VTCSOM BLOCK V PREPARATION MATERIALS

Renée LeClair
Virginia Tech Carilion School of Medicine

LibreTexts™

VTCSOM Block V Preparation Materials

This text is disseminated via the Open Education Resource (OER) LibreTexts Project (https://LibreTexts.org) and like the thousands of other texts available within this powerful platform, it is freely available for reading, printing, and "consuming."

The LibreTexts mission is to bring together students, faculty, and scholars in a collaborative effort to provide an accessible, and comprehensive platform that empowers our community to develop, curate, adapt, and adopt openly licensed resources and technologies; through these efforts we can reduce the financial burden born from traditional educational resource costs, ensuring education is more accessible for students and communities worldwide.

Most, but not all, pages in the library have licenses that may allow individuals to make changes, save, and print this book. Carefully consult the applicable license(s) before pursuing such effects. Instructors can adopt existing LibreTexts texts or Remix them to quickly build course-specific resources to meet the needs of their students. Unlike traditional textbooks, LibreTexts' web based origins allow powerful integration of advanced features and new technologies to support learning.



LibreTexts is the adaptable, user-friendly non-profit open education resource platform that educators trust for creating, customizing, and sharing accessible, interactive textbooks, adaptive homework, and ancillary materials. We collaborate with individuals and organizations to champion open education initiatives, support institutional publishing programs, drive curriculum development projects, and more.

The LibreTexts libraries are Powered by NICE CXone Expert and was supported by the Department of Education Open Textbook Pilot Project, the California Education Learning Lab, the UC Davis Office of the Provost, the UC Davis Library, the California State University Affordable Learning Solutions Program, and Merlot. This material is based upon work supported by the National Science Foundation under Grant No. 1246120, 1525057, and 1413739.

Any opinions, findings, and conclusions or recommendations expressed in this material are those of the author(s) and do not necessarily reflect the views of the National Science Foundation nor the US Department of Education.

Have questions or comments? For information about adoptions or adaptions contact info@LibreTexts.org or visit our main website at https://LibreTexts.org.

This text was compiled on 02/08/2026

TABLE OF CONTENTS

Licensing

1: Basic Microbiology and Infection Control

- 1.1: Classification - The Three Domain System
- 1.2: Sizes, Shapes, and Arrangements of Bacteria
- 1.3: The Peptidoglycan Cell Wall
  - 1.3.1: Damage of the Cell Wall
  - 1.3A: The Gram-Positive Cell Wall
  - 1.3B: The Gram-Negative Cell Wall
  - 1.3C: The Acid-Fast Cell Wall
- 1.4: Structures Outside the Cell Wall
  - 1.4A: Glycocalyx (Capsules) and Biofilms
  - 1.4B: Flagella
  - 1.4C: Fimbriae and Pili
- 1.5: Cellular Components within the Cytoplasm
  - 1.5A: Cytoplasm
  - 1.5B: The Bacterial Chromosome and Nucleoid
  - 1.5C: Plasmids and Transposons
  - 1.5D: Ribosomes
  - 1.5E: Endospores
  - 1.5F: Inclusion Bodies and Organelles Used for Photosynthesis
- 1.6: An Overview to Control of Microorganisms
- 1.7: Ways in which Chemical Control Agents Affect Bacteria
- 1.8: Ways in which Bacteria May Resist Chemical Control Agents

2: Pathogenicity

- 2.1: Overview of Microbe-Host Interactions
  - 2.1A: Normal Microbiota and Host Relationships
  - 2.1B: Opportunistic Microorganisms
  - 2.1C: Cooperation Among Microorganisms
- 2.2: Penetrating Host Defenses
  - 2.2A: Penetrating Host Defenses
  - 2.2B: Pili and Pilus Assembly
  - 2.2C: Biofilms and Infections
- 2.3: Damaging Host Cells
  - 2.3A: Toxins
  - 2.3B: Direct Damage
  - 2.3C: Type III and Type IV Secretion
  - 2.3D: Plasmids and Lysogeny
  - 2.3E: Siderophores
- 2.4: Surviving Within the Host and Exiting the Host
  - 2.4A: Intracellular Pathogens
  - 2.4B: Extracellular Immune Avoidance

- 2.4C: Regulating Virulence
- 2.4D: Portals of Exit
- 2.5: Pathogenicity and Other Microbes
  - 2.5A: Fungi
  - 2.5B: Protozoa
  - 2.5C: Helminths
  - 2.5D: Algae

3: Bacteria

- 3.1: Clostridium tetani
- 3.2: Escherichia coli
- 3.3: Haemophilus influenzae
- 3.4: Helicobacter pylori
- 3.5: Neisseria gonorrhoeae
- 3.6: Neisseria meningitidis
- 3.7: Staphylococcus aureus
- 3.8: Streptococcus pneumoniae
- 3.9: Streptococcus pyogenes
- 3.10: Vibrio cholerae

4: Culturing Bacteria

- 4.1: Culture Media
- 4.2: Complex and Synthetic Media
- 4.3: Selective and Differential Media
- 4.4: Aseptic Technique, Dilution, Streaking, and Spread Plates
- 4.5: Special Culture Techniques

5: Entry into the Host

- 5.1: Portals of Microbe Entry
- 5.2: Colonization and Growth
- 5.3: Pathogenicity Islands and Virulence Factors
- 5.4: Adherence
- 5.5: Host Risk Factors
- 5.6: Innate Resistance

6: Bacterial Infections

- 6.1: Bacterial Diseases of the Respiratory System
  - 6.1A: Pharyngitis
    - 1.1: Scarlet Fever
  - 6.1C: Diphtheria
  - 6.1D: Otitis Media
  - 6.1E: Whooping Cough
  - 6.1F: Tuberculosis
  - 6.1G: Bacterial Pneumonias
- 6.2: Bacterial Diseases of the Mouth
  - 6.2A: Tooth and Gum Infections
  - 6.2B: Dental Caries

- 6.2C: Periodontal Disease
- 6.3: Bacterial Diseases of the Digestive System
  - 6.3A: Bacterial Gastroenteritis
  - 6.3B: Staphylococcal Food Poisoning
  - 6.3C: Salmonellosis
  - 6.3D: Typhoid Fever
  - 6.3E: Cholera
  - 6.3F: Noncholera Vibrios
  - 6.3G: Pathogenic Escherichia coli
  - 6.3H: Campylobacter
  - 6.3I: Peptic Ulcer Disease
  - 6.3J: Listeriosis
- 6.4: Bacterial Diseases of the Urinary System
  - 6.4A: Urinary Tract Infection (UTI)
  - 6.4B: Cystitis
  - 6.4C: Pyelonephritis
  - 6.4D: Leptospirosis
- 6.5: Bacterial Diseases of the Reproductive System
  - 6.5A: Prostatitis
  - 6.5B: Prostatitis
  - 6.5C: Gonorrhea
  - 6.5D: Nongonococcal Urethritis (NGU)
  - 6.5E: Pelvic Inflammatory Disease (PID)
  - 6.5F: Syphilis
  - 6.5G: Genital Ulcer Diseases
  - 6.5H: Lymphogranuloma Venereum
  - 6.5I: Group B Streptococcus Colonization
  - 6.5J: Chancroid (Soft Chancre)
  - 6.5K: Bacterial Vaginosis
  - 6.5L: Chlamydia
- 6.6: Microbial Diseases of the Skin
  - 6.6A: Structure of the Skin- Epidermis
  - 6.6B: Microbiota of the Skin
  - 6.6C: Bacterial Skin Diseases
  - 6.6D: Viral Skin Diseases
  - 6.6E: Fungal Skin and Nail Diseases
  - 6.6F: Parasitic Skin Diseases
- 6.7: Microbial Diseases of the Eye
  - 6.7A: Anatomy of the Eye
  - 6.7B: Normal Eye Microbiota
  - 6.7C: Bacterial Eye Diseases
  - 6.7D: Other Infectious Eye Diseases
- 6.8: Microbial Diseases of the Nervous System
  - 6.8A: Functions of the Nervous System
  - 6.8B: Subdivisions of the Nervous System
  - 6.8C: Meningitis
  - 6.8D: Botulism
  - 6.8E: Leprosy

- 6.8F: Tetanus
- 6.8G: Paralysis-Causing Bacterial Neurotoxins

7: Innate Nonspecific Host Defenses

- 7.1: Physical Defenses
- 7.2: Chemical Defenses
- 7.3: Cellular Defenses
- 7.4: Pathogen Recognition and Phagocytosis

8: Basic Immunology Review

- 8.1: Overview of the Immune System
- 8.2: Anatomical Barriers to Infection, Mechanical Removal of Microbes, and Bacterial Antagonism by Normal Body Microbiota
- 8.3: Cells and Organs of the Immune System
- 8.4: Antimicrobial Enzymes and Antimicrobial Peptides
- 8.5: The Complement System

9: Innate Immunity

- 9.1: Overview of Immunity
- 9.2: The Innate Immune Response
- 9.3: The Innate Immune System- An Overview
- 9.4: Overview of Human-Microbial Reactions
- 9.5: Natural Killer Cells
- 9.6: Physical and Chemical Barriers
- 9.7: The Complement System
- 9.8: Pathogen Recognition
- 9.9: Defense Cells in the Blood- The Leukocytes
- 9.10: Defense Cells in the Tissue - Dendritic Cells, Macrophages, and Mast Cells
- 9.11: Early Induced Innate Immunity
  - 9.11A: Pathogen-Associated Molecular Patterns (PAMPs) and Danger-Associated Molecular Patterns (DAMPs)
  - 9.11B: Pattern-Recognition Receptors (PRRs)
  - 9.11C: Cytokines Important in Innate Immunity
  - 9.11D: Harmful Effects Associated with Abnormal Pattern-Recognition Receptor Responses, Variations in Innate Immune Signaling Pathways, and/or Levels of Cytokine Production
  - 9.11E: Phagocytosis
  - 9.11F: Natural Killer Cells (NK Cells) and Invariant Natural Killer T-Lymphocytes (iNKT Cells)
  - 9.11G: Inflammation
  - 9.11H: Nutritional Immunity
  - 9.11I: Fever
  - 9.11J: The Acute Phase Response
  - 9.11K: Intraepithelial T-lymphocytes and B-1 cells

10: Adaptive Immunity

- 10.1: Immunodeficiency
  - 10.1.E: Immunodeficiency (Exercises)
- 10.2: Hypersensitivities
  - 10.2.E: Hypersensitivities (Exercises)

- 10.3: Introduction to Adaptive Immunity
  - 10.3.1: An Overview of Innate and Adaptive Immunity
  - 10.3.2: Antigens and Epitopes
  - 10.3.3: Major Cells and Key Cell Surface Molecules Involved in Adaptive Immune Responses
    - 10.3.3A: Major Histocompatibility Complex (MHC) Molecules
    - 10.3.3B: Antigen-Presenting Cells (APCs)
    - 10.3.3C: T4-Lymphocytes (T4-Cells)
    - 10.3.3D: T8-Lymphocytes (T8-Cells)
    - 10.3.3E: Invarient Natural Killer T-Lymphocytes (iNKT Cells)
    - 10.3.3F: B-Lymphocytes (B-Cells)
    - 10.3.3G: Natural Killer Cells (NK Cells)
  - 10.3.4: The Lymphoid System
  - 10.3.5: An Overview of the Steps Involved in Adaptive Immune Responses
  - 10.3.E: Introduction to Adaptive Immunity (Exercises)
- 10.4: Humoral Immunity
  - 10.4.1: Antibodies (Immunoglobulins)
    - 10.4.1B: Antibody Structure
    - 10.4.1C: The 5 Classes (Isotypes) of Human Antibodies
    - 10.4.1D: Generation of Antibody Diversity
    - 10.4.1E: Clonal Selection and Clonal Expansion
    - 10.4.1F: Anamnestic (Memory) Response
  - 10.4.2: Ways That Antibodies Help to Defend the Body
    - 10.4.2A: Opsonization
    - 10.4.2B: Cytolysis by the Membrane Attack Complex (MAC)
    - 10.4.2C: Antibody-dependent Cellular Cytotoxicity (ADCC) by Natural Killer Cells
    - 10.4.2D: Neutralization of Exotoxins
    - 10.4.2E: Neutralization of Viruses
    - 10.4.2F: Preventing Bacterial Adherence
    - 10.4.2G: Agglutination of Microorganisms
    - 10.4.2H: Immobilization of Bacteria and Protozoans
    - 10.4.2I: Promoting an Inflammatory Response
  - 10.4.3: Naturally and Artificially Acquired Active and Passive Immunity
    - 10.4.3A: Naturally Acquired Immunity
    - 10.4.3B: Artificially Acquired Immunity
  - 10.4.E: Humoral Immunity (Exercises)
- 10.5: Cell-Mediated Immunity
  - 10.5.1: Cell-Mediated Immunity - An Overview
  - 10.5.2: Activating Antigen-Specific Cytotoxic T- Lymphocytes
  - 10.5.3: Activating Macrophages and NK Cells
  - 10.5.4: Stimulating Cells to Secrete Cytokines
  - 10.5.E: Cell-Mediated Immunity (Exercises)

11: Specific Adaptive Host Defenses

- 11.1: Architecture of the Immune System
- 11.2: Antigens, Antigen Presenting Cells, and Major Histocompatibility Complexes
- 11.3: T Lymphocytes
- 11.4: B Lymphocytes and Antibodies

12: Hypersensitivities

- 12.1: Type I (Anaphylactic) Reactions
- 12.2: Diagnosis and Treatment of Allergy
- 12.3: Type II (Cytotoxic) Reactions
- 12.4: Type III (Immune Complex) Reactions
- 12.5: Type IV (Delayed Cell-Mediated) Reactions
- 12.6: Immunity Disorders- Hypersensitivity

13: Laboratory Analysis of the Immune Response

- 13.1: Practical Applications of Monoclonal and Polyclonal Antibodies
- 13.2: Detecting Antigen-Antibody Complexes in vitro
- 13.3: Agglutination Assays
- 13.4: Enzyme Immunoassays (EIA) and Enzyme-Linked Immunosorbent Assays (ELISA)
- 13.5: Fluorescent Auto-Antibody Techniques
- 13.E: Laboratory Analysis of the Immune Response (Exercises)

14: Immunodeficiencies

- 14.1: Immunity Disorders- Autoimmune Diseases
  - 14.1A: Immunodeficiency
- 14.2: Autoimmune Disorders
- 14.3: Superantigens
- 14.4: Immunity Disorders- Immunodeficiencies
- 14.5: Cell-Mediated Autoimmune Reactions
- 14.6: Immune Complex Autoimmune Reactions
- 14.7: Cytotoxic Autoimmune Reactions
- 14.8: Primary Immunodeficiency
- 14.9: Primary Immunodeficiency Diseases
- 14.10: Secondary Immunodeficiency
- 14.11: Secondary Immunodeficiency Diseases
- 14.12: Immunotherapy for Cancer
- 14.13: The Roles of Genetics and Gender in Autoimmune Disease

15: Acellular Pathogens

- 15.1: Viruses
- 15.2: The Viral Life Cycle
- 15.3: Isolation, Culture, and Identification of Viruses
- 15.4: Viroids, Virusoids, and Prions
- 15.5: Viral Replication
  - 15.5A: General Features of Virus Replication
  - 15.5B: Steps of Virus Infections
  - 15.5C: Tissue Tropism in Animal Viruses
  - 15.5D: Animal Viruses
  - 15.5E: Plant Virus Life Cycles
- 15.6: Viral Diversity
  - 15.6A: Overview of Bacterial Viruses
  - 15.6B: RNA Bacteriophages
  - 15.6C: Single-Stranded DNA Bacteriophages

- 15.6D: Double-Stranded DNA Bacteriophages
- 15.6E: Mu- A Double-Stranded Transposable DNA Bacteriophage
- 15.6F: Virulent Bacteriophages and T4
- 15.6G: Temperate Bacteriophages - Lambda and P1
- 15.6H: Viruses of Archaea

- 15.7: Positive-Strand RNA Viruses in Animals
  - 15.7A: Positive-Strand RNA Viruses of Animals
  - 15.7B: Virus Attachment and Genome Entry
  - 15.7C: Viral Replication and Gene Expression
  - 15.7D: Viral Exit
- 15.8: Retroviruses- Double-Stranded RNA Viruses
  - 15.8A: Double-Stranded RNA Viruses - Retroviruses
  - 15.8B: HIV Attachment and Host Cell Entry
  - 15.8C: Retroviral RNA Genome
  - 15.8D: Replicative Cycle of HIV
- 15.9: Negative-Strand RNA Viruses in Animals
  - 15.9.1: Negative-Strand RNA Viruses of Animals
  - 15.9.2: Attachment and Entry to the Host Cell
  - 15.9.3: Replicative Cycle of Influenza A
- 15.10: DNA Viruses in Eukaryotes
  - 15.10.1: Plant DNA Viruses
  - 15.10.2: Replication of Double-Stranded DNA Viruses of Animals
  - 15.10.3: Double-Stranded DNA Viruses - Herpesviruses
  - 15.10.4: Attachment and Entry of Herpes Simplex
  - 15.10.5: Replication of Herpes Simplex Virus
  - 15.10.6: Immunodeficiency
  - 15.10.7: Double-Stranded DNA Viruses - Pox Viruses
  - 15.10.8: Double-Stranded DNA Viruses- Adenoviruses
  - 15.10.9: Retroviruses and Hepadnavirus
  - 15.10.10: Treatment of Animal Viral Infections
- 15.11: Viruses and Cancer
  - 15.11.1: Cancer Viruses
  - 15.11.2: DNA Oncogenic Viruses
  - 15.11.3: RNA Oncogenic Viruses
- 15.12: Overview of Viruses
  - 15.12.1: Discovery and Detection of Viruses
  - 15.12.2: Nature of the Virion
  - 15.12.3: Viral Genomes
  - 15.12.4: Host Range
  - 15.12.5: Viral Size
- 15.13: Structure of Viruses
  - 15.13A: Viral Morphology
  - 15.13B: General Morphology
  - 15.13C: Complex and Asymmetrical Virus Particles
- 15.14: Classifying Viruses
  - 15.14.1: The International Committee on Taxonomy of Viruses
  - 15.14.2: The Baltimore Virus Classification

- 15.14.3: Evolution of Viruses
- 15.14.4: Medical Importance of Viruses
- 15.15: Culturing Viruses
  - 15.15A: Batch Culture of Bacteriophages
  - 15.15B: Tissue Culture of Animal Viruses
  - 15.15C: Inoculation of Live Animals
  - 15.15D: Viral Identification
- 15.16: Subviral Entities
  - 15.16A: Defective Viruses
  - 15.16B: Viroids
  - 15.16C: Prions
- 15.17: Viral Ecology
  - 15.17A: Emergence of Viral Pathogens
  - 15.17B: Viral Roles in Ecosystems

16: The Eukaryotes of Microbiology

- 16.1: Unicellular Eukaryotic Microorganisms
- 16.2: Parasitic Helminths
- 16.3: Fungi
- 16.4: Algae
- 16.5: Lichens
- 16.E: The Eukaryotes of Microbiology (Exercises)

17: Systemic Infections

- 17.1: Respiratory System Infections
  - 17.1.1: Anatomy and Normal Microbiota of the Respiratory Tract
  - 17.1.2: Bacterial Infections of the Respiratory Tract
  - 17.1.3: Viral Infections of the Respiratory Tract
  - 17.1.4: Respiratory Mycoses
  - 17.1.E: Respiratory System Infections (Exercises)
- 17.2: Urogenital System Infections
  - 17.2.1: Anatomy and Normal Microbiota of the Urogenital Tract
  - 17.2.2: Bacterial Infections of the Urinary System
  - 17.2.3: Bacterial Infections of the Reproductive System
  - 17.2.4: Viral Infections of the Reproductive System
  - 17.2.5: Fungal Infections of the Reproductive System
  - 17.2.6: Protozoan Infections of the Reproductive System
  - 17.2.E: Urogenital System Infections (Exercises)
- 17.3: Digestive System Infections
  - 17.3.1: Anatomy and Normal Microbiota of the Digestive System
  - 17.3.2: Microbial Diseases of the Mouth and Oral Cavity
  - 17.3.3: Bacterial Infections of the Gastrointestinal Tract
  - 17.3.4: Viral Infections of the Gastrointestinal Tract
  - 17.3.5: Protozoan Infections of the Gastrointestinal Tract
  - 17.3.6: Helminthic Infections of the Gastrointestinal Tract
  - 17.3.E: Digestive System Infections (Exercises)
- 17.4: Circulatory and Lymphatic System Infections

- 17.4.1: Anatomy of the Circulatory and Lymphatic Systems
- 17.4.2: Bacterial Infections of the Circulatory and Lymphatic Systems
- 17.4.3: Viral Infections of the Circulatory and Lymphatic Systems
- 17.4.4: Parasitic Infections of the Circulatory and Lymphatic Systems
- 17.4.E: Circulatory and Lymphatic System Infections (Exercises)

- 17.5: Nervous System Infections
  - 17.5.1: Anatomy of the Nervous System
  - 17.5.2: Bacterial Diseases of the Nervous System
  - 17.5.3: Acellular Pathogenic Diseases of the Nervous System
  - 17.5.4: Neuromycoses and Parasitic Diseases of the Nervous System
  - 17.5.E: Nervous System Infections (Exercises)
- 17.6: Fungal Diseases of the Respiratory System
  - 17.6.1: Histoplasmosis
  - 17.6.2: Coccidiomycosis
  - 17.6.3: Pneumocystis Pneumonia
  - 17.6.4: Blastomycosis
  - 17.6.5: Other Fungi Involved in Respiratory Disease
- 17.7: Fungal and Protozoan Diseases of the Digestive System
  - 17.7.1: Ergot Poisoning
  - 17.7.2: Aflatoxin Poisoning
  - 17.7.3: Giardiasis
  - 17.7.4: Cryptosporidiosis
  - 17.7.5: Cyclospora Diarrheal Infection
  - 17.7.6: Amoebic Dysentery (Amoebiasis)
  - 17.7.7: Legionellosis
- 17.8: Helminthic Diseases of the Digestive System
  - 17.8.1: Tapeworms
  - 17.8.2: Hydatid Disease
  - 17.8.3: Nematodes
- 17.9: Fungal and Protozoan Diseases of the Reproductive System
  - 17.9.1: Vulvovaginal Candidiasis
  - 17.9.2: Trichomoniasis
  - 17.9.3: The TORCH Panel of Tests
- 17.10: Fungal Skin and Nail Diseases
- 17.11: Parasitic Skin Diseases
- 17.12: Other Infectious Eye Diseases
- 17.13: Fungal, Protozoan, Prion, and Other Diseases of the Nervous System
  - 17.13.1: Cryptococcosis
  - 17.13.2: African Trypanosomiasis
  - 17.13.3: Amoebic Meningoencephalitis
  - 17.13.4: Bovine Spongiform Encephalopathy
  - 17.13.5: Variant Creutzfeldt-Jakob Disease
  - 17.13.6: Chronic Fatigue Syndrome

18: Immunization

- 18.1: Passive Immunization
- 18.2: Vaccination

- 18.3: Types of Vaccines
- 18.4: Development of New Vaccines
- 18.5: Vaccine Safety

19: Vaccine Safety

- 19.1: Non-Severe Events
- 19.2: Anaphylaxis
- 19.3: Vaccine Facts
- 19.4: Self Assessment
- 19.5: Vaccine Safety
- 19.6: Evaluation of Vaccines Pre-License
- 19.7: Canada Vigilance Program
- 19.8: Reflective Questions
- 19.9: Key Takeaways
- 19.10: References

20: Human Health and Disease

- 20.1: Human Health and Disease
- 20.2: The Gut Microbiome
- 20.3: The Oral Microbiome
- 20.4: The Skin Microbiome
- 20.5: The Respiratory Microbiome
- 20.6: The Vaginal Microbiome
- 20.7: Mental Health and Multi-Microbiome Interactions

21: Cancer Immunobiology and Immunotherapy

22: Skin and Eye Infections

- 22.1: Anatomy and Normal Microbiota of the Skin and Eyes
- 22.2: Bacterial Infections of the Skin and Eyes
- 22.3: Viral Infections of the Skin and Eyes
- 22.4: Mycoses of the Skin and Eyes
- 22.5: Protozoan and Helminthic Infections of the Eyes

Index

Glossary

Detailed Licensing

Detailed Licensing

Licensing

*A detailed breakdown of this resource's licensing can be found in **Back Matter/Detailed Licensing**.*

CHAPTER OVERVIEW

1: Basic Microbiology and Infection Control

Microbiology is the study of microscopic organisms, those being unicellular (single cell), multicellular (cell colony), or acellular (lacking cells). As an application of microbiology, medical microbiology is often introduced with medical principles of immunology as microbiology and immunology. Otherwise, microbiology, virology, and immunology as basic sciences have greatly exceeded the medical variants, applied sciences.

1.1: Classification - The Three Domain System
1.2: Sizes, Shapes, and Arrangements of Bacteria
1.3: The Peptidoglycan Cell Wall
1.3.1: Damage of the Cell Wall
1.3A: The Gram-Positive Cell Wall
1.3B: The Gram-Negative Cell Wall
1.3C: The Acid-Fast Cell Wall
1.4: Structures Outside the Cell Wall
1.4A: Glycocalyx (Capsules) and Biofilms
1.4B: Flagella
1.4C: Fimbriae and Pili
1.5: Cellular Components within the Cytoplasm
1.5A: Cytoplasm
1.5B: The Bacterial Chromosome and Nucleoid
1.5C: Plasmids and Transposons
1.5D: Ribosomes
1.5E: Endospores
1.5F: Inclusion Bodies and Organelles Used for Photosynthesis
1.6: An Overview to Control of Microorganisms
1.7: Ways in which Chemical Control Agents Affect Bacteria
1.8: Ways in which Bacteria May Resist Chemical Control Agents

This page titled 1: Basic Microbiology and Infection Control is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

This page titled 1: Basic Microbiology and Infection Control is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

1.1: Classification - The Three Domain System

Learning Objectives

1. Define phylogeny.
2. Name the 3 Domains of the 3 Domain system of classification and recognize a description of each.
3. Name the four kingdoms of the Domain Eukarya and recognize a description of each.
4. Define horizontal gene transfer.

The Earth is 4.6 billion years old and microbial life is thought to have first appeared between 3.8 and 3.9 billion years ago; in fact, 80% of Earth's history was exclusively microbial life. Microbial life is still the dominant life form on Earth. It has been estimated that the total number of microbial cells on Earth on the order of 2.5 X 10^{30} cells, making it the major fraction of biomass on the planet.

Phylogeny refers to the evolutionary relationships between organisms. The Three Domain System, proposed by Woese and others, is an evolutionary model of phylogeny based on differences in the sequences of nucleotides in the cell's ribosomal RNAs (rRNA), as well as the cell's membrane lipid structure and its sensitivity to antibiotics. Comparing rRNA structure is especially useful. Because rRNA molecules throughout nature carry out the same function, their structure changes very little over time. Therefore similarities and dissimilarities in rRNA nucleotide sequences are a good indication of how related or unrelated different cells and organisms are.

There are various hypotheses as to the origin of prokaryotic and eukaryotic cells. Because all cells are similar in nature, it is generally thought that all cells came from a common ancestor cell termed the **last universal common ancestor (LUCA)**. These LUCAs eventually evolved into three different cell types, each representing a domain. The three domains are the *Archaea*, the *Bacteria*, and the *Eukarya*.

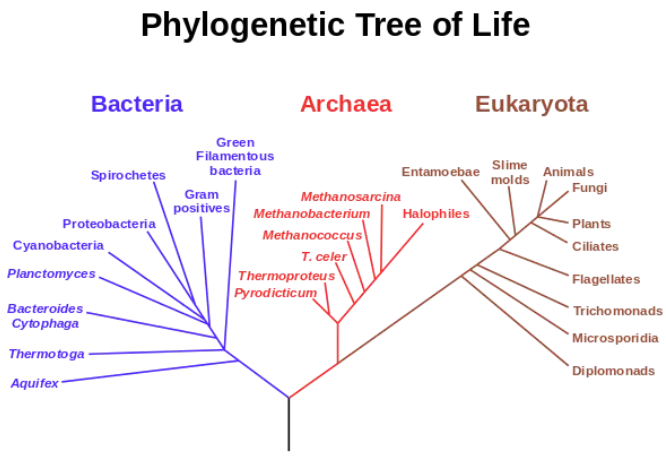


Figure **1.1.1**: A phylogenetic tree based on rRNA data, showing the separation of bacteria, archaea, and eukaryota domains.

More recently various fusion hypotheses have begun to dominate the literature. One proposes that the diploid or 2N nature of the eukaryotic genome occurred after the fusion of two haploid or 1N prokaryotic cells. Others propose that the domains *Archaea* and *Eukarya* emerged from a common archaeal-eukaryotic ancestor that itself emerged from a member of the domain *Bacteria*. Some of the evidence behind this hypothesis is based on a "superphylum" of bacteria called PVC, members of which share some characteristics with both archaea and eukaryotes. There is growing evidence that eukaryotes may have originated within a subset of archaea. In any event, it is accepted today that there are three distinct domains of organisms in nature: *Bacteria*, *Archaea*, and *Eukarya*. A description of the three domains follows.

Domains?

There is a "superphylum" of bacteria called PVC, referring to the three members of that superphylum: the Planctomycetes, the Verrucomicrobia, and the Chlamydiae. Members of the PVC, while belonging to the domain *Bacteria*, show some features of

the domains *Archaea* and *Eukarya*.

Some of these bacteria show cell compartmentalization wherein membranes surround portions of the cell interior, such as groups of ribosomes or DNA, similar to eukaryotic cells. Some divide by budding or contain sterols in their membranes, again similar to eukaryotes. Some lack peptidoglycan, similar to eukaryotes and archaea. It has been surmised that these bacteria migh be an intermediate step between an ancestor that emerged from a bacterium (domain *Bacteria*) and an archael-eukaryotic ancestor prior to its split into the domains *Archaea* and *Eukarya*.

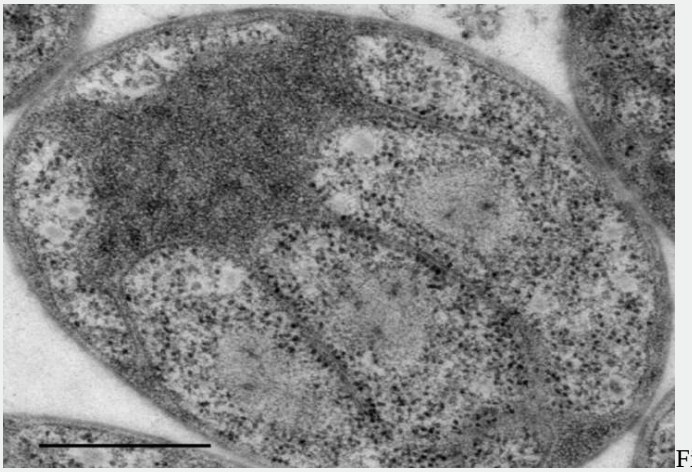


Figure **1.1.2**: Electron micrograph of the bacterium Gemmata obscuriglobus, a planctomycete noted for its highly complex membrane morphology, illustrating representative morphologies. Scale bar = 500nm. Santarella-Mellwig R, Franke J, Jaedicke A, Gorjanacz M, Bauer U, Budd A, et al. (2010) The Compartmentalized Bacteria of the Planctomycetes-Verrucomicrobia-Chlamydiae Superphylum Have Membrane Coat-Like Proteins. PLoS Biol 8(1): e1000281. doi:10.1371/journal.pbio.1000281

The Archaea (archaebacteria)

The *Archaea* possess the following characteristics:

a. *Archaea* are prokaryotic cells.
b. Unlike the *Bacteria* and the *Eukarya*, the *Archaea* have membranes composed of branched hydrocarbon chains (many also containing rings within the hydrocarbon chains) attached to glycerol by ether linkages (Figure **1.1.3**).
c. The cell walls of *Archaea* contain no peptidoglycan.
d. *Archaea* are not sensitive to some antibiotics that affect the *Bacteria*, but are sensitive to some antibiotics that affect the *Eukarya*.
e. *Archaea* contain rRNA that is unique to the *Archaea* as indicated by the presence molecular regions distinctly different from the rRNA of *Bacteria* and *Eukarya*.

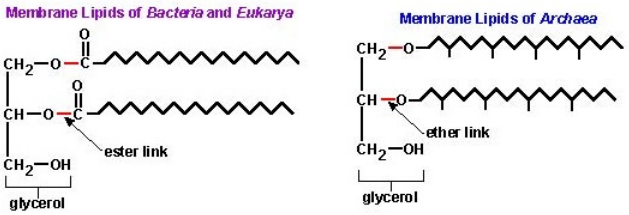


Figure **1.1.3**: Membrane Lipids of Archaea, Bacteria, and Eukarya. The Bacteria and the Eukarya have membranes composed of unbranched fatty acid chains attached to glycerol by ester linkages. The Archaea have membranes composed of branched hydrocarbon chains attached to glycerol by ether linkages.

Archaea often live in extreme environments and include methanogens, extreme halophiles, and hyperthermophiles. One reason for this is that the ether-containing linkages in the *Archaea* membranes is more stabile than the ester-containing linkages in the *Bacteria* and *Eukarya* and are better able to withstand higher temperatures and stronger acid concentrations.

The *Bacteria* (eubacteria)

Bacteria (also known as eubacteria or "true bacteria") are prokaryotic cells that are common in human daily life, encounter many more times than the archaebacteria. Eubacteria can be found almost everywhere and kill thousands upon thousands of people each year, but also serve as antibiotics producers and food digesters in our stomachs. The *Bacteria* possess the following characteristics:

a. *Bacteria* are prokaryotic cells.
b. Like the *Eukarya*, they have membranes composed of unbranched fatty acid chains attached to glycerol by ester linkages (Figure **1.1.3**).
c. The cell walls of *Bacteria*, unlike the *Archaea* and the Eukarya, contain peptidoglycan.
d. *Bacteria* are sensitive to traditional antibacterial antibiotics but are resistant to most antibiotics that affect *Eukarya*.
e. *Bacteria* contain rRNA that is unique to the *Bacteria* as indicated by the presence molecular regions distinctly different from the rRNA of *Archaea* and *Eukarya*.

Bacteria include mycoplasmas, cyanobacteria, Gram-positive bacteria, and Gram-negative bacteria.

The *Eukarya* (eukaryotes)

The *Eukarya* (also spelled *Eucarya*) possess the following characteristics:

a. *Eukarya* have eukaryotic cells.
b. Like the *Bacteria*, they have membranes composed of unbranched fatty acid chains attached to glycerol by ester linkages (Figure **1.1.3**).
c. Not all *Eukarya* possess cells with a cell wall, but for those *Eukarya* having a cell wall, that wall contains no peptidoglycan.
d. *Eukarya* are resistant to traditional antibacterial antibiotics but are sensitive to most antibiotics that affect eukaryotic cells.
e. *Eukarya* contain rRNA that is unique to the *Eukarya* as indicated by the presence molecular regions distinctly different from the rRNA of *Archaea* and *Bacteria*.

The *Eukarya* are subdivided into the following fourkingdoms:

1. Protista Kingdom: Protista are simple, predominately unicellular eukaryotic organisms. Examples includes slime molds, euglenoids, algae, and protozoans.
2. Fungi Kingdom: Fungi are unicellular or multicellular organisms with eukaryotic cell types. The cells have cell walls but are not organized into tissues. They do not carry out photosynthesis and obtain nutrients through absorption. Examples include sac fungi, club fungi, yeasts, and molds.
3. Plantae Kingdom: Plants are multicellular organisms composed of eukaryotic cells. The cells are organized into tissues and have cell walls. They obtain nutrients by photosynthesis and absorption. Examples include mosses, ferns, conifers, and flowering plants.
4. Animalia Kingdom: Animals are multicellular organisms composed of eukaryotic cells. The cells are organized into tissues and lack cell walls. They do not carry out photosynthesis and obtain nutrients primarily by ingestion. Examples include sponges, worms, insects, and vertebrates.

It used to be thought that the changes that allow microorganisms to adapt to new environments or alter their virulence capabilities was a relatively slow process occurring within an organism primarily through mutations, chromosomal rearrangements, gene deletions and gene duplications. Those changes would then be passed on to that microbe's progeny and natural selection would occur. This gene transfer from a parent organism to its offspring is called vertical gene transmission.

It is now known that microbial genes are transferred not only vertically from a parent organism to its progeny, but also horizontally to relatives that are only distantly related, e.g., other species and other genera. This latter process is known as horizontal gene transfer. Through mechanisms such as transformation, transduction, and conjugation, genetic elements such as plasmids, transposons, integrons, and even chromosomal DNA can readily be spread from one microorganism to another. As a result, the old three-branched "tree of life" in regard to microorganisms (Figure **1.1.1**) now appears to be more of a "net of life."

Microbes are known to live in remarkably diverse environments, many of which are extremely harsh. This amazing and rapid adaptability is a result of their ability to quickly modify their repertoire of protein functions by modifying, gaining, or losing their genes. This gene expansion predominantly takes place by horizontal transfer.

Summary

1. Phylogeny refers to the evolutionary relationships between organisms.
2. Organisms can be classified into one of three domains based on differences in the sequences of nucleotides in the cell's ribosomal RNAs (rRNA), the cell's membrane lipid structure, and its sensitivity to antibiotics.
3. The three domains are the Archaea, the Bacteria, and the Eukarya.
4. Prokaryotic organisms belong either to the domain Archaea or the domain Bacteria; organisms with eukaryotic cells belong to the domain Eukarya.
5. Microorganism transfer genes to other microorganisms through horizontal gene transfer - the transfer of DNA to an organism that is not its offspring.

This page titled 1.1: Classification - The Three Domain System is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **1.3: Classification - The Three Domain System** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

1.2: Sizes, Shapes, and Arrangements of Bacteria

Learning Objectives

1. List the three basic shapes of bacteria.
2. List and describe 5 different arrangements of cocci.
3. Define and give the abbreviation for the metric unit of length termed micrometer and state the average size of a coccus-shaped bacterium and a rod-shaped bacterium.
4. List and describe 2 different arrangements of bacilli.
5. List and describe 3 different spiral forms of bacteria.

Bacteria are prokaryotic, single-celled, microscopic organisms (Exceptions have been discovered that can reach sizes just visible to the naked eye. They include *Epulopiscium fishelsoni*, a bacillus-shaped bacterium that is typically 80 micrometers (µm) in diameter and 200-600 µm long, and *Thiomargarita namibiensis*, a spherical bacterium between 100 and 750 µm in diameter.)

a. generally much smaller than eukaryotic cells.
b. very complex despite their small size. Even though bacteria are single-celled organisms, they are able to communicate with one another through a process called quorum sensing. In this way they can function as a multicellular population rather than as individual bacteria. This will be discussed in greater detail in Unit 2.

For More Information: Bacterial Communication through Quorum Sensing

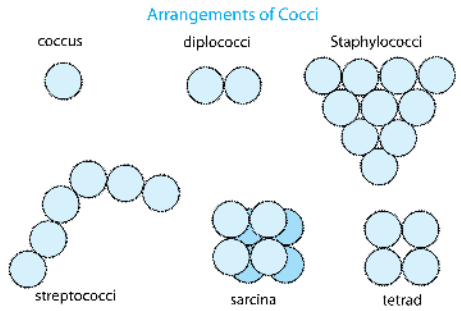


Figure 1.2.2.1.1: Arrangement of cocci bacteria. image used with permission from Mariana Ruiz.

a. Division in **one plane** produces either a diplococcus or streptococcus arrangement.

diplococcus: cocci arranged in pairs (see Figure 1.2.2)

- scanning electron micrograph of a *Streptococcus pneumoniae*, a diplococcus; courtesy of CDC
- scanning electron micrograph of a *Neisseria*, a diplococcus; courtesy of Dennis Kunkel's Microscopy

streptococcus: cocci arranged in chains (see Figure 1.2.3)

- scanning electron micrograph of a *Streptococcus pyogenes*, a streptococcus; courtesy of Dennis Kunkel's Microscopy
- transmission electron micrograph of *Streptococcus* from the Rockefeller University web page.
- scanning Electron Micrograph of *Enterococcus*

b. Division in **two planes** produces a tetrad arrangement.

tetrad: cocci arranged in squares of 4 (see Figure 1.2.4)

- scanning electron micrograph of *Micrococcus luteus* showing several tetrads

c. Division in **three planes** produces a sarcina arrangement.

sarcina: cocci in arranged cubes of 8 (see Figure 1.2.5)

d. Division in **random planes** produces a staphylococcus arrangement.

staphylococcus: cocci arranged in irregular, often grape-like clusters (see Figure 1.2.6)

- negative image of *Staphylococcus aureus*
- scanning electron micrograph of *Staphylococcus aureus*, a staphylococcus; courtesy of Dennis Kunkel's Microscopy
- Scanning electron micrograph of methicillin-resistant *Staphylococcus aureus* (MRSA); courtesy of CDC

An average coccus is about 0.5-1.0 micrometer (µm) in diameter. (A micrometer equals 1/1,000,000 of a meter.)

The rod or bacillus

Bacilli are rod-shaped bacteria. Bacilli all divide in one plane producing a bacillus, streptobacillus, or coccobacillus arrangement (see Figure 1.2.7).

a. **bacillus**: single bacilli (see Figure 1.2.8)
- scanning electron micrograph of a bacillus; courtesy of CDC
- scanning electron micrograph of *Escherichia coli* O157H7, a bacillus; courtesy of CDC

b. **streptobacillus**: bacilli arranged in chains (see Figure 1.2.9)

c. **coccobacillus**: oval and similar to a coccus (see Figure 1.2.9A and Figure 1.2.9B)

An average bacillus is 0.5-1.0 µm wide by 1.0-4.0 µm long.

The spiral

Spirals come in one of three **forms**, a vibrio, a spirillum, or a spirochete. (see Figure 1.2.10)

a. **vibrio**: a curved or comma-shaped rod (see Figure 1.2.11)

- scanning electron micrograph of a *Vibrio cholerae*, a vibrio; courtesy of Dennis Kunkel's Microscopy

b. **spirillum**: a thick, rigid spiral (see Figure 1.2.12)

c. **spirochete**: a thin, flexible spiral (see Figure 1.2.13)

- scanning electron micrograph of the spirochete *Leptospira*; courtesy of CDC
- scanning electron micrograph of the spirochete *Treponema pallidum*; courtesy of CDC

Spirals range in size from 1 µm to over 100 µm in length.

Exceptions to the above shapes

There are exceptions to the three basic shapes of coccus, bacillus, and spiral. They include sheathed, stalked, filamentous, square, star-shaped, spindle-shaped, lobed, trichome-forming, and pleomorphic bacteria.

Ultrasmall Bacteria

Ultrasmall bacteria (150 could fit in a single Escherichia coli) have been discovered in groundwater that was passed through a filter with a pore size of 0.2 micrometers µm). They showed an **average length of only 323 nanometers**(nm) and an average width of 242 nm. They contain DNA, an average of 42 ribosomes per bacterium, and possessed pili . It is thought that they use these pili to attach to other bacteria from which they scavenge nutrients. Because the surface to volume ratio is even

greater than in more traditional sized bacteria, they might be better designed to take up scarce nutrients from more nutrient-poor environments.

Concept map for Shapes and Arrangements of Bacteria

Summary

1. There are three basic shapes of bacteria: coccus, bacillus, and spiral.
2. Based on planes of division, the coccus shape can appear in several distinct arrangements: diplococcus, streptococcus, tetrad, sarcina, and staphylococcus.
3. The bacillus shape can appear as a single bacillus, a streptobacillus, or a coccobacillus.
4. The spiral shape can appear in several forms: vibrio, spirillum, and spirochete.
5. The metric unit micrometer (1/1,000,000 or 10^{-6} of a meter) is used to measure bacterial size.

This page titled 1.2: Sizes, Shapes, and Arrangements of Bacteria is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **2.1: Sizes, Shapes, and Arrangements of Bacteria** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

1.3: The Peptidoglycan Cell Wall

Learning Objectives

1. State the three parts of a peptidoglycan monomer and state the function of peptidoglycan in bacteria.
2. Briefly describe how bacteria synthesize peptidoglycan, indicating the roles of autolysins, bactoprenols, transglycosylases, and transpeptidases.
3. Briefly describe how antibiotics such as penicillins, cephalosporins, and vancomycin affect bacteria and relate this to their cell wall synthesis.
4. State what color Gram-positive bacteria stain after Gram staining.
5. State what color Gram-negative bacteria stain after Gram staining.
6. State what color acid-fast bacteria stain after acid-fast staining.

The mycoplasmas are the only bacteria that naturally lack a cell wall. Mycoplasmas maintain a nearly even pressure between the outside environment and the cytoplasm by actively pumping out sodium ions. Their cytoplasmic membranes also contain sterols that most likely provide added strength. The remaining bacteria in the domain *Bacteria*, with the exception of a few bacteria such as the Chlamydias, have a semirigid cell wall containing peptidoglycan. (While bacteria belonging to the domain *Archaea* also have a semirigid cell wall, it is composed of chemicals distinct from peptidoglycan such as protein or pseudomurein. We will not take up the *Archaea* here.)

Function of Peptidoglycan

Peptidoglycan prevents osmotic lysis. As seen earlier under the cytoplasmic membrane, bacteria concentrate dissolved nutrients (solute) through active transport. As a result, the bacterium's cytoplasm is usually hypertonic to its surrounding environment and the net flow of free water is into the bacterium. Without a strong cell wall, the bacterium would burst from the osmotic pressure of the water flowing into the cell.

Structure and Composition of Peptidoglycan

With the exceptions above, members of the domain *Bacteria* have a cell wall containing a semirigid, tight knit molecular complex called peptidoglycan. Peptidoglycan, also called murein, is a vast polymer consisting of interlocking chains of identical peptidoglycan monomers (Figure **1.3.1**). A peptidoglycan monomer consists of two joined amino sugars, N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM), with a pentapeptide coming off of the NAM (Figure **1.3.2**). The types and the order of amino acids in the pentapeptide, while almost identical in gram-positive and gram-negative bacteria, show some slight variation among the domain *Bacteria*.

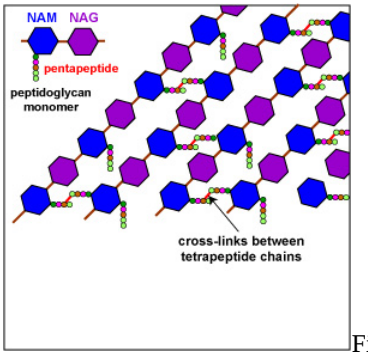


Figure **1.3.1**: Peptidoglycan is composed of cross-linked chains of peptidoglycan monomers (NAG-NAM-pentapeptide). Transglycosylase enzymes join these monomers join together to form chains. Transpeptidase enzymes then cross-link the chains to provide strength to the cell wall and enable the bacterium to resist osmotic lysis. (left) In a peptidoglycan monomer of S. aureus, the pentapeptide coming off the NAM is composed of the amino acids L-alanine, D-glutamine, L-lysine, and two D-alanines. The peptide cross-link forms by formation of a short peptide interbridge consisting of 5 glycines. In the process the terminal D-alanine is cleaved from the pentapeptide to form a tetrapeptide in the peptidogycan. (right) In a peptidoglycan monomer of E. coli, the pentapeptide coming off the NAM is composed of

the amino acids L-alanine, D-glutamic acid, meso-diaminopimelic acid, and two D-alanines. The peptide cross-link forms between the diaminopimelic acid of one peptide chain with the D-alanine of another and in the process the terminal D-alanine is cleaved from the pentapeptide to form a tetrapeptide in the peptidogycan.

The peptidoglycan monomers are synthesized in the cytosol of the bacterium where they attach to a membrane carrier molecule called bactoprenol. As discussed below, The bactoprenols transport the peptidoglycan monomers across the cytoplasmic membrane and work with the enzymes discussed below to insert the monomers into existing peptidoglycan enabling bacterial growth following binary fission.

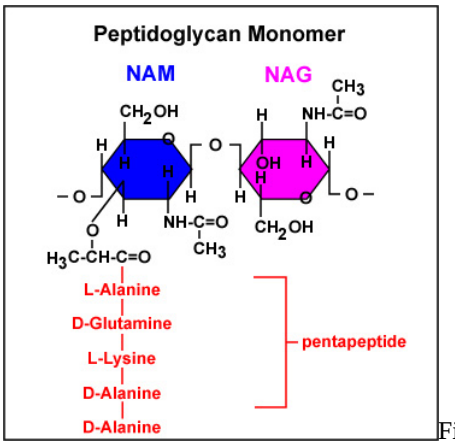


Figure 1.3.2: (left) A peptidoglycan monomer consists of two joined amino sugars, N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM), with a pentapeptide coming off of the NAM. In E. coli, the pentapeptide consists of the amino acids L-alanine, D-glutamic acid, meso diaminopimelic acid, and two D-alanines. (right) A peptidoglycan monomer consists of two joined amino sugars, N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM), with a pentapeptide coming off of the NAM. In S. aureus, the pentapeptide consists of the amino acids L-alanine, D-glutamine, L-lysine, and two D-alanines.

Once the new peptidoglycan monomers are inserted, glycosidic bonds then link these monomers into the growing chains of peptidoglycan. These long sugar chains are then joined to one another by means of peptide cross-links between the peptides coming off of the NAMs. By linking the rows and layers of sugars together in this manner, the peptide cross-links provide tremendous strength to the cell wall, enabling it to function similar to a molecular chain link fence around the bacterium (see Figure 1.3.1).

Synthesis of Peptidoglycan

In order for bacteria to increase their size following binary fission, links in the peptidoglycan must be broken, new peptidoglycan monomers must be inserted, and the peptide cross links must be resealed. The following sequence of events occur:

Step 1. Bacterial enzymes called autolysins:

a) Break the glycosidic bonds between the peptidoglycan monomers at the point of growth along the existing peptidoglycan (see Figure 1.3.3, steps 1-3); and

b) Break the peptide cross-bridges that link the rows of sugars together (see Figure 1.3.3, steps 1-3).

Flash animation showing the synthesis of peptidoglycan.

html5 version of animation for iPad showing the synthesis of peptidoglycan.

Step 2. The peptidoglycan monomers are synthesized in the cytosol (see Figure 1.3.4, step-1 and Figure 1.3.4, step-2) and bind to bactoprenol. The bactoprenols transport the peptidoglycan monomers across the cytoplasmic

membrane and interacts with transglycosidases to insert the monomers into existing peptidoglycan (see Figure 1.3.4, step-3, Figure 1.3.4, step-4, Figure 1.3.4, step-5, and Figure 1.3.4, step-6)

Flash animation showing the synthesis of peptidoglycan.

html5 version of animation for iPad showing the synthesis of peptidoglycan.

Step 3. Transglycosylase (transglycosidase) enzymes insert and link new peptidoglycan monomers into the breaks in the peptidoglycan (see Figure 1.3.5, step 1 and Figure 1.3.5, step 2).

Flash animation showing the synthesis of peptidoglycan.

html5 version of animation for iPad showing the synthesis of peptidoglycan.

Step 4. Finally, transpeptidase enzymes reform the peptide cross-links between the rows and layers of peptidoglycan to make the wall strong (see Figure 1.3.6, step 1 and see Figure 1.3.6, step 2).

In *Escherichia coli*, the terminal D-alanine is cleaved from the pentapeptides to form a tetrapeptides. This provides the energy to bond the D-alanine of one tetrapeptide to the diaminopimelic acid of another tetrapeptide (see Figure 1.3.1B). In the case of *Staphylococcus aureus*, the terminal D-alanine is cleaved from the pentapeptides to form a tetrapeptides. This provides the energy to bond a pentaglycine bridge (5 molecules of the amino acid glycine) from the D-alanine of one tetrapeptide to the L-lysine of another (see Figure 1.3.1A).

? Exercise: Think-Pair-Share Questions

1. As we will see in Unit 2, the antibiotic bacitracin binds to bactoprenol after it inserts a peptidoglycan monomer into the growing bacterial cell wall.

   Explain how this can lead to the death of that bacterium.

2. As we will see in Unit 2, the penicillin antibiotics binds to the bacterial enzyme transpeptidase.
   a. Explain how this can lead to the death of that bacterium.
   b. Could this antibiotic be used to treat protozoan infections such as giardiasis and toxoplasmosis?

In the center of the bacterium, a group of proteins called Fts (filamentous temperature sensitive) proteins interact to form a ring at the cell division plane. These proteins form the cell division apparatus known as the divisome and are directly involved in bacterial cell division by binary fission (see Figure 1.3.1 and Figure 1.3.2).

The divisome is responsible for directing the synthesis of new cytoplasmic membrane and new peptidoglycan to form the division septum.

Antimicrobial Agents that Inhibit Peptidoglycan Synthesis Causing Bacterial Lysis

Many antibiotics work by inhibiting normal synthesis of peptidoglycan in bacteria causing them to burst as a result of osmotic lysis. As just mentioned, in order for bacteria to increase their size following binary fission, enzymes called autolysins break the peptide cross links in the peptidoglycan, transglycosylase enzymes then insert and link new peptidoglycan monomers into the breaks in the peptidoglycan, and transpeptidase enzymes reform the peptide cross-links between the rows and layers of peptidoglycan to make the wall strong.

Interference with this process results in a weak cell wall and lysis of the bacterium from osmotic pressure. Examples include the penicillins (penicillin G, methicillin, oxacillin, ampicillin, amoxicillin, ticarcillin, etc.), the cephalosporins (cephalothin, cefazolin, cefoxitin, cefotaxime, cefaclor, cefoperazone, cefixime, ceftriaxone, cefuroxime, etc.), the

carbapenems (imipenem, metropenem), the monobactems (aztreonem), the carbacephems (loracarbef), and the glycopeptides (vancomycin, teichoplanin).

- For example, penicillins and cephalosporins bind to the transpeptidase enzymes (also called penicillin-binding proteins) responsible for resealing the cell wall as new peptidoglycan monomers are added during bacterial cell growth. This blocks the transpeptidase enzymes from cross-linking the sugar chains and results in a weak cell wall and subsequent osmotic lysis of the bacterium (see Figure 1.3.8).

Flash animation illustrating how penicillins inhibit peptidoglycan synthesis.

html5 version of animation for ipad showing how penicillins inhibit the synthesis of peptidoglycan.

Flash animation showing how penicillins inhibit peptidoglycan synthesis.
© Juliet V. Spencer, Stephanie K.M. Wong, authors, Licensed for use, ASM MicrobeLibrary.

YouTube movie showing lysis of *E. coli* after exposure to a penicillin

Antimicrobial chemotherapy will be discussed in greater detail later in Unit 2 under Control of Bacteria by Using Antibiotics and Disinfectants.

For More Information: Preview of Chemotherapeutic Control of Bacteria from Unit 2.

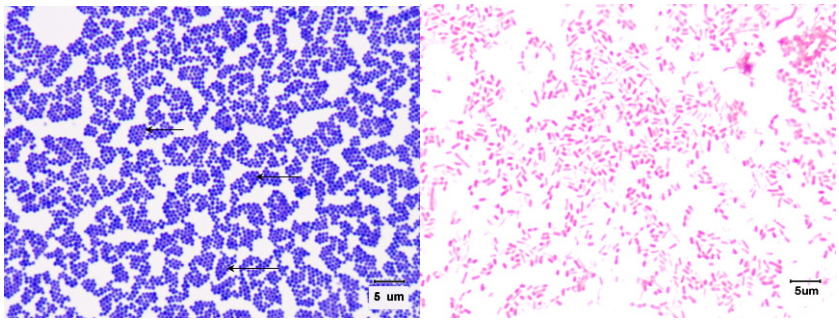
For More Information: Preview of Using Chemical Agents to Control of Bacteria from Lab 19.

Concept map for peptidoglycan and peptidoglycan synthesis.

Gram-Positive, Gram-Negative, and Acid-Fast Bacteria

Most bacteria can be placed into one of three groups based on their color after specific staining procedures are performed: Gram-positive, Gram-negative, or acid-fast.

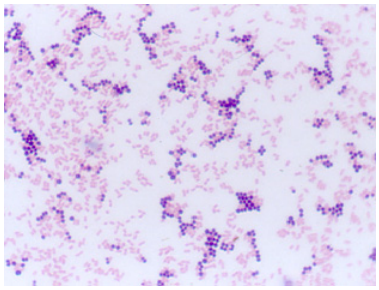
- **Gram-positive Bacteria**: These retain the initial dye crystal violet during the Gram stain procedure and appear purple when observed through the microscope. Common Gram-positive bacteria of medical importance include *Streptococcus pyogenes, Streptococcus pneumoniae, Staphylococcus aureus, Enterococcus faecalis,* and *Clostridium* species.



(left) Gram Stain of Staphylococcus aureus which are gram-positive (purple) cocci in clusters. (right) Gram Stain of Escherichia coli which are Gram-negative (pink) bacilli.

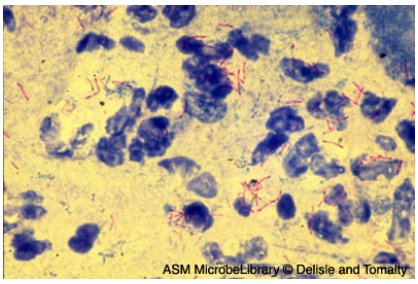
- **Gram-negative Bacteria**: These decolorize during the Gram stain procedure, pick up the counterstain safranin, and appear pink when observed through the microscope. Common Gram-negative bacteria of medical importance include *Salmonella* species, *Shigella* species, *Neisseria gonorrhoeae, Neisseria meningitidis, Haemophilus*

influenzae, Escherichia coli, Klebsiella pneumoniae, Proteus species, and *Pseudomonas aeruginosa*. Also see gram stain of a mixture of gram-positive and gram-negative bacteria.



A Gram Stain of a Mixture of Gram-Positive and Gram-Negative Bacteria. Note Gram-negative (pink) bacilli and Gram-positive (purple) cocci.

- **acid-fast Bacteria**: These resist decolorization with an acid-alcohol mixture during the acid-fast stain procedure, retain the initial dye carbolfuchsin and appear red when observed through the microscope. Common acid-fast bacteria of medical importance include *Mycobacterium tuberculosis, Mycobacterium leprae,* and *Mycobacterium avium-intracellulare* complex.



Acid-Fast Stain of Mycobacterium tuberculosis in Sputum. Note the reddish acid-fast bacilli among the blue normal flora and white blood cells in the sputum that are not acid-fast.

These staining reactions are due to fundamental differences in their cell wall as will be discussed in Lab 6 and Lab 16. We will now look at each of these three bacterial cell wall types.

The S-layer

1. Structure and Composition

The most common cell wall in species of *Archaea* is a paracrystalline surface layer (S-layer). It consists of a regularly structured layer composed of interlocking glycoprotein or protein molecules. In electron micrographs, has a pattern resembling floor tiles. Although they vary with the species, S-layers generally have a thickness between 5 and 25 nm and possess identical pores with 2-8 nm in diameter. Several species of *Bacteria* have also been found to have S-layers.

To view electron micrographs of S-layers see the following:

- S-Layer Proteins, the Structural Biology Homepage at Karl-Franzens University in Austria.
- Characteristic Properties of S-layer Proteins, at Foresight Nanotech Institute in Austria.

2. Functions and Significance to Bacteria Causing Infections

The S-layer has been associated with a number of possible functions. These include the following:

a. The S-layer may protect bacteria from harmful enzymes, from changes in pH, from the predatory bacterium *Bdellovibrio*, a parasitic bacterium that actually uses its motility to penetrate other bacteria and replicate within their cytoplasm, and from bacteriophages.

b. The S-layer can function as an adhesin, enabling the bacterium to adhere to host cells and environmental surfaces, colonize, and resist flushing.

c. The S-layer may contribute to virulence by protecting the bacterium against complement attack and phagocytosis.

d. The S-layer may act as a as a coarse molecular sieve.

Summary

1. The vast majority of the domain Bacteria have a rigid cell wall composed of peptidoglycan.
2. The peptidoglycan cell wall surrounds the cytoplasmic membrane and prevents osmotic lysis.
3. Peptidoglycan is composed of interlocking chains of building blocks called peptidoglycan monomers.
4. In order to grow following binary fission, bacteria have to synthesize new peptidoglycan monomers in the cytoplasm, transport those monomers across the cytoplasmic membrane, put breaks in the existing cell wall so the monomers can be inserted, connect the monomers to the existing peptidoglycan, and cross-link the rows and layers of peptidoglycan.
5. Many antibiotics inhibit peptidoglycan synthesis in bacteria and lead to osmotic lysis of the bacteria.
6. Most bacteria can be placed into one of three groups based on their color after specific staining procedures are performed: Gram-positive, Gram-negative, or acid-fast. These staining reactions are due to fundamental differences in the bacterial cell wall.
7. Gram-positive bacteria stain purple after Gram staining while Gram-negative bacteria stain pink.
8. Acid-fast bacteria stain red after acid-fast staining.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. A monomer of peptidoglycan consists of _____, _____, and _____. *(ans)*
2. State the function of peptidoglycan in bacteria. *(ans)*
3. State the role of the following enzymes in peptidoglycan synthesis:
   a. autolysins *(ans)*
   b. bactoprenols *(ans)*
   c. transpeptidases *(ans)*
   d. transglycosylase *(ans)*
4. A penicillin is used to treat a bacterial infection. Describe the mechanism by which this antibiotic eventually kills the bacteria. *(ans)*
5. Gram-positive bacteria stain _____ *(ans)* after Gram staining while Gram-negative bacteria stain _____ *(ans)*.
6. Bacteria normally live in a hypotonic environment. Since water flows into a cell in an environment that is hypotonic, why don't the bacteria burst from osmotic pressure? *(ans)*
7. Multiple Choice *(ans)*

This page titled 1.3: The Peptidoglycan Cell Wall is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **2.3: The Peptidoglycan Cell Wall** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

1.3.1: Damage of the Cell Wall

Learning Objectives

- Discuss the effects that damage to the cell wall has on the bacterial cell

The cell wall is the principal stress-bearing and shape-maintaining element in bacteria. Its integrity is thus of critical importance to the viability of a particular cell. In both gram-positive and gram-negative bacteria, the scaffold of the cell wall consists of a cross-linked polymer peptidoglycan. The cell wall of gram-negative bacteria is thin (approximately only 10 nanometers in thickness), and is typically comprised of only two to five layers of peptidoglycan, depending on the growth stage. In gram-positive bacteria, the cell wall is much thicker (20 to 40 nanometers thick).

While the peptidoglycan provides the structural framework of the cell wall, teichoic acids, which make up roughly 50% of the cell wall material, are thought to control the overall surface charge of the wall. This affects murein hydrolase activity, resistance to antibacterial peptides, and adherence to surfaces. Although both of these molecules are polymerized on the surface of the cytoplasmic membrane, their precursors are assembled in the cytoplasm. Any event that interferes with the assembling of the peptidoglycan precursor, and the transport of that object across the cell membrane, where it will integrate into the cell wall, would compromise the integrity of the wall. Damage to the cell wall disturbs the state of cell electrolytes, which can activate death pathways (apoptosis or programmed cell death). Regulated cell death and lysis in bacteria plays an important role in certain developmental processes, such as competence and biofilm development. They also play an important role in the elimination of damaged cells, such as those irreversibly injured by environmental or antibiotic stress. An example of an antibiotic that interferes with bacterial cell wall synthesis is Penicillin. Penicillin acts by binding to transpeptidases and inhibiting the cross-linking of peptidoglycan subunits. A bacterial cell with a damaged cell wall cannot undergo binary fission and is thus certain to die.

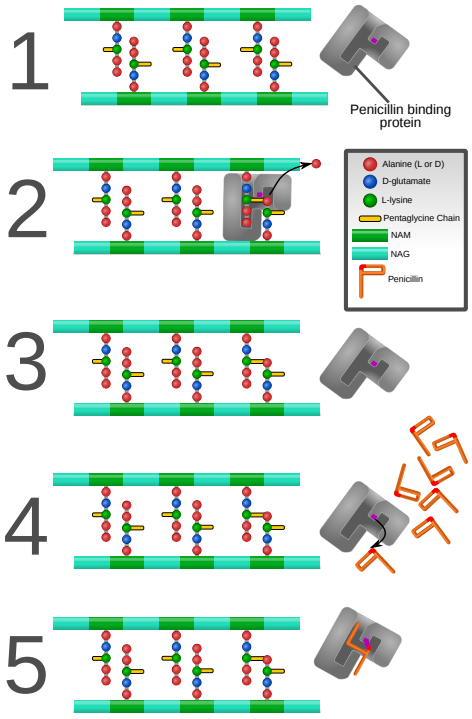


Figure: **Penicillin mechanism of action**: Penicillin acts by binding to penicillin binding proteins and inhibiting the cross-linking of peptidoglycan subunits.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- Cell wall. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Cell_wall. **License**: *CC BY-SA: Attribution-ShareAlike*

- binary fission. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/binary_fission. **License**: *CC BY-SA: Attribution-ShareAlike*
- **Provided by**: Wikimedia. **Located at**: upload.wikimedia.org/wikipedi...ll-_en.svg.png. **License**: *CC BY-SA: Attribution-ShareAlike*
- Cell envelope. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Cell_en...tive_cell_wall. **License**: *CC BY-SA: Attribution-ShareAlike*
- Gram-negative bacteria. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Gram-negative_bacteria. **License**: *CC BY-SA: Attribution-ShareAlike*
- endotoxin. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/endotoxin. **License**: *CC BY-SA: Attribution-ShareAlike*
- lipopolysaccharide. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/lipopolysaccharide. **License**: *CC BY-SA: Attribution-ShareAlike*
- **Provided by**: Wikimedia. **Located at**: upload.wikimedia.org/wikipedi...ll-_en.svg.png. **License**: *CC BY-SA: Attribution-ShareAlike*
- **Provided by**: Wikimedia. **Located at**: upload.wikimedia.org/wikipedi...l_wall.svg.png. **License**: *CC BY-SA: Attribution-ShareAlike*
- Gram positive bacteria. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Gram_positive_bacteria. **License**: *CC BY-SA: Attribution-ShareAlike*
- Gram stain. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Gram%20stain. **License**: *CC BY-SA: Attribution-ShareAlike*
- **Provided by**: Wikimedia. **Located at**: upload.wikimedia.org/wikipedi...ll-_en.svg.png. **License**: *CC BY-SA: Attribution-ShareAlike*
- **Provided by**: Wikimedia. **Located at**: upload.wikimedia.org/wikipedi...l_wall.svg.png. **License**: *CC BY-SA: Attribution-ShareAlike*
- 20110322 193829 Bacteria SMB UTI. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:20...ia_SMB_UTI.jpg. **License**: *CC BY-SA: Attribution-ShareAlike*
- Mycoplasma. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Mycoplasma. **License**: *CC BY-SA: Attribution-ShareAlike*
- osmotic environment. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/osmotic%20environment. **License**: *CC BY-SA: Attribution-ShareAlike*
- **Provided by**: Wikimedia. **Located at**: upload.wikimedia.org/wikipedi...ll-_en.svg.png. **License**: *CC BY-SA: Attribution-ShareAlike*
- **Provided by**: Wikimedia. **Located at**: upload.wikimedia.org/wikipedi...l_wall.svg.png. **License**: *CC BY-SA: Attribution-ShareAlike*
- 20110322 193829 Bacteria SMB UTI. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:20...ia_SMB_UTI.jpg. **License**: *CC BY-SA: Attribution-ShareAlike*
- TEM of L-form bacteria-Mark Leaver Newcastle University. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:TE...niversity.jpeg. **License**: *CC BY-SA: Attribution-ShareAlike*
- Cell wall. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Cell_wa...eal_cell_walls. **License**: *CC BY-SA: Attribution-ShareAlike*
- cellulose. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/cellulose. **License**: *CC BY-SA: Attribution-ShareAlike*
- cytoplasm. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/cytoplasm. **License**: *CC BY-SA: Attribution-ShareAlike*
- chitin. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/chitin. **License**: *CC BY-SA: Attribution-ShareAlike*
- **Provided by**: Wikimedia. **Located at**: upload.wikimedia.org/wikipedi...ll-_en.svg.png. **License**: *CC BY-SA: Attribution-ShareAlike*
- **Provided by**: Wikimedia. **Located at**: upload.wikimedia.org/wikipedi...l_wall.svg.png. **License**: *CC BY-SA: Attribution-ShareAlike*
- 20110322 193829 Bacteria SMB UTI. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:20...ia_SMB_UTI.jpg. **License**: *CC BY-SA: Attribution-ShareAlike*

- TEM of L-form bacteria-Mark Leaver Newcastle University. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:TE...niversity.jpeg. **License**: *CC BY-SA: Attribution-ShareAlike*
- Halobacteria. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:Halobacteria.jpg. **License**: *Public Domain: No Known Copyright*
- Peptidoglycan. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Peptido...tic_inhibition. **License**: *CC BY-SA: Attribution-ShareAlike*
- Antibiotic. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Antibiotic%23Classes. **License**: *CC BY-SA: Attribution-ShareAlike*
- transpeptidase. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/transpeptidase. **License**: *CC BY-SA: Attribution-ShareAlike*
- hydrolase. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/hydrolase. **License**: *CC BY-SA: Attribution-ShareAlike*
- **Provided by**: Wikimedia. **Located at**: upload.wikimedia.org/Wikipedia/commons/thumb/5/5a/Average_prokaryote_cell-_en.svg/500px-Average_prokaryote_cell-_en.svg.png. **License**: *CC BY-SA: Attribution-ShareAlike*
- **Provided by**: Wikimedia. **Located at**: upload.wikimedia.org/Wikipedia/commons/thumb/8/8b/Gram_negative_cell_wall.svg/1000px-Gram_negative_cell_wall.svg.png. **License**: *CC BY-SA: Attribution-ShareAlike*
- 20110322 193829 Bacteria SMB UTI. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:20110322_193829_Bacteria_SMB_UTI.jpg. **License**: *CC BY-SA: Attribution-ShareAlike*
- TEM of L-form bacteria-Mark Leaver Newcastle University. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:TEM_of_L-form_bacteria-Mark_Leaver_Newcastle_University.jpeg. **License**: *CC BY-SA: Attribution-ShareAlike*
- Halobacteria. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:Halobacteria.jpg. **License**: *Public Domain: No Known Copyright*
- **Provided by**: Wikimedia. **Located at**: upload.wikimedia.org/wikipedi...bition.svg.png. **License**: *CC BY-SA: Attribution-ShareAlike*

Key Points

- Gram-positive and Gram-negative bacteria are protected by an external cell wall composed of varying layers of peptidoglycan.
- Damage to bacterial cell wall compromises its integrity and creates imbalance of electrolytes that trigger cell death.
- Some antibiotic classes act by inhibiting the synthesis of cell wall building blocks leading to cell lysis and death.

Key Terms

- **hydrolase**: An enzyme that catalyzes the hydrolysis of a substrate.
- **transpeptidase**: Any enzyme that catalyzes the transfer of an amino or peptide group from one molecule to another

---

This page titled 1.3.1: Damage of the Cell Wall is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **4.4F: Damage of the Cell Wall** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

1.3A: The Gram-Positive Cell Wall

State what color Gram-positive bacteria stain after the Gram stain procedure.

- Describe the composition of a Gram-positive cell wall and indicate the possible beneficial functions to the bacterium of peptidoglycan, teichoic acids, and surface proteins.
- Briefly describe how PAMPs of the Gram-positive cell wall can promote inflammation.
- State the function of bacterial adhesins, secretion systems, and invasins.
- Define antigen and epitope.

Highlighted Bacterium 1. Read the description of *Enterococcus*, andmatch the bacterium with the description of the organism and the infection it causes.

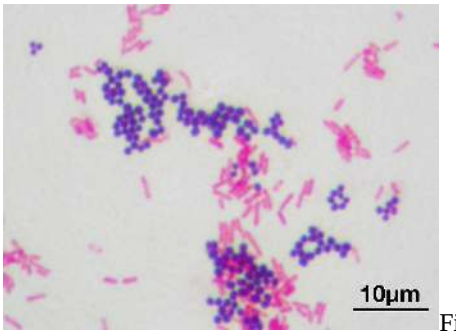


Figure **1.3A.2**A.1: Gram Stain of *V*iolet stained gram-positive cocci and pink stained gram-negative rod-shaped bacteria. from Wikipedia (Y tambe).

For More Information: Preview of the Gram stain from Lab 6.

Flash animation illustrating the interaction of the Gram's stain reagents at a molecular level
© Daniel Cavanaugh, Mark Keen, authors, Licensed for use, ASM MicrobeLibrary.

Common Gram-positive bacteria of medical importance include *Streptococcus pyogenes, Streptococcus pneumoniae, Staphylococcus aureus, Enterococcus faecalis,* and *Clostridium* species.

Structure and Composition of the Gram-Positive Cell Wall

1. In electron micrographs, the Gram-positive cell wall appears as a broad, dense wall 20-80 nm thick and consisting of numerous interconnecting layers of peptidoglycan (see Figs. 1A and 1B). Chemically, 60 to 90% of the Gram-positive cell wall is peptidoglycan. In Gram-positive bacteria it is thought that the peptidoglycan is laid down in cables of several cross-linked glycan strands approximately 50 nm wide. These cables then themselves become cross-linked for further cell wall strength.

2. Interwoven in the cell wall of Gram-positive are teichoic acids and lipoteichoic acids. Teichoic acids extend through and beyond the rest of the cell wall and are polyalcohols composed of polymers of glycerol, phosphates, and the sugar alcohol ribitol and are covalently bound to the peptidoglycan. Teichoic acids covalently bound to cytoplasmic membrane lipids are called lipoteichoic acids (see Figure **1.3A.1**B).

3. The outer surface of the peptidoglycan is studded with surface proteins that differ with the strain and species of the bacterium (see Figure **1.3A.1**B).

4. The periplasm is the gelatinous material between the peptidoglycan and the cytoplasmic membrane.

For More Information: Peptidoglycan from Unit 1.

To view an electron micrograph of *Streptococcus* showing a Gram-positive cell wall, see the Rockefeller University web page.

Functions of the Gram-Positive Cell Wall Components

1. The peptidoglycan in the Gram-positive cell wall prevents osmotic lysis.

2. The teichoic acids probably help make the cell wall stronger (see Figure 1.3A.1B).

3. The surface proteins (see Figure 1.3A.1B) in the bacterial peptidoglycan, depending on the strain and species, carry out a variety of activities.

a. Some surface proteins function as enzymes.

b. Other proteins serve as adhesins. Adhesins enable the bacterium to adhere intimately to host calls and other surfaces in order to colonize those cells and resist flushing (See Figure 1.3A.2).

Flash animation showing a bacterium using adhesins to adhere to a host cell.

html5 version of animation for iPad showing a bacterium using adhesins to adhere to a host cell.

c. Many bacteria involved in infection have the ability to co-opt the functions of host cells for the bacterium's own benefit. This is done by way of bacterial secretions systems that enable the bacterium to directly inject bacterial effector molecules into the cytoplasm of the host cell in order to alter its cellular machinery or cellular communication to the benefit of the bacteria. They do this by producing secretion systems such as the type 3 secretion system that produces hollow, needle-like tubes called injectisomes. Certain bacteria, for example, inject invasins into the cytoplasm of the host cell that enable the bacterium to enter that cell.

Flash animation showing bacteria secreting invasions into a non-immune host cell in order to enter that cell by phagocytosis.

html5 version of animation for iPad showing bacteria secreting invasions into a non-immune host cell in order to enter that cell by phagocytosis.

The role of these cell wall surface proteins will be discussed in greater detail later in Unit 3 under Bacterial Pathogenicity.

4. The periplasm contains enzymes for nutrient breakdown.

For More Information: The Ability to Adhere to Host Cells from Unit 3

For More Information: The Ability to Invade Host Cells from Unit 3

Concept map for the Gram-positive cell wall.

Significance of Gram-Positive Cell Wall Components to the Initiation of Body Defenses

The body has two immune systems: the innate immune system and the adaptive immune system.

1. Innate immunity is an antigen-nonspecific defense mechanisms that a host uses immediately or within several hours after exposure to almost any microbe. This is the immunity one is born with and is the initial response by the body to eliminate microbes and prevent infection.

2. Adaptive (acquired) immunity refers to antigen-specific defense mechanisms that take several days to become protective and are designed to react with and remove a specific antigen. This is the immunity one develops throughout life.

Initiation of Innate Immunity

In order to protect against infection, one of the things the body must initially do is detect the presence of microorganisms. The body does this by recognizing molecules unique to microorganisms that are not associated with human cells. These unique molecules are called pathogen-associated molecular patterns or PAMPs. (Because all microbes, not just pathogenic microbes, possess PAMPs, pathogen-associated molecular patterns are sometime referred to as microbe-associated molecular patterns or MAMPs.)

Fragments of peptidoglycan and teichoic acids are PAMPS associated with the cell wall of Gram-positive bacteria. In addition, bacteria and other microorganisms also possess mannose-rich glycans (short carbohydrate chains with the sugar mannose or fructose as the terminal sugar) that function as PAMPs. These mannose-rich glycans are common in microbial glycoproteins and glycolipids but rare in those of humans (see Figure 1.3A.3).

These PAMPS bind to pattern-recognition receptors or PRRs on a variety of defense cells of the body and trigger such innate immune defenses as inflammation, fever, and phagocytosis.

For More Information: Pathogen-Associated Molecular Patterns (PAMPs) from Unit 5

For More Information: Pattern-Recognition Receptors from Unit 5

Inflammation is the first response to infection and injury and is critical to body defense. Basically, the inflammatory response is an attempt by the body to restore and maintain homeostasis after injury. Most of the body defense elements are located in the blood, and inflammation is the means by which body defense cells and body defense chemicals leave the blood and enter the tissue around an injured or infected site.

Body defense cells such as macrophages, and dendritic cells have pattern recognition receptors such as toll-like receptors on their surface that are specific for the peptidoglycan fragments and lipoteichoic acids in the Gram-positive cell wall and/or to NODs in their cytoplasm that are specific for peptidoglycan fragments.

The binding of these cell wall components to their corresponding pattern recognition receptors triggers the macrophages to release various defense regulatory chemicals called cytokines, including IL-1, IL-6, IL-8, TNF-alpha, and PAF. The cytokines then bind to cytokine receptors on target cells and initiate inflammation and activate both the complement pathways and the coagulation pathway (see Figure 1.3A.4).

For More Information: Cytokines from Unit 5

For More Information: Inflammation from Unit 5

The peptidoglycan and teichoic acids also activate the alternative complement pathway and the lectin pathway, innate immune defense pathways that play a variety of roles in body defense.

For More Information: The Complement Pathways from Unit 5

Innate immunity will be discussed in greater detail in Unit 5.

Concept map for the Gram-positive cell wall.

Initiation of Adaptive Immunity

Proteins and polysaccharides associated with the Gram-positive cell wall function as antigens and initiate adaptive immunity. An antigen is defined as a molecular shape that reacts with antibody molecules and with antigen receptors on lymphocytes. We recognize those molecular shapes as foreign or different from our body's molecular shapes because they fit specific antigen receptors on our B-lymphocytes and T-lymphocytes, the cells that carry out adaptive immunity.

The actual portions or fragments of an antigen that react with antibodies and with receptors on B-lymphocytes and T-lymphocytes are called epitopes. An epitope is typically a group of 5-15 amino acids with a unique shape that makes up a portion of a protein antigen, or 3-4 sugar residues branching off of a polysaccharide antigen. A single microorganism has many hundreds of different shaped epitopes that our lymphocytes can recognize as foreign and mount an adaptive immune response against.

The body recognizes an antigen as foreign when epitopes of that antigen bind to B-lymphocytes and T-lymphocytes by means of epitope-specific receptor molecules having a shape complementary to that of the epitope. The epitope receptor on the surface of a B-lymphocyte is called a B-cell receptor and is actually an antibody molecule. The receptor on a T-lymphocyte is called a T-cell receptor (TCR).

There are two major branches of the adaptive immune responses: humoral immunity and cell-mediated immunity.

1. Humoral immunity : Humoral immunity involves the production of antibody molecules in response to an antigen and is mediated by B-lymphocytes. Through a variety of mechanisms, these antibodies are able to remove or neutralize microorganisms and their toxins after binding to their epitopes. For example, antibodies made against cell wall antigens can stick bacteria to phagocytes, a process called opsonization. Antibodies made against cell wall adhesins can prevent bacteria from adhering to and colonizing host cells.

2. Cell-mediated immunity : Cell-mediated immunity involves the production of cytotoxic T-lymphocytes, activated macrophages, activated NK cells, and cytokines in response to an antigen and is mediated by T-lymphocytes. These defense cells help to remove infected cells and cancer cells displaying foreign epitopes.

Adaptive immunity will be discussed in greater detail in Unit 6.

For More Information: Review of antigens and epitopes from Unit 6

Significance of Gram-Positive Cell Wall Components to Bacterial Pathogenicity

During severe systemic infections with large numbers of bacteria present, however, high levels of Gram-positive PAMPs are released resulting in excessive cytokine production by the macrophages and other cells and this, in turn, can harm the body (see Figure 1.3A.5).

Flash animation illustrating signaling toll-like receptors on defense cells: LTA and TLR-2/TLR-6.

html5 version of animation for iPad illustrating signaling toll-like receptors on defense cells: LTA and TLR-2/TLR-6.

For More Information: Inflammatory Gram-PositiveCell Wall Components from Unit 3

For More Information: Cytokines from Unit 5

For More Information: Inflammation from Unit 5

Summary

1. Because of the nature of their cell wall, Gram-positive bacteria stain purple after Gram staining.
2. The Gram-positive cell wall consists of many interconnected layers of peptidoglycan and lacks an outer membrane.
3. Peptidoglycan prevents osmotic lysis in the hypotonic environment in which most bacteria live.
4. Teichoic acids and lipoteichoic acids are interwoven through the peptidoglycan layers.
5. Surface proteins embedded in the cell wall can function as adhesins, secretion systems, and enzymes.
6. The Gram-positive cell wall activates both the body's innate immune defenses and its adaptive immune defenses.
7. The body activates innate immunity by recognizing molecules unique to microorganisms that are not associated with human cells called pathogen-associated molecular patterns or PAMPs. PAMPs bind to Pattern-recognition receptors (PRRs) on defense cells to trigger the production of inflammatory cytokines.
8. Inflammation is the means by which the body delivers defense cells and defense molecules to an infection site,however, excessive inflammation can be harmful and even deadly to the body.
9. PAMPs associated with the Gram-positive cell wall include peptidoglycan monomers, teichoic acids, lipoteichoic acids, and mannose-rich sugar chains.
10. An antigen is a molecular shape that reacts with antigen receptors on lymphocytes to initiate an adaptive immune response.
11. Cell wall molecules can also trigger adaptive immunity such as the production of antibody molecules against bacterial cell wall antigens.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. State what color Gram-positive bacteria appear after the Gram stain procedure. (ans)
2. Describe the structure and appearance of a Gram-positive cell wall. *(ans)*
3. State the beneficial function to the bacterium of the following components of the gram-positive cell wall:
    a. peptidoglycan *(ans)*
    b. teichoic acids *(ans)*
    c. adhesins *(ans)*
    d. invasins *(ans)*
4. Briefly describe how PAMPs of the Gram-positive cell wall can promote inflammation. *(ans)*
5. Define antigen. *(ans)*

This page titled 1.3A: The Gram-Positive Cell Wall is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **2.3A: The Gram-Positive Cell Wall** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

1.3B: The Gram-Negative Cell Wall

State what color Gram-negative bacteria stain after the Gram stain procedure.

- Describe the composition of a Gram-negative cell wall and indicate the possible beneficial functions to the bacterium of peptidoglycan, the outer membrane, lipopolysaccharides, porins, and surface proteins.
- Briefly describe how LPS and other PAMPs of the Gram-negative cell wall can promote inflammation.
- State the function of bacterial adhesins, secretion systems, and invasins.
- Define periplasm.
- Define antigen and epitope.

Highlighted Bacterium. Read the description of *Escherichia coli*, and match the bacterium with the description of the organism and the infection it causes.

Highlighted Disease: Urinary Tract Infections (UTIs). Define the following:

a. urethritis

b. cystitis

c. pyelonephritis

2. Name at least 4 risk factors for UTIs.
3. Name the most common bacterium to cause UTIs; name at least 3 other bacteria that commonly cause UTIs.
4. Name at least 3 common symptoms of UTIs.

We will now look at the Gram-negative bacterial cell wall. As mentioned in the previous section on peptidoglycan, Gram-negative bacteria are those that decolorize during the Gram stain procedure, pick up the counterstain safranin, and appear pink (Figure **1.3*B*.2**B.1).

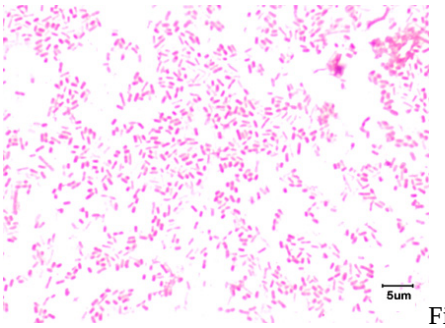


Figure **1.3*B*.2**B.1: Gram Stain of *Escherichia coli*. Note Gram-negative (pink) bacilli.

Common Gram-negative bacteria of medical importance include *Salmonella* species, *Shigella* species, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Haemophilus influenzae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus* species, and *Pseudomonas aeruginosa*.

Escherichia coli

Organism

- *Escherichia coli* is a moderately-sized Gram-negative bacillus.
- Possess a peritrichous arrangement of flagella.
- Facultative anaerobe.

Habitat

- Normal flora of the intestinal tract in humans and animals.

Source

- Usually the patient's own fecal flora; some transmission is patient-to-patient.

Clinical Disease

- *E. coli* causes around 80 percent of all uncomplicated **urinary tract infections** (UTIs) and more than 50 percent of nosocomial UTIs. UTIs account for more than 7, 000,000 physician office visits per year in the U.S. Between 35 and 40 percent of all nosocomial infections, about 900,000 per year in the U.S., are UTIs and are usually associated with urinary catheterization.
- *E. coli* causes **wound infections**, usually a result of fecal contamination of external wounds or a result of wounds that cause trauma to the intestinal tract, such as surgical wounds, gunshot wounds, knife wounds, etc.
- *E. coli* is by far the most common Gram-negative bacterium causing sepsis. **Septicemia** is a result of bacteria getting into the blood. They are usually introduced into the blood from some other infection site, such as an infected kidney, wound, or lung. There are approximately 500,000 cases of septicemia per year in the U.S. and the mortality rate is between 20 and 50 percent. Approximately 45 percent of the cases of septicemia are due to Gram-negative bacteria. *Klebsiella*, *Proteus*, *Enterobacter*, *Serratia*, and *E. coli*, are all common gram-negative bacteria causing septicemia.
- *E. coli*, along with group B streptococci, are the leading cause of **neonatal meningitis**.
- While *E. coli* is one of the dominant normal flora in the intestinal tract of humans and animals, some strains can cause **gastroenteritis**, an infection of the intestinal tract.
    - Enterotoxigenc *E. coli* (ETEC) produce enterotoxins that cause the loss of sodium ions and water from the small intestines resulting in a watery diarrhea. Over half of all travelers' diarrhea is due to ETEC; almost 80,000 cases a year in the U.S.
    - Enteropathogenic *E. coli* (EPEC) cause an endemic diarrhea in areas of the developing world, especially in infants younger than 6 months. The bacterium disrupts the normal microvilli on the epithelial cells of the small intestines resulting in maladsorbtion and diarrhea.
    - Enteroaggregative *E. coli* (EAEC) is a cause of persistant diarrhea in developing countries. It probably causes diarrhea by adhering to mucosal epithelial cells of the small intestines and interfering with their function.
    - Enteroinvasive *E. coli* (EIEC) invade and kill epithelial cells of the large intestines causing a dysentery-type syndrome similar to *Shigella* common in underdeveloped countries.
    - Enterohemorrhagic *E. coli* (EHEC), such as *E. coli* 0157:H7, produce a shiga-like toxin that kills epithelial cells of the large intestines causing hemorrhagic colitis, a bloody diarrhea. In rare cases, the shiga-toxin enters the blood and is carried to the kidneys where, usually in children, it damages vascular cells and causes hemolytic uremic syndrome. *E. coli* 0157:H7 is thought to cause more than 20,000 infections and up to 250 deaths per year in the U.S.
    - Diffuse aggreegative *E. coli*(DAEC) causes watery diarrhea in infants 1-5 years of age. They stimulate elongation of the microvilli on the epithelial cells lining the small intestines.
- For More Information: The Gram Stain from Lab 6.
- Flash animation illustrating the interaction of the Gram's stain reagents at a molecular level © Daniel Cavanaugh, Mark Keen, authors, Licensed for use, ASM MicrobeLibrary.
- Highlighted Infection: Urinary Tract Infections (UTIs)

Structure and Composition of the Gram-Negative Cell Wall

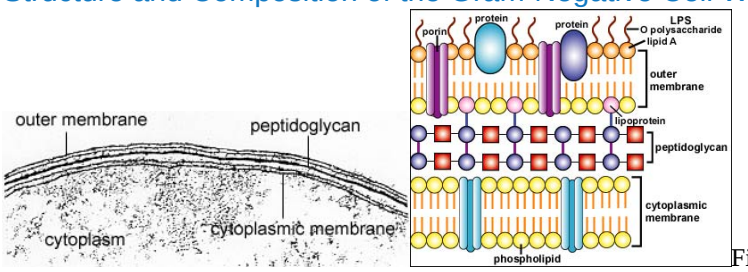


Figure 1.3*B*.1B) span the outer membrane. The porins function as channels for the entry and exit of solutes through the outer membrane of the Gram-negative cell wall. The outer membrane of the Gram-negative cell wall is studded with surface proteins that differ with the strain and species of the bacterium.

The periplasm is the gelatinous material between the outer membrane, the peptidoglycan, and the cytoplasmic membrane. This periplasmic space is about 15nm wide and contains a variety of hydrolytic enzymes for nutrient breakdown, periplasmic binding

proteins for transport via the ATP-binding cassette (ABC) system, and chemoreceptors for chemotaxis (discussed under Bacterial Flagella later in this Unit).

Concept map for the Gram-negative cell wall.

Functions of the Gram-Negative Cell Wall Components

Flash animation showing a bacterium using adhesins to adhere to a host cell.

html5 version of animation for iPad showing a bacterium using adhesins to adhere to a host cell.

Flash animation showing a bacterium using adhesins to resist being flushed out of the urethra.

html5 version of animation for iPad showing a bacterium using adhesins to resist being flushed out of the urethra.

Flash animation showing a bacterium without adhesins being flushed out of the urethra.

html5 version of animation for iPad showing a bacterium without adhesins being flushed out of the urethra.

c. Many bacteria involved in infection have the ability to **co-opt the functions of host cells for the bacterium's own benefit**. This is done by way of bacterial secretions systems that enable the bacterium to directly inject bacterial effector molecules into the cytoplasm of the host cell in order to alter its cellular machinery or cellular communication to the benefit of the bacteria. They do this by producing secretion systems such as the type 3 secretion system that produces hollow, needle-like tubes called **injectisomes**. Certain bacteria, for example, inject **invasins** into the cytoplasm of the host cell that enable the bacterium to **enter that cell.**

html5 version of animation for iPad showing a bacterium secreting invasions in order to penetrete non-immune host cells.

The role of these cell wall surface proteins will be discussed in greater detail later in Unit 3 under Bacterial Pathogenicity.

For More Information: The Ability to Adhere to Host Cells from Unit 3

For More Information: The Ability to Invade Host Cells from Unit 3

4. The **periplasm** contains **enzymes for nutrient breakdown** as well as **periplasmic binding proteins to facilitate the transfer of nutrients across the cytoplasmic membrane**.

Concept map for the Gram-negative cell wall.

The Role of Gram-Negative Cell Wall Components to the Initiation of Body Defenses

The body has two immune systems: the innate immune system and the adaptive immune system. Innate immunity is an antigen-nonspecific defense mechanisms that a host uses immediately or within several hours after exposure to almost any microbe. This is the immunity one is born with and is the initial response by the body to eliminate microbes and prevent infection. Adaptive (acquired) immunity refers to antigen-specific defense mechanisms that take several days to become protective and are designed to react with and remove a specific antigen. This is the immunity one develops throughout life.

Initiation of Innate Immunity

To protect against infection, one of the things the body must initially do is detect the presence of microorganisms. The body does this by recognizing molecules unique to microorganisms that are not associated with human cells. These unique molecules are called pathogen-associated molecular patterns or PAMPS. (Because all microbes, not just pathogenic microbes, possess PAMPs, pathogen-associated molecular patterns are sometime referred to as microbe-associated molecular patterns or MAMPs.)

LPS, porins, and fragments of peptidoglycan are PAMPs associated with the cell wall of Gram-negative bacteria. In addition, bacteria and other microorganisms also possess mannose-rich glycans (short carbohydrate chains with the sugar mannose or fructose as the terminal sugar) that function as PAMPs. These mannose-rich glycans are common in microbial glycoproteins and glycolipids but rare in those of humans (Figure **1.3*B*.3**).

These PAMPS bind to pattern-recognition receptors or PRRs on a variety of defense cells of the body and triggers innate immune defenses such as inflammation , fever, and phagocytosis.

For More Information: Pathogen-Associated Molecular Patterns (PAMPs) from Unit 5

For More Information: Pattern-Recognition Receptors from Unit 5

Inflammation is the first response to infection and injury and is critical to body defense. Basically, the inflammatory response is an attempt by the body to restore and maintain homeostasis after injury. Most of the body defense elements are located in the blood, and inflammation is the means by which body defense cells and body defense chemicals leave the blood and enter the tissue around an injured or infected site.

Body defense cells called macrophages, and dendritic cells have pattern recognition receptors such as toll-like receptors on their surface that are specific for the peptidoglycan fragments and LPS in the Gram-negative cell wall and/or to NODs in their cytoplasm that are specific for peptidoglycan fragments. The binding of these cell wall components to their corresponding pattern recognition receptors triggers the macrophages to release various defense regulatory chemicals called cytokines, including IL-1, IL-6, IL-8, TNF-alpha, and PAF. The cytokines then bind to cytokine receptors on target cells and initiate inflammation and activate both the complement pathways and the coagulation pathway (Figure **1.3*B*.4**).

The LPS binds to a LPS-binding protein circulating in the blood and this complex, in turn, binds to a receptor molecule (CD14) found on the surface of body defense cells called macrophages. This is thought to promote the ability of the toll-like receptor pair TLR-4/TLR4 to respond to the LPS. The binding of these cell wall components to their corresponding pattern recognition receptors triggers macrophages to release various defense regulatory chemicals called cytokines, including IL-1, IL-6, IL-8, TNF-alpha, and

PAF. The cytokines then bind to cytokine receptors on target cells and initiate inflammation and activate both the complement pathways and the coagulation pathway (Figure 1.3B.4).

Flash animation showing the release of LPS from the cell wall of a gram negative bacterium and its subsequent binding to pattern-recognition receptors on a macrophage.

html5 version of animation for iPad showing the release of LPS from the cell wall of a gram negative bacterium and its subsequent binding to pattern-recognition receptors on a macrophage.

For More Information: Cytokines from Unit 5

For More Information: Inflammation from Unit 5

Concept map for the Gram-negative cell wall.

Explain how the body is able to recognize these bacteria and eventually send phagocytes and defense molecules to the infected site.

- How might this mechanism lead to the symptoms of the infection?

The LPS also activates the alternative complement pathway and the lectin pathway, innate defense pathways that play a variety of roles in body defense.

Innate immunity will be discussed in greater detail in Unit 5.

For More Information: The Complement Pathways from Unit 5

Initiation of Adaptive Immunity

Proteins and polysaccharides associated with the Gram-negative cell wall function as antigens and initiate adaptive immunity. An antigen is defined as a molecular shape that reacts with antibody molecules and with antigen receptors on lymphocytes. We recognize those molecular shapes as foreign or different from our body's molecular shapes because they fit specific antigen receptors on our B-lymphocytes and T-lymphocytes, the cells that carry out adaptive immunity.

The actual portions or fragments of an antigen that react with antibodies and with receptors on B-lymphocytes and T-lymphocytes are called epitopes. An epitope is typically a group of 5-15 amino acids with a unique shape that makes up a portion of a protein antigen, or 3-4 sugar residues branching off of a polysaccharide antigen. A single microorganism has many hundreds of different shaped epitopes that our lymphocytes can recognize as foreign and mount an adaptive immune response against.

The body recognizes an antigen as foreign when epitopes of that antigen bind to B-lymphocytes and T-lymphocytes by means of epitope-specific receptor molecules having a shape complementary to that of the epitope. The epitope receptor on the surface of a B-lymphocyte is called a B-cell receptor and is actually an antibody molecule. The receptor on a T-lymphocyte is called a T-cell receptor (TCR).

There are two major branches of the adaptive immune responses: humoral immunity and cell-mediated immunity.

1. Humoral immunity: Humoral immunity involves the production of antibody molecules in response to an antigen and is mediated by B-lymphocytes. Through a variety of mechanisms, these antibodies are able to remove or neutralize microorganisms and their toxins after binding to their epitopes. For example, antibodies made against cell wall antigens can

stick bacteria to phagocytes, a process called opsonization. Antibodies made against cell wall adhesins can prevent bacteria from adhering to and colonizing host cells.

2. Cell-mediated immunity: Cell-mediated immunity involves the production of cytotoxic T-lymphocytes, activated macrophages, activated NK cells, and cytokines in response to an antigen and is mediated by T-lymphocytes. These defense cells help to remove infected cells and cancer cells displaying foreign epitopes.

Adaptive immunity will be discussed in greater detail in Unit 6.

For More Information: Review of antigens and epitopes from Unit 6

Significance of Gram-Negative Cell Wall Components to Bacterial Pathogenicity

The lipid A portion of the LPS portion in the outer membrane is also known as endotoxin. During severe systemic infections with large numbers of bacteria present, high levels of LPS are released resulting in excessive cytokine production by the macrophages and other cells and this, in turn, can harm the body (Figure 1.3*B*.5).

For More Information: Endotoxin from Unit 3

Concept map for the Gram-negative cell wall.

Summary

1. Because of the nature of their cell wall, Gram-negative bacteria stain pink after Gram staining.
2. The Gram-negative cell wall consists of 2-3 interconnected layers of peptidoglycan surrounded by an outer membrane.
3. Peptidoglycan prevents osmotic lysis in the hypotonic environment in which most bacteria live.
4. The outer membrane is a semipermeable structure that contains pore-forming proteins called porins that allow nutrients to pass through the outer membrane.
5. Surface proteins embedded in the cell wall can function as adhesins, secretion systems, and enzymes.
6. The Gram-negative cell wall activates both the body's innate immune defenses and its adaptive immune defenses.
7. The body activates innate immunity by recognizing molecules unique to microorganisms that are not associated with human cells called pathogen-associated molecular patterns or PAMPs. PAMPs bind to Pattern-recognition receptors (PRRs) on defense cells to trigger the production of inflammatory cytokines.
8. Inflammation is the means by which the body delivers defense cells and defense molecules to an infection site, however, excessive inflammation, can be harmful and even deadly to the body.
9. PAMPs associated with the Gram-negative cell wall include peptidoglycan monomers, lipopolysaccharide (LPS), porins, and mannose-rich sugar chains.
10. An antigen is a molecular shape that reacts with antigen receptors on lymphocytes to initiate an adaptive immune response.
11. Cell wall molecules can also trigger adaptive immunity such as the production of antibody molecules against bacterial cell wall antigens.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. State what color Gram-negative bacteria appear after the Gram stain procedure. (ans)
2. Describe the structure and appearance of a Gram-negative cell wall. *(ans)*
3. State the beneficial function to the bacterium of the following components of the gram-negative cell wall:
   a. peptidoglycan *(ans)*
   b. outer membrane *(ans)*

c. adhesins *(ans)*
d. invasins *(ans)*

4. Briefly describe how the LPS (endotoxin) of the Gram-negative cell wall can promote inflammation. *(ans)*
5. Define epitope. *(ans)*
6. When Gram-negative bacteria enter the blood and cause septicemia, most of the harm to the body is due to a massive inflammatory response. What might explain this? *(ans)*

This page titled 1.3B: The Gram-Negative Cell Wall is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **2.3B: The Gram-Negative Cell Wall** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

1.3C: The Acid-Fast Cell Wall

Fundamental Statements for this Learning Object:

In this section on Prokaryotic Cell Anatomy we are looking at the various anatomical parts that make up a bacterium. As mentioned in the introduction to this section, a typical bacterium usually consists of:

- a cytoplasmic membrane surrounded by a peptidoglycan cell wall and maybe an outer membrane;
- a fluid cytoplasm containing a nuclear region (nucleoid) and numerous ribosomes; and
- often various external structures such as a glycocalyx, flagella, and pili.

There are three primary types of bacterial cell wall: Gram-positive, Gram-negative, and acid-fast. We will now look at the acid-fast cell wall.

Acid-fast bacteria stain poorly with the Gram stain procedure, appearing weakly Gram-positive or Gram-variable. They are usually characterized using the acid-fast staining procedure. As mentioned in the previous section on peptidoglycan, bacteria with an acid-fast cell wall resist decolorization with an acid-alcohol mixture during the acid-fast staining procedure , retain the initial dye carbol fuchsin and appear red (Figure **1.3*C*.1;**). Common acid-fast bacteria of medical importance include *Mycobacterium tuberculosis*, *Mycobacterium leprae*,*Mycobacterium avium-intracellulare* complex, and *Nocardia* species.

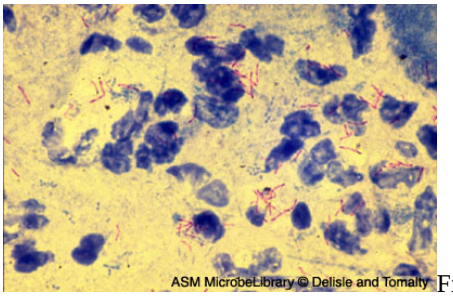


Figure **1.3*C*.1:** (left) Scanning Electron Micrograph of Mycobacterium tuberculosis. Image provided by Dr. Ray Butler and Janice Carr. Courtesy of the Centers for Disease Control and Prevention. (right) Acid-Fast Stain of Mycobacterium tuberculosis in Sputum. Note the reddish acid-fast bacilli among the blue normal flora and white blood cells in the sputum that are not acid-fast.

Structure and Composition of the Acid-Fast Cell Wall

Acid-fast bacteria are gram-positive, but in addition to peptidoglycan, the outer membrane or envelope of the acid-fast cell wall of contains large amounts of glycolipids, especially mycolic acids that in the genus *Mycobacterium*, make up approximately 60% of the acid-fast cell wall (Figure **1.3*C*.2**).

- **Layer 1:** The acid-fast cell wall of *Mycobacterium* has a thin, inner layer of peptidoglycan.
- **Layer 2:** The peptidoglycan layer is, in turn, linked to arabinogalactan (D-arabinose and D-galactose).
- **Layer 3:** The arabinogalactan is then linked to an outer membrane containing high-molecular weight mycolic acids. The arabinogalactan/mycolic acid layer is overlaid with a layer of polypeptides and mycolic acids consisting of free lipids, glycolipids, and peptidoglycolipids. Other glycolipids include lipoarabinomannan and phosphatidyinositol mannosides (PIM). Like the outer membrane of the gram-negative cell wall, porins are required to transport small hydrophilic molecules through the outer membrane of the acid-fast cell wall.
- **Layer 4:** The outer surface of the acid-fast cell wall is studded with surface proteins that differ with the strain and species of the bacterium.
- **Layer 5:**The periplasm is the gelatinous material between the peptidoglycan and the cytoplasmic membrane.

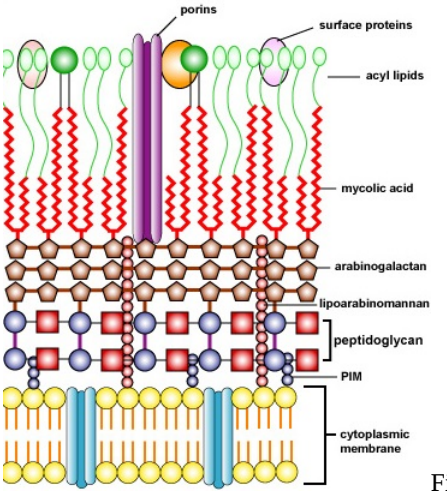


Figure **1.3*C*.2:** Structure of an Acid-Fast Cell Wall. In addition to peptidoglycan, the acid-fast cell wall of Mycobacterium contains a large amount of glycolipids, especially mycolic acids. The peptidoglycan layer is linked to arabinogalactan (D-arabinose and D-galactose) which is then linked to high-molecular weight mycolic acids. The arabinogalactan/mycolic acid layer is overlaid with a layer of polypeptides and mycolic acids consisting of free lipids, glycolipids, and peptidoglycolipids. Other glycolipids include lipoarabinomannan and phosphatidyinositol mannosides (PIM). Like the outer membrane of the gram-negative cell wall, porins are required to transport small hydrophilic molecules through the outer membrane of the acid-fast cell wall. Because of its unique cell wall, when it is stained by the acid-fast procedure, it will resist decolorization with acid-alcohol and stain red, the color of the initial stain, carbol fuchsin. With the exception of a very few other acid-fast bacteria such as Nocardia, all other bacteria will be decolorized and stain blue, the color of the methylene blue counterstain.

Functions of the Acid-Fast Cell Wall Components

- **Layer 1:** The peptidoglycan prevents osmotic lysis.
- **Layer 2:** The arabinogalactan layer is linked to both the peptidoglycan and to the mycolic acid outer membrane and probably provides additional strength to the cell wall.
- **Layer 3:** The mycolic acids and other glycolipids also impede the entry of chemicals causing the organisms to grow slowly and be more resistant to chemical agents and lysosomal components of phagocytes than most bacteria (Figure **1.3*C*.2**). There are far fewer porins in the acid-fast cell wall compared to the gram-negative cell wall and the pores are much longer. This is thought to contribute significantly to the lower permeability of acid-fast bacteria.
- **Layer 4:**The surface proteins in the acid-fast cell wall, depending on the strain and species, carry out a variety of activities, including functioning as enzymes and serving as *adhesins*, which enable the bacterium to adhere intimately to host cells and other surfaces in order to colonize and resist flushing.
- **Layer 15** The periplasm contains enzymes for nutrient breakdown.

? Exercise: Think-Pair-Share Questions

Mycobacterium tuberculosis is a very slow growing bacterium with a generation time often measured in days to weeks. It is also resistant to the vast majority of antibiotics that are commonly effective against other bacteria and treatment is typically with a combination of drugs for up to 9 months.

Based on what we just learned, explain what might account for these two characteristics.

Significance of Acid-Fast Cell Wall Components to the Initiation of Body Defenses

The body has two immune systems: the innate immune system and the adaptive immune system.

1. Innate immunity is an antigen-nonspecific defense mechanisms that a host uses immediately or within several hours after exposure to almost any microbe. This is the immunity one is born with and is the initial response by the body to eliminate microbes and prevent infection.
2. Adaptive (acquired) immunity refers to antigen-specific defense mechanisms that take several days to become protective and are designed to react with and remove a specific antigen. This is the immunity one develops throughout life.

Initiation of Innate Immunity

To protect against infection, one of the things the body must initially do is detect the presence of microorganisms. The body does this by recognizing molecules unique to microorganisms that are not associated with human cells. These unique molecules are called pathogen-associated molecular patterns or PAMPs. Pathogenic *Mycobacterium* species such as *Mycobacterium tuberculosis* and *Mycobacterium leprae* release mycolic acid, arabinogalactan, and peptidoglycan fragments from their acid-fast cell wall. (Because all microbes, not just pathogenic microbes, possess PAMPs, pathogen-associated molecular patterns are sometime referred to as microbe-associated molecular patterns or MAMPs.)

These PAMPS bind to pattern-recognition receptors or PRRs on a variety of defense cells of the body causing them to synthesize and secrete a variety of proteins called cytokines. These cytokines can, in turn promote innate immune defenses such as inflammation , phagocytosis, activation of the complement pathways , and activation of the coagulation pathway .

Inflammation is the first response to infection and injury and is critical to body defense. Basically, the inflammatory response is an attempt by the body to restore and maintain homeostasis after injury. Most of the body defense elements are located in the blood, and inflammation is the means by which body defense cells and body defense chemicals leave the blood and enter the tissue around an injured or infected site.

Body defense cells called macrophages , and dendritic cells have pattern recognition receptors such as toll-like receptors on their surface that are specific for the peptidoglycan fragments and mycolic acids in the acid-fast cell wall and/or to NODs in their cytoplasm that are specific for peptidoglycan fragments. The binding of these cell wall components to their corresponding pattern recognition receptors triggers the macrophages to release various defense regulatory chemicals called cytokines, including IL-1 and TNF-alpha. The cytokines then bind to cytokine receptors on target cells and initiate inflammation and activate both the complement pathways and the coagulation pathway.

Innate immunity will be discussed in greater detail in Unit 5.

Initiation of Adaptive Immunity

Proteins and polysaccharides associated with the acid-fast cell wall function as antigens and initiate adaptive immunity. An antigen is defined as a molecular shape that reacts with antibody molecules and with antigen receptors on lymphocytes. We recognize those molecular shapes as foreign or different from our body's molecular shapes because they fit specific antigen receptors on our B-lymphocytes and T-lymphocytes, the cells that carry out adaptive immunity.

The actual portions or fragments of an antigen that react with antibodies and with receptors on B-lymphocytes and T-lymphocytes are called epitopes . An epitope is typically a group of 5-15 amino acids with a unique shape that makes up a portion of a protein antigen, or 3-4 sugar residues branching off of a polysaccharide antigen. A single microorganism has many hundreds of different shaped epitopes that our lymphocytes can recognize as foreign and mount an adaptive immune response against.

The body recognizes an antigen as foreign when epitopes of that antigen bind to B-lymphocytes and T-lymphocytes by means of epitope-specific receptor molecules having a shape complementary to that of the epitope. The epitope receptor on the surface of a B-lymphocyte is called a B-cell receptor and is actually an antibody molecule. The receptor on a T-lymphocyte is called a T-cell receptor (TCR).

There are two major branches of the adaptive immune responses: humoral immunity and cell-mediated immunity.

1. Humoral immunity: Humoral immunity involves the production of antibody molecules in response to an antigen and is mediated by B-lymphocytes. Through a variety of mechanisms, these antibodies are able to remove or neutralize microorganisms and their toxins after binding to their epitopes.
2. Cell-mediated immunity: Cell-mediated immunity involves the production of cytotoxic T-lymphocytes, activated macrophages, activated NK cells, and cytokines in response to an antigen and is mediated by T-lymphocytes. These defense cells help to remove infected cells and cancer cells displaying foreign epitopes.

Adaptive immunity will be discussed in greater detail in Unit 6.

Significance of Acid-Fast Cell Wall Components to Bacterial Pathogenicity

Most of the damage in the lungs during tuberculosis is thought to be due to the inflammatory effects from excessive TNF-alpha production, along with the release of toxic lysosomal components of the macrophages trying to kill the *Mycobacterium tuberculosis*.

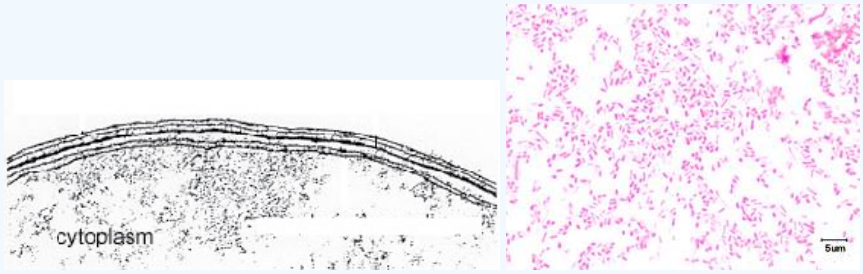
> Click on this link, read the description of *Mycobacterium tuberculosis*, and be able to match the bacterium with its description on an exam.

Antimicrobial Agents that Inhibit Acid-Fast Cell Wall Synthesis to Control *Mycobacterium* Species

INH (isoniazid) blocks the incorporation of mycolic acid into acid-fast cell walls while ethambutol interferes with the incorporation of arabinoglactan (Figure **1.3*C*.2**). Both inhibit synthesis of the acid-fast cell wall. Pyrazinamide inhibits fatty acid synthesis in *Mycobacterium tuberculosis.*

? Think-Pair-Share Questions

Look at the following transmission electron micrograph and Gram stain of the same bacterium.



(left) Transmission electron micrograph: (right) Gram stain

1. Is this organism Gram-positive, Gram-negative, or acid-fast?
2. How can you tell? State all reasons.

Summary

1. Because of the nature of their cell wall, acid-fast bacteria stain red after acid-fast staining.
2. The genus Mycobacterium and the genus Nocardia are among the few bacteria possessing an acid-fast cell wall.
3. The acid-fast cell wall consists of a thin, inner layer of peptidoglycan linked to a layer of arabinogalactin, which in turn is linked to an outer membrane containing mycolic acids and overlaid with a variety of polypeptides and glycolipids.
4. Porins are required to transport small hydrophilic molecules through the outer membrane of the acid-fast cell wall.
5. The acid-fast cell wall activates both the body's innate immune defenses and its adaptive immune defenses.
6. The body activates innate immunity by recognizing molecules unique to microorganisms that are not associated with human cells called pathogen-associated molecular patterns or PAMPs. PAMPs bind to Pattern-recognition receptors (PRRs) on defense cells to trigger the production of inflammatory cytokines.
7. Inflammation is the means by which the body delivers defense cells and defense molecules to an infection site, however, excessive inflammation, can be harmful and even deadly to the body.
8. PAMPs associated with the acid-fast cell wall include peptidoglycan monomers, arabinogalactin, and mycolic acids.
9. An antigen is a molecular shape that reacts with antigen receptors on lymphocytes to initiate an adaptive immune response.
10. Cell wall molecules can also trigger adaptive immunity such as the production of antibody molecules against bacterial cell wall antigens.
11. A few antimicrobial chemotherapeutic agents inhibit acid-fast cell wall synthesis

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. State what color acid-fast bacteria appear after the acid-fast stain procedure. *(ans)*
2. Describe the structure and appearance of an acid-fast cell wall. *(ans)*
3. State the beneficial function to the bacterium of the following components of the acid-fast cell wall:
    a. peptidoglycan *(ans)*
    b. mycolic acid and other glycolipids *(ans)*
    c. porins *(ans)*
4. *Mycobacterium tuberculosis* is much more resistant to antibiotics and disinfectants than most other bacteria. It also grows much more slowly. Why might this be? *(ans)*
5. Multiple Choice Cell Wall Quiz *(ans)*

This page titled 1.3C: The Acid-Fast Cell Wall is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **2.3C: The Acid-Fast Cell Wall** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

1.4: Structures Outside the Cell Wall

The overall purpose of this Learning Object is to list the various cellular components that are often found external to the bacterial cell wall.

In this section on Prokaryotic Cell Anatomy we are looking at the various anatomical parts that make up a bacterium. We will now look at the following structures located outside the cell wall of many bacteria: (1) glycocalyx (capsule) and S-layer, (2) flagella, and (3) pili.

This page titled 1.4: Structures Outside the Cell Wall is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **2.5: Structures Outside the Cell Wall** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

1.4A: Glycocalyx (Capsules) and Biofilms

State the chemical composition and 2 common functions of a bacterial glycocalyx.

- Briefly describe the following steps in phagocytosis:
  a. unenhanced attachment
  b. enhanced attachment
  c. engulfment
  d. destruction
- Briefly describe how a capsule might initially enable some bacteria to resist being phagocytosed by white blood cells.
- Define biofilm and state at least 3 advantages of biofilm formation to bacteria.

Highlighted Bacterium 1. Read the description of *Strepococcus pneumoniae* and match the bacterium with the description of the organism and the infection it causes.

All bacteria secrete some sort of glycocalyx (Capsules and Slime Layers), an outer viscous covering of fibers extending from the bacterium (see Figure 1.4A.1, Figure 1.4A.2, and Figure 1.4A.3). If it appears as an extensive, tightly bound accumulation of gelatinous material adhering to the cell wall, it is called a capsule as shown in the photomicrograph in Figure 1.4A.2. If the glycocalyx appears unorganized and more loosely attached, it is referred to as a slime layer.

Structure and Composition

The glycocalyx is usually a viscous polysaccharide or polypeptide slime. Actual production of a glycocalyx often depends on environmental conditions.

- A capsule stain of *Streptococcus lactis*.

Functions and Significance to Bacterial Pathogenicity

Although a number of functions have been associated with the glycocalyx, such as protecting bacteria against drying, trap nutrients, etc., for our purposes there are two very important functions. The glycocalyx enables certain bacteria to resist phagocytic engulfment by white blood cells in the body or protozoans in soil and water. The glycocalyx also enables some bacteria to adhere to environmental surfaces (rocks, root hairs, teeth, etc.), colonize, and resist flushing.

1. Preview of the Steps in Phagocytosis

As will be seen in Unit 5, there are several steps involved in phagocytosis.

a. Attachment

First the surface of the microbe must be attached to the cytoplasmic membrane of the phagocyte. Attachment of microorganisms is necessary for ingestion and may be unenhanced or enhanced.

- Unenhanced attachment is a general recognition of what are called pathogen-associated molecular patterns or PAMPs - components of common molecules such as peptidoglycan, teichoic acids, lipopolysaccharide, mannans,

and glucans common in microbial cell walls but not found on human cells - by means of glycoprotein known as endocytic pattern-recognition receptors on the surface of the phagocytes (see Figure 1.4A.4).

Flash animation illustrating the function of endocytic pattern-recognition receptors on phagocytes.

html5 version of animation for iPad illustrating the function of endocytic pattern-recognition receptors on phagocytes.

For More Information: Pathogen-Associated Molecular Patterns (PAMPs) from Unit 5

For More Information: Pattern-Recognition Receptors from Unit 5

- Enhanced attachment is the attachment of microbes to phagocytes by way of an antibody molecule called IgG or proteins produced during the complement pathways called C3b and C4b (see Figure 1.4A.5). Molecules such as IgG and C3b that promote enhanced attachment are called opsonins and the process is called opsonization. Enhanced attachment is much more specific and efficient than unenhanced.

  Flash animation illustrating the function of enhanced attachment by way of IgG.

  html5 version of animation for iPad illustrating the function of enhanced attachment by way of IgG.

  For More Information: Antibodies from Unit 6

  For More Information: The Benefits of the Complement Pathways from Unit 5

b. Engulfment

Following attachment, polymerization and then depolymerization of actin filaments send pseudopods out to engulf the microbe (see Figure 1.4A.6) and place it in a vesicle called a phagosome (see Figure 1.4A.7).

Flash animation summarizing phagocytosis through unenhanced attachment.

html5 version of animation for iPad summarizing phagocytosis through unenhanced attachment.

Flash animation summarizing phagocytosis through enhanced attachment.

html5 version of animation for iPad summarizing phagocytosis through enhanced attachment.

You Tube Movie illustrating bacterial phagocytosis by a neutrophil.

You Tube Movie illustrating a neutrophil phagocytosing MRSA

YouTube movie showing phagocytosis of yeast by a white blood cell.

You Tube animation summarizing phagocytosis by a macrophage.

c. Destruction

Finally, lysosomes, containing digestive enzymes and microbicidal chemicals, fuse with the phagosome containing the ingested microbe and the microbe is destroyed (see Figure 1.4A.8).

Role of the Glycocalyx in Resisting Phagocytosis

Capsules enable bacteria to resist phagocytosis. For example, capsules can resist unenhanced attachment by preventing the glycoprotein receptors on phagocytes from recognizing the bacterial cell wall components and mannose-containing carbohydrates (see Figure 1.4A.10). Also, some capsules simply cover the C3b that does bind to the bacterial surface and prevent the C3b receptor on phagocytes from making contact with the C3b (see Figure 1.4A.9). This will be discussed in greater detail later in Unit 3 under Bacterial Pathogenesis.

Flash animation illustrating how capsules can block unenhanced attachment of pathogen-associated molecular patterns to endocytic pattern-recognition receptors on phagocytes.

html5 version of animation for iPad illustrating how capsules can block unenhanced attachment of pathogen-associated molecular patterns to endocytic pattern-recognition receptors on phagocytes.

Examples of bacteria that use their capsule to resist phagocytic engulfment include *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, *Neisseria meningitidis*, *Bacillus anthracis* , and *Bordetella pertussis*.

- Encapsulated rod-shaped bacteria in an infected gall bladder.

For More Information: The Ability to Resist Phagocytic Engulfment from Unit 3

The body's immune defenses, however, can eventually get around the capsule by producing opsonizing antibodies (IgG) against the capsule. The antibody then sticks the capsule to the phagocyte. In vaccines against pneumococccal pneumonia and *Haemophilus influenzae* type b, it is capsular polysaccharide that is given as the antigen in order to stimulate the body to make opsonizing antibodies against the encapsulated bacterium.

Flash animation showing phagocytosis of an encapsulated bacterium through opsonization.

html5 version of animation for iPad showing phagocytosis of an encapsulated bacterium through opsonization.

- Movie of an encapsulated bacterium resisting engulfment by a neutrophil. Phagocytosis. © James Sullivan, author. Licensed for use, ASM MicrobeLibrary.

Normally when bacteria first enter the body, the innate immune defenses bind PAMPs on the bacterial cell wall to endocytic PRRs on the body's phagocytes and the organism is phagocytosed. Explain why the child's innate phagocytic defense was unable to remove the *S. pneumoniae*.

- The pneumococcal conjugate vaccine, PCV13 or Prevnar 13® is currently recommended for all children under 5 years of age. Why might prior vaccination with this vaccine have enabled the child to to remove the *S. pneumoniae* via phagocytosis?

3. Role of the Glycocalyx in Adhering to and Colonizing Environmental Surfaces

The glycocalyx also enables some bacteria to adhere to environmental surfaces (rocks, root hairs, teeth, etc.), colonize, and resist flushing. For example, many normal flora bacteria produce a capsular polysaccharide matrix or glycocalyx to form a biofilm on host tissue (see Figure 1.4A.3) as discussed below.

Significance of the glycocalyx in the Initiation of Body Defense

Initiation of Adaptive Immunity

Polysaccharides or polypeptides associated with the bacterial glycocalyx or capsule function as antigens and initiate adaptive immunity. An antigen is defined as a molecular shape that reacts with antibody molecules and with antigen receptors on lymphocytes. We recognize those molecular shapes as foreign or different from our body's molecular shapes because they fit specific antigen receptors on our B-lymphocytes and T-lymphocytes, the cells that carry out adaptive immunity.

The actual portions or fragments of an antigen that react with antibodies and with receptors on B-lymphocytes and T-lymphocytes are called epitopes. An epitope is typically a group of 5-15 amino acids with a unique shape that makes up a portion of a protein antigen, or 3-4 sugar residues branching off of a polysaccharide antigen. A single microorganism has many hundreds of different shaped epitopes that our lymphocytes can recognize as foreign and mount an adaptive immune response against.

The body recognizes an antigen as foreign when epitopes of that antigen bind to B-lymphocytes and T-lymphocytes by means of epitope-specific receptor molecules having a shape complementary to that of the epitope. The epitope receptor on the surface of a B-lymphocyte is called a B-cell receptor and is actually an antibody molecule. The receptor on a T-lymphocyte is called a T-cell receptor (TCR).

There are two major branches of the adaptive immune responses: humoral immunity and cell-mediated immunity.

1. Humoral immunity: Humoral immunity involves the production of antibody molecules in response to an antigen and is mediated by B-lymphocytes. Through a variety of mechanisms, these antibodies are able to remove or neutralize microorganisms and their toxins after binding to their epitopes. For example, antibodies made against capsular antigens can stick bacteria to phagocytes, a process called opsonization.

2. Cell-mediated immunity: Cell-mediated immunity involves the production of cytotoxic T-lymphocytes, activated macrophages, activated NK cells, and cytokines in response to an antigen and is mediated by T-lymphocytes. These defense cells help to remove infected cells and cancer cells displaying foreign epitopes.

Adaptive immunity will be discussed in greater detail in Unit 6.

Biofilms

Many pathogenic bacteria, as well as normal flora and many environmental bacteria, form complex bacterial communities as biofilms. Biofilms are groups of bacteria attached to a surface and enclosed in a common secreted adhesive matrix, typically polysaccharide in nature. Bacteria in biofilms are often able to communicate with one another by a process called quorum sensing (discussed later in Unit 2) and are able to interact with and adapt to their environment as a population of bacteria rather than as individual bacteria. By living as a community of bacteria as a biofilm, these bacteria are better able to:

- resist attack by antibiotics;
- trap nutrients for bacterial growth and remain in a favorable niche;
- adhere to environmental surfaces and resist flushing;
- live in close association and communicate with other bacteria in the biofilm; and
- resist phagocytosis and attack by the body's complement pathways.

Biofilms are, therefore, functional, interacting, and growing bacterial communities. Biofilms even contain their own water channels for delivering water and nutrients throughout the biofilm community.

- Electron micrograph of a biofilm of *Haemophilus influenzae* from Biomedcentral.com
- Photomicrograph of a biofilm with water channels from Centers for Disease Control and Prevention Rodney M. Donlan: "Biofilms: Microbial Life on Surfaces"
- Biofilm of *Pseudomonas aeruginosa* from the Ausubel Lab, Department of Molecular Biology, Massachusetts General Hospital

To initiate biofilm formation, planktonic bacteria (free individual bacteria not in a biofilm) contact an environmental surface through their motility or by random collision. These planktonic bacteria then attach to that surface using pili or cell wall adhesins. This attachment then signals the expression of genes involved in quorum sensing and, ultimately, biofilm formation. As the biofilm matrix is secreted, motile bacteria lose their flagella and become nonmotile.

Planktonic *Pseudomonas aeruginosa*, for example, uses its polar flagellum to move through water or mucus and make contact with a solid surface such as the body's mucous membranes. It then can use pili and cell wall adhesins to attach to the epithelial cells of the mucous membrane. Attachment activates signaling and quorum sensing genes to eventually enable the population of *P. aeruginosa* to start synthesizing a polysaccharide biofilm composed of alginate. As the biofilm grows, the bacteria lose their flagella to become nonmotile and secrete a variety of enzymes that enable the population to obtain nutrients from the host cells. Eventually the biofilm mushrooms up and develops water channels to deliver water and nutrients to all the bacteria within the biofilm. As the biofilm begins to get too crowded with bacteria, quorum sensing enables some of the *Pseudomonas* to again produce flagella, escape the biofilm, and colonize a new location (See Figs. 11A-11G).

Streptococcus mutans, and *Streptococcus sobrinus*, two bacteria implicated in initiating dental caries, break down sucrose into glucose and fructose. *Streptococcus mutans* can uses an enzyme called dextransucrase to convert sucrose into a sticky polysaccharide called dextran that forms a biofilm enabling the bacteria to adhere to the enamel of the tooth and form plaque. This will be discussed in greater detail later in Unit 2 under Bacterial Pathogenicity. *S.*

mutans and *S. sobrinus* also ferment glucose in order to produce energy. The fermentation of glucose results in the production of lactic acid that is released onto the surface of the tooth and initiates decay.

- Scanning electron micrograph of *Streptococcus* growing in the enamel of a tooth.© Lloyd Simonson, author. Licensed for use, ASM MicrobeLibrary.
- Scanning electron micrograph of dental plaque.© H. Busscher, H. van der Mei, W. Jongebloed, R Bos, authors. Licensed for use, ASM MicrobeLibrary.
- Scanning electron micrograph of *Staphylococcus aureus* forming a biofilm in an indwelling catheter courtesy of CDC.
- Biofilm of *Staphylococcus aureus* from Montana State University

A number of biofilm-forming bacteria, such as uropathogenic *Escherichia coli* (UPEC), enterohemorrhagic *E. coli* (EHEC), *Citrobacter* species, *Salmonella* species, and *Mycobacterium tuberculosis* are able to produce amyloid fibers that can play a role in such processes as attachment to host cells, invasion of host cells, and biofilm formation. Curli is an example of such an amyloid fiber produced by UPEC and *Salmonella*.

Many chronic and difficult-to-treat infections are caused by bacteria in biofilms. Within biofilms, bacteria grow more slowly, exhibit different gene expression than free planktonic bacteria, and are more resistant to antimicrobial agents such as antibiotics because of the reduced ability of these chemicals to penetrate the dense biofilms matrix. Biofilms have been implicated in tuberculosis, kidney stones, *Staphylococcus* infections, Legionnaires' disease, and periodontal disease. It is further estimated that as many as 10 million people a year in the US may develop biofilm-associated infections as a result of invasive medical procedures and surgical implants.

You Tube movie and animation: What are Biofilms?

Concept map for Glycocalyx and Biofilms

Summary

1. All bacteria secrete some sort of glycocalyx, an outer viscous covering of fibers extending from the bacterium.
2. An extensive, tightly bound glycocalyx adhering to the cell wall is called a capsule.
3. Phagocytosis involves several distinct steps including attachment of the microbe to the phagocyte through unenhanced or enhanced attachment, ingestion of the microbe and its placement into a phagosome, and the destruction of the microbe after fusion of lysosomes with the phagosome.
4. Capsules enable bacteria to resist unenhanced attachment by covering up bacterial PAMPs so they are unable to bind to endocytic pattern-recognition receptors.
5. The glycocalyx also enables some bacteria to adhere to environmental surfaces, colonize, and resist flushing.
6. The body's adaptive immune defenses can eventually overcome bacterial capsules by producing opsonizing antibodies (IgG) against the capsule that are able to stick the capsule to the phagocyte.
7. Biofilms are groups of bacteria attached to a surface and enclosed in a common secreted adhesive matrix and are functional, interacting, and growing bacterial communities.
8. Most bacteria in nature exist as biofilm populations.
9. Many chronic and difficult-to-treat infections are caused by bacteria in biofilms.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. State two common functions associated with the bacterial glycocalyx. (ans)
2. Briefly describe how a bacterial capsule might block phagocytosis. *(ans)*
3. State three possible functions associated with a bacterial biofilm. *(ans)*
4. Multiple Choice *(ans)*

This page titled 1.4A: Glycocalyx (Capsules) and Biofilms is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **2.5A: Glycocalyx (Capsules) and Biofilms** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

1.4B: Flagella

Describe the basic structure of a bacterial flagellum and state its function.
- State what provides the energy for bacterial flagellar rotation.
- Define the following flagellar arrangements:

a. monotrichous
b. lophotrichous
c. amphitrichous
d. peritrichous
e. axial filaments

- Define taxis.
- Compare and contrast how bacteria with peritrichous flagella and bacteria with polar flagella carry out taxis.
- State how bacterial flagella may play a role in the initiation of innate immune defenses.
- Briefly describe how bacterial flagella and chemotaxis may play a role in the pathogenocity of some bacteri

Highlighted Bacterium 1. Read the description of *Treponema pallidum* and match the bacterium with the description of the organism and the infection it causes.

Why might having flagella better enable those bacteria to cause disease?
- Our defense cells have a surface PRR called TLR-5 that recognizes bacterial flagellin. In terms of preventing infection, why is this an advantage?
- Most pathogenic spirochetes such as Treponema pallidum and Borrelia burgdorferi disseminate from the original infection site. How are they able to do this?

Structure and Composition of Flagella

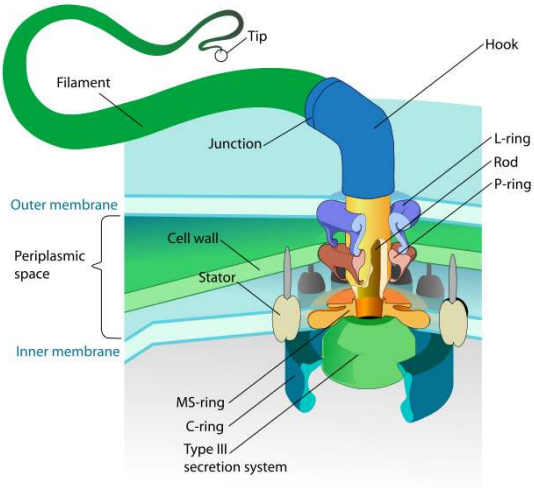


Figure **1.4*B*.4**B.1: A flagellum (plural: flagella) is a long, slender projection from the cell body, whose function is to propel a unicellular or small multicellular organism. The depicted type of flagellum is found in bacteria such as E. coli and Salmonella, and rotates like a propeller when the bacterium swims. The bacterial movement can be divided into 2 kinds: run, resulting from a counterclockwise rotation of the flagellum, and tumbling, from a clockwise rotation of the flagellum. from Wikipedia (LadyofHats)

1. The filament is the rigid, helical structure that extends from the cell surface. It is composed of the protein flagellin arranged in helical chains so as to form a hollow core. During synthesis of the flagellar filament, flagellin molecules coming off of the ribosomes are transported through the hollow core of the filament where they attach to the growing tip of the filament causing it to lengthen. With the exception of a few bacteria, such as *Bdellovibrio* and *Vibrio cholerae*, the flagellar filament is not surrounded by a sheath (see Figure **1.4*B*.1**).
2. The hook is a flexible coupling between the filament and the basal body (see Figure **1.4*B*.1**).
3. The basal body consists of a rod and a series of rings that anchor the flagellum to the cell wall and the cytoplasmic membrane (see Figure **1.4*B*.1**). Unlike eukaryotic flagella, the bacterial flagellum has no internal fibrils and does not flex. Instead, the basal body acts as a rotary molecular motor, enabling the flagellum to rotate and propel the bacterium through the surrounding fluid. In fact, the flagellar motor rotates very rapidly. (Some flagella can rotate up to 300 revolutions per second!)

The MotA and MotB proteins form the stator of the flagellar motor and function to generate torque for rotation of the flagellum. The MS and C rings function as the rotor. (See Figure **1.4*B*.1**). Energy for rotation comes from the proton motive force provided by protons moving through the Mot proteins along a concentration gradient from the peptidoglycan and periplasm towards the cytoplasm.

For More Information: Review of Proton Motive Force from Unit 7

- Electron micrograph and illustration of the basal body of bacterial flagella; Cover photo of *Molecular Biology of the Cell*, May 1, 2000.

- Animation of a rotating bacterial flagellum from the ARN Molecular Museum
- YouTube movie of the assembly and rotation of a bacterial flagellum

Bacteria flagella (see Figure 1.4B.2 and Figure 1.4B.3) are 10-20 µm long and between 0.01 and 0.02 µm in diameter.

Flagellar Arrangements (see Figure 1.4B.4)

1. monotrichous: a single flagellum, usually at one pole

- Scanning electron micrograph showing monotrichous flagellum of *Vibrio*; courtesy of CDC.

2. amphitrichous: a single flagellum at both ends of the organism

3. lophotrichous: two or more flagella at one or both poles

- Scanning electron micrograph of *Helicobacter pylori* showing lophotrichous arrangement of flagella ; from Science Photolab.com

4. peritrichous: flagella over the entire surface

- Scanning electron micrograph of *Proteus vulgaris* showing peritrichous arrangement of flagella and pili; from fineartamerica.com

5. axial filaments: internal flagella found only in the spirochetes. Axial filaments are composed of from two to over a hundred axial fibrils (or endoflagella) that extend from both ends of the bacterium between the outer membrane and the cell wall, often overlapping in the center of the cell. (see Figure 1.4B.5 and Figure 1.4B.6). A popular theory as to the mechanism behind spirochete motility presumes that as the endoflagella rotate in the periplasmic space between the outer membrane and the cell wall, this could cause the corkscrew-shaped outer membrane of the spirochete to rotate and propel the bacterium through the surrounding fluid.

- Axial filaments of the spirochete Leptospira; Midlands Technical College, Bio 255 course site

Concept map for Bacterial Flagella

Functions

Flagella are the organelles of locomotion for most of the bacteria that are capable of motility. Two proteins in the flagellar motor, called MotA and MotB, form a proton channel through the cytoplasmic membrane and rotation of the flagellum is driven by a proton gradient. This driving proton motive force occurs as protons accumulating in the space between the cytoplasmic membrane and the cell wall as a result of the electron transport system travel through the channel back into the bacterium's cytoplasm. Most bacterial flagella can rotate both counterclockwise and clockwise and this rotation contributes to the bacterium's ability to change direction as it swims. A protein switch in the molecular motor of the basal body controls the direction of rotation.

1. A bacterium with peritrichous flagella:

If a bacterium has a peritrichous arrangement of flagella, counterclockwise rotation of the flagella causes them to form a single bundle that propels the bacterium in long, straight or curved runs without a change in direction. Counterclockwise rotation causes the flagellum to exhibit a left-handed helix. During a run, that lasts about one second, the bacterium moves 10 - 20 times its length before it stops. This occurs when some of the the flagella rotate clockwise, disengage from the bundle, and trigger a tumbling motion. Clockwise rotation causes the flagellum to assume a right-handed helix. A tumble only lasts about one-tenth of a second and no real forward progress is made. After a “tumble”, the direction of the next bacterial run is random because every time the bacterium stops swimming, Brownian motion and fluid currents cause the bacterium to reorient in a new direction.

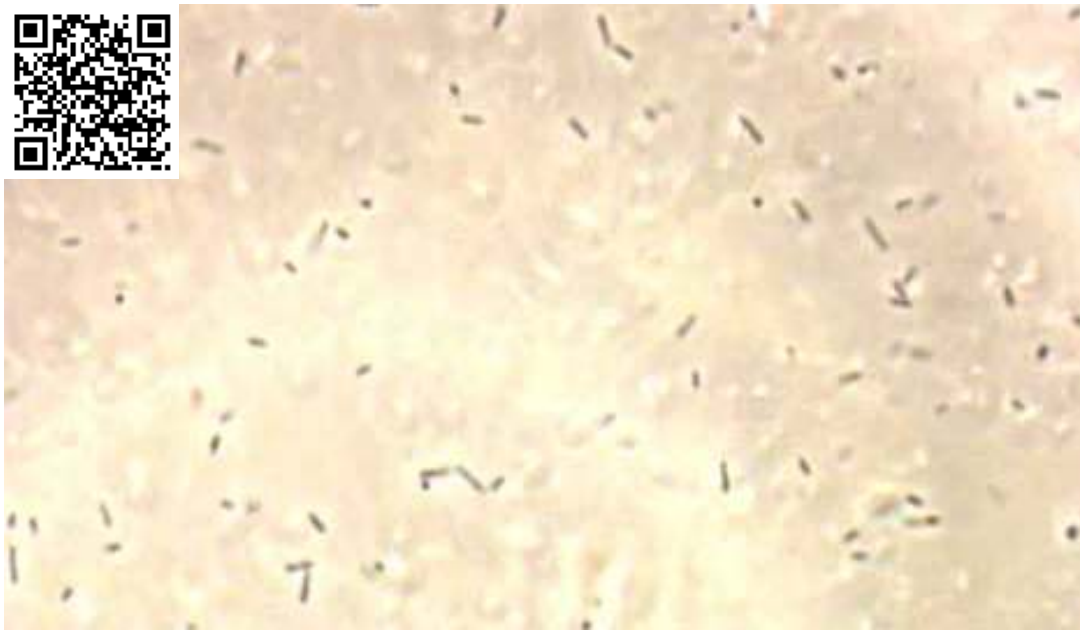
Movie of swimming *Escherichia coli* as seen with phase contrast microscopy. Flagella are not visible with under phase contrast microscopy. Note runs and tumbles. Courtesy of Dr. Howard C. Berg from the Roland Institute at Harvard.
Movie of motile *Escherichia coli* with fluorescent labelled-flagella #1. This technique allows the the flagella to be seen as the bacteria swim. Note some flagella leaving the flagellar bundle to initiate tumbling. Courtesy of Dr. Howard C. Berg from the Roland Institute at Harvard.
Movie of motile *Escherichia coli* with fluorescent labelled-flagella #2. This technique allows the the flagella to be seen as the bacteria swim. Note some flagella leaving the flagellar bundle to initiate tumbling. Courtesy of Dr. Howard C. Berg from the Roland Institute at Harvard.
Movie of tethered *Escherichia coli* showing that the bacterial flagella rotate. Courtesy of Dr. Howard C. Berg from the Roland Institute at Harvard.

When bacteria with a peritrichous arrangement grow on a nutrient-rich solid surface, they can exhibit a swarming motility wherein the bacteria elongate, synthesize additional flagella, secrete wetting agents, and move across the surface in coordinated manner.

Movie of swarming motility of *Escherichia coli*.
Courtesy of Dr. Howard C. Berg from the Roland Institute at Harvard.

2. A bacterium with polar flagella:

Most bacteria with polar flagella, like the peritrichous above, can rotate their flagella both clockwise and counterclockwise. If the flagellum is rotating counterclockwise, it pushes the bacterium forward. When it rotates clockwise, it pulls the bacterium backward. These bacteria change direction by changing the rotation of their flagella.



Video **1.4*B*.4***B.1: Phase contrast movie of motile Pseudomonas. Pseudomonas has a single polar flagellum that can rotate both counterclockwise and clockwise but is not visible under phase contrast microscopy (http://www.youtube.com/embed/EWj2TGsTQEI).*

Movie of *Spirillum volutans*, a spiral-shaped bacterium with a bundle of flagella at either end.
Courtesy of Dr. Howard C. Berg from the Roland Institute at Harvard.

Some bacteria with polar flagella can only rotate their flagellum clockwise. In this case, clockwise rotation pushes the bacterium forward. Every time the bacterium stops, Brownian motion and fluid currents cause the bacterium to reorient in a new direction.

Movie of *Rhodobacter spheroides* with fluorescent-labelled flagella.
The flagellum can only rotate clockwise.
Courtesy of Dr. Howard C. Berg from the Roland Institute at Harvard.

Concept map for Bacterial Flagella

Taxis

Around half of all known bacteria are motile. Motility serves to keep bacteria in an optimum environment via taxis. Taxis is a motile response to an environmental stimulus. Bacteria can respond to chemicals (chemotaxis), light (phototaxis), osmotic pressure (osmotaxis), oxygen (aerotaxis), and temperature (thermotaxis). Chemotaxis is a response to a chemical gradient of attractant or repellent molecules in the bacterium's environment.

- In an environment that lacks a gradient of attractant or repellent, the bacterium moves randomly. In this way the bacterium keeps searching for a gradient.

- In an environment that has a gradient of attractant or repellent, the net movement of the bacterium is towards the attractant or away from the repellent.

For More Information: Chemotaxis in *Escherichia coli*

Chemotaxis is regulated by chemoreceptors located in the cytoplasmic membrane or periplasm of the bacterium bind chemical attractants or repellents. In most cases, this leads to either the methylation or demethylation of methyl-accepting chemotaxis proteins (MCPs) that in turn, eventually trigger either a counterclockwise or clockwise rotation of the flagellum. An increasing concentration of attractant or decreasing concentration of repellent (both conditions beneficial) causes less tumbling and longer runs; a decreasing concentration of attractant or increasing concentration of repellent (both conditions harmful) causes normal tumbling and a greater chance of reorienting in a "better" direction. As a result, the organism's net movement is toward the optimum environment..

Significance of Flagella in the Initiation of Body Defense

Initiation of Innate Immunity

To protect against infection, one of the things the body must initially do is detect the presence of microorganisms. The body does this by recognizing molecules unique to microorganisms that are not associated with human cells. These unique molecules are called pathogen-associated molecular patterns or PAMPs. (Because all microbes, not just pathogenic microbes, possess PAMPs, pathogen-associated molecular patterns are sometimes referred to as microbe-associated molecular patterns or MAMPs.)

The protein flagellin in bacterial flagella is a PAMP that binds to pattern-recognition receptors or PRRs on a variety of defense cells of the body and triggers innate immune defenses such as inflammation, fever, and phagocytosis.

For More Information: Pathogen-Associated Molecular Patterns (PAMPs) from Unit 5

For More Information: Pattern-Recognition Receptors from Unit 5

Initiation of Adaptive Immunity

Proteins associated with bacterial flagella function as antigens and initiate adaptive immunity. An antigen is defined as a molecular shape that reacts with antibody molecules and with antigen receptors on lymphocytes. We recognize those molecular shapes as foreign or different from our body's molecular shapes because they fit specific antigen receptors on our B-lymphocytes and T-lymphocytes, the cells that carry out adaptive immunity.

The actual portions or fragments of an antigen that react with antibodies and with receptors on B-lymphocytes and T-lymphocytes are called epitopes. An epitope is typically a group of 5-15 amino acids with a unique shape that makes up a portion of a protein antigen, or 3-4 sugar residues branching off of a polysaccharide antigen. A single microorganism has many hundreds of different shaped epitopes that our lymphocytes can recognize as foreign and mount an adaptive immune response against.

The body recognizes an antigen as foreign when epitopes of that antigen bind to B-lymphocytes and T-lymphocytes by means of epitope-specific receptor molecules having a shape complementary to that of the epitope. The epitope receptor on the surface of a B-lymphocyte is called a B-cell receptor and is actually an antibody molecule. The receptor on a T-lymphocyte is called a T-cell receptor (TCR).

There are two major branches of the adaptive immune responses: humoral immunity and cell-mediated immunity.

1. Humoral immunity: Humoral immunity involves the production of antibody molecules in response to an antigen and is mediated by B-lymphocytes. Through a variety of mechanisms, these antibodies are able to remove or neutralize microorganisms and their toxins after binding to their epitopes. For example, antibodies made against flagellar antigens can stick bacteria to phagocytes, a process called opsonization. They can also interfere with bacterial motility.
2. Cell-mediated immunity: Cell-mediated immunity involves the production of cytotoxic T-lymphocytes, activated macrophages, activated NK cells, and cytokines in response to an antigen and is mediated by T-lymphocytes. These defense cells help to remove infected cells and cancer cells displaying foreign epitopes.

Adaptive immunity will be discussed in greater detail in Unit 6.

For More Information: Review of antigens and epitopes from Unit 6

Significance of Motility to Bacterial Pathogenicity

Motility and chemotaxis probably help some intestinal pathogens to move through the mucous layer so they can attach to the epithelial cells of the mucous membranes. In fact, many bacteria that can colonize the mucous membranes of the bladder and the intestines are motile. Motility probably

helps these bacteria move through the mucus in places where it is less viscous.

Flash animation showing a motile bacterium contacting a host cell by swimming through the mucus.

html5 version of animation for iPad showing a motile bacterium contacting a host cell by swimming through the mucus.

Motility and chemotaxis also enable spirochetes to move through viscous environments and penetrate cell membranes. Examples include *Treponema pallidum (inf)*, *Leptospira (inf)*, and *Borrelia burgdorferi*) *(inf)*. Because of their thinness, their internal flagella (axial filaments), and their motility, spirochetes are more readily able to penetrate host mucous membranes, skin abrasions, etc., and enter the body. Motility and invasins may also enable the spirochetes to penetrate deeper in tissue and enter the lymphatics and bloodstream and disseminate to other body sites.

Flash animation showing spirochetes using motility to enter a blood vessel.

html5 version of animation for iPad showing spirochetes using motility to enter a blood vessel.

Movie of motile *Borrelia bergdorferi*, the spirochete that causes Lyme disease. Note corkscrewing motility.
From You Tube, courtesy of CytoVivo.

Electron micrograph of *Treponema pallidum* invading a host cell.

This will be discussed in more detail under Bacterial Pathogenesis in Unit 3.

For More Information: The Ability to Contact Host Cells from Unit 3

For More Information: The Ability to Invade Host Cells from Unit 3

Concept map for Bacterial Flagella

Summary

1. Many bacteria are motile and use flagella to swim through liquid environments.
2. The basal body of a bacterial flagellum functions as a rotary molecular motor, enabling the flagellum to rotate and propel the bacterium through the surrounding fluid.
3. Bacterial flagella appear in several arrangements, each unique to a particular organism.
4. Motility serves to keep bacteria in an optimum environment via taxis.
5. Taxis refers to a motile response to an environmental stimulus enabling the net movement of bacteria towards some beneficial attractant or away from some harmful repellent.
6. Most bacterial flagella can rotate both clockwise and counterclockwise enabling to stop and change direction.
7. The protein flagellin that forms the filament of bacterial flagella functions as a pathogen-associated molecular pattern or PAMP that binds to pattern-recognition receptors or PRRs on a variety of defense cells of the body to trigger innate immune defenses.
8. Motility and chemotaxis probably help some intestinal pathogens to move through the mucous layer so they can attach to the epithelial cells of the mucous membranes and colonize the intestines.
9. Motility enables some spirochetes to penetrate deeper in tissue and enter the lymphatics and bloodstream and disseminate to other body sites.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. _____ a single flagellum at both ends (ans)
   A. monotrichous
   B. amphitrichous
   C. lophotrichous
   D. peritrichous
   E. axial filaments
2. State how bacterial flagella may play a role in the initiation of innate immune defenses. *(ans)*
3. Briefly describe how bacterial flagella and chemotaxis may play a role in the pathogenocity of some bacteria. *(ans)*
4. Multiple Choice *(ans)*

This page titled 1.4B: Flagella is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **2.5B: Flagella** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

1.4C: Fimbriae and Pili

Learning Objectives

1. State the chemical composition, structure, and function of the short adhesion pili of bacteria.
2. State the function of a bacterial conjugation (sex) pilus.
3. Define bacterial conjugation.
4. State how the ability to change the shape of the adhesive tip of its pili could be an advantage to a bacterium.
5. Briefly describe twitching motility induced by type IV pili.

Highlighted Bacterium

1. Read the description of *Neisseria gonorrhoeae* and match the bacterium with the description of the organism and the infection it causes.

Structure and Composition

Fimbriae and pili are thin, protein tubes originating from the cytoplasmic membrane of many bacteria. Both are able to stick bacteria to surfaces, but pili are typically longer and fewer in number than fimbriae. They are found in virtually all Gram-negative bacteria but not in many Gram-positive bacteria. The fimbriae and pili have a shaft composed of a protein called pilin. At the end of the shaft is the adhesive tip structure having a shape corresponding to that of specific glycoprotein or glycolipid receptors on a host cell (Figure **1.4*C*.1**). There are two basic types of pili: **short attachment pili** and l**ong conjugation pili**.

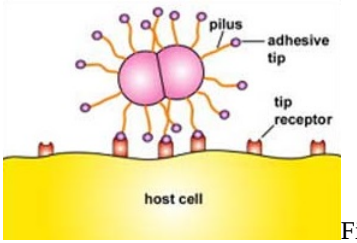


Figure **1.4*C*.1**: Adhesive Tip of Bacterial Pili Binding to Host Cell Receptors

Short attachment pili, also known as *fimbriae*, are usually short and quite numerous (Figure **1.4*C*.1**) and enable bacteria to colonize environmental surfaces or cells and resist flushing.

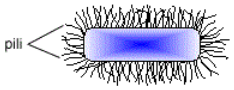
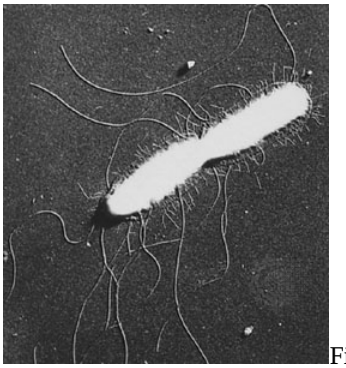


Figure **1.4*C*.2**: Bacterial Pili.


Figure **1.4*C*.3**: Electron micrograph of *Salmonella* showing both flagella and pili from the Wiki Biodiversityserene.

Long conjugation pili, also called "F" or sex pili (Figure **1.4*C*.4**), that are longer and very few in number. The conjugation pilus enables conjugation. As will be seen later in this unit, conjugation is the transfer of DNA from one bacterium to another by cell-to-cell contact. In gram-negative bacteria it is typically the transfer of DNA from a donor or "male bacterium" with a sex pilus to a recipient or "female bacterium" to enable genetic recombination.

https://med.libretexts.org/@go/page/77500

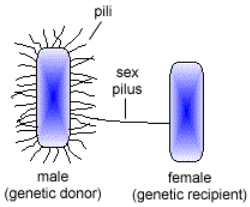
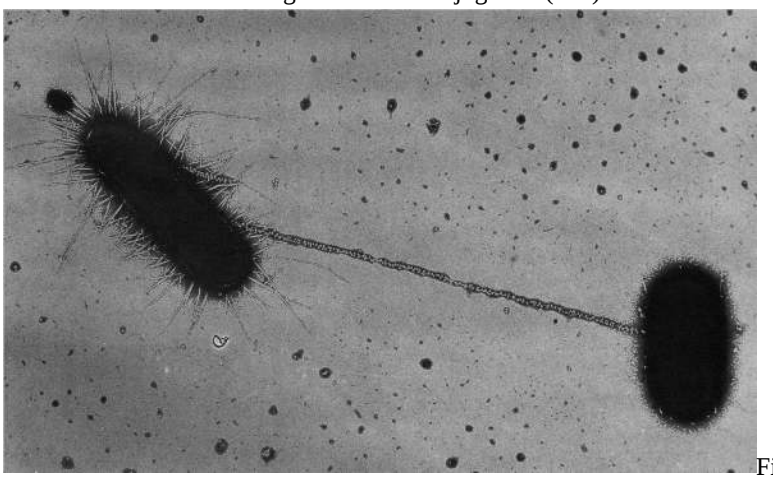


Figure 1.4*C*.4: Conjugation (Sex) Pilus


Figure 1.4*C*.5: Scanning electron micrograph of E.coli bacteria exchanging genes. Courtesy of Charles C. Brinton Jr. (NIH)

Significance of Pili to Bacterial Pathogenicity

The short attachment pili or fimbriae are organelles of adhesion allowing bacteria to colonize environmental surfaces or cells and resist flushing. The pilus has a shaft composed of a protein called *pilin*. At the end of the shaft is the adhesive tip structure having a shape corresponding to that of specific glycoprotein or glycolipid receptors on a host cell (Figure 1.4*C*.1). Because both the bacteria and the host cells have a negative charge, pili may enable the bacteria to bind to host cells without initially having to get close enough to be pushed away by electrostatic repulsion. Once attached to the host cell, the pili can depolymerize and enable adhesions in the bacterial cell wall to make more intimate contact.

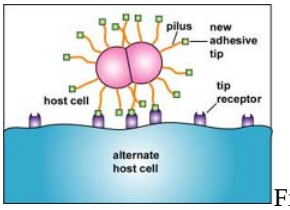


Figure 1.4*C*.6: Bacteria Altering the Adhesive Tips of Their Pili. By genetically altering the adhesive tips of their pili, certain bacteria are able to: 1) adhere to and colonize different cell types with different receptors, and 2) evade antibodies made against the previous pili. Bacteria are constantly losing and reforming pili as they grow in the body and the same bacterium may switch the adhesive tips of the pili in order to adhere to different types of cells and evade immune defenses (Figure 1.4*C*.6). This will be discussed in detail later in Unit 3 under Bacterial Pathogenesis. Bacteria that use pili to initially colonize host cells include *Neisseria gonorrhoeae*, *Neisseria meningitidis (inf)*, uropathogenic strains of *Escherichia coli*, and *Pseudomonas aeruginosa (inf)*.

Highlighted Bacterium: *Neisseria gonorrhoeae*

Click on this link, read the description of *Neisseria gonorrhoeae*, and be able to match the bacterium with its description on an exam.

Flash animation showing bacteria lacking pili being flushed out of the urethra.

Flash animation showing how bacteria with pili may resist being flushed out of the urethra.

html5 version of animation for iPad showing bacteria lacking pili being flushed out of the urethra.

html5 version of animation for iPad showing how bacteria with pili may resist being flushed out of the urethra.

One class of pili, known as type IV pili , not only allow for attachment but also enable a twitching motility. They are located at the poles of bacilli and allow for a gliding motility along a solid surface such as a host cell. Extension and retraction of these pili allows the bacterium to drag itself along the solid surface (see Figure 1.4*C*.5). In addition, bacteria can use their type IV pili to "slingshot" the bacterium over a cellular surface. In this case, as the pili contract they are thought to become taut like a stretched rubber band. When an anchoring pilus detaches, the taut pili "slingshot" the bacterium in the opposite direction (see Figure 1.4*C*.6). This motion typically alternates with the twitching motility and enables a more rapid motion and direction change than with the twitching motility because the rapid slingshotting motion reduces the viscosity of the surrounding biofilm.

This enables bacteria with these types of pili within a biofilm to move around a cellular surface and find an optimum area on that cell for attachment and growth once they have initially bound. Bacteria with type IV pili include *Pseudomonas aeruginosa*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, and *Vibrio cholerae*.

- Electron micrograph of type IV pili of *Neisseria gonorrhoeae* from Magdalene So, University of Arizona

Flash animation showing a bacterium using type IV pili to drag itself (twitching motility) along a surface.

html5 version of animation for iPad showing a bacterium using type IV pili to drag itself (twitching motility) along a surface.

Flash animation showing a bacterium using type IV pili to "slingshot" itself along a surface.

html5 version of animation for iPad showing a bacterium using type IV pili to "slingshot" itself along a surface.

You Tube movie showing twitching motility in *Pseudomonas* due to type IV pili
Courtesy of Dr. Lori Burrows You Tube videos

You Tube movie showing *Pseudomonas* using type IV pili to "walk" on end following binary fission.
Courtesy of Gerard Wong, UCLA Bioengineering, CNSI

Movie of twitching motility of *Pseudomonas*
Courtesy of Dr. Howard C. Berg from the Roland Institute at Harvard.

Retraction of pili of *Pseudomonas* used in twitching motility
Courtesy of Dr. Howard C. Berg from the Roland Institute at Harvard.

You Tube movie showing a *Pseudomonas* using pili to hop or slingshot itself over a surface.

? Exercise: Think-Pair-Share Questions

Neisseria gonorrhoeae is a gram-negative diplococcus that has multiple alleles coding for different and distinct pili adhesive tips as well as different and distinct cell wall adhesins called Opa proteins.

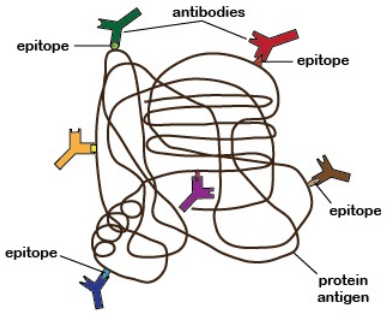
The gonococcus is able to colonize and infect a numerous sites in the body, including the urethra, the rectum, the throat, the conjunctiva of the eye, and the fallopian tubes. It can also colonize sperm.

1. Considering the locations in the body where it colonizes, why doesn't the body simply flush the bacterium out of the body?
2. Why is *N. gonorrhoea*e able to colonize so many different sites in the body?
3. We recognize pili adhesive tips and cell wall adhesins as foreign and, during adaptive immunity, make antibodies that bind to these microbial molecules. State how this might help to protect the body.

Significance of Fimbriae and Pili in the Initiation of Body Defense

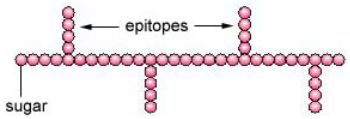
Initiation of Adaptive Immunity

Proteins associated with bacterial fimbriae and pili function as antigens and initiate adaptive immunity. An antigen is defined as a molecular shape that reacts with antibody molecules and with antigen receptors on lymphocytes. We recognize those molecular shapes as foreign or different from our body's molecular shapes because they fit specific antigen receptors on our B-lymphocytes and T-lymphocytes, the cells that carry out adaptive immunity.



Epitopes of an Antigen (Polysaccharide). Proteins have many epitopes of different specificities. During humoral immunity, antibodies are made to fit each epitope of each antigen.

The actual portions or fragments of an antigen that react with antibodies and with receptors on B-lymphocytes and T-lymphocytes are called epitopes . An epitope is typically a group of 5-15 amino acids with a unique shape that makes up a portion of a protein antigen, or 3-4 sugar residues branching off of a polysaccharide antigen. A single microorganism has many hundreds of different shaped epitopes that our lymphocytes can recognize as foreign and mount an adaptive immune response against.



Epitopes of an Antigen (Polysaccharide)

The body recognizes an antigen as foreign when epitopes of that antigen bind to B-lymphocytes and T-lymphocytes by means of epitope-specific receptor molecules having a shape complementary to that of the epitope. The epitope receptor on the surface of a B-lymphocyte is called a B-cell receptor and is actually an antibody molecule. The receptor on a T-lymphocyte is called a T-cell receptor (TCR).

There are two major branches of the adaptive immune responses: humoral immunity and cell-mediated immunity.

1. Humoral immunity: Humoral immunity involves the production of antibody molecules in response to an antigen and is mediated by B-lymphocytes. Through a variety of mechanisms, these antibodies are able to remove or neutralize microorganisms and their toxins after binding to their epitopes. For example, antibodies made against pili antigens can stick bacteria to phagocytes, a process called *opsonization*. Antibodies made against the adhesive tips of pili can prevent bacteria from adhering to and colonizing host cells.

2. Cell-mediated immunity: Cell-mediated immunity involves the production of cytotoxic T-lymphocytes, activated macrophages, activated NK cells, and cytokines in response to an antigen and is mediated by T-lymphocytes. These defense cells help to remove infected cells and cancer cells displaying foreign epitopes.

https://med.libretexts.org/@go/page/77500

Adaptive immunity will be discussed in greater detail in Unit 6.

For More Information: Review of antigens and epitopes from Unit 6

Medscape article on infections associated with organisms mentioned in this Learning Object. Registration to access this website is free.

- *Neisseria gonorrhoeae*
- *Neisseria meningitidis*
- *Escherichia coli*
- *Pseudomonas aeruginosa*
- *Vibrio cholerae*

Summary

1. Fimbriae and pili are thin, protein tubes originating from the cytoplasmic membrane found in virtually all Gram-negative bacteria but not in many Gram-positive bacteria. Pili are typically longer and fewer in number than fimbriae.
2. The short attachment pili or fimbriae are organelles of adhesion allowing bacteria to colonize environmental surfaces or cells and resist flushing.
3. The long conjugation pilus enables conjugation in Gram-negative bacteria.
4. The pilus has a shaft composed of a protein called pilin with an adhesive tip structure at the end having a shape corresponding to that of specific receptors on a host cell.
5. The same bacterium may switch the adhesive tips of the pili in order to adhere to different types of cells and evade immune defenses.
6. Type IV pili not only allow for attachment but also enable a twitching motility that enables bacteria to “crawl” or “walk” over the surfaces to which they have attached by extending and retracting their type IV pili.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. State the function of the short adhesion pili of bacteria. *(ans)*
2. Define bacterial conjugation. *(ans)*
3. State how the ability to change the shape of the adhesive tip of its pili could be an advantage to a bacterium. *(ans)*
4. Multiple Choice *(ans)*

This page titled 1.4C: Fimbriae and Pili is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **2.5C: Fimbriae and Pili** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

1.5: Cellular Components within the Cytoplasm

Name the various structures that may be located within the cytoplasm of bacteria.

In this section on Prokaryotic Cell Anatomy we are looking at the various anatomical parts that make up a bacterium. As mentioned in the introduction to this section, a typical bacterium usually consists of:

- a cytoplasmic membrane surrounded by a peptidoglycan cell wall and maybe an outer membrane;
- a fluid cytoplasm containing a nuclear region (nucleoid) and numerous ribosomes; and
- often various external structures such as a glycocalyx, flagella, and pili.

This page titled 1.5: Cellular Components within the Cytoplasm is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **2.4: Cellular Components within the Cytoplasm** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

1.5A: Cytoplasm

Define the following:

a. exoenzymes

b. endoenzymes.

c. cytosol

- State the primary function of the bacterial cytoplasm.
- Define the following:

a. metabolism

b. catabolic reactions

c. anabolic reactions.

We will now look at the bacterial cytoplasm. In bacteria, the cytoplasm refers to everything enclosed by the cytoplasmic membrane. About 80% of the cytoplasm of bacteria is composed of water. Within the cytoplasm can be found nucleic acids (DNA and RNA), enzymes and amino acids, carbohydrates, lipids, inorganic ions, and many low molecular weight compounds. The liquid component of the cytoplasm is called the cytosol. Some groups of bacteria produce cytoplasmic inclusion bodies that carry out specialized cellular functions.

Functions

While bacteria secrete exoenzymes to hydrolize macromolecules into smaller molecules capable of being transported across the cytoplasmic membrane, the cytoplasm is the site of most bacterial metabolism. This includes catabolic reactions in which molecules are broken down in order to obtain building block molecules for more complex cellular molecules and macromolecules, and anabolic reactions used to synthesize cellular molecules and macromolecules. The chemical reactions occuring within the bacterium are under the control of endoenzymes.

The various structurural filaments in the cytoplasm collectively make up the prokaryotic cytoskeleton. Prokaryotic cells possess analogs for all of the cytoskeletal proteins found in eukaryotic cells, as well as cytoskeletal proteins with no eukaryotic homologues. Cytoskeletal filaments play essential roles in determining the shape of a bacterium (coccus, bacillus, or spiral) and are also critical in the process of cell division by binary fission and in determining bacterial polarity.

Summary

1. In bacteria, the cytoplasm refers to anything enclosed by the cytoplasmic membrane.
2. The liquid portion of the cytoplasm is called the cytosol.
3. The cytoplasm is the site of most bacterial metabolism.
4. During catabolic reactions larger molecules are broken down to obtain cellular building block molecules and energy; during anabolic reactions cellular molecules and macromolecules are synthesized.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. _____ Enzymes that function within the bacterium. (ans)

   _____ Chemical reactions in which more complex molecules are synthesized. *(ans)*

   _____ Chemical reactions in which more complex molecules are broken down into smaller, more simple molecules. *(ans)*

   A. Metabolism
   B. Catabolic reactions
   C. Anabolic reactions
   D. Exoenzymes

E. Endoenzymes

2. State the primary function of bacterial cytoplasm. *(ans)*

This page titled 1.5A: Cytoplasm is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **2.4A: Cytoplasm** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

1.5B: The Bacterial Chromosome and Nucleoid

Learning Objectives

1. Define genome.
2. Describe the composition of the bacterial chromosome.
3. Name the enzymes that enables bacterial DNA to become circular, supercoiled, and unwind during DNA replication.
4. Briefly describe the process of DNA replication.
5. State the function of the following enzymes in bacterial DNA replication:
   a. DNA polymeraseIII
   b. DNA polymerase II
   c. DNA helicase
   d. primase
   e. DNA ligase
6. State the function of DNA.
7. In terms of protein synthesis, briefly describe the process of transcription and translation.
8. Briefly state how the following antibacterial chemotherapeutic agents affect bacteria:
   a. fluoroquinolones (norfloxacin, lomefloxacin, fleroxacin, ciprofloxacin, enoxacin, trovafloxacin, etc.)
   b. trimethoprim and sulfamethoxazole

We will now look at the bacterial chromosome located in the nuclear region called the nucleoid.

A. Structure and Composition of the Bacterial Chromosome

The term genome refers to the sum of an organism's genetic material. The bacterial genome is composed of a single molecule of chromosomal deoxyribonucleic acid or DNA and is located in a region of the bacterial cytoplasm visible when viewed with an electron microscope called the nucleoid. Unlike the eukaryotic nucleus, the bacterial nucleoid has no nuclear membrane or nucleoli.

In general it is thought that during DNA replication, each strand of the replicating bacterial DNA attaches to proteins at what will become the cell division plane. For example, Par proteins function to separate bacterial chromosomes to opposite poles of the cell during cell division. They bind to the origin of replication of the DNA and physically pull or push the chromosomes apart, similar to the mitotic apparatus of eukaryotic cells (Figure 1.5*B*.1).

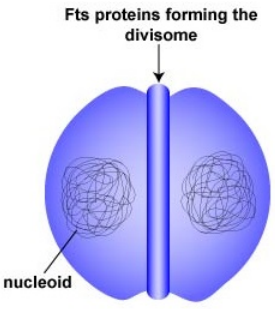


Figure 1.5*B*.1*:* Bacterial Division. In general it is thought that during DNA replication, each strand of the replicating bacterial DNA attaches to proteins at what will become the cell division plane. For example, Par proteins function to separate bacterial chromosomes to opposite poles of the cell during cell division. They bind to the origin of replication of the DNA and physically pull or push the chromosomes apart, similar to the mitotic apparatus of eukaryotic cells. In the center of the bacterium, a group of proteins called Fts (filamentous temperature sensitive) proteins interact to form a ring at the cell division plane. These proteins form the cell division apparatus known as the divisome and are directly involved in bacterial cell division by binary fission. The divisome is responsible for directing the synthesis of new cytoplasmic membrane and new peptidoglycan to form the division septum.

In the center of the bacterium, a group of proteins called Fts (filamentous temperature sensitive) proteins interact to form a ring at the cell division plane. These proteins form the cell division apparatus known as the divisome and are directly involved in bacterial cell division by binary fission. The divisome is responsible for directing the synthesis of new cytoplasmic membrane and new peptidoglycan to form the division septum.

Since bacteria are haploid, that is they have only one chromosome and only reproduce asexually, there is also no meiosis in bacteria.

The bacterial chromosome is one long, single molecule of double stranded, helical, supercoiled DNA. In most bacteria, the two ends of the double-stranded DNA covalently bond together to form both a physical and genetic circle. The chromosome is generally around 1000 µm long and frequently contains as many as 3500 genes (Figure **1.5*B*.2**). *E. coli*, a bacterium that is 2-3 µm in length, has a chromosome approximately 1400 µm long.

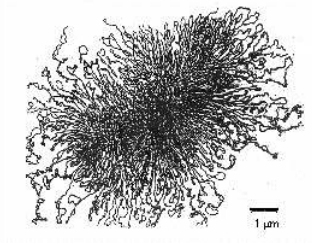


Figure **1.5*B*.2:** Electron Micrograph of a Bacterial Chromosome

To enable a macromolecule this large to fit within the bacterium, histone-like proteins bind to the DNA, segregating the DNA molecule into around 50 chromosomal domains and making it more compact. A DNA topoisomerase enzyme called DNA gyrase then supercoils each domain around itself, forming a compacted mass of DNA approximately 0.2 µm in diameter. In actively growing bacteria, projections of the nucleoid extend into the cytoplasm. Presumably, these projections contain DNA that is being transcribed into mRNA.Supercoils are both inserted and removed by *topoisomerases*.

DNA topoisomerases are, therefore, essential in the unwinding, replication, and rewinding of the circular, supercoiled bacterial DNA. In order for the long molecule of DNA to fit within the bacterium, the DNA must be supercoiled. However, this supercoiled DNA must be uncoiled and relaxed in order for DNA polymerase to bind for DNA replication and RNA polymerase to bind for transcription of the DNA. For example, a topoisomerase called DNA gyrase catalyzes the negative supercoiling of the circular DNA found in bacteria. Topoisomerase IV, on the other hand, is involved in the relaxation of the supercoiled circular DNA, enabling the separation of the interlinked daughter chromosomes at the end of bacterial DNA replication.

B. DNA Replication in Bacteria

In general, DNA is replicated by uncoiling of the helix, strand separation by breaking of the hydrogen bonds between the complementary strands, and synthesis of two new strands by complementary base pairing. Replication begins at a specific site in the DNA called the origin of replication (*ori*C).

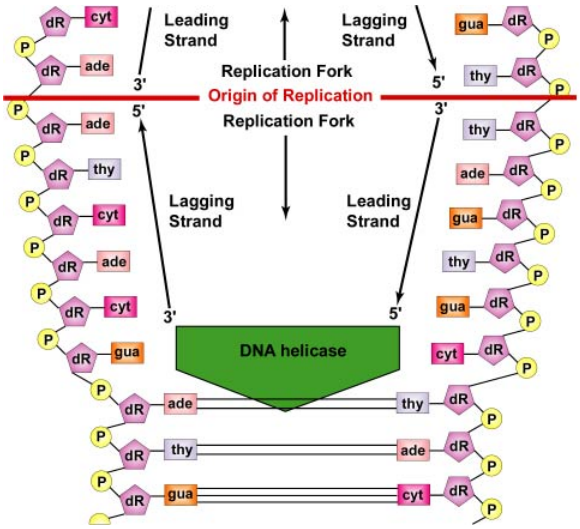


Figure 1.5*B*.3*:* DNA Replication by Complementary Base Pairing: Unwinding by DNA Helicase. Replication begins at a specific site in the DNA called the origin of replication. Unwinding enzymes called DNA helicases cause the two parent DNA strands to unwind and separate from one another in both directions at this site to form two "Y"-shaped replication forks. These replication forks are the actual site of DNA copying. During replication within the fork, helix destabilizing proteins (not shown here) bind to the single-stranded regions preventing the strands from rejoining.

DNA replication is bidirectional from the origin of replication. To begin DNA replication, unwinding enzymes called DNA helicases cause short segments of the two parent DNA strands to unwind and separate from one another at the origin of replication to form two "Y"-shaped replication forks. These replication forks are the actual site of DNA copying (Figure 1.5*B*.3). All the proteins involved in DNA replication aggregate at the replication forks to form a replication complex called a replisome (Figure 1.5*B*.4).

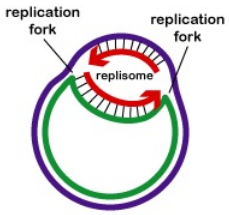


Figure 1.5*B*.4*:* Bidirectional Circular DNA Replication in Bacteria. DNA replication (arrows) occurs in both directions from the origin of replication in the circular DNA found in most bacteria. All the proteins involved in DNA replication aggregate at the replication forks to form a replication complex called a replisome. The lagging DNA strand loops out from the leading strand and this enables the replisome to move along both strands pulling the DNA through as replication occurs. It is the actual DNA, not the DNA polymerase that moves during bacterial DNA replication.

Single-strand binding proteins bind to the single-stranded regions so the two strands do not rejoin. Unwinding of the double-stranded helix generates positive supercoils ahead of the replication fork. Enzymes called *topoisomerases* counteract this by producing breaks in the DNA and then rejoin them to form negative supercoils in order to relieve this stress in the helical molecule during replication.

As the strands continue to unwind and separate in both directions around the entire DNA molecule, new complementary strands are produced by the hydrogen bonding of free DNA nucleotides with those on each parent strand. As the new nucleotides line up opposite each parent strand by hydrogen bonding, enzymes called DNA polymerases join the nucleotides by way of phosphodiester bonds. Actually, the nucleotides lining up by complementary base pairing are deoxynucleotide triphosphates, composed of a nitrogenous base, deoxyribose, and three phosphates. As the phosphodiester bond forms between the 5' phosphate group of the new nucleotide and the 3' OH of the last nucleotide in the DNA strand, two of the phosphates are removed providing energy for bonding (see Figure 1.5*B*.6). In the end, each parent strand serves as a template to synthesize a complementary copy of itself, resulting in the formation of two identical DNA molecules (see Figure 1.5*B*.7). In bacteria, Par proteins function to

separate bacterial chromosomes to opposite poles of the cell during cell division. They bind to the origin of replication of the DNA and physically pull or push the chromosomes apart, similar to the mitotic apparatus of eukaryotic cells. Fts proteins, such as FtsK in the divisome, also help in separating the replicated bacterial chromosome.

GIF animation illustrating DNA replication by complementary base pairing

In reality, DNA replication is more complicated than this because of the nature of the DNA polymerases. DNA polymerase enzymes are only able to join the phosphate group at the 5' carbon of a new nucleotide to the hydroxyl (OH) group of the 3' carbon of a nucleotide already in the chain. As a result, DNA can only be synthesized in a 5' to 3' direction while copying a parent strand running in a 3' to 5' direction.

Each DNA strand has two ends. The 5' end of the DNA is the one with the terminal phosphate group on the 5' carbon of the deoxyribose; the 3' end is the one with a terminal hydroxyl (OH) group on the deoxyribose of the 3' carbon of the deoxyribose (see Figure 1.5*B*.8). The two strands are antiparallel, that is they run in opposite directions. Therefore, one parent strand - the one running 3' to 5' and called the leading strand - can be copied directly down its entire length (see Figure 1.5*B*.9). However, the other parent strand - the one running 5' to 3' and called the lagging strand - must be copied discontinuously in short fragments (Okazaki fragments) of around 100-1000 nucleotides each as the DNA unwinds. This occurs, as mentioned above, at the replisome. The lagging DNA strand loops out from the leading strand and this enables the replisome to move along both strands pulling the DNA through as replication occurs. It is the actual DNA, not the DNA polymerase that moves during bacterial DNA replication (see Figure 1.5*B*.5).

In addition, DNA polymerase enzymes cannot begin a new DNA chain from scratch. They can only attach new nucleotides onto 3' OH group of a nucleotide in a preexisting strand. Therefore, to start the synthesis of the leading strand and each DNA fragment of the lagging strand, an RNA polymerase complex called a primase is required. The primase, which is capable of joining RNA nucleotides without requiring a preexisting strand of nucleic acid, first adds several comlementary RNA nucleotides opposite the DNA nucleotides on the parent strand. This forms what is called an RNA primer (see Figure 1.5*B*.10).

DNA polymerase III then replaces the primase and is able to add DNA nucleotides to the RNA primer (see Figure 1.5*B*.11). Later, DNA polymerase II digests away the RNA primer and replaces the RNA nucleotides of the primer with the proper DNA nucleotides to fill the gap (see Figure 1.5*B*.12). Finally, the DNA fragments themselves are hooked together by the enzyme DNA ligase (see Figure 1.5*B*.9). Yet even with this complicated procedure, a 1000 micrometer-long macromolecule of tightly-packed, supercoiled DNA can make an exact copy of itself in only about 10 minutes time under optimum conditions, inserting nucleotides at a rate of about 1000 nucleotides per second!

YouTube movie illustrating DNA replication in prokaryotic cells, #1.

YouTube movie illustrating DNA replication in prokaryotic cells, #2.

GIF animation illustrating the replication of leading and lagging strands of DNA

Animation of DNA replication.
Courtesy of HHMI's Biointeractive.

For More Information: Review of Prokaryotic DNA Replication from Unit 7

C. Functions of the Bacterial Chromosome

The chromosome is the genetic material of the bacterium. Genes located along the DNA are transcribed into RNA molecules, primarily messenger RNA (mRNA), transfer RNA (tRNA, and ribosomal RNA (rRNA). Messenger RNA is then translated into

protein at the ribosomes.

- **Transcription:** Ribonucleic acid (RNA) is synthesized by complementary base pairing of ribonucleotides with deoxyribonucleotides to match a portion of one strand of DNA called a gene. Although genes are present on both strands of DNA, only one strand is transcribed for any given gene. Following transcription of genes into mRNA, 30S and 50S ribosomal subunits attach to the mRNA and tRNA inserts the correct amino acids which are subsequently joined to form a polypeptide or a protein through a process called translation.
- **Translation**: During translation, specific tRNA molecules pick up specific amino acids, transfer those amino acids to the ribosomes, and insert them in their proper place according to the mRNA "message." This is done by the anticodon portion of the tRNA molecules complementary base pairing with the codons along the mRNA.

In general then, DNA determines what proteins and enzymes an organism can synthesize and, therefore, what chemical reactions it is able to carry out.

D. The Bacterial Epigenome

The epigenome refers to a variety of chemical compounds that modify the genome typically by adding a methyl (CH_3) group to the nucleotide base adenine at specific locations along the DNA molecule. This methylation can, in turn, either repress or activate transcription of specific genes. By basically turning genes on or off, the epigenome enables the bacterial genome to interact with and respond to the bacterium's environment. The epigenome can be inherited just like the genome.

All cells, including human cells, possess an epigenome. Just as the bacterial epigenome can affect the bacterial genome, bacteria, can affect our epigenome and subsequently modify the function of our genome by causing either DNA methylation of nucleotides or by modifying our histone proteins. The resulting modification can either help activate various genes involved in immune defenses, or, in the case of some pathogens, suppress immune response genes.

E. Significance of the Chromosome to the Initiation of Body Defense

To protect against infection, one of the things the body must initially do is detect the presence of microorganisms. The body does this by recognizing molecules unique to microorganisms that are not associated with human cells. These unique molecules are called pathogen-associated molecular patterns or PAMPS. (Because all microbes, not just pathogenic microbes, possess PAMPs, pathogen-associated molecular patterns are sometimes referred to as microbe-associated molecular patterns or MAMPs.)

Bacterial and viral genomes contain a high frequency of unmethylated cytosine-guanine (CpG) dinucleotide sequences (a cytosine lacking a methyl or CH_3 group and located adjacent to a guanine). Mammalian DNA has a low frequency of cytosine-guanine dinucleotides and most are methylated. These unmethylated cytosine-guanine dinucleotide sequences in bacterial DNA are PAMPS that bind to pattern-recognition receptors on a variety of defense cells of the body and triggers innate immune defenses such as inflammation, fever, and phagocytosis.

F. Antimicrobial Agents that Inhibiting Normal Nucleic Acid Replication in Bacteria

Some antibacterial chemotherapeutic affect bacteria by inhibiting normal nucleic acid replication.

- The fluoroquinolones (norfloxacin, lomefloxacin, fleroxacin, ciprofloxacin, enoxacin, trovafloxacin, etc.) work by inhibiting one or more of the topoisomerases, the enzymes needed for bacterial nucleic acid synthesis.
- Co-trimoxazole, a combination of sulfamethoxazole and trimethoprim, block enzymes in the bacteria pathway required for the synthesis of tetrahydrofolic acid, a cofactor needed for bacteria to make the nucleotide bases thymine, guanine, uracil, and adenine. Without the tetrahydrofolic acid, the bacteria cannot synthesize DNA or RNA.

Antimicrobial chemotherapy will be discussed in greater detail later in Unit 2 under Control of Bacteria by Using Antibiotics and Disinfectants.

? Exercise: Think-Pair-Share Questions

As we are learning, pathogen-associated molecular patterns (PAMPs) are microbial molecules many microbes share but are not found as a part of the human body and are able to initiate innate immune responses. Examples thus far include peptidoglycan fragments, lipopolysaccharide in the gram-negative cell wall, and lipoteichoic acids in the gram-positive cell wall, molecules that human cells lack. Bacterial and viral genomes also act as PAMPs.

Our cells also have DNA and RNA. How can bacterial and viral genomes initiate innate immunity when our genomes do not?

Summary

1. The genome is the sum of an organism's genetic material.
2. Bacteria contain a single chromosome of double-stranded deoxyribonucleic acid (DNA).
3. The region of the bacterial cytoplasm where the chromosome is located and visible when viewed with an electron microscope called the nucleoid.
4. The bacterial chromosome is typically a physical and genetic circle, becomes supercoiled,and is not surrounded by a nuclear membrane.
5. Bacteria do not carry out mitosis or meiosis.
6. DNA topoisomerase enzymes are used to supercoil and relax the bacterial chromosome during DNA replication and transcription.
7. Like eukaryotic DNA, prokaryotic DNA replicates by sequential unwinding of the two DNA parent strands and the subsequent complementary base pairing of DNA nucleotides with each parent strand.
8. During DNA replication the nitrogenous base adenine forms hydrogen bonds with thymine and guanine forms hydrogen bonds with cytosine.
9. Genes located along the DNA are transcribed into RNA molecules, primarily messenger RNA (mRNA), transfer RNA (tRNA), and ribosomal RNA (rRNA). Messenger RNA is then translated into protein at the ribosomes.
10. During transcription, ribonucleic acid (RNA) is synthesized by complementary base pairing of ribonucleotides with deoxyribonucleotides to match a portion of one strand of DNA called a gene.
11. During translation, specific tRNA molecules pick up specific amino acids, transfer those amino acids to the ribosomes, and insert them in their proper place according to the mRNA "message."
12. Bacterial and viral genomes act as PAMPs to stimulate innate immunity.
13. Some antibacterial chemotherapeutic agents inhibiting normal nucleic acid replication in bacteria.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. The sum of an organism's genetic material is called its_____. *(ans)*
2. Bacterial enzymes involved in in the unwinding, replication, and rewinding of the circular, supercoiled bacterial DNA called _____. *(ans)*
3. Describe the general composition of the chromosome in most bacteria. *(ans)*
4. Briefly describe the process of DNA replication. *(ans)*
5. State what enzyme carries out the following functions during DNA replication.
    a. Unwinds the helical DNA by breaking the hydrogen bonds between complementary bases. *(ans)*
    b. Synthesizes a short RNA primer at the beginning of each origin of replication. *(ans)*
    c. Adds DNA nucleotides to the RNA primer. *(ans)*
    d. Digests away the RNA primer and replaces the RNA nucleotides of the primer with the proper DNA nucleotides. *(ans)*
    e. Links the DNA fragments of the lagging strand together. *(ans)*
6. State the overall function of DNA. *(ans)*
7. Define transcription. *(ans)*

8. Define translation. *(ans)*
9. Ciprofloxacin (*Cipro*) is used to treat a variety of bacterial infections. How does it stop bacteria from growing? *(ans)*
10. Multiple Choice *(ans)*

This page titled 1.5B: The Bacterial Chromosome and Nucleoid is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **2.4B: The Bacterial Chromosome and Nucleoid** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

1.5C: Plasmids and Transposons

Learning Objectives

1. Describe plasmids and indicate their possible benefit to bacteria.
2. State the function of the following:
    a. transposons
    b. integrons
    c. episome
    d. conjugative plasmid
3. State the most common way plasmids are transmitted from one bacterium to another.
4. Define horizontal gene transfer.

In addition to the bacterial chromosome, many bacteria often contain small nonchromosomal DNA molecules called plasmids. Plasmids usually contain between 5 and 100 genes. Plasmids are not essential for normal bacterial growth and bacteria may lose or gain them without harm. They can, however, provide an advantage under certain environmental conditions. For example, under normal environmental growth conditions, bacteria are not usually exposed to antibiotics and having a plasmid coding for an enzyme capable of denaturing a particular antibiotic is of no value. However, if that bacterium finds itself in the body when the particular antibiotic that the plasmid-coded enzyme is able to degrade is being given to treat an infection, the bacterium containing the plasmid is able to survive and grow.

Structure and Composition

Plasmids are small molecules of double stranded, helical, non-chromosomal DNA. In most plasmids the two ends of the double-stranded DNA molecule that make up plasmids covalently bond together forming a physical circle. Some plasmids, however, have linear DNA. Plasmids replicate independently of the host chromosome, but some plasmids, called episomes, are able to insert or integrate into the host cell's chromosome where their replication is then regulated by the chromosome.

Although some plasmids can be transmitted from one bacterium to another by transformation and by generalized transduction, the most common mechanism of plasmid transfer is conjugation. Plasmids that can be transmitted by cell-to-cell contact are called conjugative plasmids. They contain genes coding for proteins involved in both DNA transfer and and the formation of mating pairs.

Functions

Plasmids code for synthesis of a few proteins not coded for by the bacterial chromosome. For example, R-plasmids, found in some Gram-negative bacteria, often have genes coding for both production of a conjugation pilus (discussed later in this unit) and multiple antibiotic resistance. Through a process called conjugation, the conjugation pilus enables the bacterium to transfer a copy of the R-plasmids to other bacteria, making them also multiple antibiotic resistant and able to produce a conjugation pilus. In addition, some exotoxins, such as the tetanus exotoxin, *Escherichia coli* enterotoxin, and *E. coli* shiga toxin discussed later in Unit 2 under Bacterial Pathogenicity, are also coded for by plasmids. Thousands of different plasmids are known to exist.

Transposons

Transposons (transposable elements or "jumping genes") are small pieces of DNA that encode enzymes that transpose the transposon, that is, move it from one DNA location to another, either on the same molecule of DNA or on a different molecule. Transposons may be found as part of a bacterium's nucleoid (conjugative transposons) or in plasmids and are usually between one and twelve genes long. A transposon contains a number of genes, coding for antibiotic resistance or other traits, flanked at both ends by insertion sequences coding for an enzyme called transpoase. Transpoase is the enzyme that catalyzes the cutting and resealing of the DNA during transposition. Thus, such transposons are able to cut themselves out of a bacterial nucleoid or a plasmid and insert themselves into another nucleoid or plasmid and contribute in the transmission of antibiotic resistance among a population of bacteria.

Plasmids can also acquire a number of different antibiotic resistance genes by means of integrons. Integrons are transposons that can carry multiple gene clusters called gene cassettes that move as a unit from one piece of DNA to another. An enzyme called integrase enables these gene cassettes to integrate and accumulate within the integron. In this way, a number of different antibiotic resistance genes can be transferred as a unit from one bacterium to another.

Plasmids and conjugative transposons are very important in horizontal gene transfer in bacteria. Horizontal gene transfer , also known as lateral gene transfer, is a process in which an organism transfers genetic material to another organism that is not its offspring. The ability of *Bacteria* and *Archaea* to adapt to new environments as a part of bacterial evolution most frequently results from the acquisition of new genes through horizontal gene transfer rather than by the alteration of gene functions through mutations. (It is estimated that as much as 20% of the genome of *Escherichia coli* originated from horizontal gene transfer.)

Horizontal gene transfer is able to cause rather large-scale changes in a bacterial genome. For example, certain bacteria contain multiple virulence genes called pathogenicity islands that are located on large, unstable regions of the bacterial genome. These pathogenicity islands can be transmitted to other bacteria by horizontal gene transfer. However, if these transferred genes provide no selective advantage to the bacteria that acquire them, they are usually lost by deletion. In this way the size of the bacterium's genome can remain approximately the same size over time.

CRISPR

Because bacteria are always taking in new DNA from horizontal gene transfer or being infected by bacteriophages, bacteria have developed a system for removing viral nucleic acid or DNA from self-serving or harmful plasmids. This system represents a type of adaptive immunity in bacteria, and is carried out by clustered, regularly interspaced, short palindromic repeat (CRISPR) sequences and CRISPR-associated (Cas) proteins that possess nuclease activity. The CRISPR/Cas system targets specific foreign DNA sequences in bacteria for destruction.



Video: YouTube Movie of the CRISPER/Cas9 System in Bacteria (www.youtube.com/v/ZsxIU5-s5Ds)

Applications of CRISPR technology has now become a common tool used in molecular biology for CRISPR/nuclease mediated genome editing (genetic engineering) in a wide variety of different cell types. Molecular biologists are now beginning to use this to carry out highly efficient, targeted alterations of genome sequence and gene expression and hope to eventually use it to repair damaged or dysfunctional genes.

? Exercise: Think-Pair-Share Questions

An F^+ plasmid is a conjugative plasmid that codes strictly for the ability to produce a conjugation pilus and a mating pair.

State what medically significant event might occur if a transposon located in the nucleoid of a normal flora intestinal bacterium and containing genes for antibiotic resistance were to cut out of the bacterium’s nucleoid and insert into the F^+ plasmid.

Summary

1. Many bacteria often contain small nonchromosomal DNA molecules called plasmids.
2. While plasmids are not essential for normal bacterial growth and bacteria may lose or gain them without harm, they can provide an advantage under certain environmental conditions.
3. Plasmids code for synthesis of a few proteins not coded for by the bacterial chromosome.
4. Transposons (jumping genes) are small pieces of DNA that encode enzymes that enable the transposon to, move from one DNA location to another.
5. Transposons may be found as part of a bacterium's chromosome or in plasmids
6. Integrons are transposons that can carry multiple gene clusters called gene cassettes that move as a unit from one piece of DNA to another
7. Horizontal gene transfer is a process in which an organism transfers genetic material to another cell that is not its offspring.
8. Horizontal gene transfer is able to cause rather large-scale changes in a bacterial genome.
9. The ability of Bacteria and Archaea to adapt to new environments as a part of bacterial evolution, most frequently results from the acquisition of new genes through horizontal gene transfer rather than by the alteration of gene functions through mutations.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Describe plasmids and indicate their possible benefit to bacteria. *(ans)*
2. State why R-plasmids are presenting quite a problem today in treating many Gram-negative infections. *(ans)*
3. _____ are small pieces of DNA that encode enzymes that cut segments of DNA from a location in a bacterial chromosome or in a plasmid and insert it into another chromosome or plasmid. These segments of translocated DNA often contain genes for antibiotic resistance. *(ans)*
4. The genes coding for antibiotic resistance in bacterial plasmids frequently change over time, enabling the bacterium to resist new antibiotics. What might account for this? *(ans)*
5. State the most common way plasmids are transmitted from one bacterium to another. *(ans)*
6. Define horizontal gene transfer. *(ans)*
7. Multiple Choice *(ans)*

This page titled 1.5C: Plasmids and Transposons is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **2.4C: Plasmids and Transposons** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

1.5D: Ribosomes

Learning Objectives

1. Describe the structure and chemical composition of bacterial ribosomes and state their function.
2. In terms of protein synthesis, briefly describe the process of transcription and translation.
3. State, in a general sense, how antibiotics like neomycin, tetracycline, doxycycline, erythromycin, and azithromycin affect bacterial growth.

Ribosome Structure and Composition

Ribosomes are composed of ribosomal RNA (rRNA) and protein. Prokaryotic cells have three types of rRNA: 16S rRNA, 23S rRNA, and 5S rRNA. Like transfer RNA (tRNA), rRNAs use intrastrand H-bonding between complementary nucleotide bases to form complex folded structures. Ribosomes are composed of two subunits with densities of 50S and 30S ("S" refers to a unit of density called the Svedberg unit). The 30S subunit contains 16S rRNA and 21 proteins; the 50S subunit contains 5S and 23S rRNA and 31 proteins.The two subunits combine during protein synthesis to form a complete 70S ribosome about 25nm in diameter. A typical bacterium may have as many as 15,000 ribosomes.

The Density of Ribosomal Subunits

Ribosomes are composed of two subunits that come together to translate messenger RNA (mRNA) into polypeptides and proteins during translation and are typically described in terms of their density. Density is the mass of a molecule or particle divided by its volume and is measured in Svedberg (S) units, a unit of density corresponding to the relative rate of sedimentation during ultra-high-speed centrifugation. The greater the S-value, the more dense the particle.

Ribosomal subunits are composed of ribosomal RNA (rRNA) and proteins. Ribosomal subunits with different S-values are composed of different molecules of rRNA, as well as different proteins. Remember that RNA is a polymer of ribonucleotides containing the nitrogenous base adenine, uracil, guanine, or cytosine. Different molecules of rRNA are of different lengths and have a different order of these ribonucleotide bases. Because rRNA is single stranded, many of the rRNA nucleotide bases are involved in intrastrand hydrogen bonds and this is what gives the rRNA molecule its specific shape (see Figure **1.5*D*.1**). The shape, in turn, helps determine its function - much like the the interactions between amino acids in a protein determine that protein's shape and function (see Figure **1.5*D*.2**).

Illustration of a 16S rRNA in *Escherichia coli*

Animation of a 16S rRNA

Illustration of the enzyme catalase

Prokaryotic ribosomes, for example, are composed of two subunits with densities of 50S and 30S. The 30S subunit contains 16S rRNA 1540 nucleotides long and 21 proteins; the 50S subunit contains a 5S rRNA 120 nucleotides long, a 23S rRNA 2900 nucleotides long, and 31 proteins. The two subunits combine during protein synthesis to form a complete 70S ribosome.

Eukaryotic ribosomal subunits have densities of 60S and 40S because they contain different rRNA molecules and proteins than prokaryotic ribosomal subunits. In most eukaryotes, the 40S subunit contains an 18S rRNA 1900 nucleotides long and approximately 33 proteins; the 60S subunit contains a 5S rRNA 120 nucleotides long, a 5.8S rRNA 160 nucleotides long, a 28S rRNA 4700 nucleotides long, and approximately 49 proteins. The two subunits combine during protein synthesis to form a complete 80S ribosome about 25nm in diameter.

Because of this difference in specific rRNAs and proteins the resulting "shape," there are drugs that can bind either to a 30S or 50S ribosomal subunit of a prokaryotic ribosome and subsequently block its function but are unable to bind to the equivalent 40S or 60S subunit of a eukaryotic ribosome.

Ribosome Functions

Ribosomes function as a workbench for protein synthesis, that is, they receive and translate genetic instructions for the formation of specific proteins. During protein synthesis, mRNA attaches to the 30s subunit and amino acid-carrying transfer RNAs (tRNA) attach to the 50s subunit (Figure 1.5D.1). Protein synthesis is discussed in detail in Unit 6.

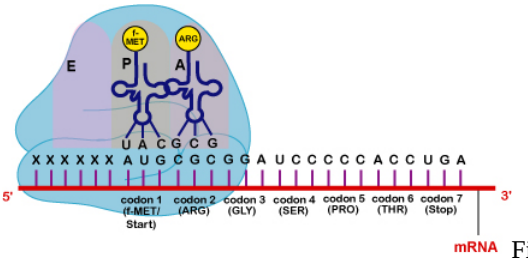


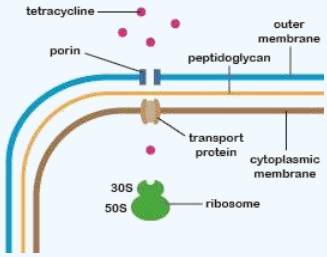
Figure 1.5D.1: 70S Ribosome During Translation. The 70S prokaryotic ribosome consists of a 50S and a 30S subunit. "S" refers to a unit of density called the Svedberg unit.

The chromosome is the genetic material of the bacterium. Genes located along the DNA are transcribed into RNA molecules, primarily messenger RNA (mRNA), transfer RNA (tRNA, and ribosomal RNA (rRNA). Messenger RNA is then translated into protein at the ribosomes.

- **Transcription:** Ribonucleic acid (RNA) is synthesized by complementary base pairing of ribonucleotides with deoxyribonucleotides to match a portion of one strand of DNA called a gene. Although genes are present on both strands of DNA, only one strand is transcribed for any given gene. Following transcription of genes into mRNA, 30S and 50S ribosomal subunits attach to the mRNA and tRNA inserts the correct amino acids which are subsequently joined to form a polypeptide or a protein through a process called translation.
- **Translation:** During translation, specific tRNA molecules pick up specific amino acids, transfer those amino acids to the ribosomes, and insert them in their proper place according to the mRNA "message." This is done by the anticodon portion of the tRNA molecules complementary base pairing with the codons along the mRNA.

? Exercise: Think-Pair-Share Questions

In order for any of the tetracycline group of antibiotics to inhibit Gram-negative bacterial growth, they must enter the cytoplasm of that bacterium and bind to the 30S subunit of its ribosomes.



Earlier we learned the composition and functions of both the Gram-negative cell wall and the cytoplasmic membrane. We have also previously learned how the order of deoxyribonucleotide bases in DNA determines the order of ribonucleotide bases in rRNA which, in turn, determines the 3-dimensional shape of that RNA. Likewise, the order of deoxyribonucleotide bases in DNA determines the order of amino acids in a protein or enzyme which determines the 3-dimensional shape of that protein.

Considering all of this and using the illustration above, think of three physical changes that could occur within the bacterium as a result of acquiring new or altered genes through mutation or horizontal gene transfer that could enable the bacterium to resist that tetracycline.

Antimicrobial Agents that Alter Prokaryotic Ribosomal Subunits and Block Translation in Bacteria

Many antibiotics alter bacterial ribosomes, interfering with translation and thereby causing faulty protein synthesis. The portion of the ribosome to which the antibiotic binds determines how translation is effected. For example:

- The **tetracyclines** (tetracycline, doxycycline, demeclocycline, minocycline, etc.) bind reversibly to the 30S subunit, distorting it in such a way that the anticodons of charged tRNAs cannot align properly with the codons of the mRNA.
- The **macrolides** (erythromycin, azithromycin, clarithromycin, dirithromycin, troleandomycin, etc.) bind reversibly to the 50S subunit. They appear to inhibit elongation of the protein by preventing the enzyme peptidyltransferase from forming peptide bonds between the amino acids. They may also prevent the transfer of the peptidyl tRNA from the A-site to the P-site.

Antimicrobial chemotherapy will be discussed in greater detail later in Unit 2 under Control of Bacteria by Using Antibiotics and Disinfectants.

Summary

1. Ribosomes are composed of ribosomal RNA (rRNA) and protein.
2. Bacterial ribosomes are composed of two subunits with densities of 50S and 30S, as opposed to 60S and 40S in eukaryotic cells.
3. Ribosomes function as a workbench for protein synthesis whereby they receive and translate genetic instructions for the formation of specific proteins.
4. During translation, specific tRNA molecules pick up specific amino acids, transfer those amino acids to the ribosomes, and insert them in their proper place according to the mRNA "message."
5. Many antibiotics bind to either the 30S or the 50S subunit of bacterial ribosomes, interfering with translation and thereby causing faulty protein synthesis.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Describe bacterial ribosomes. *(ans)*
2. State the function of ribosomes. *(ans)*
3. Define translation. *(ans)*
4. State, in a general sense, how antibiotics like neomycin, tetracycline, doxycycline, erythromycin, and azithromycin affect bacterial growth. *(ans)*
5. The tetracyclines (tetracycline, doxycycline) are antibiotics that bind to the 30S subunit of bacterial ribosomes. The macrolides (erythromycin, azithromycin, clarithromycin) are antibiotics that bind to the 50S subunit of bacterial ribosomes. Why won't these antibiotics be effective for fungal, protozoal, or viral infections? *(ans)*
6. Multiple Choice *(ans)*

This page titled 1.5D: Ribosomes is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **2.4D: Ribosomes** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

1.5E: Endospores

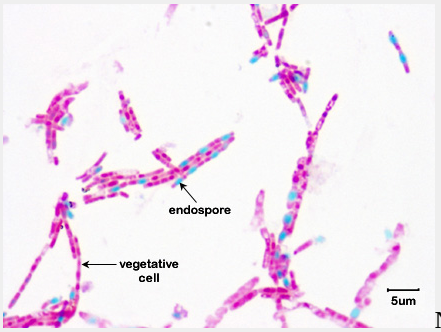
Name 2 common genera of bacteria capable of producing endospores and state which is an obligate anaerobe.

- Briefly discuss the function of a bacterial endospore.
- Describe the structure of a bacterial endospore.
- Define sporulation and germination.
- Name three infections that may be transmitted to humans by endospores.

Highlighted Bacterium1. Read the description of *Clostridium tetani* and match the bacterium with the description of the organism and the infection it causes.

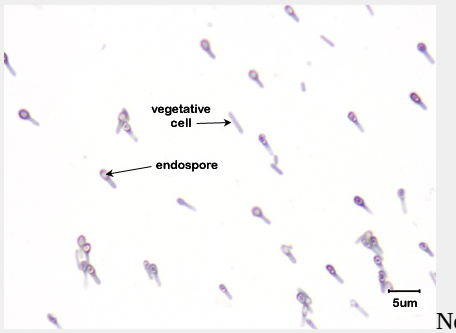
Endospores are dormant alternate life forms produced by the genus *Bacillus*, the genus *Clostridium*, and a number other genera of bacteria, including *Desulfotomaculum*, *Sporosarcina*, *Sporolactobacillus*, *Oscillospira*, and *Thermoactinomyces*. *Bacillus* species (see Figure **1.5*E*.1**) are obligate aerobes that live in soil while *Clostridium* species (see Figure **1.5*E*.2**) are obligate anaerobes often found as normal flora of the gastrointestinal tract in animals.

Figure **1.5*E*.1**: Endospore stain of *Bacillus megaterium*



Note green endospores within pink bacilli.

Figure **1.5*E*.2**: Endospore stain of *Clostridium tetani*



Note the endospore within the rod gives the bacterium a "tennis racquet" shape (arrows).

- Scanning electron micrograph of *Clostridium botulinum* with endospore; courtesy of Dennis Kunkel's Microscopy.

Formation of Endospores

Under conditions of starvation, especially the lack of carbon and nitrogen sources, a single endospores form within some of the bacteria. The process is called sporulation .

First the DNA replicates (Figure **1.5*E*.3**, step 1)and a cytoplasmic membrane septum forms at one end of the cell (Figure **1.5*E*.3**. step 3). A second layer of cytoplasmic membrane then forms around one of the DNA molecules (Figure **1.5*E*.3**, step 4) - the one that will become part of the endospore - to form a forespore (Figure **1.5*E*.3**, step 5). Both of these membrane layers then synthesize peptidoglycan in the space between them to form the first protective coat, the cortex (Figure **1.5*E*.3**, step 6) that lies adjacent to the germ cell wall that will eventually form the cell wall of the bacterium upon germination.

Calcium dipocolinate is also incorporated into the forming endospore. A spore coat composed of a keratin-like protein then forms around the cortex (Figure **1.5*E*.3**, step 7). Sometimes an outer membrane composed of lipid and protein and called an exosporium is also seen (Figure **1.5*E*.3**, step 8).

Finally, the remainder of the bacterium is degraded and the endospore is released (Figure 1.5E.3, step 9). Sporulation generally takes around 15 hours. The process is summarized in Figure 1.5E.3.

GIF animation showing endospore formation

GIF animation showing endospore germination

YouTube animation of endospore formation by Global Institute of Medical Sciences

- Scanning electron micrograph of *Bacillus anthracis* endospores; courtesy of CDC.

Endospore Structure (see Figure 1.5E.3, step 10)

The completed endospore consists of multiple layers of resistant coats (including a cortex, a spore coat, and sometimes an exosporium) surrounding a nucleoid, some ribosomes, RNA molecules, and enzymes.

- To view an electron micrograph of an endospore of *Bacillus stearothermophilus*, see the Microbe Zoo web page of Michigan State University.

(Some bacteria produce spore-like structures distinct from endospores. Exospores are heat resistant spores produced by a budding process in members of the genus *Metylosinus* and *Rhodomicrobium*. Cysts are resistant to drying and are formed singly within vegetative cells by *Azotobacter*, *Myxococcus*, and *Sporocytophaga*. Conidia are heat-susceptible asexual reproductive spores produced by various genera of branching bacteria belonging to the group Actinomycetes.)

Function of Endospores

An endospore is not a reproductive structure but rather a resistant, dormant survival form of the organism. Endospores are quite resistant to high temperatures (including boiling), most disinfectants, low energy radiation, drying, etc. The endospore can then survive until a variety of environmental stimuli trigger germination , allowing outgrowth of a single vegetative bacterium as shown in Fig 3, step 11 and step 12 and in Figure 1.5E.4. Viable endospores have reportedly been isolated from the GI tract of a bee embedded in amber between 25 and 40 million years ago. Viable endospores of a halophilic (salt-loving) bacterium have also reportedly been isolated from fluid inclusions in salt crystals dating back over 250 million years!

Bacterial endospores are resistant to antibiotics, most disinfectants, and physical agents such as radiation, boiling, and drying. The impermeability of the spore coat is thought to be responsible for the endospore's resistance to chemicals. The heat resistance of endospores is due to a variety of factors:

- Calcium-dipicolinate, abundant within the endospore, may stabilize and protect the endospore's DNA.
- Small acid-soluble proteins (SASPs) saturate the endospore's DNA and protect it from heat, drying, chemicals, and radiation. They also function as a carbon and energy source for the development of a vegetative bacterium during germination.
- The cortex may osmotically remove water from the interior of the endospore and the dehydration that results is thought to be very important in the endospore's resistance to heat and radiation.
- Finally, DNA repair enzymes contained within the endospore are able to repair damaged DNA during germination.

? , its oxygen requirements, where it normally lives, and what its exotoxin does, explain the sequence of events that led to the person contracting botulism and dying.

Endospores and Infectious Disease

Although harmless themselves until they germinate, they are involved in the transmission of some diseases to humans. Infections transmitted to humans by endospores include:

- Anthrax, caused by Bacillus anthracis; endospores can be inhaled, ingested, or enter wounds where they germinate and the vegetative bacteria subsequently replicate.
- Tetanus, caused by *Clostridium tetani*; endospores enter anaerobic wounds where they germinate and the vegetative bacteria subsequently replicate.
- Botulism, caused by *Clostridium botulinum*; endospores enter the anaerobic environment of improperly canned food where they germinate and subsequently replicate.
- Gas gangrene, caused by *Clostridium perfringens*); endospores enter anaerobic wounds where they germinate and the vegetative bacteria subsequently replicate.
- Pseudomembranous colitis (*Clostridium difficile*); antibiotics destroy the normal microbiota of the intestines that keep the growth of *C. difficile* in check while the endospores of *C. difficile* survive and subsequently germinate and replicate before the microbiota is restored.

Concept map for Bacterial Endospores

Summary

1. Endospores are dormant alternate life forms produced by a few genera of bacteria.
2. The genus Bacillus (an obligate aerobe often living in the soil) and the genus Clostridium (an obligate anaerobe living in the gastrointestinal tract of animals) produce endospores.
3. Under conditions of starvation, a single endospore forms within a bacterium through a process called sporulation, after which the remainder of the bacterium is degraded.
4. The completed endospore consists of multiple layers of resistant coats (including a cortex, a spore coat, and sometimes an exosporium) surrounding a nucleoid, some ribosomes, RNA molecules, and enzymes.
5. Endospores are quite resistant to high temperatures (including boiling), most disinfectants, low energy radiation, and drying.
6. The endospore survives until a variety of environmental stimuli trigger germination, allowing outgrowth of a single vegetative bacterium.
7. Infectious diseases such as anthrax, tetanus, gas gangrene, botulism, and pseudomembranous colitis are transmitted to humans by endospores.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Name 2 common genera of bacteria capable of producing endospores and state which is an obligate anaerobe. (ans)
2. Briefly discuss the function of a bacterial endospore. *(ans)*
3. The emergence of a vegetative bacterium from an endospore is called _____. *(ans)*
4. Name three infections transmitted to humans by bacterial endospores. *(ans)*
5. Botulism is caused by *Clostridium botulinum*, a bacterium that is normal flora of the intestinal tract of grazing animals. A person home-canned some green beans by boiling the beans and placing them in jars and screwing on lids. The lids popped down indicating a vacuum had formed within the jar. Upon ingesting these beans the person contracted botulism. Based on what was learned about *Clostridium*, explain. *(ans)*
6. Multiple Choice *(ans)*

This page titled 1.5E: Endospores is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **2.4E: Endospores** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

1.5F: Inclusion Bodies and Organelles Used for Photosynthesis

Name three major types of photosynthetic bacteria and briefly describe where its photosynthetic system is located.

- State the function of the following inclusion bodies:

A. cyanophycin granules

B. carboxysomes

C. gas vacuoles

D. polyhydroxybutyrate and glycogen granules

E. magnetosomes

F. volutin granules and sulfur granules

There are several major groups of photosynthetic bacteria: cyanobacteria, purple bacteria, green sulfur bacteria, green nonsulfur bacteria, heliobacteria, and acidobacteria. Comparing the cyanobacteria, the purple bacteria, and the green bacteria:

> The cyanobacteria carry out oxygenic photosynthesis, that is, they use water as an electron donor and generate oxygen during photosynthesis. The photosynthetic system is located in an extensive thylakoid membrane system that is lined with particles called phycobilisomes that contain light-harvesting phycobiliproteins.
>
> - Photograph of the cyanobacteria *Anabaena*.

This page titled 1.5F: Inclusion Bodies and Organelles Used for Photosynthesis is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **2.4F: Inclusion Bodies and Organelles Used for Photosynthesis** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

1.6: An Overview to Control of Microorganisms

selective toxicity
- broad spectrum antibiotic
- narrow spectrum antibiotic
- antibiotic
- chemotherapeutic synthetic drug
- cidal
- static
- sterilization
- disinfection
- disinfectant
- antiseptic
- physical agent

Control of microorganisms is essential in order to prevent the transmission of diseases and infection, stop decomposition and spoilage, and prevent unwanted microbial contamination. Microorganisms are controlled by means of physical agents and chemical agents. Physical agents include such methods of control as high or low temperature, desiccation, osmotic pressure, radiation, and filtration. Control by chemical agents refers to the use of disinfectants, antiseptics, antibiotics, and chemotherapeutic antimicrobial chemicals.

In this unit we will concentrate on the chemical control of microbial growth with a special emphasis on the antibiotics and chemotherapeutic antimicrobial chemicals used in treating bacterial infections. Control of microorganisms by means of physical agents will be covered in Lab 18 and control by means of disinfectants, antiseptics, and sanitizers will be discussed in Lab 19.

The basis of chemotherapeutic control of bacteria is selective toxicity. Selective toxicity means that the chemical being used should inhibit or kill the intended pathogen without seriously harming the host. A broad spectrum agent is one generally effective against a variety of Gram-positive and Gram-negative bacteria; a narrow spectrum agent generally works against just Gram-positives, Gram-negatives, or only a few bacteria. As mentioned above, such agents may be cidal or static in their action. A cidal agent kills the organism while a static agent inhibits the organism's growth long enough for body defenses to remove it.

There are two categories of antimicrobial chemotherapeutic agents: antibiotics and synthetic drugs. Antibiotics are metabolic products of one microorganism that inhibit or kill other microorganisms. Chemotherapeutic synthetic drugs are antimicrobial drugs synthesized by chemical procedures in the laboratory. Many of today's antibiotics are now actually semi-synthetic and some are even made synthetically.

Antibiotics are metabolic products of one microorganism that inhibit or kill other microorganisms. Why then do bacteria produce antibiotics? There is growing support for multiple actions for microbial antibiotic production:

- If produced in large enough amounts, antibiotics may be used as a weapon to inhibit or kill other microbes in the vicinity to reduce competition for food.
- Antibiotics produced in sublethal quantities may function as interspecies quorum sensing molecules enabling a number of different bacteria to form within a common biofilm where metabolic end products of one organism may serve as a substrate for another. All the organisms are protected within the same biofilm.
- Antibiotics produced in sublethal quantities may function as interspecies quorum sensing molecules enabling some bacteria to manipulate others to become motile and swim away thus reducing the competition for food.
- Antibiotics action may result in the degradation of bacterial cell walls or DNA and these products can act as cues that trigger other bacteria to produce a protective biofilm.
- Antibiotics produced in sublethal quantities may trigger intraspecies quorum sensing. Exposure to low concentrations of an antibiotic may trigger bacteria to produce quorum sensing molecules that trigger the population to produce a protective biofilm. The biofilm then protects the population from greater concentrations of the antibiotic.

Summary

1. Physical control includes such methods of control as high or low temperature, desiccation, osmotic pressure, radiation, and filtration.
2. Chemical control refers to the use of disinfectants, antiseptics, antibiotics, and chemotherapeutic antimicrobial chemicals.

3. Sterilization is the process of destroying all living organisms and viruses.
4. Disinfection is the elimination of microorganisms, but not necessarily endospores, from inanimate objects or surfaces.
5. Decontamination is the treatment of an object or inanimate surface to make it safe to handle.
6. A disinfectant is an agents used to disinfect inanimate objects but generally to toxic to use on human tissues.
7. An antiseptic is an agent that kills or inhibits growth of microbes but is safe to use on human tissue.
8. A sanitizer is an agent that reduces microbial numbers to a safe level.
9. An antibiotic is a metabolic product produced by one microorganism that inhibits or kills other microorganisms.
10. Synthetic chemicals that can be used therapeutically.
11. An agent that is cidal in action kills microorganisms.
12. An agent that is static in action inhibits the growth of microorganisms.
13. Selective toxicity means that the chemical being used should inhibit or kill the intended pathogen without seriously harming the host.
14. A broad spectrum agent is one generally effective against a variety of Gram-positive and Gram-negative bacteria.
15. A narrow spectrum agent generally works against just Gram-positives, Gram-negatives, or only a few bacteria.

Glossary

Basic terms used in discussing the control of microorganisms include:

1. **Sterilization**
   Sterilization is the process of destroying all living organisms and viruses. A sterile object is one free of all life forms, including bacterial endospores, as well as viruses.

2. **Disinfection**
   Disinfection is the elimination of microorganisms, but not necessarily endospores, from inanimate objects or surfaces.

3. **Decontamination**
   Decontamination is the treatment of an object or inanimate surface to make it safe to handle.

4. **Disinfectant**
   A disinfectant is an agents used to disinfect inanimate objects but generally to toxic to use on human tissues.

5. **Antiseptic**
   An antiseptic is an agent that kills or inhibits growth of microbes but is safe to use on human tissue.

6. **Sanitizer**
   A sanitizer is an agent that reduces microbial numbers to a safe level.

7. **Antibiotic**
   An antibiotic is a metabolic product produced by one microorganism that inhibits or kills other microorganisms.

8. **Chemotherapeutic synthetic drugs**
   Synthetic chemicals that can be used therapeutically.

9. **Cidal**
   An agent that is cidal in action will kill microorganisms and viruses.

10. **Static**
    An agent that is static in action will inhibit the growth of microorganisms.

This page titled 1.6: An Overview to Control of Microorganisms is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **4.1: An Overview to Control of Microorganisms** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

1.7: Ways in which Chemical Control Agents Affect Bacteria

Learning Objectives

- Describe six different ways antibiotics or disinfectants may affect bacterial structures or macromolecules and state how each ultimately causes harm to the cell.
- State which of the following groups of antibiotics: 1) inhibit peptidoglycan synthesis; 2) inhibit nucleic acid synthesis; 3) alter bacterial 30S ribosomal subunits blocking translation; or 4) alter bacterial 50S ribosomal subunits blocking translation.
  a. macrolides(erythromycin, azithromycin, clarithromycin, dirithromycin, troleandomycin, etc.), oxazolidinones (linezolid), and streptogramins
  b. penicillins, monobactams, carbapenems, cephalosporins, and vancomycin
  c. fluoroquinolones (norfloxacin, lomefloxacin, fleroxacin, ciprofloxacin, enoxacin, trovafloxacin, etc.), sulfonamides and trimethoprim, and metronidazole
  d. aminoglycosides (streptomycin, neomycin, netilmicin, tobramycin, gentamicin, amikacin, etc.) and tetracyclines (tetracycline, doxycycline, demeclocycline, minocycline, etc.)
- State two modes of action for disinfectants, antiseptics, and sanitizers.

The basis of chemotherapeutic control of bacteria is selective toxicity. Selective toxicity means that the chemical being used should inhibit or kill the intended pathogen without seriously harming the host. A broad spectrum agent is one generally effective against a variety of Gram-positive and Gram-negative bacteria; a narrow spectrum agent generally works against just Gram-positives, Gram-negatives, or only a few bacteria. Such agents may be cidal or static in their action. A cidal agent kills the organism while a static agent inhibits the organism's growth long enough for body defenses to remove it. There are two categories of antimicrobial chemotherapeutic agents: antibiotics and synthetic drugs. Antibiotics are metabolic products of one microorganism that inhibit or kill other microorganisms. Synthetic drugs are antimicrobial drugs synthesized by chemical procedures in the laboratory. Many of today's antibiotics are now actually semisynthetic and some are even made synthetically. We will now look at the various ways in which our control agents affect bacteria altering their structures or interfering with their cellular functions.

- Describe one way an antibiotic can inhibit peptidoglycan synthesis, state how that ultimately kills the bacterium, and give an example of such an antibiotic.
- Describe one way an antibiotic can alter bacterial ribosomes, state how that ultimately inhibits or kills the bacterium, and give an example of such an antibiotic.
- Describe one way an antibiotic can interfere with bacterial DNA synthesis, state how that ultimately kills the bacterium, and give an example of such an antibiotic

Many Antibiotics inhibit Synthesis of Peptidoglycan and cause Osmotic Lysis

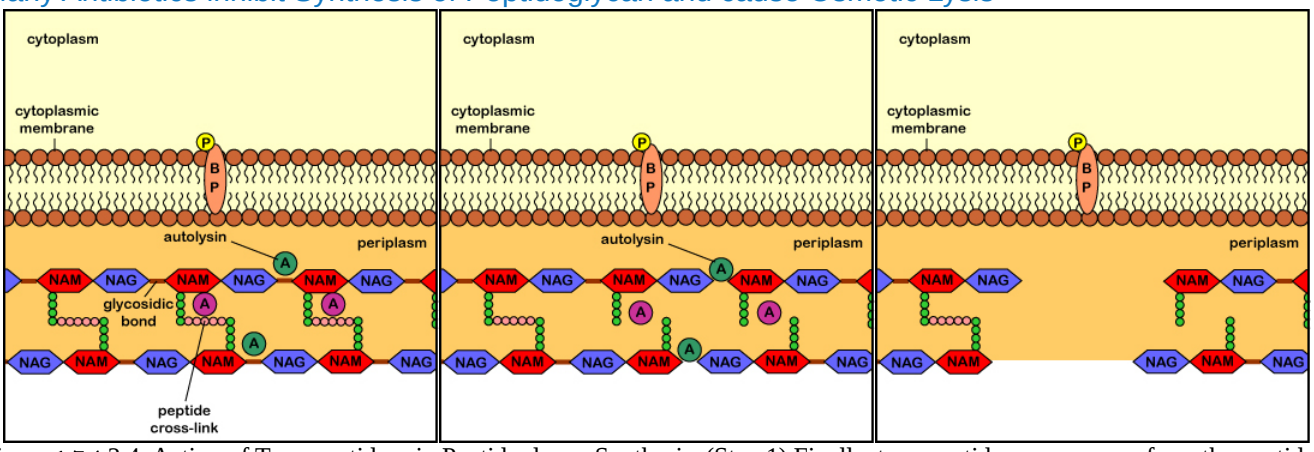


Figure 1.7.4.2.4: Action of Transpeptidase in Peptidoglycan Synthesis. (Step 1) Finally, transpeptidase enzymes reform the peptide cross-links between the rows and layers of peptidoglycan to make the wall strong.

Interference with this process results in the formation of a weak cell wall and osmotic lysis of the bacterium. Agents that inhibit peptidoglycan synthesis include the penicillins (penicillin G, methicillin, oxacillin, ampicillin, amoxicillin, ticarcillin, etc.), the cephalosporins (cephalothin, cefazolin, cefoxitin, cefotaxime, cefaclor, cefoperazone, cefixime, ceftriaxone, cefuroxime, etc.), the carbapenems (imipenem, metropenem), the monobactems (aztreonem), and the carbacephems (loracarbef). Penicillins, monobactams, carbapenems, and cephalosporins are known chemically as beta-lactam antibiotics because they all share a molecular structure called a beta-lactam ring (see Figure 1.7.5). The glycopeptides (vancomycin, teichoplanin) and lipopeptides (daptomycin) also inhibit peptidoglycan synthesis.

a. Beta lactam antibiotics such as penicillins and cephalosporins

Penicillins, cephalosporins, as well as other beta-lactam antibiotics (see Common Antibiotics), bind to the transpeptidase enzymes (also called penicillin-binding proteins) responsible for reforming the peptide cross-links between rows and layers of peptidoglycan of the cell wall as new peptidoglycan monomers are added during bacterial cell growth. This binding blocks the transpeptidase enzymes from cross-linking the sugar chains and results in a weak cell wall. In addition, these antibiotics appear to interfere with the bacterial controls that keep autolysins in check, with resulting degradation of the peptidoglycan and osmotic lysis of the bacterium (Figure 1.7.6).

Flash animation illustrating how penicillins inhibit peptidoglycan synthesis.

html5 version of animation for iPad showing how penicillins inhibit the synthesis of peptidoglycan.

Flash animation showing how penicillins inhibit peptidoglycan synthesis.
© Juliet V. Spencer, Stephanie K.M. Wong, authors, Licensed for use, ASM MicrobeLibrary.

YouTube movie showing lysis of *E. coli* after exposure to a penicillin #1

YouTube movie showing lysis of *E. coli* after exposure to a penicillin #2

b. Glycopeptides

Glycopeptides such as vancomycin (see Common Antibiotics) and the lipoglycopeptide teichoplanin bind to the D-Ala-D-Ala portion of the pentapeptides of the peptidoglycan monomers and block the formation of gycosidic bonds between

the sugars by the transgycosidase enzymes, as well as the formation of the peptide cross-links by the transpeptidase enzymes. This results in a weak cell wall and subsequent osmotic lysis of the bacterium (see Figure 1.7.7).

Flash animation illustrating how vancomycins inhibit peptidoglycan synthesis.

html5 version of animation for iPad illustrating how vancomycins inhibit peptidoglycan synthesis.

Flash animation showing how vancomycin inhibit peptidoglycan synthesis.
© Juliet V. Spencer, Stephanie K.M. Wong, authors, Licensed for use, ASM MicrobeLibrary.

c. Bacitracin

Bacitracin (see Common Antibiotics) binds to the transport protein bactoprenol after it inserts a peptidoglycan monomer into the growing cell wall. It subsequently prevents the dephosphorylation of the bactoprenol after it releases the monomer it has transported across the membrane. Bactoprenol molecules that have not lost the second phosphate group cannot assemble new monomers and transport them across the cytoplasmic membrane. As a result, no new monomers are inserted into the growing cell wall. As the autolysins continue to break the peptide cross-links and new cross-links fail to form, the bacterium bursts from osmotic lysis (see Figure 1.7.8).

Flash animation illustrating how bacitracin inhibit peptidoglycan synthesis.

html5 version of animation for iPad illustrating how bacitracin inhibit peptidoglycan synthesis.

Flash animation showing how bacitracin inhibit peptidoglycan synthesis.
© Juliet V. Spencer, Stephanie K.M. Wong, authors, Licensed for use, ASM MicrobeLibrary.

Concept map for How Antibiotics and Chemical Agents Affect Bacterial Structures and Function: Agents that Inhibit Cell Wall Synthesis, Alter the Cytoplasmic Membrane, or Inhibit DNA Synthesis

A few antimicrobial chemotherapeutic agents inhibit normal synthesis of the acid-fast cell wall

A few antimicrobial chemotherapeutic agents inhibit normal synthesis of the acid-fast cell wall of the genus *Mycobacterium* (see Common Antibiotics).. INH(isoniazid) appears to block the synthesis of mycolic acid, a key component of the acid-fast cell wall of mycobacteria (see Figure 1.7.9). Ethambutol interferes with the synthesis of the outer membrane of acid-fast cell walls (see Figure 1.7.9).

Concept map for How Antibiotics and Chemical Agents Affect Bacterial Structures and Function: Agents that Inhibit Cell Wall Synthesis, Alter the Cytoplasmic Membrane, or Inhibit DNA Synthesis

A very few antibiotics alter the bacterial cytoplasmic membrane causing leakage of molecules and enzymes needed for normal bacterial metabolism.

A very few antibiotics, such as polymyxins, colistins, and daptomycin (Common Antibiotics), as well as many disinfectants and antiseptics, such as orthophenylphenol, chlorhexidine, hexachlorophene, zephiran, alcohol, and triclosans, alter the bacterial cytoplasmic membrane causing leakage of molecules and enzymes needed for normal bacterial metabolism.

a. Polymyxins and colistins act as detergents and alter membrane permeability in Gram-negative bacteria. They cannot effectively diffuse through the thick peptidoglycan layer in gram-positives.

b. Daptomycin disrupts the bacteria cytoplasmic membrane function by apparently binding to the membrane and causing rapid depolarization. This results on a loss of membrane potential and leads to inhibition of protein, DNA and RNA synthesis, resulting in bacterial cell death.
c. Pyrazinamide inhibits fatty acid synthesis in the membranes of *Mycobacterium tuberculosis*.

Concept map for How Antibiotics and Chemical Agents Affect Bacterial Structures and Function: Agents that Inhibit Cell Wall Synthesis, Alter the Cytoplasmic Membrane, or Inhibit DNA Synthesis

Some antimicrobial chemotherapeutic agents inhibit normal nucleic acid replication in bacteria (see Common Antibiotics).

a. Fluoroquinolones

Fluoroquinolones (norfloxacin, lomefloxacin, fleroxacin, ciprofloxacin, enoxacin, trovafloxacin, gatifloxacin, etc., (Common Antibiotics)) work by inhibiting one or more of a group of enzymes called topoisomerase, enzymes needed for supercoiling, replication, and separation of circular bacterial DNA (see Figure 1.7.10). For example, DNA gyrase (topoisomerase II) catalyzes the negative supercoiling of the circular DNA found in bacteria. It is critical in bacterial DNA replication, DNA repair, transcription of DNA into RNA, and genetic recombination. Topoisomerase IV, on the other hand, is involved in the relaxation of the supercoiled circular DNA, enabling the separation of the interlinked daughter chromosomes at the end of bacterial DNA replication.

In Gram-negative bacteria, the main target for fluoroquinolones is DNA gyrase (topoisomerase II), an enzyme responsible for supercoiling of bacterial DNA during DNA replication; in Gram-positive bacteria, the primary target is topoisomerase IV, an enzyme responsible for relaxation of supercoiled circular DNA and separation of the inter-linked daughter chromosomes.

Flash animation illustrating a normal bacterial enzyme reaction.

html5 version of animation for iPad illustrating a normal bacterial enzyme reaction.

Flash animation illustrating antimicrobial agents may inactivate a bacterial enzyme.

html5 version of animation for iPad illustrating antimicrobial agents may inactivate a bacterial enzyme.

For More Information: The Nucleoid from Unit 1.

b. Sulfonamides

Sulfonamides (sulfamethoxazole, sulfanilamide) and diaminopyrimidines (trimethoprim) (see Common Antibiotics) block enzymes in the bacteria pathway required for the synthesis of tetrahydrofolic acid, a cofactor needed for bacteria to make the nucleotide bases thymine, guanine, uracil, and adenine (see Figure 1.7.11).

This is done through a process called competitive antagonism whereby a drug chemically resembles a substrate in a metabolic pathway. Because of their similarity, either the drug or the substrate can bind to the substrate's enzyme. While the enzyme is bound to the drug, it is unable to bind to its natural substrate and that blocks that step in the

metabolic pathway (see Figure 1.7.12). Typically, a sulfonamide and a diaminopyrimidine are combined. Co-trimoxazole, for example, is a combination of sulfamethoxazole and trimethoprim.

Flash animation showing competitive antagonism.

html5 version of animation for iPad showing competitive antagonism.

Sulfonamides such as sulfamethoxazole tie up the first enzyme in the pathway, the conversion of para-aminobenzoic acid to dihydropteroic acid (see Figure 1.7.11). Trimethoprim binds to the third enzyme in the pathway, an enzyme that is responsible for converting dihydrofolic acid to tetrahydrofolic acid (see Figure 1.7.11). Without the tetrahydrofolic acid, the bacteria cannot synthesize DNA or RNA.

c. Metronidazole

Metronidazole (see Common Antibiotics) is a drug that is activated by the microbial proteins flavodoxin and feredoxin found in microaerophilc and anaerobic bacteria and certain protozoans. Once activated, the metronidazole puts nicks in the microbial DNA strands.

Concept map for How Antibiotics and Chemical Agents Affect Bacterial Structures and Function: Agents that Inhibit Cell Wall Synthesis, Alter the Cytoplasmic Membrane, or Inhibit DNA Synthesis

d. Rifampin

Rifampin (rifamycin) (see Common Antibiotics) blocks transcription by inhibiting bacterial RNA polymerase, the enzyme responsible for transcription of DNA to mRNA.

For More Information: Transcription from Unit 7

Concept map for How Antibiotics and Chemical Agents Affect Bacterial Structures and Function: Agents that Alter Prokaryotic Ribosomal Subunits, Inhibit RNA Polymerase, and Denature Enzymes

Many antibiotics alter bacterial ribosomes, interfering with translation of mRNA into proteins and thereby causing faulty protein synthesis (see Common Antibiotics).

To learn more detail about the specific steps involved in translation during bacterial protein synthesis, see the animation that follows. Protein synthesis is discussed in greater detail in Unit 6.

For More Information: Ribosomes from Unit 1

For More Information: Translation from Unit 7

Flash animation illustrating the early stages of translation during bacterial protein synthesis.

html5 version of animation for iPad illustrating the early stages of translation during bacterial protein synthesis.

a. Aminoglycosides

The aminoglycosides (streptomycin, neomycin, netilmicin, tobramycin, gentamicin, amikacin, etc. (see Common Antibiotics)) bind irreversibly to the 16S rRNA in the 30S subunit of bacterial ribosomes. Although the exact mechanism of action is still uncertain, there is evidence that some prevent the transfer of the peptidyl tRNA from the A-site to the P-

site, thus preventing the elongation of the polypeptide chain. Some aminoglycosides also appear to interfere with the proofreading process that helps assure the accuracy of translation (see Figure 1.7.13). Possibly the antibiotics reduce the rejection rate for tRNAs that are near matches for the codon. This leads to misreading of the codons or premature termination of protein synthesis (see Figure 1.7.14). Aminoglycosides may also interfere directly or indirectly with the function of the bacterial cytoplasmic membrane. Because of their toxicity, aminoglycosides are generally used only when other first line antibiotics are not effective.

Flash animation illustrating aminoglycosides preventing the translocation of tRNA from the A-site to the P-site of bacterial ribosomes.

html5 version of animation for iPad illustrating aminoglycosides preventing the translocation of tRNA from the A-site to the P-site of bacterial ribosomes.

Flash animation illustrating aminoglycosides causing a misreading of codons.

html5 version of animation for iPad illustrating aminoglycosides causing a misreading of codons.

b. Tetracyclines

The tetracyclines (tetracycline, doxycycline, demeclocycline, minocycline, etc. (see Common Antibiotics)) bind reversibly to the 16S rRNA in the 30S ribosomal subunit, distorting it in such a way that the anticodons of charged tRNAs cannot align properly with the codons of the mRNA (see Figure 1.7.15).

Flash animation illustrating how tetracyclines bind to the 30S ribosomal subunit and block translation.

html5 version of animation for iPad illustrating how tetracyclines bind to the 30S ribosomal subunit and block translation.

c. Macrolides

The macrolides (erythromycin, azithromycin, clarithromycin, dirithromycin, troleandomycin, etc. (see Common Antibiotics)) bind reversibly to the 23S rRNA in the 50S subunit of bacterial ribosomes. They appear to inhibit elongation of the protein by preventing the enzyme peptidyltransferase from forming peptide bonds between the amino acids (see Figure 1.7.16). They may also prevent the transfer of the peptidyl tRNA from the A-site to the P-site (see Figure 1.7.17) as the beginning peptide chain on the peptidyl tRNA adheres to the ribosome, creates friction, and blocks the exit tunnel of the 50S ribosomal subunit.

Flash animation illustrating how macrolides bind to the 50S ribosomal subunit and block translation by blocking peptidyltransferase.

Flash animation illustrating how macrolides bind to the 50S ribosomal subunit and block translation by preventing the transfer of the peptidyl tRNA from the A-site to the P-site.

html5 version of animation for iPad illustrating how macrolides bind to the 50S ribosomal subunit and block translation by blocking peptidyltransferase.

html5 version of animation for iPad illustrating how macrolides bind to the 50S ribosomal subunit and block translation by preventing the transfer of the peptidyl tRNA from the A-site to the P-site.

d. Oxazolidinones

The oxazolidinones (linezolid, sivextro) (see Common Antibiotics), following the first cycle of protein synthesis, interfere with translation sometime before the initiation phases. They appear to bind to the 50S ribosomal subunit and interfere

with its binding to the initiation complex (see Figure 1.7.18).

Flash animation illustrating how oxazolidinones block the binding of the 50S ribosomal subunit to the initiation complex.

html5 version of animation for iPad illustrating how oxazolidinones block the binding of the 50S ribosomal subunit to the initiation complex.

e. Streptogramins

The streptogramins (synercid, a combination of quinupristin and dalfopristin (see Common Antibiotics)) bind to two different locations on the 23S rRNA in the 50S ribosomal subunit and work synergistically to block translation. There are reports that the streptogramins may inhibit the attachment of the charged tRNA to the A-site or may block the peptide exit tunnel of the 50S ribosomal subunit.

Concept map for How Antibiotics and Chemical Agents Affect Bacterial Structures and Function: Agents that Alter Prokaryotic Ribosomal Subunits, Inhibit RNA Polymerase, and Denature Enzymes

For a more detailed description of any specific antimicrobial agent, see the website of RxList - The Internet Drug Index.

Modes of action for disinfectants, antiseptics, and sanitizers

Disinfection is the elimination of microorganisms, but not necessarily endospores, from inanimate objects or surfaces, whereas decontamination is the treatment of an object or inanimate surface to make it safe to handle. Sterilization is the process of destroying all living organisms and viruses. A sterile object is one free of all life forms, including bacterial endospores, as well as viruses.

The term disinfectant is used for an agent used to disinfect inanimate objects or surfaces but is generally too toxic to use on human tissues. An antiseptic refers to an agent that kills or inhibits growth of microbes but is safe to use on human tissue. A sanitizer describes an agent that reduces microbial numbers to a safe level. Because disinfectants and antiseptics often work slowly on some viruses - such as the hepatitis viruses, bacteria with an acid-fast cell wall such as *Mycobacterium tuberculosis*, and especially bacterial endospores, produced by the genus *Bacillus* and the genus *Clostridium*, they are usually unreliable for sterilization - the destruction of all life forms.

There are a number of factors which influence the antimicrobial action of disinfectants and antiseptics, including:

1. The concentration of the chemical agent.
2. The temperature at which the agent is being used. Generally, the lower the temperature, the longer it takes to disinfect or decontaminate.
3. The kinds of microorganisms present. Endospore producers such as *Bacillus* species, *Clostridium* species, and acid-fast bacteria like *Mycobacterium tuberculosis* are harder to eliminate.
4. The number of microorganisms present. The more microorganisms present, the harder it is to disinfect or decontaminate.
5. The nature of the material bearing the microorganisms. Organic material such as dirt and excreta interferes with some agents.

The best results are generally obtained when the initial microbial numbers are low and when the surface to be disinfected is clean and free of possible interfering substances.

Concept map for Lab 19 - Using disinfectants, antisepticics, and sanitizers to control microorganisms

There are 2 common antimicrobial modes of action for disinfectants, antiseptics, and sanitizers:

1. They may damage the lipids and/or proteins of the semipermeable cytoplasmic membrane of microorganisms resulting in leakage of cellular materials needed to sustain life.

2. They may denature microbial enzymes and other proteins, usually by disrupting the hydrogen and disulfide bonds that give the protein its three-dimensional functional shape. This blocks metabolism.

A large number of such chemical agents are in common use. Some of the more common groups are listed below:

1. Phenol and phenol derivatives: Phenol (5-10%) was the first disinfectant commonly used. However, because of its toxicity and odor, phenol derivatives (phenolics) are now generally used. The most common phenolic is orthophenylphenol, the agent found in O-syl®, Staphene®, and Amphyl®. Bisphenols contain two phenolic groups and typically have chlorine as a part of their structure. They include hexachlorophene and triclosan. Hexachlorophene in a 3% solution is combined with detergent and is found in PhisoHex®. Triclosan is an antiseptic very common in antimicrobial soaps and other products. Biguanides include chlorhexadine and alexidine. A 4% solution of chlorhexidine in isopropyl alcohol and combined with detergent (Hibiclens® and Hibitane®) is a common hand washing agent and surgical handscrub. These agents kill most bacteria, most fungi, and some viruses, but are usually ineffective against endospores. Chloroxylenol (4-chloro-3,5-dimethylphenol) is a broad spectrum antimicrobial chemical compound used to control bacteria, algae, fungi and virus and is often used in antimicrobial soaps and antiseptics. Phenol and phenolics alter membrane permeability and denature proteins. Bisphenols, biguanides, and chloroxylenol alter membrane permeability.

2. Soaps and detergents: Soaps are only mildly microbicidal. Their use aids in the mechanical removal of microorganisms by breaking up the oily film on the skin (emulsification) and reducing the surface tension of water so it spreads and penetrates more readily. Some cosmetic soaps contain added antiseptics to increase antimicrobial activity.

Detergents may be anionic or cationic. Anionic (negatively charged) detergents, such as laundry powders, mechanically remove microorganisms and other materials but are not very microbicidal. Cationic (positively charged) detergents alter membrane permeability and denature proteins. They are effective against many vegetative bacteria, some fungi, and some viruses. However, bacterial endospores and certain bacteria such as *Mycobacterium tuberculosis and Pseudomonas* species are usually resistant. Soaps and organic materials like excreta also inactivate them. Cationic detergents include the quaternary ammonium compounds such as benzalkonium chloride, zephiran®, diaprene, roccal, ceepryn, and phemerol. Household Lysol® contains alkyl dimethyl benzyl ammonium chloride and alcohols.

3. Alcohols

70% solutions of ethyl or isopropyl alcohol are effective in killing vegetative bacteria, enveloped viruses, and fungi. However, they are usually ineffective against endospores and non-enveloped viruses. Once they evaporate, their cidal activity will cease. Alcohols denature membranes and proteins and are often combined with other disinfectants, such as iodine, mercurials, and cationic detergents for increased effectiveness.

4. Acids and alkalies

Acids and alkalies alter membrane permeability and denature proteins and other molecules. Salts of organic acids, such as calcium propionate, potassium sorbate, and methylparaben, are commonly used as food preservatives. Undecylenic acid (Desenex®) is used for dermatophyte infections of the skin. An example of an alkali is lye (sodium hydroxide).

5. Heavy metals

Heavy metals, such as mercury, silver, and copper, denature proteins. Mercury compounds (mercurochrome, metaphen, merthiolate) are only bacteriostatic and are not effective against endospores. Silver nitrate (1%) is sometimes put in the eyes of newborns to prevent gonococcal ophthalmia. Copper sulfate is used to combat fungal diseases of plants and is also a common algicide. Selinium sulfide kills fungi and their spores.

6. Chlorine

Chlorine gas reacts with water to form hypochlorite ions, which in turn denature microbial enzymes. Chlorine is used in the chlorination of drinking water, swimming pools, and sewage. Sodium hypochlorite is the active agent in household bleach. Calcium hypochlorite, sodium hypochlorite, and chloramines (chlorine plus ammonia) are used to sanitize glassware, eating utensils, dairy and food processing equipment, hemodialysis systems, and treating water supplies.

7. Iodine and iodophores

Iodine also denatures microbial proteins. Iodine tincture contains a 2% solution of iodine and sodium iodide in 70% alcohol. Aqueous iodine solutions containing 2% iodine and 2.4% sodium iodide are commonly used as a topical antiseptic. Iodophores are a combination of iodine and an inert polymer such as polyvinylpyrrolidone that reduces surface tension and slowly releases

the iodine. Iodophores are less irritating than iodine and do not stain. They are generally effective against vegetative bacteria, *Mycobacterium tuberculosis*, fungi, some viruses, and some endospores. Examples include Wescodyne®, Ioprep®, Ioclide®, Betadine®, and Isodine®.

8. Aldehydes

Aldehydes, such as formaldehyde and glutaraldehyde, denature microbial proteins. Formalin (37% aqueous solution of formaldehyde gas) is extremely active and kills most forms of microbial life. It is used in embalming, preserving biological specimens, and in preparing vaccines. Alkaline glutaraldehyde (Cidex®), acid glutaraldehyde (Sonacide®), and glutaraldehyde phenate solutions (Sporocidin®) kill vegetative bacteria in 10-30 minutes and endospores in about 4 hours. A 10 hour exposure to a 2% glutaraldehyde solution can be used for cold sterilization of materials. *Ortho*-phthalaldehyde (OPA) is dialdehyde used as a high-level disinfectant for medical instruments.

9. Peroxygens

Peroxygens are oxidizing agents that include hydrogen peroxide and peracetic acid. Hydrogen peroxide is broken down into water and oxygen by the enzyme catalase in human cells and is not that good of an antiseptic for open wounds but is useful for disinfecting inanimate objects. The high concentrations of hydrogen peroxide overwhelm the catalase found in microbes. Peracetic acid is a disinfectant that kills microorganisms by oxidation and subsequent disruption of their cytoplasmic membrane. It is widely used in health care, food processing, and water treatment.

10. Ethylene oxide gas

Ethylene oxide is one of the very few chemicals that can be relied upon for sterilization (after 4-12 hours exposure). Since it is explosive, it is usually mixed with inert gases such as freon or carbon dioxide. Gaseous chemosterilizers, using ethylene oxide, are commonly used to sterilize heat-sensitive items such as plastic syringes, petri plates, textiles, sutures, artificial heart valves, heart-lung machines, and mattresses. Ethylene oxide has very high penetrating power and denatures microbial proteins. Vapors are toxic to the skin, eyes, and mucous membranes and are also carcinogenic. Another gas that is used as a sterilant is chlorine dioxide which denatures proteins in vegetative bacteria, bacterial endospores, viruses, and fungi.

Concept map for How Antibiotics and Chemical Agents Affect Bacterial Structures and Function:
Agents that Alter Prokaryotic Ribosomal Subunits,
Inhibit RNA Polymerase, and Denature Enzymes

Summary

1. Many antibiotics (penicillins, cephalosporins, vancomycin, bacitracin) inhibit normal synthesis of peptidoglycan by bacteria and cause osmotic lysis. They do this by inactivating the enzymes or the transporters involved in peptidoglycan synthesis.
2. A few antimicrobial chemotherapeutic agents (INH, ethambutol) inhibit normal synthesis of the acid-fast cell wall.
3. A very few antibiotics (polymyxin, colistin, daptomycin) alter the bacterial cytoplasmic membrane causing leakage of molecules and enzymes needed for normal bacterial metabolism.
4. Some antimicrobial chemotherapeutic agents (fluoroquinolones, sulfonamides, trimethoprim) inhibit normal nucleic acid replication in bacteria.
5. Many antibiotics (tetracyclines, macrolides, oxazolidinones, streptogramins) alter bacterial ribosomes, interfering with translation of mRNA into proteins and thereby causing faulty protein synthesis.
6. There are 2 common antimicrobial modes of action for disinfectants, antiseptics, and sanitizers: damaging the lipids and/or proteins of the semipermeable cytoplasmic membrane of microorganisms resulting in leakage of cellular materials; and denaturing microbial enzymes and other proteins.
7. A number of factors which influence the antimicrobial action of disinfectants and antiseptics, including the concentration of the chemical agent, the temperature at which the agent is being used, the kinds of microorganisms present, the number of microorganisms present, and the nature of the material bearing the microorganisms.
8. Endospore producers such as Bacillus species, Clostridium species, and acid-fast bacteria like Mycobacterium tuberculosis are harder to eliminate.

This page titled 1.7: Ways in which Chemical Control Agents Affect Bacteria is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **4.2: Ways in which Chemical Control Agents Affect Bacteria** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

1.8: Ways in which Bacteria May Resist Chemical Control Agents

Name two bacteria that have low-permeability membrane barriers and are thereby intrinsically resistant to many antibiotics.
- Briefly describe 4 different mechanisms as a result of genetic changes in a bacterium that may enable that bacterium to resist an antibiotic.
- Describe R (Resistance) plasmids and state their significance to medical microbiology.
- State what the following stand for: MRSA, VRE,CRE, and XDR TB.
- Define antibiotic tolerance.

The basis of chemotherapeutic control of bacteria is selective toxicity. Selective toxicity means that the chemical being used should inhibit or kill the intended pathogen without seriously harming the host. A broad spectrum agent is one generally effective against a variety of gram-positive and gram-negative bacteria; a narrow spectrum agent generally works against just gram-positives, gram-negatives, or only a few bacteria. Such agents may be cidal or static in their action. A cidal agent kills the organism while a static agent inhibits the organism's growth long enough for body defenses to remove it. There are two categories of antimicrobial chemotherapeutic agents: antibiotics and synthetic drugs. Antibiotics are metabolic products of one microorganism that inhibit or kill other microorganisms. Synthetic drugs are antimicrobial drugs synthesized by chemical procedures in the laboratory. Many of today's antibiotics are now actually semisynthetic and some are even made synthetically.

We will now look at the two sides of the story with regards to controlling bacteria by means of chemicals:

1. Ways in which Our Control Agents Affect Bacterial Structures or Function
2. Ways in which Bacteria May Resist Our Control Agents

We will now look at the various ways in which bacteria become resistant to our control agents.

Some opportunistic pathogens, such as *Pseudomonas aeruginosa*, *Mycobacterium tuberculosis*, and *Enterococcus* species, have low-permeability membrane barriers and are thereby intrinsically resistant to many antibiotics. Most bacteria, however, become resistant to antibiotics as a result of mutation or horizontal gene transfer. Mutation in bacterial DNA can alter the order of nucleotide bases in a gene and alter that gene product. Horizontal gene transfer can alter or add bacterial genes, again altering the bacterium's gene products. See function of DNA.

Most bacteria, become resistant to antibiotics by way of one or more of the following mechanisms that are coded for by genes in the bacterial chromosomeor in plasmids:

1. Producing an enzyme capable of inactivating the antibiotic;
2. Altering the target site receptor for the antibiotic to reduce or block its binding;
3. Preventing the entry of the antibiotic into the bacterium and/or using an efflux pump to transport the antibiotic out of the bacterium; and/or
4. Modulating gene expression to produce more of the bacterial enzyme that is being tied up or altered by the antibiotic.

Nice summary of antibiotic resistant cases and associated deaths; from the CDC.
Improving antibiotic use among hospitalized patients; from CDC.
Estimates of Healthcare-Associated Infections (HCIs) 2011; from CDC.
Getting Smart About Antibiotics; from CDC.

We will now look at each of these mechanisms of resistance.

Producing to inactivate the antibiotic

(see Figure 1.8.1).

Bacteria may acquire new genes that code for an enzyme that inactivates a particular antibiotic or group of antibiotics. For example:

a. Bacteria typically become resistant to penicillins, monobactams, carbapenems, and cephalosporins are known chemically as beta-lactam antibiotics (see Figure 1.8.2) and many bacteria become resistant to these antibiotics by producing various beta-lactamases that are able to inactivate some forms of these drugs. Beta-lactamases break the beta-lactam ring of the antibiotic, thus inactivating the drug. (Penicillinase is a beta-lactamase that inactivates certain penicillins.) To overcome this mechanism of resistance, sometimes beta-lactam antibiotics such as amoxicillin, ticarcillin, imipenem, or ampicillin are combined with beta-lactamase inhibitors such as clavulanate, tazobactam, or sulbactam (see Common Antibiotics) - chemicals that resemble beta-lactam antibiotic (see Figure 1.8.2). These agents bind to the bacterial beta-lactamases and neutralize them.

b. Bacteria may become resistant to aminoglycosides (streptomycin, neomycin, netilmicin, tobramycin, gentamicin, amikacin, etc.) and streptogramins by enzymatically adding new chemical groups to these antibiotics, thus inactivating the drug.

Flash animation showing a bacterium producing an enzyme capable of destroying the antibiotic.

html5 version of animation for iPad showing a bacterium producing an enzyme capable of destroying the antibiotic.

Altering the target site receptor for the antibiotic in the bacterium to reduce or block its binding.

Antibiotics work by binding to some bacterial target site, such as a 50S ribosomal subunit, a 30S ribosomal subunit, or a particular bacterial enzyme such as a transpeptidases or a DNA topoisomerase. Bacteria may acquire new genes that alter the molecular shape of the portion of the ribosomal subunit or the enzyme to which the drug normally binds. For example:

a. Bacteria may become resistant to to macrolides (erythromycin, azithromycin, clarithromycin, dirithromycin, troleandomycin, etc.) by producing a slightly altered 50S ribosomal subunit that still functions but to which the antibiotic can no longer bind (see Figure 1.8.3).

b. Bacteria may become resistant to beta-lactam antibiotics (penicillins, monobactams, carbapenems, and cephalosporins) by producing altered transpeptidases (penicillin-binding proteins) with greatly reduced affinity for the binding of beta-lactam antibiotics.

c. Bacteria may become resistant to vancomycin by producing altered cross-linking peptides in the peptidoglycan to which the antibiotic no longer bonds.

d. Bacteria may become resistant to fluoroquinolones (norfloxacin, lomefloxacin, fleroxacin, ciprofloxacin, enoxacin, trovafloxacin, etc.) by producing altered DNA gyrase or other topoisomerases to which the drug no longer binds (see Figure 1.8.4).

Flash animation showing a bacterium producing an altered ribosomal subunit to which the antibiotic no longer binds.

html5 version of animation for iPad showing a bacterium producing an altered ribosomal subunit to which the antibiotic no longer binds.

Flash animation showing a bacterium producing an altered enzyme to which the antibiotic no longer binds.

html5 version of animation for iPad showing a bacterium producing an altered enzyme to which the antibiotic no longer binds.

For More Information: Ribosomes from Unit 1

For More Information: Peptidoglycan from Unit 1.

For More Information: The Nucleoid from Unit 1.

Altering the membranes and transport systems to prevent the entry of the antibiotic into the bacterium and/or using an efflux pump to transport the antibiotic out of the bacterium.

Antibiotics that target ribosomes or enzymes within the bacterium must first pass through the porins in the outer membrane of gram-negative and acid-fast bacterial cell walls, and then the cytoplasmic membrane in the case of all bacteria. Subsequently, the antibiotic has to accumulate to a high enough concentration within the bacterium to inhibit or kill the organism.

a. A Gram-negative or an acid-fast bacterium may block the entry of an antmicrobial drug by acquiring genes that alter the porins in the cell wall's outer membrane (see Figure 1.8.5).

b. A bacterium may block the entry of an antmicrobial drug by acquiring genes that alter the carrier (transport) proteins used to transport the drug through the bacterium's cytoplasmic membrane (see Figure 1.8.6). This is generally not a common mechanism of antibiotic resistance.

c. A bacterium may acquire genes coding for an energy-driven efflux pump in its the cytoplasmic membrane that is able to to pump the antibiotic out of the bacterium and preventing it from accumulating to a high enough concentration to inhibit or kill the

organism (see Figure 1.8.7). This is the most common method bacteria use to prevent toxic levels of antimicrobial drugs from accumulating within the cytoplasm.

Flash animation showing a bacterium producing altered porins to block transport of the drug across the outer membrane.

Flash animation showing a bacterium producing an altered carrier protein to block transport of the drug across the cytoplasmic membrane.

Flash animation showing a bacterium producing new transporter protein able to pump the drug out of the bacterium.

html5 version of animation for iPad showing a bacterium producing altered porins to block transport of the drug across the outer membrane.

html5 version of animation for iPad showing a bacterium producing an altered carrier protein to block transport of the drug across the cytoplasmic membrane.

html5 version of animation for iPad showing a bacterium producing new transporter protein able to pump the drug out of the bacterium.

For More Information: The Cytoplasmic Membrane from Unit 1.

Modulating gene expression to produce more of the bacterial enzyme that is being tied up or altered by the antibiotic.

Remember that enzymes function as catalysts and are present in cells in small amounts because they are not altered as they carry out their specific biochemical reactions. As mentioned in the previous section, numerous antimicrobial drugs work by inactivating bacterial enzymes and blocking metabolic reactions. Making a particular enzyme and the amount of enzyme that is made is under genetic control.

Genetic control of enzyme activity refers to controlling transcription of the mRNA needed for an enzyme's synthesis. In prokaryotic cells, this involves the induction or repression of enzyme synthesis by regulatory proteins that can bind to DNA and either block or enhance the function of RNA polymerase, the enzyme required for transcription.

Bacteria also use translational control of enzyme synthesis. In this case, the bacteria produce noncoding RNAs (ncRNAs) or antisense RNAa such as microRNAs (miRNAs) that are complementary to an early portion of the mRNA coding for the enzyme. When the noncoding RNA binds to the mRNA by complementary base pairing, ribosomes cannot attach, the mRNA cannot be translated into protein, and the enzyme is not made (See Figure 1.8.8).

For More Information: Enzyme Regulation from Unit 2.

Mutations or horizontal gene transfer may result in a modulation of gene expression or translational events that favor increased production of the enzyme being tied up or altered by the antimicrobial agent (see Figure 1.8.9). Since enzymes are normally

produced in limited amounts, production of excessive amounts of enzyme may allow for the metabolic activity being blocked by the agent to still occur.

Flash animation showing competitive antagonism.

html5 version of animation for iPad showing competitie antagonism.

Flash animation showing a bacterium producing more of a limited enzyme.

html5 version of animation for iPad showing a bacterium producing more of a limited enzyme.

GIF animation showing antisense RNA.

Many pathogenic bacteria, as well as normal flora, form complex bacterial communities as biofilms.

Bacteria in biofilms are often able to communicate with one another by a process called quorum sensing and are able to interact with and adapt to their environment as a population of bacteria rather than as individual bacteria. By living as a community of bacteria as a biofilm, these bacteria are:

- better able to resist attack by antibiotics, and
- are better able to resist the host immune system.

Why bacterium within a biofilm are more antibiotic resistant isn't completely understood but various mechanisms have been preposed. The extracellular polysaccharide may make it more difficult for the antibiotic to reach all of the bacteria. Bacteria within a biofilm are generally in a metabolically more inert state and this could slow down antibacterial action of the drug. Many antibiotics are static, not cidal in action; the body depends on phagocytes to remove the inhibited bacteria. The biofilm structure makes engulfment by phagocytes pretty much impossible.

Exposure to antibiotics doesn't "cause" bacteria to become drug resistant. The above changes in the bacterium that enable it to resist the antibiotic occur naturally as a result of mutation or as a result of horizontal gene transfer. For example, when under stress from antibiotics, some bacteria switch on genes whose protein products can increase the mutation rate within the bacterium 10,000 times as fast as the mutation rate that occurs during normal binary fission. This causes a sort of hyperevolution where mutation acts as a self defense mechanism for the bacterial population by increasing the chance of forming an antibiotic-resistant mutant that is able to survive at the expense of the majority of the population. (Remember that most mutations are harmful to a cell.)

For More Information: Mutation from Unit 7.

In addition, horizontal gene transfer as a result of transformation, transduction, and conjugation can transfer antibiotic resistance from one bacterium to another. Horizontal gene transfer enables bacteria to respond and adapt to their environment much more rapidly than mutation by acquiring large DNA sequences from another bacterium in a single transfer.

For More Information: Horizontal Gene Transfer from Unit 2

Concept map for Ways in Which Bacteria Resist Antibiotics and Chemical Agents

Briefly describe 3 different mechanisms, as a result of mutation or horizontal gene transfer in a bacterium, that may enable that bacterium to resist an antibiotic

- State at least 4 medical dangers associated with the improper use of antibiotics and list 3 common examples of antibiotic misuse.

Exposure to the antibiotic typically selects for strains of the organism that have become resistant through these natural processes. Misuse of antibiotics, such as prescribing them for non-bacterial infections (colds, influenza, most upper respiratory infections, etc.) or prescribing the "newest" antibiotic on the market when older brands may still be as effective simply inceases the rate at which this natural selection for resistance occurs. According to the Centers for Disease Control and Prevention, as many as one-third (50 million out of 150 million) of antibiotic prescriptions given on an outpatient basis are unneeded. Patient noncompliance with antimicrobial therapy, namely, not taking the prescribed amount of the antibiotic at the proper intervals for the appropriate length of time, also plays a role in selecting for resistant strains of bacteria.

The spread of antibiotic resistance in pathogenic bacteria is due to both direct selection and indirect selection.

- Direct selection refers to the selection of antibiotic resistant pathogens at the site of infection.
- Indirect selection is the selection of antibiotic-resistant normal floras within an individual anytime an antibiotic is given. At a later date, these resistant normal flora may transfer resistance genes to pathogens that enter the body. In addition, these resistant normal flora may be transmitted from person to person through such means as the fecal-oral route or through respiratory secretions.

As an example, many Gram-negative bacteria possess R (Resistance) plasmids that have genes coding for multiple antibiotic resistance through the mechanisms stated above, as well as transfer genes coding for a conjugation (sex) pilus (see Figs. 10A-10F). It is possible for R-plasmids to accumulate transposons to increase bacterial resistance. Such an organism can conjugate with other bacteria and transfer to them an R plasmid. *E. coli*, *Proteus*, *Serratia*, *Enterobacter*, *Salmonella*, *Shigella*, and *Pseudomonas* are bacteria that frequently have R-factor plasmids.

Flash animation illustrating R plasmid conjugation.

html5 version of animation for iPad illustrating R plasmid conjugation.

In addition to plasmids, conjugative transposons also frequently transmit antibiotic resistance from one bacterium to another. Conjugative transposons, like conjugative plasmids, carry the genes that enable mating pairs to form for conjugation. Therefore, conjugative transposons also enable mobilizable plasmids and nonconjugative transposons to be transferred to a recipient bacterium during conjugation.

For More Information: Horizontal Gene Transfer from Unit 2

Examples of Antibilotic Resistant Bacteria

Examples of resistant strains of bacteria of ever increasing medical importance include:

- Penicillinase-Producing *Neisseria gonorrhoeae* (PPNG): Most strains of *Neisseria gonorrhoeae* have penicillinase plasmids and are known as PPNG (penicillinase-producing *Neisseria gonorrhoeae*). As a result, penicillin is no longer the drug of choice for gonorrhea.
- Carbapenem-Resistant Enterobacteriaceae (CRE): More recently, carbapenemase-producing *Klebsiella pneumoniae* (KPC) strains are frequently being identified among nosocomial pathogens globally. Carbapenemase is a broad-spectrum beta-lactamase enzyme first found in *K. pneumoniae* isolates that results in resistance to all penicillins, cephalosporins, carbapenems (i.e., imipenem, ertapenem, metropenem), and monobactams (i.e., aztreonam). These broad-spectrum beta-lactamases are also known as extended spectrum beta-lactamases or ESBLs. These ESBLs are now being seen in a variety *Enterobacteriaceae* including *Enterobacter* spp., *E. coli*, *Serratia* spp., and *Salmonella enterica*. These ESBL-producing *Enterobacteriaceae* are known as carbapenem-resistant *Enterobacteriaceae*, or CRE.
- Methicillin-Resistant Staphylococcus aureus (MRSA): *Staphylococcus aureus* resistance to methicillin confers resistance to all penicillins and cephalosporins.
- Vancomycin-Resistant Enterococcus (VRE): Vancomycin-resistant *Enterococcus* (VRE) are intrinsically resistant to most antibiotics and have acquired resistance to the first line drug of choice, vancomycin.
- XDR TB: Extensively drug-resistant tuberculosis (XDR TB), a relatively rare type of multidrug-resistant *Mycobacterium tuberculosis* that is resistant to almost all drugs used to treat TB, including the two best first-line drugs: isoniazid and rifampin. XDR TB is also resistant to the best second-line medications: fluoroquinolones and at least one of three injectable drugs i.e., amikacin, kanamycin, or capreomycin.

Dormant persisters: Another mechanism that protects some bacteria from antibiotics is antibiotic tolerance. In the case of antibiotic tolerance, the tolerant bacterium is not killed but simply stops growing when the antibiotic is present. It then is able to recover once the antibiotic is no longer in the host. For example, *Streptococcus pneumoniae* tolerant to vancomycin appear to repress their autolysins in the presence of the drug and don't undergo osmotic lysis. Antibiotic tolerance is especially significant in terms of bacteria that form biofilms associated with catheters, heart valves, orthopedic devices, and people with cystic fibrosis. These biofilms often contain a small percentage of dormant persisters that, because they are not dividing, tolerate the antibiotics.

Its been found that bacteria simultaneously produce toxins that inhibit their own growth and antitoxins that bind to the toxin and cause its neutralizion. Small numbers of bacteria in the population, however, become persisters because they produce lower levels of antitoxin or the antitoxin is degraded by stress. As a result, the free toxin arrests bacterial growth enabling a persistent state that is able to survive stressors such as antibiotics and starvation.

Bacteria such as *E. coli*, *Proteus*, *Enterobacter*, *Serratia*, *Pseudomonas*, *Staphylococcus aureus*, and *Enterococcus* mentioned above, are the leading cause of health care-associated infections. According to the Centers for Disease Control and Prevention (CDC) Healthcare-associated infection's website, "In American hospitals alone, healthcare-associated infections account for an estimated 1.7 million infections and 99,000 associated deaths each year" in the U.S. The CDC also estimates that “more than two million people in the United States get infections that are resistant to antibiotics and at least 23,000 people die as a result.”

Finally, Bacterial endospores, such as those produced by *Bacillus* and *Clostridium*, are also resistant to antibiotics, most disinfectants, and physical agents such as boiling and drying. Although harmless themselves, they are involved in the transmission of some diseases to humans. Examples include anthrax (*Bacillus anthracis*), tetanus (*Clostridium tetani*), botulism (*Clostridium botulinum*), gas gangrene (*Clostridium perfringens*), and pseudomembranous colitis (*Clostridium difficile*).

Summary

1. Most bacteria become resistant to antibiotics by way of one or more mechanisms that are coded for by genes in the bacterial chromosome and/or in bacterial plasmids.
2. Bacterial genes may code for production of an enzyme that inactivates the antibiotic.
3. Bacterial genes may code for an altered target site receptor (ribosomal subunit, enzyme, etc.) for the antibiotic to reduce or block its binding.
4. Bacterial genes may code for altered membrane components that prevent the entry of the antibiotic into the bacterium and/or using an efflux pump to transport the antibiotic out of the bacterium.

5. Bacterial genes may code for modulated gene expression to produce more of the bacterial enzyme that is being tied up or altered by the antibiotic.
6. When under stress from antibiotics, some bacteria switch on genes whose protein products can increase the mutation rate within the bacterium causing a hyperevolution to increase the chance of forming an antibiotic-resistant mutant that is able to survive.
7. Horizontal gene transfer as a result of transformation, transduction, and conjugation can transfer antibiotic resistance from one bacterium to another. Horizontal gene transfer enables bacteria to respond and adapt to their environment much more rapidly than mutation by acquiring large DNA sequences from another bacterium in a single transfer.
8. Another mechanism that protects some bacteria from antibiotics is antibiotic tolerance whereby the tolerant bacterium, called a dormant persister, is not killed but simply stops growing when the antibiotic is present.
9. CDC estimates that “more than two million people in the United States get infections that are resistant to antibiotics and at least 23,000 people die as a result.”

This page titled 1.8: Ways in which Bacteria May Resist Chemical Control Agents is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **4.3: Ways in which Bacteria May Resist Chemical Control Agents** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

CHAPTER OVERVIEW

2: Pathogenicity

Pathogenicity refers to the ability of an organism to cause disease (ie, harm the host). This ability represents a genetic component of the pathogen and the overt damage done to the host is a property of the host-pathogen interactions. Commensals and opportunistic pathogens lack this inherent ability to cause disease.

2.1: Overview of Microbe-Host Interactions

2.1A: Normal Microbiota and Host Relationships

2.1B: Opportunistic Microorganisms

2.1C: Cooperation Among Microorganisms

2.2: Penetrating Host Defenses

2.2A: Penetrating Host Defenses

2.2B: Pili and Pilus Assembly

2.2C: Biofilms and Infections

2.3: Damaging Host Cells

2.3A: Toxins

2.3B: Direct Damage

2.3C: Type III and Type IV Secretion

2.3D: Plasmids and Lysogeny

2.3E: Siderophores

2.4: Surviving Within the Host and Exiting the Host

2.4A: Intracellular Pathogens

2.4B: Extracellular Immune Avoidance

2.4C: Regulating Virulence

2.4D: Portals of Exit

2.5: Pathogenicity and Other Microbes

2.5A: Fungi

2.5B: Protozoa

2.5C: Helminths

2.5D: Algae

This page titled 2: Pathogenicity is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

This page titled 2: Pathogenicity is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

2.1: Overview of Microbe-Host Interactions

This page titled 2.1: Overview of Microbe-Host Interactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **14.2: Overview of Microbe-Host Interactions** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

2.1A: Normal Microbiota and Host Relationships

Learning Objectives

- Explain the relationship between the normal microbiota and the host upon infection of a pathogen

Normal Microbiota

The phrase “normal microbiota” refers to the microorganisms that reside on the surface and deep layers of skin, in the saliva and oral mucosa, in the conjunctiva, and in the gastrointestinal tracts of every human being. These microorganisms are not harmful to humans; in fact, some are even beneficial and all help maintain our health. Our normal microbiota consists of various bacteria, fungi, and archaea. An example of our bacterial microbiota is *E. coli* . Many people think of *E. coli* as the bacteria that makes you sick; however while it has that capacity, it can also remain dormant and benign in your gastrointestinal tract for your entire life. All humans actually acquire *E. coli*shortly after birth with the intake of food or water. Other forms of bacteria present in the human gut are necessary for proper digestion of carbohydrates.

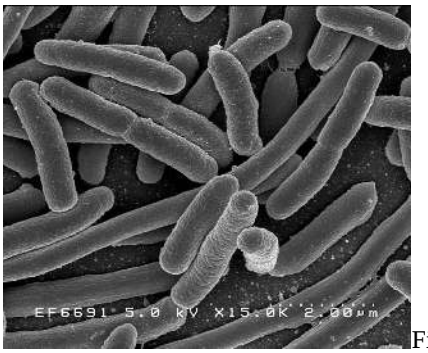


Figure: **Escherichia coli**: This is a magnified view of Escherichia coli (or E. coli).

Host Relationships

While our bodies are happy to host the array of microbiota that are considered “normal,” the human body does not take a back seat when infection tries to use it as a host. Interestingly, normal microbiota can be key players helping the body fight off infection. Resistance to and recovery from viral infections depends on the interactions that occur between the virus and its host. The host has a variety of defenses that it uses to prevent infection. One of the first lines of defense is mucus, which has a range of normal microbiota that compete with and may even attack invading bacteria and virae.

Once a virus or bacteria makes its way past the skin and mucosa, there may be changes that occur in the host to diminish the invader’s effectiveness. An example of such a change is a fever. There are a number of other humoral components of the nonspecific immune system as well. Specific immune responses are produced by antibodies. Different interferons (IgA, IgG, IgM, etc.) play roles in defeating viruses located in our membranes. The body does not easily become a host to infection; it has a line up of defenses to try to protect you from harm.

Key Points

- The phrase “normal microbiota ” refers to the microorganisms that reside on the surface and deep layers of skin, in the saliva and oral mucosa, in the conjunctiva, and in the gastrointestinal tracts of every human being.
- These microbiota are not harmful to humans; some are even beneficial and most help maintain our health.
- Our normal microbiota consists of various bacteria, fungi, and archaea.
- While our bodies are happy to host the array of microbiota that are considered “normal,” the human body does not take a back seat when infection tries to use it as a host.
- Resistance to and recovery from viral infections depends on the interactions that occur between virus and host. The host has a variety of barriers that it uses to prevent infection. One of the first lines of defense is mucus, which has a range of normal microbiota.
- There are a number of other humoral components of the nonspecific immune system as well.

Key Terms

- **host**: A cell or organism which harbors another organism or biological entity, usually a parasite.
- **microorganism**: An organism that is too small to be seen by the unaided eye, especially a single-celled organism, such as a bacterium.
- **interferon**: Any of a group of glycoproteins, produced by the immune system, that prevent viral replication in infected cells.

This page titled 2.1A: Normal Microbiota and Host Relationships is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **14.2A: Normal Microbiota and Host Relationships** is licensed CC BY-SA 4.0.

2.1B: Opportunistic Microorganisms

Learning Objectives

- Describe the traits of an opportunistic microorganism

In the general realm of biology, an opportunist is an organism that is able sustain its life from a number of different sources, but when favorable conditions arise, the organism immediately takes advantage of the opportunity to thrive. When the focus is turned more specifically to microbiology, scientists call organisms that behave this way opportunistic microorganisms. A microorganism is a microscopic organism that can either be a single cell, cell cluster, or multicellular. Microorganisms are very diverse and include bacteria, fungi, algae, and protozoa. Opportunistic microorganisms are typically non-pathogenic microorganisms that act as a pathogen in certain circumstances. They lay dormant for long periods of time until the hosts' immune system is suppressed and then they seize the opportunity to attack.

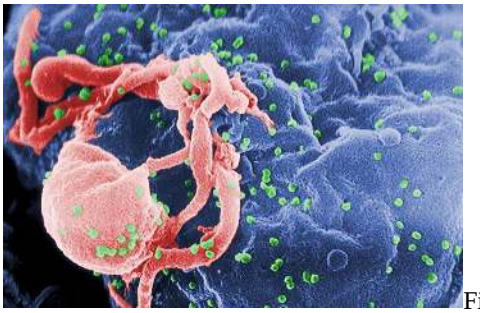


Figure: **HIV**: This is a magnified view of HIV budding from a lymphocyte.

Patients with Human Immunodeficiency Virus (HIV) are particularly susceptible to opportunistic infections. HIV can develop into Acquired Immune Deficiency Syndrome (AIDS), which infects and destroys helper T cells (specifically CD4+ T cells). When the number of CD4+ T cell numbers fall below a critical level, cell-mediated immunity is lost. When immunity is lost, the opportunistic microorganisms can easily infect the AIDS patient without being destroyed by the immune system. These opportunistic pathogens thrive while the human body slowly deteriorates.

An example of an opportunistic microorganism is *Haemophilus ducreyi*. This microorganism infects its host through broken skin or epidermis. In other words, without an open wound, this sexually transmitted disease would be unable to use the human body as a host. It takes advantage of the opportunity to infect the lymphocytes, macrophages and granulocytes as soon as it enters the area of broken skin.

Key Points

- A microorganism is a microscopic organism that can either be a single cell, cell cluster, or multicellular. Microorganisms are very diverse and include bacteria, fungi, algae, and protozoa.
- Opportunistic microorganisms are typically non-pathogenic microorganisms that act as a pathogen in certain circumstances. They lay dormant for long periods of time until the host 's immune system is suppressed and then they take that opportunity to attack.
- Haemophilus ducreyi, a microorganism, infects its host through broken skin or epidermis. Without the open wound, this sexually transmitted disease would be unable to use the human body as a host.

Key Terms

- **microorganism**: An organism that is too small to be seen by the unaided eye, especially a single-celled organism, such as a bacterium.
- **Opportunistic**: Taking advantage of situations that arise.
- **immunodeficiency**: A depletion in the body's natural immune system, or in some component of it.

This page titled 2.1B: Opportunistic Microorganisms is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **14.2B: Opportunistic Microorganisms** is licensed CC BY-SA 4.0.

2.1C: Cooperation Among Microorganisms

Learning Objectives

- Compare and contrast the following cooperative behavior: mutalism and altruism

Microbial Cooperation



Figure: **Methanogenic Bacteria in Termites**: Methanogenic bacteria have a syntrophic relationship with protozoans living in the guts of termites. The protozoans break down cellulose, releasing H2 which is then used in methanogenesis.

A cooperative behavior benefits one party while the other performs a certain behavior or takes a particular action. In microbial systems, there are two main types of cooperation, altruism and mutualism. It is important to remember that microorganisms include bacteria, archaea, fungi, and protists. They are too small to be seen with the naked eye, but they play a huge role in the world as we know it and have a great deal of biological diversity.

Mutualism

Mutualism is a relationship between microorganisms that is mutually beneficial (+/+). This means that both parties benefit from their interaction. A microbial example is the interaction between protozoa and archaea in the digestive tracts of some animals. These animals eat cellulose which is broken down by the protozoa to obtain energy. This process releases hydrogen as a waste product, which in turn reduces energy production. Specialized archaea convert the hydrogen (which they need) to methane, which allows energy production to increase. Both the protozoa and archaea benefit from this relationship.

Altruism

Altruism is a relationship between microorganisms that is beneficial to one party, but harmful to the the (+/-). Most scientists believe that the individual that is harmed, or at a loss, performs the action because they believe it will ultimately benefit others whom it is close to or share a relationship with (like family). On a microscopic level, this happens with programmed cell death, or apoptosis. Although it does not seem like it would be beneficial for the cell to die, it has been suggested that the resources it was using could be better utilized by other cells for growth and survival.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: ***CC BY-SA: Attribution-ShareAlike***

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- Escherichia coli. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Escheri...mal_microbiota**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Human microbiome. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Human_microbiome**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- host. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/host**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- interferon. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/interferon**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- microorganism. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/microorganism**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- EscherichiaColi NIAID. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Es...Coli_NIAID.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Haemophilus ducreyi. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Haemophilus_ducreyi**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Opportunistic infection. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Opportunistic_infection**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Hiv. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Hiv**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Microorganisms. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Microorganisms**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Opportunism. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Opportu...al_opportunism**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- immunodeficiency. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/immunodeficiency**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Opportunistic. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/Opportunistic**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- microorganism. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/microorganism**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- EscherichiaColi NIAID. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Es...Coli_NIAID.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- HIV-budding-Color. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:HI...ding-Color.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Archaea. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Archaea%23Mutualism**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Microbial cooperation. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Microbial_cooperation**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- altruism. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/altruism**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Cooperation. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/Cooperation**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- mutualism. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/mutualism**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- EscherichiaColi NIAID. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Es...Coli_NIAID.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- HIV-budding-Color. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:HI...ding-Color.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Coptotermes formosanus shiraki USGov k8204-7. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Co...ov_k8204-7.jpg**. **License**: ***Public Domain: No Known Copyright***

Key Points

- In microbial systems, there are two main types of cooperation, altruism and mutualism.
- Mutualism is a relationship between microorganisms that is mutually beneficial (+/+). This means that both parties are receiving positive things from their interaction.
- Altruism is a relationship between microorganisms that is beneficial to one party, but harmful to the the (+/-). Scientists believe that the individual that is at a loss performs the action because they believe it will ultimately benefit others whom they share a relationship with (like family).

Key Terms

- **Cooperation**: Association for mutual benefit.
- **mutualism**: A relationship between individuals of different species in which both individuals benefit
- **altruism**: Regard for others, both natural and moral; devotion to the interests of others; brotherly kindness; – opposed to egoism or selfishness.

This page titled 2.1C: Cooperation Among Microorganisms is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **14.2C: Cooperation Among Microorganisms** is licensed CC BY-SA 4.0.

2.2: Penetrating Host Defenses

This page titled 2.2: Penetrating Host Defenses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **14.3: Penetrating Host Defenses** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

2.2A: Penetrating Host Defenses

Learning Objectives

- Recognize the ways a host can be infected by, and resist, pathogens

The human microbiome (or human microbiota) is the aggregate of microorganisms that reside on the surface and in deep layers of skin, in the saliva and oral mucosa, in the conjunctiva, and in the gastrointestinal tracts. They include bacteria, fungi, and archaea. Some of these organisms perform tasks that are useful for the human host. However, the majority have no known beneficial or harmful effect. Organisms that are expected to be present, and that under normal circumstances do not cause disease, but participate in maintaining health, are deemed members of the normal flora.

Many of the bacteria in the digestive tract, collectively referred to as the gut flora, are able to break down certain nutrients such as carbohydrates that humans otherwise could not digest. The majority of these commensal bacteria are anaerobes, meaning they survive in an environment with no oxygen. Normal flora bacteria can act as opportunistic pathogens at times of lowered immunity. *Escherichia coli* (*E. coli*) is a bacterium that lives in the colon. It is an extensively studied model organism. Certain mutated strains of these gut bacteria do cause disease. An example is *E. coli* O157:H7.

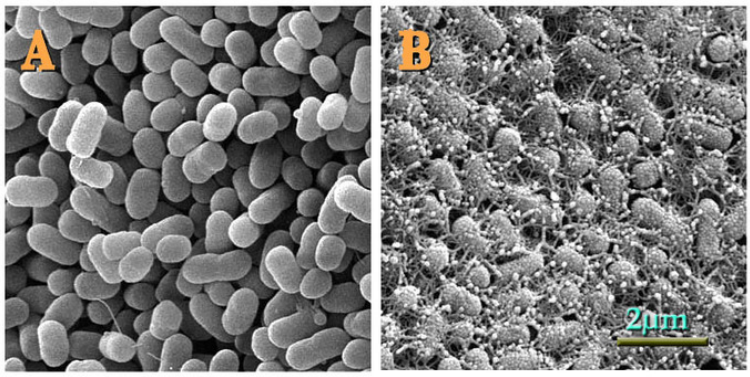


Figure: **Escherichia coli O157:H7**: Topographical images of colonies of *E. coli* O157:H7 strains (A) 43895OW (curli non-producing) and (B) 43895OR (curli producing) grown on agar for 48 h at 28°C. Escherichia coli O157:H7 is an enterohemorrhagic strain of the bacterium Escherichia coli and a cause of food borne illness. Infection often leads to hemorrhagic diarrhea and occasionally to kidney failure, especially in young children and elderly persons. Transmission is via the fecal-oral route. Most illness has been associated with eating under cooked, contaminated ground beef or ground pork, swimming in or drinking contaminated water, or eating contaminated vegetables.

Infection is the invasion of a host organism's bodily tissues by disease-causing organisms, their multiplication, and the host's reaction to these organisms and the toxins they produce. Infections are caused by pathogens such as viruses, prions, bacteria, and viroids, and larger organisms like macroparasites and fungi.

It is important to keep in mind that although the immune system has evolved to be able to control many pathogens, pathogens themselves have evolved ways to evade the immune response. An example already mentioned is in *Mycobactrium tuberculosis*, which has evolved a complex cell wall that is resistant to the digestive enzymes of the macrophages that ingest them, and thus persists in the host, causing the chronic disease tuberculosis. This section briefly summarizes other ways in which pathogens can "outwit" immune responses. But keep in mind, although it seems as if pathogens have a will of their own, they do not. All of these evasive "strategies" arose strictly by evolution, driven by selection.

Bacteria sometimes evade immune responses because they exist in multiple strains, such as different groups of *Staphylococcus aureus*. *S. aureus* is commonly found in minor skin infections, such as boils, and some healthy people harbor it in their nose. One small group of strains of this bacterium, however, called methicillin-resistant *Staphylococcus aureus*, has become resistant to multiple antibiotics and is essentially untreatable. Different bacterial strains differ in the antigens on their surfaces. The immune response against one strain (antigen) does not affect the other; thus, the species survives.

Another method of immune evasion is mutation. Because viruses' surface molecules mutate continuously, viruses like influenza change enough each year that the flu vaccine for one year may not protect against the flu common to the next. New vaccine

formulations must be derived for each flu season.

Genetic recombination—the combining of gene segments from two different pathogens—is an efficient form of immune evasion. For example, the influenza virus contains gene segments that can recombine when two different viruses infect the same cell. Recombination between human and pig influenza viruses led to the 2010 H1N1 swine flu outbreak.

Pathogens can produce immunosuppressive molecules that impair immune function, and there are several different types. Viruses are especially good at evading the immune response in this way, and many types of viruses have been shown to suppress the host immune response in ways much more subtle than the wholesale destruction caused by HIV.

Key Points

- Infections are caused by pathogens such as viruses, prions, bacteria, and viroids, and larger organisms like macroparasites and fungi.
- Mammalian hosts react to infections with an innate response, often involving inflammation, followed by an adaptive response.
- Pathogens can evade the body's immune responses through means that include specialized adaptations, mutation, evolved resistance to treatments, genetic recombination, and the production of immunosuppressive molecules that impair immune function.

Key Terms

- **Human microbiome**: The aggregate of microorganisms that reside on the surface and in deep layers of skin, in the saliva and oral mucosa, in the conjunctiva, and in the gastrointestinal tracts.

This page titled 2.2A: Penetrating Host Defenses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **14.3A: Penetrating Host Defenses** is licensed CC BY-SA 4.0.

2.2B: Pili and Pilus Assembly

Learning Objectives

- Describe the function of the pili in regards to pathogenecity

A pilus (Latin for “hair;” plural: pili) is a hairlike appendage found on the surface of many bacteria. The terms pilus and fimbria (Latin for “thread” or “fiber,” plural: fimbriae) can be used interchangeably, although some researchers reserve the term pilus for the appendage required for bacterial conjugation. All pili are primarily composed of oligomeric pilin proteins.

Dozens of these structures can exist on the bacteria. Some bacterial viruses or bacteriophages attach to receptors on pili at the start of their reproductive cycle. Pili are antigenic. They are also fragile and constantly replaced, sometimes with pili of different composition, resulting in altered antigenicity. Specific host responses to old pili structure are not effective on the new structure. Recombination genes of pili code for variable (V) and constant (C) regions of the pili (similar to immunoglobulin diversity).

Conjugative pili allow the transfer of DNA between bacteria, in the process of bacterial conjugation. They are sometimes called “sex pili”, in analogy to sexual reproduction, because they allow for the exchange of genes via the formation of “mating pairs”. Perhaps the most well-studied is the F pilus of Escherichia coli, encoded by the F plasmid or fertility factor.

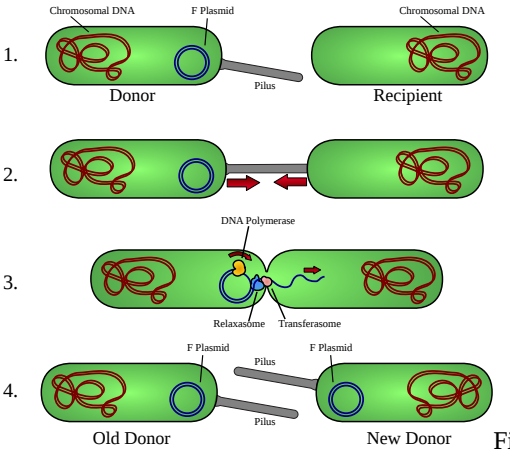


Figure: **Bacterial Conjugation**: A schematic drawing of bacterial conjugation. Conjugation diagram 1- Donor cell produces pilus. 2- Pilus attaches to recipient cell, brings the two cells together. 3- The mobile plasmid is nicked, and a single strand of DNA is then transferred to the recipient cell. 4- Both cells recircularize their plasmids, synthesize second strands, and reproduce pili; both cells are now viable donors.

A pilus is typically 6 to 7 nm in diameter. During conjugation, a pilus emerging from donor bacterium ensnares the recipient bacterium, draws it in close, and eventually triggers the formation of a mating bridge, which establishes direct contact and the formation of a controlled pore that allows transfer of DNA from the donor to the recipient. Typically, the DNA transferred consists of the genes required to make and transfer pili (often encoded on a plasmid), and is a kind of selfish DNA; however, other pieces of DNA often are co-transferred, and this can result in dissemination of genetic traits, such as antibiotic resistance, among a bacterial population. Not all bacteria can make conjugative pili, but conjugation can occur between bacteria of different species.

Some pili, called “type IV pili,” generate motile forces. The external ends of the pili adhere to a solid substrate, either the surface to which the bacteria are attached or to other bacteria, and when the pilus contracts, it pulls the bacteria forward, like a grappling hook. Movement produced by type IV pili is typically jerky, and so it is called “twitching motility,” as distinct from other forms of bacterial motility, such as motility produced by flagella. However, some bacteria, for example Myxococcus xanthus, exhibit gliding motility. Bacterial type IV pilins are similar in structure to the component flagellins of Archaeal flagella.

Attachment of bacteria to host surfaces is required for colonization during infection or to initiate formation of a biofilm. A fimbria is a short pilus that is used to attach the bacterium to a surface. Fimbriae are either located at the poles of a cell or are evenly spread over its entire surface. Mutant bacteria that lack fimbriae cannot adhere to their usual target surfaces and, thus, cannot cause diseases. Some fimbriae can contain lectins. The lectins are necessary to adhere to target cells, because they can recognize

oligosaccharide units on the surface of these target cells. Other fimbriae bind to components of the extracellular matrix. Fimbriae are found in both Gram-negative and Gram-positive bacteria. In Gram-positive bacteria, the pilin subunits are covalently linked.

Key Points

- The process of bacterial conjugation allow for the exchange of genes via the formation of “sex pili”.
- All pili are primarily composed of oligomeric pilin proteins.
- Conjugative pili allow the transfer of DNA between bacteria in the process of bacterial conjugation.

Key Terms

- **pilus**: A hair-like appendage found on the cell surface of many bacteria.

This page titled 2.2B: Pili and Pilus Assembly is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **14.3B: Pili and Pilus Assembly** is licensed CC BY-SA 4.0.

2.2C: Biofilms and Infections

Learning Objectives

- Discuss the importance of biofilms in the biomedical community

A biofilm is an aggregate of microorganisms in which cells adhere to each other on a surface. These adherent cells are frequently embedded within a self-produced matrix of extracellular polymeric substance (EPS).

Microbes form a biofilm in response to many factors, which may include cellular recognition of specific or non-specific attachment sites on a surface, nutritional cues, or in some cases, by exposure of planktonic cells to sub-inhibitory concentrations of antibiotics. When a cell switches to the biofilm mode of growth, it undergoes a phenotypic shift in behavior in which large suites of genes are differentially regulated.

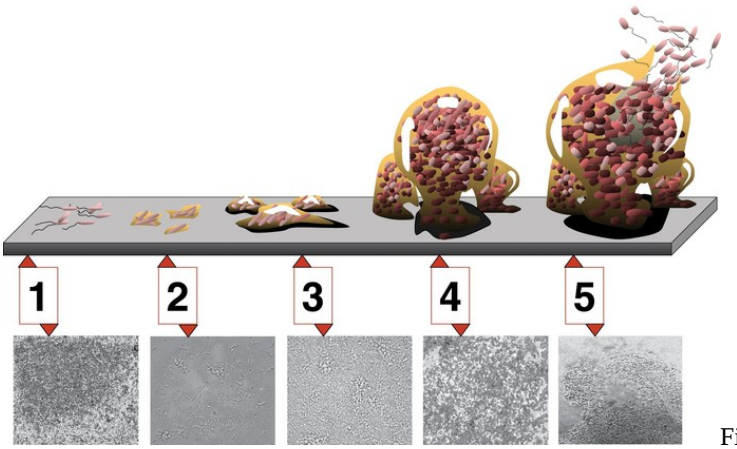


Figure: **Biofilm development**: 5 stages of biofilm development. Stage 1, initial attachment; stage 2, irreversible attachment; stage 3, maturation I; stage 4, maturation II; stage 5, dispersion. Each stage of development in the diagram is paired with a photomicrograph of a developing Pseudomonas aeruginosa biofilm. All photomicrographs are shown to same scale.

Biofilms are ubiquitous. Nearly every species of microorganism, not only bacteria and archaea, have mechanisms by which they can adhere to surfaces and to each other. Biofilms will form on virtually every non-shedding surface in a non-sterile aqueous (or very humid) environment.

Biofilms have been found to be involved in a wide variety of microbial infections in the body, by one estimate in 80% of all infections. Infectious processes in which biofilms have been implicated include common problems such as urinary tract infections, catheter infections, middle-ear infections, formation of dental plaque, gingivitis, and coating contact lenses. Biofilms have also been implicated in less common but more lethal processes such as endocarditis, infections in cystic fibrosis, and infections of permanent indwelling devices such as joint prostheses and heart valves.

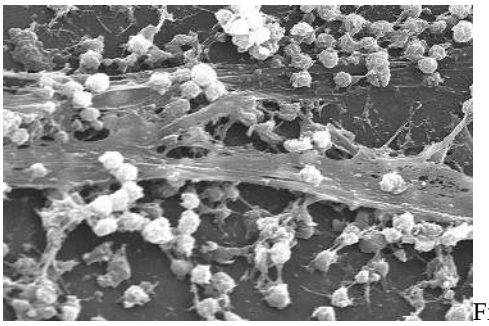


Figure: **Staphylococcus aureus biofilm**: Staphylococcus aureus forming a biofilm on a catheter.

More recently it has been noted that bacterial biofilms may impair cutaneous wound healing and reduce topical antibacterial efficiency in healing or treating infected skin wounds. It has recently been shown that biofilms are present on the removed tissue of

80% of patients undergoing surgery for chronic sinusitis. The patients with biofilms were shown to have been denuded of cilia and goblet cells, unlike the controls without biofilms who had normal cilia and goblet cell morphology. Biofilms were also found on samples from two of 10 healthy controls mentioned. The species of bacteria from interoperative cultures did not correspond to the bacteria species in the biofilm on the respective patient's tissue. In other words, the cultures were negative though the bacteria were present.

Biofilms can also be formed on the inert surfaces of implanted devices such as catheters, prosthetic cardiac valves, and intrauterine devices. New staining techniques are being developed to differentiate bacterial cells growing in living animals, e.g. from tissues with allergy-inflammations.

Pseudomonas aeruginosa biofilms

The achievements of medical care in industrialized societies are markedly impaired due to chronic opportunistic infections that have become increasingly apparent in immunocompromised patients and the aging population. Chronic infections remain a major challenge for the medical profession and are of great economic relevance because traditional antibiotic therapy is usually not sufficient to eradicate these infections.

Pseudomonas aeruginosa is not only an important opportunistic pathogen and causative agent of emerging nosocomial infections but can also be considered a model organism for the study of diverse bacterial mechanisms that contribute to bacterial persistence. In this context the elucidation of the molecular mechanisms responsible for the switch from planktonic growth to a biofilm phenotype and the role of inter-bacterial communication in persistent disease should provide new insights. It should help researchers learn about the pathogenicity of P. aeruginosa, contribute to a better clinical management of chronically infected patients, and lead to the identification of new drug targets for the development of alternative anti-infective treatment strategies.

Dental plaque

Dental plaque is a biofilm that adheres to teeth surfaces and consists of bacterial cells, salivary polymers, and bacterial extracellular products. This accumulation of microorganisms subject the teeth and gingival tissues to high concentrations of bacterial metabolites which results in dental disease. The biofilms attached to the surfaces of some dental alloys, impression materials, dental implants, restorative and cement materials play an essential role concerning the biofilms establishment dynamics toward the physical-chemical properties of the materials which biofilms are attached to.

Legionellosis

Legionella bacteria are known to grow under certain conditions in biofilms, in which they are protected against disinfectants. Workers in cooling towers, persons working in air conditioned rooms, and people taking a shower are exposed to Legionella by inhalation when the systems are not well designed, constructed, or maintained. Neisseria gonorrhoeae is an exclusive human pathogen. Recent studies have demonstrated that it utilizes two distinct mechanisms for entry into human urethral and cervical epithelial cells involving different bacterial surface ligands and host receptors. In addition, it has been demonstrated that the gonococcus can form biofilms on glass surfaces and over human cells. There is evidence for the formation of gonococcal biofilms on human cervical epithelial cells during natural disease. Evidence also suggests that the outer membrane blebbing by the gonococcus is crucial in biofilm formation over human cervical epithelial cells.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: ***CC BY-SA: Attribution-ShareAlike***

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- Normal flora. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Normal_flora**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Infection. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Infection**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- OpenStax College, The Immune Response against Pathogens. January 16, 2014. **Provided by**: OpenStax CNX. **Located at**: **http://cnx.org/contents/bcad1027-425...9d445dfe425f@4**. **License**: ***CC BY: Attribution***

- Human microbiome. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Human%20microbiome**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- EColiCRIS051-Fig2. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:EC...IS051-Fig2.jpg**. **License**: ***Public Domain: No Known Copyright***
- Pilus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Pilus**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- pilus. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/pilus**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- EColiCRIS051-Fig2. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:EC...IS051-Fig2.jpg**. **License**: ***Public Domain: No Known Copyright***
- Conjugation. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...onjugation.svg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Biofilms. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Biofilms**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- sterile. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/sterile**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- biofilm. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/biofilm**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- EColiCRIS051-Fig2. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:EC...IS051-Fig2.jpg**. **License**: ***Public Domain: No Known Copyright***
- Conjugation. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...onjugation.svg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Biofilm. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Biofilm.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Staphylococcus aureus biofilm 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:St...pg%23filelinks**. **License**: ***Public Domain: No Known Copyright***

Key Points

- Biofilms have been found to be involved in a wide variety of microbial infections in the body.
- Microbes form a biofilm in response to many factors, which may include cellular recognition of specific or non-specific attachment sites on a surface and nutritional cues.
- Bacterial biofilms may impair cutaneous wound healing and reduce topical antibacterial efficiency in healing or treating infected skin wounds.

Key Terms

- **biofilm**: A thin film of mucus created by and containing a colony of bacteria and other microorganisms.
- **sterile**: unable to reproduce (or procreate)

This page titled 2.2C: Biofilms and Infections is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **14.3C: Biofilms and Infections** is licensed CC BY-SA 4.0.

2.3: Damaging Host Cells

This page titled 2.3: Damaging Host Cells is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **14.4: Damaging Host Cells** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

2.3A: Toxins

Learning Objectives

- Describe the major toxin types (bacterial toxins and mycotoxins) and their mechanisms of action

Toxins are poisonous substances produced within living cells or organisms and can include various classes of small molecules or proteins that cause disease on contact. The severity and type of diseases caused by toxins can range from minor effects to deadly effects. The organisms which are capable of producing toxins include bacteria, fungi, algae, and plants. Some of the major types of toxins include, but are not limited to, environmental, marine, and microbial toxins. Microbial toxins may include those produced by the microorganisms bacteria (i.e. bacterial toxins) and fungi (i.e. mycotoxins).

Bacterial Toxins

Bacterial toxins are typically classified under two major categories: exotoxins or endotoxins. Exotoxins are immediately released into the surrounding environment whereas endotoxins are not released until the bacteria is killed by the immune system. The release of toxins into the surrounding environment, regardless of when released, results in the disruption of metabolic pathways in the host eukaryote. These metabolic pathways include damaging cell membranes, disrupting protein synthesis, inhibiting neurotransmitter release, or activating the host immune system. The mechanisms of action by which toxins disrupt eukaryotic cell processes are dependent on the target. For example, the bacteria *Listeria monocytogenes*, associated with food-borne illnesses, specifically targets cholesterol by producing a pore-forming toxin protein, listeriolysin O. This exotoxin affects intracellular processes and creates unregulated pores within the cell membranes of the host. Another example of an exotoxin includes an enterotoxin produced by the bacteria *Staphlycoccal aureus. S. aureus* can producestaphylococcal enterotoxin B (SEB), associated with intestinal illness, which promotes activation of the immune system. Upon activation of the immune system, the release of large amounts of cytokines, inflammatory related molecules, causes significant inflammation. Lastly, an example of an endotoxin, includes the protein lipopolysaccharide (LPS) produced by gram-negative bacteria. The LPS is a component of the bacteria's outer membrane and promotes structural integrity. Upon destruction of the membrane by an immune response, the LPS is released and functions as a toxin.

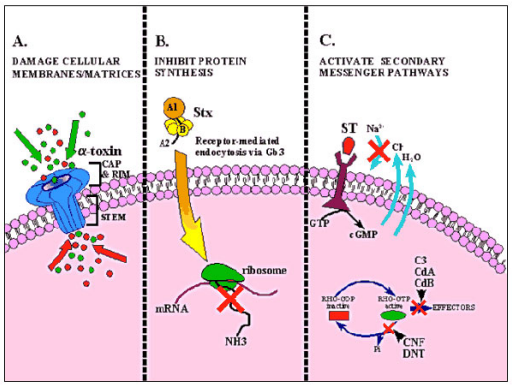


Figure: ***Bacterial Toxin Mechanism of Action****: A schematic of various processes utilized by bacterial toxins to damage host cells.*

However, bacterial toxins are also currently serving as new sources for potential drug development. Toxins have been shown to exhibit anticancer characteristics and fight again microbial virulence. The investigation of toxins as potential medicinal compounds is currently underway.

Mycotoxins

Mycotoxins are the classes of toxins produced by fungi. Mycotoxins are numerous and production of a specific mycotoxin is not restricted to one specific species. Mycotoxins are secondary metabolites that are toxic to humans and produced by fungi. There are various types of mycotoxins including, but not limited to, aflatoxins, ochratoxins, citrinin, and ergot alkaloids.

Aflatoxins

Aflatoxins are a type of mycotoxin that are produced by certain strains of *Aspergillus* fungi. The aflatoxins are further broken down into types: AFB1, AFB2, AFG1, and AFG2. These strains are present in a wide range of agricultural commodities associated with tropic and subtropic zones. These commodities include species of peanuts and corn. The most potent toxin is AFB1 and it is associated with carcinogenic effects.

Ochratoxin

Ochratoxin is a type of toxin produced by both *Penicillium* and *Aspergillus* species. Ochratoxins are further classified in types A, B and C and differ in structure. Ochratoxins have demonstrated carcinogenic properties and are often found in beverages such as beer and wine, as the fungal species which produce ochratoxins are often found on the plants used to produce these products.

Citrinin

Citrinin is a mycotoxin that has been isolated in numerous species of both *Penicillium* and *Aspergillus*. Many of these fungal species are utilized in food processing and are often found in foods including cheese, wheat, rice, corn, and soy sauce. Citrinin is known to function as a nephrotoxin, indicating it has toxic effects on kidney function.

Ergot Alkaloids

Ergot Alkaloids are specific compounds that are produced as toxic alkaloids in *Claviceps*, a group of fungi associated with grasses, rye, and related plants. The disease caused by ingestion of this fungi is called ergotism. Ergotism is characterized by detrimental effects on the vascular system in particular, including vasoconstriction of blood vessels resulting in gangrene, and eventually, limb loss if left untreated. Additionally, ergotism can present as hallucinations and convulsions as ergot alkaloids target the central nervous system. Due to the vascular system effects of ergot alkaloids, they have been used for medicinal purposes.

Key Points

- Microbial toxins may include those produced by the microorganisms bacteria (i.e. bacterial toxins) and fungi (i.e. mycotoxins).
- Bacterial toxins can include both endotoxins and exotoxins, which vary in mechanism of action and are species -specific.
- Exotoxins are immediately released into the surrounding environment whereas endotoxins are not released until the bacteria is killed by the immune system.
- Mycotoxins can be classified into numerous categories and are not species-specific because the same mycotoxin can be produced by different fungal species.

Key Terms

- **endotoxin**: Any toxin secreted by a microorganism and released into the surrounding environment only when it dies.
- **exotoxin**: Any toxin secreted by a microorganism into the surrounding environment.
- **cytokines**: Regulatory proteins that function in the regulation of the cells involved in immune system function

This page titled 2.3A: Toxins is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **14.4A: Toxins** is licensed CC BY-SA 4.0.

2.3B: Direct Damage

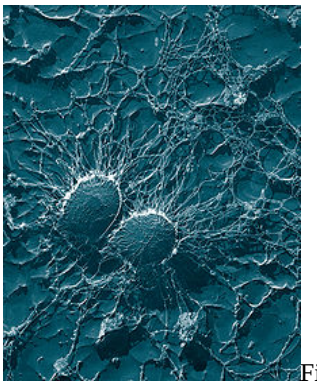
Learning Objectives

- Describe the different processes used by pathogens to damage the host and ensure infection

Direct damage to the host is a general mechanism utilized by pathogenic organisms to ensure infection and destruction of the host cell. The pathogenic organism typically causes damage due to its own growth process. The promotion of disease is characterized by the ability of a pathogenic organism to enter a host and inflict damage and destruction onto the host cell. The pathogenic organism must exhibit specific characteristics that promote its growth into a host cell including, but not limited to, the ability to invade, colonize, and attach to host cells.

The ability of a pathogen to gain entrance to a host cell is fundamental in the ability of the pathogen to promote and cause disease. The ability to manipulate the process of phagocytosis is a mechanism often utilized by bacteria to ensure they effectively invade a host. Phagocytosis is a process utilized by phagocytes (white blood cells) as a defense mechanism to protect from foreign bodies. The phagocytes engulf invaders and present them to additional factors within the immune system that result in their destruction. However, a successful and destructive pathogen often exhibits the ability to evade phagocytosis.

The mechanism(s) utilized by pathogens to avoid phagocytosis include avoiding both contact and engulfment. Pathogens that exhibit the ability to avoid contact utilize various processes to accomplish this, including: the ability to grow in regions of the body where phagocytes are incapable of reaching; the ability to inhibit the activation of an immune response; inhibiting and interfering with chemotaxis which drives the phagocytes to site of infection; and 'tricking' the immune system to identify the bacteria as 'self. ' Additional mechanism(s) by which bacteria can avoid destruction is by avoiding engulfment. This is accomplished by the ability of the bacteria to exhibit produce molecules that interfere with the phagocytes ability to internalize the bacteria. Molecules that interfere with this process include certain types of proteins and sugars that block engulfment.

 Figure: **Protected from Phagocytosis**: Staphylococcus aureus exhibit physical properties, specifically a capsule, that protect the bacteria from phagocytosis.

Once the pathogen has successfully evaded engulfment and destruction by the immune system, it is detrimental because the bacteria then multiply. Often times, bacteria will directly attach themselves to host cells and utilize nutrients from the host cell for their own cellular processes. Upon the use of host nutrients for its own cellular processes, the bacteria may also produce toxins or enzymes that will infiltrate and destroy the host cell. The production of these destructive products results in the direct damage of the host cell. The waste products of the microbes will also damage to the cell. Examples of bacteria that will damage tissue by producing toxins, include, *Corynebacterium diphtheriae* and *Streptococcus pyogenes.* Specifically, *Corynebacterium diphtheriae* causes diphtheria, which isa disease of the upper respiratory tract. It produces a toxin, diphtheria toxin, which alters host protein function. The toxin can then result in damage to additional tissues including the heart, liver, and nerves. *Streptococcus pyogenes* is associated with strep throat and "flesh-eating disease. " The bacteria produce enzymes which function in disrupting fibrin clots. Fibrin clots will form at sites of injury, in this case, at the site of foreign invasion. The enzymes, capable of digesting fibrin, will open an area within the epithelial cells and promote invasion of the bacteria into the tissues.

Key Points

- Pathogenic organisms must have mechanisms in place to evade attack by the immune system.
- Pathogens can produce enzymes that disrupt normal tissue and allow for further invasion into the tissues.
- Pathogens can produce toxins that interfere with protein function deemed necessary by the host cell for proper maintenance.

Key Terms

- **diphtheria**: A disease of the upper respiratory tract caused by a toxin secreted by Corynebacterium diphtheriae.
- **phagocytosis**: the process by which a cell incorporates foreign particles intracellularly.

This page titled 2.3B: Direct Damage is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **14.4B: Direct Damage** is licensed CC BY-SA 4.0.

2.3C: Type III and Type IV Secretion

Learning Objectives

- Distinguish between Type III and IV secretion systems

In regards to pathogenecity, secretion in microorganisms such as bacterial species involves the movement of effector molecules from the interior of a pathogenic organism to the exterior. The secretion of specific molecules allows for adaptation to occur, thereby promoting survival. Effector molecules secreted include proteins, enzymes or toxins. The mechanisms by which pathogenic bacteria secrete proteins involve complex and specialized secretion systems. Specifically, Type III and Type IV secretion systems are utilized by gram-negative pathogenic bacteria to transport proteins that function as pathogenic components.

Type III Secretion Systems

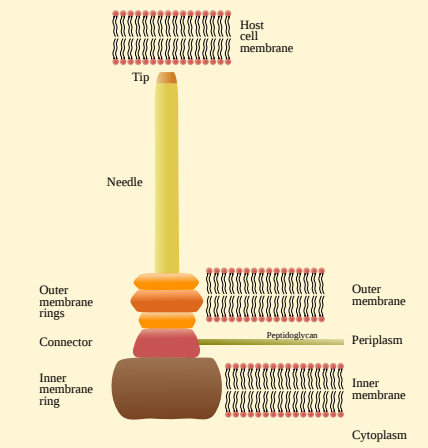


Figure: **Type III Secretion System**: The type III secretion system is characterized by the ability to inject secretory molecules into the host eukaryotic cell.

Type III secretion systems are characterized by the ability to inject a protein directly from the bacterial cell to the eukaryotic cell. It is often compared to the bacterial flagellar basal body which functions as a motor unit and extracellular appendage that is comprised of numerous proteins. The pathogenic bacteria which exhibit this capability contain a critical structural component, considered a protein appendage, that allows the injection of the protein into the host cell. The type III secretion system involves the formation of a complex, roughly ~20 proteins, that reside within the cytoplasmic membrane of the bacterial cell. The process of injecting or transferring the secretory protein from the bacterial cell to the host eukaryotic cell requires a membrane-associated ATPase. Certain species of pathogenic bacteria, including: *Salmonella*, *Shigella*, *Yersinia* and *Vibrio* exhibit type III secretion systems. The system is regulated by Ca2+ concentrations which regulate the opening and closing of gates present in the membrane by which the type III secretion system complexes can utilize for translocation. For example, in *Salmonella*, most commonly associated with *Enteritis salmonellosis*, or food poisoning, the bacteria injects a toxin, AvrA, that inhibits activation of the innate immune system of the host. The mechanism by which AvrA is injected involves exact and proper assembly of proteins which promote invasion of the host cell. Misalignment or improper organization of proteins involved in the type III secretion system prevent injection of secretory substances from the pathogen into the host cell. Another pathogen, *Shigella*, which utilizes type III secretion systems is able to successfully carry out its infection by evading the immune system. The movement between neighboring cells and evading the immune system, enhances its ability to inject its secretory protein into the host cell.

Type IV Secretion Systems

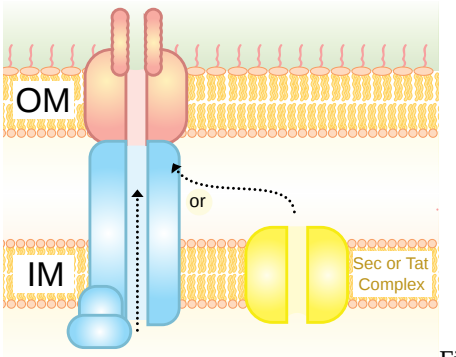


Figure: **Type IV Secretion System**: Type IV secretion systems are characterized by the ability to transfer material using machinery similar to the bacterial conjugation machinery.

Type IV secretion systems are characterized by the ability to transfer secretory molecules via a mechanism similar to the bacterial conjugation machinery. The type IV secretion systems can either secrete or receive molecules. The bacterial conjugation machinery allows transfer of genetic material to occur via direct cell-to-cell contact or by a bridge-like apparatus between the two cells. The type IV secretion system utilizes a process similar to this. However, the exact mechanism(s) this process utilizes is unknown but there is a general understanding.

This specific secretion system can transport both DNA and proteins. An example of a pathogenic bacteria that utilizes the type IV secretion system is *Helicobacter pylori*. *H. pylori*, most commonly associated with stomach ulcers, attaches itself to epithelial cells within the stomach, then via a type IV secretion system, injects a secretory molecule. The secretory molecule injected into the epithelial cells is an inflammation-inducing agent derived from their own cellular wall. The secretory molecule, peptidoglycan, is recognized by the host system as a foreign substance and activates expression of cytokines which promotes an inflammatory response. This inflammatory response of the stomach is a key characteristic of individuals with ulcers. Peptidoglycan is not the only secretory molecule transferred to the stomach epithelial cells but additional proteins, such as CagA, which function in disruption of host cell cellular activities can be transferred as well.

Key Points

- Type III secretion system use a process which injects the secretory molecule into the host cell.
- Type IV secretion systems use a process which is similar to the bacterial conjugation machinery.
- Type IV secretion systems require attachment to the host cell by direct cell-to-cell contact or via a bridge-like apparatus.
- Type IV secretion systems can be used to both transport and receive molecules.
- Type III secretion systems requires a large protein complex to ensure proper transfer of secretory molecules.

Key Terms

- **peptidoglycan**: A polymer of glycan and peptides found in bacterial cell walls.
- **effector**: a small molecule that effects additional molecules
- **bacterial conjugation**: transfer of genetic material between bacterial cells by direct contact

This page titled 2.3C: Type III and Type IV Secretion is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **14.4C: Type III and Type IV Secretion** is licensed CC BY-SA 4.0.

2.3D: Plasmids and Lysogeny

Learning Objectives

- Distinguish between plasmids and lysogeny in regards to pathogenecity

Plasmids

Plasmids are DNA molecules that are capable of replicating independently from the chromosomal DNA. Plasmids are often characterized by their circular appearance and double-strands; they also vary in size and number. Plasmids are present in the three major domains (Archaea, Bacteria and Eukarya) and are considered to be ‘naked DNA’. ‘Naked DNA’ refers to a specific type of DNA which does not encode for genes promoting the transfer of genetic material to a new host. The plasmids are present within the cells as extra chromosomal genomes and are a common tool used in molecular biology to integrate new DNA into a host. In the field of molecular biology, plasmid DNA is often referred to as ‘ vectors ‘ due to their ability to transfer DNA between organisms. The use of plasmid DNA in molecular biology is considered to be recombinant DNA technology. In addition, plasmid DNA provides a mechanism by which horizontal gene transfer can occur, contributing to antibiotic resistance.

Horizontal gene transfer is a major mechanism promoting bacterial antibiotic resistance, as the plasmid DNA can transfer genes from one species of bacteria to another. The plasmid DNA which is transferred often has developed genes that encode for resistance against antibiotics. The ability to transfer this resistance from one species to another is increasingly becoming an issue in clinics for treatment of bacterial infections. The process of horizontal gene transfer can occur via three mechanisms: transformation, transduction and conjugation. Plasmid DNA transfer is associated with conjugation as the host-to-host transfer requires direct mechanical transfer. The advantages of plasmid DNA transfer allow for survival advantages.

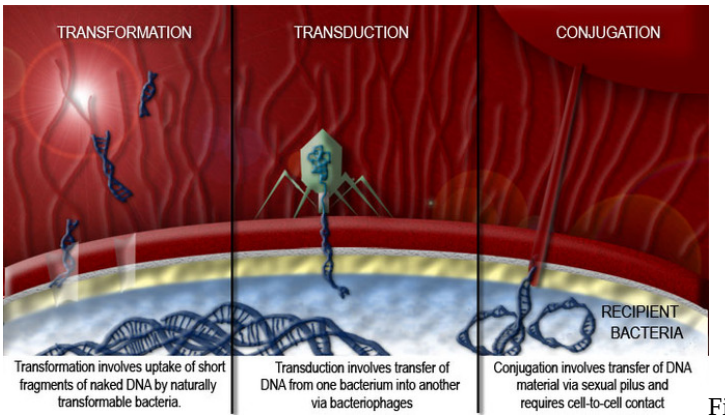


Figure: **Horizontal Gene Transfer**: There are three mechanisms by which horizontal gene transfer can occur. Specifically, the exchange of plasmid DNA falls under transformation.

Lysogeny

Lysogeny is the process by which a bacteriophageintegrates its nucleic acids into a host bacterium’s genome. Lysogeny is utilized by viruses to ensure the maintenance of viral nucleic acids within the genome of the bacterium host. The virus displays the ability to infect the bacterium host and integrate its own genetic materials into the host bacterium genome. The bacteriophages newly integrated genetic material, called a prophage, is transferred to new bacterial daughter cells upon cell division. The prophage is integrated into the bacterium genome at this point. The lysogenic cycle is key to ensure the transmittance of bacteriophage nucleic acids to host bacterium’s genome. Lysogeny is one of two major methods of viral reproduction utilized by viruses.

Lysogenic cycles are utilized by specific types of viruses to ensure viral reproduction, but they also need the second major method of viral reproduction, the lytic cycle, as well. The lytic cycle, considered the primary method of viral replication, results in the actual destruction of the infected cell. Upon destruction of the infected cell, the new viruses, which have developed after undergoing biosynthesis and maturation, are free to infect other cells. The lytic cycle is characterized by the breakdown of the bacteria cell wall intracellularly. The viruses cause disruption of the bacterial cell by producing enzymes which facilitate this process. An example of a virus which can promote the transformation of bacterium from a nontoxic to toxic strain via lysogeny is

the CTXφ virus. Specifically, the bacterium, *Vibrio cholerae*, is transformed into a toxic strain upon infection with the bacteriophage. This bacterium is then able to produce a cholera toxin, the cause of the disease cholera.

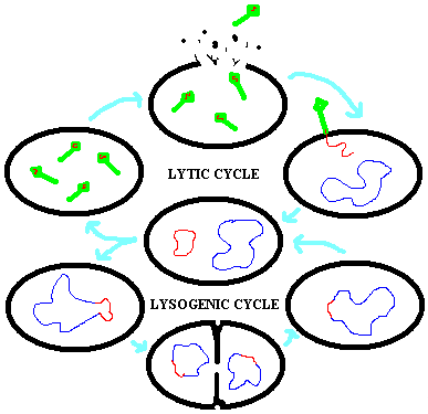


Figure: ***Lysogenic and lytic cycles****: Schematic of lysogenic and lytic cycle utilized by viruses to ensure viral reproduction.*

Key Points

- Plasmids are double-stranded circular forms of ‘naked DNA ‘.
- Plasmids are responsible for horizontal gene transfer which promotes the development of antibiotic resistance in bacterium.
- Lysogeny is a major method of viral reproduction characterized by the integration of viral nucleic acids in the bacterium genome.

Key Terms

- **bacteriophage**: A virus that specifically infects bacteria.
- **lysogeny**: the process by which a bacteriophage incorporates its nucleic acids into a host bacterium

---

This page titled 2.3D: Plasmids and Lysogeny is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **14.4D: Plasmids and Lysogeny** is licensed CC BY-SA 4.0.

2.3E: Siderophores

Learning Objectives

- Compare and contrast the role of various siderophores in pathogenecity, including: yersiniabactin, enterobactin and ferrichromes

Siderophores are specific types of molecules utilized by microorganisms to obtain iron from the environment. Specifically, in regards to pathogenicity, organisms that exhibit the ability to produce siderophores release these iron-specific molecules and scavenge iron from their hosts organisms. The siderophores are then utilized by the pathogen to obtain iron. Therefore, siderophores are chelating agents that bind the iron ions. The ability of pathogens to obtain iron from the host is essential for survival because the iron is limited in the host environment, in particular, the host tissues and fluids. The iron is used to allow for formation of soluble ferric ion (Fe^{3+}) complexes that are necessary for maintenance of homeostatic mechanisms within the pathogen.

The ability to form water soluble Fe^{3+} complexes is a key component to the active transport of the Fe-siderophore complex across the cellular membrane. In iron deficient environments, the siderophores are released and allow for the formation of water soluble-Fe^{3+} complexes to increase iron acquisition. The complexes then generally bind to the cellular membrane using cell specific receptors. They are transported across the membrane utilized for the necessary processes. However, there are differences in the mechanisms employed by various sideorophobes to obtain iron and the specific type of siderophore utilized varies.

Yersiniabactin

The pathogenic bacteria, *Yersinia pestis*, *Yersinia pseduotuberculosis*, and *Yersinia enterocolitica* have the ability to produce a siderophore called yersiniabactin. Pathogenic yersinia is responsible for numerous diseases including the bubonic plague. The ability of pathogenic Yersinia to establish and spread disease is based on its ability to obtain iron for fundamental cellular processes. In areas of low iron, the organism will release yersiniabactin to form Fe^{3+} complexes. The yersiniabactin-Fe^{3+} complex will then bind to the outer membrane of the bacteria based on specific receptor recognition. The complex is then translocated through the membrane via membrane-embedded proteins and iron is released from the yersiniabactin. The iron will then be utilized in numerous cellular processes.

Enterobactin

Pathogenic bacteria such as *Escherichia coli* and *Salmonella typhimurium* have the ability to produce a siderophore called enterobactin. This specific type of siderophore is the strongest identified siderophore, to date, with an extremely high binding affinity to Fe^{3+}. Upon a decrease in iron, the bacterial cells release enterobactin which forms a complex with Fe^{3+}. The complex is then transported intracellularly via an ATP-binding cassette transporter. Once the enterobactin-Fe^{3+} complex arrives intracellularly, it is necessary to remove the Fe^{3+} from the complex. Due to the high-binding affinity of enterobactin, the bacteria require a highly specific enzyme, ferrienterobactin esterase, to cleave the iron from the complex. The iron released from the complex will then be utilized in metabolic processes.

Ferrichrome

Another type of siderophore produced by pathogenic fungi includes a ferrichrome. Fungi that have been shown to produce ferrichromes include those in the genera Aspergillus, Ustilago, and Penicillum. The ferrichrome allows for formation of a ferrichrome-iron complex which can then interact with a protein receptor on the cell surface. The ferrichrome promotes iron transport within the organism to allow metabolic processes to occur.

The discovery and identification of siderophores have allowed for the development of treatments targeting these siderophore-iron complexes. By targeting these complexes, the pathogenic microorganisms can be targeted by inhibiting necessary cellular processes. The production and importance of these siderophores to pathogenic organisms is key to their survival.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: ***CC BY-SA: Attribution-ShareAlike***

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- Microbial toxins. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Microbial_toxins**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- **Provided by**: U.S. Food and Drug Administration. **Located at**: **www.fda.gov/downloads/Food/Fo.../UCM297627.pdf**. **License**: ***Public Domain: No Known Copyright***
- Bacterial Toxins: Friends or Foes?. **Provided by**: Centers for Disease Control and Prevention. **Located at**: **http://wwwnc.cdc.gov/eid/article/5/2...06_article.htm**. **License**: ***Public Domain: No Known Copyright***
- Claviceps. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Claviceps**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Microbial toxins. **Provided by**: Wikipedia. **Located at**: **http://en.Wikipedia.org/wiki/Microbial_toxins**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Claviceps. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Claviceps**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Staphylococcal Enterotoxin B. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Staphylococcal_Enterotoxin_B**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Microbial toxins. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Microbi...s%23Mycotoxins**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Listeriolysin O. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Listeriolysin_O**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Toxins: MedlinePlus Medical Encyclopedia. **Provided by**: National Insitute of Health. **Located at**: **http://www.nlm.nih.gov/medlineplus/e...cle/002331.htm**. **License**: ***Public Domain: No Known Copyright***
- Mycotoxin. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Mycotoxin**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Lipopolysaccharide. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Lipopolysaccharide**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Toxin. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Toxin**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Mycotoxin. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Mycotoxin**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- cytokines. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/cytokines**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- exotoxin. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/exotoxin**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- endotoxin. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/endotoxin**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Figure 1 - Bacterial Toxins: Friends or Foes?n- Volume 5, Number 2u2014April 1999 - Emerging Infectious Disease journal - CDC. **Provided by**: Centers for Disease Control and Prevention. **Located at**: **http://wwwnc.cdc.gov/eid/article/5/2/99-0206-f1.htm**. **License**: ***Public Domain: No Known Copyright***
- Phagocyte. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Phagocy..._by_phagocytes**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Diseases - Understanding Infectious Diseases, page 1. **Provided by**: National Insitute of Health. **Located at**: **science.education.nih.gov/sup...rstanding1.htm**. **License**: ***Public Domain: No Known Copyright***
- Phagocyte. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Phagocy..._by_phagocytes**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Corynebacterium diphtheriae. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Corynebacterium_diphtheriae**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- phagocytosis. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/phagocytosis**. **License**: ***CC BY-SA: Attribution-ShareAlike***

- diphtheria. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/diphtheria**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Figure 1 - Bacterial Toxins: Friends or Foes?n- Volume 5, Number 2u2014April 1999 - Emerging Infectious Disease journal - CDC. **Provided by**: Centers for Disease Control and Prevention. **Located at**: http://wwwnc.cdc.gov/eid/article/5/2/99-0206-f1.htm. **License**: ***Public Domain: No Known Copyright***
- Phagocyte. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Phagocy..._by_phagocytes**. **License**: ***Public Domain: No Known Copyright***
- Secretion. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Secreti...tem_.28T2SS.29**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Helicobacter pylori. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Helicobacter_pylori**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Bacterial conjugation. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Bacterial_conjugation**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Salmonella. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Salmonella**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Secretion. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Secreti...4SS_or_TFSS.29**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Type three secretion system. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Type_th...cretion_system**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Secretion. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Secreti...tem_.28T2SS.29**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Secretion. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Secretion%23Type_II_secretion_system_.28T2SS.29**. **License**: *CC BY-SA: Attribution-ShareAlike*
- effector. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/effector**. **License**: *CC BY-SA: Attribution-ShareAlike*
- bacterial conjugation. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/bacterial%20conjugation**. **License**: *CC BY-SA: Attribution-ShareAlike*
- peptidoglycan. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/peptidoglycan**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Figure 1 - Bacterial Toxins: Friends or Foes?n- Volume 5, Number 2u2014April 1999 - Emerging Infectious Disease journal - CDC. **Provided by**: Centers for Disease Control and Prevention. **Located at**: http://wwwnc.cdc.gov/eid/article/5/2/99-0206-f1.htm. **License**: ***Public Domain: No Known Copyright***
- Phagocyte. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Phagocyte%23Host_damage_by_phagocytes**. **License**: ***Public Domain: No Known Copyright***
- File:T4SS.svg - Wikipedia, the free encyclopedia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/w/index.php?...4SS.svg&page=1**. **License**: *CC BY-SA: Attribution-ShareAlike*
- T3SS needle complex. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:T3...le_complex.svg**. **License**: ***Public Domain: No Known Copyright***
- Lysogenic cycle - wikidoc. **Provided by**: Wikidoc. **Located at**: **ro.wikidoc.org/index.php/Lysogenic_cycle**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Lytic cycle - wikidoc. **Provided by**: Wikidoc. **Located at**: **ro.wikidoc.org/index.php/Lytic_cycle**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Vibrio cholerae. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Vibrio_cholerae%23Bacteriophage_CTX.CF.86**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Horizontal gene transfer. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Horizontal_gene_transfer**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Plasmids. **Provided by**: Ask a Biologist. **Located at**: http://askabiologist.asu.edu/plasmids. **License**: *CC BY-SA: Attribution-ShareAlike*
- Lysogenic cycle. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Lysogenic_cycle**. **License**: *CC BY-SA: Attribution-ShareAlike*

- Lytic cycle - wikidoc. **Provided by**: Wikidoc. **Located at**: **ro.wikidoc.org/index.php/Lytic_cycle**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Plasmids. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Plasmids**. **License**: *CC BY-SA: Attribution-ShareAlike*
- bacteriophage. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/bacteriophage**. **License**: *CC BY-SA: Attribution-ShareAlike*
- lysogeny. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/lysogeny**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Figure 1 - Bacterial Toxins: Friends or Foes?n- Volume 5, Number 2u2014April 1999 - Emerging Infectious Disease journal - CDC. **Provided by**: Centers for Disease Control and Prevention. **Located at**: **http://wwwnc.cdc.gov/eid/article/5/2/99-0206-f1.htm**. **License**: ***Public Domain: No Known Copyright***
- Phagocyte. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Phagocyte%23Host_damage_by_phagocytes**. **License**: ***Public Domain: No Known Copyright***
- File:T4SS.svg - Wikipedia, the free encyclopedia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/w/index.php?...4SS.svg&page=1**. **License**: *CC BY-SA: Attribution-ShareAlike*
- T3SS needle complex. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:T3...le_complex.svg**. **License**: *Public Domain: No Known Copyright*
- Horizontal%20Gene%20Transfer%20%E2%80%94%20Antimicrobial%20Resistance%20Learning%20Site%20For%20Veterinary%20Students. **Provided by**: Michigan%20State%20University. **Located at**: **amrls.cvm.msu.edu/microbiology/molecular-basis-for-antimicrobial-resistance/acquired-resistance/acquisition-of-antimicrobial-resistance-via-horizontal-gene-transfer**. **License**: ***CC BY: Attribution***
- File:Viral%20Reproduction%20Chart.png%20-%20wikidoc. **Provided by**: Wikidoc. **Located at**: **ro.wikidoc.org/index.php/File...tion_Chart.png**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Iron in microbiology. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Iron_in_microbiology**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Siderophore. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Siderophore**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Enterobactin. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Enterobactin**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Iron in microbiology. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Iron_in_microbiology**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Enterobactin. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Enterobactin**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Yersiniabactin. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Yersiniabactin**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Ferrichrome. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Ferrichrome**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Yersiniabactin. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Yersiniabactin**. **License**: *CC BY-SA: Attribution-ShareAlike*
- siderophore. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/siderophore**. **License**: *CC BY-SA: Attribution-ShareAlike*
- chelating agent. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/chelating_agent**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Figure 1 - Bacterial Toxins: Friends or Foes?n- Volume 5, Number 2u2014April 1999 - Emerging Infectious Disease journal - CDC. **Provided by**: Centers for Disease Control and Prevention. **Located at**: **http://wwwnc.cdc.gov/eid/article/5/2/99-0206-f1.htm**. **License**: *Public Domain: No Known Copyright*
- Phagocyte. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Phagocyte%23Host_damage_by_phagocytes**. **License**: *Public Domain: No Known Copyright*
- File:T4SS.svg - Wikipedia, the free encyclopedia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/w/index.php?...4SS.svg&page=1**. **License**: *CC BY-SA: Attribution-ShareAlike*

- T3SS needle complex. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:T3...le_complex.svg**. **License**: ***Public Domain: No Known Copyright***
- Horizontal%20Gene%20Transfer%20%E2%80%94%20Antimicrobial%20Resistance%20Learning%20Site%20For%20Veterinary%20Students. **Provided by**: Michigan%20State%20University. **Located at**: **amrls.cvm.msu.edu/microbiology/molecular-basis-for-antimicrobial-resistance/acquired-resistance/acquisition-of-antimicrobial-resistance-via-horizontal-gene-transfer**. **License**: ***CC BY: Attribution***
- File:Viral%20Reproduction%20Chart.png%20-%20wikidoc. **Provided by**: Wikidoc. **Located at**: **ro.wikidoc.org/index.php/File:Viral_Reproduction_Chart.png**. **License**: ***CC BY-SA: Attribution-ShareAlike***

Key Points

- Siderophore – iron complexes are necessary for iron acquisition to various pathogenic organisms for metabolic processes.
- The types of siderophores produced are species specific and exhibit different properties.
- The siderophores are necessary to obtain iron by binding to cell surfaces and transporting the siderophore-iron complexes intracellularly.
- Siderophores are produced in environments that have low iron concentration, such as host tissues and fluids. They are considered advantageous to pathogenic organisms.

Key Terms

- **siderophore**: Any medium-sized molecule that has a high specificity for binding or chelating iron; they are employed by microorganisms to obtain iron from the environment
- **chelating agent**: A compound that reacts with a metal ion to produce a chelate.

This page titled 2.3E: Siderophores is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **14.4E: Siderophores** is licensed CC BY-SA 4.0.

2.4: Surviving Within the Host and Exiting the Host

This page titled 2.4: Surviving Within the Host and Exiting the Host is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **14.5: Surviving Within the Host and Exiting the Host** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

2.4A: Intracellular Pathogens

Learning Objectives

- Recognize examples of intracellular pathogens

A pathogen or infectious agent is a microorganism such as a virus, bacterium, prion, or fungus that causes disease in its host. The host may be an animal, a plant, or even another microorganism. Not all pathogens are undesirable to humans. In entomology, pathogens are one of the "Three P's" (predators, pathogens, and parasitoids) that serve as natural or introduced biological controls to suppress arthropod pest populations.

There are several types of intracellular pathogens. Pathogenic viruses are mainly those of the families of Adenoviridae, bacteria Picornaviridae, Herpesviridae, Hepadnaviridae, Flaviviridae, Retroviridae, Orthomyxoviridae, Paramyxoviridae, Papovaviridae, Polyomavirus, Rhabdoviridae, and Togaviridae. Viruses typically range between 20 to 300 nanometers in length. Although the vast majority of bacteria are harmless or beneficial, a few pathogenic bacteria can cause infectious diseases. Bacteria can often be killed by antibiotics because the cell wall in the outside is destroyed, expelling the DNA out of the body of the pathogen, therefore making the pathogen incapable of producing proteins, so it dies. They typically range between 1 and 5 micrometers in length.

 Figure: ***Stanley Prusiner****: Stanley Prusiner discovered prions, which are a class of infectious self-reproducing pathogens primarily or solely composed of protein.*

Pathogenic fungi comprise a eukaryotic kingdom of microbes that are usually saprophytes but can cause diseases in humans, animals, and plants. Fungi are the most common cause of diseases in crops and other plants. The typical fungal spore size is 1 to 40 micrometers in length.

Some eukaryotic organisms, such as protists and helminths, cause disease. According to the prion theory, prions are infectious pathogens that do not contain nucleic acids. These abnormally-folded proteins are found characteristically in some diseases such as scrapie, bovine spongiform encephalopathy (mad cow disease), and Creutzfeldt–Jakob disease. Although prions fail to meet the requirements laid out by Koch's postulates, the hypothesis of prions as a new class of pathogen led Stanley B. Prusiner to receive the Nobel Prize in Physiology or Medicine in 1997.

Key Points

- The host may be an animal, a plant, or even another microorganism.
- Pathogenic viruses are mainly those of the families of Adenoviridae, bacteria Picornaviridae, Herpesviridae, Hepadnaviridae, Flaviviridae, Retroviridae, Orthomyxoviridae, Paramyxoviridae, Papovaviridae, Polyomavirus, Rhabdoviridae, and Togaviridae.
- Although the vast majority of bacteria are harmless or beneficial, a few pathogenic bacteria can cause infectious diseases.

Key Terms

- **prion**: A self-propagating misfolded conformer of a protein that is responsible for a number of diseases that affect the brain and other neural tissue.
- **pathogen**: Any organism or substance, especially a microorganism, capable of causing disease, such as bacteria, viruses, protozoa, or fungi. Microorganisms are not considered to be pathogenic until they have reached a population size that is large enough to cause disease.

This page titled 2.4A: Intracellular Pathogens is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **14.5A: Intracellular Pathogens** is licensed CC BY-SA 4.0.

2.4B: Extracellular Immune Avoidance

Learning Objectives

- List the mechanisms that bacteria use for intracellular pathogenesis

Extracellular Immune Avoidance

A pathogen's success depends on its ability to evade the host's immune responses. Thus, pathogens have evolved several methods that allow them to successfully infect a host by evading the immune system's detection and destruction. Bacteria usually overcome physical barriers by secreting enzymes that digest the barrier in the manner of a type II secretion system. They also use a type III secretion system that allows bacteria to insert a hallow tube, which provides proteins a direct route to enter the host cell. These proteins often shutdown the defenses of the host.

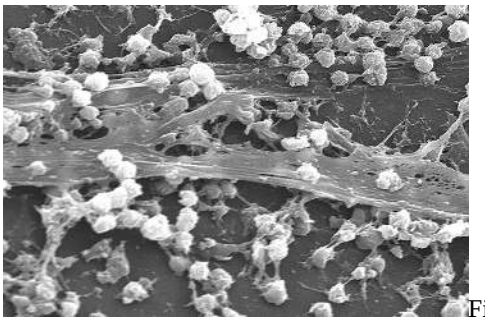


Figure: **Staphylococcus aureus biofilm**: Staphylococcus aureus forming a biofilm on a catheter.

Some pathogens avoid the immune system by hiding within the cells of the host, a process referred to as intracellular pathogenesis. The pathogen hides inside the host cell where it is protected from direct contact with the complement, antibodies, and immune cells. A lot of pathogens release compounds that misdirect or diminish the host's immune response. Some bacteria even form biofilms which protect them from the proteins and cells of the immune system. Many successful infections often involve biofilms. Some bacteria create surface proteins, such as Streptococcus, that will bind to antibodies making them ineffective.

Other pathogens invade the body by changing the non-essential epitopes on their surface rapidly while keeping the essential epitopes hidden. This is referred to as antigenic variation. HIV rapidly mutates so the proteins that are on its viral envelope, which are essential for its entry into the host's target cell, are consistently changing. The constant change of these antigens is why vaccines have not been created. Another common strategy that is used is to mask antigens with host molecules in order to evade detection by the immune system. With HIV, the envelope covering the viron is created from the host cell's outermost membrane making it difficult for the immune system to identify as a non-self structure.

Key Points

- Bacteria usually overcome physical barriers by secreting enzymes to digest the barrier in the manner of a type II secretion system.
- Some pathogens avoid the immune system by hiding within the cells of the host, a process referred to as intracellular pathogenesis.
- Other pathogens invade the body by changing the non-essential epitopes on their surface rapidly, while keeping the essential epitopes hidden.

Key Terms

- **pathogen**: Any organism or substance, especially a microorganism, capable of causing disease, such as bacteria, viruses, protozoa, or fungi. Microorganisms are not considered to be pathogenic until they have reached a population size that is large enough to cause disease.
- **biofilm**: A thin film of mucus created by and containing a colony of bacteria and other microorganisms.
- **antigenic variation**: The mechanism by which an infectious organism changes its surface proteins in favor of circumventing a host immune response.

This page titled 2.4B: Extracellular Immune Avoidance is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **14.5B: Extracellular Immune Avoidance** is licensed CC BY-SA 4.0.

2.4C: Regulating Virulence

Learning Objectives

- Compare and contrast the hypotheses that explain why a pathogen evolves as it does: Trade-Off, Short-Sighted Evolution and Coincidental Evolution Hypotheses

Virulence is the degree of pathogenicity within a group or species of parasites as indicated by case fatality rates and/or the ability of the organism to invade the tissues of the host. The pathogenicity of an organism – its ability to cause disease – is determined by its virulence factors. In an ecological context, virulence can be defined as the host's parasite-induced loss of fitness. Virulence can be understood in terms of proximate causes—those specific traits of the pathogen that help make the host ill—and ultimate causes—the evolutionary pressures that lead to virulent traits occurring in a pathogen strain.

The ability of a microorganism to cause disease is described in terms of the number of infecting bacteria, the route of entry into the body, the effects of host defense mechanisms, and intrinsic characteristics of the microorganism called virulence factors. Host-mediated pathogenesis is often important because the host can respond aggressively to infection with the result that host defense mechanisms do damage to host tissues while the infection is being countered.

According to evolutionary medicine, optimal virulence increases with horizontal transmission (between non-relatives) and decreases with vertical transmission (from parent to child). This is because the fitness of the host is bound to the fitness in vertical transmission but is not so bound in horizontal transmission.The pathogen population can evolve once it is in the host. There are three main hypotheses about why a pathogen evolves as it does. These three models help to explain the life history strategies of parasites, including reproduction, migration within the host, virulence, etc.



Figure: **Tuberculosis Culture**: The bacteria Mycobacterium tuberculosis can evolve to subvert the protection offered by immune defenses. This close-up reveals this organism's colonial morphology. Note the colorless rough surface, which are typical morphologic characteristics seen in Mycobacterium tuberculosis colonial growth. Macroscopic examination of colonial growth patterns is still one of the ways microorganisms are often identified.

1. Trade-off hypothesis argues that pathogens tend to evolve toward ever decreasing virulence because the death of the host (or even serious disability) is ultimately harmful to the pathogen living inside. For example, if the host dies, the pathogen population inside may die out entirely. Therefore, it was believed that less virulent pathogens that allowed the host to move around and interact with other hosts should have greater success reproducing and dispersing. But this is not necessarily the case. Pathogen strains that kill the host can increase in frequency as long as the pathogen can transmit itself to a new host, whether before or after the host dies. The evolution of virulence in pathogens is a balance between the costs and benefits of virulence to the pathogen.
2. Short-sighted evolution hypothesis suggests that the traits that increase reproduction rate and transmission to a new host will rise to high frequency within the pathogen population. These traits include the ability to reproduce sooner, reproduce faster, reproduce in higher numbers, live longer, survive against antibodies, or survive in parts of the body the pathogen does not normally infiltrate. These traits typically arise due to mutations, which occur more frequently in pathogen populations than in host populations, due to the pathogens' rapid generation time and immense numbers. After only a few generations, the mutations that enhance rapid reproduction or dispersal will increase in frequency. The same mutations that enhance the reproduction and dispersal of the pathogen also enhance its virulence in the host, causing much harm (disease and death). If the

pathogen's virulence kills the host and interferes with its own transmission to a new host, virulence will be selected against. But as long as transmission continues despite the virulence, virulent pathogens will have the advantage.

3. Coincidental evolution hypothesis argues that some forms of pathogenic virulence did not co-evolve with the host. For example, tetanus is caused by the soil bacterium Clostridium tetani. After C. tetani bacteria enter a human wound, the bacteria may grow and divide rapidly, even though the human body is not their normal habitat. While dividing, C. tetani produce a neurotoxin that is lethal to humans. But it is selection in the bacterium's normal life cycle in the soil that leads it to produce this toxin, not any evolution with a human host. The bacterium finds itself inside a human instead of in the soil by mere happenstance. We can say that the neurotoxin is not directed at the human host.

Key Points

- Virulence is the degree of pathogenicity within a group or species of parasites as indicated by case fatality rates and/or the ability of the organism to invade the tissues of the host.
- The ability of a microorganism to cause disease is described in terms of the number of infecting bacteria, the route of entry into the body, the effects of host defense mechanisms, and intrinsic characteristics of the microorganism called virulence factors.
- Optimal virulence increases with horizontal transmission (between non-relatives) and decreases with vertical transmission (from parent to child).
- The pathogen population can evolve once it is in the host.
- The three main hypotheses about why a pathogen evolves as it does are the Trade-Off Hypothesis, the Short-Sighted Evolution Hypothesis, and the Coincidental Evolution Hypothesis.

Key Terms

- **virulence**: The degree of pathogenicity within a group or species of parasites as indicated by case fatality rates and/or the ability of the organism to invade the tissues of the host and it is determined by virulence factors.

This page titled 2.4C: Regulating Virulence is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **14.5C: Regulating Virulence** is licensed CC BY-SA 4.0.

2.4D: Portals of Exit

Learning Objectives

- Distinguish between horizontal and vertical disease transmission

Transmission is the passing of a communicable disease from an infected host individual or group to a conspecific individual or group by one or more of the following means: droplet contact, direct physical contact, indirect physical contact, airborne transmission, and fecal-oral transmission.

Transmission can also be indirect, via another organism. Indirect transmission could involve zoonoses or, more typically, larger pathogens like macroparasites with more complex life cycles. Disease can be directly transmitted in two ways. The first is horizontal disease transmission – from one individual to another in the same generation by either direct contact, or indirect contact air, such as via a cough or sneeze. The second is vertical disease transmission – passing a disease causing agent vertically from parent to offspring, such as through perinatal transmission.

Pathogens must have a way to be transmitted from one host to another to ensure their species ‘ survival. Infectious agents are generally specialized for a particular method of transmission. For example, a virus or bacteria that causes its host to develop coughing and sneezing symptoms has a great survival advantage – it is much more likely to be ejected from one host and carried to another. This is also the reason that many microorganisms cause diarrhea.

The respiratory route is a typical mode of transmission among many infectious agents. If an infected person coughs or sneezes on another person, the microorganisms, suspended in warm, moist droplets, may enter the body through the nose, mouth, or eye surfaces. Diseases that are commonly spread by coughing or sneezing include: bacterial meningitis and chickenpox.



Figure: **Sneezing**: Sneezing can spread disease by launching disease vectors into the air.

When viruses are shed by an infected person through coughing or sneezing into the air, the mucus coating on the virus starts to evaporate. Once this mucus shell evaporates the remaining viron is called a droplet nucleus or quanta. The mucus evaporation rate is determined by the temperature and humidity inside the room. The lower the humidity, the quicker the mucus shell evaporates thus allowing the droplet nuclei to stay airborne and not drop to the ground. The low indoor humidity levels in wintertime buildings ensure that higher levels of droplet nuclei will survive: droplet nuclei are so microscopic that they are able to stay airborne indefinitely on the air currents present within indoor spaces. When an infected person coughs or sneezes, a percentage of their viruses will become droplet nuclei. If these droplet nuclei gain access to the eyes, nose, or mouth of an uninfected person (known as a susceptible) – either directly, or indirectly by touching a contaminated surface – then the droplet nuclei may penetrate into the deep recesses of their lungs. Viral diseases that are commonly spread by coughing or sneezing droplet nuclei include the common cold and influenza.

Direct fecal-oral transmission is rare for humans at least. More common are the indirect routes: foodstuffs or water become contaminated and the people who eat and drink them become infected. This is the typical mode of transmission for infectious agents such as cholera, hepatitis A, and polio.

Sexual transmission refers to any disease that can be caught during sexual activity with another person, including vaginal or anal sex or (less commonly) through oral sex. Transmission is either directly between surfaces in contact during intercourse or from

secretions which carry infectious agents that get into the partner's blood stream through tiny tears in the penis, vagina, or rectum. Some diseases transmissible by the sexual route include: HIV/AIDS and chlamydia.

Sexually transmitted diseases such as HIV and Hepatitis B are thought to not normally be transmitted through mouth-to-mouth contact, although it is possible to transmit some STDs between the genitals and the mouth during oral sex. In the case of HIV this possibility has been established. It is also responsible for the increased incidence of herpes simplex virus 1 (which is usually responsible for oral infections) in genital infections and the increased incidence of the type 2 virus (more common genitally) in oral infections.

Diseases that can be transmitted by direct contact are called contagious. These diseases can also be transmitted by sharing a towel (where the towel is rubbed vigorously on both bodies) or items of clothing in close contact with the body (socks, for example) if they are not washed thoroughly between uses.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: ***CC BY-SA: Attribution-ShareAlike***

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- Pathogen. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Pathoge...es_of_pathogen**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Pathogen. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Pathoge...es_of_pathogen**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- pathogen. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/pathogen**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- prion. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/prion**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Prusiner 1. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Pr...PG%23filelinks**. **License**: ***Public Domain: No Known Copyright***
- Structural Biochemistry/Genetic code/Immune System. **Provided by**: Wikibooks. **Located at**: **en.wikibooks.org/wiki/Structu..._Immune_System**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- biofilm. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/biofilm**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- pathogen. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/pathogen**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- antigenic variation. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/antigenic_variation**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Prusiner 1. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Pr...PG%23filelinks**. **License**: ***Public Domain: No Known Copyright***
- Staphylococcus%20aureus%20biofilm%2001. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:St...pg%23filelinks**. **License**: ***Public Domain: No Known Copyright***
- Virulence. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Virulence**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Virulence. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Virulence**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Virulence. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Virulence**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Virulence factor. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Virulence_factor**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- virulence. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/virulence**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Prusiner 1. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Pr...PG%23filelinks**. **License**: ***Public Domain: No Known Copyright***

- Staphylococcus%20aureus%20biofilm%2001. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:St...pg%23filelinks**. **License**: ***Public Domain: No Known Copyright***
- TB Culture. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:TB_Culture.jpg**. **License**: ***Public Domain: No Known Copyright***
- Transmission (medicine). **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Transmission_(medicine)**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- transmission. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/transmission**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Prusiner 1. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Pr...PG%23filelinks**. **License**: ***Public Domain: No Known Copyright***
- Staphylococcus%20aureus%20biofilm%2001. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:St...pg%23filelinks**. **License**: ***Public Domain: No Known Copyright***
- TB Culture. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:TB_Culture.jpg**. **License**: ***Public Domain: No Known Copyright***
- Sneeze. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Sn...PG%23filelinks**. **License**: ***Public Domain: No Known Copyright***

Key Points

- Transmission of microorganisms can happen directly from one person to another by: droplet contact, direct physical contact, indirect physical contact, airborne transmission, or fecal-oral transmission.
- Transmission can also be indirect, via another organism, either a vector or an intermediate host.
- Disease can also be transmitted in two ways: horizontally from one individual to another in the same generation and vertically from parent to offspring, such as through perinatal transmission.

Key Terms

- **transmission**: Transmission is the passing of a communicable disease from an infected host individual or group to a conspecific individual or group, regardless of whether the other individual was previously infected.

This page titled 2.4D: Portals of Exit is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **14.5D: Portals of Exit** is licensed CC BY-SA 4.0.

2.5: Pathogenicity and Other Microbes

This page titled 2.5: Pathogenicity and Other Microbes is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **14.6: Pathogenicity and Other Microbes** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

2.5A: Fungi

Learning Objectives

- Give examples of pathogenic fungi

A fungus is a member of a large group of eukaryotic organisms that includes microorganisms such as yeasts and molds. These organisms are classified as kingdom Fungi, separate from plants, animals, and bacteria. Fungi have a worldwide distribution and cangrow in a wide range of habitats, including extreme environments such as deserts or areas with high salt concentrations or ionizing radiation, as well as in deep sea sediments. Most fungi are inconspicuous because of the small size of their structures and their cryptic lifestyles in soil, on dead matter, and as symbionts of plants, animals, or other fungi. Fungi perform an essential role in the decomposition of organic matter and have fundamental roles in nutrient cycling and exchange. Many fungal species produce bioactive compounds called mycotoxins, such as alkaloids and polyketides that are toxic to animals including humans, contributing to pathogenecity and disease.

The study of pathogenic fungi is referred to as a medical mycology. There are various examples of pathogenic fungi including but not limited too: Candida species, Aspergillosis, Cryptococcus, Histoplasma, Pneumocystis and Stachybotrys.

Candida species are commonly known to cause opportunist infections in immunocompromised hosts. The immunocompromised hosts that commonly become infected with Candida include transplant patients, cancer patients and AIDS sufferers. Candida infections are difficult to treat and can result in systemic infections leading to death.

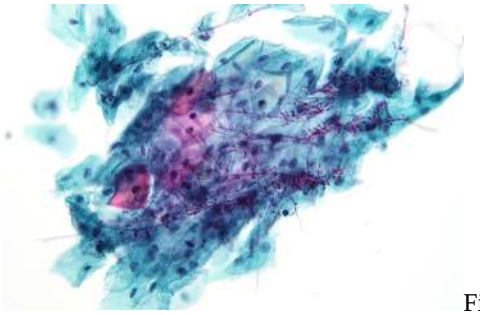


Figure: **Candida**: A Candida infection seen from a pap test specimen.

One of the most commons fungal pathogenic species includes Aspergillus strains, specifically Aspergillus fumigatus and Aspergillus flavus. Aspergillus can cause disease via production of mycotoxins, induction of allergic responses and through localized or systemic infections. Aspergillus flavus specifically produces aflatoxin which is both a toxin and carcinogen whereas Aspergillus fumigatus causes allergic disease. Symptoms of diseases caused by Aspergillus can include fever, cough, chest pain or breathlessness.

Cryptococcus neoformans causes severe forms of meningitis and meningo-encephalitis in patients with HIV infection and AIDS. Cryptococcus species live in the soil and do not cause disease in humans thus, Cryptococcus neoformans is the major pathogen in both human and animals.

Histoplasma capsulatum results in the formation of histoplasmosis in humans, dogs and cats. This specific fungus is endemic in certain areas of the United States and infection is due to inhaling contaminated air.

Pneumocystis jirovecii results in the formation of pneumonia in individuals with weakened immune systems including premature children, the elderly and AIDS patients.

Stachybotrys chartarum, also referred to as black mold, causes respiratory damage and severe headaches. This type of black mold frequently occurs in households that are chronically damp.

Key Points

- There are various examples of pathogenic fungi including but not limited too: Candida species, Aspergillosis, Cryptococcus, Histoplasma, Pneumocystis and Stachybotrys.

- Many fungal species produce bioactive compounds called mycotoxins, such as alkaloids and polyketides that are toxic to animals including humans, contributing to pathogenecity and disease.
- The study of pathogenic fungi is referred to as a medical mycology.

Key Terms

- **symbiont**: An organism that lives in a symbiotic relationship; a symbiote.
- **mycotoxin**: Any substance produced by a mold or fungus that is injurious to vertebrates upon ingestion, inhalation, or skin contact.
- **opportunist**: when an organism takes advantage of any opportunity to advance its own situation.

This page titled 2.5A: Fungi is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **14.6A: Fungi** is licensed CC BY-SA 4.0.

2.5B: Protozoa

Learning Objectives

- Compare and contrast the proliferative and dormant stages in pathogenic protozoa and the diseases protazoa cause

Protozoa (or protozoans) are a diverse group of unicellular eukaryotic organisms, many of which are motile. Originally, protozoa had been defined as unicellular protists with animal-like behavior (e.g., movement). Protozoa were regarded as the partner-group of protists to protophyta, which have plant-like behavior (e.g., photosynthesis). In general, protozoa are referred to as animal-like protists because they are capable of movement, or *motile*. While there is no exact definition for the term protozoa, it often refers to a unicellular heterotrophic protist, such as the amoebas and ciliates.

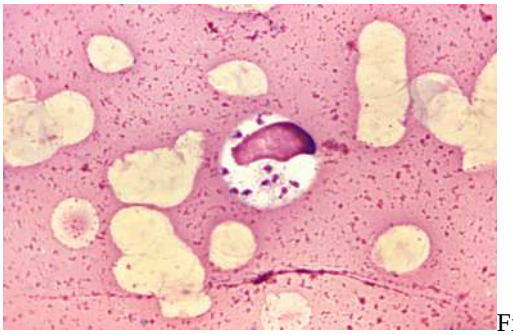


Figure: **Leishmania donovani**: Leishmania donovani, (a species of protozoa) in a bone marrow cell.

Protozoa can display pathogenicity and are the cause of various diseases. The life stages of these protozoa play a major role in their ability to function as pathogens and infect various hosts. Some protozoa have life stages alternating between proliferative stages (e.g., trophozoites) and dormant cysts. As cysts, protozoa can survive harsh conditions, such as exposure to extreme temperatures or harmful chemicals, or long periods without access to nutrients, water, or oxygen for a period of time. The ability of protozoa to thrive under extreme environments contributes to their ability to evade immune system responses, drug therapies and survive for prolonged periods of time before infection. Being a cyst enables parasitic species to survive outside of a host, and allows their transmission from one host to another. When protozoa are in the form of trophozoites they actively feed. The conversion of a trophozoite to cyst form is known as encystation, while the process of transforming back into a trophozoite is known as excystation.

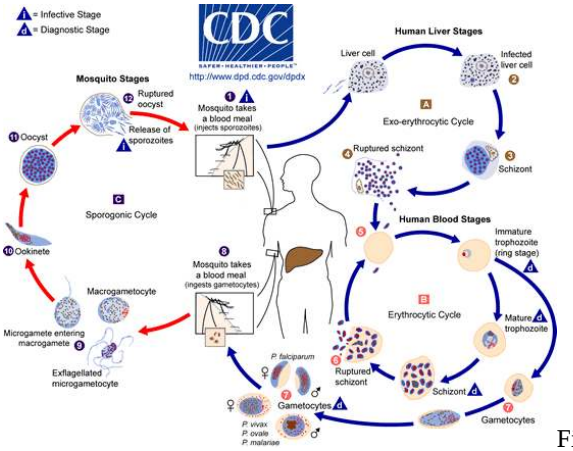


Figure: **Malaria Life Cycle**: Example of a life cycle promoting pathogenicity of a protozoa, specifically the malaria parasite.

Protozoa such as the malaria parasites (Plasmodium spp.), trypanosomes, and leishmania are also important as parasites and symbionts of multicellular animals. Examples of human diseases caused by protozoa are: malaria, amoebiasis, giardiasis, toxoplasmosis, cryptosporidiosis, trichomoniasis, Chagas disease, leishmaniasis, and dysentery. The life cycle of protozoan are successful based on successful transmission between hosts and host and environment. Infection and disease by protozoan parasites

are often times associated with developing countries with poor hygiene and sanitation conditions that may promote transmission of these protozoa.

Key Points

- Examples of human diseases caused by protozoa are: malaria, amoebiasis, giardiasis, toxoplasmosis, cryptosporidiosis, trichomoniasis, Chagas disease, leishmaniasis, and dysentery.
- The life stages of these protozoa play a major role in their ability to function as pathogens and infect various hosts.
- Protozoa were regarded as the partner-group of protists to protophyta, which have plant-like behavior (e.g., photosynthesis). In general, protozoa are referred to as animal-like protists because they are capable of movement, or motile.
- Some protozoa are human parasites, causing diseases.

Key Terms

- **trophozoite**: A protozoan in the feeding stage of its life cycle.
- **protozoa**: Protozoa are a diverse group of unicellular eukaryotic organisms, many of which are motile. Originally, protozoa had been defined as unicellular protists with animal-like behavior, e.g., movement. Protozoa were regarded as the partner group of protists to protophyta, which have plant-like behavior, e.g., photosynthesis.
- **dormant cyst**: A resting or dormant stage of a microorganism
- **cyst**: a pouch or sac without opening, usually membranous and containing morbid matter, which develops in one of the natural cavities or in the substance of an organ

---

This page titled 2.5B: Protozoa is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **14.6B: Protozoa** is licensed CC BY-SA 4.0.

2.5C: Helminths

Learning Objectives

- List the four groups of parasitic worms (helminths), routes of transmission and risk factors

Parasitic worms, often referred to as helminths, are a division of eukaryotic parasites. They are worm-like organisms that live and feed off of living hosts, receiving nourishment and protection while disrupting the nutrient absorption of their hosts, which causes weakness and disease. Those that live inside the digestive tract are called intestinal parasites. They can live inside humans as well as other animals.


Figure: **Hookworms**: The hookworms attached to the intestinal mucosa.

Parasitic worms belong to four groups:

- Monogeneans
- Cestodes (tapeworms)
- Nematodes (roundworms)
- Trematodes (flukes)

Helminths often find their way into a host through contaminated food or water, soil, mosquito bites, and even sexual acts. Poorly washed vegetables eaten raw may contain eggs of nematodes such as Ascaris, Enterobius, Thichuris, and or cestodes such as Taenia, Hymenolepis, and Echinococcus. Plants may also be contaminated with fluke metacercaria, such as Fasciola. Schistosomes and nematodes such as hookworms (Ancylostoma an Necator) and Strongyloides can penetrate the skin. Finally, Wuchereria, Onchocerca, and Dracunculus are transmitted by mosquitoes and flies.

Populations in the developing world are at particular risk for infestation with parasitic worms. Risk factors include the following:

- Inadequate water treatment
- Use of contaminated water for drinking, cooking, washing food, and irrigation
- Undercooked food of animal origin
- Walking barefoot

Simple measures—such as use of shoes, soaking vegetables with 1.5% bleach, adequate cooking of foods (not microwaving), and sleeping under mosquito-proof nets—can have a strong impact on prevention.

Response to worm infection in humans is a Th2 response in the majority of cases. Inflammation of the gut may also occur, resulting in cyst-like structures forming around the egg deposits throughout the body. The host's lymphatic system is also increasingly taxed the longer helminths propagate, as they excrete toxins after feeding. These toxins are released into the intestines and absorbed by the host's bloodstream, making the host susceptible to more common diseases such as seasonal viruses and bacterial infections.

Parasitic worms have been used as a medical treatment for various diseases, particularly those involving an overactive immune response. As humans have evolved with parasitic worms, proponents argue that they are needed for a healthy immune system. Scientists are looking to see if there is a connection between the prevention and control of parasitic worms and the increase in allergies such as hay-fever in developed countries. Parasitic worms may be able to damp down the immune system of their host,

making it easier for them to live in the intestine without coming under attack. This may be one mechanism for their proposed medicinal effect.

Key Points

- Helminths are worm-like organisms that live and feed off of living hosts, receiving nourishment and protection while disrupting the nutrient absorption of their hosts, which causes weakness and disease.
- Helminths that live inside the digestive tract are called intestinal parasites.
- Helminths often find their way into a host through contaminated food or water, soil, mosquito bites, and sexual acts.
- Response to worm infection in humans is a Th2 response in the majority of cases.

Key Terms

- **helminth**: A parasitic roundworm or flatworm.
- **lymphatic system**: In mammals, including humans, a network of lymph vessels and lymph nodes that transport fluid, fats, proteins, and lymphocytes to the bloodstream as lymph, and remove microorganisms and other debris from tissues.

This page titled 2.5C: Helminths is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **14.6C: Helminths** is licensed CC BY-SA 4.0.

2.5D: Algae

Learning Objectives

- Discuss the various types of pathogenic algae



Figure: **Cephaleuros virescens**: Infestation of the algal leaf spot (Cephaleuros virescens) on ther southern magnolia (Magnolia grandiflora); Green-orange algal spots or “green scruf” on leaf surface. The grayish-white and darker “crusts” are lichens of the genus Strigula resulting from fungal colonization of the alga.

Algae, are not normally considered common pathogens. Algal blooms are often associated with negative impacts on humans and the surrounding environment in which they occur. A harmful algal bloom (HAB) is an algal bloom that causes negative impacts to other organisms via production of natural toxins, mechanical damage to other organisms, or by other means. HABs are often associated with large-scale marine mortality events and have been associated with various types of shellfish poisonings. However, the damage to other organisms is not due to the algae infecting a host but rather indirectly excreting a toxin, or in some cases blocking out light or competing for resources.

However notable examples of algae acting as pathogens are known. For example Cephaleuros which is a genus of parasitic thalloid alga comprising approximately 14 species. Its common name is red rust. Chrooderma is its basionym. Specimens can reach around 10 mm in size. Dichotomous branches are formed. The alga is parasitic on some important economic plants of the tropics and subtropics such as tea, coffee, mango and guava causing damage limited to the area of algal growth on leaves (algal leaf spot), or killing new shoots, or disfiguring fruit. Members of the genera may also grow with a fungus to form a lichen that does not damage the plants.

Examples of algae acting as a mammalian pathogen are known as well, notably the disease Protothecosis. Protothecosis is a disease found in dogs, cats, cattle, and humans caused by a type of green alga known as Prototheca that lacks chlorophyll. It and its close relative Helicosporidium are unusual in that they are actually green algae that have become parasites.The two most common species are Prototheca wickerhamii and Prototheca zopfii. Both are known to cause disease in dogs, while most human cases are caused by P. wickerhami. Prototheca is found worldwide in sewage and soil. Infection is rare despite high exposure, and can be related to a defective immune system. In dogs, females and Collies are most commonly affected. The first human case was identified in 1964 in Sierra Leone.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: ***CC BY-SA: Attribution-ShareAlike***

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- Fungi. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Fungi**. **License**: ***CC BY-SA: Attribution-ShareAlike***

- Pathogenic fungi. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Pathogenic_fungi**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- opportunist. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/opportunist**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- mycotoxin. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/mycotoxin**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- symbiont. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/symbiont**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Candida pap 1. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Candida_pap_1.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Protozoa. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Protozoa**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- cyst. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/cyst**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- trophozoite. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/trophozoite**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- dormant cyst. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/dormant%20cyst**. **License**: *CC BY-SA: Attribution-ShareAlike*
- protozoa. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/protozoa**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Candida pap 1. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Candida_pap_1.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- CDC - Malaria - About Malaria - Biology. **Provided by**: Centers for Disease Control and Prevention. **Located at**: **http://www.cdc.gov/malaria/about/biology/**. **License**: ***Public Domain: No Known Copyright***
- Leishmania donovani 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Le...onovani_01.png**. **License**: ***Public Domain: No Known Copyright***
- Helminthes. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Helminthes**. **License**: *CC BY-SA: Attribution-ShareAlike*
- helminth. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/helminth**. **License**: *CC BY-SA: Attribution-ShareAlike*
- lymphatic system. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/lymphatic_system**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Candida pap 1. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Candida_pap_1.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- CDC - Malaria - About Malaria - Biology. **Provided by**: Centers for Disease Control and Prevention. **Located at**: **http://www.cdc.gov/malaria/about/biology/**. **License**: ***Public Domain: No Known Copyright***
- Leishmania donovani 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Le...onovani_01.png**. **License**: ***Public Domain: No Known Copyright***
- Hookworms. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Hookworms.JPG**. **License**: *Public Domain: No Known Copyright*
- Protothecosis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Protothecosis**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Cephaleuros. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Cephaleuros**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Cephaleuros virescens01. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Cephaleuros_virescens01.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Protothecosis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Protothecosis**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Algal bloom. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Algal_bloom**. **License**: *CC BY-SA: Attribution-ShareAlike*
- thalloid. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/thalloid**. **License**: *CC BY-SA: Attribution-ShareAlike*

- alga. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/alga**. **License**: *CC BY-SA: Attribution-ShareAlike*
- basionym. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/basionym**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Candida pap 1. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Candida_pap_1.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- CDC - Malaria - About Malaria - Biology. **Provided by**: Centers for Disease Control and Prevention. **Located at**: **http://www.cdc.gov/malaria/about/biology/**. **License**: *Public Domain: No Known Copyright*
- Leishmania donovani 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Leishmania_donovani_01.png**. **License**: *Public Domain: No Known Copyright*
- Hookworms. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Hookworms.JPG**. **License**: *Public Domain: No Known Copyright*
- Cephaleuros virescens01. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...irescens01.jpg**. **License**: *CC BY: Attribution*

Key Points

- While algal blooms can lead to negative consequences, the effect of an algal bloom are often indirect, the alga is not directly infecting a host.
- Cephaleuros are a genus of parasitic alga which infect plants, causing red rust, which affects many commercial crops that humans consume.
- Prototheca are a type of green alga that lack chlorophyll, that can infect mammals including humans causing the disease protothecosis.
- To some degree the distribution of algae is subject to floristic discontinuities caused by geographical features, such as Antarctica, long distances of ocean, or general land masses.

Key Terms

- **thalloid**: Of a plant, alga, or fungus lacking complex organization, especially lacking distinct stems, roots, or leaves.
- **alga**: any of many aquatic photosynthetic organisms, whose size ranges from a single cell to giant kelps and whose form is very diverse
- **basionym**: An earlier valid scientific name of a species that has since been renamed and from which the new name is partially derived.

This page titled 2.5D: Algae is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **14.6D: Algae** is licensed CC BY-SA 4.0.

CHAPTER OVERVIEW

3: Bacteria

3.1: Clostridium tetani
3.2: Escherichia coli
3.3: Haemophilus influenzae
3.4: Helicobacter pylori
3.5: Neisseria gonorrhoeae
3.6: Neisseria meningitidis
3.7: Staphylococcus aureus
3.8: Streptococcus pneumoniae
3.9: Streptococcus pyogenes
3.10: Vibrio cholerae

This page titled 3: Bacteria is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

This page titled 3: Bacteria is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

3.1: Clostridium tetani

Organism

- *Clostridium tetani* is a moderately-sized Gram-positive, endospore-producing bacillus.
- Motile with a peritrichous arrangement of flagella.
- Produce round, terminal endospores that give the bacterium a "tennis-racquet" appearance.
- An obligate anaerobe*(def)*.

Habitat

- Colonizes the intestinal tract in humans and animals.

Source

- Endospores found in fertile soil or feces.

Epidemiology

- Endospores are found in most soils and in the intestinal tract of many animals and humans.
- Although exposure to endospores is commom, disease is uncommon except in countries with poor medical care and vaccination compliance.
- Fewer than 50 cases per year in the U.S.; most in elderly individuals with waning immunity.
- It is estimated that there is more than one million cases a year worldwide, with a mortality rate of 20% to 50%.
- Most deaths occur in neonates and originates from infection of umbilical stumps in mothers that have no immunity.

Clinical Disease

- Generalized tetanus is most common. Typical presenting symptoms include lockjaw and sardonic smile, arrising as a result of spastic paralysis of the masseter muscles and other facial muscles. Difficulty in swallowing, drooling, irritability, and persistent back spasms are other early symptoms. When the autonomic nervous system is involved, symptoms include perfuse sweating, hyperthermia , cardiac arrhythmias , and fluctuations in blood pressure.
- Cephalic infection primarily infects the head and involves cranial nerves.
- Localized infection involves the muscles in the area of primary injury.
- Neonatal tetanus is in newborns and originates from infection of umbilical stumps in mothers that have no immunity.
- The infection begins when endospores of *C. tetani* enter an anaerobic wound . Since the bacterium is an obligate anaerobe, an anaerobic environment is needed for the endospores to germinate and the vegetative bacteria to grow. Vegetative bacteria eventually produce tetanospasmin, the toxin responsible for symptoms of tetanus.

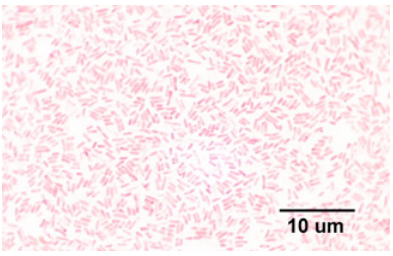
** CDC Recommendations for tetanus prophylaxis.

From Tetanus, by Daniel J Dire, MD, FACEP, FAAEM, Associate Professor, Department of Emergency Medicine, University of Alabama at Birmingham and Daniel J Dire, MD, FACEP, FAAEM, is a member of the following medical societies: American Academy of Clinical Toxicology, American Academy of Emergency Medicine, Association of Military Surgeons of the US, and Society for Academic Emergency Medicine

---

This page titled 3.1: Clostridium tetani is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

3.2: Escherichia coli



Gram Stain of *Escherichia coli*. Note gram-negative (pink) bacilli.

This page titled 3.2: Escherichia coli is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

3.3: Haemophilus influenzae

Organism

- *Haemophilus influenzae* is a small Gram-negative bacillus.
- It is nonmotile.
- Facultative anaerobe *(def)*.
- Fastideous growth needs. Requires enrichments for growth.

Habitat

- Mucous membranes of the respiratory tract in humans.

Source

- The patient's own mucous membranes or transmitted patient-to-patient.

Epidemiology

- *Haemophilus parainfluenzae* and nonencapsulated *H. influenzae* typically colonize the upper respiratory tract in humans within the first few months of life. These bacteria typically cause sinusitis, otitis media *(def)*, bronchitis*(def)*, and pneumonia *(def)*.
- Encapsulated *H. influenzae*, primarily *H. influenzae* type b, is uncommon as normal flora of the upper respiratory tract but can be a common cause of serious infection in children.
- Until immunization of children against *H. influenzae* type b became routine in developed countries, this bacterium was the most common cause of pneumonia, septicemia*(def)*, meningitis *(def)*, and epiglottitis *(def)* in children under the age of four. Immunization has reduced the incidence of systemic infection by this bacterium 95%.

Clinical Disease

- *Haemophilus influenzae* does not cause influenza. Influenza is a viral infection.
- *Haemophilus parainfluenzae* and nonencapsulated *H. influenzae* typically cause sinusitis, otitis media *(def)*, bronchitis *(def)*, and pneumonia *(def)*.
- *H. influenzae* type b is the most common cause of pneumonia, septicemia *(def)*, meningitis *(def)*, epiglottitis *(def)*, and cellulitis in children under the age of four who are not immunized.

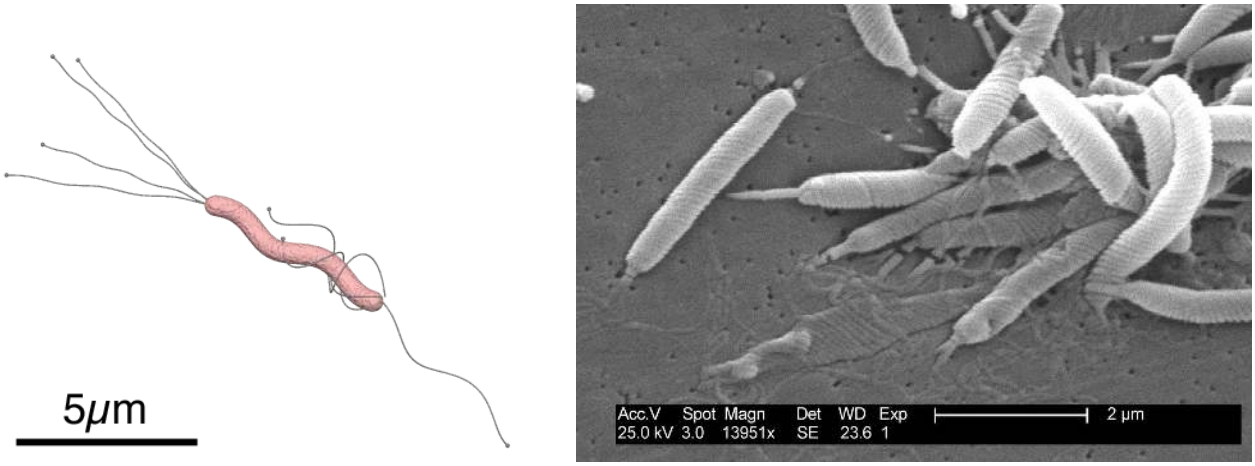
From *Haemophilus influenzae* Infections, by Mark R Schleiss, MD, Associate Professor, Department of Pediatrics, Division of Infectious Diseases, University of Cincinnati and Children's Hospital Research Foundation.

This page titled 3.3: Haemophilus influenzae is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

3.4: Helicobacter pylori

Organism

- *Helicobacter* is a gram-negative spiral-shaped bacterium with polar flagella.
- Microaerophilic *(def)*.



(left) Structure of Helicobacter pylori. (right) Scanning electron micrograph of ***Helicobacter*** *bacteria (originally classified as Flexispira rappini, now deprecated). Obtained from the CDC Public Health Image Library. Image credit: CDC/Dr. Patricia Fields, Dr. Collette Fitzgerald (PHIL #5715), 2004.*

Habitat

- The human gastrointestinal tract is the primary source.

Source

- Person-to-person spread by the fecal-oral route.

Epidemiology

- In developing countries, 70%-90% of individuals are colonized by the age of 10; in developed countries, colonization is low during children but increases to around 45% in older adults.
- Between 70% and 90% of people with gastritis, peptic ulcers, or doedonal ulcers are infected with *H. pylori*.

Clinical Disease

- Appears as gastritis *(def)*, peptic ulcers *(def)*, gastric adenocarcinoma *(def)*, and certain B-cell lymphomas *(def)*.
- Chronic gastritis is a risk factor for gastric carcinoma.

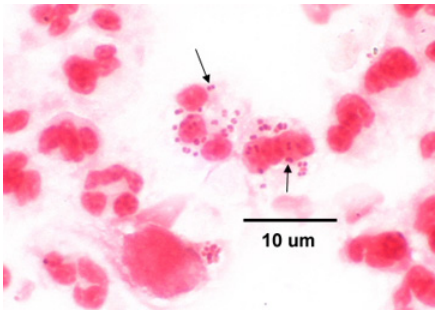
From *Helicobacter pylori* Infection, by Luigi Santacroce, MD, Assistant Professor, Department of Dentistry and Surgery, Section of General Surgery, Medical and Dentistry School, State University at Bari, Italy and Giuseppe Miragliotta, MD, Chairman, Professor, Section of Microbiology, University Hospital of Bari, Italy; Manoop S Bhutani, MD, Associate Professor of Medicine, Division of Gastroenterology, University of Texas Medical Branch at Galveston

This page titled 3.4: Helicobacter pylori is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

This page titled 3.4: Helicobacter pylori is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

3.5: Neisseria gonorrhoeae

Positive GC smear for gonorrhea.



Note the *Neisseria gonorrhoeae* (gram-negative diplococci) inside the white blood cells.

This page titled 3.5: Neisseria gonorrhoeae is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

3.6: Neisseria meningitidis

Organism

- *Neisseria meningitidis* is a Gram-negative diplococcus, typically flattened where the cocci meet.
- Aerobic *(def)*.
- There are 13 serogroups of meningococci. Serogroups B and C commonly cause meningitis *(def)* and meningococcemia *(def)* in developed countries; serogroups Y and W135 typically cause pneumonia.

Habitat

- Humans are the only natural host.

Source

- Transmitted person-to-person by aerosolized respiratory tract secretions.

Clinical Disease

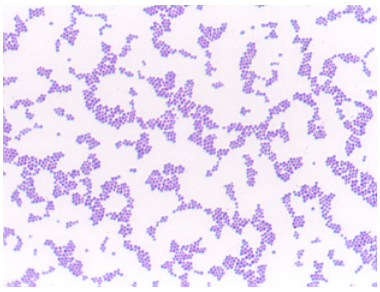
- There are between 2000 and 3000 cases of meningococcal meningitis per year in the U.S. A total of 2725 cases were reported to CDC in 1998.
- *N. meningitidis* infects the nasopharynx of humans causing a usually mild or subclinical upper respiratory infection. However in about 15% of these individuals, the organism invades the blood and disseminates, causing septicemia and from the there may cross the blood-brain barrier causing meningitis *(def)*. A petechial skin rash, caused by endotoxin in the blood, appears in about 75 percent of the septic cases and fatality rates for meningococcal septicemia are as high as 30 percent as a result of the shock cascade. A fulminating form of the disease, called Waterhouse-Frederichsen syndrome, can be fatal within several hours due to massive intravascular coagulation and resulting shock, probably a result of massive endotoxin release. *N. meningitidis* is especially dangerous in young children.
- Typical symptoms are headache, meningeal signs, and fever.
- Mortality is close to 100% if untreated; less than 10% with prompt and appropriate antibiotic therapy.

From Meningococcal Infections, by Thomas A Hoffman, MD, Professor, Department of Internal Medicine, Division of Infectious Diseases, Jackson Memorial Hospital, University of Miami.

This page titled 3.6: Neisseria meningitidis is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

3.7: Staphylococcus aureus

Gram Stain of *Staphylococcus aureus*



Note gram-positive (purple) cocci in clusters.

This page titled 3.7: Staphylococcus aureus is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

3.8: Streptococcus pneumoniae

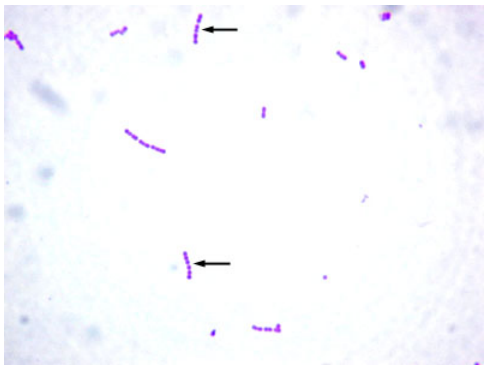
Streptococcus pneumoniae, or the pneumococcus, is a gram-positive lanceolate coccus usually appearing as a diplococcus, but occasionally appearing singularly or in short chains. Pneumococci are frequently found as normal flora of the nasopharynx of healthy carriers. From 10% to 40% of adults carry the bacterium in the nasopharynx. In the U.S., they are the most common cause of community-acquired pneumonia requiring hospitalization, causing around 500,000 cases per year and usually occurring as a secondary infection in the debilitated or immunocompromised host. The pneumococci also cause over 7,000,000 cases of otitis media per year, are the leading cause of sinusitis in people of all ages, are responsible for 500,000 cases of bacteremia, and 3000 cases of meningitis, being the most common cause of meningitis in adults and children over 4 years of age. Note gram-positive encapsulated diplococci. The large cells with the dark red nuclei are while blood cells.



Encapsulated Streptococcus pneumoniae. Encapsulated Streptococcus pneumoniae. © Gloria Delisle and Lewis Tomalty, authors. Licensed for use, ASM MicrobeLibrary.

This page titled 3.8: Streptococcus pneumoniae is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

3.9: Streptococcus pyogenes



Note gram-positive (purple) cocci in chains (arrows).

Organism

- *Streptococcus pyogenes*, a group A beta streptococcus, is a Gram-positive coccus typically arranged in chains.
- Facultative anaerobe *(def)*.

Habitat

- Asymptomatic colonization of the upper respiratory tract in humans.

Source

- Pharyngitis is pread person to person primarily by respiratory droplets; skin infections are spread by direct contact with an infected person or through fomites *(def)*.

Epidemiology

- The group A beta hemolytic streptococci are responsible for most acute human streptococcal infections. Between 5% and 20% of children are asymptomatic carriers. The most common infection is pharyngitis *(def)* with the organism usually being limited to the mucous membranes and lymphatic tissue of the upper respiratory tract. Children are at greatest risk for infection.

Clinical Disease

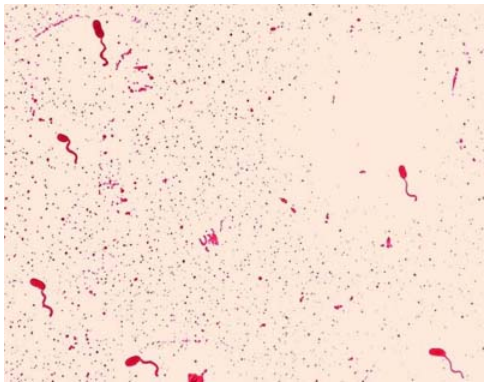
- The most common infection is pharyngitis (streptococcal sore throat) with the organism usually being limited to the mucous membranes and lymphatic tissue of the upper respiratory tract. From the pharynx, however, the streptococci sometimes spread to other areas of the respiratory tract resulting in laryngitis *(def)*, bronchitis *(def)*, pneumonia, and otitis media *(def)*.
- Occasionally, it may enter the lymphatic vessels or the blood and disseminate to other areas of the body, causing septicemia *(def)*, osteomyelitis *(def)*, endocarditis*(def)*, septic arthritis *(def)*, and meningitis *(def)*.
- If it enters injured skin, it may cause pyogenic *(def)* cutaneous infections such as impetigo , erysipelas *(def)*, orcellulitis *(def)*.

- Group A beta streptococcus infections can result in two autoimmune diseases *(def)*, rheumatic fever and acute glomerulonephritis, where antibodies made against streptococcal antigens cross react with joint membranes and heart valve tissue in the case of rheumatic fever, or glomerular cells and basement membranes of the kidneys in the case of acute glomerulonephritis.
- Certain strains of *S. pyogenes* cause invasive group A beta streptococcal infections. Each year in the U.S. there are between 750 and 1500 cases of necrotizing fasciitis where a streptococcal-coded protease called Exotoxin B destroys the muscle (myositis) or the muscle covering (necrotizing fasciitis). There are another 750 - 1500 cases of toxic shock-like syndrome *(def)* due to group A beta streptococci producing Streptococcal pyrogenic exotoxin (Spe).

From Streptococcus Group A Infections, by Sat Sharma, MD, FRCPC, FACP, FCCP, DABSM, Program Director, Associate Professor, Department of Internal Medicine, Divisions of Pulmonary and Critical Care Medicine, University of Manitoba; Site Coordinator of Respiratory Medicine, St Boniface General Hospital; and Godfrey Harding, MD, FRCPC, Program Director of Medical Microbiology, Professor, Department of Medicine, Section of Infectious Diseases and Microbiology, St Boniface Hospital, University of Manitoba, Canada.

This page titled 3.9: Streptococcus pyogenes is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

3.10: Vibrio cholerae



Monotrichous Flagellum of Vibrio cholerae. Courtesy of the Centers for Disease Control and Prevention.

This page titled 3.10: Vibrio cholerae is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

4: Culturing Bacteria

This page titled 4: Culturing Bacteria is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **6.3: Culturing Bacteria** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

4.1: Culture Media

Learning Objectives

- Classify culture media

Culture medium or growth medium is a liquid or gel designed to support the growth of microorganisms. There are different types of media suitable for growing different types of cells. Here, we will discuss microbiological cultures used for growing microbes, such as bacteria or yeast.

NUTRIENT BROTHS AND AGAR PLATES

These are the most common growth media, although specialized media are sometimes required for microorganism and cell culture growth. Some organisms, termed fastidious organisms, need specialized environments due to complex nutritional requirements. Viruses, for example, are obligate intracellular parasites and require a growth medium containing living cells. Many human microbial pathogens also require the use of human cells or cell lysates to grow on a media.

The most common growth media nutrient broths (liquid nutrient medium) or LB medium (Lysogeny Broth) are liquid. These are often mixed with agar and poured into Petri dishes to solidify. These agar plates provide a solid medium on which microbes may be cultured. They remain solid, as very few bacteria are able to decompose agar. Many microbes can also be grown in liquid cultures comprised of liquid nutrient media without agar.



Figure: **Microbial pathogen growing on blood-agar plate**: Red blood cells are used to make an agar plate. Different pathogens that can use red blood cells to grow are shown on these plates. On the left is staphylococcus and the right streptococcus.

DEFINED VS UNDEFINED MEDIA

This is an important distinction between growth media types. A *defined* medium will have known quantities of all ingredients. For microorganisms, it provides trace elements and vitamins required by the microbe and especially a defined carbon and nitrogen source. Glucose or glycerol are often used as carbon sources, and ammonium salts or nitrates as inorganic nitrogen sources. An *undefined* medium has some complex ingredients, such as yeast extract, which consists of a mixture of many, many chemical species in unknown proportions. Undefined media are sometimes chosen based on price and sometimes by necessity – some microorganisms have never been cultured on defined media.

There are many different types of media that can be used to grow specific microbes, and even promote certain cellular processes; such as wort, the medium which is the growth media for the yeast that makes beer. Without wort in certain conditions, fermentation cannot occur and the beer will not contain alcohol or be carbonated (bubbly).

COMMON BROADLY-DEFINED CULTURE MEDIA

Nutrient media – A source of amino acids and nitrogen (e.g., beef, yeast extract). This is an undefined medium because the amino acid source contains a variety of compounds with the exact composition being unknown. These media contain all the elements that most bacteria need for growth and are non-selective, so they are used for the general cultivation and maintenance of bacteria kept in laboratory-culture collections.

Minimal media – Media that contains the minimum nutrients possible for colony growth, generally without the presence of amino acids, and are often used by microbiologists and geneticists to grow "wild type" microorganisms. These media can also be used to select for or against the growth of specific microbes. Usually a fair amount of information must be known about the microbe to determine its minimal media requirements.

Selective media – Used for the growth of only selected microorganisms. For example, if a microorganism is resistant to a certain antibiotic, such as ampicillin or tetracycline, then that antibiotic can be added to the medium in order to prevent other cells, which do not possess the resistance, from growing.

Differential media – Also known as indicator media, are used to distinguish one microorganism type from another growing on the same media. This type of media uses the biochemical characteristics of a microorganism growing in the presence of specific nutrients or indicators (such as neutral red, phenol red, eosin y, or methylene blue) added to the medium to visibly indicate the defining characteristics of a microorganism. This type of media is used for the detection and identification of microorganisms.

These few examples of general media types provide some indication only; there are a myriad of different types of media that can be used to grow and control microbes.

Key Points

- Culture media contains the nutrients needed to sustain a microbe.
- Culture media can vary in many ingredients allowing the media to select for or against microbes.
- Glucose or glycerol are often used as carbon sources, and ammonium salts or nitrates as inorganic nitrogen sources in culture media.

Key Terms

- **culture**: The process of growing a bacterial or other biological entity in an artificial medium.
- **lysogeny broth**: Lysogeny broth (LB) is a nutritionally-rich medium; primarily used for the growth of bacteria.

This page titled 4.1: Culture Media is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **6.3A: Culture Media** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

4.2: Complex and Synthetic Media

Learning Objectives

- Differentiate complex and synthetic medias

There are many types of culture media, which is food that microbes can live on. Two major sub types of media are complex and synthetic medias, known as undefined and defined media.



Figure: **Undefined Media**: Luria Broth as shown here is made with yeast extract, as yeast extract is not completely chemically defined Luria Broth is therefore an undefined media. By Lilly_M [GFDL (http://www.gnu.org/copyleft/fdl.html), CC-BY-SA, via Wikimedia Commons

An undefined medium has some complex ingredients, such as yeast extract or casein hydrolysate, which consist of a mixture of many, many chemical species in unknown proportions. Undefined media are sometimes chosen based on price and sometimes by necessity – some microorganisms have never been cultured on defined media.A defined medium (also known as chemically defined medium or synthetic medium) is a medium in which all the chemicals used are known, no yeast, animal, or plant tissue is present. A chemically defined medium is a growth medium suitable for the culture of microbes or animal cells (including human) of which all of the chemical components are known. The term chemically defined medium was defined by Jayme and Smith as a 'Basal formulation which may also be protein-free and is comprised solely of biochemically-defined low molecular weight constituents.

A chemically defined medium is entirely free of animal-derived components (including microbial derived components such as yeast extract) and represents the purest and most consistent cell culture environment. By definition chemically defined media cannot contain either fetal bovine serum, bovine serum albumin, or human serum albumin as these products are derived from bovine or human sources and contain complex mixes of albumins and lipids. The term 'chemically defined media' is often misused in the literature to refer to serum albumin-containing media. Animal serum or albumin is routinely added to culture media as a source of nutrients and other ill-defined factors, despite technical disadvantages to its inclusion and its high cost. Technical disadvantages to using serum include the undefined nature of serum, batch-to-batch variability in composition, and the risk of contamination. There are increasing concerns about animal suffering inflicted during serum collection that add an ethical imperative to move away from the use of serum wherever possible. Chemically defined media differ from serum-free media in that bovine serum albumin or human serum albumin with either a chemically defined recombinant version (which lacks the albumin associated lipids) or synthetic chemical such as the polymer polyvinyl alcohol which can reproduce some of the functions of serums.

Key Points

- Defined media is made from constituents that are completely understood.
- Undefined media has some part of which is not entirely defined.
- The presence of extracts from animals or other microbes makes a media undefined as the entire chemical composition of extracts are not completely known.

Key Terms

- **recombinant**: This term refers to something formed by combining existing elements in a new combination. Thus, the phrase recombinant DNA refers to an organism created in the lab by adding DNA from another species.
- **serum**: The clear yellowish fluid obtained upon separating whole blood into its solid and liquid components after it has been allowed to clot. Also called blood serum.

This page titled 4.2: Complex and Synthetic Media is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **6.3B: Complex and Synthetic Media** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

4.3: Selective and Differential Media

Learning Objectives

- Compare selective and differential media

There are many types of media used in the studies of microbes. Two types of media with similar implying names but very different functions, referred to as selective and differential media, are defined as follows.

Selective media are used for the growth of only selected microorganisms. For example, if a microorganism is resistant to a certain antibiotic, such as ampicillin or tetracycline, then that antibiotic can be added to the medium in order to prevent other cells, which do not possess the resistance, from growing. Media lacking an amino acid such as proline in conjunction with *E. coli* unable to synthesize it were commonly used by geneticists before the emergence of genomics to map bacterial chromosomes. Selective growth media are also used in cell culture to ensure the survival or proliferation of cells with certain properties, such as antibiotic resistance or the ability to synthesize a certain metabolite. Normally, the presence of a specific gene or an allele of a gene confers upon the cell the ability to grow in the selective medium. In such cases, the gene is termed a marker. Selective growth media for eukaryotic cells commonly contain neomycin to select cells that have been successfully transfected with a plasmid carrying the neomycin resistance gene as a marker. Gancyclovir is an exception to the rule as it is used to specifically kill cells that carry its respective marker, the Herpes simplex virus thymidine kinase (HSV TK). Some examples of selective media include:

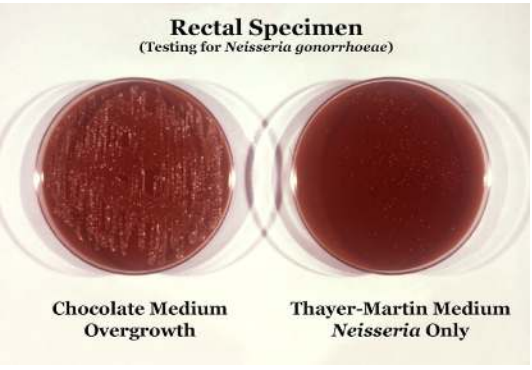


Figure: **Non-selective versus selective media.**: The non-selective media on the right allows of the growth of several different bactarial species and is overgrown with bacteria (whitish lines). While the plate on the right selectively only allows the bacteria Neisseria gonorrhoeae, to grow (white dots).

- Eosin methylene blue (EMB) that contains methylene blue – toxic to Gram-positive bacteria, allowing only the growth of Gram negative bacteria.
- YM (yeast and mold) which has a low pH, deterring bacterial growth.
- MacConkey agar for Gram-negative bacteria.
- Hektoen enteric agar (HE) which is selective for Gram-negative bacteria.
- Mannitol salt agar (MSA) which is selective for Gram-positive bacteria and differential for mannitol. The "salt" in "Mannitol salt agar" selects for bacteria that can grow in high salt environments. *Staphylococci* thrive on the medium, largely because of their adaptation to salty habitats such as human skin.
- Terrific Broth (TB) is used with glycerol in cultivating recombinant strains of Escherichia coli.
- Xylose lysine desoxyscholate (XLD), which is selective for Gram-negative bacteria buffered charcoal yeast extract agar, which is selective for certain gram-negative bacteria, especially Legionella pneumophila.

Differential media or indicator media distinguish one microorganism type from another growing on the same media. This type of media uses the biochemical characteristics of a microorganism growing in the presence of specific nutrients or indicators (such as neutral red, phenol red, eosin y, or methylene blue) added to the medium to visibly indicate the defining characteristics of a microorganism. This type of media is used for the detection of microorganisms and by molecular biologists to detect recombinant strains of bacteria. Examples of differential media include:

- Blood agar (used in strep tests), which contains bovine heart blood that becomes transparent in the presence of hemolytic.
- Streptococcuseosin methylene blue (EMB), which is differential for lactose and sucrose fermentation.

- MacConkey (MCK), which is differential for lactose fermentationmannitol salt agar (MSA), which is differential for mannitol fermentation.
- X-gal plates, which are differential for lac operon mutants.

Key Points

- Selective media generally selects for the growth of a desired organism, stopping the growth of or altogether killing non-desired organisms.
- Differential media takes advantage of biochemical properties of target organisms, often leading to a visible change when growth of target organisms are present.
- Differential media, unlike selective media, does not kill organisms. It indicates if a target organism is present.

Key Terms

- **recombinant**: This term refers to something formed by combining existing elements in a new combination. Thus, the phrase recombinant DNA refers to an organism created in the lab by adding DNA from another species.
- **gene**: A unit of heredity; a segment of DNA or RNA that is transmitted from one generation to the next. It carries genetic information such as the sequence of amino acids for a protein.
- **allele**: One of a number of alternative forms of the same gene occupying a given position on a chromosome.

This page titled 4.3: Selective and Differential Media is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **6.3C: Selective and Differential Media** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

4.4: Aseptic Technique, Dilution, Streaking, and Spread Plates

Learning Objectives

- Recall aseptic technique, dilution series, streaking and spreading plates

Microbiologists have many tools, but four relatively simple techniques are used by microbiologists daily, these are outlined here.

Aseptic technique or sterile technique is used to avoid contamination of sterile media and equipment during cell culture. Sterile technique should always be employed when working with live cell cultures and reagents/media that will be used for such cultures. This technique involves using flame to kill contaminating organisms, and a general mode of operation that minimizes exposure of sterile media and equipment to contaminants.

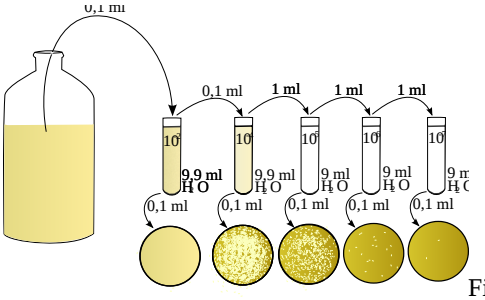


Figure: **Serial Dilution**: Example of Serial dilution of bacteria in five steps. The diluted bacteria were then spread plated. By Leberechtc (Own work) [GFDL (http://www.gnu.org/copyleft/fdl.html) and CC-BY-3.0 (http://creativecommons.org/licenses/by/3.0)], via Wikimedia Commons

When working with cultures of living organisms, it is extremely important to maintain the environments in which cells are cultured and manipulated as free of other organisms as possible. This requires that exposure of containers of sterilized culture media to outside air should be minimized, and that flame is used to "re-sterilize" container lids and rims. This means passing rims and lids through the flame produced by a Bunsen burner in order to kill microorganisms coming in contact with those surfaces.

Sterile technique, in general, is a learned state-of-being, or mantra, where every utilization of any sterile material comes with the caveat of taking every precaution to ensure it remains as free of contaminants as possible for as long as possible. Heat is an excellent means of killing microorganisms, and the Bunsen burner is the sterile technician's best friend.

A serial dilution is the step-wise dilution of a substance in solution. Usually the dilution factor at each step is constant, resulting in a geometric progression of the concentration in a logarithmic fashion. A ten-fold serial dilution could be 1 M, 0.1 M, 0.01 M, 0.001 M… Serial dilutions are used to accurately create highly-diluted solutions as well. A culture of microbes can be diluted in the same fashion. For a ten-fold dilution on a 1 mL scale, vials are filled with 900 microliters of water or media, and 100 microliters of the stock microbial solution are serially transferred, with thorough mixing after every dilution step. The dilution of microbes is very important to get to microbes diluted enough to count on a spread plate (described later).

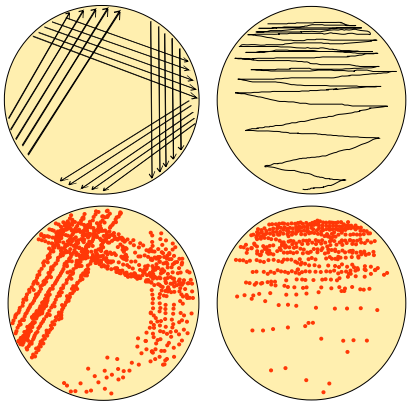


Figure: **Streak plate**: Four streak plates. Successful streaks lead to individual colonies of microbes.

https://med.libretexts.org/@go/page/77633

In microbiology, streaking is a technique used to isolate a pure strain from a single species of microorganism, often bacteria. Samples can then be taken from the resulting colonies and a microbiological culture can be grown on a new plate so that the organism can be identified, studied, or tested.The streaking is done using a sterile tool, such as a cotton swab or commonly an inoculation loop. This is dipped in an inoculum such as a broth or patient specimen containing many species of bacteria.The sample is spread across one quadrant of a petri dish containing a growth medium, usually an agar plate which has been sterilized in an autoclave. Choice of which growth medium is used depends on which microorganism is being cultured, or selected for. Growth media are usually forms of agar, a gelatinous substance derived from seaweed.

Spread plates are simply microbes spread on a media plate. Microbes are in a solution, and can be diluted. They are then transferred to a petri dish with media specific for the growth of the microbe of interest. The solution is then spread uniformly through a number of possible means, the most popular is the use of sterile glass beads that are shook on top of the media, spreading the microbe-containing liquid evenly on the plate. Also common is the use of a bent-glass rod, often referred to as a hockey stick, due to its similar shape. The glass rod is sterilized and used to spread the microbe-containing liquid uniformly on the plate.

Key Points

- Aseptic technique is basically the mindset of keeping things free of contamination, as the world we live in has so many microbes that can interfere with experiments.
- Colony streaking leads to to the isolation of individual colonies, which are a group of microbes that came from one single progenitor mircrobe.
- Spread plates allow for the even spreading of bacteria onto a petri dish; allowing for the isolation of individual colonies, for counting or further experiments.

Key Terms

- **colony**: A bacterial colony is defined as a visible cluster of bacteria growing on the surface of or within a solid medium, presumably cultured from a single cell.
- **bunsen burner**: A small laboratory gas burner whose air supply may be controlled with an adjustable hole.

This page titled 4.4: Aseptic Technique, Dilution, Streaking, and Spread Plates is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **6.3D: Aseptic Technique, Dilution, Streaking, and Spread Plates** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

4.5: Special Culture Techniques

Learning Objectives

- Evaluate special culture techniques

Microbiologists would prefer to use well-defined media to grow a microbe, making the microbe easier to control. However, microbes are incredibly varied in what they use as a food source, the environments they live in, and the danger levels they may have for humans and other organisms they may compete with. Therefore they need special nutrient and growth environments. To grow these difficult microbes, microbiologists often turn to undefined media which is chosen based on price and more-so in this case by necessity as some microorganisms have never been cultured on defined media. Some special culture conditions are relatively simple as demonstrated by microaerophile.

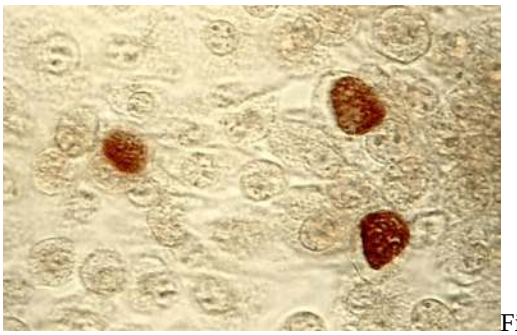
A microaerophile is a microorganism that requires oxygen to survive, but requires environments containing lower levels of oxygen than are present in the atmosphere (~20% concentration). Many microphiles are also capnophiles, as they require an elevated concentration of carbon dioxide. In the laboratory they can be easily cultivated in a candle jar. A candle jar is a container into which a lit candle is introduced before sealing the container's airtight lid. The candle's flame burns until extinguished by oxygen deprivation, which creates a carbon dioxide-rich, oxygen-poor atmosphere in the jar. Many labs also have access directly to carbon dioxide and can add the desired carbon dioxide levels directly to incubators where they want to grow microaerophiles.



Figure: ***Candle jar****: A candle is lit in a jar with a culture plate. The lid is put on, as the burns it increases the carbon dioxide levels in the jar.*

Animals can often be used to culture microbes. For example, armadillos are often used in the study of leprosy. They are particularly susceptible due to their unusually low body temperature, which is hospitable to the leprosy bacterium, Mycobacterium leprae. The leprosy bacterium is difficult to culture and armadillos have a body temperature of 34°C, similar to human skin. Likewise, humans can acquire a leprosy infection from armadillos by handling them or consuming armadillo meat. Additionally, Syphillis which is caused by the bacteria *Treponema pallidum* is difficult to grow with defined media, so rabbits are used to culture *Treponema pallidum*. *Treponema pallidum* belongs to the Spirochaetesphylum of bacteria.

To date Spirochaetes are very difficult if not impossible to rear in a controlled laboratory environment. This also includes other human pathogens like the bacterium that causes Lyme disease. Using animals to culture human-pathogens has problems. First, the use of animals is always difficult for technical and ethical reasons. Also, a microbe growing on animal other than a human may behave very differently from how that same microbe will behave on a human. Some human pathogens are grown directly on cells cultured from humans. Exemplified by the bacteria *Chlamydia trachomatis*, the bacteria responsible for the sexually transmitted infection (STI) in humans known as Chlamydia. As *Chlamydia trachomatis* only grows in humans. The human cell culture known as McCoy cell culture is used to culture this bacteria.

 Figure: ***Chlamydias bacteria group****: Light microscope view of cells infected with chlamydiae as shown by the brown inclusion bodies.*

A large concern of microbiology is trying to find ways in which humans can avoid or get rid of microbrial infections. As typified by some of the above examples, some microbes have to be grown in the lab, and some of them can infect humans. To deal with this, microbiologists use a classification of biosafety levels. A biosafety level is the level of the biocontainment precautions required to isolate dangerous biological agents in an enclosed facility. The levels of containment range from the lowest biosafety level 1 (BSL-1) to the highest at level 4 (BSL-4). In the United States, the Centers for Disease Control and Prevention (CDC) have specified these levels.

- **Biosafety Level 1**: This level is suitable for work involving well-characterized agents not known to consistently cause disease in healthy adult humans, with minimal potential hazard to laboratory personnel and the environment.
- **Biosafety Level 2**: This level is similar to Biosafety Level 1 and is suitable for work involving agents of moderate potential hazard to personnel and the environment. It includes various bacteria and viruses that cause only mild disease to humans or are difficult to contract via aerosol in a lab setting such as chlamydia.
- **Biosafety Level 3**: This level is applicable to clinical, diagnostic, teaching, research, or production facilities in which work is done with indigenous or exotic agents that may cause serious or potentially lethal disease after inhalation. It includes various bacteria, parasites, and viruses that can cause severe to fatal disease in humans, but for which treatments exist (eg. yellow fever).
- **Biosafety Level 4**: This level is reserved for work with dangerous and exotic agents that pose a high individual risk of aerosol-transmitted laboratory infections, agents that cause severe to fatal disease in humans for which vaccines or other treatments are not available, such as Bolivian and Argentine hemorrhagic fevers, Marburg virus, and the Ebola virus. Very few laboratories are biosafety level 4.

 Figure: **Positive pressure suit**: A scientist puts on a positive pressure suit, something needed to work with the most dangerous human pathogens in a biosafety level 4 laboratory.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- Culture media. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Culture_media. **License**: *CC BY-SA: Attribution-ShareAlike*
- Culture media. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Culture_media. **License**: *CC BY-SA: Attribution-ShareAlike*
- Culture media. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Culture_media. **License**: *CC BY-SA: Attribution-ShareAlike*
- Culture media. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Culture_media. **License**: *CC BY-SA: Attribution-ShareAlike*
- Culture media. **Provided by**: Wikipedia. **Located at**: http://en.Wikipedia.org/wiki/Culture_media. **License**: *CC BY-SA: Attribution-ShareAlike*
- Culture media. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Culture_media. **License**: *CC BY-SA: Attribution-ShareAlike*
- Culture media. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Culture_media. **License**: *CC BY-SA: Attribution-ShareAlike*
- culture. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/culture. **License**: *CC BY-SA: Attribution-ShareAlike*
- lysogeny broth. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/lysogeny%20broth. **License**: *CC BY-SA: Attribution-ShareAlike*
- Agarplate redbloodcells edit. **Provided by**: Wikimedia. **Located at**: commons.wikimedia.org/wiki/Fi...cells_edit.jpg. **License**: *Public Domain: No Known Copyright*
- Growth medium. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Growth_medium. **License**: *CC BY-SA: Attribution-ShareAlike*
- Chemically defined medium. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Chemically_defined_medium. **License**: *CC BY-SA: Attribution-ShareAlike*

- Growth medium. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Growth_medium. **License**: *CC BY-SA: Attribution-ShareAlike*
- serum. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/serum. **License**: *CC BY-SA: Attribution-ShareAlike*
- recombinant. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/recombinant. **License**: *CC BY-SA: Attribution-ShareAlike*
- Agarplate redbloodcells edit. **Provided by**: Wikimedia. **Located at**: commons.wikimedia.org/wiki/Fi...cells_edit.jpg. **License**: *Public Domain: No Known Copyright*
- **Provided by**: Wikimedia. **Located at**: upload.wikimedia.org/wikipedi..._bottle-01.jpg. **License**: *CC BY-SA: Attribution-ShareAlike*
- Growth medium. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Growth_medium. **License**: *CC BY-SA: Attribution-ShareAlike*
- Growth medium. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Growth_medium. **License**: *CC BY-SA: Attribution-ShareAlike*
- allele. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/allele. **License**: *CC BY-SA: Attribution-ShareAlike*
- recombinant. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/recombinant. **License**: *CC BY-SA: Attribution-ShareAlike*
- gene. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/gene. **License**: *CC BY-SA: Attribution-ShareAlike*
- Agarplate redbloodcells edit. **Provided by**: Wikimedia. **Located at**: commons.wikimedia.org/wiki/Fi...cells_edit.jpg. **License**: *Public Domain: No Known Copyright*
- **Provided by**: Wikimedia. **Located at**: upload.wikimedia.org/wikipedi..._bottle-01.jpg. **License**: *CC BY-SA: Attribution-ShareAlike*
- Neisseria gonorrhoeae 01. **Provided by**: Wikimedia. **Located at**: commons.wikimedia.org/wiki/Fi...rrhoeae_01.png. **License**: *Public Domain: No Known Copyright*
- Sterile Technique. **Provided by**: Laboratory Wiki. **Located at**: http://lab.wikia.com/wiki/Sterile_Technique. **License**: *CC BY-SA: Attribution-ShareAlike*
- Serial dilution. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Serial_dilution. **License**: *CC BY-SA: Attribution-ShareAlike*
- Streaking (microbiology). **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Streaking_(microbiology). **License**: *CC BY-SA: Attribution-ShareAlike*
- Serial dilution. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Serial_dilution. **License**: *CC BY-SA: Attribution-ShareAlike*
- colony. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/colony. **License**: *CC BY-SA: Attribution-ShareAlike*
- bunsen burner. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/bunsen_burner. **License**: *CC BY-SA: Attribution-ShareAlike*
- Agarplate redbloodcells edit. **Provided by**: Wikimedia. **Located at**: commons.wikimedia.org/wiki/Fi...cells_edit.jpg. **License**: *Public Domain: No Known Copyright*
- **Provided by**: Wikimedia. **Located at**: upload.wikimedia.org/wikipedi..._bottle-01.jpg. **License**: *CC BY-SA: Attribution-ShareAlike*
- Neisseria gonorrhoeae 01. **Provided by**: Wikimedia. **Located at**: commons.wikimedia.org/wiki/Fi...rrhoeae_01.png. **License**: *Public Domain: No Known Copyright*
- Sembra%20en%20estria. **Provided by**: Wikimedia. **Located at**: commons.wikimedia.org/wiki/Fi..._en_estria.svg. **License**: *CC BY-SA: Attribution-ShareAlike*
- Verd%C3%BCnnungsreihe%20mit%20Ausplattieren. **Provided by**: Wikimedia. **Located at**: commons.wikimedia.org/wiki/Fi...plattieren.svg. **License**: *CC BY: Attribution*
- Biosafety level. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Biosafety_level. **License**: *CC BY-SA: Attribution-ShareAlike*
- Biosafety level. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Biosafety_level. **License**: *CC BY-SA: Attribution-ShareAlike*
- Biosafety level. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Biosafety_level. **License**: *CC BY-SA: Attribution-ShareAlike*

- Biosafety level. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Biosafety_level. **License**: *CC BY-SA: Attribution-ShareAlike*
- Growth medium. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Growth_medium. **License**: *CC BY-SA: Attribution-ShareAlike*
- Microaerophile. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Microaerophile. **License**: *CC BY-SA: Attribution-ShareAlike*
- Armadillo. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Armadillo. **License**: *CC BY-SA: Attribution-ShareAlike*
- Chlamydia infection. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Chlamydia_infection. **License**: *CC BY-SA: Attribution-ShareAlike*
- ChlamydiaTrachomatisEinschlussku00f6rperchen. **Provided by**: Wikimedia. **Located at**: commons.wikimedia.org/wiki/Fi...B6rperchen.jpg. **License**: *CC BY-SA: Attribution-ShareAlike*
- Biosafety level. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Biosafety_level. **License**: *CC BY-SA: Attribution-ShareAlike*
- Growth medium. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Growth_medium. **License**: *CC BY-SA: Attribution-ShareAlike*
- Armadillo. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Armadillo. **License**: *CC BY-SA: Attribution-ShareAlike*
- yellow fever. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/yellow%20fever. **License**: *CC BY-SA: Attribution-ShareAlike*
- Lyme disease. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/Lyme_disease. **License**: *CC BY-SA: Attribution-ShareAlike*
- Agarplate redbloodcells edit. **Provided by**: Wikimedia. **Located at**: commons.wikimedia.org/wiki/File:Agarplate_redbloodcells_edit.jpg. **License**: *Public Domain: No Known Copyright*
- **Provided by**: Wikimedia. **Located at**: upload.wikimedia.org/wikipedi..._bottle-01.jpg. **License**: *CC BY-SA: Attribution-ShareAlike*
- Neisseria gonorrhoeae 01. **Provided by**: Wikimedia. **Located at**: commons.wikimedia.org/wiki/File:Neisseria_gonorrhoeae_01.png. **License**: *Public Domain: No Known Copyright*
- Sembra%20en%20estria. **Provided by**: Wikimedia. **Located at**: commons.wikimedia.org/wiki/File:Sembra_en_estria.svg. **License**: *CC BY-SA: Attribution-ShareAlike*
- Verd%C3%BCnnungsreihe%20mit%20Ausplattieren. **Provided by**: Wikimedia. **Located at**: commons.wikimedia.org/wiki/File:Verd%C3%BCnnungsreihe_mit_Ausplattieren.svg. **License**: *CC BY: Attribution*
- ChlamydiaTrachomatisEinschlussku00f6rperchen. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:ChlamydiaTrachomatisEinschlussk%C3%B6rperchen.jpg. **License**: *CC BY: Attribution*
- Positive-pressure biosafety suit. **Provided by**: Wikimedia. **Located at**: commons.wikimedia.org/wiki/File:Positive-pressure_biosafety_suit.jpg. **License**: *Public Domain: No Known Copyright*
- Anaerobic chamber. **Provided by**: Wikimedia. **Located at**: commons.wikimedia.org/wiki/File:Anaerobic_chamber.JPG. **License**: *CC BY-SA: Attribution-ShareAlike*

Key Points

- Microbes, often those that we know little about, have to be cultured with undefined media or growth conditions.
- The use of animals to culture animals is sometimes necessary as no simple media can be used, this presents technical and ethical issues.
- As human pathogens are often studied by microbiologists, special safety conditions know as biosafety levels are used to keep researches free of infection from the pathogens they study.

Key Terms

- **yellow fever**: An acute febrile illness of tropical regions, caused by a flavivirus and spread by mosquitoes, characterized by jaundice, black vomit, and the absence of urination.
- **Lyme disease**: Infection by a bacterium of the genus Borrelia which is transmitted by ticks. Symptoms include a rash followed by fever, joint pain, and headaches.

This page titled 4.5: Special Culture Techniques is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **6.3E: Special Culture Techniques** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

5: Entry into the Host

This page titled 5: Entry into the Host is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **14.1: Entry into the Host** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

5.1: Portals of Microbe Entry

Learning Objectives

- Recognize the various methods and types of microorganism transmission: vectors, hosts, horizontal, vertical transmissions

Microbes gain access to human tissues via two main types of routes: mucosal surfaces within the body (linings of the respiratory, digestive, reproductive, or urinary tracts) or epithelial surfaces on the outside of the body (areas of skin that are either undamaged or compromised due to insect bites, cuts/scrapes, or other wounds).

Transmission of Microorganisms

Transmission of microorganisms occurs directly from one person to another by one or more of the following means:

- droplet contact by coughing or sneezing on another person
- direct physical contact by touching an infected person
- direct physical contact (usually by touching soil contamination or a contaminated surface)
- airborne transmission (if the microorganism can remain in the air for long periods)
- fecal-oral transmission (usually from contaminated food or water sources)
- contamination via intravenous drug us
- contamination from blood given via transfusion or organ transplants

Transmission can also be indirect via another organism, either a vector (like a mosquito) or an intermediate host (like how a tapeworm from a pig can be transmitted to humans who ingest improperly cooked pork).

Horizontal or Vertical Transmission

Disease can also be directly transmitted in two ways: horizontally or vertically. Horizontal disease transmission occurs from one individual to another in the same generation (peers in the same age group), and can occur by either direct contact (licking, touching, biting), or indirect contact. Vertical disease transmission involves passing a disease causing agent vertically from parent to offspring.

Pathogens must have a way to be transmitted from one host to another to ensure their species ‘ survival. Infectious agents are generally specialized for a particular method of transmission. Taking an example from the respiratory route, from an evolutionary perspective a virus or bacteria that causes its host to develop coughing and sneezing symptoms has a great survival advantage: it is much more likely to be ejected from one host and carried to another.

A locus is the point on the body where a pathogen enters. In droplet contact and other airborne transmission it is generally the respiratory system through the nose, mouth, or eye surfaces. In direct physical and indirect contact it is generally through a wound in the skin or through a mucous membrane. In fecal-oral transmission, it is through the mouth. In vector-borne transmission, it is at the bite or sting of the vector. Other common indirect routes include contaminated food or water.

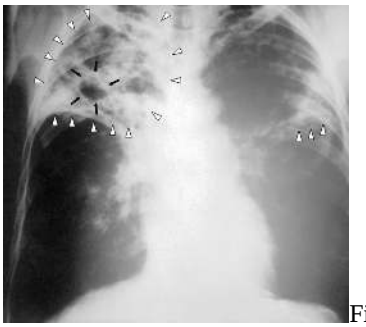


Figure: **Chest x-ray of a patient with tuberculosis.**: In this chest X-ray of a person with advanced tuberculosis, the infections in both lungs are marked by white arrowheads and the formation of a cavity is marked by black arrows. The boundary between contagious and non-contagious infectious diseases is not perfectly drawn, as illustrated by tuberculosis, which is clearly transmissible from person to person, but was not classically considered a contagious disease.

Sexual Transmission

In sexual transmission, infection originates directly between surfaces in contact during intercourse (the usual route for bacterial infections and those infections causing sores) or from secretions (semen or the fluid secreted by the excited female). Sexually transmitted diseases such as HIV and Hepatitis B are thought to be transmitted through unprotected sexual intercourse (including anal and oral routes), contaminated blood transfusions, sharing hypodermic needles, and from mother to child during pregnancy, delivery, or breastfeeding. Bodily fluids such as saliva and tears do not transmit HIV. Oral sexual practices have increased the incidence of herpes simplex virus 1 (which is usually responsible for oral infections) in genital infections and the increased incidence of the type 2 virus (more common genitally) in oral infections. Herpes diseases that are transmitted primarily by oral means may be caught through direct contact with an infectious area of the skin.

Direct Contact: Contagious Diseases

Diseases that can be transmitted by direct contact are called contagious (contagious is not the same as infectious). Although all contagious diseases are infectious, not all infectious diseases are contagious. Interestingly, some contagious diseases like tuberculosis were not classically considered to be contagious even though they are transmissible from person to person. Direct transmission can also occur by sharing a towel (where the towel is rubbed vigorously on both bodies) or items of clothing in close contact with the body (socks, for example) if they are not washed thoroughly between uses. Some diseases that are transmissible by direct contact include Athlete's foot and impetigo.

Key Points

- Transmission can be direct (vertically or horizontally) or indirect.
- Infectious agents are generally specialized for a particular method of transmission.
- A locus is the point on the body where a pathogen enters.

Key Terms

- **infectious**: Infectious diseases, also known as transmissible diseases or communicable diseases, comprise clinically evident illness (i.e., characteristic medical signs and/or symptoms of disease) resulting from the infection, presence, and growth of pathogenic biological agents in an individual host organism.
- **pathogen**: Any organism or substance, especially a microorganism, capable of causing disease, such as bacteria, viruses, protozoa, or fungi. Microorganisms are not considered to be pathogenic until they have reached a population size that is large enough to cause disease.
- **contagious**: Of a person, having a disease that can be transmitted to another person by touch.

This page titled 5.1: Portals of Microbe Entry is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **14.1A: Portals of Microbe Entry** is licensed CC BY-SA 4.0.

5.2: Colonization and Growth

Learning Objectives

- Distinguish between colonization and infection

Infection begins when an organism successfully colonizes by entering the body, growing and multiplying from there. Most humans are not easily infected. Those who are weak, sick, malnourished, have cancer or are diabetic possess an increased susceptibility to chronic or persistent infections. Individuals who have a suppressed immune system are particularly susceptible to opportunistic infections.

Entrance to the host generally occurs through the mucosa in orifices like the oral cavity, nose, eyes, genitalia, anus, or open wounds. While a few organisms can grow at the initial site of entry, many migrate and cause systemic infection in different organs. Some pathogens grow within the host cells (intracellular) whereas others grow freely in bodily fluids. Some virulent bacteria produce special proteins that allow them to colonize parts of the host body. Helicobacter pylori is able to survive in the acidic environment of the human stomach by producing the enzyme urease. Colonization of the stomach lining by this bacterium can lead to gastric ulcer and cancer. The virulence of various strains of Helicobacter pylori tends to correlate with the level of production of urease.

Wound colonization refers to nonreplicating microorganisms within the wound, while in infected wounds replicating organisms exist and tissue is injured. All multicellular organisms are colonized to some degree by extrinsic organisms and the vast majority of these exist in either a mutualistic or commensal relationship with the host. An example of the former is the anaerobic bacteria species, which colonizes the mammalian colon, and an example of the latter is various species of staphylococcus that exist on human skin. Neither of these colonizations are considered infections.

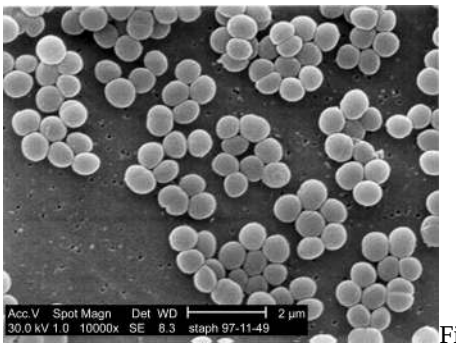


Figure: **Staphylococcus aureus**: Staphylococcus is a Gram-positive bacteria which includes several species that can cause a wide variety of infections in humans and other animals through infection or the production of toxins.

The difference between an infection and a colonization is often only a matter of circumstance. Non-pathogenic organisms can become pathogenic given specific conditions and even the most virulent organism requires certain circumstances to cause a compromising infection. Some colonizing bacteria, such as Corynebacteria sp. and viridans streptococci, prevent the adhesion and colonization of pathogenic bacteria. They thus have a symbiotic relationship with the host, preventing infection and speeding wound healing.

The variables involved in the outcome of a host becoming inoculated by a pathogen and the ultimate outcome include: the route of entry of the pathogen and the access to host regions that it gains, the intrinsic virulence of the particular organism, the quantity or load of the initial inoculant, and the immune status of the host being colonized. As an example, the Staphylococcus species remains harmless on the skin. But when present in a normally sterile space, such as in the capsule of a joint or the peritoneum the Staphylococcus species multiplies without resistance and creates a burden on the host.

Key Points

- Some virulent bacteria produce special proteins that allow them to colonize parts of the host body.
- Wound colonization refers to nonreplicating microorganisms within the wound, while in infected wounds replicating organisms exist and tissue is injured.

- While a few organisms can grow at the initial site of entry, many migrate and cause systemic infection in different organs.

Key Terms

- **infection**: An uncontrolled growth of harmful microorganisms in a host.

This page titled 5.2: Colonization and Growth is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **14.1B: Colonization and Growth** is licensed CC BY-SA 4.0.

5.3: Pathogenicity Islands and Virulence Factors

Learning Objectives

- Describe the traits characterizing a pathogenicity island and its advantages

Pathogenicity Islands and Virulence Factors

Pathogenicity islands (PAIs) are a distinct class of genomic islands acquired by microorganisms through horizontal gene transfer. They are incorporated in the genome of pathogenic organisms, but are usually absent from those nonpathogenic organisms of the same or closely related species. These mobile genetic elements may range from 10-200 kb, and may encode genes contributing to the virulence of the respective pathogen. Typical examples are adherence factors, toxins, iron uptake systems, invasion factors and secretion systems.

Pathogenicity islands are discrete genetic units flanked by direct repeats, insertion sequences or tRNA genes, which act as sites for recombination into the DNA. Cryptic mobility genes may also be present, indicating the provenance as transduction.

One species of bacteria may have more than one PAI (i.e. salmonella has at least five). PAIs are transferred through horizontal gene transfer events such as transfer by a plasmid, phage, or conjugative transposon. PAIs carry genes encoding one or more virulence factors, including, but not limited to, adhesins, toxins, or invasins. They may be located on a bacterial chromosome or may be transferred within a plasmid. The GC-content of pathogenicity islands often differs from that of the rest of the genome, potentially aiding in their detection within a given DNA sequence.

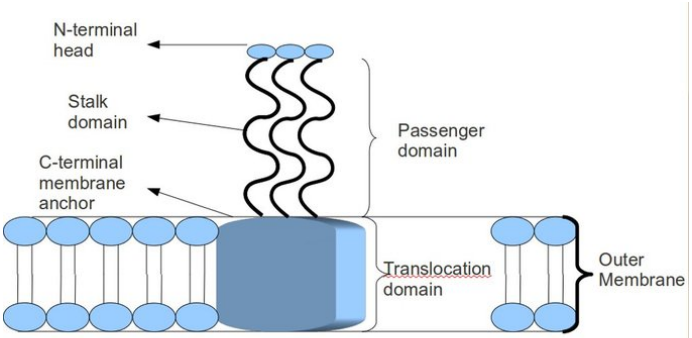


Figure: **Trimeric Autotransporter Adhesin structure**: The structure on the top (outside) of the outer membrane is a TAA protein. Various parts of the TAA are labelled, including the N-terminal head, stalk domain and C-terminal membrane anchor.

PAIs are flanked by direct repeats; the sequence of bases at two ends of the inserted sequence are the same. They carry functional genes such as integrases, transposases, or part of insertion sequences, to enable insertion into host DNA. PAIs are often associated with tRNA genes, which target sites for this integration event. They can be transferred as a single unit to new bacterial cells, thus conferring virulence to formerly benign strains.

Key Points

- Pathogenicity islands are discrete genetic units flanked by direct repeats, insertion sequences or tRNA genes, which act as sites for recombination into the DNA.
- PAIs are incorporated in the genome of pathogenic organisms, but are usually absent from those nonpathogenic organisms of the same or closely related species.
- PAIs carry genes encoding one or more virulence factors, including, but not limited to, adhesins, toxins, or invasins.

Key Terms

- **pathogenicity island**: A distinct class of genomic islands acquired by microorganisms through horizontal gene transfer.
- **virulence factor**: Molecules expressed and secreted by pathogens (bacteria, viruses, fungi and protozoa) that enable them to achieve colonization of a niche in the host, immunoevasion, immunosuppression, entry into and out of the cells, and obtaining

nutrition from the host.

This page titled 5.3: Pathogenicity Islands and Virulence Factors is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **14.1C: Pathogenicity Islands and Virulence Factors** is licensed CC BY-SA 4.0.

5.4: Adherence

Learning Objectives

- Review the role of adhesins, including fimbriae and the Dr family, in pathogenic bacteria

Adhesins are cell-surface components or appendages of bacteria that facilitate bacterial adhesion or adherence to other cells or to inanimate surfaces. Adhesins are a type of virulence factor. Adherence is an essential step in bacterial pathogenesis or infection, required for colonizing a new host. For example, nontypeable Haemophilus influenzae expresses the adhesins Hia, Hap, Oap, and a hemagglutinating pili.

Fimbriae are fine filaments of protein, just 3–10 nanometers in diameter and up to several micrometers in length. They are distributed over the surface of the cell, and resemble fine hairs when seen under the electron microscope. Fimbriae are believed to be involved in attachment to solid surfaces or to other cells, and are essential for the virulence of some bacterial pathogens. Most fimbriae of Gram-negative bacteria function as adhesins, but in many cases the actual adhesin is a minor subunit protein at the tip of the fimbriae. In Gram-positive bacteria, a protein or polysaccharide surface layer serves as the specific adhesin. To effectively achieve adherence to host surfaces, many bacteria produce multiple adherence factors called adhesins.

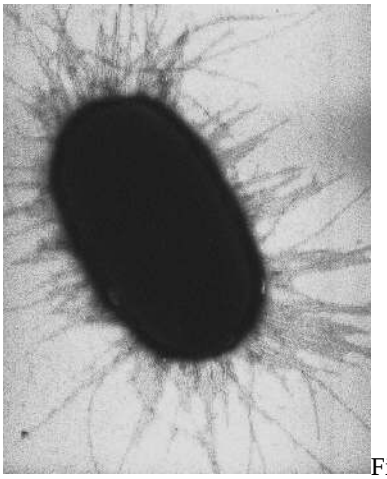


Figure: **E. coli fimbriae**: In bacteriology, a fimbria (plural fimbriae; abbreviated FIM) is an appendage composed of curlin proteins that can be found on many Gram-negative and some Gram-positive bacteria that is thinner and shorter than a flagellum. This appendage ranges from 3-10 nanometers in diameter and can be up to several micrometers long.

The Dr family of adhesins bind to the Dr blood group antigen component of decay-accelerating factor (DAF). These proteins contain both fimbriated and afimbriated adherence structures and mediate adherence of uropathogenic Escherichia coli to the urinary tract. They do so by inducing the development of long cellular extensions that wrap around the bacteria. They also confer the mannose-resistant hemagglutination phenotype, which can be inhibited by chloramphenicol. The N-terminal portion of the mature protein is thought to be responsible for chloramphenicol sensitivity. Also, they induce activation of several signal transduction cascades, including activation of PI-3 kinase. The Dr family of adhesins are particularly associated with cystitis and pregnancy-associated pyelonephritis.

Adhesins are attractive vaccine candidates because they are often essential to infection and are surface-located, making them readily accessible to antibodies. The effectiveness of anti-adhesin antibodies is illustrated by studies with FimH, the adhesin of uropathogenic Escherichia coli (UPEC). In animal models, passive immunization with anti FimH-antibodies and vaccination with the protein significantly reduced colonization by UPEC. Moreover, the Bordetella pertussis adhesins FHA and pertactin are components of 3 of the 4 acellular pertussis vaccines currently licensed for use in the U.S.

Key Points

- Adhesins are a type of virulence factor.
- Adherence is an essential step in bacterial pathogenesis or infection, required for colonizing a new host.

- Fimbriae are believed to be involved in attachment to solid surfaces or to other cells and are essential for the virulence of some bacterial pathogens.

Key Terms

- **adhesin**: Any of several factors that enable bacteria to adhere to epithelial surfaces as a step towards infection.
- **fimbriae**: Fine filaments of protein distributed over the surface of bacteria that are believed to be involved in attachment to solid surfaces or to other cells, and are essential for the virulence of some bacterial pathogens.

This page titled 5.4: Adherence is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **14.1D: Adherence** is licensed CC BY-SA 4.0.

5.5: Host Risk Factors

Learning Objectives

- Recognize the risk factors that increase chance of disease

Most humans are not easily infected. Those who are weak, sick, malnourished, have cancer, or are diabetic have increased susceptibility to chronic or persistent infections. Individuals who have a suppressed immune system or who are on immunosuppressive drugs are particularly susceptible to opportunistic infections.

Risk of infection is a nursing diagnosis which is defined as “the state in which an individual is at risk to be invaded by an opportunistic or pathogenic agent (virus, fungus, bacteria, protozoa, or other parasite) from endogenous or exogenous sources. ” The risk of infection depends on a number of endogenous sources. Skin damage from incision can increase a patient’s risk of infection, as can very young or old age, due to a naive or compromised immune system respectively. Examples of risk factors include decreased immune system resulting from disease, compromised circulation caused by peripheral vascular disease, compromised skin integrity as a result of surgery, or repeated contact with contagious agents.

Risk Reduction

Techniques like hand washing, wearing gowns, and wearing face masks can help prevent infections from being passed between the surgeon and the patient. Frequent hand washing remains the most important defense against the spread of unwanted organisms. Good nutrition is necessary to reduce risk. So is a healthy lifestyle. By avoiding illicit drugs, using a condom, and entering an exercise program one can improve one’s risk factors. Foods should be cooked to recommended temperatures; avoid foods that have been left outside for long. One should not take antibiotics for longer than needed or when they are not needed—long term use of antibiotics leads to resistance and increased the chance of developing opportunistic infections like clostridium difficile colitis. Vaccination is another vital means of preventing infections by encouraging the development of immune resistance in vaccinated hosts.

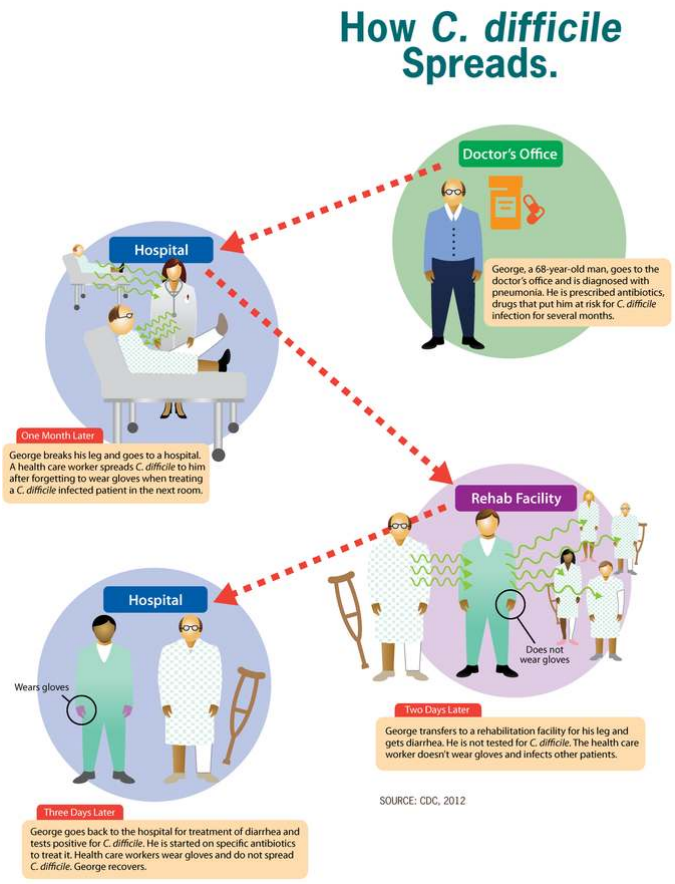


Figure: **How C. difficile spreads**: C. difficile is transmitted from person to person by the fecal-oral route. The organism forms large numbers of heat-resistant spores. These are not killed by alcohol-based hand cleansers or routine cleaning of surfaces. These spores remain viable in the hospital or nursing home environment for long periods of time. Because of this, the bacteria can be cultured from almost any surface in the hospital. Once spores are ingested by a patient, they pass through the stomach unscathed because of their acid-resistance. They germinate into vegetative cells in the colon upon exposure to bile acids, and multiply.

Key Points

- Risk of infection is a nursing diagnosis; “the state in which an individual is at risk to be invaded by an opportunistic or pathogenic agent (virus, fungus, bacteria, protozoa, or other parasite) from endogenous or exogenous sources” is the diagnostic definition of risk.
- Examples of risk factors includes decreased immune system secondary to disease, compromised circulation secondary to peripheral vascular disease, compromised skin integrity secondary to surgery, or repeated contact with contagious agents.
- Techniques like hand washing, wearing gowns, and wearing face masks can help prevent infections from being passed from the surgeon to the patient or vice versa.

Key Terms

- **opportunistic infection**: Any infection that causes disease and occurs only when the host’s immune system is impaired.
- **colitis**: inflammation of the colon.
- **vaccination**: inoculation with a vaccine in order to protect a particular disease or strain of disease.

This page titled 5.5: Host Risk Factors is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **14.1E: Host Risk Factors** is licensed CC BY-SA 4.0.

5.6: Innate Resistance

Learning Objectives

- Discuss the various innate barriers within humans that provide protection from infection

Several barriers protect organisms from infection, including mechanical, chemical, and biological barriers. However, as organisms cannot be completely sealed against their environments, other systems act to protect body openings such as the lungs, intestines, and the genitourinary tract. In the lungs, coughing and sneezing mechanically eject pathogens and other irritants from the respiratory tract. The flushing action of tears and urine also mechanically expels pathogens, while mucus secreted by the respiratory and gastrointestinal tract serves to trap and entangle microorganisms.

Chemical barriers also protect against infection. The skin and respiratory tract secrete antimicrobial peptides such as the β-defensins. Enzymes such as lysozyme and phospholipase A2 in saliva, tears, and breast milk are also antibacterials. Vaginal secretions serve as a chemical barrier following menarche, when they become slightly acidic, while semen contains defensins and zinc to kill pathogens. In the stomach, gastric acid and proteases serve as powerful chemical defenses against ingested pathogens. Within the genitourinary and gastrointestinal tracts, commensal flora serve as biological barriers by competing with pathogenic bacteria for food and space and, in some cases, by changing the conditions in their environment, such as pH or available iron. This reduces the probability that pathogens will reach sufficient numbers to cause illness. However, since most antibiotics non-specifically target bacteria and do not affect fungi, oral antibiotics can lead to an “overgrowth” of fungi and cause conditions such as a vaginal candidiasis (a yeast infection). There is good evidence that re-introduction of probiotic flora, such as pure cultures of the lactobacilli normally found in unpasteurized yogurt, helps restore a healthy balance of microbial populations in intestinal infections in children and encouraging preliminary data in studies on bacterial gastroenteritis and inflammatory bowel diseases. Inflammation is one of the first responses of the immune system to infection.

The human microbiome (or human microbiota) is the aggregate of microorganisms that reside on the surface and in deep layers of skin, in the saliva and oral mucosa, in the conjunctiva, and in the gastrointestinal tracts. They include bacteria, fungi, and archaea. Some of these organisms perform tasks that are useful for the human host. However, the majority have no known beneficial or harmful effect. Those that are expected to be present, and that under normal circumstances do not cause disease, but instead participate in maintaining health, are deemed members of the normal flora.

Populations of microbes (such as bacteria and yeasts) inhabit the skin and mucosa. Their role forms part of normal, healthy human physiology. However, if microbe numbers grow beyond their typical ranges (often due to a compromised immune system) or if microbes populate atypical areas of the body (such as through poor hygiene or injury), disease can result.

Many of the bacteria in the digestive tract are collectively referred to as the gut flora. In this context, *gut* is synonymous with intestinal, and *flora* with microbiota and microflora, the word microbiome is also in use. They are able to break down certain nutrients such as carbohydrates that humans otherwise could not digest. The majority of these commensal bacteria are anaerobes, meaning they survive in an environment with no oxygen. Normal flora bacteria can act as opportunistic pathogens at times of lowered immunity.

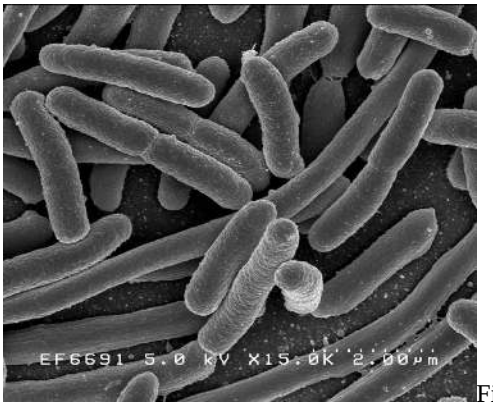


Figure: **Gut Flora**: Gut flora consists of microorganisms such as Escherichia Coli that live in the digestive tracts of animals. It is the largest reservoir of human flora. In this context, gut is synonymous with

intestinal, and flora with microbiota and microflora. The word microbiome is also in use.

Archaea are present in the human gut, but, in contrast to the enormous variety of bacteria in this organ, the numbers of archaeal species are much more limited. Fungi, in particular yeasts, are present in the human gut. The best-studied of these are Candida species. This is because of their ability to become pathogenic in immune compromised hosts. Yeasts are also present on the skin, particularly Malassezia species, where they consume oils secreted from the sebaceous glands.

A small number of bacteria are normally present in the conjunctiva. Staphylococcus epidermidis and certain coryneforms such as Propionibacterium acnes are dominant. The lachrymal glands continuously secrete, keeping the conjunctiva moist, while intermittent blinking lubricates the conjunctiva and washes away foreign material. Tears contain bactericides such as lysozyme, so that microorganisms have difficulty in surviving the lysozyme and settling on the epithelial surfaces.

The gut flora is the human flora of microorganisms that normally live in the digestive tract and can perform a number of useful functions for their hosts. Though people can survive with no gut flora, the microorganisms perform a host of useful functions such as fermenting unused energy substrates, training the immune system, preventing growth of harmful species, regulating the development of the gut, producing vitamins for the host (such as biotin and vitamin K), and producing hormones to direct the host to store fats. However, in certain conditions, some species are thought to be capable of causing disease by causing infection or increasing cancer risk for the host.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: *CC BY-SA: Attribution-ShareAlike*

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- Routes of infection. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Routes_...ection%23Locus**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Infectious disease. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Infecti...23Transmission**. **License**: *CC BY-SA: Attribution-ShareAlike*
- infectious. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/infectious**. **License**: *CC BY-SA: Attribution-ShareAlike*
- pathogen. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/pathogen**. **License**: *CC BY-SA: Attribution-ShareAlike*
- contagious. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/contagious**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Tuberculosis-x-ray-1. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Tu...is-x-ray-1.jpg**. **License**: ***Public Domain: No Known Copyright***
- Infection. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Infection%23Colonization**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Virulence. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Virulence**. **License**: *CC BY-SA: Attribution-ShareAlike*
- infection. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/infection**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Tuberculosis-x-ray-1. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Tuberculosis-x-ray-1.jpg**. **License**: ***Public Domain: No Known Copyright***
- Staphylococcus aureus 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:St...pg%23filelinks**. **License**: ***Public Domain: No Known Copyright***
- Structural Biochemistry/Three Domains of Life/Bacteria. **Provided by**: Wikibooks. **Located at**: **en.wikibooks.org/wiki/Structural_Biochemistry/Three_Domains_of_Life/Bacteria%23Virulence_Factors**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Virulence factor. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Virulence_factor**. **License**: *CC BY-SA: Attribution-ShareAlike*

- Pathogenicity island. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Pathogenicity_island. **License**: *CC BY-SA: Attribution-ShareAlike*
- virulence factor. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/virulence%20factor. **License**: *CC BY-SA: Attribution-ShareAlike*
- pathogenicity island. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/pathogenicity%20island. **License**: *CC BY-SA: Attribution-ShareAlike*
- Tuberculosis-x-ray-1. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:Tuberculosis-x-ray-1.jpg. **License**: ***Public Domain: No Known Copyright***
- Staphylococcus aureus 01. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:St...pg%23filelinks. **License**: ***Public Domain: No Known Copyright***
- Taabasic1. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:Taabasic1.jpg. **License**: *CC BY-SA: Attribution-ShareAlike*
- Bacteria. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Bacteria. **License**: *CC BY-SA: Attribution-ShareAlike*
- Adhesins. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Adhesins. **License**: *CC BY-SA: Attribution-ShareAlike*
- fimbriae. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/fimbriae. **License**: *CC BY-SA: Attribution-ShareAlike*
- adhesin. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/adhesin. **License**: *CC BY-SA: Attribution-ShareAlike*
- Tuberculosis-x-ray-1. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:Tuberculosis-x-ray-1.jpg. **License**: ***Public Domain: No Known Copyright***
- Staphylococcus aureus 01. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:St...pg%23filelinks. **License**: ***Public Domain: No Known Copyright***
- Taabasic1. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:Taabasic1.jpg. **License**: *CC BY-SA: Attribution-ShareAlike*
- E. coli fimbriae. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:E....i_fimbriae.png. **License**: *CC BY: Attribution*
- Risk of infection. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Risk_of_infection. **License**: *CC BY-SA: Attribution-ShareAlike*
- Infection. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Infecti...and_prevention. **License**: *CC BY-SA: Attribution-ShareAlike*
- Cellulitis. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Celluli...23Risk_factors. **License**: *CC BY-SA: Attribution-ShareAlike*
- Infection. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Infection%23Colonization. **License**: *CC BY-SA: Attribution-ShareAlike*
- colitis. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/colitis. **License**: *CC BY-SA: Attribution-ShareAlike*
- vaccination. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/vaccination. **License**: *CC BY-SA: Attribution-ShareAlike*
- opportunistic infection. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/opportunistic_infection. **License**: *CC BY-SA: Attribution-ShareAlike*
- Tuberculosis-x-ray-1. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:Tuberculosis-x-ray-1.jpg. **License**: ***Public Domain: No Known Copyright***
- Staphylococcus aureus 01. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:Staphylococcus_aureus_01.jpg%23filelinks. **License**: ***Public Domain: No Known Copyright***
- Taabasic1. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:Taabasic1.jpg. **License**: *CC BY-SA: Attribution-ShareAlike*
- E. coli fimbriae. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:E....i_fimbriae.png. **License**: *CC BY: Attribution*
- How C. difficile spreads. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:Ho...le_spreads.png. **License**: *Public Domain: No Known Copyright*
- Human flora. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Human_flora%23cite_note-11. **License**: *CC BY-SA: Attribution-ShareAlike*

- Immune system. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Immune_system**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- flora. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/flora**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- lysozyme. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/lysozyme**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- microbiota. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/microbiota**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Tuberculosis-x-ray-1. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Tuberculosis-x-ray-1.jpg**. **License**: ***Public Domain: No Known Copyright***
- Staphylococcus aureus 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Staphylococcus_aureus_01.jpg%23filelinks**. **License**: ***Public Domain: No Known Copyright***
- Taabasic1. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Taabasic1.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- E. coli fimbriae. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:E._coli_fimbriae.png**. **License**: ***CC BY: Attribution***
- How C. difficile spreads. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:How_C._difficile_spreads.png**. **License**: ***Public Domain: No Known Copyright***
- **Provided by**: Wikimedia. **Located at**: **upload.wikimedia.org/wikipedi...Coli_NIAID.jpg**. **License**: ***Public Domain: No Known Copyright***

Key Points

- The flushing action of tears and urine also mechanically expels pathogens, while mucus secreted by the respiratory and gastrointestinal tract serves to trap and entangle microorganisms.
- The human microbiome (or human microbiota) is the aggregate of microorganisms that reside on the surface and in deep layers of skin, in the saliva and oral mucosa, in the conjunctiva, and in the gastrointestinal tracts.
- Some of these organisms perform tasks that are useful for the human host, but the majority have no known beneficial or harmful effect.

Key Terms

- **lysozyme**: A bacteriolytic (or antibiotic) enzyme found in many animal secretions and in egg white.
- **microbiota**: The microbial flora harbored by normal, healthy individuals.
- **flora**: the microorganisms that inhabit some part of the body, such as intestinal flora

---

This page titled 5.6: Innate Resistance is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **14.1F: Innate Resistance** is licensed CC BY-SA 4.0.

CHAPTER OVERVIEW

6: Bacterial Infections

- 6.1: Bacterial Diseases of the Respiratory System
  - 6.1A: Pharyngitis
    - 1.1: Scarlet Fever
  - 6.1C: Diphtheria
  - 6.1D: Otitis Media
  - 6.1E: Whooping Cough
  - 6.1F: Tuberculosis
  - 6.1G: Bacterial Pneumonias
- 6.2: Bacterial Diseases of the Mouth
  - 6.2A: Tooth and Gum Infections
  - 6.2B: Dental Caries
  - 6.2C: Periodontal Disease
- 6.3: Bacterial Diseases of the Digestive System
  - 6.3A: Bacterial Gastroenteritis
  - 6.3B: Staphylococcal Food Poisoning
  - 6.3C: Salmonellosis
  - 6.3D: Typhoid Fever
  - 6.3E: Cholera
  - 6.3F: Noncholera Vibrios
  - 6.3G: Pathogenic Escherichia coli
  - 6.3H: Campylobacter
  - 6.3I: Peptic Ulcer Disease
  - 6.3J: Listeriosis
- 6.4: Bacterial Diseases of the Urinary System
  - 6.4A: Urinary Tract Infection (UTI)
  - 6.4B: Cystitis
  - 6.4C: Pyelonephritis
  - 6.4D: Leptospirosis
- 6.5: Bacterial Diseases of the Reproductive System
  - 6.5A: Prostatitis
  - 6.5B: Prostatitis
  - 6.5C: Gonorrhea
  - 6.5D: Nongonococcal Urethritis (NGU)
  - 6.5E: Pelvic Inflammatory Disease (PID)
  - 6.5F: Syphilis
  - 6.5G: Genital Ulcer Diseases
  - 6.5H: Lymphogranuloma Venereum
  - 6.5I: Group B Streptococcus Colonization
  - 6.5J: Chancroid (Soft Chancre)

6.5K: Bacterial Vaginosis
6.5L: Chlamydia
6.6: Microbial Diseases of the Skin
6.6A: Structure of the Skin- Epidermis
6.6B: Microbiota of the Skin
6.6C: Bacterial Skin Diseases
6.6D: Viral Skin Diseases
6.6E: Fungal Skin and Nail Diseases
6.6F: Parasitic Skin Diseases
6.7: Microbial Diseases of the Eye
6.7A: Anatomy of the Eye
6.7B: Normal Eye Microbiota
6.7C: Bacterial Eye Diseases
6.7D: Other Infectious Eye Diseases
6.8: Microbial Diseases of the Nervous System
6.8A: Functions of the Nervous System
6.8B: Subdivisions of the Nervous System
6.8C: Meningitis
6.8D: Botulism
6.8E: Leprosy
6.8F: Tetanus
6.8G: Paralysis-Causing Bacterial Neurotoxins

This page titled 6: Bacterial Infections is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

This page titled 6: Bacterial Infections is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

6.1: Bacterial Diseases of the Respiratory System

This page titled 6.1: Bacterial Diseases of the Respiratory System is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.3: Bacterial Diseases of the Respiratory System** is licensed CC BY-SA 4.0.

6.1A: Pharyngitis

Learning Objectives

- List the symptoms and bacterial causes associated with pharyngitis

Pharyngitis

Pharyngitis is an inflammation of the throat. In most cases, it is quite painful and is the most common cause of a sore throat. Like many types of inflammation, pharyngitis can be acute or chronic. Acute cases are characterized by a rapid onset and, typically, a relatively short course of inflammation. Pharyngitis can result in very large tonsils. This can make swallowing and breathing difficult. It can be accompanied by a cough or fever, for example, if it is caused by a systemic infection. Most acute cases are caused by viral infections (40–80%). The remainder are caused by bacterial infections, fungal infections, or irritants such as pollutants or chemical substances. The treatment of viral causes is mainly symptomatic. Bacterial or fungal causes are often amenable to antibiotics and anti-fungal treatments, respectively.

Bacterial Causes of Pharyngitis

A number of different bacteria can infect the human throat. The most common is Group A streptococcus, but others include Corynebacterium diphtheriae, Neisseria gonorrhoeae, Chlamydophila pneumoniae, and Mycoplasma pneumoniae.



Figure: **Streptococcal pharyngitis**: A severe case of strep throat or Streptococcal pharyngitis.

Streptococcal pharyngitis, more commonly known as strep throat, is caused by group A beta-hemolytic streptococcus (GAS). This is the most common bacterial cause of pharyngitis (15–30%). Common symptoms of strep throat include fever, sore throat, and large lymph nodes. It is a contagious infection, spread by close contact with an infected individual. A throat culture is the gold standard for the diagnosis of streptococcal pharyngitis, with a sensitivity of 90–95%. A rapid strep test (also called rapid antigen detection testing, or RADT) is also occasionally used as a diagnostic. While the rapid strep test is quicker, it has a lower sensitivity (70%) and a statistically equal specificity (98%) as a throat culture. For step throat, antibiotics are useful in preventing complications and expediting recovery.

Fusobacterium necrophorum are normal inhabitants of the oropharyngeal flora. Occasionally, however, these bacteria can create a peritonsillar abscess. In 1 out of 400 untreated cases, Lemierre's syndrome can occur as a result of these abscesses.

Diphtheria is a potentially life threatening upper respiratory infection caused by Corynebacterium diphtheriae. As a result of childhood vaccination programs, diphtheria has has been largely eradicated in developed nations, but it is still reported in the Third World, and, increasingly, in some areas in Eastern Europe. Antibiotics are effective in the early stages, but recovery is generally slow.

Key Points

- In most cases, pharyngitis is caused by a systemic viral infection and is typified by a painful swelling inflammation of the throat. This can cause difficulty swallowing or breathing.
- The most common bacterial cause of pharyngitis is streptococcus.

- Several types of bacteria can cause pharyngitis. The most common and effective treatment for these infections are antibiotics.

Key Terms

- **hemolytic**: producing hemolysis; destroying red blood cells
- **peritonsillar abscess**: Peritonsillar abscess (PTA), also called a quinsy, or abbreviated as a PTA, is a recognized complication of tonsillitis. It consists of a collection of pus beside the tonsil in what is referred to as Peritonsilar space (Peri – meaning surrounding).

This page titled 6.1A: Pharyngitis is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.3A: Pharyngitis** is licensed CC BY-SA 4.0.

1.1: Scarlet Fever

Learning Objectives

- Describe the bacterium *Streptococcus pyogenes* that causes scarlet fever

A Bacteriophage Hitchhiker

Scarlet fever is an infectious disease which most commonly affects 4-8 year-old children. Symptoms include sore throat, fever, and a characteristic red rash. It is usually spread by inhalation. There is no vaccine, but the disease is effectively treated with antibiotics. Scarlet fever is caused by an erythrogenic toxin, a substance produced by the bacterium Streptococcus pyogenes (group A strep.) when it is infected by a certain bacteriophage.

 Figure: **Scarlet Fever**: The rosy cheeks and white area around the mouth are typical symptoms of scarlet fever.

Scarlet fever is caused by secretion of pyrogenic (fever inducing) exotoxins by the infected Streptococcus. Exotoxin A (speA) is probably the best studied of these toxins. It is carried by the bacteriophage T12, which integrates into the Streptococcal genome, from where the toxin is transcribed.

The phage itself integrates into a serine tRNA gene on the chromosome. The T12 virus itself has not been placed into a taxon by the International Committee on Taxonomy of Viruses. It has a double stranded DNA genome; on morphological grounds it appears to be a member of the Siphoviridae. The speA gene was cloned and sequenced in 1986. It is 753 base pairs in length and encodes a 29.244 kiloDalton (kDa) protein. The protein contains a putative 30 amino acid signal peptide. Removal of the signal sequence gives a predicted molecular weight of 25.787 (kDa) for the secreted protein. Both a promoter and a ribosome-binding site (Shine-Dalgarno sequence) are present upstream of the gene. A transcriptional terminator is located 69 bases downstream from the translational termination codon. The carboxy terminal portion of the protein exhibits extensive homology with the carboxy terminus of Staphylococcus aureus enterotoxins B and C1. Streptococcal phages other than T12 may also carry the speA gene.

Key Points

- Scarlet fever usually affects children. Historically, it had devastating effects.
- While antibiotics are effective against scarlet fever, the illness is actually caused by a bacteriophage infecting Streptococcus that has infected a person.
- The bacteriophage T12 inserts into the genome of Streptococcus. This leads to the expression of an exotoxin, which causes scarlet fever.

Key Terms

- **scarlet fever**: a streptococcal infection, mainly occurring among children, and characterized by a red skin rash, sore throat and fever
- **Shine-Dalgarno sequence**: A ribosomal binding site in the mRNA of prokaryotes.
- **exotoxin**: Any toxin secreted by a microorganism into the surrounding environment.
- **enterotoxin**: Any of several toxins produced by intestinal bacteria

This page titled 1.1: Scarlet Fever is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **1.1: Scarlet Fever** is licensed CC BY-SA 4.0.

6.1C: Diphtheria

Learning Objectives

- Discuss the role of diphtheria toxin in diphtheria

Overview of Diphtheria

Diphtheria is an upper respiratory tract illness caused by *Corynebacterium diphtheriae*, a facultative, anaerobic, Gram-positive bacterium. It is characterized by sore throat, low fever, and an adherent membrane (a pseudomembrane) on the tonsils, pharynx, and/or nasal cavity. A milder form of diphtheria can be restricted to the skin. Less common consequences include myocarditis (about 20% of cases) and peripheral neuropathy (about 10% of cases).

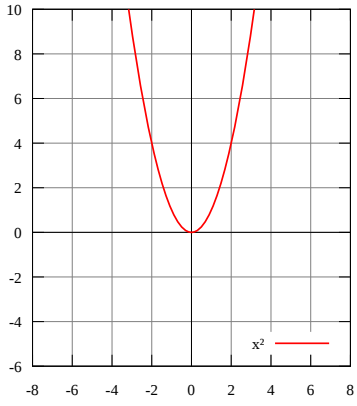


Figure: **Graph of $y=x^2$**

Diphtheria is a contagious disease spread by direct physical contact or breathing the aerosolized secretions of infected individuals. Historically quite common, diphtheria has largely been eradicated in industrialized nations through widespread vaccination. In the United States, for example, there were 52 reported cases of diphtheria between 1980 and 2000; between 2000 and 2007, there were only three cases as the diphtheria–pertussis–tetanus (DPT) vaccine is recommended for all school-age children. Boosters of the vaccine are recommended for adults, since the benefits of the vaccine decrease with age without constant re-exposure; they are particularly recommended for those traveling to areas where the disease has not been eradicated.

Advanced Cases of Diphtheria

In cases that progress beyond a throat infection, diphtheria toxin spreads through the blood and can lead to potentially life-threatening complications that affect other organs, such as the heart and kidneys. The toxin can cause damage to the heart that affects its ability to pump blood or the kidneys' ability to clear wastes. It can also cause nerve damage, eventually leading to paralysis. About 40% to 50% of those left untreated can die.

Diphtheria toxin is produced by *C. diphtheriae* only when it is infected with a bacteriophage that integrates the toxin-encoding genetic elements into the bacteria. Diphtheria toxin is a single, 60,000 dalton molecular weight protein composed of two peptide chains, fragment A and fragment B, held together by a disulfide bond. Fragment B is a recognition subunit that gains the toxin entry into the host cell by binding to the EGF-like domain of heparin-binding EGF-like growth factor (HB-EGF) on the cell surface. This signals the cell to internalize the toxin within an endosome via receptor-mediated endocytosis. Inside the endosome, the toxin is split by a trypsin-like protease into its individual A and B fragments. The acidity of the endosome causes fragment B to create pores in the endosome membrane, thereby catalyzing the release of fragment A into the cell's cytoplasm.

Fragment A inhibits the synthesis of new proteins in the affected cell. It does this by catalyzing ADP-ribosylation of elongation factor EF-2—a protein that is essential to the translation step of protein synthesis. This ADP-ribosylation involves the transfer of an ADP-ribose from NAD+ to a diphthamide (a modified histidine) residue within the EF-2 protein. Since EF-2 is needed for the moving of tRNA from the A-site to the P-site of the ribosome during protein translation, ADP-ribosylation of EF-2 prevents protein synthesis. ADP-ribosylation of EF-2 is reversed by giving high doses of nicotinamide (a form of vitamin B3), since this is one of the reaction ‘s end-products, thus high amounts will drive the reaction in the opposite direction counteracting the toxin.

 Figure: **Diphtheria toxin induced lesion**: Corynebacterium diphtheriae produces toxins that can affect the skin by causing skin lesions, as shown here.

Key Points

- Diptheria is caused bu the bacteria Corynebacterium diphtheriae, and is easily treated with antibiotics. It is now a fairly rare disease in developed countries.
- If left untreated and if infected by a bacteriophage, then Corynebacterium diphtheriae produces toxins that can lead to mortality.
- Diphtheria toxinis comprised of two fragments, fragment A and fragment B;. Fragment B binds to the target cell surface and allows entry into cells through endosomes; fragment A inhibits protein translation.
- Fragment A inhibits protein synthesis by catalyzing EF-2 a protein essential for tRNA movement during protein translation.

Key Terms

- **ribosylation**: The attachment of a ribose or ribosyl group to a molecule, especially to a polypeptide or protein
- **translation**: A process occurring in the ribosome, in which a strand of messenger RNA (mRNA) guides assembly of a sequence of amino acids to make a protein.

This page titled 6.1C: Diphtheria is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.3C: Diphtheria** is licensed CC BY-SA 4.0.

6.1D: Otitis Media

Learning Objectives

- Discuss the causes and symptoms associated with otitis media

Otitis media is inflammation of the middle ear. It occurs in the area between the tympanic membrane and the inner ear, also effecting a duct known as the eustachian tube. It is one of the two most common causes of earache – the other being otitis externa. Diseases other than ear infections can also cause ear pain, including various cancers of any structure that share nerve supply with the ear. Though painful, otitis media is not threatening and usually heals on its own within 2–6 weeks. Typically, acute otitis media follows a cold. After a few days of a stuffy nose, the ear becomes involved and can cause severe pain. The pain will usually settle within a day or two, but can last over a week. Sometimes the ear drum ruptures, discharging pus from the ear, but the ruptured drum will usually heal rapidly.

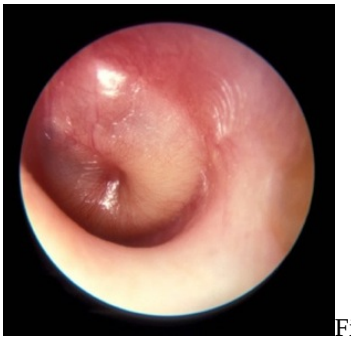


Figure: **Acute Otitis Media**: This is a view of the tympanic membrane showing inflammation and redness, typical of acute otitis media.

Otitis media is most commonly caused by infection with viral, bacterial, or fungal pathogens. The most common bacterial pathogen is Streptococcus pneumoniae. Others include Pseudomonas aeruginosa, nontypeable Haemophilus influenzae and Moraxella catarrhalis. Among older adolescents and young adults, the most common cause of ear infections is Haemophilus influenzae. Viruses like respiratory syncytial virus (RSV) and those that cause the common cold may also result in otitis media by damaging the normal defenses of the epithelial cells in the upper respiratory tract. A major risk factor for developing otitis media is Eustachian tube dysfunction, which leads to the ineffective clearing of bacteria from the middle ear.

Otitis media caused by bacterial infections are due to Trimeric Autotransporter Adhesins (TAA; proteins found on the outer membrane of Gram-negative bacteria. Bacteria use TAAs in order to infect their host cells via a process called cell adhesion. TAAs are virulence factors; an infective agent that infects the host cell by attaching to them and secreting the virulence factor by a secretion pathway. The UspA1 protein domain is a TAA found in the bacteria Moraxella catarrhalis, which causes middle ear infections in humans.

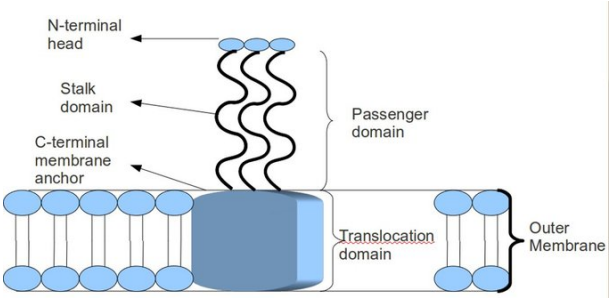


Figure: **Trimeric Autotransporter Adhesin structure**: The structure on the top (outside) of the outer membrane is a TAA protein. Various parts of the TAA are labelled, including the N-terminal head, stalk domain and C-terminal membrane anchor.

Key Points

- Bacterial-caused earaches are often due to Streptococcus pneumoniae, a common bacterial infection.
- Trimeric Autotransporter Adhesins on the surface of bacteria are the proteins responsible for earaches.
- TAA proteins bind to host cells, allowing the invading bacteria to transfer virulence factors which then cause inflammation of the middle ear.

Key Terms

- **Eustachian tube**: In humans and other land vertebrates, a tube that links the pharynx to the cavity of the middle ear to allow the equalization of the pressure on both sides of the eardrum.
- **tympanic**: relating to the eardrum or middle ear; tympanal

---

This page titled 6.1D: Otitis Media is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.3D: Otitis Media** is licensed CC BY-SA 4.0.

6.1E: Whooping Cough

Learning Objectives

- Describe the mechanism of action and causes of pertussis causing bacteria

Pertussis

Pertussis, also known as whooping cough, is an infection of the respiratory system characterized by a “whooping” sound that an afflicted person makes when breathing inwards. Only 50% of patients actually display the classic sound as they attempt to draw breath over a partially closed glottis. In the U.S., the infection was responsible for 5,000 to 10,000 deaths per year before a vaccine was developed and made available. Vaccination has transformed this. Between 1985 and 1988, fewer than 100 children died from pertussis. In 2000, according to the WHO, around 39 million people worldwide were being infected annually. Of these, about 297,000 died.

Causes of Pertussis

Pertussis is caused by the bacteria, Bordetella pertussis, a gram-negative, aerobic coccobacillus capsulate of the genus Bordetella. Bordetella pertussis infects its host by colonizing lung epithelial cells. The bacterium contains a surface protein, filamentous haemagglutinin adhesin, which binds to the sulfatides found on the cilia of epithelial cells. Once anchored, the bacterium produces tracheal cytotoxin, which stops the cilia from beating. This prevents the cilia from clearing debris from an organism ‘s lungs, and the body responds by sending the host into a coughing fit. These coughs expel some bacteria into the air, which are free to infect other hosts. There does not appear to be a zoonotic reservoir for B. pertussis. Humans are its only host. The bacterium is spread by airborne droplets, and its incubation period is one to two weeks.

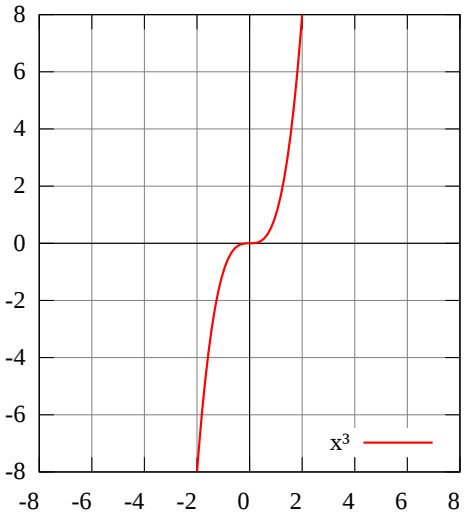


Figure: **Graph of $y=x^3$**

B. pertussis has the ability to inhibit the function of a host’s immune system, through virulence factors. Its virulence factors include pertussis toxin, filamentous hæmagglutinin, pertactin, fimbria, and tracheal cytotoxin. The pertussis toxin, or PTx, inhibits G protein coupling that regulates an adenylate cyclase-mediated conversion of ATP to cyclic AMP. The end result is that phagocytes convert too much ATP to cyclic AMP, which can cause disturbances in cellular signaling mechanisms. This prevents phagocytes from correctly responding to an infection. PTx, formerly known as lymphocytosis -promoting factor, causes a decrease in the entry of lymphocytes into lymph nodes. This can lead to a condition known as lymphocytosis, which is a large increase in the number of lymphocytes in an organism’s blood.

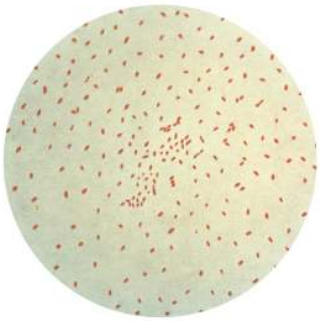


Figure: **Bordetella pertussis**: Bordetella pertussis, the bacteria that causes whooping cough

Key Points

- Whooping cough is caused by the bacteria Bordetella pertussis, which infects the respiratory system.
- There is no zoonotic reservoir of Bordetella pertussis, meaning that humans appear to be the only host of this bacteria.
- Bordetella pertussis produces a number of virulence factors, notably Ptx, which inhibits the ability of phagocytes to respond to infections. This helps Bordetella pertussis spread throughout a host.

Key Terms

- **zoonotic**: of or relating to zoonosis, the transmission of an infectious disease between species.
- **glottis**: an organ of speech, located in the larynx, and consisting of the true vocal cords and the opening between them
- **lymphocytes**: type of white blood cells in the vertebrate immune system

---

This page titled 6.1E: Whooping Cough is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.3E: Whooping Cough** is licensed CC BY-SA 4.0.

6.1F: Tuberculosis

Learning Objectives

- Summarize the risk factors associated with tuberculosis (TB)

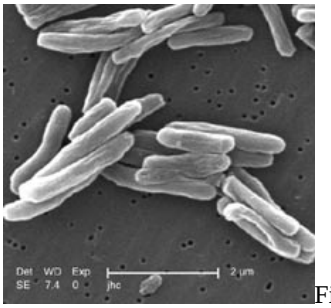


Figure: **Electron micrograph of Mycobacterium tuberculosis.**: This bacteria is primarily responsible for TB.

Tuberculosis (TB; short for tubercle bacillus) is a common, and in many cases lethal, infectious disease caused by various strains of mycobacteria, usually Mycobacterium tuberculosis . Tuberculosis typically attacks the lungs, but can also affect other parts of the body. It is spread through the air when people who have an active TB infection cough, sneeze, or otherwise transmit their saliva through the air. Most infections are asymptomatic and latent, but about one in 10 latent infections eventually progresses to active disease which, if left untreated, kills more than 50% of those infected. One third of the world's population is thought to have been infected with M. tuberculosis with new infections occurring at a rate of about one per second.

Symptoms

The classic symptoms of active TB infection are a chronic cough with blood-tinged sputum, fever, chills night sweats, and weight loss. Tuberculosis may infect any part of the body, but most commonly occurs in the lungs, known as pulmonary tuberculosis. Extrapulmonary TB occurs when tuberculosis develops outside of the lungs, but may co-exist with pulmonary TB as well. Extrapulmonary TB occurs more commonly in immunosuppressed persons and young children. In those with HIV this occurs in more than 50% of cases. Notable extrapulmonary infection sites include the pleura (in tuberculous pleurisy), the central nervous system (in tuberculous meningitis), the lymphatic system (in scrofula of the neck), the genitourinary system (in urogenital tuberculosis), and the bones and joints (osseous tuberculosis). Tuberculosis may become a chronic illness and cause extensive scarring in the upper lobes of the lungs.

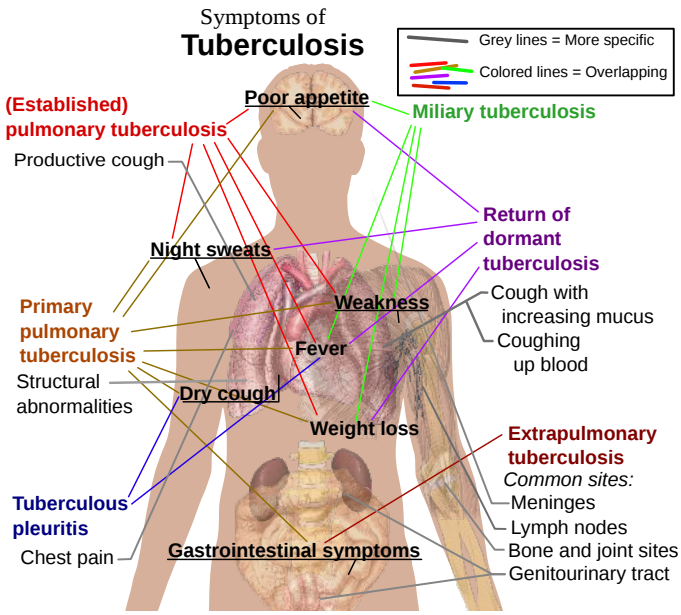


Figure: **Tuberculosis Symptoms.**: Diagram depicting various TB symptoms.

Diagnostics

Diagnosing active tuberculosis based merely on signs and symptoms is difficult, as is diagnosing the disease in those who are immunosuppressed. A diagnosis of TB should, however, be considered in those with signs of lung disease or constitutional symptoms lasting longer than two weeks. A chest x-ray and multiple sputum cultures for acid-fast bacilli are typically part of the initial evaluation. A definitive diagnosis of TB is made by identifying M. tuberculosis in a clinical sample such as sputum, pus, or a tissue biopsy. However, the difficult culture process for this slow-growing organism can take two to six weeks for blood or sputum culture.

The Mantoux tuberculin skin test is often used to screen people at high risk for TB. It involves injecting an protein extraction of the tuberculosis bacteria under the skin, and then examining the site 36-48 hours later. A person who has been exposed to the bacteria and has previously formed antibodies is expected to mount an immune response, displaying a raised, red area of skin at the site of injection. The test does have limited accuracy, especially in immunosuppressed people, and is typically used in combination with clinical findings and x-rays to reach a diagnosis.

Risk Factors

A number of factors make people more susceptible to TB infections. The most important risk factor globally is HIV; 13% of all TB cases are infected by the virus. This is a particular problem in sub-Saharan Africa, where rates of HIV are high. Tuberculosis is closely linked to both overcrowding and malnutrition, making it one of the principal diseases of poverty. Those at high risk thus include: people who inject illicit drugs, inhabitants and employees of locales where vulnerable people gather, such as prisons and homeless shelters; medically underprivileged and resource-poor communities; high-risk ethnic minorities, children in close contact with high-risk category patients, and health care providers serving these clients. Chronic lung disease is another significant risk factor. Those who smoke cigarettes have nearly twice the risk of TB than non-smokers. Other disease states can also increase the risk of developing tuberculosis, including alcoholism and diabetes mellitus. Certain medications that cause immunosuppression such as corticosteroids and infliximab, are becoming increasingly important risk factors, especially in the developed world.

Treatment

Treatment of TB uses antibiotics to kill the bacteria. Effective TB treatment is difficult, due to the unusual structure and chemical composition of the mycobacterial cell wall, which hinders the entry of drugs and makes many antibiotics ineffective. The two antibiotics commonly used are isoniazid and rifampicin. Treatments can be prolonged, from months to even years. A barrier to effective treatment is patient noncompliance. Due to the long duration of treatment, patients will often forget to take their

antibiotics periodically or stop taking them altogether. This contributes to the development of drug-resistant tuberculosis. Many strains of tuberculosis have already become resistant to previous treatments, including a strain that is resistant to all antibiotics.

Latent TB treatment usually employs a single antibiotic, while active TB disease is best treated with combinations of several antibiotics to reduce the risk of the bacteria developing antibiotic resistance. People with latent infections are also treated to prevent them from progressing to active TB disease later in life.

Key Points

- Tuberculosis is spread through the air when people who have an active TB infection cough, sneeze, or otherwise transmit their saliva through the air.
- The classic symptoms of active TB infection are a chronic cough with blood -tinged sputum, fever, night sweats, and weight loss.
- Diagnosis of active TB relies on radiology (commonly chest x-rays) as well as microscopic examination and microbiological culture of body fluids. Diagnosis of latent TB relies on the Mantoux tuberculin skin test.
- Antibiotic resistance is a growing problem in the treatment of tuberculosis.

Key Terms

- **latent**: Existing or present but concealed or inactive.
- **tuberculosis**: An infectious disease of humans and animals caused by a species of mycobacterium mainly infecting the lungs where it causes tubercles characterized by the expectoration of mucus and sputum, fever, weight loss, and chest pain. It is transmitted through inhalation or ingestion of bacteria.
- **pleurisy**: inflammation of lung pleura
- **sputum**: Matter coughed up and expectorated from the mouth, composed of saliva and discharges from the respiratory passages such as mucus, phlegm, or pus.

This page titled 6.1F: Tuberculosis is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.3F: Tuberculosis** is licensed CC BY-SA 4.0.

6.1G: Bacterial Pneumonias

Learning Objectives

- List the various causes of bacterial pneumonia

Pneumonia is an inflammatory condition of the lung, affecting primarily the microscopic air sacs known as alveoli. It is usually caused by infection with viruses or bacteria and less commonly other microorganisms, certain drugs and other conditions such as autoimmune diseases. Typical symptoms include a cough, chest pain, fever, and difficulty breathing. Diagnostic tools include x-rays and culture of the sputum. Vaccines to prevent certain types of pneumonia are available. Treatment depends on the underlying cause. Presumed bacterial pneumonia is treated with antibiotics. If the pneumonia is severe, the affected person is generally admitted to hospital.

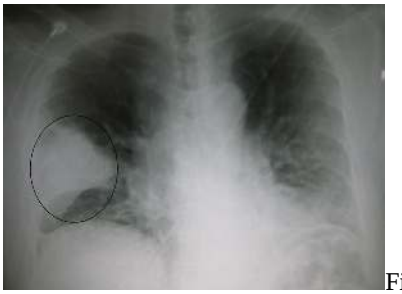


Figure: **Bacterial pneumonia**: A chest X-ray showing a very prominent wedge-shaped bacterial pneumonia in the right lung.

Bacteria are the most common cause of community-acquired pneumonia (CAP), with Streptococcus pneumoniae isolated in nearly 50% of cases. Other commonly isolated bacteria include: Haemophilus influenzae in 20%, Chlamydophila pneumoniae in 13%, and Mycoplasma pneumoniae in 3% of cases; Staphylococcus aureus; Moraxella catarrhalis; Legionella pneumophila and Gram-negative bacilli. A number of drug-resistant versions of the above infections are becoming more common, including drug-resistant Streptococcus pneumoniae (DRSP) and methicillin-resistant Staphylococcus aureus (MRSA). The spreading of organisms is facilitated when risk factors are present. Alcoholism is associated with Streptococcus pneumoniae, anaerobic organisms and Mycobacterium tuberculosis; smoking facilitates the effects of Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, and Legionella pneumophila. Exposure to birds is associated with Chlamydia psittaci; farm animals with Coxiella burnetti; aspiration of stomach contents with anaerobic organisms; and cystic fibrosis with Pseudomonas aeruginosa and Staphylococcus aureus. Streptococcus pneumoniae is more common in the winter, and should be suspected in persons who aspirate a large amount anaerobic organisms.

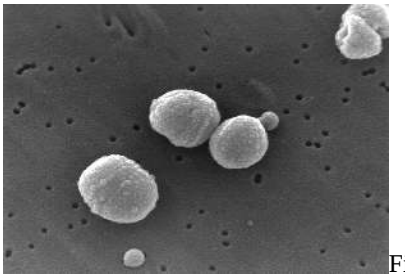


Figure: **Streptococcus pneumoniae**: The bacterium Streptococcus pneumoniae, a common cause of pneumonia, imaged by an electron microscope

Bacteria caused pneumonia fall into 3 groups:

1. Gram Positive. Streptococcus pneumoniae is the most common bacterial cause of pneumonia in all age groups except newborn infants. Streptococcus pneumoniae is a Gram-positive bacterium that often lives in the throat of people who do not have pneumonia. Other important Gram-positive causes of pneumonia are Staphylococcus aureus and Bacillus anthracis.
2. Gram Negative. Gram-negative bacteria are seen less frequently: Haemophilus influenzae, Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa, and Moraxella catarrhalis are the most common. These bacteria often live in the gut and enter the lungs when contents of the gut (such as vomit or faeces) are inhaled.

3. Atypical bacteria. “Atypical” bacteria are Coxiella burnetii, Chlamydophila pneumoniae, Mycoplasma pneumoniae, and Legionella pneumophila. Many people falsely believe they are called “atypical” because they are uncommon and/or do not respond to common antibiotics and/or cause atypical symptoms. In reality, they are “atypical” because they do not gram stain as well as gram-negative and gram-positive organisms. Pneumonia caused by Yersinia pestis is usually called pneumonic plague.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: ***CC BY-SA: Attribution-ShareAlike***

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- Peritonsillar abscess. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Peritonsillar_abscess**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Pharyngitis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Pharyngitis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Pharyngitis. **Provided by**: Wikipedia. **Located at**: **http://en.Wikipedia.org/wiki/Pharyngitis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Streptococcal pharyngitis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Strepto...al_pharyngitis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- peritonsillar abscess. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/peritonsillar%20abscess**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- hemolytic. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/hemolytic**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Pos strep. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Pos_strep.JPG**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Scarlett fever. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Scarlett_fever**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Scarlett fever. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Scarlett_fever**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Scarlett fever. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Scarlett_fever**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- enterotoxin. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/enterotoxin**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- exotoxin. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/exotoxin**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Shine-Dalgarno sequence. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/Shine-Dalgarno_sequence**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- scarlet fever. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/scarlet_fever**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Pos strep. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Pos_strep.JPG**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Scarlet fever 1.1. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi..._fever_1.1.JPG**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Diptheria. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Diptheria**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Diptheria. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Diptheria**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Diptheria. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Diptheria**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- translation. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/translation**. **License**: ***CC BY-SA: Attribution-ShareAlike***

- ribosylation. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/ribosylation**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Pos strep. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Pos_strep.JPG**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Scarlet fever 1.1. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi..._fever_1.1.JPG**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- A diphtheria skin lesion on the leg.nPHIL 1941 lores. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...1941_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- Function x^2. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Function_x%5E2.svg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Eustachian tube. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/Eustachian_tube**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Otitis media. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Otitis_media**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Otitis media. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Otitis_media**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Otitis media. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Otitis_media**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Trimeric Autotransporter Adhesins. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Trimeri...orter_Adhesins**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Otitis media. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Otitis_media**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Trimeric Autotransporter Adhesins. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Trimeri...orter_Adhesins**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Otitis media. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Otitis_media**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- tympanic. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/tympanic**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Pos strep. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Pos_strep.JPG**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Scarlet fever 1.1. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi..._fever_1.1.JPG**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- A diphtheria skin lesion on the leg.nPHIL 1941 lores. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...1941_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- Function x^2. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Function_x%5E2.svg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Acute Otitis Media. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...itis_Media.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Taabasic1. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Taabasic1.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Whooping cough. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Whooping_cough**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Whooping cough. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Whooping_cough**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Whooping cough. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Whooping_cough**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Whooping cough. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Whooping_cough**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- lymphocytes. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/lymphocytes**. **License**: ***CC BY-SA: Attribution-ShareAlike***

- glottis. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/glottis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- zoonotic. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/zoonotic**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Pos strep. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Pos_strep.JPG**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Scarlet fever 1.1. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi..._fever_1.1.JPG**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- A diphtheria skin lesion on the leg.nPHIL 1941 lores. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...1941_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- Function x^2. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Function_x%5E2.svg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Acute Otitis Media. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...itis_Media.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Taabasic1. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Taabasic1.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Function x^3. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Function_x%5E3.svg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Bordetella pertussis. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi..._pertussis.jpg**. **License**: ***Public Domain: No Known Copyright***
- Tuberculosis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Tuberculosis**. **License**: *CC BY-SA: Attribution-ShareAlike*
- pleurisy. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/pleurisy**. **License**: *CC BY-SA: Attribution-ShareAlike*
- sputum. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/sputum**. **License**: *CC BY-SA: Attribution-ShareAlike*
- latent. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/latent**. **License**: *CC BY-SA: Attribution-ShareAlike*
- tuberculosis. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/tuberculosis**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Pos strep. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Pos_strep.JPG**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Scarlet fever 1.1. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi..._fever_1.1.JPG**. **License**: *CC BY-SA: Attribution-ShareAlike*
- A diphtheria skin lesion on the leg.nPHIL 1941 lores. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...1941_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- Function x^2. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Function_x%5E2.svg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Acute Otitis Media. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...itis_Media.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Taabasic1. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Taabasic1.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Function x^3. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Function_x%5E3.svg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Bordetella pertussis. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi..._pertussis.jpg**. **License**: ***Public Domain: No Known Copyright***
- Mycobacterium tuberculosis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:My...berculosis.jpg**. **License**: ***Public Domain: No Known Copyright***
- Tuberculosis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Tuberculosis**. **License**: ***Public Domain: No Known Copyright***
- Pneumonia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Pneumonia**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Pneumonia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Pneumonia**. **License**: *CC BY-SA: Attribution-ShareAlike*

- Pneumonia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Pneumonia**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Bacterial pneumonia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Bacterial_pneumonia**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Pneumonia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Pneumonia**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- infection. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/infection**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Boundless. **Provided by**: Boundless Learning. **Located at**: **www.boundless.com//physics/de...ion/alveoli--2**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- pneumonia. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/pneumonia**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Pos strep. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Pos_strep.JPG**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Scarlet fever 1.1. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi..._fever_1.1.JPG**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- A diphtheria skin lesion on the leg.nPHIL 1941 lores. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...1941_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- Function x^2. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Function_x%5E2.svg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Acute Otitis Media. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...itis_Media.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Taabasic1. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Taabasic1.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Function x^3. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Function_x%5E3.svg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Bordetella pertussis. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi..._pertussis.jpg**. **License**: ***Public Domain: No Known Copyright***
- Mycobacterium tuberculosis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:My...berculosis.jpg**. **License**: ***Public Domain: No Known Copyright***
- Tuberculosis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Tuberculosis**. **License**: ***Public Domain: No Known Copyright***
- Streptococcus pneumoniae. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...pneumoniae.jpg**. **License**: ***Public Domain: No Known Copyright***
- PneumonisWedge09. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...nisWedge09.JPG**. **License**: ***CC BY-SA: Attribution-ShareAlike***

Key Points

- Most cases of pneumonia are caused by bacterial infections, and most of the bacterial infections are caused by the bacteria Streptococcus pneumoniae.
- The bacteria that cause pneumonia are split into three groups, gram-negative, gram-positive and atypical.
- Alcoholism is asociated with Streptococcus pneumoniae induced pneumonia and smoking exacerbates the situation.

Key Terms

- **pneumonia**: Pneumonia is an inflammatory condition of the lung, affecting primarily the microscopic air sacs known as alveoli.
- **infection**: An uncontrolled growth of harmful microorganisms in a host.
- **Alveoli**: alveolus (plural alveoli) a small air sac in the lungs, where oxygen and carbon dioxide are exchanged with the blood.

This page titled 6.1G: Bacterial Pneumonias is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.3G: Bacterial Pneumonias** is licensed CC BY-SA 4.0.

6.2: Bacterial Diseases of the Mouth

This page titled 6.2: Bacterial Diseases of the Mouth is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.7: Bacterial Diseases of the Mouth** is licensed CC BY-SA 4.0.

6.2A: Tooth and Gum Infections

Learning Objectives

- List the types of bacteria and issues associated with oral bacteria: Streptococci spp and Lactobaccilus acidophilus

Tooth and Gum Infections

Dental caries, also known as tooth decay or cavity, is a bacterial infection that causes demineralization and destruction of the hard tissues (enamel, dentin, and cementum). This usually happens from the production of acid by bacterial fermentation of the food debris accumulated on the tooth surface. If demineralization exceeds saliva and other remineralization factors, such as from calcium and fluoridated toothpastes, these hard tissues progressively break down, producing dental caries (cavities, holes in the teeth). The bacteria most responsible for dental cavities are the mutans streptococci, most prominently Streptococcus mutans and Streptococcus sobrinus, and lactobacilli. If left untreated, the disease can lead to pain, tooth loss, and infection. Today, caries remain one of the most common diseases throughout the world.

The mouth contains a wide variety of oral bacteria, but only a few specific species of bacteria are believed to cause dental caries: Streptococcus mutans and Lactobacilli among them. Lactobacillus acidophilus, Actinomyces viscosus, Nocardia spp., and Streptococcus mutans are most closely associated with caries, in particular root caries. Bacteria collect around the teeth and gums in a sticky, creamy-colored mass called plaque, which serves as a biofilm. Some sites collect plaque more commonly than others. Grooves on the occlusal surfaces of molar and premolar teeth provide microscopic retention sites for plaque bacteria, as do the approximal sites. Plaque may also collect above or below the gingiva where it is referred to as supra- or sub-gingival plaque respectively.

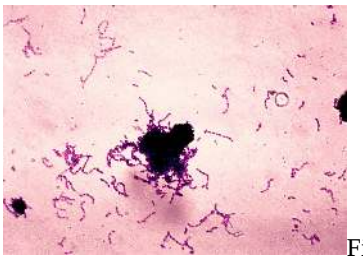


Figure: **Gram stain of Streptococcus mutans.**: Morphology is rod-like with chains when cultured on broth. Can cause subacute bacterial endocarditis and dental caries.

Oral bacteria have evolved mechanisms to sense their environment and evade or modify the host. Bacteria occupy the ecological niche provided by both the tooth surface and gingival epithelium. However, a highly efficient innate host defense system constantly monitors the bacterial colonization and prevents bacterial invasion of local tissues. A dynamic equilibrium exists between dental plaque bacteria and the innate host defense system. The oral cavity of the newborn baby does not contain bacteria but rapidly becomes colonized with bacteria such as Streptococcus salivarius. With the appearance of the teeth during the first year, colonization by Streptococcus mutans and Streptococcus sanguinis occurs as these organisms colonize the dental surface and gingiva. Other strains of streptococci adhere strongly to the gums and cheeks but not to the teeth. The gingival crevice area (supporting structures of the teeth) provides a habitat for a variety of anaerobic species. Bacteroides and spirochetes colonize the mouth around puberty.



Figure: **Dental caries**: This image shows destruction of a tooth by cervical decay from dental caries. This type of decay is also known as root decay.

The levels of oral spirochetes are elevated in patients with periodontal diseases. Among this group, Treponema denticola is the most studied and is considered one of the main etiological bacteria of periodontitis. Treponema denticola is a motile and highly proteolytic bacterium.

Spirochetes and fusi-form bacilli live as normal flora in the mouth, but the bacteria can cause infection and diseases to the oral cavity.

Porphyromonas gingivalis is a Gram-negative oral anaerobe strongly associated with chronic adult periodontitis. The bacterium produces a number of well-characterized virulence factors and can be manipulated genetically. The availability of the genome sequence is aiding our understanding of the biology of P. gingivalis and how it interacts with the environment, other bacteria, and the human host.

Aggregatibacter actinomycetemcomitans is considered an oral pathogen due to its virulence factors, its association with localized aggressive periodontitis in young adolescents, and studies indicating that it can cause bone loss.

Dental plaque is the material that adheres to the teeth and consists of bacterial cells (mainly S. mutans and S. sanguis), salivary polymers, and bacterial extracellular products. Plaque is a biofilm on the surfaces of the teeth. This accumulation of microorganisms subject the teeth and gingival tissues to high concentrations of bacterial metabolites which results in dental disease. If not taken care of, via brushing or flossing, the plaque can turn into tartar (its hardened form) and lead to gingivitis or periodontal disease.

Key Points

- Dental caries, also known as tooth decay or cavity, is a bacterial infection that causes demineralization and destruction of the hard tissues (enamel, dentin, and cementum).
- Tooth decay results from the production of acid by bacterial fermentation of the food debris accumulated on the tooth surface.
- Bacteria occupy the ecological niche provided by both the tooth surface and gingival epithelium. However, a highly efficient innate host defense system constantly monitors the bacterial colonization and prevents bacterial invasion of local tissues.
- Porphyromonas gingivalis is a Gram-negative oral anaerobe strongly associated with chronic adult periodontitis.
- Dental plaque is the material that adheres to the teeth and consists of bacterial cells (mainly S. mutans and S. sanguis), salivary polymers, and bacterial extracellular products.

Key Terms

- **cavity**: A soft area in a decayed tooth.
- **plaque**: a clearing in a bacterial lawn caused by a virus
- **dental plaque**: Dental plaque is the material that adheres to the teeth and consists of bacterial cells (mainly S. mutans and S. sanguis), salivary polymers, and bacterial extracellular products.
- **biofilm**: A thin film of mucus created by and containing a colony of bacteria and other microorganisms.

This page titled 6.2A: Tooth and Gum Infections is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.7A: Tooth and Gum Infections** is licensed CC BY-SA 4.0.

6.2B: Dental Caries

Learning Objectives

- Explain how dental caries can be prevented

Dental caries, also known as tooth decay or a cavity, is an infection, usually bacterial in origin, that causes demineralization of the hard tissues (enamel, dentin, and cementum) and destruction of the organic matter of the tooth, usually by production of acid by hydrolysis of the food debris accumulated on the tooth surface. If demineralization exceeds saliva and other remineralization factors such as from calcium and fluoridated toothpastes, these tissues progressively break down, producing dental caries (cavities, holes in the teeth). The two bacteria most commonly responsible for dental cavities are Streptococcus mutans and Lactobacillus. If left untreated, the disease can lead to pain, tooth loss, and infection. Today, caries remain one of the most common diseases throughout the world.

Caries can be classified by location, etiology, rate of progression, and affected hard tissues. These forms of classification can be used to characterize a particular case of tooth decay in order to more accurately represent the condition to others and also indicate the severity of tooth destruction.

Tooth decay disease is caused by specific types of bacteria that produce acid in the presence of fermentable carbohydrates such as sucrose, fructose, and glucose. The mineral content of teeth is sensitive to increases in acidity from the production of lactic acid. To be specific, a tooth (which is primarily mineral in content) is in a constant state of back-and-forth demineralization and remineralization between the tooth and surrounding saliva. For people with little saliva, especially due to radiation therapies that may destroy the salivary glands, there also exists remineralization gel. These patients are particularly susceptible to dental caries. When the pH at the surface of the tooth drops below 5.5, demineralization proceeds faster than remineralization (meaning that there is a net loss of mineral structure on the tooth's surface). Most foods are in this acidic range and without remineralization result in the ensuing decay.

As the enamel and dentin are destroyed, the cavity becomes more noticeable. The affected areas of the tooth change color and become soft to the touch. Once the decay passes through enamel, the dentinal tubules, which have passages to the nerve of the tooth, become exposed, causing a toothache. The pain may worsen with exposure to heat, cold, or sweet foods and drinks. Dental caries can also cause bad breath and foul tastes. In highly progressed cases, infection can spread from the tooth to the surrounding soft tissues. Complications such as cavernous sinus thrombosis and Ludwig's angina can be life-threatening.

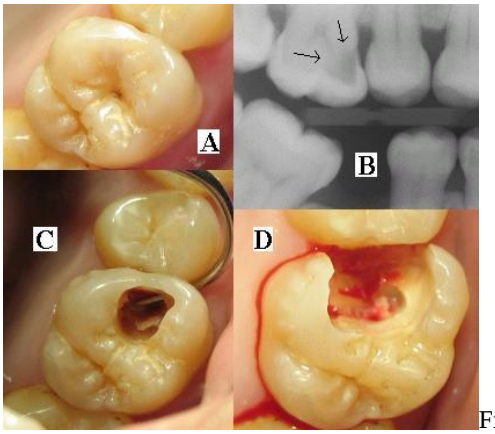


Figure: **Dental caries**: (A) A small spot of decay visible on the surface of a tooth. (B) The radiograph reveals an extensive region of demineralization within the dentin (arrows). (C) A hole is discovered on the side of the tooth at the beginning of decay removal. (D) All decay removed.

There are four main criteria required for caries formation: a tooth surface (enamel or dentin) caries-causing bacteria, fermentable carbohydrates (such as sucrose), and time. The caries process does not have an inevitable outcome, and different individuals will be susceptible to different degrees depending on the shape of their teeth, oral hygiene habits, and the buffering capacity of their saliva. Dental caries can occur on any surface of a tooth that is exposed to the oral cavity, but not the structures that are retained within the bone. All caries occur from acid demineralization that exceeds saliva and fluoride remineralization, and almost all acid

demineralization occurs where food (containing carbohydrate like sugar) is left on teeth. Though most trapped food is left between teeth, over 80% of cavities occur inside pits and fissures on chewing surfaces where brushing, fluoride, and saliva cannot reach to remineralize the tooth as they do on easy-to-reach surfaces that develop few cavities.

In most people, disorders or diseases affecting teeth are not the primary cause of dental caries. Ninety-six percent of tooth enamel is composed of minerals. These minerals, especially hydroxyapatite, will become soluble when exposed to acidic environments. Enamel begins to demineralize at a pH of 5.5. Dentin and cementum are more susceptible to caries than enamel because they have lower mineral content. Thus, when root surfaces of teeth are exposed from gingival recession or periodontal disease, caries can develop more readily. Even in a healthy oral environment, however, the tooth is susceptible to dental caries.

Bacteria in a person's mouth convert glucose, fructose, and most commonly sucrose (table sugar) into acids such as lactic acid through a glycolytic process called fermentation. If left in contact with the tooth, these acids may cause demineralization, which is the dissolution of its mineral content. The process is dynamic, however, as remineralization can also occur if the acid is neutralized by saliva or mouthwash.

At times, pit and fissure caries may be difficult to detect. Bacteria can penetrate the enamel to reach dentin, but then the outer surface may remineralize, especially if fluoride is present. These caries, sometimes referred to as "hidden caries", will still be visible on x-ray radiographs, but visual examination of the tooth would show the enamel intact or minimally perforated.

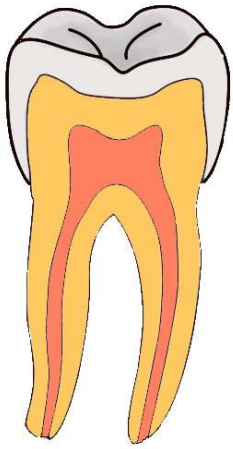


Figure: **Pit and fissure caries.**: The progression of pit and fissure caries resembles two triangles with their bases meeting along the junction of enamel and dentin.

Key Points

- Dentin is produced continuously throughout life by odontoblasts.
- Caries can be classified by location, etiology, rate of progression, and affected hard tissues.
- Enamel is a highly mineralized acellular tissue. Enamel rods, which are the basic unit of the enamel structure, run perpendicularly from the surface of the tooth to the dentin.
- There are four main criteria required for caries formation: a tooth surface (enamel or dentin), caries-causing bacteria, fermentable carbohydrates (such as sucrose), and time.
- Dental caries can occur on any surface of a tooth that is exposed to the oral cavity, but not the structures that are retained within the bone.
- The two bacteria most commonly responsible for dental cavities are Streptococcus mutans and Lactobacillus.
- The use of dental sealants is a means of prevention.
- Professional hygiene care consists of regular dental examinations and cleanings.
- An extraction can also serve as treatment for dental caries.
- In general, early treatment is less painful and less expensive than treatment of extensive decay.
- Recurrent caries, also described as secondary, are caries that appears at a location with a previous history of caries.
- Dentin is produced continuously throughout life by odontoblasts.
- Personal hygiene care consists of proper brushing and flossing daily. The purpose of oral hygiene is to minimize any etiologic agents of disease in the mouth.

- Primary diagnosis involves inspection of all visible tooth surfaces using a good light source, dental mirror and explorer. Dental radiographs (X-rays) may show dental caries before it is otherwise visible, in particular caries between the teeth.
- Caries can be classified by location, etiology, rate of progression, and affected hard tissues.
- In dentin from the deepest layer to the enamel, the distinct areas affected by caries are the advancing front, the zone of bacterial penetration, and the zone of destruction.
- Intrauterine and neonatal lead exposure promote tooth decay. Other divalent cations, such as cadmium, mimic the calcium ion and therefore exposure may promote tooth decay.
- From the deepest layer of the enamel to the enamel surface, the identified areas are the: translucent zone, dark zones, body of the lesion, and surface zone.
- Enamel is a highly mineralized acellular tissue. Enamel rods, which are the basic unit of the enamel structure, run perpendicularly from the surface of the tooth to the dentin.
- Some brands of smokeless tobacco contain high sugar content, increasing susceptibility to caries. Tobacco use is a significant risk factor for periodontal disease, which can cause the gingiva to recede.
- Reduced saliva is associated with increased caries.
- There are four main criteria required for caries formation: a tooth surface (enamel or dentin); caries-causing bacteria; fermentable carbohydrates (such as sucrose); and time.
- If demineralization exceeds saliva and other remineralization factors such as from calcium and fluoridated toothpastes, these tissues progressively break down, producing dental caries (cavities, holes in the teeth).
- The presentation of caries is highly variable.
- Bacteria collect around the teeth and gums in a sticky, creamy-coloured mass called plaque, which serves as a biofilm.
- Dental caries can occur on any surface of a tooth that is exposed to the oral cavity, but not the structures that are retained within the bone.
- The mineral content of teeth is sensitive to increases in acidity from the production of lactic acid.
- Radiographs are used for less visible areas of teeth and to judge the extent of destruction.
- Depending on the extent of tooth destruction, various treatments can be used to restore teeth to proper form, function, and aesthetics, but there is no known method to regenerate large amounts of tooth structure. Instead, dental health organizations advocate preventive and prophylactic measures, such as regular oral hygiene and dietary modifications, to avoid dental caries.
- Tooth decay disease is caused by specific types of bacteria that produce acid in the presence of fermentable carbohydrates such as sucrose, fructose, and glucose.
- Before the cavity forms, the process is reversible, but once a cavity forms, the lost tooth structure cannot be regenerated.
- The two bacteria most commonly responsible for dental cavities are Streptococcus mutans and Lactobacillus.

Key Terms

- **cementum**: A bony substance that covers the root of a tooth; cement.
- **enamel**: The hard covering on the exposed part of a tooth.
- **dentin**: The hard, dense calcareous material that makes up the bulk of a tooth

This page titled 6.2B: Dental Caries is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.7B: Dental Caries** is licensed CC BY-SA 4.0.

6.2C: Periodontal Disease

Learning Objectives

- Differentiate between peridontitis and gingivitis

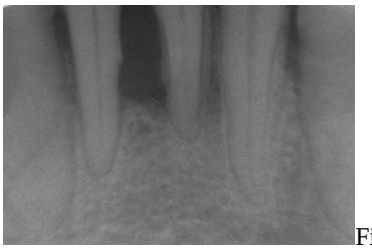
Periodontal disease is a type of disease that affects one or more of the periodontal tissues, which include:

- the cementum, or the outer layer of the roots of teeth
- the gingiva, or gum tissue
- the alveolar bone, or the bony sockets into which the teeth are anchored
- the periodontal ligament, which are the connective tissue fibers that run between the cementum and the alveolar bone.

While many different diseases affect the tooth-supporting structures, plaque-induced inflammatory lesions make up the vast majority of periodontal diseases and have traditionally been divided into two categories: peridontitis or gingivitis.

Peridontitis

Periodontitis is an inflammatory disease affecting the periodontium, or the tissues that surround and support the teeth. Periodontitis involves progressive loss of the alveolar bone around the teeth, and if left untreated, can lead to the loosening and subsequent loss of teeth. Periodontitis is caused by microorganisms that adhere to and grow on the tooth's surfaces, along with an overly aggressive immune response against these microorganisms.


Figure: **Periodontal disease**: This radiograph shows significant bone loss between the two roots of a tooth (black region). The spongy bone has receded due to infection under the tooth, reducing the bony support for the tooth.

In the early stages, periodontitis has very few symptoms and in many individuals the disease has progressed significantly before they seek treatment. Symptoms may include the following:

- Redness or bleeding of gums while brushing teeth, using dental floss, or biting into hard food
- Gum swelling that recurs
- Spitting out blood after brushing teeth
- Halitosis, or bad breath, and a persistent metallic taste in the mouth
- Gingival recession, resulting in apparent lengthening of teeth
- Deep pockets between the teeth and the gums, that are sites where the attachment has been gradually destroyed by collagen-destroying enzymes, known as collagenases
- Loose teeth, in the later stages

The gingival inflammation and bone destruction of peridontitis are largely painless. Hence, people may wrongly assume that painless bleeding after teeth cleaning is insignificant, although this may be a symptom of progressing periodontitis in that patient.

A diagnosis of periodontitis is established by inspecting the soft gum tissues around the teeth with a probe and by evaluating the patient's x-ray films to determine the amount of bone loss around the teeth.


Figure: **Gingivitis**: Severe gingivitis before (top) and after (bottom) treatment.

Gingivitis

Gingivitis, or inflammation of the gums, is a non-destructive peridontal disease. The primary cause of gingivitis is poor oral hygiene which leads to the accumulation of bacterial matrix at the gum line, called dental plaque. Other contributors are poor nutrition and underlying medical issues such as diabetes.

In some people, gingivitis progresses to periodontitis –- with the destruction of the gingival fibers, the gum tissues separate from the tooth, forming pockets between the tooth and gum. Subgingival microorganism (those that exist under the gum line) colonize the periodontal pockets and cause further inflammation in the gum tissues and progressive bone loss.

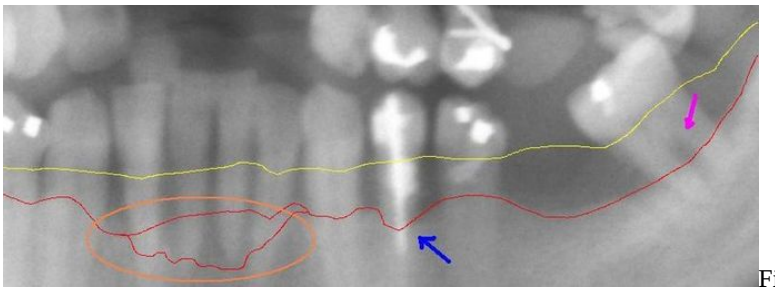
If left undisturbed, microbic plaque calcifies to form calculus, which is commonly called tartar. Calculus above and below the gum line must be removed completely by the dental hygienist or dentist to treat gingivitis and periodontitis. Although the primary cause of both gingivitis and periodontitis is the microbic plaque that adheres to the tooth surface, there are many other modifying factors. A very strong risk factor is one's genetic susceptibility. Several conditions and diseases, including Down syndrome, diabetes, and other diseases that affect one's resistance to infection also increase susceptibility to periodontitis.

Prevention

Daily oral hygiene measures to prevent periodontal disease include:

- Brushing teeth properly at least twice daily, with the patient attempting to direct the toothbrush bristles underneath the gum-line, to help disrupt the bacterial-mycotic growth and formation of subgingival plaque.
- Flossing daily and using interdental brushes as well as cleaning behind the last tooth, the third molar, in each quarter.
- Using an antiseptic mouthwash. Chlorhexidine gluconate-based mouthwash in combination with careful oral hygiene may cure gingivitis, although they cannot reverse any attachment loss due to periodontitis.
- Using periodontal trays to maintain dentist-prescribed medications at the source of the disease. The use of trays allows the medication to stay in place long enough to penetrate the biofilms where the microorganism are found.

Regular dental check-ups and professional teeth cleaning as required. Dental check-ups serve to monitor the person's oral hygiene methods and levels of attachment around teeth, identify any early signs of periodontitis, and monitor response to treatment.

 Figure: **Extensive periodontal disease**: This section from a panoramic x-ray film depicts the teeth of the lower left quadrant, exhibiting generalized severe bone loss of 30–80%. The red line depicts the existing bone level, and the yellow line depicts where the gingiva was originally (1–2 mm above the bone), prior to the patient developing periodontal disease. The pink arrow, on the right, points to a furcation involvement, or the loss of enough bone to reveal the location at which the individual roots of a molar begin to branch from the single root trunk; this is a sign of advanced periodontal disease.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: ***CC BY-SA: Attribution-ShareAlike***

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- Dental caries. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Dental_caries**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Oral microbiology. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Oral_microbiology**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- cavity. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/cavity**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- biofilm. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/biofilm**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- plaque. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/plaque**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- dental plaque. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/dental%20plaque**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Streptococcus mutans 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:St..._mutans_01.jpg**. **License**: ***Public Domain: No Known Copyright***
- Toothdecay. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Toothdecay.png**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Dental caries. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Dental_caries**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- dentin. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/dentin**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- cementum. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/cementum**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- enamel. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/enamel**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Streptococcus mutans 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:St..._mutans_01.jpg**. **License**: ***Public Domain: No Known Copyright***
- Toothdecay. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Toothdecay.png**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Pit-and-Fissure-Caries-GIF. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Pi...Caries-GIF.gif**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- ToothMontage3. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:ToothMontage3.jpg**. **License**: ***CC BY: Attribution***
- Periodontal Disease. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Periodontal_Disease**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- gingivitis. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/gingivitis**. **License**: ***CC BY-SA: Attribution-ShareAlike***

- periodontium. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/periodontium**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- periodontitis. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/periodontitis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Streptococcus mutans 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:St..._mutans_01.jpg**. **License**: ***Public Domain: No Known Copyright***
- Toothdecay. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Toothdecay.png**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Pit-and-Fissure-Caries-GIF. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Pi...Caries-GIF.gif**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- ToothMontage3. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:ToothMontage3.jpg**. **License**: ***CC BY: Attribution***
- Paro1. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Paro1.JPG**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Gingivitis before and after-2. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Gi...nd_after-2.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Generalized perio -touched up. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ge...touched_up.jpg**. **License**: ***Public Domain: No Known Copyright***

Key Points

- Peridontal tissues are the cementum, or the outer layer of the roots of teeth; the gingiva, or gums; the alveolar bone, or the bony sockets into which the teeth are anchored; and the periodontal ligament, which are the connective tissue fibers that run between the cementum and the alveolar bone.
- Periodontitis is an inflammatory disease affecting the periodontium, or the tissues that surround and support the teeth. Periodontitis involves progressive loss of the alveolar bone around the teeth, and if left untreated, can lead to the loosening and subsequent loss of teeth.
- Periodontitis is caused by microorganisms that adhere to and grow on the tooth ‘s surfaces, along with an overly aggressive immune response against these microorganisms.
- In the early stages, periodontitis has very few symptoms and in many individuals the disease has progressed significantly before they seek treatment. The gingival inflammation and bone destruction of peridontitis are largely painless.
- Gingivitis, or inflammation of the gums, is a non-destructive peridontal disease. The primary cause of gingivitis is poor oral hygiene which leads to the accumulation dental plaque at the gum line. Gingivitis can progress to periodontitis.
- Daily oral hygiene measures to prevent periodontal disease include brushing and flossing daily and using an antiseptic mouthwash.
- There are many surgical approaches used in treatment of advanced periodontitis, including open flap debridement, osseous surgery, as well as guided tissue regeneration and bone grafting.
- Several conditions and diseases, including Down syndrome, diabetes, and other diseases that affect one’s resistance to infection also increase susceptibility to periodontitis.
- The primary etiology (cause) of gingivitis is poor oral hygiene which leads to the accumulation of a mycotic and bacterial matrix at the gum line, called dental plaque. Other contributors are poor nutrition and underlying medical issues such as diabetes.
- Once successful periodontal treatment has been completed, with or without surgery, an ongoing regimen of “periodontal maintenance” is required.
- In the early stages, periodontitis has very few symptoms and in many individuals the disease has progressed significantly before they seek treatment. Symptoms may include the following: redness or bleeding of gums, gum swelling that recurs, spitting out blood after brushing teeth, halitosis, or bad breath, and a persistent metallic taste in the mouth, gingival recession, resulting in apparent lengthening of teeth, deep pockets between the teeth and the gums, and loose teeth
- Periodontitis is caused by microorganisms that adhere to and grow on the tooth’s surfaces.
- The extent of disease refers to the proportion of the dentition affected by the disease in terms of percentage of sites. Generally, six probing sites around each tooth are recorded, as follows: mesiobuccal, mid-buccal, distobuccal, mesiolingual, mid-lingual,

and distolingual.

- The severity of disease refers to the amount of periodontal ligament fibers that have been lost, termed clinical attachment loss.
- Smoking is a factor that increases the occurrence of periodontitis
- The 1999 classification system for periodontal diseases and conditions listed seven major categories of periodontal diseases, of which the last six are termed destructive periodontal disease because the damage is essentially irreversible. The seven categories are as follows:
- Gingivitis
- Chronic periodontitis
- Aggressive periodontitis
- Periodontitis as a manifestation of systemic disease
- Necrotizing ulcerative gingivitis/periodontitis
- Abscesses of the periodontium
- Combined periodontic-endodontic lesions

Key Terms

- **periodontitis**: An inflammatory disease that affects the periodontium—the tissues that surround and support the teeth–and can lead to tooth loss.
- **periodontium**: The specialized tissues that both surround and support the teeth, maintaining them in the maxillary and mandibular bones; the tissues including alveolar bone, cementum, gums, and periodontal ligament.
- **gingivitis**: Inflammation of the gums or gingivae.

This page titled 6.2C: Periodontal Disease is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.7C: Periodontal Disease** is licensed CC BY-SA 4.0.

6.3: Bacterial Diseases of the Digestive System

This page titled 6.3: Bacterial Diseases of the Digestive System is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.8: Bacterial Diseases of the Digestive System** is licensed CC BY-SA 4.0.

6.3A: Bacterial Gastroenteritis

Learning Objectives

- Describe the cause and effect of bacterial gastroenteritis

Gastroenteritis is a medical condition characterized by inflammation ("-itis") of the gastrointestinal tract that involves both the stomach ("gastro"-) and the small intestine ("entero"-), resulting in some combination of diarrhea, vomiting, and abdominal pain and cramping. Although unrelated to influenza, it has also been called 'stomach flu' and 'gastric flu'.

Globally, most cases in children are caused by rotavirus. Less common causes include other bacteria (or their toxins) and parasites. Transmission may occur due to consumption of improperly prepared foods, contaminated water, or via close contact with individuals who are infectious. The foundation of management for this illness is adequate hydration. For mild or moderate cases, this can typically be achieved via oral rehydration solution. For more severe cases, intravenous fluids may be needed. Gastroenteritis primarily affects children and those in the developing world. Gastroenteritis typically involves both diarrhea and vomiting, or less commonly, presents with only one or the other. Abdominal cramping may also be present.

Signs and symptoms usually begin 12–72 hours after contracting the infectious agent. Some bacterial infections may be associated with severe abdominal pain and may persist for several weeks. In the developed world, *Campylobacter jejuni* is the primary cause of bacterial gastroenteritis, with half of these cases associated with exposure to poultry. In children, bacteria are the cause in about 15% of cases, with the most common types being *Escherichia coli*, *Salmonella*, *Shigella*, and *Campylobacter* species. If food becomes contaminated with bacteria and remains at room temperature for a period of several hours, the bacteria multiply and increase the risk of infection in those who consume the food. Toxigenic *Clostridium difficile* is an important cause of diarrhea that occurs more often in the elderly. Infants can carry these bacteria without developing symptoms. It is a common cause of diarrhea in those who are hospitalized and is frequently associated with antibiotic use. *Staphylococcus aureus* infectious diarrhea may also occur in those who have used antibiotics. "Traveler's diarrhea" is usually a type of bacterial gastroenteritis. Acid-suppressing medication appears to increase the risk of significant infection after exposure to a number of organisms, including *Clostridium difficile*, *Salmonella*, and *Campylobacter* species.

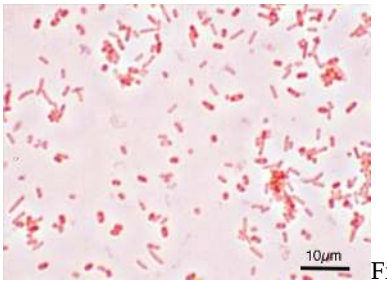


Figure: **Salmonella Typhimurium**: Salmonella enterica serovar Typhimurium as seen with a microscope at 1000 fold magnification and following Gram staining. Salmonella is a common cause of gastroenteritis in children.

Transmission rates are also related to poor hygiene, especially among children, in crowded households, and in those with pre-existing poor nutritional status. After developing tolerance, adults may carry certain organisms without exhibiting signs or symptoms, and thus act as natural reservoirs of contagion. While some agents (such as *Shigella*) only occur in primates, others may occur in a wide variety of animals (such as *Giardia*).

Gastroenteritis is typically diagnosed clinically, based on a person's signs and symptoms. Determining the exact cause is usually not needed as it does not alter management of the condition. However, stool cultures should be performed in those with blood in the stool, those who might have been exposed to food poisoning, and those who have recently traveled to the developing world. Electrolytes and kidney function should also be checked when there is a concern about severe dehydration.

A supply of easily accessible uncontaminated water and good sanitation practices are important for reducing rates of infection and clinically significant gastroenteritis. Personal measures (such as hand washing) have been found to decrease incidence and prevalence rates of gastroenteritis in both the developing and developed world by as much as 30%.

Key Points

- Gastroenteritis typically involves both diarrhea and vomiting, or less commonly, presents with only one or the other.
- Transmission rates are also related to poor hygiene, especially among children, in crowded households, and in those with pre-existing poor nutritional status.
- A supply of easily accessible uncontaminated water and good sanitation practices are important for reducing rates of infection and clinically significant gastroenteritis.

Key Terms

- **inflammation**: A condition of any part of the body, consisting in congestion of the blood vessels, with obstruction of the blood current, and growth of morbid tissue. It is manifested outwardly by redness and swelling, attended with heat and pain.
- **gastroenteritis**: Inflammation of the mucous membranes of the stomach and intestine; often caused by an infection.

This page titled 6.3A: Bacterial Gastroenteritis is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.8A: Bacterial Gastroenteritis** is licensed CC BY-SA 4.0.

6.3B: Staphylococcal Food Poisoning

Learning Objectives

- Recognize the causes of staphylococcal food poisoning

Staphylococcus is a Gram-positive bacteria which includes several species that can cause a wide variety of infections in humans and other animals through infection or the production of toxins. Staphylococcal toxins are a common cause of food poisoning, as they can be produced in improperly-stored food. The main coagulase-positive staphylococcus is *Staphylococcus aureus*. These bacteria can survive on dry surfaces, increasing the chance of transmission.

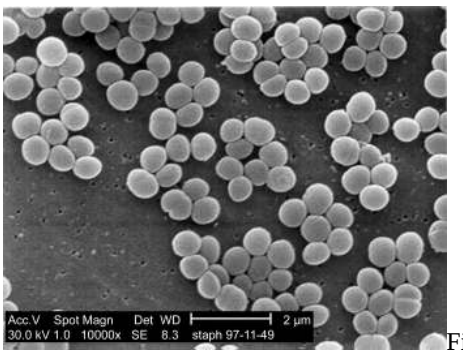


Figure: **Staphylococcus aureus**: Staphylococcus is a Gram-positive bacteria which includes several species that can cause a wide variety of infections in humans and other animals through infection or the production of toxins.

Any *S. aureus* infection can cause the staphylococcal scalded skin syndrome, a cutaneous reaction to exotoxin absorbed into the bloodstream. It can also cause a type of septicaemia called pyaemia. The infection can be life-threatening. Problematically, Methicillin-resistant *Staphylococcus aureus* (MRSA) has become a major cause of hospital-acquired infections and is being recognized with increasing frequency in community-acquired infections.

Foodborne illness usually arises from improper handling, preparation, or food storage. Good hygiene practices before, during, and after food preparation can reduce the chances of contracting an illness. There is a consensus in the public health community that regular hand-washing is one of the most effective defenses against the spread of foodborne illness. The action of monitoring food to ensure that it will not cause foodborne illness is known as food safety.

Foodborne disease can also be caused by a large variety of toxins that affect the environment, such as pesticides or medicines in food, and naturally toxic substances such as poisonous mushrooms or reef fish. In the past, bacterial infections were thought to be more prevalent because few places had the capability to test for norovirus and no active surveillance was being done for this particular agent. Toxins for bacterial infections are delayed because the bacteria need time to multiply. Their symptoms are usually not seen until 12–72 hours or more after eating contaminated food.

Key Points

- Staphylococcus is a Gram-positive bacteria which includes several species that can cause a wide variety of infections in humans and other animals through infection or the production of toxins.
- Foodborne illness usually arises from improper handling, preparation, or storage of food.
- Good hygiene practices before, during, and after food preparation can reduce the chances of contracting an illness.

Key Terms

- **toxin**: A toxic or poisonous substance produced by the biological processes of biological organisms.
- **norovirus**: The genus of a number of species of virus, family Caliciviridae, causing human gastroenteritis, of which Norwalk virus is the prototype.

This page titled 6.3B: Staphylococcal Food Poisoning is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.8B: Staphylococcal Food Poisoning** is licensed CC BY-SA 4.0.

6.3C: Salmonellosis

Learning Objectives

- Distinguish between nontyphoidal and typhoidal Salmonella

Salmonellosis is an infection with the Salmonella bacteria. Most people infected with Salmonella develop diarrhea, fever, vomiting, and abdominal cramps 12 to 72 hours after infection. In most cases, the illness lasts four to seven days, and most people recover without treatment. However, in some cases the diarrhea may be so severe that the patient becomes dangerously dehydrated and must be taken to a hospital. At the hospital, the patient may receive intravenous fluids to treat the dehydration, and may be given medications to relieve symptoms, such as fever reducers. In severe cases, the Salmonella infection may spread from the intestines to the bloodstream, and then to other body sites, and can cause death unless the person is promptly treated with antibiotics. The elderly, infants, and those with impaired immune systems are more likely to develop severe illness. Some people afflicted with Salmonellosis later experience reactive arthritis, which can have long-lasting, disabling effects.

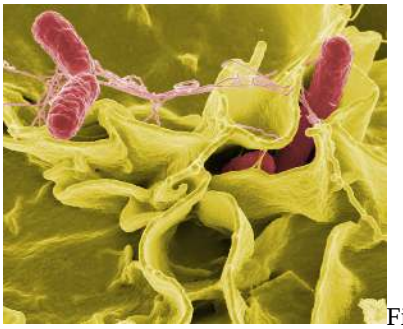


Figure: **Salmonella**: Salmonella is a genus of rod-shaped, gram-negative, non-spore-forming, predominantly motile enterobacteria (shown here in red).

Different Kinds of Salmonella

The different kinds of Salmonella include *S. bongori* and *S. enterica*. The type of Salmonella usually associated with infections in humans, nontyphoidal Salmonella, is usually contracted from: poultry, pork, and beef when the meat is prepared incorrectly or is infected with the bacteria after preparation; infected eggs, egg products, and milk when not prepared, handled, or refrigerated properly; reptiles (such as turtles, lizards, and snakes) which can carry the bacteria in their intestines; and tainted fruits and vegetables.

The typhoidal form of Salmonella can lead to typhoid fever. Typhoid fever is a life-threatening illness, and about four hundred cases are reported in the United States each year, with 75% of those acquired while traveling out of the country. It is carried only by humans and is usually contracted through direct contact with the fecal matter of an infected person. Typhoidal Salmonella is more commonly found in poorer countries, where unsanitary conditions are more likely to occur, and can affect as many as 21.5 million people a year.

Salmonella Infection

The Salmonella bacterium induces responses in the animal it is infecting, and this is what typically causes the symptoms rather than any direct toxin that is produced. Symptoms are usually gastrointestinal, including nausea, vomiting, abdominal cramps, and bloody diarrhea with mucus. Headache, fatigue, and rose spots are also possible. These symptoms can be severe, especially in young children and the elderly. Symptoms last generally up to a week, and can appear 12 to 72 hours after ingesting the bacterium. After bacterial infections, reactive arthritis (Reiter's syndrome) can develop.

An infectious process can only begin after living salmonellae (not only their toxins) reach the gastrointestinal tract. Some of the microorganisms are killed in the stomach, while the surviving salmonellae enter the small intestine and multiply in tissues (this is the localized form). By the end of the incubation period, the macro-organisms are poisoned by endotoxins that are released from the dead salmonellae. The local response to the endotoxins is enteritis and gastrointestinal disorder. In the generalized form of the

disease, salmonellae pass through the lymphatic system of the intestine into the blood of the patients (typhoid form) and are carried to various organs (liver, spleen, kidneys) to form secondary foci (septic form).

Endotoxins first act on affected organs' vascular and nervous systems, manifested by: increased permeability and decreased tone of the vessels, upset thermal regulation, vomiting, and diarrhea. In severe forms of the disease, enough liquid and electrolytes are lost to upset the body's metabolism of water and salt, decreasing the circulating blood volume and arterial pressure to enough of a degree to cause hypovolemic shock. Septic shock may also develop. Shock of mixed character (with signs of both hypovolemic and septic shock) is more common in severe salmonellosis. Oliguria and azotemia develop in severe cases as a result of kidney involvement due to hypoxia and bacteremia.

Key Points

- In severe cases, the Salmonella infection may spread from the intestines to the bloodstream, and then to other body sites, and can cause death unless the person is treated with antibiotics.
- The type of Salmonella usually associated with infections in humans, nontyphoidal Salmonella, is often contracted from contaminated food or reptiles.
- The Salmonella bacterium induces responses in the animal it is infecting, and this is what typically causes the symptoms, rather than any direct toxin that is produced.

Key Terms

- **typhoid fever**: An illness caused by the bacterium Salmonella typhi. Not to be confused with typhus.
- **endotoxin**: Any toxin secreted by a microorganism and released into the surrounding environment only when it dies.
- **arthritis**: Inflammation of a joint or joints causing pain and/or disability, swelling, and stiffness; and due to various causes such as infection, trauma, degenerative changes, or metabolic disorders.

This page titled 6.3C: Salmonellosis is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.8C: Salmonellosis** is licensed CC BY-SA 4.0.

6.3D: Typhoid Fever

Learning Objectives

- Summarize the four stages of untreated typhoid fever and methods of preventing it

Typhoid fever, also known as typhoid, is a common, worldwide bacterial disease. It is transmitted by the ingestion of food or water that has been contaminated with the feces of a person infected by the bacterium Salmonella typhi, serotype Typhi. The disease has been known by many names, such as gastric fever, abdominal typhus, infantile remittant fever, slow fever, nervous fever or pythogenic (originating from filth or putrefaction) fever. The name "typhoid" means "resembling typhus" and comes from the neuropsychiatric symptoms common to typhoid and typhus. The term "enteric fever" is a collective term that refers to typhoid and paratyphoid. The impact of this disease fell sharply with the improved sanitation techniques of the 20th century.

STAGES

Classically, the course of untreated typhoid fever is divided into four individual stages, each lasting approximately one week.

First stage: the temperature rises slowly and fever fluctuations are seen with relative bradycardia (slow pulse), malaise, headache and cough. Nose bleeds (epistaxis) are seen in 25% of cases and abdominal pain can occur. There is leukopenia (a decrease in the number of circulating white blood cells), with eosinopenia and relative lymphocytosis. The classic Widal test is negative in the first week.

Second stage: the patient lies prostrate with high fever in plateau around 40 °C (104 °F) and bradycardia, classically with a dicrotic pulse wave. Delirium is frequent; patients may be calm, but sometimes agitated. This delirium gives typhoid its nickname of "nervous fever". Rose spots appear on the lower chest and abdomen in around a third of patients. The Widal test is strongly positive with antiO and antiH antibodies. Blood cultures may be still positive at this stage. (The major symptom of typhoid is that the fever usually rises in the afternoon in the first and second stages.)


Figure: **Typhoid Fever**: Rose spots on the chest of a patient with typhoid fever due to the bacterium Salmonella typhi

Third stage: a number of complications can occur: intestinal hemorrhage due to bleeding in congested Peyer's patches and intestinal perforation in the distal ileum.

Fourth stage: by the end of the third week the fever starts subsiding (defervescence). This carries on into the fourth and final week.

PREVENTION

The bacteria which cause typhoid fever may be spread through poor hygiene habits and public sanitation conditions and, sometimes, also by flying insects feeding on infected feces. Public education campaigns encouraging people to wash their hands after defecating and before handling food are an important component in controlling the spread of the disease. A person may become an asymptomatic carrier of typhoid fever, suffering no symptoms, but capable of infecting others.

DIAGNOSIS

Diagnosis is made by any blood, bone marrow or stool cultures and with the Widal test (demonstration of salmonella antibodies against antigens O-somatic and H-flagellar). In epidemics and less wealthy countries, after excluding malaria, dysentery or pneumonia, a therapeutic trial time with chloramphenicol is generally undertaken while awaiting the results of the Widal test, and

cultures of the blood and stool. The Widal test is time-consuming and often, when a diagnosis is reached, it is too late to start an antibiotic regimen.

VACCINATION

There are two vaccines licensed for use for the prevention of typhoid: the live, oral Ty21a vaccine (sold as Vivotif Berna) and the injectable Typhoid polysaccharide vaccine (sold as Typhim Vi by Sanofi Pasteur and Typherix by GlaxoSmithKline).

TREATMENT

The rediscovery of oral rehydration therapy in the 1960s provided a simple way to prevent many of the deaths of diarrheal diseases in general. Where resistance is uncommon, the treatment of choice is a fluoroquinolone such as ciprofloxacin otherwise, a third-generation cephalosporin such as ceftriaxone or cefotaxime. Cefixime is a suitable oral alternative. Typhoid fever in most cases is not fatal. Antibiotics, such as ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole, amoxicillin and ciprofloxacin have been commonly used to treat typhoid fever.

Key Points

- The impact of Typhoid fever fell sharply with the improved sanitation techniques of the 20th century.
- Classically, the course of untreated typhoid fever is divided into four individual stages, each lasting approximately one week.
- Diagnosis is made by any blood, bone marrow or stool cultures and with the Widal test (demonstration of salmonella antibodies against antigens O-somatic and H-flagellar).

Key Terms

- **dicrotic**: A type of pulse associated with low systemic vascular resistance and a compliant aorta, e.g sepsis
- **Peyer's patch**: Peyer's patches (or aggregated lymphoid nodules) are usually found in the lowest portion of the small intestine, the ileum, in humans.
- **Widal test**: The agglutination test for typhoid fever.
- **eosinopenia**: Eosinopenia is a form of agranulocytosis where the number of eosinophil granulocyte is lower than expected; usually a predictor of bacterial infection.
- **lymphocytosis**: An increase in the number or proportion of lymphocytes in the blood.

This page titled 6.3D: Typhoid Fever is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.8D: Typhoid Fever** is licensed CC BY-SA 4.0.

6.3E: Cholera

Learning Objectives

- Describe the mode of transmission for Vibrio cholerae and the steps that can be taken to prevent this

Vibrio Cholerae

Cholera is an infection in the small intestine caused by the bacterium *Vibrio cholerae*. The primary symptoms of cholera are profuse, painless diarrhea and vomiting of clear fluid. These symptoms usually start suddenly, one to five days after ingestion of the bacteria. The diarrhea is frequently described as “rice water” in nature and may have a fishy odor. If the severe diarrhea is not treated with intravenous rehydration, it can result in life-threatening dehydration and electrolyte imbalances.



Figure: **Adult cholera patient**: A person with severe dehydration due to cholera – note the sunken eyes and decreased skin turgor which produces wrinkled hands.

Transmission

Cholera is typically transmitted by either contaminated food or water. In the developed world, seafood is the usual cause, while in the developing world it is more often water. Cholera is rarely spread directly from person to person. Both toxic and nontoxic strains exist.

Most *V. cholerae* bacteria, when consumed, do not survive the acidic conditions of the human stomach. The few surviving bacteria conserve their energy and stored nutrients during the passage through the stomach by shutting down much protein production. When the surviving bacteria exit the stomach and reach the small intestine, they need to propel themselves through the thick mucus that lines the small intestine to get to the intestinal walls, where they can thrive. *V. cholerae* bacteria begin production of the hollow cylindrical protein flagellin to make flagella. These flagella are cork-screw helical fibers that rotate to propel the bacteria through the mucus of the small intestine.

Once the cholera bacteria reach the intestinal wall, they no longer need the flagella to move. The bacteria stop producing the protein flagellin, again conserving energy and nutrients by changing the mix of proteins they manufacture in response to the changed chemical surroundings. The *V. cholerae* start producing the toxic proteins that give the infected person a watery diarrhea.

The diarrhea carries new generations of *V. cholerae* bacteria out into the drinking water of the next host if proper sanitation measures are not in place. A rapid dip-stick test is available to determine the presence of *V. cholerae* in a water supply. Samples that test positive should be further tested to determine antibiotic resistance. In epidemic situations, a clinical diagnosis may be made by taking a patient history and doing a brief examination. Treatment is usually started without or before confirmation by laboratory analysis. Although cholera may be life-threatening, prevention of the disease is normally straightforward if proper sanitation practices are followed. In developed countries, due to nearly universal advanced water treatment and sanitation practices, cholera is no longer a major health threat.

Breaking the Transmission Path

Effective sanitation practices, if instituted and adhered to in time, are usually sufficient to stop an epidemic. There are several points along the cholera transmission path at which its spread may be halted.

- Sterilization or proper disposal and treatment of infected fecal waste water produced by cholera victims and all contaminated materials (e.g. clothing, bedding, etc.) is essential. All materials that come in contact with cholera patients should be sanitized by washing in hot water, using chlorine bleach if possible. Hands that touch cholera patients or their clothing, bedding, etc., should be thoroughly cleaned and disinfected with chlorinated water or other effective antimicrobial agents.
- Antibacterial treatment of general sewage by chlorine, ozone, ultraviolet light or other effective treatment before it enters the waterways or underground water supplies helps prevent undiagnosed patients from inadvertently spreading the disease.
- Warnings about possible cholera contamination should be posted around contaminated water sources with directions on how to decontaminate the water (boiling, chlorination etc.) for possible use.
- All water used for drinking, washing, or cooking should be sterilized by either boiling, chlorination, ozone water treatment, ultraviolet light sterilization (e.g. by solar water disinfection), or antimicrobial filtration in any area where cholera may be present.
- Public health education and adherence to appropriate sanitation practices are of primary importance to help prevent and control transmission of cholera and other diseases.

Prevention and Treatment

A number of safe and effective oral vaccines for cholera are available. In most cases, cholera can be successfully treated with oral rehydration therapy (ORT), which is effective, safe, and simple to administer. Rice-based solutions are more efficient than glucose-based ones. In cases of severe dehydration, intravenous rehydration may be necessary. Antibiotic treatments for one to three days shorten the course of the disease and reduce the symptoms. People will recover without them, however, if sufficient hydration is maintained. Doxycycline is typically used first line, although some strains of V. cholerae have shown resistance. Testing for resistance during an outbreak can help determine appropriate future choices. Other antibiotics proven to be effective include cotrimoxazole, erythromycin, tetracycline, chloramphenicol, and furazolidone. Fluoroquinolones, such as norfloxacin, also may be used, but resistance has been reported.

Key Points

- The primary symptoms of cholera are profuse, painless diarrhea and vomiting of clear fluid.
- V. cholerae bacteria that survive the gastric juices produce the hollow cylindrical protein flagellin to make flagella, the cork-screw helical fibers they rotate to propel themselves through the mucus of the small intestine.
- A number of safe and effective oral vaccines for cholera are available.

Key Terms

- **flagella**: A flagellum is a lash-like appendage that protrudes from the cell body of certain prokaryotic and eukaryotic cells.
- **electrolyte**: any of the various ions (such as sodium or chloride) that regulate the electric charge on cells and the flow of water across their membranes

---

This page titled 6.3E: Cholera is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.8E: Cholera** is licensed CC BY-SA 4.0.

6.3F: Noncholera Vibrios

Learning Objectives

- Discuss the difference between cholera and noncholera causing Vibrios

Vibrio is a genus of Gram-negative bacteria possessing a curved rod shape (comma shape). Several species of Vibro can cause food borne infection, usually associated with eating undercooked seafood. Vibrio species are prevalent in estuarine and marine environments. Seven species can cause food borne infections associated with seafood. Vibrio cholerae O1 and O139 serovtypes produce cholera toxin and are agents of cholera. Vibrio species are facultative anaerobes that test positive for oxidase and do not form spores. All members of the genus are motile and have polar flagella with sheaths.

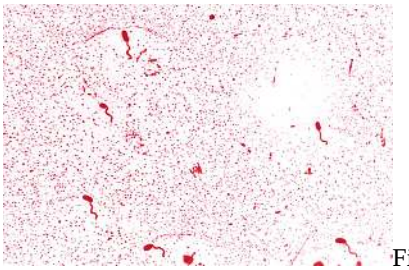


Figure: **Vibrio Cholerae**: Flagellar stain of V. cholerae

Patients with noncholera Vibrio wound infection or septicemia are much more ill and frequently have other medical conditions. Medical therapy consists of the following: prompt initiation of effective antibiotic therapy (doxycycline or a quinolone), intensive medical therapy with aggressive fluid replacement, vasopressors for hypotension and septic shock, early fasciotomy within 24 hours after development of clinical symptoms in patients with necrotizing fasciitis, early debridement of the infected wound, expeditious and serial surgical evaluation and intervention to prevent rapid deterioration, especially in patients with necrotizing fasciitis or compartment syndrome. Reconstructive surgery, such as skin graft, is indicated in the recovery phase.

Fecal-oral route infections in the terrestrial environment are responsible for epidemic cholera. Most strains cause gastroenteritis such as V. cholerae non-O1/O139 strains and Vibrio parahaemolytitcus strains capable of producing thermostable direct hemolysin (TDH) and/or TDH-related hemolysin. Vibrio vulnificus is responsible for seafood borne primary septicemia. Its infectivity depends primarily on the risk factors of the host. V. vulnificus infection has the highest fatality rate (50%) of any food borne pathogen. Four other species (V. mimicus, V. hollisae, V. fluvialis, and V. furnissii) can cause gastroenteritis. Some strains of these species produce known toxins, but the pathogenic mechanism is largely not understood.

Key Points

- Vibrio species are prevalent in estuarine and marine environments. Seven species can cause food borne infections associated with seafood.
- Patients with noncholera Vibrio wound infection or septicemia are much more ill and frequently have other medical conditions.
- Early medical intervention is paramount and consists of antimicrobial therapy, intensive medical therapy for disease symptoms, and surgical removal of infected tissues if necessary.

Key Terms

- **necrotizing fasciitis**: Necrotizing fasciitis, commonly known as flesh-eating disease or flesh-eating bacteria syndrome, is a rare infection of the deeper layers of skin and subcutaneous tissues, that easily spreads across the fascial plane within the subcutaneous tissue.
- **hemolysin**: any substance that damages the membranes of red blood cells and thus releases hemoglobin
- **septicemia**: A disease caused by the presence of pathogenic organisms, especially bacteria or their toxins in the bloodstream, characterized by chills and fever.
- **vibrio**: Any of several bacteria, of the genus Vibrio, shaped like a curved rod.

This page titled 6.3F: Noncholera Vibrios is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.8F: Noncholera Vibrios** is licensed CC BY-SA 4.0.

6.3G: Pathogenic Escherichia coli

Learning Objectives

- Distinguish between the different types of pathogenic E. coli in regards to classification and mode of transmission

Escherichia coli (E. coli) is a Gram-negative, rod-shaped bacterium that is commonly found in the lower intestine of warm-blooded organisms (endotherms). Most E. coli strains are harmless, but some serotypes are pathogenic and can cause serious food poisoning in humans and other species. The harmless strains are part of the normal flora of the gut, and can benefit their hosts by producing vitamin K2, and by preventing the establishment of pathogenic bacteria within the intestine.

Pathogenic E. coli

Pathogenic E. coli strains can be categorized based on elements that can elicit an immune response in animals, namely: O antigen, K antigen, H antigen, and F antigen in the lipopolysaccharide (LPS) molecules found in the outer membrane of the E. coli cell. The O antigen is a polymer of immunogenic repeating oligosaccharides which is used for serotyping E.coli. It should be noted though that antibodies towards several O antigens cross-react with other O antigens and partially to K antigens not only from E. coli, but also from other Escherichia species and Enterobacteriaceae species. There are two separate groups of K-antigen groups, named group I and group II (while a small in-between subset (K3, K10, and K54/K96) has been classified as group III). Group I consists of 100 kDa (large) capsular polysaccharides, while those in Group II, associated with extraintestinal diseases, are under 50 kDa in size.

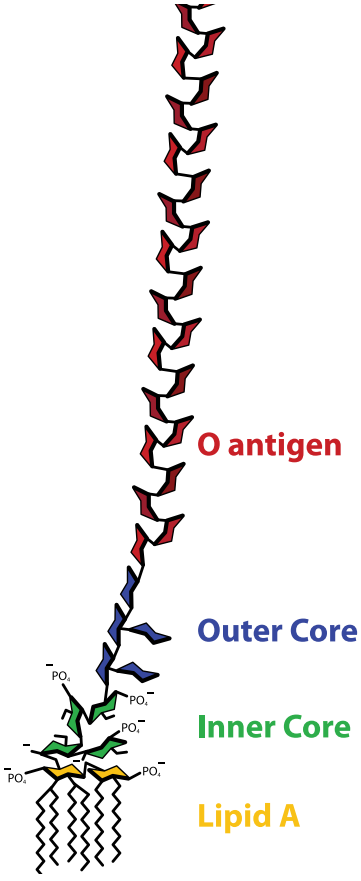


Figure: **Lipopolysaccharide**: Structure of a lipopolysaccharide showing the O antigen, core region and lipid A.

In humans and in domestic animals, virulent strains of E. coli can cause various diseases. In humans, gastroenteritis, urinary tract infections, and neonatal meningitis can occur. In rarer cases, virulent strains are also responsible for haemolytic-uremic syndrome, peritonitis, mastitis, septicemia, and Gram-negative pneumonia. Certain strains of E. coli produce potentially lethal toxins. Food poisoning caused by E. coli can result from eating unwashed vegetables or undercooked meat. If E. coli bacteria escape the

intestinal tract through a perforation (for example from an ulcer, a ruptured appendix, or due to a surgical error) and enter the abdomen, they usually cause peritonitis that can be fatal without prompt treatment.

Transmission of pathogenic E. coli often occurs via fecal–oral transmission. Common routes of transmission include unhygienic food preparation, farm contamination due to manure fertilization, irrigation of crops with contaminated greywater or raw sewage, feral pigs on cropland, or direct consumption of sewage-contaminated water. According to the U.S. Food and Drug Administration, the fecal-oral cycle of transmission can be disrupted by cooking food properly, preventing cross-contamination, instituting barriers such as gloves for food workers, instituting health care policies so food industry employees seek treatment when they are ill, pasteurization of juice or dairy products and proper hand washing requirements.

Uropathogenic E. coli

Uropathogenic E. coli (UPEC) is responsible for approximately 90% of urinary tract infections (UTI) seen in individuals with ordinary anatomy. In ascending infections, fecal bacteria colonize the urethra and spread up the urinary tract to the bladder, as well as to the kidneys (causing pyelonephritis), or the prostate in males. Because women have a shorter urethra than men, they are 14 times more likely to suffer from an ascending UTI. Uropathogenic E. coli use P fimbriae (pyelonephritis-associated pili) to bind urinary tract endothelial cells and colonize the bladder. UPEC can evade the body's innate immune defences (e.g. the complement system) by invading superficial umbrella cells to form intracellular bacterial communities (IBCs). They also have the ability to form K antigen, capsular polysaccharides that contribute to biofilm formation. Descending infections in turn, though relatively rare, occur when E. coli cells enter the upper urinary tract organs (kidneys, bladder or ureters) from the blood stream.

E. coli and Meningitis

Neonatal meningitis is produced by a serotype of E. coli that contains a capsular antigen called K1. The colonization of the newborn's intestines with these stems, that are present in the mother's vagina, lead to bacteraemia, which leads to meningitis. Severe meningitis in the neonates are caused because of the absence of the IgM antibodies from the mother (these do not cross the placenta because FcRn only mediates the transfer of IgG), plus the fact that the body recognizes as self the K1 antigen, as it resembles the cerebral glicopeptides. In stool samples, microscopy will show Gram-negative rods, with no particular cell arrangement.

Treating E. coli

Bacterial infections are usually treated with antibiotics. However, the antibiotic sensitivities of different strains of E. coli vary widely. As Gram-negative organisms, E. coli are resistant to many antibiotics that are effective against Gram-positive organisms. Antibiotics which may be used to treat E. coli infection include amoxicillin, as well as other semisynthetic penicillins, many cephalosporins, carbapenems, aztreonam, trimethoprim-sulfamethoxazole, ciprofloxacin, nitrofurantoin, and the aminoglycosides. Researchers have actively been working to develop safe, effective vaccines to lower the worldwide incidence of E. coli infection.

Key Points

- Pathogenic E. coli strains can be categorized based on elements that can elicit an immune response in animals. The different categories are: O antigen, K antigen, H antigen, and F antigen in the lipopolysaccharide.
- In humans and in domestic animals, virulent strains of E. coli can cause gastroenteritis, urinary tract infections, and neonatal meningitis.
- Bacterial infections are usually treated with antibiotics.

Key Terms

- **bacteraemia**: The medical condition of having bacteria in the bloodstream.
- **lipopolysaccharide**: any of a large class of lipids conjugated with polysaccharides
- **flora**: the microorganisms that inhabit some part of the body, such as intestinal flora
- **enterohemorrhagic E. coli**: strains of the bacterium Escherichia coli that, when infecting humans, have been linked with the severe complication hemolytic-uremic syndrome

This page titled 6.3G: Pathogenic Escherichia coli is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.8G: Pathogenic Escherichia coli** is licensed CC BY-SA 4.0.

6.3H: Campylobacter

Learning Objectives

- Discuss the method of transmission for Campylobacter

Description of Campylobacter Bacteria

Campylobacter is a genus of bacteria that are Gram-negative, spiral, and microaerophilic. The name means “twisted bacteria” because of the spiral formation; motile, with either unipolar or bipolar flagella, the organisms have a characteristic spiral/corkscrew appearance and are oxidase-positive.



Figure: **Epsilonproteobacteria**: Campylobacter bacteria are the number-one cause of food-related gastrointestinal illness in the United States. To learn more about this pathogen, ARS scientists are sequencing multiple Campylobacter genomes. This scanning electron microscope image shows the characteristic spiral, or corkscrew, shape of C. jejuni cells and related structures.

Campylobacter jejuni is now recognized as one of the main causes of bacterial foodborne disease in many developed countries. At least a dozen species of Campylobacter have been implicated in human disease, with C. jejuni and C. coli the most common. C. fetus is a cause of spontaneous abortions in cattle and sheep, as well as an opportunistic pathogen in humans.

Campylobacter species contain two flagellin genes in tandem for motility: flaA and flaB. These genes undergo intergenic recombination, further contributing to their virulence. Nonmotile mutants do not colonize.

Methods of Transmission and Treatment

The common routes of transmission are fecal-oral; the bacteria are introducted through ingestion of contaminated food or water and by the eating of raw meat. Infection produces an inflammatory, sometimes bloody diarrhea, periodontitis, or dysentery syndrome, mostly including cramps, fever and pain. The infection is usually self-limiting. In most cases symptomatic treatment by liquid and electrolyte replacement is enough in human infections. The use of antibiotics, on the other hand, is controversial.

Diagnosis

Symptoms typically last for five to seven days. The sites of tissue injury include the jejunum, the ileum, and the colon. Most strains of C. jejuni produce a toxin (cytolethal distending toxin) that hinders the cells from dividing and activating the immune system. This symptom helps the bacteria evade the immune system and survive for a limited time in the cells. A cholera-like enterotoxin was also once thought to be made, but this appears not to be the case. The organism produces diffuse, bloody, edematous, and exudative enteritis. Although rarely has the infection been considered a cause of hemolytic uremic syndrome and thrombotic thrombocytopenic purpura, no unequivocal case reports exist. In some cases, a Campylobacter infection can be the underlying cause of Guillain-Barré syndrome. Gastrointestinal perforation is a rare complication of ileal infection.

Diagnosis of the illness is made by testing a specimen of faeces (bowel motion). Standard treatment is now azithromycin and, on occassion, terbinafine. Quinolone antibiotics such as ciprofloxacin or levofloxacin are no longer as effective due to resistance.

Dehydrated children may require intravenous (by vein) fluid treatment in a hospital. The illness is contagious, and children must be kept at home until they have been clear of symptoms for at least two days. Good hygiene is important to avoid contracting the illness or spreading it to others.

Key Points

- Campylobacter jejuni is now recognized as one of the main causes of bacterial foodborne disease in many developed countries.
- The common routes of transmission are fecal-oral, ingestion of contaminated food or water, and the eating of raw meat.
- It produces an inflammatory, sometimes bloody, diarrhea, periodontitis or dysentery syndrome, mostly including cramps, fever and pain.

Key Terms

- **microaerophilic**: living and thriving in an environment low in oxygen
- **enteritis**: Inflammation of the intestines, generally the small intestine, that may lead to diarrhea.
- **flagella**: A flagellum is a lash-like appendage that protrudes from the cell body of certain prokaryotic and eukaryotic cells.

This page titled 6.3H: Campylobacter is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.8H: Campylobacter** is licensed CC BY-SA 4.0.

6.3I: Peptic Ulcer Disease

Learning Objectives

- List the causes of and treatments for peptic ulcer disease

A peptic ulcer, also known as peptic ulcer disease, is an erosion in the wall of the stomach, duodenum, or esophagus. As many as 70–90% of such ulcers are associated with Helicobacter pylori, a spiral-shaped bacterium that lives in the acidic environment of the stomach. Ulcers can also be caused or worsened by drugs such as aspirin, ibuprofen, and other NSAIDs.



Figure: **Deep gastric ulcer**: This image, acquired via endoscope, shows a deep gastric ulcer.

Symptoms

Symptoms of a peptic ulcer include abdominal pain, classically near the stomach with severity relating to mealtimes, about three hours after eating a meal; bloating and abdominal fullness; nausea; copious vomiting; loss of appetite and weight loss; vomiting of blood; and melena, which are tarry, foul-smelling feces due to oxidized iron from hemoglobin. Rarely, an ulcer can lead to a gastric or duodenal perforation, which leads to acute peritonitis. This is extremely serious and requires immediate surgery.

Causes

A major causative factor of ulcers is chronic inflammation due to Helicobacter pylori that colonizes the mucosa. The immune system is unable to clear the infection, despite the appearance of antibodies. Thus, the bacterium can cause a chronic active gastritis, resulting in a defect in the regulation of gastrin production by that part of the stomach. Gastrin secretion can either be increased, or as in most cases, decreased, resulting in a too basic or too acidic stomach environment, respectively. A decrease in acid can promote H. pylori growth and an increase in acid can contribute to the erosion of the mucosa and therefore ulcer formation.

Another major cause is the use of NSAIDs. The gastric mucosa protects itself from gastric acid with a layer of mucus, the secretion of which is stimulated by certain prostaglandins. NSAIDs block the function of cyclooxygenase 1 (cox-1), which is essential for the production of these prostaglandins.

Researchers also continue to look at stress as a possible cause, or at least complication, in the development of ulcers. There is debate as to whether psychological stress can influence the development of peptic ulcers. Burns and head trauma, however, can lead to physiologic stress ulcers, which are reported in many patients who are on mechanical ventilation.

Diagnosis

The diagnosis is mainly established based on the characteristic symptoms. Stomach pain is usually the first signal of a peptic ulcer. In some cases, doctors may treat ulcers without diagnosing them with specific tests and observe whether the symptoms resolve, this indicating that their primary diagnosis was accurate.

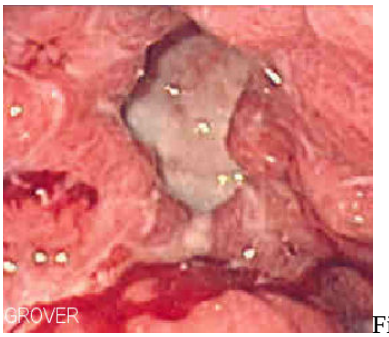


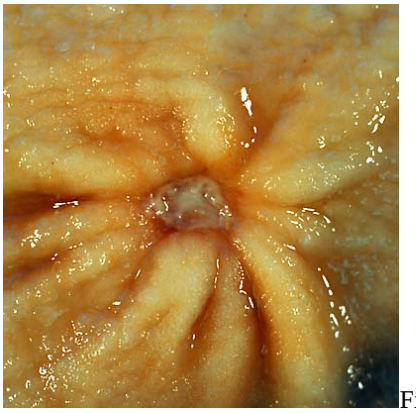
Figure: **Gastric ulcer**: This endoscopic image shows a gastric ulcer, which upon biopsy was shown to be gastric cancer.

Confirmation of the diagnosis is made with the help of tests such as endoscopies or barium contrast x-rays. The tests are typically ordered if the symptoms do not resolve after a few weeks of treatment. Tests are also given when first appear in a person who is over age 45 or who has other symptoms such as weight loss, because stomach cancer can cause similar symptoms. Also, when severe ulcers resist treatment, particularly if a person has several ulcers or the ulcers are in unusual places, a doctor may suspect an underlying condition that causes the stomach to overproduce acid.

An esophagogastroduodenoscopy (EGD), a form of endoscopy, also known as a gastroscopy, is carried out on patients in whom a peptic ulcer is suspected. By direct visual identification, the location and severity of an ulcer can be described. Moreover, if no ulcer is present, EGD can often provide an alternative diagnosis.

If a peptic ulcer perforates, air will leak from the inside of the gastrointestinal tract (which always contains some air) to the peritoneal cavity (which normally never contains air). This leads to “free gas” within the peritoneal cavity. If the patient stands erect, as when having a chest x-ray, the gas will float to a position underneath the diaphragm. Therefore, gas in the peritoneal cavity, shown on an erect chest x-ray or supine lateral abdominal x-ray, is an omen of perforated peptic ulcer disease.

Treatment


Figure: **Benign gastric ulcer**: This gastric ulcer was found in tissue removed during a gastrectomy.

Younger patients with ulcer-like symptoms are often treated with antacids. The ability of antacids to neutralize acidity by increasing the pH or blocking the secretion of acid by gastric cells is critical in reducing acidity in the stomach. Patients who are taking NSAIDs may also be prescribed a prostaglandin analogue in order to help prevent peptic ulcers by replacing the prostaglandins whose formation is blocked by NSAID use.

When H. pylori infection is present, the most effective treatments are combinations of two antibiotics, such as Clarithromycin, Amoxicillin, Tetracycline, and Metronidazole; and one proton pump inhibitor, sometimes in combination with antacids. In complicated, treatment-resistant cases, three antibiotics may be used together with a proton pump inhibitor. Treatment of H. pylori usually leads to clearing of infection, relief of symptoms and eventual healing of ulcers. Recurrence of infection can occur and retreatment may be required, if necessary with other antibiotics.

Perforated peptic ulcer is a surgical emergency and requires surgical repair of the perforation. Most bleeding ulcers require endoscopy urgently to stop bleeding with cautery, injection, or clipping.

Key Points

- 70–90% of peptic ulcers are associated with Helicobacter pylori, a spiral-shaped bacterium that lives in the acidic environment of the stomach.
- Diagnosis is mainly established based on the characteristic symptoms. Stomach pain is usually the first signal of a peptic ulcer.
- Treatment of H. pylori usually leads to clearing of infection, relief of symptoms, and eventual healing of ulcers.
- Gas in the peritoneal cavity, shown on an erect chest x-ray or supine lateral abdominal x-ray, is an omen of perforated peptic ulcer disease, which requires emergency surgery.
- Gastrointestinal bleeding is the most common complication. Sudden large bleeding can be life-threatening. It occurs when the ulcer erodes one of the blood vessels, such as the gastroduodenal artery.
- Most bleeding ulcers require endoscopy urgently to stop bleeding with cautery, injection, or clipping.
- During the active phase, the base of the ulcer shows 4 zones: inflammatory exudate, fibrinoid necrosis, granulation tissue and fibrous tissue.
- A gastric peptic ulcer is a mucosal defect which penetrates the muscularis mucosae and muscularis propria, produced by acid-pepsin aggression.
- Ulcers are not purely an infectious disease and that psychological factors do play a significant role.
- Diagnosis is mainly established based on the characteristic symptoms. Stomach pain is usually the first signal of a peptic ulcer.
- Gastric ulcers are most often localized on the lesser curvature of the stomach.
- Gas in the peritoneal cavity, shown on an erect chest X-ray or supine lateral abdominal X-ray, is an omen of perforated peptic ulcer disease.
- Gastrointestinal bleeding is the most common complication. Sudden large bleeding can be life-threatening. It occurs when the ulcer erodes one of the blood vessels, such as the gastroduodenal artery.
- Burning or gnawing feeling in the stomach area lasting between 30 minutes and 3 hours commonly accompanies ulcers.
- Typical ulcers tend to heal and recur and as a result the pain may occur for few days and weeks and then wane or disappear.

Key Terms

- **prostaglandin**: Any of a group of naturally occurring lipids derived from the C20 acid prostanoic acid; they have a number of physiological functions and may be considered to be hormones.
- **NSAID**: Any drug of the non-steroidal anti-inflammatory class used as a pain reliever.
- **gastrin**: A hormone that stimulates the production of gastric acid in the stomach.
- **gastritis**: Inflammation of the lining of the stomach, characterized by nausea, loss of appetite, and upper abdominal discomfort or pain.

This page titled 6.3I: Peptic Ulcer Disease is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.8I: Peptic Ulcer Disease** is licensed CC BY-SA 4.0.

6.3J: Listeriosis

Learning Objectives

- Discuss the mechanism of action for listeriosis

Listeriosis is a bacterial infection caused by a Gram-positive, motile bacterium, *Listeria monocytogenes*. Listeriosis has a low incidence in humans and occurs in pregnant women, newborn infants, elderly patients, and patients who are immunocompromised. Pregnant women are the most susceptible and infection can lead to early delivery, infection of the newborn, and death of the baby.

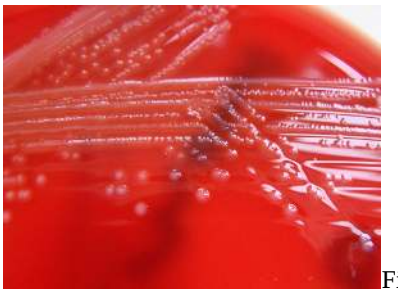


Figure: **Listeria monocytogenes**: A bacterial infection caused by a Gram-positive, motile bacterium, Listeria monocytogenes which is shown here on a blood agar plate.

The symptoms of listeriosis usually last 7–10 days, with the most common symptoms being fever, muscle aches, and vomiting. Diarrhea is another symptom, but less common. If the infection spreads to the nervous system it can cause meningitis, an infection of the covering of the brain and spinal cord.

Listeria originally evolved to invade membranes of the intestines, as an intracellular infection, and developed a chemical mechanism to do so. This involves a bacterial protein “internalin” which attaches to a protein on the intestinal cell membrane “cadherin. ” These adhesion molecules are also to be found in two other unusually tough barriers in humans – the blood-brain barrier and the feto-placental barrier, and this may explain the apparent affinity that Listeria has for causing meningitis and affecting babies in-utero. Particular strains of a food-borne bacteria are able to invade the heart, leading to serious and difficult-to-treat heart infections.

Listeria monocytogenes is ubiquitous in the environment. The main route of acquisition is by the ingestion of contaminated food products. Listeria has been isolated from raw meat, dairy products, vegetables, fruit and seafood. Soft cheeses, unpasteurized milk and unpasteurised pâté are potential dangers too. The main prevention is through the promotion of safe handling, cooking and consumption of food. This includes washing raw vegetables and cooking raw food thoroughly, as well as reheating leftover or ready-to-eat foods, like hot dogs, until steaming hot. Another preventative measure is to advise high-risk groups such as pregnant women and immunocompromised patients to avoid unpasteurized pâtés and foods such as soft cheeses.

In the advent of listeriosis, bacteremia should be treated for two weeks, meningitis for three weeks, and brain abscess for at least six weeks. Ampicillin generally is considered the antibiotic of choice and gentamicin is added frequently for its synergistic effects. About 10 percent of serious listeria infections involve cardiac infections that are difficult to treat, with more than one-third proving fatal.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: ***CC BY-SA: Attribution-ShareAlike***

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- Bacterial gastroenteritis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Bacterial_gastroenteritis%23Classification**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- inflammation. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/inflammation**. **License**: ***CC BY-SA: Attribution-ShareAlike***

- gastroenteritis. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/gastroenteritis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Salmonella Typhimurium Gram. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Sa...urium_Gram.jpg**. **License**: ***Public Domain: No Known Copyright***
- Staphylococcal infection. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Staphylococcal_infection**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Food poisoning. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Food_poisoning**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- norovirus. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/norovirus**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- toxin. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/toxin**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Salmonella Typhimurium Gram. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Sa...urium_Gram.jpg**. **License**: ***Public Domain: No Known Copyright***
- Staphylococcus aureus 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:St...pg%23filelinks**. **License**: ***Public Domain: No Known Copyright***
- Salmonella typhi typhoid fever PHIL 2215 lores. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Sa...2215_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- Salmonellosis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Salmonellosis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- arthritis. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/arthritis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- endotoxin. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/endotoxin**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- typhoid fever. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/typhoid_fever**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Salmonella Typhimurium Gram. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Sa...urium_Gram.jpg**. **License**: ***Public Domain: No Known Copyright***
- Staphylococcus aureus 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:St...pg%23filelinks**. **License**: ***Public Domain: No Known Copyright***
- Salmonella typhi typhoid fever PHIL 2215 lores. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Sa...2215_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- SalmonellaNIAID. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:SalmonellaNIAID.jpg**. **License**: ***Public Domain: No Known Copyright***
- Typhoid fever. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Typhoid_fever**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- lymphocytosis. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/lymphocytosis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- eosinopenia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/eosinopenia**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Peyer's patch. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Peyer's%20patch**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- dicrotic. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/dicrotic**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Widal test. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/Widal_test**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Salmonella Typhimurium Gram. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Sa...urium_Gram.jpg**. **License**: ***Public Domain: No Known Copyright***
- Staphylococcus aureus 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:St...pg%23filelinks**. **License**: ***Public Domain: No Known Copyright***
- Salmonella typhi typhoid fever PHIL 2215 lores. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Sa...2215_lores.jpg**. **License**: ***Public Domain: No Known Copyright***

- SalmonellaNIAID. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:SalmonellaNIAID.jpg**. **License**: ***Public Domain: No Known Copyright***
- Salmonella typhi typhoid fever PHIL 2215 lores. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Sa...2215_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- Cholera. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Cholera**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- flagella. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/flagella**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- electrolyte. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/electrolyte**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Salmonella Typhimurium Gram. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Sa...urium_Gram.jpg**. **License**: ***Public Domain: No Known Copyright***
- Staphylococcus aureus 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:St...pg%23filelinks**. **License**: ***Public Domain: No Known Copyright***
- Salmonella typhi typhoid fever PHIL 2215 lores. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Sa...2215_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- SalmonellaNIAID. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:SalmonellaNIAID.jpg**. **License**: ***Public Domain: No Known Copyright***
- Salmonella typhi typhoid fever PHIL 2215 lores. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Sa...2215_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- Adult cholera patient. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ad...ra_patient.jpg**. **License**: ***Public Domain: No Known Copyright***
- Food microbiology. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Food_mi...ology%23Vibrio**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Vibrio. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Vibrio%...rio_infections**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- septicemia. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/septicemia**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- hemolysin. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/hemolysin**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- necrotizing fasciitis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/necrotizing%20fasciitis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- vibrio. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/vibrio**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Salmonella Typhimurium Gram. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Salmonella_Typhimurium_Gram.jpg**. **License**: ***Public Domain: No Known Copyright***
- Staphylococcus aureus 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:St...pg%23filelinks**. **License**: ***Public Domain: No Known Copyright***
- Salmonella typhi typhoid fever PHIL 2215 lores. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Sa...2215_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- SalmonellaNIAID. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:SalmonellaNIAID.jpg**. **License**: ***Public Domain: No Known Copyright***
- Salmonella typhi typhoid fever PHIL 2215 lores. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Sa...2215_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- Adult cholera patient. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ad...ra_patient.jpg**. **License**: ***Public Domain: No Known Copyright***
- Vibrio cholerae 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Vi...holerae_01.jpg**. **License**: ***Public Domain: No Known Copyright***
- Pathogenic Escherichia coli. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Pathogenic_Escherichia_coli**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- bacteraemia. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/bacteraemia**. **License**: ***CC BY-SA: Attribution-ShareAlike***

- lipopolysaccharide. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/lipopolysaccharide**. **License**: *CC BY-SA: Attribution-ShareAlike*
- flora. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/flora**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Enterohemorrhagic E. coli. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Enterohemorrhagic_E._coli**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Salmonella Typhimurium Gram. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Salmonella_Typhimurium_Gram.jpg**. **License**: ***Public Domain: No Known Copyright***
- Staphylococcus aureus 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:St...pg%23filelinks**. **License**: ***Public Domain: No Known Copyright***
- Salmonella typhi typhoid fever PHIL 2215 lores. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Sa...2215_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- SalmonellaNIAID. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:SalmonellaNIAID.jpg**. **License**: ***Public Domain: No Known Copyright***
- Salmonella typhi typhoid fever PHIL 2215 lores. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Sa...2215_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- Adult cholera patient. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ad...ra_patient.jpg**. **License**: ***Public Domain: No Known Copyright***
- Vibrio cholerae 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Vi...holerae_01.jpg**. **License**: ***Public Domain: No Known Copyright***
- File:LPS.svg - Wikipedia, the free encyclopedia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/w/index.php?...LPS.svg&page=1**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Campylobacter. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Campylobacter**. **License**: *CC BY-SA: Attribution-ShareAlike*
- flagella. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/flagella**. **License**: *CC BY-SA: Attribution-ShareAlike*
- enteritis. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/enteritis**. **License**: *CC BY-SA: Attribution-ShareAlike*
- microaerophilic. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/microaerophilic**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Salmonella Typhimurium Gram. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Salmonella_Typhimurium_Gram.jpg**. **License**: ***Public Domain: No Known Copyright***
- Staphylococcus aureus 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:St...pg%23filelinks**. **License**: ***Public Domain: No Known Copyright***
- Salmonella typhi typhoid fever PHIL 2215 lores. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Sa...2215_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- SalmonellaNIAID. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:SalmonellaNIAID.jpg**. **License**: ***Public Domain: No Known Copyright***
- Salmonella typhi typhoid fever PHIL 2215 lores. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Salmonella_typhi_typhoid_fever_PHIL_2215_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- Adult cholera patient. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ad...ra_patient.jpg**. **License**: ***Public Domain: No Known Copyright***
- Vibrio cholerae 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Vi...holerae_01.jpg**. **License**: ***Public Domain: No Known Copyright***
- File:LPS.svg - Wikipedia, the free encyclopedia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/w/index.php?...LPS.svg&page=1**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Campylobacter. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Campylobacter.jpg**. **License**: ***Public Domain: No Known Copyright***
- Peptic ulcer disease. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Peptic_ulcer_disease**. **License**: *CC BY-SA: Attribution-ShareAlike*
- gastrin. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/gastrin**. **License**: *CC BY-SA: Attribution-ShareAlike*

- prostaglandin. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/prostaglandin**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- NSAID. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/NSAID**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- gastritis. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/gastritis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Salmonella Typhimurium Gram. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Salmonella_Typhimurium_Gram.jpg**. **License**: ***Public Domain: No Known Copyright***
- Staphylococcus aureus 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:St...pg%23filelinks**. **License**: ***Public Domain: No Known Copyright***
- Salmonella typhi typhoid fever PHIL 2215 lores. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Salmonella_typhi_typhoid_fever_PHIL_2215_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- SalmonellaNIAID. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:SalmonellaNIAID.jpg**. **License**: ***Public Domain: No Known Copyright***
- Salmonella typhi typhoid fever PHIL 2215 lores. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Salmonella_typhi_typhoid_fever_PHIL_2215_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- Adult cholera patient. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ad...ra_patient.jpg**. **License**: ***Public Domain: No Known Copyright***
- Vibrio cholerae 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Vi...holerae_01.jpg**. **License**: ***Public Domain: No Known Copyright***
- File:LPS.svg - Wikipedia, the free encyclopedia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/w/index.php?...LPS.svg&page=1**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Campylobacter. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Campylobacter.jpg**. **License**: ***Public Domain: No Known Copyright***
- Deep gastric ulcer. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:De...tric_ulcer.png**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Benign gastric ulcer 1. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Be...ic_ulcer_1.jpg**. **License**: ***Public Domain: No Known Copyright***
- Gastric ulcer 3. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Gastric_ulcer_3.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Listeriosis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Listeriosis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- incidence. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/incidence**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- listeriosis. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/listeriosis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- cadherin. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/cadherin**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- meningitis. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/meningitis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- blood-brain barrier. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/blood-brain_barrier**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Salmonella Typhimurium Gram. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Salmonella_Typhimurium_Gram.jpg**. **License**: ***Public Domain: No Known Copyright***
- Staphylococcus aureus 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Staphylococcus_aureus_01.jpg%23filelinks**. **License**: ***Public Domain: No Known Copyright***
- Salmonella typhi typhoid fever PHIL 2215 lores. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Salmonella_typhi_typhoid_fever_PHIL_2215_lores.jpg**. **License**: ***Public Domain: No Known Copyright***

- SalmonellaNIAID. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:SalmonellaNIAID.jpg**. **License**: ***Public Domain: No Known Copyright***
- Salmonella typhi typhoid fever PHIL 2215 lores. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Salmonella_typhi_typhoid_fever_PHIL_2215_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- Adult cholera patient. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ad...ra_patient.jpg**. **License**: ***Public Domain: No Known Copyright***
- Vibrio cholerae 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Vi...holerae_01.jpg**. **License**: ***Public Domain: No Known Copyright***
- File:LPS.svg - Wikipedia, the free encyclopedia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/w/index.php?...LPS.svg&page=1**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Campylobacter. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Campylobacter.jpg**. **License**: ***Public Domain: No Known Copyright***
- Deep gastric ulcer. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:De...tric_ulcer.png**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Benign gastric ulcer 1. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Be...ic_ulcer_1.jpg**. **License**: ***Public Domain: No Known Copyright***
- Gastric ulcer 3. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Gastric_ulcer_3.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Listeria monocytogenes - Columbia Horse Blood Agar -Detail | Flickr - Photo Sharing!. **Provided by**: Flickr. **Located at**: **http://www.flickr.com/photos/nathanreading/6268795918/**. **License**: ***CC BY: Attribution***

Key Points

- Listeriosis has a low incidence in humans and occurs in pregnant women, newborn infants, elderly patients, and patients who are immunocompromised.
- Listeria can invade through unusually tough barriers in humans: the blood-brain barrier and the feto-placental barrier, which contain high levels of cadherin protein on their membrane.
- The main route of acquisition of Listeria is through the ingestion of contaminated food products.

Key Terms

- **incidence**: a measure of the risk that a person develops a new condition within a specified period of time, usually a year
- **listeriosis**: An infectious disease of humans and animals caused by the bacteria Listeria monocytogenes and Listeria ivanovii, often through contaminated food.
- **meningitis**: Inflammation of the meninges, characterized by headache, neck stiffness and photophobia and also fever, chills, vomiting, and myalgia.
- **cadherin**: Any of a class of transmembrane proteins important in maintaining tissue structure.
- **blood-brain barrier**: a structure in the central nervous system (CNS) that keeps various substances found in the bloodstream out of the brain while allowing in the substances essential to metabolic function

---

This page titled 6.3J: Listeriosis is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.8J: Listeriosis** is licensed CC BY-SA 4.0.

6.4: Bacterial Diseases of the Urinary System

This page titled 6.4: Bacterial Diseases of the Urinary System is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.14: Bacterial Diseases of the Urinary System** is licensed CC BY-SA 4.0.

6.4A: Urinary Tract Infection (UTI)

A urinary tract infection (UTI) is an infection affecting the urinary tract; about 150 million people develop UTIs each year.

LEARNING OBJECTIVES

Summarize the various categories of urinary tract infection (UTI): complicated, uncomplicated, upper and lower UTIs

KEY TAKEAWAYS

Key Points

- About 150 million people develop a urinary tract infection each year, and they are more common in women than men.
- A urinary tract infection (UTI) is an infection that affects part of the urinary tract. When it affects the lower urinary tract it is known as a bladder infection (cystitis); when it affects the upper urinary tract it is known as kidney infection (pyelonephritis).
- UTIs are generally treatable with antibiotics, though resistance to some of the medications is growing.

Key Terms

- **urinary tract infection**: A bacterial infection that affects part of the urinary tract.

About 150 million people develop a urinary tract infection each year. They are more common in women than men. In women, they are the most common form of bacterial infection. Up to 10% of women have a urinary tract infection in a given year and half of women having at least one infection at some point in their lives. They occur most frequently between the ages of 16 and 35 years. Recurrences are common. Urinary tract infections have been described since ancient times with the first documented description in the Ebers Papyrus dated to c. 1550 BC.

A urinary tract infection (UTI) is an infection that affects part of the urinary tract. When it affects the lower urinary tract it is known as a bladder infection (cystitis); when it affects the upper urinary tract it is known as kidney infection (pyelonephritis). Symptoms from a lower urinary tract include pain with urination, frequent urination, and feeling the need to urinate despite having an empty bladder. Symptoms of a kidney infection include fever and flank pain usually in addition to the symptoms of a lower UTI. Rarely the urine may appear bloody. In the very old and the very young, symptoms may be vague or non-specific.

The most common cause of infection is Escherichia coli, though other bacteria or fungi may rarely be the cause. Risk factors include female anatomy, sexual intercourse, diabetes, obesity, and family history. Although sexual intercourse is a risk factor, UTIs are not classified as sexually transmitted infections (STIs). Kidney infection, if it occurs, usually follows a bladder infection but may also result from a blood-borne infection. Diagnosis in young healthy women can be based on symptoms alone. In those with vague symptoms, diagnosis can be difficult because bacteria may be present without there being an infection. In complicated cases or if treatment fails, a urine culture may be useful.

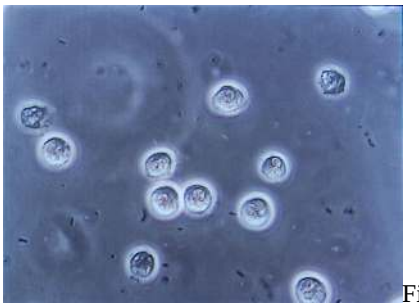
Categories of UTI

Uncomplicated UTIs

In uncomplicated cases, a diagnosis may be made and treatment given based on symptoms alone without further laboratory confirmation, and treatment involves a short course of antibiotics such as nitrofurantoin or trimethoprim / sulfamethoxazole. Resistance to many of the antibiotics used to treat this condition is increasing.

Complicated UTIs

In complicated cases, it may be useful to confirm the diagnosis via urinalysis, looking for the presence of urinary nitrites, white blood cells (leukocytes), or leukocyte esterase. Another test, urine microscopy, looks for the presence of red blood cells, white blood cells, or bacteria. A longer course or intravenous antibiotics may be needed. If symptoms do not improved in two or three days, further diagnostic testing may be needed. Phenazopyridine may help with symptoms. In those who have bacteria or white blood cells in their urine but have no symptoms, antibiotics are generally not needed, although during pregnancy is an exception. In those with frequent infections, a short course of antibiotics may be taken as soon as symptoms begin or long term antibiotics may be used as a preventative measure.

 Figure: **Bacteriuria and Pyuria**: Multiple bacilli (rod-shaped bacteria, here shown as black and bean-shaped) shown between white blood cells in urinary microscopy. These changes are indicative of a urinary tract infection.

Lower UTI

Lower urinary tract infection is also referred to as a bladder infection. The most common symptoms are burning with urination and having to urinate frequently (or an urge to urinate) in the absence of vaginal discharge and significant pain. These symptoms may vary from mild to severe and in healthy women last an average of six days. Some pain above the pubic bone or in the lower back may be present.

Upper UTI

People experiencing an upper urinary tract infection, or pyelonephritis, may experience flank pain, fever, or nausea and vomiting in addition to the classic symptoms of a lower urinary tract infection. Rarely the urine may appear bloody or contain visible pus in the urine.

Prevention

A number of measures have not been confirmed to affect UTI frequency including: urinating immediately after intercourse, the type of underwear used, personal hygiene methods used after urinating or defecating, or whether a person typically bathes or showers. There is similarly a lack of evidence surrounding the effect of holding one's urine, tampon use, and douching. In those with frequent urinary tract infections who use spermicide or a diaphragm as a method of contraception, they are advised to use alternative methods. In those with benign prostatic hyperplasia urinating in a sitting position appears to improve bladder emptying which might decrease urinary tract infections in this group.

For those with recurrent infections, taking a short course of antibiotics when each infection occurs is associated with the lowest antibiotic use. A prolonged course of daily antibiotics is also effective. Medications frequently used include nitrofurantoin and trimethoprim/sulfamethoxazole (TMP/SMX). Methenamine is another agent used for this purpose as in the bladder where the acidity is low it produces formaldehyde to which resistance does not develop. Some recommend against prolonged use due to concerns of antibiotic resistance.

This page titled 6.4A: Urinary Tract Infection (UTI) is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.14A: Urinary Tract Infection (UTI)** is licensed CC BY-SA 4.0.

6.4B: Cystitis

Learning Objectives

- Differentiate among the distinct types of cystitis: traumatic, interstitial, eosinophilic, hemorrhagic cystitis, and cystitis cystica, recognizing their causes and risk factors

A urinary tract infection (UTI), a bacterial infection that affects the lower urinary tract, is also known as a simple cystitis (a bladder infection). Symptoms from a lower urinary tract infection include painful urination and either frequent urination or the urge to urinate (or both). Cystitis is a urinary bladder inflammation that can result from any one of a number of distinct syndromes. It is most commonly caused by a bacterial infection in which case it is referred to as a urinary tract infection.

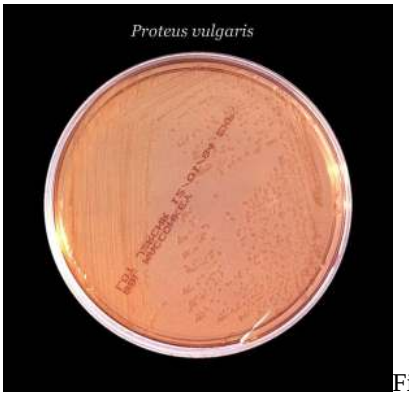


Figure: ***Proteus vulgaris on MacConkey agar****: After 24 hours, this inoculated MacConkey agar culture plate cultivated colonial growth of Gram-negative, rod-shaped, and facultatively anaerobic Proteus vulgaris bacteria. Normally found in the humans gastrointestinal tract, Proteus spp. are opportunistic pathogens, which means that they usually do not cause disease. However, under immunocompromised circumstances, i.e., weakened immunity, these bacteria can be found the culprit responsible for urinary tract infections such as cystitis and pyelonephritis.*

Signs and Symptoms

- Pressure in the lower pelvis
- Painful urination (dysuria)
- Frequent urination (polyuria) or urgent need to urinate (urinary urgency)
- Need to urinate at night (nocturia)
- Urine that contains traces of blood (haematuria)
- Dark, cloudy or strong-smelling urine
- Pain above the pubic bone, or in the lower back or abdomen
- Feeling unwell, weak, or feverish

There are several medically distinct types of cystitis, each having a unique etiology and therapeutic approach:

- Traumatic cystitis is probably the most common form of cystitis in the female. It is due to bruising of the bladder, usually by abnormally forceful sexual intercourse. This is often followed by bacterial cystitis, frequently by coliform bacteria being transferred from the bowel through the urethra into the bladder.
- Interstitial cystitis (IC) is considered more of an injury to the bladder resulting in constant irritation and rarely involves the presence of infection. IC patients are often misdiagnosed with UTI/cystitis for years before they are told that their urine cultures are negative. Antibiotics are not used to treatment of IC. The cause of IC is unknown, although some suspect it may be autoimmune where the immune system attacks the bladder. Several therapies are now available.
- Eosinophilic cystitis (EC) is a rare form of cystitis that is diagnosed via biopsy. In these cases, the bladder wall is infiltrated with a high number of eosinophils. The cause of EC may be attributed to infection by Schistosoma haematobium or by certain medications in afflicted children. Some consider it a form of interstitial cystitis.

- Hemorrhagic cystitis can occur as a side effect of cyclophosphamide, ifosfamide, and radiation therapy. Radiation cystitis, one form of hemorrhagic cystitis is a rare consequence of patients undergoing radiation therapy for the treatment of cancer. Several adenovirus serotypes have been associated with an acute, self-limited hemorrhagic cystitis, which occurs primarily in boys. It is characterized by hematuria, and virus can usually be recovered from the urine. In sexually active women the most common cause of urinary tract infection is from E. coli and Staphylococcus saprophyticus.
- Cystitis cystica is a chronic cystitis glandularis accompanied by the formation of cysts. This disease can cause chronic urinary tract infections. It appears as small cysts filled with fluid and lined by one or more layers of epithelial cells. These are due to hydropic degeneration in center of Brunn's nests

Key Points

- Cystitis is a urinary bladder inflammation that is most commonly caused by a bacterial infection in which case it is referred to as a urinary tract infection. Symptoms from a lower urinary tract include painful urination and either frequent urination or urge to urinate (or both), but neither may be present.
- Traumatic cystitis is probably the most common form of cystitis in the female. It is due to bruising of the bladder, usually by abnormally forceful sexual intercourse.
- Interstitial cystitis (IC) is considered more of an injury to the bladder resulting in constant irritation and rarely involves the presence of infection.

Key Terms

- **cystitis**: Cystitis is a urinary bladder inflammation that can result from any one of a number of distinct syndromes. It is most commonly caused by a bacterial infection in which case it is referred to as a urinary tract infection.

This page titled 6.4B: Cystitis is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.14B: Cystitis** is licensed CC BY-SA 4.0.

6.4C: Pyelonephritis

Learning Objectives

- Identify the main symptoms of pyelonephritis

Pyelonephritis is an inflammation of the kidney tissue, calyces, and renal pelvis. It is commonly caused by bacterial infection that has spread up the urinary tract or travelled through the bloodstream to the kidneys. A similar term is “pyelitis” which means inflammation of the pelvis and calyces. In other words, pyelitis together with nephritis is collectively known as pyelonephritis. Severe cases of pyelonephritis can lead to pyonephrosis (pus accumulation around the kidney), sepsis (a systemic inflammatory response of the body to infection), kidney failure and even death.

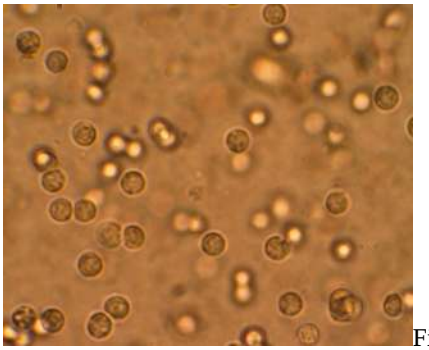


Figure: ***Urinary tract infection (UTI)****: White blood cells in the urine of someone with a UTI, seen under a microscope.*

Pyelonephritis presents with fever, accelerated heart rate, painful urination, abdominal pain radiating to the back, nausea, and tenderness at the costovertebral angle on the affected side. Pyelonephritis that has progressed to urosepsis may be accompanied by signs of septic shock, including rapid breathing, decreased blood pressure, violent shivering, and occasionally delirium. Pyelonephritis requires antibiotic therapy, and sometimes surgical intervention, as well as treatment of any underlying causes to prevent its recurrence.

Key Points

- Pyelonephritis is an inflammation of the kidney tissue and renal area of the pelvis.
- Pyelonephritis is most commonly caused by a bacterial infection ascending up the upper urinary tract.
- Severe cases of pyelonephritis can lead to sepsis, kidney failure, and death.
- Pyelonephritis presents with fever, accelerated heart rate, painful urination, abdominal pain, and nausea.
- Pyelonephritis requires antibiotic therapy, and sometimes surgical intervention, as well as treatment of any underlying causes to prevent recurrence.

Key Terms

- **pyelonephritis**: An ascending urinary tract infection that has reached the pelvis or the kidney.
- **Urinary tract**: The organ system that produces, stores, and eliminates urine. In humans it includes two kidneys, two ureters, the bladder, and the urethra.

This page titled 6.4C: Pyelonephritis is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.14C: Pyelonephritis** is licensed CC BY-SA 4.0.

6.4D: Leptospirosis

Learning Objectives

- Generalize the causes and mode of transmission for leptospirosis

Leptospirosis (also known as Weil's Syndrome, canicola fever, canefield fever, nanukayami fever, 7-day fever, Rat Catcher's Yellows, Fort Bragg fever, black jaundice, and Pretibial fever) is caused by bacteria of the genus *Leptospira*, and affects humans as well as other animals. Symptoms can range from none to mild such as headaches, muscle pains, and fevers; to severe with bleeding from the lungs or meningitis. If the infection causes the person to turn yellow, have kidney failure and bleeding it is then known as Weil's disease. If the infection causes lots of bleeding from the lungs it is known as severe pulmonary haemorrhage syndrome.

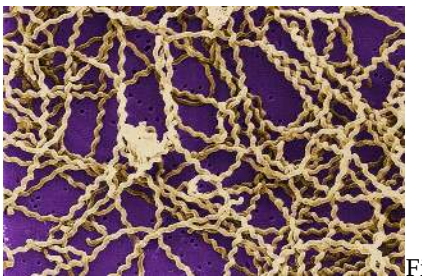


Figure: ***Leptospira bactera that cause Leptospirosis****: Scanning electron micrograph of a number of Leptospira sp. bacteria atop a 0.1 µm polycarbonate filter.*

Leptospirosis is among the world's most common diseases transmitted to people from animals. The infection is commonly transmitted to humans by allowing water that has been contaminated by animal urine to come in contact with unhealed breaks in the skin, eyes, or mucous membranes. Outside of tropical areas, leptospirosis cases have a relatively distinct seasonality, with most cases occurring in spring and autumn.

Leptospirosis is caused by a spirochaete bacterium called *Leptospira spp*. There are at least five serotypes of importance in the United States and Canada, all of which cause disease in dogs (Icterohaemorrhagiae, Canicola, Pomona, Grippotyphosa, and Bratislava).There are other (less common) infectious strains as well. Leptospirosis is transmitted by the urine of an infected animal and is contagious as long as it is still moist. Although rats, mice, and moles are important primary hosts, a wide range of other mammals (including dogs, deer, rabbits, hedgehogs, cows, sheep, raccoons, opossums, skunks, and certain marine mammals) are able to carry and transmit the disease as secondary hosts. Dogs may lick the urine of an infected animal off the grass or soil or drink from an infected puddle.

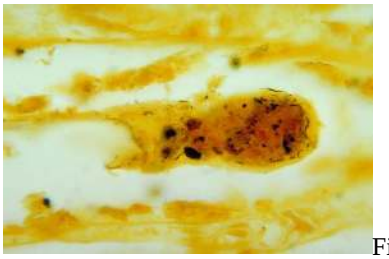


Figure: ***Leptospirosis in kidney****: Photomicrograph of kidney tissue, using a silver staining technique, revealing the presence of Leptospira bacteria.*

There have been reports of "house dogs" contracting leptospirosis from licking the urine of infected mice that enter the house. The type of habitats most likely to carry infectious bacteria are muddy riverbanks, ditches, gullies, and muddy livestock-rearing areas where there is regular passage of either wild or farm mammals. There is a direct correlation between the amount of rainfall and the incidence of leptospirosis, making it seasonal in temperate climates and year-round in tropical climates. Leptospirosis is also transmitted by the semen of infected animals. Humans become infected through contact with water, food, or soil containing urine from these infected animals. This may result from swallowing contaminated food and water or through skin contact. The disease is not known to be spread from person to person, and cases of bacterial dissemination in convalescence are extremely rare in humans. Leptospirosis is common among water-sport enthusiasts in specific areas, as prolonged immersion in water is known to promote the entry of the bacteria. Surfers and whitewater paddlers are at especially high risk in areas that have been shown to contain the

bacteria, and can contract the disease by swallowing contaminated water, splashing contaminated water into their eyes or nose, or exposing open wounds to infected water.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: ***CC BY-SA: Attribution-ShareAlike***

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- Urinary tract infection. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Urinary_tract_infection**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Boundless. **Provided by**: Boundless Learning. **Located at**: **www.boundless.com//microbiolo...ract-infection**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Bacteriuria pyuria 4. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ba...a_pyuria_4.jpg**. **License**: ***Public Domain: No Known Copyright***
- Cystitis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Cystitis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Urinary tract infection. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Urinary_tract_infection**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- cystitis. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/cystitis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Bacteriuria pyuria 4. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ba...a_pyuria_4.jpg**. **License**: ***Public Domain: No Known Copyright***
- Proteus McConkey. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...s_McConkey.jpg**. **License**: ***Public Domain: No Known Copyright***
- Pyelonephritis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Pyelonephritis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Urinary tract infection. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Urinary_tract_infection**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Urinary tract. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Urinary%20tract**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- pyelonephritis. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/pyelonephritis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Bacteriuria pyuria 4. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ba...a_pyuria_4.jpg**. **License**: ***Public Domain: No Known Copyright***
- Proteus McConkey. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...s_McConkey.jpg**. **License**: ***Public Domain: No Known Copyright***
- Pyuria. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Pyuria.JPG**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Leptospirosis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Leptospirosis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- leptospirosis. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/leptospirosis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Bacteriuria pyuria 4. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ba...a_pyuria_4.jpg**. **License**: ***Public Domain: No Known Copyright***
- Proteus McConkey. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...s_McConkey.jpg**. **License**: ***Public Domain: No Known Copyright***
- Pyuria. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Pyuria.JPG**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Leptospirosis%20in%20kidney. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Le..._in_kidney.jpg**. **License**: ***Public Domain: No Known Copyright***
- Scanning electron micrographu00a0of a number of Leptospira sp. bacteria atop a 0.1 u00b5mu00a0polycarbonateu00a0filter. **Provided by**: Wikimedia Commons. **Located at**: **en.Wikipedia.org/wiki/Leptosp...micrograph.jpg**. **License**: ***Public***

Domain: No Known Copyright

Key Points

- Leptospirosis symptoms can range from none to mild such as headaches, muscle pains, and fevers; to severe with bleeding from the lungs or meningitis.
- Outside of tropical areas, leptospirosis cases have a relatively distinct seasonality, with most cases occurring in spring and autumn.
- Leptospirosis is transmitted by the urine of an infected animal and is contagious as long as it remains moist.
- There is a direct correlation between the amount of rainfall and the incidence of leptospirosis, making it seasonal in temperate climates and year-round in tropical climates.

Key Terms

- **leptospirosis**: an acute, infectious, febrile disease of both humans and animals, caused by spirochetes of the genus Leptospira

---

This page titled 6.4D: Leptospirosis is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.14D: Leptospirosis** is licensed CC BY-SA 4.0.

6.5: Bacterial Diseases of the Reproductive System

This page titled 6.5: Bacterial Diseases of the Reproductive System is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.15: Bacterial Diseases of the Reproductive System** is licensed CC BY-SA 4.0.

6.5A: Prostatitis

Learning Objectives

- Define the symptoms, diagnostic tests and treatments used for prostatitis

Prostatitis is an inflammation of the prostate which can be caused by bacteria. Bacterial infections can cause both acute and chronic prostatitis.

Symptoms and diagnosis

Acute prostatitis is relatively easy to diagnose because it presents the general infection symptoms which may include: fever, chills, groin and lower back pain, issues during urination, and general body aches. The prostate is usually enlarged. Testing of urine samples reveals the presence of bacteria and white blood cells. Blood samples can contain bacteria. White blood cells counts are elevated in the complete blood count.

Chronic prostatitis is a rare condition. It usually causes intermittent urinary tract infections (UTIs) which can lead to cystitis. Sometimes there are no symptoms. The diagnosis is made after culturing urine or prostate liquid. Semen analysis can also be used for diagnosis it. PSA (prostate specific antigen) levels may be elevated.

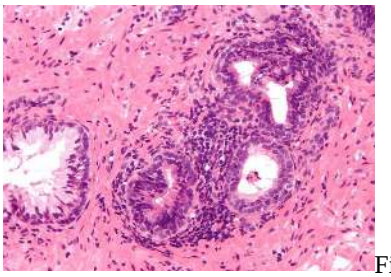


Figure: **Histologic image of chronic prostatitis**: The single gland on the left is healthy, while the glands on the right are inflamed

INFECTIOUS AGENTS

Common bacteria that cause acute prostatitis include gram negative bacteria such as *Escherichia coli*, *Klebsiella*, *Proteus*, *Enterobacter*, *Pseudomonas*, as well as gram positive bacteria such as *Staphylococcus aureus*. E. coli is the major infectious agent that causes chronic prostatitis.

TREATMENT

Acute prostatitis is a serious condition that requires immediate treatment to prevent complications such as sepsis. The antibiotics of choice should be bactericidal (e.g., quinolone) not bacteriostatic (e.g., tetracycline) if the infection is life-threatening. Other commonly used antibiotics are doxycycline and ciprofloxacin. Severe infections may require hospitalization, while milder cases (no sepsis) can be treated with antibiotic administration combined with bed rest at home. The infection is usually cured successfully with antibiotics and the recovery is complete without further complications. Treatment of chronic prostatitis requires courses of antibiotic administration for one to two months or a longer course with low doses. The recurrence of the disease is high. In these cases higher success rates of treatment are achieved when a combination of antibiotics is used. Animal studies have shown that *E. coli* extract with cranberry can prevent chronic prostatitis. The choice of antibiotic for chronic prostatitis also depends on its ability to penetrate the prostatic capsule. Good penetrators of the barrier are quinolones, doxycycline, macrolides and sulfas (Bactrim). In the case of acute prostatitis, the prostate-blood barrier is damaged by the infection so the penetrating ability of the antibiotic is not as important.

Key Points

- Bacteria can cause acute and chronic prostatitis.
- Acute prostatitis is a serious condition that needs immediate treatment with antibiotics. If treated promptly complications are rare.

- Chronic prostatitis is a rare disease that is harder to treat and has high recurrence rate. In the case of remission, combinations of antibiotics may be a better therapy than a single antibiotic.

Key Terms

- **bactericidal**: An agent that kills bacteria.
- **bacteriostatic**: A drug that prevents bacterial growth and reproduction but does not necessarily kill them. When it is removed from the environment the bacteria start growing again.
- **cystitis**: An inflammation of the urinary bladder.

This page titled 6.5A: Prostatitis is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.15A: Prostatitis** is licensed CC BY-SA 4.0.

6.5B: Prostatitis

Learning Objectives

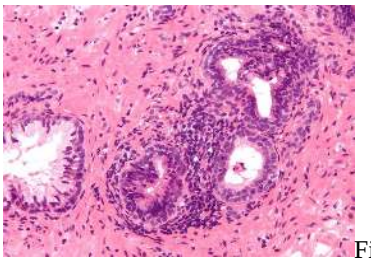
- Define the symptoms, diagnostic tests and treatments used for prostatitis

Prostatitis is an inflammation of the prostate which can be caused by bacteria. Bacterial infections can cause both acute and chronic prostatitis.

Symptoms and diagnosis

Acute prostatitis is relatively easy to diagnose because it presents the general infection symptoms which may include: fever, chills, groin and lower back pain, issues during urination, and general body aches. The prostate is usually enlarged. Testing of urine samples reveals the presence of bacteria and white blood cells. Blood samples can contain bacteria. White blood cells counts are elevated in the complete blood count.

Chronic prostatitis is a rare condition. It usually causes intermittent urinary tract infections (UTIs) which can lead to cystitis. Sometimes there are no symptoms. The diagnosis is made after culturing urine or prostate liquid. Semen analysis can also be used for diagnosis it. PSA (prostate specific antigen) levels may be elevated.


Figure: **Histologic image of chronic prostatitis**: The single gland on the left is healthy, while the glands on the right are inflamed

INFECTIOUS AGENTS

Common bacteria that cause acute prostatitis include gram negative bacteria such as *Escherichia coli*, *Klebsiella*, *Proteus*, *Enterobacter*, *Pseudomonas*, as well as gram positive bacteria such as *Staphylococcus aureus*. E. coli is the major infectious agent that causes chronic prostatitis.

TREATMENT

Acute prostatitis is a serious condition that requires immediate treatment to prevent complications such as sepsis. The antibiotics of choice should be bactericidal (e.g., quinolone) not bacteriostatic (e.g., tetracycline) if the infection is life-threatening. Other commonly used antibiotics are doxycycline and ciprofloxacin. Severe infections may require hospitalization, while milder cases (no sepsis) can be treated with antibiotic administration combined with bed rest at home. The infection is usually cured successfully with antibiotics and the recovery is complete without further complications. Treatment of chronic prostatitis requires courses of antibiotic administration for one to two months or a longer course with low doses. The recurrence of the disease is high. In these cases higher success rates of treatment are achieved when a combination of antibiotics is used. Animal studies have shown that *E. coli* extract with cranberry can prevent chronic prostatitis. The choice of antibiotic for chronic prostatitis also depends on its ability to penetrate the prostatic capsule. Good penetrators of the barrier are quinolones, doxycycline, macrolides and sulfas (Bactrim). In the case of acute prostatitis, the prostate-blood barrier is damaged by the infection so the penetrating ability of the antibiotic is not as important.

Key Points

- Bacteria can cause acute and chronic prostatitis.
- Acute prostatitis is a serious condition that needs immediate treatment with antibiotics. If treated promptly complications are rare.

- Chronic prostatitis is a rare disease that is harder to treat and has high recurrence rate. In the case of remission, combinations of antibiotics may be a better therapy than a single antibiotic.

Key Terms

- **bactericidal**: An agent that kills bacteria.
- **bacteriostatic**: A drug that prevents bacterial growth and reproduction but does not necessarily kill them. When it is removed from the environment the bacteria start growing again.
- **cystitis**: An inflammation of the urinary bladder.

This page titled 6.5B: Prostatitis is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.15B: Prostatitis** is licensed CC BY-SA 4.0.

6.5C: Gonorrhea

Learning Objectives

- Describe gonorrhea

Gonorrhea (also colloquially known as the clap) is a common human sexually transmitted infection. The usual symptoms in men are burning with urination and penile discharge. Women, on the other hand, are asymptomatic half the time or have vaginal discharge and pelvic pain. In both men and women if gonorrhea is left untreated, it may spread locally causing epididymitis or pelvic inflammatory disease or throughout the body, affecting joints and heart valves.Treatment is commonly with ceftriaxone as antibiotic resistance has developed to many previously used medications. In 2011, there were reports of some strains of gonorrhea showing resistance to ceftriaxone. Half of women with gonorrhea are asymptomatic while others have vaginal discharge, lower abdominal pain or pain with intercourse.

The most common male symptoms are urethritis associated with burning with urination and discharge from the penis. Either sex may also acquire gonorrhea of the throat from performing oral sex on an infected partner, usually a male partner. Such infection is asymptomatic in 90% of cases, and produces a sore throat in the remaining 10%. The incubation period is 2 to 14 days with most of these symptoms occurring between 4–6 days after being infected. Rarely, gonorrhea may cause skin lesions and joint infection (pain and swelling in the joints) after traveling through the blood stream. Very rarely it may settle in the heart causing endocarditis or in the spinal column causing meningitis (both are more likely among individuals with suppressed immune systems, however).

CAUSE

Gonorrhea is caused by the bacteria Neisseria gonorrhoeae. The infection is transmitted from one person to another through vaginal, oral, or anal sex. Men have a 20% risk of getting the infection from a single act of vaginal intercourse with an infected woman. The risk for men who have sex with men is higher. Women have a 60–80% risk of getting the infection from a single act of vaginal intercourse with an infected man. A mother may transmit gonorrhea to her newborn during childbirth; when affecting the infant's eyes, it is referred to as ophthalmia neonatorum. It cannot be spread by toilets or bathrooms.

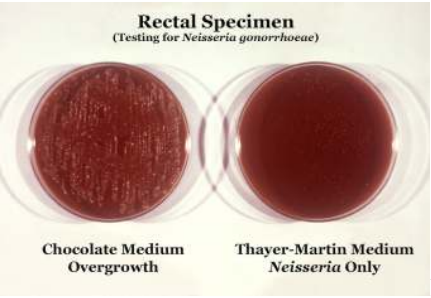


Figure: **Neisseria gonorrhoeae**: Neisseria gonorrhoeae cultured on two different media types and presented in stereoscopic 3d.

Key Points

- The usual symptoms of gonorrhea in men are burning with urination and penile discharge.
- Women with gonorrhea, on the other hand, are asymptomatic half the time or have vaginal discharge and pelvic pain.
- If gonorrhea is left untreated, it may spread locally causing epididymitis or pelvic inflammatory disease or throughout the body, affecting joints and heart valves.Treatment is commonly with ceftriaxone as antibiotic resistance has developed to many previously used medications.

Key Terms

- **ceftriaxone**: A synthetic cephalosporin antibiotic used to treat gonorrhea.

This page titled 6.5C: Gonorrhea is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.15C: Gonorrhea** is licensed CC BY-SA 4.0.

6.5D: Nongonococcal Urethritis (NGU)

Learning Objectives

- Recognize the symptoms, causes and treatments for nongonococcal urethritis (NGU)

Nongonococcal urethritis (NGU) is a urethral inflammation that is not caused by *Neisseria gonorrhoeae*, *a* classification used by doctors for treatment purposes. The general symptoms are pain on urination, frequent need to urinate and white or cloudy discharge. The most common symptoms unique to men are discharge from the penis, itching, and tenderness. In women, the symptoms include vaginal discharge, abdominal pain. If irregular menstrual bleeding is present it may indicate that the infection has progressed into pelvic inflammatory disease.

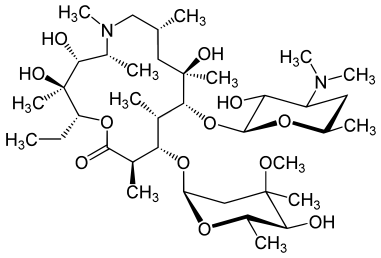


Figure: **Azithromycin**: The structure of azithromycin, a microlide antibiotic used to treat NGU.

Diagnosing NGU is based on the lack of *Neisseria gonorrhoeae* in laboratory testsin a patient with urethritis. In men, it can be diagnosed with Gram staining of urethral discharge; the same is not true for women, since they may have other Gram negative bacteria that are part of their normal vaginal microflora. There are multiple infectious agents that can cause nongonococcal inflammation of the urethra. The most common bacterial agent is *Chlamydia trachomatis* (about a quarter to half of all NGU cases), though others include *Ureaplasma urealyticum*, *Haemophilus vaginalis* and *Mycoplasma genitalium*. Viral infections can be caused sometimes by the Herpes simplex virus or adenovirus. Parasites such as *Trichomonas vaginalis* can cause inflammation too, although rarely. NGU can be caused by reasons different than infection, such as the use of some chemicals or physical injuries. Since many different infectious agents can be causing NGU, the initial treatment should be with a broad spectrum antibiotic. Studies indicate that therapies with doxycycline or azithromycin with tinidazole can be more effective than doxycycline or azithromycin alone. Sexual partners of infected patients should be treated as well. Prompt treatment is critical in both men and women. Women are at risk of developing pelvic inflammatory disease (PID), while in men the infection can progress to epididymitis and cause infertility.

Key Points

- The general symptoms are pain on urination, frequent urination, and white or cloudy discharge.
- It can be caused by many infectious agents, with the most common being chlamydia.
- Since many different infectious agents can be causing NGU, the initial treatment should be with a broad spectrum antibiotic.

Key Terms

- **epididymitis**: An inflammation of the epididymis, a structure in the testicles where sperm matures.

This page titled 6.5D: Nongonococcal Urethritis (NGU) is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.15D: Nongonococcal Urethritis (NGU)** is licensed CC BY-SA 4.0.

6.5E: Pelvic Inflammatory Disease (PID)

Learning Objectives

- Describe the causes, symptoms and long-term effects of pelvic inflammatory disease

Pelvic inflammatory disease (PID) is an inflammation of the uterus, fallopian tubes and/or the ovaries. It is most often caused by a sexually transmitted infection (STI) but there are other predisposing conditions (e.g., postpartum period, the use of intrauterine device). It should be treated promptly to avoid serious complications like scarring and adhesions which can cause infertility, ectopic pregnancy and chronic pelvic pain.

Symptoms and diagnosis

PID can be asymptomatic or present with acute symptoms. About two thirds of patients whose laparoscopies indicated a previous PID were unaware of it. Asymptomatic infections should be treated as well, since they can still cause permanent damage to the reproductive tract.

Symptoms include fever, lower abdominal pain, unusual discharge, irregular menstrual bleeding, painful intercourse.

Different tests can be used for diagnosis such as pelvic ultrasound and laboratory tests for STIs. Usually, more than one test is needed for proper diagnosis. Early diagnosis and treatment are critical to limit the spread of the infection to the lower part of the tract and to avoid long term consequences.

Infectious agents

PID can be caused by many different infectious agents like viruses, fungi or bacteria. The most common infectious agents are *Chlamydia trachomatis* and *Neisseria gonorrhoeae* which are sexually transmitted.

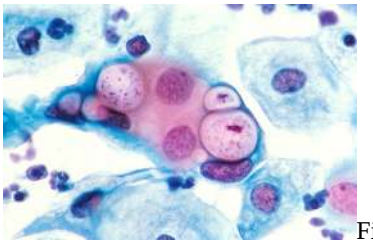


Figure: **Pap smear with Chlamydia**: Cells of Chlamydia are visible in the vacuoles. Magnification 500x, stained with hematoxylin and eosin stain (HE)

The normal vaginal flora can also cause PID under certain circumstances. Co-infection with multiple species is also possible.

Treatment

The primary mode of therapy is an antibiotic regimen. In serious cases, intravenous administration of drugs may be necessary. Usually, improvement of symptoms should be noticed within a few days.

Sexual partners of patients with PID should be treated as well. Some of the most commonly used antibiotics and combinations of antibiotics are: *cefoxitin* or *cefotetan* plus *doxycycline*, *cefoxitin* plus *doxycycline*, *clindamycin* plus *gentamycin*, *ampicillin* and *sublactam* plus *doxycycline.*

Key Points

- Different agents can cause the infection but the most common are Chlamydia trachomatis and Neisseria gonorrhoeae.
- PID can cause permanent damage to the affected organs leading to issues such as infertility and chronic pelvic pain.
- Single antibiotics or combinations of antibiotics are used for the treatment of PID.

Key Terms

- **ectopic**: Being out of place, such as a pregnancy occurring inside the fallopian tubes instead of the uterus.

- **pelvic inflammatory disease**: inflammation of the uterus, fallopian tubes, and/or ovaries as it progresses to scar formation with adhesions to nearby tissues and organs
- **asymptomatic**: not exhibiting any symptoms of disease.

This page titled 6.5E: Pelvic Inflammatory Disease (PID) is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.15E: Pelvic Inflammatory Disease (PID)** is licensed CC BY-SA 4.0.

6.5F: Syphilis

Learning Objectives

- Describe syphilis, its affect on the spinal cord, and its methods of transmission

Syphilis is a sexually transmitted infection (STI) caused by the spirochete bacterium *Treponema pallidum*.

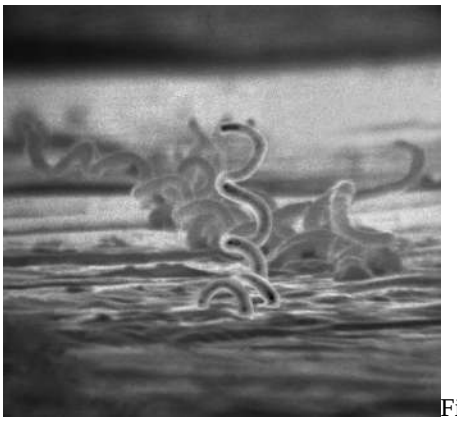


Figure: **Electron Microscopy of Treponema Pallidum**: This electron micrograph shows Treponema pallidum on cultures of cotton-tail rabbit epithelium cells (Sf1Ep). It is the causative agent of syphilis.

FOUR STAGES OF SYPHILIS

The signs and symptoms of syphilis vary depending on which of the four stages it presents (primary, secondary, latent, or tertiary). The primary stage classically presents itself with a single chancre (a firm, painless, non-itchy skin ulceration) as shown in. Secondary syphilis shows itself with a diffuse rash that frequently involves the palms of the hands and soles of the feet. Latent syphilis displays little to no symptoms, and neurosyphilis (tertiary) can result in neurological and cardiac symptoms because the syphilis has been undiagnosed or untreated for many years.



Figure: **Secondary Syphilitic Infection on the Posterior Aspect of the Torso**: Dermatologic manifestations are the hallmark of secondary syphilis. Copper-red papules are most common, but macular, pustular, acneiform, psoriasiform, nodular, annular, or follicular variants can appear. The lesions characteristically do not itch, but may itch in some patients.



Figure: **Primary Syphilitic Infection of the Finger**: The chancre is usually firm, round, small, and painless, appearing at the spot where syphilis entered the body. It lasts three to six weeks and heals on its own. If adequate treatment is not administered, the infection progresses to the secondary stage.

DIAGNOSIS AND TREATMENT

Diagnosis is usually via blood tests, but the bacteria can also be visualized under a microscope. Syphilis can be effectively treated with antibiotics, specifically the preferred intramuscular penicillin G (given intravenously for neurosyphilis), or else ceftriaxone, and in those who have a severe penicillin allergy, oral doxycycline or azithromycin.

Syphilis is believed to have infected 12 million people globally in 1999, with more than 90 percent of cases in the developing world. Rates decreased dramatically after the widespread availability of penicillin in the 1940s. However, rates of infection have increased since the turn of the century in many countries, often in combination with human immunodeficiency virus (HIV). By some accounts, this has been attributed, in part, to unsafe sexual practices among men who have sex with men, increased promiscuity among all genders, prostitution, and decreasing use of barrier protection.

PRIMARY SYPHILIS

Primary syphilis is typically acquired by direct sexual contact with the infectious lesions of another person. Approximately three to 90 days after the initial exposure (average 21 days) a skin lesion, called a chancre, appears at the point of contact. This chancre is classically a single, firm, painless, non-itchy skin ulceration with a clean base and sharp borders between 0.3 and 3.0 cm in size. However, the lesion may take on almost any form. In the classic form, it evolves from a macule to a papule and finally to an erosion or ulcer. Occasionally, multiple lesions may be present, with multiple lesions more common when co-infected with HIV. Lesions may be painful or tender (in 30 percent of those infected), and they may occur outside of the genitals (2 to 7 percent). The lesion may persist for three to six weeks without treatment.

SECONDARY SYPHILIS

Secondary syphilis occurs approximately four to 10 weeks after the primary infection. While secondary disease is known for the many different ways it can manifest, symptoms most commonly involve the skin, mucous membranes, and lymph nodes. There may be a symmetrical, reddish-pink, non-itchy rash on the trunk and extremities, including the palms and soles of the feet. The rash may become maculopapular or pustular. It may form flat, broad, whitish, wart-like lesions known as condyloma latum on mucous membranes. All of these lesions harbor bacteria and are infectious.

Other symptoms may include fever, sore throat, malaise, weight loss, hair loss, and headache. Rare manifestations include hepatitis, kidney disease, arthritis, periostitis, optic neuritis, uveitis, and interstitial keratitis. The acute symptoms usually resolve after three to six weeks; however, about 25 percent of people may experience a recurrence of secondary symptoms.

NEUROSYPHILIS

Neurosyphilis occurs when syphilis is left untreated from many years. The brain and spinal cord become infected with the syphilis bacterium, Treponema pallidum, during the secondary stage of infection and can remain latent for 10 to 20 years after the initial infection. Eventually, this infection begins to damage the tissues of the brain and spinal cord, resulting in neurosyphilis. Neurosyphilis is characterized by neurological and psychiatric symptoms, such as confusion, blindness, abnormal gait and dementia. Left untreated, neurosyphilis symptoms will worsen over time and can lead to death. Treatment for neurosyphilis is the same as any other stage of syphilis, requiring only a short course of penicillin.

TRANSMISSION AND PREVENTION

Syphilis is transmitted primarily by sexual contact or during pregnancy from a mother to her fetus. The spirochete is able to pass through intact mucous membranes or compromised skin. Therefore, it is transmissible by kissing, or oral, vaginal, and anal sex. Approximately 30 to 60 percent of those exposed to primary or secondary syphilis will get the disease. It can be transmitted via blood products, but, many countries test for it, and thus the risk is low. The risk of transmission from sharing needles appears limited. Syphilis cannot be contracted through toilet seats, daily activities, hot tubs, or sharing eating utensils or clothing.

As of 2010, there is no vaccine effective for prevention. Abstinence from intimate physical contact with an infected person is effective at reducing the transmission of syphilis, as is the proper use of a latex condom. However, condom use does not completely eliminate the risk.

Key Points

- In addition to sexual contact, syphilis may also be transmitted from mother to child during pregnancy or at birth, resulting in congenital syphilis.
- Primary syphilis is typically acquired by direct sexual contact with the infectious lesions of another person, and usually presents with a single skin ulceration called a chancre.
- Secondary syphilis occurs approximately four to 10 weeks after the primary infection and may present as a symmetrical, reddish-pink, non-itchy rash on the trunk and extremities, including the palms and soles of the feet.
- Primary syphilis typically presents with a single skin ulceration called a chancre.
- Neurosyphilis refers to a syphilis infection that affects the central nervous system, and cardiovascular syphilis affects the cardiovascular system.
- Blood tests for syphilis are either treponemal or nontreponemal.
- The Tuskegee syphilis study, where African American men in rural Alabama were told they were receiving free health care and instead were given syphilis in order to study its symptoms and progression, is one of the most infamous cases of questionable medical ethics in US history.

Key Terms

- **congenital syphilis**: syphilis present in utero and at birth
- **Treponema pallidum**: A Gram-negative spirochaete bacterium with subspecies that cause treponemal diseases such as syphilis, bejel, pinta, and yaws.
- **chancre**: A skin lesion, sometimes associated with certain contagious diseases like syphilis.
- **syphilis**: a disease spread via sexual activity, caused by the bacterium Treponema pallidum
- **syphilis**: A disease spread via sexual activity, caused by the bacterium Treponema pallidum.

This page titled 6.5F: Syphilis is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.15F: Syphilis** is licensed CC BY-SA 4.0.

6.5G: Genital Ulcer Diseases

Learning Objectives

- List the causes and symptoms of genital ulcers

Genital ulcers are skin ulcers located on the genital area and can be caused by a number of sexually transmitted diseases or other noninfectious conditions such as yeasts, trauma, lupus, rheumatoid arthritis or Behcet's syndrome.

Sexually Transmitted Genital Ulcers

When the reason for a genital ulcer is an infection, it can be caused by a number of sexually transmitted diseases. Among the most common are Herpes simplex virus (HSV), the genital herpes agent; *Treponema pallidum*, that causes syphilis; *Chlamydia trachomatis*, the cause of chlamydia; and *Haemophilus ducreyi*, the chancroid agent. In the United States, the most common reasons for genital ulcers in young and sexually active patients are genital herpes and syphilis.

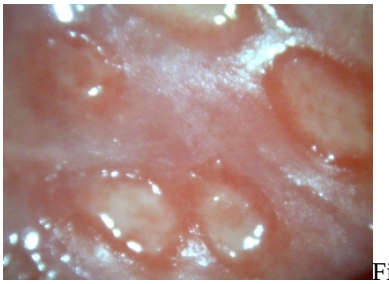


Figure: **Genital Ulcers**: Ulcers caused by genital herpes.

Symptoms and Diagnosis

Genital ulcers can be painful or painless depending on the type of infection. Their appearance can be slightly different from one disease to another. Other than ulceration, enlarged lymph nodes in the groin area can be present, along with blisters and sores. Proper diagnosis cannot be obtained solely through examination and medical history. Testing for a specific infectious agent depends on the likelihood of its presence. In the U.S., testing is recommended for syphilis (by serology and darkfield microscopy) and HSV (culture, serology or PCR), and in cases of chancroid outbreaks or based on the medical history, for the presence of *Haemophilus ducreyi*. In about 25% of the cases, the reason for the ulcer will not be identified by laboratory testing. Syphilis, genital herpes and chancroid have all been associated with increasing the risk for HIV transmission. The CDC recommends routine HIV screening for all patients who present with genital ulcers.

Treatment

Since the ulcers are symptoms of a number of infectious agents, the treatment is chosen according to the disease agent if it can be identified. Quite often, therapy has to start before identification is complete in order to decrease the chances for transmission and to increase the probability of successful treatment. The choice of medication is made, after careful examination of the symptoms and all epidemiological circumstances, based on the most likely causative agent.

Key Points

- The most common STDs that present with genital ulcers are genital herpes, syphilis, chlamydia and chancroid.
- Other than ulceration, enlarged lymph nodes in the groin area may be present, along with blisters and sores.
- To improve the outcome, treatment often starts before identification is complete, with medications chosen based on symptoms and epidemiological circumstances.

Key Terms

- **Behcet's syndrome**: Behcet's syndrome, or Behcet's disease, is an immune disorder that leads to inflammation of the blood vessels. Common symptoms include mouth and genital ulcers, as well as ocular issues.

This page titled 6.5G: Genital Ulcer Diseases is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.15G: Genital Ulcer Diseases** is licensed CC BY-SA 4.0.

6.5H: Lymphogranuloma Venereum

Learning Objectives

- Outline the causes and disease stages for lymphogranuloma venereum (LGV)

Lymphogranuloma venereum (LGV) is a sexually transmitted disease which was considered rare in the developed world until about a decade ago. LGV is an infection of the lymph nodes. The infectious agent enters the body through breaks in the skin or through the epithelial layer of mucous membranes.

Infectious Agents

The infectious agents are a few serovars of *Chlamydia trachomatis:* L1, L2, L2a, L2b and L3.

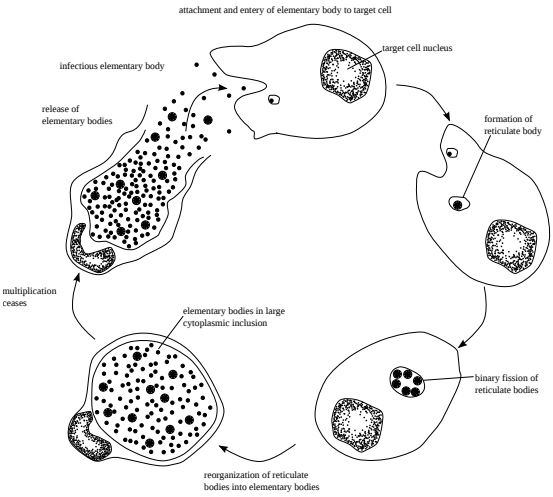


Figure: **Chlamydiae Life Cycle**: Basic diagram of the life cycle of the Chlamydiae. The infectious agents of Lymphogranuloma venereum are a few serovars of Chlamydia trachomatis: L1, L2, L2a, L2b and L3.

Symptoms and Diagnosis

The general symptoms may include fever, malaise and decreased appetite. The disease progresses in stages. In the primary stage, symptoms appear within days after infection. The first symptom is usually painless ulcers at the contact area.The secondary stage can manifest from days to months later. The infectious agent spreads to the lymph nodes through the lymphatic drainage pathways, causing inflammation of the lymph nodes and lymphatic channels. In males with genital infection, these symptoms will usually be in the inguinal or/and femoral areas. In women, an inflammation of the cervix, the fallopian tubes or/and peritonitis may appear as well as inflammation and infection of the lymphatic system. If the infection started in the anal area, it may cause inflammation of the rectum or the colonic mucosa, presenting with symptoms such as anorectal pain, discharge, abdominal cramps and diarrhea.

The enlarged lymph nodes are called buboes and are painful, inflamed and can fixate to the skin. These changes can further progress to necrosis, abscesses and fistulas. As healing starts, fibrosis may occur in the inflamed areas and cause obstruction of the lymphatic system and edema. The fibrosis and edema are considered the third stage of LGV and are mainly permanent. Diagnosis is made after serological analysis and exclusion of other reasons for genital ulcers and lymphatic issues. Culturing is also used for identification of serotypes. Other tests include direct fluorescent antibody analysis (DFA) and PCR tests.

Treatment

Treatment is performed with antibiotics, usually tetracycline, doxycycline or erythromycin. Sometimes drainage of the buboes or abscesses is performed as well. Prognosis is best if treatment starts early in the infection process. Severe complications include bowel obstruction or perforation, which can lead to death.

Key Points

- The infectious agents are a few serovars of Chlamydia trachomatis: L1, L2, L2a, L2b and L3.
- The symptoms of LGV include enlarged and inflamed lymph nodes and lymph passages as well as infection of the surrounding tissues in the genital and abdominal areas.
- Treatment of LGV includes antibiotics and may require drainage of inflamed nodes.

Key Terms

- **serovar**: A group of microorganisms (viruses or bacteria), belonging to the same species, that are characterized by the presence of a specific antigen on their surface.
- **bubo**: An inflamed swelling of a lymph node, especially in the armpit or the groin, due to an infection such as bubonic plague, gonorrhea, tuberculosis or syphilis.

This page titled 6.5H: Lymphogranuloma Venereum is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.15H: Lymphogranuloma Venereum** is licensed CC BY-SA 4.0.

6.5I: Group B Streptococcus Colonization

Learning Objectives

- Describe the pathogenic characteristics, symptoms and diagnostic test used for Group B streptococcus (GBS)

Group B Streptococcus Colonization

Group B streptococcus (GBS), also called *streptococcus agalactiae* or simply strep B, is part of the natural genital and intestinal microflora in some people. Studies indicate that as many as 40% of women can be carriers. It is usually harmless but under certain circumstances (in newborns, the elderly, and in people with compromised immune systems) it can cause life-threatening infections. The bacteria is gram-positive streptococcus, and possesses the group B antigen from the Lancefield classification. Its infectivity is due to the presence of a antiphagocytic polysaccharide capsule. If a pregnant woman is a carrier of strep B, the baby can become infected during vaginal delivery.



Figure: **The CAMP Test**: The collected sample is streaked on a blood agar plate (vertical streaks) next to staphylococcus aureus culture (horizontal streak). Strep B has weak hemolytic activity, which is enhanced substantially (arrow-like area) when streaked next to s. aureus. The reason for that is the interaction between the CAMP factor from strep B and the s. aureus hemolysin.

Symptoms and diagnosis

Healthy adults are usually asymptomatic carriers of the bacteria. Sometimes it can manifest with urinary tract infections (UTIs) in both pregnant and nonpregnant women. In newborns, the first symptoms are breathing difficulties and pneumonia, which can progress to meningitis and sepsis. In elderly people, it can cause pneumonia and/or UTI and is linked to congestive heart failure. A number of different tests are used as diagnostic tools. Screening pregnant women for GBS, usually in the third trimester, is currently routine in many countries. In the cases of positive status, antibiotics are administered during labor to substantially lower the risk of infection for the baby. This strategy has lead to a significant drop in the rates of infant infection in these countries. A very common diagnostic test is the CAMP test named after the three people that discovered it. Sometimes, before plating, enrichment of the gathered probe is performed. This includes sample growth in special medium that will favor its growth over the other bacteria collected with the specimen. The method of enrichment followed by the CAMP tests is currently the gold standard for GBS diagnosis. It lowers significantly the rates of false negatives. However, culturing takes days and is not feasible if labor starts before screening was completed or in cases when it was not performed at all. The best diagnostic tool will allow identification during labor. PCR techniques are faster but they are still complicated and not fast enough to be used widely for diagnostics once labor has started. TreatmentPregnant women who are carriers of GBS are administered penicillin or ampicillin during labor. These antibiotics are the primary choice for GBS therapy in general, since the bacteria are becoming increasingly resistant to many other common antibiotics.

Key Points

- The most vulnerable groups of people to infection are newborns, the elderly, and people with compromised immune system.
- To prevent infections in infants, many countries routinely screen pregnant women for GBS in the third trimester.
- GBS infection is treated with antibiotics, with penicillin and ampicillin as the primary choice.

Key Terms

- **sepsis**: A life-threatening medical condition caused by a severe inflammatory response of the human body triggered by the presence of an infectious agent.

This page titled 6.5I: Group B Streptococcus Colonization is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.15I: Group B Streptococcus Colonization** is licensed CC BY-SA 4.0.

6.5J: Chancroid (Soft Chancre)

Learning Objectives

- Recognize the symptoms, causes and treatment for chancroid

Chancroid (soft chancre) is a sexually transmitted disease and can only be spread through sexual contact. It is becoming rarer worldwide with sporadic outbreaks in countries where it is uncommon. This disease is a risk factor for HIV infection.

Infectious Agent

Chancroid is caused by *Haemophilus ducreyi*, a gram-negative fastidious organism. It enters the body through breaks in the skin.

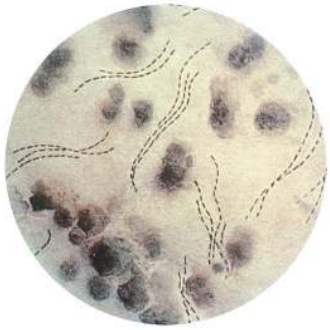


Figure: **Haemophilus ducreyi**: A microscopic image of the bacteria that causes chancroid. The stain used is Gentian Violet and the bacteria are bacilli organized in chains.

Symptoms and Diagnosis

The incubation period of chancroid is between one to fourteen days. The area of infection gets inflamed as cells of the immune system gather to fight the invading organism. Between 30-60% of the patients can also develop lymphadenopathy. Quite often, these enlarged lymph nodes can rupture through the skin and produce draining abscesses.The first symptoms after infection are small painless bumps which quickly become painful ulcers. These ulcers can be quite different in size. The base of the ulcers is usually covered in a gray or yellow substance and bleeds easily. They are typically located in specific ares for men and women. Men often have only one ulcer while women present with multiple ulcers. Women have other symptoms as well such as pain during urination and intercourse. For proper diagnosis, the other two infectious agents that can present with similar although not identical ulcers need to be excluded. Tests for the identification of *Treponema pallidium* (causes syphilis) and HSV (Herpes Simplex Virus, type 2) may be performed to exclude the possibility that ulcers are caused by those agents instead of *Haemophilus ducreyi.* For identification, samples from patients are cultured on chocolate agar. Even though serological and genetic tests can be used for identification, they are not widely used and culturing is the main tool for identifying *Haemophilus ducreyi*.

Treatment

Chancroid is treated with single doses of antibiotics like azythromycin or ceftriaxone, or with erythromycin for a week.

Key Points

- Chancroid is becoming rarer worldwide but there are sporadic outbreaks even in countries where it is uncommon.
- The most common symptoms for chancroid are enlarged lymph nodes and painful, bleeding ulcers with distinctive characteristics.
- Chancroid is treated with single doses of antibiotics like azythromycin or ceftriaxone, or with erythromycin for a week.

Key Terms

- **fastidious**: Microorganisms that are difficult to culture since they need specific nutrients in their medium to grow.
- **lymphadenopathy**: An abnormal enlargement of the lymph nodes

This page titled 6.5J: Chancroid (Soft Chancre) is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.15J: Chancroid (Soft Chancre)** is licensed CC BY-SA 4.0.

6.5K: Bacterial Vaginosis

Learning Objectives

- Describe the symptoms, causes and methods of diagnosis for bacterial vaginosis

Bacterial vaginosis (BV) is a condition where the vaginal microflora in women have become disrupted. BV is not a typical sexually transmitted disease since women who have never had sexual contact can suffer from this condition, too. However, having sex with a new partner or multiple partners increases the risk of getting BV but it is unclear how and why that happens. BV is a very common condition and it is estimated that about 1 in 3 women will develop it in their lifetime.

Symptoms and diagnosis

Bacterial vaginosis may be completely asymptomatic. The most common symptom is white or gray discharge, that can be thin, with fish-like odor (especially strong after intercourse). Sometimes itching outside of the vagina or/and burning during urination can also be present. For diagnosis in the clinical practice, a swab from the vaginal wall is obtained and examined with a few different tests called the *Amsel* criteria:

- the discharge should be thin, white, yellow and homogenous
- clue cells must be present in the specimen when observed under the microscope
- pH > 4.5
- the release of fishy odor after the addition of 10% KOH to the specimen

At least three of these tests have to be positive for conclusive diagnosis. Alternative tests can be performed as well and they usually involve Gram staining of the specimen and observing the types of bacteria present in it. Infectious agentsThe normal vaginal microflora contains many species with *Lactobacillus* as the dominant representative. Some *Lactobacilli* produce hydrogen peroxide which can prevent the overgrowth of bacteria that will disturb the balance and cause BV. Some of the bacteria that will produce BV symptoms are *Gardnerella vaginalis*, *Mobiluncus*, *Bacteroides*, and *Mycoplasma*. Factors that are known to disturb the balance are: antibiotics, pH imbalance (douching can alter vaginal pH), psychosocial stress, iron deficiency anemia in pregnant women and women with STD.

Women who already have BV are at increased risk for sexually transmitted diseases including HIV. Bacterial vaginosis during pregnancy increases the risk of premature birth. TreatmentThe treatment regimen is most often *metronidizole* (for seven days) or *clindamycin*. The treatment is usually successful but BV has high rates of recurrence. Treatment of male sex partners is usually not recommended but BV can be transferred to female sex partners.

Key Points

- The most common symptom is white or gray discharge, that can be thin, with fish-like odor (especially strong after intercourse).
- Common bacterial species that can overgrow and cause symptoms of BV are Gardnerella vaginalis, Mobiluncus, Bacteroides and Mycoplasma.
- The treatment regimen is most often metronidizole (for seven days) or clindamycin. BV has high recurrence rates.

Key Terms

- **recurrence**: The returning of a disease that was already treated successfuly.

This page titled 6.5K: Bacterial Vaginosis is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.15K: Bacterial Vaginosis** is licensed CC BY-SA 4.0.

6.5L: Chlamydia

Learning Objectives

- Describe the effects of chlamydia in men and women

Chlamydia infection (from the Greek meaning “cloak”) is a common sexually transmitted infection (STI) in humans caused by the bacterium Chlamydia trachomatis. The term Chlamydia infection can also refer to infection caused by any species belonging to the bacterial family Chlamydiaceae. C. trachomatis is found only in humans.

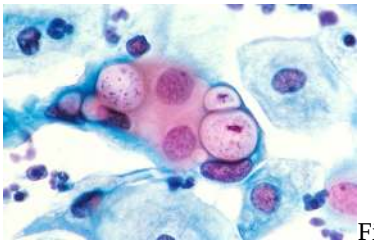


Figure: **Chlamydia**: Pap smear showing C. trachomatis (H&E stain).

Chlamydia is a major infectious cause of human genital and eye disease. Chlamydia infection is one of the most common sexually transmitted infections worldwide; it is estimated that about 1 million individuals in the United States are infected with chlamydia. C. trachomatis is naturally found living only inside human cells. Chlamydia can be transmitted during vaginal, anal, or oral sex, and can be passed from an infected mother to her baby during vaginal childbirth. Between half and three-quarters of all women who have a chlamydia infection of the cervix (cervicitis) have no symptoms and do not know that they are infected. In men, infection of the urethra (urethritis) is usually symptomatic, causing a white discharge from the penis with or without pain on urinating (dysuria).

Occasionally, the condition spreads to the upper genital tract in women (causing pelvic inflammatory disease) or to the epididymis in men (causing epididymitis). If untreated, chlamydial infections can cause serious reproductive and other health problems with both short-term and long-term consequences.

Genital disease

Chlamydial cervicitis in a female patient characterized by mucopurulent cervical discharge, erythema, and inflammation. Male patients may develop a white, cloudy or watery discharge from the tip of the penis.

Women

Chlamydial infection of the neck of the womb (cervicitis) is a sexually transmitted infection which is asymptomatic for about 50-70% of women infected with the disease. The infection can be passed through vaginal, anal, or oral sex. Of those who have an asymptomatic infection that is not detected by their doctor, approximately half will develop pelvic inflammatory disease (PID), a generic term for infection of the uterus, fallopian tubes, and/or ovaries. PID can cause scarring inside the reproductive organs, which can later cause serious complications, including chronic pelvic pain, difficulty becoming pregnant, ectopic (tubal) pregnancy, and other dangerous complications of pregnancy.Chlamydia is known as the “Silent Epidemic” because in women, it may not cause any symptoms in 75% of cases, and can linger for months or years before being discovered. Symptoms that may occur include unusual vaginal bleeding or discharge, pain in the abdomen, painful sexual intercourse (dyspareunia), fever, painful urination or the urge to urinate more frequently than usual (urinary urgency).

Men

In men, chlamydia shows symptoms of infectious urethritis (inflammation of the urethra) in about 50% of cases. Symptoms that may occur include: a painful or burning sensation when urinating, an unusual discharge from the penis, swollen or tender testicles, or fever. Discharge, or the purulent exudate, is generally less viscous and lighter in color than for gonorrhea. If left untreated, it is possible for chlamydia in men to spread to the testicles causing epididymitis, which in rare cases can cause sterility if not treated within 6 to 8 weeks. Chlamydia is also a potential cause of prostatitis in men, although the exact relevance in prostatitis is difficult to ascertain due to possible contamination from urethritis.

Treatment

C. trachomatis infection can be effectively cured with antibiotics once it is detected. Current guidelines recommend azithromycin, doxycycline, erythromycin, or ofloxacin. Agents recommended for pregnant women include erythromycin or amoxicillin.

An option for treating partners of patients (index cases) diagnosed with chlamydia or gonorrhea is *patient-delivered partner therapy*(PDT or PDPT), which is the clinical practice of treating the sex partners of index cases by providing prescriptions or medications to the patient to take to his/her partner without the health care provider first examining the partner.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: ***CC BY-SA: Attribution-ShareAlike***

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- Prostate. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Prostate**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Acute prostatitis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Acute_prostatitis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Prostatitis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Prostatitis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Chronic bacterial prostatitis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Chronic_bacterial_prostatitis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- bacteriostatic. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/bacteriostatic**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- bactericidal. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/bactericidal**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- cystitis. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/cystitis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Inflammation of prostate. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...f_prostate.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Prostate. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Prostate**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Acute prostatitis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Acute_prostatitis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Prostatitis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Prostatitis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Chronic bacterial prostatitis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Chronic_bacterial_prostatitis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- bacteriostatic. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/bacteriostatic**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- bactericidal. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/bactericidal**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- cystitis. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/cystitis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Inflammation of prostate. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...f_prostate.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Inflammation of prostate. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...f_prostate.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Sexually transmitted. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Sexually_transmitted**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Genital herpes. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Genital_herpes**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- HPV. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/HPV**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Chlamydia infection. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Chlamydia_infection**. **License**: ***CC BY-SA: Attribution-ShareAlike***

- Gonorrhea. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Gonorrhea**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- HIV. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/HIV**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Syphilis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Syphilis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Genital warts. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Genital_warts**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- ceftriaxone. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/ceftriaxone**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Inflammation of prostate. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...f_prostate.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Inflammation of prostate. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...f_prostate.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Neisseria gonorrhoeae 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ne...rrhoeae_01.png**. **License**: ***Public Domain: No Known Copyright***
- Non-gonococcal urethritis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Non-gon...cal_urethritis**. **License**: *CC BY-SA: Attribution-ShareAlike*
- epididymitis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/epididymitis**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Inflammation of prostate. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...f_prostate.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Inflammation of prostate. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...f_prostate.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Neisseria gonorrhoeae 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ne...rrhoeae_01.png**. **License**: ***Public Domain: No Known Copyright***
- File:Azithromycin structure.svg - Wikipedia, the free encyclopedia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/w/index.php?...ure.svg&page=1**. **License**: ***Public Domain: No Known Copyright***
- Pelvic inflammatory disease. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Pelvic_inflammatory_disease**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Pelvic inflammatory disease. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Pelvic_inflammatory_disease**. **License**: *CC BY-SA: Attribution-ShareAlike*
- ectopic. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/ectopic**. **License**: *CC BY-SA: Attribution-ShareAlike*
- asymptomatic. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/asymptomatic**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Inflammation of prostate. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...f_prostate.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Inflammation of prostate. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...f_prostate.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Neisseria gonorrhoeae 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ne...rrhoeae_01.png**. **License**: ***Public Domain: No Known Copyright***
- File:Azithromycin structure.svg - Wikipedia, the free encyclopedia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/w/index.php?...ure.svg&page=1**. **License**: ***Public Domain: No Known Copyright***
- Pap smear showing clamydia in the vacuoles 500x H&E. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...s_500x_H&E.jpg**. **License**: ***Public Domain: No Known Copyright***
- Neurosyphilis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Neurosyphilis**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Syphilis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Syphilis**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Neurosyphilis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Neurosyphilis**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Syphilis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Syphilis**. **License**: *CC BY-SA: Attribution-ShareAlike*

- Congenital syphilis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Congenital_syphilis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- chancre. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/chancre**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Treponema pallidum. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Treponema%20pallidum**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- syphilis. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/syphilis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Inflammation of prostate. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...f_prostate.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Inflammation of prostate. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...f_prostate.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Neisseria gonorrhoeae 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ne...rrhoeae_01.png**. **License**: ***Public Domain: No Known Copyright***
- File:Azithromycin structure.svg - Wikipedia, the free encyclopedia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/w/index.php?...ure.svg&page=1**. **License**: ***Public Domain: No Known Copyright***
- Pap smear showing clamydia in the vacuoles 500x H&E. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...s_500x_H&E.jpg**. **License**: ***Public Domain: No Known Copyright***
- Extragenital syphilitic chancre of the left index finger PHIL 4147 lores. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ex...4147_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- 2ndsyphil2. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:2ndsyphil2.jpg**. **License**: ***CC BY: Attribution***
- Treponema pallidum. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Tr...a_pallidum.jpg**. **License**: ***Public Domain: No Known Copyright***
- Diseases Characterized by Genital, Anal, or Perianal Ulcers. **Provided by**: Centers for Disease Control and Prevention. **Located at**: **www.cdc.gov/std/treatment/201...tal-ulcers.htm**. **License**: ***Public Domain: No Known Copyright***
- Sexually transmitted disease. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Sexuall...mitted_disease**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Genital herpes. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Genital_herpes**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Genital ulcer. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Genital_ulcer**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Syphilis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Syphilis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Genital herpes. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Genital_herpes**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Behcet's syndrome. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Behcet's%20syndrome**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Inflammation of prostate. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...f_prostate.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Inflammation of prostate. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...f_prostate.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Neisseria gonorrhoeae 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ne...rrhoeae_01.png**. **License**: ***Public Domain: No Known Copyright***
- File:Azithromycin structure.svg - Wikipedia, the free encyclopedia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/w/index.php?...ure.svg&page=1**. **License**: ***Public Domain: No Known Copyright***
- Pap smear showing clamydia in the vacuoles 500x H&E. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...s_500x_H&E.jpg**. **License**: ***Public Domain: No Known Copyright***
- Extragenital syphilitic chancre of the left index finger PHIL 4147 lores. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ex...4147_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- 2ndsyphil2. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:2ndsyphil2.jpg**. **License**: ***CC BY: Attribution***
- Treponema pallidum. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Tr...a_pallidum.jpg**. **License**: ***Public Domain: No Known Copyright***

- Herpes genitalis. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi..._genitalis.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Lymphogranuloma venereum. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Lymphogranuloma_venereum**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- serovar. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/serovar**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- bubo. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/bubo**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Inflammation of prostate. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Inflammation_of_prostate.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Inflammation of prostate. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Inflammation_of_prostate.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Neisseria gonorrhoeae 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ne...rrhoeae_01.png**. **License**: ***Public Domain: No Known Copyright***
- File:Azithromycin structure.svg - Wikipedia, the free encyclopedia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/w/index.php?...ure.svg&page=1**. **License**: ***Public Domain: No Known Copyright***
- Pap smear showing clamydia in the vacuoles 500x H&E. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...s_500x_H&E.jpg**. **License**: ***Public Domain: No Known Copyright***
- Extragenital syphilitic chancre of the left index finger PHIL 4147 lores. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ex...4147_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- 2ndsyphil2. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:2ndsyphil2.jpg**. **License**: ***CC BY: Attribution***
- Treponema pallidum. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Tr...a_pallidum.jpg**. **License**: ***Public Domain: No Known Copyright***
- Herpes genitalis. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi..._genitalis.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Chlamydae Life Cycle. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ch...Life_Cycle.svg**. **License**: ***Public Domain: No Known Copyright***
- Group B streptococcal infection. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Group_B...ccal_infection**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- CAMP test. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/CAMP_test**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- sepsis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/sepsis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Inflammation of prostate. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Inflammation_of_prostate.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Inflammation of prostate. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Inflammation_of_prostate.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Neisseria gonorrhoeae 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Neisseria_gonorrhoeae_01.png**. **License**: ***Public Domain: No Known Copyright***
- File:Azithromycin structure.svg - Wikipedia, the free encyclopedia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/w/index.php?title=File:Azithromycin_structure.svg&page=1**. **License**: ***Public Domain: No Known Copyright***
- Pap smear showing clamydia in the vacuoles 500x H&E. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...s_500x_H&E.jpg**. **License**: ***Public Domain: No Known Copyright***
- Extragenital syphilitic chancre of the left index finger PHIL 4147 lores. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ex...4147_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- 2ndsyphil2. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:2ndsyphil2.jpg**. **License**: ***CC BY: Attribution***
- Treponema pallidum. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Tr...a_pallidum.jpg**. **License**: ***Public Domain: No Known Copyright***
- Herpes genitalis. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi..._genitalis.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Chlamydae Life Cycle. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ch...Life_Cycle.svg**. **License**: ***Public Domain: No Known Copyright***

- CAMP test. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:CAMP_test.JPG**. **License**: ***Public Domain: No Known Copyright***
- Diseases Characterized by Genital, Anal, or Perianal Ulcers. **Provided by**: Centers for Disease Control and Prevention. **Located at**: **www.cdc.gov/std/treatment/201...tal-ulcers.htm**. **License**: ***Public Domain: No Known Copyright***
- Haemophilus ducreyi. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Haemophilus_ducreyi**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Chancroid. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Chancroid**. **License**: *CC BY-SA: Attribution-ShareAlike*
- lymphadenopathy. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/lymphadenopathy**. **License**: *CC BY-SA: Attribution-ShareAlike*
- fastidious. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/fastidious**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Inflammation of prostate. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Inflammation_of_prostate.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Inflammation of prostate. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Inflammation_of_prostate.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Neisseria gonorrhoeae 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Neisseria_gonorrhoeae_01.png**. **License**: ***Public Domain: No Known Copyright***
- File:Azithromycin structure.svg - Wikipedia, the free encyclopedia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/w/index.php?title=File:Azithromycin_structure.svg&page=1**. **License**: ***Public Domain: No Known Copyright***
- Pap smear showing clamydia in the vacuoles 500x H&E. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...s_500x_H&E.jpg**. **License**: ***Public Domain: No Known Copyright***
- Extragenital syphilitic chancre of the left index finger PHIL 4147 lores. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ex...4147_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- 2ndsyphil2. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:2ndsyphil2.jpg**. **License**: *CC BY: Attribution*
- Treponema pallidum. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Tr...a_pallidum.jpg**. **License**: ***Public Domain: No Known Copyright***
- Herpes genitalis. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi..._genitalis.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Chlamydae Life Cycle. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ch...Life_Cycle.svg**. **License**: ***Public Domain: No Known Copyright***
- CAMP test. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:CAMP_test.JPG**. **License**: ***Public Domain: No Known Copyright***
- Haemophilus ducreyi 01. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...ducreyi_01.jpg**. **License**: ***Public Domain: No Known Copyright***
- Bacterial Vaginosis (BV): Bacterial Vaginosis u2013 CDC Fact Sheet. **Provided by**: Centers for Disease Control and Prevention. **Located at**: **http://www.cdc.gov/std/bv/STDFact-Ba...-Vaginosis.htm**. **License**: ***Public Domain: No Known Copyright***
- Bacterial vaginosis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Bacterial_vaginosis**. **License**: *CC BY-SA: Attribution-ShareAlike*
- recurrence. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/recurrence**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Inflammation of prostate. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Inflammation_of_prostate.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Inflammation of prostate. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Inflammation_of_prostate.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Neisseria gonorrhoeae 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Neisseria_gonorrhoeae_01.png**. **License**: ***Public Domain: No Known Copyright***

- File:Azithromycin structure.svg - Wikipedia, the free encyclopedia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/w/index.php?title=File:Azithromycin_structure.svg&page=1**. **License**: ***Public Domain: No Known Copyright***
- Pap smear showing clamydia in the vacuoles 500x H&E. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...s_500x_H&E.jpg**. **License**: ***Public Domain: No Known Copyright***
- Extragenital syphilitic chancre of the left index finger PHIL 4147 lores. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Extragenital_syphilitic_chancre_of_the_left_index_finger_PHIL_4147_lores.jpg**. **License**: *Public Domain: No Known Copyright*
- 2ndsyphil2. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:2ndsyphil2.jpg**. **License**: *CC BY: Attribution*
- Treponema pallidum. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Treponema_pallidum.jpg**. **License**: *Public Domain: No Known Copyright*
- Herpes genitalis. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Herpes_genitalis.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Chlamydae Life Cycle. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Chlamydae_Life_Cycle.svg**. **License**: *Public Domain: No Known Copyright*
- CAMP test. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:CAMP_test.JPG**. **License**: *Public Domain: No Known Copyright*
- Haemophilus ducreyi 01. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Haemophilus_ducreyi_01.jpg**. **License**: *Public Domain: No Known Copyright*
- Chlamydia infection. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Chlamydia_infection**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Genital warts. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Genital_warts**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Sexually transmitted. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Sexually_transmitted**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Genital herpes. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Genital_herpes**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Syphilis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Syphilis**. **License**: *CC BY-SA: Attribution-ShareAlike*
- HIV. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/HIV**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Gonorrhea. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Gonorrhea**. **License**: *CC BY-SA: Attribution-ShareAlike*
- HPV. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/HPV**. **License**: *CC BY-SA: Attribution-ShareAlike*
- azithromycin. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/azithromycin**. **License**: *CC BY-SA: Attribution-ShareAlike*
- sexually transmitted disease. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/sexually_transmitted_disease**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Inflammation of prostate. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Inflammation_of_prostate.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Inflammation of prostate. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Inflammation_of_prostate.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Neisseria gonorrhoeae 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Neisseria_gonorrhoeae_01.png**. **License**: *Public Domain: No Known Copyright*
- File:Azithromycin structure.svg - Wikipedia, the free encyclopedia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/w/index.php?title=File:Azithromycin_structure.svg&page=1**. **License**: *Public Domain: No Known Copyright*
- Pap smear showing clamydia in the vacuoles 500x H&E. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...s_500x_H&E.jpg**. **License**: *Public Domain: No Known Copyright*
- Extragenital syphilitic chancre of the left index finger PHIL 4147 lores. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Extragenital_syphilitic_chancre_of_the_left_index_finger_PHIL_4147_lores.jpg**. **License**: *Public Domain: No Known Copyright*

- 2ndsyphil2. **Provided by**: Wikipedia. **Located at**: http://en.Wikipedia.org/wiki/File:2ndsyphil2.jpg. **License**: *CC BY: Attribution*
- Treponema pallidum. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:Treponema_pallidum.jpg. **License**: *Public Domain: No Known Copyright*
- Herpes genitalis. **Provided by**: Wikimedia. **Located at**: commons.wikimedia.org/wiki/File:Herpes_genitalis.jpg. **License**: *CC BY-SA: Attribution-ShareAlike*
- Chlamydae Life Cycle. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:Chlamydae_Life_Cycle.svg. **License**: *Public Domain: No Known Copyright*
- CAMP test. **Provided by**: Wikimedia. **Located at**: commons.wikimedia.org/wiki/File:CAMP_test.JPG. **License**: *Public Domain: No Known Copyright*
- Haemophilus ducreyi 01. **Provided by**: Wikimedia. **Located at**: commons.wikimedia.org/wiki/File:Haemophilus_ducreyi_01.jpg. **License**: *Public Domain: No Known Copyright*
- Pap smear showing clamydia in the vacuoles 500x H&E. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:Pa...s_500x_H&E.jpg. **License**: *Public Domain: No Known Copyright*

Key Points

- Chlamydia infection is one of the most common sexually transmitted infections worldwide; it is estimated that about 1 million individuals in the United States are infected with chlamydia.
- Between half and three-quarters of all women who have a chlamydia infection of the cervix (cervicitis) have no symptoms and do not know that they are infected.
- C. trachomatis infection can be effectively cured with antibiotics once it is detected. Current guidelines recommend azithromycin, doxycycline, erythromycin, or ofloxacin.Agents recommended for pregnant women include erythromycin or amoxicillin.

Key Terms

- **azithromycin**: A macrolide antibiotic derived from erythromycin.
- **sexually transmitted disease**: any of various diseases that are usually contracted through sexual contact

---

This page titled 6.5L: Chlamydia is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.15L: Chlamydia** is licensed CC BY-SA 4.0.

6.6: Microbial Diseases of the Skin

This page titled 6.6: Microbial Diseases of the Skin is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **15.18: Microbial Diseases of the Skin** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

6.6A: Structure of the Skin- Epidermis

The epidermis includes five main layers: the stratum corneum, stratum lucidium, stratum granulosum, stratum spinosum, and stratum germinativum.

LEARNING OBJECTIVES

Describe the layers of the epidermis

KEY TAKEAWAYS

Key Points

- The epidermis provides a protective waterproof barrier that also keeps pathogens at bay and regulates body temperature.
- The main layers of the epidermis are: stratum corneum, stratum lucidium, stratum granulosm, stratum spinosum, stratum germinativum (also called stratum basale).
- Keratinocytes in the stratum basale proliferate during mitosis and the daughter cells move up the strata, changing shape and composition as they undergo multiple stages of cell differentiation.

Key Terms

- **keratinocyte**: the predominant cell type in the epidermis, the outermost layer of the skin, constituting 95% of the cells found there. Those keratinocytes found in the basal layer (stratum germinativum) of the skin are sometimes referred to as basal cells or basal keratinocytes.
- **stratum germinativum**: the basal layer—sometimes referred to as stratum basale—is the deepest of the five layers of the epidermis.
- **stratum corneum**: the most superficial layer of the epidermis from which dead skin sheds.
- **epidermis**: the outermost layer of skin.
- **stratum lucidum**: a layer of our skin that is found on the palms of our hands and the soles of our feet.

Layers of the Epidermis

The epidermis is the outermost layer of our skin. It is the layer we see with our eyes. It contains no blood supply of its own—which is why you can shave your skin and not cause any bleeding despite losing many cells in the process. Assuming, that is, you don't nick your skin to deep, where the blood supply is actually found. The epidermis is itself divided into at least four separate parts. A fifth part is present in some areas of our body. In order from the deepest layer of the epidermis to the most superficial, these layers (strata) are the:

- Stratum basale
- Stratum spinosum
- Stratum granulosum
- Stratum lucidum
- Stratum corneum

Stratum Basale

The stratum basale, also called the stratum germinativum, is the basal (base) layer of the epidermis. It is the layer that's closest to the blood supply lying underneath the epidermis.

This layer is one of the most important layers of our skin. This is because it contains the only cells of the epidermis that can divide via the process of mitosis, which means that skin cells germinate here, hence the word germinativum.

In this layer, the most numerous cells of the epidermis, called keratinocytes, arise thanks to mitosis. Keratinocytes produce the most important protein of the epidermis.

This protein is appropriately called keratin. Keratin makes our skin tough and provides us with much-needed protection from microorganisms, physical harm, and chemical irritation.

Millions of these new cells arise in the stratum basale on a daily basis. The newly produced cells push older cells into the upper layers of the epidermis with time. As these older cells move up toward the surface, they change their shape, nuclear, and chemical composition. These changes are, in part, what give the strata their unique characteristics.

Stratum Spinosum and Granulosum

From the stratum basale, the keratinocytes move into the stratum spinosum, a layer so called because its cells are spiny-shaped cells. The stratum spinosum is partly responsible for the skin's strength and flexibility. From there the keratinocytes move into the next layer, called the stratum granulosum. This layer gets its name from the fact that the cells located here contain many granules. The keratinocytes produce a lot of keratin in this layer—they become filled with keratin. This process is known as keratinization. The keratinocytes become flatter, more brittle, and lose their nuclei in the stratum granulosum as well.

Stratum Lucidum

Once the keratinocytes leave the stratum granulosum, they die and help form the stratum lucidum. This death occurs largely as a result of the distance the keratinocytes find themselves from the rich blood supply the cells of the stratum basale lie on top off. Devoid of nutrients and oxygen, the keratinocytes die as they are pushed towards the surface of our skin. The stratum lucidum is a layer that derives its name from the lucid (clear/transparent) appearance it gives off under a microscope. This layer is only easily found in certain hairless parts of our body, namely the palms of our hands and the soles of our feet. Meaning, the places where our skin is usually the thickest.

Stratum Corneum

From the stratum lucidum, the keratinocytes enter the next layer, called the stratum corneum (the horny layer filled with cornified cells). This the only layer of skin we see with our eyes. The keratinocytes in this layer are called corneocytes. They are devoid of almost all of their water and they are completely devoid of a nucleus at this point. They are dead skin cells filled with the tough protein keratin. In essence, they are a protein mass more so than they are a cell. The corneocytes serve as a hard protective layer against environmental trauma, such as abrasions, light, heat, chemicals, and microorganism. The cells of the stratum corneum are also surrounded by lipids (fats) that help repel water as well. These corneocytes are eventually shed into the environment and become part of the dandruff in our hair or the dust around us, which dust mites readily munch on. This entire cycle, from new keratinocyte in the straum basale to a dead cell flaked off into the air, takes between 25–45 days.

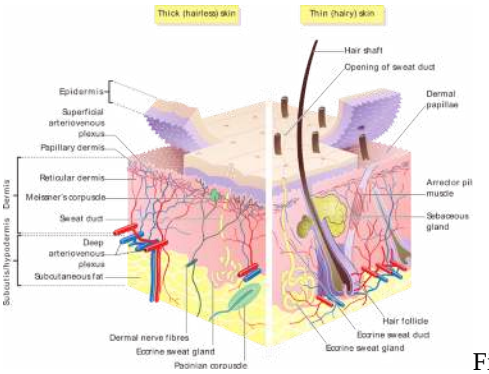


Figure: **Skin overview**: skin layers, of both hairy and hairless skin.

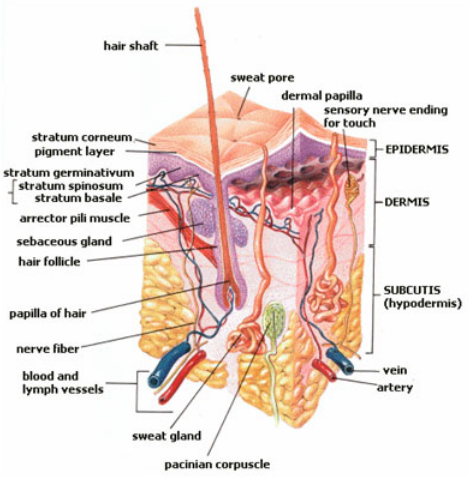
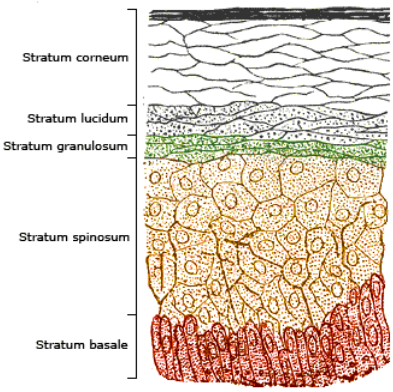


Figure: **Human skin**: This image details the parts of the integumentary system.



Layers of the epidermis: The epidermis is made up of 95% keratinocytes but also contains melanocytes, Langerhans cells, Merkel cells, and inflammatory cells. The stratum basale is primarily made up of basal keratinocyte cells, which can be considered the stem cells of the epidermis. They divide to form the keratinocytes of the stratum spinosum, which migrate superficially.

This page titled 6.6A: Structure of the Skin- Epidermis is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.18A: Structure of the Skin- Epidermis** is licensed CC BY-SA 4.0.

6.6B: Microbiota of the Skin

Learning Objectives

- Describe the types of skin flora and how they can be beneficial for the organism

The skin flora, more properly referred to as the skin microbiome or skin microbiota, are the microorganisms that reside on the skin. Most bacteria on the skin are found in the superficial layers of the epidermis and the upper parts of hair follicles. Skin flora are usually non-pathogenic, and either commensals (are not harmful to their host) or mutualistic (offer a benefit). The benefits bacteria can offer include preventing transient pathogenic organisms from colonizing the skin surface, either by competing for nutrients, secreting chemicals against them, or stimulating the skin's immune system. However, resident microbes can cause skin diseases and enter the blood system creating life-threatening diseases particularly in immunosuppressed people. Hygiene to control such flora is important in preventing the transmission of antibiotic resistant hospital-acquired infections.

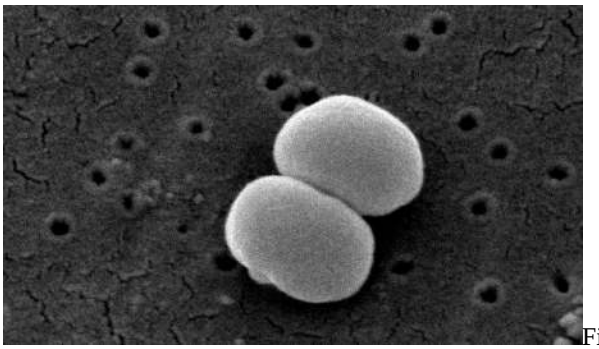
A major nonhuman skin flora is Batrachochytrium dendrobatidis, a chytrid and non-hyphal zoosporic fungus that causes chytridiomycosis, an infectious disease thought to be responsible for the decline in amphibian populations. The estimate of the number of species present on skin bacteria has been radically changed by the use of 16S ribosomal RNA to identify bacterial species present on skin samples direct from their genetic material. Previously such identification had depended upon microbiological culture upon which many varieties of bacteria did not grow and so were hidden to science. Staphylococcus epidermidis and Staphylococcus aureus were thought from cultural based research to be dominant. However, 16S ribosomal RNA research found that while common these species make up only 5% of skin bacteria. However, skin variety provides a rich and diverse habitat for bacteria. Most come from four phyla: Actinobacteria (51.8%), Firmicutes (24.4%), Proteobacteria (16.5%), and Bacteroidetes (6.3%).

There are three main ecological areas for skin flora: sebaceous, moist, and dry. Propionibacteria and Staphylococci species are the main species in sebaceous areas. In moist places on the body Corynebacteria together with Staphylococci dominate. In dry areas, there is a mixture of species, but b-Proteobacteria and Flavobacteriales are dominant. Ecologically, sebaceous areas have greater species richness than moist and dry ones. The areas with least similarity between people in species are the spaces between fingers, the spaces between toes, axillae, and umbilical cord stump. Most similar are beside the nostril, nares (inside the nostril), and on the back.

Skin microflora can be commensals, mutualistic, or pathogens. Often they can be all three depending upon the strength of the person's immune system. Research on the immune system in the gut and lungs has shown that microflora aids immunity development. However, such research has only started upon whether this is the case with the skin. Pseudomonas aeruginosa is an example of a mutualistic bacterium that can turn into a pathogen and cause disease. If it gains entry into the blood system it can result in infections in bone, joint, gastrointestinal, and respiratory systems and it can also cause dermatitis. However,

Pseudomonas aeruginosa produces antimicrobial substances such as pseudomonic acid (that are exploited commercially such as Mupirocin). This works against staphylococcal and streptococcal infections. Pseudomonas aeruginosa also produces substances that inhibit the growth of fungus species such as Candida krusei, Candida albicans, Torulopsis glabrata, Saccharomyces cerevisiae, and Aspergillus fumigatus. It can also inhibit the growth of Helicobacter pylori. Fatty acids (caproic acid) on the skin inhibit bacteria, especially after puberty, when undecylic acid becomes the primary fatty acid on the skin. Undecylic acid provides resistance to ringworm fungus and other skin infections.

Another aspect of bacteria is the generation of body odor. Sweat is odorless. However, several bacteria may consume it and create byproducts which may be considered putrid by man (as in contrast to flies, for example, that may find them attractive/appealing). For example, Propionibacteria in adolescent and adult produce propionic acid in sebaceous glands.

 Figure: **Staphylococcus epidermidis**: Scanning electron microscope image of Staphylococcus epidermidis one of roughly 1,000 bacteria species present on human skin. Though usually not pathogenic, it can cause skin infections and even life threatening illnesses in those that are immunocompromised.

Key Points

- Most bacteria on the skin are found in the superficial layers of the epidermis and the upper parts of hair follicles.
- Skin flora are usually non-pathogenic, and either commensals (are not harmful to their host) or mutualistic (offer a benefit).
- The benefits bacteria can offer include preventing transient pathogenic organisms from colonizing the skin surface, either by competing for nutrients, secreting chemicals against them, or stimulating the skin's immune system.
- Resident microbes can cause skin diseases and enter the blood system creating life-threatening diseases particularly in immunosuppressed people.

Key Terms

- **skin flora**: the skin flora, more properly referred to as the skin microbiome or skin microbiota, are the microorganisms which reside on the skin.
- **commensal**: a term for a form of symbiosis in which one organism derives a benefit while the other is unaffected
- **mutualistic**: mutually beneficial.

This page titled 6.6B: Microbiota of the Skin is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.18B: Microbiota of the Skin** is licensed CC BY-SA 4.0.

6.6C: Bacterial Skin Diseases

Bacterial skin infections include impetigo, erysipelas, and cellulitis.

LEARNING OBJECTIVES

Describe how impetigo, erysipelas and cellulitis are acquired and the treatment options available

KEY TAKEAWAYS

Key Points

- Impetigo is a highly contagious bacterial skin infection most common among pre-school children primarily caused by Staphylococcus aureus and sometimes by Streptococcus pyogenes.
- Erysipelas is an acute streptococcus bacterial infection of the upper dermis and superficial lymphatics.
- Cellulitis is a diffuse inflammation of connective tissue with severe inflammation of dermal and subcutaneous layers of the skin.
- Antimicrobial therapy is available for impetigo, erysipelas, and cellulitis.

Key Terms

- **erysipelas**: a severe skin disease caused by streptococcus infection in surface and surrounding tissue, marked by continued spreading inflammation
- **impetigo**: a contagious bacterial skin disease forming pustules and yellow crusty sores, chiefly on the face and hands. It is common in children. Infection is often through cuts or insect bites.
- **cellulitis**: an inflammation of subcutaneous or connective tissue caused by a bacterial infection

 Figure: Facial impetigo.

Common Bacterial Skin Infections

Bacterial skin infections include impetigo, erysipelas, and cellulitis.

IMPETIGO

Impetigo is a highly contagious bacterial skin infection most common among pre-school children. It is primarily caused by Staphylococcus aureus and sometimes by Streptococcus pyogenes. The infection is spread by direct contact with lesions or with nasal carriers. The incubation period is 1–3 days. Dried streptococci in the air are not infectious to intact skin. Scratching may spread the lesions. Impetigo generally appears as honey-colored scabs formed from dried serum and is often found on the arms, legs, or face . For generations, the disease was treated with an application of the antiseptic *gentian violet*. Today, topical or oral antibiotics are usually prescribed.


Figure: **Facial erysipelas**. Erysipelas of the face due to invasive Streptococcus.

ERYSIPELAS

Erysipelas is an acute streptococcus bacterial infection of the upper dermis and superficial lymphatics. This disease is most common among the elderly, infants, and children. People with immune deficiency, diabetes, alcoholism, skin ulceration, fungal infections, and impaired lymphatic drainage (e.g., after mastectomy, pelvic surgery, bypass grafting) are also at increased risk. Patients typically develop symptoms including high fevers, shaking, chills, fatigue, headaches, vomiting, and general illness within 48 hours of the initial infection. The erythematous skin lesion enlarges rapidly and has a sharply demarcated raised edge. It appears as a red, swollen, warm, hardened and painful rash, similar in consistency to an orange peel. More severe infections can result in vesicles, bullae, and petechiae, with possible skin necrosis. Lymph nodes may be swollen and lymphedema may occur. Occasionally, a red streak extending to the lymph node can be seen. Most cases of erysipelas are due to Streptococcus pyogenes (also known as beta-hemolytic group A streptococci), although non-group A streptococci can also be the causative agent. Beta-hemolytic, non-group A streptococci include Streptococcus agalactiae, also known as group B strep or GBS. Depending on the severity, treatment involves either oral or intravenous antibiotics, using penicillins, clindamycin, or erythromycin. While illness symptoms resolve in a day or two, the skin may take weeks to return to normal.


Figure: **Cellulitis**. Left shin infected with cellulitis.

CELLULITIS

Cellulitis is a diffuse inflammation of connective tissue with severe inflammation of dermal and subcutaneous layers of the skin. Cellulitis can be caused by normal skin flora or by exogenous bacteria, and often occurs where the skin has previously been broken. Common points of infection include cracks in the skin, cuts, blisters, burns, insect bites, surgical wounds, intravenous drug injection, or sites of intravenous catheter insertion. Group A Streptococcus and Staphylococcus are the most common of these bacteria, which are part of the normal flora of the skin, but normally cause no actual infection while on the skin's outer surface. Skin on the face or lower legs is most commonly affected by this infection, though cellulitis can occur on any part of the body. The mainstay of therapy remains treatment with appropriate antibiotics Recovery periods last from 48 hours to six months. The typical signature symptom of cellulitis is an area which is red, hot, and tender . Cellulitis is most often a clinical diagnosis, and local cultures do not always identify the causative organism. Blood cultures usually are positive only if the patient develops generalized

sepsis.Treatment consists of resting the affected area, cutting away dead tissue, and administration of antibiotics (either oral or intravenous).

This page titled 6.6C: Bacterial Skin Diseases is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.18C: Bacterial Skin Diseases** is licensed CC BY-SA 4.0.

6.6D: Viral Skin Diseases

Learning Objectives

- Describe what causes cold sores, shingles and warts and the treatment options available

Virus-related cutaneous conditions are caused by two main groups of viruses–DNA and RNA types–both of which are obligatory intracellular parasites.

A cutaneous condition is any medical condition that affects the integumentary system — the organ system that comprises the entire surface of the body and includes skin, hair, nails, and related muscle and glands. Conditions of the human integumentary system constitute a broad spectrum of diseases, also known as dermatoses. While only a small number of skin diseases account for most visits to the physician, thousands of skin conditions have been described. Three common skin conditions that result from viral infections are cold sores, shingles, and warts.

Herpes

Herpes simplex is a viral disease from the herpesviridae family caused by both Herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2). Infection with the herpes virus is categorized into one of several distinct disorders based on the site of infection. Oral herpes , the visible symptoms of which are colloquially called cold sores or fever blisters, is an infection of the face or mouth and is the most common form of infection. Genital herpes, known simply as herpes, is the second most common form of herpes. Herpes simplex is most easily transmitted by direct contact with a lesion or the body fluid of an infected individual. Transmission may also occur through skin-to-skin contact during periods of asymptomatic shedding. Barrier protection methods are the most reliable method of preventing transmission of herpes, but they merely reduce rather than eliminate risk. Oral herpes is easily diagnosed if the patient presents with visible sores or ulcers. Once infected, the virus remains in the body for life. Recurrent infections (outbreaks) may occur from time to time, especially in times of immune impairment such as HIV and cancer-related immune suppression. However, after several years, outbreaks become less severe and more sporadic, and some people will become perpetually asymptomatic and will no longer experience outbreaks, though they may still be contagious to others. Treatments with antivirals can reduce viral shedding and alleviate the severity of symptomatic episodes.

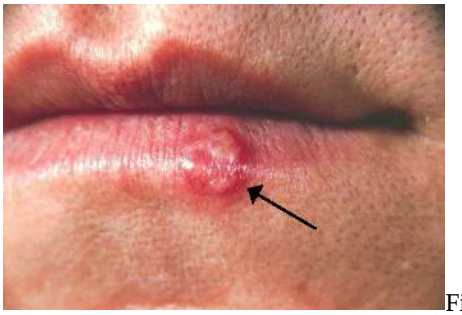


Figure: **Herpes simplex**. Herpes labialis or cold sore of the lower lip. Note the blisters in a group marked by an arrow.

Herpes Zoster

Herpes zoster (or simply zoster), commonly known as shingles, is a viral disease characterized by a painful skin rash with blisters in a limited area on one side of the body, often in a stripe. The initial infection with varicella zoster virus (VZV) causes the acute (short-lived) illness chickenpox which generally occurs in children and young people. Once an episode of chickenpox has resolved, the virus is not eliminated from the body but remains latent and can go on to cause shingles—an illness with very different symptoms—often many years after the initial infection. Although the zoster rash usually heals within two to four weeks, some sufferers experience residual nerve pain for months or years, a condition called postherpetic neuralgia. Exactly how the virus remains latent in the body, and subsequently re-activates is not understood. The earliest symptoms of herpes zoster, which include headache, fever, and malaise, are nonspecific, and may result in an incorrect diagnosis. In most cases after 1–2 days, but sometimes as long as three weeks, the initial phase is followed by the appearance of the characteristic skin rash. The pain and rash most commonly occurs on the torso, but can appear on the face, eyes, or other parts of the body.

At first the rash appears similar to the first appearance of hives. However, unlike hives, herpes zoster causes skin changes limited to a dermatome, normally resulting in a stripe or belt-like pattern that is limited to one side of the body and does not cross the midline. The goals of treatment are to limit the severity and duration of pain, shorten the duration of a shingles episode, and reduce complications. Symptomatic treatment is often needed for the complication of postherpetic neuralgia. Topical lotions containing calamine can be used on the rash or blisters and may be soothing. Antiviral drugs inhibit VZV replication and reduce the severity and duration of herpes zoster with minimal side effects, but do not reliably prevent postherpetic neuralgia. Of these drugs, acyclovir has been the standard treatment.


Figure: **Herpes Zoster**. Neck Herpes zoster blisters on the neck and shoulder.

A wart is generally a small, rough growth, typically on a human's hands or feet , but often other locations, that can resemble a cauliflower or a solid blister. They are caused by a viral infection, specifically by one of the many types of human papillomavirus (HPV). It is possible to get warts from others. They are contagious and usually enter the body in an area of broken skin. They typically disappear after a few months but can last for years and can recur. Gardasil is an HPV vaccine aimed at preventing cervical cancers and genital warts. There are many treatments and procedures associated with wart removal.


Figure: Warts. Warts on the big toe.

Key Points

- Oral herpes, the visible symptoms of which are colloquially called cold sores or fever blisters, is an infection of the face or mouth and is the most common form of infection by herpes simplex.
- Herpes zoster (or simply zoster), commonly known as shingles, is a viral disease caused by reactivation of latent varizella zoster virus and characterized by a painful skin rash with blisters in a limited area on one side of the body, often in a stripe.
- A wart is generally a small, rough growth, typically on a human's hands or feet that can resemble a cauliflower or a solid blister and it is caused by infection by the human papilloma virus.

Key Terms

- **shingles**: a viral disease characterized by a painful skin rash with blisters in a limited area on one side of the body, often in a stripe
- **wart**: a type of deformed growth occurring on the skin caused by the human papillomavirus (HPV).
- **cold sore**: a small bump on the lips resulting from infection by the herpes virus.
- **zoster**: the disease called herpes zoster (from the typically beltlike pattern of its rash); shingles.

This page titled 6.6D: Viral Skin Diseases is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.18D: Viral Skin Diseases** is licensed CC BY-SA 4.0.

6.6E: Fungal Skin and Nail Diseases

Learning Objectives

- Describe how fungal skin and nail diseases arise, their characteristic symptoms and the treatment options available

A cutaneous condition is any medical condition that affects the integumentary system — the organ system that comprises the entire surface of the body and includes skin, hair, nails, and related muscle and glands. Conditions of the human integumentary system constitute a broad spectrum of diseases, also known as dermatoses, as well as many nonpathologic states (like, in certain circumstances, melanonychia and racquet nails). Common fungal skin and nail diseases include athlete's foot, jock itch, and ringworm.

Athlete's foot (also known as ringworm of the foot and tinea pedis;) is an infection of the skin that is caused by a fungi in the genus Trichophyton. While it is typically transmitted in moist communal areas where people walk barefoot, the disease requires a warm moist environment, such as the inside of a shoe, in order to incubate. Athlete's foot causes scaling, flaking, and itching of the affected skin. Blisters and cracked skin may also occur, leading to exposed raw tissue, pain, swelling, and inflammation. Secondary bacterial infection can accompany the fungal infection, sometimes requiring a course of oral antibiotics. Athlete's foot can usually be diagnosed by visual inspection of the skin, but where the diagnosis is in doubt direct microscopy of a potassium hydroxide preparation (known as a KOH test) may help rule out other possible causes, such as eczema or psoriasis. Without medication athlete's foot resolves in 30–40% of cases and topical antifungal medication consistently produce much higher percentages of a cure. Conventional treatment typically involves daily or twice daily application of a topical medication in conjunction with hygiene measures outlined in the above section on prevention. Keeping feet dry and practicing good hygiene is crucial to preventing reinfection. Severe or prolonged fungal skin infections may require treatment with oral antifungal medication.



Figure: **Athlete's Foot**. A severe case of athlete's foot.

Tinea cruris, also known as crotch itch, crotch rot, Dhobie itch, eczema marginatum, gym itch, jock itch, jock rot, and ringworm of the groin is a dermatophyte fungal infection of the groin region in any sex, though more often seen in males. As the common name for this condition implies, it causes itching or a burning sensation in the groin area, thigh skin folds, or anus. It may involve the inner thighs and genital areas, as well as extending back to the perineum and perianal areas. Affected areas may appear red, tan, or brown, with flaking, rippling, peeling, or cracking skin. Opportunistic infections (infections that are caused by a diminished immune system) are frequent. Fungus from other parts of the body (commonly tinea pedis or 'athlete's foot') can contribute to this itch. A warm, damp environment allowing the fungus to cultivate greatly contributes; especially with tight, sweaty, or rubbing clothing such as a jockstrap. Medical professionals suggest keeping the groin area clean and dry by drying off thoroughly after bathing and putting on dry clothing right away after swimming or perspiring. Other recommendations to prevent this infection are: not sharing clothing or towels with others, showering immediately after athletic activities, wearing loose cotton underwear, avoiding tight-fitting clothes, and using antifungal powders. Tinea cruris is best treated with topical antifungal medications of the allylamine or azole type.

Dermatophytosis or ringworm is a clinical condition caused by fungal infection of the skin in humans, pets such as cats, and domesticated animals such as sheep and cattle. The term "ringworm" is a misnomer, since the condition is caused by fungi of several different species and not by parasitic worms. The fungi that cause parasitic infection (dermatophytes) feed on keratin, the material found in the outer layer of skin, hair, and nails. These fungi thrive on skin that is warm and moist, but may also survive directly on the outsides of hair shafts or in their interiors. In pets, the fungus responsible for the disease survives in skin and on the

outer surface of hairs. Advice often given to prevent this infection includes: avoiding sharing clothing, sports equipment, towels, or sheets and washing clothes in hot water with fungicidal soap after suspected exposure to ringworm. After being exposed to places where the potential of being infected is high, one should wash with an antibacterial and anti-fungal soap or one that contains tea tree oil, which contains terpinen-4-ol. Antifungal treatments include topical agents such as miconazole, terbinafine, clotrimazole, ketoconazole, or tolnaftate applied twice daily until symptoms resolve — usually within one or two weeks

Key Points

- Athlete's foot (also known as ringworm of the foot and tinea pedis) is an infection of the skin that causes scaling, flaking, and itching of affected areas and is caused by a fungi in the genus Trichophyton.
- Tinea cruris, also known as jock itch, is a dermatophyte fungal infection of the groin region in any sex, though more often seen in males.
- Dermatophytosis or ringworm is a clinical condition caused by fungal infection of the skin in humans, pets such as cats, and domesticated animals such as sheep and cattle.

Key Terms

- **jock itch**: a fungal infection, tinea cruris, of the groin region, due to the fungus Trichophyton rubrum and others.
- **ringworm**: a contagious fungal affliction of the skin, characterized by ring-shaped discoloured patches, covered by vesicles or scales.
- **athlete's foot**: a fungal infection of the skin of the foot, usually between the toes, caused by the pathogen fungi. Scientific name: tinea pedis.

This page titled 6.6E: Fungal Skin and Nail Diseases is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.18E: Fungal Skin and Nail Diseases** is licensed CC BY-SA 4.0.

6.6F: Parasitic Skin Diseases

Learning Objectives

- Describe how the parasitic skin infections creeping eruption, lice and scabies arise and the treatment options available

A cutaneous condition is any medical condition that affects the integumentary system — the organ system that comprises the entire surface of the body and includes skin, hair, nails, and related muscle and glands. The major function of this system is as a barrier against the external environment. Conditions of the human integumentary system constitute a broad spectrum of diseases, also known as dermatoses, as well as many nonpathologic states (like, in certain circumstances, melanonychia and racquet nails). Common parasitic skin diseases include creeping eruption, lice, and scabies.

Cutaneous larva migrans (abbreviated CLM) is a skin disease in humans caused by the larvae of various nematode parasites of the hookworm family (Ancylostomatidae). The most common species that cayse this disease in the Americas is Ancylostoma braziliense. Colloquially called creeping eruption due to the way it looks, the disease is also somewhat ambiguously known as “ground itch” or (in some parts of the southern U.S.) “sandworms,” as the larvae like to live in sandy soil. Another vernacular name is plumber’s itch. The medical term CLM literally means “wandering larvae in the skin. ” These parasites are found in dog and cat feces and although they are able to infect the deeper tissues of these animals (through to the lungs and then the intestinal tract), in humans they are only able to penetrate the outer layers of the skin and thus create the typical wormlike burrows visible underneath the skin . The parasites apparently lack the collagenase enzymes required to penetrate through the basement membrane deeper into the skin. The infection causes a red, intense itching eruption. The itching can become very painful and if scratched may allow a secondary bacterial infection to develop but it will stop after the parasites are dead. Systemic (oral) agents to treat this infection include albendazole (trade name Albenza) and ivermectin (trade name Stromectol).



Figure: **Larva Migrans Cutanea**. Typical “creeping eruption” associated with cutaneous larva migrans.

Louse (plural: lice) is the common name for members of over 3,000 species of wingless insects of the order Phthiraptera, three of which are classified as human disease agents. They are obligate ectoparasites of every avian and mammalian order except for monotremes (the platypus and echidnas), bats, whales, dolphins, porpoises, and pangolins. Most lice are scavengers, feeding on skin and other debris found on the host’s body, but some species feed on sebaceous secretions and blood. Most are found only on specific types of animals, and, in some cases, only to a particular part of the body. Some animals are known to host up to 15 different species, although one to three is typical for mammals, and two to six for birds. For example, in humans, different species of louse inhabit the scalp and pubic hair. Lice generally cannot survive for long if removed from their host. Humans host three different kinds of lice: head lice, body lice, and pubic lice. Lice infestations can be controlled with lice combs and medicated shampoos or washes.

Scabies (from Latin: scabere, “to scratch”), known colloquially as the seven-year itch, is a contagious skin infection that occurs among humans and other animals. The disease may be transmitted from objects, but is most often transmitted by direct skin-to-skin contact, with a higher risk with prolonged contact. Initial infections require four to six weeks to become symptomatic. Reinfection, however, may manifest symptoms within as little as 24 hours. Because the symptoms are allergic, their delay in onset is often mirrored by a significant delay in relief after the parasites have been eradicated. The characteristic symptoms of a scabies infection include intense itching and superficial burrows . The burrow tracks are often linear, to the point that a neat “line” of four or more

closely placed and equally developed mosquito-like “bites” is almost diagnostic of the disease. Scabies may be diagnosed clinically in geographical areas where it is common when diffuse itching presents along with either lesions in two typical spots or there is itchiness of another household member. The classical sign of scabies is the burrows made by the mites within the skin. To detect the burrow, the suspected area is rubbed with ink from a fountain pen or a topical tetracycline solution, which glows under a special light. A number of medications are effective in treating scabies with permethrin being the most effective treatment. However, treatment must often involve the entire household or community to prevent re-infection. Options to improve itchiness include antihistamines.


Figure: **Acarodermatitis**. Scabies of the foot.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Structures of the Skin. **Provided by**: Boundless Learning. **Located at**: **http://%20**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- skin. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Skin**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- stratum germinativum. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/stratum%20germinativum**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Epidermis (skin). **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Epidermis_(skin)**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- keratinocyte. **Located at**: **en.Wikipedia.org/wiki/keratinocyte**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Integumentary system. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Integumentary_system**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Human Physiology/Integumentary System. **Provided by**: Wikibooks. **Located at**: **en.wikibooks.org/wiki/Human_P..._System%23Skin**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Merkel cells. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Merkel%20cells**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- human skin. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Human_skin**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Vitamin D. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Vitamin...on_in_the_skin**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- skin flora. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Skin_flora**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- mutualistic. **Provided by**: Wikipedia. **Located at**: **en.wiktionary.org/wiki/mutualistic**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- commensal. **Provided by**: Wikipedia. **Located at**: **en.wiktionary.org/wiki/commensal**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Staphylococcus epidermidis 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Staphylococcus_epidermidis_01.png**. **License**: ***Public Domain: No Known Copyright***
- skin infection. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Skin_infection**. **License**: ***CC BY-SA: Attribution-ShareAlike***

- cellulitis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Cellulitis**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Erysipelas. **Located at**: **en.Wikipedia.org/wiki/Erysipelas**. **License**: *CC BY-SA: Attribution-ShareAlike*
- impetigo. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Impetigo**. **License**: *CC BY-SA: Attribution-ShareAlike*
- cellulitis. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/cellulitis**. **License**: *CC BY-SA: Attribution-ShareAlike*
- erysipelas. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/erysipelas**. **License**: *CC BY-SA: Attribution-ShareAlike*
- impetigo. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/impetigo**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Cellulitis3. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Cellulitis3.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- facial erysipelas. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Fa...erysipelas.jpg**. **License**: ***Public Domain: No Known Copyright***
- Impetigo2011. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Impetigo2011.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- wart. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Wart**. **License**: *CC BY-SA: Attribution-ShareAlike*
- cold sore. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/cold_sore**. **License**: *CC BY-SA: Attribution-ShareAlike*
- skin disease. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Skin_disease**. **License**: *CC BY-SA: Attribution-ShareAlike*
- wart. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/wart**. **License**: *CC BY-SA: Attribution-ShareAlike*
- shingles. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/shingles**. **License**: *CC BY-SA: Attribution-ShareAlike*
- herpes simplex. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Herpes_simplex**. **License**: *CC BY-SA: Attribution-ShareAlike*
- zoster. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/zoster**. **License**: *CC BY-SA: Attribution-ShareAlike*
- herpes zoster neck. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Herpes_zoster_neck.png**. **License**: *CC BY-SA: Attribution-ShareAlike*
- dornwarzen. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Dornwarzen.jpg**. **License**: ***Public Domain: No Known Copyright***
- herpes. **Provided by**: Wikimedia. **Located at**: **upload.wikimedia.org/Wikipedia/commons/d/da/Herpes(PHIL_1573_lores).jpg**. **License**: ***Public Domain: No Known Copyright***
- jock itch. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Jock_itch**. **License**: *CC BY-SA: Attribution-ShareAlike*
- athlete's foot. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Athlete's_foot**. **License**: *CC BY-SA: Attribution-ShareAlike*
- ringworm. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Ringworm**. **License**: *CC BY-SA: Attribution-ShareAlike*
- ringworm. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/ringworm**. **License**: *CC BY-SA: Attribution-ShareAlike*
- jock itch. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/jock_itch**. **License**: *CC BY-SA: Attribution-ShareAlike*
- athlete's foot. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/athlete's_foot**. **License**: *CC BY-SA: Attribution-ShareAlike*
- feet fungus. **Provided by**: Wikimedia. **Located at**: **upload.wikimedia.org/wikipedi...FeetFungal.JPG**. **License**: *CC BY-SA: Attribution-ShareAlike*
- scabies. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Scabies**. **License**: *CC BY-SA: Attribution-ShareAlike*

- cutaneous larva migrans. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/cutaneo...arva%20migrans**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- lice. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Lice**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- scabies. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/scabies**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- creeping eruption. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Creeping_eruption**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- louse. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/louse**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- larva mirgrans cutanea. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:La...ns_Cutanea.jpg**. **License**: ***Public Domain: No Known Copyright***
- scabies. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Scabies**. **License**: *Other*. **License Terms**: GNU: http://www.gnu.org/copyleft/fdl.html
- Curation and Revision. **Provided by**: Boundless.com. **License**: ***CC BY-SA: Attribution-ShareAlike***

Key Points

- Cutaneous larva migrans is a skin disease in humans caused by the larvae of various nematode parasites of the hookworm family (Ancylostomatidae) and characterized by a red, intense itching eruption.
- Humans host three different kinds of lice (head lice, body lice, and pubic lice). Lice infestations can be controlled with lice combs and medicated shampoos or washes.
- Scabies, known colloquially as the seven-year itch, is a contagious skin infection that occurs among humans and other animals.

Key Terms

- **scabies**: an infestation of parasitic mites, Sarcoptes scabiei, causing intense itching caused by the mites burrowing into the skin of humans and other animals. It is easily transmissible from human to human; secondary skin infection may occur.
- **cutaneous larva migrans**: a skin disease in humans, caused by the larvae of various nematode parasites of the hookworm family (Ancylostomatidae).
- **louse**: a small parasitic wingless insect of the order Phthiraptera.

This page titled 6.6F: Parasitic Skin Diseases is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.18F: Parasitic Skin Diseases** is licensed CC BY-SA 4.0.

6.7: Microbial Diseases of the Eye

This page titled 6.7: Microbial Diseases of the Eye is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **15.19: Microbial Diseases of the Eye** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

6.7A: Anatomy of the Eye

Learning Objectives

- Explain how eyes have evolved to benefit organisms

Anatomy of the Eye

The retina, a thin layer of cells located on the inner surface of the back of the eye, consists of photoreceptive cells, which are responsible for the transduction of light into nervous impulses. However, light does not enter the retina unaltered; it must first pass through other layers that process it so that it can be interpreted by the retina.

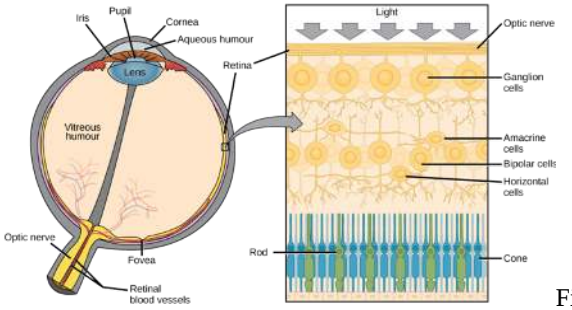


Figure: **Retina**: (a) The human eye is shown in cross section. The human eye contains structures, such as the cornea, iris, lens, and fovea, that process light so it can be deciphered by the retina. Other structures like the aqueous humor and the vitreous humor help maintain the shape of the eye. (b) A blowup shows the layers of the retina. The retina contains photoreceptive cells. In the retina, light is converted into neural signals sent to the brain.

The cornea, the front transparent layer of the eye, along with the crystalline lens, refract (bend) light to focus the image on the retina. After passing through the cornea, light passes through the aqueous humour, which connects the cornea to the lens. This clear gelatinous mass also provides the corneal epithelium with nutrients and helps maintain the convex shape of the cornea. The iris, which is visible as the colored part of the eye, is a circular muscular ring lying between the lens and the aqueous humour that regulates the amount of light entering the eye. Light passes through the center of the iris, the pupil, which actively adjusts its size to maintain a constant level of light entering the eye. In conditions of high ambient light, the iris contracts, reducing the size of the pupil. In conditions of low light, the iris relaxes and the pupil enlarges.

The main function of the lens is to focus light on the retina and fovea centralis. The lens is a transparent, convex structure located behind the cornea. On the other side of the lens is the vitreous humour, which lets light through without refraction, maintains the shape of the eye, and suspends the delicate lens. The lens focuses and re-focuses light as the eye rests on near and far objects in the visual field. The lens is operated by muscles that stretch it flat or allow it to thicken, changing the focal length of light coming through to focus it sharply on the retina. With age comes the loss of the flexibility of the lens; a form of farsightedness called presbyopia results. Presbyopia occurs because the image focuses behind the retina. It is a deficit similar to a different type of farsightedness, hyperopia, caused by an eyeball that is too short. For both defects, images in the distance are clear, but images nearby are blurry. Myopia (nearsightedness) occurs when an eyeball is elongated and the image focus falls in front of the retina. In this case, images in the distance are blurry, but images nearby are clear.

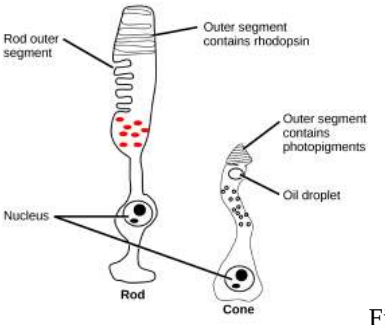


Figure: **Rods and cones**: Rods and cones are photoreceptors in the retina. Rods respond in low light and can detect only shades of gray. Cones respond in intense light and are responsible for color vision.

There are two types of photoreceptors in the retina: rods and cones. Both are named for their general appearance. Rods, strongly photosensitive, are located in the outer edges of the retina. They detect dim light and are used primarily for peripheral and nighttime vision. Cones, weakly photosensitive, are located near the center of the retina. They respond to bright light; their primary role is in daytime, color vision.

The fovea is the region in the center back of the eye that is responsible for acute (central) vision. The fovea has a high density of cones. When you bring your gaze to an object to examine it intently in bright light, the eyes orient so that the object's image falls on the fovea. However, when looking at a star in the night sky or other object in dim light, the object can be better viewed by the peripheral vision because it is the rods at the edges of the retina, rather than the cones at the center, that operate better in low light. In humans, cones far outnumber rods in the fovea.

Key Points

- The cornea and the lens bend light to focus the image on the retina; the iris and pupil regulate the amount of light entering the eye.
- The aqueous humour maintains the convex shape of the cornea; the vitreous humour supports the lens and maintains the shape of the entire eye.
- Presbyopia occurs because the image focuses behind the retina; it is similar to hyperopia (farsightedness), which is caused by an eyeball that is too short.
- Myopia (nearsightedness) occurs when an eyeball is elongated; images in the distance appear blurry, but images nearby are clear.
- Rods are used for peripheral and nighttime vision; cones are used for daytime and color vision.
- The fovea is responsible for acute vision because it has a high density of cones.

Key Terms

- **rod**: a rod-shaped cell located in the outer retina of the eye that is extremely sensitive to light
- **retina**: the thin layer of cells at the back of the eyeball where light is converted into neural signals sent to the brain
- **cone**: cell located near the center of the retina that is weakly photosensitive and is responsible for color vision in relatively bright light

---

This page titled 6.7A: Anatomy of the Eye is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.19A: Anatomy of the Eye** is licensed CC BY-SA 4.0.

6.7B: Normal Eye Microbiota

Learning Objectives

- Give examples of the microorganisms found in the normal eye microbiota

Normal Eye Microbiota

The human microbiome (or human microbiota) is the aggregate of microorganisms that reside on the surface and in deep layers of skin, in the saliva and oral mucosa, in the conjunctiva, and in the gastrointestinal tracts. They include bacteria, fungi, and archaea. Some of these organisms perform tasks that are useful for the human host. However, the majority have been too poorly researched to understand the role they play. Those that are expected to be present and do not cause disease (under normal circumstances), but instead participate in maintaining health, are deemed members of the normal flora.

A small number of bacteria are normally present in the conjunctiva. These include: Chlamydia trachomatis, Chlamydophila pneumoniae, Haemophilus aegyptius, Haemophilus influenzae, Moraxella spp, Neisseria spp, Staphylococcus aureus, Staphylococcus epidermidis and Streptococcus viridians. Staphylococcus epidermidis and certain coryneforms such as Propionibacterium acnes are dominant. Staphylococcus aureus, streptococci, Haemophilus sp. and Neisseria sp. sometimes occur. The lachrymal glands continuously secrete tears keeping the conjunctiva moist, while intermittent blinking lubricates the conjunctiva and washes away foreign material. Tears contain bactericides such as lysozyme, so that microorganisms have difficulty in surviving the lysozyme and settling on the epithelial surfaces.

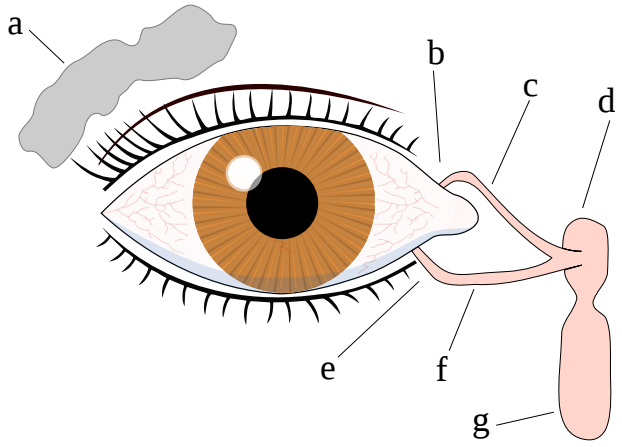


Figure: **The Tear System**: The tear system. Tears are secretions that clean and lubricate the eyes: A) Tear gland/Lacrimal gland, B) Superior lacrimal punctum, C) Superior lacrimal canal lacrimation leads to tears, D) Tear sac/Lacrimal sac, E) Inferior lacrimal punctum, F) Inferior lacrimal canal, G) Nasolacrimal canal.

Some pathogens able to infect the conjunctiva, such as Neisseria gonorrhoeae and Chlamydia trachomatis, are thought to have special processes allowing them to attach to the conjunctival epithelium. Newborn infants are particularly prone to bacterial attachment. Chlamydia and Neisseria may be present in an infected mother and show up on the cervical and vaginal epithelium. In such cases the newborn's eyes may be treated with silver nitrate or antibiotics.

Key Points

- The lachrymal glands continuously secrete tears keeping the conjunctiva moist, while intermittent blinking lubricates the conjunctiva and washes away foreign material.
- Tears contain bactericides such as lysozyme, so that microorganisms have difficulty in surviving the lysozyme and settling on the epithelial surfaces.
- Some pathogens able to infect the conjunctiva, such as Neisseria gonorrhoeae and Chlamydia trachomatis are thought to have special processes allowing them to attach to the conjunctival epithelium.

Key Terms

- **lachrymal gland**: The lacrimal glands are paired almond-shaped glands, one for each eye, that secrete the aqueous layer of the tear film.
- **conjunctiva**: A clear mucous membrane that lines the inner surface of the eyelid and the exposed surface of the eyeball or sclera.
- **lysozyme**: A bacteriolytic (or antibiotic) enzyme found in many animal secretions and in egg white.

This page titled 6.7B: Normal Eye Microbiota is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.19B: Normal Eye Microbiota** is licensed CC BY-SA 4.0.

6.7C: Bacterial Eye Diseases

Conjunctivitis is inflammation of the conjunctiva, most commonly due to an infection.

LEARNING OBJECTIVES

Describe the various causes of conjunctivitis and keratitis and its symptoms

KEY TAKEAWAYS

Key Points

- Classification can be either by extent of the inflamed area or by cause (allergic, bacterial, viral, or chemical).
- Red eye (hyperaemia), irritation (chemosis) and watering (epiphora) of the eyes are symptoms common to all forms of conjunctivitis.
- Keratitis, a condition in which the eye's cornea becomes inflamed, is often marked by moderate to intense pain and usually involves impaired eyesight.

Key Terms

- **conjunctivitis**: An inflammation of the conjunctiva often due to infection.
- **keratitis**: Inflammation of the cornea.

Common Eye Infections

CONJUNCTIVITIS

Conjunctivitis, also called pink eye or Madras eye, is inflammation of the conjunctiva, which consists of the outermost layer of the eye and the inner surface of the eyelids. Conjunctivitis most commonly caused by a viral infection or, less commonly, a bacterial infection, or by an allergic reaction. Classification can be either by extent of the inflamed area or by cause (allergic, bacterial, viral or chemical). Neonatal conjunctivitis is often defined separately due to different organisms.

Symptoms and Diagnosis

An inflamed, red eye (hyperaemia), irritation (chemosis), and watering (epiphora) of the eyes are symptoms common to all forms of conjunctivitis. However, the pupils should be normally reactive and the visual acuity normal. Bacterial conjunctivitis due to common pyogenic (pus-producing) bacteria causes marked grittiness/irritation and a stringy, opaque, greyish or yellowish mucopurulent discharge that may cause the lids to stick together, especially after sleep. Another symptom that could be caused by bacterial conjunctivitis is severe crusting of the infected eye and the surrounding skin.



Figure: **Conjunctivitis**: An eye with bacterial conjunctivitis.

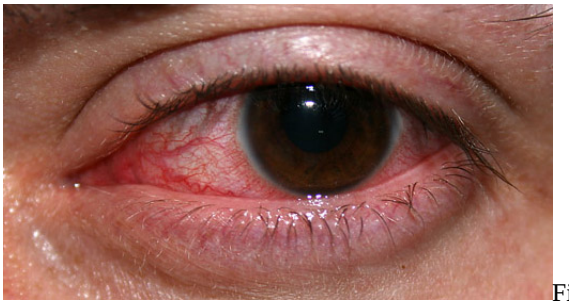
Contrary to popular belief, discharge is not essential to the diagnosis. Bacteria such as *Chlamydia trachomatis* or *Moraxella* can cause a non-exudative but persistent conjunctivitis without much redness. The gritty and/or scratchy feeling is sometimes localized enough for patients to insist they must have a foreign body in the eye. The more acute pyogenic infections can be painful. Like viral conjunctivitis, it usually affects only one eye but may spread easily to the other eye.

Corynebacterium diphtheriae causes membrane formation in conjunctiva of non immunized children. Bacterial conjunctivitis usually resolves without treatment. Antibiotics, eye drops, or ointment may only be needed if no improvement is observed after three days.

Chlamydiaconjunctivitis or *trachoma* was once the most important cause of blindness worldwide. The infection can be spread from eye to eye by fingers, shared towels or cloths, coughing and sneezing, and by eye-seeking flies. Newborns can also develop *chlamydia* eye infection through childbirth. *Chlamydia* can affect infants by causing spontaneous abortion, premature birth, and conjunctivitis, which may lead to blindness and pneumonia. Conjunctivitis due to *chlamydia* typically occurs one week after birth (compared with chemical causes (within hours) or gonorrhea (2–5 days)).

KERATITIS

Keratitis is a condition in which the eye's cornea, the front part of the eye, becomes inflamed. The condition is often marked by moderate to intense pain and usually involves impaired eyesight. Superficial keratitis involves the superficial layers (i.e. the epithelium) of the cornea. After healing, this form of keratitis does not generally leave a scar. Deep keratitis involves deeper layers of the cornea (i.e. the epithelium, Bowman's membrane and often stroma), and the natural course leaves a scar upon healing that impairs vision if it occurs on or near the visual axis. This can be reduced or avoided with the use of topical corticosteroid eyedrops.


Figure: **Keratitis**: An eye with non-ulcerative sterile keratitis.

Causes and Treatment

Keratitis has multiple causes. Bacterial infection of the cornea can follow from an injury or from result from wearing contact lenses. The bacteria involved are *Staphylococcus aureus* and, for contact lens wearers, *Pseudomonas aeruginosa*. *Pseudomonas aeruginosa* contains enzymes that can digest the cornea. Treatment depends on the cause of the keratitis. Infectious keratitis can progress rapidly, and generally requires urgent antibacterial, antifungal, or antiviral therapy to eliminate the pathogen. Treatment is usually carried out by an ophthalmologist and can involve prescription eye medications, systemic medication, or even intravenous therapy. It is inadvisable to use over-the-counter eye drops as they are typically not helpful in treating infections; using them could also delay crucial correct treatment, increasing the likelihood of sight-threatening complications. In addition, contact lens wearers are typically advised to discontinue contact lens wear and replace contaminated contact lenses and contact lens cases.

This page titled 6.7C: Bacterial Eye Diseases is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.19C: Bacterial Eye Diseases** is licensed CC BY-SA 4.0.

6.7D: Other Infectious Eye Diseases

Fungi and viruses such as herpes simplex can cause eye infections.

LEARNING OBJECTIVES

Summarize the various types of herpes simplex keratitis: dendritic ulcer (epithelial keratitis) and disciform keratitis (stromal keratitis)

KEY TAKEAWAYS

Key Points

- Improper hygiene is a major cause of fungal contamination of contact lenses.
- Herpetic simplex keratitis is a form of keratitis caused by recurrent herpes simplex virus in cornea.
- Primary infection most commonly manifests as blepharoconjunctivitis i.e. infection of lids and conjunctiva that heals without scarring.

Key Terms

- **ulcer**: An open sore of the skin, eyes, or mucous membrane, often caused by an initial abrasion and generally maintained by an inflammation and/or an infection.
- **keratitis**: Inflammation of the cornea.
- **conjunctivitis**: An inflammation of the conjunctiva often due to infection.

Microbial corneal infection is the most serious and “most common vision threatening” complication of wearing contact lenses, which is believed to be strongly associated with contact lens cases. Such infections “are being increasingly recognized as an important cause of morbidity and blindness” and “may even be life-threatening. ” While the cornea is believed to be the most common site for fungal eye infections, other parts of the eye such as the orbit, sclera, and eyelids may also be involved.

Fungal Infections of the Eye

Factors that contribute to fungal contamination of contact lenses include, but not limited to, hygiene negligence such as: improper sterilization and disinfection of contact lenses, use of contaminated lenses, contaminated contact lens case, contaminated contact lens solution, wearing of contact lenses during eye infections and introduction of micro-organisms from the environment.

Diagnosis is determined”by recognition of typical clinical features and through direct microscopic detection of fungi in scrapes, biopsy specimens, and other samples. “Ultimately, cultures that are made from the samples isolated from patients is what “confirms diagnosis. ” Other tests that may also be used if needed include “histopathological, immunohistochemical, or DNA -based tests. Pathogenesis of the fungal contaminants includes a wide range of factors such as invasiveness, toxigenicity, and host factors. Once diagnosis is accessed, specific anti-fungal therapy can be administered. One of the most popular and common treatments used”for life-threatening and severe ophthalmic mycoses is amphotericin B which is a specific anti-fungal drug. For the treatment for filamentous fungal keratitis, “topical natamycin is usually the first choice. For the treatment of yeast keratitis, topical amphotericin B is usually the first choice. Current advances in further treatments include evaluations of triazoles such as itraconazole and fluconazole” as therapeutic options in ophthalmic mycoses.

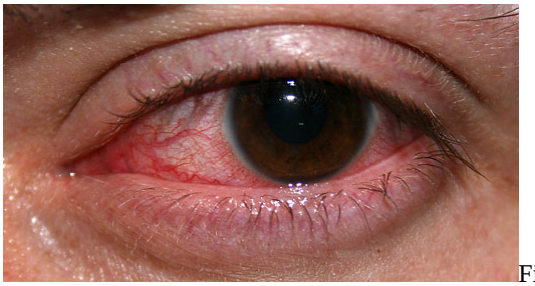


Figure: **Keratitis**: An eye with non-ulcerative sterile keratitis.

Viral Infections of the Eye

Herpes Simplex Virus

Herpetic simplex keratitis is a form of keratitis caused by recurrent herpes simplex virus in cornea. Herpes simplex virus (HSV) infection is very common in humans. HSV is a double-stranded DNA virus that has icosahedral capsid. HSV-1 infections are found more commonly in the oral area and HSV-2 in the genital area. Primary infection most commonly manifests as blepharoconjunctivitis i.e. infection of lids and conjunctiva that heals without scarring. Lid vesicles and conjunctivitis are seen in primary infection. Corneal involvement is rarely seen in primary infection. Recurrent herpes of the eye in turn is caused by reactivation of the virus in a latently infected sensory ganglion, transport of the virus down the nerve axon to sensory nerve endings, and subsequent infection of ocular surface. The following classification of herpes simplex keratitis is important for understanding this disease:



Figure: **Herpes simplex blepharitis**: Primary eye infection with herpes simplex virus most commonly manifests as blepharoconjunctivitis i.e. infection of lids and conjunctiva that heals without scarring. Lid vesicles and conjunctivitis are seen in primary infection.

Dendritic Ulcer (Epithelial Keratitis)

This classic herpetic lesion consists of a linear branching corneal ulcer (dendritic ulcer). During eye exam the defect is examined after staining with fluorescein dye. The underlying corneal has minimal inflammation. Patients with epithelial keratitis complain of foreign-body sensation, light sensitivity, redness, and blurred vision. Focal or diffuse reduction in corneal sensation develops following recurrent epithelial keratitis. In immune deficient patients or with the use of corticosteroids the ulcer may become large and in these cases it is called geographic ulcer.

Disciform Keratitis (Stromal Kieratitis)

Stromal keratitis manifests as a disc-shaped area of corneal edema. Longstanding corneal edema leads to permanent scarring. It is the major cause of decreased vision associated with HSV. Localized endotheliis (localized inflammation of corneal endothelial layer) is the cause of disciform keratitis.

Diagnostic testing is seldom needed because of its classic clinical features and is not useful in stromal keratitis as there is usually no live virus. Laboratory tests are indicated in complicated cases when the clinical diagnosis is uncertain and in all cases of suspected neonatal herpes infection. Corneal smears or impression cytology specimens can be analyzed by culture, antigen detection, or fluorescent antibody testing. Demonstration of HSV is possible with viral culture. Serologic tests in turn may show a rising antibody titer during primary infection but are of no diagnostic assistance during recurrent episodes.

Treatment of herpes of the eye is different based on its presentation. Epithelial keratitis is caused by live virus. Stromal disease is an immune response. Metaherpetic ulcer results from inability of the corneal epithelium to heal. Epithelial keratitis is treated with topical antivirals, which are very effective with low incidence of resistance. Acyclovir ophthalmic ointment and Trifluridine eye drops have similar effectiveness but are more effective than Idoxuridine and Vidarabine eye drops. Topical antiviral medications are not absorbed by the cornea through an intact epithelium, but orally administered acyclovir penetrates an intact cornea and anterior chamber.

Cytomegalovirus Retinitis

Cytomegalovirus retinitis, also known as CMV retinitis, is an inflammation of the retina of the eye that can lead to blindness. Caused by human cytomegalovirus, it occurs predominantly in people whose immune system has been compromised.

Parasitic Infections of the Eye

Acanthamoeba

Acanthamoeba is a microscopic, free-living ameba (single-celled living organism) commonly found in the environment that can cause rare, but severe, eye illness. Acanthamoeba causes three main types of illness involving the eye (Acanthamoeba keratitis), the brain and spinal cord (Granulomatous Encephalitis), and infections that can spread throughout the entire body (disseminated infection).

Toxoplasma gondii

A single-celled parasite called Toxoplasma gondii causes a disease known as toxoplasmosis. While the parasite is found throughout the world, more than 60 million people in the United States may be infected with the Toxoplasma parasite. Of those who are infected, very few have symptoms because a healthy person's immune system usually keeps the parasite from causing illness.

Signs and symptoms of ocular toxoplasmosis can include reduced vision, blurred vision, pain (often with bright light), redness of the eye, and sometimes tearing. Ophthalmologists sometimes prescribe medicine to treat active disease. Whether or not medication is recommended depends on the size of the eye lesion, the location, and the characteristics of the lesion (acute active, versus chronic not progressing). An ophthalmologist will provide the best care for ocular toxoplasmosis.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: ***CC BY-SA: Attribution-ShareAlike***

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- OpenStax College, Biology. October 17, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44761/latest...ol11448/latest. **License**: ***CC BY: Attribution***
- Ophthalmology/Anatomy of the Eye. **Provided by**: Wikibooks. **Located at**: http://en.wikibooks.org/wiki/Ophthal...omy_of_the_Eye. **License**: ***CC BY-SA: Attribution-ShareAlike***
- rod. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/rod. **License**: ***CC BY-SA: Attribution-ShareAlike***
- cone. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/cone. **License**: ***CC BY-SA: Attribution-ShareAlike***
- retina. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/retina. **License**: ***CC BY-SA: Attribution-ShareAlike***
- OpenStax College, Vision. October 17, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44761/latest...e_36_05_02.png. **License**: ***CC BY: Attribution***
- OpenStax College, Vision. October 17, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44761/latest...e_36_05_03.jpg. **License**: ***CC BY: Attribution***
- Human microbiome. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Human_m...unctival_flora. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Human flora. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Human_flora. **License**: ***CC BY-SA: Attribution-ShareAlike***
- List of human flora. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/List_of...an_flora%23Eye. **License**: ***CC BY-SA: Attribution-ShareAlike***
- lysozyme. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/lysozyme. **License**: ***CC BY-SA: Attribution-ShareAlike***
- lachrymal gland. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/lachrymal%20gland. **License**: ***CC BY-SA: Attribution-ShareAlike***
- conjunctiva. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/conjunctiva. **License**: ***CC BY-SA: Attribution-ShareAlike***

- OpenStax College, Vision. October 17, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44761/latest...e_36_05_02.png. **License**: *CC BY: Attribution*
- OpenStax College, Vision. October 17, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44761/latest...e_36_05_03.jpg. **License**: *CC BY: Attribution*
- Tear system. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:Te...tem.svg%23file. **License**: *CC BY-SA: Attribution-ShareAlike*
- Conjunctivitis. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Conjunctivitis. **License**: *CC BY-SA: Attribution-ShareAlike*
- Chlamydial infection. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Chlamyd...%23Eye_disease. **License**: *CC BY-SA: Attribution-ShareAlike*
- Keratitis. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Keratitis. **License**: *CC BY-SA: Attribution-ShareAlike*
- keratitis. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/keratitis. **License**: *CC BY-SA: Attribution-ShareAlike*
- conjunctivitis. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/conjunctivitis. **License**: *CC BY-SA: Attribution-ShareAlike*
- OpenStax College, Vision. October 17, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44761/latest...e_36_05_02.png. **License**: *CC BY: Attribution*
- OpenStax College, Vision. October 17, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44761/latest...e_36_05_03.jpg. **License**: *CC BY: Attribution*
- Tear system. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:Te...tem.svg%23file. **License**: *CC BY-SA: Attribution-ShareAlike*
- Clare-314. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:Clare-314.jpg. **License**: *CC BY-SA: Attribution-ShareAlike*
- Conjunctivitis. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Conjunctivitis. **License**: *CC BY: Attribution*
- Fungal contamination of contact lenses. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Fungal_...contact_lenses. **License**: *CC BY-SA: Attribution-ShareAlike*
- Ocular herpes. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Ocular_herpes. **License**: *CC BY-SA: Attribution-ShareAlike*
- ulcer. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/ulcer. **License**: *CC BY-SA: Attribution-ShareAlike*
- keratitis. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/keratitis. **License**: *CC BY-SA: Attribution-ShareAlike*
- conjunctivitis. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/conjunctivitis. **License**: *CC BY-SA: Attribution-ShareAlike*
- Cytomegalovirus retinitis. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Cytomegalovirus_retinitis. **License**: *CC BY-SA: Attribution-ShareAlike*
- Toxoplasmosis. **Provided by**: Centers for Disease Control and Prevention. **Located at**: http://www.cdc.gov/parasites/toxoplasmosis/gen_info/faqs.html. **License**: ***Public Domain: No Known Copyright***
- Acanthamoeba Infection FAQs. **Provided by**: Centers for Disease Control and Prevention. **Located at**: http://www.cdc.gov/parasites/acanthamoeba/gen_info/acanthamoeba.html. **License**: ***Public Domain: No Known Copyright***
- OpenStax College, Vision. October 17, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44761/latest...e_36_05_02.png. **License**: *CC BY: Attribution*
- OpenStax College, Vision. October 17, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44761/latest...e_36_05_03.jpg. **License**: *CC BY: Attribution*
- Tear system. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:Te...tem.svg%23file. **License**: *CC BY-SA: Attribution-ShareAlike*
- Clare-314. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:Clare-314.jpg. **License**: *CC BY-SA: Attribution-ShareAlike*
- Conjunctivitis. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Conjunctivitis. **License**: *CC BY: Attribution*

- Clare-314. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Clare-314.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Herpes%25252520simplex%25252520blepharitis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:He...lepharitis.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***

This page titled 6.7D: Other Infectious Eye Diseases is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.19D: Other Infectious Eye Diseases** is licensed CC BY-SA 4.0.

6.8: Microbial Diseases of the Nervous System

This page titled 6.8: Microbial Diseases of the Nervous System is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **15.20: Microbial Diseases of the Nervous System** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

6.8A: Functions of the Nervous System

Learning Objectives

- Describe the functions of the nervous system

The nervous system has three overlapping functions based on the sensory input, integration, and motor output. The nervous system is a highly integrated system.

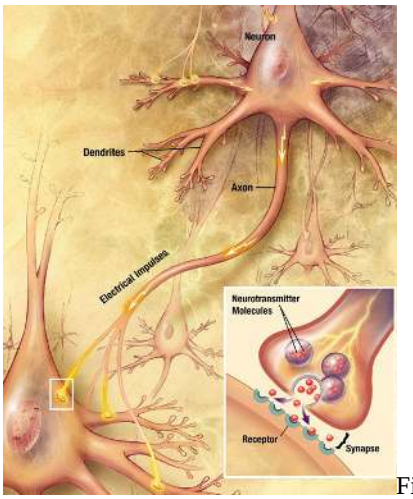


Figure: **Major elements in neuron-to-neuron communication**: Electrical impulses travel along the axon of a neuron. When this signal reaches a synapse, it provokes release of neurotransmitter molecules, which bind to receptor molecules located in the the target cell.

Sensory Input

Sensory input comes from the many sensory receptors that monitor changes occurring both inside and outside the body. The total sum of the information gathered by these receptors is called sensory input. The nervous system processes and interprets sensory input and decides what actions should be taken. The nervous system activates effector organs such as muscles and glands to cause a response called motor output.

Integration

At a more integrative level, the primary function of the nervous system is to control and communicate information throughout the body. It does this by extracting information from the environment using sensory receptors. This sensory input is sent to the central nervous system, which determines an appropriate response.

Motor Response

Once the response is activated, the nervous system sends signals via motor output to muscles or glands to initiate the response.

In humans, the sophistication of the nervous system allows for language, abstract representation of concepts, transmission of culture, and many other features of society that would not otherwise exist.

Key Points

- The nervous system is a highly integrated system. The nervous system has three overlapping functions based on sensory input, integration, and motor output.
- At a more integrative level, the primary function of the nervous system is to control and communicate information throughout the body.

Key Terms

- **hormone**: A molecule released by a cell or a gland in one part of the body that sends out messages affecting cells in other parts of the organism.
- **nervous system**: The organ system that coordinates the activities of muscles, monitors organs, constructs and processes data received from the senses, and initiates actions.

This page titled 6.8A: Functions of the Nervous System is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.20A: Functions of the Nervous System** is licensed CC BY-SA 4.0.

6.8B: Subdivisions of the Nervous System

Learning Objectives

- Describe the subdivisions of the nervous system

Key Points

- The nervous system is often divided into components called gray matter and white matter. Gray matter contains a relatively high proportion of neuron cell bodies and white matter is composed mainly of axons.
- The peripheral nervous system is subdivided into nerves, the autonomic system, and the somatic system. The autonomic nervous system is further subdivided into the parasympathetic and sympathetic nervous systems.
- The enteric nervous system is an independent subsystem of the peripheral nervous system.
- The central nervous system includes the brain and spinal cord and has various centers that integrate of all the information in the body. These can be subdivided into lower centers that carry out essential body functions and higher centers that control more sophisticated information processing.

Key Terms

- **gray matter**: A major component of the central nervous system, consisting of neuronal cell bodies, neuropil (dendrites and unmyelinated axons), glial cells (astroglia and oligodendrocytes), and capillaries.
- **central nervous system**: In vertebrates, the part of the nervous system comprising the brain, brainstem, and spinal cord.
- **white matter**: A region of the central nervous system containing myelinated nerve fibers and no dendrites.
- **peripheral nervous system**: This system consists of the nerves and ganglia outside of the brain and spinal cord.

The nervous system is comprised of two major subdivisions, the central nervous system (CNS) and the peripheral nervous system (PNS).

Central Nervous System

The CNS includes the brain and spinal cord along with various centers that integrate all the sensory and motor information in the body. These centers can be broadly subdivided into lower centers, including the spinal cord and brain stem, that carry out essential body and organ-control functions and higher centers within the brain that control more sophisticated information processing, including our thoughts and perceptions. Further subdivisions of the brain will be discussed in a later section.

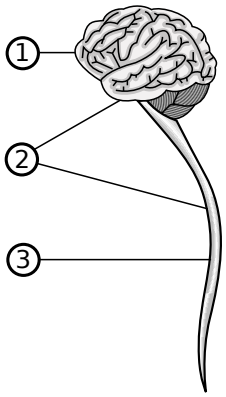


Figure: **The Central Nervous System**: The central nervous system (2) is a combination of the brain (1) and the spinal cord (3).

Gray Matter and White Matter

The nervous system is often divided into components called gray matter and white matter. Gray matter, which is gray in preserved tissue but pink or light brown in living tissue, contains a relatively high proportion of neuron cell bodies. Conversely, white matter is composed mainly of axons and is named because of the color of the fatty insulation called myelin that coats many axons. White

matter includes all of the nerves of the PNS and much of the interior of the brain and spinal cord. Gray matter is found in clusters of neurons in the brain and spinal cord and in cortical layers that line their surfaces.

By convention, a cluster of neuron cell bodies in the gray matter of the brain or spinal cord is called a nucleus, whereas a cluster of neuron cell bodies in the periphery is called a ganglion. However, there are a few notable exceptions to this rule, including a part of the brain called the basal ganglia, which will be discussed later.

Peripheral Nervous System

The PNS is a vast network of nerves consisting of bundles of axons that link the body to the brain and the spinal cord. Sensory nerves of the PNS contain sensory receptors that detect changes in the internal and external environment. This information is sent to the CNS via afferent sensory nerves. Following information processing in the CNS, signals are relayed back to the PNS by way of efferent peripheral nerves.

Autonomic and Somatic Nervous Systems

The PNS is further subdivided into the autonomic nervous system (ANS) and the somatic nervous system. The autonomic system has involuntary control of internal organs, blood vessels, and smooth and cardiac muscles. The somatic system has voluntary control of our movements via skeletal muscle.

As mentioned, the autonomic nervous system acts as a control system and most functions occur without conscious thought. The ANS affects heart rate, digestion, respiratory rate, salivation, perspiration, pupil diameter, urination, and sexual arousal. While most of its actions are involuntary, some, such as breathing, work in tandem with the conscious mind. The ANS is classically divided into two subsystems: the parasympathetic nervous system (PSNS) and sympathetic nervous system (SNS).

Parasympathetic and Sympathetic Nervous Systems

Broadly, the parasympathetic system is responsible for stimulation of “rest-and-digest” activities that occur when the body is at rest, including sexual arousal, salivation, lacrimation (tears), urination, digestion, and defecation. The sympathetic nervous syste is responsible for stimulating activities associated with the “fight-or-flight” response: mobilizing the systems of the body for escape or attacking sources of danger. In truth, the functions of both the parasympathetic and sympathetic nervous systems are not so straightforward, but this division is a useful rule of thumb.

The enteric nervous system (ENS) controls the gastrointestinal system and is sometimes considered part of the autonomic nervous system. However, it is sometimes considered an independent system because it can operate independently of the brain and the spinal cord.

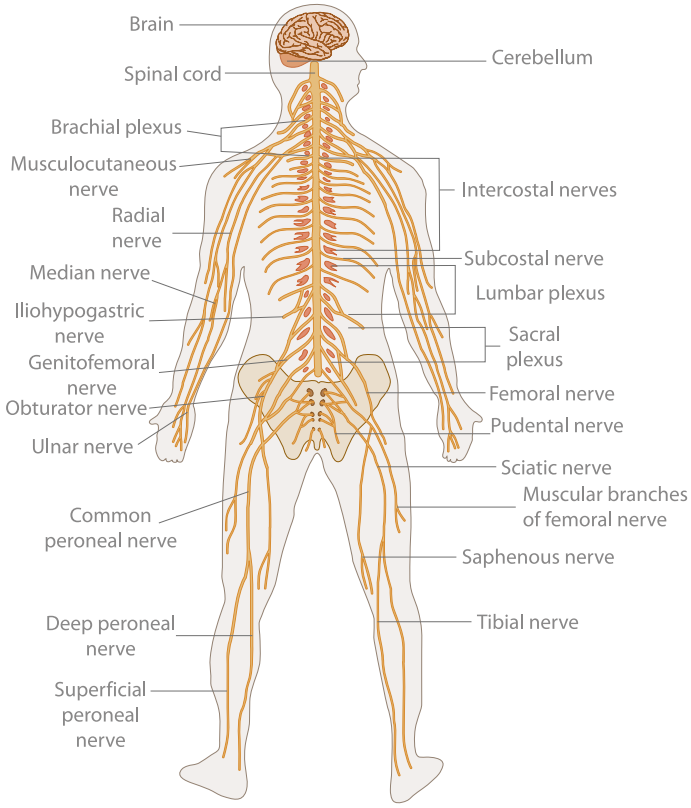


Figure: **The Nervous System of a Vertebrate**: The brain and the spinal cord are the central nervous system (CNS) (shown in yellow). The left-right pair of cranial nerves, spinal nerves, and ganglia make up the peripheral nervous system (shown in dark gold).

This page titled 6.8B: Subdivisions of the Nervous System is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.20B: Subdivisions of the Nervous System** is licensed CC BY-SA 4.0.

6.8C: Meningitis

Learning Objectives

- Discuss the various causes (viral, bacteria, fungi and protozoa) and modes of transmission for meningitis

Meningitis is inflammation of the protective membranes covering the brain and spinal cord, known collectively as the meninges. The inflammation may be caused by infection with viruses, bacteria, or other microorganisms, and less commonly by certain drugs. Meningitis can be life-threatening because of the inflammation's proximity to the brain and spinal cord. Therefore, the condition is classified as a medical emergency.

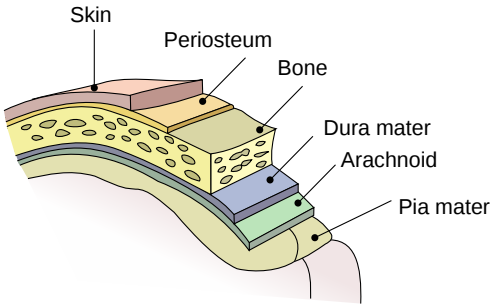


Figure: **The Meninges**: This figure displays the meninges with respect to the skull and surface of the brain.

The most common symptoms of meningitis are headache and neck stiffness associated with fever, confusion or altered consciousness, vomiting, and an inability to tolerate light (photophobia) or loud noises (phonophobia). Children often exhibit only nonspecific symptoms, such as irritability and drowsiness. If a rash is present, it may indicate a particular cause of meningitis. For instance, meningitis caused by the bacterium Neisseria meningitidis (known as "meningococcal menigitis") can be differentiated from meningitis with other causes by a rapidly spreading petechial rash, which may precede other symptoms. The rash consists of numerous small, irregular purple or red spots ("petechiae") on the trunk, lower extremities, mucous membranes, conjuctiva, and (occasionally) the palms of the hands or soles of the feet. Meningococcal bacteria may be accompanied by a characteristic rash. Seizures may also occur for various reasons. In children, seizures are common in the early stages of meningitis and do not necessarily indicate an underlying cause.

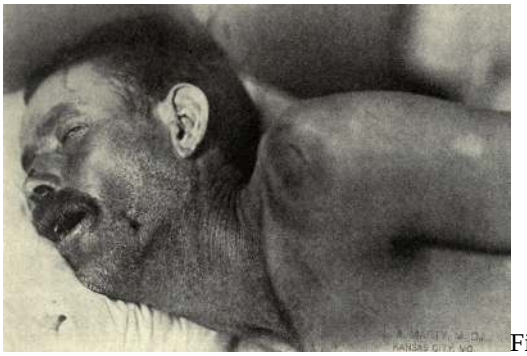


Figure: **Neck stiffness**: Neck stiffness, Texas meningitis epidemic of 1911–12. Nuchal rigidity occurs in 70% of bacterial meningitis in adults.

Meningitis can lead to serious long-term consequences such as deafness, epilepsy, hydrocephalus, and cognitive deficits, especially if not treated quickly. Some forms of meningitis (such as those associated with meningococci, Haemophilus influenzae type B, pneumococci, or mumps virus infections) may be prevented by immunization.

Meningitis is typically caused by an infection with microorganisms. Most infections are due to viruses (such as enteroviruses or herpes simplex virus), with bacteria (for example group B streptococci), fungi, and protozoa being the next most common causes. It may also result from various non-infectious causes. The term aseptic meningitis refers to cases of meningitis in which no bacterial infection can be demonstrated. This type of meningitis is usually caused by viruses, but it may be due to bacterial infection that has already been partially treated, when bacteria disappear from the meninges, or pathogens infect a space adjacent to the meninges

(e.g. sinusitis). Endocarditis (an infection of the heart valves which spreads small clusters of bacteria through the bloodstream) may cause aseptic meningitis. Aseptic meningitis may also result from infection with spirochetes, a type of bacteria that includes Treponema pallidum (the cause of syphilis) and Borrelia burgdorferi (known for causing Lyme disease).

A lumbar puncture diagnoses or excludes meningitis. A needle is inserted into the spinal canal to extract a sample of cerebrospinal fluid (CSF) which envelops the brain and spinal cord. The CSF is examined in a medical laboratory. In someone suspected of having meningitis, blood tests are performed for markers of inflammation (e.g. C-reactive protein, complete blood count) as well as blood cultures.

The first treatment in acute meningitis consists of antimicrobial and sometimes antiviral therapy. In addition, corticosteroids can also be used to prevent complications from excessive inflammation. The introduction of pneumococcal vaccine has lowered rates of pneumococcal meningitis in both children and adults. Recent skull trauma potentially allows nasal cavity bacteria to enter the meningeal space. Similarly, devices in the brain and meninges such as cerebral shunts carry an increased risk of meningitis.

Bacterial and viral meningitis are contagious and can be transmitted through droplets of respiratory secretions during close contact such as kissing, sneezing, or coughing on someone, but cannot be spread by only breathing the air where a person with meningitis has been. Since the 1980's, many countries have included immunization against Haemophilus influenzae type B in their routine childhood vaccination schemes. This has practically eliminated this pathogen as a cause of meningitis in young children in those countries.

Key Points

- Meningitis can be caused by viruses, bacteria, fungi, and protozoa.
- The most common symptoms of meningitis are headache and neck stiffness associated with fever, confusion or altered consciousness, vomiting, and an inability to tolerate light (photophobia) or loud noises (phonophobia).
- A lumbar puncture diagnoses or excludes meningitis.
- The first treatment in acute meningitis consists of antimicrobial and sometimes antiviral therapy.

Key Terms

- **meninges**: The three membranes that envelop the brain and spinal cord.
- **meningitis**: Inflammation of the meninges, characterized by headache, neck stiffness and photophobia and also fever, chills, vomiting, and myalgia.
- **lumbar puncture**: A diagnostic and at times therapeutic procedure performed to collect a sample of cerebrospinal fluid for biochemical, microbiological, and cytological analysis, or rarely to relieve increased intracranial pressure.

This page titled 6.8C: Meningitis is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.20C: Meningitis** is licensed CC BY-SA 4.0.

6.8D: Botulism

Learning Objectives

- Compare and contrast the three major modes of entry for Botulinium toxin (infant botulism or adult intestinal toxemia, foodborne botulism, and wound botulism) and describe its mechanism of action

Overview of Botulism

Botulism is a rare, but sometimes fatal, paralytic illness caused by botulinum toxin. It can affect a wide range of mammals, birds and fish. This toxin is a protein produced under anaerobic conditions by the bacterium Clostridium botulinum. The toxin enters the human body in one of three ways: by colonization of the digestive tract by the bacterium in children (infant botulism) or adults (adult intestinal toxemia), by ingestion of toxin from foods (foodborne botulism), or by contamination of a wound by the bacterium (wound botulism). Person-to-person transmission of botulism does not occur. All forms lead to paralysis that typically starts with the muscles of the face and then spreads towards the limbs. In severe forms, it leads to paralysis of the breathing muscles and causes respiratory failure. In light of this life-threatening complication, all suspected cases of botulism are treated as medical emergencies, and public health officials are usually involved to prevent further cases from the same source. Botulism can be prevented by killing the spores by pressure cooking or autoclaving at 121 °C (250 °F) for 30 minutes or providing conditions that prevent the spores from growing. Additional precautions for infants include not feeding them honey.



Figure: **Botulism**: A 14-year-old with botulism. Note the bilateral total ophthalmoplegia with ptosis in the left image and the dilated, fixed pupils in the right image. This child was fully conscious.

C. botulinum is an anaerobic, Gram positive, spore-forming rod. Botulinium toxin is one of the most powerful known toxins: about one microgram is lethal to humans. It acts by blocking nerve function (neuromuscular blockade) through inhibition of the release of the excitatory neurotransmitter acetyl choline from the presynaptic membrane of neuromuscular junctions in the somatic nervous system. This causes paralysis. Advanced botulism can cause respiratory failure by paralyzing the muscles of the chest, which can progress to respiratory arrest. In all cases, illness is caused by the botulinium toxin produced by the bacterium C. botulinum in anaerobic conditions, and not by the bacterium itself. The pattern of damage occurs because the toxin affects nerves that fire (depolarize) at a higher frequency first.

MODES OF ENTRY

Three main modes of entry for the toxin are known. The most common form in Western countries is infant botulism. This occurs in small children who are colonized with the bacterium during the early stages of their lives. The bacterium then releases the toxin into the intestine, which is absorbed into the bloodstream. The consumption of honey during the first year of life has been identified as a risk factor for infant botulism and it is a factor in a fifth of all cases. The adult form of infant botulism is termed adult intestinal toxemia, and is exceedingly rare. Foodborne botulism results from contaminated foodstuffs in which C. botulinum spores have been allowed to germinate in anaerobic conditions. This typically occurs in home-canned food substances and fermented uncooked dishes. Given that multiple people often consume food from the same source, it is common for more than a single person to be affected simultaneously. Symptoms usually appear 12–36 hours after eating, but can also appear within 6 hours to 10 days. Wound botulism results from the contamination of a wound with the bacteria, which then secrete the toxin into the bloodstream. This has

become more common in intravenous drug users since the 1990s, especially people using black tar heroin and those injecting heroin into the skin rather than the veins

TREATMENT

The only drug currently available to treat infant botulism is Botulism Immune Globulin Intravenous-Human (BIG-IV or BabyBIG). BabyBIG was developed by the Infant Botulism Treatment and Prevention Program at the California Department of Public Health. There are two primary Botulinum Antitoxins available for treatment of wound and foodborne botulism. Trivalent (A,B,E) Botulinum Antitoxin is derived from equine sources utilizing whole antibodies (Fab & Fc portions). This antitoxin is available from the local health department via the CDC. The second antitoxin is heptavalent (A,B,C,D,E,F,G) Botulinum Antitoxin which is derived from “despeciated” equine IgG antibodies which have had the Fc portion cleaved off leaving the F(ab’)2 portions. This is a less immunogenic antitoxin that is effective against all known strains of botulism where not contraindicated. This is available from the US Army.

Key Points

- The toxin (s) enters the human body by colonization of the digestive tract by the bacterium, by ingestion of toxin from foods or by contamination of a wound by the bacterium.
- All forms lead to paralysis that typically starts with the muscles of the face and then spreads towards the limbs.
- Botulism can be prevented by killing the spores by pressure cooking or autoclaving at 121 °C (250 °F) for 30 minutes or providing conditions that prevent the spores from growing.

Key Terms

- **infant botulism**: poisoning caused by the toxin from Clostridium botulinum where the gastro-intestinal tract is colonized by spores prior to the protective intestinal bacterial flora having developed
- **spore**: A thick resistant particle produced by a bacterium or protist to survive in harsh or unfavorable conditions.
- **botulism**: Poisoning caused by the toxin from Clostridium botulinum, a type of anaerobic bacteria that grows in improperly-prepared food.
- **wound botulism**: poisoning caused by the toxin from Clostridium botulinum when spores enter a wound under the skin, and, in the absence of oxygen are activated and release toxin
- **toxin**: A toxic or poisonous substance produced by the biological processes of biological organisms.

This page titled 6.8D: Botulism is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.20D: Botulism** is licensed CC BY-SA 4.0.

6.8E: Leprosy

Learning Objectives

- Describe the causative agents of leprosy: Mycobacterium leprae and Mycobacterium lepromatosis

Leprosy, also known as Hansen's disease (HD), is a chronic disease caused by the bacteria Mycobacterium leprae and Mycobacterium lepromatosis. Named after physician Gerhard Armauer Hansen, leprosy is primarily a granulomatous disease of the peripheral nerves and mucosa of the upper respiratory tract. Skin lesions are the primary external sign. Left untreated, leprosy can be progressive, causing permanent damage to the skin, nerves, limbs, and eyes.


Figure: **Leprosy**: A 23-year-old man infected with leprosy.

Diagnosis

Diagnosis in the U.S. is often delayed because healthcare providers are unaware of leprosy and its symptoms. Early diagnosis and treatment prevents nerve involvement, the hallmark of leprosy, and the disability it causes. There are many kinds of leprosy, but there are common symptoms, including:

- Runny nose
- Dry scalp
- Eye problems
- Skin lesions
- Muscle weakness
- Reddish skin
- Smooth, shiny, diffuse thickening of skin on the face, ears, and hands
- Loss of sensation in fingers and toes
- Thickening of peripheral nerves
- Flat nose due to destruction of nasal cartilage

There is also phonation and resonation of sound during speech. Often there is atrophy of the testes and impotency.

Causative Agents

Mycobacterium leprae and *Mycobacterium lepromatosis* are the causative agents of leprosy. *M. lepromatosis* is a comparatively recently identified mycobacterium that was isolated from a fatal case of diffuse lepromatous leprosy in 2008. An intracellular, acid-fast bacterium, *M. leprae* is aerobic and rod-shaped, and is surrounded by the waxy cell membrane coating characteristic of Mycobacterium species. Due to extensive loss of genes necessary for independent growth, *M. leprae* and *M. lepromatosis* are obligate pathogens, and are unculturable in the laboratory, a factor that leads to difficulty in definitively identifying the organism under a strict interpretation of Koch's postulates. The use of non-culture-based techniques such as molecular genetics has allowed for alternative establishment of causation.

Routes of Infection

M. leprae is usually spread from person to person in respiratory droplets. Studies have shown that leprosy can be transmitted to humans through contact with armadillos, too. Leprosy is not known to be either sexually transmitted or highly infectious after treatment. Approximately 95% of people are naturally immune, and sufferers are no longer infectious after as little as two weeks of treatment. In 1988, Jacinto Convit was nominated for the Nobel Prize in Medicine for developing a vaccine to fight leprosy using a combination of tuberculosis (TB) vaccines with Mycobacterium Leprae. A number of synthetic pharmaceuticals that are effective against leprosy have now been identified, allowing doctors a flexible choice of treatments.

Key Points

- Left untreated, leprosy can be progressive, causing permanent damage to the skin, nerves, limbs, and eyes.
- M. leprae and M. lepromatosis are obligate pathogens, and are unculturable in the laboratory, a factor that leads to difficulty in definitively identifying the organism under a strict interpretation of Koch's postulates.
- There is now a vaccination and extensive pharmaceutical options for treatment and prevention of leprosy.

Key Terms

- **leprosy**: Leprosy, also known as Hansen's disease (HD), is a chronic disease caused by the bacteria Mycobacterium leprae and Mycobacterium lepromatosis.
- **mycobacterium**: Any of many rod-shaped, aerobic bacteria, of the genus Mycobacterium, that cause diseases such as tuberculosis and leprosy

This page titled 6.8E: Leprosy is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.20E: Leprosy** is licensed CC BY-SA 4.0.

6.8F: Tetanus

Learning Objectives

- Describe the mode of transmission and mechanism of action for *Clostridium tetani*

Overview

Tetanus is a medical condition characterized by a prolonged contraction of skeletal muscle fibers. The primary symptoms are caused by tetanospasmin, a neurotoxin produced by the Gram-positive, rod-shaped, obligate anaerobic bacterium *Clostridium tetani*.

Infection and Symptomatic Effects

Infection generally occurs through wound contamination and often involves a cut or deep puncture wound. C. tetani is not invasive, and the infection is normally confined to a wound. Here the bacteria multiply and produce tetanospasmin, which is able to travel throughout the body. Tetanospasmin is an A-B toxin. The B subunit binds to the receptors on motor neurons, while the A subunit induces endocytosis to enter the neuron. Early symptoms of the disease include restlessness, irritability and difficulty swallowing. As the infection progresses, muscle spasms develop in the jaw (thus the name “lockjaw”) and elsewhere in the body. Infection can be prevented by proper immunization and by post-exposure prophylaxis. Tetanus often begins with mild spasms in the jaw muscles (lockjaw). The spasms can also affect the chest, neck, back, and abdominal muscles. Back muscle spasms often cause arching, called opisthotonos. Prolonged muscular action causes sudden, powerful, and painful contractions of muscle groups. This is called tetany.



Figure: **Opisthotonus**: Muscular spasms (specifically opisthotonos) in a patient suffering from tetanus. Painting by Sir Charles Bell, 1809.

Tetanus affects skeletal muscle, a type of striated muscle used in voluntary movement. The other type of striated muscle, cardiac or heart muscle, is not affected by the toxin because of its intrinsic electrical properties. The incubation period of tetanus can be long, and may be as long several months, but is usually about eight days. In general, the further the injury site is from the central nervous system, the longer the incubation period. The shorter the incubation period, the more severe the symptoms.

Sources of Infection

Tetanus is often associated with rust, especially rusty nails, but this concept is somewhat misleading. Objects that accumulate rust are often found outdoors, or in places that harbor anaerobic bacteria, but the rust itself does not cause tetanus nor does it contain *C. tetani* bacteria. The rough surface of rusty metal merely provides a prime habitat for a *C. tetani* endospore to reside, and the nail affords a means to puncture skin and deliver endospore into the wound. An endospore is a non-metabolizing survival structure that begins to metabolize and cause infection once in an adequate environment. Because *C. tetani* is an anaerobic bacterium, it and its endospores survive well in an environment that lacks oxygen. Hence, stepping on a nail, rusty or not, may result in a tetanus infection, as the low-oxygen (anaerobic) environment is provided by the same object that causes a puncture wound, delivering endospores to a suitable environment for growth.

Diagnosis, Treatment, and Prevention

There are currently no blood tests that can be used to diagnose tetanus. The diagnosis is based on the presentation of tetanus symptoms. Diagnosis does not depend upon isolation of the bacteria, which is recovered from the wound in only 30% of cases and can be isolated from patients without tetanus. The “spatula test” is a clinical test for tetanus that involves touching the posterior pharyngeal wall with a sterile, soft-tipped instrument, and observing the effect. A positive test result is the involuntary contraction of the jaw (biting down on the “spatula”); a negative test result would normally be a gag reflex attempting to expel the foreign object.

Unlike many infectious diseases, recovery from naturally acquired tetanus does not usually result in immunity to tetanus. This is due to the extreme potency of the tetanospasmin toxin; even a lethal dose of tetanospasmin is insufficient to provoke an immune response.Tetanus can be prevented by vaccination with tetanus toxoid. The CDC recommends that adults receive a booster vaccine every ten years, and standard care practice in many places is to give the booster to any patient with a puncture wound who is uncertain of when he or she was last vaccinated, or if he or she has had fewer than three lifetime doses of the vaccine. The booster may not prevent a potentially fatal case of tetanus from the current wound as it can take up to two weeks for tetanus antibodies to form.

A person infected with *C. tetani* can be treated with antibiotics, which will kill the multiplying bacteria but will have no effect on the endospores or the toxin. To combat the effects of the toxin, tetanus immune globulin (TIG) antitoxin can be given to the patient. These antibodies are able to neutralize the tetanospasmin if they are not already bound to motor neurons, and can confer passive immunity.

Key Points

- Infection generally occurs through wound contamination and often involves a cut or deep puncture wound.
- There are currently no blood tests that can be used to diagnose tetanus.
- Tetanus can be prevented by vaccination with tetanus toxoid.

Key Terms

- **tetanus**: A serious and often fatal disease caused by the infection of an open wound with the anaerobic bacterium Clostridium tetani, found in soil and the intestines and feces of animals.
- **opisthotonos**: A tetanic spasm in which the body is bent backwards and stiffened.
- **neurotoxin**: A toxin that specifically acts upon neurons, their synapses, or the nervous system in its entirety.
- **tetanospasmin**: The A-B toxin produced by C. tetani which is responsible for the symptoms of tetanus.

This page titled 6.8F: Tetanus is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.20F: Tetanus** is licensed CC BY-SA 4.0.

6.8G: Paralysis-Causing Bacterial Neurotoxins

Learning Objectives

- Describe the mechanism of action for botulinum toxin

Botulinum toxin is a protein and neurotoxin produced by Clostridium botulinum, C. butyricum, C. baratii and C. argentinense. Botulinum toxin can cause botulism, a serious and life-threatening illness in humans and animals. In 1949, Arnold Burgen's group discovered, through an elegant experiment, that botulinum toxin blocks neuromuscular transmission through decreased acetylcholine release. In 1973, Alan Scott used botulinum toxin type A (BTX-A) in monkey experiments. In 1980, he officially used BTX-A for the first time in humans to treat "crossed eyes" (strabismus), a condition in which the eyes are not properly aligned with each other, as well as "uncontrollable blinking" (blepharospasm). In 1993, Pasricha and colleagues showed that botulinum toxin could be used for the treatment of achalasia, a spasm of the lower esophageal sphincter. In 1994, Bushara showed botulinum toxin injections inhibit sweating; this was the first demonstration of non-muscular use of BTX-A in humans. The cosmetic effect of BTX-A on wrinkles was first reported by J. D. and J. A. Carruthers in a 1992 study on BTX-A for the treatment of glabellar frown lines. The acceptance of BTX-A use for the treatment of muscle pain disorders is growing, with approvals pending in many European countries. The efficacy of BTX-A in treating a variety of other medical conditions (including prostatic dysfunction, asthma, and others) is an area of continued study.

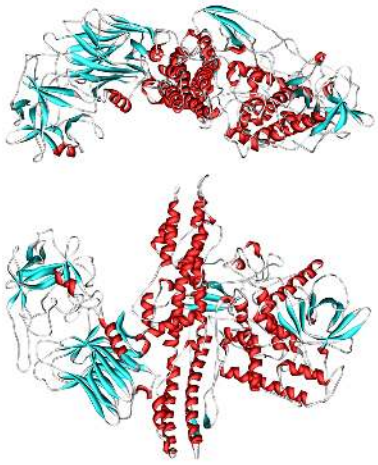


Figure: **Botulinum Toxin**: Structure of Botulinum toxin, a protein and neurotoxin produced by the bacterium Clostridium botulinum

Foodborne botulism can be transmitted through food that has not been heated correctly prior to being canned, or food from a can that has not been cooked correctly. Most infant botulism cases cannot be prevented because the bacteria that cause this disease are in soil and dust. The bacteria can also be found inside homes on floors, carpet, and countertops, even after cleaning. Honey can contain the bacteria that cause infant botulism, so children less than 12 months old should not be fed honey.

Botulinum toxin is a two-chain polypeptide with a 100-kDa heavy chain joined by a disulfide bond to a 50-kDa light chain. This light chain is an enzyme (a protease) that attacks one of the fusion proteins (SNAP-25, syntaxin or synaptobrevin) at a neuromuscular junction, preventing vesicles from anchoring to the membrane to release acetylcholine. By inhibiting acetylcholine release, the toxin interferes with nerve impulses and causes flaccid (sagging) paralysis of muscles in botulism, as opposed to the spastic paralysis seen in tetanus. The heavy chain of the toxin is particularly important for targeting the toxin to specific types of axon terminals. The toxin must get inside the axon terminals to cause paralysis. Following the attachment of the toxin heavy chain to proteins on the surface of axon terminals, the toxin can be taken into neurons by endocytosis. The light chain is able to cleave endocytotic vesicles and reach the cytoplasm. The light chain of the toxin has protease activity. The type A toxin proteolytically degrades the SNAP-25 protein, a type of SNARE protein. The SNAP-25 protein is required for vesicle fusion that releases neurotransmitters from the axon endings (in particular acetylcholine). Botulinum toxin specifically cleaves these SNAREs, and so prevents neurosecretory vesicles from docking/fusing with the nerve synapse plasma membrane and releasing their neurotransmitters.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: ***CC BY-SA: Attribution-ShareAlike***

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- Nervous system. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Nervous_system%23Neural_circuits_and_systems**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Nervous system. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Nervous...tem%23Function**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- hormone. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/hormone**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- nervous system. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/nervous_system**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Nervous system. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Nervous...tem%23Function**. **License**: ***Public Domain: No Known Copyright***
- Autonomic nervous system. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Autonomic_nervous_system**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Enteric nervous system. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Enteric_nervous_system**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Parasympathetic nervous system. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Parasympathetic_nervous_system**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Nervous system. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Nervous_system%23Anatomy_in_vertebrates**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Human Physiology/The Nervous System. **Provided by**: Wikibooks. **Located at**: **en.wikibooks.org/wiki/Human_P...nervous_system**. **License**: *CC BY-SA: Attribution-ShareAlike*
- gray matter. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/gray%20matter**. **License**: *CC BY-SA: Attribution-ShareAlike*
- peripheral nervous system. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/peripheral%20nervous%20system**. **License**: *CC BY-SA: Attribution-ShareAlike*
- white matter. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/white_matter**. **License**: *CC BY-SA: Attribution-ShareAlike*
- central nervous system. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/central_nervous_system**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Nervous system. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Nervous...tem%23Function**. **License**: ***Public Domain: No Known Copyright***
- Human Physiology/The Nervous System. **Provided by**: Wikibooks. **Located at**: **en.wikibooks.org/wiki/Human_P...nervous_system**. **License**: *CC BY-SA: Attribution-ShareAlike*
- TE-Nervous system diagram. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...em_diagram.svg**. **License**: ***CC BY: Attribution***
- meningitis. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/meningitis**. **License**: *CC BY-SA: Attribution-ShareAlike*
- meninges. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/meninges**. **License**: *CC BY-SA: Attribution-ShareAlike*
- lumbar puncture. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/lumbar_puncture**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Nervous system. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Nervous...tem%23Function**. **License**: ***Public Domain: No Known Copyright***
- Human Physiology/The Nervous System. **Provided by**: Wikibooks. **Located at**: **en.wikibooks.org/wiki/Human_P...nervous_system**. **License**: *CC BY-SA: Attribution-ShareAlike*

- TE-Nervous system diagram. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:TE-Nervous_system_diagram.svg**. **License**: ***CC BY: Attribution***
- Meninges-en. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Meninges-en.svg**. **License**: ***Public Domain: No Known Copyright***
- Neck stiffness. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Neck_stiffness.jpg**. **License**: ***Public Domain: No Known Copyright***
- botulism. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/botulism**. **License**: *CC BY-SA: Attribution-ShareAlike*
- spore. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/spore**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Boundless. **Provided by**: Boundless Learning. **Located at**: **www.boundless.com//microbiolo...wound-botulism**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Boundless. **Provided by**: Boundless Learning. **Located at**: **www.boundless.com//microbiolo...nfant-botulism**. **License**: *CC BY-SA: Attribution-ShareAlike*
- toxin. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/toxin**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Nervous system. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Nervous...tem%23Function**. **License**: ***Public Domain: No Known Copyright***
- Human Physiology/The Nervous System. **Provided by**: Wikibooks. **Located at**: **en.wikibooks.org/wiki/Human_P...nervous_system**. **License**: *CC BY-SA: Attribution-ShareAlike*
- TE-Nervous system diagram. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:TE-Nervous_system_diagram.svg**. **License**: ***CC BY: Attribution***
- Meninges-en. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Meninges-en.svg**. **License**: ***Public Domain: No Known Copyright***
- Neck stiffness. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Neck_stiffness.jpg**. **License**: ***Public Domain: No Known Copyright***
- Botulism1and2. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Botulism1and2.JPG**. **License**: *CC BY: Attribution*
- mycobacterium. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/mycobacterium**. **License**: *CC BY-SA: Attribution-ShareAlike*
- leprosy. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/leprosy**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Nervous system. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Nervous_system%23Function**. **License**: ***Public Domain: No Known Copyright***
- Human Physiology/The Nervous System. **Provided by**: Wikibooks. **Located at**: **en.wikibooks.org/wiki/Human_P...nervous_system**. **License**: *CC BY-SA: Attribution-ShareAlike*
- TE-Nervous system diagram. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:TE-Nervous_system_diagram.svg**. **License**: *CC BY: Attribution*
- Meninges-en. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Meninges-en.svg**. **License**: ***Public Domain: No Known Copyright***
- Neck stiffness. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Neck_stiffness.jpg**. **License**: ***Public Domain: No Known Copyright***
- Botulism1and2. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Botulism1and2.JPG**. **License**: *CC BY: Attribution*
- Leprosy. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Leprosy.jpg**. **License**: ***Public Domain: No Known Copyright***
- Tetanus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Tetanus**. **License**: *CC BY-SA: Attribution-ShareAlike*
- opisthotonos. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/opisthotonos**. **License**: *CC BY-SA: Attribution-ShareAlike*
- tetanus. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/tetanus**. **License**: *CC BY-SA: Attribution-ShareAlike*
- neurotoxin. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/neurotoxin**. **License**: *CC BY-SA: Attribution-ShareAlike*

- Nervous system. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Nervous_system%23Function**. **License**: ***Public Domain: No Known Copyright***
- Human Physiology/The Nervous System. **Provided by**: Wikibooks. **Located at**: **en.wikibooks.org/wiki/Human_Physiology/The_Nervous_System%23Overview_of_the_entire_nervous_system**. **License**: *CC BY-SA: Attribution-ShareAlike*
- TE-Nervous system diagram. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:TE-Nervous_system_diagram.svg**. **License**: *CC BY: Attribution*
- Meninges-en. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Meninges-en.svg**. **License**: ***Public Domain: No Known Copyright***
- Neck stiffness. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Neck_stiffness.jpg**. **License**: ***Public Domain: No Known Copyright***
- Botulism1and2. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Botulism1and2.JPG**. **License**: *CC BY: Attribution*
- Leprosy. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Leprosy.jpg**. **License**: ***Public Domain: No Known Copyright***
- Opisthotonus in a patient suffering from tetanus - Painting by Sir Charles Bell - 1809. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Op...ell_-_1809.jpg**. **License**: ***Public Domain: No Known Copyright***
- acetylcholine. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/acetylcholine**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Botulinum toxin. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Botulinum_toxin**. **License**: *CC BY-SA: Attribution-ShareAlike*
- neurotoxin. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/neurotoxin**. **License**: *CC BY-SA: Attribution-ShareAlike*
- axon. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/axon**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Nervous system. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Nervous_system%23Function**. **License**: ***Public Domain: No Known Copyright***
- Human Physiology/The Nervous System. **Provided by**: Wikibooks. **Located at**: **en.wikibooks.org/wiki/Human_Physiology/The_Nervous_System%23Overview_of_the_entire_nervous_system**. **License**: *CC BY-SA: Attribution-ShareAlike*
- TE-Nervous system diagram. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:TE-Nervous_system_diagram.svg**. **License**: *CC BY: Attribution*
- Meninges-en. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Meninges-en.svg**. **License**: ***Public Domain: No Known Copyright***
- Neck stiffness. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Neck_stiffness.jpg**. **License**: *Public Domain: No Known Copyright*
- Botulism1and2. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Botulism1and2.JPG**. **License**: *CC BY: Attribution*
- Leprosy. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Leprosy.jpg**. **License**: *Public Domain: No Known Copyright*
- Opisthotonus in a patient suffering from tetanus - Painting by Sir Charles Bell - 1809. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Op...ell_-_1809.jpg**. **License**: *Public Domain: No Known Copyright*
- Botulinum toxin 3BTA. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Bo...toxin_3BTA.png**. **License**: *Public Domain: No Known Copyright*

Key Points

- Botulinum toxin is produced by Clostridium botulinum, C. butyricum, C. baratii and C. argentinense.
- The light chain of botulinum toxin is an enzyme (a protease) that attacks one of the fusion proteins (SNAP-25, syntaxin or synaptobrevin) at a neuromuscular junction, preventing vesicles from anchoring to the membrane and releasing acetylcholine.
- The heavy chain of the toxin is particularly important for targeting the toxin to specific types of axon terminals.

Key Terms

- **neurotoxin**: A toxin that specifically acts upon neurons, their synapses, or the nervous system in its entirety.
- **acetylcholine**: A neurotransmitter in humans and other animals. It is an ester of acetic acid and choline with chemical formula CH3COOCH2CH2N⁺(CH3)3.
- **axon**: A nerve fibre, which is a long slender projection of a nerve cell, and which conducts nerve impulses away from the body of the cell to a synapse.

This page titled 6.8G: Paralysis-Causing Bacterial Neurotoxins is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.20G: Paralysis-Causing Bacterial Neurotoxins** is licensed CC BY-SA 4.0.

CHAPTER OVERVIEW

7: Innate Nonspecific Host Defenses

Despite relatively constant exposure to pathogenic microbes in the environment, humans do not generally suffer from constant infection or disease. Under most circumstances, the body is able to defend itself from the threat of infection thanks to a complex immune system designed to repel, kill, and expel disease-causing invaders. Immunity as a whole can be described as two interrelated parts: nonspecific innate immunity, which is the subject of this chapter, and specific adaptive host defenses, which are discussed in the next chapter.

The nonspecific innate immune response provides a first line of defense that can often prevent infections from gaining a solid foothold in the body. These defenses are described as *nonspecific* because they do not target any specific pathogen; rather, they defend against a wide range of potential pathogens. They are called *innate* because they are built-in mechanisms of the human organism. Unlike the specific adaptive defenses, they are not acquired over time and they have no “memory” (they do not improve after repeated exposures to specific pathogens).

Broadly speaking, nonspecific innate defenses provide an immediate (or very rapid) response against potential pathogens. However, these responses are neither perfect nor impenetrable. They can be circumvented by pathogens on occasion, and sometimes they can even cause damage to the body, contributing to the signs and symptoms of infection (Figure 7.1).



Figure 7.1: Varicella, or chickenpox, is caused by the highly contagious varicella-zoster virus. The characteristic rash seen here is partly a result of inflammation associated with the body’s immune response to the virus. Inflammation is a response mechanism of innate immunity that helps the body fight off a wide range of infections. (credit: John Noble / CDC; Public Domain)

7.1: Physical Defenses
7.2: Chemical Defenses
7.3: Cellular Defenses

This page titled 7: Innate Nonspecific Host Defenses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

7.1: Physical Defenses

Learning Objectives

- Describe the various physical barriers and mechanical defenses that protect the human body against infection and disease
- Describe the role of microbiota as a first-line defense against infection and disease

Clinical Focus: Part 1

Angela, a 25-year-old female patient in the emergency department, is having some trouble communicating verbally because of shortness of breath. A nurse observes constriction and swelling of the airway and labored breathing. The nurse asks Angela if she has a history of asthma or allergies. Angela shakes her head no, but there is fear in her eyes. With some difficulty, she explains that her father died suddenly at age 27, when she was just a little girl, of a similar respiratory attack. The underlying cause had never been identified.

Exercise 7.1.1

1. What are some possible causes of constriction and swelling of the airway?
2. What causes swelling of body tissues in general?

Nonspecific innate immunity can be characterized as a multifaceted system of defenses that targets invading pathogens in a nonspecific manner. In this chapter, we have divided the numerous defenses that make up this system into three categories: physical defenses, chemical defenses, and cellular defenses. However, it is important to keep in mind that these defenses do not function independently, and the categories often overlap. Table **7.1.1** provides an overview of the nonspecific defenses discussed in this chapter.

Table **7.1.1**: Overview of Nonspecific Innate Immune Defenses

Overview of Nonspecific Innate Immune Defenses	
Physical defenses	Physical barriers
	Mechanical defenses
	Microbiome
Chemical defenses	Chemicals and enzymes in body fluids
	Antimicrobial peptides
	Plasma protein mediators
	Cytokines
	Inflammation-eliciting mediators
Cellular defenses	Granulocytes
	Agranulocytes

Physical defenses provide the body's most basic form of nonspecific defense. They include physical barriers to microbes, such as the skin and mucous membranes, as well as mechanical defenses that physically remove microbes and debris from areas of the body where they might cause harm or infection. In addition, the microbiome provides a measure of physical protection against disease, as microbes of the normal microbiota compete with pathogens for nutrients and cellular binding sites necessary to cause infection.

Physical Barriers

Physical barriers play an important role in preventing microbes from reaching tissues that are susceptible to infection. At the cellular level, barriers consist of cells that are tightly joined to prevent invaders from crossing through to deeper tissue. For example, the endothelial cells that line blood vessels have very tight cell-to-cell junctions, blocking microbes from gaining access to the bloodstream. Cell junctions are generally composed of cell membrane proteins that may connect with the extracellular matrix or with complementary proteins from neighboring cells. Tissues in various parts of the body have different types of cell junctions. These include tight junctions, desmosomes, and gap junctions, as illustrated in Figure **7.1.1**. Invading microorganisms may attempt to break down these substances chemically, using enzymes such as proteases that can cause structural damage to create a point of entry for pathogens.

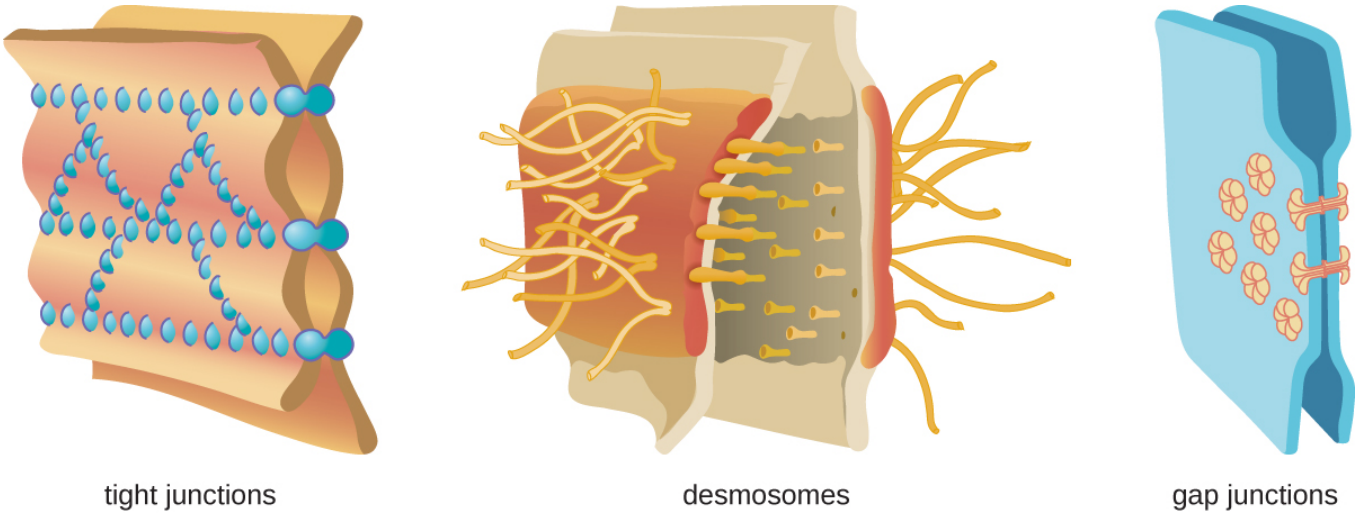


Figure **7.1.1**: There are multiple types of cell junctions in human tissue, three of which are shown here. Tight junctions rivet two adjacent cells together, preventing or limiting material exchange through the spaces between them. Desmosomes have intermediate fibers that act like shoelaces, tying two cells together, allowing small materials to pass through the resulting spaces. Gap junctions are channels between two cells that permit their communication via signals. (credit: modification of work by Mariana Ruiz Villareal)

The Skin Barrier

One of the body's most important physical barriers is the skin barrier, which is composed of three layers of closely packed cells. The thin upper layer is called the epidermis. A second, thicker layer, called the dermis, contains hair follicles, sweat glands, nerves, and blood vessels. A layer of fatty tissue called the hypodermis lies beneath the dermis and contains blood and lymph vessels (Figure **7.1.2**).

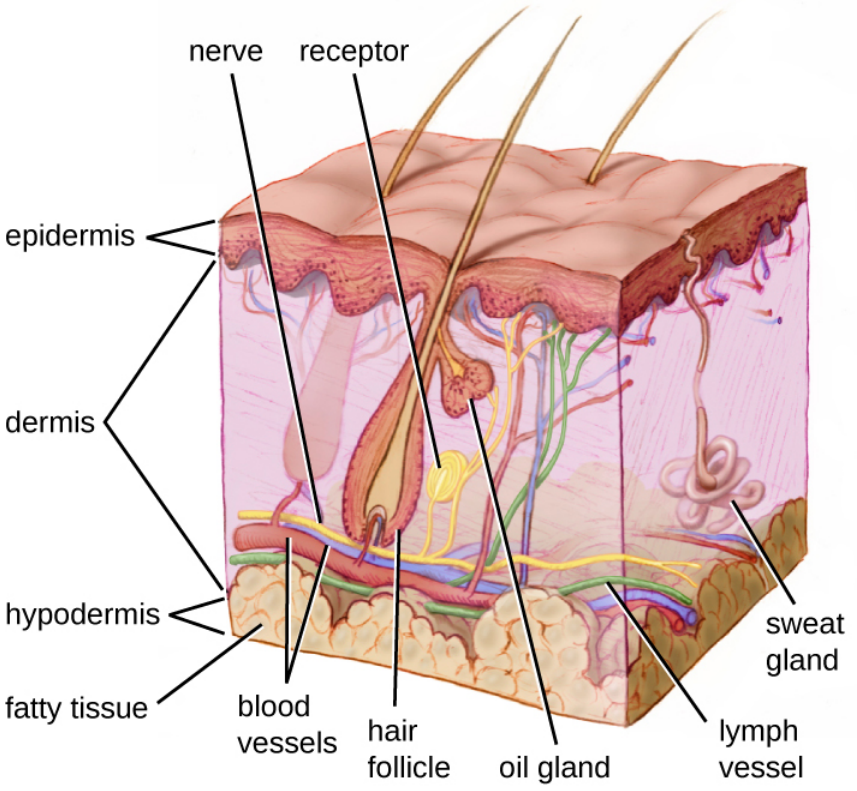


Figure **7.1.2**: Human skin has three layers, the epidermis, the dermis, and the hypodermis, which provide a thick barrier between microbes outside the body and deeper tissues. Dead skin cells on the surface of the epidermis are continually shed, taking with them microbes on the skin's surface. (credit: modification of work by National Institutes of Health)

The topmost layer of skin, the epidermis, consists of cells that are packed with keratin. These dead cells remain as a tightly connected, dense layer of protein-filled cell husks on the surface of the skin. The keratin makes the skin's surface mechanically tough and resistant to degradation by bacterial enzymes. Fatty acids on the skin's surface create a dry, salty, and acidic environment that inhibits the growth of some microbes and is highly resistant to breakdown by bacterial enzymes. In addition, the dead cells of the epidermis are frequently shed, along with any microbes that may be clinging to them. Shed skin cells are continually replaced with new cells from below, providing a new barrier that will soon be shed in the same way.

Infections can occur when the skin barrier is compromised or broken. A wound can serve as a point of entry for opportunistic pathogens, which can infect the skin tissue surrounding the wound and possibly spread to deeper tissues.

Every Rose Has its Thorn

Mike, a gardener from southern California, recently noticed a small red bump on his left forearm. Initially, he did not think much of it, but soon it grew larger and then ulcerated (opened up), becoming a painful lesion that extended across a large part of his forearm (Figure **7.1.3**). He went to an urgent care facility, where a physician asked about his occupation. When he said he was a landscaper, the physician immediately suspected a case of sporotrichosis, a type of fungal infection known as rose gardener's disease because it often afflicts landscapers and gardening enthusiasts.

Under most conditions, fungi cannot produce skin infections in healthy individuals. Fungi grow filaments known as hyphae, which are not particularly invasive and can be easily kept at bay by the physical barriers of the skin and mucous membranes. However, small wounds in the skin, such as those caused by thorns, can provide an opening for opportunistic pathogens like *Sporothrix schenkii*, a soil-dwelling fungus and the causative agent of rose gardener's disease. Once it breaches the skin barrier, *S. schenkii* can infect the skin and underlying tissues, producing ulcerated lesions like Mike's. Compounding matters, other pathogens may enter the infected tissue, causing secondary bacterial infections.

Luckily, rose gardener's disease is treatable. Mike's physician wrote him a prescription for some antifungal drugs as well as a course of antibiotics to combat secondary bacterial infections. His lesions eventually healed, and Mike returned to work with a

new appreciation for gloves and protective clothing.





Figure 7.1.3: Rose gardener's disease can occur when the fungus *Sporothrix schenkii* breaches the skin through small cuts, such as might be inflicted by thorns. (credit left: modification of work by Elisa Self; credit right: modification of work by Centers for Disease Control and Prevention)

Mucous Membranes

The mucous membranes lining the nose, mouth, lungs, and urinary and digestive tracts provide another nonspecific barrier against potential pathogens. Mucous membranes consist of a layer of epithelial cells bound by tight junctions. The epithelial cells secrete a moist, sticky substance called mucus, which covers and protects the more fragile cell layers beneath it and traps debris and particulate matter, including microbes. Mucus secretions also contain antimicrobial peptides.

In many regions of the body, mechanical actions serve to flush mucus (along with trapped or dead microbes) out of the body or away from potential sites of infection. For example, in the respiratory system, inhalation can bring microbes, dust, mold spores, and other small airborne debris into the body. This debris becomes trapped in the mucus lining the respiratory tract, a layer known as the mucociliary blanket. The epithelial cells lining the upper parts of the respiratory tract are called ciliated epithelial cells because they have hair-like appendages known as cilia. Movement of the cilia propels debris-laden mucus out and away from the lungs. The expelled mucus is then swallowed and destroyed in the stomach, or coughed up, or sneezed out (Figure 7.1.4). This system of removal is often called the mucociliary escalator.

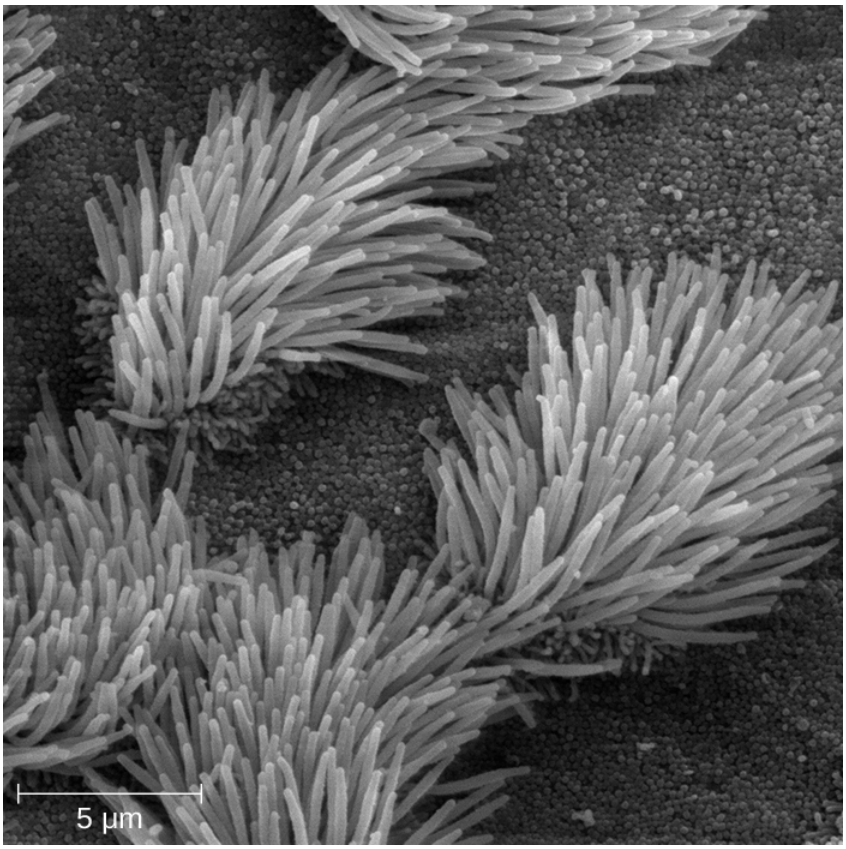


Figure **7.1.4**: This scanning electron micrograph shows ciliated and nonciliated epithelial cells from the human trachea. The mucociliary escalator pushes mucus away from the lungs, along with any debris or microorganisms that may be trapped in the sticky mucus, and the mucus moves up to the esophagus where it can be removed by swallowing.

The mucociliary escalator is such an effective barrier to microbes that the lungs, the lowermost (and most sensitive) portion of the respiratory tract, were long considered to be a sterile environment in healthy individuals. Only recently has research suggested that healthy lungs may have a small normal microbiota. Disruption of the mucociliary escalator by the damaging effects of smoking or diseases such as cystic fibrosis can lead to increased colonization of bacteria in the lower respiratory tract and frequent infections, which highlights the importance of this physical barrier to host defenses.

Like the respiratory tract, the digestive tract is a portal of entry through which microbes enter the body, and the mucous membranes lining the digestive tract provide a nonspecific physical barrier against ingested microbes. The intestinal tract is lined with epithelial cells, interspersed with mucus-secreting goblet cells (Figure **7.1.5**). This mucus mixes with material received from the stomach, trapping foodborne microbes and debris. The mechanical action of peristalsis, a series of muscular contractions in the digestive tract, moves the sloughed mucus and other material through the intestines, rectum, and anus, excreting the material in feces.

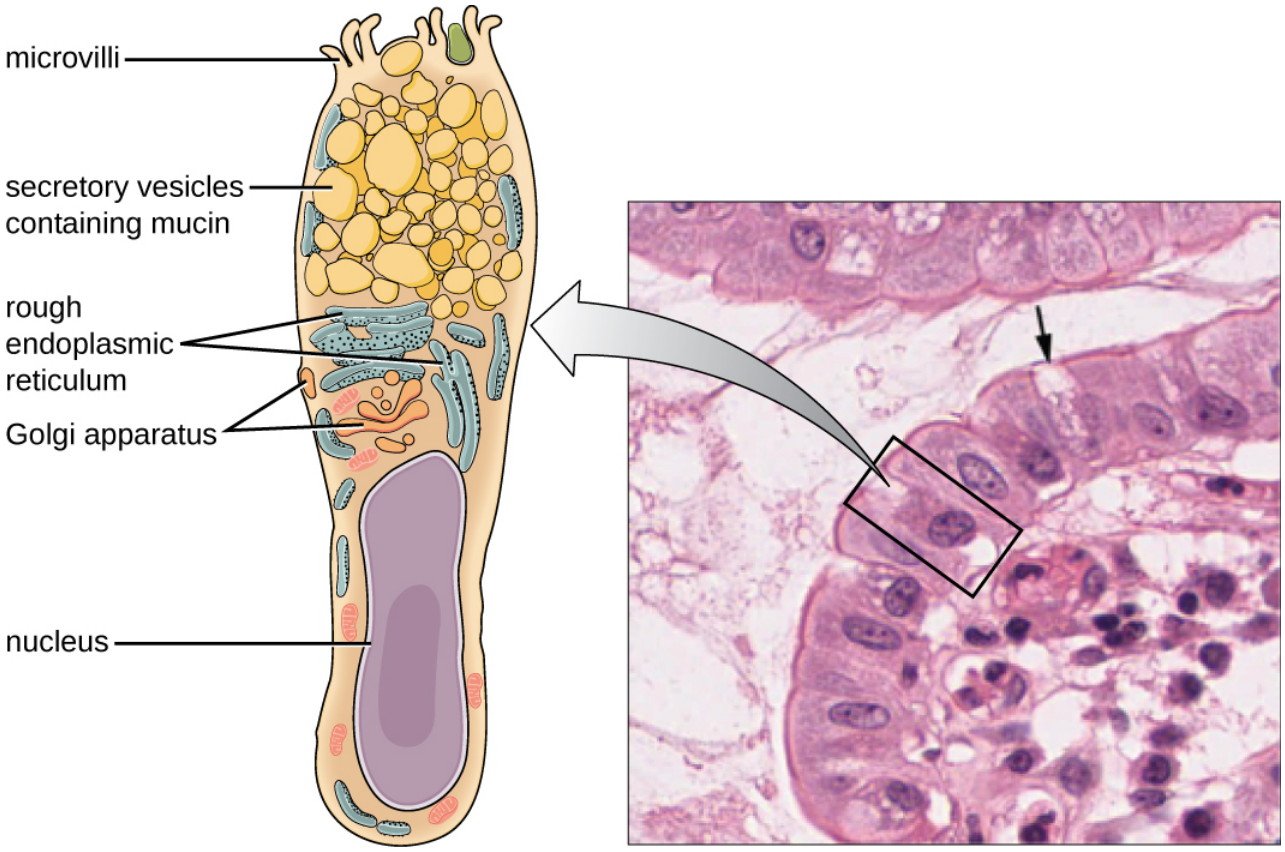


Figure **7.1.5**: Goblet cells produce and secrete mucus. The arrows in this micrograph point to the mucus-secreting goblet cells (magnification 1600×) in the intestinal epithelium. (credit micrograph: Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Endothelia

The epithelial cells lining the urogenital tract, blood vessels, lymphatic vessels, and certain other tissues are known as endothelia. These tightly packed cells provide a particularly effective frontline barrier against invaders. The endothelia of the blood-brain barrier, for example, protect the central nervous system (CNS), which consists of the brain and the spinal cord. The CNS is one of the most sensitive and important areas of the body, as microbial infection of the CNS can quickly lead to serious and often fatal inflammation. The cell junctions in the blood vessels traveling through the CNS are some of the tightest and toughest in the body, preventing any transient microbes in the bloodstream from entering the CNS. This keeps the cerebrospinal fluid that surrounds and bathes the brain and spinal cord sterile under normal conditions.

? Exercise 7.1.2

1. Describe how the mucociliary escalator functions.
2. Name two places you would find endothelia.

Mechanical Defenses

In addition to physical barriers that keep microbes out, the body has a number of mechanical defenses that physically remove pathogens from the body, preventing them from taking up residence. We have already discussed several examples of mechanical defenses, including the shedding of skin cells, the expulsion of mucus via the mucociliary escalator, and the excretion of feces through intestinal peristalsis. Other important examples of mechanical defenses include the flushing action of urine and tears, which both serve to carry microbes away from the body. The flushing action of urine is largely responsible for the normally sterile environment of the urinary tract, which includes the kidneys, ureters, and urinary bladder. Urine passing out of the body washes out transient microorganisms, preventing them from taking up residence. The eyes also have physical barriers and mechanical mechanisms for preventing infections. The eyelashes and eyelids prevent dust and airborne microorganisms from reaching the

surface of the eye. Any microbes or debris that make it past these physical barriers may be flushed out by the mechanical action of blinking, which bathes the eye in tears, washing debris away (Figure **7.1.6**).

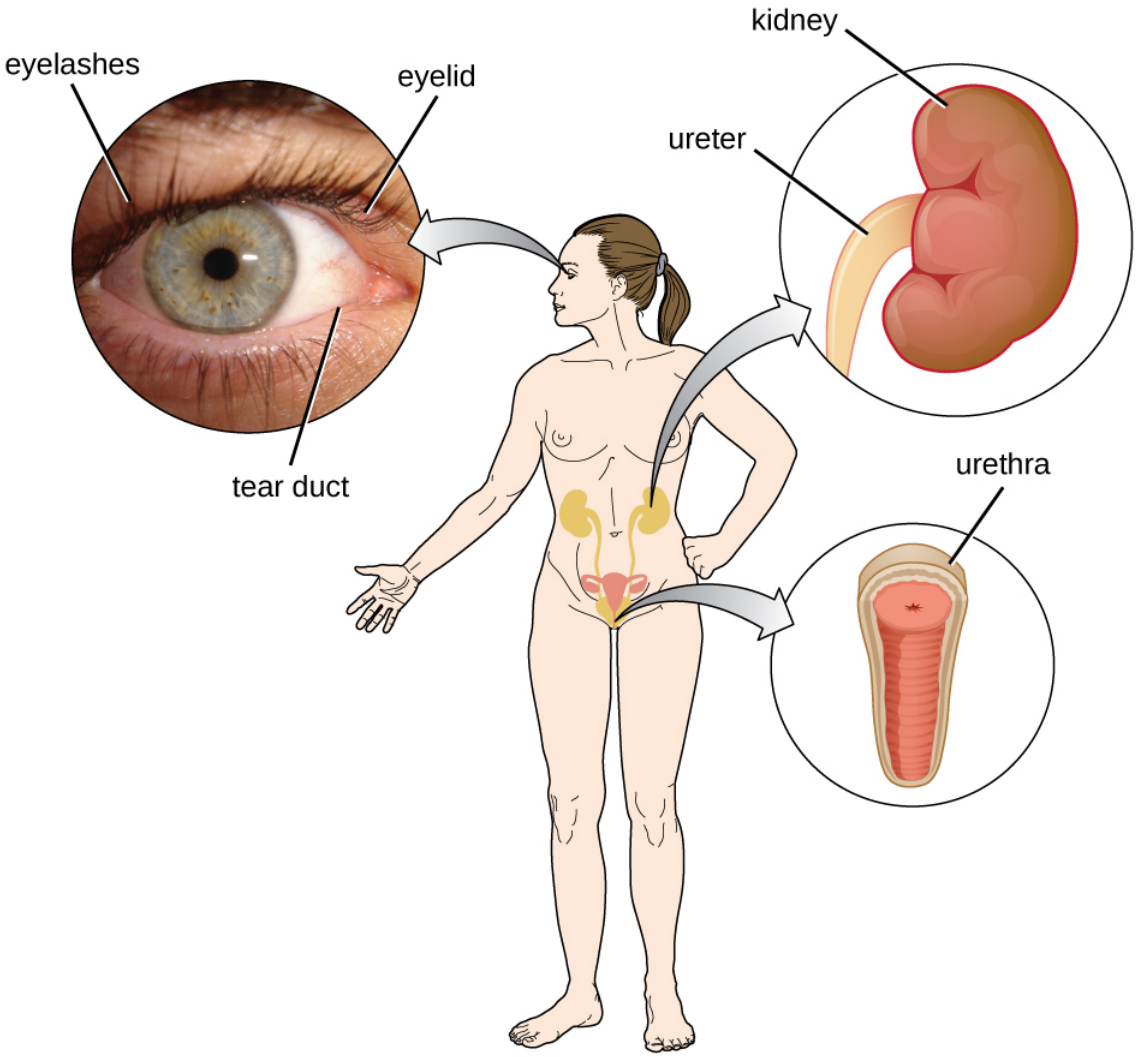


Figure **7.1.6**: Tears flush microbes away from the surface of the eye. Urine washes microbes out of the urinary tract as it passes through; as a result, the urinary system is normally sterile.

? Exercise 7.1.3

Name two mechanical defenses that protect the eyes.

Microbiome

In various regions of the body, resident microbiota serve as an important first-line defense against invading pathogens. Through their occupation of cellular binding sites and competition for available nutrients, the resident microbiota prevent the critical early steps of pathogen attachment and proliferation required for the establishment of an infection. For example, in the vagina, members of the resident microbiota compete with opportunistic pathogens like the yeast *Candida*. This competition prevents infections by limiting the availability of nutrients, thus inhibiting the growth of *Candida*, keeping its population in check. Similar competitions occur between the microbiota and potential pathogens on the skin, in the upper respiratory tract, and in the gastrointestinal tract. As will be discussed later in this chapter, the resident microbiota also contribute to the chemical defenses of the innate nonspecific host defenses.

The importance of the normal microbiota in host defenses is highlighted by the increased susceptibility to infectious diseases when the microbiota is disrupted or eliminated. Treatment with antibiotics can significantly deplete the normal microbiota of the

gastrointestinal tract, providing an advantage for pathogenic bacteria to colonize and cause diarrheal infection. In the case of diarrhea caused by *Clostridium difficile*, the infection can be severe and potentially lethal. One strategy for treating *C. difficile* infections is fecal transplantation, which involves the transfer of fecal material from a donor (screened for potential pathogens) into the intestines of the recipient patient as a method of restoring the normal microbiota and combating *C. difficile* infections.

Table **7.1.2** provides a summary of the physical defenses discussed in this section.

Table **7.1.2**: Physical Defenses of Nonspecific Innate Immunity

Defense	Examples	Function
Cellular barriers	Skin, mucous membranes, endothelial cells	Deny entry to pathogens
Mechanical defenses	Shedding of skin cells, mucociliary sweeping, peristalsis, flushing action of urine and tears	Remove pathogens from potential sites of infection
Microbiome	Resident bacteria of the skin, upper respiratory tract, gastrointestinal tract, and genitourinary tract	Compete with pathogens for cellular binding sites and nutrients

? Exercise 7.1.4

List two ways resident microbiota defend against pathogens.

Key Concepts and Summary

- **Nonspecific innate immunity** provides a first line of defense against infection by nonspecifically blocking entry of microbes and targeting them for destruction or removal from the body.
- The physical defenses of innate immunity include physical barriers, mechanical actions that remove microbes and debris, and the microbiome, which competes with and inhibits the growth of pathogens.
- The skin, mucous membranes, and endothelia throughout the body serve as physical barriers that prevent microbes from reaching potential sites of infection. Tight cell junctions in these tissues prevent microbes from passing through.
- Microbes trapped in dead skin cells or **mucus** are removed from the body by mechanical actions such as shedding of skin cells, mucociliary sweeping, coughing, **peristalsis**, and flushing of bodily fluids (e.g., urination, tears)
- The resident microbiota provide a physical defense by occupying available cellular binding sites and competing with pathogens for available nutrients.

This page titled 7.1: Physical Defenses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **17.1: Physical Defenses** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

7.2: Chemical Defenses

Learning Objectives

- Describe how enzymes in body fluids provide protection against infection or disease
- List and describe the function of antimicrobial peptides, complement components, cytokines, and acute-phase proteins
- Describe similarities and differences among classic, alternate, and lectin complement pathways

In addition to physical defenses, the innate nonspecific immune system uses a number of chemical mediators that inhibit microbial invaders. The term “chemical mediators” encompasses a wide array of substances found in various body fluids and tissues throughout the body. Chemical mediators may work alone or in conjunction with each other to inhibit microbial colonization and infection.

Some chemical mediators are endogenously produced, meaning they are produced by human body cells; others are produced exogenously, meaning that they are produced by certain microbes that are part of the microbiome. Some mediators are produced continually, bathing the area in the antimicrobial substance; others are produced or activated primarily in response to some stimulus, such as the presence of microbes.

Chemical and Enzymatic Mediators Found in Body Fluids

Fluids produced by the skin include examples of both endogenous and exogenous mediators. Sebaceous glands in the dermis secrete an oil called sebum that is released onto the skin surface through hair follicles. This sebum is an endogenous mediator, providing an additional layer of defense by helping seal off the pore of the hair follicle, preventing bacteria on the skin’s surface from invading sweat glands and surrounding tissue (Figure **7.2.1**). Certain members of the microbiome, such as the bacterium *Propionibacterium acnes* and the fungus *Malassezia*, among others, can use lipase enzymes to degrade sebum, using it as a food source. This produces oleic acid, which creates a mildly acidic environment on the surface of the skin that is inhospitable to many pathogenic microbes. Oleic acid is an example of an exogenously produced mediator because it is produced by resident microbes and not directly by body cells.

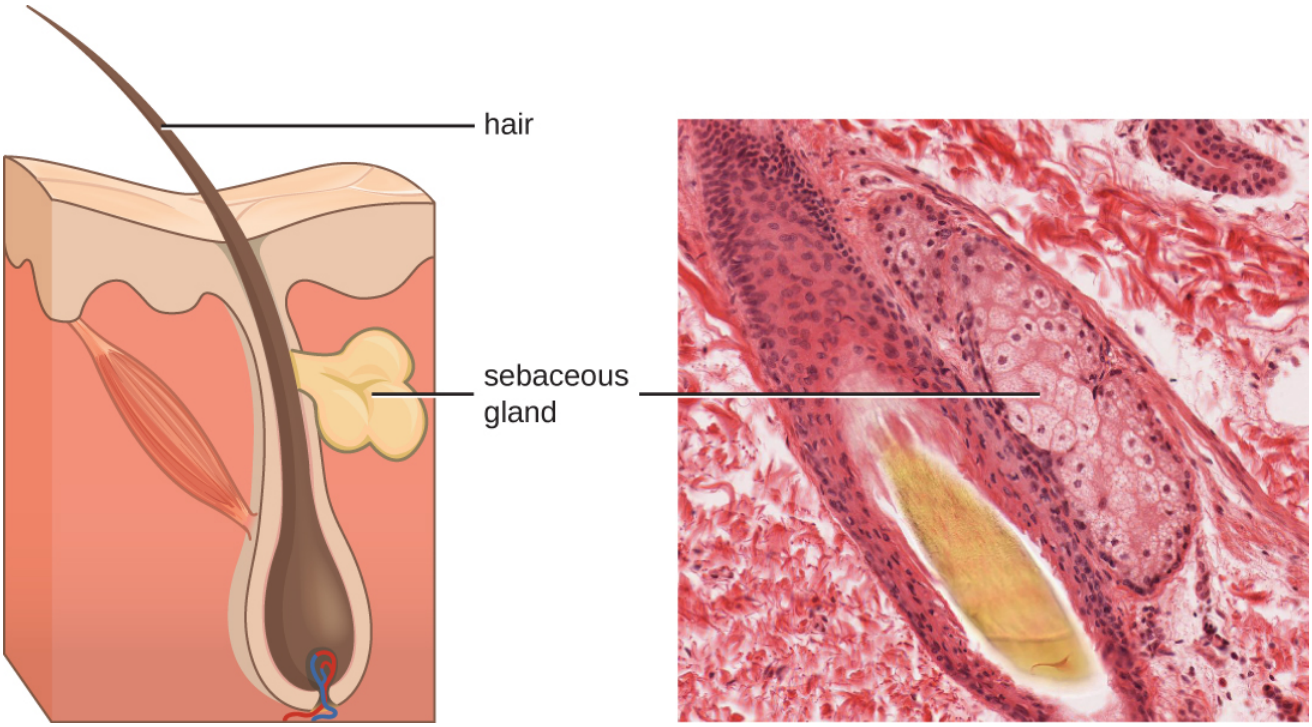


Figure **7.2.1**: Sebaceous glands secrete sebum, a chemical mediator that lubricates and protect the skin from invading microbes. Sebum is also a food source for resident microbes that produce oleic acid, an exogenously produced mediator. (credit micrograph: Micrograph provided by the Regents of University of Michigan Medical School © 2012)

Environmental factors that affect the microbiota of the skin can have a direct impact on the production of chemical mediators. Low humidity or decreased sebum production, for example, could make the skin less habitable for microbes that produce oleic acid, thus making the skin more susceptible to pathogens normally inhibited by the skin's low pH. Many skin moisturizers are formulated to counter such effects by restoring moisture and essential oils to the skin.

The digestive tract also produces a large number of chemical mediators that inhibit or kill microbes. In the oral cavity, saliva contains mediators such as lactoperoxidase enzymes, and mucus secreted by the esophagus contains the antibacterial enzyme lysozyme. In the stomach, highly acidic gastric fluid kills most microbes. In the lower digestive tract, the intestines have pancreatic and intestinal enzymes, antibacterial peptides (cryptins), bile produced from the liver, and specialized Paneth cells that produce lysozyme. Together, these mediators are able to eliminate most pathogens that manage to survive the acidic environment of the stomach.

In the urinary tract, urine flushes microbes out of the body during urination. Furthermore, the slight acidity of urine (the average pH is about 6) inhibits the growth of many microbes and potential pathogens in the urinary tract.

The female reproductive system employs lactate, an exogenously produced chemical mediator, to inhibit microbial growth. The cells and tissue layers composing the vagina produce glycogen, a branched and more complex polymer of glucose. Lactobacilli in the area ferment glycogen to produce lactate, lowering the pH in the vagina and inhibiting transient microbiota, opportunistic pathogens like *Candida* (a yeast associated with vaginal infections), and other pathogens responsible for sexually transmitted diseases.

In the eyes, tears contain the chemical mediators lysozyme and lactoferrin, both of which are capable of eliminating microbes that have found their way to the surface of the eyes. Lysozyme cleaves the bond between NAG and NAM in peptidoglycan, a component of the cell wall in bacteria. It is more effective against gram-positive bacteria, which lack the protective outer membrane associated with gram-negative bacteria. Lactoferrin inhibits microbial growth by chemically binding and sequestering iron. This effectually starves many microbes that require iron for growth.

In the ears, cerumen (earwax) exhibits antimicrobial properties due to the presence of fatty acids, which lower the pH to between 3 and 5.

The respiratory tract uses various chemical mediators in the nasal passages, trachea, and lungs. The mucus produced in the nasal passages contains a mix of antimicrobial molecules similar to those found in tears and saliva (e.g., lysozyme, lactoferrin, lactoperoxidase). Secretions in the trachea and lungs also contain lysozyme and lactoferrin, as well as a diverse group of additional chemical mediators, such as the lipoprotein complex called surfactant, which has antibacterial properties.

? Exercise 7.2.1

1. Explain the difference between endogenous and exogenous mediators
2. Describe how pH affects antimicrobial defenses

Antimicrobial Peptides

The antimicrobial peptides (AMPs) are a special class of nonspecific cell-derived mediators with broad-spectrum antimicrobial properties. Some AMPs are produced routinely by the body, whereas others are primarily produced (or produced in greater quantities) in response to the presence of an invading pathogen. Research has begun exploring how AMPs can be used in the diagnosis and treatment of disease.

AMPs may induce cell damage in microorganisms in a variety of ways, including by inflicting damage to membranes, destroying DNA and RNA, or interfering with cell-wall synthesis. Depending on the specific antimicrobial mechanism, a particular AMP may inhibit only certain groups of microbes (e.g., gram-positive or gram-negative bacteria) or it may be more broadly effective against bacteria, fungi, protozoa, and viruses. Many AMPs are found on the skin, but they can also be found in other regions of the body.

A family of AMPs called defensins can be produced by epithelial cells throughout the body as well as by cellular defenses such as macrophages and neutrophils (see Cellular Defenses). Defensins may be secreted or act inside host cells; they combat microorganisms by damaging their plasma membranes. AMPs called bacteriocins are produced exogenously by certain members of

the resident microbiota within the gastrointestinal tract. The genes coding for these types of AMPs are often carried on plasmids and can be passed between different species within the resident microbiota through lateral or horizontal gene transfer.

There are numerous other AMPs throughout the body. The characteristics of a few of the more significant AMPs are summarized in Table **7.2.1**.

Table **7.2.1**: Characteristics of Selected Antimicrobial Peptides (AMPs)

AMP	Secreted by	Body site	Pathogens inhibited	Mode of action
Bacteriocins	Resident microbiota	Gastrointestinal tract	Bacteria	Disrupt membrane
Cathelicidin	Epithelial cells, macrophages, and other cell types	Skin	Bacteria and fungi	Disrupts membrane
Defensins	Epithelial cells, macrophages, neutrophils	Throughout the body	Fungi, bacteria, and many viruses	Disrupt membrane
Dermicidin	Sweat glands	Skin	Bacteria and fungi	Disrupts membrane integrity and ion channels
Histatins	Salivary glands	Oral cavity	Fungi	Disrupt intracellular function

? Exercise 7.2.2

Why are antimicrobial peptides (AMPs) considered nonspecific defenses?

Plasma Protein Mediators

Many nonspecific innate immune factors are found in plasma, the fluid portion of blood. Plasma contains electrolytes, sugars, lipids, and proteins, each of which helps to maintain homeostasis (i.e., stable internal body functioning), and contains the proteins involved in the clotting of blood. Additional proteins found in blood plasma, such as acute-phase proteins, complement proteins, and cytokines, are involved in the nonspecific innate immune response.

Plasma versus Serum

There are two terms for the fluid portion of blood: plasma and serum. How do they differ if they are both fluid and lack cells? The fluid portion of blood left over after coagulation (blood cell clotting) has taken place is serum. Although molecules such as many vitamins, electrolytes, certain sugars, complement proteins, and antibodies are still present in serum, clotting factors are largely depleted. Plasma, conversely, still contains all the clotting elements. To obtain plasma from blood, an anticoagulant must be used to prevent clotting. Examples of anticoagulants include heparin and ethylene diamine tetraacetic acid (EDTA). Because clotting is inhibited, once obtained, the sample must be gently spun down in a centrifuge. The heavier, denser blood cells form a pellet at the bottom of a centrifuge tube, while the fluid plasma portion, which is lighter and less dense, remains above the cell pellet.

Acute-Phase Proteins

The acute-phase proteins are another class of antimicrobial mediators. Acute-phase proteins are primarily produced in the liver and secreted into the blood in response to inflammatory molecules from the immune system. Examples of acute-phase proteins include C-reactive protein, serum amyloid A, ferritin, transferrin, fibrinogen, and mannose-binding lectin. Each of these proteins has a different chemical structure and inhibits or destroys microbes in some way (Table **7.2.1**).

Table **7.2.2**: Some Acute-Phase Proteins and Their Functions

Some Acute-Phase Proteins and Their Functions	
C-reactive protein	Coats bacteria (opsonization), preparing them for ingestion by phagocytes
Serum amyloid A	
Ferritin	Bind and sequester iron, thereby inhibiting the growth of pathogens
Transferrin	
Fibrinogen	Involved in formation of blood clots that trap bacterial pathogens
Mannose-binding lectin	Activates complement cascade

The Complement System

The complement system is a group of plasma protein mediators that can act as an innate nonspecific defense while also serving to connect innate and adaptive immunity (discussed in the next chapter). The complement system is composed of more than 30 proteins (including C1 through C9) that normally circulate as precursor proteins in blood. These precursor proteins become activated when stimulated or triggered by a variety of factors, including the presence of microorganisms. Complement proteins are considered part of innate nonspecific immunity because they are always present in the blood and tissue fluids, allowing them to be activated quickly. Also, when activated through the alternative pathway (described later in this section), complement proteins target pathogens in a nonspecific manner.

The process by which circulating complement precursors become functional is called complement activation. This process is a cascade that can be triggered by one of three different mechanisms, known as the alternative, classical, and lectin pathways.

The alternative pathway is initiated by the spontaneous activation of the complement protein C3. The hydrolysis of C3 produces two products, C3a and C3b. When no invader microbes are present, C3b is very quickly degraded in a hydrolysis reaction using the water in the blood. However, if invading microbes are present, C3b attaches to the surface of these microbes. Once attached, C3b will recruit other complement proteins in a cascade (Figure **7.2.2**).

The classical pathway provides a more efficient mechanism of activating the complement cascade, but it depends upon the production of antibodies by the specific adaptive immune defenses. To initiate the classical pathway, a specific antibody must first bind to the pathogen to form an antibody-antigen complex. This activates the first protein in the complement cascade, the C1 complex. The C1 complex is a multipart protein complex, and each component participates in the full activation of the overall complex. Following recruitment and activation of the C1 complex, the remaining classical pathway complement proteins are recruited and activated in a cascading sequence (Figure **7.2.2**).

The lectin activation pathway is similar to the classical pathway, but it is triggered by the binding of mannose-binding lectin, an acute-phase protein, to carbohydrates on the microbial surface. Like other acute-phase proteins, lectins are produced by liver cells and are commonly upregulated in response to inflammatory signals received by the body during an infection (Figure **7.2.2**).

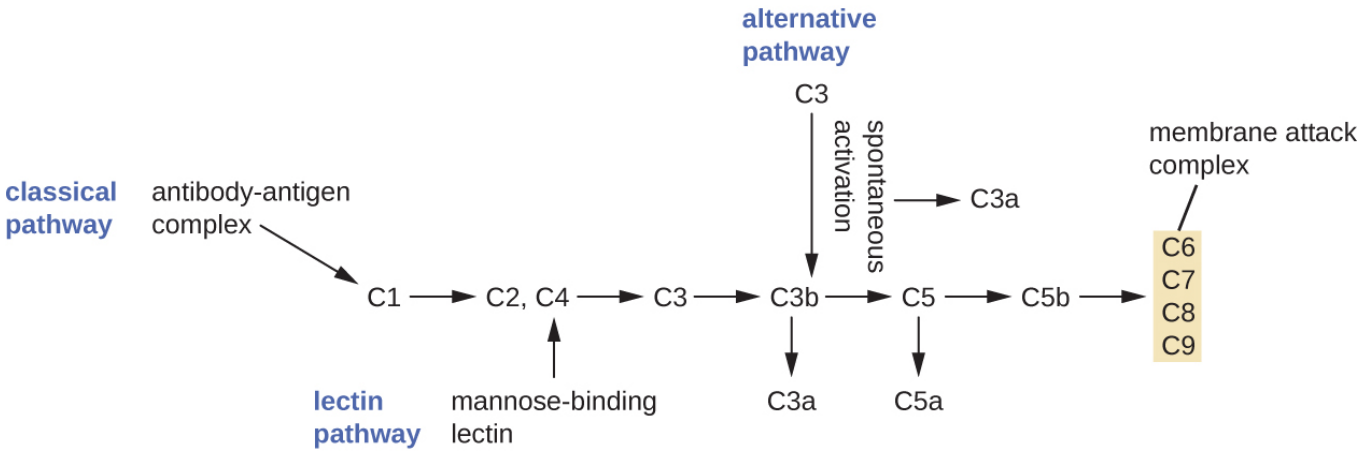


Figure **7.2.2**: The three complement activation pathways have different triggers, as shown here, but all three result in the activation

of the complement protein C3, which produces C3a and C3b. The latter binds to the surface of the target cell and then works with other complement proteins to cleave C5 into C5a and C5b. C5b also binds to the cell surface and then recruits C6 through C9; these molecules form a ring structure called the membrane attack complex (MAC), which punches through the cell membrane of the invading pathogen, causing it to swell and burst.

Although each complement activation pathway is initiated in a different way, they all provide the same protective outcomes: opsonization, inflammation, chemotaxis, and cytolysis. The term opsonization refers to the coating of a pathogen by a chemical substance (called an opsonin) that allows phagocytic cells to recognize, engulf, and destroy it more easily. Opsonins from the complement cascade include C1q, C3b, and C4b. Additional important opsonins include mannose-binding proteins and antibodies. The complement fragments C3a and C5a are well-characterized anaphylatoxins with potent proinflammatory functions. Anaphylatoxins activate mast cells, causing degranulation and the release of inflammatory chemical signals, including mediators that cause vasodilation and increased vascular permeability. C5a is also one of the most potent chemoattractants for neutrophils and other white blood cells, cellular defenses that will be discussed in the next section.

The complement proteins C6, C7, C8, and C9 assemble into a membrane attack complex (MAC), which allows C9 to polymerize into pores in the membranes of gram-negative bacteria. These pores allow water, ions, and other molecules to move freely in and out of the targeted cells, eventually leading to cell lysis and death of the pathogen (Figure **7.2.2**). However, the MAC is only effective against gram-negative bacteria; it cannot penetrate the thick layer of peptidoglycan associated with cell walls of gram-positive bacteria. Since the MAC does not pose a lethal threat to gram-positive bacterial pathogens, complement-mediated opsonization is more important for their clearance.

Cytokines

Cytokines are soluble proteins that act as communication signals between cells. In a nonspecific innate immune response, various cytokines may be released to stimulate production of chemical mediators or other cell functions, such as cell proliferation, cell differentiation, inhibition of cell division, apoptosis, and chemotaxis.

When a cytokine binds to its target receptor, the effect can vary widely depending on the type of cytokine and the type of cell or receptor to which it has bound. The function of a particular cytokine can be described as autocrine, paracrine, or endocrine (Figure **7.2.3**). In autocrine function, the same cell that releases the cytokine is the recipient of the signal; in other words, autocrine function is a form of self-stimulation by a cell. In contrast, paracrine function involves the release of cytokines from one cell to other nearby cells, stimulating some response from the recipient cells. Last, endocrine function occurs when cells release cytokines into the bloodstream to be carried to target cells much farther away.

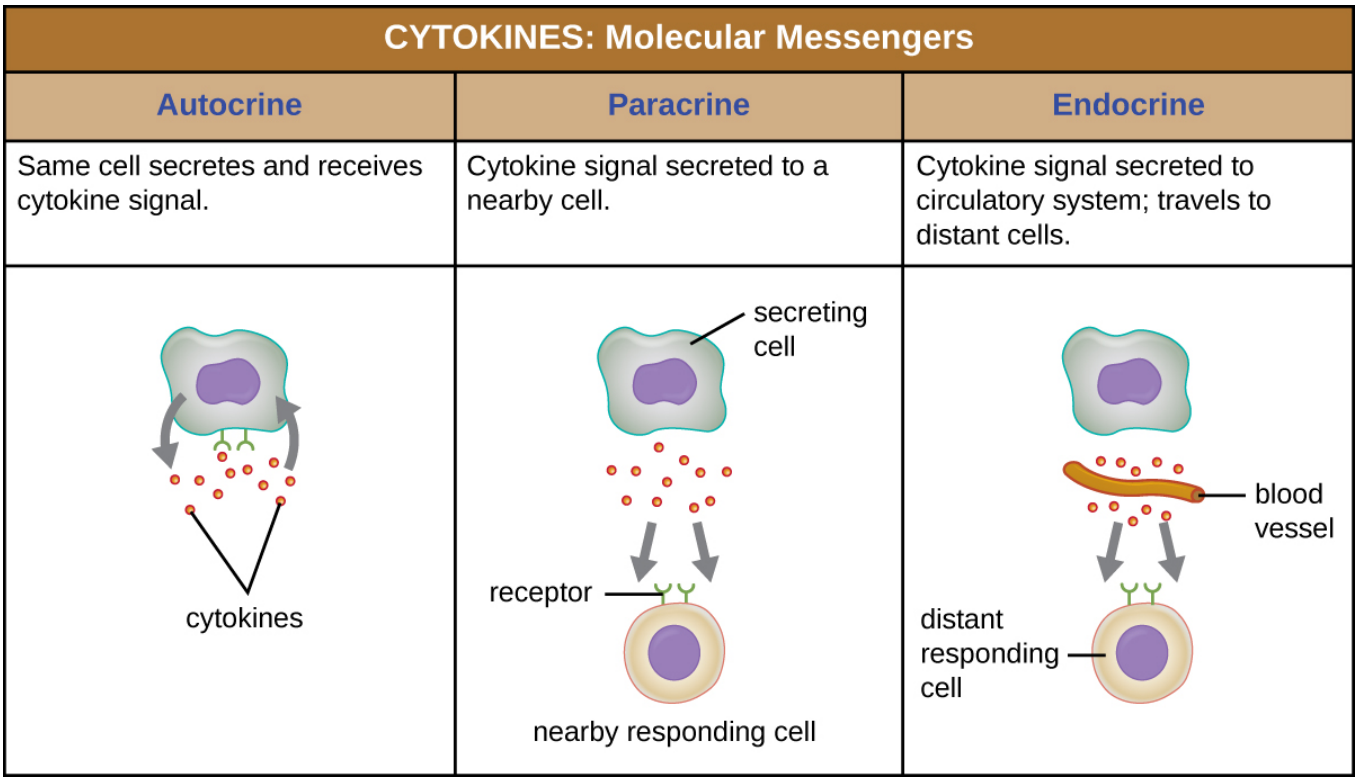


Figure 7.2.3: Autocrine, paracrine, and endocrine actions describe which cells are targeted by cytokines and how far the cytokines must travel to bind to their intended target cells' receptors.

Three important classes of cytokines are the interleukins, chemokines, and interferons. The interleukins were originally thought to be produced only by leukocytes (white blood cells) and to only stimulate leukocytes, thus the reasons for their name. Although interleukins are involved in modulating almost every function of the immune system, their role in the body is not restricted to immunity. Interleukins are also produced by and stimulate a variety of cells unrelated to immune defenses.

The chemokines are chemotactic factors that recruit leukocytes to sites of infection, tissue damage, and inflammation. In contrast to more general chemotactic factors, like complement factor C5a, chemokines are very specific in the subsets of leukocytes they recruit.

Interferons are a diverse group of immune signaling molecules and are especially important in our defense against viruses. Type I interferons (interferon-α and interferon-β) are produced and released by cells infected with virus. These interferons stimulate nearby cells to stop production of mRNA, destroy RNA already produced, and reduce protein synthesis. These cellular changes inhibit viral replication and production of mature virus, slowing the spread of the virus. Type I interferons also stimulate various immune cells involved in viral clearance to more aggressively attack virus-infected cells. Type II interferon (interferon-γ) is an important activator of immune cells (Figure 7.2.4).

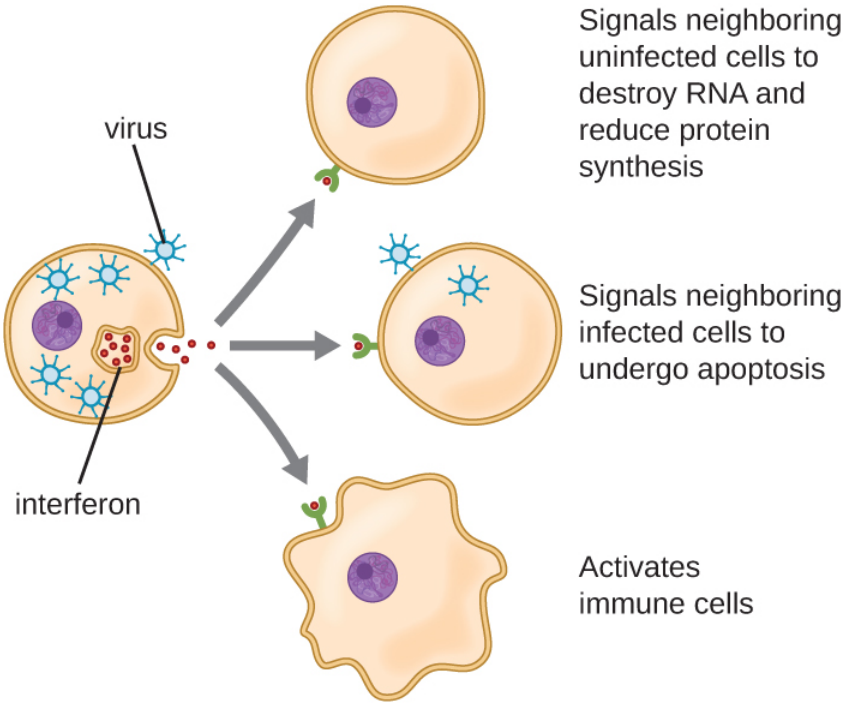


Figure **7.2.4**: Interferons are cytokines released by a cell infected with a virus. Interferon-α and interferon-β signal uninfected neighboring cells to inhibit mRNA synthesis, destroy RNA, and reduce protein synthesis (top arrow). Interferon-α and interferon-β also promote apoptosis in cells infected with the virus (middle arrow). Interferon-γ alerts neighboring immune cells to an attack (bottom arrow). Although interferons do not cure the cell releasing them or other infected cells, which will soon die, their release may prevent additional cells from becoming infected, thus stemming the infection.

Inflammation-Eliciting Mediators

Many of the chemical mediators discussed in this section contribute in some way to inflammation and fever, which are nonspecific immune responses discussed in more detail in Inflammation and Fever. Cytokines stimulate the production of acute-phase proteins such as C-reactive protein and mannose-binding lectin in the liver. These acute-phase proteins act as opsonins, activating complement cascades through the lectin pathway.

Some cytokines also bind mast cells and basophils, inducing them to release histamine, a proinflammatory compound. Histamine receptors are found on a variety of cells and mediate proinflammatory events, such as bronchoconstriction (tightening of the airways) and smooth muscle contraction.

In addition to histamine, mast cells may release other chemical mediators, such as leukotrienes. Leukotrienes are lipid-based proinflammatory mediators that are produced from the metabolism of arachidonic acid in the cell membrane of leukocytes and tissue cells. Compared with the proinflammatory effects of histamine, those of leukotrienes are more potent and longer lasting. Together, these chemical mediators can induce coughing, vomiting, and diarrhea, which serve to expel pathogens from the body.

Certain cytokines also stimulate the production of prostaglandins, chemical mediators that promote the inflammatory effects of kinins and histamines. Prostaglandins can also help to set the body temperature higher, leading to fever, which promotes the activities of white blood cells and slightly inhibits the growth of pathogenic microbes (see Inflammation and Fever).

Another inflammatory mediator, bradykinin, contributes to edema, which occurs when fluids and leukocytes leak out of the bloodstream and into tissues. It binds to receptors on cells in the capillary walls, causing the capillaries to dilate and become more permeable to fluids.

? Exercise 7.2.3

1. What do the three complement activation pathways have in common?
2. Explain autocrine, paracrine, and endocrine signals.
3. Name two important inflammation-eliciting mediators.

Clinical Focus: Part 2

To relieve the constriction of her airways, Angela is immediately treated with antihistamines and administered corticosteroids through an inhaler, and then monitored for a period of time. Though her condition does not worsen, the drugs do not seem to be alleviating her condition. She is admitted to the hospital for further observation, testing, and treatment.

Following admission, a clinician conducts allergy testing to try to determine if something in her environment might be triggering an allergic inflammatory response. A doctor orders blood analysis to check for levels of particular cytokines. A sputum sample is also taken and sent to the lab for microbial staining, culturing, and identification of pathogens that could be causing an infection.

Exercise 7.2.4

1. Which aspects of the innate immune system could be contributing to Angela's airway constriction?
2. Why was Angela treated with antihistamines?
3. Why would the doctor be interested in levels of cytokines in Angela's blood?

Table **7.2.3** provides a summary of the chemical defenses discussed in this section.

Table **7.2.3**: Chemical Defenses of Nonspecific Innate Immunity

Defense	Examples	Function
Chemicals and enzymes in body fluids	Sebum from sebaceous glands	Provides oil barrier protecting hair follicle pores from pathogens
	Oleic acid from sebum and skin microbiota	Lowers pH to inhibit pathogens
	Lysozyme in secretions	Kills bacteria by attacking cell wall
	Acid in stomach, urine, and vagina	Inhibits or kills bacteria
	Digestive enzymes and bile	Kill bacteria
	Lactoferrin and transferrin	Bind and sequester iron, inhibiting bacterial growth
	Surfactant in lungs	Kills bacteria
Antimicrobial peptides	Defensins, bacteriocins, dermicidin, cathelicidin, histatins,	Kill bacteria by attacking membranes or interfering with cell functions
Plasma protein mediators	Acute-phase proteins (C-reactive protein, serum amyloid A, ferritin, fibrinogen, transferrin, and mannose-binding lectin)	Inhibit the growth of bacteria and assist in the trapping and killing of bacteria
	Complements C3b and C4b	Opsonization of pathogens to aid phagocytosis
	Complement C5a	Chemoattractant for phagocytes
	Complements C3a and C5a	Proinflammatory anaphylatoxins
Cytokines	Interleukins	Stimulate and modulate most functions of immune system
	Chemokines	Recruit white blood cells to infected area
	Interferons	Alert cells to viral infection, induce apoptosis of virus-infected cells, induce antiviral defenses in infected and nearby uninfected cells, stimulate immune cells to attack virus-infected cells
Inflammation-eliciting mediators	Histamine	Promotes vasodilation, bronchoconstriction, smooth muscle contraction, increased secretion and mucus production
	Leukotrienes	Promote inflammation; stronger and longer lasting than histamine
	Prostaglandins	Promote inflammation and fever
	Bradykinin	Increases vasodilation and vascular permeability, leading to edema

Key Concepts and Summary

- Numerous **chemical mediators** produced endogenously and exogenously exhibit nonspecific antimicrobial functions.
- Many chemical mediators are found in body fluids such as sebum, saliva, mucus, gastric and intestinal fluids, urine, tears, cerumen, and vaginal secretions.

- **Antimicrobial peptides (AMPs)** found on the skin and in other areas of the body are largely produced in response to the presence of pathogens. These include dermcidin, cathelicidin, defensins, histatins, and bacteriocins.
- **Plasma** contains various proteins that serve as chemical mediators, including **acute-phase proteins**, **complement proteins**, and **cytokines**.
- The **complement system** involves numerous precursor proteins that circulate in plasma. These proteins become activated in a cascading sequence in the presence of microbes, resulting in the **opsonization** of pathogens, chemoattraction of leukocytes, induction of inflammation, and cytolysis through the formation of a **membrane attack complex (MAC)**.
- **Cytokines** are proteins that facilitate various nonspecific responses by innate immune cells, including production of other chemical mediators, cell proliferation, cell death, and differentiation.
- Cytokines play a key role in the inflammatory response, triggering production of inflammation-eliciting mediators such as acute-phase proteins, **histamine**, leukotrienes, **prostaglandins**, and **bradykinin**.

This page titled 7.2: Chemical Defenses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **17.2: Chemical Defenses** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

7.3: Cellular Defenses

Learning Objectives

- Identify and describe the components of blood
- Explain the process by which the formed elements of blood are formed (hematopoiesis)
- Describe the characteristics of formed elements found in peripheral blood, as well as their respective functions within the innate immune system

In the previous section, we discussed some of the chemical mediators found in plasma, the fluid portion of blood. The nonfluid portion of blood consists of various types of formed elements, so called because they are all formed from the same stem cells found in bone marrow. The three major categories of formed elements are: red blood cells (RBCs), also called erythrocytes; platelets, also called thrombocytes; and white blood cells (WBCs), also called leukocytes.

Red blood cells are primarily responsible for carrying oxygen to tissues. Platelets are cellular fragments that participate in blood clot formation and tissue repair. Several different types of WBCs participate in various nonspecific mechanisms of innate and adaptive immunity. In this section, we will focus primarily on the innate mechanisms of various types of WBCs.

Hematopoiesis

All of the formed elements of blood are derived from pluripotent hematopoietic stem cells (HSCs) in the bone marrow. As the HSCs make copies of themselves in the bone marrow, individual cells receive different cues from the body that control how they develop and mature. As a result, the HSCs differentiate into different types of blood cells that, once mature, circulate in peripheral blood. This process of differentiation, called hematopoiesis, is shown in more detail in Figure **7.3.1**.

In terms of sheer numbers, the vast majority of HSCs become erythrocytes. Much smaller numbers become leukocytes and platelets. Leukocytes can be further subdivided into granulocytes, which are characterized by numerous granules visible in the cytoplasm, and agranulocytes, which lack granules. Figure **7.3.2** provides an overview of the various types of formed elements, including their relative numbers, primary function, and lifespans.

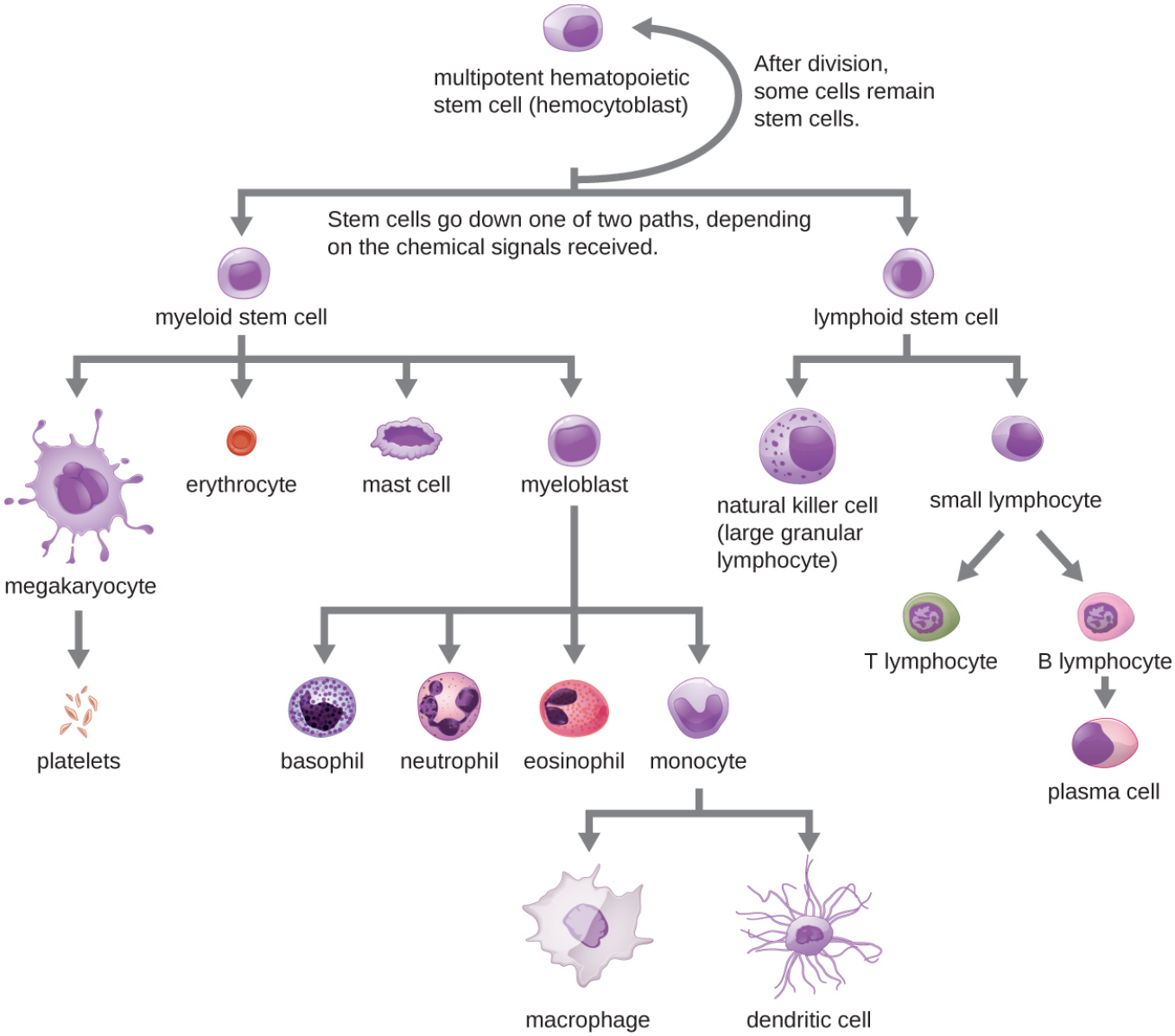


Figure 7.3.1: All the formed elements of the blood arise by differentiation of hematopoietic stem cells in the bone marrow.

Formed Element	Major Subtypes		Numbers Present per Microliter (μL) and Mean (Range)	Appearance in a Standard Blood Smear	Summary of Functions	Comments
Erythrocytes (red blood cells) 			5.2 million (4.4–6.0 million)	Flattened biconcave disk; no nucleus; pale red	Transport oxygen and some carbon dioxide between tissue and lungs	Lifespan of approximately 120 days
Leukocytes (white blood cells)			7000 (5000–10,000)	Obvious dark-staining nucleus	All function in body defenses	Exit capillaries and move into tissues; lifespan of usually a few hours or days
	Granulocytes, including neutrophils, eosinophils, and basophils	***Total leukocytes (%)***	4360 (1800–9950)	Abundant granules in cytoplasm; nucleus normally lobed	Nonspecific (innate) resistance to disease	Classified according to membrane-bound granules in cytoplasm
	Neutrophils 	50–70	4150 (1800–7300)	Nucleus lobes increase with age; pale lilac granules	Phagocytic; particularly effective against bacteria; release cytotoxic chemicals from granules	Most common leukocyte; lifespan of minutes to days
	Eosinophils 	1–3	165 (0–700)	Nucleus generally two-lobed; bright red-orange granules	Phagocytic cells; particularly effective with antigen-antibody complexes; release antihistamines; combat parasitic infections	Lifespan of minutes to days
	Basophils 	<1	44 (0–150)	Nucleus generally two-lobed but difficult to see due to presence of heavy, dense, dark purple granules	Pro-inflammatory	Least common leukocyte; lifespan unknown
	Agranulocytes, including lymphocytes and monocytes		2640 (1700–4950)	Lack abundant granules in cytoplasm; have a simple-shaped nucleus that may be indented	Body defenses	Group consists of two major cell types from different lineages
	Lymphocytes 	20–40	2185 (1500–4000)	Spherical cells with a single, often large, nucleus occupying much of the cell's volume; stains purple; seen in large (natural killer cells) and small (B and T cells) variants	Primarily specific (adaptive) immunity: T cells directly attack other cells (cellular immunity); B cells release antibodies (humoral immunity); natural killer cells are similar to T cells but nonspecific	Initial cells originate in bone marrow, but secondary production occurs in lymphatic tissue; several distinct subtypes; memory cells form after exposure to a pathogen and rapidly increase responses to subsequent exposure; lifespan of many years
	Monocytes 	1–6	455 (200–950)	Largest leukocyte; has an indented or horseshoe-shaped nucleus	Very effective phagocytic cells engulfing pathogens or worn-out cells; also serve as antigen-presenting cells (APCs) or other components of the immune system	Produced in red bone marrow; referred to as macrophages and dendritic cells after leaving the circulation
Platelets 			350,000 (150,000–500,000)	Cellular fragments surrounded by a plasma membrane and containing granules; stains purple	Hemostasis; release growth factors for repair and healing of tissue	Formed from megakaryocytes that remain in the red bone marrow and shed platelets into circulation

Figure **7.3.2**: Formed elements of blood include erythrocytes (red blood cells), leukocytes (white blood cells), and platelets.

Granulocytes

The various types of granulocytes can be distinguished from one another in a blood smear by the appearance of their nuclei and the contents of their granules, which confer different traits, functions, and staining properties. The neutrophils, also called polymorphonuclear neutrophils (PMNs), have a nucleus with three to five lobes and small, numerous, lilac-colored granules. Each lobe of the nucleus is connected by a thin strand of material to the other lobes. The eosinophils have fewer lobes in the nucleus (typically 2–3) and larger granules that stain reddish-orange. The basophils have a two-lobed nucleus and large granules that stain dark blue or purple (Figure **7.3.3**).

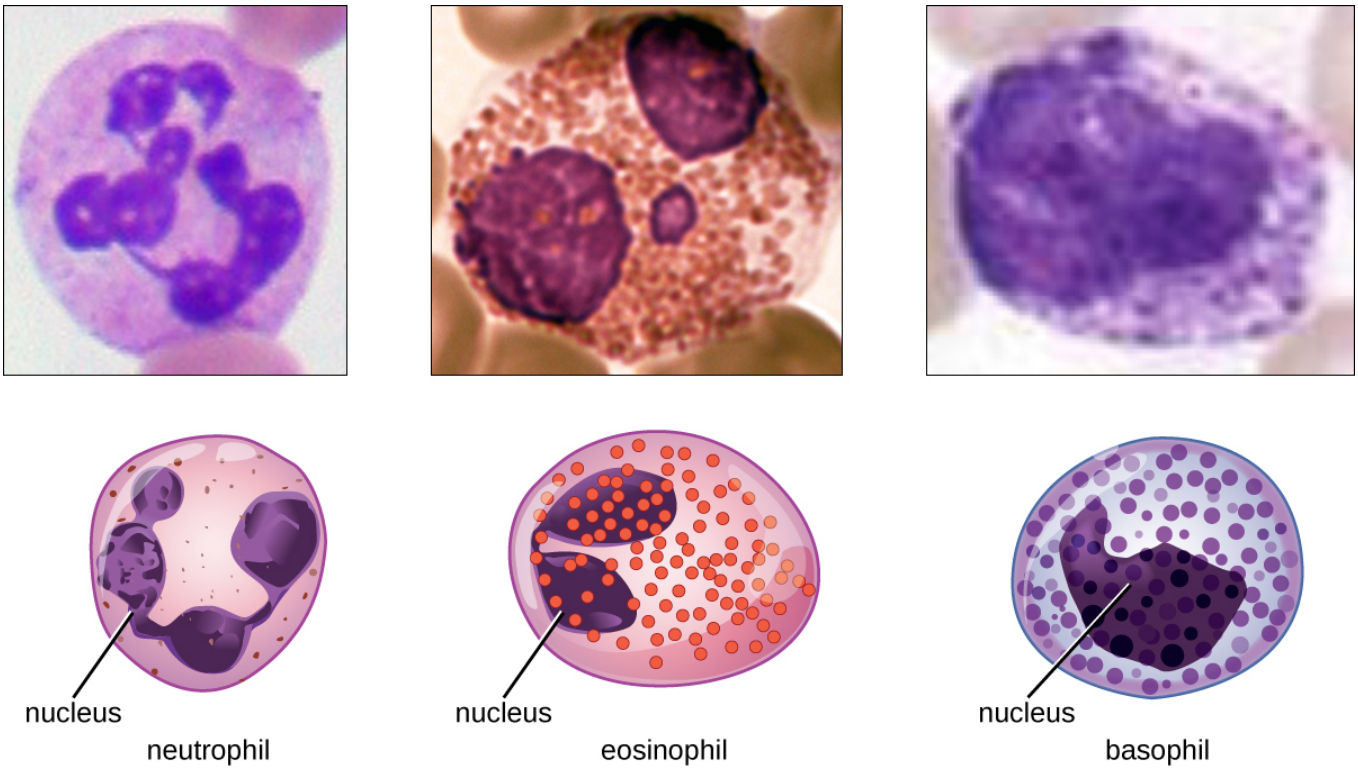


Figure **7.3.3**: Granulocytes can be distinguished by the number of lobes in their nuclei and the staining properties of their granules. (credit “neutrophil” micrograph: modification of work by Ed Uthman)

Neutrophils (PMNs)

Neutrophils (PMNs) are frequently involved in the elimination and destruction of extracellular bacteria. They are capable of migrating through the walls of blood vessels to areas of bacterial infection and tissue damage, where they seek out and kill infectious bacteria. PMN granules contain a variety of defensins and hydrolytic enzymes that help them destroy bacteria through phagocytosis (described in more detail in Pathogen Recognition and Phagocytosis) In addition, when many neutrophils are brought into an infected area, they can be stimulated to release toxic molecules into the surrounding tissue to better clear infectious agents. This is called degranulation.

Another mechanism used by neutrophils is neutrophil extracellular traps (NETs), which are extruded meshes of chromatin that are closely associated with antimicrobial granule proteins and components. Chromatin is DNA with associated proteins (usually histone proteins, around which DNA wraps for organization and packing within a cell). By creating and releasing a mesh or lattice-like structure of chromatin that is coupled with antimicrobial proteins, the neutrophils can mount a highly concentrated and efficient attack against nearby pathogens. Proteins frequently associated with NETs include lactoferrin, gelatinase, cathepsin G, and myeloperoxidase. Each has a different means of promoting antimicrobial activity, helping neutrophils eliminate pathogens. The toxic proteins in NETs may kill some of the body’s own cells along with invading pathogens. However, this collateral damage can be repaired after the danger of the infection has been eliminated.

As neutrophils fight an infection, a visible accumulation of leukocytes, cellular debris, and bacteria at the site of infection can be observed. This buildup is what we call pus (also known as purulent or suppurative discharge or drainage). The presence of pus is a

sign that the immune defenses have been activated against an infection; historically, some physicians believed that inducing pus formation could actually promote the healing of wounds. The practice of promoting “laudable pus” (by, for instance, wrapping a wound in greasy wool soaked in wine) dates back to the ancient physician Galen in the 2nd century AD, and was practiced in variant forms until the 17th century (though it was not universally accepted). Today, this method is no longer practiced because we now know that it is not effective. Although a small amount of pus formation can indicate a strong immune response, artificially inducing pus formation does not promote recovery.

Eosinophils

Eosinophils are granulocytes that protect against protozoa and helminths; they also play a role in allergic reactions. The granules of eosinophils, which readily absorb the acidic reddish dye eosin, contain histamine, degradative enzymes, and a compound known as major basic protein (MBP) (Figure **7.3.3**). MBP binds to the surface carbohydrates of parasites, and this binding is associated with disruption of the cell membrane and membrane permeability.

Basophils

Basophils have cytoplasmic granules of varied size and are named for their granules’ ability to absorb the basic dye methylene blue (Figure **7.3.3**). Their stimulation and degranulation can result from multiple triggering events. Activated complement fragments C3a and C5a, produced in the activation cascades of complement proteins, act as anaphylatoxins by inducing degranulation of basophils and inflammatory responses. This cell type is important in allergic reactions and other responses that involve inflammation. One of the most abundant components of basophil granules is histamine, which is released along with other chemical factors when the basophil is stimulated. These chemicals can be chemotactic and can help to open the gaps between cells in the blood vessels. Other mechanisms for basophil triggering require the assistance of antibodies, as discussed in B Lymphocytes and Humoral Immunity.

Mast Cells

Hematopoiesis also gives rise to mast cells, which appear to be derived from the same common myeloid progenitor cell as neutrophils, eosinophils, and basophils. Functionally, mast cells are very similar to basophils, containing many of the same components in their granules (e.g., histamine) and playing a similar role in allergic responses and other inflammatory reactions. However, unlike basophils, mast cells leave the circulating blood and are most frequently found residing in tissues. They are often associated with blood vessels and nerves or found close to surfaces that interface with the external environment, such as the skin and mucous membranes in various regions of the body (Figure **7.3.4**).

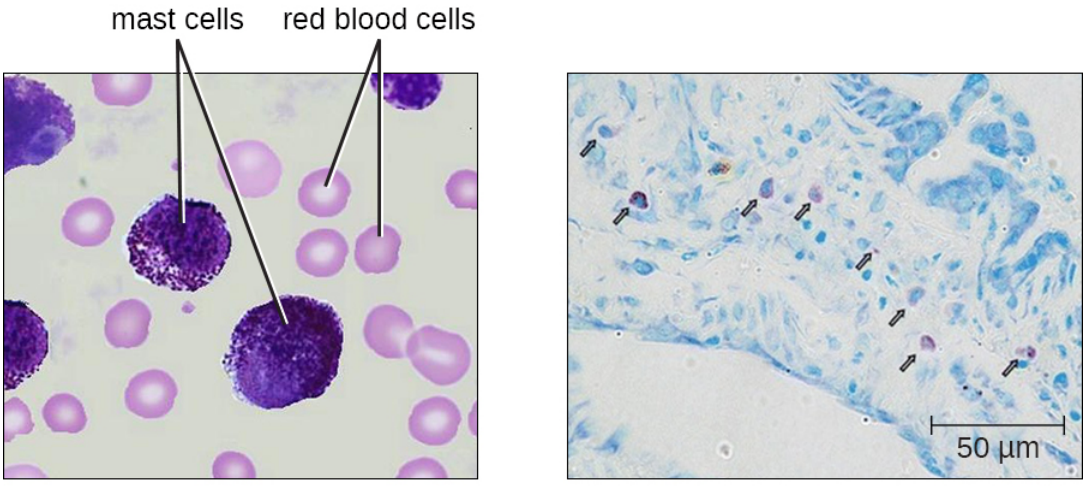


Figure **7.3.4**: Mast cells function similarly to basophils by inducing and promoting inflammatory responses. (a) This figure shows mast cells in blood. In a blood smear, they are difficult to differentiate from basophils (b). Unlike basophils, mast cells migrate from the blood into various tissues. (credit right: modification of work by Greenland JR, Xu X, Sayah DM, Liu FC, Jones KD, Looney MR, Caughey GH)

Exercise 7.3.1

1. Describe the granules and nuclei of neutrophils, eosinophils, basophils, and mast cells.
2. Name three antimicrobial mechanisms of neutrophils

Clinical Focus: Part 3

Angela's tests come back negative for all common allergens, and her sputum samples contain no abnormal presence of pathogenic microbes or elevated levels of members of the normal respiratory microbiota. She does, however, have elevated levels of inflammatory cytokines in her blood.

The swelling of her airway has still not responded to treatment with antihistamines or corticosteroids. Additional blood work shows that Angela has a mildly elevated white blood cell count but normal antibody levels. Also, she has a lower-than-normal level of the complement protein C4.

Exercise 7.3.2

1. What does this new information reveal about the cause of Angela's constricted airways?
2. What are some possible conditions that could lead to low levels of complement proteins?

Agranulocytes

As their name suggests, agranulocytes lack visible granules in the cytoplasm. Agranulocytes can be categorized as lymphocytes or monocytes (Figure **7.3.2**). Among the lymphocytes are natural killer cells, which play an important role in nonspecific innate immune defenses. Lymphocytes also include the B cells and T cells, which are discussed in the next chapter because they are central players in the specific adaptive immune defenses. The monocytes differentiate into macrophages and dendritic cells, which are collectively referred to as the mononuclear phagocyte system.

Natural Killer Cells

Most lymphocytes are primarily involved in the specific adaptive immune response, and thus will be discussed in the following chapter. An exception is the natural killer cells (NK cells); these mononuclear lymphocytes use nonspecific mechanisms to recognize and destroy cells that are abnormal in some way. Cancer cells and cells infected with viruses are two examples of cellular abnormalities that are targeted by NK cells. Recognition of such cells involves a complex process of identifying inhibitory and activating molecular markers on the surface of the target cell. Molecular markers that make up the major histocompatibility complex (MHC) are expressed by healthy cells as an indication of "self." This will be covered in more detail in next chapter. NK cells are able to recognize normal MHC markers on the surface of healthy cells, and these MHC markers serve as an inhibitory signal preventing NK cell activation. However, cancer cells and virus-infected cells actively diminish or eliminate expression of MHC markers on their surface. When these MHC markers are diminished or absent, the NK cell interprets this as an abnormality and a cell in distress. This is one part of the NK cell activation process (Figure **7.3.5**). NK cells are also activated by binding to activating molecular molecules on the target cell. These activating molecular molecules include "altered self" or "nonself" molecules. When a NK cell recognizes a decrease in inhibitory normal MHC molecules and an increase in activating molecules on the surface of a cell, the NK cell will be activated to eliminate the cell in distress.

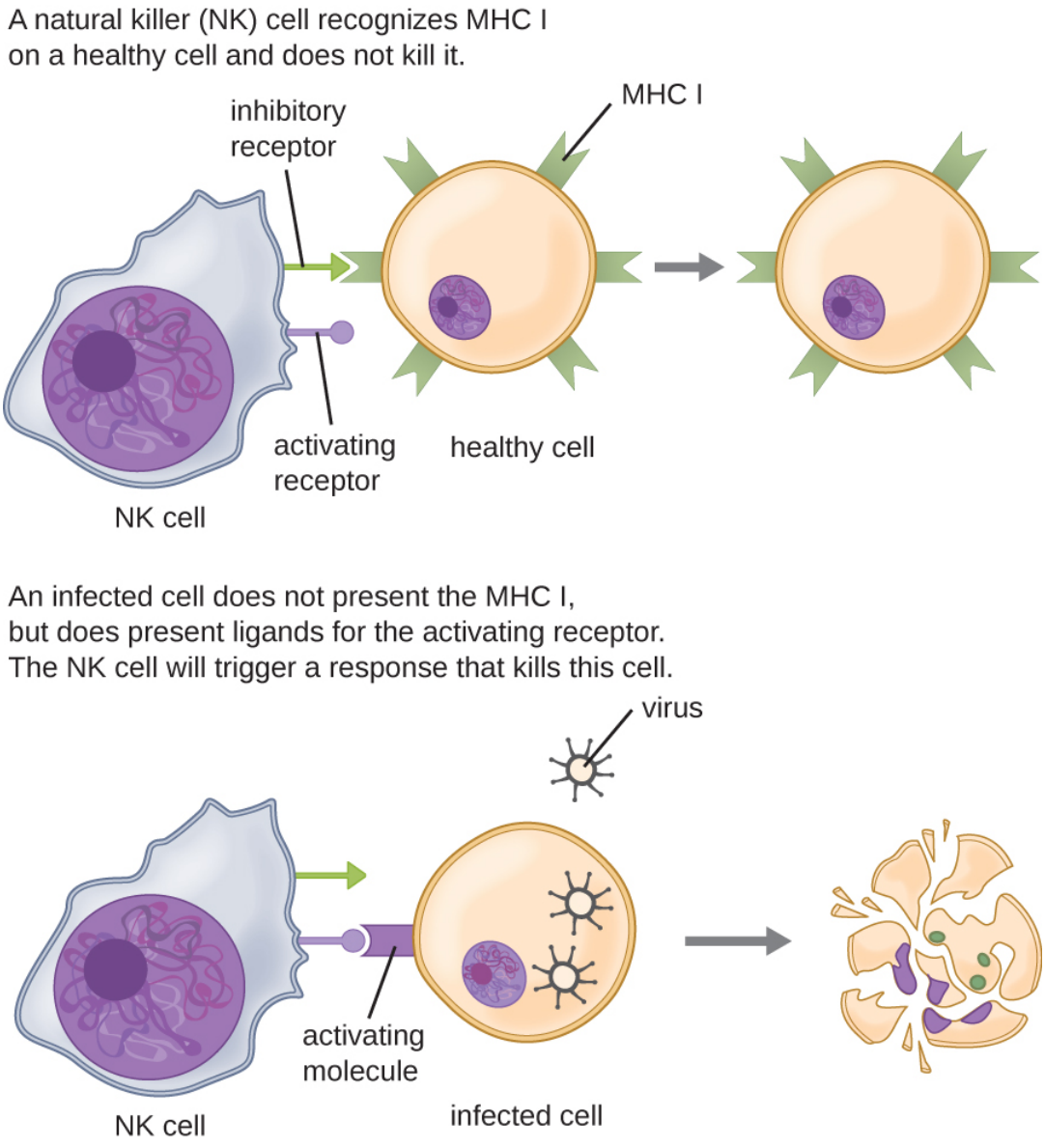


Figure **7.3.5**: Natural killer (NK) cells are inhibited by the presence of the major histocompatibility cell (MHC) receptor on healthy cells. Cancer cells and virus-infected cells have reduced expression of MHC and increased expression of activating molecules. When a NK cell recognizes decreased MHC and increased activating molecules, it will kill the abnormal cell.

Once a cell has been recognized as a target, the NK cell can use several different mechanisms to kill its target. For example, it may express cytotoxic membrane proteins and cytokines that stimulate the target cell to undergo apoptosis, or controlled cell suicide. NK cells may also use perforin-mediated cytotoxicity to induce apoptosis in target cells. This mechanism relies on two toxins released from granules in the cytoplasm of the NK cell: perforin, a protein that creates pores in the target cell, and granzymes, proteases that enter through the pores into the target cell's cytoplasm, where they trigger a cascade of protein activation that leads to apoptosis. The NK cell binds to the abnormal target cell, releases its destructive payload, and detaches from the target cell. While the target cell undergoes apoptosis, the NK cell synthesizes more perforin and proteases to use on its next target.

NK cells contain these toxic compounds in granules in their cytoplasm. When stained, the granules are azurophilic and can be visualized under a light microscope (Figure **7.3.6**). Even though they have granules, NK cells are not considered granulocytes because their granules are far less numerous than those found in true granulocytes. Furthermore, NK cells have a different lineage than granulocytes, arising from lymphoid rather than myeloid stem cells (Figure **7.3.1**).

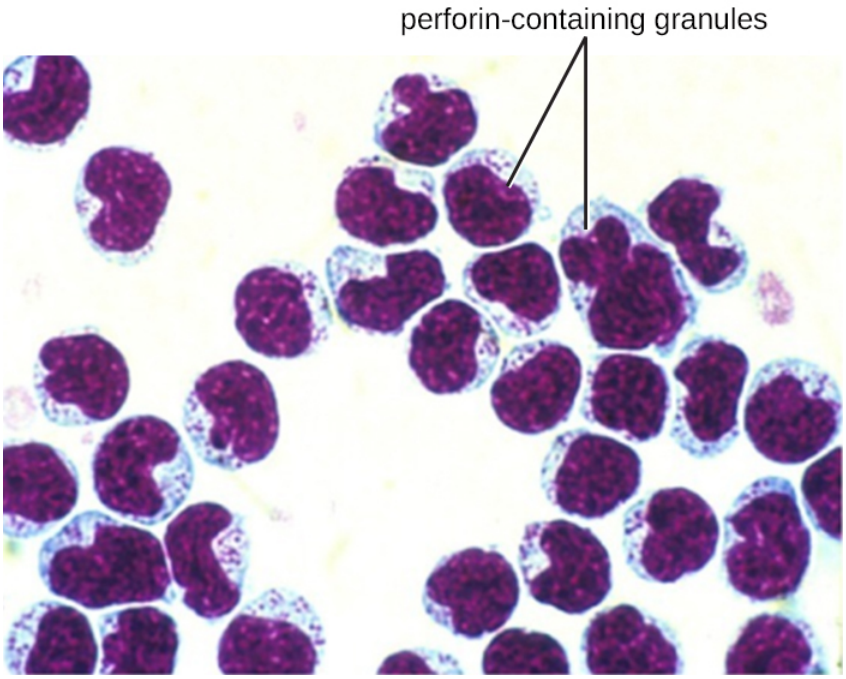


Figure **7.3.6**: Natural killer cell with perforin-containing granules. (credit: modification of work by Rolstad B)

Monocytes

The largest of the white blood cells, monocytes have a nucleus that lacks lobes, and they also lack granules in the cytoplasm (Figure **7.3.7**). Nevertheless, they are effective phagocytes, engulfing pathogens and apoptotic cells to help fight infection.

When monocytes leave the bloodstream and enter a specific body tissue, they differentiate into tissue-specific phagocytes called macrophages and dendritic cells. They are particularly important residents of lymphoid tissue, as well as nonlymphoid sites and organs. Macrophages and dendritic cells can reside in body tissues for significant lengths of time. Macrophages in specific body tissues develop characteristics suited to the particular tissue. Not only do they provide immune protection for the tissue in which they reside but they also support normal function of their neighboring tissue cells through the production of cytokines. Macrophages are given tissue-specific names, and a few examples of tissue-specific macrophages are listed in Table **7.3.1**. Dendritic cells are important sentinels residing in the skin and mucous membranes, which are portals of entry for many pathogens. Monocytes, macrophages, and dendritic cells are all highly phagocytic and important promoters of the immune response through their production and release of cytokines. These cells provide an essential bridge between innate and adaptive immune responses, as discussed in the next section as well as the next chapter.

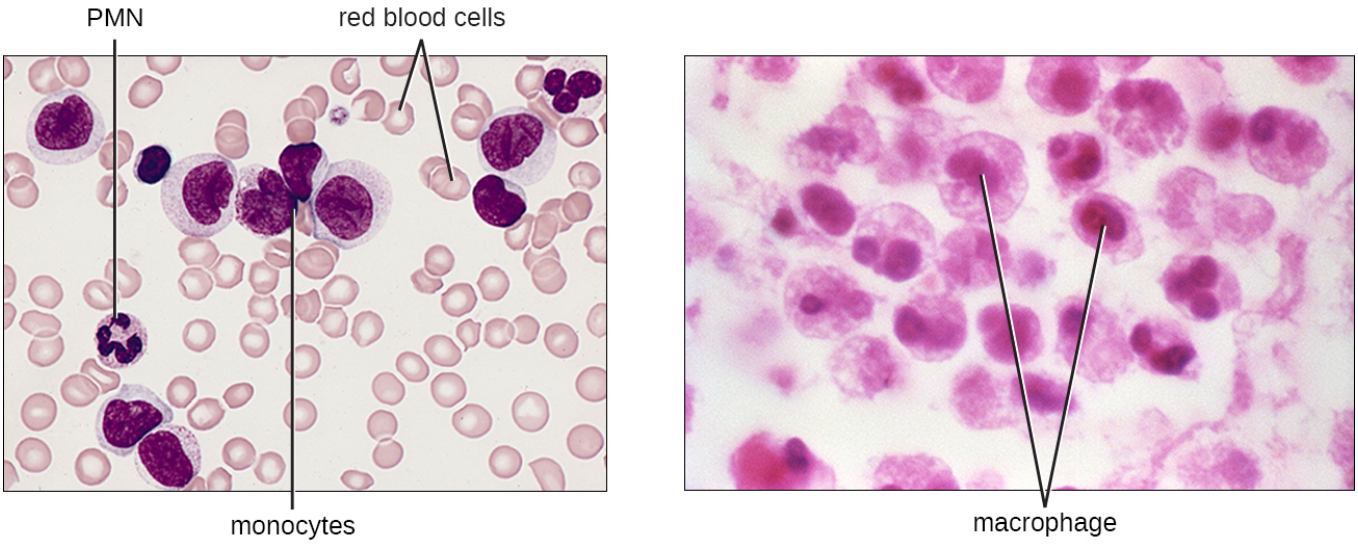


Figure **7.3.7**: Monocytes are large, agranular white blood cells with a nucleus that lacks lobes. When monocytes leave the bloodstream, they differentiate and become macrophages with tissue-specific properties. (credit left: modification of work by Armed Forces Institute of Pathology; credit right: modification of work by Centers for Disease Control and Prevention)

Table **7.3.1**: Macrophages Found in Various Body Tissues

Tissue	Macrophage
Brain and central nervous system	Microglial cells
Liver	Kupffer cells
Lungs	Alveolar macrophages (dust cells)
Peritoneal cavity	Peritoneal macrophages

? Exercise 7.3.3

1. Describe the signals that activate natural killer cells.
2. What is the difference between monocytes and macrophages?

Key Concepts and Summary

- The **formed elements** of the blood include red blood cells (**erythrocytes**), white blood cells (**leukocytes**), and **platelets (thrombocytes**). Of these, leukocytes are primarily involved in the immune response.
- All formed elements originate in the bone marrow as stem cells (HSCs) that differentiate through **hematopoiesis**.
- **Granulocytes** are leukocytes characterized by a lobed nucleus and granules in the cytoplasm. These include **neutrophils (PMNs)**, **eosinophils**, and **basophils**.
- Neutrophils are the leukocytes found in the largest numbers in the bloodstream and they primarily fight bacterial infections.
- Eosinophils target parasitic infections. Eosinophils and basophils are involved in allergic reactions. Both release histamine and other proinflammatory compounds from their granules upon stimulation.
- **Mast cells** function similarly to basophils but can be found in tissues outside the bloodstream.
- **Natural killer** (**NK**) cells are lymphocytes that recognize and kill abnormal or infected cells by releasing proteins that trigger apoptosis.
- **Monocytes** are large, mononuclear leukocytes that circulate in the bloodstream. They may leave the bloodstream and take up residence in body tissues, where they differentiate and become tissue-specific **macrophages** and **dendritic cells**.

This page titled 7.3: Cellular Defenses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **17.3: Cellular Defenses** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

7.4: Pathogen Recognition and Phagocytosis

Learning Objectives

- Explain how leukocytes migrate from peripheral blood into infected tissues
- Explain the mechanisms by which leukocytes recognize pathogens
- Explain the process of phagocytosis and the mechanisms by which phagocytes destroy and degrade pathogens

Several of the cell types discussed in the previous section can be described as phagocytes—cells whose main function is to seek, ingest, and kill pathogens. This process, called phagocytosis, was first observed in starfish in the 1880s by Nobel Prize-winning zoologist Ilya Metchnikoff (1845–1916), who made the connection to white blood cells (WBCs) in humans and other animals. At the time, Pasteur and other scientists believed that WBCs were spreading pathogens rather than killing them (which is true for some diseases, such as tuberculosis). But in most cases, phagocytes provide a strong, swift, and effective defense against a broad range of microbes, making them a critical component of innate nonspecific immunity. This section will focus on the mechanisms by which phagocytes are able to seek, recognize, and destroy pathogens.

Extravasation (Diapedesis) of Leukocytes

Some phagocytes are leukocytes (WBCs) that normally circulate in the bloodstream. To reach pathogens located in infected tissue, leukocytes must pass through the walls of small capillary blood vessels within tissues. This process, called extravasation, or diapedesis, is initiated by complement factor C5a, as well as cytokines released into the immediate vicinity by resident macrophages and tissue cells responding to the presence of the infectious agent (Figure **7.4.1**). Similar to C5a, many of these cytokines are proinflammatory and chemotactic, and they bind to cells of small capillary blood vessels, initiating a response in the endothelial cells lining the inside of the blood vessel walls. This response involves the upregulation and expression of various cellular adhesion molecules and receptors. Leukocytes passing through will stick slightly to the adhesion molecules, slowing down and rolling along the blood vessel walls near the infected area. When they reach a cellular junction, they will bind to even more of these adhesion molecules, flattening out and squeezing through the cellular junction in a process known as transendothelial migration. This mechanism of “rolling adhesion” allows leukocytes to exit the bloodstream and enter the infected areas, where they can begin phagocytosing the invading pathogens.

Note that extravasation does not occur in arteries or veins. These blood vessels are surrounded by thicker, multilayer protective walls, in contrast to the thin single-cell-layer walls of capillaries. Furthermore, the blood flow in arteries is too turbulent to allow for rolling adhesion. Also, some leukocytes tend to respond to an infection more quickly than others. The first to arrive typically are neutrophils, often within hours of a bacterial infection. By contract, monocytes may take several days to leave the bloodstream and differentiate into macrophages.

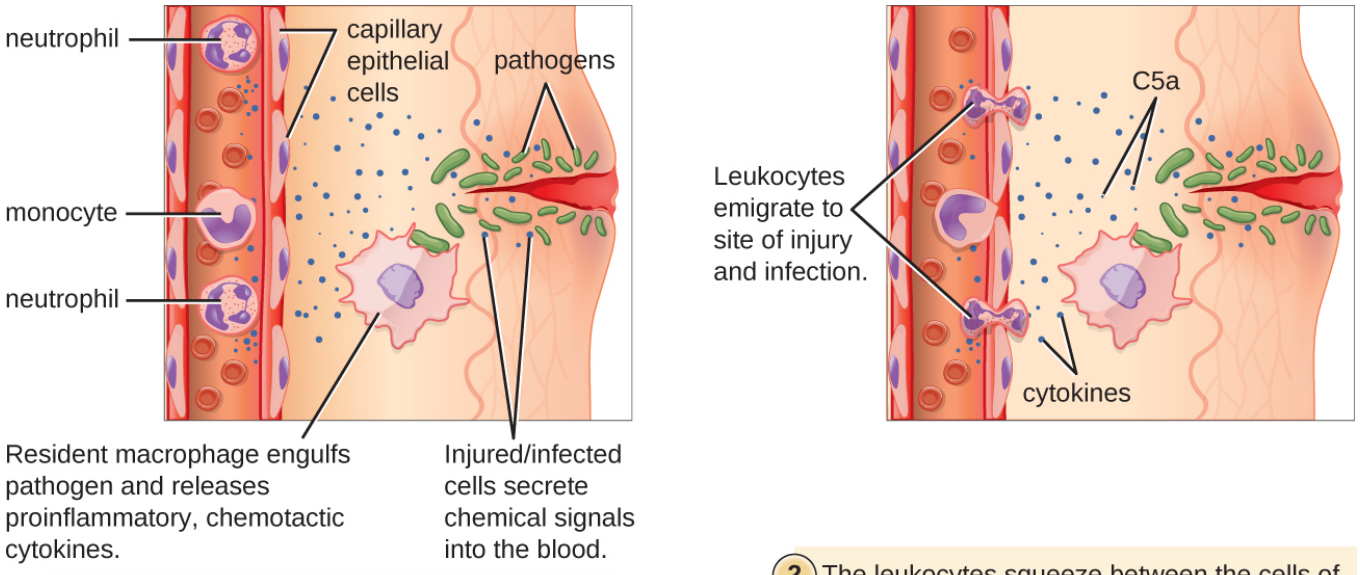


Figure **7.4.1**: Damaged cells and macrophages that have ingested pathogens release cytokines that are proinflammatory and chemotactic for leukocytes. In addition, activation of complement at the site of infection results in production of the chemotactic and proinflammatory C5a. Leukocytes exit the blood vessel and follow the chemoattractant signal of cytokines and C5a to the site of infection. Granulocytes such as neutrophils release chemicals that destroy pathogens. They are also capable of phagocytosis and intracellular killing of bacterial pathogens.

Link to Learning

Watch the following videos on leukocyte extravasation and leukocyte rolling to learn more.

? Exercise 7.4.1

Explain the role of adhesion molecules in the process of extravasation.

Pathogen Recognition

As described in the previous section, opsonization of pathogens by antibody; complement factors C1q, C3b, and C4b; and lectins can assist phagocytic cells in recognition of pathogens and attachment to initiate phagocytosis. However, not all pathogen recognition is opsonin dependent. Phagocytes can also recognize molecular structures that are common to many groups of pathogenic microbes. Such structures are called pathogen-associated molecular patterns (PAMPs). Common PAMPs include the following:

- peptidoglycan, found in bacterial cell walls;
- flagellin, a protein found in bacterial flagella;
- lipopolysaccharide (LPS) from the outer membrane of gram-negative bacteria;
- lipopeptides, molecules expressed by most bacteria; and
- nucleic acids such as viral DNA or RNA.

Like numerous other PAMPs, these substances are integral to the structure of broad classes of microbes.

The structures that allow phagocytic cells to detect PAMPs are called pattern recognition receptors (PRRs). One group of PRRs is the toll-like receptors (TLRs), which bind to various PAMPs and communicate with the nucleus of the phagocyte to elicit a response. Many TLRs (and other PRRs) are located on the surface of a phagocyte, but some can also be found embedded in the membranes of interior compartments and organelles (Figure **7.4.2**). These interior PRRs can be useful for the binding and recognition of intracellular pathogens that may have gained access to the inside of the cell before phagocytosis could take place. Viral nucleic acids, for example, might encounter an interior PRR, triggering production of the antiviral cytokine interferon.

In addition to providing the first step of pathogen recognition, the interaction between PAMPs and PRRs on macrophages provides an intracellular signal that activates the phagocyte, causing it to transition from a dormant state of readiness and slow proliferation to a state of hyperactivity, proliferation, production/secretion of cytokines, and enhanced intracellular killing. PRRs on macrophages also respond to chemical distress signals from damaged or stressed cells. This allows macrophages to extend their responses beyond protection from infectious diseases to a broader role in the inflammatory response initiated from injuries or other diseases.

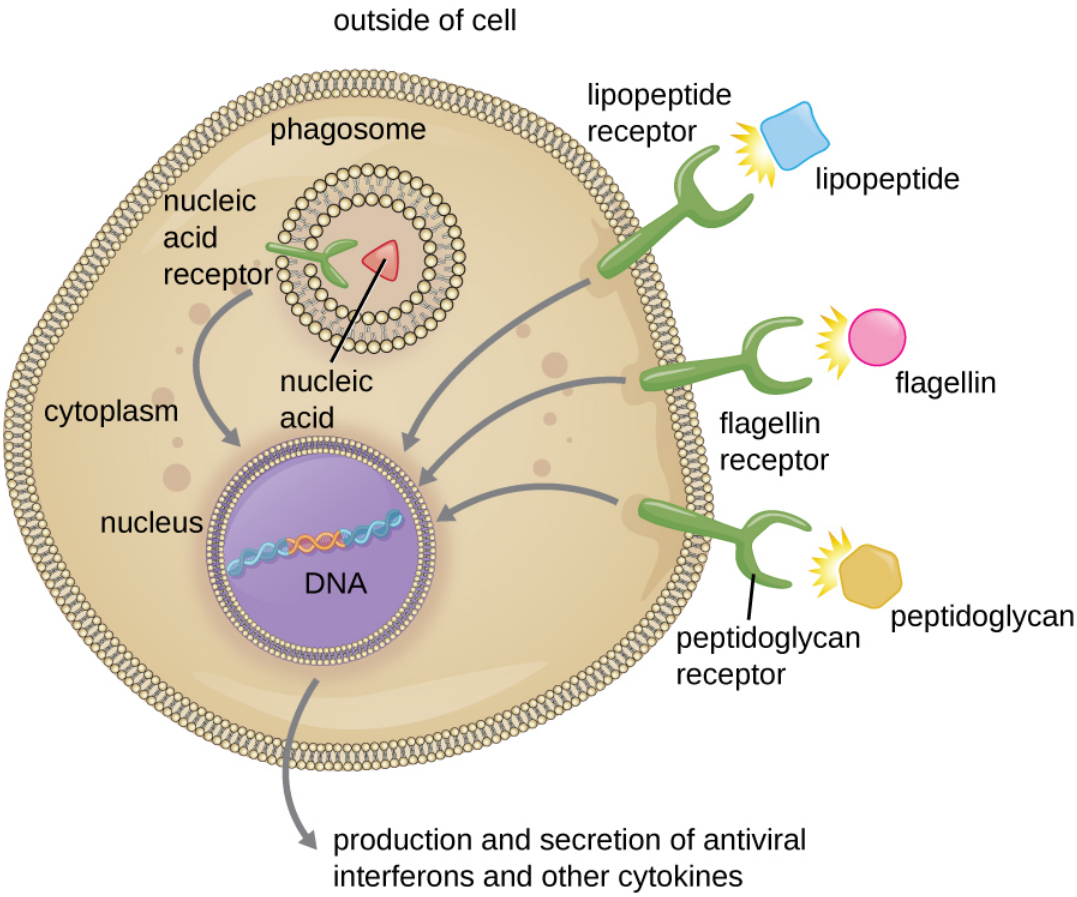


Figure **7.4.2**: Phagocytic cells contain pattern recognition receptors (PRRs) capable of recognizing various pathogen-associated molecular patterns (PAMPs). These PRRs can be found on the plasma membrane or in internal phagosomes. When a PRR recognizes a PAMP, it sends a signal to the nucleus that activates genes involved in phagocytosis, cellular proliferation, production and secretion of antiviral interferons and proinflammatory cytokines, and enhanced intracellular killing.

? Exercise 7.4.2

1. Name four pathogen-associated molecular patterns (PAMPs).
2. Describe the process of phagocyte activation.

Pathogen Degradation

Once pathogen recognition and attachment occurs, the pathogen is engulfed in a vesicle and brought into the internal compartment of the phagocyte in a process called phagocytosis (Figure **7.4.3**). PRRs can aid in phagocytosis by first binding to the pathogen's surface, but phagocytes are also capable of engulfing nearby items even if they are not bound to specific receptors. To engulf the pathogen, the phagocyte forms a pseudopod that wraps around the pathogen and then pinches it off into a membrane vesicle called a phagosome. Acidification of the phagosome (pH decreases to the range of 4–5) provides an important early antibacterial mechanism. The phagosome containing the pathogen fuses with one or more lysosomes, forming a phagolysosome. Formation of the phagolysosome enhances the acidification, which is essential for activation of pH-dependent digestive lysosomal enzymes and production of hydrogen peroxide and toxic reactive oxygen species. Lysosomal enzymes such as lysozyme, phospholipase, and proteases digest the pathogen. Other enzymes are involved a respiratory burst. During the respiratory burst, phagocytes will increase their uptake and consumption of oxygen, but not for energy production. The increased oxygen consumption is focused on the production of superoxide anion, hydrogen peroxide, hydroxyl radicals, and other reactive oxygen species that are antibacterial.

In addition to the reactive oxygen species produced by the respiratory burst, reactive nitrogen compounds with cytotoxic (cell-killing) potential can also form. For example, nitric oxide can react with superoxide to form peroxynitrite, a highly reactive nitrogen compound with degrading capabilities similar to those of the reactive oxygen species. Some phagocytes even contain an

internal storehouse of microbicidal defensin proteins (e.g., neutrophil granules). These destructive forces can be released into the area around the cell to degrade microbes externally. Neutrophils, especially, can be quite efficient at this secondary antimicrobial mechanism.

Once degradation is complete, leftover waste products are excreted from the cell in an exocytic vesicle. However, it is important to note that not all remains of the pathogen are excreted as waste. Macrophages and dendritic cells are also antigen-presenting cells involved in the specific adaptive immune response. These cells further process the remains of the degraded pathogen and present key antigens (specific pathogen proteins) on their cellular surface. This is an important step for stimulation of some adaptive immune responses, as will be discussed in more detail in the next chapter.

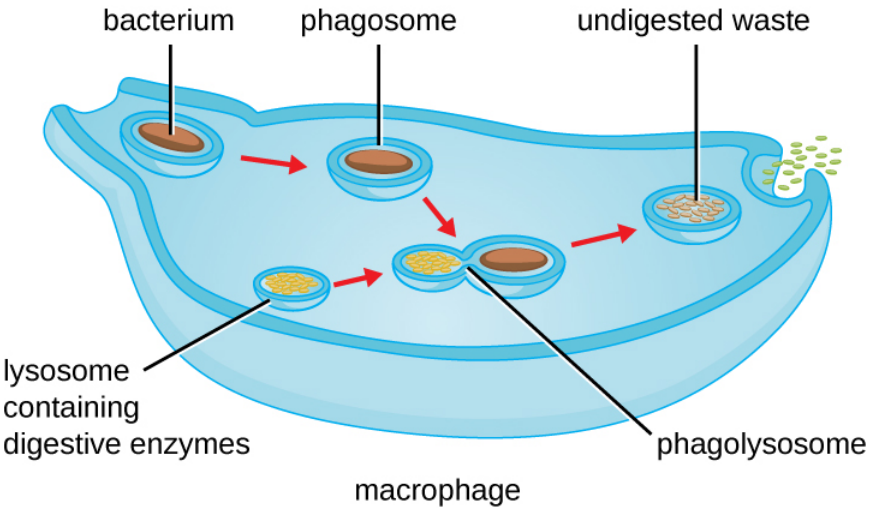


Figure **7.4.3**: The stages of phagocytosis include the engulfment of a pathogen, the formation of a phagosome, the digestion of the pathogenic particle in the phagolysosome, and the expulsion of undigested materials from the cell.

Link to Learning

Visit this link to view a phagocyte chasing and engulfing a pathogen.

Exercise 7.4.3

What is the difference between a phagosome and a lysosome?

When Phagocytosis Fails

Although phagocytosis successfully destroys many pathogens, some are able to survive and even exploit this defense mechanism to multiply in the body and cause widespread infection. Protozoans of the genus *Leishmania* are one example. These obligate intracellular parasites are flagellates transmitted to humans by the bite of a sand fly. Infections cause serious and sometimes disfiguring sores and ulcers in the skin and other tissues (Figure **7.4.4**). Worldwide, an estimated 1.3 million people are newly infected with leishmaniasis annually.

Salivary peptides from the sand fly activate host macrophages at the site of their bite. The classic or alternate pathway for complement activation ensues with C3b opsonization of the parasite. *Leishmania* cells are phagocytosed, lose their flagella, and multiply in a form known as an amastigote (Leishman-Donovan body) within the phagolysosome. Although many other pathogens are destroyed in the phagolysosome, survival of the *Leishmania* amastigotes is maintained by the presence of surface lipophosphoglycan and acid phosphatase. These substances inhibit the macrophage respiratory burst and lysosomal enzymes. The parasite then multiplies inside the cell and lyses the infected macrophage, releasing the amastigotes to infect other macrophages within the same host. Should another sand fly bite an infected person, it might ingest amastigotes and then transmit them to another individual through another bite.

There are several different forms of leishmaniasis. The most common is a localized cutaneous form of the illness caused by *L. tropica*, which typically resolves spontaneously over time but with some significant lymphocyte infiltration and permanent scarring. A mucocutaneous form of the disease, caused by *L. viannia brasilienfsis*, produces lesions in the tissue of the nose and mouth and can be life threatening. A visceral form of the illness can be caused by several of the different *Leishmania* species. It affects various organ systems and causes abnormal enlargement of the liver and spleen. Irregular fevers, anemia, liver dysfunction, and weight loss are all signs and symptoms of visceral leishmaniasis. If left untreated, it is typically fatal.

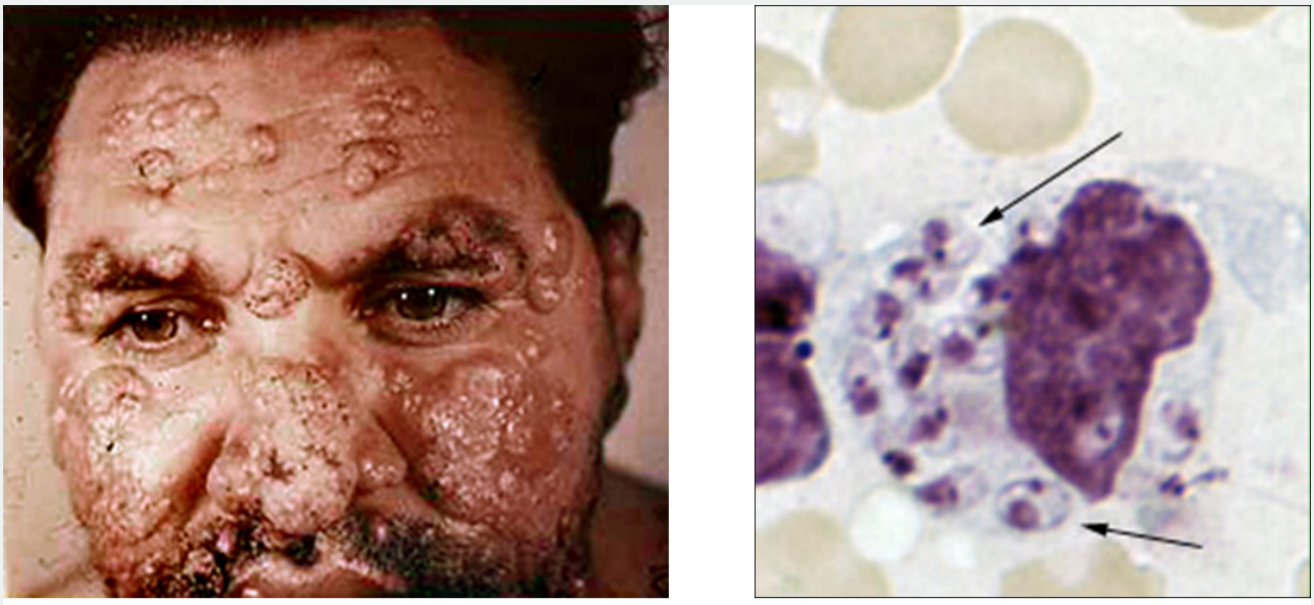


Figure **7.4.4**: (a) Cutaneous leishmaniasis is a disfiguring disease caused by the intracellular flagellate *Leishmania tropica*, transmitted by the bite of a sand fly. (b) This light micrograph of a sample taken from a skin lesion shows a large cell, which is a macrophage infected with *L. tropica* amastigotes (arrows). The amastigotes have lost their flagella but their nuclei are visible. Soon the amastigotes will lyse the macrophage and be engulfed by other phagocytes, spreading the infection. (credit a: modification of work by Otis Historical Archives of "National Museum of Health & Medicine"; credit b: modification of work by Centers for Disease Control and Prevention)

Key Concepts and Summary

- Phagocytes are cells that recognize pathogens and destroy them through phagocytosis.
- Recognition often takes place by the use of phagocyte receptors that bind molecules commonly found on pathogens, known as **pathogen-associated molecular patterns (PAMPs)**.
- The receptors that bind PAMPs are called **pattern recognition receptors**, or **PRRs**. **Toll-like receptors** (**TLRs**) are one type of PRR found on phagocytes.
- **Extravasation** of white blood cells from the bloodstream into infected tissue occurs through the process of **transendothelial migration**.
- Phagocytes degrade pathogens through **phagocytosis**, which involves engulfing the pathogen, killing and digesting it within a **phagolysosome**, and then excreting undigested matter.

Footnotes

1. 1 World Health Organization. "Leishmaniasis." 2016. http://www.who.int/mediacentre/factsheets/fs375/en/.

This page titled 7.4: Pathogen Recognition and Phagocytosis is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **17.4: Pathogen Recognition and Phagocytosis** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

8: Basic Immunology Review

Immediate innate immunity begins 0-4 hours after exposure to an infectious agent and involves the action of soluble preformed antimicrobial molecules that circulate in the blood, our found in extracellular tissue fluids, and are secreted by epithelial cells. These include: antimicrobial enzymes and peptides, and complement system proteins. These preformed antimicrobial molecules are designed to immediately begin to remove infectious agents as soon as they enter the body. In addition to preformed antimicrobial molecules, the following also play a role in immediate innate immunity: anatomical barriers to infection, mechanical removal of microbes, and bacterial antagonism by the body's normal microbiota

This page titled 8: Basic Immunology Review is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **11.3: Immediate Innate Immunity** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

8.1: Overview of the Immune System

Learning Objectives

- Distinguish between innate and adaptive immunity

The immune system is a system of biological structures and processes within an organism that protects against disease. To function properly, an immune system must detect a wide variety of agents, from viruses to parasitic worms, and distinguish them from the organism's own healthy tissue.

Pathogens can rapidly evolve and adapt to avoid detection and neutralization by the immune system. As a result, multiple defense mechanisms have also evolved to recognize and neutralize pathogens. Even simple unicellular organisms, such as bacteria, possess a rudimentary immune system in the form of enzymes that protect against bacteriophage infections. Other basic immune mechanisms including include phagocytosis, antimicrobial peptides called defensins, and the complement system, which evolved in ancient eukaryotes and remain in modern descendants, such as plants and insects. Jawed vertebrates have even more sophisticated defense mechanisms, including the ability to adapt over time to recognize specific pathogens more efficiently. Adaptive (acquired) immunity creates immunological memory after an initial response to a specific pathogen, leading to an enhanced response to subsequent encounters with that same pathogen. This process of acquired immunity is the basis of vaccination.

Innate and Adaptive Immunity

The immune system protects organisms from infection with layered defenses of increasing specificity. Physical barriers prevent pathogens, such as bacteria and viruses, from entering the organism. If a pathogen breaches these barriers, the innate immune system provides an immediate, but non-specific response. Innate immune systems are found in all plants and animals. If pathogens successfully evade the innate response, vertebrates possess a second layer of protection, the adaptive immune system, which is activated by the innate response. The immune system adapts its response during an infection in order to improve its recognition of the pathogen. This improved response is then retained after the pathogen has been eliminated, in the form of an immunological memory, and allows the adaptive immune system to mount faster and stronger attacks when this pathogen is encountered. Both innate and adaptive immunity depend on the ability of the immune system to distinguish between self and non- self molecules, where self molecules are those components of an organism's body that can be distinguished from foreign substances by the immune system.

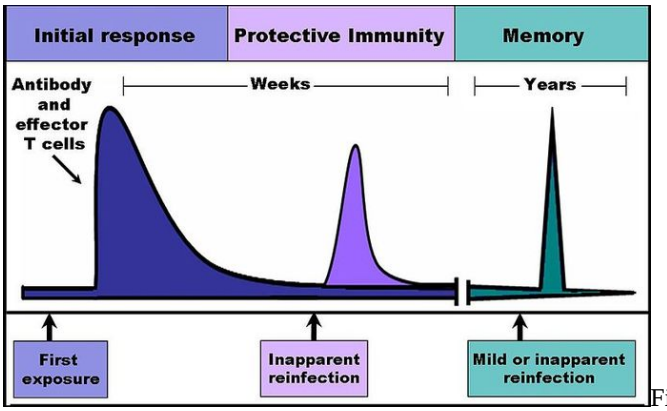


Figure: **The Time Course of an Immune Response**: Immune reactants, such as antibodies and effector T-cells, work to eliminate an infection, and their levels and activity rapidly increase following an encounter with an infectious agent, whether that agent is a pathogen or a vaccine. For several weeks these reactants remain in the serum and lymphatic tissues and provide protective immunity against reinfection by the same agent. During an early reinfection, few outward symptoms of illness are present, but the levels of immune reactants increase and are detectable in the blood and/or lymph. Following clearance of the infection, antibody level and effector T cell activity gradually declines. Because immunological memory has developed, reinfection at later times leads to a rapid increase in antibody production and effector T cell activity. These later infections can be mild or even inapparent.

Immunity is a biological term that describes a state of having sufficient biological defences to avoid infection, disease, or other unwanted biological invasion. Immunity involves both specific and non-specific components.

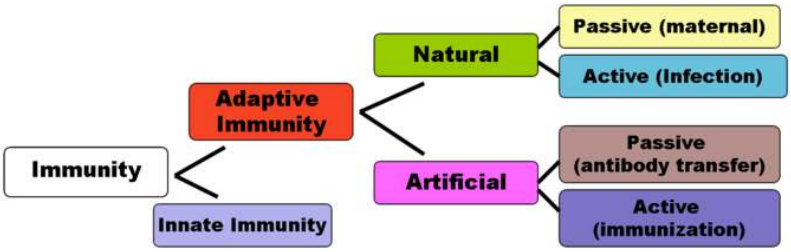


Figure: **Immunity**: Natural immunity occurs through contact with a disease causing agent, when the contact was not deliberate, where as artificial immunity develops only through deliberate actions of exposure. Both natural and artificial immunity can be further subdivided, depending on the amount of time the protection lasts. Passive immunity is short lived, and usually lasts only a few months, whereas protection via active immunity lasts much longer, and is sometimes life-long.

INNATE IMMUNITY

Innate, or nonspecific, immunity is the natural resistance with which a person is born. It provides resistance through several physical, chemical, and cellular approaches. Microbes first encounter the epithelial layers (physical barriers that line our skin and mucous membranes). Subsequent general defenses include secreted chemical signals (cytokines), antimicrobial substances, fever, and phagocytic activity associated with the inflammatory response. The phagocytes express cell surface receptors that can bind and respond to common molecular patterns expressed on the surface of invading microbes. Through these approaches, innate immunity can prevent the colonization, entry, and spread of microbes.

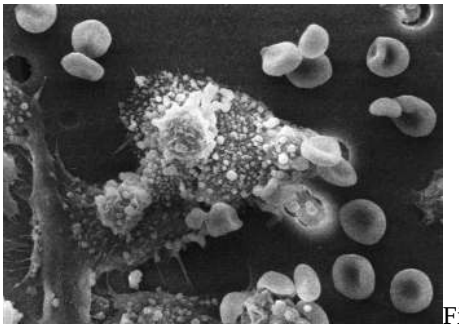


Figure: **An animal's immune response to a foreign body**: Macrophages begin to fuse with, and inject its toxins into, the cancer cell. The cell starts rounding up and loses its spikes. As the macrophage cell becomes smooth. The cancer cell appears lumpy in the last stage before it dies. These lumps are actually the macrophages fused within the cancer cell. The cancer cell then loses its morphology, shrinks up and dies. Photo magnification: 3: x8,000 Type: B & W print

ADAPTIVE IMMUNITY

Adaptive immunity is often sub-divided into two major types depending on how the immunity was introduced. Naturally acquired immunity occurs through contact with a disease causing agent, when the contact was not deliberate, whereas artificially acquired immunity develops only through deliberate actions such as vaccination. Both naturally and artificially acquired immunity can be further subdivided depending on whether immunity is induced in the host or passively transferred from an immune host. Passive immunity is acquired through transfer of antibodies or activated T cells from an immune host, and is short lived—usually lasting only a few months. Active immunity is induced in the host itself by antigen, and lasts much longer, sometimes the entire lifetime.

A further subdivision of adaptive immunity is characterized by the cells involved; humoral immunity is the aspect of immunity that is mediated by secreted antibodies, whereas the protection provided by cell-mediated immunity involves T lymphocytes alone. Humoral immunity is active when the organism generates its own antibodies, and passive when antibodies are transferred between individuals. Similarly, cell-mediated immunity is active when the organism's own T cells are stimulated and passive when T cells come from another organism.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: ***CC BY-SA: Attribution-ShareAlike***

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- Lymph node. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Lymph_node**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Liver. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Liver%23Physiology**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Adenoid. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Adenoid**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Skin. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Skin%23Functions**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- White blood cell. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/White_blood_cell**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Tonsil. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Tonsil**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Immune system. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Immune_...lular_barriers**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Lymphatic system. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Lymphatic_system**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Immunology. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Immunology**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Spleen. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Spleen**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Bone marrow. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Bone_marrow**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Thymus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Thymus%23Function**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Leukocytes. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Leukocytes**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- lymphocytes. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/lymphocytes**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Neutrophil with anthrax copy. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ne...thrax_copy.jpg**. **License**: ***CC BY: Attribution***
- Illu lymphatic system. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...tic_system.jpg**. **License**: ***Public Domain: No Known Copyright***
- **Provided by**: Wikimedia. **Located at**: **upload.wikimedia.org/wikipedi...lood_cells.jpg**. **License**: ***Public Domain: No Known Copyright***
- Gut flora. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Gut_flora**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- List of human diseases associated with infectious pathogens. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/List_of...ious_pathogens**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Immune system. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Immune_...n_by_pathogens**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Human Microbiome Project. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Human_Microbiome_Project**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Human pathogen. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Human_pathogen**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Skin flora. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Skin_flora**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Primary pathogen. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Primary%20pathogen**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Opportunistic pathogen. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Opportunistic%20pathogen**. **License**: ***CC BY-SA: Attribution-ShareAlike***

- Human microbiome. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Human%20microbiome**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Neutrophil with anthrax copy. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Neutrophil_with_anthrax_copy.jpg**. **License**: *CC BY: Attribution*
- Illu lymphatic system. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...tic_system.jpg**. **License**: ***Public Domain: No Known Copyright***
- **Provided by**: Wikimedia. **Located at**: **upload.wikimedia.org/wikipedi...lood_cells.jpg**. **License**: ***Public Domain: No Known Copyright***
- Skin Microbiome20169-300. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Sk...e20169-300.jpg**. **License**: ***Public Domain: No Known Copyright***
- Malaria. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Malaria.jpg**. **License**: *CC BY: Attribution*
- Adaptive (acquired) immunity. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Adaptiv...ed)%20immunity**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Immunity (medical). **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Immunity_(medical)**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Immunology. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Immunology**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Immune system. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Immune_system**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Innate immunity. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Innate%20immunity**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Self molecules. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Self%20molecules**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Neutrophil with anthrax copy. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Neutrophil_with_anthrax_copy.jpg**. **License**: *CC BY: Attribution*
- Illu lymphatic system. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Illu_lymphatic_system.jpg**. **License**: ***Public Domain: No Known Copyright***
- **Provided by**: Wikimedia. **Located at**: **upload.wikimedia.org/Wikipedia/commons/thumb/8/82/SEM_blood_cells.jpg/482px-SEM_blood_cells.jpg**. **License**: ***Public Domain: No Known Copyright***
- Skin Microbiome20169-300. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Skin_Microbiome20169-300.jpg**. **License**: ***Public Domain: No Known Copyright***
- Malaria. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Malaria.jpg**. **License**: *CC BY: Attribution*
- Immunity. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Immunity.png**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Macs killing cancer cell. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...ancer_cell.jpg**. **License**: ***Public Domain: No Known Copyright***
- Immune response. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Immune_response.jpg**. **License**: ***Public Domain: No Known Copyright***

Key Points

- Pathogens can rapidly evolve and adapt to avoid detection and neutralization by the immune system. As a result, multiple defense mechanisms have also evolved to recognize and neutralize pathogens. The immune system protects from infection with layered defenses of increasing specificity.
- Physical barriers prevent pathogens from entering the organism. If these barriers are breached, the innate immune system provides an immediate, non-specific response. If pathogens successfully evade the innate response, vertebrates possess a second layer of protection, the adaptive immune system.
- Immunity is a biological term that describes a state of having sufficient biological defences to avoid infection, disease, or other unwanted biological invasion.

- Innate, or nonspecific, immunity is the natural resistance with which a person is born. It provides resistance through several physical, chemical, and cellular approaches.
- Adaptive immunity is often sub-divided into two major types acording to how the immunity was introduced. Naturally acquired immunity occurs through non-deliberate contact with a disease causing agent, whereas artificially acquired immunity develops through deliberate actions such as vaccination.
- Immunology is a branch of biomedical science that covers the study of all aspects of the immune system in all organisms. It deals with the physiological functioning of the immune system in states of both health and disease.

Key Terms

- **Adaptive (acquired) immunity**: The creation of immunological memory after an initial response to a specific pathogen, leading to an enhanced response to subsequent encounters with that same pathogen. This process of acquired immunity is the basis of vaccination.
- **Innate immunity**: The natural resistance with which a person is born. It provides resistance through several physical, chemical, and cellular approaches.
- **Self molecules**: Those components of an organism's body that can be distinguished by the immune system from foreign substances.

This page titled 8.1: Overview of the Immune System is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **11.1C: Overview of the Immune System** is licensed CC BY-SA 4.0.

8.2: Anatomical Barriers to Infection, Mechanical Removal of Microbes, and Bacterial Antagonism by Normal Body Microbiota

Describe what is meant by anatomical barriers to infection.
- List 4 ways in which the body can physically remove microorganisms or their products.
- Briefly describe how intraepithelial T-lymphocytes and B-1 cells play a role in innate immunity.
- Describe how bacterial antagonism by normal microbiota acts as a non-specific body defense mechanism and name 2 opportunistic microbes that may cause superinfection upon destruction of the normal microbiota.
- Briefly describe the process involved in the development of antibiotic-associated colitis.

Anatomical barriers are tough, intact barriers that prevent the entry and colonization of many microbes. Examples include the skin, the mucous membranes, and bony encasements.

The skin

The skin, consisting of the epidermis and the dermis, is dry, acidic, and has a temperature lower than 37 degrees Celsius (body temperature). These conditions are not favorable to bacterial growth. Resident normal microbiota of the skin also inhibits potentially harmful microbes. In addition, the dead, keratinized cells that make up the surface of the skin are continuously being sloughed off so that microbes that do colonize these cells are constantly being removed. Hair follicles and sweat glands produce lysozyme and toxic lipids that can kill bacteria. Epithelial cells also produce defensins and cathelicidins to kill microbes. Beneath the epidermis of the skin are Langerhans' cells - immature dendritic cells - that phagocytose and kill microbes, carry them to nearby lymph nodes, and present antigens of these microbes to T-lymphocytes to begin adaptive immune responses against them. Finally, intraepithelial T-lymphocytes and B-1 lymphocytes are associated with the epidermis and the mucosal epithelium. These cells recognize microbes common to the epidermis and mucous membranes and start immediate adaptive immune responses against these commonly encountered microbes.

The mucous membranes

Mucous membranes line body cavities that open to the exterior, such as the respiratory tract, the gastrointestinal tract, and the genitourinary tract. Mucous membranes are composed of an epithelial layer that secretes mucus, and a connective tissue layer. The mucus is a physical barrier that traps microbes. Mucus also contains lysozyme to degrade bacterial peptidoglycan, an antibody called secretory IgA that prevents microbes from attaching to mucosal cells and traps them in the mucous, lactoferrin to bind iron and keep it from from being used by microbes, and lactoperoxidase to generate toxic superoxide radicals that kill microbes. Resident normal microbiota of the mucosa also inhibits potentially harmful microbes. In addition, the mucous membrane, like the skin, is constantly sloughing cells to remove microbes that have attached to the mucous membranes. Beneath the mucosal membrane is mucosa-associated lymphoid tissue (MALT) that contains Langerhans' cells - immature dendritic cells - that phagocytose and kill microbes, carry them to nearby lymph nodes, and present antigens of these microbes to T-lymphocytes to begin adaptive immune responses against them. Intraepithelial T-lymphocytes and B-1 lymphocytes are associated with the epidermis and the mucosal epithelium. These cells recognize microbes common to the epidermis and mucous membranes and start immediate adaptive immune responses against these commonly encountered microbes.

Bony encasements

Bony encasements, such as the skull and the thoracic cage, protect vital organs from injury and entry of microbes.

Mechanical removal is the process of physically flushing microbes from the body. Methods include:

1. **Mucus and cilia:** Mucus traps microorganisms and prevents them from reaching and colonizing the mucosal epithelium. Mucus also contains lysozyme to degrade bacterial peptidoglycan, an antibody called secretory IgA that prevents microbes from attaching to mucosal cells and traps them in the mucus, lactoferrin to bind iron and keep it from from being used by microbes, and lactoperoxidase to generate toxic superoxide radicals that kill microbes. Cilia on the surface of the epithelial cells propel mucus and trapped microbes upwards towards the throat where it is swallowed and the microbes are killed in the stomach. This is sometimes called the tracheal toilet.
2. **The cough and sneeze reflex:** Coughing and sneezing removes mucus and trapped microbes.
3. **Vomiting and diarrhea:** These processes remove pathogens and toxins in the gastrointestinal tract.

4. **he physical flushing action of body fluids:** Fluids such as urine, tears, saliva, perspiration, and blood from injured blood vessels also flush microbes from the body.

Bacterial Antagonism by Normal Microbiota

Approximately 100 trillion bacteria and other microorganisms reside in or on the human body. The normal body microbiota keeps potentially harmful opportunistic pathogens in check and also inhibits the colonization of pathogens by:

1. Producing metabolic products (fatty acids, bacteriocins, etc.) that inhibit the growth of many pathogens;
2. Adhering to target host cells so as to cover them and preventing pathogens from colonizing;
3. Depleting nutrients essential for the growth of pathogens; and
4. Non-specifically stimulating the immune system.

Destruction of normal bacterial microbiota by the use of broad spectrum antibiotics may result in superinfections or overgrowth by antibiotic-resistant opportunistic microbiota. For example, the yeast *Candida*, that causes infections such as vaginitis and thrush, and the bacterium *Clostridium difficile*, that causes potentially severe antibiotic-associated colitis, are opportunistic microorganisms normally held in check by the normal microbiota.

In the case of *Candida* infections, the *Candida* resists the antibacterial antibiotics because being a yeast, it is eukaryotic, not prokaryotic like the bacteria. Once the bacteria are eliminated by the antibiotics, the *Candida* has no competition and can overgrow the area.

Clostridium difficile is an opportunistic Gram-positive, endospore-producing bacillus transmitted by the fecal-oral route that causes severe antibiotic-associated colitis. *C. difficile* is a common healthcare-associated infection (HAIs) and is the most frequent cause of health-care-associated diarrhea. *C. difficile* infection often recurs and can progress to sepsis and death. CDC has estimated that there are about 500,000 *C. difficile* infections (CDI) in health-care associated patients each year and is linked to 15,000 American deaths each year.

Antibiotic-associated colitis is especially common in older adults. It is thought that *C. difficile* survives the exposure to the antibiotic by sporulation. After the antibiotic is no longer in the body, the endospores germinate and *C. difficile* overgrows the intestinal tract and secretes toxin A and toxin B that have a cytotoxic effect on the epithelial cells of the colon. *C. difficile* has become increasingly resistant to antibiotics in recent years making treatment often difficult. There has been a great deal of success in treating the infection with fecal transplants, still primarily an experimental procedure. Polymerase chain reaction (PCRs) assays, which test for the bacterial gene encoding toxin B, are highly sensitive and specific for the presence of a toxin-producing *Clostridium difficile* organism. The most successful technique in restricting *C. difficile* infections has been the restriction of the use of antimicrobial agents.

A patient is given large doses of broad spectrum antibiotics and subsequently develops a *Candida albicans* infection of the vagina. Discuss why this might happen in terms of immediate innate immunity. Why didn't the antibiotic kill the *Candida albicans* too?

- Often during intestinal infections drugs are given to suppress diarrhea. Discuss why this may not always be a good idea, especially with microbial infections that cause ulceration of the intestines.

Summary

Anatomical barriers such as the skin, the mucous membranes, and bony encasements are tough, intact barriers that prevent the entry and colonization of many microbes. Mechanical removal is the process of physically flushing microbes from the body. Examples include mucus and cilia, coughing and sneezing, vomiting and diarrhea, and the flushing action of bodily fluids. The normal microbiota keeps potentially harmful opportunistic pathogens in check and also inhibits the colonization of pathogens by producing metabolic products that inhibit the growth of many pathogens, adhering to target host cells so as to cover them and prevent pathogens from colonizing, depleting nutrients essential for the growth of pathogens, and non-specifically stimulating the immune system.

Destruction of normal bacterial microbiota by the use of broad spectrum antibiotics may result in superinfections or overgrowth by antibiotic-resistant opportunistic microbiota such as *Candida* and *Clostridium difficile*.

This page titled 8.2: Anatomical Barriers to Infection, Mechanical Removal of Microbes, and Bacterial Antagonism by Normal Body Microbiota is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the

style and standards of the LibreTexts platform.

- **11.3C: Anatomical Barriers to Infection, Mechanical Removal of Microbes, and Bacterial Antagonism by Normal Body Microbiota** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

8.3: Cells and Organs of the Immune System

Learning Objectives

- Recognize the cells and organs of the immune system and their functions

Immune System Organs

The key primary lymphoid organs of the immune system include the thymus and bone marrow, as well as secondary lymphatic tissues including spleen, tonsils, lymph vessels, lymph nodes, adenoids, skin, and liver.

The thymus “educates” T cells and provides an inductive environment for the development of T cells from hematopoietic progenitor cells. The thymus is largest and most active during the neonatal and pre-adolescent periods of development. By the early teens, the thymus begins to atrophy and thymic stroma is replaced by adipose tissue. Nevertheless, residual T-lymphopoiesis continues throughout adult life.

Bone marrow is the flexible tissue found in the interior of bones. In humans, red blood cells are produced in the heads of long bones. The red bone marrow is a key element of the lymphatic system, being one of the primary lymphoid organs that generate lymphocytes from immature hematopoietic progenitor cells. Bone marrow and thymus constitute the primary lymphoid tissues involved in the production and early selection of lymphocytes.

The lymphatic system is a part of the circulatory system, comprising a network of conduits called lymphatic vessels that carry a clear fluid, called lymph, unidirectionally towards the heart. The lymphatic system has multiple interrelated functions including the transportation of white blood cells to and from the lymph nodes into the bones, and the transportation of antigen -presenting cells (such as dendritic cells) to the lymph nodes where an immune response is stimulated. Lymphoid tissue is found in many organs, particularly the lymph nodes.

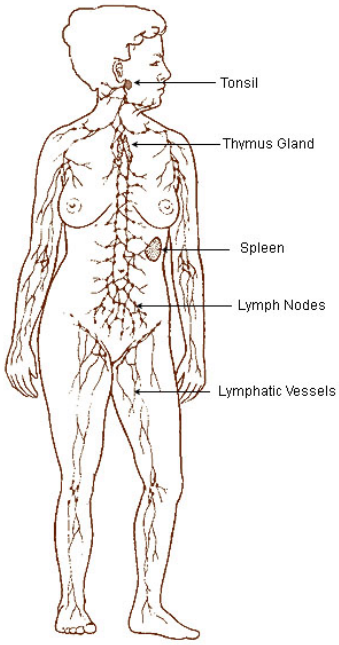


Figure: **The Lymph Nodes and Lymph Vessels in Human Beings**: The lymphatic system is a part of the circulatory system, comprising a network of conduits called lymphatic vessels that carry a clear fluid called lymph.

The spleen is similar in structure to a large lymph node and acts primarily as a blood filter. It synthesizes antibodies in its white pulp and removes antibody-coated bacteria along with antibody-coated blood cells by way of blood and lymph node circulation.

The palatine tonsils and the nasopharyngeal tonsil are lymphoepithelial tissues located near the oropharynx and nasopharynx. These immunocompetent tissues are the immune system’s first line of defense against ingested or inhaled foreign pathogens. The fundamental immunological roles of tonsils aren’t yet understood.

Lymph nodes are distributed widely throughout areas of the body, including the armpit and stomach, and linked by lymphatic vessels. Lymph nodes are garrisons of B, T and other immune cells. Lymph nodes act as filters or traps for foreign particles and are important in the proper functioning of the immune system. They are packed tightly with the white blood cells, called lymphocytes and macrophages.

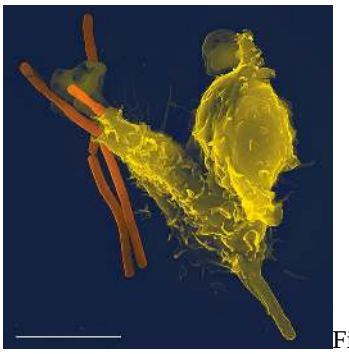
The skin is one of the most important parts of the body because it interfaces with the environment, and is the first line of defense from external factors, acting as an anatomical barrier from pathogens and damage between the internal and external environment in bodily defense. Langerhans cells in the skin are part of the adaptive immune system.

The liver has a wide range of functions, including immunological effects—the reticuloendothelial system of the liver contains many immunologically active cells, acting as a “sieve” for antigens carried to it via the portal system.

Immune System Cells

Leukocytes (white blood cells) are immune system cells involved in defending the body against infectious disease and foreign materials. Five different types of leukocytes exist, all produced and derived from a multipotent cell in the bone marrow known as a hematopoietic stem cell. The innate leukocytes include the phagocytes, mast cells, eosinophils, basophils, and natural killer cells. These cells identify and eliminate pathogens and are important mediators in the activation of the adaptive immune system.

Neutrophils and macrophages are phagocytes that travel throughout the body in pursuit of invading pathogens. Neutrophils are normally found in the bloodstream and are the most abundant type of phagocyte. During the acute phase of inflammation neutrophils migrate toward the site of inflammation and are usually the first cells to arrive at the scene of infection. Macrophages reside within tissues and produce a wide array of chemicals. They also act as scavengers, ridding the body of worn-out cells and other debris, and as antigen-presenting cells that activate the adaptive immune system. Dendritic cells are phagocytes in tissues that are in contact with the external environment, and are located mainly in the skin, nose, lungs, stomach, and intestines. These cells serve as a link between the bodily tissues and the innate and adaptive immune systems, as they present antigen to T-cells, one of the key cell types of the adaptive immune system.

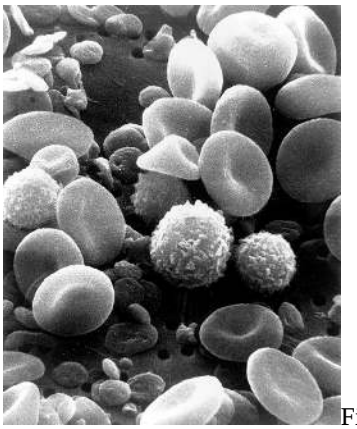

Figure: **A Phagocyte in Action**: Neutrophil engulfing anthrax bacteria. Taken with a Leo 1550 scanning electron microscope. Scale bar is 5 micrometers.

Mast cells reside in connective tissues and mucous membranes, and regulate the inflammatory response. They are most often associated with allergy and anaphylaxis.

Basophils and eosinophils are related to neutrophils. They secrete chemical mediators that are involved in defending against parasites, and play a role in allergic reactions, such as asthma.

Natural killer cells are leukocytes that attack and destroy tumor cells, or cells that have been infected by viruses.

The cells of the adaptive immune system are special types of leukocytes, called lymphocytes. B cells and T cells are the major types of lymphocytes and are derived from hematopoietic stem cells in the bone marrow.

 Figure: **Blood Cells**: Red blood cells, several white blood cells including lymphocytes, a monocyte, a neutrophil, and many small disc-shaped platelets.

T cells recognize a “non-self” target, such as a pathogen, only after antigens have been processed and presented in combination with a “self” receptor, called a major histocompatibility complex (MHC) molecule. There are two major subtypes of T cells: the killer T cell, which kills cells that are infected with viruses (and other pathogens) or are otherwise damaged or dysfunctional, and the helper T cell, which regulates both innate and adaptive immune responses and helps determine which immune responses the body makes to a particular pathogen. These cells have no cytotoxic activity and do not kill infected cells or clear pathogens directly. A third, minor subtype are the γ T cells that recognize intact antigens not bound to MHC receptors.

In contrast, the B cell antigen-specific receptor is an antibody molecule on the B cell surface, which recognizes whole pathogens without any need for antigen processing. Each lineage of B cell expresses a different antibody, so the complete set of B cell antigen receptors represent all the antibodies that the body can manufacture.

Key Points

- The key primary lymphoid organs of the immune system are the thymus and bone marrow, and secondary lymphatic tissues such as spleen, tonsils, lymph vessels, lymph nodes, adenoids, and skin and liver.
- Leukocytes (white blood cells) act like independent, single-celled organisms and are the second arm of the innate immune system.
- The innate leukocytes include the phagocytes (macrophages, neutrophils, and dendritic cells), mast cells, eosinophils, basophils, and natural killer cells. These cells identify and eliminate pathogens and are also important mediators in the activation of the adaptive immune system.
- The cells of the adaptive immune system are special types of leukocytes, called lymphocytes. B cells and T cells are the major types of lymphocytes and are derived from hematopoietic stem cells in the bone marrow.
- The lymphatic system is a part of the circulatory system, comprising a network of conduits called lymphatic vessels. The lymphatic system has multiple functions such as the transportation of white blood cells to and from the lymph nodes into the bones.

Key Terms

- **lymphocytes**: A lymphocyte is a type of white blood cell in the vertebrate immune system. The three major types of lymphocyte are T cells, B cells and natural killer (NK) cells. T cells (thymus cells) and B cells (bursa-derived cells) are the major cellular components of the adaptive immune response.
- **Leukocytes**: Cells of the immune system involved in defending the body against both infectious disease and foreign materials. Five different and diverse types of leukocytes exist.

This page titled 8.3: Cells and Organs of the Immune System is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **11.1A: Cells and Organs of the Immune System** is licensed CC BY-SA 4.0.

8.4: Antimicrobial Enzymes and Antimicrobial Peptides

State how long it takes for immediate innate immunity to become activated and what it involves.

- State the function of the following antimicrobial enzymes and peptides:

a. lysozyme
b. phospholipase A_2
c. defensins
d. cathelicidins
e. lactotransferrin and transferrin

Examples include:

a. Lysozyme , found in in tears, mucous, saliva, plasma , tissue fluid, etc., breaks down peptidoglycan in bacteria causing osmotic lysis. Specifically, it breaks the bond between the N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM), the two sugars that make up the backbone of peptidoglycan (see Figure 8.4.1).

b. Phospholipase A_2 is an enzyme that penetrates the bacterial cell wall and hydrolyzes the phospholipids in the bacterial cytoplasmic membrane.

c. Human defensins) are short cationic peptides 30-40 amino acids long that are directly toxic by disrupting the cytoplasmic membrane of a variety of microorganisms causing leakage of cellular needs (see Figure 8.4.2). They also activate cells for an inflammatory response. Defensins are produced by leukocytes, epithelial cells, and other cells. They are also found in blood plasma and mucus. Certain defensins also disrupt the envelopes of some viruses.

d. Cathelicidins are proteins produced by skin and mucosal epithelial cells. The two peptides produced upon cleavage of the cathelicidin are directly toxic to a variety of microorganisms. One pepitide also can bind to and neutralize LPS from Gram-negative cell walls to reduce inflammation.

e. Lactic and fatty acids, found in perspiration and sebaceous secretions , inhibit microbes on the skin.

f. Lactoferrin and transferrin , found in body secretions, plasma, and tissue fluid, trap iron for use by human cells while preventing its use by microorganisms.

g. Hydrochloric acid and enzymes found in gastric secretions destroy microbes that are swallowed.

Keep in mind that in Unit 3 under "Virulence Factors that Promote Bacterial Colonization of the Host" we learned several mechanisms that various bacteria use to resist the body's antibacterial peptides. By resisting these immediate innate immune defenses, some bacteria have a better chance of colonizing their host.

Concept Map for Antibacterial Enzymes and Peptides

Summary

1. Immediate innate immunity begins 0-4 hours after exposure to an infectious agent and involves the action of soluble preformed antimicrobial molecules that circulate in the blood and are found in extracellular tissue fluids.
2. Lysozyme, found in in tears, mucous, saliva, plasma, tissue fluid, etc., breaks down peptidoglycan in bacteria causing osmotic lysis.
3. Phospholipase A2 is an enzyme that penetrates the bacterial cell wall and hydrolyzes the phospholipids in the bacterial cytoplasmic membrane.
4. Human defensins are short cationic peptides 30-40 amino acids long that are directly toxic by disrupting the cytoplasmic membrane of a variety of microorganisms causing leakage of cellular needs.
5. Cathelicidins are proteins produced by skin and mucosal epithelial cells that are directly toxic to a variety of microorganisms.

6. Lactoferrin and transferrin, found in body secretions, plasma, and tissue fluid, trap iron for use by human cells while preventing its use by microorganisms.

This page titled 8.4: Antimicrobial Enzymes and Antimicrobial Peptides is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **11.3A: Antimicrobial Enzymes and Antimicrobial Peptides** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

8.5: The Complement System

Briefly describe how the classical complement pathway is activated.
- Briefly describe the beneficial effects of the following complement pathway products:

a. C5a
b. C3a
c. C3b
d. C4b
e. C3d
f. $C5b6789_n$ (MAC)

- Briefly describe how the lectin pathway is activated.
- Briefly describe how the alternative complement pathway is activated.

In this section we will look at how the body's complement system functions to remove infectious agents. The complement system refers to a series of more than 30 soluble, preformed proteins circulating in the blood and bathing the fluids surrounding tissues. The proteins circulate in an inactive form, but in response to the recognition of molecular components of microorganism, they become sequentially activated, working in a cascade where in the binding of one protein promotes the binding of the next protein in the cascade. There are 3 complement pathways that make up the complement system: the classical complement pathway, the lectin pathway, and the alternative complement pathway. The pathways differ in the manner in which they are initiated and ultimately produce a key enzyme called C3 convertase:

- The **classical complement pathway** is initiated by activation of C1. C1 is primarily activated by interacting with the Fc portion of the antibody molecules IgG or IgM after they have bound to their specific antigen. C1 is also able to directly bind to the surfaces of some pathogens as well as with the C-reactive protein (CRP) that is produced during the acute phase response of innate immunity.
- The **lectin pathway** is activated by the interaction of microbial carbohydrates (lectins) with mannose-binding lectin (MBL) or ficolins found in the plasma and tissue fluids.
- The **alternative complement pathway** is activated by C3b binding to microbial surfaces and to antibody molecules.

The end results and defense benefits of each pathway, however, are the same. All complement pathways carry out 6 beneficial innate defense functions. Proteins produced by the complement pathways:

1. Trigger inflammation,
2. Chemotactically attract phagocytes to the infection site,
3. Promote the attachment of antigens to phagocytes (enhanced attachment or opsonization),
4. Cause lysis of Gram-negative bacteria, human cells displaying foreign epitopes,and viral envelopes,
5. Play a role in the activation of naive B-lymphocytes during adaptive immunity, and
6. Remove harmful immune complexes from the body.

We will now look at each of these complement pathways and see how they function to protect the body.

The Classical Complement Pathway

The classical complement pathway is primarily activated when a complement protein complex called C1 interacts with the Fc portion of the antibody molecules IgG or IgM after they have bound to their specific antigen via their Fab portion. C1 is also able to directly bind to the surfaces of some pathogens as well as with the C-reactive protein (CRP) that is produced during the acute phase response of innate immunity. The C1 complex is composed of three complement proteins called C1q, C1r, and C1s.

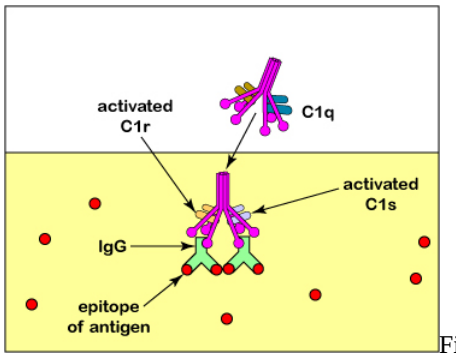


Figure 8.5.1: Activation of C1 during the Classical Complement Pathway. The Fab of 2 molecules of IgG or 1 molecule of IgM bind to epitopes on an antigen. C1, consisting of C1q, C1r, and C1s then binds to the Fc portion of the antibodies. The binding of C1q to the antibody molecules activates the C1r portion of C1 which, in turn, activates C1s. This activation gives C1s enzymatic activity to cleave complement protein C4 into C4a and C4b and complement protein C2 into C2a and C2b.

C1 is also able to directly bind to the surfaces of some pathogens as well as with the C-reactive protein (CRP) that is produced during the acute phase response of innate immunity.

Flash animation showing assembly of C1 during the classical complement pathway.

html5 version of animation for iPad showing assembly of C1 during the classical complement pathway.

2. The binding of C1q activates the C1r portion of C1 which, in turn, activates C1s. This activation gives C1s enzymatic activity to cleave complement protein C4 into C4a and C4b (see Figure 8.5.2A and Figure 8.5.2B).

3. C2 then binds to C4b and is cleaved by C1 into C2a and C2b (see Figure 8.5.3A and Figure 8.5.3B).

4. C4b and C2a combine to form C4b2a, the C3 convertase. C3 convertase can now cleave hundreds of molecules of C3 into C3a and C3b (see Figure 8.5.4).

5. Some molecules of C3b bind to C4b2a, the C3 convertase, to form C4b2a3b, a C5 convertase that cleaves C5 into C5a and C5b (see Figure 8.5.5).

Flash animation showing formation of C3 convertase and C5 convertase during the classical complement pathway.

html5 version of animation for iPad showing formation of C3 convertase and C5 convertase during the classical complement pathway.

6. C5b binds to the surface of the target cell and subsequently binds C6, C7, C8, and a number of monomers of C9 to form $C5b6789_n$, the Membrane Attack Complex (MAC) (see Figure 8.5.6 and Figure 8.5.7).

Flash animation showing the formation of the Membrane Attack Complex (MAC) and cytolysis during the complement pathways.

html5 version of animation for iPad showing the formation of the Membrane Attack Complex (MAC) and cytolysis during the complement pathways.

For More Information: Antigens and Immunogens from Unit 5

For More Information: Antibodies from Unit 6

As mentioned above, proteins of the complement pathways carry out 6 beneficial innate defense functions. These include:

1. Triggering inflammation: C5a is the most potent complement protein triggering inflammation. It reacts with blood vessels causing vasodilation. It also causes mast cells to release vasodilators such as histamine,increasing blood vessel permeability as well as increasing the expression of adhesion molecules on leukocytes and the vascular endothelium so that leukocytes can squeeze out of the blood vessels and enter the tissue (diapedesis). C5a also causes neutrophils to release toxic oxygen radicals for extracellular killing and induces fever. To a lesser extent C3a and C4a also promote inflammation. As we will see later in this unit, inflammation is a process in which blood vessels dilate and become more permeable, thus enabling body defense cells and defense chemicals to leave the blood and enter the tissues.

2. Chemotactically attracting phagocytes to the infection site: C5a also functions as a chemoattractant for phagocytes. Phagocytes will move towards increasing concentrations of C5a and subsequently attach, via their CR1 receptors to the C3b molecules attached to the antigen. This will be discussed in greater detail later in this unit under phagocytosis.

3. Promoting the attachment of antigens to phagocytes (enhanced attachment or opsonization): C3b and to a lesser extent, C4b can function as opsonins, that is, they can attach antigens to phagocytes. One portion of the C3b binds to proteins and polysaccharides on microbial surfaces; another portion attaches to CR1 receptors on phagocytes, B-lymphocytes, and dendritic cells for enhanced phagocytosis. (see Figure 8.5.8). In actuality, C3b molecule can bind to pretty much any protein or polysaccharide. Human cells, however, produce Factor H that binds to C3b and allows Factor I to inactivate the C3b. On the other hand, substances such as LPS on bacterial cells facilitate the binding of Factor B to C3b and this protects the C3b from inactivation by Factor I. In this way,

C3b does not interact with our own cells but is able to interact with microbial cells. C3a and C5a increase the expression of C3b receptors on phagocytes and increase their metabolic activity.

Flash animation showing the role of C5a in vasodilation, the chemotaxis of phagocytes towards C5a, and their attachment to the opsonin C3b as a result of the complement pathways.

html5 version of animation for iPad showing the role of C5a in vasodilation, the chemotaxis of phagocytes towards C5a, and their attachment to the opsonin C3b as a result of the complement pathways.

4. Causing lysis of Gram-negative bacteria, human cells displaying foreign epitopes,and viral envelopes: $C5b6789_n$, functions as a Membrane Attack Complex (MAC). This helps to destroy gram-negative bacteria as well as human cells displaying foreign antigens (virus-infected cells, tumor cells, etc.) by causing their lysis; see Figure 8.5.6 and Figure 8.5.7. It can also damage the envelope of enveloped viruses.

Flash animation showing the formation of the Membrane Attack Complex (MAC) and cytolysis during the complement pathways.

html5 version of animation for iPad showing the formation of the Membrane Attack Complex (MAC) and cytolysis during the complement pathways.

5. Serving as a second signal for activating naive B-lymphocytes during adaptive immunity: Some C3b is converted to C3d. C3d binds to CR2 receptors on B-lymphocytes. This serves as a second signal for the activation of B-lymphocytes whose B-cell receptors have just interacted with their corresponding antigen.

6. Removing harmful immune complexes from the body: C3b and to a lesser extent, C4b help to remove harmful immune complexes from the body. The C3b and C4b attach the immune complexes to CR1 receptors on erythrocytes. The erythrocytes then deliver the complexes to fixed macrophages within the spleen and liver for destruction. Immune complexes can lead to a harmful Type III hypersensitivity, as will be discussed later in Unit 5 under Hypersensitivities.

YouTube animation illustrating benefits of the complement pathways.

Concept Map for the Complement Pathways

Some bacterial capsules are rich in sialic acid, a common component of host cell glycoprotein, that has an affinity for serum protein H, a complement regulatory protein that leads to the degradation of C3b.
Describe what significance this has in the bacterium resisting phagocytosis and why.

2. *S. pyogenes* produces a protease that cleaves the complement protein C5a.

Describe what significance this has in the bacterium resisting phagocytosis and why.

The Lectin Pathway

The lectin pathway is activated by the interaction of microbial carbohydrates with mannose-binding lectin (MBL) or ficolins found in the plasma and tissue fluids. (Lectins are carbohydrate-binding proteins.) The lectin pathway is

mediated by two groups of proteins found in the plasma of the blood and in tissue fluids:

1. Mannose-binding lectin (MBL) - also known as mannose-binding protein or MBP. MBL is a soluble pattern-recognition receptor that binds to various microbial carbohydrates such as those rich in mannose or fucose, and to N-acetylglucosamine (NAG). These glycans are common in microbial glycoproteins and glycolipids but rare in those of humans. MBL is synthesized by the liver and released into the bloodstream as part of the acute phase response that will be discussed later in this unit. The MBL is equivalent to C1q in the classical complement pathway.

   Ficolins are similar in their structure to MBL and bind to microbial carbohydrates such as N-acetylglucosamine (NAG), lipoteichoic acids, and lipopolysaccharide (LPS). Ficolin is also equivalent to C1q in the classical complement pathway.

2. Both mannose-binding lectin (MBL) and ficolin form complexes with MBL-associated serine proteases called MASP1 and MASP2, which are equivalent to C1r and C1s of the classical pathway.

   a. The binding of the MBL (or the ficolin) to the microbial carbohydrate activates the associated MASP2 giving it the enzymatic activity to split C4 into C4a and C4b (see Figure 8.5.9A and Figure 8.5.9B).

   b. C2 then binds to C4b and is cleaved by MASP2 into C2a and C2b (see Figure 8.5.10A and Figure 8.5.10B).

   c. C4b and C2a combine to form C4b2a, the C3 convertase. C3 convertase can now cleave hundreds of molecules of C3 into C3a and C3b (see Figure 8.5.11).

   d. Some molecules of C3b bind to C4b2a, the C3 convertase, to form C4b2a3b, a C5 convertase that cleaves C5 into C5a and C5b (see Figure 8.5.12).

   e. C5b binds to the surface of the target cell and subsequently binds C6, C7, C8, and a number of monomers of C9 to form $C5b6789_n$, the Membrane Attack Complex (MAC) (see Figure 8.5.6 and Figure 8.5.7).

Flash animation showing activation of the lectin pathway

html5 version of animation for iPad showing activation of the lectin pathway

Flash animation showing formation of C3 convertase and C5 convertase during the lectin pathway.

html5 version of animation for iPad showing formation of C3 convertase and C5 convertase during the lectin pathway.

Flash animation showing the formation of the Membrane Attack Complex (MAC) and cytolysis during the complement pathways.

html5 version of animation for iPad showing the formation of the Membrane Attack Complex (MAC) and cytolysis during the complement pathways.

The beneficial results of the activated complement proteins are the same as in the classical complement pathway above. The complement proteins:

1. Trigger inflammation : C5a>C3a>c4a;

2. Chemotactically attract phagocytes to the infection site: C5a;

3. Promote the attachment of antigens to phagocytes via enhanced attachment or opsonization : C3b>C4b;

4. Cause lysis of Gram-negative bacteria and human cells displaying foreign epitopes : MAC;

5. Serve as a second signal for the activation of naive B-lymphocytes): C3d; and

6 Remove harmful immune complexes from the body: C3b>C4b.

Flash animation showing the role of C5a in vasodilation, the chemotaxis of phagocytes towards C5a, and their attachment to the opsonin C3b as a result of the complement pathways.

html5 version of animation for iPad showing the role of C5a in vasodilation, the chemotaxis of phagocytes towards C5a, and their attachment to the opsonin C3b as a result of the complement pathways.

Flash animation showing the formation of the Membrane Attack Complex (MAC) during the complement pathways.

html5 version of animation for iPad showing the formation of the Membrane Attack Complex (MAC) during the complement pathways.

Concept Map for the Complement Pathways

YouTube animation illustrating benefits of the complement pathways.

The Alternative Complement Pathway

The alternative complement pathway is mediated by C3b, produced either by the classical or lectin pathways or from C3 hydrolysis by water. (Water can hydrolyze C3 and form C3i, a molecule that functions in a manner similar to C3b.)

Activation of the alternative complement pathway begins when C3b (or C3i) binds to the cell wall and other surface components of microbes. C3b can also bind to IgG antibodies. Alternative pathway protein Factor B then combines with the cell-bound C3b to form C3bB. Factor D then splits the bound Factor B into Bb and Ba, forming C3bBb. A serum protein called properdin then binds to the Bb to form C3bBbP that functions as a C3 convertase (see Figure 8.5.13) capable of enzymatically splitting hundreds of molecules of C3 into C3a and C3b. The alternative complement pathway is now activated.

Some of the C3b subsequently binds to some of the C3bBb to form C3bBb3b, a C5 convertase capable of splitting molecules of C5 into C5a and C5b (see Figure 8.5.14). From here, the alternative complement pathway is identical to the other complement pathways.

Flash animation showing the activation of the alternative complement pathway, the formation of C3 convertase, and the formation of C5 convertase.

html5 version of animation for iPad showing the activation of the alternative complement pathway, the formation of C3 convertase, and the formation of C5 convertase.

The beneficial results are the same as in the classical complement pathway above. The complement proteins:

1. Trigger inflammation : C5a>C3a>c4a;
2. Chemotactically attract phagocytes to the infection site: C5a;
3. Promote the attachment of antigens to phagocytes via enhanced attachment or opsonization : C3b>C4b;
4. Cause lysis of Gram-negative bacteria, human cells displaying foreign epitopes,and viral envelopes: MAC; and
5. Serve as a second signal for the activation of naive B-lymphocytes): C3d;
6. Remove harmful immune complexes from the body: C3b>C4b.

Flash animation showing the role of C5a in vasodilation, the chemotaxis of phagocytes towards C5a, and their attachment to the opsonin C3b as a result of the complement pathways.

html5 version of animation for iPad showing the role of C5a in vasodilation, the chemotaxis of phagocytes towards C5a, and their attachment to the opsonin C3b as a result of the complement pathways.

Flash animation showing the formation of the Membrane Attack Complex (MAC) during the complement pathways.

html5 version of animation for iPad showing the formation of the Membrane Attack Complex (MAC) during the complement pathways.

Concept Map for the Complement Pathways

YouTube animation illustrating benefits of the complement pathways.

Keep in mind that in Unit 3, we learned several mechanisms that various bacteria use to resist the body's complement pathways. By resisting these immediate innate immune defenses, some bacteria have a better chance of colonizing their host.

Summary

1. The proteins of the complement system circulate in an inactive form, but in response to the recognition of molecular components of microorganism, they become sequentially activated, working in a cascade where in the binding of one protein

promotes the binding of the next protein in the cascade.

2. There are 3 complement pathways that make up the complement system: the classical complement pathway, the lectin pathway, and the alternative complement pathway.
3. The classical complement pathway is initiated by activation of C1. C1 is primarily activated by interacting with the Fc portion of the antibody molecules IgG or IgM after they have bound to their specific antigen. C1 is also able to directly bind to the surfaces of some pathogens as well as with the C-reactive protein (CRP) that is produced during the acute phase response of innate immunity.
4. The lectin pathway is activated by the interaction of microbial carbohydrates (lectins) with mannose-binding lectin (MBL) or ficolins found in the plasma and tissue fluids.
5. The alternative complement pathway is activated by C3b binding to microbial surfaces and to antibody molecules.
6. All complement pathways carry out the same 6 beneficial innate defense functions.
7. The complement proteins C5a and, to a lesser extent, C3a, and C4a trigger vasodilation and inflammation in order to deliver defense cells and defense chemicals to the infection site.
8. The complement protein C5a also functions as a chemoattractant for phagocytes.
9. The complement proteins C3b and to a lesser extent, C4b can function as opsonins, that is, they can attach antigens to phagocytes.
10. The complement proteins C5b6789n, functions as a Membrane Attack Complex (MAC) causing lysis of Gram-negative bacteria, human cells displaying foreign epitopes, and viral envelopes.
11. The complement protein C3d serves as a second signal for activating naive B-lymphocytes during adaptive immunity.
12. The complement proteins C3b and to a lesser extent, C4b help to remove harmful immune complexes from the body.

This page titled 8.5: The Complement System is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **11.3B: The Complement System** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

CHAPTER OVERVIEW

9: Innate Immunity

Innate immunity is an antigen-nonspecific defence mechanisms that a host uses immediately or within several hours after exposure to almost any microbe. This is the immunity one is born with and is the initial response by the body to eliminate microbes and prevent infection. Innate immunity can be divided into immediate innate immunity and early induced innate immunity. In this section we will learn about immediate innate immunity.

9.1: Overview of Immunity
9.2: The Innate Immune Response
9.3: The Innate Immune System- An Overview
9.4: Overview of Human-Microbial Reactions
9.5: Natural Killer Cells
9.6: Physical and Chemical Barriers
9.7: The Complement System
9.8: Pathogen Recognition
9.9: Defense Cells in the Blood- The Leukocytes
9.10: Defense Cells in the Tissue - Dendritic Cells, Macrophages, and Mast Cells
9.11: Early Induced Innate Immunity
9.11A: Pathogen-Associated Molecular Patterns (PAMPs) and Danger-Associated Molecular Patterns (DAMPs)
9.11B: Pattern-Recognition Receptors (PRRs)
9.11C: Cytokines Important in Innate Immunity
9.11D: Harmful Effects Associated with Abnormal Pattern-Recognition Receptor Responses, Variations in Innate Immune Signaling Pathways, and/or Levels of Cytokine Production
9.11E: Phagocytosis
9.11F: Natural Killer Cells (NK Cells) and Invariant Natural Killer T-Lymphocytes (iNKT Cells)
9.11G: Inflammation
9.11H: Nutritional Immunity
9.11I: Fever
9.11J: The Acute Phase Response
9.11K: Intraepithelial T-lymphocytes and B-1 cells

Template:HideTOC

This page titled 9: Innate Immunity is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

This page titled 9: Innate Immunity is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

9.1: Overview of Immunity

This page titled 9.1: Overview of Immunity is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **11.1: Overview of Immunity** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

9.2: The Innate Immune Response

This page titled 9.2: The Innate Immune Response is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **11.2: The Innate Immune Response** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

9.3: The Innate Immune System- An Overview

Compare adaptive (acquired) immunity with innate immunity.
- Compare immediate innate immunity with early induced innate immunity.
- Define the following:

a. pathogen-associated molecular patterns (PAMPs)
b. pattern-recognition receptors (PRRs)
c. antigen
d. immunogen
e. epitope.

In Units 1-4 we looked at microorganisms: how they replicate, why some are potentially more pathogenic than others, and how we can control them with antimicrobial agents. Units 4 and 5 are devoted to the ways in which the body defends itself against microbes and other potentially harmful cells and molecules. The body has two immune systems: the innate immune system and the adaptive immune system. Unit 5 deals with innate immunity while Unit 6 will cover adaptive immunity. Let's first briefly compare acquired and innate immunity.

Innate immunity

Innate immunity is an antigen-nonspecific defense mechanisms that a host uses immediately or within several hours after exposure to almost any microbe. This is the immunity one is born with and is the initial response by the body to eliminate microbes and prevent infection. Innate immunity can be divided into immediate innate immunity and early induced innate immunity.

Immediate innate immunity begins 0 - 4 hours after exposure to an infectious agent and involves the action of soluble preformed antimicrobial molecules that circulate in the blood, our found in extracellular tissue fluids, and are secreted by epithelial cells. These include:

- antimicrobial enzymes and peptides;
- complement system proteins; and
- anatomical barriers to infection, mechanical removal of microbes, and bacterial antagonism by normal body microbiota

These preformed innate defense molecules will be discussed in greater detail later in this unit.

Early induced innate immunity begins 4 - 96 hours after exposure to an infectious agent and involves the recruitment of defense cells as a result of pathogen-associated molecular patterns or PAMPS binding to pattern-recognition receptors or PRRs . These recruited defense cells include:

- phagocytic cells: leukocytes such as neutrophils, eosinophils, and monocytes; tissue phagocytic cells in the tissue such as macrophages ;
- cells that release inflammatory mediators: inflammatory cells in the tissue such as macrophages and mast cells ; leukocytes such as basophils and eosinophils; and
- natural killer cells (NK cells).

Unlike adaptive immunity, innate immunity does not recognize every possible antigen. Instead, it is designed to recognize molecules shared by groups of related microbes that are essential for the survival of those organisms and are not found associated with mammalian cells. These unique microbial molecules are called pathogen-associated molecular patterns or PAMPS and include LPS from the gram-negative cell wall, peptidoglycan and lipotechoic acids from the gram-positive cell wall, the sugar mannose (a terminal sugar common in microbial glycolipids and glycoproteins but rare in those of humans), bacterial and viral unmethylated CpG DNA, bacterial flagellin, the amino acid N-formylmethionine found in bacterial proteins, double-stranded and single-stranded RNA from viruses, and glucans from fungal cell walls. In addition, unique molecules displayed on stressed, injured, infected, or transformed

human cells also act as PAMPS. (Because all microbes, not just pathogenic microbes, possess PAMPs, pathogen-associated molecular patterns are sometimes referred to as microbe-associated molecular patterns or MAMPs.)

Most body defense cells have pattern-recognition receptors or PRRs for these common PAMPS (see Figure 9.3.1) and so there is an immediate response against the invading microorganism. Pathogen-associated molecular patterns can also be recognized by a series of soluble pattern-recognition receptors in the blood that function as opsonins and initiate the complement pathways. In all, the innate immune system is thought to recognize approximately 10^3 of these microbial molecular patterns.

Flash animation illustrating signaling toll-like receptors on defense cells: LPS and TLR-4.

html5 version of animation for iPad illustrating signaling toll-like receptors on defense cells: LPS and TLR-4.

For More Information: Pathogen-Associated Molecular Patterns (PAMPs) from Unit 5

For More Information: Pattern-Recognition Receptors (PRRs) from Unit 5

For More Information: Leukocytes from Unit 5

Examples of innate immunity include anatomical barriers, mechanical removal, bacterial antagonism, antigen-nonspecific defense chemicals, the complement pathways, phagocytosis, inflammation, fever, and the acute-phase response. In this current unit we will look at each of these in greater detail.

Concept Map for Innate Versus Adaptive Immunity

Adaptive (acquired) immunity

Adaptive (acquired) immunity refers to antigen-specific defense mechanisms that take several days to become protective and are designed to react with and remove a specific antigen . This is the immunity one develops throughout life. During adaptive immunity, antigens are transported to lymphoid organs where they are recognized by naive B-lymphocytes and T-lymphocytes. These activated B- and T-lymphocytes subsequently proliferate and differentiate into effector cells.

An antigen is defined as a substance that reacts with antibody molecules and antigen receptors on lymphocytes. An immunogen is an antigen that is recognized by the body as nonself and stimulates an adaptive immune response. For simplicity we will use the term antigen when referring to both antigens and immunogens. The actual portions or fragments of an antigen that react with antibodies and lymphocyte receptors are called epitopes .

For More Information: Antigens and Immunogens from Unit 5

For More Information: Antibodies from Unit 6

As we will see later in Unit 5, the body recognizes an antigen as foreign when epitopes of that antigen bind to B-lymphocytes and T-lymphocytes by means of epitope-specific receptor molecules having a shape complementary to that of the epitope. The epitope receptor on the surface of a B-lymphocyte is called a B-cell receptor and is actually an antibody molecule . The receptor on a T-lymphocyte is called a T-cell receptor (TCR).

It is estimated that the human body has the ability to recognize 10^7 or more different epitopes and make up to 10^9 different antibodies, each with a unique specificity. In order to recognize this immense number of different epitopes, the body produces 10^7 or more distinct clones of both B-lymphocytes and T-lymphocytes, each with a unique B-cell receptor or T-cell receptor. Among this large variety of B-cell receptors and T-cell receptors there is bound to be at least one that has an epitope-binding site able to fit, at least to some degree, any antigen the immune system eventually encounters. With the adaptive immune responses, the body is able to recognize any conceivable antigen it may eventually encounter.

The downside to the specificity of adaptive immunity is that only a few B-cells and T-cells in the body recognize any one epitope. These few cells then must rapidly proliferate in order to produce enough cells to mount an effective immune response against that particular epitope, and that typically takes several days. During this time the pathogen could be causing considerable harm, and that is why innate immunity is also essential.

For More Information: B-Lymphocytes from Unit 6

For More Information: T4-Lymphocytes from Unit 6

For More Information: T8-Lymphocytes from Unit 6

html5 version of animation for iPad showing epitopes reacting with specific B-cell receptor on a B-lymphocytes.

Flash animation showing epitopes reacting with a specific TCR on a T8-lymphocyte.

html5 version of animation for iPad showing epitopes reacting with a specific TCR on a T8-lymphocyte.

Adaptive immunity usually improves upon repeated exposure to a given infection and involves the following:

- antigen-presenting cells (APCs) such as macrophages and dendritic cells ;
- the activation and proliferation of antigen-specific B-lymphocytes ;
- the activation and proliferation of antigen-specific T-lymphocytes ; and
- the production of antibody molecules , cytotoxic T-lymphocytes (CTLs) , activated macrophages , and cytokines .

Acquired immunity includes both humoral immunity and cell-mediated immunity and will be the topic of Unit 6.

Concept Map for Innate Versus Adaptive Immunity

? Compare and contrast how innate immunity and adaptive immunity are typically initiated in response to microbes.

We will now take a closer look at innate immunity.

Summary

1. The body has two immune systems: the innate immune system and the adaptive immune system.
2. Innate immunity is an antigen-nonspecific defense mechanisms that a host uses immediately or within several hours after exposure to almost any microbe.
3. Innate immunity is the immunity one is born with and is the initial response by the body to eliminate microbes and prevent infection.
4. Immediate innate immunity begins 0 - 4 hours after exposure to an infectious agent and involves the action of soluble preformed antimicrobial molecules that circulate in the blood and in extracellular tissue fluids.
5. Early induced innate immunity begins 4 - 96 hours after exposure to an infectious agent and involves the recruitment of defense cells as a result of pathogen-associated molecular patterns or PAMPS binding to pattern-recognition receptors or PRRs.
6. Adaptive (acquired) immunity refers to antigen-specific defense mechanisms that take several days to become protective and are designed to react with and remove a specific antigen.
7. Adaptive immunity is the immunity one develops throughout life.
8. An antigen is defined as a substance that reacts with antibody molecules and antigen receptors on lymphocytes.
9. The actual portions or fragments of an antigen that react with antibodies and lymphocyte receptors are called epitopes.

This page titled 9.3: The Innate Immune System- An Overview is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **11.1: The Innate Immune System: An Overview** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

9.4: Overview of Human-Microbial Reactions

Learning Objectives

- Outline the relationships between humans and microbes: non-pathogenic and pathogenic

The Human Microbiome Project

The Human Microbiome Project (HMP) is a United States National Institutes of Health initiative aimed at identifying and characterizing the microorganisms which are found in association with both healthy and diseased humans.

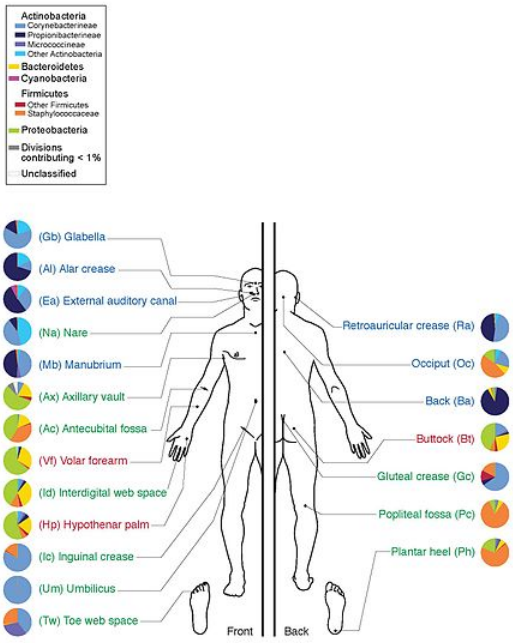


Figure: ***Bacteria commonly found in and on humans****: This is a depiction of the human body and bacteria that predominates throughout it.*

Total microbial cells found in association with humans may exceed the total number of cells making up the human body by a factor of ten-to-one. The total number of genes associated with the human microbiome could exceed the total number of human genes by a factor of 100-to-one.

Organisms expected to be found in the human microbiome may generally be categorized as bacteria (the majority), archaea, yeasts, and single-celled eukaryotes as well as various helminth parasites and viruses, such as those that infect cellular microbiome organisms.

The HMP project discovered several “surprises”, including:

- Bacterial protein -coding genes are estimated as 360 times more abundant than human genes.
- Microbial metabolic activities, for example, digestion of fats, are not always provided by the same bacterial species.
- Components of the human microbiome change over time, affected by a patient disease state and medication.

Examples of Non-pathogenic Interactions

Gut flora consists of microorganisms that live in the digestive tracts of animals and is the largest reservoir of human flora. The human body, consisting of about 10 trillion cells, carries about ten times as many microorganisms in the intestines. The metabolic activities performed by these bacteria resemble those of an organ, leading some to liken gut bacteria to a “forgotten” organ.

Bacteria make up most of the flora in the colon and up to 60% of the dry mass of feces. Between 300 and 1000 different species live in the gut. It is probable that 99% of the bacteria come from about 30 or 40 species. Fungi and protozoa also make up a part of

the gut flora, but little is known about their activities.

The relationship between gut flora and humans is thought to be not merely commensal, but rather a mutualistic relationship. Though people can survive without gut flora, the microorganisms perform a host of useful functions, such as fermenting unused energy substrates, training the immune system, preventing growth of harmful, pathogenic bacteria, regulating the development of the gut, producing vitamins for the host, and producing hormones to direct the host to store fats. In certain conditions, some species can cause disease by producing infection or increasing the host's cancer risk.

The skin microbiota are composed mostly of bacteria of which there are around 1000 species upon human skin from 19 phyla. The total number of bacteria on an average human has been estimated at 10^{12}.

Skin flora are usually non-pathogenic and either commensal or mutualistic. The benefits of bacteria include preventing transient pathogenic organisms from colonizing the skin surface, either by competing for nutrients, secreting chemicals against them, or stimulating the skin's immune system. Resident microbes can cause skin diseases and enter the blood system creating life-threatening diseases particularly in immunosuppressed people.

Pathogenic Interactions

Among the almost infinite varieties of microorganisms, relatively few cause disease in otherwise healthy individuals. Infectious disease results from the interplay between those few pathogens and the defenses of the hosts they infect. Infectious diseases comprise clinically evident illness resulting from the infection, and the presence and growth of pathogenic biological agents in an individual host organism. Infectious pathogens include some viruses, bacteria, fungi, protozoa, multicellular parasites, and aberrant proteins known as prions. Primary pathogens cause disease as a result of their presence or activity within the normal, healthy host. Their intrinsic virulence is due to their need to reproduce and spread.



Figure: ***The malaria plasmodium****: Malaria is transmitted to people and animals by mosquitoes. Malarial sporozoites develop inside oocysts and are released in large numbers into the hemocoel of Anopheles stephensi mosquitoes. This false-colored electron micrograph shows a sporozoite migrating through the cytoplasm of midgut epithelia.*

Organisms which cause an infectious disease in a host with depressed resistance are classified as opportunistic pathogens. Opportunistic disease may be caused by microbes that are ordinarily in contact with the host, such as pathogenic bacteria or fungi in the gastrointestinal tract. They may also result from (otherwise innocuous) microbes acquired from other hosts or from the environment as a result of traumatic introduction (as in surgical wound infections). An opportunistic disease requires impairment of host defenses, which may occur as a result of genetic defects, exposure to antimicrobial drugs or immunosuppressive chemicals, exposure to ionizing radiation, or as a result of an infectious disease with immunosuppressive activity.

The success of any pathogen depends on its ability to elude host immune responses. Therefore, pathogens evolved several methods that allow them to successfully infect a host, while evading the immune system. Bacteria often overcome physical barriers by secreting enzymes that digest the barrier. An evasion strategy used by several pathogens to avoid the innate immune system is to hide within the cells of their host. The mechanisms used to evade the adaptive immune system are more complicated. The simplest approach is antigenic variation: rapid changes of non-essential epitopes on the surface of the pathogen, while keeping essential epitopes concealed.

Key Points

- Though people can survive without gut flora, the microorganisms perform a host of useful functions: fermenting unused energy substrates, training the immune system, preventing growth of harmful bacteria, regulating the development of the gut, and producing vitamins and hormones for the host.
- Organisms expected to be found in the human microbiome may generally be categorized as bacteria (the majority), archaea, yeasts, and single-celled eukaryotes as well as various helminth parasites and viruses.
- Skin flora are usually either commensal or mutualistic. The benefits of bacteria include preventing transient pathogenic organisms from colonizing the skin surface. Resident microbes can cause skin diseases and create life-threatening illness particularly in immunosuppressed people.
- Among the almost infinite varieties of microorganisms, relatively few cause disease in otherwise healthy individuals. Infectious disease results from the interplay between those few pathogens and the defenses of the hosts they infect.
- Primary pathogens cause disease as a result of their activity in the healthy host and their intrinsic virulence is due to their need to reproduce and spread. Organisms that cause an infectious disease in a host with depressed resistance are classified as opportunistic.
- The success of any pathogen depends on its ability to elude host immune responses. Therefore, pathogens evolved several methods that allow them to successfully infect a host, while evading the immune system.

Key Terms

- **Human microbiome**: The aggregate of microorganisms that reside on the surface and in deep layers of skin, in the saliva and oral mucosa, in the conjunctiva, and in the gastrointestinal tracts. They include bacteria, fungi, and archaea. Some of these organisms perform tasks that are useful for the human host. However, the majority have no known beneficial or harmful effect.
- **Primary pathogen**: These pathogens cause disease as a result of their presence or activity within the normal, healthy host. Their intrinsic virulence (the severity of the disease they cause) is due to their need to reproduce and spread.
- **Opportunistic pathogen**: Organisms which cause an infectious disease in a host with depressed resistance are classified as opportunistic pathogens. Opportunistic disease may be caused by microbes that are ordinarily in contact with the host, such as pathogenic bacteria or fungi in the gastrointestinal or the upper respiratory tract. They may also result from (otherwise innocuous) microbes acquired from other hosts or from the environment as a result of traumatic introduction. An opportunistic disease requires impairment of host defenses.

This page titled 9.4: Overview of Human-Microbial Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **11.1B: Overview of Human-Microbial Reactions** is licensed CC BY-SA 4.0.

9.5: Natural Killer Cells

LEARNING OBJECTIVe

- Describe the role of natural killer cells in the immune response

Lymphocytes are leukocytes (white blood cells) that are histologically identifiable by their large, darkly-staining nuclei; they are small cells with very little cytoplasm. After a pathogen enters the body, infected cells are identified and destroyed by natural killer (NK) cells, which are a type of lymphocyte that can kill cells infected with viruses or tumor cells (abnormal cells that uncontrollably divide and invade other tissue). While NK cells are part of the innate immune response, they are best understood relative to their counterparts in the adaptive immune response,T cells, which are also classified as lymphocytes.

T cells are lymphocytes that mature in the thymus gland and identify intracellular infections, especially from viruses, by the altered expression of major histocompatibility class (MHC) I molecules on the surface of infected cells. MHC I molecules are proteins on the surfaces of all nucleated cells which help the immune system distinguish between “self” and “non-self.” If the cell is infected, the MHC I molecules display fragments of proteins from the infectious agents to T-cells. Healthy cells do not display any proteins and will be ignored by the immune system, while the cells identified as “non-self” by foreign proteins will be attacked by the immune system.

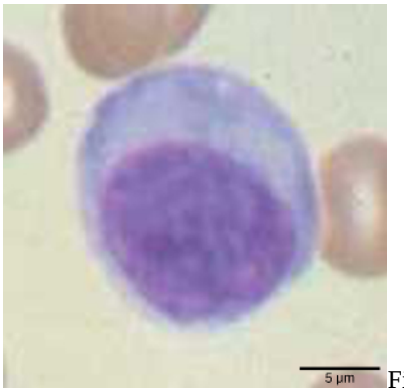


Figure: ***Lymphocytes****: Lymphocytes, such as NK cells, are characterized by their large nuclei that actively absorb Wright stain and, therefore, appear dark colored under a microscope.*

An infected cell (or a tumor cell) is often incapable of synthesizing and displaying MHC I molecules appropriately. The metabolic resources of cells infected by some viruses produce proteins that interfere with MHC I processing and/or trafficking to the cell surface. The reduced MHC I on host cells varies from virus to virus and results from active inhibitors being produced by the viruses. This process can deplete host MHC I molecules on the cell surface, which prevents T-cells from recognizing them, but which NK cells detect as “unhealthy” or “abnormal” while searching for cellular MHC I molecules. As such, NK cells offer a complementary check for unhealthy cells, relative to T cells. Similarly, the dramatically-altered gene expression of tumor cells leads to expression of extremely- deformed or absent MHC I molecules that also signal “unhealthy” or “abnormal.”

NK cells are always active; an interaction with normal, intact MHC I molecules on a healthy cell disables the killing sequence, causing the NK cell to move on. After the NK cell detects an infected or tumor cell, its cytoplasm secretes granules comprised of perforin: a destructive protein that creates a pore in the target cell. Granzymes are released along with the perforin in the immunological synapse. A granzyme, a protease that digests cellular proteins, induces the target cell to undergo programmed cell death, or apoptosis. Phagocytic cells then digest the cell debris left behind. NK cells are constantly patrolling the body. They are an effective mechanism for controlling potential infections and preventing cancer progression.

Key Points

- Natural killer (NK) cells are lymphocytes (a subclass of white blood cells) that recognize infected or tumorogenic cells and kill them.
- Unlike the related T cells, NK cells do not recognize fragments of the infecting particle, but rather the incorrect display of major histocompatibility complex (MHC) I molecules.
- NK cells are always active, but will not perform their killing function on cells with intact MHC I molecules.

- When NK cells detect an infected or tumor cell, they secrete granules that contain perforin, creating a pore in the target cell; granzymes then pass through these pores, degrading cellular proteins, causing cells to undergo apoptosis.

Key Terms

- **lymphocyte**: a type of white blood cell or leukocyte that is divided into two principal groups and a null group: B-cells, T-cells, and natural killer (NK) cells
- **major histocompatibility complex**: a protein present on the extracellular surface of the cell that displays portions of the proteins that are degraded inside the cell
- **T cell**: a lymphocyte, from the thymus, that can recognize specific antigens and can activate or deactivate other immune cells

---

This page titled 9.5: Natural Killer Cells is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **11.2A: Natural Killer Cells** is licensed CC BY-SA 4.0.

9.6: Physical and Chemical Barriers

Learning Objectives

- Describe physical and chemical barriers in the innate immune response

Physical and chemical barriers

The immune system comprises both innate and adaptive immune responses. Innate immunity occurs naturally due to genetic factors or physiology. It is not induced by infection or vaccination, but is constantly available to reduce the workload for the adaptive immune response. The adaptive immune response expands over time, storing information about past infections and mounting pathogen-specific defenses. Both the innate and adaptive levels of the immune response involve secreted proteins, receptor-mediated signaling, and intricate cell -to-cell communication. From an historical perspective, the innate immune system developed early in animal evolution, roughly a billion years ago, as an essential response to infection. In the innate immune response, any pathogenic threat triggers a consistent sequence of events that can identify the type of pathogen and either clear the infection independently or mobilize a highly-specialized adaptive immune response.

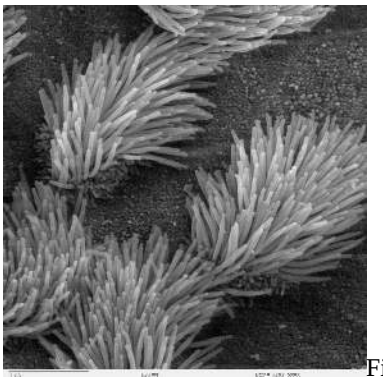


Figure: **Cilia up close**: Cilia are a type of organelle found in eukaryotic cells. In the innate immune system, they serve to move pathogens out of the respiratory system via a concerted sweeping motion.

Before any immune factors are triggered, the skin (also known as the epithelial surface) functions as a continuous, impassable barrier to potentially-infectious pathogens. The skin is considered the first defense of the innate immune system; it is the first of the nonspecific barrier defenses. Pathogens are killed or inactivated on the skin by desiccation (drying out) and by the skin's acidity. In addition, beneficial microorganisms that coexist on the skin compete with invading pathogens, preventing infection. Desquamation, or peeling skin, also serves to dislodge organisms that have adhered to the surface of the body and are awaiting entry. Regions of the body that are not protected by skin (such as the eyes and mucous membranes) have alternative methods of defense. These include tears in the eyes; mucous membranes that provide partial protection despite having to allow absorption and secretion; mucus secretions that trap and rinse away pathogens; and cilia (singular cilium) in the nasal passages and respiratory tract that push the mucus with the pathogens out of the body. Furthermore, tears and mucus secretions contain microbicidal factors that prevent many infections from entering via these routes.

Despite these barriers, pathogens may enter the body through skin abrasions or punctures, or by collecting on mucosal surfaces in large numbers that overcome the mucus or cilia. Some pathogens have evolved specific mechanisms that allow them to overcome physical and chemical barriers.

Once inside, the body still has many other defenses, including chemical barriers. Some of these include the low pH of the stomach, which inhibits the growth of pathogens; blood proteins that bind and disrupt bacterial cell membranes; and the process of urination, which flushes pathogens from the urinary tract. The blood-brain barrier also protects the nervous system from pathogens that have already entered the blood stream, but would do significantly more damage if they entered the central nervous system.

Key Points

- The skin, or epithelial surface, serves as the primary barrier to microbial entry into the body; skin peeling, drying out, and the skin's acidity all serve to dislodge or kill foreign pathogens.

- Orifices such as the eyes and mouth, which are not covered by skin, have other mechanisms by which they prevent entry; tears wash away microbes, while cilia in the nasal passages and respiratory tract push mucus (which traps pathogens) out of the body.
- Many chemical barriers also exist once pathogens make it past the outer physical barriers; the acidity of the stomach ensures that few organisms arriving with food survive the digestive system.

Key Terms

- **cilium**: a hairlike organelle projecting from a eukaryotic cell (such as unicellular organism or one cell of a multicelled organism), which serves either for locomotion by moving or as sensors
- **microbicidal**: functioning to reduce the infectivity of microbes

---

This page titled 9.6: Physical and Chemical Barriers is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **11.2B: Physical and Chemical Barriers** is licensed CC BY-SA 4.0.

9.7: The Complement System

Learning Objectives

- Explain how the complement system aids antibody response

Complement

The innate immune system serves as a first responder to pathogenic threats that bypass natural physical and chemical barriers of the body. Using a combination of cellular and molecular attacks, the innate immune system identifies the nature of a pathogen and responds with inflammation, phagocytosis (where a cell engulfs a foreign particle), cytokine release, destruction by NK cells, and/or a complement system. In this concept, we will discuss the complement system.

An array of approximately 20 types of soluble proteins, called a complement system, functions to destroy extracellular pathogens. Cells of the liver and macrophages synthesize complement proteins continuously. These proteins are abundant in the blood serum and are capable of responding immediately to infecting microorganisms. The complement system is so named because it is complementary to the antibody response of the adaptive immune system. Complement proteins bind to the surfaces of microorganisms and are particularly attracted to pathogens that are already bound by antibodies. Binding of complement proteins occurs in a specific and highly-regulated sequence, with each successive protein being activated by cleavage and/or structural changes induced upon binding of the preceding protein(s). After the first few complement proteins bind, a cascade of sequential binding events follows in which the pathogen rapidly becomes coated in complement proteins.

Complement proteins perform several functions. They serve as a marker to indicate the presence of a pathogen to phagocytic cells, such as macrophages and B cells, to enhance engulfment. This process is called opsonization. Certain complement proteins can combine to form attack complexes that open pores in microbial cell membranes. These structures destroy pathogens by causing their contents to leak. When innate mechanisms are insufficient to clear an infection, the adaptive immune response is informed and mobilized.

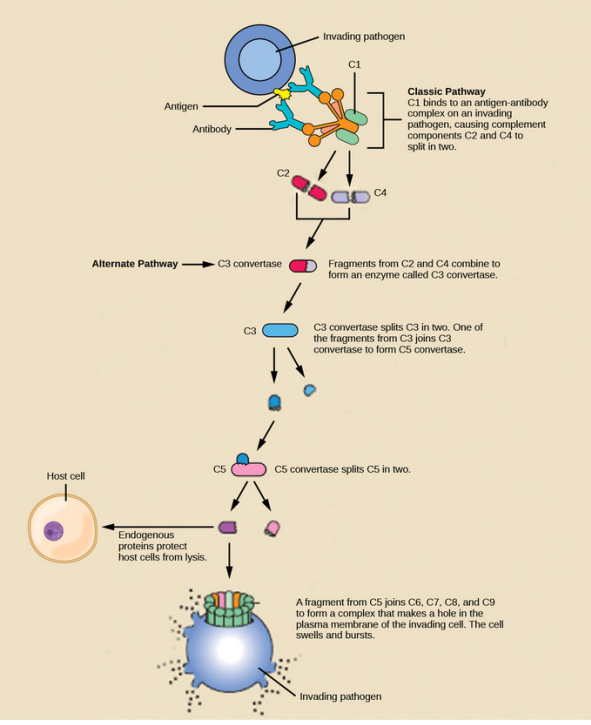


Figure: **Complement cascade in the innate immune response**: The classic pathway for the complement cascade involves the attachment of several initial complement proteins to an antibody-bound pathogen, followed by rapid activation and binding of many more complement proteins and the creation of destructive pores in the microbial cell envelope and cell wall. The alternate pathway does not involve antibody activation. Rather, C3 convertase spontaneously breaks down C3. Endogenous regulatory proteins prevent the complement complex from binding to host cells. Pathogens lacking these regulatory proteins are lysed.

Key Points

- The complement system is so named because it is complementary to the antibody response of the adaptive immune system.
- The complement system proteins are produced continuously by the liver and macrophages, are abundant in the blood serum, and are capable of immediate response to infecting microorganisms.
- The complement system works by first having several proteins bind to a target; this binding event then begins a series of highly-specific and regulated sequences wherein successive proteins are activated by cleavage and/or structural changes of the preceding proteins.
- The complement system serves as a marker to indicate targets for phagocytic cells; complement proteins can also combine to form attack complexes capable of opening pores in microbial cell membranes.

Key Terms

- **opsonization**: the process by which a pathogen is marked for ingestion and destruction by a phagocyte
- **complement system**: an aspect of the innate immune system that supplements the actions of the antibodies and phagocytic cells in clearing out pathogens from an organism

---

This page titled 9.7: The Complement System is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **11.2C: The Complement System** is licensed CC BY-SA 4.0.

9.8: Pathogen Recognition

Learning Objectives

- Describe the role of PAMPs and PRRs, interferons, and other cytokines in innate immunity

Pathogen recognition

When a pathogen enters the body, cells in the blood and lymph detect the specific pathogen-associated molecular patterns (PAMPs) on the pathogen's surface. PAMPs are carbohydrate, polypeptide, and nucleic acid "signatures" that are expressed by viruses, bacteria, and parasites, but which differ from molecules on host cells. These PAMPs allow the immune system to recognize "self" from "other" so as not to destroy the host.

The immune system has specific cells with receptors that recognize these PAMPs. A macrophage is a large, phagocytic cell that engulfs foreign particles and pathogens. Macrophages recognize PAMPs via complementary pattern recognition receptors (PRRs). PRRs are molecules on macrophages and dendritic cells which are in contact with the external environment and can thus recognize PAMPs when present. A monocyte, a type of leukocyte (white blood cell) that circulates in the blood and lymph, differentiates into macrophages after it moves into infected tissue. Dendritic cells bind molecular signatures of pathogens, promoting pathogen engulfment and destruction.

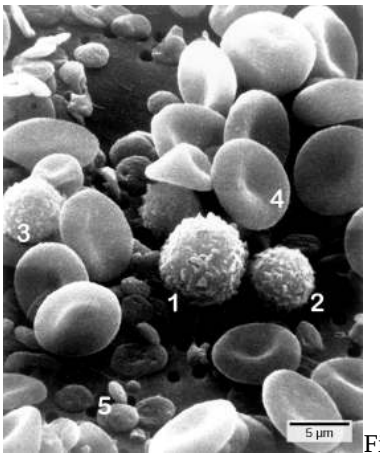
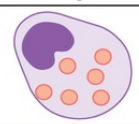
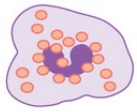


Figure: **Blood cells related to the innate immune response**: Cells of the blood include (1) monocytes, (2) lymphocytes, (3) neutrophils, (4) red blood cells, and (5) platelets. Leukocytes (1, 2, 3) are white blood cells that

Cell type	Characteristics	Location	Image
Mast cell	Dilates blood vessels and induces inflammation through release of histamines and heparin. Recruits macrophages and neutrophils. Involved in wound healing and defense against pathogens but can also be responsible for allergic reactions.	Connective tissues, mucous membranes	
Macrophage	Phagocytic cell that consumes foreign pathogens and cancer cells. Stimulates response of other immune cells.	Migrates from blood vessels into tissues.	
Natural killer cell	Kills tumor cells and virus-infected cells.	Circulates in blood and migrates into tissues.	
Dendritic cell	Presents antigens on its surface, thereby triggering adaptive immunity.	Present in epithelial tissue, including skin, lung and tissues of the digestive tract. Migrates to lymph nodes upon activation.	
Monocyte	Differentiates into macrophages and dendritic cells in response to inflammation.	Stored in spleen, moves through blood vessels to infected tissues.	
Neutrophil	First responders at the site of infection or trauma, this abundant phagocytic cell represents 50-60 percent of all leukocytes. Releases toxins that kill or inhibit bacteria and fungi and recruits other immune cells to the site of infection.	Migrates from blood vessels into tissues.	
Basophil	Responsible for defense against parasites. Releases histamines that cause inflammation and may be responsible for allergic reactions.	Circulates in blood and migrates to tissues.	
Eosinophil	Releases toxins that kill bacteria and parasites but also causes tissue damage.	Circulates in blood and migrates to tissues.	

play an important role in the body's immune system. Figure: **Cells involved in the innate immune system**: The immune system has specific cells whose job is to recognize pathogen-associated molecular patterns. The characteristics and location of cells involved in the innate immune system are described in this chart.

Once a pathogen is detected, the immune system must also track whether it is replicating intracellularly (inside the cell, as with most viruses and some bacteria) or extracellularly (outside of the cell, as with other bacteria, but not viruses). The innate immune system must respond accordingly by identifying the extracellular pathogen and/or by identifying host cells that have already been infected.

Cytokine release affect

The binding of PRRs with PAMPs triggers the release of cytokines, which signal that a pathogen is present and needs to be destroyed along with any infected cells. A cytokine is a chemical messenger that regulates cell differentiation (form and function), proliferation (production), and gene expression to affect immune responses. At least 40 types of cytokines exist in humans that differ in terms of the cell type that produces them, the cell type that responds to them, and the changes they produce.

One subclass of cytokines is the interleukin (IL), which mediates interactions between leukocytes (white blood cells). Interleukins are involved in bridging the innate and adaptive immune responses. In addition to being released from cells after PAMP recognition, cytokines are released by the infected cells which bind to nearby uninfected cells, inducing those cells to release cytokines, resulting in a cytokine burst.

A second class of cytokines is interferons, which are released by infected cells as a warning to nearby uninfected cells. A function an interferons is to inhibit viral replication, making them particularly effective against viruses. They also have other important functions, such as tumor surveillance. Interferons work by signaling neighboring uninfected cells to destroy RNA (often a very important biomolecule for viruses) and reduce protein synthesis; signaling neighboring infected cells to undergo apoptosis (programmed cell death); and activating immune cells.

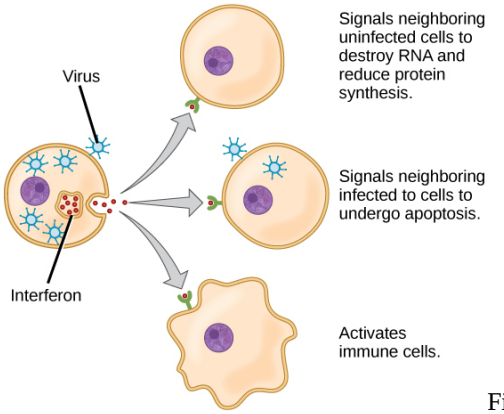


Figure: **Interferon release**: Interferons are cytokines that are released by a cell infected with a virus. The response of neighboring cells to interferons helps stem the infection.

Cytokines also send feedback to cells of the nervous system to bring about the overall symptoms of feeling sick, which include lethargy, muscle pain, and nausea. These effects may have evolved because the symptoms encourage the individual to rest, preventing them from spreading the infection to others. Cytokines also increase the core body temperature, causing a fever, which causes the liver to withhold iron from the blood. Without iron, certain pathogens (such as some bacteria) are unable to replicate; this is called nutritional immunity.

Phagocytosis and inflammation

The first cytokines to be produced are pro-inflammatory; that is, they encourage inflammation, or the localized redness, swelling (edema), heat, loss of function, and pain that result from the movement of leukocytes and fluid through increasingly-permeable capillaries to a site of infection. The population of leukocytes that arrives at an infection site depends on the nature of the infecting pathogen. Both macrophages and dendritic cells engulf pathogens and cellular debris through phagocytosis. A neutrophil is also a phagocytic leukocyte that engulfs and digests pathogens. Neutrophils, the most-abundant leukocytes of the immune system, have a nucleus with two to five lobes and contain organelles (lysosomes) that digest engulfed pathogens. An eosinophil is a leukocyte that works with other eosinophils to surround a parasite. It is involved in the allergic response and in protection against helminthes (parasitic worms).

Neutrophils and eosinophils are particularly important leukocytes that engulf large pathogens, such as bacteria and fungi. A mast cell is a leukocyte that produces inflammatory molecules, such as histamine, in response to large pathogens. A basophil is a leukocyte that, like a neutrophil, releases chemicals to stimulate the inflammatory response. Basophils are also involved in allergy and hypersensitivity responses and induce specific types of inflammatory responses. Eosinophils and basophils produce additional inflammatory mediators to recruit more leukocytes. A hypersensitive immune response to harmless antigens, such as in pollen, often involves the release of histamine by basophils and mast cells; this is why many anti-allergy medications are anti-histamines.

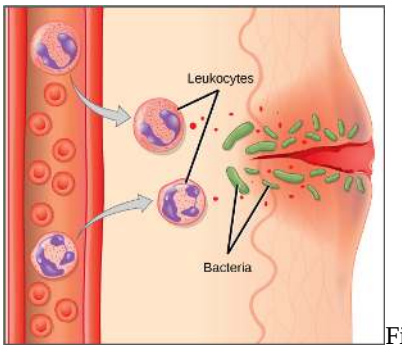


Figure: **Innate immune response to cuts**: In response to a cut, mast cells secrete histamines that cause nearby capillaries to dilate. Neutrophils and monocytes leave the capillaries. Monocytes mature into macrophages. Neutrophils, dendritic cells, and macrophages release chemicals to stimulate the inflammatory response. Neutrophils and macrophages also consume invading bacteria by phagocytosis.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: ***CC BY-SA: Attribution-ShareAlike***

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- OpenStax College, Biology. October 17, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44820/latest...ol11448/latest. **License**: ***CC BY: Attribution***
- major histocompatibility complex. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/major+...bility+complex**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- lymphocyte. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/lymphocyte**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- T cell. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/T_cell**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- OpenStax College, Innate Immune Response. October 17, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44820/latest...e_42_01_05.jpg. **License**: ***CC BY: Attribution***
- OpenStax College, Biology. October 17, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44820/latest...ol11448/latest. **License**: ***CC BY: Attribution***
- Innate immune system. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Innate_immune_system**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- OpenStax College, Biology. December 4, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44820/latest...ol11448/latest. **License**: ***CC BY: Attribution***
- cilium. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/cilium**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- microbicidal. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/microbicidal**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- OpenStax College, Innate Immune Response. October 17, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44820/latest...e_42_01_05.jpg. **License**: ***CC BY: Attribution***
- Bronchiolar epithelium 3 - SEM. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Br...um_3_-_SEM.jpg**. **License**: ***Public Domain: No Known Copyright***
- complement system. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/complement_system**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- OpenStax College, Biology. October 17, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44820/latest...ol11448/latest. **License**: ***CC BY: Attribution***
- opsonization. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/opsonization**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- OpenStax College, Innate Immune Response. October 17, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44820/latest...e_42_01_05.jpg. **License**: ***CC BY: Attribution***
- Bronchiolar epithelium 3 - SEM. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Br...um_3_-_SEM.jpg**. **License**: ***Public Domain: No Known Copyright***
- OpenStax College, Innate Immune Response. October 17, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44820/latest...e_42_01_06.jpg. **License**: ***CC BY: Attribution***
- OpenStax College, Biology. October 17, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44820/latest...ol11448/latest. **License**: ***CC BY: Attribution***
- phagocytosis. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/phagocytosis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- macrophage. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/macrophage**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- cytokine. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/cytokine**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- OpenStax College, Innate Immune Response. October 17, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44820/latest...e_42_01_05.jpg. **License**: ***CC BY: Attribution***
- Bronchiolar epithelium 3 - SEM. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Br...um_3_-_SEM.jpg**. **License**: ***Public Domain: No Known Copyright***

- OpenStax College, Innate Immune Response. October 17, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44820/latest...e_42_01_06.jpg. **License**: ***CC BY: Attribution***
- OpenStax College, Innate Immune Response. October 17, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44820/latest...e_42_01_04.jpg. **License**: ***CC BY: Attribution***
- OpenStax College, Innate Immune Response. October 17, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44820/latest...e_42_01_03.jpg. **License**: ***CC BY: Attribution***
- OpenStax College, Innate Immune Response. October 17, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44820/latest...e_42_01_01.jpg. **License**: ***CC BY: Attribution***
- OpenStax College, Innate Immune Response. October 17, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44820/latest...e_42_01_02.jpg. **License**: ***CC BY: Attribution***

Key Points

- Pathogens are recognized by a variety of immune cells, such as macrophages and dendritic cells, via pathogen-associated molecular patterns (PAMPs) on the pathogen surface, which interact with complementary pattern-recognition receptors (PRRs) on the immune cells' surfaces.
- Upon binding of PRRs with PAMPs (pathogen recognition), immune cells release cytokines to tell other cells to start fighting back.
- One class of cytokines, interferons, warn nearby uninfected cells of impending infection, cause cells to start cleaving RNA and reduce protein synthesis, and signal nearby infected cells to undergo apoptosis.
- Another class of cytokines, called inerleukins, mediate interactions between white blood cells (leukocytes) and help bridge the innate and adaptive immune responses.
- Inflammation (hot, red, swollen, painful tissue associated with infection) is encouraged by cytokines that are produced immediately upon pathogen recognition; the increase in blood flow associated with inflammation allows more leukocytes (a type of innate immune cell) to reach the infected area.

Key Terms

- **macrophage**: a white blood cell that phagocytizes necrotic cell debris and foreign material, including viruses, bacteria, and tattoo ink; part of the innate immune system
- **phagocytosis**: the process where a cell incorporates a particle by extending pseudopodia and drawing the particle into a vacuole of its cytoplasm
- **cytokine**: any of various small regulatory proteins that regulate the cells of the immune system; they are released upon binding of PRRs to PAMPS

This page titled 9.8: Pathogen Recognition is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **11.2D: Pathogen Recognition** is licensed CC BY-SA 4.0.

9.9: Defense Cells in the Blood- The Leukocytes

State what each of the following determine: CBC and leukocyte differential count.

- State the significance of the following:
  a. an elevated white blood cell count
  b. a shift to the left (elevated bands)
- Describe and state the major functions of the following leukocytes:
  a. neutrophils
  b. basophils
  c. eosinophils
  d. monocytes
  e. B-lymphocytes
  f. T4-lymphocytes
  g. T8-lymphocytes
  h. NK cells
- State what type of cell monocytes differentiate into when they enter tissue.
- State 2 functions of platelets.

All leukocytes are critical to body defense. There are normally between 5,000-10,000 leukocytes per cubic millimeter (mm^3) of blood and these can be divided into five major types: neutrophils, basophils, eosinophils, monocytes, and lymphocytes. The production of colonies of the different types of leukocytes is called leukopoiesis and is induced by various cytokines known as colony stimulating factors or CSFs .

The complete blood count (CBC) is a laboratory test which, among other things, determines the total number of both leukocytes and erythrocytes per ml of blood. In general, an elevated WBC count (leukocytosis) is seen in infection, inflammation, leukemia, and parasitic infestations. A decreased WBC count (leukopenia) is generally seen in bone marrow depression, severe infection, viral infections, autoimmune diseases, malignancies, and malnutrition. For example, infections may increase the total leukocyte count two to three times the normal level by dramatically increasing the number of neutrophils.

The differential white blood cell count (leukocyte differential count) determines the number of each type of leukocyte calculated as a percentage of the total number of leukocytes. This information can be useful diagnostically because different diseases or disorders can cause an increase or a decrease in the various types of WBCs. For example, when doing a differential WBC count, neutrophils are usually divided into segs (a mature neutrophile having a segmented nucleus) and bands (an immature neutrophil with an incompletely segmented or banded nucleus). During an active infection, people are generally producing large numbers of new neutrophils and therefore will have a higher percentage of the immature band forms. (An increase in band forms is sometimes referred to as a "shift to the left" because on laboratory slips used for differential WBC counts, the heading for bands is to the left of the heading for mature neutrophils or segs.)

The five types of leukocytes fall into one of two groups: the polymorphonuclear leukocytes and the mononuclear leukocytes.

Polymorphonuclear Leukocytes

Polymorphonuclear leukocytes (granulocytes) have irregular shaped nuclei with several lobes and their cytoplasm is filled with granules containing enzymes and antimicrobial chemicals. They include the following:

Neutrophils

Neutrophils are the most abundant of the leukocytes, normally accounting for 54-75% of the WBCs. An adult typically has 3,000-7,500 neutrophils/mm^3 of blood but the number may increase two- to three-fold during active infections.

They are called neutrophils because their granules stain poorly - they have a neutral color - with the mixture of dyes used in staining leukocytes. The nucleus of a neutrophil has multiple lobes.

Neutrophils are important phagocytes. Their granules contain various agents for killing microbes. Primary azurophil granules contain acid hydrolase, myeloperoxidase, defensins, cathepsin G, cationic proteins, and bactericidal permeability increasing protein (BPI). Secondary specific granules contain such defense chemicals as lysozyme, lactoferrin, collagenase, and elastase. These agents kill microbes intracellularly during phagocytosis but are also often released extracellularly where they kill not only microbes but also surrounding cells and tissue, as will be discussed later under phagocytosis.

They release the enzyme kallikrein that catalyzes the generation of bradykinins. Bradykinins promote inflammation by causing vasodilation, increasing vascular permeability, and increasing mucous production. They are also chemotactic for leukocytes and stimulate pain. They produce enzymes that catalyze the synthesis of prostaglandins from arachidonic acid in cell membranes. Certain prostaglandins promote inflammation by causing vasodilation and increasing capillary permeability. They also cause constriction of smooth muscles, enhance pain, and induce fever.

They are short-lived, having a life span of a few hours to a few days, and do not multiply. They circulate in the blood for around 6 hours and if the are not recruited, they undergo apoptosis. In tissue, they function for several hours and die. However, the bone marrow makes about 80,000,000 new neutrophils per minute to replace these.

- To view an electron micrograph of a neutrophil, see the Web page for the University of Illinois College of Medicine.
- Scanning electron micrograph of a neutrophil engulfing *Escherichia coli* from sciencephotogallery.com.
- Transmission electron micrograph of a neutrophil engulfing *Neisseria gonorrhoeae* from sciencephotogallery.com.

Eosinophils

Eosinophils normally comprise 1-4% of the WBCs (50-400/mm^3 of blood). They are called eosinophils because their granules stain red with the acidic dye eosin, one of the mixture of dyes used when staining leukocytes. The nucleus of an eosinophil typically appears lobed.

Their granules contain destructive enzymes for killing infectious organisms. These enzymes include acid phosphatase, peroxidases, major basic protein, RNase, DNases, lipase, and plasminogen. They are capable of phagocytosis but primarily they release their contents into the surrounding environment to kill microbes extracellularly. The substances they release defend primarily against fungi, protozoa, and parasitic worms (helminths), pathogens that are too big to be consumed by phagocytosis. They secrete leukotrienes, prostaglandins, chemicals that promotes inflammation by causing vasodilation and increasing capillary permeability. They also secrete various cytokines such as IL-1, IL-2, IL-4, IL-5, IL-6, IL-8, IL-13, and TNF alpha. Their life span is 8-12 days.

- To view an electron micrograph of an eosinophil, see the Web page for the University of Illinois College of Medicine.
- Transmission electron micrograph of an eosinophil from sciencephotogallery.com.

Basophils

Basophils normally make up 0-1% of the WBCs (25-100/mm^3 of blood). They are called basophils because their granules stain a dark purplish blue with the basic dye methylene blue, one of the dyes that are used when staining leukocytes. Basophils have a lobed nucleus. Basophils release histamine, leukotrienes, and prostaglandins, chemicals that promotes inflammation by causing vasodilation, increasing capillary permeability, and increasing mucous production. Basophils also produce heparin, platelet-activating factor (PAF) and the cytokine IL-4. Their life span is probably a few hours to a few days.

Mononuclear Leukocytes

Mononuclear leukocytes (agranulocytes) have compact nuclei and have no visible cytoplasmic granules. The following are agranulocytes:

Monocytes

Monocytes normally make up 2-8% of the WBCs (100-500/mm^3 of blood). Monocytes are important phagocytes. Monocytes differentiate into macrophages and dendritic cells when they leave the blood and enter the tissue. Macrophages and dendritic cells are very important in phagocytosis and serve as antigen-presenting cells in the adaptive immune responses (see below). They produce a variety of cytokines that play numerous roles in body defense. They are long-lived (life span of months) and can multiply.

- To view an electron micrograph of a monocyte, see the Web page for the University of Illinois College of Medicine.
- Transmission electron micrograph of a monocyte from sciencephotogallery.com.

Lymphocytes

Lymphocytes normally represent 25-40% of the WBCs (1,500-4,500/mm^3 of blood). Lymphocytes mediate the adaptive immune responses (Unit 6). Only a small proportion of the body's lymphocytes are found in the blood. The majority are found in lymphoid tissue. In fact the collective mass of all the lymphocytes in the human body is about the same as the mass of the brain! Lymphocytes circulate back and forth between the blood and the lymphoid system of the body. They have a life span of days to years. There are 3 major populations of lymphocytes:

B-lymphocytes (B-cells) mediate humoral immunity, the production of antibody molecules against a specific antigen,and have B-cell receptors (BCR) on their surface for antigen recognition. Generally 10-20% of the lymphocytes are B-lymphocytes. Once activated, most B-lymphocytes differentiate into antibody-secreting plasma cells.

T-lymphocytes (T-cells) are responsible for cell-mediated immunity, the production of cytotoxic T-lymphocytes (CTLs), activated macrophages, activated NK cells, and cytokines against a specific antigen. They also regulate the adaptive immune responses. Generally 60-80% of the lymphocytes are T-lymphocytes. Based on biochemical markers on their surface, there are two major classes of T-lymphocytes:

- T4-lymphocytes ($CD4^+$ T-lymphocytes) have CD4 molecules and T-cell receptors (TCRs) on their surface for protein antigen recognition. They function to regulate the adaptive immune responses through cytokine production. Once activated, they differentiate into effector T4-lymphocytes such as Th1 cells, Th2 cells, and Th17 cells.
- T8-lymphocytes ($CD8^+$ T-lymphocytes) have CD8 molecules and T-cell receptors (TCRs) on their surface for protein antigen recognition. Once activated, they differentiate into cytotoxic T-lymphocytes (CTLs).

Invariant natural killer T (iNKT) cells are a subset of lymphocytes that bridge the gap between innate and adaptive immunity. They have T-cell receptors (TCRs) on their surface for glycolipid antigen recognition. Through the cytokines they produce once activated,i NKT cells are essential in both innate and adaptive immune protection against pathogens and tumors. They also play a regulatory role in the development of autoimmune diseases and transplantation tolerance.

NK cells (natural killer cells) are lymphocytes that lack B-cell receptors and T-cell receptors. They function to kill infected cells and tumor cells. NK cells are able to kill cells to which antibody molecules have attached through a process called antibody-dependent cellular cytotoxicity (ADCC). They also kill human cells lacking MHC-I molecules on their surface. Lymphocytes will be discussed in greater detail in Unit 6.

Although not white blood cells, platelets (thrombocytes) are another formed element in the blood. They promote clotting by sticking together after becoming activated and forming platelet plugs to close up damaged capillaries. They also secrete cytokines and chemokines to promote inflammation.

Why are there more neutrophils and, specifically, more band form neutrophils found in the blood during an active infection?

- Compare and contrast the functions of B-lymphocytes, T4-lymphocytes, and T8-lymphocytes in immune responses.

Concept Map for Defense Cells in the Blood: Leukocytes

Summary

1. The complete blood count (CBC) is a laboratory test that, among other things, determines the total number of both leukocytes and erythrocytes per ml of blood.
2. In general, an elevated WBC count (leukocytosis) is seen in infection, inflammation, leukemia, and parasitic infestations.
3. Neutrophils are the most abundant of the leukocytes, normally accounting for 54-75% of the WBCs. Neutrophils are important phagocytes and also promote inflammation.
4. Eosinophils normally comprise 1-4% of the WBCs. They are capable of phagocytosis but primarily they release their contents into the surrounding environment to kill microbes, especially parasitic worms, extracellularly. They also promote inflammation.
5. Basophils normally make up 0-1% of the WBCs and release histamine, leukotrienes, and prostaglandins, chemicals that promotes inflammation.
6. Monocytes normally make up 2-8% of the WBCs and differentiate into macrophages and dendritic cells when they leave the blood and enter the tissue.
7. Lymphocytes normally represent 25-40% of the WBCs and mediate the specific immune responses.
8. B-lymphocytes (B-cells) mediate humoral immunity, the production of antibody molecules against a specific antigen, and have B-cell receptors (BCR) on their surface for antigen recognition. Most B-lymphocytes differentiate into antibody-secreting plasma cells.
9. T-lymphocytes (T-cells) are responsible for cell-mediated immunity, the production of cytotoxic T-lymphocytes (CTLs), activated macrophages, activated NK cells, and cytokines against a specific antigen.
10. T4-lymphocytes have CD4 molecules and T-cell receptors on their surface for antigen recognition. They function to regulate the adaptive immune responses through cytokine production. Once activated, they differentiate into effector T4-lymphocytes.
11. T8-lymphocytes have CD8 molecules and T-cell receptors on their surface for antigen recognition. Once activated, they differentiate into T8-suppressor cells and cytotoxic T-lymphocytes (CTLs).
12. NK cells (natural killer cells) are lymphocytes that lack B-cell receptors and T-cell receptors. They function to kill infected cells and tumor cells.

This page titled 9.9: Defense Cells in the Blood- The Leukocytes is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **11.2: Defense Cells in the Blood: The Leukocytes** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

9.10: Defense Cells in the Tissue - Dendritic Cells, Macrophages, and Mast Cells

Learning Objectives

1. State 3 different functions of macrophages in body defense.
2. State the primary function of dendritic cells in body defense.
3. Name the cells in the tissue whose primary function is to present antigen to naive T-lymphocytes.
4. Name the cells in the tissue whose primary function is to present antigen to effector T-lymphocytes.
5. State the primary function of mast cells in body defense.

Dendritic Cells

Most dendritic cells are derived from monocytes and are referred to as myeloid dendritic cells. They are located throughout the epithelium of the skin, the respiratory tract, and the gastrointestinal tract, as well as lymphoid tissues and organ parenchyma. In these locations, in their immature form, they are attached by long cytoplasmic processes. Upon capturing antigens through pinocytosis and phagocytosis and becoming activated by inflammatory cytokines, the dendritic cells detach from their initial site, enter lymph vessels, and are carried to regional lymph nodes. By the time they enter the lymph nodes, they have matured and are now able to present antigen to the ever changing populations of naive T-lymphocytes located in the cortex of the lymph nodes.

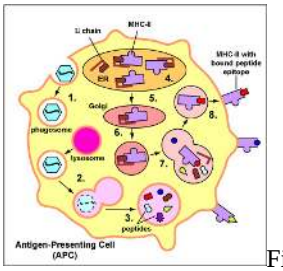


Figure 9.10.1: Binding of Peptide Epitopes from Exogenous Antigens to MHC-II Molecules. Exogenous antigens are those from outside cells of the body. Examples include bacteria, free viruses, yeasts, protozoa, and toxins. These exogenous antigens enter antigen-presenting cells or APCs (macrophages, dendritic cells, and B-lymphocytes) through phagocytosis. The microbes are engulfed and placed in a phagosome. After lysosomes fuse with the phagosome, protein antigens are degraded by proteases into a series of peptides. These peptides eventually bind to grooves in MHC-II milecules and are transported to the surface of the APC. T4-lymphocytes are then able to recognize peptide/MHC-II complexes by means of their T-cell receptors (TCRs) and CD4 molecules. 1. Exogenous antigens, such as viruses, are engulfed and placed in a phagosome. 2. Lysosomes fuse with the phagosome forming an phagolysosome. 3. Protein antigens are degraded into a series of peptides. 4. MHC-II molecules are synthesized in the endoplasmic reticulum and transported to the Golgi complex. Once assembled, within the endoplasmic reticulum, a protein called the invarient chain (Ii) attaches to the the peptide-binding groove of the MHC-II molecules and in this way prevents peptides designated for binding to MHC-I molecules within the ER from attaching to the MHC-II. 5&6. The MHC-II molecules with bound Ii chain are now transported to the Golgi complex, and placed in vesicles. 7. The vesicles containing the MHC-II molecules fuse with the peptide-containing phaglysosomes. The Ii chain is removed and the peptides are now free to bind to the grooves of the MHC-II molecules. 8. The MHC-II molecules with bound peptides are transported to the cytoplasmic membrane where they become anchored. Here, the peptide and MHC-II complexes can be recognized by T4-lymphocytes by way of TCRs and CD4 molecules having a complementary shape.

The primary function of dendritic cells is to capture and present protein antigens to naive T-lymphocytes. (Naive lymphocytes are those that have not yet encountered an antigen.) Dendritic cells engulf microorganisms and other materials and degrade them with their lysosomes. Peptides from microbial proteins are then bound to a groove of unique molecules called MHC-II molecules produced by macrophages, dendritic cells, and B-lymphocytes. The peptide epitopes bound to the MHC-II molecules are then put on the surface of the dendritic cell (Figure 9.10.1) where they can be recognized by complementary shaped T-cell receptors (TCR) and CD4 molecules on naive T4-lymphocyte (see Figure 9.10.2).

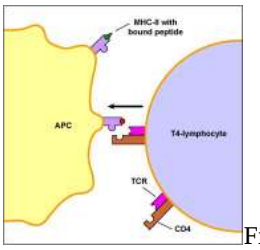


Figure 9.10.2: A T4-Lymphocyte Recognizing Epitope/MHC-II on an Antigen-Presenting Cell (APC).

Exogenous antigens are those from outside cells of the body. Examples include bacteria, free viruses, yeasts, protozoa, and toxins. These exogenous antigens enter antigen-presenting cells or APCs (macrophages, dendritic cells, and B-lymphocytes) through phagocytosis. The microbes are engulfed and placed in a phagosome. After lysosomes fuse with the phagosome, protein antigens are degraded by proteases into a series of peptides. These peptides eventually bind to grooves in MHC-II milecules and are transported to the surface of the APC. T4-lymphocytes are then able to recognize peptide/MHC-II complexes by means of their T-cell receptors (TCRs) and CD4 molecules.

In addition, dendritic cells can bind peptide epitopes to MHC-I molecules and present them to naiveT8-lymphocytes. The MHC-I molecules with bound peptide on the dendritic cell are recognized by complementary shaped T-cell receptors (TCR) and CD8 molecules on naive T8-lymphocyte (Figure 9.10.3).

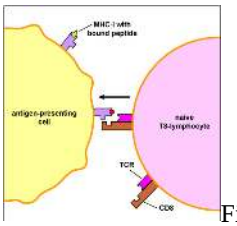
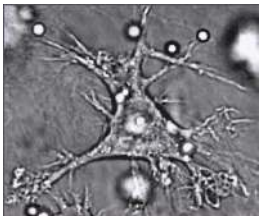


Figure 9.10.3: An Antigen-Presenting Cell Presenting MHC-I with Bound Peptide to a Naive T8-lymphocyte having a Complementary T-Cell Receptor. Antigen-presenting cells (APCs) such as dendritic cells and macrophages produce both MHC-I and MHC-II molecules. These APCs can phagocytose infected cells and tumor cells, place them in phagosomes, and degrade them with lysosomes. During this process, some of the proteins escape from the phagosome into the surrounding cytosol. Here they can be degraded into peptides by proteasomes, bound to MHC-I molecules, and placed on the surface of the APC. Now the peptide/MHC-I complexes can be recognized by a naive T8-lymphocyte having a complementary shaped T-cell receptor (TCR) and CD8 molecule. This activates the naive T8-lymphocyte enabling it to eventually proliferate and differentiate into cytotoxic T-lymphocytes (CTLs).



A dendritic cell. (CC BY-SA 2.5; Judith Behnsen, Priyanka Narang, Mike Hasenberg, Frank Gunzer, Ursula Bilitewski, Nina Klippel, Manfred Rohde, Matthias Brock, Axel A. Brakhage, Matthias Gunzer - Source: PLoS Pathogens).

These interactions enable the T4-lymphocytes or T8-lymphocytes to become activated, proliferate, and differentiate into effector cells. This will be discussed in detail in Unit 6. Myeloid dendritic cells also use pattern-recognition receptors called toll-like receptors (TLRs) to recognize pathogen-associated molecular patterns or PAMPs (Figure 9.10.4). The interaction of the PAMP with its TLR stimulates the production of co-stimulatory molecules that are also required for T-lymphocyte activation. Dendritic cells produce many of the same inflammatory cytokines as macrophages, such as tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (IL-1), interleukin-6 (IL-6), and interleukin-8 (IL-8). They also can produce interleukin-12 (IL-12), a cytokine that can activate natural killer T-lymphocytes (NKT cells).

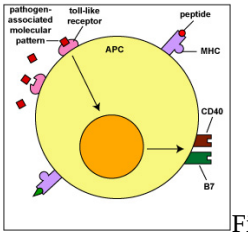


Figure 9.10.4: Production of Co-stimulatory Molecules by Antgen-Presenting Cells (APCs). Antigen-presenting cells such as dendritic cells and macrophages can produce both MHC-I and MHC-II molecules. MHC-I molecules with bound peptides can be recognized by a complementary-shaped TCR/CD8 on the surface of a naive T8-lymphocyte while MHC-II molecules with bound peptides can be recognized by a complementary-shaped TCR/CD4 on the surface of a naive T4-lymphocyte. This represents the first signal necessary for activation of the naive T4- or T8-lymphocyte. Co-stimulatory signals involving the interaction of co-stimulatory molecules such as CD40 and B7 molecules on the APC with their corresponding ligands on the T4- or T8-lymphocyte are also necessary for activation. These co-stimulatory molecules are only synthesized when toll-like receptors on APCs bind to pathogen-associated molecular patterns of microbes. This is another backup system to help assure that the TCR of the lymphocyte is recognizing a nonself peptide and not a self peptide on the MHC molecules of the APC. Without the interaction of the co-stimulatory molecules, the naive T4- or T8-lymphocyte is not activated and undergoes apoptosis.

Another type of dendritic cell, the plasmacytoid dendritic cell, uses its TLRs to recognize viral PAMPs. This interaction results in the production and secretion of type I interferons. Antigen-presenting cells or APCs will be discussed in greater detail in Unit 6.

Macrophages

When monocytes leave the blood and enter the tissue, they become activated and differentiate into macrophages. Those that have recently left the blood during inflammation and move to the site of infection through positive chemotaxis are sometimes referred to as wandering macrophages. In addition, the body has macrophages already stationed throughout all tissues and organs of the body. These are sometimes referred to as fixed macrophages.

Many fixed macrophages are part of the mononuclear phagocytic (reticuloendothelial) system. They, along with B-lymphocytes and T-lymphocytes, are found supported by reticular fibers in lymph nodules, lymph nodes, and the spleen where they filter out and phagocytose foreign matter such as microbes. Similar cells are also found in the liver (Kupffer cells), the kidneys (mesangial cells), the brain (microglia), the bones (osteoclasts), the lungs (alveolar macrophages), and the gastrointestinal tract (peritoneal macrophages). Macrophages actually have a number of very important functions in body defense including:

Function 1

Killing of microbes, infected cells, and tumor cells by phagocytosis. Macrophages that have engulfed microorganisms become activated by a subset of T-helper lymphocytes called T_h1 cells (Figure 9.10.6). Activated macrophages develop a ruffled cytoplasmic membrane and produce increased numbers of lysosomes.

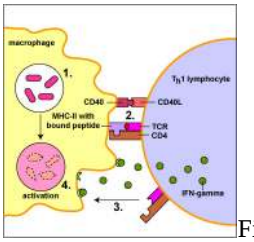


Figure 9.10.6: Activation of a Macrophage by a T_h1 Lymphocyte. 1. Engulfed bacteria inside a phagosome or a phagolysosome. 2. An activated T_h1 lymphocyte binds to a peptide/MHC-II complex on a macrophage by way of its TCR and CD4 molecule. Co-stimulatory molecules such as CD40L on the T_h1 cell then bind toCD40 on a macrophage. 3. This triggers the T_h1 lymphocyte to secrete the cytokine interferon-gamma (IFN-gamma) that binds to IFN-gamma receptors receptors on the macrophage. 4. The IFN-gamma activates the macrophage enabling it to produce more hydrolytic lysosomal enzymes, nitric oxide, and toxic oxygen radicals that destroy the microorganisms within the phagosomes and phagolysosomes.

Function 2

Processing antigens so they can be recognized by effector T-lymphocytes during the adaptive immune responses. Macrophages, as well as the dendritic cells mentioned below, process antigens through phagocytosis and present them to T-lymphocytes. Because of this function, they are often referred to as antigen-presenting cells or APCs.

Macrophages primarily capture and present protein antigens to effector T-lymphocytes. (Effector lymphocytes are lymphocytes that have encountered an antigen, proliferated, and matured into a form capable of actively carrying out immune defenses.) Macrophages engulf the microorganism and degrade it with their lysosomes. Peptides from microbial proteins are then bound to a groove of unique molecules called MHC-II molecules produced by macrophages, dendritic cells, and B-lymphocytes. The peptide epitopes bound to the MHC-II molecules are then put on the surface of the macrophage (Figure **9.10.1**) where they can be recognized by complementary shaped T-cell receptors (TCR) and CD4 molecules on an effector T4-lymphocyte (Figure **9.10.2**). This interaction leads to the activation of that macrophage.

Like dendritic cells discussed above, macrophages are also capable of capturing and presenting protein antigens to naive T-lymphocytes although they are not as important in this function.

Function 3

Secreting lipid mediators of inflammation such as leukotrienes, prostaglandins, and platelet-activating factor (PAF).

Function 4

Secreting proteins called cytokines that play a variety of roles in non-specific body defense. Macrophage-produced cytokines promote inflammation and induce fever, increase phagocytosis and energy output, promote sleep, activate resting T-lymphocytes , attract and activate neutrophils, and stimulate the replication of endothelial cells to form capillaries and fibroblasts to form connective scar tissue. Four important cytokines that macrophages produce (as mentioned in Unit 1 under endotoxin) are tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (IL-1), interleukin-6 (IL-6), and interleukin-8 (IL-8).

There is growing evidence that monocytes and macrophages can be “trained” by an earlier infection to do better in future infections, that is, develop memory. It is thought that microbial pathogen-associated molecular patterns (PAMPs) binding to pattern-recognition (PRRs) on monocytes and macrophages triggers the cell’s epigenome to reprogram or train that cell to react better against new infections.

Macrophages show great functional diversity. In addition to the populations of macrophages involved in body defense and immunity, there are populations of macrophages that play important roles in:

1. The development of a variety of tissues and organs within the body, including the brain, blood cells, mammary gland, pancreas, and kidneys.
2. Modulating normal physiology and maintaining homeostasis in the body, including insulin resistance and sensitivity, long term nutrient storage, thermogenesis, and liver and pancreas function in response to caloric intake.
3. Tissue repair, including the formation of scar tissue and the growth of new capillaries into injured tissues.

Mast Cells

Mast cells are typically the immunological first responders to infection and carry out many of the same inflammatory-mediating functions as basophils. There are two types of mast cells in the body: mast cells found in the connective tissue and mast cells found throughout the mucous membranes. The granules of mast cells contain such mediators as histamine, eosinophil chemotactic factor, neutrophil chemotactic factor, platelet activating factor, and cytokines such as IL-3, IL-4, IL-5, IL-6, and TNF-alpha. They also possess pathways for synthesizing leukotrienes and prostaglandins, chemicals that promote inflammation by causing vasodilation, increasing capillary permeability, and increasing mucous production.

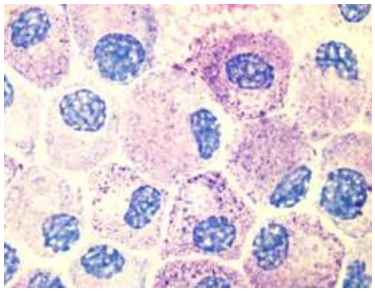


Photo of cultured mast cells at 100X using an oil immersion lens and an olympus digital camera. The cells are stained with Tol Blue, and might appear slightly degranulated as they were activated using an artificial antigen during the course of an experiment.

Image use with permission (Kauczuk).

Mast cells have pattern-recognition receptors or PRRs on their surface that interact with pathogen-associated molecular patterns or PAMPs of microbes. After the PAMPs bind to their respective PRRs, they release the contents of their granules. These chemical mediators promote inflammation and attract neutrophils to the infected site.

Summary

1. Most dendritic cells are derived from monocytes and are referred to as myeloid dendritic cells and are located throughout the epithelium of the skin, the respiratory tract, and the gastrointestinal tract, as well as lymphoid tissues and organ parenchyma.
2. Upon capturing antigens through pinocytosis and, the dendritic cells detach from their initial site, enter lymph vessels, and are carried to regional lymph nodes where they present antigens to the ever changing populations of naive T-lymphocytes.
3. The primary function of dendritic cells is to capture and present protein antigens to naive T-lymphocytes.
4. When monocytes leave the blood and enter the tissue, many become activated and differentiate into macrophages. These macrophages that have recently left the blood during inflammation and move to the site of infection through positive chemotaxis are sometimes referred to as wandering macrophages.
5. The body has macrophages already stationed throughout the tissues and organs of the body and these are sometimes referred to as fixed macrophages.
6. Functions of macrophages include killing of microbes, infected cells, and tumor cells by phagocytosis, processing antigens so they can be recognized by effector T-lymphocytes during the adaptive immune responses, and secreting mediators of inflammation such as leukotrienes, prostaglandins, and platelet-activating factor, and cytokines.
7. Mast cells are typically the immunological first responders to infection and carry out many of the same inflammatory-mediating functions as basophils.

This page titled 9.10: Defense Cells in the Tissue - Dendritic Cells, Macrophages, and Mast Cells is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **11.3: Defense Cells in the Tissue - Dendritic Cells, Macrophages, and Mast Cells** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

9.11: Early Induced Innate Immunity

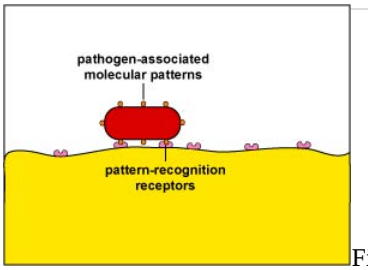


Figure **9.11.1**: Pathogen-Associated Molecular Patterns Binding to Pattern-Recognition Receptors on Defense Cells. Glycoprotein molecules known as pattern-recognition receptors are found on the surface of a variety of body defense cells. They are so named because they recognize and bind to pathogen-associated molecular patterns - molecular components associated with microorganisms but not found as a part of eukaryotic cells. These include bacterial molecules such as peptidoglycan, teichoic acids, lipopolysaccharide, mannans, flagellin, pilin, and bacterial DNA. There are also pattern-recognition molecules for viral double-stranded RNA (dsRNA) and fungal cell walls components such as lipoteichoic acids, glycolipids, mannans, and zymosan. Many of these pattern recognition receptors are known as toll-like receptors.

Most body defense cells have pattern-recognition receptors or PRRs for these common PAMPs enabling an immediate response against the invading microorganism. Pathogen-associated molecular patterns can also be recognized by a series of soluble pattern-recognition receptors in the blood that function as opsonins and initiate the complement pathways. In all, the innate immune system is thought to recognize approximately 10^3 of these microbial molecular patterns.

This page titled 9.11: Early Induced Innate Immunity is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **11.4: Early Induced Innate Immunity** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

9.11A: Pathogen-Associated Molecular Patterns (PAMPs) and Danger-Associated Molecular Patterns (DAMPs)

State how long it takes for early induced innate immunity to become activated and what it involves.
- State what is meant by pathogen-associated molecular patterns (PAMPs), and the role PAMPs play in inducing innate immunity.
- Name at least 5 PAMPS associated with bacteria.
- Name at least 2 PAMPS associated with viruses.
- Define DAMPs and give two examples.

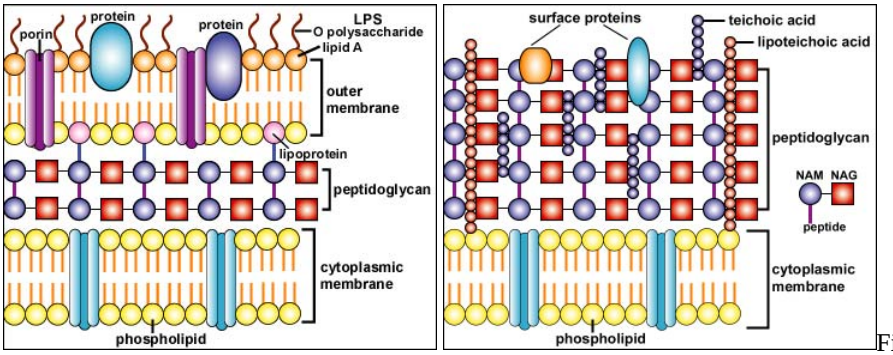


Figure **9.11*A*.1**: (left) Structure of a Gram-Negative Cell Wall. The Gram-negative cell wall is composed of a thin, inner layer of peptidoglycan and an outer membrane consisting of molecules of phospholipids, lipopolysaccharides (LPS), lipoproteins and surface proteins. The lipopolysaccharide consists of lipid A and O polysaccharide. (right) The Gram-positive cell wall appears as dense layer typically composed of numerous rows of peptidoglycan, and molecules of lipoteichoic acid, wall teichoic acid and surface proteins.

Examples of microbial-associated PAMPs include:

a. lipopolysaccharide (LPS) from the outer membrane of the Gram-negative cell wall (see Figure **9.11*A*.1**A);
b. bacterial lipoproteins and lipopeptides (see Figure **9.11*A*.1**A);
c. porins in the outer membrane of the Gram-negative cell wall (see Figure **9.11*A*.1**A);
d. peptidoglycan found abundantly in the Gram-positive cell wall and to a lesser degree in the gram-negative cell wall (see Figure **9.11*A*.1**B);
e. lipoteichoic acids found in the Gram-positive cell wall (Figure **9.11*A*.1**B);
f. lipoarabinomannan and mycolic acids found in acid-fast cell walls (Figure **9.11*A*.2**B)
g. mannose-rich glycans (short carbohydrate chains with the sugar mannose or fructose as the terminal sugar). These are common in microbial glycoproteins and glycolipids but rare in those of humans (see Figure **9.11*A*.6**).
h. flagellin found in bacterial flagella;
i. bacterial and viral nucleic acid. Bacterial and viral genomes contain a high frequency of unmethylated cytosine-guanine dinucleotide or CpG sequences (a cytosine lacking a methyl or CH_3 group and located adjacent to a guanine). Mammalian DNA has a low frequency of CpG sequences and most are methylated which may mask recognition by pattern-recognition receptors . Also, human DNA and RNA does not normally enter cellular endosomes where the pattern-recognition receptors for microbial DNA and RNA are located;
j. *N*-formylmethionine , an amino acid common to bacterial proteins;
k. double-stranded viral RNA unique to many viruses in some stage of their replication;
l. single-stranded viral RNA from many` viruses having an RNA genome;
m. lipoteichoic acids, glycolipids, and zymosan from yeast cell walls; and
n. phosphorylcholine and other lipids common to microbial membranes.

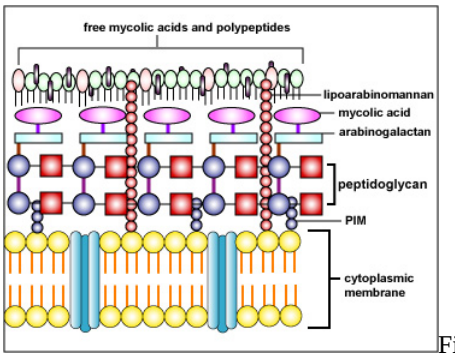


Figure **9.11*A*.2**: Structure of an Acid-Fast Cell Wall. In addition to peptidoglycan, the acid-fast cell wall of Mycobacterium contains a large amount of glycolipids, especially mycolic acids. The peptidoglycan layer is linked to arabinogalactan (D-arabinose and D-galactose) which is then linked to high-molecular weight mycolic acids. The arabinogalactan/mycolic acid layer is overlaid with a layer of polypeptides and mycolic acids consisting of free lipids, glycolipids, and peptidoglycolipids. Other glycolipids include lipoarabinomannan and phosphatidyinositol mannosides (PIM). Because of its unique cell wall, when it is stained by the acid-fast procedure, it will resist decolorization with acid-alcohol and stain red, the color of the initial stain, carbol fuchsin. With the exception of a very few other acid-fast bacteria such as Nocardia, all other bacteria will be decolorized and stain blue, the color of the methylene blue counterstain.

Examples of DAMPs associated with stressed, injured, infected, or transformed host cells and not found on normal cells include:

a. heat-shock proteins;
b. altered membrane phospholipids; and
c. molecules normally located inside phagosomes and lysosomes that enter the cytosol only when these membrane-bound compartments are damaged as a result of infection, including antibodies bound to microbes from opsonization.
d. molecules normally found within cells, such as ATP, DNA, and RNA, that spill out of damaged cells.

To recognize PAMPs such as those listed above, various body cells have a variety of corresponding receptors called pattern-recognition receptors or PRRs capable of binding specifically to conserved portions of these molecules. Cells that typically have pattern recognition receptors include macrophages , dendritic cells , endothelial cells , mucosal epithelial cells, and lymphocytes .

? What are DAMPs and why would it be an advantage for them to initiate an inflammatory response similar to PAMPs?

Summary

1. Early induced innate immunity begins 4 - 96 hours after exposure to an infectious agent and involves the recruitment of defense cells as a result of pathogen-associated molecular patterns or PAMPS binding to pattern-recognition receptors or PRRs.
2. Pathogen-associated molecular patterns or PAMPs are molecules shared by groups of related microbes that are essential for the survival of those organisms and are not found associated with mammalian cells. Examples include LPS, porins, peptidoglycan, lipoteichoic acids, mannose-rich glycans, flagellin, bacterial and viral genomes, mycolic acid, and lipoarabinomannan.
3. Danger-associated molecular patterns or DAMPs are unique molecules displayed on stressed, injured, infected, or transformed human cells also be recognized as a part of innate immunity. Examples include heat-shock proteins and altered membrane phospholipids.
4. PAMPs and DAMPs bind to pattern-recognition receptors or PRRs associated with body cells to induce innate immunity.

This page titled 9.11A: Pathogen-Associated Molecular Patterns (PAMPs) and Danger-Associated Molecular Patterns (DAMPs) is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **11.3A: Pathogen-Associated Molecular Patterns (PAMPs) and Danger-Associated Molecular Patterns (DAMPs)** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

9.11B: Pattern-Recognition Receptors (PRRs)

State the function of the following as they relate to innate immunity.

a. pattern recognition receptors (PRRs)
b. endocytic pattern recognition receptors
c. signaling pattern recognition receptors
d. danger-associated molecular patterns
e. danger recognition receptors
f. inflammasome
g. pyroptosis

- Name 2 endocytic PRRs.
- Name 2 signaling PRRs found on host cell surfaces.
- Name 2 signaling PRRs found in the endosomes of phagocytic cells.
- Name 2 signaling PRRs found on the host cell cytoplasm.
- Briefly describe the major difference between the effect of the cytokines produced in response to PAMPs that bind to cell surface signaling PRRs and endosomal PRRs.

In order to recognize PAMPs, various body cells have a variety of corresponding receptors called pattern-recognition receptors or PRRs (see Figure 9.11B.5) capable of binding specifically to conserved portions of these molecules. Cells that typically have pattern recognition receptors include macrophages, dendritic cells, endothelial cells, mucosal epithelial cells, and lymphocytes.

Many pattern-recognition receptors are located on the surface of these cells where they can interact with PAMPs on the surface of microbes. Others PRRs are found within the phagolysosomes of phagocytes where they can interact with PAMPs located within microbes that have been phagocytosed. Some PRRs are found in the cytosol of the cell.

There are two functionally different major classes of pattern-recognition receptors: endocytic pattern-recognition receptors and signaling pattern-recognition receptors.

Endocytic (Phagocytic) Pattern-Recognition Receptors

Endocytic pattern-recognition receptors, also called phagocytic pattern-recognition receptors, are found on the surface of phagocytes and promote the attachment of microorganisms to phagocytes leading to their subsequent engulfment and destruction. They include:

1. Mannose receptors

Mannose receptors on the surface of phagocytes bind to various microbial carbohydrates such as those rich in mannose or fucose, and to N-acetylglucosamine (NAG). Human glycoproteins and glycolipids typically have terminal N-acetylglucosamine and sialic acid groups. C-type lectins found on the surface of phagocytes are mannose receptors (see Figure 9.11B.6).

It is now thought that mannose receptors may be quite important in removing potentially harmful mannose-containing glycoproteins such as lysosomal hydrolases that are produced in increased amounts during inflammation.

2. Dectin-1

Dectin-1 recognizes beta-glucans (polymers of glucose) commonly found in fungal cell walls.

3. Scavenger receptors

Scavenger receptors found on the surface of phagocytic cells bind to bacterial cell wall components such as LPS, peptidoglycan and teichoic acids (see Figure 9.11B.7). There are also scavenger receptors for certain components of other types of microorganisms, as well as for stressed, infected, or injured cells. Scavenger receptors include CD-36, CD-68, and SRB-1.

4. Opsonin receptors

Opsonins are soluble molecules produced as a part of the body's immune defenses that bind microbes to phagocytes. One portion of the opsonin binds to a PAMP on the microbial surface and another portion binds to a specific receptor on the phagocytic cell.

- Acute phase proteins circulating in the plasma, such as:
  - mannose-binding lectin (also called mannose-binding protein) that binds to various microbial carbohydrates such as those rich in mannose or fucose, and to N-acetylglucosamine (NAG); and
  - C-reactive protein (CRP) that binds to phosphorylcholine portion of teichoic acids and lipopolysaccharides of bacterial and fungal cell walls. It also binds to the phosphocholine found on the surface of damaged or dead human cells.
- Complement pathway proteins, such as C3b (see Figure 9.11B.8) and C4b recognize a variety of PAMPS.
- Surfactant proteins in the alveoli of the lungs, such as SP-A and SP-D are opsonins.
- During adaptive immunity, the antibody molecule IgG can function as an opsonin (see Figure 9.11B.16).

Flash animation illustrating the function of endocytic pattern-recognition receptors on phagocytes.

html5 version of animation for iPad illustrating the function of endocytic pattern-recognition receptors on phagocytes.

5. *N*-formyl Met receptors

N-formyl methionine is the first amino acid produced in bacterial proteins since the f-met-tRNA in bacteria has an anticodon complementary to the AUG start codon (see Figure 9.11B.17). This form of the amino acid is not typically seen in mammalian proteins. FPR and FPRL1 are *N*-formyl receptors on neutrophils and macrophages. Binding of *N*-formyl Met to its receptor promotes the motility and the chemotaxis of these phagocytes. It also promotes phagocytosis.

Signaling Pattern-Recognition Receptors

Signaling pattern-recognition receptors bind a number of microbial molecules: LPS, peptidoglycan, teichoic acids, flagellin, pilin, unmethylated cytosine-guanine dinucleotide or CpG sequences from bacterial and viral genomes; lipoteichoic acid, glycolipids, and zymosan from fungi; double-stranded viral RNA, and certain single-stranded viral RNAs. Binding of microbial PAMPs to signaling PRRs promotes the production of:

- inflammatory cytokines, such as such as interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-alpha), and interleukin-12 (IL-12);
- antiviral cytokines called type-1 interferons (IFN), such as IFN-alpha and IFN-beta;
- chemotactic factors, such as the chemokines interleukin-8 (IL-8), MCP-1, and RANTES; and
- antimicrobial peptides, such as human defensins *)* and cathelicidins.

These molecules are crucial to initiating innate immunity and adaptive immunity.

1. Signaling PRRs found on cell surfaces (see Figure 9.11B.5):

A series of signaling pattern-recognition receptors known as toll-like receptors (TLRs) are found on the surface of a variety of defense cells and other cells. These TLRs play a major role in the induction of innate immunity and contribute to the induction of adaptive immunity.

Different combinations of TLRs appear in different cell types and may occur in pairs. Different TLRs directly or indirectly bind different microbial molecules. For example:

a. TLR-2 - recognizes peptidoglycan, bacterial lipoproteins, lipoteichoic acid (Gram-positive bacteria), and porins (gram-negative bacteria).

b. TLR-4 - recognizes lipopolysaccharide (Gram-negative bacteria), fungal mannans, viral envelope proteins, parasitic phospholipids, heat-shock proteins.
c. TLR-5 - recognizes bacterial flagellin;
d. TLR-1/TLR-2 pairs - binds to bacterial lipopeptides, lipomannans (mycobacteria) lipoteichoic acids (Gram-positive bacteria), cell wall beta gucans (bacteria and fungi), zymosan (fungi) and glycosylphosphatidylinositol (GPI)-anchored proteins (protozoa).
e. TLR-2/TL6 pairs - also binds to bacterial lipopeptides, lipomannans (mycobacteria) lipoteichoic acids (Gram-positive bacteria), cell wall beta gucans (bacteria and fungi), zymosan (fungi) and glycosylphosphatidylinositol (GPI)-anchored proteins (protozoa).

Many of the TLRs, especially those that bind to bacterial and fungal cell wall components, stimulate the transcription and translation of inflammatory cytokines such as interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-alpha), and interleukin-12 (IL-12), as well as chemokines such as interleukin-8 (IL-8), MCP-1, and RANTES. These cytokines trigger innate immune defenses such as inflammation, fever, and phagocytosis in order to provide an immediate response against the invading microorganism (see Figure 9.11B.9). Because cytokines such as IL-I, TNF-alpha, and IL-12 that trigger an inflammatory response, they are often referred to as inflammatory cytokines. Chemokines are a group of cytokines that enable the migration of leukocytes from the blood to the tissues at the site of inflammation. To counter inflammation, anti-inflammatory cytokines such as IL-1 receptor antagonist, IL-4, and IL-10 are produced.

Another cell surface PRR is CD14. CD14 is found on monocytes, macrophages, and neutrophils and promotes the ability of TLR-4 to respond to LPS. LPS typically binds to LPS-binding protein in the plasma and tissue fluid. The LPS-binding protein promotes the binding of LPS to the CD14 receptors. At that point the LPS-binding protein comes off and the LPS-CD14 bind to TLR-4. Interaction of LPS and CD14 with TLR-4 leads to an elevated synthesis and secretion of inflammatory cytokines such as IL-1, IL-6, IL-8, TNF-alpha, and platelet-activating factor (PAF). These cytokines then bind to cytokine receptors on target cells and initiate inflammation and activate both the complement pathways and the coagulation pathway (see Figure 9.11B.9).

The signaling process for the CD14 and TLR-4 response to LPS is shown in Figure 9.11B.15.

Flash animation illustrating signaling toll-like receptors on defense cells: LPS and TLR-4.

html5 version of animation for iPad illustrating signaling toll-like receptors on defense cells: LPS and TLR-4.

Flash animation illustrating signaling toll-like receptors on defense cells: LTA and TLR-2/TLR-6.

html5 version of animation for iPad illustrating signaling toll-like receptors on defense cells: LTA and TLR-2/TLR-6.

For More Information: Inflammation from Unit 5

TLRs also participate in adaptive immunity by triggering various secondary signals needed for humoral immunity (the production of antibodies) and cell-mediated immunity (the production of cytotoxic T-lymphocytes, activated macrophages, and additional cytokines). Without innate immune responses there could be no adaptive immunity.

a. T-independent (TI) antigens allow B-lymphocytes to mount an antibody response without the requirement of interaction with effector T4-lymphocytes. The resulting antibody molecules are generally of the IgM isotype and do

not give rise to a memory response. There are two basic types of T-independent antigens: TI-1 and TI-2. TI-1 antigens are pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharide (LPS) from the outer membrane of the gram-negative cell wall and lipoteichoic acids from the gram-positive cell wall. These antigens activate B-lymphocytes by binding to their specific toll-like receptors rather than to B-cell receptors (see Figure 9.11B.11). Antibody molecules generated against TI-1 antigens are often called "natural antibodies" because they are always being made against bacteria present in the body.

b. The activation of naive T-lymphocytes requires co-stimulatory signals involving the interaction of accessory molecules on antigen-presenting cells or APCs with their corresponding ligands on T-lymphocytes. These co-stimulatory molecules are only synthesized when toll-like receptors on APCs bind to pathogen-associated molecular patterns of microbes (see Figure 9.11B.12).

2. Signaling PRRs found in the membranes of the endosomes (phagolysosomes) used to degrade pathogens (see Figure 9.11B.5):

a. TLR-3 - binds double-stranded viral RNA;
b. TLR-7 - binds single-stranded viral RNA, such as in HIV, rich in guanine/uracil nucleotide pairs;
c. TLR-8 - binds single-stranded viral RNA;
d. TLR-9 - binds unmethylated cytosine-guanine dinucleotide sequences (CpG DNA) found in bacterial and viral genomes but uncommon or masked in human DNA and RNA.

Most of the TLRs that bind to viral components trigger the synthesis of cytokines called interferons that block viral replication within infected host cells as well as inflammatory cytokines.

Flash animation showing toll-like receptors (TLRs) recognizing viral double-stranded RNA.

html5 version of animation for iPad showing showing toll-like receptors (TLRs) recognizing viral double-stranded RNA.

GIF animation showing the antiviral nature of interferon.

3. Signaling PRRs and DRRs found in the cytoplasm (see Figure 9.11B.5)

Pattern-recognition receptors or PRRs found in the cytoplasm include:

a. NODs (nucleotide-binding oligomerization domain)

NOD proteins, including NOD-1 and NOD-2, are cytostolic proteins that allow intracellular recognition of peptidoglycan components.

1. NOD-1 recognizes peptidoglycan containing the muramyl dipeptide NAG-NAM-gamma-D-glutamyl-meso diaminopimelic acid, part of the peptidoglycan monomer in common gram-negative bacteria and just a few gram-positive bacteria.

2. NOD-2 recognizes peptidoglycan containing the muramyl dipeptide NAG-NAM-L-alanyl-isoglutamine found in practically all bacteria (see Figure 9.11B.5).

As macrophages phagocytose either whole bacteria or peptidoglycan fragments released during bacterial growth, the peptidoglycan is broken down into muramyl dipeptides. Binding of the muramyl dipetides to NOD-1 or NOD-2 leads to the activation of genes coding for inflammatory cytokines such as IL-1, TNF-alpha, IL-8, and IL-12 in a manner similar to the cell surface TLRs. Activation of NOD-2 also induces the production of antimicrobial peptides such as defensins as well as microbicidal reactive oxygen species (ROS).

b. CARD-containing proteins

CARD (caspase activating and recruitment domain)-containing proteins, such as RIG-1 (retinoic acid-inducible gene-1) and MDA-5 (melanoma differentiation-associated gene-5), are cytoplasmic sensors of viral RNA molecules that trigger the synthesis of type-1 interferons, antiviral cytokines that block viral replication within infected host cells in a manner similar to the endosomal TLRs. RIG-1 recognizes 5'-PPPs on viral RNAs. The 5'-PPPs on host cell RNAs are either capped or removed and are not recognized by RIG-1. Rig-1 and MDA-5 can also, through another regulatory pathway, stimulate the production of inflammatory cytokines.

Detection of PAMPs by PRRs in the cytosol trigger the formation of multi-protein complexes called inflammasomes which, in turn, leads to the activation of caspase-1. Caspase-1 triggers the formation of inflammatory cytokines and can also result in an inflammatory response-induced cell suicide called pyroptosis. Pyroptosis, unlike apoptosis, leads to the release of PAMPS as well as inflammatory cytokines from the lysed cell.

Pyroptosis is initiated by PAMPs binding to pattern-recognition receptors (PRRs) on various defense cells which then triggers the production of inflammatory cytokines and type-1 interferons. Other PRRs, called nod-like receptors (NLRs) located in the cytosol of these defense cells recognize PAMPs and DAMPs that have entered the host cell's cytosol. Some NLRs trigger the production of inflammatory cytokines while others activate caspase 1-dependent pyroptosis of the cell causing the release of its intracellular inflammatory cytokines (see Figure 9.11*B*.1). The binding of PAMPs or DAMPs to their respective NLRs triggers the assembly of multiprotein complexes called inflammasomes in the cytosol of the host cell. It is these inflammasomes that activate caspase 1 and induce inflammation and pyroptosis. Pyroptosis results in production of proinflammatory cytokines, rupture of the cell's plasma membrane, and subsequent release of proinflammatory intracellular contents. It plays an essential role in innate immunity by promoting inflammation to control microbial infections. At highly elevated levels, however, it can cause considerable harm to the body and even death.

c. Danger recognition receptors or DRRs

Danger recognition receptors or DRRs found in the cytoplasm recognize danger-associated molecular patterns (DAMPS) in the cytosol such as altered membrane phospholipids, and materials released from damaged phagosomes and damaged lysosomes, including antibodies bound to microbes from opsonization. DAMPs are also produced as a result of tissue injury during cancer, heart attack, and stroke. Detection of DAMPs by DRRs in the cytosol also triggers the activation of inflammasomes, release of inflammatory cytokines, and pyroptosis.

4. Secreted signaling PRRs found in plasma and tissue fluid

In addition to the PRRs found on or within cells, there are also secreted pattern-recognition receptors. These PRRs bind to microbial cell walls and enable them to activate the complement pathways, as well as by phagocytes. For example, mannan-binding lectin -also known as mannan-binding protein - is synthesized by the liver and released into the bloodstream as part of the acute phase response discussed later in Unit 4. Here it can bind to the carbohydrates on bacteria, yeast, some viruses, and some parasites (see Figure 9.11*B*.6). This, in turn, activates the lectin complement pathway (discussed later in Unit 4) and results in the production of a variety of activated complement proteins that are able to trigger inflammation, chemotactically attract phagocytes to the infection site, promote the attachment of antigens to phagocytes via enhanced attachment or opsonization, and cause lysis of gram-negative bacteria and infected or transformed human cells.

Other secreted PRRs include C-reactive protein (CRP), surfactant protein A (SP-A), surfactant protein D (SP-D), collectin liver 1 (CL-L1), and ficolins.

Flash animation showing activation of the lectin pathway, formation of C3 convertase, and formation of C5 convertase.

html5 version of animation for iPad showing activation of the lectin pathway, formation of C3 convertase, and formation of C5 convertase.

Compare and contrast the functions of endocytic pattern-recognition receptors and signaling pattern-recognition receptors.

- Compare and contrast signaling pattern-recognition receptors found on cell surfaces with those found in the membranes of endosomes (phagolysosomes).

Concept Map for PRRs and DRRs

Summary

1. Early induced innate immunity begins 4 - 96 hours after exposure to an infectious agent and involves the recruitment of defense cells as a result of pathogen-associated molecular patterns or PAMPS binding to pattern-recognition receptors or PRRs and danger-associated molecular patterns or DAMPs binding to danger-recognition receptors or DRRs.
2. Endocytic pattern-recognition receptors are found on the surface of phagocytes and promote the attachment of microorganisms to phagocytes leading to their subsequent engulfment and destruction. They include mannose receptors, scavenger receptors, and opsonin receptors.
3. Binding of microbial PAMPs to signaling PRRs promotes the production of inflammatory cytokines, antiviral cytokines called type-1 interferons (IFN), chemotactic factors, and antimicrobial peptides. They include toll-like receptors (TLRs) and NODs.
4. PRRs found on the surface of the body's cells typically bind to surface PAMPs on microbes and stimulate the production of inflammatory cytokines.
5. PRRs found within cellular phagolysosomes (endosomes) typically detect nucleic acid PAMPs released during the phagocytic destruction of viruses and stimulate the production of antiviral cytokines called type-1 interferons.
6. PRRs and DRRs found within the cytoplasm of host cells typically trigger the formation of multi-protein complexes called inflammasomes which, in turn, triggers the formation of inflammatory cytokines and can also leads to an inflammatory response-induced cell suicide called pyroptosis.
7. PRRs circulating in the blood and tissue fluid activate the complement pathways and may function as opsonins.

This page titled 9.11B: Pattern-Recognition Receptors (PRRs) is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **11.3B: Pattern-Recognition Receptors (PRRs)** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

9.11C: Cytokines Important in Innate Immunity

Learning Objectives

1. Describe the following:
   a. cytokines
   b. chemokines
   c. interferons
2. State what is meant by the phrase "Cytokines are pleiotropic, redundant, and multifunctional."
3. Name the two cytokines that are most important in stimulating acute inflammation.
4. Describe specifically how type I interferons are able to block viral replication within an infected host cell.

Cytokines are low molecular weight, soluble proteins that are produced in response to an antigen and function as chemical messengers for regulating the innate and adaptive immune systems. They are produced by virtually all cells involved in innate and adaptive immunity, but especially by T- helper (Th) lymphocytes. The activation of cytokine-producing cells triggers them to synthesize and secrete their cytokines. The cytokines, in turn, are then able to bind to specific cytokine receptors on other cells of the immune system and influence their activity in some manner.

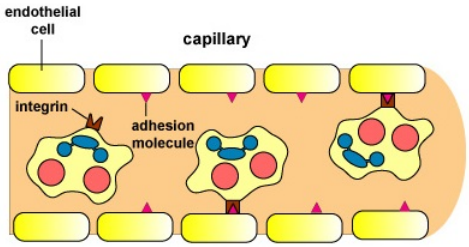
Cytokines are pleiotropic, redundant, and multifunctional.

- Pleiotropic means that a particular cytokine can act on a number of different types of cells rather than a single cell type.
- Redundant refers to to the ability of a number of different cytokines to carry out the same function.
- Multifunctional means the same cytokine is able to regulate a number of different functions.

Some cytokines are antagonistic in that one cytokine stimulates a particular defense function while another cytokine inhibits that function. Other cytokines are synergistic wherein two different cytokines have a greater effect in combination than either of the two would by themselves. There are three functional categories of cytokines:

1. cytokines that regulate innate immune responses,
2. cytokines that regulate adaptive Immune responses, and
3. cytokines that stimulate hematopoiesis.

Cytokines that regulate innate immunity are produced primarily by mononuclear phagocytes such as macrophages and dendritic cells, although they can also be produced by T-lymphocytes, NK cells, endothelial cells, and mucosal epithelial cells. They are produced primarily in response to pathogen-associated molecular patterns (PAMPs) such as LPS, peptidoglycan monomers, teichoic acids, unmethylated cytosine-guanine dinucleotide or CpG sequences in bacterial and viral genomes, and double-stranded viral RNA. Cytokines produced in response to PRRs on cell surfaces, such as the inflammatory cytokines IL-1, IL-6, IL-8, and TNF-alpha, mainly act on leukocytes and the endothelial cells that form blood vessels in order to promote and control early inflammatory responses (Figure 9.11C.1). Cytokines produced in response to PRRs that recognize viral nucleic acids, such as type I interferons, primarily block viral replication within infected host cells (see Figure 9.11C.2A and Figure 9.11C.2B).



https://med.libretexts.org/@go/page/77724

Figure **9.11*C*.1:** *Integrins on the surface of the leukocyte bind to adhesion molecules on the inner surface of the vascular endothelial cells. The leukocytes flatten out and squeeze between the endothelial cells to leave the blood vessels and enter the tissue. The increased capillary permeability also allows plasma to enter the tissue.*

Examples include:

a. Tumor necrosis factor-alpha (TNF-a)

TNF-a is the principle cytokine that mediates acute inflammation. In excessive amounts it also is the principal cause of systemic complications such as the shock cascade. Functions include acting on endothelial cells to stimulate inflammation and the coagulation pathway; stimulating endothelial cells to produce selectins and ligands for leukocyte integrins during diapedesis ; stimulating endothelial cells and macrophages to produce chemokines that contribute to diapedesis, chemotaxis, and the recruitment of leukocytes; stimulating macrophages to secrete interleukin-1 (IL-1) for redundancy; activating neutrophils and promoting extracellular killing by neutrophils; stimulating the liver to produce acute phase proteins, and acting on muscles and fat to stimulate catabolism for energy conversion. TNF-a stimulates the endothelial cells that form capillaries to express proteins that activate blood clot formation within the capillaries. This occludes local blood flow to help prevent microbes from entering the bloodstream. In addition, TNF is cytotoxic for some tumor cells; interacts with the hypothalamus to induce fever and sleep; stimulates the synthesis of collagen and collagenase for scar tissue formation; and activates macrophages. TNF is produced by monocytes,macrophages, dendritic cells, T_H1 cells, and other cells.

b. Interleukin-1 (IL-1)

IL-1 function similarly to TNF in that it mediates acute inflammatory responses. It also works synergistically with TNF to enhance inflammation. Functions of IL-1 include promoting inflammation ; activating the coagulation pathway, stimulating the liver to produce acute phase proteins, catabolism of fat for energy conversion, inducing fever and sleep; stimulates the synthesis of collagen and collagenase for scar tissue formation; stimulates the synthesis of adhesion factors on endothelial cells and leukocytes (see Figure 9.11*C*.1) for diapedesis ; and activates macrophages. IL-1 is produced primarily by monocytes, macrophages, dendritic cells, endothelial cells, and some epithelial cell.

c. Chemokines

Chemokines are a group of cytokines that enable the migration of leukocytes from the blood to the tissues at the site of inflammation. They increase the affinity of integrins on leukocytes for ligands on the vascular wall (see Figure 9.11*C*.1 during diapedesis, regulate the polymerization and depolymerization of actin in leukocytes for movement and migration, and function as chemoattractants for leukocytes. In addition, they trigger some WBCs to release their killing agents for extracellular killing and induce some WBCs to ingest the remains of damaged tissue. Certain chemokines promote angiogenesis. Chemokines also regulate the movement of B-lymphocytes, T-lymphocytes, and dendritic cells through the lymph nodes and the spleen. When produced in excess amounts, chemokines can lead to damage of healthy tissue as seen in such disorders as rheumatoid arthritis, pneumonia, asthma, adult respiratory distress syndrome (ARDS), and septic shock. Examples of chemokines include IL-8, MIP-1a, MIP-1b, MCP-1, MCP-2, MCP-3, GRO-a, GRO-b, GRO-g, RANTES, and eotaxin. Chemokines are produced by many cells including leukocytes, endothelial cells, epithelial cells, and fibroblasts.

d. Interleukin-12 (IL-12)

IL-12 is a primary mediator of early innate immune responses to intracellular microbes. It is also an inducer of cell-mediated immunity. It functions to stimulate the synthesis of interferon-gamma by T-lymphocytes and NK cells ; increases the killing activity of cytotoxic T-lymphocytes and NK cells; and stimulates the differentiation of naive T4-lymphocytes into interferon-gamma producing T_H1 cells. It is produced mainly by macrophages and dendritic cells.

e. Type I Interferons

Interferons modulate the activity of virtually every component of the immune system. Type I interferons include 13 subtypes of interferon-alpha, interferon-beta, interferon omega, interferon-kappa, and interferon tau. (There is only one type II interferon, interferon-gamma, which is involved in the inflammatory response.)

The most powerful stimulus for type I interferons is the binding of viral DNA or RNA to toll-like receptors TLR-3, TLR-7, and TLR-9 in endosomal membranes.

a. TLR-3 - binds double-stranded viral RNA;
b. TLR-7 - binds single-stranded viral RNA, such as in HIV, rich in guanine/uracil nucleotide pairs;
c. TLR-9 - binds unmethylated cytosine-guanine dinucleotide sequences (CpG DNA) found in bacterial and viral genomes but uncommon or masked in human DNA and RNA.

Flash animation showing toll-like receptors (TLRs) recognizing viral double-stranded RNA.

html5 version of animation for iPad showing toll-like receptors (TLRs) recognizing viral double-stranded RNA.

Signaling pattern recognition receptors located in the cytoplasm of cells such as RIG-1 and MDA-5 also signal synthesis and secretion of type-I interferons.

For More Information: Pattern-Recognition Receptors (PRRs) from Unit 5

Type I interferons, produced abundantly by plasmacytoid dendritic cells, by virtually any virus-infected cell, and by other defense cells provide an early innate immune response against viruses. Interferons induce uninfected cells to produce an enzyme capable of degrading viral mRNA, as well as one that blocks translation in eukaryotic cells. These enzymes remain inactive until the uninfected cell becomes infected with a virus. At this point, the enzymes are activated and begin to degrade viral mRNA and block translation in the host cell. This not only blocks viral protein synthesis, it also eventually kills the infected cell (see Figure $9.11C.2$A and Figure $9.11C.2$B). In addition, type I interferons also cause infected cells to produce enzymes that interfere with transcription of viral RNA or DNA. They also promote body defenses by enhancing the activities of CTLs, macrophages, dendritic cells, NK cells, and antibody-producing cells, as well as induce chemokine production to attract leukocytes to the area.

GIF animation showing the antiviral nature of interferon.

Type I interferons also induce MHC-I antigen expression needed for recognition of antigens by cytotoxic T-lymphocytes ; augment macrophages, NK cells, cytotoxic T-lymphocytes, and B-lymphocytes activity; and induce fever. Interferon-alpha is produced by T-lymphocytes, B-lymphocytes, NK cells, monocytes/macrophages; interferon-beta by virus-infected cells, fibroblasts, macrophages, epithelial cells, and endothelial cells.

f. Interleukin-6 (IL-6)

IL-6 functions to stimulate the liver to produce acute phase proteins ; stimulates the proliferation of B-lymphocytes ; and increases neutrophil production. IL-6 is produced by many cells including T-lymphocytes, macrophages, monocytes, endothelial cells, and fibroblasts.

g. Interleukin-10 (IL-10)

IL-10 is an inhibitor of activated macrophages and dendritic cells and as such, regulates innate immunity and cell-mediated immunity. IL-10 inhibits their production of IL-12, co-stimulator molecules, and MHC-II molecules, all of which are needed for cell-mediated immunity. IL-10 is produced mainly by macrophages, and T_H2 cells.

h. Interleukin 15 (IL-15)

IL-15 stimulates NK cell proliferation and proliferation of memory T8-lymphocytes. IL-15 is produced by various cells including macrophages.

i. Interleukin-18 (IL-18)

IL-18 stimulates the production of interferon-gamma by NK cells and T-lymphocytes and thus induces cell-mediated immunity. It is produced mainly by macrophages.

A number of human cytokines produced by recombinant DNA technologies are now being used to treat various infections or immune disorders. These include:

1. recombinant interferon alfa-2a (*Roferon-A*): a cytokine used to treat Kaposi's sarcoma, chronic myelogenous leukemia, and hairy cell leukemia.
2. peginterferon alfa-2a (*Pegasys*) : used to treat hepatitis C (HCV).
3. recombinant interferon-alpha 2b (*Intron A*): a cytokine produced by recombinant DNA technology and used to treat Hepatitis B; malignant melanoma, Kaposi's sarcoma, follicular lymphoma, hairy cell leukemia, warts, and Hepatitis C.
4. peginterferon alfa-2b (*PEG-Intron; PEG-Intron Redipen*): used to treat hepatitis C (HCV).
5. recombinant Interferon alfa-2b plus the antiviral drug ribavirin (*Rebetron*): used to treat hepatitis C (HCV).
6. recombinant interferon-alpha n3 (*Alferon N*): used to treat warts.
7. recombinant iInterferon alfacon-1 *(Infergen*) : used to treat hepatitis C (HCV).
8. G-CSF (granulocyte colony stimulating factor): for reduction of infection in people after myelotoxic anticancer therapy for solid tumors.
9. GM-CSF (granulocyte-macrophage colony stimulating factor): for hematopoietic reconstruction after bone marrow transplant in people with lymphoid cancers.

Concept Map for Cytokines Important in Innate Immunity

Summary

1. Cytokines are low molecular weight, soluble proteins that are produced in response to an antigen and function as chemical messengers for regulating the innate and adaptive immune systems.
2. Cytokines are pleiotropic, meaning meaning that a particular cytokine can act on a number of different types of cells rather than a single cell type.
3. Cytokines are redundant, meaning that a number of different cytokines are able to carry out the same function.
4. Cytokines are multifunctional, meaning that the same cytokine is able to regulate a number of different functions.
5. Tumor necrosis factor-alpha (TNF-a) and interleukin-1 (IL-1) are the principle cytokines that mediates acute inflammation.
6. Chemokines are a group of cytokines that enable the migration of leukocytes from the blood to the tissues at the site of inflammation.
7. Type I interferons, produced abundantly by plasmacytoid dendritic cells, by virtually any virus-infected cell, and by other defense cells provide an early innate immune response against viruses by inducing uninfected cells to produce enzymes capable of degrading viral mRNA and blocking translation in eukaryotic cells. They also enhancing the activities of CTLs, macrophages, dendritic cells, NK cells, and antibody-producing cells and induce chemokine production to attract leukocytes to the area.
8. Type II interferon is involved in stimulating an inflammatory response.

This page titled 9.11C: Cytokines Important in Innate Immunity is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **11.3C: Cytokines Important in Innate Immunity** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

9.11D: Harmful Effects Associated with Abnormal Pattern-Recognition Receptor Responses, Variations in Innate Immune Signaling Pathways, and/or Levels of Cytokine Production

Describe how an overactive TLR-4 receptor can increase the risk of SIRS in a person if Gram-negative bacteria enter the bloodstream.
- Briefly describe two specific examples of how an improper functioning PRR can lead to an increased risk of a specific infection or disease.

The Ability of Pathogen-Associated Molecular Patterns or PAMPs to Trigger the Synthesis and Secretion of Excessive Levels of Inflammatory Cytokines and Chemokines

As learned in Unit 3 under sepsis and systemic inflammatory response syndrome (SIRS), during severe systemic infections with large numbers of bacteria present, high levels of cell wall PAMPs are released resulting in excessive cytokine production by the defense cells and this can harm the body (see Figure 9.11*D*.10). In addition, neutrophils start releasing their proteases and toxic oxygen radicals that kill not only the bacteria, but the surrounding tissue as well. Harmful effects include high fever, hypotension, tissue destruction, wasting, acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), and damage to the vascular endothelium. This can result in shock, multiple system organ failure (MOSF), and death.

For More Information: Review of The Ability of PAMPs to Trigger the Production of Inflammatory Cytokines that Result in an Excessive Inflammatory Response from Unit 3

Harmful Effects Associated with either an Overactive or an Underactive Innate Immune Response

There are a number of harmful effects that are known to occur as a result of either an overactive or an underactive innate immune response. This occurs as a result of people possessing different polymorphisms in the various genes participating in PRR signaling.

- People born with underactive PRRs or deficient PRR immune signaling pathways are at increased risk of infection by specific pathogens due to a decrease innate immune response.
- People born with overactive PRRs or deficient PRR immune signaling pathways are at increased risk of inflammatory damage by lower numbers of specific pathogens.

Examples include:

1. People with an underactive form of TLR-4, the toll-like receptor for bacterial LPS, have been found to be five times as likely to contract a severe bacterial infection over a five year period than those with normal TLR-4. People with overactive TLR-4 receptors may be more prone to developing SIRS from gram-negative bacteria.

2. Most people that die as a result of Legionnaire's disease have been found to have a mutation in the gene coding for TLR-5 that enables the body to recognize the flagella of *Legionella pneumophila*.

3. B-lymphocytes, the cells responsible for recognizing foreign antigens and producing antibodies against those antigens, normally don't make antibodies against the body's own DNA and RNA. The reason is that any B-lymphocytes that bind the body's own antigens normally undergo apoptosis, a programmed cell suicide. People with the autoimmune disease systemic lupus erythematosus have a mutation in a gene that signals the cell to undergo apoptosis. As a result, these B-cells are able to bind and engulf the body's own DNA and RNA and place them in an endosome or phagolysosome where the the DNA can be recognized by TLR-9 and the RNA by TLR-7. This, in turn, triggers those B-lymphocytes to make antibody molecules against the body's own DNA and RNA. Another gene error enables these B- cells to increase the expression of TLR-7.

4. TLR-4, MyD88, TLR-1 and TLR-2 have been implicated in the production of atherosclerosis in mice and some humans.

5. Mutations resulting in loss-of-function in the gene coding for NOD-2 that prevents the NOD-2 from recognizing muramyl dipeptide make a person more susceptible to Crohn's disease, an inflammatory disease of the large intestines. Mutations resulting in over-activation in the gene coding for NOD-2 can lead to an inflammatory disorder called Blau syndrome.

6. People with chronic sinusitis that does not respond well to treatment have decreased activity of TLR-9 and produce reduced levels of human beta-defensin 2, as well as mannan-binding lectin needed to initiate the lectin complement pathway.

7. Pathogenic strains of *Staphylococcus aureus* producing leukocidin and protein A, including MRSA, cause an increased inflammatory response. Protein A, a protein that blocks opsonization and functions as an adhesin, binds to cytokine receptors for TNF-alpha. It mimics the cytokine and induces a strong inflammatory response. As the inflammatory response attracts neutrophils to the infected area, the leukocidin causes lysis of the neutrophils. As a result, tissue is damaged and the bacteria are not phagocytosed.

8. People with chronic mucocutaneous candidiasis disease have a mutation either in the gene coding for IL-17F or the gene encoding IL-17F receptor. T_H17 cells secrete cytokines such as IL-17 that are important for innate immunity against organisms that infect mucous membranes.

9. A polymorphism in the gene for TLR-2 makes individuals less responsive to *Treponema pallidum* and *Borrelia burgdorferi* and possibly more susceptible to tuberculosis and staphylococcal infections.

10. Polymorphisms in a gene locus called *A20*, a gene that helps to control inflammation, are considered as risk alleles for rheumatoid arthritis, systemic lupus erythematosus, psoriasis, type I diabetes, and Chron's disease.

11. The innate immune response to *Mycobacterium tuberculosis* and the severity of tuberculosis depends on the response of TLRs 1/2, TLR 6, and TLR 9 to the bacterium. Polymorphisms in Toll-interacting protein (TOLLIP), a negative regulator of TLR signaling, influence the response of the patient to *M. tuberculosis*.

What is the significance of underactive and overactive PRRs in innate immunity?

Therapeutic Possibilities

Researchers are now looking at various ways to either artificially activate TLRs in order to enhance immune responses or inactivate TLRs to lessen inflammatory disorders. Examples of agents being evaluated in clinical studies or animal studies include:

1. TLR activators to activate immune responses

    a. Both TLR-4 and TLR-9 activators are being tried in early clinical trials as vaccine adjuvants to improve the immune response to vaccines. TLR-9 activators are being tried as an adjuvant for the hepatitis B and anthrax vaccines and a TLR-4 activator is being tried as an adjuvant for the vaccine against the human papillomaviruses that cause most cervical cancer.
    b. Both TLR-7 and TLR-9 activators are being tried in early clinical trials as an antiviral against hepatitis C. Activation of these TLRs triggers the synthesis and secretion of type I interferons that block viral replication within infected host cells.
    c. TLR-9 activators are being tried in early clinical trials as an adjuvant for chemotherapy in the treatment of lung cancer.
    d. TLR-9 activators are being tried in early clinical trials to help in the treatment and prevention of allergies and asthma. Activation of TLR-9 in macrophages and other cells stimulates these cells to kill T_H2 cells, the subclass of T-helper lymphocytes responsible for most allergies and asthma.

2. TLR inhibitors to suppress immune responses

    a. General TLR inhibitors might one day be used to treat autoimmune disorders.
    b. A TLR-4 inhibitor, a mimic of the endotoxin from the gram-negative cell wall, is being tried in early clinical trials to block or reduce the death rate from Gram-negative sepsis and SIRS.
    c. TLR-4, TLR-2, and MyD88 inhibitors might possibly one day lessen atherosclerotic plaques and the risk of heart disease.

Of course using TLR activators or TLR inhibitors to turn up or turn down immune responses also carries risks. Trying to suppress harmful inflammatory responses may also result in increased susceptibility to infections; trying to activate immune responses could lead to SIRS or autoimmune disease.

For More Information: Pattern-Recognition Receptors (PRRs) from Unit 5

Summary

1. In severe bacterial infections, pathogen-associated molecular patterns or PAMPs can trigger the synthesis and secretion of excessive levels of inflammatory cytokines and chemokines leading to systemic inflammatory response syndrome or SIRS.
2. People born with underactive PRRs or deficient PRR immune signaling pathways are at increased risk of infection by specific pathogens due to a decrease innate immune response.
3. People born with overactive PRRs or deficient PRR immune signaling pathways are at increased risk of inflammatory damage by lower numbers of specific pathogens.
4. Researchers are now looking at various ways to either artificially activate underactive PRRs in order to enhance immune responses, or inactivate overactive PRRs to lessen inflammatory disorders.

This page titled 9.11D: Harmful Effects Associated with Abnormal Pattern-Recognition Receptor Responses, Variations in Innate Immune Signaling Pathways, and/or Levels of Cytokine Production is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **11.3D: Harmful Effects Associated with Abnormal Pattern-Recognition Receptor Responses, Variations in Innate Immune Signaling Pathways, and/or Levels of Cytokine Production** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

9.11E: Phagocytosis

Briefly describe the role of the following as they relate to phagocytosis:

a. inflammation

b. lymph nodules

c. lymph nodes

d. spleen

- Describe the following steps in phagocytosis:

a. activation

b. chemotaxis

c. attachment (both unenhanced and enhanced)

d. ingestion

e. destruction

- State what happens when either phagocytes are overwhelmed with microbes or they adhere to cells to large to be phagocytosed.
- Describe what causes most of the tissue destruction seen during microbial infections.
- Compare the oxygen-dependent and oxygen-independent killing systems of neutrophils and macrophages.
- Briefly describe the role of autophagy in removing intracellular microbes.

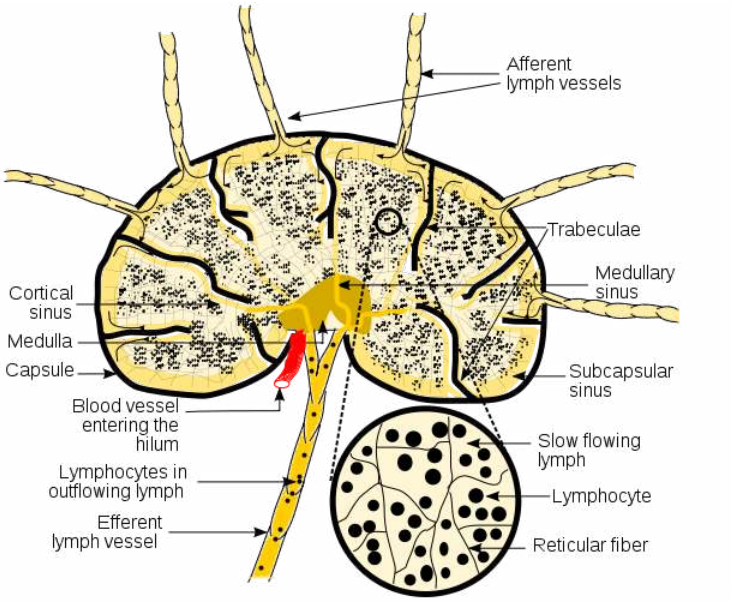


Figure **9.11*E*.1**: Diagram of a Lymph Node. Schematic diagram of a lymph node showing flow of lymph through lymph sinuses. Image used wtih permission (Public Domain; KC Panchal).

In addition, Langerhans' cells (immature dendritic cells) are located throughout the epithelium of the skin, the respiratory tract, and the gastrointestinal tract where in their immature form they are attached by long cytoplasmic processes. Upon capturing antigens through pinocytosis and phagocytosis and becoming activated by proinflammatory cytokines, the dendritic cells detach from the epithelium, enter lymph vessels, and are carried to regional lymph nodes. By the time they enter the lymph nodes, they have matured and are now able to present antigen to the ever changing populations of naive T-lymphocytes located in the cortex of the lymph nodes.

The spleen contains many reticular fibers that support fixed macrophages and dendritic cells, as well as ever changing populations of circulating B-lymphocytes and T-lymphocytes. Blood carries microorganisms to the spleen where they are filtered out and phagocytosed by the fixed macrophages and dendritic cells and presented to the circulating B-lymphocytes and T-lymphocytes to initiate adaptive immune responses. There are also specialized macrophages and dendritic cells located in the brain (microglia), lungs (alveolar macrophages), liver (Kupffer cells), kidneys (mesangial cells), bones (osteoclasts), and the gastrointestinal tract (peritoneal macrophages).

The Steps Involved in Phagocytosis

There are a number of distinct steps involved in phagocytosis:

Step 1: Activation of the Phagocyte

Resting phagocytes are activated by inflammatory mediators such as bacterial products (bacterial proteins, capsules, LPS, peptidoglycan, teichoic acids, etc.), complement proteins, inflammatory cytokines, and prostaglandins. As a result, the circulating phagocytes produce surface glycoprotein receptors that increase their ability to adhere to the inner surface of capillary walls, enabling them to squeeze out of the capillary and be attracted to the site of infection.

In addition, they produce endocytic pattern-recognition receptors that recognize and bind to pathogen-associated molecular patterns or PAMPs - components of common microbial molecules such as peptidoglycan, teichoic acids, lipopolysaccharide, and mannose-rich glycans that are not found in human cells - to attach the microbe to the phagocyte for what is called unenhanced attachment (discussed below). They also exhibit increased metabolic and microbicidal activity by increasing their production of ATPs, lysosomal enzymes, lethal oxidants, etc.

Step 2: Chemotaxis of Phagocytes (for wandering macrophages, neutrophils, and eosinophils)

Chemotaxis is the movement of phagocytes toward an increasing concentration of some attractant such as bacterial factors (bacterial proteins, capsules, LPS, peptidoglycan, teichoic acids, etc.), complement proteins (C5a), chemokines (chemotactic cytokines such as interleukin-8 secreted by various cells), fibrin split products, kinins, and phospholipids released by injured host cells.

Flash animation showing the role of C5a in vasodilation, the chemotaxis of phagocytes towards C5a, and their attachment to the opsonin C3b as a result of the complement pathways.

html5 version of animation for iPad showing the role of C5a in vasodilation, the chemotaxis of phagocytes towards C5a, and their attachment to the opsonin C3b as a result of the complement pathways.

Movie showing chemotaxis by neutrophil. Chemotaxis of Neutrophils. © From Intimate Strangers: Unseen Life on Earth. Created by Mondo Media. Peter Baker, Executive Producer. Licensed for use, ASM MicrobeLibrary.

You Tube animation summarizing phagocytosis by a macrophage.

You Tube movie illustrating chemotaxis.

Some microbes, such as the influenza A viruses, *Mycobacterium tuberculosis*, blood invasive strains of *Neisseria gonorrhoeae*, and *Bordetella pertussis* have been shown to block chemotaxis.

Step 3: Attachment of the Phagocyte to the Microbe or Cell

Attachment of microorganisms is necessary for ingestion. Attachment may be unenhanced or enhanced.

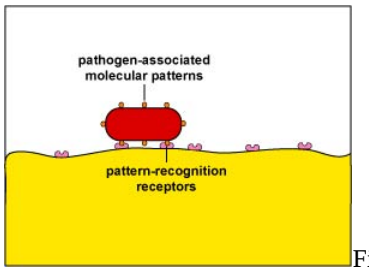


Figure 9.11*E*.2: Unenhanced Attachment of Bacteria to Phagocytes. Glycoprotein molecules known as pattern-recognition receptors are found on the surface of phagocytes. They are so named because they recognize and bind to pathogen-associated molecular patterns - components of common molecules such as peptidoglycan, teichoic acids, lipopolysaccharide, mannans, and glucans - found in many microorganisms.

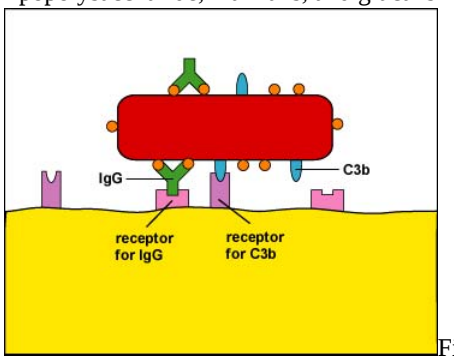


Figure 9.11*E*.3: Enhanced Attachment of Bacteria to Phagocytes. One of the functions of certain antibody molecules known as IgG is to stick antigens such as bacterial proteins and polysaccharides to phagocytes. The "tips" of the antibody, the Fab portion, have a shape that fits epitopes, portions of an antigen with a complementary shape. The "stalk" of the antibody is called the Fc portion and is able to bind to Fc receptors on phagocytes. Also, when body defense pathways known as the complement pathways are activated, one of the beneficial defense proteins made is called C3b. C3b binds by one end to bacterial surface proteins and by the other end to C3b receptors on phagocytes. The IgG and C3b are also known as opsonins and the process of enhanced attachment is also called opsonization.

Flash animation illustrating the function of enhanced attachment by way of IgG.

html5 version of animation for iPad illustrating the function of enhanced attachment by way of IgG.

Flash animation showing the role of C5a in vasodilation, the chemotaxis of phagocytes towards C5a, and their attachment to the opsonin C3b as a result of the complement pathways.

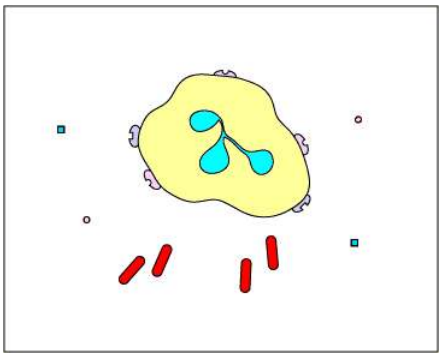
html5 version of animation for iPad showing the role of C5a in vasodilation, the chemotaxis of phagocytes towards C5a, and their attachment to the opsonin C3b as a result of the complement pathways.

For More Information: Antibodies from Unit 6

For More Information: The Complement Pathways from Unit 5

c. Extracellular trapping with NETs: In response to certain pathogen associated molecular patterns such as LPS, and certain cytokines such as IL-8, neutrophils release DNA and antimicrobial granular proteins. These neutrophil extracellular traps

(NETs) bind to bacteria, prevent them from spreading, and kill them with antimicrobial proteins (see Figure 9.11*E*.15 and Figure 9.11*E*.16).



Neutrophil NETS Trapping and Killing Bacteria. In response to certain pathogen associated molecular patterns such as LPS, and certain cytokines such as IL-8, neutrophils release DNA and antimicrobial granular proteins. These neutrophil extracellular traps (NETs) bind to bacteria, prevent them from spreading,andkill them with antimicrobial proteins such as histones and elastins. One hypothesis, shown in this animation, proposes that the NETs are produced by living neutrophils in response to bacteria. Alternately, NETs may be released as a result of necrotic cell death of neutrophils.

Some microorganisms are more resistant to phagocytic attachment.

a. Capsules can resist unenhanced attachment by preventing the endocytic pattern recognition receptors on phagocytes from recognizing the bacterial cell wall components and mannose-containing carbohydrates (see Figure 9.11*E*.14). *Streptococcus. pneumonia* activates the classical complement pathway, but resists C3b opsonization, and complement causes further inflammation in the lungs.

Flash animation illustrating how capsules can block unenhanced attachment of pathogen-associated molecular patterns to endocytic pattern-recognition receptors on phagocytes.

html5 version of animation for iPad illustrating how capsules can block unenhanced attachment of pathogen-associated molecular patterns to endocytic pattern-recognition receptors on phagocytes.

Movie of an encapsulated bacterium resisting engulfment by a neutrophil. Phagocytosis. © James Sullivan, author. Licensed for use, ASM MicrobeLibrary.

b. Some capsules prevent the formation of C3 convertase, an early enzyme in the complement pathways. Without this enzyme, the opsonins C3b and C4b, as well as the other beneficial proteins are not produced.

Flash animation showing an encapsulated bacterium resisting phagocytosis by blocking C3b.

html5 version of animation for iPad showing an encapsulated bacterium resisting phagocytosis by blocking C3b.

c. Other capsules, rich in sialic acid, a common component of host cell glycoprotein, have an affinity for serum protein H, a complement regulatory protein that leads to the degradation of the opsonin C3b by factor I and the formation of C3 convertase. (Serum protein H is what normally leads to the degradation of any C3b that binds to host glycoproteins so that we don't stick our own phagocytes to our own cells with C3b.)

d. Some capsules simply cover the C3b that does bind to the bacterial surface and prevent the C3b receptor on phagocytes from making contact with the C3b (see Figure 9.11*E*.3). This is seen with the capsule of *Streptococcus pneumoniae*.

Flash animation showing an encapsulated bacterium resisting phagocytosis by blocking C3b.

html5 version of animation for iPad showing an encapsulated bacterium resisting phagocytosis by blocking C3b.

e. *Neisseria meningitidis* has a capsule composed of sialic acid *while Streptococcus pyogenes* (group A beta streptococci) has a capsule made of hyaluronic acid. Both of these polysaccharides closely resemble carbohydrates found in human tissue polysaccharides and because they are not recognized as foreign by the lymphocytes that carry out the immune responses, antibodies are not made against these capsules. Likewise, some bacteria are able to coat themselves with host proteins such as fibronectin, lactoferrin, or transferrin and in this way avoid antibodies.

f. An outer membrane molecule of *Neisseria gonorrhoeae* called Protein II and the M-protein of *Streptococcus pyogenes* allow these bacteria to be more resistant to phagocytic engulfment. The M-protein of *S. pyogenes*, for example, binds factor H of the complement pathway and this results in the degradation of the opsonin C3b by factor I and the formation of C3 convertase. *S. pyogenes* also produces a protease that cleaves the complement protein C5a.

g. *Staphylococcus aureus* produces protein A while *Streptococcus pyogenes* produces protein G. Both of these proteins bind to the Fc portion of antibodies (see Figure 9.11*E*.4) and in this way the bacteria become coated with antibodies in a way that does not result in opsonization (see Figure 9.11*E*.5).

Step 4: Ingestion of the Microbe or Cell by the Phagocyte

Following attachment, polymerization and then depolymerization of actin filaments send pseudopods out to engulf the microbe (see Figure 9.11*E*.6) and place it in an endocytic vesicle called a phagosome (see Figure 9.11*E*.7).

Flash animation showing ingestion and phagosome formation.

html5 version of animation for iPad showing ingestion and phagosome formation.

During this process, an electron pump brings protons (H^+) into the phagosome. This lowers the pH within the phagosome to 3.5 - 4.0 so that when a lysosome fuses with the phagosome, the pH is correct for the acid hydrolases to effectively break down cellular proteins. The acidification also releases defensins, cathelicidin, and bacterial permeability inducing protein (BPI), peptides and enzymes that can kill microbes, from a matrix and enabling their activation.

Flash animation showing acidification of the phagosome following ingestion.

html5 version of animation for iPad showing acidification of the phagosome following ingestion.

Scanning electron micrographs of a macrophage with pseudopods and a macrophage phagocytozing *E. coli* on a blood vessel; courtesy of Dennis Kunkel's Microscopy.

You Tube Movie illustrating bacterial phagocytosis by a neutrophil.

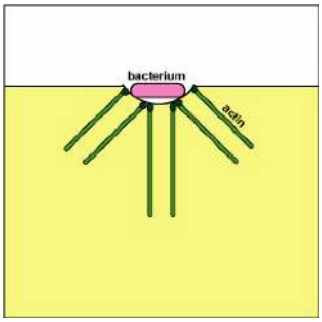
You Tube Movie illustrating a neutrophil phagocytosing MRSA

Intracellular microbes, such as viruses and bacteria that invade host cells, can also be engulfed once they enter the cytosol of the cell by a process called autophagy. A membrane-bound compartment called an autophagosome grows around the microbe and the surrounding cytosol and subsequently delivers it to lysosomes for destruction (see Figure 9.11*E*.17). (This process is also used by eukaryotic cells to engulf and degrade unnecessary or dysfunctional cellular components such as damaged organelles.)

Some microorganisms are more resistant to phagocytic ingestion

a. Pathogenic *Yersinia*, such as the one that causes plague, contact phagocytes and, by means of a type III secretion system, deliver proteins which depolymerize the actin microfilaments needed for phagocytic engulfment into the phagocytes (see Figure 9.11*E*.8). Another *Yersinia* protein degrades C3b and C5a.

b. Some bacteria, like *Mycobacterium tuberculosis*, *Salmonella*, and *Listeria monocytogenes* can block autophagy.



Blocking Phagosome Formation by Depolymerizing Actin. Molecules of some bacteria, through a type III secretion system, deliver proteins which depolymerize the phagocyte's actin microfilaments used for phagocytic engulfment.

Step 5: Destruction of the Microbe or Cell

Phagocytes contain membranous sacs called lysosomes produced by the Golgi apparatus that contain various digestive enzymes, microbicidal chemicals, and toxic oxygen radicals. The lysosomes travel along microtubules within the phagocyte and fuse with the phagosomes containing the ingested microbes and the microbes are destroyed (see Figure 9.11*E*.9).

To view an electron micrograph of a phagolysosome, see the Web page for the University of Illinois College of Medicine.

Flash animation showing intracellular destruction.

html5 version of animation for iPad showing intracellular destruction.

Flash animation summarizing phagocytosis by unenhanced attachment.

html5 version of animation for iPad summarizing phagocytosis by unenhanced attachment.

Flash animation summarizing phagocytosis by enhanced attachment (opsonization).

html5 version of animation for iPad summarizing phagocytosis by enhanced attachment (opsonization).

You Tube animation summarizing phagocytosis by a macrophage.

Some bacteria are more resistant to phagocytic destruction once engulfed.

a. Some bacteria, such as *Legionella pneumophilia* and *Mycobacterium* species, cause the phagocytic cell to place them into an endocytic vacuole via a pathway that decreases their exposure to toxic oxygen compounds.

b. Some bacteria, such as *Salmonella*, are more resistant to toxic forms of oxygen and to defensins (toxic peptides that kill bacteria).

c. Some bacteria, such as *Shigella flexneri* and the spotted fever *Rickettsia*, escape from the phagosome into the cytoplasm prior to the phagosome fusing with a lysosome (see Figure 9.11*E*.10).

Flash animation showing a bacterium resisting phagocytosis by escaping from a phagosome prior to the phagosome fusing with the lysosome.

html5 version of animation for iPad showing a bacterium resisting phagocytosis by escaping from a phagosome prior to the phagosome fusing with the lysosome.

d. *Neisseria gonorrhoeae* produces Por protein (protein I) that prevents phagosomes from fusing with lysosomes enabling the bacteria to survive inside phagocytes.

Flash animation showing a bacterium resisting phagocytosis by blocking the fusion of the phagosome with the lysosome.

html5 version of animation for iPad showing a bacterium resisting phagocytosis by blocking the fusion of the phagosome with the lysosome.

e. Some bacteria, such as species of *Salmonella*, *Mycobacterium*, *Legionella*, and *Chlamydia*, block the vesicular transport machinery that enables the phagosome to fuse with the lysosome.

Flash animation showing a bacterium resisting phagocytosis by blocking the lysosome from moving to the phagosome.

html5 version of animation for iPad showing a bacterium resisting phagocytosis by blocking the lysosome from moving to the phagosome.

f. Some bacteria, such as pathogenic *Mycobacterium* and *Legionella pneumophilia*, prevent the acidification of the phagosome which is needed for effective killing of microbes by lysosomal enzymes. (Normally after the phagosome forms, the contents become acidified because the lysosomal enzymes used for killing function much more effectively at an acidic pH.)

Flash animation showing a bacterium preventing acidification of the phagosome following ingestion.

html5 version of animation for iPad showing a bacterium preventing acidification of the phagosome following ingestion.

g. The carotenoid pigments that give *Staphylococcus aureus* its golden color and group B streptococci (GBS) its orange tint shield the bacteria from the toxic oxidants that neutrophils use to kill bacteria.

h. Cell wall lipids of *Mycobacterium tuberculosis*, such as lipoarabinomannan, arrest the maturation of phagosomes preventing delivery of the bacteria to lysosomes.

i. Some bacteria are able to kill phagocytes. Bacteria such as *Staphylococcus aureus* and *Streptococcus pyogenes* produce the exotoxin leukocidin which damages the cytoplasmic membrane of the phagocyte. On the other hand, bacteria, such as *Shigella* and *Salmonella*, induce macrophage apoptosis, a programmed cell death.

Flash animation showing a bacterium using leukocidin to kill a phagocyte.

html5 version of animation for iPad showing a bacterium using leukocidin to kill a phagocyte.

If the the infection site contains very large numbers of microorganisms and high levels of inflammatory cytokines and chemokines are being produced in response to PAMPs, the phagocyte will empty the contents of its lysosomes by a process called degranulation in order to kill the microorganisms or cell extracellularly.

These released lysosomal contents, however, also kill surrounding host cells and tissue. Most tissue destruction associated with infections is a result of this process (see Figure 9.11*E*.11).

The phagocyte will also empty the contents of its lysosomes for extracellular killing if the cell to which the phagocyte adheres is too large to be engulfed (see Figure 9.11*E*.12 and Figure 9.11*E*.13).

Flash animation summarizing extracellular killing by phagocytosis.

html5 version of animation for iPad summarizing extracellular killing by phagocytosis.

There are 2 killing systems in neutrophils and macrophages: the oxygen-dependent system and the oxygen-independent system.

1. The oxygen-dependent system: production of reactive oxygen species (ROS)

The cytoplasmic membrane of phagocytes contains the enzyme oxidase which converts oxygen into superoxide anion (O^{2-}). This can combine with water by way of the enzyme dismutase to form hydrogen peroxide (H_2O_2) and hydroxyl (OH) radicals.

In the case of neutrophils, but not macrophages, the hydrogen peroxide can then combine with chloride (Cl^{2-}) ions by the action of the enzyme myeloperoxidase (MPO) to form hypochlorous acid (HOCL), and singlet oxygen.

In macrophages, nitric oxide (NO) can combine with hydrogen peroxide to form peroxynitrite radicals. (In addition to ROS and NO, macrophages secrete inflammatory cytokines such as TNF-alpha, IL-1, IL-8, and IL-12 to promote an inflammatory response.)

These compounds are very microbicidal because they are powerful oxidizing agents which oxidize most of the chemical groups found in proteins, enzymes, carbohydrates, DNA, and lipids. Lipid oxidation can break down cytoplasmic membranes. Collectively, these oxidizing free radicals are called reactive oxygen species (ROS).

Oxidase also acts as an electron pump that brings protons (H^+) into the phagosome. This lowers the pH within the phagosome so that when lysosomes fuse with the phagosome, the pH is correct for the acid hydrolases, like elastase, to effectively break down cellular proteins.

In addition to phagocytes using this oxygen-dependant system to kill microbes intracellularly, neutrophils also routinely release these oxidizing agents, as well as acid hydrolases, for the purpose of killing microbes extracellularly. These agents, however, also wind up killing the neutrophils themselves as well as some surrounding body cells and tissues as mentioned above.

2. The oxygen-independent system

Some lysosomes contain defensins), cationic peptides that alter cytoplasmic membranes; lysozyme, an enzyme that breaks down peptidoglycan, lactoferrin, a protein that deprives bacteria of needed iron; cathepsin G, a protease that causes damage to microbial membranes; elastase, a protease that kills many types of bacteria; cathelicidins, proteins that upon cleavage are directly toxic to a variety of microorganisms; bactericidal permeability inducing protein (BPI), proteins used by neutrophils to kill certain bacteria by damaging their membranes; collagenase ; and various other digestive enzymes that exhibit antimicrobial activity by breaking down proteins, RNA, phosphate compounds, lipids, and carbohydrates.

Concept Map for Phagocytosis

Streptococcus pyogenes has a capsule made of hyaluronic acid, a polysaccharide also found on human cells. Describe what significance this has in the bacterium resisting phagocytosis and why.

2. *Streptococcus pyogenes* produces a protein called protein G that binds to the Fc portion of human IgG. Describe what significance this has in the bacterium resisting phagocytosis and why.

3. Many bacteria produces capsules that cover their cell wall. Describe what significance this has in the bacterium resisting phagocytosis and why.

4. People born with chronic granulomatious disease have neutrophils that lack the enzyme oxidase in their cytoplasmic membrane. Describe what significance this has in the bacterium resisting phagocytosis and why.

Summary

Phagocytosis is the primary method used by the body to remove free microorganisms in the blood and tissue fluids. An inflammatory response to injury and/or infection allows phagocytes to leave the bloodstream, enter the tissue, and go to the site of infection or injury. Microorganisms entering lymph nodules found in the respiratory, gastrointestinal, and genitourinary tract can be phagocytosed by fixed macrophages and dendritic cells and presented to B-lymphocytes and T-lymphocytes to initiate adaptive immune responses.Tissue fluid picks up microbes in the tissue, enters the lymph vessels as lymph, and carries the microbes to regional lymph nodes where they are filtered out and phagocytosed by fixed macrophages and dendritic cells and presented to the circulating B-lymphocytes and T-lymphocytes to initiate adaptive immune responses.

Dendritic cells located throughout the epithelium of the skin, the respiratory tract, and the gastrointestinal tract phagocytize microbes, enter lymph vessels, and carry the microbes to regional lymph nodes where the dendritic cells present antigens associated with the microbes to the ever changing populations of naive T-lymphocytes.Blood carries microorganisms to the spleen where they are filtered out and phagocytosed by fixed macrophages and dendritic cells and presented to the circulating B-lymphocytes and T-lymphocytes to initiate adaptive immune responses. There are also specialized macrophages and dendritic cells located in the brain (microglia), lungs (alveolar macrophages), liver (Kupffer cells), kidneys (mesangial cells), bones (osteoclasts), and the gastrointestinal tract (peritoneal macrophages.

1. Resting phagocytes are activated by inflammatory mediators and produce surface receptors that increase their ability to adhere to the inner surface of capillary walls enabling them to squeeze out of the capillary and enter the tissue, a process called diapedesis.
2. Activation also enables phagocytes to produce endocytic pattern-recognition receptors that recognize and bind to microbial PAMPs in order to attach the microbe to the phagocyte, as well as to exhibit increased metabolic and microbicidal activity.
3. Phagocytes then use chemotaxis to move towards an increasing concentration of some attractant such as bacterial factors or defense molecules.
4. Attachment of phagocytes to the microbes or cells can be through unenhanced attachment or enhanced attachment.
5. Unenhanced attachment is the recognition of pathogen-associated molecular patterns or PAMPs by endocytic pattern-recognition receptors on the surface of the phagocytes.
6. Enhanced attachment, or opsonization, is the attachment of microbes to phagocytes by way of an antibody molecule called IgG, the complement proteins C3b and C4b, and acute phase proteins such as mannose-binding lectin (MBL) and C-reactive protein (CRP).
7. Following attachment, polymerization and then depolymerization of actin filaments send pseudopods out to engulf the microbe and place it in an endocytic vesicle called a phagosome.
8. During this process, an electron pump brings protons (H+) into the phagosome to lowers the pH within the phagosome to a pH that is correct for the acid hydrolases to effectively break down cellular proteins.
9. Phagocytes contain membranous sacs called lysosomes that contain various digestive enzymes, microbicidal chemicals, and toxic oxygen radicals. The lysosomes fuse with the phagosomes containing the ingested microbes and the microbes are destroyed.

10. If the infection site contains very large numbers of microorganisms and high levels of inflammatory cytokines and chemokines are being produced in response to PAMPs, the phagocyte will empty the contents of its lysosomes in order to kill the microorganisms or cell extracellularly.
11. Lysosomal contents released during extracellular killing also kill surrounding host cells and tissue. Most tissue destruction associated with infections is a result of extracellular killing by phagocytes.

This page titled 9.11E: Phagocytosis is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **11.3E: Phagocytosis** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

9.11F: Natural Killer Cells (NK Cells) and Invariant Natural Killer T-Lymphocytes (iNKT Cells)

Describe how NK cells are able to recognize and kill infected cells and cancer cells lacking MHC-I molecules.
- State two factors that can result in a nucleated human cell not producing MHC-I molecules.
- State how iNKT cells recognize glycolipids in order to become activated.
- Describe the overall function of iNKT cells in terms how they promote both innate and adaptive immunity and may also help to regulate the immune responses.

We will now take a closer look at natural killer (NK) cells and invariant natural killer T-lymphocytes (iNKT cells).

Natural Killer Cells (NK Cells)

NK cells are important in innate immunity because they are able to recognize infected cells, cancer cells, and stressed cells and kill them. In addition, they produce a variety of cytokines, including proinflammatory cytokines, chemokines, colony-stimulating factors, and other cytokines that function as regulators of body defenses. For example, through cytokine production NK cells also suppress and/or activate macrophages , suppress and/or activate the antigen-presenting capabilities of dendritic cells, and suppress and/or activate T-lymphocyte responses.

NK cells use a dual receptor system in determining whether to kill or not kill human cells. When cells are either under stress, are turning into tumors, or are infected, various stress-induced molecules such as MHC class I polypeptide-related sequence A (MICA) and MHC class I polypeptide-related sequence B (MICB) are produced and are put on the surface of that cell.

The first receptor, called the killer-activating receptor, can bind to these stress-induced molecules, and this sends a positive signal that enables the NK cell to kill the cell to which it has bound unless the second receptor cancels that signal.

This second receptor, called the killer-ihibitory receptor, recognizes MHC-I molecules that are usually present on all nucleated human cells. MHC-I molecules, produced by all nucleated cells in the body, possess a deep groove that can bind peptides from proteins found within the cytosol of human cells, transport them to the surface of that cell, and display the MHC-!/peptide complex to receptors on cytotoxic T-lymphocytes or CTLs. If the MHC-I molecules have peptides from the body's own proteins bound to them, CTLs do not recognize those cells as foreign and the cell is not killed. If, on the other hand, the MHC-I molecules have peptides from viral, bacterial, or mutant proteins bound to them, CTLs recognize that cell as foreign and kill that cell. (CTLs will be discussed in greater detail in Unit 6.)

For More Information: CTLs from Unit 6

If MHC-I molecules/self peptide complexes are expressed on the cell, the killer-inhibitory receptors on the NK cell recognize this MHC-I/peptide complex and sends a negative signal that overrides the original kill signal and prevents the NK cell from killing the cell to which it has bound (see Figure 9.11F.3).

Viruses, stress, and malignant transformation, however, can often interfere with the ability of the infected cell or tumor cell to express MHC-I molecules. Without the signal from the killer-inhibitory receptor, the kill signal from the killer-activating signal is not overridden and the NK cell kills the cell to which it has bound (see Figure 9.11F.4).

The NK cell then releases pore-forming proteins called perforins, proteolytic enzymes called granzymes, and chemokines. Granzymes pass through the pores and activate the enzymes that lead to apoptosis of the infected cell by means of destruction of its

structural cytoskeleton proteins and by chromosomal degradation. As a result, the cell breaks into fragments that are subsequently removed by phagocytes (see Figure 9.11*F*.5). Perforins can also sometimes result in cell lysis.

Flash animation of a NK cell interacting with a normal body cell.

Flash animation of a NK cell interacting with a virus-infected cell or tumor cell not expressing MHC-I molecules.

html5 version of animation for iPad of a NK cell interacting with a normal body cell.

html5 version of animation for iPad of a NK cell interacting with a virus-infected cell or tumor cell not expressing MHC-I molecules.

Flash animation of apoptosis by NK cells

html5 version of animation for iPad of apoptosis by NK cells

Cytokines such as interleukin-2 (IL-2) and interferon-gamma (IFN-gamma) produced by T_H1 lymphocytes activate NK cells.

NK cells also play a role in adaptive immune responses. As will be seen in Unit 6, NK cells are also capable of antibody-dependent cellular cytotoxicity or ADCC where they kill cells to which antibody molecules have bound.

For More Information: ADCC from Unit 6

Invariant Natural Killer T-Lymphocytes (iNKT Cells)

iNKT cells are a subset of lymphocytes that bridge the gap between innate and adaptive immunity. They have T-cell receptors (TCRs) on their surface for glycolipid antigen recognition. They also have natural killer (NK) cell receptors.

Through the cytokines they produce once activated, iNKT cells are essential in both innate and adaptive immune protection against pathogens and tumors. They also play a regulatory role in the development of autoimmune diseases, asthma, and transplantation tolerance. It has been shown that iNKT cell deficiency or disfunction can lead to the development of autoimmune diseases, human asthma, and cancers.

Pathogens may not directly activate iNKT cells. The TCR of iNKT cells recognize exogenous glycolipid antigens , as well as endogenous self glycolipid antigens presented by MHC-I-like CD1d molecules on antigen presenting dendritic cells. iNKT cells can also be activated by the cytokine interleukin-12 (IL-12) produced by dendritic cells that have themselves become activated by pathogen-associated molecular patterns (PAMPs) of microbes binding to the pattern-recognition receptors (PRRs) of the dendritic cell.

Once activated, the iNKT cells rapidly produce large quantities of cytokines, including interferon-gamma (IFN-?), interleukin-4 (IL-4), interleukin-2 (IL-2), interleukin-10 (IL-10), tumor necrosis factor-alpha (TNF-a), interleukin-13 (IL-13), and chemokines. Through the rapid productions of such cytokines, iNKT cells are able to promote and suppress different innate and adaptive immune responses. For example, large amounts of IFN-? are produced by activated iNKT cells. IFN-? activates NK cells and macrophages as a part of innate immunity.

It has been proposed that if the iNKT cell is repeatedly stimulated by the body's own glycolipids in the absence of microbes that this might stimulate the iNKT cell /dendritic cell interaction to produce tolerizing signals that inhibit the T_H1 cell response and possibly stimulate the production of regulatory T-lymphocytes (T_{reg} cells). In this way it might suppress autoimmune responses and prevent tissue damage.

There is also growing evidence that early childhood exposure to microbes is associated with protection against allergic diseases, asthma, and inflammatory diseases such as ulcerative colitis. It has been found that germ-free mice have large accumulations of mucosal iNKT cells in the lungs and intestines and increased morbidity from allergic asthma and inflammatory bowel disease. However, colonization of neonatal germ-free mice with normal microbiota resulted in mucosal iNKT cell tolerance to these diseases. It has been proposed that microbes the human body has been traditionally exposed to from early childhood throughout most of human history might play a role in developing normal iNKT cell numbers and iNKT cell responses.

iNKT cells will be discussed in further detail in Unit 6.

Concept Map for NK Cells and iNKT Cells

Summary

1. Natural Killer (NK) cells are able to recognize infected cells, cancer cells, and stressed cells and kill them. In addition, they produce a variety of cytokines, including proinflammatory cytokines, chemokines, colony-stimulating factors, and other cytokines that function as regulators of body defenses.
2. When body cells are either under stress, are turning into tumors, or are infected, various stress-induced molecules are produced and are put on the surface of that cell.
3. NK cells use a dual receptor system in determining whether to kill or not kill human cells.
4. The first receptor, called the killer-activating receptor, can bind to these stress-induced molecules, and this sends a positive signal that enables the NK cell to kill the cell to which it has bound unless the second receptor cancels that signal.
5. The second receptor, called the killer-ihibitory receptor, recognizes MHC-I molecules that are usually present on all nucleated human cells. If MHC-I molecules/self peptide complexes are expressed on the cell, the killer-inhibitory receptors on the NK cell recognize this MHC-I/peptide complex and sends a negative signal that overrides the original kill signal and prevents the NK cell from killing the cell to which it has bound.
6. Viruses, stress, and malignant transformation can often interfere with the ability of the infected cell or tumor cell to express MHC-I molecules. Without the signal from the killer-inhibitory receptor, the kill signal from the killer-activating signal is not overridden and the NK cell kills the cell to which it has bound.
7. NK cells kill their target cells by inducing apoptosis, a programmed cell suicide.
8. NK cells also play a role in adaptive immune responses by way of antibody-dependent cellular cytotoxicity or ADCC where they bind to and kill cells to which antibody molecules have bound.
9. Invariant natural killer T-lymphocytes (iNKT cells) are a subset of lymphocytes that have T-cell receptors on their surface for glycolipid antigen recognition. They also have natural killer (NK) cell receptors.
10. Through the cytokines they produce, iNKT cells are able to promote and suppress different innate and adaptive immune responses. They also play a regulatory role in the development of autoimmune diseases, asthma, and transplantation tolerance. iNKT cell deficiency or disfunction can lead to the development of autoimmune diseases, human asthma, and cancers.

This page titled 9.11F: Natural Killer Cells (NK Cells) and Invariant Natural Killer T-Lymphocytes (iNKT Cells) is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **11.3F: Natural Killer Cells (NK Cells) and Invariant Natural Killer T-Lymphocytes (iNKT Cells)** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

https://med.libretexts.org/@go/page/77727

9.11G: Inflammation

Describe the 4 processes that make up the inflammatory mechanism.
- Briefly describe the various beneficial effects of inflammation that are associated with plasma leakage and with diapedesis.
- Briefly describe the process of diapedesis, indicating the role of P-selectins, integrins, and adhesion molecules.
- Briefly describe the healing stage of inflammation.
- Briefly describe the problems that arise from chronic inflammation.

The inflammatory response is an attempt by the body to restore and maintain homeostasis after injury and is an integral part of body defense. Most of the body defense elements are located in the blood and inflammation is the means by which body defense cells and defense chemicals leave the blood and enter the tissue around the injured or infected site. Inflammation is essentially beneficial, however, excess or prolonged inflammation can cause harm.

The Mechanism of Inflammation

Essentially, four processes make up the inflammatory mechanism:

a. Smooth muscles around larger blood vessels contract to slow the flow of blood through the capillary beds at the infected or injured site. This gives more opportunity for leukocytes to adhere to the walls of the capillary and squeeze out into the surrounding tissue.

b. The endothelial cells that make up the wall of the smaller blood vessels contract. This increases the space between the endothelial cells resulting in increased capillary permeability. Since these blood vessels get larger in diameter as a result of this, the process is called vasodilation (see Figure 9.11*G*.1).

Scanning electron micrographs of a cross section of a capillary showing an endothelial cell and a capillary with a red blood cell; courtesy of Dennis Kunkel's Microscopy).

Animation showing a capillary prior to vasodilation.

Animation showing vasodilation.

html5 version of animation for iPad showing a capillary prior to vasodilation.

html5 version of animation for iPad showing vasodilation.

c. Molecules called selectins are produced on the membrane of the leukocyte and are able to reversibly bind to corresponding selectin glycoprotein receptors on the inner wall of the venule. This reversible binding enables the leukocyte to roll along the inner wall of the venule. This reversible binding enables the leukocyte to roll along the inner wall of the venule. Adhesion molecules are activated on the surface of the endothelial cells on the inner wall of the capillaries. Corresponding molecules on the surface of leukocytes called integrins attach to these adhesion molecules allowing the leukocytes to flatten and squeeze through the space between the endothelial cells. This process is called diapedesis or extravasation.

d. Activation of the coagulation pathway causes fibrin clots to physically trap the infectious microbes and prevent their entry into the bloodstream. This also triggers blood clotting within the surrounding small blood vessels to both

stop bleeding and further prevent the microorganisms from entering the bloodstream.

You Tube animation illustrating leukocyte rolling along the inner wall of a blood vessel.

You Tube movie and animation of leukocyte extravasation (diapedesis)
from ImmuneDocumentary

These four events are triggered and enhanced by a variety of chemical inflammatory mediators. We will now divide the inflammatory response into two stages: early inflammation and late inflammation.

Early Inflammation and Diapedesis

Most leukocyte diapedesis (extravasation) occurs in post-capillary venules because hemodynamic shear forces are lower in these venules. This makes it easier for leukocytes to attach to the inner wall of the vessel and squeeze out between the endothelial cells. We will look at this process in more detail below.

1. During the very early stages of inflammation, stimuli such as injury or infection trigger the release of a variety of mediators of inflammation such as leukotrienes, prostaglandins, and histamine. The binding of these mediators to their receptors on endothelial cells leads to vasodilation, contraction of endothelial cells, and increased blood vessel permeability. In addition, the basement membrane surrounding the capillaries becoming rearranged so as to promote the migration of leukocytes and the movement of plasma macromolecules from the capillaries into the surrounding tissue. Mast cells in the connective tissue as well as basophils, neutrophils and platelets leaving the blood from injured capillaries, release or stimulate the synthesis of vasodilators such as histamine, leukotrienes, kinins, and prostaglandins. Certain products of the complement pathways (C5a and C3a) can bind to mast cells and trigger their release their vasoactive agents. In addition, tissue damage activates the coagulation cascade and production of inflammatory mediators like bradykinins.
2. The binding of histamine to histamine receptors on endothelial cells triggers an upregulation of P-selectin molecules and platelet-activating factor or PAF on the endothelial cells that line the venules.
3. The P-selectins then are able to reversibly bind to corresponding P-selectin glycoprotein ligands (PSGL-1) on leukocytes. This reversible binding enables the leukocyte to now roll along the inner wall of the venule.
4. The binding of PAF to its corresponding receptor PAF-R on the leukocyte upregulates the surface expression of an integrin called leukocyte function-associated molecule-1 (LFA-1) on the surface of the leukocyte.
5. The LFA-1 molecules on the rolling leukocytes can now bind firmly to an an adhesion molecule called intercellular adhesion molecule-1 (ICAM-1) found on the surface of the endothelial cells forming the inner wall of the blood vessel (see Figure 9.11*G*.4).
6. The leukocytes flatten out, squeeze between the constricted endothelial cells, and use enzymes to breakdown the matrix that forms the basement membrane surrounding the blood vessel. The leukocytes then migrate towards chemotactic agents such as the complement protein C5a and leukotriene B_4 generated by cells at the site of infection or injury (see Figure 9.11*G*.5).

Late Inflammation and Diapedesis

1) Usually within two to four hours of the early stages of inflammation, activated macrophages and vascular endothelial cells release inflammatory cytokines such as TNF and IL-1 when their toll-like receptors bind pathogen-associated molecular patterns - molecular components associated with microorganisms but not found as a part of eukaryotic cells.

This enables vascular endothelial cells of nearby venules to increase their expression of adhesion molecules such as P-selectins, E-selectins, intercellular adhesion molecules (ICAMs), and chemokines.

For More Information: Pathogen-Associated Molecular Patterns (PAMPs) from Unit 5

For More Information: Pattern-Recognition Receptors (PRRs) from Unit 5

For More Information: Cytokines from Unit 5

2) The binding of TNF and IL-1 to receptors on endothelial cells triggers an maintains the inflammatory response by upregulation the production of the adhesion molecule E-selectin and maintaining P-selectin expression on the endothelial cells that line the venules.

3). The E-selectins on the inner surface of the endothelial cells can now bind firmly to its corresponding integrin E-selectin ligand-1 (ESL-1) on leukocytes (see Figure 9.11G.4).

4) The leukocytes flatten out, squeeze between the constricted endothelial cells, and move across the basement membrane as they are are attracted towards chemokines such as interleukin-8 (IL-8) and monocyte chemotactic protein-1 (MCP-1) generated by cells at the site of infection or injury (see Figure 9.11G.5). Leakage of fibrinogen and plasma fibronectin then forms a molecular scaffold that enhances the migration and retention of leukocytes at the infected site.

Animation summarizing late inflammation and diapedesis.

html5 version of animation for iPad summarizing late inflammation and diapedesis.

Benefits of Inflammation

As a result of this increased permeability:

a. Plasma flows out of the blood into the tissue.

Beneficial molecules in the plasma (see Figure 9.11G.2) include:

1. Clotting factors. Tissue damage activates the coagulation cascade causing fibrin clots to form to localize the infection, stop the bleeding, and chemotactically attract phagocytes.

2. Antibodies. These help remove or block the action of microbes through a variety of methods that will be explained in Unit 6.

For More Information: Antibodies from Unit 6

3. Proteins of the complement pathways. These, in turn: 1) stimulate more inflammation (C5a, C3a, and C4a), 2) stick microorganisms to phagocytes (C3b and C4b), 3) chemotactically attract phagocytes (C5a), and 4) lyse membrane-bound cells displaying foreign antigens (membrane attack complex or MAC).

For More Information: The Benefits of the Complement Pathways from Unit 5

4. Nutrients. These feed the cells of the inflamed tissue.

5. Lysozyme, cathelicidins, phospholipase A_2,and human defensins. Lysozyme degrades peptidoglycan. Cathelicidins are cleaved into two peptides that are directly toxic to microbes and can neutralize LPS from the gram-negative bacterial cell wall. Phospholipase A_2 hydrolyzes the phospholipids in the bacterial cytoplasmic membrane. Human defensins put pores in the cytoplasmic membranes of many bacteria. Defensins also activate cells involved in the inflammatory response.

6. Transferrin.Transferrin deprives microbes of needed iron.

b. Leukocytes enter the tissue through a process called diapedesis or extravasation, discussed above under early inflammation and late inflammation.

Benefits of diapedesis include (see Figure 9.11*G*.2):

1. Increased phagocytosis. Neutrophils, monocytes that differentiate into macrophages when they enter the tissue, and eosinophils are phagocytic leukocytes.

2. More vasodilation. Basophils, eosinophils, neutrophils, and platelets enter the tissue and release or stimulate the production of vasoactive agents that promote inflammation.

3. Cytotoxic T-lymphocytes (CTLs), effector T4-cells, and NK cells enter the tissue to kill cells such as infected cells and cancer cells that are displaying foreign antigens on their surface (discussed in Unit 6).

For More Information: Leukocytes from Unit 5

Concept Map for Inflammation

Cytokines called chemokines are especially important in this part of the inflammatory response. They play key roles in diapedesis -enabling white blood cells to adhere to the inner surface of blood vessels, migrate out of the blood vessels into the tissue, and be chemotactically attracted to the injured or infected site. They also trigger extracellular killing by neutrophils.

Finally, within 1 to 3 days, macrophages release the cytokines interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-a). These cytokines stimulate NK cells and T-lymphocytes to produce the cytokine interferon-gamma. (IF-?). The IF-? then binds to receptors on macrophages causing them to produce fibroblast growth factor and angiogenic factors for tissue remodeling. With the proliferation of endothelial cells and fibroblasts, endothelial cells form a fine network of new capillaries into the injured area to supply blood, oxygen, and nutrients to the inflamed tissue. The fibroblasts deposit the protein collagen in the injured area and form a bridge of connective scar tissue to close the open, exposed area. This is called fibrosis or scarring, and represents the final healing stage.

Inflammation is normally carefully regulated by cytokines. Inflammatory cytokines such as interferon-gamma and interleukin-12 enhance the inflammatory response whereas the cytokine interleukin-10 inhibits inflammation by decreasing the expression of inflammatory cytokines.

So as can be seen, acute inflammation is essential to body defense. Chronic inflammation, however, can result in considerable tissue damage and scarring. With prolonged increased capillary permeability, neutrophils continually leave the blood and accumulate in the tissue at the infected or injured site. As they discharge their lysosomal contents and reactive oxygen species or ROS, surrounding tissue is destroyed and eventually replaced with scar tissue. Anti-inflammatory agents such as antihistamines or corticosteroids may have to be given to relieve symptoms or reduce tissue damage.

For example, as learned in Unit 3, during severe systemic infections with large numbers of microorganisms present, high levels of pathogen-associated molecular patterns (PAMPs) are released resulting in excessive cytokine production by macrophages and this can harm the body. In addition, neutrophils start releasing their proteases and reactive oxygen species that kill not only the bacteria, but the surrounding tissue as well. Harmful effects include high fever, hypotension, tissue destruction, wasting, acute respiratory distress syndrome or ARDS, disseminated intravascular coagulation or DIC, damage to the vascular endothelium, hypovolemia, and reduced perfusion of blood through tissues and organs resulting to shock, multiple system organ failure (MOSF), and often death. This excessive inflammatory response is referred to as Systemic Inflammatory Response Syndrome or SIRS or the Shock Cascade.

For More Information: The Shock Cascade from Unit 3

Briefly describe the mechanisms that enable to slow the flow of blood at an infection site and get phagocytes, complement proteins and antibodies to the infection site.
- Why is it important to deliver plasma to an infection site?
- Why is it important for diapedesis to occur during inflammation?

Chronic inflammation also contributes to heart disease, Alzheimer's disease, diabetes, and cancer.

- In the case of cancer,it is proposed that when macrophages produce inflammatory cytokines, such as TNF-alpha, these cytokines activate a gene switch in the cancer cell that turns on the synthesis of proteins that promote cell replication and inflammation while blocking apoptosis of the cancer cell.
- In heart disease, it is thought that macrophages digest low density lipoprotein or LDL, the bad cholesterol, and are then encased in a fibrous cap that forms arterial plaque.
- With diabetes, it is thought that the metabolic stress of obesity triggers innate immune cells and fat cells to produce cytokines such as TNF-alpha that can interfere with the normal function of insulin.
- In the case of Alzheimer's disease, microglial cells, macrophage-like cells in the brain, interact with the beta-amyloid proteins that build up in neurons of those with Alzheimer's and subsequently produce inflammatory cytokines and free radicals that destroy the neurons.

Concept Map for Inflammation

Summary

1. Most of the body defense elements are located in the blood and inflammation is the means by which body defense cells and defense chemicals leave the blood and enter the tissue around the injured or infected site.
2. As part of the mechanism for inflammation, smooth muscles around larger blood vessels contract to slow the flow of blood through the capillary beds at the infected or injured site. This gives more opportunity for leukocytes to adhere to the walls of the capillary and squeeze out into the surrounding tissue.
3. As part of the mechanism for inflammation, the endothelial cells that make up the wall of the smaller blood vessels contract. This increases the space between the endothelial cells resulting in increased capillary permeability.
4. As part of the mechanism for inflammation, adhesion molecules are activated on the surface of the endothelial cells on the inner wall of the capillaries and corresponding molecules on the surface of leukocytes called integrins attach to these adhesion

molecules allowing the leukocytes to flatten and squeeze through the space between the endothelial cells. This process is called diapedesis or extravasation.

5. As part of the mechanism for inflammation, activation of the coagulation pathway causes fibrin clots to physically trap the infectious microbes and prevent their entry into the bloodstream.
6. Acute inflammation is essential to body defense.
7. As a result of this increased permeability, plasma flows out of the blood into the tissue delivering clotting factors, antibody molecules, complement pathway proteins, nutrients, antibacterial enzymes and peptides, and transferrin for innate body defense.
8. As a result of this increased permeability, leukocytes enter the tissue delivering phagocytic cells, inflammation-inducing cells, cytotoxic T-lymphocytes, effector T4-lymphocytes, and NK cells.
9. Inflammatory cytokines also, enable endothelial cells form a fine network of new capillaries into the injured area to supply blood, oxygen, and nutrients to the inflamed tissue, and enable fibroblasts to deposit the protein collagen in the injured area and form a bridge of connective scar tissue to close the open, exposed area.
10. Chronic inflammation can result in considerable tissue damage and scarring, primarily to extracellular killing by phagocytes and hypoperfusion.
11. Chronic inflammation is thought to also contribute to heart disease, Alzheimer's disease, diabetes, and cancer.

This page titled 9.11G: Inflammation is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **11.3G: Inflammation** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

9.11H: Nutritional Immunity

Learning Objectives

- Describe at least four ways the body deprives microorganisms of iron.

We will now take a closer look at nutritional immunity. Iron is needed as a cofactor for certain enzymes in both bacteria and humans. Both bacteria and human cells produce iron chelators that trap free iron from their environment and transport it into the cell. During infection, the body makes considerable metabolic adjustment in order to make iron unavailable to microorganisms. Much of this is due to production of a defense chemical called leukocyte-endogenous mediator (LEM). As a result of infection, there is:

1. decreased intestinal absorption of iron from the diet;
2. a decrease of iron in the plasma and an increase in iron in storage as ferritin;
3. increased synthesis of the human iron-binding proteins (iron chelators) such as lactoferrin, transferrin, ferritin, and hemin that trap iron for use by human cells while making it unavailable to most microbes;
4. coupled with the febrile response, decreased ability of bacteria to synthesize their own iron chelators called siderophores;
5. prior stationing of lactoferrin at common sites of microbial invasion such as in the mucous of mucous membranes, and the entry of transferrin into the tissue during inflammation.

This lack of iron, which is needed as a cofactor for certain enzyme reactions, can inhibit the growth of many bacteria.

As seen in Unit 3, some bacteria produce in addition to their own siderophore, receptors for siderophores of other bacteria in this way take iron from other bacteria. Furthermore, a number of pathogenic bacteria are able to bind human transferrin, lactoferrin, ferritin, and hemin and use that as their iron source. For example, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, and *Haemophilus influenzae*are able to use iron bound to human transferrin and lactoferrin for their iron needs, while pathogenic *Yersinia* species are able to use transferrin and hemin as iron sources. *Borrelia burgdorferi* doesn't even use iron as a cofactor, but instead uses manganese. Furthermore, a number of bacteria are able to produce exotoxins that kill host cells only when iron concentrations are low. Perhaps in this way the bacteria can gain access to the iron that was in those cells.

Summary

1. Iron is needed as a cofactor for certain enzymes in both bacteria and humans.
2. Both bacteria and human cells produce iron chelators that trap free iron from their environment and transport it into the cell.
3. During infection, the body makes considerable metabolic adjustment in order to make iron unavailable to microorganisms.
4. The lack of iron can inhibit the growth of many bacteria.
5. Some bacteria in addition to their own siderophores, produce receptors for iron chelators of other bacteria and/or human cells and in this way take iron being trapped for use by other organisms.
6. A number of bacteria are able to produce toxins that kill host cells only when iron concentrations are low and in this way gain access to the iron that was in those cells.

This page titled 9.11H: Nutritional Immunity is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **11.3H: Nutritional Immunity** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

9.11I: Fever

Describe the mechanism behind fever induction and indicate its possible benefits.
- Define hyperpyrexia.

Activated macrophages and other leukocytes release inflammatory cytokines such as TNF-alpha, IL-1, and IL-6 when their pattern-recognition receptors (PRRs) bind pathogen associated molecular patterns or PAMPs - molecular components associated with microorganisms but not found as a part of eukaryotic cells. These include bacterial molecules such as peptidoglycan, teichoic acids, lipopolysaccharide, mannans, flagellin, and bacterial DNA. There are also pattern-recognition molecules for viral double-stranded RNA (dsRNA) and fungal cell walls components such as lipoteichoic acids, glycolipids, mannans, and zymosan.

These cytokines stimulate the anterior hypothalamus of the brain, the part of the brain that regulates body temperature, to produce prostaglandin E2, which leads to an increase bodily heat production and increased vasoconstriction. This, in turn, decreases the loss of heat from the skin and increases body temperature. Up to a certain point, fever is beneficial:

1. Fever increases the environmental temperature above the optimum growth temperature for many microorganisms. If the microorganisms are growing more slowly, the body's defenses have a better chance of removing them all.
2. Fever leads to the production of heat shock proteins that are recognized by some intraepithelial T-lymphocytes called delta gamma T-cells, resulting in the production of inflammation-promoting cytokines.
3. Fever elevates the temperature of the body increasing the rate of enzyme reactions, and speeding up metabolism within the body. An elevation in the rate of metabolism can increase the production and activity of phagocytes, speed up the multiplication of lymphocytes, increase the rate of antibody and cytokine production, increase the rate at which leukocytes are released from the bone marrow into the bloodstream, and speed up tissue repair.

Too high of a body temperature, however, may cause damage by denaturing the body's enzymes. Hyperpyrexia is a fever with an extreme elevation of body temperature greater than or equal to 41.5 °C (106.7 °F). Body temperature this elevated often indicates a serious underlying condition and may lead to potentially hazardous side effects. As a result, hyperpyrexia is considered as a medical emergency.

Summary

1. Activated macrophages and other leukocytes release inflammatory cytokines such as TNF-alpha, IL-1, and IL-6 when their pattern-recognition receptors (PRRs) bind pathogen associated molecular patterns or PAMPs.
2. These cytokines stimulate the anterior hypothalamus of the brain, the part of the brain that regulates body temperature, to produce prostaglandin E2, which leads to an increase bodily heat production and increased vasoconstriction.
3. Vasoconstriction decreases the loss of heat from the skin and increases body temperature.
4. Fever increases the environmental temperature above the optimum growth temperature for many microorganisms.
5. Fever leads to the production of heat shock proteins that are recognized by some intraepithelial T-lymphocytes resulting in the production of inflammation-promoting cytokines.
6. Fever elevates the temperature of the body increasing the rate of enzyme reactions, and speeding up metabolism within the body including that involved in innate and adaptive immunity as well as tissue repair.

This page titled 9.11I: Fever is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **11.3I: Fever** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

9.11J: The Acute Phase Response

Briefly describe the mechanism behind the acute phase response.
- State the functions of the following acute phase proteins:

a. C-reactive protein

b. mannose-binding lectin

We will now take a closer look at the acute phase response. The acute phase response is an innate body defense seen during acute illnesses and involves the increased production of certain blood proteins termed acute phase proteins.

Activated macrophages and other leukocytes release inflammatory cytokines such as tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (IL-1), and interleukin-6 (IL-6) when their pattern-recognition receptors (PRRs) bind pathogen associated molecular patterns or PAMPs - molecular components associated with microorganisms but not found as a part of eukaryotic cells. These include bacterial molecules such as peptidoglycan, teichoic acids, lipopolysaccharide, mannans, flagellin, pilin, and bacterial DNA. There are also pattern-recognition molecules for viral double-stranded RNA (dsRNA) and fungal cell walls components such as lipoteichoic acids, glycolipids, mannans, and zymosan.

These cytokines travel through the blood and stimulate hepatocytes in the liver to synthesize and secrete acute phase proteins. This response provides an early defense and enables the body to recognize foreign substances early on in the infection process prior to the full activation and implementation of the immune responses. Two important acute phase proteins are C-reactive protein and mannose-binding protein. They function as soluble pattern-recognition receptors.

1. C-reactive protein (CRP) binds to the phosphorylcholine portion of teichoic acids and lipopolysaccharides of bacterial and fungal cell walls. It also binds to the phosphocholine found on the surface of damaged or dead human cells. It functions as an opsonin, sticking the microorganism to phagocytes, and activates the classical complement pathway by binding C1q, the first component in the pathway.
2. Mannan-bindinglectin (MBL) - also known as mannan-binding protein or MBP -binds to mannose-richglycans (short carbohydrate chains with the sugar mannose or fructose as the terminal sugar). These are common in microbial glycoproteins and glycolipids but rare in those of humans. It functions as an opsonin, sticking the microorganism to phagocytes, and activates the lectin pathway.

Products of the complement pathways, in turn, promote inflammation, attach microbes to phagocytes, cause to MAC cytolysis, and chemotactically attract phagocytes to the infected area.

Summary

1. The acute phase response is an innate body defense seen during acute illnesses and involves the increased production of certain blood proteins termed acute phase proteins.
2. Inflammatory cytokines produced during innate immunity travel through the blood and stimulate hepatocytes in the liver to synthesize and secrete acute phase proteins.
3. Two important acute phase proteins are C-reactive protein and mannose-binding protein, both functioning as soluble pattern-recognition receptors.
4. C-reactive protein (CRP) binds to certain PAMPs bacterial and fungal cell walls as well as to phosphocholine found on the surface of damaged or dead human cells.
5. CRP functions as an opsonin, sticking the microorganism to phagocytes, and activates the classical complement pathway by binding C1q, the first component in the pathway.
6. Mannan-binding lectin (MBL) - also known as mannan-binding protein or MBP - binds to mannose-rich glycans on microbial cell walls.
7. MBL functions as an opsonin, sticking the microorganism to phagocytes, and activates the lectin pathway.

This page titled 9.11J: The Acute Phase Response is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **11.3J: The Acute Phase Response** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

9.11K: Intraepithelial T-lymphocytes and B-1 cells

Briefly describe how intraepithelial T-lymphocytes (gamma:delta T-lymphocytes) play a role in innate immunity.
- Briefly describe how B-1 cells play a role in innate immunity.

We will now take a closer look at Intraepithelial T-lymphocytes (e.g., T4 and T8) and B-1 cells. Most of the T-lymphocytes and B-lymphocytes in the body are involved in the adaptive immune responses that will be discussed in Unit 6. In adaptive immunity, specific receptors on T-lymphocytes (T-cell receptors or TCRs) and B-lymphocytes (B-cell receptors or BCRs) recognize specific antigens of specific microbes.

Intraepithelial T-lymphocytes and B-1 cells, on the other hand, are subpopulations of T-lymphocytes and B-lymphocytes that possess a more limited diversity of receptors and are designed to directly recognize the more common microbes that enter the epidermis or the mucosal epithelia. As such, they function more as effector cells for innate immunity rather than adaptive immunity.

a. Intraepithelial T-lymphocytes (IELs) are found in the epidermis of the skin and the mucosal epithelia. These T-lymphocytes, known as gamma:delta T-lymphocytes, differ from the T-lymphocytes (alpha:beta T-lymphocytes) associated with adaptive immunity. The alpha:beta T-lymphocytes are designed to recognize peptide antigens bound to MHC-I molecules of infected cells and tumor cells.

   Although their exact function is unknown, it has been proposed that they recognize molecules associated with epithelial cells but expressed only when those cells are infected, such as MHC-I molecules and heat shock proteins. They then trigger apoptosis of these stressed or infected cells using perforins and granzymes similar to cytotoxic T-lymphocytes (CTLs) of adaptive immunity. Rather than recognizing antigens specific to an infectious microorganism, they recognize molecules associated with the epithelium as a consequence of infection. Their T-cell receptors may also function as PRRs for recognizing certain PAMPs. As such, they function more as effector cells for innate immunity rather than adaptive immunity. They probably help defend the body by producing cytokines that play a variety of roles in body defense. IELs are also thought to aid in repair of mucous membranes following inflammatory damage. Excessive or inappropriate activation of IELs can also lead to damage of the intestines as in the case of celiac disease.

b. B-1 lymphocytes, or B-1 cells are found mostly in the peritoneal and pleural cavities . B-1 cells have a limited diversity of antigen receptors that initially produce a class of antibody molecule called IgM against common polysaccharide and lipid antigens of microbes and against PAMPs. As such they function more as effector cells for innate immunity rather than adaptive immunity. Antibodies produced by B-1 cells are often called natural antibodies that help to protect against bacteria in body cavities. Similar B-lymphocytes called marginal zone B cells are found in the marginal zone of the white pulp of the spleen. These are thought to make IgM to protect against bacteria that enter the bloodstream.

Summary

1. Most of the T-lymphocytes and B-lymphocytes in the body are involved in the adaptive immune responses wherein specific receptors on T-lymphocytes (T-cell receptors or TCRs) and B-lymphocytes (B-cell receptors or BCRs) recognize specific antigens of specific microbes.
2. Intraepithelial T-lymphocytes and B-1 cells, however, are subpopulations of T-lymphocytes and B-lymphocytes that possess a more limited diversity of receptors and are designed to directly recognize the more common microbes that enter the epidermis or the mucosal epithelia and function more as effector cells for innate immunity rather than adaptive immunity.
3. Intraepithelial T-lymphocytes (IELs) are found in the epidermis of the skin and the mucosal epithelia.
4. It has been proposed that they recognize molecules such as MHC-I molecules and heat shock proteins associated with epithelial cells but expressed only when those cells are infected and trigger apoptosis of these stressed or infected cells. They may also aid in repair of mucous membranes following inflammatory damage.
5. B-1 lymphocytes, or B-1 cells, are found mostly in the peritoneal and pleural cavities.
6. B-1 cells have a limited diversity of antigen receptors that initially produce a class of antibody molecule called IgM against common polysaccharide and lipid antigens of microbes and against PAMPs.

7. Similar B-lymphocytes called marginal zone B cells are found in the spleen.\ and are thought to make IgM to protect against bacteria that enter the bloodstream.

This page titled 9.11K: Intraepithelial T-lymphocytes and B-1 cells is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **11.3K: Intraepithelial T-lymphocytes and B-1 cells** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

CHAPTER OVERVIEW

10: Adaptive Immunity

The adaptive immune system is a subsystem of the overall immune system that is composed of highly specialized, systemic cells and processes that eliminate or prevent pathogen growth. Adaptive immunity creates immunological memory after an initial response to a specific pathogen, and leads to an enhanced response to subsequent encounters with that pathogen. This process of acquired immunity is the basis of vaccination.

10.1: Immunodeficiency
10.1.E: Immunodeficiency (Exercises)
10.2: Hypersensitivities
10.2.E: Hypersensitivities (Exercises)
10.3: Introduction to Adaptive Immunity
10.3.1: An Overview of Innate and Adaptive Immunity
10.3.2: Antigens and Epitopes
10.3.3: Major Cells and Key Cell Surface Molecules Involved in Adaptive Immune Responses
10.3.3A: Major Histocompatibility Complex (MHC) Molecules
10.3.3B: Antigen-Presenting Cells (APCs)
10.3.3C: T4-Lymphocytes (T4-Cells)
10.3.3D: T8-Lymphocytes (T8-Cells)
10.3.3E: Invarient Natural Killer T-Lymphocytes (iNKT Cells)
10.3.3F: B-Lymphocytes (B-Cells)
10.3.3G: Natural Killer Cells (NK Cells)
10.3.4: The Lymphoid System
10.3.5: An Overview of the Steps Involved in Adaptive Immune Responses
10.3.E: Introduction to Adaptive Immunity (Exercises)
10.4: Humoral Immunity
10.4.1: Antibodies (Immunoglobulins)
10.4.1B: Antibody Structure
10.4.1C: The 5 Classes (Isotypes) of Human Antibodies
10.4.1D: Generation of Antibody Diversity
10.4.1E: Clonal Selection and Clonal Expansion
10.4.1F: Anamnestic (Memory) Response
10.4.2: Ways That Antibodies Help to Defend the Body
10.4.2A: Opsonization
10.4.2B: Cytolysis by the Membrane Attack Complex (MAC)
10.4.2C: Antibody-dependent Cellular Cytotoxicity (ADCC) by Natural Killer Cells
10.4.2D: Neutralization of Exotoxins
10.4.2E: Neutralization of Viruses
10.4.2F: Preventing Bacterial Adherence
10.4.2G: Agglutination of Microorganisms
10.4.2H: Immobilization of Bacteria and Protozoans
10.4.2I: Promoting an Inflammatory Response

10.4.3: Naturally and Artificially Acquired Active and Passive Immunity
10.4.3A: Naturally Acquired Immunity
10.4.3B: Artificially Acquired Immunity
10.4.E: Humoral Immunity (Exercises)
10.5: Cell-Mediated Immunity
10.5.1: Cell-Mediated Immunity - An Overview
10.5.2: Activating Antigen-Specific Cytotoxic T- Lymphocytes
10.5.3: Activating Macrophages and NK Cells
10.5.4: Stimulating Cells to Secrete Cytokines
10.5.E: Cell-Mediated Immunity (Exercises)

This page titled 10: Adaptive Immunity is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

This page titled 10: Adaptive Immunity is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

10.1: Immunodeficiency

This page titled 10.1: Immunodeficiency is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

This page titled 10.1: Immunodeficiency is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

10.1.E: Immunodeficiency (Exercises)

These are homework exercises to accompany Kaiser's "Microbiology" TextMap. Microbiology is the study of microorganisms, which are defined as any microscopic organism that comprises either a single cell (unicellular), cell clusters or no cell at all (acellular). This includes eukaryotes, such as fungi and protists, and prokaryotes. Viruses and prions, though not strictly classed as living organisms, are also studied.

15.1: Primary Immunodeficiency

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Match the following:

   _____ Rare but severe primary immunodeficiencies occuring as the result of a rare recessive genetic defect in the immune responses that involves the development of B-lymphocytes, T-lymphocytes, or both and results in multiple, recurrent infections during infancy.

   _____ Common, less severe primary immunodeficiencies involving just one or more of the huge number of genes involved in the immune responses. They involve the decreased ability to combat just a single type of infection or a narrow range of infections and relate to an individual's own unique genetics.

   _____ There may be greatly decreased humoral immunity but cell-mediated immunity remains normal. X-linked agammaglobulinemia and selective IgA deficiency are examples. May be treated with artificially-acquired passive immunization.

   _____ Primary immunodeficiencies that affect both humoral immunity and cell-mediated immunity. There is a defect in both B-lymphocytes and T-lymphocytes, or just T-lymphocytes in which case the humoral deficiency is due to the lack of T4-helper lymphocytes.

   a. B-lymphocyte disorder
   b. combined B-lymphocyte and T-lymphocyte disorder
   c. novel primary immunodeficiency
   d. conventional primary immunodeficiency

2. Infants born with a nonfunctional thymus develop frequent and severe infections. Explain.

15.2: Secondary Immunodeficiency

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. State what is meant by secondary immunodeficiency and list 4 possible contributing factors.
2. Briefly give three mechanisms of HIV-induced immunodeficiency.

This page titled 10.1.E: Immunodeficiency (Exercises) is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **15.E: Immunodeficiency (Exercises)** has no license indicated.

SECTION OVERVIEW

10.2: Hypersensitivities

Hypersensitivities are a set of undesirable reactions produced by the normal immune system, including allergies and autoimmunity. These reactions may be damaging, uncomfortable, or occasionally fatal. Hypersensitivity reactions require a pre-sensitized (immune) state of the host. Immediate hypersensitivities refer to humoral immunity (antigen/antibody reactions) causing harm. Delayed hypersensitivities refer to cell-mediated immunity (cytotoxic T-lymphocytes, macrophages, and cytokines) leading to harm.

Topic hierarchy

10.2.E: Hypersensitivities (Exercises)

Template:HideTOC

This page titled 10.2: Hypersensitivities is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

This page titled 10.2: Hypersensitivities is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

10.2.E: Hypersensitivities (Exercises)

These are homework exercises to accompany Kaiser's "Microbiology" TextMap. Microbiology is the study of microorganisms, which are defined as any microscopic organism that comprises either a single cell (unicellular), cell clusters or no cell at all (acellular). This includes eukaryotes, such as fungi and protists, and prokaryotes. Viruses and prions, though not strictly classed as living organisms, are also studied.

1. When humoral immunity (antigen/antibody reactions) cause harm to the body it is termed _____.

2. When cell-mediated immunity (cytotoxic T-lymphocytes, macrophages, and cytokines) cause harm to the body it is termed _____.

3. **Describe** the mechanism for Type I (IgE-mediated) hypersensitivity and give two examples. State how they are treated symptomatically.

4. When a person has hay fever, common symptoms include runny eyes, runny nose, swollen sinuses, and difficulty in breathing. In terms of humoral immunity, discuss the mechanism behind these symptoms. Also state the reason for giving antihistamines and describe how allergy shots may lessen the severity of this type of hypersensitivity.

5. Researchers are hoping that the injection of monoclonal antibodies against IgE may someday be used to prevent virtually any Type I hypersensitivity. Explain.

6. Describe the mechanism for Type II (antibody-dependent cytotoxicity) hypersensitivity and give 2 examples.

7. Describe the mechanism for Type III (immune complex-mediated) hypersensitivity and give 2 examples.

8. Describe the mechanism for Type IV (Stimulatory) hypersensitivity and give an example.

9. Describe the mechanism for Type IV (delayed) hypersensitivity and give 2 examples.

10. Define superantigen .

11. Briefly describe the mechanism by which superantigens cause harm to the body.

12. Name 2 superantigens and give an example of a bacterium that produces each.

A.

B.

This page titled 10.2.E: Hypersensitivities (Exercises) is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **16.E: Hypersensitivities (Exercises)** has no license indicated.

10.3: Introduction to Adaptive Immunity

This page titled 10.3: Introduction to Adaptive Immunity is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

This page titled 10.3: Introduction to Adaptive Immunity is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

10.3.1: An Overview of Innate and Adaptive Immunity

Compare adaptive (acquired) immunity with innate immunity.
- Define the following:
  a. antigen
  b. immunogen
  c. epitope
  d. humoral immunity
  e. cell-mediated immunity

As mentioned in Unit 5, the body has two immune systems: innate immunity and adaptive immunity. Unit 5 dealt with innate immunity. In Unit 6 we will cover adaptive immunity. Let's first again briefly compare acquired and innate immunity.

Innate Immunity

Innate immunity is an antigen-nonspecific defense mechanisms that a host uses immediately or within several hours after exposure to almost any microbe. This is the immunity one is born with and is the initial response by the body to eliminate microbes and prevent infection. Innate immunity can be divided into immediate innate immunity and early induced innate immunity.

Immediate innate immunity begins 0 - 4 hours after exposure to an infectious agent and involves the action of soluble preformed antimicrobial molecules that circulate in the blood, our found in extracellular tissue fluids, and are secreted by epithelial cells. These include: antimicrobial enzymes and peptides; complement system proteins; and anatomical barriers to infection, mechanical removal of microbes, and bacterial antagonism by normal flora bacteria. These preformed innate defense molecules will be discussed in greater detail later in this unit.

Early induced innate immunity begins 4 - 96 hours after exposure to an infectious agent and involves the recruitment of defense cells as a result of pathogen-associated molecular patterns or PAMPS binding to pattern-recognition receptors or PRRs. These recruited defense cells include: phagocytic cells: leukocytes such as neutrophils, eosinophils, and monocytes; tissue phagocytic cells in the tissue such as macrophages; cells that release inflammatory mediators: inflammatory cells in the tissue such as macrophages and mast cells; leukocytes such as basophils and eosinophils; and natural killer cells (NK cells).

Unlike adaptive immunity, innate immunity does not recognize every possible antigen. Instead, it is designed to recognize molecules shared by groups of related microbes that are essential for the survival of those organisms and are not found associated with mammalian cells. These unique microbial molecules are called pathogen-associated molecular patterns or PAMPS and include LPS from the gram-negative cell wall, peptidoglycan and lipotechoic acids from the gram-positive cell wall, the sugar mannose (a terminal sugar common in microbial glycolipids and glycoproteins but rare in those of humans), bacterial and viral unmethylated CpG DNA, bacterial flagellin, the amino acid *N*-formylmethionine found in bacterial proteins, double-stranded and single-stranded RNA from viruses, and glucans from fungal cell walls. In addition, unique molecules displayed on stressed, injured, infected, or transformed human cells also act as PAMPS. (Because all microbes, not just pathogenic microbes, possess PAMPs, pathogen-associated molecular patterns are sometimes referred to as microbe-associated molecular patterns or MAMPs.)

Most body defense cells have pattern-recognition receptors or PRRs for these common PAMPS (Figure 10.3.1.1) and so there is an immediate response against the invading microorganism. Pathogen-associated molecular patterns can also be recognized by a series of soluble pattern-recognition receptors in the blood that function as opsonins and

initiate the complement pathways. In all, the innate immune system is thought to recognize approximately 10^3 of these microbial molecular patterns.

For More Information: Leukocytes from Unit 5

Examples of innate immunity include anatomical barriers, mechanical removal, bacterial antagonism, antigen-nonspecific defense chemicals, the complement pathways, phagocytosis, inflammation, fever, and the acute-phase response. In this current unit we will look at each of these in greater detail.

Adaptive Immunity

Adaptive (acquired) immunity refers to antigen-specific defense mechanisms that take several days to become protective and are designed to react with and remove a specific antigen. This is the immunity one develops throughout life. There are two major branches of the adaptive immune responses: humoral immunity and cell-mediated immunity.

1. humoral immunity: humoral immunity involves the production of antibody molecules in response to an antigen and is mediated by B-lymphocytes.
2. cell-mediated immunity: Cell-mediated immunity involves the production of cytotoxic T-lymphocytes, activated macrophages, activated NK cells, and cytokines in response to an antigen and is mediated by T-lymphocytes.

During adaptive immunity, antigens are transported to lymphoid organs where they are recognized by naive B-lymphocytes and T-lymphocytes. These activated B- and T-lymphocytes subsequently proliferate and differentiate into effector cells. An antigen is defined as a substance that reacts with antibody molecules and antigen receptors on lymphocytes. An immunogen is an antigen that is recognized by the body as nonself and stimulates an adaptive immune response. For simplicity we will use the term antigen when referring to both antigens and immunogens. The actual portions or fragments of an antigen that react with antibodies and lymphocyte receptors are called epitopes. The size of an epitope is generally thought to be equivalent to 5-15 amino acids in the case of protein antigens (Figure **10.3.1.2**); 3-4 sugar residues in the case of polysaccharide antigens (Figure **10.3.1.3**).

For More Information: Antigens and Immunogens

For More Information: Antibodies from Unit 6

The body recognizes an antigen as foreign when epitopes of that antigen bind to epitope-specific receptor molecules on the surface of B-lymphocytes and/or T-lymphocytes. The epitope receptor on the surface of a B-lymphocyte is called a B-cell receptor (BCR) and is actually an antibody molecule. The receptor on a T-lymphocyte is called a T-cell receptor (TCR).

- B-cell receptors (BCRs) can bind directly to epitopes on peptide, protein, polysaccharide, nucleic acid, and lipid antigens (Figure **10.3.1.4**).
- T-cell receptors (TCRs) of most T4-lymphocytes and T8-lymphocytes can only recognize peptide epitopes from protein antigens presented by the body's own cells by way of special molecules called MHC molecules (Figure **10.3.1.4**).

It is estimated that the human body has the ability to recognize 10^7 or more different epitopes and make up to 10^9 different antibodies, each with a unique specificity. In order to recognize this immense number of different epitopes, the body produces 10^7 or more distinct clones of both B-lymphocytes and T-lymphocytes, each with a unique B-cell receptor or T-cell receptor. Among this large variety of B-cell receptors and T-cell receptors there is bound to be at least one that has an epitope-binding site able to fit, at least to some degree, any antigen the immune system eventually

encounters. With the adaptive immune responses, the body is able to recognize any conceivable antigen it may eventually encounter.

The downside to the specificity of adaptive immunity is that only a few B-cells and T-cells in the body recognize any one epitope. These few cells then must rapidly proliferate in order to produce enough cells to mount an effective immune response against that particular epitope, and that typically takes several days. During this time the pathogen could be causing considerable harm, and that is why innate immunity is also essential.

Flash animation of epitopes reacting with a specific TCR on a T8-lymphocyte.

Adaptive immunity usually improves upon repeated exposure to a given infection and involves the following:

- antigen-presenting cells (APCs) such as macrophages and dendritic cells;
- the activation and proliferation of antigen-specific B-lymphocytes;
- the activation and proliferation of antigen-specific T-lymphocytes; and
- the production of antibody molecules, cytotoxic T-lymphocytes (CTLs), activated macrophages, and cytokines.

Acquired immunity includes both humoral immunity and cell-mediated immunity and will be the topic of Unit 5.

Concept Map for Innate Versus Adaptive Immunity

We will now take a closer look at adaptive immunity.

Summary

1. The body has two immune systems: the innate immune system and the adaptive immune system.
2. Innate immunity is an antigen-nonspecific defense mechanisms that a host uses immediately or within several hours after exposure to almost any microbe.
3. Innate immunity is the immunity one is born with and is the initial response by the body to eliminate microbes and prevent infection.
4. Immediate innate immunity begins 0 - 4 hours after exposure to an infectious agent and involves the action of soluble preformed antimicrobial molecules that circulate in the blood and in extracellular tissue fluids.
5. Early induced innate immunity begins 4 - 96 hours after exposure to an infectious agent and involves the recruitment of defense cells as a result of pathogen-associated molecular patterns or PAMPS binding to pattern-recognition receptors or PRRs.
6. Adaptive (acquired) immunity refers to antigen-specific defense mechanisms that take several days to become protective and are designed to react with and remove a specific antigen.
7. Adaptive immunity is the immunity one develops throughout life.
8. An antigen is defined as a substance that reacts with antibody molecules and antigen receptors on lymphocytes.
9. The actual portions or fragments of an antigen that react with antibodies and lymphocyte receptors are called epitopes.

This page titled 10.3.1: An Overview of Innate and Adaptive Immunity is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **12.1: An Overview of Innate and Adaptive Immunity** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

10.3.2: Antigens and Epitopes

Define antigen and immunogen.
- State what antigens are composed of chemically.
- List 3 characteristics an antigen must have to be immunogenic.
- Define epitope.
- Briefly describe how the body recognizes an antigen as foreign.
- Compare B-cell receptors and T-cell receptors in terms of how they recognize epitopes.
- In terms of infectious diseases, list 2 categories of microbial materials that may act as an antigen.
- List 3 groups of noninfectious materials that may act as an antigen.
- Define the following:

a. endogenous antigen
b. exogenous antigen
c. autoantigen
d. hapten

An antigen is defined as a substance that reacts with antibody molecules and antigen receptors on lymphocytes. An immunogen is an antigen that is recognized by the body as non-self and stimulates an adaptive immune response. For simplicity, both antigens and immunogens are usually referred to as antigens.

To be immunogenic, an antigen must possess three characteristics:

- be of high molecular weight,
- exhibit chemical complexity, and
- exhibit foreignness (recognized as non-self by the body).

Chemically, antigens are large molecular weight proteins (including conjugated proteins such as glycoproteins, lipoproteins, and nucleoproteins) and polysaccharides (including lipopolysaccharides). These protein and polysaccharide antigens are found on the surfaces of viruses and cells, including microbial cells (bacteria, fungi, protozoans) and human cells.

Epitopes of an antigen

The actual portions or fragments of an antigen that react with receptors on B-lymphocytes and T-lymphocytes, as well as with free antibody molecules, are called epitopes or antigenic determinants. The size of an epitope is generally thought to be equivalent to 5-15 amino acids or 3-4 sugar residues.

Some antigens, such as polysaccharides, usually have many epitopes, but all of the same specificity. This is because polysaccharides may be composed of hundreds of sugars with branching sugar side chains, but usually contain only one or two different sugars. As a result, most "shapes" along the polysaccharide are the same (see Figure **10.3.2.1**).

Other antigens such as proteins usually have many epitopes of different specificities. This is because proteins are usually hundreds of amino acids long and are composed of 20 different amino acids. Certain amino acids are able to interact with other amino acids in the protein chain and this causes the protein to fold over upon itself and assume a complex three-dimensional shape. As a result, there are many different "shapes" on the protein (see Figure **10.3.2.2**). That is why proteins are more immunogenic than polysaccharides; they are chemically more complex.

A microbe, such as a single bacterium, has many different proteins (and polysaccharides) on its surface that collectively form its various structures, and each different protein may have many different epitopes. Therefore, immune responses are directed against many different epitopes of many different antigens of the same microbe. (For example, a bacterial cell wall alone may contain over 100 different epitopes.) Even simple viruses possess many different epitopes. (see Figure **10.3.2.3**).

Recognizing an antigen as foreign

As we saw earlier in Unit 5, the B-lymphocytes and T-lymphocytes are the cells that carry out the immune responses. The body recognizes an antigen as foreign when epitopes of that antigen bind to B-lymphocytes and T-lymphocytes by means of epitope-specific receptor molecules having a shape complementary to that of the epitope (similar to interlocking pieces of a puzzle).

a. B-cell receptors

The antigen receptors on the cytoplasmic membrane of B-lymphocytes are called B-cell receptors and are actually antibody molecules made by that cell and anchored to the outer surface of its cytoplasmic membrane. As will be seen in a later section, antibodies are "Y"-shaped macromolecules composed of four glycoprotein chains connected to one another by disulfide (S-S) bonds and noncovalent bonds (see Figure **10.3.2.4**). Additional S-S bonds fold the individual glycoprotein chains into a number of distinct globular domains (see Figure **10.3.2.5**).

The two tips of the "Y" are referred to as the Fab portions of the antibody (see Figure **10.3.2.4** and Figure **10.3.2.5**). The first 110 amino acids or first domain of both the heavy and light chain of the Fab region of the antibody provide specificity for binding an epitope on an antigen. Because they recognize molecular shapes that occur as a result of the 3-dimensional folding of an antigen, B-cell receptors can bind directly to epitopes on peptide, protein, polysaccharide, nucleic acid, and lipid antigens.

The bottom part of the "Y", the C terminal region of each glycoprotein chain, is called the Fc portion. The Fc portion has a constant amino acid sequence that defines the class and subclass of each antibody. The terminal portion of the Fc region of the B-cell receptor is the part that becomes anchored to the cytoplasmic membrane of B-lymphocyte (see Figure **10.3.2.6**).

b. T-cell receptors

The receptors on the membrane of T-lymphocytes are called T-cell receptors or TCRs. They are analogous to the B-cell receptor, but are composed of just two glycoprotein chains, each having a variable domain and a constant domain (see Figure **10.3.2.7**).

Unlike B-cell receptors that can directly bind to epitopes on antigens, the T-cell receptor or TCR of most T4-lymphocytes and T8-lymphocytes can only recognize peptide epitopes from protein antigens presented by the body's own cells by way of special molecules called MHC molecules as seen in Figure **10.3.2.6**. The terminal portion of the variable domains provides specificity for binding peptides of protein antigens after the protein has been unfolded, broken into peptides, and bound to a MHC molecule, while the terminus of the constant region becomes anchored to the cytoplasmic membrane of the T-lymphocyte.

The TCR of $CD4^-CD8^-$ T-lymphocytes and non-MHC restricted $CD4^+$ and $CD8^+$ lymphocytes can recognize epitopes of lipid or glycolipid antigens after they have been attached to CD1 molecules on antigen-presenting cells or in some cases, epitopes directly on antigens.

It is estimated that the human body has the ability to recognize 10^7or more different epitopes and make up to 10^9 different antibodies, each with a unique specificity. In order to recognize this immense number of different epitopes, the body produces 10^7 or more distinct clones of both B-lymphocytes and T-lymphocytes, each with a unique B-cell receptor or T-cell receptor. Among this large variety of B-cell receptors and T-cell receptors there is bound to be at least one that has an epitope-binding site able to fit, at least to some degree, any antigen the immune system eventually

encounters. With the adaptive immune responses, the body is able to recognize any conceivable antigen it may eventually encounter.

Flash animation of epitopes reacting with specific B-cell receptors on B-lymphocytes.

html5 version of animation for iPad showing epitopes reacting with specific B-cell receptor on a B-lymphocytes.

Flash animation showing epitopes reacting with a specific TCR on a T8-lymphocyte.

html5 version of animation for iPad showing epitopes reacting with a specific TCR on a T8-lymphocyte.

For More Information: B-Lymphocytes from Unit 6

For More Information: T4-Lymphocytes from Unit 6

For More Information: T8-Lymphocytes from Unit 6

Substances that act as antigens

In terms of infectious diseases, the following may act as antigens:

a. microbial structures, such as bacterial and fungal cell walls, protozoan cell membranes, bacterial and fungal capsules, microbial flagella, bacterial pili, viral capsids, viral envelope-associated glycoproteins, etc.; and

b. microbial toxins

Certain non-infectious materials may also act as antigens if they are recognized as "nonself" by the body. These include:

a. allergens, including dust, pollen, hair, foods, dander, bee venom, drugs, and other agents causing allergic reactions;

b. foreign tissues and cells from transplants and transfusions; and

c. the body's own cells that the body fails to recognize as "normal self," such as cancer cells, infected cells, cells involved in autoimmune diseases.

There are three broad categories of antigens: endogenous antigens, exogenous antigens, and autoantigens.

1. Endogenous antigens are proteins found within the cytosol of human cells. Examples of endogenous antigens include:

a. viral proteins produced during viral replication;
b. proteins produced by intracellular bacteria such as Rickettsias and Chlamydias during their replication;
c. proteins that have escaped into the cytosol from the phagosome of phagocytes such as antigen-presenting cells;

d. tumor antigens produced by cancer cells; and
e. self-peptides from host cellular proteins.

2. Exogenous antigens are antigens that enter from outside the body, such as bacteria, fungi, protozoa, and free viruses. These exogenous antigens enter macrophages, dendritic cells, and B-lymphocytes through phagocytosis or pinocytosis.

3. Autoantigens are any of an organism's own antigens (self-antigens) that stimulate an autoimmune reaction, that is humoral immunity or cell-mediated against self.

A hapten is a small molecule that by itself is not immunogenic but can act as an antigen when it binds to a larger protein molecule. The hapten then acts as an epitope on the protein. For example with penicillin and poison ivy allergies, the penicillin molecules and the oil urushiol from the poison ivy plant function as haptens, binding to tissue proteins to form an antigen and stimulating an allergic immune response.

How is the body able to distinguish epitopes of microorganisms from "self" epitopes present as a part of our body?
- What is the difference between how B-lymphocytes and T-lymphocytes recognize antigens?

Summary

1. An antigen is defined as a substance that reacts with antibody molecules and antigen receptors on lymphocytes.
2. An immunogen is an antigen that is recognized by the body as non-self and stimulates an adaptive immune response.
3. Chemically, antigens are large molecular weight proteins and polysaccharides.
4. The actual portions or fragments of an antigen that react with receptors on B-lymphocytes and T-lymphocytes, as well as with free antibody molecules, are called epitopes.
5. The size of an epitope is generally thought to be equivalent to 5-15 amino acids or 3-4 sugar residues.
6. Polysaccharides antigens usually have many epitopes but all of the same specificity.
7. Proteins antigens usually have many epitopes of different specificities.
8. Immune responses are directed against many different epitopes of many different antigens of the same microbe.
9. The body recognizes an antigen as foreign when epitopes of that antigen bind to B-lymphocytes and T-lymphocytes by means of epitope-specific receptor molecules having a shape complementary to that of the epitope.
10. The antigen receptors on the cytoplasmic membrane of B-lymphocytes are called B-cell receptors and are actually antibody molecules made by that cell and anchored to the outer surface of its cytoplasmic membrane and is composed of composed of four interconnected glycoprotein chains.
11. The receptors on the membrane of T-lymphocytes are called T-cell receptors or TCRs and are composed of just two glycoprotein chains.
12. During its development, each different B-lymphocyte and T-lymphocyte becomes genetically programmed to produce a B-cell receptor or T-cell receptor with a unique three-dimensional shape.
13. The body produces 107 or more distinct clones of both B-lymphocytes and T-lymphocytes, each with a unique B-cell receptor or T-cell receptor and with this large variety of B-cell receptors and T-cell receptors there is bound to be at least one that has an epitope-binding site able to fit, at least to some degree, any antigen the immune system eventually encounters.
14. In terms of infectious diseases, microbial structures and microbial toxins act as antigens.
15. Certain noninfectious materials also act as antigens, including allergens, foreign tissues and cells from transplants and transfusions, and the body's own cells that the body fails to recognize as "normal self," such as cancer cells, infected cells, and cells involved in autoimmune diseases.
16. Endogenous antigens are antigens found within the cytosol of human cells such as viral proteins, proteins from intracellular bacteria, and tumor antigens.
17. Exogenous antigens are antigens that enter from outside the body, such as bacteria, fungi, protozoa, and free viruses.
18. Autoantigens are any of an organism's own antigens (self-antigens) that stimulate an autoimmune reaction.

This page titled 10.3.2: Antigens and Epitopes is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **12.2: Antigens and Epitopes** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

10.3.3: Major Cells and Key Cell Surface Molecules Involved in Adaptive Immune Responses

We will now take a look at major cells and key cell-surface molecules involved in adaptive immune responses. Template:HideTOC

This page titled 10.3.3: Major Cells and Key Cell Surface Molecules Involved in Adaptive Immune Responses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **12.3: Major Cells and Key Cell Surface Molecules Involved in Adaptive Immune Responses** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

10.3.3A: Major Histocompatibility Complex (MHC) Molecules

Learning Objectives

- State which body cells display MHC-I surface molecules and which cells normally display MHC-II surface molecules.
- Define endogenous antigen and exogenous antigen and state which class of MHC molecule primarily binds each.
- State which type of T-lymphocyte recognizes epitopes from protein antigens on MHC-I molecules and which type recognizes epitopes from protein antigens on MHC-II molecules.
- State the role of proteasomes in binding of peptides from endogenous antigens by MHC-I molecules.
- State the role of lysosomes in binding of peptides from exogenous antigens by MHC-II molecules.

The Roles of MHC Molecules In Adaptive Immune Responses

MHC molecules enable T-lymphocytes to recognize epitopes of antigens and discriminate self from non-self. Unlike B-cell receptors on B-lymphocytes that are able to directly bind epitopes on antigens, the T-cell receptors (TCRs) of T-lymphocytes can only recognize epitopes - typically short chains of amino acids called peptides - after they are bound to MHC molecules (Figure 10.3.3A.1).

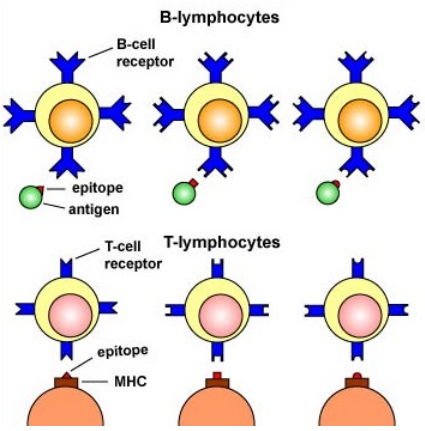


Figure 10.3.3A.1: Epitope-Specific Receptors on the Surface of B- and T-Lymphocytes. B-lymphocytes have B-cell receptors that recognize epitopes directly on antigens. T-lymphocytes have TCR molecules that recognize epitopes only after they have been placed on cells of the body by way of MHC molecules.

The MHC genes are the most polymorphic genes in the human genome, possessing many alleles for each gene. The MHC genes are co-dominantly expressed so that an individual expresses the alleles inherited from each parent. In this way, the number of MHC molecules that bind peptide for presentation to T-lymphocytes is maximized. In addition, each MHC molecule is able to bind a wide variety of different peptides, both self-peptides and foreign peptides. There are two classes of MHC molecules: MHC-I and MHC-II.

- MHC-I molecules present epitopes to T8-lymphocytes.
- MHC-II molecules presents epitopes to T4-lymphocytes .

The expression of MHC molecules is increased by cytokines produced during both innate immune responses and adaptive immune responses. Cytokines such as interferon-alpha, interferon-beta, interferon-gamma, tumor necrosis factor increase the expression of MHC-I molecules, while interferon-gamma is the main cytokine to increase the expression of MHC-II molecules.

MHC-I molecules

MHC-I molecules are designed to enable the body to recognize infected cells and tumor cells and destroy them with cytotoxic T-lymphocytes or CTLs. CTLs are effector defense cells derived from naive T8-lymphocytes. MHC-I molecules are:

- Made by all nucleated cells in the body.
- Possess a deep groove that can bind peptide epitopes, typically 8-11 amino acids long, typically from endogenous antigens .

- Present MHC-I/peptide complexes to naive T8-lymphocytes and cytotoxic T-lymphocytes possessing a complementary-shaped T-cell receptor or TCR.
- Through the process of cross-presentation, some antigen-presenting dendritic cells can cross-present epitopes of exogenous antigens to MHC-I molecules for eventual presentation to naive T8-lymphocytes.

Endogenous antigens are proteins found within the cytosol of human cells. Examples of endogenous antigens include:

a. Viral proteins produced during viral replication;
b. Proteins produced by intracellular bacteria such as Rickettsias and Chlamydias during their replication;
c. Proteins that have escaped into the cytosol from the phagosome of phagocytes such as antigen-presenting cells;
d. Tumor antigens produced by cancer cells; and
e. Self-peptides from host cellular proteins.

During the replication of viruses and intracellular bacteria within their host cell, as well as during the replication of tumor cells, viral, bacterial, or tumor proteins are degraded into a variety of peptide epitopes by cylindrical organelles called proteasomes. The body's own cytosolic proteins are also degraded into peptides by proteasomes.

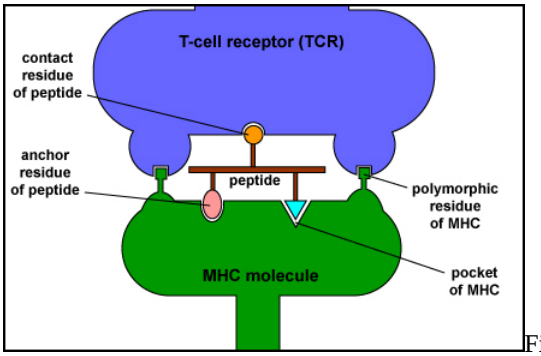


Figure 10.3.3A.2: MHC Molecule with Bound Peptide Binding to a Complementary T-Cell Receptor. This illustration shows a T-cell receptor (TCR) on the surface of a T-lymphocyte recognizing two polymorphic residues of a MHC molecule and one residue of its bound peptide epitope.

These peptide epitopes are then attached to a groove of MHC-I molecules that are then transported to the surface of that cell where they can be recognized by a complementary-shaped T-cell receptor (TCR) and a CD8 molecule, a co-receptor, on the surface of either a naive T8-lymphocyte or a cytotoxic T-lymphocyte (CTL). The TCRs recognize both the foreign peptide antigen and the MHC molecule (Figure 10.3.3A.2). TCRs, however, will not recognize self-peptides bound to MHC-I. As a result, normal cells are not attacked and killed.

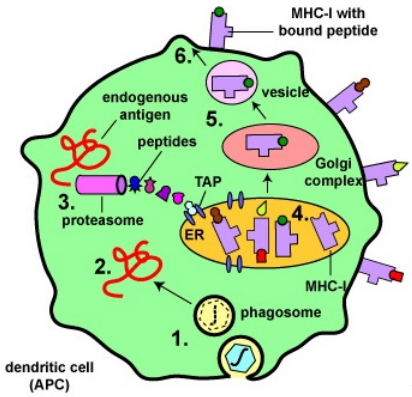


Figure 10.3.3A.3: Binding of Peptide Epitopes from Endogenous Antigens to MHC-I Molecules by a Dendritic Cell.Endogenous antigens are those located within the cytosol of the cells of the body. Examples include: a. viral proteins produced during viral replication, b. proteins produced by intracellular bacteria such as Rickettsias and Chlamydias during their replication, c. proteins that have escaped into the cytosol from the phagosome of phagocytes such as antigen-presenting cells, d. tumor antigens produced by cancer cells, e. and self peptides from human cell proteins.

> Dendritic cells bind epitopes from endogenous antigens to MHC-I molecules and present them to naive T8-lymphocytes in order to activate these naive T8-lymphocytes.

1. Antigens are engulfed by dendritic cells and placed in a phagosome. Some of the proteins escape from the phagosome into the cytosol of the dendritic cell where they become endogenous antigens.
2. These endogenous antigens pass through proteasomes where they are degraded into a series of peptides.
3. The peptides are transported into the rough endoplasmic reticulum (ER) by a transporter protein called TAP.
4. The peptides then bind to the grooves of newly synthesized MHC-I molecules.
5. The endoplasmic reticulum transports the MHC-I molecules with bound peptides to the Golgi complex.
6. The Golgi complex, in turn, transports the MHC-I/peptide complexes by way of an exocytic vesicle to the cytoplasmic membrane where they become anchored. Here, the peptide and MHC-I/peptide complexes can be recognized by naive T8-lymphocytes by way of TCRs and CD8 molecules having a complementary shape.

Through the process of cross-presentation, some antigen-presenting dendritic cells can cross-present epitopes of exogenous antigens to MHC-I molecules for eventual presentation to naive T8-lymphocytes.

MHC-I molecule with bound peptide on the surface of antigen-presenting dendritic cells (Figure **10.3.3*A*.3**) can be recognized by a complementary-shaped TCR/CD8 on the surface of a naive T8-lymphocyte to initiate cell-mediated immunity (Figure **10.3.3*A*.4**). (Certain dendritic cells, as discussed later, can also cross-present exogenous antigens to MHC-I molecules).

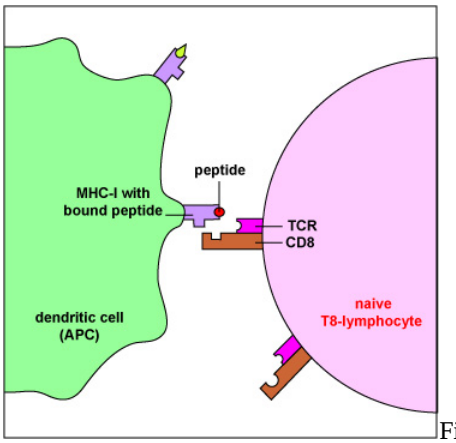


Figure **10.3.3*A*.4**: An Antigen-Presenting Dendritic Cell Presenting MHC-I with Bound Peptide to a Naive T8-lymphocyte having a Complementary T-Cell Receptor. Antigen-presenting dendritic cells produce both MHC-I and MHC-II molecules. These APCs can phagocytose infected cells and tumor cells, place them in phagosomes, and degrade them with lysosomes. During this process, some of the proteins escape from the phagosome into the surrounding cytosol. Here they can be degraded into peptides by proteasomes, bound to MHC-I molecules, and placed on the surface of the dendritic cell. Now the peptide/MHC-I complexes can be recognized by a naive T8-lymphocyte having a complementary shaped T-cell receptor (TCR) and CD8 molecule. This activates the naive T8-lymphocyte enabling it to eventually proliferate and differentiate into cytotoxic T-lymphocytes (CTLs).

MHC-I molecule with bound peptide on the surface of infected cells and tumor cells (Figure **10.3.3*A*.5**) can be recognized by a complementary-shaped TCR/CD8 on the surface of a cytotoxic T-lymphocyte or CTL to initiate destruction of the cell containing the endogenous antigen (Figure **10.3.3*A*.6**). (CTLs are effector cells derived from naive T8-lymphocytes.)

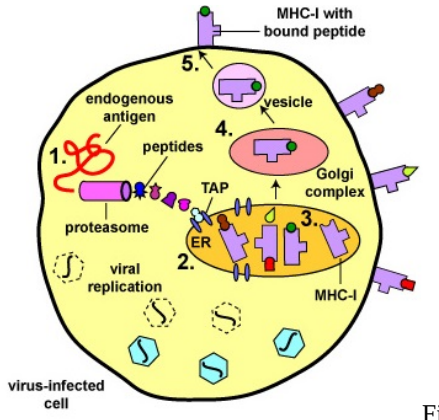


Figure **10.3.3A.5**: Binding of Peptide Epitopes from Endogenous Antigens to MHC-I Molecules by a Virus-Infected Cell. Endogenous antigens are those being produced within the cytosol of the cells of the body. Examples include: a. viral proteins produced during viral replication, b. proteins produced by intracellular bacteria such as Rickettsias and Chlamydias during their replication, c. proteins that have escaped into the cytosol from the phagosome of phagocytes such as antigen-presenting cellsd. tumor antigens produced by cancer cells, e. and self peptides from human cell proteins. The body marks infected cells and tumor cells for destruction by placing peptide epitopes from these endogenous antigens on their surface by way of MHC-I molecules.

Cytotoxic T-lymphocytes (CTLs) are then able to recognize peptide/MHC-I complexes by means of their T-cell receptors (TCRs) and CD8 molecules and kill the cells to which they bind.

1. During viral replication within the host cell, endogenous antigens, such as viral proteins, pass through proteasomes where they are degraded into a series of peptides.
2. The peptides are transported into the rough endoplasmic reticulum (ER) by a transporter protein called TAP.
3. The peptides then bind to the grooves of newly synthesized MHC-I molecules.
4. The endoplasmic reticulum transports the MHC-I molecules with bound peptides to the Golgi complex.
5. The Golgi complex, in turn, transports the MHC-I/peptide complexes by way of an exocytic vesicle to the cytoplasmic membrane where they become anchored. Here, the peptide and MHC-I/peptide complexes can be recognized by CTLs by way of TCRs and CD8 molecules having a complementary shape.

MHC-I molecules are coded for by three MHC-I genes, *HLA-A*, *HLA-B*, and *HLA-C*. As mentioned above, however, there are many different alleles for each gene that a person inherits. In this way, the number of MHC-I molecules that bind peptides for presentation to T-8 lymphocytes is maximized. The expression of MHC-I molecules on all cell types is increased by the cytokines interferon-alpha (IFN-a) and interferon-beta (IFN-ß).

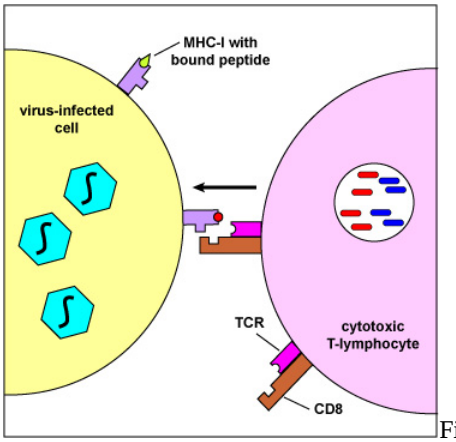


Figure **10.3.3A.6**: A Cytotoxic T-lymphocyte Recognizing a Virus-Infected Cell. Endogenous antigens are those being produced within the cytosol of the cells of the body. Examples include proteins from replicating viruses, proteins from intracellular bacteria, and tumor antigens. The body marks infected cells and tumor cells for destruction by placing peptide epitopes from these endogenous antigens on their surface by way of MHC-I molecules. Cytotoxic T-

lymphocytes (CTLs) are then able to recognize peptide/MHC-I complexes by means of their T-cell receptors (TCRs) and CD8 molecules and kill the cells to which they bind.

? Exercise: Think-Pair-Share Questions

All nucleated cells produce MHC-I molecules. MHC-I molecules bind peptide epitopes of antigens found within our cells. Peptide epitopes bound to MHC-I molecules are recognized by TCRs and CD8 molecules on the surfaces of naive T8-lymphocytes and on cytotoxic T-lymphocytes (CTLs).

Why is it important that all nucleated cells in our body are able to produce MHC-I molecules?

MHC-II molecules

MHC-II molecules are designed to enable T4-lymphocytes to recognize epitopes of exogenous antigens and discriminate self from non-self. MHC-II molecules are:

- Made by antigen-presenting cells or APCs, such as dendritic cells, macrophages, and B-lymphocytes .
- Possess a deep groove that can bind peptide epitopes, often 10-30 amino acids long but with an optimum length of 12-16 amino acids, typically from exogenous antigens. The peptides interact along their entire length with the groove.
- Present MHC-II/peptide complexes to naive T4-lymphocytes or effector T4-lymphocytes that have a complementary shaped T-cell receptor or TCR.
- Through the process of cross-presentation, some antigen-presenting dendritic cells can cross-present epitopes of endogenous antigens to MHC-II molecules for eventual presentation to naive T4-lymphocytes.

Exogenous antigens are antigens that enter from outside the body, such as bacteria, fungi, protozoa, and free viruses. These exogenous antigens enter macrophages, dendritic cells, and B-lymphocytes through phagocytosis. The microbes are engulfed and placed in a phagosome which then fuses with lysosomes. Following this fusion, the phagolysosome becomes acidified. Acidification, in turn, activates the proteases within the phagolysosome enabling protein antigens from the microbe to be degraded into a series of short peptides. These peptide epitopes are then attached to MHC-II molecules and are then transported to the surface of the antigen-presenting cell (APC) (Figure **10.3.3A.7**). (Certain dendritic cells, as discussed later, can also cross-present endogenous antigens to MHC-II molecules.)

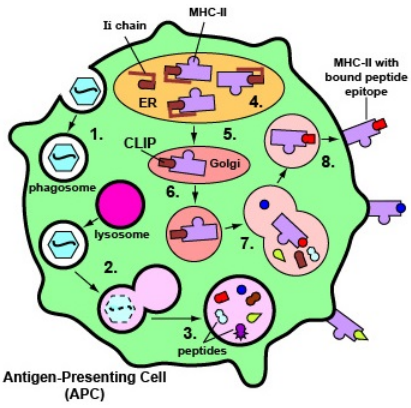


Figure **10.3.3A.7**: Binding of Peptide Epitopes from Exogenous Antigens to MHC-II Molecules Exogenous antigens are those from outside cells of the body. Examples include bacteria, free viruses, yeasts, protozoa, and toxins. These exogenous antigens enter antigen-presenting cells or APCs (macrophages, dendritic cells, and B-lymphocytes) through phagocytosis. The microbes are engulfed and placed in a phagosome. After lysosomes fuse with the phagosome, protein antigens are degraded by proteases into a series of peptides. These peptides eventually bind to grooves in MHC-II milecules and are transported to the surface of the APC. T4-lymphocytes are then able to recognize peptide/MHC-II complexes by means of their T-cell receptors (TCRs) and CD4 molecules. 1. Exogenous antigens, such as viruses, are engulfed and placed in a phagosome.2. Lysosomes fuse with the phagosome forming an phagolysosome. 3. Protein antigens are degraded into a series of peptides. 4. MHC-II molecules are synthesized in the endoplasmic reticulum and transported to the Golgi complex. Once assembled, within the endoplasmic reticulum, a protein called the invarient chain (Ii) attaches to the the peptide-binding groove of the MHC-II molecules and in this way prevents peptides designated for binding to MHC-I molecules within the ER from attaching to the MHC-II. 5. As the MHC-II molecules with bound Ii chain are transported to the Golgi complex, the Ii is cleaved, leaving a short peptide called

CLIP in the groove of the MHC molecule. 6&7. The vesicles containing the MHC-II molecules fuse with the peptide-containing phaglysosomes. The CLIP peptide is removed from the MHC=II molecules and the peptide epitopes are now free to bind to the grooves of the MHC-II molecules. 8. The MHC-II molecules with bound peptides are transported to the cytoplasmic membrane where they become anchored. Here, the peptide and MHC-II complexes can be recognized by T4-lymphocytes by way of TCRs and CD4 molecules having a complementary shape. (Through the process of cross-presentation, some antigen-presenting dendritic cells can cross-present epitopes of endogenous antigens to MHC-II molecules for eventual presentation to naive T4-lymphocytes.)

Some pathogens, such as *Mycobacterium tuberculosis*, *Mycobacterium leprae*, and *Leishmania*, are able to grow in the endocytic vesicles of macrophages without being killed by lysosomes. These macrophages can, however, become activated by T4-effector lymphocytes called T_H1 cells and subsequently use intravesicular proteases to degrade the proteins from these pathogens into peptides for presentation to MHC-II molecules that pass through on their way to the cell surface.

Here the MHC-II molecules with bound peptides can be recognized by a complementary-shaped T-cell receptor and a CD4 molecule, a co-receptor, on the surface of a T4-lymphocyte (Figure 10.3.3A.8). T4-lymphocytes are the cells the body uses to regulate both humoral immunity and cell-mediated immunity.

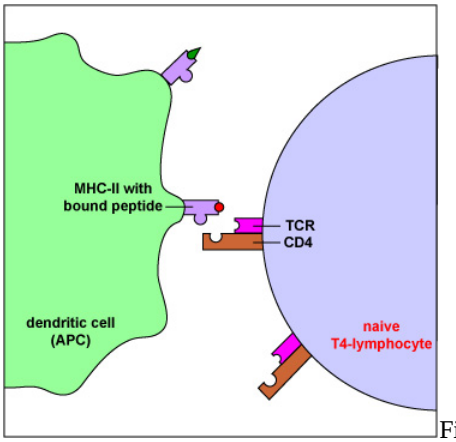


Figure 10.3.3A.8: A T4-Lymphocyte Recognizing Epitope/MHC-II on an Antigen-Presenting Dendritic Cell.Exogenous antigens are those from outside cells of the body. Examples include bacteria, free viruses, yeasts, protozoa, and toxins. These exogenous antigens enter antigen-presenting dendritic cells through phagocytosis. The microbes are engulfed and placed in a phagosome. After lysosomes fuse with the phagosome, protein antigens are degraded by proteases into a series of peptides. These peptides eventually bind to grooves in MHC-II milecules and are transported to the surface of the APC. T4-lymphocytes are then able to recognize peptide/MHC-II complexes by means of their T-cell receptors (TCRs) and CD4 molecules.

MHC-II molecules are coded for by three MHC-II genes, *HLA-DR*, *HLA-DP*, and *HLA-DQ*. Interferon-gamma (IFN- ?) increases the expression of both MHC-I and MHC-II molecules.

? Think-Pair-Share Questions

Only antigen-presenting cells such as dendritic cells, macrophages, and B-lymphocytes produce MHC-II molecules. Peptide epitopes bound to MHC-II molecules are recognized by TCRs and CD4 molecules on the surfaces of naive T4-lymphocytes and on effector T4-lymphocytes.

Why don't all nucleated cells in our body produce MHC-II molecules as well as MHC-I molecules?

Why is it important for dendritic cells to produce both MHC-I and MHC-II molecules?

Summary

1. MHC molecules enable T-lymphocytes to recognize epitopes and discriminate self from non-self.
2. T-cell receptors (TCRs) of T-lymphocytes can only recognize epitopes - typically short chains of amino acids called peptides - after they are bound to MHC molecules.
3. MHC-I presents epitopes to T8-lymphocytes; MHC-II presents epitopes to T4-lymphocytes.
4. MHC-I molecules are designed to enable the body to recognize infected cells and tumor cells and destroy them with cytotoxic T-lymphocytes or CTLs. (CTLs are effector defense cells derived from naïve T8-lymphocytes.)

5. MHC-I molecules are made by all nucleated cells in the body; bind peptide epitopes typically from endogenous antigens; present MHC-I/peptide complexes to naive T8-lymphocytes and cytotoxic T-lymphocytes possessing a complementary-shaped T-cell receptor or TCR.
6. Through the process of cross-presentation, some antigen-presenting dendritic cells can cross-present epitopes of exogenous antigens to MHC-I molecules for eventual presentation to naive T8-lymphocytes.
7. Endogenous antigens are proteins found within the cytosol of human cells and include viral proteins produced during viral replication, proteins produced by intracellular bacteria, proteins that have escaped into the cytosol from the phagosome of phagocytes such as antigen-presenting cells, and tumor antigens produced by cancer cells.
8. During the replication of viruses and intracellular bacteria within their host cell, as well as during the replication of tumor cells, viral, bacterial, or tumor proteins are degraded into a variety of peptide epitopes by cylindrical organelles called proteasomes. The resulting peptide epitopes are then attached to MHC-I molecules that are then transported to the surface of that cell.
9. Exogenous antigens are antigens that enter from outside the body such as bacteria, fungi, protozoa, and free viruses.
10. MHC-II molecules are made by antigen-presenting cells or APCs, such as dendritic cells, macrophages, and B-lymphocytes; bind peptide epitopes typically from exogenous antigens; and present MHC-II/peptide complexes to naive T4-lymphocytes or effector T4-lymphocytes that have a complementary shaped T-cell receptor or TCR.
11. Through the process of cross-presentation, some antigen-presenting dendritic cells can cross-present epitopes of endogenous antigens to MHC-II molecules for eventual presentation to naive T4-lymphocytes.
12. Exogenous antigens enter antigen-presenting macrophages, dendritic cells, and B-lymphocytes through phagocytosis, and are engulfed and placed in a phagosome where protein antigens from the microbe are degraded by proteases into a series of peptides. These peptides are then attached to MHC-II molecules that are then put on the surface of the APC.

This page titled 10.3.3A: Major Histocompatibility Complex (MHC) Molecules is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **12.3A: Major Histocompatibility Complex (MHC) Molecules** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

10.3.3B: Antigen-Presenting Cells (APCs)

Describe the overall function of antigen-presenting cells (APCs) such as dendritic cells, macrophages, and B-lymphocytes in terms of the following:

a. how they "process" exogenous antigens

b. how they "process" endogenous antigens

c. the types of MHC molecule to which they attach peptides

d. the role of proteasomes in the binding of peptides from endogenous antigens by MHC-I molecules.

e. the role of lysosomes in the binding of peptides from exogenous antigens by MHC-II molecules.

f. the types of cells to which they present peptides

- Name the primary type of cell that functions as an antigen-presenting cell to naive T4-lymphocytes and naive T8-lymphocytes.
- State the role of T4-effector cells in activating macrophages.
- State the role of T4-effector cells in the proliferation and differentiation of activated B-lymphocytes.

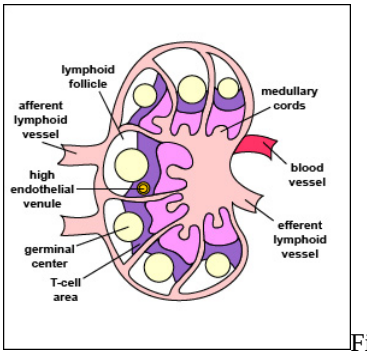


Figure 10.3.3*B*.1: Structure of a Lymph Nodes Antigens enter lymph nodes through afferent lymphoid vessels. Antigen-presenting dendritic cells, B-lAntigens enter lymph nodes through afferent lymphoid vessels. Antigen-presenting dendritic cells enter the lymph node through afferent lymphatic vessels while naive B-lymphocytes, and naive T-lymphocytes enter through high endothelial venules. Non-activated and effector lymphocytes leave the lymph node through efferent lymphatic vessels. Naive B-lymphocytes become activated, proliferate, and differentiate into plasma cells in the germinal centers of lymphoid follicles while naive T-lymphocytes become activated, proliferate and differentiate into T-effector lymphocytes in the T-cell area.

The primary function of dendritic cells, then, is to capture and present protein antigens to naive T-lymphocytes. (Naive lymphocytes are those that have not yet encountered an antigen.) Since dendritic cells are able to express both MHC-I and MHC-II molecules, they are able to present antigens to both naive T8-lymphocytes and naive T4-lymphocytes.

You Tube movie of a dendritic cell engulfing melanoma cells (red).

These interactions enable the naiveT4-lymphocyte or T8-lymphocyte to become activated, proliferate, and differentiate into effector lymphocytes. (Effector lymphocytes are lymphocytes that have encountered an antigen, proliferated, and matured into a form capable of actively carrying out immune defenses.)

1. MHC-II presentation of protein antigens to naive T4-lymphocytes

    a. MHC-II presentation of exogenous antigens to naive T4-lymphocytes

    Immature dendritic cells take in protein antigens for attachment to MHC-II molecules and subsequent presentation to naive T4-lymphocytes by:

    1. Receptor-mediated phagocytosis, e.g., PAMPs binding to endocytic PRRs, IgG or C3b attachment of microbes to phagocytes during opsonization (see Figure 10.3.3*B*.2).

    2. Macropinocytosis, a process where large volumes of surrounding fluid containing microbes are engulfed. This also enables dendritic cells to take in some encapsulated bacteria that might resist classical

phagocytosis (see Figure 10.3.3B.3).

The binding of microbial PAMPs to the PRRs of the immature dendritic cell activates that dendritic cell and promotes production of the chemokine receptor CCR7 that directs the dendritic cell into local lymphoid tissue. Following maturation, the dendritic cell can now present protein epitopes bound to MHC molecules to all the various naive T-lymphocytes passing through the lymphoid system (See Figure 10.3.3B.4 and Figure 10.3.3B.5).

The MHC-II molecules bind peptide epitopes from exogenous antigens and place them on the surface of the dendritic cell (see Figure 10.3.3B.6). Here the MHC-II/peptide complexes can be recognized by complementary shaped TCRs and CD4 molecules on naive T4-lymphocytes (see Figure 10.3.3B.7).

Flash animation of MHC-II molecules binding epitopes from exogenous antigens.

html5 version of animation for iPad showing MHC-II molecules binding epitopes from exogenous antigens.

Flash animation of a naive T4-lymphocyte recognizing epitopes bound to MHC-II molecules on an antigen-presenting dendritic cell.

html5 version of animation for iPad showing a naive T4-lymphocyte recognizing epitopes bound to MHC-II molecules on an antigen-presenting dendritic cell.

b. MHC-II cross-presentation of endogenous antigens to naive T4-lymphocytes

While most dendritic cells present exogenous antigens to naive T4-lymphocytes, certain dendritic cells are capable of cross-presentation of endogenous antigens to naive T4-lymphocytes. In this way, T4-lymphocytes can play a role in defending against both exogenous and endogenous antigens. This is done via autophagy, the cellular process whereby the cell's own cytoplasm is taken into specialized vesicles called autophagosomes (See Figure 10.3.3B.8). The autophagosomes subsequently fuse with lysosomes containing proteases that will degrade the proteins in the autophagosome into peptides. From here, the peptides are transported into the vesicles containing MHC-II molecules where they can bind to the MHC-II groove, be transported to the surface of the denritic cell, and interact with the TCRs and CD4 molecules of naive T4-lymphocytes (See Figure 10.3.3B.8).

2. MHC-I presentation of protein antigens to naive T8-lymphocytes

Immature dendritic cells take in protein antigens for attachment to MHC-I molecules and subsequent presentation to naive T8-lymphocytes.

a. MHC-I presentation of endogenous antigens to naive T8-lymphocytes

During the replication of viruses and intracellular bacteria within their host cell, as well as during the replication of tumor cells, viral, bacterial, or tumor proteins are degraded into a variety of peptide epitopes by cylindrical organelles called proteasomes. The body's own cytosolic proteins are also degraded into peptides by proteasomes.

These peptide epitopes are then attached to a groove of MHC-I molecules that are then transported to the surface of that cell where they can be recognized by a complementary-shaped T-cell receptor (TCR) and a CD8 molecule, a co-receptor, on the surface of either a naive T8-lymphocyte or a cytotoxic T-lymphocyte (CTL). The TCRs recognize both the foreign peptide antigen and the MHC molecule. TCRs, however, will not recognize self-peptides bound to MHC-I. As a result, normal cells are not attacked and killed.

MHC-I molecule with bound peptide on the surface of antigen-presenting dendritic cells ; see Figure 10.3.3*B*.9 can be recognized by a complementary-shaped TCR/CD8 on the surface of a naive T8-lymphocyte to initiate cell-mediated immunity (see Figure 10.3.3*B*.10).

Flash animation of MHC-I molecules binding epitopes from endogenous antigens by an antigen-presenting cell.

html5 version of animation for iPad showing MHC-I molecules binding epitopes from endogenous antigens by an antigen-presenting cell.

Flash animation of a naive T8-lymphocyte recognizing epitopes bound to MHC-I molecules on an antigen-presenting dendritic cell.

html5 version of animation for iPad showing a naive T8-lymphocyte recognizing epitopes bound to MHC-I molecules on an antigen-presenting dendritic cell.

b. MHC-I cross-presentation of exogenous antigens to naive T8-lymphocytes

While most dendritic cells present endogenous antigens to naive T8-lymphocytes, certain dendritic cells are capable of cross-presentation of exogenous antigens to naive T8-lymphocytes. In this way, T8-lymphocytes can play a role in defending against both exogenous and endogenous antigens. There are two proposed mechanisms for cross-presentation of exogenous antigens to T8-lymphocytes:

1. The dendritic cell engulfs the exogenous antigen and places it in a phagosome which then fuses with a lysosome to form a phagolysosome. The antigen is partially degraded in the phagolysosome where proteins are translocated into the cytoplasm where they are processed into peptides by proteasomes, enter the endoplasmic reticulum, and are bound to MHC-I molecules (see Figure 10.3.3*B*.11).

2. The dendritic cell engulfs the exogenous antigen and places it in a phagosome which then fuses with a lysosome to form a phagolysosome. The protein antigens are degraded into peptides within the phagolysosome which then directly fuses with vesicles containing MHC-I molecules to which the peptides subsequently bind (see Figure 10.3.3*B*.12).

In addition, dendritic cells are very susceptible to infection by many different viruses. Once inside the cell, the viruses become endogenous antigens in the cytosol. Once in the cytosol, the viral proteins from the replicating viruses are degraded into peptides by proteasomes where they subsequently bind to MHC-I molecules.

The binding of microbial PAMPs to the PRRs of the immature dendritic cell activates that dendritic cell and promotes production of the chemokine receptor CCR7 that directs the dendritic cell into local lymphoid tissue. Following maturation, the dendritic cell can now present protein epitopes bound to MHC molecules to all the various naive T-lymphocytes passing through the lymphoid system.

To view an electron micrograph of a dendritic cell presenting antigen to T-lymphocytes, #1 see the Web page for the University of Illinois College of Medicine.

To view an electron micrograph of a dendritic cell presenting antigen to T-lymphocytes, #2 see the Web page for the University of Illinois College of Medicine.

? Why is this essential for effective adaptive immunity ?

For a Summary of Key Surface Molecules and Cellular Interactions of Antigen-Presenting Dendritic Cells, see Figure 10.3.3B.13.

Concept Map for Antigen-Presenting Cells (APCs)

Macrophages

As we learned in Unit 5, when monocytes leave the blood and enter the tissue, they become activated and differentiate into macrophages. Those that have recently left the blood during inflammation and move to the site of infection are sometimes referred to as wandering macrophages. In addition, the body has macrophages already stationed throughout the tissues and organs of the body. These are sometimes referred to as fixed macrophages. Many fixed macrophages are part of the mononuclear phagocytic (reticuloendothelial) system. They, along with B-lymphocytes and T-lymphocytes, are found supported by reticular fibers in lymph nodules, lymph nodes, and the spleen where they filter out and phagocytose foreign matter such as microbes. Similar cells derived from stem cells, monocytes, or macrophages are also found in the liver (Kupffer cells), the kidneys (mesangial cells), the brain (microglia), the bones (osteoclasts), the lungs (alveolar macrophages), and the gastrointestinal tract (peritoneal macrophages).

The primary function of macrophages, then, is to capture and present protein antigens to effector T-lymphocytes. (Effector lymphocytes are lymphocytes that have encountered an antigen, proliferated, and matured into a form capable of actively carrying out immune defenses.)

The MHC-II molecules bind peptide epitopes from exogenous antigens and place them on the surface of the macrophages. Here the MHC-II/peptide complexes can be recognized by complementary shaped T-cell receptors (TCRs) and CD4 molecules on an effector T4-lymphocytes ; see Fig.14.

Effector T4-lymphocytes called T_H1 cells coordinate immunity against intracellular bacteria and promote opsonization by macrophages.

1. They produce cytokines such as interferon-gamma (IFN-?) that promote cell-mediated immunity against intracellular pathogens, especially by activating macrophages that have either ingested pathogens or have become infected with intracellular microbes such as *Mycobacterium tuberculosis, Mycobacterium leprae, Leishmania donovani*, and *Pneumocystis jiroveci* that are able to grow in the endocytic vesicles of macrophages. Activation of the macrophage by T_H1 cells greatly enhances their antimicrobial effectiveness (see Figure 10.3.3B.14).

2. They produce cytokines that promote the production of opsonizing and complement activating IgG that enhances phagocytosis (see Figure 10.3.3B.15).

3. They produce receptors that bind to and kill chronically infected cells, releasing the bacteria that were growing within the cell so they can be engulfed and killed by macrophages.

4. They produce cytokines such as tumor necrosis factor-alpha (TNF-a) that promote diapedesis of macrophages.

5. They produce the chemokine CXCL2 to attract macrophages to the infection site.

Flash animation of the activation of a macrophage by a T_H1 cell.

html5 version of animation for iPad showing the activation of a macrophage by a T_H1 cell.

There is growing evidence that monocytes and macrophages can be “trained” by an earlier infection to do better in future infections, that is, develop memory. It is thought that microbial pathogen-associated molecular patterns (PAMPs) binding to pattern-recognition (PRRs) on monocytes and macrophages triggers the cell’s epigenome to reprogram or train that cell to react better against new infections.

For a Summary of Key Surface Molecules and Cellular Interactions of Antigen-Presenting Macrophages, see Figure 10.3.3B.16.

Concept Map for Antigen-Presenting Cells (APCs)

B-lymphocytes

Like all lymphocytes, B-lymphocytes circulate back and forth between the blood and the lymphoid system of the body. B-lymphocytes are able to capture and present peptide epitopes from exogenous antigens to effector T4-lymphocytes. The MHC-II molecules bind peptide epitopes from exogenous antigens and place them on the surface of the B-lymphocytes. Here the MHC-II/peptide complexes can be recognized by complementary shaped T-cell receptors (TCRs) and CD4 molecules on an effector T4-lymphocytes (see Figure 10.3.3B.17). This interaction eventually triggers the effector T4-lymphocyte to produce and secrete various cytokines that enable that B-lymphocyte to proliferate and differentiate into antibody-secreting plasma cells (see Figure 10.3.3B.18).

Flash animation of the binding of peptide epitopes to MHC-II molecules by a B-lymphocyte.

Flash animation of an effector T4-lymphocyte recognizing epitopes bound to MHC-II molecules on a B-lymphocyte.

html5 version of animation for iPad showing the binding of peptide epitopes to MHC-II molecules by a B-lymphocyte

html5 version of animation for iPad showing an effector T4-lymphocyte recognizing epitopes bound to MHC-II molecules on a B-lymphocyte.

For a Summary of Key Surface Molecules and Cellular Interactions of Antigen-Presenting B-Lymphocytes, see Figure 10.3.3B.19.

Summary

1. Antigen-presenting cells (APCs) include dendritic cells, macrophages, and B-lymphocytes.
2. APCs express both MHC-I and MHC-II molecules and serve two major functions during adaptive immunity: they capture and process antigens for presentation to T-lymphocytes, and they produce signals required for the proliferation and differentiation of lymphocytes.
3. Most dendritic cells are derived from monocytes and are referred to as myeloid dendritic cells and are located under the surface epithelium of the skin, the mucous membranes of the respiratory tract, genitourinary tract, and the gastrointestinal tract, and throughout the body's lymphoid tissues and in most solid organs.
4. The primary function of dendritic cells is to capture and present protein antigens to naive T-lymphocytes which enables the naïve T4-lymphocytes or T8-lymphocytes to become activated, proliferate, and differentiate into effector cells.
5. Naïve lymphocytes are B-lymphocytes and T-lymphocytes that have not yet reacted with an epitope of an antigen.
6. Dendritic cells use MHC-II molecules to present protein antigens to naïve T4-lymphocytes and MHC-I molecules to present protein antigens to naïve T8-lymphocytes.
7. When monocytes leave the blood and enter the tissue, they become activated and differentiate into macrophages.

8. When functioning as APCs, macrophages capture and present peptide epitopes from exogenous antigens to effector T4-lymphocytes.
9. Effector lymphocytes are lymphocytes that have encountered an antigen, proliferated, and matured into a form capable of actively carrying out immune defenses.
10. B-lymphocytes mediate antibody production.
11. When functioning as APCs, B-lymphocytes are able to capture and present peptide epitopes from exogenous antigens to effector T4-lymphocytes.
12. To activate naïve T4-lymphocytes, dendritic cells engulf exogenous antigens, place them in a phagosome, degrade protein antigens into peptides via lysosomes, bind those peptides to MHC-II molecules and transport them to the surface of the dendritic cell where they can be recognized by the T-cell receptors and CD4 molecules of naïve T4-lymphocytes.
13. To activate naïve T8-lymphocytes, dendritic cells degrade endogenous protein antigens into peptides via their proteasomes, bind those peptides to MHC-I molecules and transport them to the surface of the dendritic cell where they can be recognized by the T-cell receptors and CD8 molecules of naïve T8-lymphocytes.

This page titled 10.3.3B: Antigen-Presenting Cells (APCs) is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **12.3B: Antigen-Presenting Cells (APCs)** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

10.3.3C: T4-Lymphocytes (T4-Cells)

Describe the overall function of T4-lymphocytes and their activation in terms of the following:

a. the role of their TCRs and CD4 molecules

b. what they recognize on antigen-presenting cells (APCs) such as dendritic cells, macrophages, and B-lymphocytes.

c. the role of antigen-presenting dendritic cells in the activation of naive T4-lymphocytes.

- Compare T_H1, T_H2, T_H17, T_{reg}, and T_{FH} lymphocytes in terms of their primary function(s) in immunity.

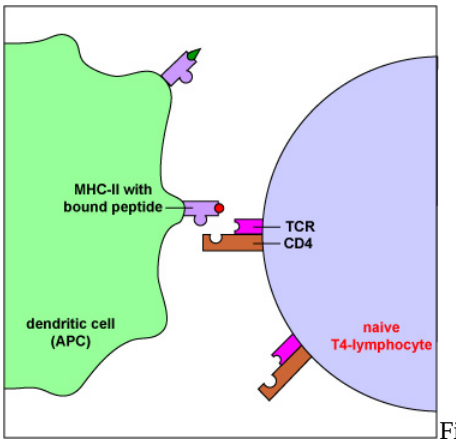


Figure **10.3.3*C*.6**: Binding of Peptide Epitopes from Exogenous Antigens to MHC-II Molecules. Exogenous antigens are those from outside cells of the body. Examples include bacteria, free viruses, yeasts, protozoa, and toxins. These exogenous antigens enter antigen-presenting cells or APCs (macrophages, dendritic cells, and B-lymphocytes) through phagocytosis. The microbes are engulfed and placed in a phagosome. After lysosomes fuse with the phagosome, protein antigens are degraded by proteases into a series of peptides. These peptides eventually bind to grooves in MHC-II milecules and are transported to the surface of the APC. T4-lymphocytes are then able to recognize peptide/MHC-II complexes by means of their T-cell receptors (TCRs) and CD4 molecules.

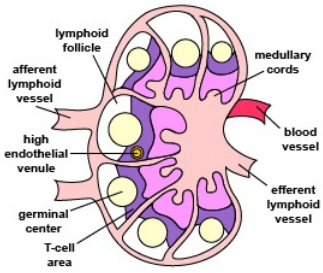


Figure **10.3.3*C*.8**: Transient binding of T4-Lymphocytes to Dendritic Cells.As naive T4-lymphocytes migrate through the cortical region of lymph nodes, they use surface cell adhesion molecules such as LFA-1 and CD2 to bind transiently to corresponding receptors such as ICAM-1, ICAM-2 and CD58 on the surface of dentritic cells. This transient binding allows time for the TCRs on the T8-lymphocyte to sample large numbers of MHC-II/peptide complexes on the antigen-presenting dendritic cells.

- To view an electron micrograph of a dendritic cell presenting antigen to T-lymphocytes, #1 see the Web page for the University of Illinois College of Medicine.
- To view an electron micrograph of a dendritic cell presenting antigen to T-lymphocytes, #2 see the Web page for the University of Illinois College of Medicine.

Those naive T4-lymphocytes not activated by epitopes of antigens on the dendritic cells exit the lymph node (or other lymphoid tissue) and eventually re-enter the bloodstream. However, if a TCR and CD4 molecule of the naive T4-lymphocyte detects a corresponding MHC-II/peptide complex on a mature dendritic cell, this will send a first signal for the activation of that naive T-lymphocyte. Next, a second signal that promotes survival of that T-lymphocyte is sent when co-stimulatory molecules such as B7.1 and B7.2 on the dendritic cell bind to CD28 molecules on the T4-lymphocyte. Finally, the dendritic cell produces cytokines such as interleukin-6 (IL-6), IL-4, IL-12, and T-cell growth

factor-beta (TGF-ß) that contribute to proliferation of the T4-lymphocytes and their differentiation into effector T4-lymphocytes, the cells the body uses to regulate both humoral immunity and cell-mediated immunity through the cytokines they produce. (Activated T4-lymphocytes remain in the lymph node as they proliferate (clonal expansion) and only leave the lymphoid tissues and re-enter the bloodstream after they have differentiated into effector T4-lymphocytes.)

CD28-dependent co-stimulation of the T4-lymphocyte also stimulates it to synthesize the cytokine interleukin-2 (IL-2) as well as a high-affinity IL-2 receptor. The binding of IL-2 to its high affinity receptor allows for cell proliferation and formation of a clone of thousands of identical T4-lymphocytes after several days. IL-2 also contributes to survival of those activated T4-lymphocytes and their differentiation into T4-effector cells. In addition, some of the T4-lymphocytes differentiate into circulating T4-memory cells. Circulating T4-memory cells allow for a more rapid and greater production of effector T4-lymphocytes upon subsequent exposure to the same antigen.

Differentiation of naive T4-lymphocyte into T4-effector lymphocytes

Functionally, there are many different types or subpopulations of effector T4-lymphocytes based on the cytokines they produce. Immune reactions are typically dominated by five primary types: T_H1 cells, T_H2 cells, T_H17 cells, T_{reg} cells, and T_{FH} cells.

CD4 T_H1 cells

Coordinate immunity against intracellular bacteria and promote opsonization. They:

1. Produce cytokines such as interferon-gamma (IFN-?) that promote cell-mediated immunity against intracellular pathogens, especially by activating macrophages that have either ingested pathogens or have become infected with intracellular microbes such as *Mycobacterium tuberculosis, Mycobacterium leprae, Leishmania donovani*, and *Pneumocystis jjroveci* that are able to grow in the endocytic vesicles of macrophages. Activation of the macrophage by T_H1 cells greatly enhances their antimicrobial effectiveness.
2. They produce cytokines that promote the production of opsonizing antibodies that enhance phagocytosis (Figure 10.3.3C.9).
3. Produce receptors that bind to and kill chronically infected cells, releasing the bacteria that were growing within the cell so the can be engulfed and killed by macrophages.
4. Produce the cytokine interleukin-2 (IL-2) that induces T-lymphocyte proliferation.
5. Produce cytokines such as tumor necrosis factor-alpha (TNF-a) that promote diapedesis of macrophages.
6. Produces the chemokine CXCL2 to attract macrophages to the infection site.
7. Produce cytokines that block the production of T_H2 cells.

CD4 T_H2 cells

Coordinate immunity against helminths and microbes that colonize mucous membranes

1. Produce the cytokine interleukin-4 (IL-4) that promotes the production of the antibody isotype IgE in response to helminths and allergens. IgE is able to stick eosinophils to helminths for extracellular killing of the helminth (Figure 10.3.3C.10); it also promotes many allergic reactions.
2. Produce cytokines that attract and activate eosinophils and mast cells.
3. Promote the production of antibodies that neutralize microbes (Figure 10.3.3C.11) and toxins (Figure 10.3.3C.12) preventing their attachment to host cells.
4. Produce cytokines that function as B-lymphocyte growth factors such as IL-4, IL-5, IL-9. and IL-13 (Figure 10.3.3C.13).
5. Produce interleukin-22 (IL-22) that promotes the removal of microbes in mucosal tissues.
6. Produce cytokines that block the production of T_H1 cells.

CD4 T_H17 cells

Promote a local inflammatory response to stimulate a strong neutrophil response and promote the integrity of the skin and mucous membranes

Produce cytokines like interleukin-17 (IL-17) and interleukin-6 (IL-6) that trigger local epithelial cells and fibroblasts to produce chemokines that recruit neutrophils to remove extracellular pathogens.

CD4 T_{reg} cells

Suppress immune responses

1. Produce inhibitory cytokines such as Interleukin-10 (IL-10) and TGF-ß that help to limit immune responses and prevent autoimmunity by suppressing T-lymphocyte activity.
2. Promoting anamnestic response (immunologic memory) to resist repeat infections by the same microbe.
3. Protecting beneficial normal flora in the intestines from being destroyed by the immune system.
4. Aiding in sustaining pregnancy so that the immune system doesn't recognize a fetus as foreign and try to destroy it.
5. Controlling established inflammation in tissues.

T_{FH} cells

Promote humoral immunity by stimulating antibody production and antibody isotype switching by B-lymphocytes

1. T follicular helper cells (T_{FH} cells) are located in lymphoid follicles.
2. T_{FH} cells are now thought to be the primary effector T-lymphocytes that stimulate antibody production and isotype switching by B-lymphocytes. They are able to produce cytokines that are characteristic of both T_H2 cells and T_H1 cells.
3. T_{FH} cells producing (IFN-?) promote the production of opsonizing antibodies; those producing IL-4 promote the production of IgE.

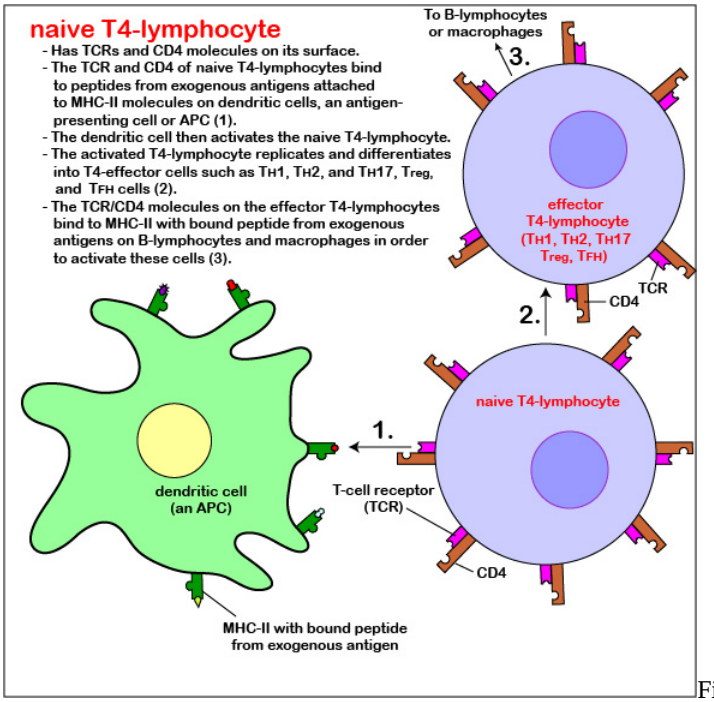


Figure **10.3.3*C*.14**: A Summary of Key Surface Molecules and Cellular Interactions of Naive T4-Lymphocytes

? Macrophages and B-lymphocytes are antigen-presenting cells but they do not activate naive T4- and T8-lymphocytes. Why must macrophages and B-lymphocytes be antigen-presenting cells?

Regulation of effector T4-lymphocyte activity: A role for commensals and helminths?

It is now recognized that genes associated with the normal flora (microbiota) of the intestinal tract aid in digestion of many foods (especially plant polysaccharides that would normally be indigestible by humans), may play a role in normal growth and regulating appetite, and also help to regulate immune defenses. There is ever growing evidence that commensal bacteria of the gastrointestinal tract, as well as parasitic gastrointestinal helminths, may have coevolved with the human body over the past 200,000 year in such a way that genes from the human microbiota may play a significant role in regulating the human immune responses by providing a series of checks and balances that prevent the immune system from being too aggressive and causing an autoimmune attack upon the body's own cells, while still remaining aggressive enough to recognize and remove harmful pathogens. As exposure to and colonization with these once common human organisms has drastically changed over time as a result of less exposure to mud, animal and human feces,and helminth ova, coupled with ever increasing antibiotic use, improved sanitation, changes in the human diet, increased rate of cesarean sections, and improved methods of processing and preserving of food, the rate of allergies, allergic asthma, and autoimmune diseases (inflammatory bowel disease, Crone's disease, type-1 diabetes, and multiple sclerosis for example) has dramatically increased in developed countries while remaining relatively low in undeveloped and more agrarian parts of the world.

Numerous experiments in germ-free mice (mice with no intestinal commensals) have shown them to be much more susceptible to allergic asthma and autoimmune diseases such as colitis then normal mice. Feeding commensals or nematode ova to newborn germ-free mice, in turn, reduces the occurrence to these disorders. An imbalance in the relationship between proinflammatory T_H17 cells and inflammation-suppressing T_{reg} cells appears to increase the risk of inflammatory autoimmune diseases, while an imbalance between T_H1 and T_H2 cells seems to contribute to the risk of allergies and asthma. For example, a common commensal colon bacterium *Bacteroides fragilis* produces a molecule called polysaccharide A that dendritic cells engulf, process and present to naive T4-lymphocytes. This interaction stimulates the differentiation of the naive T4-lymphocytes into anti-inflammatory T_{reg} cells that suppress the activity of proinflammatory T_H17 cells. Without colonization with *B. fragilis*, the proinflammatory T_H17 cells are not suppressed and there is an increased risk of inflammatory autoimmune diseases.

Normal intestinal microbiota also appear to regulate the intestinal levels of the invariant natural killer (iNKT) cells discussed under innate immune responses in Unit 4. iNKT cells recognize endogenous and exogenous lipid antigens presented on CD1d molecules by dendritic cells and in response, secrete proinflammatory cytokines. Germ free mice show an accumulation of iNKT cells in the colon and in the lungs and have an increased risk of intestinal bowel disease and allergic asthma. Neonatal germ free mice that were subsequently colonized with normal microbiota were protected from this iNKT cell accumulation and the resulting inflammatory pathology.

For More Information: MHC Molecules from Unit 6

For More Information: B-Lymphocytes from Unit 6

For More Information: Macrophages and NK cells from Unit 6

For More Information: Cytotoxic T-Lymphocytes from Unit 6

Summary

1. T-lymphocytes refer to lymphocytes that are produced in the bone marrow but require interaction with the thymus for their maturation.
2. The primary role of T4-lymphocytes is to regulate the body's immune responses through the production of cytokines.
3. T4-lymphocytes display CD4 molecules and T-cell receptors (TCRs) on their surface.
4. The TCR on T4-lymphocytes, in cooperation with CD4, typically bind peptides from exogenous antigens bound to MHC-II molecules.
5. During its development, each T4-lymphocyte becomes genetically programmed to produce a TCR with a unique specificity that is able to bind an epitope/MHC-II complex on an APC such as a dendritic cell, a macrophage, or a B-lymphocyte possessing a corresponding shape.
6. To become activated, naive T4-lymphocytes migrate through lymph nodes where the TCRs on the T4-lymphocyte are able to sample large numbers of MHC-II/peptide complexes on the antigen-presenting dendritic cells for ones that “fit”, thus enabling activation of that naïve T4-lymphocyte.
7. After activation, the dendritic cell produces cytokines that contribute to proliferation of the T4-lymphocytes and their differentiation into effector T4-lymphocytes, the cells the body uses to regulate both humoral immunity and cell-mediated immunity through the cytokines they produce.
8. Some of the T4-lymphocytes differentiate into circulating T4-memory cells that enable a more 9.rapid and greater production of effector T4-lymphocytes upon subsequent exposure to the same antigen.
9. Functionally, there are many different types or subpopulations of effector T4-lymphocytes based on the cytokines they produce. Immune reactions are typically dominated by five primary types: TH1 cells, TH2 cells, TH17 cells, Treg cells, and TFH cells.
10. CD4 TH1 cells coordinate immunity against intracellular bacteria and promote opsonization.
11. CD4 TH2 cells coordinate immunity against helminths and microbes that colonize mucous membranes.
12. CD4 TH17 cells promote a local inflammatory response to stimulate a strong neutrophil response and promote the integrity of the skin and mucous membranes.
13. CD4 Treg cells suppress immune responses.
14. TFH cells promote humoral immunity by stimulating antibody production and antibody isotype switching by B-lymphocytes.
15. There is ever growing evidence that commensal bacteria of the gastrointestinal tract, as well as parasitic gastrointestinal helminths, may have coevolved with the human body over the past 200,000 year in such a way that genes from the human microbiota may play a significant role in regulating the human immune responses by providing a series of checks and balances that prevent the immune system from being too aggressive and causing an autoimmune attack upon the body's own cells, while still remaining aggressive enough to recognize and remove harmful pathogens.

This page titled 10.3.3C: T4-Lymphocytes (T4-Cells) is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **12.3C: T4-Lymphocytes (T4-Cells)** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

10.3.3D: T8-Lymphocytes (T8-Cells)

Describe the overall function of T8-lymphocytes and their activation in terms of the following:
a. the role of their TCRs and CD8 molecules
b. how they are activated by antigen-presenting dendritic cells
c. the type of effector cells into which activated T8-lymphocytes differentiate
d. what CTLs recognize on infected cells and tumor cells
e. how CTLs kill infected cells and tumor cells

- State the overall function of T8-lymphocytes in adaptive immunity.

The primary role of T8-lymphocytes (T8-Cells; $CD8^+$ Cells; Cytotoxic T-Lymphocytes) is to kill infected cells and tumor cells by inducing apoptosis of those cells. Once naive T8-lymphocytes are activated by dendritic cells , they proliferate and differentiate into T8-effector lymphocytes called cytotoxic T-lymphocytes (CTLs) that bind to and kill infected cells and tumor cells.

T8-lymphocytes are T-lymphocytes displaying a surface molecule called CD8. T8-lymphocytes also have on their surface, T-cell receptors or TCRs similar to those on T4-lymphocytes. The TCR on T8-lymphocytes, in cooperation with CD8, bind peptides from endogenous antigens bound to MHC-I molecules .

During its development, each T8-lymphocyte becomes genetically programmed, by gene-splicing reactions similar to those in B-lymphocytes and T4-lymphocytes, to produce a TCR with a unique shape capable of binding epitope/MHC-I complex with a corresponding shape. It is estimated that the human body has the ability to recognize 10^7 or more different epitopes . In order to recognize this immense number of different epitopes, the body produces 10^7 or more distinct clones of T-lymphocytes, each with a unique T-cell receptor. In this variety of T-cell receptors there is bound to be at least one that has an epitope-binding site able to fit, at least to some degree, peptides of any antigen the immune system eventually encounters.

Activation of a naive T8-lymphocyte by a dendritic cell

One of the body's major defenses against viruses, intracellular bacteria, and cancers is the destruction of infected cells and tumor cells by cytotoxic T-lymphocytes or CTLs . These CTLs are effector cells derived from naive T8-lymphocytes during cell-mediated immunity. However, in order to become CTLs, naive T8-lymphocytes must become activated by dendritic cells as shown in Figure $10.3.3D.1$ and Figure $10.3.3D.2$.

Flash animation of MHC-I molecules binding epitopes from endogenous antigens by an antigen-presenting dendritic cell.

html5 version of animation for iPad showing MHC-I molecules binding epitopes from endogenous antigens by an antigen-presenting dendritic cell.

- To view an electron micrograph of a dendritic cell presenting antigen to T-lymphocytes, #1 see the Web page for the University of Illinois College of Medicine.
- To view an electron micrograph of a dendritic cell presenting antigen to T-lymphocytes, #2 see the Web page for the University of Illinois College of Medicine.

Certain dendritic cells are capable of cross-presentation of exogenous antigens to naive T8-lymphocytes . In this way, T8-lymphocytes can play a role in defending against both exogenous and endogenous antigens.

Naive T-lymphocytes circulate in the blood. In response to chemokines produced by lymphoid tissues, they leave the vascular endothelium in regions called high endothelial venules and enter lymph nodes (see Figure $10.3.3D.3$) or other

lymphoid tissues, a process called diapedesis .

As naive T8-lymphocytes migrate through the cortical region of lymph nodes, they use surface cell adhesion molecules such as LFA-1 and CD2 to bind transiently to corresponding receptors such as ICAM-1, ICAM-2 and CD58 on the surface of dendritic cells. This transient binding allows time for the TCRs on the T8-lymphocyte to sample large numbers of MHC-I/peptide complexes on the antigen-presenting dendritic cells (see Figure 10.3.3D.4).

Flash animation of the activation of a naive T8-lymphocyte recognizing epitopes bound to MHC-I molecules on an antigen-presenting dendritic cell.

html5 version of animation for iPad showing the activation of a naive T8-lymphocyte recognizing epitopes bound to MHC-I molecules on an antigen-presenting dendritic cell.

Those naive T8-lymphocytes not activated by epitopes of antigens on the dendritic cells exit the lymph node (or other lymphoid tissue) and eventually re-enter the bloodstream. However, if a TCR and CD8 molecule of the naive T8-lymphocyte detects a corresponding MHC-I/peptide complex on a mature dendritic cell, this will send a first signal for the activation of that naive T-lymphocyte. Next, a second signal that promotes survival of that T-lymphocyte is sent when co-stimulatory molecules such as B7.1 and B7.2 on the dendritic cell bind to CD28 molecules on the T8-lymphocyte. Finally, the dendritic cell produces cytokines such as interleukin-6 (IL-6), IL-4, IL-12, and T-cell growth factor-beta (TGF-ß) that contribute to proliferation of the T8-lymphocytes and their differentiation into effector T8-lymphocytes called cytotoxic T-lymphocytes (CTLs) that are able to bind to and kill infected cells and tumor cells displaying the same peptide/MHC-I complex on their surface. (Activated T8-lymphocytes remain in the lymph node as they proliferate (clonal expansion) and only leave the lymphoid tissues and re-enter the bloodstream after they have differentiated into CTLs.)

While activated T8-lymphocytes produce interleukin-2 (IL-2) as well as a high-affinity IL-2 receptor themselves, in most cases it is the IL-2 produced by effector T4-lymphocytes that enables cell proliferation and formation of a clone of thousands of identical T8-lymphocytes after several days. IL-2 also contributes to survival of those activated T8-lymphocytes and their differentiation into T8-effector cells called a cytotoxic T-lymphocytes or CTLs .

CTLs leave the secondary lymphoid organs and enter the bloodstream where they can be delivered anywhere in the body via the circulatory system and the inflammatory response. In addition, some of the T8-lymphocytes differentiate into circulating T8-memory cells . Circulating T8-memory cells allow for a more rapid and greater production of CTLs upon subsequent exposure to the same antigen.

Marking an infected cell or tumor cell for destruction by cytotoxic T-lymphocytes (CTLs)

During the replication of viruses and intracellular bacteria within their host cell, as well as during the replication of tumor cells, viral, bacterial, or tumor proteins in the cytosol of that cell are degraded into a variety of peptide epitopes by cylindrical organelles called proteasomes . Other endogenous antigens such as proteins released into the cytosol from the phagosomes of antigen-presenting cells, such as macrophages and dendritic cells as well, as a variety of the human cell's own proteins (self-proteins) are also degraded by proteasomes. As these various endogenous antigens pass through proteasomes, proteases and peptidases chop the protein up into a series of peptides, typically 8-11 amino acids long (see Figure 10.3.3D.5).

A transporter protein called TAP located in the membrane of the cell's endoplasmic reticulum then transports these peptide epitopes into the endoplasmic reticulum where they bind to the grooves of various newly made MHC-I molecules. The MHC-I molecules with bound peptides are then transported to the Golgi complex and placed in exocytic vesicles. The exocytic vesicles carry the MHC-I/peptide complexes to the cytoplasmic membrane of the cell where they

become anchored to its surface (see Figure 10.3.3D.6). A single cell may have up to 250,000 molecules of MHC-I with bound epitope on its surface.

Flash animation of MHC-I molecules binding epitopes from endogenous antigens in an infected cell.

html5 version of animation for iPad showing MHC-I molecules binding epitopes from endogenous antigens in an infected cell.

CTLs binding to infected cells or tumor cells and inducing apoptosis

CTLs are, by way of their TCRs and CD8 molecules, able to recognize infected cells and tumor cells displaying MHC-I molecules with bound peptides on their surface (see Figure 10.3.3D.7) and destroy them through apoptosis , a programmed cell suicide.

Apoptosis involves a complex of intracellular granules. This complex of granules in a protected state including:

1. Pore-forming proteins called perforins ;
2. Proteolytic enzymes called granzymes ; and
3. A proteoglycan called granulysin.

When the TCR and CD8 of the CTL binds to the MHC-I/epitope on the surface of the virus-infected cell or tumor cell (see Figure 10.3.3D.7), this sends a signal through a CD3 molecule which triggers the release of the perforins/granzymes/granulysin complexes from the CTL.

The exact mechanism of entry of the granzymes into the infected cell or tumor cell is still debated. It is, however, dependent on perforins. Possibilities include:

- The perforins/granzymes/granulysin complex may be taken into the target cell by receptor-mediated endocytosis . The perforin molecules may then act on the endosomal membrane allowing granzymes to enter the cytosol.
- The perforin molecules may put pores in the membrane of the target cell allowing the granzymes to directly enter the cytosol (see Figure 10.3.3D.7).

Killing of the infected cell or tumor cell by apoptosis involves a variety of mechanisms:

- Certain granzymes can activate the caspase enzymes that lead to apoptosis of the infected cell. The caspases are proteases that destroy the protein structural scaffolding of the cell - the cytoskeleton - and nucleases that degrade both the target cell's nucleoprotein and any microbial DNA within the cell (see Figure 10.3.3D.8).
- Granzymes cleave a variety of other cellular substrates that contribute to cell death.
- The perforin molecules may also polymerize and form pores in the membrane of the infected cell, similar to those produced by MAC. This can increase the permeability of the infected cell and contribute to cell death. If enough perforin pores form, the cell might not be able to exclude ions and water and may undergo cytolysis.
- Granulysin has antimicrobial actions and can also induce apoptosis.
    - Electron micrograph of a CTL binding to a tumor cell.

- Electron micrograph showing a killed tumor cell.

Flash animation of a CTL triggering apoptosis by way of perforins and granzymes.

html5 version of animation for iPad showing a CTL triggering apoptosis by way of perforins and granzymes.

Flash animation of CTL-induced apoptosis of a virus-infected cell.

html5 version of animation for iPad showing CTL-induced apoptosis of a virus-infected cell.

YouTube animation illustrating the MHC-I system marking an infected cell for destruction and its subsequent killing by CTLs.
Howard Hughes Medical Institute.

Movie illustrating apoptosis. Found on You Tube.

Concept Map for T-lymphocytes

TPS Question: T8-Lymphocytes

For a Summary of Key Surface Molecules and Cellular Interactions of Naive T8-Lymphocytes, see Figure 10.3.3*D*.9.

Summary

1. T-lymphocytes refer to lymphocytes that are produced in the bone marrow but require interaction with the thymus for their maturation.
2. The primary role of T8-lymphocytes is to kill infected cells and tumor cells by inducing apoptosis of those cells.
3. Once naive T8-lymphocytes are activated by dendritic cells, they proliferate and differentiate into T8-effector lymphocytes called cytotoxic T-lymphocytes (CTLs) that bind to and kill infected cells and tumor cells.
4. T8-lymphocytes display CD8 molecules and T-cell receptors (TCRs) on their surface.
5. The TCR on T8-lymphocytes, in cooperation with CD8, typically bind peptides from endogenous antigens bound to MHC-I molecules.
6. During its development, each T8-lymphocyte becomes genetically programmed, by gene-splicing reactions similar to those in B-lymphocytes and T4-lymphocytes, to produce a TCR with a unique shape capable of binding epitope/MHC-I complex with a corresponding shape.
7. To become activated, naive T8-lymphocytes migrate through lymph nodes where the TCRs on the T8-lymphocyte are able to sample large numbers of MHC-I/peptide complexes on the antigen-presenting dendritic cells for ones that “fit”, thus enabling activation of that naïve T8-lymphocyte.
8. After activation, the dendritic cell produces cytokines that contribute to proliferation of the T8-lymphocytes and their differentiation into effector T4-lymphocytes called cytotoxic T-lymphocytes (CTLs) that are able to bind to and kill infected cells and tumor cells displaying the same peptide/MHC-I complex on their surface.

9. Some of the T8-lymphocytes differentiate into circulating T8-memory cells that enable a more rapid and greater production of CTLs upon subsequent exposure to the same antigen.
10. During the replication of viruses and intracellular bacteria within their host cell, as well as during the replication of tumor cells, viral, bacterial, or tumor proteins in the cytosol of that cell are degraded into a variety of peptide epitopes by cylindrical organelles called proteasomes.
11. As these various endogenous antigens pass through proteasomes, proteases and peptidases chop the protein up into a series of peptides that are transported into the endoplasmic reticulum where they bind to newly made MHC-I molecules.
12. The MHC-I molecules with bound peptides are then transported to the Golgi complex and placed in exocytic vesicles that carry the MHC-I/peptide complexes to the cytoplasmic membrane of the cell where they become anchored to its surface.
13. CTLs are, by way of their TCRs and CD8 molecules, are then able to recognize infected cells and tumor cells displaying MHC-I molecules with bound peptides on their surface. This sends a signal that triggers the release of the perforins/granzymes/granulysin complexes from the CTL to destroy the infected cell or tumor cell through apoptosis.
14. The perforin molecules may put pores in the membrane of the target cell allowing the granzymes to directly enter the cytosol, and certain granzymes activate the caspase enzymes that lead to apoptosis of the infected cell or tumor cell by destroying the cytoskeleton of the cell and degrading both the target cell's nucleoprotein and any microbial DNA within the cell.

This page titled 10.3.3D: T8-Lymphocytes (T8-Cells) is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **12.3D: T8-Lymphocytes (T8-Cells)** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

10.3.3E: Invarient Natural Killer T-Lymphocytes (iNKT Cells)

Describe the overall function of iNKT cells and their activation in terms of the following:
a. the role of their TCRs
b. how they are activated by antigen-presenting cells
c. how they promote both innate and adaptive immunity and may also help to regulate the immune responses

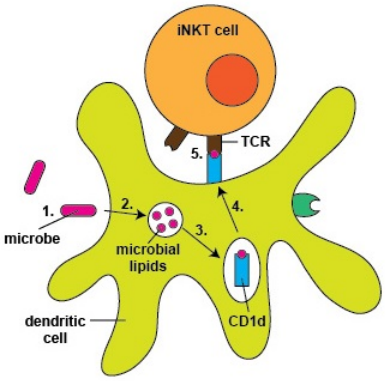


Figure **10.3.3*E*.1**: An iNKT-Lymphocyte Recognizing Microbial Glycolipid Antigen Bound to a CD1d Molecule on a Dendritic Cell. 1. Antigen-presenting dendritic cells engulf certain microbes or microbial glycolipids (exogenous glycolipids). 2. The glycolipids are degrade into epitopes by lysosomes. 3. The glycolipid epitopes are then bound to CD1d molecules produced in the endoplasmic reticulum by the dendritic cell. 4. The glycolipid epitope/CD1d complexs are transported by the Golgi apparatus to the surface of the dendritic cell. 5. Here the glycolipid epitope can be presented to theTCR of iNKT cells to induce iNKT cell activation.

Once activated, the iNKT cells rapidly produce large quantities of both T_H1 cell and T_H2 cell cytokines, including interferon-gamma (IFN-?), interleukin-4 (IL-4), interleukin-2 (IL-2), interleukin-10 (IL-10), tumor necrosis factor-alpha (TNF-a), interleukin-13 (IL-13), and chemokines. Through the rapid productions of such cytokines, iNKT cells are able to promote and suppress different innate and adaptive immune responses. For example, large amounts of IFN-? are produced by activated iNKT cells. IFN-? activates NK cells and macrophages as a part of innate immunity; it also promotes the maturation of dendritic cells so that they induce a T_H1 cell response to induce adaptive immunity.

It has been proposed that if the iNKT cell is repeatedly stimulated by the body's own glycolipids in the ab sense of microbes that this might stimulate the iNKT cell /dendritic cell interaction to produce tolerizing signals that inhibit the T_H1 cell response and possibly stimulate the production of regulatory T-lymphocytes (T_{reg} cells). In this way it might suppress autoimmune responses and prevent tissue damage.

There is also growing evidence that early childhood exposure to microbes is associated with protection against allergic diseases, asthma, and inflammatory diseases such as ulcerative colitis. It has been found that germ-free mice have large accumulations of mucosal iNKT cells in the lungs and intestines and increased morbidity from allergic asthma and inflammatory bowel disease. However, colonization of neonatal germ-free mice with normal microbiota resulted in mucosal iNKT cell tolerance to these diseases. It has been proposed that microbes the human body has been traditionally exposed to from early childhood throughout most of human history might play a role in developing normal iNKT cell numbers and iNKT cell responses.

This page titled 10.3.3E: Invarient Natural Killer T-Lymphocytes (iNKT Cells) is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **12.3E: Invarient Natural Killer T-Lymphocytes (iNKT Cells)** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

10.3.3F: B-Lymphocytes (B-Cells)

Learning Objectives

Describe the overall function of B-lymphocytes and their activation by T-dependent antigens in terms of the following:

a. the antigen receptor on their surface
b. how they "process" exogenous antigens
c. the type of MHC molecule to which they attach peptides
d. the role of lysosomes in binding of peptides from exogenous antigens by MHC-II molecules.
e. the type of cell to which they present peptides
f. the types of cells into which activated B-lymphocytes differentiate

B-lymphocytes (B-cells) are responsible for the production of antibody molecules **during adaptive immunity**. Antibodies are critical in removing extracellular microorganisms and toxins. B-lymphocytes refer to lymphocytes that are produced in the bone marrow and require bone marrow stromal cells and their cytokines for maturation. During its development, each B-lymphocyte becomes genetically programmed through a series of gene-splicing reactions to produce an antibody molecule with a unique specificity - a specific 3-dimensional shape capable of binding a specific epitope of an antigen (Figure $\mathbf{10.3.3F.1}$).

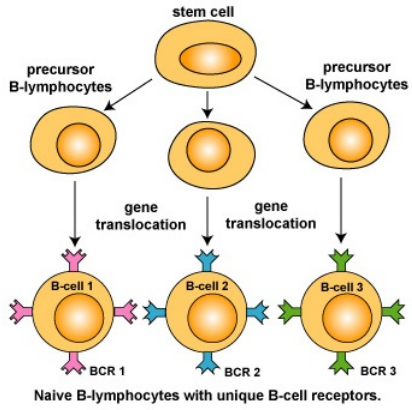


Figure $\mathbf{10.3.3F.1}$: B-Lymphocyte Precursors Making B-Cell Receptors (BCRs). During its development, each B-lymphocyte becomes genetically programmed, through a process called gene translocation, to make a unique B-cell receptor. Molecules of that B-cell receptor are placed on its surface where it can react with epitopes of an antigen.

It is estimated that the human body has the ability to recognize 10^7 or more different epitopes and make up to 10^9 different antibodies, each with a unique specificity. In order to recognize this immense number of different epitopes, the body produces 10^7 or more distinct clones of B-lymphocytes, each with a unique B-cell receptor or BCR. In this variety of B-cell receptors there is bound to be at least one that has an epitope-binding site able to fit, at least to some degree, any antigen the immune system eventually encounters.

Typically, over 100,000 identical molecules of that unique antibody are placed on the surface of the B-lymphocyte where they can function as B-cell receptors capable of binding specific epitopes of a corresponding shape (Figure $\mathbf{10.3.3F.2}$). Naive B-lymphocytes can be activated by both T-dependent antigens and T-independent antigens.

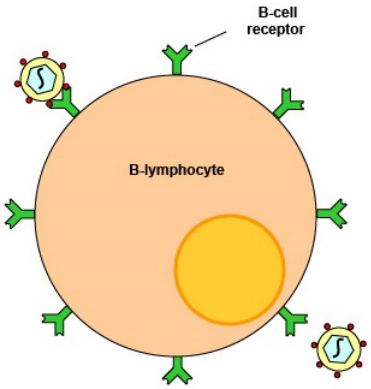


Figure 10.3.3F.2: A B-lymphocyte Recognizing Epitopes of a Virus by way of B-cell Receptors. Epitopes of the virus bind to a B-lymphocyte by way of a specific B-cell receptor.

Activation of naive B-lymphocytes by T-dependent antigens

In order for naive B-lymphocytes to proliferate, differentiate, and mount an antibody response against T-dependent antigens, such as most proteins, these B-lymphocytes must interact with effector T4-lymphocytes called T_{FH} cells. All classes of antibody molecules can be made against T-dependent antigens and there is usually a memory response against such antigens.

B-Lymphocytes and T4-lymphocytes encounter antigens in secondary lymphoid organs such as the lymph nodes and the spleen. Using a lymph node as an example (Figure 10.3.3F.3A), soluble antigens, such as microbial polysaccharides and proteins and toxins, as well as **microbes such as bacteria and viruses**, **enter the lymph node** through afferent lymphatic vessels. By this time, complement pathway activation has coated these soluble antigens or microbes with opsonins such as C3b, which in turn can be degraded to C3d.

Located within the lymphoid tissues are specialized macrophages and specialized dendritic cells called follicular dendritic cells (FDCs). These macrophages have poor endocytic ability and produce few lysosomes. The FDCs are nonphagocytic. Both cell types, however, have complement receptors called CR1 and CR2 that bind to the C3b and C3d, enabling the antigens and microbes to stick to the surface of the macrophages and FDCs. However,because of the poor endocytic ability of the macrophages and the lack of endocytosis by the FDCs, the antigens and microbes are not engulfed but rather remain on the surface of the cells. In addition, the macrophages can transfer their bound antigens or microbes to FDCs (Figure 10.3.3F.3B).

Here the antigens and microbes in the lymph node can bind to complementary-shaped BCRs on naive B-lymphocytes **directly, by way of macrophages, or via the FDCs** (Figure 10.3.3F.3B).

Circulating naive B-lymphocytes, as a result of chemotaxis, enter lymph nodes through high endothelial venules. Any naive B-lymphocyte that bind antigens become activated and remain in the lymphoid nodes to proliferate and differentiate. Any B-lymphocytes not activated leave the lymphoid node through efferent lymphatic vessels and are returned to the bloodstream.

The first signal for the activation of a naive B-lymphocyte occurs when BCRs on the surface of the B-lymphocyte bind epitopes of antigens having a corresponding shape. A second signal is also needed for the activation of the naive B-lymphocyte. This is provided when the complement protein C3d on the microbial surface or soluble antigen binds to a complement receptor called CR2 on the surface of the naive B-lymphocyte.

Once bound, the antigen is engulfed, placed in a phagosome , and degraded with lysosomes. During this process, protein antigens are broken down into a series of peptide epitopes.These peptides eventually bind to grooves in MHC-II molecules that are then transported to the surface of the B-lymphocyte (Figure 10.3.3F.4).

Meanwhile, naïve T4-lymphocytes are being activated by epitopes of antigens bound to MHC-II molecules on antigen-presenting dendritic cells in the T-cell area of the lymph node and subsequently proliferate and differentiate into T4-effector lymphocytes such

as T_{FH} cells which remain in the lymph node. The T-cell receptors and CD4 molecules on T_{FH} cells bind to the MHC-II molecules with bound peptide epitope on the B-lymphocyte. The binding of co-receptor molecules such as CD40L and CD28 on the surface of the effector T4-lymphocyte to the corresponding molecules CD40 and B7 on the surface of the B-lymphocyte further contribute to the interaction between these two cells (Figure 10.3.3F.5). This enables the T_{FH} cells to produce cytokines such as interleukin-2 (IL-2) , interleukin-4 (IL-4), interleukin-5 (IL-5), and interleukin-6 (IL-6) (Figure 10.3.3F.5).

Flash animation of the binding of peptide epitopes to MHC-II molecules by a B-lymphocyte.

Flash animation of an effector T4-lymphocyte recognizing epitopes bound to MHC-II molecules on a B-lymphocyte.

html5 version of animation for iPad showing the binding of peptide epitopes to MHC-II molecules by a B-lymphocyte

html5 version of animation for iPad showing an effector T4-lymphocyte recognizing epitopes bound to MHC-II molecules on a B-lymphocyte.

Collectively these cytokines:

a. Enable activated B-lymphocytes to proliferate.
b. Stimulate activated B-lymphocytes to synthesize and secrete antibodies.
c. Promote the differentiation of B-lymphocytes into antibody-secreting plasma cells. See Figure 10.3.3F.6.
d. Enable antibody producing cells to switch the class or isotype of antibodies being produced.

YouTube animation illustrating production of antibodies by B-lymphocytes.

YouTube animation illustrating production of antibodies by B-lymphocytes against Streptococcus pyogenes.

Effector T4-lymphocytes also enable B-lymphocytes to undergo affinity maturation through a high rate of somatic mutation. This allows the B-lymphocytes to eventually "fine-tune" the shape of the antibody for better fit with the original epitope. After mutation, some antibodies fit better, some worse. To select for B-lymphocytes displaying antibodies with a better fit, the variant B-lymphocytes interact with cells called follicular dendritic cells (FDCs) in the germinal centers of the secondary lymphoid organs. The FDCs display the same antigens that activated the original B-lymphocyte. If the B-lymphocytes have high affinity antibodies for the antigen on the FDC, they are selected to survive. Those B-lymphocytes with low affinity antibodies undergo apoptosis.

With the exception of T_{FH} cells which remain in the germinal centers of the lymph nodes and spleen, progeny of the activated B-lymphocytes and T4 effector lymphocytes leave the secondary lymphoid organs and migrate to tissues where they continue to respond to the invading antigen as long as it is present.

In the case of systemic infections or vaccinations where the antigens enter the bloodstream, plasma cells migrate to the bone marrow where antibodies can be produced for decades. After the antibodies are secreted by the plasma cells, they are found dissolved in the blood plasma and lymph. From here they can be delivered anywhere in the body via the circulatory system and the inflammatory response. In the case of infections of the mucous membranes, however, plasma cells only enter the mucous membranes where antibodies are only produced for a few months to a year or so.

During the proliferation and differentiation that follows lymphocyte activation, some of the B-lymphocytes stop replicating and become circulating, long-lived memory cells. Memory cells are capable of what is called anamnestic response or "memory", that is, they "remember" the original antigen. If that same antigen again enters the body while the B-memory cells (and T4-memory cells) are still present, these memory cells will initiate a rapid, heightened secondary response against that antigen (Figure 10.3.3F.7). This is why the body sometimes develops a permanent immunity after an infectious disease and is also the principle behind immunization.

Activation of B-lymphocytes by T-independent antigens

T-independent (TI) antigens are usually large carbohydrate and lipid molecules with multiple, repeating subunits. B-lymphocytes mount an antibody response to T-independent antigens without the requirement of interaction with effector T4-lymphocytes. Bacterial LPS from the Gram-negative cell wall and capsular polysaccharides are examples of TI antigens. The resulting antibody molecules are generally of the IgM isotype and do not give rise to a memory response. There are two basic types of T-independent antigens: TI-1 and TI-2.

a. TI-1 antigens arepathogen-associated molecular patterns or PAMPS such as lipopolysaccharide (LPS) from the outer membrane of the gram-negative cell wall and bacterial nucleic acid. These antigens activate B-lymphocytes by binding to their specific pattern-recognition receptors , in this case toll-like receptors, rather than to B-cell receptors (Figure $10.3.3F.8$). Antibody molecules generated against TI-1 antigens are often called "natural antibodies" because they are always being made against bacteria present in the body.

For More Information: Pathogen-Associated Molecular Patterns from Unit 5

For More Information: Pattern-Recognition Receptors from Unit 5

b. TI-2 antigens, such as capsular polysaccharides, are molecules with multiple, repeating subunits. These repeating subunits activate B-lymphocytes by simultaneously cross-linking a number of B-cell receptors (Figure $10.3.3F.9$).

For More Information: T4-Lymphocytes from Unit 6

For More Information: MHC Molecules from Unit 6

For a Summary of Key Surface Molecules and Cellular Interactions of Naive B-Lymphocytes, see Figure $10.3.3F.10$.

Concept Map for B-lymphocytes

Summary

1. B-lymphocytes are responsible for the production of antibody molecules during adaptive immunity.
2. Antibodies are critical in removing extracellular microorganisms and toxins.
3. B-lymphocytes refer to lymphocytes that are produced in the bone marrow and require bone marrow stromal cells and their cytokines for maturation.
4. During its development, each B-lymphocyte becomes genetically programmed to produce an antibody molecule with a unique 3-dimensional shape capable of binding a specific epitope of an antigen, and puts molecules of that antibody on its surface that function as B-cell receptors or BCRs.
5. Naive B-lymphocytes can be activated by both T-dependent antigens and T-independent antigens.
6. In order for naive B-lymphocytes to proliferate, differentiate, and mount an antibody response against T-dependent antigens, such as most proteins, these B-lymphocytes must interact with effector T4-lymphocytes called TFH cells.
7. The first signal for the activation of a naive B-lymphocyte occurs when BCRs on the surface of the B-lymphocyte bind epitopes of antigens having a corresponding shape.
8. Once bound to the BCR, the antigen is engulfed, placed in a phagosome, and degraded with lysosomes. During this process, protein antigens are broken down into a series of peptide epitopes, bind to MHC-II molecules, and are transported to the surface of the B-lymphocyte.

9. The T-cell receptors and CD4 molecules on TFH cells bind to the MHC-II molecules with bound peptide epitope on the B-lymphocyte which enables the TFH cells to produce cytokines that collectively enable the B-lymphocytes to proliferate, synthesize and secrete antibodies, differentiate into antibody-secreting plasma cells, and switch the class of antibodies being produced.
10. By way of a mutation process called affinity maturation, activated B-lymphocytes are able over time to “fine-tune" the shape of the antibody for better fit with the original epitope.
11. During the proliferation and differentiation that follows lymphocyte activation, some of the B-lymphocytes stop replicating and become circulating, long-lived memory cells that will initiate a rapid, heightened secondary response against that antigen if it again enters the body.
12. T-independent (TI) antigens are usually large carbohydrate and lipid molecules with multiple, repeating subunits. B-lymphocytes mount an antibody response to T-independent antigens without the requirement of interaction with effector T4-lymphocytes, but the resulting antibody molecules are generally of the IgM isotype only and do not give rise to a memory response.

This page titled 10.3.3F: B-Lymphocytes (B-Cells) is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **12.3F: B-Lymphocytes (B-Cells)** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

10.3.3G: Natural Killer Cells (NK Cells)

Briefly describe how NK cells bind to and kill infected cells and tumor cells through ADCC.
- Briefly describe how NK cells recognize and kill infected cells and tumor cells that suppress MHC-I production.

NK cells are another group of cytolytic lymphocytes that are distinct from B-lymphocytes and T-lymphocytes, and participate in both innate immunity and adaptive immunity. NK cells are lymphocytes that lack B-cell receptors and T-cell receptors. They are designed to kill certain mutant cells and virus-infected cells in one of two ways:

Antibody-dependent Cellular Cytotoxicity

NK cells kill cells to which antibody molecules have attached through a process called antibody-dependent cellular cytotoxicity (ADCC) as shown in Figure 10.3.3G.1, Figure 10.3.3G.2, and Figure 10.3.3G.3. The Fab portion of the antibody binds to epitopes on the "foreign" cell. The NK cell then binds to the Fc portion of the antibody. The NK cell is then able to contact the cell and by inducing a programmed cell suicide called apoptosis.

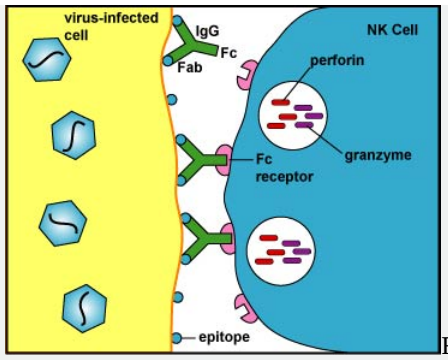


Figure 10.3.3G.3

As a result, the infected cell breaks into membrane-bound fragments that are subsequently removed by phagocytes. If very large numbers of perforins are inserted into the plasma membrane of the infected cell, this can result in a weakening of the membrane and lead to cell lysis rather than apoptosis. An advantage to killing infected cells by apoptosis is that the cell's contents, including viable virus particles and mediators of inflammation, are not released as they are during cell lysis.

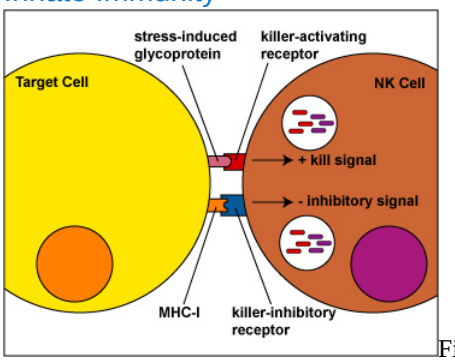


Figure **10.3.3*G*.6**). Perforins can also sometimes result in cell lysis.

Flash animation of a NK cell interacting with a normal body cell.

Flash animation of a NK cell interacting with a virus-infected cell or tumor cell not expressing MHC-I molecules.

Flash animation of apoptosis by NK cells

html5 version of animation for iPad showing a NK cell interacting with a normal body cell.

html5 version of animation for iPad showing a NK cell interacting with a virus-infected cell or tumor cell not expressing MHC-I molecules.

html5 version of animation for iPad showing apoptosis by NK cells.

In addition, NK cells produce a variety of cytokines, including proinflammatory cytokines, chemokines, colony-stimulating factors, and other cytokines that function as regulators of body defenses. For example, through cytokine production NK cells also suppress and/or activate macrophages, suppress and/or activate the antigen-presenting capabilities of dendritic cells, and suppress and/or activate T-lymphocyte responses.

Summary

1. Natural Killer (NK) cells are able to recognize infected cells, cancer cells, and stressed cells and kill them. In addition, they produce a variety of cytokines, including proinflammatory cytokines, chemokines, colony-stimulating factors, and other cytokines that function as regulators of body defenses.
2. NK cells play a role in adaptive immune responses by way of antibody-dependent cellular cytotoxicity or ADCC where they bind to and kill cells to which antibody molecules have bound.
3. During ADCC, the Fab portion of the antibody binds to epitopes on the "foreign" cell. The NK cell then binds to the Fc portion of the antibody and the NK cell is then able to contact and kill the cell by inducing a programmed cell suicide called apoptosis.
4. During innate immunity, NK cells use a dual receptor system in determining whether to kill or not kill human cells.
5. When body cells are either under stress, are turning into tumors, or are infected, various stress-induced molecules are produced and are put on the surface of that cell.
6. The first receptor, called the killer-activating receptor, can bind to these stress-induced molecules, and this sends a positive signal that enables the NK cell to kill the cell to which it has bound unless the second receptor cancels that signal.

7. The second receptor, called the killer-ihibitory receptor, recognizes MHC-I molecules that are usually present on all nucleated human cells. If MHC-I molecules/self peptide complexes are expressed on the cell, the killer-inhibitory receptors on the NK cell recognize this MHC-I/peptide complex and sends a negative signal that overrides the original kill signal and prevents the NK cell from killing the cell to which it has bound.
8. NK cells kill their target cells by inducing apoptosis, a programmed cell suicide.

This page titled 10.3.3G: Natural Killer Cells (NK Cells) is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **12.3G: Natural Killer Cells (NK Cells)** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

10.3.4: The Lymphoid System

Learning Objectives

1. Compare and give examples of the following:
   a. primary lymphoid organs
   b. secondary lymphoid organs
2. Define the following:
   a. plasma
   b. tissue fluid
   c. lymph
   d. lymph vessels
   e. MALT
3. Briefly describe the importance of the lymphoid system in adaptive immune responses and how microbes and other antigens encounter naive B-lymphocytes and T-lymphocytes.

The body uses the lymphoid system to enable lymphocytes to encounter antigens and it is here that adaptive immune responses are initiated. The lymphoid system consists of primary lymphoid organs, secondary lymphoid organs, and lymphatic vessels.

The bone marrow and the thymus constitute the primary lymphoid organs. Both B-lymphocytes and T-lymphocytes are produced from stem cells in the bone marrow. B-lymphocytes mature in the bone marrow while T-lymphocytes migrate to the thymus and mature there. After maturation, both naive B-lymphocytes and naive T-lymphocytes circulate between the blood and the secondary lymphoid organs.

Lymphatic vessels are responsible for flow of lymph within the lymphoid system and are a part of the body's fluid recirculation system. The liquid portion of the blood, called plasma, constantly leaks out of capillaries to deliver oxygen and nutrients to cells of the surrounding tissue. Once in the tissue, the plasma is now called tissue fluid. While most of this tissue fluid re-enters capillaries and is returned directly to the bloodstream, some fluid enters lymph vessels as lymph. The lymph flows through regional lymph nodes and eventually enters the circulatory system at the heart to maintain the fluid volume of the circulation.

Secondary lymphoid organs

Adaptive immune responses require antigen-presenting cells, such as macrophages and dendritic cells, and ever changing populations of B-lymphocytes and T- lymphocytes. These cells gather to detect and present antigens in secondary lymphoid organs. The secondary lymphoid organs include highly organized lymphoid organs such as lymph nodes and the spleen, as well as less organized accumulations of lymphoid organs scattered strategically throughout the body.

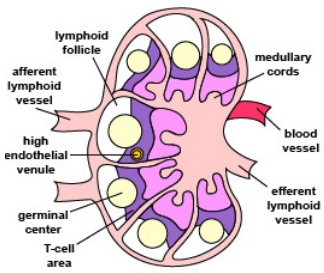


Figure **10.3.4.1**: Structure of a Lymph Nodes. Antigens enter lymph nodes through afferent lymphoid vessels. Antigen-presenting dendritic cells enter the lymph node through afferent lymphatic vessels while naive B-lymphocytes, and naive T-lymphocytes enter through high endothelial venules. Non-activated and effector lymphocytes leave the lymph node through efferent lymphatic vessels. Naive B-lymphocytes become activated, proliferate, and differentiate into plasma cells in the

germinal centers of lymphoid follicles while naive T-lymphocytes become activated, proliferate and differentiate into T-effector lymphocytes in the T-cell area.

Lymph nodes (Figure **10.3.4.1**) contain many reticular fibers that support fixed macrophages and dendritic cells as well as ever changing populations of circulating B-lymphocytes and T-lymphocytes. When microorganisms and other antigens enter tissues, they are transported by tissue fluid into the lymph vessels. Lymph vessels, in turn, carry these antigens, now in the lymph, to regional lymph nodes. In addition, immature dendritic cells located under the surface epithelium of the skin and the surface epithelium of the mucous membranes of the respiratory tract, genitourinary tract, and the gastrointestinal tract capture antigens through pinocytosis and phagocytosis. The dendritic cells detach from their initial site, enter lymph vessels, and are carried to regional lymph nodes. Here the microbes and other antigens in the lymph encounter changing populations of B-lymphocytes, are filtered out and phagocytosed by the fixed macrophages and dendritic cells, and are presented to changing populations of T-lymphocytes (Figure **10.3.4.2**). Approximately 25 billion different lymphocytes migrate through each lymph node every day.

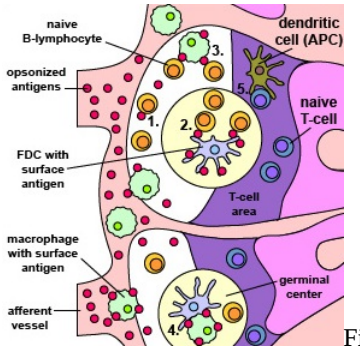


Figure **10.3.4.2**: B-lymphocyte and T-Lymphocytes Recognizing Antigens in a Lymph Node. Opsonized antigens (those coated with C3b and Ced from the complement pathways) enter a lymph node through afferent lymphoid vessels. These opsonized antigens bind to and remain on the surface of specialized macrophages and follicular dendritic cells (FDCs). In addition, macrophages can transfer antigens to FDCs (see 4. above). Using their B-cell receptor (BCR), naive B-lymphocytes are able to recognize antigens directly (see 1. above), or more commonly, on the surface of FDCs (see 2. above), or on the surface of macrophages (see 3. above) in the germinal centers and lymphoid follicles of the lymph node. Meanwhile, naive T-lymphocytes are being activated by antigen-presenting dendritic cells in the T-cell areas of the lymph node (see 5. above). T4-effector cells and activated B-lymphcytes then interact with one another at the interface between the geminal centers and the T-cell areas.

Like the lymph nodes, the spleen contains many reticular fibers that support fixed macrophages and dendritic cells as well as ever changing populations of circulating B-lymphocytes and T-lymphocytes. When microorganisms and other antigens enter the blood, they are transported by the blood vessels to the spleen. Most of the spleen is referred to as red pulp. This area is involved in the disposal of old red blood cells. Scattered throughout the spleen are isolated areas called the white pulp (Figure **10.3.4.3**). Here antigens in the blood encounter macrophages, dendritic cells, and ever-changing populations of B-lymphocytes and T-lymphocytes.

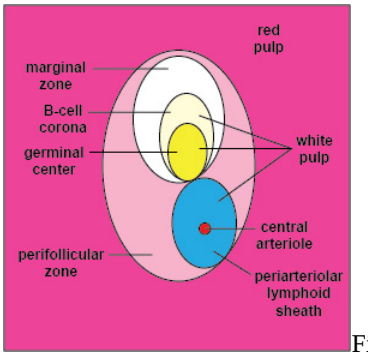


Figure **10.3.4.3**: Section of a Spleen Showing Red Pulp and White Pulp. The red pulp makes up the majority of the spleen. This is where old red blood cells are destroyed. Scattered throughout the spleen are areas of white pulp where microbes, cells, and antigens encounter macrophages, dendritic cells, and changing populations of B-lymphocytes and T-lymphocytes. Soluble antigens, blood-borne microbes, and antigen-antibody complexes are filtered out of the blood and phagocytosed by immature dendritic cells and macrophages within the marginal zone. After maturation, dendritic cells migrate to

the periphery of the periarteriolar lymphoid sheath, The T-cell area of the white pulp, and present antigens bound to MHC molecules to the TCRs of T-lymphocytes. Secondary follicles consisting of germinal centers surrounded by a B-cell corona are where B-lymphocytes encounter microbes and soluble antigens.

Mucosal surfaces within the body, the most common sites of microbial invasion, are protected by the mucosal immune system consisting of the mucosa-associated lymphoid tissue or MALT, an extensive diffuse system of small concentrations of lymphoid tissue found in various sites of the body such as the gastrointestinal tract, thyroid, breast, lung, salivary glands, eye, and skin. MALT is populated by loose clusters of T-lymphocytes, B-lymphocytes, plasma cells, activated T_H cells, and macrophages. MALT can be subdivided into:

- GALT (gut-associated lymphoid tissue, such as the Peyer's patches (Figure 10.3.4.4) in the lining of the small intestines, as well as the adenoids, tonsils, and appendix)
- BALT (bronchial-associated lymphoid tissue in the bronchi)
- SALT (skin-associated lymphoid tissue beneath the epidermis)
- NALT (nose-associated lymphoid tissue)
- LALT (larynx-associated lymphoid tissue)
- CALT (conjunctiva-associated lymphoid tissue in the eye)

As can be seen, no matter how microbes and other antigens enter the body, they will eventually encounter the lymphoid system to initiate adaptive immune responses.

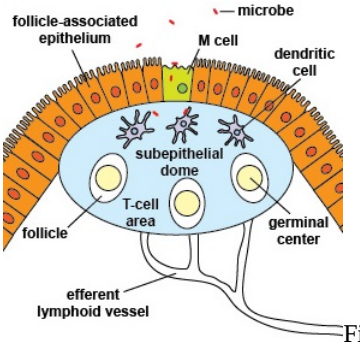


Figure 10.3.4.4: Diagram of a Peyer's Patch. Peyer's patches are part of the mucosa-associated lymphoid tissue (MALT) in the small intestines. Microbes and antigens enter through specialized epithelial cells called microfold (M) cells. Changing populations of naive B-lymphocytes and naive T-lymphocytes enter the Peyer's patch via blood vessels with B-lymphocytes entering the follicles and germinal centers and T-lymphocytes entering the T-cell area. Dendritic cells engulf and process antigens and present them by way of MHC molecules to the TCRs of naive T-lymphocytes.

Summary

1. The body uses the lymphoid system to enable lymphocytes to encounter antigens and it is here that adaptive immune responses are initiated.
2. The lymphoid system consists of primary lymphoid organs, secondary lymphoid organs, and lymphatic vessels.
3. The bone marrow and the thymus constitute the primary lymphoid organs.
4. While both B-lymphocytes and T-lymphocytes are produced from stem cells in the bone marrow, B-lymphocytes mature in the bone marrow and T-lymphocytes migrate to the thymus to mature.
5. After maturation, both naive B-lymphocytes and naive T-lymphocytes circulate between the blood and the secondary lymphoid organs.
6. Adaptive immune responses require antigen-presenting cells, such as macrophages and dendritic cells, and ever changing populations of B-lymphocytes and T- lymphocytes. These cells gather to detect and present antigens in secondary lymphoid organs.
7. The secondary lymphoid organs include highly organized lymphoid organs such as lymph nodes and the spleen, as well as less organized accumulations of lymphoid organs scattered strategically throughout the body.
8. Lymphatic vessels are responsible for flow of lymph within the lymphoid system and are a part of the body's fluid recirculation system. The lymph flows through regional lymph nodes and eventually enters the circulatory system at

the heart to maintain the fluid volume of the circulation.

This page titled 10.3.4: The Lymphoid System is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **12.4: The Lymphoid System** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

10.3.5: An Overview of the Steps Involved in Adaptive Immune Responses

Learning Objectives

1. List the 5 general steps involved in the immune responses in their correct order.
2. State where antigens may encounter APCs, B-lymphocytes, and T-lymphocytes if they enter the following:
    a. the blood
    b. tissues
    c. the respiratory tract
    d. the gastrointestinal tract
    e. the genitourinary tract
3. Briefly describe how the receptor molecules on the surface of naive B-lymphocytes, T4-helper lymphocytes, and T8-lymphocytes eventually recognize or bind epitope, indicating the roles of BCR, TCR, CD4, CD8, MHC-I, and MHC-II molecules in lymphocyte activation.
4. State the overall function of T4-effector lymphocytes and the importance behind rapid proliferation of activated lymphocytes.
5. State what types of effector cells the proliferating B-lymphocytes and T8-lymphocytes differentiate into in order to destroy or neutralize the antigen.
6. Define cytokine.
7. State the function of memory cells.
8. State what is meant by immunologic tolerance.

Whether considering *humoral immunity* or *cell-mediated immunity*, there are several general steps involved in the immune responses.

Step 1. The antigen must encounter the B-lymphocytes, T-lymphocytes, and antigen-presenting cells (APCs) capable of carrying out an adaptive immune response.

Fundamental Statement for this Step:

1. Antigens encounter the APCs, B-lymphocytes, and T-lymphocytes in the secondary lymphoid organs of the lymphoid system.

Antigens encounter the APCs, B-lymphocytes, and T-lymphocytes in the secondary lymphoid organs of the lymphoid system. Tissue fluid carries antigens to lymph nodes, blood carries antigens to the spleen, and immature dendritic cells under the skin and mucosal epithelium carry antigens to regional lymph nodes. Here they encounter ever changing populations of naive B-lymphocytes, T4-lymphocytes, and T8-lymphocytes as they circulate back and forth between the blood and the lymphatics.

a. Antigens that enter through the bloodstream, encounter the APCs, B-lymphocytes, and T-lymphocytes in the spleen ; see Figure 10.3.5.1.
b. Antigens that enter through the tissue, are picked up by tissue fluid, enter the lymph vessels, and are carried to the lymph nodes where they encounter APCs, B-lymphocytes, and T-lymphocytes; see Figure 10.3.5.2.
c. Antigens that enter the respiratory tract, encounter APCs, B-lymphocytes, and T-lymphocytes in the tonsils and the mucosa-associated lymphoid tissue (MALT), including the bronchial-associated lymphoid tissue (BALT), the nose-associated lymphoid tissue (NALT), and the larynx-associated lymphoid tissue (LALT).
d. Antigens that enter the intestinal tract, encounter APCs, B-lymphocytes, and T-lymphocytes in the Peyer's patches (see Figure 10.3.5.3) and other gut-associated lymphoid tissues (GALT).
e. Antigens that enter the genitourinary tract, encounter APCs, B-lymphocytes, and T-lymphocytes in the mucosa-associated lymphoid tissue (MALT) found there.

f. Finally, antigens that penetrate the skin, encounter APCs, B-lymphocytes, and T-lymphocytes of the skin-associated lymphoid tissue (SALT).

Step 2. Naive B-lymphocytes, T4-lymphocytes, and T8-lymphocytes must recognize epitopes of an antigen by means of antigen-specific receptor molecules on their surface and become activated. This is known as clonal selection.

Fundamental Statements for this Step:

1. Dendritic cells bind peptide epitopes to MHC-II molecules to enable them to be recognized by complementary shaped T-cell receptors (TCR) and CD4 molecules on naive T4-lymphocyte.
2. Dendritic cells bind peptide epitopes to MHC-I molecules to enable them to be recognized by complementary shaped T-cell receptors (TCR) and CD8 molecules on naive T8-lymphocytes.
3. These interactions are required to enable the T4-lymphocyte or T8-lymphocyte to become activated, proliferate, and differentiate into effector cells.
4. Naive T4-lymphocytes have T cell receptors (TCRs) that, in cooperation with CD4 molecules, bind to MHC-II molecules with attached epitope from an antigen found on the surface of an antigen-presenting dendritic cell.
5. Naive T8-lymphocytes have T cell receptors (TCRs) that, in cooperation with CD8 molecules, bind to MHC-I molecules with attached epitope from an antigen found on the surface of antigen-presenting dendritic cells.
6. Most proteins are T-dependent antigens. In order for naive B-lymphocytes to proliferate, differentiate and mount an antibody response against T-dependent antigens, these B-lymphocytes must interact with effector T4-lymphocytes.
7. Specialized macrophages and specialized dendritic cells called FDCs are located in the lymphoid tissues. Antigens and microbes are are found on the surface of these FDCs and macrophages which present them to complementary-shaped BCRs on naive B-lymphocytes**.**
8. A few antigens are called T-independent antigens. T-independent (TI) antigens are usually large carbohydrate and lipid molecules with multiple, repeating subunits. B-lymphocytes mount an antibody response to T-independent antigens without the requirement of interaction with effector T4-lymphocytes but the antibody response is much more limited than with T-dependent antigens.

a. The role of antigen-presenting dendritic cells

The primary function of dendritic cells is to capture and present protein antigens to naive T-lymphocytes.

- Dendritic cells bind peptide epitopes to MHC-II molecules (see Figure 10.3.5.4) to enable them to be recognized by complementary shaped T-cell receptors (TCR) and CD4 molecules on naive T4-lymphocyte.
- Dendritic cells bind peptide epitopes to MHC-I molecules (see Figure 10.3.5.5) to enable them to be recognized by complementary shaped T-cell receptors (TCR) and CD8 molecules on naive T8-lymphocytes.

These interactions are required to enable the T4-lymphocyte or T8-lymphocyte to become activated, proliferate, and differentiate into effector cells.

Flash animation of MHC-II molecules binding epitopes from exogenous antigens.

html5 version of animation for iPad showing MHC-II molecules binding epitopes from exogenous antigens.

Flash animation of MHC-I molecules binding epitopes from endogenous antigens by an antigen-presenting dendritic cell.

html5 version of animation for iPad showing MHC-I molecules binding epitopes from endogenous antigens by an antigen-presenting dendritic cell.

Most dendritic cells are derived from monocytes and are referred to as myeloid dendritic cells. They are located under the surface epithelium of the skin and the surface epithelium of the mucous membranes of the respiratory tract, genitourinary tract, and the gastrointestinal tract. They are also found throughout the body's lymphoid tissues and in most solid organs.

Upon capturing antigens through pinocytosis and phagocytosis and becoming activated by proinflammatory cytokines, the dendritic cells detach from the epithelium, enter lymph vessels, and are carried to regional lymph nodes (see Figure 10.3.5.6). By the time they enter the lymph nodes, they have matured and are now able to present antigen to the ever changing populations of naive T-lymphocytes located in the T-cell area of the lymph nodes (see Figure 10.3.5.7).

- To view an electron micrograph of a dendritic cell presenting antigen to T-lymphocytes, #1 see the Web page for the University of Illinois College of Medicine.
- To view an electron micrograph of a dendritic cell presenting antigen to T-lymphocytes, #2 see the Web page for the University of Illinois College of Medicine.

For More Information: Antigen-presenting cells from Unit 6

b. Naive T4-helper lymphocytes recognizing peptide epitopes

Naive T4-lymphocytes circulate in the blood. In response to chemokines produced by lymphoid tissues, they leave the vascular endothelium in regions called high endothelial venules and enter lymph nodes or other secondary lymphoid tissues, a process called diapedesis.

Naive T4-lymphocytes have T-cell receptors (TCRs) that, in cooperation with CD4 molecules, bind to MHC-II molecules with attached epitope from an antigen found on the surface of an antigen-presenting dendritic cells ; (see Figure 10.3.5.8). Each T4-lymphocyte is genetically programmed to make a unique TCR. The TCR recognizes the peptide while the CD4 molecule recognizes the MHC-II molecule.

Flash animation of a naive T4-lymphocyte recognizing epitopes on MHC-II via its TCR and CD4.

html5 version of animation for iPad showing a naive T4-lymphocyte recognizing epitopes on MHC-II via its TCR and CD4.

For More Information: MHC Molecules from Unit 6

For More Information: Antigen-presenting cells from Unit 6

For More Information: T4-Lymphocytes from Unit 6

c. Naive T8-lymphocytes recognizing peptide epitopes

Naive T8-lymphocytes circulate in the blood. In response to chemokines produced by lymphoid tissues, they leave the vascular endothelium in regions called high endothelial venules and enter lymph nodes or other secondary lymphoid tissues, a process called diapedesis.

Naive T8-lymphocytes have T-cell receptors (TCRs) that, in cooperation with CD8 molecules, bind to MHC-I molecules with attached epitope from an antigen found on the surface of antigen-presenting dendritic cells (see

Figure 10.3.5.9). Each T8-lymphocyte is genetically programmed to make a unique TCR. The TCR recognizes the peptide while the CD8 molecule recognizes the MHC-I molecule.

Flash animation of a naive T8-lymphocyte recognizing epitopes on MHC-I via its TCR and CD8.

html5 version of animation for iPad showing a naive T8-lymphocyte recognizing epitopes on MHC-I via its TCR and CD8.

For More Information: MHC Molecules from Unit 6

For More Information: Antigen-presenting cells from Unit 6

For More Information: T8-Lymphocytes from Unit 6

d. Naive B-lymphocytes recognizing epitopes of antigens

Most proteins are T-dependent antigens. In order for naive B-lymphocytes to proliferate, differentiate and mount an antibody response against T-dependent antigens, these B-lymphocytes must interact with effector T4-lymphocytes. All classes or isotypes of antibody molecules can be made against T-dependent antigens and there is usually a memory response against such antigens.

Naive B-Lymphocytes encounter antigens in secondary lymphoid organs such as the lymph nodes and the spleen. Using a lymph node as an example, soluble antigens, such as microbial polysaccharides and proteins and toxins, as well as **microbes such as bacteria and viruses**, **enter the lymph node** through afferent lymphatic vessels. By this time, complement pathway activation has coated these soluble antigens or microbes with opsonins such as C3b, which in turn can be degraded to C3d.

Located within the lymphoid tissues are specialized macrophages and specialized dendritic cells called follicular dendritic cells (FDCs). These macrophages have poor endocytic ability and produce few lysosomes. The FDCs are nonphagocytic. Both cell types, however, have complement receptors called CR1 and CR2 that bind to the C3b and C3d, enabling the antigens and microbes to stick to the surface of the macrophages and FDCs. However,because of the poor endocytic ability of the macrophages and the lack of endocytosis by the FDCs, the antigens and microbes are not engulfed but rather remain on the surface of the cells. In addition, the macrophages can transfer their bound antigens or microbes to FDCs (see Figure 10.3.5.10). Here the antigens and microbes in the lymph node can bind to complementary-shaped BCRs on naive B-lymphocytes **directly, by way of macrophages, or via the FDCs** (see Figure 10.3.5.10).

Flash animation of the binding of peptide epitopes to MHC-II molecules by a B-lymphocyte.

Flash animation of an effector T4-lymphocyte recognizing epitopes bound to MHC-II molecules on a B-lymphocyte.

html5 version of animation for iPad showing the binding of peptide epitopes to MHC-II molecules by a B-lymphocyte.

html5 version of animation for iPad showing an effector T4-lymphocyte recognizing epitopes bound to MHC-II molecules on a B-lymphocyte.

For More Information: B-Lymphocytes from Unit 6

For More Information: Antigen-presenting cells from Unit 6

A few antigens are called T-independent antigens. T-independent (TI) antigens are usually large carbohydrate and lipid molecules with multiple, repeating subunits. B-lymphocytes mount an antibody response to T-independent antigens without the requirement of interaction with effector T4-lymphocytes. Bacterial lipopolysaccharide (LPS) from the Gram-negative cell wall and capsular polysaccharides are examples of TI antigens. The resulting antibody molecules are generally of the IgM isotype and do not give rise to a memory response. There are two basic types of T-independent antigens: TI-1 and TI-2.

1. TI-1 antigens are pathogen-associated molecular patterns or PAMPS such as lipopolysaccharide (LPS) from the outer membrane of the Gram-negative cell wall and bacterial nucleic acid. These antigens activate B-lymphocytes by binding to their specific pattern-recognition receptors, in this case toll-like receptors, rather than to B-cell receptors (see Figure 10.3.5.11). Antibody molecules generated against TI-1 antigens are often called "natural antibodies" because they are always being made against bacteria present in the body.

For More Information: Pathogen-Associated Molecular Patterns from Unit 5

For More Information: Pattern-Recognition Receptors from Unit 5

2. TI-2 antigens, such as capsular polysaccharides, are molecules with multiple, repeating subunits. These repeating subunits activate B-lymphocytes by simultaneously cross-linking a number of B-cell receptors (see Figure 10.3.5.12).

Those naive B-lymphocytes not activated by epitopes of antigens exit the lymph node or other lymphoid tissue and eventually re-enter the bloodstream.

3. After the naive B-lymphocytes, T4-lymphocytes, and T8-lymphocytes bind their corresponding epitopes, they must proliferate into large clones of identical cells in order to mount a successful immune response against that antigen. This is known as clonal expansion.

Fundamental Statements for this Step:

1. With the exception of T-independent antigens, naive B-lymphocytes must be stimulated to proliferate by means of cytokines called interleukins produced primarily by effector T4- lymphocytes such as T_{FH} cells.
2. In the case of T4-lymphocytes and T8-lymphocytes, dendritic cells produces cytokines that contribute to proliferation of the activated T-lymphocytes. CD28-dependent co-stimulation of the T4-lymphocyte also stimulates it to synthesize the cytokine interleukin-2 (IL-2) as well as a high-affinity IL-2 receptor. The binding of IL-2 to its high affinity receptor allows for cell proliferation and formation of a clone of thousands of identical T-lymphocytes after several days.

With the exception of T-independent antigens, the naive B-lymphocytes that were activated in step 2 must be stimulated to proliferate by means of cytokines called interleukins (such as IL-2, IL-4, IL-5, Il-6, and IL-10) produced primarily by effector T4- lymphocytes such as T_{FH} cells (see Figure 10.3.5.13).

For More Information: T4-Lymphocytes from Unit 6

Flash animation of an effectorT4-lymphocyte interacting with an activated B-lymphocyte.

html5 version of animation for iPad showing an effectorT4-lymphocyte interacting with an activated B-lymphocyte.

In the case of T4-lymphocytes and T8-lymphocytes, dendritic cells produces cytokines such as interleukin-6 (IL-6), IL-4, IL-12, and T-cell growth factor-beta (TGF-ß) that contribute to proliferation of the activated T-lymphocytes. CD28-dependent co-stimulation of the T4-lymphocyte also stimulates it to synthesize the cytokine interleukin-2 (IL-

2) as well as a high-affinity IL-2 receptor. The binding of IL-2 to its high affinity receptor allows for cell proliferation and formation of a clone of thousands of identical T-lymphocytes after several days.

It is thought that in most immune responses, only around 1/1000 to 1/10,000 lymphocytes will have a receptor capable of binding the initiating antigen. Thus, proliferation allows the production of clones of thousands of identical lymphocytes having specificity for the original antigen. This is essential to give enough cells to mount a successful immune response against that antigen.

GIF Animation showing proliferation of a B-lymphocyte.

GIF Animation showing proliferation of a T4-lymphocyte.

GIF Animation showing proliferation of a T8-lymphocyte.

4. The large clones of identical B-lymphocytes, T4-lymphocytes, and T8-lymphocytes now differentiate into effector cells capable of directing body defenses against the original antigen resulting in its destruction or neutralization.

Fundamental Statements for this Step:

1. Cytokines produced by dendritic cells and T4-effector lymphocytes enable the clones of B-lymphocytes and T-lymphocytes above to differentiate into effector cells.
2. In the case of humoral immunity, B-lymphocytes differentiate into effector cells called plasma cells. These cells synthesize and secrete vast quantities of antibodies capable of reacting with and eliminating or neutralizing the original antigen.
3. T4-lymphocytes differentiate into T4-effector lymphocytes. Functionally, there are many different types or subpopulations of effector T4-lymphocytes based on the cytokines they produce. Examples include T_H1 cells, T_H2 cells, T_H17 cells, T_{reg} cells, and T_{FH} cells.
4. In the case of cell-mediated immunity, the T8-lymphocytes differentiate into cytotoxic T-lymphocytes (CTLs) capable of destroying body cells having the original epitope on their surface, such as viral infected cells, bacterial infected cells, and tumor cells by inducing apoptosis.
5. Antibodies, cytokines, activated macrophages, and cytotoxic T-lymphocytes eventually destroy or remove the antigen.

Cytokines produced by dendritic cells and T4-effector lymphocytes enable the clones of B-lymphocytes and T-lymphocytes from step 3 above to differentiate into effector cells.

a. In the case of humoral immunity, B-lymphocytes differentiate into effector cells calledplasma cells. These cells synthesize and secrete vast quantities of antibodies capable of reacting with and eliminating or neutralizing the original antigen (see Figure 10.3.5.14).

GIF Animation showing proliferation of a B-lymphocyte
and its differentiation into an effector cell.

For More Information: B-Lymphocytes from Unit 6

b. T4-lymphocytes differentiate into T4-effector lymphocytes. Functionally, there are many different types or subpopulations of effector T4-lymphocytes based on the cytokines they produce. Immune reactions are typically dominated by five primary types: T_H1 cells, T_H2 cells, T_H17 cells, T_{reg} cells, and T_{FH} cells.

1. CD4 T_H1 cells: Coordinate immunity against intracellular bacteria and promote opsonization. They:

- Produce cytokines such as interferon-gamma (IFN-?) that promote cell-mediated immunity against intracellular pathogens, especially by activating macrophages that have either ingested pathogens or have become infected with intracellular microbes such as *Mycobacterium tuberculosis,*

Mycobacterium leprae, Leishmania donovani, and *Pneumocystis jiroveci* that are able to grow in the endocytic vesicles of macrophages. Activation of the macrophage by T_H1 cells greatly enhances their antimicrobial effectiveness.

- They produce cytokines that promote the production of opsonizing antibodies that enhance phagocytosis (see Figure 10.3.5.15).
- Produce receptors that bind to and kill chronically infected cells, releasing the bacteria that were growing within the cell so the can be engulfed and killed by macrophages.
- Produce the cytokine interleukin-2 (IL-2) that induces T-lymphocyte proliferation.
- Produce cytokines such as tumor necrosis factor-alpha (TNF-a) that promote diapedesis of macrophages.
- Produces the chemokine CXCL2 to attract macrophages to the infection site.
- Produce cytokines that block the production of T_H2 cells.

2. CD4 T_H2 cells: Coordinate immunity against helminths and microbes that colonize mucous membranes

- Produce the cytokine interleukin-4 (IL-4) that promotes the production of the antibody isotype IgE in response to helminths and allergens. IgE is able to stick eosinophils to helminths for extracellular killing of the helminth (see Figure 10.3.5.16); it also promotes many allergic reactions.
- Produce cytokines that attract and activate eosinophils and mast cells.
- Promote the production of antibodies that neutralize microbes (see Figure 10.3.5.17) and toxins (see Figure 10.3.5.18) preventing their attachment to host cells.
- Produce cytokines that function as B-lymphocyte growth factors such as IL-4, IL-5, IL-9. and IL-13 (see Figure 10.3.5.13).
- Produce interleukin-22 (IL-22) that promotes the removal of microbes in mucosal tissues.
- Produce cytokines that block the production of T_H1 cells.

3. CD4 T_H17 cells: Promote a local inflammatory response to stimulate a strong neutrophil response and promote the integrity of the skin and mucous membranes

- Produce cytokines like interleukin-17 (IL-17) and interleukin-6 (IL-6) that trigger local epithelial cells and fibroblasts to produce chemokines that recruit neutrophils to remove extracellular pathogens.

4. CD4 T_{reg} cells: Suppress immune responses

- Produce inhibitory cytokines such as Interleukin-10 (IL-10) and TGF-ß that help to limit immune responses and prevent autoimmunity by suppressing T-lymphocyte activity.
- Promoting anamnestic response (immunologic memory) to resist repeat infections by the same microbe.
- Protecting beneficial normal flora in the intestines from being destroyed by the immune system.
- Aiding in sustaining pregnancy so that the immune system doesn't recognize a fetus as foreign and try to destroy it.
- Controlling established inflammation in tissues.

5. T_{FH} cells: Promote humoral immunity by stimulating antibody production and antibody isotype switching by B-lymphocytes

- T follicular helper cells (T_{FH} cells) are located in lymphoid follicles.
- T_{FH} cells are now thought to be the primary effector T-lymphocytes that stimulate antibody production and isotype switching by B-lymphocytes. They are able to produce cytokines that are characteristic of both T_H2 cells and T_H1 cells.

- T_{FH} cells producing (IFN-?) promote the production of opsonizing antibodies; those producing IL-4 promote the production of IgE.

c. In the case of cell-mediated immunity , the T8-lymphocytes differentiate into cytotoxic T-lymphocytes (CTLs) capable of destroying body cells having the original epitope on their surface, such as viral infected cells, bacterial infected cells, and tumor cells. They do this by inducing apoptosis, a programmed cell suicide (see Figure 10.3.5.19 and Figure 10.3.5.20). T-lymphocytes also secrete various cytokines that participate in various aspects of adoptive and innate immunity.

GIF Animation showing proliferation of a T8-lymphocyte and its differentiation into an effector cell.

Flash animation of a CTL triggering apoptosis by way of perforins and granzymes.

html5 version of animation for iPad showing a CTL triggering apoptosis by way of perforins and granzymes.

Flash animation of CTL-induced apoptosis of a virus-infected cell.

html5 version of animation for iPad showing CTL-induced apoptosis of a virus-infected cell.

For More Information: T8-Lymphocytes from Unit 6

For More Information: Cytotoxic T-Lymphocytes from Unit 6

Progeny of the original lymphocytes leave the secondary lymphoid organs and migrate to tissues where they continue to respond to the invading antigen.

Antibodies, cytokines, activated macrophages, and cytotoxic T-lymphocytes eventually destroy or remove the antigen. Antibodies and cytokines amplify defense functions and collaborate with cells of the innate immune system, such as phagocytes and NK cells, as well as with molecules of the innate immune system, such as those of the complement system and the acute phase response. Cytotoxic T-lymphocytes (CTLs) destroy body cells having the original epitope on their surface, e.g., viral infected cells, bacterial infected cells, and tumor cells. Cytokines also amplify innate immune defenses such as inflammation, fever, and the acute phase response.

5. Some of the B-lymphocytes, T4-lymphocytes, and T8-lymphocytes differentiate into long-lived, circulating memory cells.

Fundamental Statements for this Step:

1. During the proliferation and differentiation that follows lymphocyte activation, some of the B-lymphocytes and T-lymphocytes stop replicating and become circulating, long-lived memory cells.
2. Memory cells are capable of what is called anamnestic response or "memory", that is, they "remember" the original antigen. If that same antigen again enters the body while the memory cells are still present, these memory cells will initiate a rapid, heightened secondary response against that antigen.

During the proliferation and differentiation that follows lymphocyte activation, some of the B-lymphocytes and T-lymphocytes stop replicating and become circulating, long-lived memory cells. Memory cells are capable of what is called *anamnestic response* or "memory", that is, they "remember" the original antigen. If that same antigen

again enters the body while the memory cells are still present, these memory cells will initiate a rapid, heightened secondary response against that antigen (see Figure 10.3.5.14 and Figure 10.3.5.21).

This is why the body sometimes develops a permanent immunity after an infectious disease and is also the principle behind immunization.

Concept Map for The General Steps in Adaptive Immunity

.

Immune Regulation

The immune responses are carefully regulated by a variety of mechanisms. They are turned on only in response to an antigen and are turned off once the antigen has been removed.

Fundamental Statements for this Process:

1. *The immune responses are carefully regulated by a variety of mechanisms. They are turned on only in response to an antigen and are turned off once the antigen has been removed.*
2. *The immune responses are also able to discriminate between self and non-self in order to prevent autoimmune tissue damage.*
3. *During the random gene-splicing reactions mentioned earlier, some lymphocytes are bound to produce receptors that fit the body's own proteins and polysaccharides. The body develops immunologic tolerance to these self antigens by triggering apoptosis in self-reactive lymphocytes.*
4. *Alternately, immature B-lymphocytes with self-reactive B-cell receptors may be stimulated to undergo a new gene rearrangement to make a new receptor that is no longer self-reactive. This process is called receptor editing.*
5. *Some autoreactive T-lymphocytes are able to slip through the system but a group of T4-effector lymphocytes called T_{reg} cells are able to suppress their action.*
6. *If there is a breakdown in this normal elimination or suppression of self-reacting cells, autoimmune diseases may develop.*

The immune responses are also able to discriminate between self and non-self in order to prevent autoimmune tissue damage. During the random gene-splicing reactions mentioned earlier, some lymphocytes are bound to produce receptors that fit the body's own proteins and polysaccharides. Through mechanisms that are not fully understood, the body develops immunologic tolerance to these self antigens. In other words, the immune system becomes tolerant of the body's own molecules.

During lymphocyte development, the body eliminates self-reactive lymphocytes. Self-reactive B-lymphocytes undergo negative selection. Since the bone marrow, where the B-lymphocytes are produced and mature, is normally free of foreign substances, any B-lymphocytes that bind substances there must be recognizing "self" and are eliminated by apoptosis, a programmed cell suicide. Apoptosis results in the activation of proteases within the target cell which then degrade the cell's structural proteins and DNA. Alternately, immature B-lymphocytes with self-reactive B-cell receptors may be stimulated to undergo a new gene rearrangement to make a new receptor that is no longer self-reactive. This process is called receptor editing.

This negative selection also occurs in secondary lymphoid organs whenever a T-dependent B-lymphocyte binds to an antigen but is then unable to react with its specific T-4 lymphocyte because the T4-lymphocyte does not recognize that antigen as foreign.

Self-reactive T-lymphocytes undergo both negative selection and positive selection. Positive selection occurs in the thymus and eliminates T-lymphocytes that cannot recognize MHC molecules. Because T4-lymphocytes and T8-lymphocytes can only recognize peptide epitopes bound to MHC molecules, any T-lymphocytes that cannot recognize

MHC molecules fail this positive selection, do not develop any further, and are eventually eliminated. Then, each T-lymphocyte that passes positive selection by being able to recognize a MHC molecule must undergo negative selection. Any T-lymphocytes recognizing "self" peptides bound to MHC molecules are eliminated by apoptosis. Like with B-lymphocytes, this negative selection also occurs in secondary lymphoid organs whenever a T-lymphocyte binds to a peptide on a MHC molecule but is then unable to react with its specific T-4 lymphocyte because the T4-lymphocyte does not recognize that peptide as foreign.

Some autoreactive T-lymphocytes are able to slip through the system but a group of T4-effector lymphocytes called T_{reg} cells are able to suppress their action. If there is a breakdown in this normal elimination or suppression of self-reacting cells, autoimmune diseases may develop.

We will now look at the various events discussed above in greater detail as they apply to both humoral immunity and cell-mediated immunity with special emphasis on infectious diseases. Keep in mind that some infectious agents live outside human cells (e.g., most bacteria), a few live inside the phagosomes and lysosomes of human cells through which they enter (e.g., *Mycobacterium tuberculosis, Mycobacterium leprae*), and others live in the fluid interior of human cells (e.g., viruses, Rickettsias, and Chlamydias). Through a combination of humoral immunity and cell-mediated immunity, all types of infectious agents, as well as many types of tumor cells, may be eliminated from the body.

This page titled 10.3.5: An Overview of the Steps Involved in Adaptive Immune Responses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **12.5: An Overview of the Steps Involved in Adaptive Immune Responses** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

10.3.E: Introduction to Adaptive Immunity (Exercises)

These are homework exercises to accompany Kaiser's "Microbiology" TextMap. Microbiology is the study of microorganisms, which are defined as any microscopic organism that comprises either a single cell (unicellular), cell clusters or no cell at all (acellular). This includes eukaryotes, such as fungi and protists, and prokaryotes. Viruses and prions, though not strictly classed as living organisms, are also studied.

12.1: An Overview of Innate and Adaptive Immunity

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Describe what is meant by the following:
    a. innate immunity
    b. adaptive (acquired) immunity
2. Define the following:
    a. antigen
    b. immunogen
    c. epitope
    d. humoral immunity
    e. cell-mediated immunity

12.2: Antigens and Epitopes

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Match the following:

    _____ Asubstance that reacts with antibody molecules and antigen receptors on lymphocytes.

    _____ An antigen that is recognized by the body as non-self and stimulates an adaptive immune response.

    _____ The actual portions or fragments of an antigen that react with receptors on B-lymphocytes and T-lymphocytes as well as with free antibody molecules.

    _____ An antibody molecule composed of 4 glycoprotein chains whose Fc portion is anchored to the membrane of certain lymphocytes; able to recognize epitopes on protein and polysaccharide antigens.

    _____ A molecule composed of 2 glycoprotein chains anchored to the membrane of certain lymphocytes; able to recognize peptide epitopes from protein antigens presented by the body's own cells by way of MHC molecules.

    _____ Antigens are proteins found within the cytosol of human cells such as viral proteins, proteins from intracellular bacteria, and tumor antigens.

    _____ An organism’s own antigens (self-antigens) that stimulate an autoimmune reaction.

    _____ Antigens that enter from outside the body, such as bacteria, fungi, protozoa, and free viruses.

    a. B-cell receptor
    b. T-cell receptor
    c. immunogen
    d. hapten
    e. epitope
    f. antigen
    g. autoantigens

h. endogenous antigens
i. exogenous antigens.

2. Briefly describe how the body recognizes an antigen as foreign.
3. In terms of infectious diseases, describe 2 categories of microbial materials that may act as an antigen.
   a.
   b.
4. Describe 3 groups of noninfectious materials that may act as an antigen.
   a.
   b.
   c.

12.3: Major Cells and Key Cell Surface Molecules Involved in Adaptive Immune Responses

12.3A: Major Histocompatibility Complex (MHC) Molecules

12.3B: Antigen-Presenting Cells (APCs)

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Match the following in terms of antigen-presenting dendritic cells presenting antigens to naive T4-lymphocytes:

   _____ Dendritic cells engulf _____ antigens.

   _____ Once engulfed by dendritic cells, protein antigens are degraded into peptides by organelles called _____.

   _____ Dendritic cells bind peptides to grooves in _____.

   _____ The dendritic cell then presents the MHC/peptide complex to the _____.

   _____ Dendritic cells produce co-stimulatory signals after pathogen-associated molecular patterns bind to _____.

   a. TCR of T4-lymphocytes
   b. TCR of T8-lymphocytes
   c. MHC-I molecules
   d. MHC-II molecules
   e. exogenous
   f. endogenous
   g. toll-like receptors
   h. lysosomes
   i. proteasomes
   j. cytosol

2. Match the following in terms of ntigen-presenting dendritic cells presenting antigens to naive T8-lymphocytes:

   _____ Dendritic cells engulf _____ antigens.

   _____ Once engulfed by dendritic cells, protein antigens are degraded into peptides by organelles called _____.

   _____ Some proteins escape from phagosomes and phagolysosomes into the _____.

   _____ Once in the cytosol, protein antigens are degraded into peptides by organelles called _____.

   _____ Dendritic cells then bind peptides to grooves in _____.

   _____ The Dendritic cell then presents the MHC/peptide complex to the _____.

a. TCR of T4-lymphocytes
b. TCR of T8-lymphocytes
c. MHC-I molecules
d. MHC-II molecules
e. exogenous
f. endogenous
g. toll-like receptors
h. lysosomes
i. proteasomes
j. cytosol

3. Name the primary type of cell that functions as an antigen-presenting cell to naive T4-lymphocytes and naive T8-lymphocytes.
4. State the role of T4-effector cells in activating macrophages .
5. State the role of T4-effector cells in the proliferation and differentiation of activated B-lymphocytes.

12.3C: T4-Lymphocytes (T4-Cells)

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Match the following in terms of activation and function of T4-lymphocytes:

_____ Epitopes of antigens are recognized by T4-lymphocytes by way of their _____.

_____ The TCR/CD4 molecules of T4-lymphocytes recognize _____ on antigen-presenting cells (APCs) such as dendritic cells, macrophages, and B-lymphocytes.

a. peptides from exogenous antigens bound to MHC-II molecules
b. peptides from endogenous antigens bound to MHC-I molecules
c. MHC-I molecules
d. toll-like receptors
e. B-cell receptors
f. T-cell receptors
g. plasma cells
h. lysosomes
i. proteasomes

2. Matching

_____ Promote cell-mediated immunity against intracellular pathogens; enhance the killing ability of macrophages, promote diapedesis and chemotaxis of macrophages, and promote the production of opsonizing antibodies.

_____ Help to limit immune responses and prevent autoimmunity by suppressing T-lymphocyte activies, promote immune memory, help to sustain pregnancy, and control established inflammation.

_____ Promote a local inflammatory response to stimulate a strong neutrophil response and promote the integrity of the skin and mucous membranes.

_____ Promote the production of the antibody isotype IgE in response to helminthsand allergens, attract and activate eosinophils and mast cells, promote the production of antibodies that neutralize microbesand toxins, and promote the removal of microbes in mucosal tissues.

A. CD4 T_H2 cells
B. CD4 T_H1 cells

C. CD4 T_{reg} cells
D. CD4 T_H17 cells
E. CD4 T_{FH} cells

12.3D: T8-Lymphocytes (T8-Cells)

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Match the following in terms of activation and function of T8-lymphocytes:

_____ Epitopes of antigens are recognized by T8-lymphocytes by way of their _____.

_____ The TCR/CD8 molecules of naive T8-lymphocytes recognize _____ on antigen-presenting dendritic cells.

_____ After activation, T8-lymphocytes proliferate and differentiate into _____

a. peptides from exogenous antigens bound to MHC-II molecules
b. peptides from endogenous antigens bound to MHC-I molecules
c. MHC-I molecules
d. toll-like receptors
e. B-cell receptors
f. T-cell receptors
g. plasma cells
h. cytotoxic T-lymphocytes (CTLs)
i. natural killer cells (NK cells)

2. State the overall function of activated T8-lymphocytes in adaptive immunity.

12.3E: Invarient Natural Killer T-Lymphocytes (iNKT Cells)

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Epitopes of glycolipid antigens are recognized by iNKT lymphocytes by way of their _____.
2. The TCR molecules of iNKT lymphocytes recognize _____ on antigen-presenting dendritic cells.
3. iNKT lymphocytes can also be activated by the cytokine _____ produced by activated dendritic cells.
4. iNKT cells promote both innate and adaptive immunity and may also regulate immune responses by way of the _____ they produce once activated.

12.3F: B-Lymphocytes (B-Cells)

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Match the following in terms of activation of B-lymphocytes by T-dependent antigens:

_____ Epitopes of antigens are recognized by B-lymphocytes by way of their _____.

_____ Once engulfed by APCs, protein antigens are degraded into peptides by organelles called _____.

_____ B-lymphocytes bind peptides to grooves in _____.

_____ The B-lymphocyte then presents the MHC/peptide complex to the _____.

_____ B-lymphocytes eventually differentiate into antibody-secreting cells called _____.

a. TCR of T4-lymphocytes
b. TCR of T8-lymphocytes
c. MHC-I molecules
d. MHC-II molecules
e. B-cell receptors
f. CD4 molecules
g. plasma cells
h. lysosomes
i. proteasomes

2. State the overall function of B-lymphocytes in adaptive immunity.

12.3G: Natural Killer Cells (NK Cells)

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Briefly describe how NK cells bind to and kill infected cells and tumor cells through ADCC.
2. Briefly describe how NK cells recognize and kill infected cells and tumor cells that suppress MHC-I production.

12.3A: Major Histocompatibility Complex (MHC) Molecules

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Match the following:

_____ Produced by all nucleated cells in the body.

_____ Produced primarily by antigen-presenting cells such as macrophages, dendritic cells, and B-lymphocytes.

_____ Primarily bind peptides from exogenous antigens.

_____ Primarily bind peptides from endogenous antigens.

_____ Recognize peptides bound to MHC-II molecules.

_____ Recognize peptides bound to MHC-I molecules.

a. TCR of T4-lymphocytes
b. TCR of T8-lymphocytes
c. MHC-I molecules
d. MHC-II molecules

2. State the role of proteasomes in binding of peptides from endogenous antigens by MHC-I molecules.
3. State the role of lysosomes in binding of peptides from exogenous antigens by MHC-II molecules.
4. Multiple Choice

12.3B: Antigen-Presenting Cells (APCs)

12.3C: T4-Lymphocytes (T4-Cells)

12.3D: T8-Lymphocytes (T8-Cells)

12.3E: Invarient Natural Killer T-Lymphocytes (iNKT Cells)

12.3F: B-Lymphocytes (B-Cells)

12.3G: Natural Killer Cells (NK Cells)

12.4: The Lymphoid System

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Match the following with the BEST answer:

   _____ Contain antigen-presenting cells, such as macrophages and dendritic cells, and ever changing populations ofB-lymphocytes and T- lymphocytes. Examples include the tonsils, the appendix, Peyer's patches, MALT, SALT, lymph nodes, and the spleen.

   _____ Produce B-lymphocytes and T-lymphocytes. The bone marrow and the thymus.

   _____ The fluid surrounding cells in the body.

   _____ The liquid portion of the blood.

   _____ A diffuse system of small concentrations of lymphoid tissue found in various sites of the body such as the gastrointestinal tract, respiratory tract, eye, and skin. It is populated by loose clusters of T-lymphocytes, B-lymphocytes, plasma cells, activated T_H cells, and macrophages.

   _____ The liquid found in lymph vessels.

   _____ Expose antigens found in the lymph to dendritic cells, B-lymphocytes, and T-lymphocytes.

   _____ Expose antigens found in the blood to dendritic cells, B-lymphocytes, and T-lymphocytes.

   a. plasma
   b. lymph
   c. tissue fluid
   d. primary lymphoid organs
   e. secondary lymphoid organs
   f. the spleen
   g. lymph nodes
   h. MALT

2. Briefly describe the importance of the lymphoid system in adaptive immune responses.

12.5: An Overview of the Steps Involved in Adaptive Immune Responses

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. State where antigens may encounter APCs, B-lymphocytes, and T-lymphocytes if they enter the following:
   a. the blood
   b. tissues
   c. the respiratory tract
   d. the gastrointestinal tract
   e. the genitourinary tract
2. Match the following:

   _____ Use lysosomes to degrade exogenous antigens into peptides, bind them to MHC-II molecules, and present them to naive T4-lymphocytes.

_____ Uses BCR to recognize epitopes of antigens; a few antigens are recognized by toll-like receptors.

_____ Uses TCR and CD4 to recognize peptide epitopes from exogenous antigens bound to MHC-II molecules of antigen-presenting dendritic cells, macrophages, and B-lymphocytes.

_____ Uses TCR and CD8 to recognize peptide epitopes from endogenous antigens bound to MHC-I molecules of cells.

_____ Cells that allow for a heightened secondary response upon subsequent exposure to the same antigen.

_____ Once activated itself, secretes cytokines that enable activated B-lymphocytes and T-lymphocytes to proliferate and differentiate.

_____ Use proteasomes to degrade endogenous antigens into peptides, bind them to MHC-I molecules, and present them to naive T8-lymphocytes.

_____ Differentiate into antibody secreting plasma cells.

_____ Differentiate into cytotoxic T-lymphocytes (CTLs).

a. T4-lymphocytes
b. T8-lymphocytes
c. dendritic cells
d. B-lymphocytes
e. memory cells

3. State the overall function of T4-effector lymphocytes and the importance behind rapid proliferation of activated lymphocytes.
4. The ability of the body to initiate and direct adaptive immune responses against antigenic molecules foreign to the body but not against antigenic molecules that are a normal component of the body is called _____.

This page titled 10.3.E: Introduction to Adaptive Immunity (Exercises) is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **12.E: Introduction to Adaptive Immunity (Exercises)** has no license indicated.

SECTION OVERVIEW

10.4: Humoral Immunity

Humoral Immunity refers to the production of antibody molecules in response to an antigen. These antibody molecules circulate in the plasma of the blood and enter tissue and organs via the inflammatory response. Humoral immunity is most effective microbes or their toxins located in the extracellular spaces of the body. Antibodies or immunoglobulins are specific glycoprotein configurations produced by B-lymphocytes and plasma cells in response to a specific antigen and capable of reacting with that antigen.

10.4.1: Antibodies (Immunoglobulins)

- 10.4.1B: Antibody Structure
- 10.4.1C: The 5 Classes (Isotypes) of Human Antibodies
- 10.4.1D: Generation of Antibody Diversity
- 10.4.1E: Clonal Selection and Clonal Expansion
- 10.4.1F: Anamnestic (Memory) Response

10.4.2: Ways That Antibodies Help to Defend the Body

- 10.4.2A: Opsonization
- 10.4.2B: Cytolysis by the Membrane Attack Complex (MAC)
- 10.4.2C: Antibody-dependent Cellular Cytotoxicity (ADCC) by Natural Killer Cells
- 10.4.2D: Neutralization of Exotoxins
- 10.4.2E: Neutralization of Viruses
- 10.4.2F: Preventing Bacterial Adherence
- 10.4.2G: Agglutination of Microorganisms
- 10.4.2H: Immobilization of Bacteria and Protozoans
- 10.4.2I: Promoting an Inflammatory Response

10.4.3: Naturally and Artificially Acquired Active and Passive Immunity

- 10.4.3A: Naturally Acquired Immunity
- 10.4.3B: Artificially Acquired Immunity

10.4.E: Humoral Immunity (Exercises)

Template:HideTOC

This page titled 10.4: Humoral Immunity is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

This page titled 10.4: Humoral Immunity is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

10.4.1: Antibodies (Immunoglobulins)

Humoral Immunity refers to the production of antibody molecules in response to an antigen. These antibody molecules circulate in the plasma of the blood and enter tissue and organs via the inflammatory response. Humoral immunity is most effective microbes or their toxins located in the extracellular spaces of the body. Antibodies or immunoglobulins are specific glycoprotein configurations produced by B-lymphocytes and plasma cells in response to a specific antigen and capable of reacting with that antigen. In this section we will look at the structure of antibodies, the 5 classes or isotypes of human antibodies, generation of antibody diversity, clonal selection and clonal expansion, and memory (anamnestic) response.

Template:HideTOC

This page titled 10.4.1: Antibodies (Immunoglobulins) is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **13.1: Antibodies (Immunoglobulins)** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

10.4.1B: Antibody Structure

Learning Objectives

1. Describe an antibody molecule.
2. Draw the "stick figure" structure of IgG, indicating the Fab portion (variable region) and the Fc portion (constant region).
3. State the functions of the Fab and the Fc portions of an antibody.
4. State what is meant by the biological activity of an antibody.
5. Compare the structure of IgM and secretory IgA with that of IgG.

In this section we will look at the structure of antibodies. There are five classes or isotypes of human antibodies :

a. immunoglobulin G (IgG),
b. immunoglobulin M (IgM),
c. immunoglobulin A (IgA),
d. immunoglobulin D (IgD), and
e. immunoglobulin E (IgE).

The simplest antibodies, such as IgG, IgD, and IgE, are "Y"-shaped macromolecules called monomers. A monomer is composed of four glycoprotein chains: two identical heavy chains and two identical light chains. The two heavy chains have a high molecular weight that varies with the class of antibody. The light chains come in two varieties: kappa or lambda and have a lower molecular weight than the heavy chains. The four glycoprotein chains are connected to one another by disulfide (S-S) bonds and non-covalent bonds (Figure 10.4.1*B*.1).

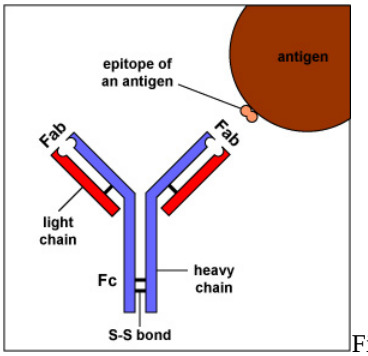


Figure 10.4.1*B*.1: IgG.The Fab portion of the antibody has specificity for binding an epitope of an antigen. The Fc portion directs the biological activity of the antibody.

Additional S-S bonds fold the individual glycoprotein chains into a number of distinct globular domains (Figure 10.4.1*B*.2). The area where the top of the "Y" joins the bottom is called the hinge. This area is flexible to enable the antibody to bind to pairs of epitopes various distances apart on an antigen.

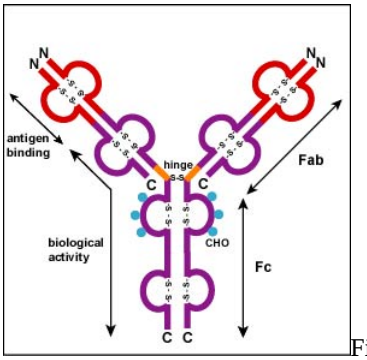


Figure 10.4.1*B*.2: Folding Domains of an Antibody. The Fab portion of the antibody, the first domain of the antibody shown in red has the complementarity-determining regions providing specificity for binding an epitope of

an antigen. The Fc portion, shown in purple directs the biological activity of the antibody. (S-S = disulfide bond; N = amino terminal of glycoprotein; C = carboxy terminal of glycoprotein; CHO = carbohydrate.)

The two tips of the "Y" monomer are referred to as the antigen-binding fragments or Fab portions of the antibody (Figures 1-3). The first 110 amino acids or first domain of both the heavy and light chain of the Fab region of the antibody provide specificity for binding an epitope on an antigen. The amino acid sequence of this first domain of both the light chain and the heavy chain shows tremendous variation from antibody to antibody and constitutes the variable region (V region). This is because each B-lymphocyte, early in its development, becomes genetically programmed through a series of gene-splicing reactions to produce a Fab with a unique 3-dimensional shape capable of fitting some epitope with a corresponding shape.

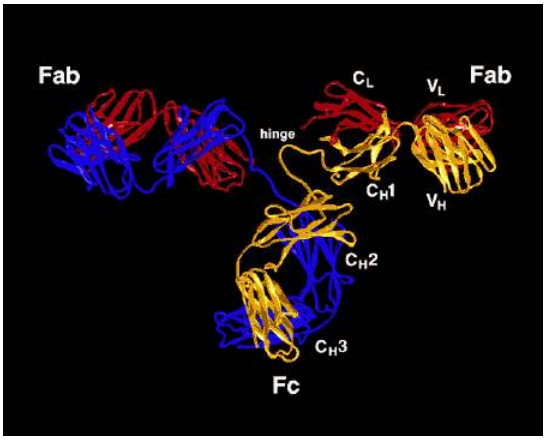


Figure **10.4.1*B*.3*:*** *Ribbon Drawing of the Antibody Molecule IgG2a, A ribbon drawing of the first intact antibody molecule ever crystallized (IgG2a). The Fab portion of the antibody has specificity for binding an epitope of an antigen. The Fc portion directs the biological activity of the antibody.*

The various genes the cell splices together determine the order of amino acids of the Fab portion of both the light and heavy chain; the amino acid sequence determines the final 3-dimensional shape (Figure **10.4.1*B*.4**). Therefore, different antibody molecules produced by different B-lymphocytes will have different orders of amino acids at the tips of the Fab to give them unique shapes for binding epitope. The antigen-binding site is large enough to hold an epitope of about 5-7 amino acids or 3-4 sugar residues. Epitopes bind to the Fab portion of the antibody by reversible, non-covalent bonds.

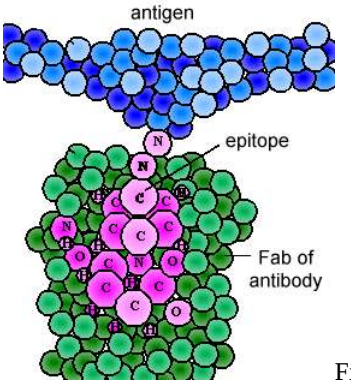


Figure **10.4.1*B*.4**: Epitope of an Antigen Binding to Fab of an Antibody

The bottom part of the "Y", the C terminal region of each glycoprotein chain, is called the Fc portion. The Fc portion, as well as one domain of both the heavy and light chain of the Fab region has a constant amino acid sequence and is referred to as the constant region (C region) of the antibody and defines the class and subclass of each antibody. The Fc portion is responsible for the biological activity of the antibody (Figures 1-3), however, the Fc portion only becomes

biologically active after the Fab component has bound to its corresponding antigen. Depending on the class and subclass of antibody, biological activities of the Fc portion of antibodies include the ability to:

- Activate the classical complement pathway (IgG & IgM); see Figure 10.4.1*B*.5.
- Activate the lectin complement pathway and the alternative complement pathway (IgA)
- Bind to receptors on phagocytes (IgG); see Figure 10.4.1*B*.6.
- Bind to receptors on mast cells, basophils, and eosinophils (IgE); see Fig 7 and Figure 10.4.1*B*.8.
- Bind to receptors on NK cells (IgG); see Figure 10.4.1*B*.9.
- Determine the tissue distribution of the antibodies, that is, to what tissues types the antibody molecules are able to go.

 Figure 10.4.1*B*.12: Rotating GIF Animation of Humanized IgG

Individual "Y"-shaped antibody molecules are called monomers and can bind to two identical epitopes. Antibodies of the classes IgG, IgD, and IgE are monomers.

Two classes of antibodies are more complex. IgM (see Figure 10.4.1*B*.10) is a pentamer, consisting of 5 "Y"-like molecules connected at their Fc portions by a "J" or joining chain. Secretory IgA (see Figure 10.4.1*B*.11) is a dimer consisting of 2 "Y"-like molecules connected at their Fc portions by a "J" chain and stabilized to resist enzymatic digestion in body secretions by means of a secretory component.

Summary

1. There are 5 classes or isotypes of human antibodies or immunoglobulins: IgG, IgM, IgA, IgD, and IgE.
2. The simplest antibodies, such as IgG, IgD, and IgE, are "Y"-shaped macromolecules called monomers and are composed of four glycoprotein chains: two identical heavy chains and two identical light chains.
3. The two tips of the "Y" monomer are referred to as the antigen-binding fragments or Fab portions of the antibody and these portions provide specificity for binding an epitope on an antigen.
4. Early in its development, each B-lymphocyte becomes genetically programmed through a series of gene-splicing reactions to produce a Fab with a unique 3-dimensional shape capable of fitting some epitope with a corresponding shape.
5. The Fc portion only becomes biologically active after the Fab component has bound to its corresponding antigen. Biological activities include activating the complement pathways, and binding to receptors on phagocytes and other defense cells to promote adaptive immunity.
6. IgM is a pentamer, consisting of 5 monomers joined at their Fc portions.
7. IgA is a dimer, consisting of 2 monomers joined at their Fc portions.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Describe an antibody molecule. *(ans)*
2. Match the following:

    _____ The region of the antibody that provide specificity for binding an epitope on an antigen. *(ans)*

    _____ The region of the antibody that is responsible for the biological activity of the antibody. *(ans)*

    _____ Composed of four glycoprotein chains. There are two identical heavy chains having a high molecular weight and two identical light chains. *(ans)*

_____ A pentamer, consisting of 5 "Y"-like molecules connected at their Fc portions by a "J" or joining chain. *(ans)*

_____ A dimer consisting of 2 "Y"-like molecules connected at their Fc portions by a "J" chain and stabilized to resist enzymatic digestion. *(ans)*

a. IgM
b. secretory IgA
c. IgG
d. Fab
e. Fc

3. Multiple Choice *(ans)*

This page titled 10.4.1B: Antibody Structure is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **13.1B: Antibody Structure** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

10.4.1C: The 5 Classes (Isotypes) of Human Antibodies

State which classes (isotypes) of human antibodies possess the following characteristics:

a. are monomers
b. is a pentamer
c. is a dimer
d. activates the classical complement pathway by its Fc portion
e. binds to macrophages and neutrophils by its Fc portion
f. binds to NK cells by its Fc portion
g. crosses the placenta
h. functions as a B-cell receptor
i. the first antibody produced during an adaptive immune response
j. binds to components of mucous by its Fc portion
k. found mainly in body secretions
l. binds to mast cells and basophils by its Fc portion and promotes inflammation, coughing, sneezing, vomiting, and allergic reactions
m. binds to eosinophils by its Fc portion and promotes the removal of parasitic worms and arthropods

- Match the antibody isotype with its description.

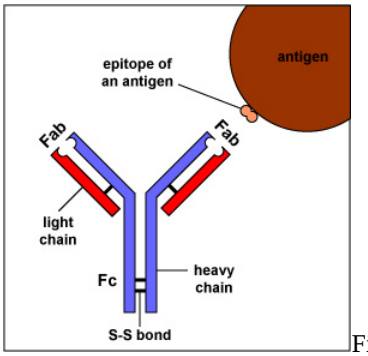


Figure 10.4.1C.13.3.3: Opsonization (Enhanced Attachment). The Fab portion of IgG binds to epitopes of an antigen. The Fc portion can now attach the antigen to Fc receptors on phagocytes for enhanced attachment. This is especially important against encapsulated microbes. C3b and C4b from the complement pathways can also attach antigens to phagocytes.

For More Information: Classical complement pathway from Unit 5

For More Information: Opsonization from Unit 6

For More Information: Antibody-dependent cellular cytotoxicity (ADCC) from Unit 6

IgM (Immunoglobulin M)

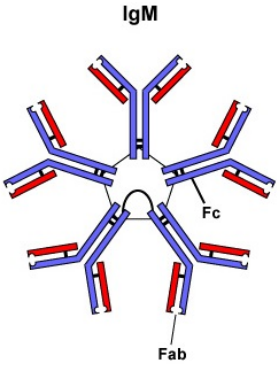


Figure 10.4.1C.13.3.6).

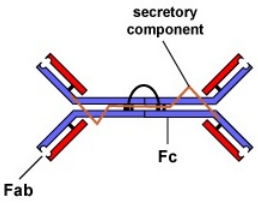


Figure 10.4.1C.13.3.6: Secretory IgA is a dimer and has 4 Fab sites. A secretory component helps protect it from digestion in body secretions.

The Fc portion of secretory IgA binds to components of mucous and contributes to the ability of mucous to trap microbes. The Fc portion of secretory IgA can bind to macrophages and neutrophils for enhanced attachment (opsonization). IgA can activate the lectin complement pathway and the alternative complement pathway.

IgD: (Immunoglobulin D)

IgD makes up approximately 0.2% of the serum antibodies. IgD is a monomer and has 2 epitope-binding sites and is found on the surface of B-lymphocytes (along with monomeric IgM) as a B-cell receptor where it may control of B-lymphocyte activation and suppression. IgD may play a role in eliminating B-lymphocytes generating self-reactive autoantibodies.

IgE (Immunoglobulin E)

IgE makes up about 0.002% of the serum antibodies with a half-life of 2 days. Most IgE is tightly bound to basophils and mast cells via its Fc region . IgE is a monomer and has 2 epitope-binding sites. IgE is made in response to parasitic worms (helminths) and arthropods. It is also often made in response to allergens(allergens are antigens causing allergic reactions). IgE may protect external mucosal surfaces by promoting inflammation, enabling IgG, complement proteins, and leukocytes to enter the tissues, as well as by triggering coughing, sneezing, and vomiting for mechanical removal of microbes and toxins. .

The Fc portion of IgE can bind to mast cells and basophils where it mediates many allergic reactions. Cross linking of cell-bound IgE by antigen triggers the release of vasodilators for an inflammatory response (Fig 7). The Fc portion of IgE made against parasitic worms and arthropods can bind to eosinophils enabling opsonization (Figure 10.4.1C.8). This is a major defense against parasitic worms and arthropods.

For More Information: IgE-mediated hypersensitivity (Type-I) from Unit 6

Each day an average adult produces approximately three grams of antibodies, about two-thirds of this IgA.

Summary

1. IgG makes up approximately 80% of the serum antibodies, is a monomer with 2 Fab sites. The Fc portion can activate the classical complement pathway, bind to macrophages and neutrophils to enable opsonization, bind to NK cells to promote ADCC, and can cross the placenta.
2. IgM makes up approximately 13% of the serum antibodies, is the first antibody produced during an immune response, is found mainly in the blood, and is a pentamer with 10 Fab sites. The Fc portion can activate the classical complement pathway. Monomeric forms of IgM are found on the surface of B-lymphocytes as B-cell receptors.
3. IgA makes up approximately 6% of the serum antibodies, is a dimer with 4 epitope-binding sites and is found mainly in body secretions as secretory IgA (sIgA) where it protects internal body surfaces exposed to the environment by blocking the

attachment of bacteria and viruses to mucous membranes.

4. The Fc portion of secretory IgA binds to components of mucous and contributes to the ability of mucous to trap microbes, and can bind to macrophages and neutrophils to enable opsonization, and can activate the lectin complement pathway and the alternative complement pathway.
5. IgD makes up approximately 0.2% of the serum antibodies, is a monomer with 2 Fab sites, is found on the surface of B-lymphocytes as a B-cell receptor, and may play a role in eliminating B-lymphocytes generating self-reactive autoantibodies.
6. IgE makes up about 0.002% of the serum antibodies, is a monomer with 2 Fab sites, and is made in response to parasitic worms (helminths) and arthropods. It is also often made in response to allergens. The Fc portion of IgE can bind to mast cells and basophils (see Figure **10.4.1*C*.8**) where it mediates many allergic reactions, and the Fc portion of IgE made against parasitic worms can bind to eosinophils enabling opsonization. IgE may also protect external mucosal surfaces by promoting inflammation.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Match the class (isotype) of human antibody with its description.
2. Multiple Choice *(ans)*

This page titled 10.4.1C: The 5 Classes (Isotypes) of Human Antibodies is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **13.1C: The 5 Classes (Isotypes) of Human Antibodies** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

10.4.1D: Generation of Antibody Diversity

Define gene translocation and relate it to each B-lymphocyte being able to produce an antibody with a unique shaped Fab.

- Define the following:
  a. combinatorial diversity
  b. junctional diversity
  c. affinity maturation

In this section we will look at generation of antibody diversity through gene translocation. As mentioned earlier, the immune system of the body has no idea as to what antigens it may eventually encounter. Therefore, it has evolved a system that possesses the capability of responding to any conceivable antigen. The immune system can do this because both B-lymphocytes and T-lymphocytes have evolved a unique system of gene-splicing called gene translocation, a type of gene-shuffling process where various different genes along a chromosome are cut out of one location and joined with other genes along the chromosome.

To demonstrate this gene translocation process, we will look at how each B-lymphocyte becomes genetically programmed to produce an antibody functioning as a B-cell receptor(BCR) having a unique shaped Fab. As mentioned above, the Fab portion of an antibody is composed of 2 protein chains: a heavy and a light (see Figure $\mathbf{10.4.1}D\mathbf{.1}$).

The variable heavy chain portion of the Fab is coded for by a combination of 3 genes, called VH (variable heavy), DH (diversity heavy), and JH (joining heavy). The variable light chain portion of the Fab consists of either a kappa chain or a lambda chain coded for by a combination of 2 genes, VL (variable light) and JL (joining light). In the DNA of each B-lymphocyte there are multiple forms of each one of these variable determinant genes. Although the exact number of each gene isn't known and varies from person, there are approximately 38-46 VH genes; 23 DH genes; 6 JH genes; 34-38 kappa VL genes; 5 kappa JL genes; 29-33 lambda VL genes; and 4-5 lambda JL genes.

While a person inherits alleles for the various V(D)J genes from each parent, an individual B-lymphocyte will only express an inherited allele set from one parent. This increases a greater diversity of antibodies in that individual.

Through random gene translocation, any combination of the multiple forms of each gene can join together (see Figure $\mathbf{10.4.1}D\mathbf{.2}$) resulting in thousands of possible gene combinations. This is known as combinatorial diversity.

Gene translocation of the V(D)J genes is initiated when an enzyme called V(D)J recombinase recognizes recombination signal sequences located at the 3' end of V genes, the 5' end of J genes, and both ends of D genes. As a result, the chromosome forms a loop allowing different genes from different regions along the chromosome to align (see Figure $\mathbf{10.4.1}D\mathbf{.3}$). In the heavy chain any J-heavy gene and any D-heavy gene align and bind together as the genes are cut from one location and pasted into another. Subsequently, any one of the V-heavy genes is attached to this DJ segment. In the light chain, chromosomal looping enables any V-light gene to attach to any J-light gene.

Flash animation showing gene translocation and combinatorial diversity.

html5 version of animation for iPad showing gene translocation and combinatorial diversity.

During gene translocation, specialized enzymes in the B-lymphocyte cause splicing inaccuracies wherein additional nucleotides are added or deleted at the various gene junctions. This change in the nucleotide base sequence generates even greater diversity in Fab shape. This is called junctional diversity.

Furthermore, as B-lymphocytes proliferate, they undergo affinity maturation, a process that "fine tunes" the shape of the Fab epitope binding site. This is because the immunoglobulin V genes of B-lymphocytes have a mutation rate

between 1000 to 10,000 times greater than other human genes in the body. This somatic hypermutation creates a great opportunity for selection of variant B-lymphocytes with even better fitting antigen-binding sites that fit the epitope more precisely. The longer and more tightly the antigen binds to the B-cell receptor, the greater the chance that B-lymphocyte has of surviving and replicating. In other words, the "fit" of the antibody can be improved over time. Affinity maturation occurs in the germinal centers of the lymph nodes.

Most likely humans produce at least 10^{11} different shaped BCRs. Keep in mind that the 3-dimensional shape of a protein is ultimately determined by the sequence of its amino acids and the sequence of amino acids is determined by the order of nitrogenous bases in the genes coding for that protein. Between combinatorial diversity, junctional diversity, and affinity maturation, there are probably billions of possible gene combinations and rearrangements that can code for the Fab portions of an antibody. Chances are, then, each B-lymphocyte will carry out a unique series of gene translocations and be able to produce an antibody with a unique shaped epitope-binding site.

Because gene translocation is a random process, some immature B-lymphocytes do wind up making B-cell receptors that fit the body's own antigens. Immature B-lymphocytes with self-reactive B-cell receptors may be stimulated to undergo a new gene rearrangement to make a new receptor that is no longer self-reactive. Recognition of self antigen can reactivate genes that allow the B-lymphocyte to carry out new light chain V-J recombinations and enabling that cell to express a new B-cell receptor. This process is called receptor editing.

Alternately, self-reactive B-lymphocytes can also undergo negative selection. Since the bone marrow, where the B-lymphocytes are produced and mature, is normally free of foreign substances, any B-lymphocytes that bind substances there must be recognizing "self" and are eliminated by apoptosis, a programmed cell suicide. Apoptosis results in the activation of proteases within the target cell which then degrade the cell's structural proteins and DNA.

Summary

1. The adaptive immune responses have evolved a system that possesses the capability of responding to any conceivable antigen the body might eventually encounter through a process called gene translocation.
2. Gene translocation is a type of gene-shuffling process where various different genes along a chromosome are cut out of one location and joined with other genes along the chromosome to create a maximum number of different B-cell and T-cell receptors.
3. Each B-lymphocyte becomes genetically programmed to produce an antibody functioning as a B-cell receptor (BCR) having a unique shaped Fab.
4. The variable portion of both the heavy and light chain of the antibody is coded for by multiple genes and there are multiple forms of each one of these variable genes.
5. Through random gene translocations, any combination of the multiple forms of each gene can join together resulting in thousands of possible gene combinations. This is known as combinatorial diversity.
6. During gene translocation, specialized enzymes in the B-lymphocyte cause splicing inaccuracies wherein additional nucleotides are added or deleted at the various gene junctions and this change in the nucleotide base sequence generates even greater diversity in Fab shape. This is called junctional diversity.
7. As B-lymphocytes proliferate, they undergo affinity maturation, a process that "fine tunes" the shape of the Fab epitope binding site through a high rate of somatic hypermutation. This creates a great opportunity for selection of variant B-lymphocytes with even better fitting antigen-binding sites that fit the epitope more precisely.
8. Immature B-lymphocytes with self-reactive B-cell receptors may be stimulated to undergo a new gene rearrangement to make a new receptor that is no longer self-reactive through a process called receptor editing. Alternately, self-reactive B-lymphocytes can also undergo negative selection whereby any B-lymphocytes that bind substances recognized as "self" and are eliminated by apoptosis.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Define gene translocation. *(ans)*
2. Relate gene translocation to each B-lymphocyte being able to produce an antibody with a unique shaped Fab. (ans)
3. Define the following:
    a. combinatorial diversity *(ans)*
    b. affinity maturation *(ans)*

This page titled 10.4.1D: Generation of Antibody Diversity is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **13.1D: Generation of Antibody Diversity** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

10.4.1E: Clonal Selection and Clonal Expansion

Learning Objectives

- Briefly describe the process of clonal selection and clonal expansion.

As mentioned above, during early differentiation of naive B-lymphocytes in the bone marrow, each B-lymphocyte becomes genetically programmed to make an antibody with a unique antigen-binding site (Fab) through a series of gene translocations, and molecules of that antibody are put on its surface to function as the B-cell receptor (Figure 10.4.1*E*.1).

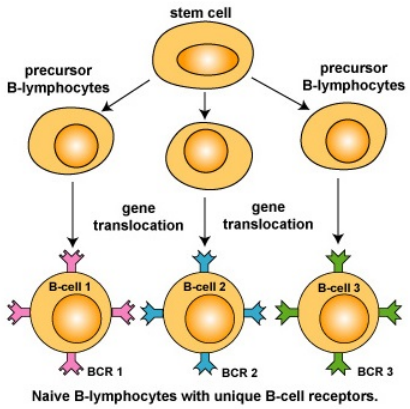


Figure 10.4.1*E*.1: Clonal Selection, Step-1. During its development, each B-lymphocyte becomes genetically programmed, through a process called gene translocation, to make a unique B-cell receptor. Molecules of that B-cell receptor are placed on its surface where it can react with epitopes of an antigen.

When an antigen encounters the immune system, its epitopes eventually will react only with B-lymphocytes with B-cell receptors on their surface that more or less fit and this activates those B-lymphocytes. This process is known as *clonal selection* (Figure 10.4.1*E*.2).

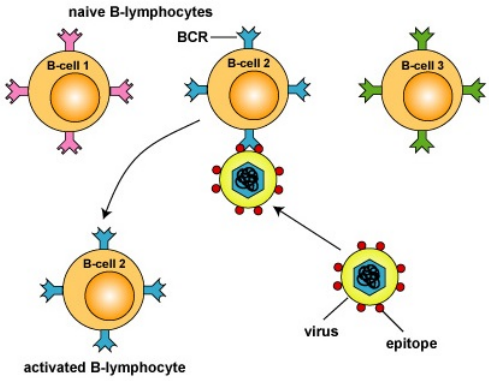


Figure 10.4.1*E*.2: Clonal Selection, Step-2. A B-lymphocyte with an appropriately fitting B-cell receptor can now react with epitopes of an antigen having a corresponding shape. This activates the B-lymphocyte.

Cytokines produced by effector T4-helper lymphocytes enable those activated B-lymphocytes to rapidly proliferate to produce large clones of thousands of identical B-lymphocytes. In this way, even though only a few B-lymphocytes in the body may have an antibody molecule able to fit a particular epitope, eventually many thousands of cells are produced with the right specificity. This is referred to as *clonal expansion* (Figure 10.4.1*E*.3).

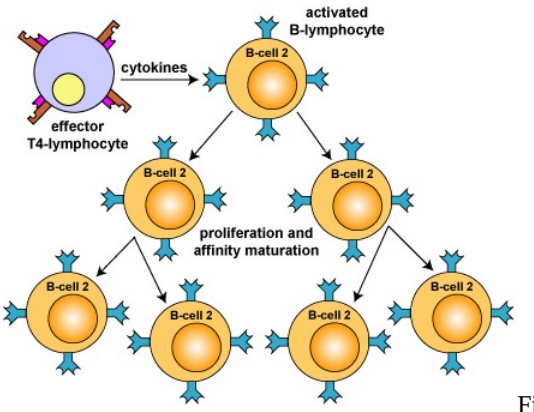


Figure **10.4.1*E*.3**: Clonal Expansion. Cytokines from an effector T4-lymphocyte now enable the activated B-lymphocyte to proliferate into a large clone of identical B-lymphocytes. During this time, "fine-tuning" of the B-cell receptor occurs through affinity maturation.

Furthermore, as the B-lymphocytes proliferate, they undergo affinity maturation as a result of somatic hypermutations. This allows the B-lymphocytes to "fine-tune" the shape of the antibody for better fit with the original epitope. B-lymphocytes having better fitting B-cell receptor on their surface bind epitope longer and more tightly allowing these cells to selectively replicate. Eventually these variant B-lymphocytes differentiate intoplasma cells that synthesize and secrete vast quantities of antibodies that have Fab sites which fit the original epitope very precisely (Figure 10.4.1*E*.4). It generally takes 4-5 days for a naive B- lymphocyte that has been activated to complete clonal expansion and differentiate into effector B-lymphocytes.

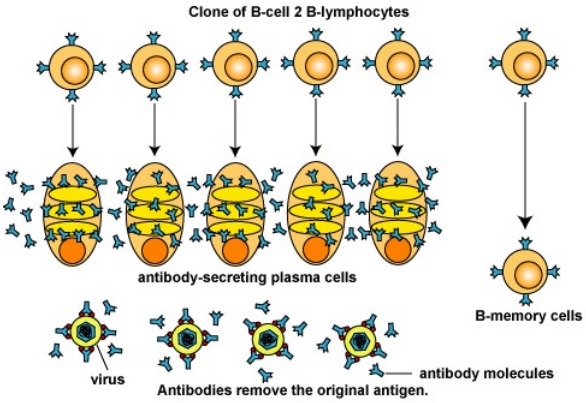
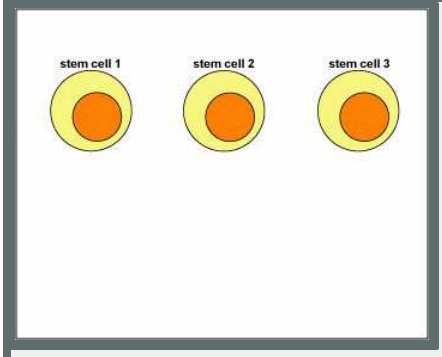


Figure **10.4.1*E*.4**: Differentiation of B-lymphocytes into Plasma Cells and B-Memory Cells. The B-lymphocytes now differentiate into antibody-secreting B-lymphocytes and plasma cells that secrete large quantities of antibodies that "fit" the original epitope. Some B-lymphocytes differentiate into B-memory cells capable of anamnestic response.

A single activated B-lymphocyte can, within seven days, give rise to approximately 4000 antibody-secreting cells. Over 2000 antibody molecules can be produced per plasma cell per second for typically up to four to five days. The B-memory cells that eventually form also have these high affinity antibodies on their surface.

Animation Overview: Clonal Selection and Clonal Expansion



During its development, each B-lymphocyte becomes genetically programmed, through a process called gene translocation, to make a unique antibody molecule that will function as a B-cell receptor. Molecules of that antibody are then placed on the cell's surface where it can react with epitopes of an antigen. A B-lymphocyte with an appropriately fitting B-cell receptor can now react with epitopes of an antigen having a corresponding shape. This activates the B-lymphocyte. Cytokines from an activated T4-lymphocyte now enable the activated B-lymphocyte to proliferate into a large clone of identical B-lymphocytes. During this time, "fine-tuning" of the B-cell receptor occurs as a result of affinity maturation. The B-lymphocytes now differentiate into antibody-secreting B-lymphocytes and plasma cells that secrete large quantities of antibodies "fitting" the original epitope. Some B-lymphocytes differentiate into B-memory cells capable of anamnestic response.

As with naive B-lymphocytes, during its development, each naive T4-lymphocyte becomes genetically programmed by gene-splicing reactions similar to those in B-lymphocytes, to produce a TCR with a unique specificity. Identical molecules of that TCR are placed on its surface where they are able to bind an epitope/MHC-II complex on an antigen-presenting dendritic cell with a corresponding shape (Figure **10.4.1*E*.5**). This is clonal selection of the T4-lymphocytes that are required for the body's response to T-dependent antigens.

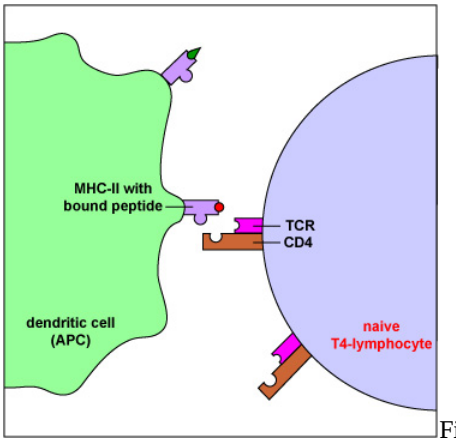


Figure **10.4.1*E*.5**: A Naive T4-Lymphocyte Recognizing Epitope/MHC-II on an Antigen-Presenting Dendritic Cell. Exogenous antigens are those from outside cells of the body. Examples include bacteria, free viruses, yeasts, protozoa, and toxins. These exogenous antigens enter antigen-presenting dendriticcells through phagocytosis. The microbes are engulfed and placed in a phagosome. After lysosomes fuse with the phagosome, protein antigens are degraded by proteases into a series of peptides. These peptides eventually bind to grooves in MHC-II milecules and are transported to the surface of the dendritic cell. Naive T4-lymphocytes are then able to recognize peptide/MHC-II complexes by means of their T-cell receptors (TCRs) and CD4 molecules.

In response to cytokines, these activated T4-lymphocytes now rapidly proliferate and differentiate into effector T4-lymphocytes. This is clonal expansion of the T4-lymphocytes. Before an antigen enters the body, the number of naive

T4-lymphocytes specific for any particular antigen is between 1 in 10^5 to 10^6 lymphocytes. After antigen exposure, the number of T4-lymphocytes specific for that antigen may increase to 1 in 100 to 1000 lymphocytes.

Summary

1. Each naïve B-cell becomes genetically programmed to make an antibody with a unique antigen-binding site (Fab) through a series of gene translocations, and molecules of that antibody are put on its surface to function as the B-cell receptor.
2. When an antigen encounters the immune system, its epitopes eventually will react only with B-lymphocytes with B-cell receptors on their surface that more or less fit and this activates those B-lymphocytes. This process is known as clonal selection.
3. Cytokines produced by activated T4-helper lymphocytes enable those activated B-lymphocytes to rapidly proliferate to produce large clones of thousands of identical B-lymphocytes.
4. In this way, even though only a few B-lymphocytes in the body may have an antibody molecule able to fit a particular epitope, eventually eventually many thousands of cells are produced with the right specificity. This is referred to as clonal expansion.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Briefly describe the process of clonal selection and clonal expansion. *(ans)*
2. Multiple Choice *(ans)*

This page titled 10.4.1E: Clonal Selection and Clonal Expansion is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **13.1E: Clonal Selection and Clonal Expansion** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

10.4.1F: Anamnestic (Memory) Response

Learning Objectives

1. In terms of humoral immunity, statewhat is meant by anamnestic response and discuss its role in immune defense.
2. Briefly describe why there is a heightened secondary response during anamestic response.

As a result of B-lymphocytes recognizing T-dependent antigens (proteins) during humoral immunity, numerous circulating B-memory cells and T4-memory cells develop (Figure **10.4.1*F*.1**), which possess anamnestic response or memory. (During cell-mediated immunity, T8-memory cells also develop.) A subsequent exposure to that same antigen results in:

- A more rapid production of antibodies;
- Produced in greater amounts; and
- Produced for a longer period of time.

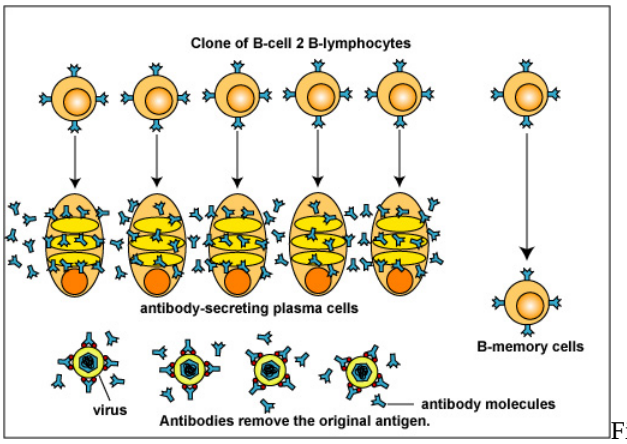


Figure **10.4.1*F*.1:** Differentiation of B-lymphocytes into Plasma Cells and B-Memory Cells. The B-lymphocytes now differentiate into plasma cells that secrete large quantities of antibodies that fit the original epitope. Some B-lymphocytes differentiate into B-memory cells capable of anamnestic response.

The primary response to a new antigen generally peaks at 5-10 days. IgM is made first later to be replaced by IgG. Because of the numerous circulating B-memory cells and T4-memory cells from the primary response, however, the secondary anamnestic response peaks in only 1-3 days (Figure **10.4.1*F*.2**). There is an increase in the amount of IgG made and under certain conditions, IgA or IgE may be made.

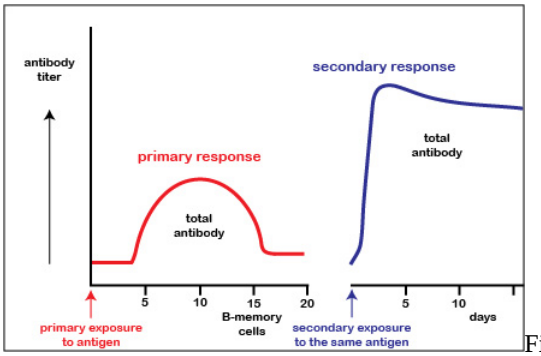


Figure **10.4.1*F*.2:** Anamnestic Response. After the primary exposure to an antigen, there is an inductive period of generally several days to a week when no measurable antibodies are detected in the serum. This is the period when the antigen is being exposed to immunocompetent cells, being processed by APCs, clonal selection and clonal expansion are taking place, and B-lymphocytes are differentiating into plasma cells and B-memory cells. Because of the memory cells, however, a second exposure to the same antigen results in more antibodies being made faster for a longer period of time, as shown in the secondary response.

Because of clonal expansion and affinity maturation , there is now a pool of B-memory cells having the "fine-tuned" B-cell receptors on their surface. The pool of B-memory cells migrate to lymph nodes, to mucosal tissue, and circulate in the blood waiting to encounter the original antigen if it again enters the body. B-memory cells have a long life and also replicate and produce

antibodies periodically when they are exposed to persisting epitope remaining on the surface of follicular dendritic cells in the lymphoid organs. In addition to the B-memory cells, a pool of circulating T4-effector memory cells (CD4 T_{EM} cells), as well T4 tissue resident memory cells (CD4 T_{RM} cells) located in the mucosa enable an accelerated helper function.

This memory response applies to T-dependent antigens . In the case of the T-independent antigens, there is usually no anamnestic response.

In the case of systemic infections and most vaccinations, many of the plasma cells migrate to the bone marrow where they may continue to secrete antibodies for months or years after the antigen has been eliminated. Plasma cells produced in the mucous membranes generally remain in the mucous membranes and secrete antibodies for only around a year.

Memory is better in preventing systemic infections than preventing mucosal infections because infections limited to the mucous membranes generally do not provide enough time for the development of effector cells such as plasma cells, effector T4-lymphocytes , and cytotoxic T-lymphocytes from the activated memory cells.

Summary

1. As a result of B-lymphocytes recognizing T-dependent antigens (proteins) during humoral immunity, numerous circulating B-memory cells and T4-memory cells develop which possess anamnestic response or memory.
2. A subsequent exposure to that same antigen results in a more rapid production of antibodies that are produced in greater amounts for a longer period of time.
3. The primary response to a new antigen generally peaks at 5 - 10 days.
4. Because of the numerous circulating B-memory cells and T4-memory cells from the primary response, the secondary anamnestic response peaks in only 1 - 3 days.
5. In the case of systemic infections and most vaccinations, many of the plasma cells migrate to the bone marrow where they may continue to secrete antibodies for months or years after the antigen has been eliminated.
6. Plasma cells produced in the mucous membranes generally remain in the mucous membranes and secrete antibodies for only around a year. Therefore, anamnestic response is better at preventing systemic infections than preventing mucosal infections.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. In terms of humoral immunity, discusswhat is meant by anamnestic response. *(ans)*
2. Briefly describe why there is a heightened secondary response during anamestic response. *(ans)*

This page titled 10.4.1F: Anamnestic (Memory) Response is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **13.1F: Anamnestic (Memory) Response** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

10.4.2: Ways That Antibodies Help to Defend the Body

The antibodies produced during humoral immunity ultimately defend the body through a variety of different means.

Template:HideTOC

This page titled 10.4.2: Ways That Antibodies Help to Defend the Body is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **13.2: Ways That Antibodies Help to Defend the Body** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

10.4.2A: Opsonization

Learning Objectives

- Discuss how antibodies defend the body by way of opsonization. (Include what classes or isotypes of immunoglobulins are involved, the role of the Fab portion of the antibody, the role, if any, of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.)
- Briefly describe two different ways bacteria may resist opsonization.

Opsonization, or enhanced attachment, refers to the antibody molecules IgG and IgE, the complement proteins C3b and C4b, and other opsonins attaching antigens to phagocytes. This results in a much more efficient phagocytosis.

Opsonization with IgG, IgA, C3b, and C4b

The process starts with antibodies of the isotype IgG, IgA, or IgM being made against a surface antigen of the organism or cell to be phagocytosed. The Fab portions of the antibody react with epitopes of the antigen. The Fc portion of IgG (but not IgM) can then bind to receptors on neutrophils and macrophages thus sticking the antigen to the phagocyte (Figure **10.4.2*A*.1**). The Fc portion of secretory IgA can also bind to macrophages and neutrophils for opsonization.

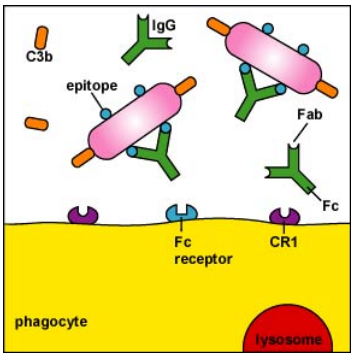


Figure **10.4.2*A*.1**: Opsonization (Enhanced Attachment). The Fab portion of IgG binds to epitopes of an antigen. The Fc portion can now attach the antigen to Fc receptors on phagocytes for enhanced attachment. This is especially important against encapsulated microbes. C3b and C4b from the complement pathways can also attach antigens to phagocytes.

The Fc portion of secretory IgA can also bind to macrophages and neutrophils for opsonization.

Alternately, IgG, IgA, and IgM can activate the complement pathways (Figure **10.4.2*A*.2**) and C3b or C4b can stick the antigen to phagocytes (Figure **10.4.2*A*.1**). Like IgG, C3b, and to a lesser extent C4b, can function as opsonins, that is, they can attach antigens to phagocytes.One portion of the C3b binds to proteins and polysaccharides on microbial surfaces; another portion attaches to CR1 receptors on phagocytes, B-lymphocytes, and dendritic cells for enhanced phagocytosis (Figure **10.4.2*A*.3**). (Remember that C3b and C4b are also produced during the alternative complement pathway and the lectin pathway as was discussed in Unit 5.) Activation of the complement pathway also promotes inflammation to bring phagocytes and defense chemicals from the bloodstream to the infection site as discussed later under this topic.

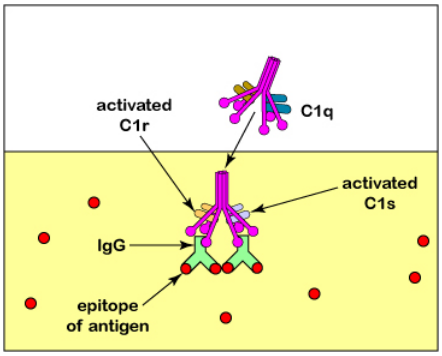


Figure **10.4.2*A*.2**: Activation of C1 during the Classical Complement Pathway. The Fab of 2 molecules of IgG or 1 molecule of IgM bind to epitopes on an antigen. C1, consisting of C1q, C1r, and C1s then binds to the

https://med.libretexts.org/@go/page/77756

Fc portion of the antibodies. The binding of C1q to the antibody molecules activates the C1r portion of C1 which, in turn, activates C1s. This activation gives C1s enzymatic activity to cleave complement protein C4 into C4a and C4b and complement protein C2 into C2a and C2b.

Actually, C3b molecule can bind to pretty much any protein or polysaccharide. Human cells, however, produce Factor H that binds to C3b and allows Factor I to inactivate the C3b. On the other hand, substances such as LPS on bacterial cells facilitate the binding of Factor B to C3b and this protects the C3b from inactivation by Factor I. In this way, C3b does not interact with our own cells but is able to interact with microbial cells.

Attachment then promotes destruction of the antigen. Microorganisms are placed in phagosomes (Figure 10.4.2A.4) where they are ultimately digested by lysosomes (Figure 10.4.2A.5). If the antigen is a cell too large to be ingested - such as virus-infected host cells, transplant cells, and cancer cells - the phagocyte empties the contents of its lysosomes directly on the cell for extracellular killing (Figure 10.4.2A.6 and Figure 10.4.2A.7).

Opsonization is especially important against microorganisms with antiphagocytic structures such as capsules since opsonizing antibodies made against the capsule are able to stick capsules to phagocytes (Figure 10.4.2A.8). In vaccines against pneumococccal pneumonia and *Haemophilus influenzae* type b, it is capsular polysaccharide that is given as the antigen in order to stimulate the body to make opsonizing antibodies against the encapsulated bacterium.

Opsonization with IgE and the promotion of inflammation

The antibody isotype IgE is made against parasitic worms (helminths) and arthropods. The Fab portions of IgE bind to epitopes on the helminth or arthropod while the Fc portion binds to receptors on eosinophils enabling opsonization. In other words, IgE sticks phagocytic eosinophils to helminths and arthropods for the extracellular killing of that organism (Figure 10.4.2A.9).

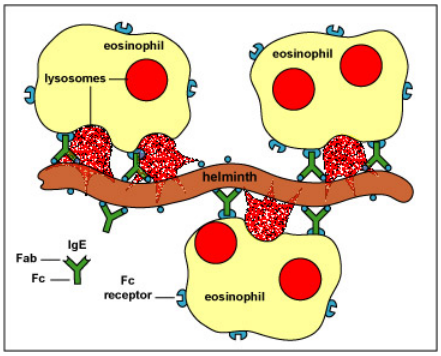


Figure 10.4.2A.9: Opsonization of a Helminth by IgE and Eosinophils. A major function of the cytokines produced by T_H2 cells is to enable B-lymphocytes to activate eosinophils and produce increased amounts of a class of antibodies called IgE against helminths (parasitic worms) and arthropods. IgE act as an opsonizing antibody to stick phagocytic eosinophils to helminths for extracellular killing of the helminths. The Fab portion of IgE reacts with epitopes on the helminth while the Fc portion binds to Fc receptors of activated eosinophils. The lysosomal proteases of eosinophils are able to destroy the tough integument of helminths. IgE also promotes inflammation to recruit phagocytes.

The Fc portion of IgE also binds to receptors on mast cells and basophils to trigger the release of *inflammatory mediators* (Figure 10.4.2A.10). The inflammatory response then enables phagocytes and defense chemicals to leave the bloodstream and go to the infected site as will be discussed later under this topic.

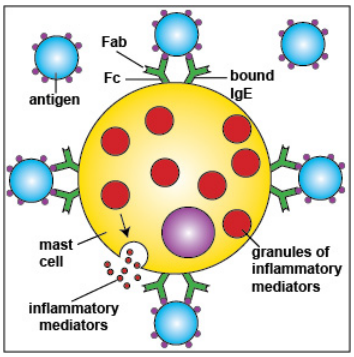


Figure 10.4.2A.10: IgE Binding to Mast Cells and Basophils and Promoting an Inflammatory Response. The Fc portion of IgE is able to bind to receptors on mast cells and basophils. The cross-binding of antigens to the Fab portion of IgE triggers the release of inflammatory mediators. The resulting inflammatory response subsequently delivers defense cells and defense molecules from the bloodstream to the infection site.

? Exercise: Think-Pair-Share Questions

Compare and contrast how IgG, IgM, and IgE promote opsonization..

Because of a particular immunodeficiency disorder, a person is unable to produce C3 convertase. Which of the above antibody isotypes could still participate in opsonization? Briefly explain why.

How Bacteria Resist Attachment to Phagocytes

As we learned previously, some bacteria by means of the activities described below are able to resist phagocytic attachment :

- An outer membrane molecule of *Neisseria gonorrhoeae* called Protein II and the M-protein of *Streptococcus pyogenes* allow these bacteria to be more resistant to phagocytic engulfment. The M-protein of *S. pyogenes*, for example, binds factor H of the complement pathway and this leads to the degradation of the opsonin C3b by factor I and the formation of C3 convertase.
- Some capsules simply cover the C3b that does bind to the bacterial surface and prevent the C3b receptor on phagocytes from making contact with the C3b (Figure 10.4.2A.11). This is seen with the capsule of *Streptococcus pneumoniae*.
- Capsules can also resist unenhanced attachment by preventing the glycoprotein receptors on phagocytes from recognizing the bacterial cell wall components and mannose-containing carbohydrates.
- *S. pneumonia* activates the classical complement pathway, but resists C3b opsonization, and complement causes further inflammation in the lungs.
- *Neisseria meningitidis* has a capsule composed of sialic acid *while Streptococcus pyogenes* (group A beta streptococci) has a capsule made of hyaluronic acid. Both of these polysaccharides closely resemble carbohydrates found in human tissue polysaccharides and because they are not recognized as foreign by the lymphocytes that carry out the immune responses, antibodies are not made against these capsules.
- Some bacteria are able to coat themselves with host proteins such as fibronectin, lactoferrin, or transferrin. This prevents antibody molecules from binding to epitopes on the bacterial surface.
- *Staphylococcus aureus* produces protein A while *Streptococcus pyogenes* produces protein G. Both of these proteins bind to the Fc portion of antibodies, the portion that normally binds to receptors on phagocytes (Figure 10.4.2A.12). In this way the bacteria become coated with antibodies in a way that does not result in opsonization (Figure 10.4.2A.13).
- *Streptococcus pyogenes* produces Mac proteins that are able to bind to the receptors on phagocytes to which IgG and C3b normally attach (Figure 10.4.2A.14.and Figure 10.4.2A.15). This blocks opsonization.
- Pathogenic *Yersinia*, such as the one that causes plague, contact phagocytes and, by means of a type III secretion system, deliver proteins which depolymerize the actin microfilaments needed for phagocytic engulfment into the

phagocytes. Another *Yersinia* protein degrades C3b and C5a.

Summary

Opsonization, or enhanced attachment, refers to the antibody molecules IgG and IgE, the complement proteins C3b and C4b, and other opsonins attaching antigens to phagocytes. The Fab portions of the antibody IgG react with epitopes of the antigen. The Fc portion of IgG can then bind to neutrophils and macrophages thus sticking the antigen to the phagocyte. The Fc portion of secretory IgA can also bind to macrophages and neutrophils for opsonization. IgG and IgM can activate the classical complement pathway and C3b or C4b can stick the antigen to phagocytes. IgE is made against parasitic worms (helminths) and arthropods. The Fab portions of IgE bind to epitopes on the helminth or arthropod while the Fc portion binds to receptors on eosinophils enabling opsonization.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Discuss how antibodies defend the body by way of opsonization. (Include what classes or isotypes of immunoglobulins are involved, the role of the Fab portion of the antibody, the role, if any, of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.) *(ans)*
2. We know *Streptococcus pneumoniae* is encapsulated and capsules resist phagocytosis. Yet the body is eventually able to phagocytose this organism. Describe how. *(ans)*
3. *Staphylococcus aureus* produces an exotoxin called Protein A. Protein A is able to react with the Fc portion of IgG. In terms of humoral immunity, discuss how Protein A may help the *Staphylococcus* resist phagocytosis. *(ans)*
4. The M-protein of *Streptococcus pyogenes* binds factor H of the complement pathway and allows these bacteria to be more resistant to phagocytic engulfment. Explain how. *(ans)*
5. Multiple Choice *(ans)*

This page titled 10.4.2A: Opsonization is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **13.2A: Opsonization** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

10.4.2B: Cytolysis by the Membrane Attack Complex (MAC)

Learning Objectives

1. Discuss how antibodies defend the body by way of MAC cytolysis. (Include what classes or isotypes of immunoglobulins are involved, the role of the Fab portion of the antibody, the role, if any, of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.)
2. State specifically how MAC cytolysis protects against the following:
   a. Gram-negative bacteria
   b. human cells recognized as nonself
   c. enveloped viruses
3. Describe one way Gram-negative bacteria may resist cytolysis.

The process starts with the antibody isotypes IgG or IgM being made against epitopes on membranes. The Fab portion of IgG or IgM reacts with the epitopes on the membrane and the Fc portion of the antibody then activates the classical complement pathway. $C5b6789_n$ (the membrane attack complex or MAC) then puts holes in the membrane. (Remember that MAC is also produced during the alternative complement pathway and the lectin pathway as was discussed in Unit 5.)

a. In the case of bacteria, MAC can put holes in the outer membrane and possibly the cytoplasmic membrane of the Gram-negative cell wall (Figure 10.4.2*B*.1 left) causing lysis (Figure 10.4.2*B*.1 right).

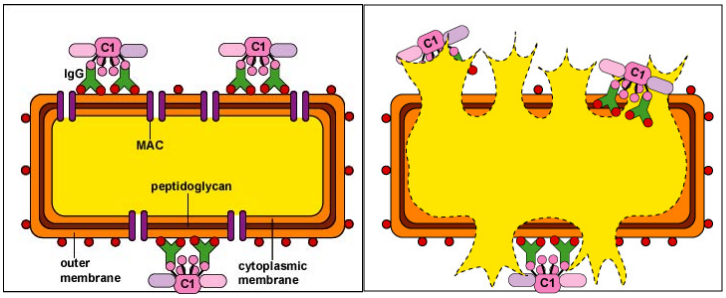


Figure 10.4.2*B*.1: (left) Cytolysis of Gram-Negative Bacteria, Step 1. The Fab portion of IgG or IgM binds to epitopes on the outer membrane of the gram-negative cell wall. This activates the complement pathway enabling the membrane attack complex (MAC) to insert through the outer membrane and cytoplasmic membrane causing the bacterium to lyse. (right)Lysis of the gram-negative bacterium.

b. With enveloped viruses, the MAC can damage the viral envelope (Figure \(\PageIndex{12}\).3.2).

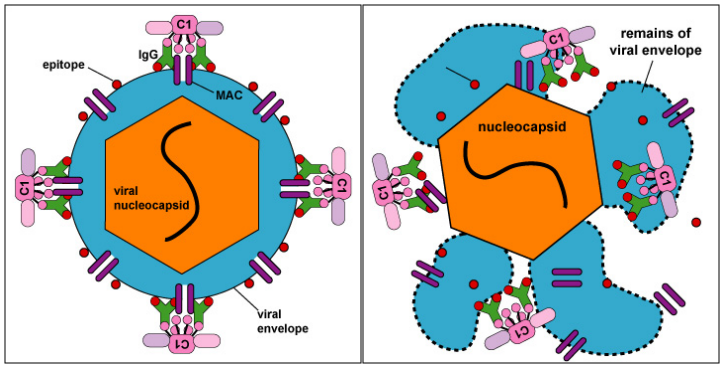


Figure 10.4.2*B*.2: (left) MAC Damage to the Viral Envelope, Step 1: MAC (membrane attack complex) from the activated complement pathways is able to damage the envelope of enveloped viruses causing viral inactivation. (right) Step 2: Without its envelope, the virus is unable to infect new host cells.

c. In the case of human cells recognized as nonself- virus-infected cells, transplanted cells, transfused cells, cancer cells - the MAC causes direct cell lysis (see Figure 10.4.2*B*.5 and Figure 10.4.2*B*.6).

However, as learned in Unit 3, some bacteria by means of the activities described below are more resistant to MAC lysis.

- The LPS of the cell wall is the principle target for complement in Gram-negative bacteria by activating the alternative complement pathway and serving as a binding site for C3b as well as the site for formation of MAC. Some Gram-negative bacteria attach sialic acid to the LPS O antigen (see Figure $10.4.2B.7$) and this prevents the formation of the complement enzyme C3 convertase that is needed for the eventual formation of all the beneficial complement proteins such as C3b, C5a, and MAC. Blood-invasive strains of *Neisseria gonorrhoeae ,* as well as *Bordetella pertussis* and *Hemophilus influenzae* are examples of Gram-negative bacteria that are able to alter their LPS in this manner.
- Some Gram-negative bacteria, such as *Salmonella* , lengthen the LPS O antigen side chain (see Figure $10.4.2B.7$) and this prevents the formation of MAC. *Neisseria meningitidis* and Group B Streptococcus , on the other hand, produces capsular polysaccharides composed of sialic acid and as mentioned above, sialic acid prevents MAC lysis.
- An outer membrane molecule of *Neisseria gonorrhoeae* called Protein II binds factor H of the complement pathway and this leads to the degradation of the opsonin C3b by factor I and the formation of C3 convertase. Without C3 convertase, no MAC is produced.

Summary

The Fab portion of IgG or IgM reacts with the epitopes on the membrane and the Fc portion of the antibody then activates the classical complement pathway. C5b6789n (the membrane attack complex or MAC) then puts holes in the membrane. In the case of bacteria, MAC can put holes in the outer membrane and possibly the cytoplasmic membrane of the Gram-negative cell wall causing lysis. In the case of enveloped viruses, MAC can damage the viral envelope. In the case of human cells recognized as nonself - virus-infected cells, transplanted cells, transfused cells, cancer cells- the MAC causes direct cell lysis.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Discuss how antibodies defend the body by way of MAC cytolysis. (Include what classes or isotypes of immunoglobulins are involved, the role of the Fab portion of the antibody, the role, if any, of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.) *(ans)*
2. Some Gram-negative bacteria attach sialic acid to the LPS O antigen of their outer membrane. Briefly describe how this may protect that Gram-negative bacterium from MAC cytolysis. *(ans)*
3. How does MAC affect viruses? *(ans)*
4. Multiple Choice *(ans)*

This page titled 10.4.2B: Cytolysis by the Membrane Attack Complex (MAC) is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **13.2B: Cytolysis by the Membrane Attack Complex (MAC)** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

10.4.2C: Antibody-dependent Cellular Cytotoxicity (ADCC) by Natural Killer Cells

Learning Objectives

1. **Discuss** how antibodies defend the body by way of **ADCC by Natural Killer cells**. (Include what classes or isotypes of immunoglobulins are involved, the role of the Fab portion of the antibody, the role, if any, of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.)

Natural killer (NK) cells are capable of antibody-dependent cellular cytotoxicity or ADCC. NK cells have receptors on their surface for the Fc portion of certain subclasses of IgG. When the antibody IgG is made against epitopes on "foreign" membrane-bound cells, such as virus-infected cells and cancer cells, the Fab portions of the antibodies react with the "foreign" cell. The NK cells then bind to the Fc portion of the antibody (Figure **10.4.2*C*.1**).

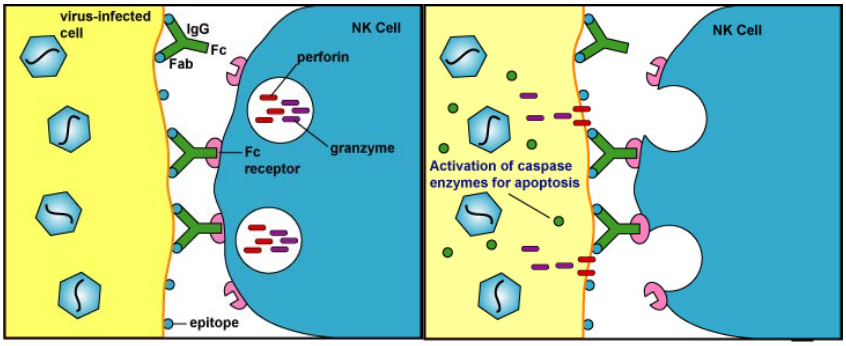


Figure **10.4.2*C*.1**: Destruction of Virus-Infected Cells by NK Cells through Antibody-Dependent Cellular Cytotoxicity (ADCC), (left) Step 1: The Fab portion of the antibody binds to epitopes on the "foreign" cell. The NK cell then binds to the Fc portion of the antibody. (right) Step 2: The NK cell is then able to contact the cell and release pore-forming proteins called perforins and proteolytic enzymes called granzymes. Granzymes pass through the pores and activate the enzymes that lead to apoptosis of the infected cell by means of destruction of its structural cytoskeleton proteins and by chromosomal degradation. As a result, the cell breaks into fragments that are subsequently removed by phagocytes. Perforins can also sometimes result in cell lysis.

The NK cell then **releases pore-forming proteins called perforins, proteolytic enzymes called granzymes**, and chemokines. Granzymes pass through the pores and activate the enzymes that lead to **apoptosis** of the infected cell by means of destruction of its structural cytoskeleton proteins and by chromosomal degradation (Figure **10.4.2*C*.13**.5.1; right panel and Figure **10.4.2*C*.2**). As a result, the cell breaks into fragments that are subsequently removed by phagocytes. Perforins can also sometimes result in cell lysis. (When NK cells are carrying out ADCC, they are sometimes also referred to as killer cells.)

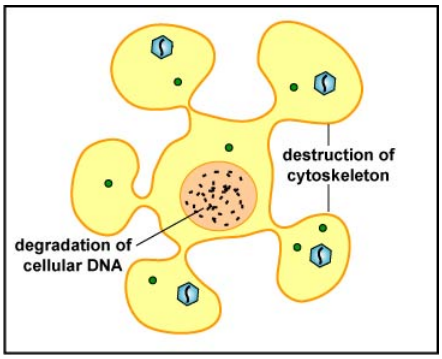


Figure **10.4.2*C*.2**: NK cells release pore-forming proteins called perforins and proteolytic enzymes called granzymes. Granzymes pass through the pores and activate the enzymes that lead to apoptosis, a programmed suicide of the infected cell. Apoptosis occurs when certain granzymes activate a group of protease enzymes called caspases that destroy the protein structural scaffolding of the cell, degrade the cell's nucleoprotein, and activate enzymes that degrade the cell's DNA. As a result, the infected cell breaks into membrane-bound fragments that are subsequently removed by phagocytes. If very large numbers of perforins are inserted into the plasma membrane of the infected cell, this can result in a weakening of the membrane and lead to cell lysis rather than apoptosis. An advantage to killing infected cells by apoptosis is that the cell's contents, including viable virus particles and mediators of inflammation, are not released as they are during cell lysis.

Summary

NK cells are capable of antibody-dependent cellular cytotoxicity or ADCC. When IgG is made against epitopes on "foreign" membrane-bound cells, such as virus-infected cells and cancer cells, the Fab portions of the antibodies react with epitopes on the "foreign" cell and then NK cells bind to the Fc portion of the antibody. The NK cell then releases pore-forming proteins called perforins and proteolytic enzymes called granzymes. Granzymes pass through the pores and activate the enzymes that lead to apoptosis of the infected cell and the cell breaks into fragments that are subsequently removed by phagocytes.

Questions

Study the material in this section and then **write out the answers** to these questions. **Do not** just click on the answers and write them out. This will not test your understanding of this tutorial.

1. **Discuss** how antibodies defend the body by way of **ADCC by NK cells**. (Include what classes or isotypes of immunoglobulins are involved, the role of the Fab portion of the antibody, the role, if any, of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.)
2. Antibody-dependent cellular cytotoxicity (ADCC) is a result of:
    a. Antibodies sticking infected cells and cancer cells to phagocytes.
    b. Antibodies sticking infected cells and cancer cells to cytotoxic T-lymphocytes (CTLs).
    c. Antibodies sticking infected cells and cancer cells to NK cells.
    d. MAC lysing the membranes of infected cells and cancer cells.
3. During ADCC, the Fab portion of the antibody _____while the Fc portion _____.
    a. binds to epitopes of an antigen; activates the complement pathway.
    b. activates the complement pathway; binds to epitopes of an antigen.
    c. binds to epitopes of an antigen; binds to cytotoxic T-lymphocytes.
    d. binds to epitopes of an antigen; binds to NK cells.
4. NK cells kill the cells they bind to by:
    a. Triggering apoptosis.
    b. Dumping the contents of their lysosomes on the cell.
    c. Producing cytolytic exotoxins that lyse the cell.
    d. Inducing extracellular killing by eosinophils.

This page titled 10.4.2C: Antibody-dependent Cellular Cytotoxicity (ADCC) by Natural Killer Cells is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **13.2C: Antibody-dependent Cellular Cytotoxicity (ADCC) by Natural Killer Cells** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

10.4.2D: Neutralization of Exotoxins

Learning Objectives

- Discuss how antibodies defend the body by way of neutralizing exotoxins. (Include what classes or isotypes of immunoglobulins are involved, the role of the Fab portion of the antibody, the role, if any, of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.)
- Describe how the ability of bacteria to sense their own population density, communicate with each other by way of secreted factors (cell-to-cell signaling), and behave as a population rather than as individual bacteria most likely plays an important role in pathogenicity for many bacteria.

For an exotoxin to cause harm it must first bind to receptors on a susceptible host cell. Antitoxin antibodies are made against microbial exotoxins. The Fab portion binds to the exotoxin molecules before they can interact with host target cells and thus neutralizes the toxin (Figure **10.4.2*D*.1**). IgG neutralizes toxins in tissues while IgA neutralizes toxins at mucosal surfaces within the body.

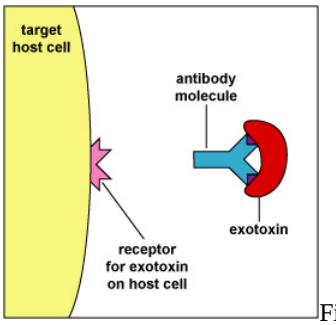


Figure **10.4.2*D*.1:** Neutralization of Exotoxins. The Fab portion of the antibodies made against epitopes of the binding site of an exotoxin blocks the exotoxin from binding to the exotoxin receptor on the host cell membrane. As a result, the toxin can not enter the cell and cause harm.

However, as learned in Unit 2, many Gram-negative and Gram-positive are able to sense their own population density, communicate with each other by way of secreted factors, and behave as a population rather than as individual bacteria. This is referred to as quorum sensing and most likely plays an important role in pathogenicity for many bacteria.

- For example, *Pseudomonas aeruginosa* causes severe nosocomial infections, chronic infections in people with cystic fibrosis, and potentially fatal infections in those who are immunocompromised. Its virulence depends on the secretion of a variety of harmful exotoxins and enzymes. If there was an isolated production of these virulence toxins and enzymes by a small number of *Pseudomonas*, the body's immune responses would most likely be able effectively neutralize these harmful agents with antibodies. However, through a coordination of the expression of the genes coding for these toxins and enzymes by the entire population of bacteria, *P. aeruginosa* appears to only secrete these extracellular virulence factors when the density of bacteria is large enough that they can be produced at high enough levels to overcome body defenses.

Summary

For an exotoxin to cause harm it must first bind to receptors on a susceptible host cell. Antitoxin antibodies are made against microbial exotoxins. The Fab portion binds to the exotoxin molecules before they can interact with host target cells and thus neutralizes the toxin.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Discuss how antibodies defend the body by way of neutralizing exotoxins. (Include what classes or isotypes of immunoglobulins are involved, the role of the Fab portion of the antibody, the role, if any, of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.) *(ans)*
2. Describe how the ability of *Pseudomonas aeruginosa* to sense its own population density, communicate with other *Pseudomonas* by way of secreted factors (cell-to-cell signaling), and behave as a population rather than as individual bacteria most likely plays an important role in pathogenicity of this organism. *(ans)*
3. Multiple Choice *(ans)*

This page titled 10.4.2D: Neutralization of Exotoxins is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **13.2D: Neutralization of Exotoxins** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

10.4.2E: Neutralization of Viruses

Discuss how antibodies defend the body by way of neutralizing viruses. (Include what classes or isotypes of immunoglobulins are involved, the role of the Fab portion of the antibody, the role, if any, of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.)

- Briefly describe 2 different ways viruses may resist neutralizing antibodies.

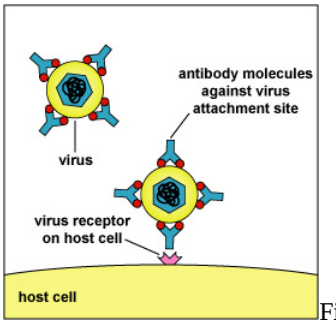


Figure 10.4.2*E*.1: Neutralization of Viruses. The Fab portion of the antibodies made against epitopes of the virus attachment site blocks the virus from adsorbing to the receptor site on the host cell membrane. As a result, the virus can not penetrate and replicate.

However, as learned in Unit 4, some viruses by means of the activities described below are able to overcome this antibody defense.

- The influenza viruses undergo what is called antigenic drift and antigenic shift. With antigenic drift, mutations cause a gradual change in the hemagglutinin antigen that adsorbs to receptors on host cells. Antigenic shift is caused by a human influenza virus acquiring a new genome segment from an influenza virus capable of infecting other animals such as a ducks or swine. This new genome segment causes a major change in the hemagglutinin antigen. Antibodies made against the original human influenza virus can no longer bind to the new strain of virus or stick the virus to phagocytes.
- Likewise HIV, because of its high rate of mutation and its intracellular recombination with other strains of HIV, as mentioned earlier in this unit, produces altered gp120 to which antibodies made against the earlier strains of HIV can no longer bind.
- The hepatitis C virus (HCV) frequently, through mutation, produces viral variants ("escape mutants") to resist antibodies.

? A child is fully immunized against measles, mumps, and rubella with the MMR vaccine. The child is subsequently exposed to measles but doesn't get the disease. Explain why the virus was unable to replicate and cause disease symptoms.

Summary

In order for viruses to infect a cell and replicate, they must first adsorb to receptors on the host cell's plasma membrane. Antibodies are made against viral capsids or envelope glycoproteins where the Fab portion binds to and covers the viral attachment molecules. This prevents viral adsorption to host cells. Neutralizing antibodies are especially important in preventing viral reinfection.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Discuss how antibodies defend the body by way of neutralizing viruses. (Include what classes or isotypes of immunoglobulins are involved, the role of the Fab portion of the antibody, the role, if any, of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.) *(ans)*
2. Describe one way a virus can resist virus-neutralizing antibodies and give an example. *(ans)*
3. Multiple Choice *(ans)*

This page titled 10.4.2E: Neutralization of Viruses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **13.2E: Neutralization of Viruses** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

10.4.2F: Preventing Bacterial Adherence

Learning Objectives

1. Discuss how antibodies defend the body by way of preventing bacterial adherence to host cells. (Include what classes or isotypes of immunoglobulins are involved, the role of the Fab portion of the antibody, the role, if any, of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.)
2. Briefly describe 2 different ways bacteria may resist antibodies that block bacterial adherence to host cells.

One of the body's innate defenses is the ability to physically remove bacteria from the body through such means as the constant shedding of surface epithelial cells from the skin and mucous membranes, the removal of bacteria by such means as coughing, sneezing, vomiting, and diarrhea, and bacterial removal by bodily fluids such as saliva, blood, mucous, and urine. Bacteria may resist this physical removal producing pili, cell wall adhesin proteins, and/or biofilm-producing capsules.

Antibodies are made against pili, capsules, and cell wall adhesins. The binding of the Fab portion of the antibody to the adhesive tip of the pili, the cell wall adhesins, or the capsular molecules prevents the bacteria from adhering to and colonizing host cells (see Figure $\mathbf{10.4.2F.1}$ and Figure $\mathbf{10.4.2F.2}$.) IgG blocks adherence of bacteria in tissues while IgA blocks adherence of bacteria at mucosal surfaces within the body.

? The body is able to make antibody molecules against the adhesive tips of Escherichia coli pili and yet E. coli is still the most common cause of urinary tract infections. State what might account for this.

However, as learned in Unit 3, some bacteria by means of the activities described below are able to overcome this antibody defense.

- Some bacteria can produce immunoglobulin proteases which can degrade the protective IgA found in mucus. Examples include bacteria that colonize the mucous membranes such as *Streptococcus pneumoniae*, *Hemophilus influenzae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Helicobacter pylori*, *Shigella flexneri* and enteropathogenic *Escherichia coli*.
- Another way certain bacteria can evade antibodies is by changing the adhesive tips of their pili as seen with *Neisseria gonorrhoeae* (see Figure $\mathbf{10.4.2F.3}$). Bacteria can also vary other surface proteins so that antibodies already made will no longer "fit."

Summary

Bacteria resist physical removal by means of pili, cell wall adhesin proteins, and/or biofilm-producing capsules. The binding of the Fab portion of the antibody to the adhesive tip of the pili, the cell wall adhesins, or the capsular molecules prevents the bacteria from adhering to and colonizing host cells.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Discuss how antibodies defend the body by way of preventing bacterial adherence to host cells. (Include what classes or isotypes of immunoglobulins are involved, the role of the Fab portion of the antibody, the role, if any, of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.) *(ans)*
2. Describe how immunoglobulin proteases may protect bacteria from antibodies that block bacterial adhence to host cells. *(ans)*
3. Multiple Choice *(ans)*

This page titled 10.4.2F: Preventing Bacterial Adherence is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **13.2F: Preventing Bacterial Adherence** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

10.4.2G: Agglutination of Microorganisms

Learning Objectives

1. Discuss the how antibodies defend the body by agglutinating microorganisms. (Include what classes or isotypes of immunoglobulins are involved, the role of the Fab portion of the antibody, the role - if any - of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.)

Agglutination is mainly a function of antibodies with multiple reactive Fab sites such as IgM and IgA. The Fab portion of the antibodies links microorganisms together (causes them to agglutinate) so they can be phagocytosed more effectively (see Figure 10.4.2G.1).

Summary

Agglutination is mainly a function of antibodies with multiple reactive Fab sites such as IgM and IgA. The Fab portion of the antibodies links microorganisms together (causes them to agglutinate) so they can be phagocytosed more effectively.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Discuss how antibodies defend the body by agglutinating microorganisms. (Include what classes or isotypes of immunoglobulins are involved, the role of the Fab portion of the antibody, the role, if any, of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.) *(ans)*
2. State why IgM and IgA are good at causing agglutination of microorganisms. *(ans)*

This page titled 10.4.2G: Agglutination of Microorganisms is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **13.2G: Agglutination of Microorganisms** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

10.4.2H: Immobilization of Bacteria and Protozoans

Learning Objectives

1. Discuss how antibodies defend the body by immobilizing bacteria and protozoans. (Include the role of the Fab portion of the antibody, the role, if any, of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.)

Flagella and cilia are organelles of locomotion and enable motile microorganisms to move towards or away from environmental molecules through a process called taxis. The mucosal surfaces of the bladder and the intestines constantly flush bacteria away in order to prevent colonization.Motile bacteria that can swim chemotactically toward mucosal surfaces may have a better chance to make contact with the mucous membranes, attach, and colonize.

Antibodies are made against the flagella of motile bacteria or the flagella or cilia of motile protozoans. The Fab portions of the antibodies bind to these locomotor organelles and arrest the organism's movement blocking its ability to spread.

Summary

1. Flagella and cilia are organelles of locomotion and enable motile microorganisms to move towards or away from environmental molecules through a process called taxis.
2. Antibodies are made against the flagella of motile bacteria or the flagella or cilia of motile protozoans.
3. The Fab portions of the antibodies bind to these locomotor organelles and arrest the organism's movement blocking its ability to spread.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Discusshow antibodies defend the body by immobilizing bacteria and protozoans. (Include the role of the Fab portion of the antibody, the role, if any, of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.) *(ans)*

This page titled 10.4.2H: Immobilization of Bacteria and Protozoans is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **13.2H: Immobilization of Bacteria and Protozoans** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

10.4.2I: Promoting an Inflammatory Response

Learning Objectives

1. Describe two different ways antibodies defend the body by promoting an inflammatory response and state the importance of inflammation. (Include the role of the Fab portion of the antibody, the role, if any, of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.)

Antigen-antibody reactions can also promote an inflammatory response:

a. IgG and IgM can activate the classical complement pathway (see Figure **10.4.2*I*.1**).

As learned under innate immunity in Unit 5, the classical complement pathway is primarily activated when a complement protein complex called C1 interacts with the Fc portion of the antibody molecules IgG or IgM after they have bound to their specific antigen via their Fab portion . C1 is also able to directly bind to the surfaces of some pathogens.

The C1 complex is composed of three complement proteins called C1q, C1r, and C1s.

- The C1q is the portion of the C1 complex that binds to the antibodies or the microbe.
- The binding of C1q activates the C1r portion of C1 which, in turn, activates C1s. This activation gives C1s enzymatic activity to cleave complement protein C4 into C4a and C4b and C2 into C2a and C2b and begin the classical complement pathway.

The beneficial results of the activated complement proteins include :

1. Triggering inflammation : C5a>C3a>C4a.

2. Chemotactically attracting phagocytes to the infection site: C5a;

3. Promoting the attachment of antigens to phagocytes via enhanced attachment or opsonization : C3b>C4b (discussed earlier under opsonization);

4. Causing the lysis of Gram-negative bacteria, viral envelopes, and human cells displaying foreign epitopes (discussed earlier under MAC cytolysis).

b. IgA can activate the lectin complement pathway and the alternative complement pathway and C5a, C3a, and C4a can trigger inflammation.

c. IgE can bind to mast cells and basophils and trigger the release of inflammatory mediators.

The Fc portion of IgE can bind to receptors on mast cells and basophils . Cross linking of the cell-bound IgE by antigen triggers the release of vasodilators and other inflammatory mediators for an inflammatory response (see Fig 2).

As learned under inflammation in Unit 5, most of the body defense elements are located in the blood and inflammation is the means by which body defense cells and defense chemicals leave the blood and enter the tissue around the injured or infected site.

The inflammatory response produces vasodilators that increase capillary permeability. As a result of this increased permeability:

a. Plasma flows out of the blood into the tissue.

Beneficial molecules in the plasma include:

1. Clotting factors. Tissue damage activates the coagulation cascade causing fibrin clots to form to localize the infection, stop the bleeding, and chemotactically attract phagocytes.

2. Antibodies . These help remove or block the action of microbes through a variety of methods described in this section.
3. Proteins of the complement pathways . These, in turn: 1) stimulate more inflammation (C5a, C3a, and C4a), 2) stick microorganisms to phagocytes (C3b and C4b), 3) chemotactically attract phagocytes (C5a), and 4) lyse membrane-bound cells displaying foreign antigens (membrane attack complex or MAC).
4. Nutrients. These feed the cells of the inflamed tissue.
5. Lysozyme, cathelicidins, phospholipase A_2, and human defensins . Lysozyme degrades peptidoglycan. Cathelicidins are cleaved into two peptides that are directly toxic to microbes and can neutralize LPS from the gram-negative bacterial cell wall. Phospholipase A_2 hydrolyzes the phospholipids in the bacterial cytoplasmic membrane. Human defensins put pores in the cytoplasmic membranes of many bacteria. Defensins also activate cells involved in the inflammatory response.
6. Transferrin . Transferrin deprives microbes of needed iron.

b. Leukocytes enter the tissue through a process called diapedesis or extravasation.

Benefits of diapedesis include:

1. Increased phagocytosis. Phagocytes such as neutrophils, monocytes that differentiate into macrophages when they enter the tissue, and eosinophils are phagocytic leukocytes.
2. More vasodilation. Basophils, eosinophils, neutrophils, and platelets enter the tissue and release or stimulate the production of vasoactive agents that promote inflammation.
3. Cytotoxic T-lymphocytes (CTLs) , effector T4-cells , and NK cells enter the tissue to kill cells such as infected cells and cancer cells that are displaying foreign antigens on their surface (discussed in Unit 6).

Summary

1. IgG and IgM can activate the classical complement pathway and C5a, C3a, and C4a can trigger inflammation.
2. IgA can activate the lectin complement pathway and the alternative complement pathway and C5a, C3a, and C4a can trigger inflammation.
3. IgE can bind to mast cells and basophils and trigger the release of inflammatory mediators.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Describe one way antibodies defend the body by promoting an inflammatory response and state the importance of inflammation. (Include the role of the Fab portion of the antibody, the role, if any, of the Fc portion of the antibody, and the role of any complement proteins, if any, involved.) *(ans)*

This page titled 10.4.2I: Promoting an Inflammatory Response is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **13.2I: Promoting an Inflammatory Response** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

SECTION OVERVIEW

10.4.3: Naturally and Artificially Acquired Active and Passive Immunity

Immunity may be passive or active. During **passive immunity**, antibodies made in another person or animal enter the body and the immunity is short-lived and Active Immunity: In the case of **active immunity**, antigens enter the body and the body responds by making its own antibodies and B-memory cells. In this case, immunity is longer lived although duration depends on the persistence of the antigen and the memory cells in the body. Both passive and active immunity can be either naturally or artificially acquired.

10.4.3A: Naturally Acquired Immunity

10.4.3B: Artificially Acquired Immunity

This page titled 10.4.3: Naturally and Artificially Acquired Active and Passive Immunity is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **13.3: Naturally and Artificially Acquired Active and Passive Immunity** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

10.4.3A: Naturally Acquired Immunity

Learning Objectives

1. Give an example of naturally acquired active immunity.
2. Give two examples of naturally acquired passive immunity and state why this is important to newborns and infants.

Active Naturally Acquired Immunity

Active naturally acquired immunity refers to the natural exposure to an infectious agent or other antigen by the body. The body responds by making its own antibodies.

Passive Naturally Acquired Immunity

There are two examples of passive naturally acquired immunity: (1) The placental transfer of IgG from mother to fetus during pregnancy. These antibodies generally last 4 to 6 months following birth. The immune responses reach full strength at about age 5. (2) The IgA and IgG found in human colostrum and milk of babies who are nursed. In addition to the IgA and IgG, human milk also contains:

- Oligosaccharides and mucins that adhere to bacteria and viruses to interfere with their attachment to host cells;
- Lactoferrin to bind iron and make it unavailable to most bacteria;
- B_{12} binding protein to deprive bacteria of needed vitamin $B_{12;}$
- Bifidus factor that promotes the growth of *Lactobacillus bifidus*, normal flora in the gastrointestinal tract of infants that crowds out harmful bacteria;
- Fibronectin that increases the antimicrobial activity of macrophages and helps repair tissue damage from infection in the gastrointestinal tract;
- Gamma-interferon, a cytokine that enhances the activity of certain immune cells;
- Hormones and growth factors that stimulate the baby's gastrointestinal tract to mature faster and be less susceptible to infection;
- Lysozyme to break down peptidoglycan in bacterial cell walls.

Benefits of Breast Feeding

According to the Centers for Disease Control and Prevention (CDC), breast-fed infants have a lower incidence of gastrointestinal infections, ear infections, atopic dermatitis, respiratory infections, urinary tract infections, meningitis, type 2 diabetes, and sudden infant death syndrome. Benefits to the mother include a decreased risk of breast cancer, ovarian cancer, and type 2 diabetes, as well stopping post-birth bleeding and temporarily suppressing ovulation. It may also be associated with a reduced risk of pediatric overweight.

Summary

Active naturally acquired immunity refers to the natural exposure to an infectious agent or other antigen by the body. The body responds by making its own antibodies. There are two examples of passive naturally acquired immunity: The placental transfer of IgG from mother to fetus during pregnancy that generally lasts 4 to 6 months after birth; and The IgA and IgG found in human colostrum and milk of babies who are nursed.

This page titled 10.4.3A: Naturally Acquired Immunity is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **13.3A: Naturally Acquired Immunity** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

10.4.3B: Artificially Acquired Immunity

Define and give at least one example of each of the following types of immunity:

a. artificially acquired active immunity

b. artificially acquired passive immunity

- List 3 different forms of antigen that may be used for artificially acquired active immunity and state 2 common examples of each.
- State what DTaP stands for and what specifically is being injected with the DTaP vaccine.
- Briefly compare active immunization with passive immunization in terms of tetanus prophylaxis.
- Define adjuvant.
- In artificially acquired immunity, active immunization is preferred over passive immunization. Explain why.
- Describe what is meant by herd immunity (community immunity).

Active Artificially Acquired Immunity

Active artificially acquired immunity refers to any immunization with an antigen. By giving a safe form of the antigen artificially, the body will produce its own antibodies and, more importantly, develop circulating, long-lived B-memory cells with high affinity B-cell receptors on their surface. If at a later date the body is again exposed to that same antigen, the memory cells will cause immediate and rapid production of the appropriate antibodies for protection. With artificially acquired active immunity, one is immunized with one or more of the following:

Attenuated microbes

Attenuated microbes are living, non-virulent strains of a microbe. Viruses are attenuated by growing them in non-human cells until they mutate and adapt to the non-human host. In the process, they lose virulence for humans. Viruses can also be attenuated using recombinant DNA techniques to either mutate or delete virulence genes in the viral genome.

Attenuated viral vaccines tend to be immunologically quite effective since the viruses can multiply slowly in the body, thus increasing the amount and persistence of the antigen for a greater antibody response. In addition, attenuated viruses enter the cytosol of cells and peptides from viral antigens can be presented by MHC-I molecules to activate naive T8-lymphocytes and stimulate the production of cytotoxic T-lymphocytes (CTLs). Living attenuated microbes can, however, sometimes be potentially dangerous to highly immunosuppressed individuals in whom they may cause opportunistic infections.

Examples of vaccines that contain attenuated microbes include:

- The MMR vaccine containing attenuated measles, mumps, and rubella viruses;
- The MMRV vaccine containing attenuated measles, mumps, rubella viruses and varicella zoster (chickenpox) viruses;
- The TOPV or trivalent oral polio vaccine containing attenuated poliomyelitis viruses types 1, 2, and 3;
- The yellow fever vaccine containing attenuated yellow fever viruses;
- The Var or varicella zoster virus vaccine containing attenuated varicella zoster viruses.

The body responds by producing antibodies that block viral adsorption to host cells.

Flash animation showing neutralization of a virus.

html5 version of animation for iPad showing neutralization of a virus.

Killed organisms, fragmented microorganisms, or antigens produced by recombinant DNA technology

Examples of vaccines containing killed or inactivated microbes include:

- The IPV or inactivated poliomyelitis vaccine containing inactivated poliomyelitis viruses types 1, 2, and 3;
- The rabies vaccines containing whole, killed rabies viruses;
- The influenza vaccines consist of inactivated influenza viruses, either whole or broken down;
- The hepatitis A vaccine containing inactivated hepatitis A virus;

- RV1, an attenuated strain of a human rotavirus. Rotaviruses are the most common cause of gastroenteritis in children.

Examples of vaccines containing fragments of microorganisms include the immunizations for:

- Meningococcal meningitis; contains capsular polysaccharide from 4 strains of *Neisseria meningitidis*;
- Pneumococcal pneumonia; PCV13 containing capsular material from the 13 most serious strains of *Streptococcus pneumoniae* in children conjugated to diphtheria toxoid protein; PCV 23 containing capsular material from the 23 most serious strains of *S. pneumoniae* in adults conjugated to diphtheria toxoid protein;
- *Hemophilus influenzae* type b containing capsular polysaccharide from *H. influenzae* type B conjugated to protein (either diphtheria toxoid or an outer membrane protein from *Neisseria meningitidis*).

These vaccines contain polysaccharide capsular material from the bacteria, usually conjugated to protein for greater immunogenicity. The body responds by producing opsonizing antibodies against the capsule.

Flash animation showing phagocytosis of an encapsulated bacterium through opsonization.

html5 version of animation for iPad showing phagocytosis of an encapsulated bacterium through opsonization.

While the B-cell receptors of B-lymphocytes can recognize epitopes on polysaccharides, T4-lymphocytes can only recognize peptide epitopes bound to MHC-II molecules. The protein conjugate added to the polysaccharide in the vaccine is degraded into peptides and bound to MHC-II molecules by APCs. They then present the peptide to the TCRs on T4-lymphocytes for their activation. In this way the cytokines produced by the activated T4-lymphocytes become available for use by the B-lymphocytes sensitized to the polysaccharide component of the vaccine.

c. Examples of vaccines produced by recombinant DNA technology include:

- The hepatitis B vaccine, the first human vaccine produced by recombinant DNA technology, contains hepatitis B virus surface antigen (HBsAG);
- The acellular pertussis part of the diphtheria, tetanus, and acellular pertussis vaccine (DTaP) containing diphtheria toxoid, tetanus toxoid, and antigens from the whooping cough bacterium *Bordetella pertussis* (Acellular pertussis vaccines contain inactivated pertussis toxin (PT) and may contain one or more other bacterial components (e.g., filamentous hemagglutinin [FHA], an outer-membrane protein; pertactin [Pn], and fimbriae [Fim] types 2 and 3);
- The vaccine against Lyme disease;
- Gardasil, a vaccine against human papilloma virus (HPV) types 6, 11 that cause about 90% of genital warts, and types 16, and 18 responsible for around 70% of cervical cancer in the US; and Cervarix, a vaccine against HPV types 16 and 18. Both contain recombinant L1 capsid protein from the different strains of HPV;
- RV5, an oral vaccine against human rotavirus gastroenteritis. Capsid proteins from human rotaviruses have been expressed on the surface of harmless non-human rotavirus strains.

Toxoid

A toxoid is an exotoxin treated so as to be non-poisonous but still immunogenic. Examples of vaccines containing toxoids include the diphtheria and tetanus components of the DTaP and Td vaccines. The body responds by making antibodies capable of neutralizing the exotoxin. The antigen may be adsorbed to an adjuvant, a substance such as aluminum hydroxide or aluminum phosphate that is not immunogenic but enhances the immunogenicity of antigens.

Flash animation showing neutralization of an exotoxin.

html5 version of animation for iPad showing neutralization of an exotoxin.

Routine immunization practices protect more than just the individuals receiving the vaccine. When a critical portion of a community becomes immunized against a particular infectious disease, most members of the community - including those who were not immunized - are protected against that disease because there is little opportunity for an outbreak. This is known as herd immunity or community immunity.

Passive Artificially Acquired Immunity

Passive artificially acquired immunity refers to the injection of antibody-containing serum, or immune globulin (IG), from another person or animal. Since the body is not making its own antibodies and memory cells are not produced, passive artificially acquired immunity is short lived and offers only mediate, short term protection. Also, the injection of serum during passive immunization carries a greater risk of allergic reactions than the injection of antigens during active immunization. These allergic reactions are referred to as serum sickness and will be discussed later under hypersensitivities.

Examples include:

- The use of pooled adult human immune globulin (IG) to prevent hepatitis A and measles and to prevent infections in people with certain immunodeficiency diseases;
- Human HBIG to prevent hepatitis B in those not actively immunized with the HepB vaccine;
- Human TIG to prevent tetanus in those not actively immunized with the DTP, DTaP, or Td vaccines;
- RhoGAM to prevent Rh hemolytic disease of newborns;
- VZIG to prevent varicella;
- CMV-IGIV to prevent cytomegalovirus infections in highly immunosuppressed individuals;
- RIG to prevent rabies, given concurrently with active immunization with the rabies vaccine;
- The antisera used for botulism; and
- IVIG (intravenous immune globulin), now being used to reduce infections in people with certain immunosuppressive diseases such as primary immunodeficiency syndrome and chronic lymphocytic leukemia as well as to treat certain autoimmune diseases such as immune thrombocytopenia purpura (ITP) and Kawasaki disease.

Tetanus provides a nice example of how active immunization (DTaP) and passive immunization (TIG) may be used in preventing a disease (Table **10.4.3*B*.13**.3B.1:).

Table **10.4.3*B*.13**.3B.1: Tetanus prophylaxis in Routine Wound Management

History of tetanus toxoid doses	**Clean, minor wound**		**All other wounds (1)**	
	Td (2)	TIG (3)	Td	TIG
Unknown or < 3	Yes	No	Yes	Yes
Three or more	No (4)	No	No (5)	No

(1) Such as, but not limited to, wounds contaminated with dirt, feces, soil, saliva, etc.: puncture wounds, avulsions, and wounds resulting from missles, crushing, burns, and frostbite.
(2) Tetanus toxoid, diphtheria toxoid (active immunization).
(3) Tetanus Immune Globulin (passive immunization).
(4) Yes, if more than 10 years since last dose.
(5) Yes, if more than 5 years since last dose. (More frequent boosters are not needed and can accentuate side effects.)

There is also some early evidence that immunization may be of value in the treatment of some infections as well as in their prevention, possibly by supercharging the immune system of those already infected. Vaccine therapies in various stages of testing include those against diseases such as herpes, leprosy, tuberculosis, and hepatitis B.

? A patient with a deep puncture wound who has never received a DTaP vaccination is given both Td and TIG. Another patient with an identical wound and who had 4 DTaP vaccinations as a child and a Td booster 3 years ago is given nothing. Discuss the reasoning behind this.

This page titled 10.4.3B: Artificially Acquired Immunity is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **13.3B: Artificially Acquired Immunity** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

10.4.E: Humoral Immunity (Exercises)

These are homework exercises to accompany Kaiser's "Microbiology" TextMap. Microbiology is the study of microorganisms, which are defined as any microscopic organism that comprises either a single cell (unicellular), cell clusters or no cell at all (acellular). This includes eukaryotes, such as fungi and protists, and prokaryotes. Viruses and prions, though not strictly classed as living organisms, are also studied.

13.1: Antibodies (Immunoglobulins)

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Define antibody.
2. In terms of infectious disease, state what humoral immunity is most effective against.

13.1A: An Overview

13.1B: Antibody Structure

13.1C: The 5 Classes (Isotypes) of Human Antibodies

13.1D: Generation of Antibody Diversity

13.1E: Clonal Selection and Clonal Expansion

13.1F: Anamnestic (Memory) Response

13.2: Ways That Antibodies Help to Defend the Body

- List 9 ways that antibodies help to defend the body.

13.2A: Opsonization

13.2B: Cytolysis by the Membrane Attack Complex (MAC)

13.2C: Antibody-dependent Cellular Cytotoxicity (ADCC) by Natural Killer Cells

13.2D: Neutralization of Exotoxins

13.2E: Neutralization of Viruses

13.2F: Preventing Bacterial Adherence

13.2G: Agglutination of Microorganisms

13.2H: Immobilization of Bacteria and Protozoans

13.2I: Promoting an Inflammatory Response

13.3: Naturally and Artificially Acquired Active and Passive Immunity

1. Define the following:
    a. active immunity
    b. passive immunity
2. Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

    1.Matching

_____ Antibodies made in another person or animal enter the body and the immunity is short-lived.

_____ Antigens enter the body and the body responds by making its own antibodies and B-memory cells.

A. active immunity
B. passive immunity

13.3A: Naturally Acquired Immunity

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Give an example of naturally acquired active immunity.
2. Give two examples of naturally acquired passive immunity.
   A.
   B.
3. State why naturally acquired passive immunity is important to newborns and infants.

13.3B: Artificially Acquired Immunity

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Define and give an example of artifically acquired passive immunity.
2. Define and give an example of artifically acquired active immunity.
3. List 3 different forms of antigen that may be used for artificially acquired active immunity and state 2 common examples of each.
   A.
   B.
   C.
4. A patient with a deep puncture wound who has never received a DTP vaccinationis given both Td and TIG. Another patient with an identical wound and who had 4 DTP vaccinationsas a child and a Td booster 3 years ago is given nothing. Discuss the reasoning behind this. (hint: see Fig. 1)

This page titled 10.4.E: Humoral Immunity (Exercises) is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **13.E: Humoral Immunity (Exercises)** has no license indicated.

SECTION OVERVIEW

10.5: Cell-Mediated Immunity

Cell-mediated immunity (CMI) is an immune response that does not involve antibodies but rather involves the activation of macrophages and NK-cells, the production of antigen-specific cytotoxic T-lymphocytes, and the release of various cytokines in response to an antigen. Cellular immunity protects the body by:

- Activating antigen-specific cytotoxic T-lymphocytes (CTLs) that are able to lyse body cells displaying epitopes of foreign antigen on their surface, such as virus-infected cells, cells with intracellular bacteria, and cancer cells displaying tumor antigens;
- Activating macrophages and NK cells, enabling them to destroy intracellular pathogens; and
- Stimulating cells to secrete a variety of cytokines that influence the function of other cells involved in adaptive immune responses and innate immune responses.

Cell-mediated immunity is directed primarily microbes that survive in phagocytes and microbes that infect non-phagocytic cells. It is most effective in destroying virus-infected cells, intracellular bacteria, and cancers. It also plays a major role in delayed transplant rejection.

Topic hierarchy

10.5.1: Cell-Mediated Immunity - An Overview

10.5.2: Activating Antigen-Specific Cytotoxic T- Lymphocytes

10.5.3: Activating Macrophages and NK Cells

10.5.4: Stimulating Cells to Secrete Cytokines

10.5.E: Cell-Mediated Immunity (Exercises)

Template:HideTOC

This page titled 10.5: Cell-Mediated Immunity is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

This page titled 10.5: Cell-Mediated Immunity is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

10.5.1: Cell-Mediated Immunity - An Overview

Learning Objectives

1. Briefly compare humoral immunity with cell-mediated immunity.
2. Define cell-mediated immunity and state what it is most effective against.
3. State three different ways by which cell-mediated immunity protects the body.
4. Define gene translocation and relate it to each T-lymphocyte being able to produce T-cell receptor with a unique shape.
5. Define the following:
    a. combinatorial diversity
    b. junctional diversity
6. In terms of cell-mediated immunity, state what is meant by anamnestic response and discuss its role in immune defense.
7. Briefly describe why there is a heightened secondary response during anamestic response.

Cell-mediated immunity (CMI) is an immune response that does not involve antibodies but rather involves the activation of macrophages and NK-cells, the production of antigen-specific cytotoxic T-lymphocytes, and the release of various cytokines in response to an antigen . Cellular immunity protects the body by:

1. Activating antigen-specific cytotoxic T-lymphocytes (CTLs) that are able to destroy body cells displaying epitopes of foreign antigen on their surface, such as virus-infected cells, cells with intracellular bacteria, and cancer cells displaying tumor antigens;
2. Activating macrophages and NK cells, enabling them to destroy intracellular pathogens; and
3. Stimulating cells to secrete a variety of cytokines that influence the function of other cells involved in adaptive immune responses and innate immune responses.

Cell-mediated immunity is directed primarily microbes that survive in phagocytes and microbes that infect non-phagocytic cells. It is most effective in destroying virus-infected cells, intracellular bacteria, and cancers. It also plays a major role in delayed transplant rejection.

Generation of T-cell receptor (TCR) diversity through gene translocation

As mentioned earlier, the immune system of the body has no idea as to what antigens it may eventually encounter. Therefore, it has evolved a system that possesses the capability of responding to any conceivable antigen. The immune system can do this because both B-lymphocytes and T-lymphocytes have evolved a unique system of gene-splicing called gene translocation, a type of gene-shuffling process where various different genes along a chromosome move and join with other genes from the chromosome. To demonstrate this gene translocation process, we will look at how each T-lymphocyte becomes genetically programmed to produce a T-cell receptor (TCR) having a unique shape to fit a specific epitope.

In a manner similar to B-lymphocytes, T-lymphocytes are able to cut out and splice together different combinations of genes along their chromosomes. Through random gene translocation, any combination of the multiple forms of each gene can join together. This is known as *combinatorial diversity*. The T-cell receptors or TCRs (Figure **10.5.1.1**) of most T-lymphocytes involved in adaptive immunity consist of an alpha (a) and a beta (ß) chain. There are 70-80 different V_a genes and 61 different J_a genes that code for the variable portion of the a chain of the TCR. Likewise, there are 52 $V_ß$ genes, 1 $D_{ß1}$ gene, 1 $D_{ß2}$ gene, and 6-7 $J_ß$ genes that can recombine to form the variable portion of the TCR.

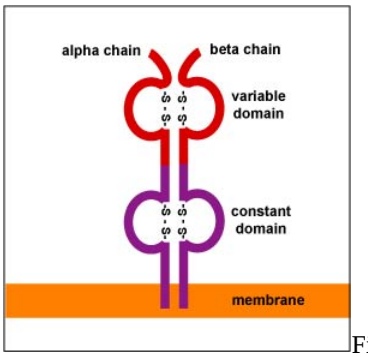


Figure **10.5.1.1**:The T-Cell Receptor. Most T-cell receptors are composed of two polypeptide chains, an alpha (α) chain and a beta (β) chain. The variable domains of the α and β chains (red) provide specificity for binding a peptide bound to a MHC molecule. The terminus of the constant domains (purple) anchors the receptor to the cytoplasmic membrane of the T-lymphocyte. (S-S = disulfide bond)

During gene translocation, specialized enzymes in the T-lymphocyte cause splicing inaccuracies wherein additional nucleotides are added or deleted at the various gene junctions. This change in the nucleotide base sequence generates even greater diversity in Fab shape. This is called *junctional diversity*. Unlike the BCR, somatic hypermutation does not occur during the production of the TCRs. As a result of combinatorial diversity and junctional diversity, each T-lymphocyte is able to produce a unique shaped T-cell receptor (TCR) capable of reacting with complementary-shaped peptide bound to a MHC molecule.

Anamnestic Response (Memory)

As a result of T-lymphocytes recognizing epitopes of protein antigens during cell-mediated immunity, numerous circulating **T8-memory cells** and **T4-memory cells** develop which possess anamnestic response or memory. These T-memory cells persist for the remainder of a person's life. Effector memory T-cells (T_{EM} cells) circulate in the blood whereas tissue resident memory T-cells (T_{RM} cells) are found within the epithelium of the skin and mucous membranes. CD8 T_{RM} cells are typically activated by viral antigens and subsequently produce inflammatory cytokines that trigger an innate immune response for nonspecific antiviral activity. CD4 T_{RM} cells are found in clusters surrounding macrophages in the mucosa. Unlike T_{EM} cells, T_{RM} cells do not circulate in the blood and are not replenished from the blood. They remain in peripheral tissues.

A subsequent exposure to that same antigen results in:

- A more rapid and longer production of cytotoxic T-lymphocytes (CTLs);
- A more rapid and longer production of T4-effector lymphocytes; and
- Triggering of nonspecific innate immune responses.

Clonal Selection and Clonal Expansion

As mentioned above, during early differentiation of naive T-lymphocytes in the thymus marrow, each T4-lymphocyte and each T8-lymphocyte becomes genetically programmed to make a T-cell receptor or TCR with a unique shape through a series of gene translocations, and molecules of that TCR are put on its surface of that T-lymphocyte to function as its epitope receptor. When an antigen encounters the immune system, epitopes from protein antigens bound to MHC-I or MHC-II molecules eventually will react with a naive T4- and T8-lymphocyte with TCRs and CD4 or CD8 molecules on its surface that more or less fit and this activates that T-lymphocyte. This process is known as *clonal selection*.

Cytokines produced by effector T4-helper lymphocytes enable the now activated T4- and T8-lymphocyte to rapidly proliferate to produce large clones of thousands of identical T4- and T8-lymphocytes. In this way, even though only a few T-lymphocytes in the body may have TCR molecule able to fit a particular epitope, eventually many thousands of cells are produced with the right specificity. This is referred to as clonal expansion. These cells then differentiate into effector T4-lymphocytes and cytotoxic T-lymphocytes or CTLs.

Cellular immunity is also the mechanism behind delayed hypersensitivity (discussed later in this unit). Delayed hypersensitivity is generally used to refer to the harmful effects of cell-mediated immunity (tissue and transplant rejections, contact dermatitis, positive skin tests like the PPD test for tuberculosis, granuloma formation during tuberculosis and deep mycoses, and destruction of virus-infected cells).

Summary

1. Cell-mediated immunity (CMI) is an immune response that does not involve antibodies but rather involves the activation of macrophages and NK-cells, the production of antigen-specific cytotoxic T-lymphocytes, and the release of various cytokines in response to an antigen.
2. Cell-mediated immunity is directed primarily microbes that survive in phagocytes and microbes that infect non-phagocytic cells. It is most effective in destroying virus-infected cells, intracellular bacteria, and cancers.
3. In a manner similar to B-lymphocytes, T-lymphocytes are able to randomly cut out and splice together different combinations of genes along their chromosomes through a process called gene translocation. This is known as combinatorial diversity and results in each T-lymphocyte generating a unique T-cell receptor (TCR).
4. During gene translocation, specialized enzymes in the T-lymphocyte cause splicing inaccuracies wherein additional nucleotides are added or deleted at the various gene junctions. This change in the nucleotide base sequence generates even greater diversity in the shape of the TCR. This is called junctional diversity.
5. As a result of combinatorial diversity and junctional diversity, each T-lymphocyte is able to produce a unique shaped T-cell receptor (TCR) capable of reacting with complementary-shaped peptide bound to a MHC molecule.
6. As a result of T-lymphocytes recognizing epitopes of protein antigens during cell-mediated immunity, numerous circulating T8-memory cells and T4-memory cells) develop which possess anamnestic response or memory.
7. A subsequent exposure to that same antigen results in a more rapid and longer production of cytotoxic T-lymphocytes (CTLs), and a more rapid and longer production of T4-effector lymphocytes.
8. When an antigen encounters the immune system, epitopes from protein antigens bound to MHC-I or MHC-II molecules eventually will react with a naive T4- and T8-lymphocyte with TCRs and CD4 or CD8 molecules on its surface that more or less fit and this activates that T-lymphocyte. This process is known as clonal selection.
9. Cytokines produced by effector T4-helper lymphocytes enable the now activated T4- and T8-lymphocyte to rapidly proliferate to produce large clones of thousands of identical T4- and T8-lymphocytes. This is referred to as clonal expansion.

This page titled 10.5.1: Cell-Mediated Immunity - An Overview is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **14.1: Cell-Mediated Immunity - An Overview** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

10.5.2: Activating Antigen-Specific Cytotoxic T- Lymphocytes

Learning Objectives

1. In terms of the role of cytotoxic T-lymphocytes (CTLs) in body defense:
   a. State from what cells cytotoxic T-lymphocytes are derived.
   b. Describe how they can react with and destroy virus-infected cells, cells containing intracellular bacteria, and cancer cells without harming normal cells. (Indicate the role of following: TCR, CD4, MHC-I, and peptides from endogenous antigens.)
   c. State the mechanism by which cytotoxic T-lymphocytes kill the cells to which they bind. (Indicate the role of the following: perforins, granzymes, caspases, and macrophages in the process.)
2. Briefly describe two ways certain viruses may evade cell-mediated immunity.

Marking an Infected Cell or a Tumor Cell for Destruction by Cytotoxic T-Lymphocytes

One of the body's major defenses against viruses, intracellular bacteria, and cancers is the destruction of infected cells and tumor cells by cytotoxic T-lymphocytes (CTLs). These CTLs are effector cells derived from naive T8-lymphocytes during cell-mediated immunity. Both T8-lymphocytes and CTLs produce T-cell receptors or TCRs and CD8 molecules that are anchored to their surface.

a. The TCRs and CD8 molecules on the surface of naive T8-lymphocytes are designed to recognize peptide epitopes bound to MHC-I molecules on antigen-presenting cells or APCs .
b. The TCRs and CD8 molecules on the surface of cytotoxic T-lymphocytes (CTLs) are designed to recognize peptide epitopes bound to MHC-I molecules on infected cells and tumor cells.

During the replication of viruses and intracellular bacteria within their host cell, as well as during the replication of tumor cells, viral, bacterial, or tumor proteins in the cytosol of that cell are degraded into a variety of peptide epitopes by cylindrical organelles called proteasomes . Other endogenous antigens such as proteins released into the cytosol from the phagosomes of antigen-presenting cells, such as macrophages and dendritic cells as well, as a variety of the human cell's own proteins (self-proteins) are also degraded by proteasomes. As these various endogenous antigens pass through proteasomes, proteases and peptidases chop the protein up into a series of peptides, typically 8-11 amino acids long (Figure 10.5.2.1).

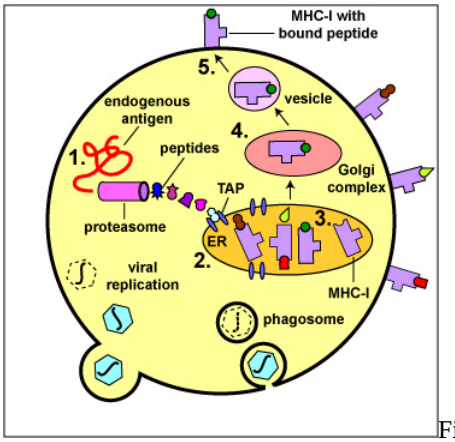
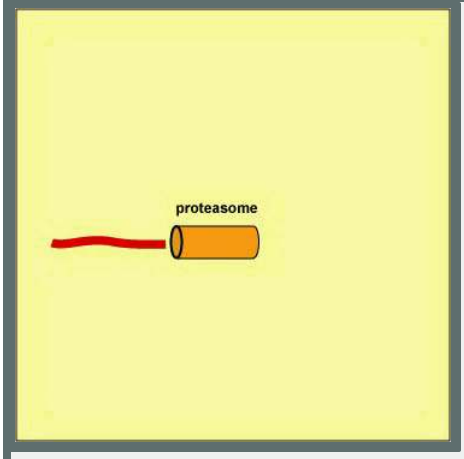


Figure 10.5.2.1: Binding of Peptide Epitopes from Endogenous Antigens to MHC-I Molecules. Endogenous antigens are those located within the cytosol of cells of the body. Examples include: a. viral proteins produced during viral replication, b. proteins produced by intracellular bacteria such as Rickettsias and Chlamydias during their replication, c. proteins that have escaped into the cytosol from the phagosome of phagocytes such as antigen-presenting cells d. tumor antigens produced by cancer cells, e. and self peptides from human cell proteins. The body marks infected cells and tumor cells for destruction by placing peptide epitopes from these endogenous antigens on their surface by way of MHC-I molecules. Cytotoxic T-lymphocytes (CTLs) are then able to recognize peptide/MHC-I complexes by means of their T-cell receptors (TCRs)

and CD8 molecules and kill the cells to which they bind. 1. Endogenous antigens, such as viral proteins, pass through proteasomes where they are degraded into a series of peptides. 2. The peptides are transported into the rough endoplasmic reticulum (ER) by a transporter protein called TAP. 3. The peptides then bind to the grooves of newly synthesized MHC-I molecules. 4. The endoplasmic reticulum transports the MHC-I molecules with bound peptides to the Golgi complex. 5. The Golgi complex, in turn, transports the MHC-I/peptide complexes by way of an exocytic vesicle to the cytoplasmic membrane where they become anchored. Here, the peptide and MHC-I/peptide complexes can be recognized by CTLs by way of TCRs and CD8 molecules having a complementary shape.

of a proteasome degrading proteins into peptides



During the replication of viruses and intracellular bacteria within their host cell, as well as during the replication of tumor cells, viral, bacterial, or tumor proteins, as well proteins released from phagosomes of phagocytes and various human cell or self-proteins, are degraded into a variety of peptide epitopes by cylindrical organelles called proteasomes. As endogenous antigens pass through proteasomes, proteases and peptidases chop the protein up into a series of peptides, typically 8-11 amino acids long.

A transporter protein called TAP located in the membrane of the cell's endoplasmic reticulum then transports these peptide epitopes into the endoplasmic reticulum where they bind to the grooves of various newly made MHC-I molecules. The MHC-I molecules with bound peptides are then transported to the Golgi complex and placed in exocytic vesicles. The exocytic vesicles carry the MHC-I/peptide complexes to the cytoplasmic membrane of the cell where they become anchored to its surface (Figure **10.5.2.2**). A single cell may have up to 250,000 molecules of MHC-I with bound epitope on its surface.

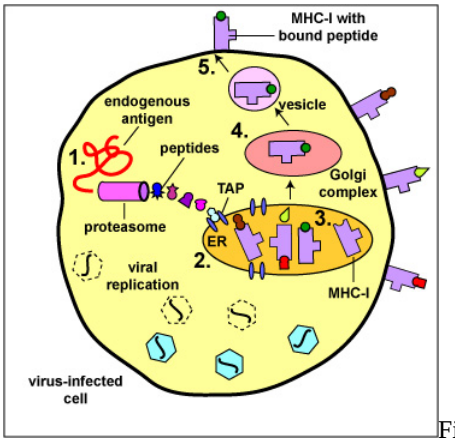


Figure **10.5.2.2**: Binding of Peptide Epitopes from Endogenous Antigens to MHC-I Moleculesby a Virus-Infected Cell. *The body marks infected cells and tumor cells for destruction by placing peptide epitopes from these endogenous antigens on their surface by way of MHC-I molecules. Cytotoxic T-lymphocytes (CTLs) are then able to recognize peptide/MHC-I complexes by means of their T-cell receptors (TCRs) and CD8 molecules and kill the cells to which they bind: (1) During viral replication within the host cell, endogenous antigens,*

such as viral proteins, pass through proteasomes where they are degraded into a series of peptides. (2) The peptides are transported into the rough endoplasmic reticulum (ER) by a transporter protein called TAP. (3) The peptides then bind to the grooves of newly synthesized MHC-I molecules. (4) The endoplasmic reticulum transports the MHC-I molecules with bound peptides to the Golgi complex. (5) The Golgi complex, in turn, transports the MHC-I/peptide complexes by way of an exocytic vesicle to the cytoplasmic membrane where they become anchored. Here, the peptide and MHC-I/peptide complexes can be recognized by CTLs by way of TCRs and CD8 molecules having a complementary shape.

During cell-mediated immunity, MHC-I molecule with bound peptide on the surface of infected cells and tumor cells can be recognized by a complementary-shaped TCR/CD8 on the surface of a cytotoxic T-lymphocyte (CTL) to initiate destruction of the cell containing the endogenous antigen (Figure **10.5.2.3**).

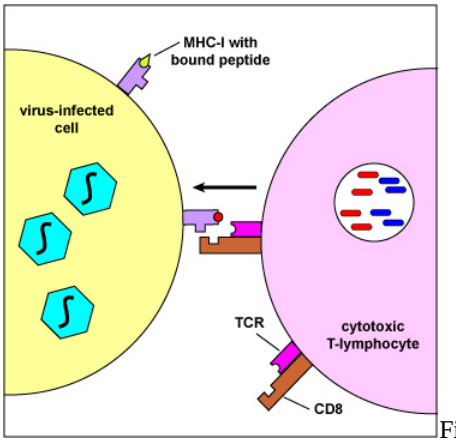


Figure **10.5.2.3**: A Cytotoxic T-lymphocyte Recognizing a Virus-Infected Cell. Endogenous antigens are those being produced within cells of the body. Examples include proteins from replicating viruses, proteins from intracellular bacteria, and tumor antigens. The body marks infected cells and tumor cells for destruction by placing peptide epitopes from these endogenous antigens on their surface by way of MHC-I molecules. Cytotoxic T-lymphocytes (CTLs) are then able to recognize peptide/MHC-I complexes by means of their T-cell receptors (TCRs) and CD8 molecules and kill the cells to which they bind.

Endogenous antigens

Endogenous antigens are those located within the cytosol of cells of the body. Examples include:

a. viral proteins produced during viral replication,
b. proteins produced by intracellular bacteria such as Rickettsias and Chlamydias during their replication,
c. proteins that have escaped into the cytosol from the phagosome of phagocytes such as antigen-presenting cells
d. tumor antigens produced by cancer cells,
e. and self peptides from human cell proteins.

The body marks infected cells and tumor cells for destruction by placing peptide epitopes from these endogenous antigens on their surface by way of MHC-I molecules. Cytotoxic T-lymphocytes (CTLs) are then able to recognize peptide/MHC-I complexes by means of their T-cell receptors (TCRs) and CD8 molecules and kill the cells to which they bind.

1. Endogenous antigens, such as viral proteins, pass through proteasomes where they are degraded into a series of peptides.
2. The peptides are transported into the rough endoplasmic reticulum (ER) by a transporter protein called TAP.
3. The peptides then bind to the grooves of newly synthesized MHC-I molecules.
4. The endoplasmic reticulum transports the MHC-I molecules with bound peptides to the Golgi complex.
5. The Golgi complex, in turn, transports the MHC-I/peptide complexes by way of an exocytic vesicle to the cytoplasmic membrane where they become anchored. Here, the peptide and MHC-I/peptide complexes can be recognized by CTLs by way of TCRs and CD8 molecules having a complementary shape.

Cytotoxic T-Lymphocyte (CTL) Destruction of Body Cells Displaying Epitopes of Foreign Antigen on their Surface

The cytotoxic T-lymphocytes (CTLs) produced during cell-mediated immunity are designed to remove body cells displaying "foreign" epitope, such as virus-infected cells, cells containing intracellular bacteria, and cancer cells with mutant surface proteins. The CTLs are able to kill these cells by inducing a programmed cell death known as apoptosis. Using virus-infected cells as an example, the CTLs circulate throughout the body where they encounter virus-infected cells and induce apoptosis. This involves involves a complex of intracellular cytotoxic granules containing:

1. Pore-forming proteins called perforins
2. Proteolytic enzymes called granzymes and
3. Granulysin

When the TCR and CD8 of the CTL binds to the MHC-I/epitope on the surface of the virus-infected cell or tumor cell (Figure **10.5.2.4**), this sends a signal through a CD3 molecule which triggers the release of the cytotoxic perforins/granzymes/granulysin granules from the CTL.

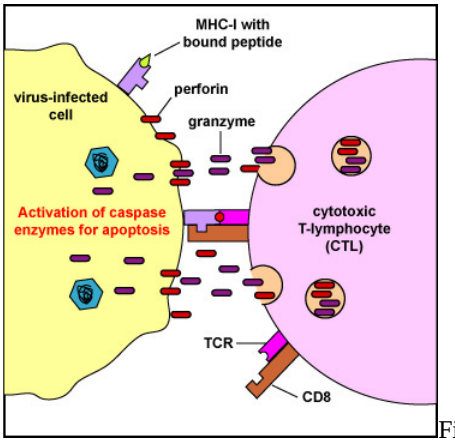


Figure **10.5.2.4**: Cytotoxic T-lymphocyte (CTL)-Induced Apoptosis of a Virus-Infected Cell. Binding of the CTL to the infected cell triggers the CTL to release pore-forming proteins called perforins, proteolytic enzymes called granzymes, and chemokines. Granzymes pass through the pores and activate the caspase enzymes that lead to apoptosis of the infected cell by means of destruction of its structural cytoskeleton proteins and by chromosomal degradation. As a result, the cell breaks into fragments that are subsequently removed by phagocytes.

The exact mechanism of entry of the granzymes into the infected cell or tumor cell is still debated. It is, however, dependent on perforins. Possibilities include:

1. The perforins/granzymes/granulysin complex may be taken into the target cell by receptor-mediated endocytosis. The perforin molecules may then act on the endosomal membrane allowing granzymes to enter the cytosol.
2. The perforin molecules may put pores in the membrane of the target cell allowing the granzymes to directly enter the cytosol (Figure **10.5.2.5**).

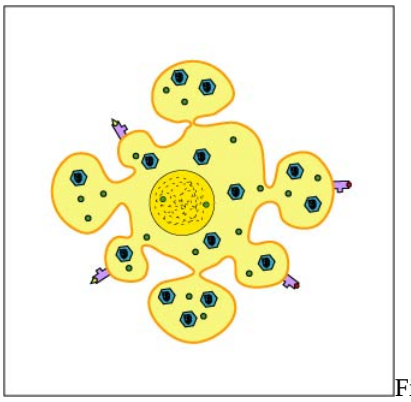


Figure 10.5.2.5: CTL-Induced Apoptosis of a Virus-Infected Cell. Binding of the CTL to the infected cell triggers the CTL to release pore-forming proteins called perforins, proteolytic enzymes called granzymes, and chemokines. Granzymes pass through the perforin pores and activate the enzymes that lead to apoptosis of the infected cell by means of destruction of its structural cytoskeleton proteins and by chromosomal degradation. As a result, the cell breaks into fragments that are subsequently removed by phagocytes. This prevents the release of any mature viruses that might occur if the infected cell was lysed.

Killing of the infected cell or tumor cell by apoptosis involves a variety of mechanisms:

1. Certain granzymes can activate the caspase enzymes that lead to apoptosis of the infected cell. The caspases are proteases that destroy the protein structural scaffolding of the cell - the cytoskeleton - and nucleases that degrade both the target cell's nucleoprotein and any microbial DNA within the cell (Figure 10.5.2.5).
2. Granzymes cleave a variety of other cellular substrates that contribute to cell death.
3. The perforin molecules may also polymerize and form pores in the membrane of the infected cell, similar to those produced by MAC. This can increase the permeability of the infected cell and contribute to cell death. If enough perforin pores form, the cell might not be able to exclude ions and water and may undergo cytolysis.
4. Granulysin has antimicrobial actions and can also induce apoptosis.
    - Electron micrograph of a CTL binding to a tumor cell.
    - Electron micrograph showing a killed tumor cell.

- CTLs can also trigger apoptosis through FasL/Fas interactions. Activated lymphocytes express both death receptors called Fas and Fas ligand or FasL (Figure 10.5.2.6) on their surface. This FasL/Fas interaction triggers an intracellular transduction that activates the caspase enzymes that lead to apoptosis. In this way, CTLs can kill other lymphocytes and terminate lymphocyte proliferation after the immune responses have eradicated an infection.

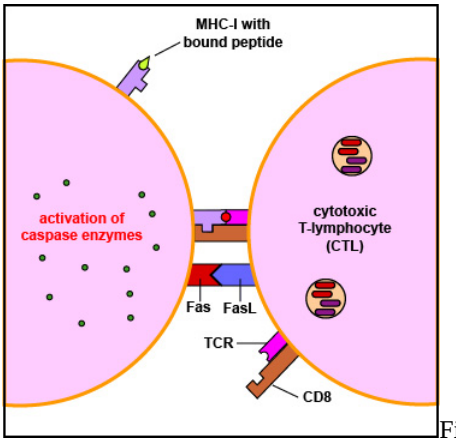


Figure 10.5.2.6: A Cytotoxic T-Lymphocyte (CTL) Inducing Apoptosis by Fas/FasL Interaction. A cytotoxic T-lymphocyte (CTL), by way of its TCR and CD8, can bind to MHC-I/epitope on a virus-infected and cause apoptosis by way of perforins and granzymes. In addition, a Fas ligand (FasL) on the CTL can bind to a Fas molecule on the surface of many cell types and activate the enzymes that lead to apoptosis. Most likely this mechanism is used to remove effector lymphocytes once they are no longer needed after an adaptive immune response.

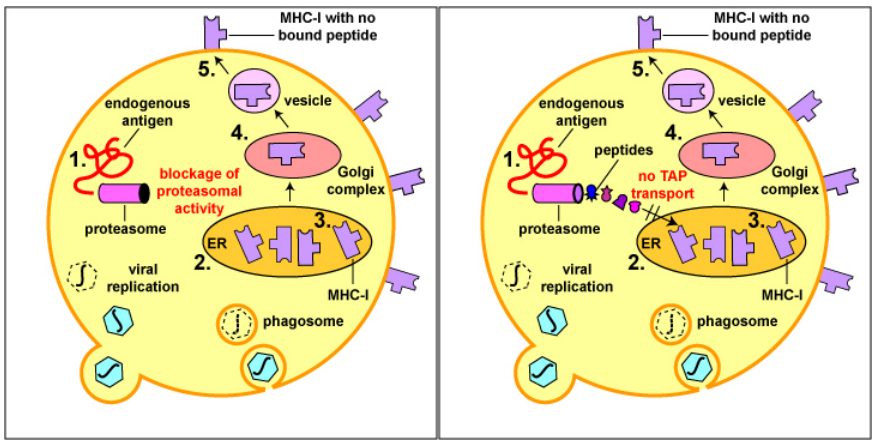
Death by apoptosis does not result in the release of cellular contents such as inflammatory mediators or viruses as occurs during immune-induced cell lysis. Instead, the cell breaks into membrane-bound apoptoptic fragments that are subsequently removed by macrophages. This reduces inflammation and also prevents the release of viruses that have assembled within the infected cell and their spread into uninfected cells. Since the CTLs are not destroyed in these reactions, they can function over and over again to destroy more virus-infected cells.

? Exercise: Think-Pair-Share Questions

1. Some viruses inhibit proteasomal activity in the cells they infect. Explain specifically how this might better enable the virus to resist adaptive immunity.
2. Some viruses suppress the production of MHC-I molecules in the cells they infect. Explain specifically how this might better enable the virus to resist adaptive immunity.
3. Some viruses block the TAP transport of peptides into the endoplasmic reticulum of the cells they infect. Explain specifically how this might better enable the virus to resist adaptive immunity.
4. Some viruses block apoptosis of the cells they infect. Explain specifically how this might better enable the virus to resist adaptive immunity.

As with humoral immunity, certain microbes are able to evade to some degree cell-mediated immunity:

- Epstein-Barr virus (EBV) and cytomegalovirus (CMV) inhibit proteasomal activity so that viral proteins are not degraded into viral peptides. (see Figure 10.5.2.7A)
- Herpes simplex viruses (HSV) can block the TAP transport of peptides into the endoplasmic reticulum (see Figure 10.5.2.7B).
- Numerous viruses, such as the cytomegalovirus (CMV) and adenoviruses can block the formation of MHC-I molecules by the infected cell. As a result, no viral peptide is displayed on the infected cell and the CTLs are no longer able to recognize that the cell is infected and kill it (see Figure 10.5.2.7C).
- Epstein-Barr virus (EBV) down regulates several host proteins involved in attaching viral epitopes to MHC-I molecules and displaying them on the host cell's surface (see Figure 10.5.2.7D).
- Adenoviruses and Epstein-Barr Viruses (EBV) code for proteins that blocks apoptosis, the programmed cell suicide mechanism triggered by various defense mechanisms in order to destroy virus-infected cells.



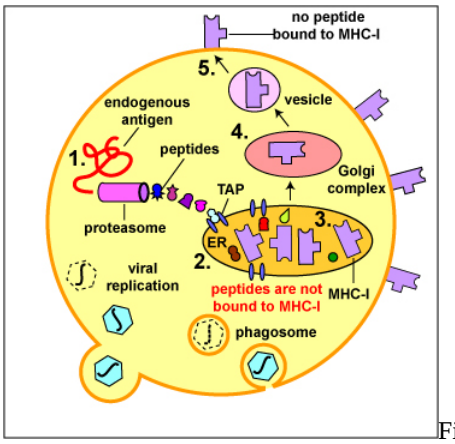


Figure **10.5.2.7**: (top left) Inhibition of Proteasome Activity. Epstein-Barr virus (EBV) and cytomegalovirus (CMV) inhibit proteosomal activity so that viral proteins are not degraded into viral peptides. (top right) Blockage of TAP Transport of Peptides into the Endoplasmic Reticulum. Herpes simplex viruses (HSV) can block the TAP transport of peptides into the endoplasmic reticulum. (bottom left) Suppression of the Synthesis of MHC-I Molecules. Numerous viruses, such as the cytomegalovirus (CMV) and adenoviruses can block the formation of MHC-I molecules by the infected cell. As a result, no viral peptide is displayed on the infected cell and the CTLs are no longer able to recognize that the cell is infected and kill it. (bottom right) Blockage of the Binding of Peptide Epitopes from Viruses to MHC-I Molecules. Epstein-Barr virus (EBV) down regulates several host proteins involved in attaching viral epitopes to MHC-I molecules and displaying them on the surface of the host cell. As a result, no viral peptide is displayed on the infected cell and the CTLs are no longer able to recognize that the cell is infected and kill it.

Summary

1. Cell-mediated immunity (CMI) is an immune response that does not involve antibodies but rather involves the activation of macrophages and NK-cells, the production of antigen-specific cytotoxic T-lymphocytes, and the release of various cytokines in response to an antigen.
2. Cell-mediated immunity is directed primarily microbes that survive in phagocytes and microbes that infect non-phagocytic cells.
3. One of the body's major defenses against viruses, intracellular bacteria, and cancers is the destruction of infected cells and tumor cells by cytotoxic T-lymphocytes or CTLs, effector cells derived from naïve T8-lymphocytes during cell-mediated immunity.
4. The TCRs and CD8 molecules on the surface of naive T8-lymphocytes are designed to recognize peptide epitopes bound to MHC-I molecules on antigen-presenting cells (APCs).
5. During the replication of viruses and intracellular bacteria within their host cell, as well as during the replication of tumor cells, viral, bacterial, or tumor proteins (endogenous antigens) in the cytosol of that cell are degraded into a variety of peptide epitopes by cylindrical organelles called proteasomes.
6. These peptide epitopes bind to MHC-I molecules being synthesized in the endoplasmic reticulum which are eventually transported to the cytoplasmic membrane of that cell.
7. During cell-mediated immunity, MHC-I molecule with bound peptide on the surface of infected cells and tumor cells can be recognized by a complementary-shaped TCR/CD8 on the surface of a cytotoxic T-lymphocyte (CTL) to initiate destruction of the cell containing the endogenous antigens.
8. When the TCR and CD8 of the CTL binds to the MHC-I/epitope on the surface of the virus-infected cell or tumor cell, this triggers the release of cytotoxic perforins/granzymes/ granulysin granules from the CTL that lead to apoptosis, a programmed cell suicide of that cell.
9. Cell death by apoptosis does not result in the release of cellular contents such as inflammatory mediators or viruses as occurs during immune-induced cell lysis.
10. During apoptosis, the cell breaks into membrane-bound apoptotic fragments that are subsequently removed by macrophages.

This page titled 10.5.2: Activating Antigen-Specific Cytotoxic T- Lymphocytes is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **14.2: Activating Antigen-Specific Cytotoxic T- Lymphocytes** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

10.5.3: Activating Macrophages and NK Cells

Learning Objectives

1. Describe how T_H1 effector cells are able to interact with and activate macrophages.
2. Describe how NK cells are able to recognize and destroy infected cells and cancer cells lacking MHC-I molecules.

After interacting with APCs, some naive T4-lymphocytes differentiate into a subset of effector cells called T_H1 cells. T_H1 cells function primarily to promote phagocytosis of microbes and the killing of intracellular microbes.

Activation of Macrophages

Effector T4-lymphocytes called T_H1 cells coordinate immunity against intracellular bacteria and promote opsonization by macrophages. They produce cytokines such as interferon-gamma (IFN-?) that promote cell-mediated immunity against intracellular pathogens, especially by activating macrophages that have either ingested pathogens or have become infected with intracellular microbes such as *Mycobacterium tuberculosis*, *Mycobacterium leprae*, *Leishmania donovani*, and *Pneumocystis jiroveci* that are able to grow in the endocytic vesicles of macrophages. Activation of the macrophage by T_H1 cells greatly enhances their antimicrobial effectiveness (Figure **10.5.3.1**).

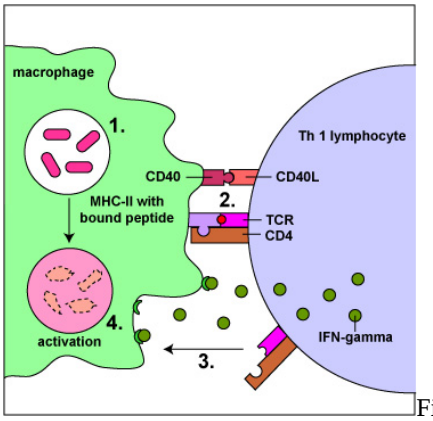


Figure **10.5.3.1:** Activation of a Macrophage by a T_H1 Lymphocyte. (1) Engulfed bacteria inside a phagosome or a phagolysosome. (2) An activated T_H1 lymphocyte binds to a peptide/MHC-II complex on a macrophage by way of its TCR and CD4 molecule. Co-stimulatory molecules such as CD40L on the T_H1 cell then bind toCD40 on a macrophage. (3) This triggers the T_H1 lymphocyte to secrete the cytokine interferon-gamma (IFN-Î³) that binds to IFN-Î³ receptors receptors on the macrophage. (4) The IFN-Î³ activates the macrophage enabling it to produce more hydrolytic lysosomal enzymes, nitric oxide, and toxic oxygen radicals that destroy the microorganisms within the phagosomes and phagolysosomes.

They produce cytokines that promote the production of increases the production of opsonizing and complement activating IgG that enhances phagocytosis (Figure **10.5.3.1**).

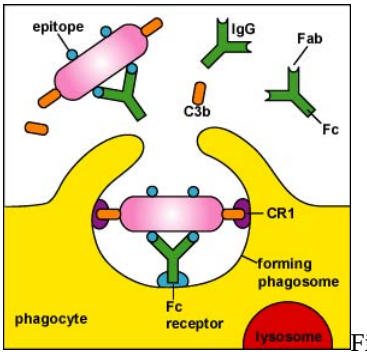


Figure **10.5.3.2**: Opsonization (Enhanced Attachment). The Fab portion of the antibody IgG binds to epitopes of an antigen such as this bacterium. The Fc portion of IgG then binds to Fc receptors on phagocytes

for opsonization or enhanced attachment. Once attached to the phagocyte the microbe can be engulfed more efficiently and placed in a phagosome. Complement pathway proteins such as C3b and C4b can also function as opsonins.

- They produce receptors that bind to and kill chronically infected cells, releasing the bacteria that were growing within the cell so they can be engulfed and killed by macrophages.
- They produce cytokines such as tumor necrosis factor-alpha (TNF-a) that promote diapedesis of macrophages.
- They produce the chemokine CXCL2 to attract macrophages to the infection site.

Activated natural killer T-lymphocytes (NKT cells) also produce large amounts of IFN-gamma to activate macrophages.

Activation of macrophages Increases their production of toxic oxygen radicals, nitric oxide, and hydrolytic lysosomal enzymes enabling the killing of microbes within their phagolysosomes. It also causes the macrophages to secrete cytokines such as TNF-a, IL-1, and IL-12. TNF-a and IL-1 promote inflammation to recruit phagocytic leukocytes. lL-12 enables naive T4-lymphocytes to differentiate into T_H1 cells. Moreover activation increases the production of B7 co-stimulator molecules and MHC-1 molecules by macrophages for increased T-lymphocyte activation.

Activation of NK Cells

Cytokines such as interleukin-2 (IL-2) and interferon-gamma (IFN-gamma) produced by T_H1 lymphocytes activate NK cells. NK cells are another group of cytolytic lymphocytes, distinct from B-lymphocytes and T-lymphocytes, that participate in both innate immunity and adaptive immunity. NK cells are lymphocytes that lack B-cell receptors and T-cell receptors. They are designed to kill certain mutant cells and virus-infected cells in one of two ways:

1. NK cells kill cells to which antibody molecules have attached through a process called antibody-dependent cellular cytotoxicity (ADCC) as shown in Figure 10.5.3.3 , Figure 10.5.3.4, and Figure 10.5.3.5 . The Fab portion of the antibody binds to epitopes on the "foreign" cell. The NK cell then binds to the Fc portion of the antibody. The NK cell is then able to contact the cell and by inducing a programmed cell suicide called **apoptosis**.

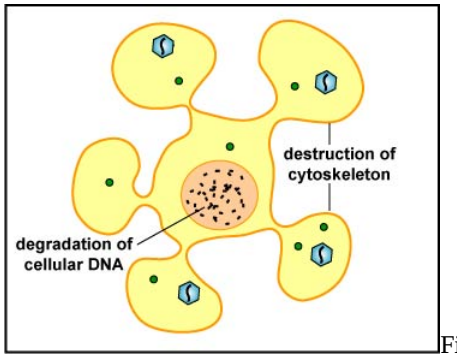


Figure 10.5.3.5: Destruction of Virus-Infected Cells by NK Cells through Antibody-Dependent Cellular Cytotoxicity (ADCC), Step-3. NK cells release pore-forming proteins called perforins and proteolytic enzymes called granzymes. Granzymes pass through the pores and activate the enzymes that lead to apoptosis, a programmed suicide of the infected cell. Apoptosis occurs when certain granzymes activate a group of protease enzymes called caspases that destroy the protein structural scaffolding of the cell, degrade the cell's nucleoprotein, and activate enzymes that degrade the cell's DNA. As a result, the infected cell breaks into membrane-bound fragments that are subsequently removed by phagocytes. If very large numbers of perforins are inserted into the plasma membrane of the infected cell, this can result in a weakening of the membrane and lead to cell lysis rather than apoptosis. An advantage to killing infected cells by apoptosis is that the cell's contents, including viable virus particles and mediators of inflammation, are not released as they are during cell lysis.

2. NK cells to use a duel receptor system in determining whether to kill or not kill human cells. When cells are either under stress, are turning into tumors, or are infected, various molecules such as MICA and MICB are produced and are put on the surface of that cell. The first receptor, called the **killer-activating receptor**, can bind to various molecules such as MICA and MICB that are produced and are put on the surface of that cell, and this sends a positive signal that enables the NK cell to kill the cell to which it has bound unless the second receptor cancels that signal. This second receptor, called the **killer-ihibitory receptor**, recognizes MHC-I molecules that are also usually present on all nucleated human cells. If MHC-I molecules are expressed on the cell, the killer-inhibitory receptor sends a negative signal that overrides the kill signal and prevents the NK cell from killing that cell (Figure 10.5.3.6).

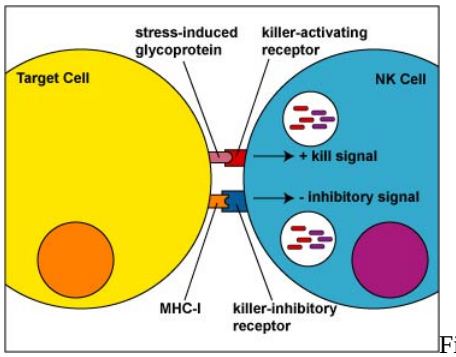


Figure 10.5.3.6: NK Cell Interacting with a Normal Body Cell. NK cells appear to use a duel receptor system in determining whether to kill or not kill human cells. NK cells appear to use a duel receptor system in determining whether to kill or not kill human cells. When cells are either under stress, are turning into tumors, or are infected, various stress-induced molecules are produced and are put on the surface of that cell. The first NK cell receptor, called thekiller-activating receptor, recognizes these stress-induced molecules. This interaction sends a positive signal which enables the NK cell to kill the cell to which it has bound unless the second receptor cancels that signal. This second receptor, called the killer-inhibitory receptor, recognizes MHC-I molecules that are also usually present on all nucleated human cells. If MHC-I molecules are expressed on the cell, the killer-inhibitory receptor sends a negative signal that overrides the kill signal and prevents the NK cell from killing that cell.

Viruses and malignant transformation can sometimes interfere with the ability of the infected cell or tumor cell to express MHC-I molecules. Without the signal from the killer-inhibitory receptor, the kill signal from the killer-activating signal is not overridden and the NK cell kills the cell to which it has bound (Figure 10.5.3.7).

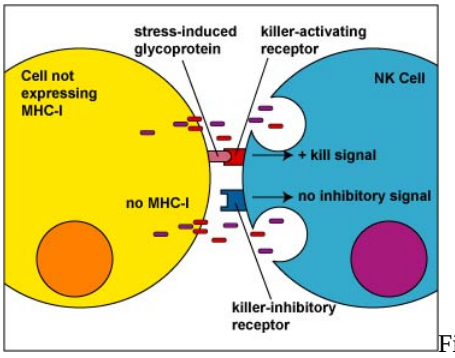


Figure 10.5.3.7: NK Cell Interacting with a Virus-Infected Cell or a Mutant Cell Not Expressing MHC-I Molecules. When cells are either under stress, are turning into tumors, or are infected, various stress-induced molecules are produced and are put on the surface of that cell. In addition, v iruses and malignant transformation can sometimes interfere with the ability of the infected cell or tumor cell to express MHC-I molecules. Without the signal from the killer-inhibitory receptor, the kill signal from the killer-activating signal is not overridden and the NK cell releases pore-forming proteins called perforins, proteolytic enzymes called granzymes, and chemokines. Granzymes pass through the pores and activate the enzymes that lead to apoptosis of the infected cell by means of destruction of its structural cytoskeleton proteins and by chromosomal degradation. As a result, the cell breaks into fragments that are subsequently removed by phagocytes. Perforins can also sometimes result in cell lysis.

The NK cell releases pore-forming proteins called perforins and proteolytic enzymes called granzymes. Granzymes pass through the pores and activate the enzymes that lead to apoptosis of the infected cell by means of destruction of its structural cytoskeleton proteins and by chromosomal degradation. As a result, the cell breaks into fragments that are subsequently removed by macrophages (Figure 10.5.3.5). Perforins can also sometimes result in cell lysis. The distinction between causing apoptosis versus causing cell lysis is important because lysing a virus-infected cell would only release the virions, whereas apoptosis leads to destruction of the virus inside.

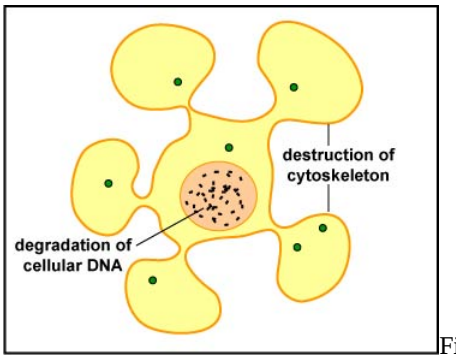


Figure 10.5.3.8: Apoptosis by NK Cells. Viruses and malignant transformation can sometimes interfere with the ability of the infected cell or tumor cell to express MHC-I molecules. Without the signal from the killer-inhibitory receptor, the kill signal from the killer-activating signal is not overridden and the NK cell kills the cell to which it has bound. The NK cell releases pore-forming proteins called perforins, proteolytic enzymes called granzymes, and chemokines. Granzymes pass through the pores and activate the enzymes that lead to apoptosis of the infected cell by means of destruction of its structural cytoskeleton proteins and by chromosomal degradation. As a result, the cell breaks into fragments that are subsequently removed by phagocytes. Perforins can also sometimes result in cell lysis.

NK cells also produce a variety of cytokines, including proinflammatory cytokines, chemokines, colony-stimulating factors, and other cytokines that function as regulators of body defenses. For example, through cytokine production NK cells also suppress and/or activate macrophages, suppress and/or activate the antigen-presenting capabilities of dendritic cells, and suppress and/or activate T-lymphocyte responses.

As with humoral immunity, certain microbes are able to evade to some degree NK cells:

- The cytomegalovirus (CMV) can also trigger its host cell to produce altered MHC-I molecules that are unable to bind viral epitopes, and, therefore, are not recognized by CTLs. However, NK cells are also unable to kill this infected cell because it is still displaying "MHC-I molecules" on its surface.
- CMV also produces microRNAs (miRNAs), small non-coding RNA molecules that down-regulates the production of stress-induced proteins that the killer-activating receptor of NK cells first recognizes. The miRNAs do this by binding to the host cell's mRNA coding for stress-induced proteins (Figure 10.5.3.14.3.9). Without this binding there is no kill signal by the NK cell.
- Cytomegalovirus (CMV) and herpes simplex type 1 virus (HSV-1) produce microRNAs (miRNAs), small non-coding RNA molecules that block protein involved in apoptosis, a programmed cell suicide. The miRNAs do this by binding to the host cell's mRNA coding for apoptosis-inducing proteins (Figure 10.5.3.9).



Figure 10.5.3.9: *Antisense RNA (microRNA or miRNA). When an antisense RNA (microRNA or miRNA) that is complementary to a mRNA coding for a particular protein or enzyme binds to the mRNA by complementary base pairing, that mRNA cannot be translated and the protein or enzyme is not made.*

Summary

1. Effector T4-lymphocytes called T_H1 cells coordinate immunity against intracellular bacteria and promote opsonization by macrophages.
2. Cytokines produced by T_H1 cells promote cell-mediated immunity against intracellular pathogens by activating macrophages and enhancing their antimicrobial effectiveness, increasing the production of opsonizing and complement activating IgG that enhances phagocytosis, and promoting diapedesis and chemotaxis of macrophages to the infection site.
3. Activation of natural killer T-lymphocytes (NKT cells) produces large amounts of IFN-gamma to activate macrophages.
4. Cytokines such as interleukin-2 (IL-2) and interferon-gamma (IFN-gamma) produced by T_H1 lymphocytes activate NK cells.
5. Activated NK cells kill cells to which antibody molecules have attached through a process called antibody-dependent cellular cytotoxicity (ADCC).

6. Activated NK cells also use a duel receptor system in determining whether to kill or not kill cells such as cancer cells and infected cells that are displaying stress molecules and are not producing MHC-I molecules.
7. NK cells kill infected cells and cancer cells by inducing apoptosis, a programmed cell suicide.

This page titled 10.5.3: Activating Macrophages and NK Cells is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **14.3: Activating Macrophages and NK Cells** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

10.5.4: Stimulating Cells to Secrete Cytokines

Learning Objectives

1. Define cytokine and explain what is meant by "cytokines are pleiotropic, redundant, and multifunctional."
2. Name 3 cytokines that regulate innate immune responses by triggering an inflammatory response.
3. Name the group of cytokines that regulates innate immunity by preventing translation of viral mRNA and by degrading both viral and host cell RNA.
4. Name 4 cytokines that regulate adaptive immune responses.
5. Name 2 cytokines that stimulate hematopoiesis.

Cytokines are low molecular weight, soluble proteins that are produced in response to an antigen and function as chemical messengers for regulating the innate and adaptive immune systems. They are produced by virtually all cells involved in innate and adaptive immunity, but especially by T helper (T_H) lymphocytes. The activation of cytokine-producing cells triggers them to synthesize and secrete their cytokines. The cytokines, in turn, are then able to bind to specific cytokine receptors on other cells of the immune system and influence their activity in some manner. Cytokines are pleiotropic, redundant, and multifunctional.

- Pleiotropic means that a particular cytokine can act on a number of different types of cells rather than a single cell type.
- Redundant refers to to the ability of a number of different cytokines to carry out the same function.
- Multifunctional means the same cytokine is able to regulate a number of different functions.

Some cytokines are antagonistic in that one cytokine stimulates a particular defense function while another cytokine inhibits that function. Other cytokines are synergistic wherein two different cytokines have a greater effect in combination than either of the two would by themselves. There are three functional categories of cytokines:

1. Cytokines that regulate innate immune responses,
2. Cytokines that regulate adaptive Immune responses, and
3. Cytokines that stimulate hematopoiesis.

Cytokines that Regulate Innate Immunity

a. Cytokines that regulate innate immunity are produced primarily by mononuclear phagocytes such as macrophages and dendritic cells, although they can also be produced by T-lymphocytes, NK cells, endothelial cells, and mucosal epithelial cells. They are produced primarily in response to pathogen-associated molecular patterns (PAMPs) such as LPS, peptidoglycan monomers, teichoic acids, unmethylated cytosine-guanine dinucleotide or CpG sequences in bacterial and viral genomes, and double-stranded viral RNA. Cytokines produced in response to PRRs on cell surfaces, such as the inflammatory cytokines IL-1, IL-6, IL-8, and TNF-alpha, mainly act on leukocytes and the endothelial cells that form blood vessels in order to promote and control early inflammatory responses (Figure 10.5.4.1).

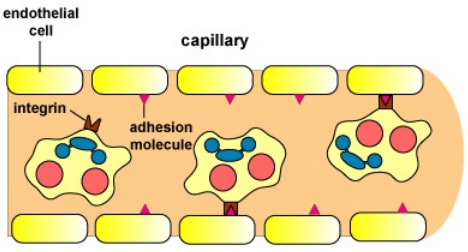


Figure 10.5.4.1: Diapedesis During Inflammation. Integrins on the surface of the leukocyte bind to adhesion molecules on the inner surface of the vascular endothelial cells. The leukocytes flatten out and squeeze between the endothelial cells to leave the blood vessels and enter the tissue. The increased capillary permeability also allows plasma to enter the tissue.

Cytokines produced in response to PRRs that recognize viral nucleic acids, such as type I interferons, primarily block viral replication within infected host cells (Figure 10.5.4.2).

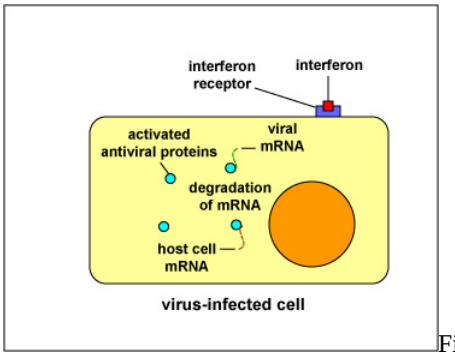


Figure 10.5.4.2: Antiviral Action of Interferon. Step 1 (left) Viral replication stimulates the infected host cell to produce type I interferons. Step 2 (right) Produced by immune-activated cells or virus-infected cells in response to the double-stranded RNA (dsRNA) that many viruses produce as a part of their life cycle, interferons exert their antiviral activity by binding to uninfected neighboring cells and inducing them to produce enzymes that degrade mRNA. This not only prevents translation of viral mRNA into viral proteinit also eventually kills the host cell, the factory producing the viruses. Interferons also enhance body defenses against viruses by enhancing the activities of CTLs, macrophages, NK cells, and antibody-producing cells.

Examples include:

1. Tumor necrosis factor-alpha (TNF-a): TNF-a is the principle cytokine that mediates acute inflammation. In excessive amounts it also is the principal cause of systemic complications such as the shock cascade. Functions include acting on endothelial cells to stimulate inflammation and the coagulation pathway; stimulating endothelial cells to produce selectins and ligands for leukocyte integrins (Figure 10.5.4.1) during diapedesis; stimulating endothelial cells and macrophages to produce chemokines that contribute to diapedesis, chemotaxis, and the recruitment of leukocytes; stimulating macrophages to secrete interleukin-1 (IL-1) for redundancy; activating neutrophils and promoting extracellular killing by neutrophils; stimulating the liver to produce acute phase proteins, and acting on muscles and fat to stimulate catabolism for energy conversion. In addition, TNF is cytotoxic for some tumor cells; interacts with the hypothalamus to induce fever and sleep; stimulates the synthesis of collagen and collagenase for scar tissue formation; and activates macrophages. TNF is produced by monocytes,macrophages, dendritic cells, T_H1 cells, and other cells.
2. Interleukin-1 (IL-1): IL-1 function similarly to TNF in that it mediates acute inflammatory responses. It also works synergistically with TNF to enhance inflammation. Functions of IL-1 include promoting inflammation; activating the coagulation pathway, stimulating the liver to produce acute phase proteins, catabolism of fat for energy conversion, inducing fever and sleep; stimulates the synthesis of collagen and collagenase for scar tissue formation; stimulates the synthesis of adhesion factors on endothelial cells and leukocytes (Figure 10.5.4.1) for diapedesis; and activates macrophages. IL-1 is produced primarily by monocytes, macrophages, dendritic cells, endothelial cells, and some epithelial cell.
3. Chemokines: Chemokines are a group of cytokines that enable the migration of leukocytes from the blood to the tissues at the site of inflammation. They increase the affinity of integrins on leukocytes for ligands on the vascular wall (Figure 10.5.4.1) during diapedesis, regulate the polymerization and depolymerization of actin in leukocytes for movement and migration, and function as chemoattractants for leukocytes. In addition, they trigger some WBCs to release their killing agents for extracellular killing and induce some WBCs to ingest the remains of damaged tissue. Chemokines also regulate the movement of B-lymphocytes, T-lymphocytes, and dendritic cells through the lymph nodes and the spleen. When produced in excess amounts, chemokines can lead to damage of healthy tissue as seen in such disorders as rheumatoid arthritis, pneumonia, asthma, adult respiratory distress syndrome (ARDS), and septic shock. Examples of chemokines include IL-8, MIP-1a, MIP-1b, MCP-1, MCP-2, MCP-3, GRO-a, GRO-b,

GRO-g, RANTES, and eotaxin. Chemokines are produced by many cells including leukocytes, endothelial cells, epithelial cells, and fibroblasts.

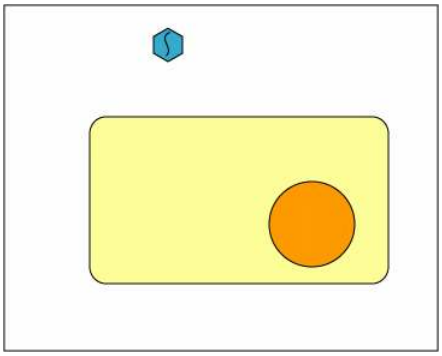
4. Interleukin-12 (IL-12): IL-12 is a primary mediator of early innate immune responses to intracellular microbes. It is also an inducer of cell-mediated immunity. It functions to stimulate the synthesis of interferon-gamma by T-lymphocytes and NK cells; increases the killing activity of cytotoxic T-lymphocytes and NK cells; and stimulates the differentiation of naive T4-lymphocytes into interferon-gamma producing T_H1 cells. It is produced mainly by macrophages and dendritic cells.
5. Type I Interferons: Interferons modulate the activity of virtually every component of the immune system. Type I interferons include 13 subtypes of interferon-alpha, interferon-beta, interferon omega, interferon-kappa, and interferon tau. (There is only one type II interferon, interferon-gamma, which is involved in the inflammatory response.)

The most powerful stimulus for type I interferons is the binding of viral DNA or RNA to toll-like receptors TLR-3, TLR-7, and TLR-9 in endosomal membranes.

a. TLR-3 - binds double-stranded viral RNA;
b. TLR-7 - binds single-stranded viral RNA, such as in HIV, rich in guanine/uracil nucleotide pairs;
c. TLR-9 - binds unmethylated cytosine-guanine dinucleotide sequences (CpG DNA) found in bacterial and viral genomes but uncommon or masked in human DNA and RNA.

Signaling pattern recognition receptors located in the cytoplasm of cells such as RIG-1 and MDA-5 also signal synthesis and secretion of type-I interferons.

Type I interferons, produced by virtually any virus-infected cell, provide an early innate immune response against viruses. Interferons induce uninfected cells to produce enzymes capable of degrading mRNA. These enzymes remain inactive until the uninfected cell becomes infected with a virus. At this point, the enzymes are activated and begin to degrade both viral and cellular mRNA. This not only blocks viral protein synthesis, it also eventually kills the infected cell (Figure 10.5.4.2). In addition, type I interferons also cause infected cells to produce enzymes that interfere with transcription of viral RNA or DNA. They also promote body defenses by enhancing the activities of CTLs, macrophages, dendritic cells, NK cells, and antibody-producing cells.



Antiviral Action of Interferon Interferon induces uninfected cells to produce enzymes capable of degrading mRNA. These enzymes remain inactive until the uninfected cell becomes infected with a virus. At this point, the enzymes are activated and begin to degrade both viral and cellular mRNA. Thisnot only blocks viral protein synthesis, it also eventually kills the infected cell.

Type I interferons also induce MHC-I antigen expression needed for recognition of antigens by cytotoxic T-lymphocytes; augment macrophage, NK cell, cytotoxic T-lymphocytes, and B-lymphocyte activity; and induce fever. Interferon-alpha is produced by T-lymphocytes, B-lymphocytes, NK cells, monocytes/macrophages; interferon-beta by virus-infected cells, fibroblasts, macrophages, epithelial cells, and endothelial cells.

6. Interleukin-6 (IL-6): IL-6 functions to stimulate the liver to produce acute phase proteins; stimulates the proliferation of B-lymphocytes; and increases neutrophil production. IL-6 is produced by many cells including T-lymphocytes,

macrophages, monocytes, endothelial cells, and fibroblasts.

7. Interleukin-10 (IL-10): IL-10 is an inhibitor of activated macrophages and dendritic cells and as such, regulates innate immunity and cell-mediated immunity. IL-10 inhibits their production of IL-12, co-stimulator molecules, and MHC-II molecules, all of which are needed for cell-mediated immunity. IL-10 is produced mainly by macrophages, and T_H2 cells.

8. Interleukin 15 (IL-15): IL-15 stimulates NK cell proliferation and proliferation of memory T8-lymphocytes. IL-15 is produced by various cells including macrophages.

9. Interleukin-18 (IL-18): IL-18 stimulates the production of interferon-gamma by NK cells and T-lymphocytes and thus induces cell-mediated immunity. It is produced mainly by macrophages.

Cytokines that Regulate Adaptive Immune Responses (Humoral Immunity and Cell-Mediated Immunity)

Cytokines that regulate adaptive immunity are produced primarily by T-lymphocytes that have recognized an antigen specific for that cell. These cytokines function in the proliferation and differentiation of B-lymphocytes and T-lymphocytes after antigen recognition and in the activation of effector cells.

Examples include:

1. Interleukin-2 (IL-2): IL-2 is a growth factor for NK cells and antigen-stimulated T-lymphocytes and B-lymphocytes. IL-2 also increases the killing ability of NK cells; increases the synthesis of other cytokines; increases Fas-mediated apoptosis; and stimulates antibody synthesis by B-lymphocytes. IL-2 is produced mainly by T4-lymphocytes and to a lesser extent T8-lymphocytes.
2. Interleukin-4 (IL-4): IL-4 is a major stimulus for production of the antibody isotype IgE and the development of T_h2 cells for defense against helminths and arthropods. It also antagonizes the effects of interferon-gamma and thus inhibits cell-mediated immunity. IL-4 is produced mainly by T_H2 cells and mast cells.
3. Interleukin-5 (IL-5): IL-5 is a growth and activating factor for eosinophils as a defense against helminths and arthropods. It also stimulates the proliferation and differentiation of antigen-activated B-lymphocytes and the production of IgA. IL-5 is produced mainly by T_H2 cells.
4. Interferon-gamma (IFN-?):Interferons modulate the activity of virtually every component of the immune system. Type I interferons include more than 20 types of interferon-alpha, interferon-beta, interferon omega, and interferon tau. There is only one type II interferon, interferon-gamma. Type II interferon is produced by activated T-lymphocytes as part of an immune response and functions mainly to promote the activity of the components of the cell-mediated immune system such as CTLs, macrophages, and NK cells. IFN-? is the principal cytokine for activating macrophages. It also induces the production of MHC-I molecules, MHC-II molecules, and co-stimulatory molecules by APCs in order to promote cell-mediated immunity and activates and increases the antimicrobial and tumoricidal activity of monocytes, macrophages, neutrophils, and NK cells. IFN-? stimulates the differentiation of T4-lymphocytes into T_H1 cells and inhibits the proliferation of T_H2 cells; stimulates the production of IgG subclasses that activate the complement pathway and promote opsonization; and augments or inhibits other cytokine activities. IFN-? is produced primarily by T_H1 cells, $CD8^+$ cells, and NK cells.
5. Transforming growth factor-beta (TGF-ß): TGF-ß functions to inhibit the proliferation and effector function of T-lymphocytes; inhibit the proliferation of B-lymphocytes; and inhibits macrophage function. It also promotes tissue repair. TGF-ß is produced by T-lymphocytes, macrophages, and other cells.
6. Lymphotoxin (LT): LT plays a role in the recruitment and activation of neutrophils and in lymphoid organogenesis. Being chemically similar to TNF, LT is also a mediator of acute inflammatory responses. LT is made by T-lymphocytes.
7. Interleukin-13 (IL-13): IL-13 increases the production of IgE by B-lymphocytes, inhibits macrophages, and increases mucus production. IL-13 is made primarily by T_H2 cells.

Cytokines that Stimulate Hematopoiesis

Produced by bone marrow stromal cells, these cytokines stimulate the growth and differentiation of immature leukocytes.

Examples include:

1. *Colony-stimulating factors (CSF)*: Promote the production of colonies of the different leukocytes in the bone marrow and enhance their activity. Examples include granulocyte macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), and macrophage colony stimulating factor (M-CSF). In addition to their role in promoting production of leukocyte colonies, the CSFs also appear to promote their function. For example, when GM-CSF binds to receptors on neutrophils, eosinophils, and monocytes, it activates these cells and inhibits their apoptosis. GM-CSF increases adhesion of these cells to capillary walls during diapedesis, enhances their phagocytosis and extracellular killing, and increases both superoxide anion generation and antibody-dependent cytotoxicity. The various CSFs are produced by T-lymphocytes, macrophages, and other cells.
2. *Stem cell factor*: Stem cell factor makes stem cells in the bone marrow mor responsive to the various CSFs. It is made mainly by bone marrow stromal cells.
3. *Interleukin-3 (IL-3)*: IL-3 supports the growth of multilineage bone marrow stem cells. IL-3 is made primarily by T-lymphocytes.
4. *Interleukin-7 (IL-7)*: IL-7 plays a role in the survival and proliferation of immature B-lymphocyte and T-lymphocyte precursors. Il-7 is produced mainly my fibroblasts and bone marrow stromal cells.

Some viruses cause infected host cells to secrete molecules that bind and tie up cytokines, preventing them from binding to normal cytokine receptors on host cells.

- Poxviruses cause infected host cells to secrete molecules that bind interleukin-1 (IL-1) and interferon-gamma (IFN-gamma).
- Cytomegaloviruses (CMV) cause infected host cells to secrete molecules that bind chemokines.

Summary

1. Cytokines are low molecular weight, soluble proteins that are produced in response to an antigen and function as chemical messengers for regulating the innate and adaptive immune systems.
2. Cytokines are pleiotropic, meaning that a particular cytokine can act on a number of different types of cells rather than a single cell type.
3. Cytokines are redundant, meaning that a number of different cytokines to carry out the same function.
4. Cytokines are multifunctional, meaning the same cytokine is able to regulate a number of different functions.
5. There are three functional categories of cytokines: Cytokines that regulate innate immune responses; cytokines that regulate adaptive Immune responses; and cytokines that stimulate hematopoiesis.
6. Type I interferons provide an early innate immune response against viruses. Interferons induce uninfected cells to produce enzymes capable of degrading mRNA. These enzymes remain inactive until the uninfected cell becomes infected with a virus. At this point, the enzymes are activated and begin to degrade both viral and cellular mRNA. This not only blocks viral protein synthesis, it also eventually kills the infected cell.

This page titled 10.5.4: Stimulating Cells to Secrete Cytokines is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **14.4: Stimulating Cells to Secrete Cytokines** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

10.5.E: Cell-Mediated Immunity (Exercises)

These are homework exercises to accompany Kaiser's "Microbiology" TextMap. Microbiology is the study of microorganisms, which are defined as any microscopic organism that comprises either a single cell (unicellular), cell clusters or no cell at all (acellular). This includes eukaryotes, such as fungi and protists, and prokaryotes. Viruses and prions, though not strictly classed as living organisms, are also studied.

14.1: Cell-Mediated Immunity: An Overview

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. State three different ways by which cell-mediated immunity protects the body.
   A.
   B.
   C.
2. Define gene translocation.
3. Relate gene translocation to each T-lymphocyte being able to produce a T-cell receptor with a unique shape.
4. Define the following:
   a. combinatorial diversity
5. In terms of humoral immunity, discuss what is meant by anamnestic response.
6. Briefly describe why there is a heightened secondary response during anamestic response.

14.2: Activating Antigen-Specific Cytotoxic T- Lymphocytes

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. The role of cytotoxic T-lymphocytes (CTLs) in body defense.
   a. State from what cells cytotoxic T-lymphocytes are derived.
   b. Describe how they can react with and destroy virus-infected cells, cells containing intracellular bacteria, and cancer cells without harming normal cells. (Indicate the role of following: TCR, CD4, MHC-I, and peptides from endogenous antigens.)
   c. State the mechanism by which cytotoxic T-lymphocytes kill the cells to which they bind. (Indicate the role of the following: perforins, granzymes, caspases, and macrophages in the process.)

14.3: Activating Macrophages and NK Cells

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Viruses and malignant transformation can sometimes interfere with the ability of the infected cell or tumor cell to express MHC-I molecules. This enables them to resist destruction by cytoyoxic T-lymphocytes. However the body is still able to kill these infected cells and tumor cells. Describe how.
2. Describe how T_H1 effector cells are able to interact with and activate macrophages.

14.4: Stimulating Cells to Secrete Cytokines

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Name 4 cytokines that regulate adaptive immune responses.
2. Name 3 cytokines that regulate innate immune responses by triggering an inflammatory response.

3. Name 2 cytokines that stimulate hematopoiesis.
4. Name the group of cytokines that regulates innate immunity by preventing translation of viral mRNA and by degrading both viral and host cell RNA.

This page titled 10.5.E: Cell-Mediated Immunity (Exercises) is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **14.E: Cell-Mediated Immunity (Exercises)** has no license indicated.

CHAPTER OVERVIEW

11: Specific Adaptive Host Defenses

People living in developed nations and born in the 1960s or later may have difficulty understanding the once heavy burden of devastating infectious diseases. For example, smallpox, a deadly viral disease, once destroyed entire civilizations but has since been eradicated. Thanks to the vaccination efforts by multiple groups, including the World Health Organization, Rotary International, and the United Nations Children's Fund (UNICEF), smallpox has not been diagnosed in a patient since 1977. Polio is another excellent example. This crippling viral disease paralyzed patients, who were often kept alive in "iron lung wards" as recently as the 1950s (Figure **11.1**). Today, vaccination against polio has nearly eradicated the disease. Vaccines have also reduced the prevalence of once-common infectious diseases such as chickenpox, German measles, measles, mumps, and whooping cough. The success of these and other vaccines is due to the very specific and adaptive host defenses that are the focus of this chapter.

Innate Nonspecific Host Defenses described innate immunity against microbial pathogens. Higher animals, such as humans, also possess an adaptive immune defense, which is highly specific for individual microbial pathogens. This specific adaptive immunity is acquired through active infection or vaccination and serves as an important defense against pathogens that evade the defenses of innate immunity.



Figure **11.1**: Polio was once a common disease with potentially serious consequences, including paralysis. Vaccination has all but eliminated the disease from most countries around the world. An iron-lung ward, such as the one shown in this 1953 photograph, housed patients paralyzed from polio and unable to breathe for themselves.

11.1: Architecture of the Immune System

11.2: Antigens, Antigen Presenting Cells, and Major Histocompatibility Complexes

11.3: T Lymphocytes

11.4: B Lymphocytes and Antibodies

This page titled 11: Specific Adaptive Host Defenses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

11.1: Architecture of the Immune System

Learning Objectives

- Define memory, primary response, secondary response, and specificity
- Distinguish between humoral and cellular immunity
- Differentiate between antigens, epitopes, and haptens
- Describe the structure and function of antibodies and distinguish between the different classes of antibodies

Clinical Focus: Part 1

Olivia, a one-year old infant, is brought to the emergency room by her parents, who report her symptoms: excessive crying, irritability, sensitivity to light, unusual lethargy, and vomiting. A physician feels swollen lymph nodes in Olivia's throat and armpits. In addition, the area of the abdomen over the spleen is swollen and tender.

Exercise 11.1.1

1. What do these symptoms suggest?
2. What tests might be ordered to try to diagnose the problem?

Adaptive immunity is defined by two important characteristics: specificity and memory. Specificity refers to the adaptive immune system's ability to target specific pathogens, and memory refers to its ability to quickly respond to pathogens to which it has previously been exposed. For example, when an individual recovers from chickenpox, the body develops a *memory* of the infection that will *specifically* protect it from the causative agent, the varicella-zoster virus, if it is exposed to the virus again later.

Specificity and memory are achieved by essentially programming certain cells involved in the immune response to respond rapidly to subsequent exposures of the pathogen. This programming occurs as a result of the first exposure to a pathogen or vaccine, which triggers a primary response. Subsequent exposures result in a secondary response that is faster and stronger as a result of the body's memory of the first exposure (Figure **11.1.1**). This secondary response, however, is specific to the pathogen in question. For example, exposure to one virus (e.g., varicella-zoster virus) will not provide protection against other viral diseases (e.g., measles, mumps, or polio).

Adaptive specific immunity involves the actions of two distinct cell types: B lymphocytes (B cells) and T lymphocytes (T cells). Although B cells and T cells arise from a common hematopoietic stem cell differentiation pathway, their sites of maturation and their roles in adaptive immunity are very different.

B cells mature in the bone marrow and are responsible for the production of glycoproteins called antibodies, or immunoglobulins. Antibodies are involved in the body's defense against pathogens and toxins in the extracellular environment. Mechanisms of adaptive specific immunity that involve B cells and antibody production are referred to as humoral immunity. The maturation of T cells occurs in the thymus. T cells function as the central orchestrator of both innate and adaptive immune responses. They are also responsible for destruction of cells infected with intracellular pathogens. The targeting and destruction of intracellular pathogens by T cells is called cell-mediated immunity, or cellular immunity.

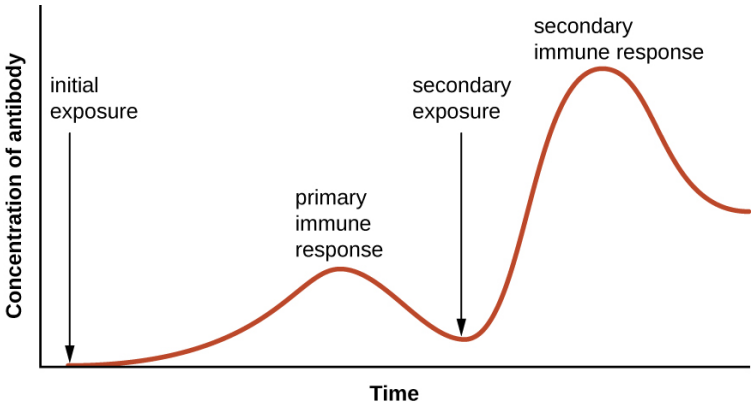


Figure **11.1.1**: This graph illustrates the primary and secondary immune responses related to antibody production after an initial and secondary exposure to an antigen. Notice that the secondary response is faster and provides a much higher concentration of antibody.

? Exercise 11.1.2

1. List the two defining characteristics of adaptive immunity.
2. Explain the difference between a primary and secondary immune response.
3. How do humoral and cellular immunity differ?

Antigens

Activation of the adaptive immune defenses is triggered by pathogen-specific molecular structures called antigens. Antigens are similar to the pathogen-associated molecular patterns (PAMPs) discussed in Pathogen Recognition and Phagocytosis; however, whereas PAMPs are molecular structures found on numerous pathogens, antigens are unique to a specific pathogen. The antigens that stimulate adaptive immunity to chickenpox, for example, are unique to the varicella-zoster virus but significantly different from the antigens associated with other viral pathogens.

The term *antigen* was initially used to describe molecules that stimulate the production of antibodies; in fact, the term comes from a combination of the words antibody and generator, and a molecule that stimulates antibody production is said to be antigenic. However, the role of antigens is not limited to humoral immunity and the production of antibodies; antigens also play an essential role in stimulating cellular immunity, and for this reason antigens are sometimes more accurately referred to as immunogens. In this text, however, we will typically refer to them as antigens.

Pathogens possess a variety of structures that may contain antigens. For example, antigens from bacterial cells may be associated with their capsules, cell walls, fimbriae, flagella, or pili. Bacterial antigens may also be associated with extracellular toxins and enzymes that they secrete. Viruses possess a variety of antigens associated with their capsids, envelopes, and the spike structures they use for attachment to cells.

Antigens may belong to any number of molecular classes, including carbohydrates, lipids, nucleic acids, proteins, and combinations of these molecules. Antigens of different classes vary in their ability to stimulate adaptive immune defenses as well as in the type of response they stimulate (humoral or cellular). The structural complexity of an antigenic molecule is an important factor in its antigenic potential. In general, more complex molecules are more effective as antigens. For example, the three-dimensional complex structure of proteins make them the most effective and potent antigens, capable of stimulating both humoral and cellular immunity. In comparison, carbohydrates are less complex in structure and therefore less effective as antigens; they can only stimulate humoral immune defenses. Lipids and nucleic acids are the least antigenic molecules, and in some cases may only become antigenic when combined with proteins or carbohydrates to form glycolipids, lipoproteins, or nucleoproteins.

One reason the three-dimensional complexity of antigens is so important is that antibodies and T cells do not recognize and interact with an entire antigen but with smaller exposed regions on the surface of antigens called epitopes. A single antigen may possess several different epitopes (Figure **11.1.2**), and different antibodies may bind to different epitopes on the same antigen (Figure **11.1.3**). For example, the bacterial flagellum is a large, complex protein structure that can possess hundreds or even thousands of

epitopes with unique three-dimensional structures. Moreover, flagella from different bacterial species (or even strains of the same species) contain unique epitopes that can only be bound by specific antibodies.

An antigen's size is another important factor in its antigenic potential. Whereas large antigenic structures like flagella possess multiple epitopes, some molecules are too small to be antigenic by themselves. Such molecules, called haptens, are essentially free epitopes that are not part of the complex three-dimensional structure of a larger antigen. For a hapten to become antigenic, it must first attach to a larger carrier molecule (usually a protein) to produce a conjugate antigen. The hapten-specific antibodies produced in response to the conjugate antigen are then able to interact with unconjugated free hapten molecules. Haptens are not known to be associated with any specific pathogens, but they are responsible for some allergic responses. For example, the hapten urushiol, a molecule found in the oil of plants that cause poison ivy, causes an immune response that can result in a severe rash (called contact dermatitis). Similarly, the hapten penicillin can cause allergic reactions to drugs in the penicillin class.

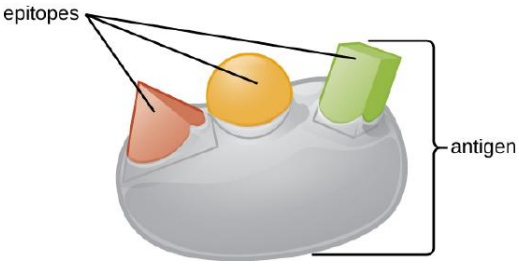


Figure **11.1.2**: An antigen is a macromolecule that reacts with components of the immune system. A given antigen may contain several motifs that are recognized by immune cells.

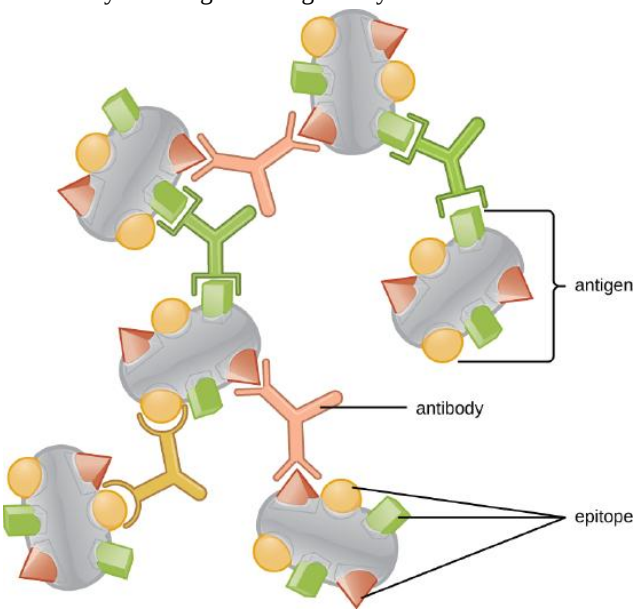


Figure **11.1.3**: A typical protein antigen has multiple epitopes, shown by the ability of three different antibodies to bind to different epitopes of the same antigen.

? Exercise 11.1.3

1. What is the difference between an antigen and an epitope?
2. What factors affect an antigen's antigenic potential?
3. Why are haptens typically not antigenic, and how do they become antigenic?

Antibodies

Antibodies (also called immunoglobulins) are glycoproteins that are present in both the blood and tissue fluids. The basic structure of an antibody monomer consists of four protein chains held together by disulfide bonds (Figure **11.1.4**). A disulfide bond is a covalent bond between the sulfhydryl *R* groups found on two cysteine amino acids. The two largest chains are identical to each other and are called the heavy chains. The two smaller chains are also identical to each other and are called the light chains. Joined together, the heavy and light chains form a basic Y-shaped structure.

The two ‘arms’ of the Y-shaped antibody molecule are known as the Fab region, for “fragment of antigen binding.” The far end of the Fab region is the variable region, which serves as the site of antigen binding. The amino acid sequence in the variable region dictates the three-dimensional structure, and thus the specific three-dimensional epitope to which the Fab region is capable of binding. Although the epitope specificity of the Fab regions is identical for each arm of a single antibody molecule, this region displays a high degree of variability between antibodies with different epitope specificities. Binding to the Fab region is necessary for neutralization of pathogens, agglutination or aggregation of pathogens, and antibody-dependent cell-mediated cytotoxicity.

The constant region of the antibody molecule includes the trunk of the Y and lower portion of each arm of the Y. The trunk of the Y is also called the Fc region, for “fragment of crystallization,” and is the site of complement factor binding and binding to phagocytic cells during antibody-mediated opsonization.

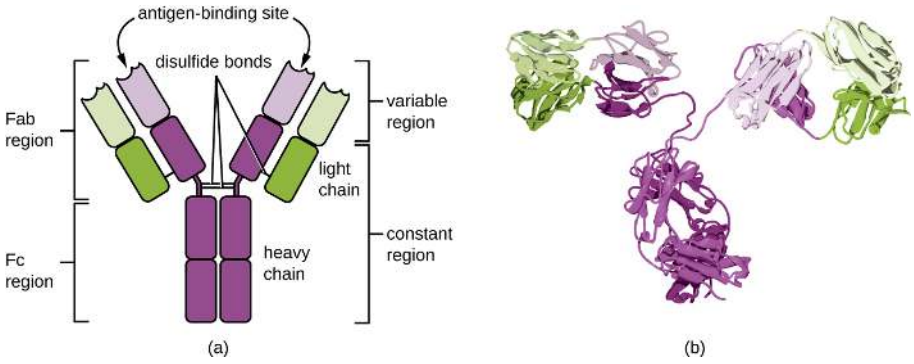


Figure **11.1.4**: (a) The typical four-chain structure of a generic antibody monomer. (b) The corresponding three-dimensional structure of the antibody IgG. (credit b: modification of work by Tim Vickers)

? Exercise 11.1.4

Describe the different functions of the Fab region and the Fc region.

Antibody Classes

The constant region of an antibody molecule determines its class, or isotype. The five classes of antibodies are IgG, IgM, IgA, IgD, and IgE. Each class possesses unique heavy chains designated by Greek letters γ, μ, α, δ, and ε, respectively. Antibody classes also exhibit important differences in abundance in serum, arrangement, body sites of action, functional roles, and size (Figure **11.1.5**).

IgG is a monomer that is by far the most abundant antibody in human blood, accounting for about 80% of total serum antibody. IgG penetrates efficiently into tissue spaces, and is the only antibody class with the ability to cross the placental barrier, providing passive immunity to the developing fetus during pregnancy. IgG is also the most versatile antibody class in terms of its role in the body’s defense against pathogens.

IgM is initially produced in a monomeric membrane-bound form that serves as an antigen-binding receptor on B cells. The secreted form of IgM assembles into a pentamer with five monomers of IgM bound together by a protein structure called the J chain. Although the location of the J chain relative to the Fc regions of the five monomers prevents IgM from performing some of the functions of IgG, the ten available Fab sites associated with a pentameric IgM make it an important antibody in the body’s arsenal of defenses. IgM is the first antibody produced and secreted by B cells during the primary and secondary immune responses, making pathogen-specific IgM a valuable diagnostic marker during active or recent infections.

IgA accounts for about 13% of total serum antibody, and secretory IgA is the most common and abundant antibody class found in the mucus secretions that protect the mucous membranes. IgA can also be found in other secretions such as breast milk, tears, and saliva. Secretory IgA is assembled into a dimeric form with two monomers joined by a protein structure called the secretory component. One of the important functions of secretory IgA is to trap pathogens in mucus so that they can later be eliminated from the body.

Similar to IgM, IgD is a membrane-bound monomer found on the surface of B cells, where it serves as an antigen-binding receptor. However, IgD is not secreted by B cells, and only trace amounts are detected in serum. These trace amounts most likely come from the degradation of old B cells and the release of IgD molecules from their cytoplasmic membranes.

IgE is the least abundant antibody class in serum. Like IgG, it is secreted as a monomer, but its role in adaptive immunity is restricted to anti-parasitic defenses. The Fc region of IgE binds to basophils and mast cells. The Fab region of the bound IgE then interacts with specific antigen epitopes, causing the cells to release potent pro-inflammatory mediators. The inflammatory reaction resulting from the activation of mast cells and basophils aids in the defense against parasites, but this reaction is also central to allergic reactions (see Diseases of the Immune System.)

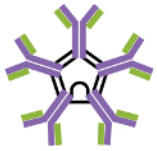
The Five Immunoglobulin (Ig) Classes					
Properties	**IgG monomer**	**IgM pentamer**	**Secretory IgA dimer**	**IgD monomer**	**IgE monomer**
Structure			 Secretory component		
Heavy chains	γ	μ	α	δ	ε
Number of antigen-binding sites	2	10	4	2	2
Molecular weight (Daltons)	150,000	900,000	385,000	180,000	200,000
Percentage of total antibody in serum	80%	6%	13% (monomer)	<1%	<1%
Crosses placenta	yes	no	no	no	no
Fixes complement	yes	yes	no	no	no
Fc binds to	phagocytes				mast cells and basophils
Function	Neutralization, agglutination, complement activation, opsonization, and antibody-dependent cell-mediated cytotoxicity.	Neutralization, agglutination, and complement activation. The monomer form serves as the B-cell receptor.	Neutralization and trapping of pathogens in mucus.	B-cell receptor.	Activation of basophils and mast cells against parasites and allergens.

Figure 11.1.5: The five Immunoglobulin classes

? Exercise 11.1.5

1. What part of an antibody molecule determines its class?
2. What class of antibody is involved in protection against parasites?
3. Describe the difference in structure between IgM and IgG.

Antigen-Antibody Interactions

Different classes of antibody play important roles in the body's defense against pathogens. These functions include neutralization of pathogens, opsonization for phagocytosis, agglutination, complement activation, and antibody-dependent cell-mediated cytotoxicity. For most of these functions, antibodies also provide an important link between adaptive specific immunity and innate nonspecific immunity.

Neutralization involves the binding of certain antibodies (IgG, IgM, or IgA) to epitopes on the surface of pathogens or toxins, preventing their attachment to cells. For example, Secretory IgA can bind to specific pathogens and block initial attachment to intestinal mucosal cells. Similarly, specific antibodies can bind to certain toxins, blocking them from attaching to target cells and thus neutralizing their toxic effects. Viruses can be neutralized and prevented from infecting a cell by the same mechanism (Figure 11.1.6).

As described in Chemical Defenses, opsonization is the coating of a pathogen with molecules, such as complementfactors, C-reactive protein, and serum amyloid A, to assist in phagocyte binding to facilitate phagocytosis. IgG antibodies also serve as excellent opsonins, binding their Fab sites to specific epitopes on the surface of pathogens. Phagocytic cells such as macrophages, dendritic cells, and neutrophils have receptors on their surfaces that recognize and bind to the Fc portion of the IgG molecules; thus, IgG helps such phagocytes attach to and engulf the pathogens they have bound (Figure **11.1.7**).

Agglutination or aggregation involves the cross-linking of pathogens by antibodies to create large aggregates (Figure **11.1.8**). IgG has two Fab antigen-binding sites, which can bind to two separate pathogen cells, clumping them together. When multiple IgG antibodies are involved, large aggregates can develop; these aggregates are easier for the kidneys and spleen to filter from the blood and easier for phagocytes to ingest for destruction. The pentameric structure of IgMprovides ten Fab binding sites per molecule, making it the most efficient antibody for agglutination.

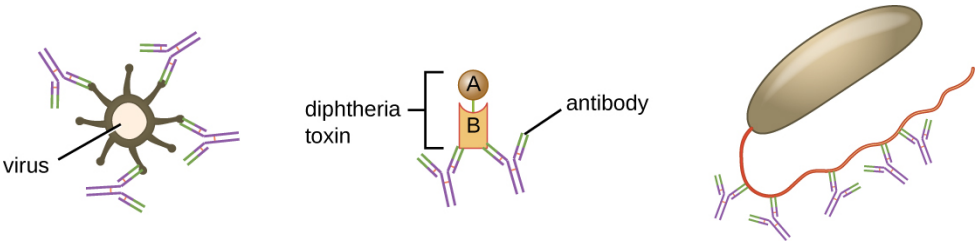


Figure **11.1.6**: Neutralization involves the binding of specific antibodies to antigens found on bacteria, viruses, and toxins, preventing them from attaching to target cells.

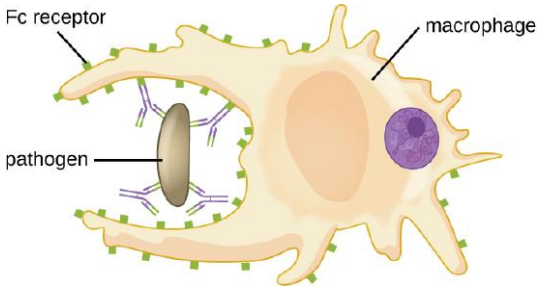


Figure **11.1.7**: Antibodies serve as opsonins and inhibit infection by tagging pathogens for destruction by macrophages, dendritic cells, and neutrophils. These phagocytic cells use Fc receptors to bind to IgG-opsonized pathogens and initiate the first step of attachment before phagocytosis.

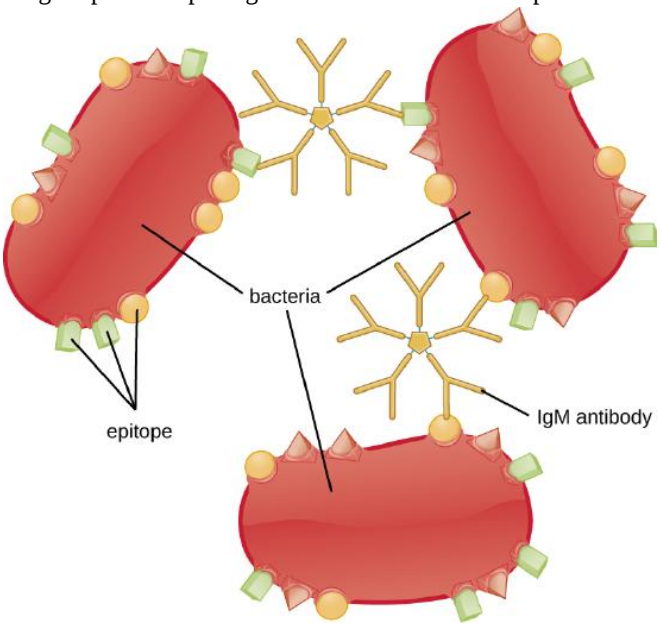


Figure **11.1.8**: Antibodies, especially IgM antibodies, agglutinate bacteria by binding to epitopes on two or more bacteria simultaneously. When multiple pathogens and antibodies are present, aggregates form when the binding sites of antibodies bind with separate pathogens.

Another important function of antibodies is activation of the complement cascade. As discussed in the previous chapter, the complement system is an important component of the innate defenses, promoting the inflammatory response, recruiting phagocytes

to site of infection, enhancing phagocytosis by opsonization, and killing gram-negative bacterial pathogens with the membrane attack complex (MAC). Complement activation can occur through three different pathways (see Figure 17.2.2), but the most efficient is the classical pathway, which requires the initial binding of IgG or IgM antibodies to the surface of a pathogen cell, allowing for recruitment and activation of the C1 complex.

Yet another important function of antibodies is antibody-dependent cell-mediated cytotoxicity (ADCC), which enhances killing of pathogens that are too large to be phagocytosed. This process is best characterized for natural killer cells (NK cells), as shown in Figure **11.1.9**, but it can also involve macrophages and eosinophils. ADCC occurs when the Fab region of an IgG antibody binds to a large pathogen; Fc receptors on effector cells (e.g., NK cells) then bind to the Fc region of the antibody, bringing them into close proximity with the target pathogen. The effector cell then secretes powerful cytotoxins (e.g., perforin and granzymes) that kill the pathogen.

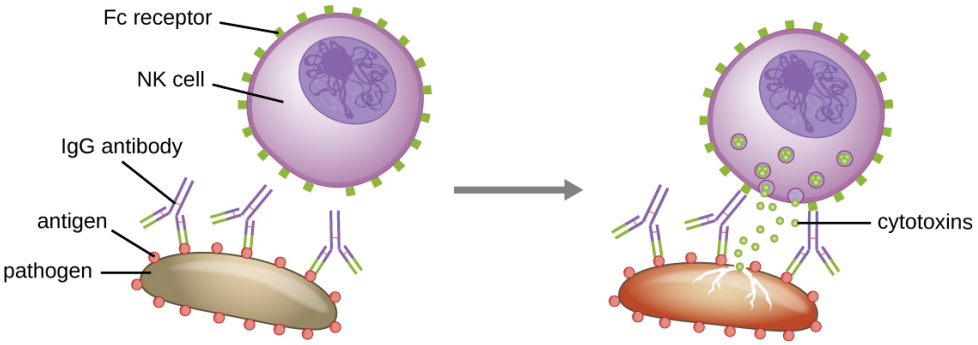


Figure **11.1.9**: In this example of ADCC, antibodies bind to a large pathogenic cell that is too big for phagocytosis and then bind to Fc receptors on the membrane of a natural killer cell. This interaction brings the NK cell into close proximity, where it can kill the pathogen through release of lethal extracellular cytotoxins.

? Exercise 11.1.6

1. Where is IgA normally found?
2. Which class of antibody crosses the placenta, providing protection to the fetus?
3. Compare the mechanisms of opsonization and antibody-dependent cell-mediated cytotoxicity.

Key Concepts and Summary

- **Adaptive immunity** is an acquired defense against foreign pathogens that is characterized by **specificity** and **memory.** The first exposure to an antigen stimulates a **primary response**, and subsequent exposures stimulate a faster and strong **secondary response.**
- Adaptive immunity is a dual system involving **humoral immunity** (antibodies produced by B cells) and **cellular immunity** (T cells directed against intracellular pathogens).
- **Antigens**, also called **immunogens**, are molecules that activate adaptive immunity. A single antigen possesses smaller **epitopes**, each capable of inducing a specific adaptive immune response.
- An antigen's ability to stimulate an immune response depends on several factors, including its molecular class, molecular complexity, and size.
- **Antibodies** (**immunoglobulins**) are Y-shaped glycoproteins with two Fab sites for binding antigens and an Fc portion involved in complement activation and opsonization.
- The five classes of antibody are **IgM**, **IgG**, **IgA**, **IgE**, and **IgD**, each differing in size, arrangement, location within the body, and function. The five primary functions of antibodies are neutralization, opsonization, agglutination, complement activation, and antibody-dependent cell-mediated cytotoxicity (ADCC).

This page titled 11.1: Architecture of the Immune System is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **18.1: Architecture of the Immune System** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

https://med.libretexts.org/@go/page/77793

11.2: Antigens, Antigen Presenting Cells, and Major Histocompatibility Complexes

Learning Objectives

- Identify cells that express MHC I and/or MHC II molecules and describe the structures and cellular location of MHC I and MHC II molecules
- Identify the cells that are antigen-presenting cells
- Describe the process of antigen processing and presentation with MHC I and MHC II

As discussed in Cellular Defenses, major histocompatibility complex (MHC) molecules are expressed on the surface of healthy cells, identifying them as normal and "self" to natural killer (NK) cells. MHC molecules also play an important role in the presentation of foreign antigens, which is a critical step in the activation of T cells and thus an important mechanism of the adaptive immune system.

Major Histocompatibility Complex Molecules

The major histocompatibility complex (MHC) is a collection of genes coding for MHC molecules found on the surface of all nucleated cells of the body. In humans, the MHC genes are also referred to as human leukocyte antigen (HLA) genes. Mature red blood cells, which lack a nucleus, are the only cells that do not express MHC molecules on their surface.

There are two classes of MHC molecules involved in adaptive immunity, MHC I and MHC II (Figure **11.2.1**). MHC I molecules are found on all nucleated cells; they present normal self-antigens as well as abnormal or nonself pathogens to the effector T cells involved in cellular immunity. In contrast, MHC II molecules are only found on macrophages, dendritic cells, and B cells; they present abnormal or nonself pathogen antigens for the initial activation of T cells.

Both types of MHC molecules are transmembrane glycoproteins that assemble as dimers in the cytoplasmic membrane of cells, but their structures are quite different. MHC I molecules are composed of a longer α protein chain coupled with a smaller β_2 microglobulin protein, and only the α chain spans the cytoplasmic membrane. The α chain of the MHC I molecule folds into three separate domains: α_1, α_2 and α_3. MHC II molecules are composed of two protein chains (an α and a β chain) that are approximately similar in length. Both chains of the MHC II molecule possess portions that span the plasma membrane, and each chain folds into two separate domains: α_1 and α_2, and β_1, and β_2. In order to present abnormal or non-self-antigens to T cells, MHC molecules have a cleft that serves as the antigen-binding site near the "top" (or outermost) portion of the MHC-I or MHC-II dimer. For MHC I, the antigen-binding cleft is formed by the α_1 and α_2 domains, whereas for MHC II, the cleft is formed by the α_1 and β_1 domains (Figure **11.2.1**).

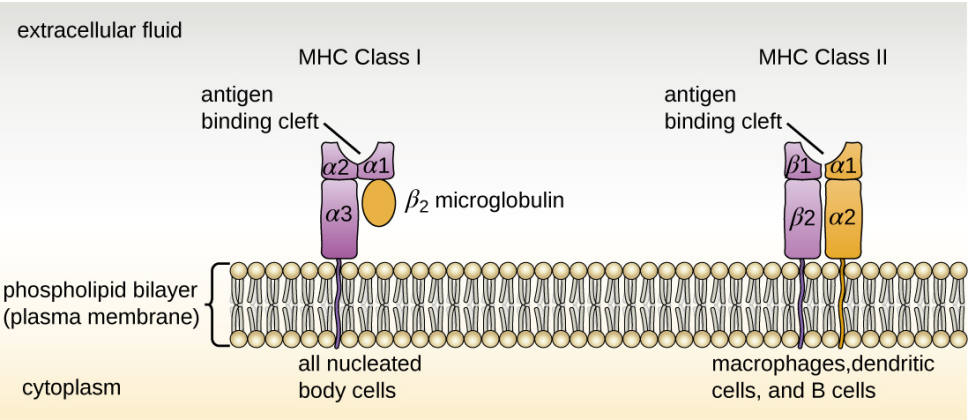


Figure **11.2.1**: MHC I are found on all nucleated body cells, and MHC II are found on macrophages, dendritic cells, and B cells (along with MHC I). The antigen-binding cleft of MHC I is formed by domains α_1 and α_2. The antigen-binding cleft of MHC II is formed by domains α_1 and β_1.

? Exercise 11.2.1

Compare the structures of the MHC I and MHC II molecules.

Antigen-Presenting Cells (APCs)

All nucleated cells in the body have mechanisms for processing and presenting antigens in association with MHC molecules. This signals the immune system, indicating whether the cell is normal and healthy or infected with an intracellular pathogen. However, only macrophages, dendritic cells, and B cells have the ability to present antigens specifically for the purpose of activating T cells; for this reason, these types of cells are sometimes referred to as antigen-presenting cells (APCs).

While all APCs play a similar role in adaptive immunity, there are some important differences to consider. Macrophages and dendritic cells are phagocytes that ingest and kill pathogens that penetrate the first-line barriers (i.e., skin and mucous membranes). B cells, on the other hand, do not function as phagocytes but play a primary role in the production and secretion of antibodies. In addition, whereas macrophages and dendritic cells recognize pathogens through nonspecific receptor interactions (e.g., PAMPs, toll-like receptors, and receptors for opsonizing complement or antibody), B cells interact with foreign pathogens or their free antigens using antigen-specific immunoglobulin as receptors (monomeric IgD and IgM). When the immunoglobulin receptors bind to an antigen, the B cell internalizes the antigen by endocytosis before processing and presentting the antigen to T cells.

Antigen Presentation with MHC II Molecules

MHC II molecules are only found on the surface of APCs. Macrophages and dendritic cells use similar mechanisms for processing and presentation of antigens and their epitopes in association with MHC II; B cells use somewhat different mechanisms that will be described further in B Lymphocytes and Humoral Immunity. For now, we will focus on the steps of the process as they pertain to dendritic cells.

After a dendritic cell recognizes and attaches to a pathogen cell, the pathogen is internalized by phagocytosis and is initially contained within a phagosome. Lysosomes containing antimicrobial enzymes and chemicals fuse with the phagosome to create a phagolysosome, where degradation of the pathogen for antigen processing begins. Proteases (protein-degrading) are especially important in antigen processing because only protein antigen epitopes are presented to T cells by MHC II (Figure **11.2.2**).

APCs do not present all possible epitopes to T cells; only a selection of the most antigenic or immunodominantepitopes are presented. The mechanism by which epitopes are selected for processing and presentation by an APC is complicated and not well understood; however, once the most antigenic, immunodominant epitopes have been processed, they associate within the antigen-binding cleft of MHC II molecules and are translocated to the cell surface of the dendritic cell for presentation to T cells.

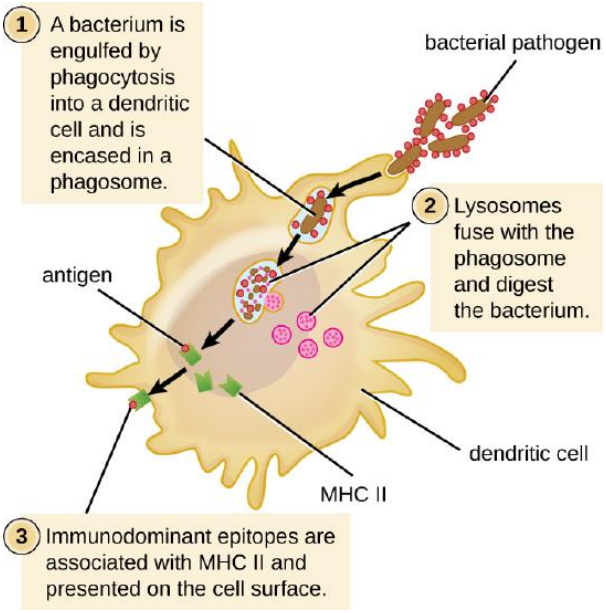


Figure **11.2.2**: A dendritic cell phagocytoses a bacterial cell and brings it into a phagosome. Lysosomes fuse with the phagosome to create a phagolysosome, where antimicrobial chemicals and enzymes

degrade the bacterial cell. Proteases process bacterial antigens, and the most antigenic epitopes are selected and presented on the cell's surface in conjunction with MHC II molecules. T cells recognize the presented antigens and are thus activated.

? Exercise 11.2.2

1. What are the three kinds of APCs?
2. What role to MHC II molecules play in antigen presentation?
3. What is the role of antigen presentation in adaptive immunity?

Antigen Presentation with MHC I Molecules

MHC I molecules, found on all normal, healthy, nucleated cells, signal to the immune system that the cell is a normal "self" cell. In a healthy cell, proteins normally found in the cytoplasm are degraded by proteasomes (enzyme complexes responsible for degradation and processing of proteins) and processed into self-antigen epitopes; these self-antigen epitopes bind within the MHC I antigen-binding cleft and are then presented on the cell surface. Immune cells, such as NK cells, recognize these self-antigens and do not target the cell for destruction. However, if a cell becomes infected with an intracellular pathogen (e.g., a virus), protein antigens specific to the pathogen are processed in the proteasomes and bind with MHC I molecules for presentation on the cell surface. This presentation of pathogen-specific antigens with MHC I signals that the infected cell must be targeted for destruction along with the pathogen.

Before elimination of infected cells can begin, APCs must first activate the T cells involved in cellular immunity. If an intracellular pathogen directly infects the cytoplasm of an APC, then the processing and presentation of antigens can occur as described (in proteasomes and on the cell surface with MHC I). However, if the intracellular pathogen does not directly infect APCs, an alternative strategy called cross-presentation is utilized. In cross-presentation, antigens are brought into the APC by mechanisms normally leading to presentation with MHC II (i.e., through phagocytosis), but the antigen is presented on an MHC I molecule for CD8 T cells. The exact mechanisms by which cross-presentation occur are not yet well understood, but it appears that cross-presentation is primarily a function of dendritic cells and not macrophages or B cells.

? Exercise 11.2.3

1. Compare and contrast antigen processing and presentation associated with MHC I and MHC II molecules.
2. What is cross-presentation, and when is it likely to occur?

Key Concepts and Summary

- **Major histocompatibility complex (MHC)** is a collection of genes coding for glycoprotein molecules expressed on the surface of all nucleated cells.
- **MHC I** molecules are expressed on all nucleated cells and are essential for presentation of normal "self" antigens. Cells that become infected by intracellular pathogens can present foreign antigens on MHC I as well, marking the infected cell for destruction.
- **MHC II** molecules are expressed only on the surface of **antigen-presenting cells** (macrophages, dendritic cells, and B cells). Antigen presentation with MHC II is essential for the activation of T cells.
- **Antigen-presenting cells (APCs)** primarily ingest pathogens by phagocytosis, destroy them in the phagolysosomes, process the protein antigens, and select the most antigenic/immunodominant epitopes with MHC II for presentation to T cells.
- **Cross-presentation** is a mechanism of antigen presentation and T-cell activation used by dendritic cells not directly infected by the pathogen; it involves phagocytosis of the pathogen but presentation on MHC I rather than MHC II.

This page titled 11.2: Antigens, Antigen Presenting Cells, and Major Histocompatibility Complexes is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **18.2: Antigens, Antigen Presenting Cells, and Major Histocompatibility Complexes** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

11.3: T Lymphocytes

Learning Objectives

- Describe the process of T-cell maturation and thymic selection
- Explain the genetic events that lead to diversity of T-cell receptors
- Compare and contrast the various classes and subtypes of T cells in terms of activation and function
- Explain the mechanism by which superantigens effect unregulated T-cell activation

As explained in Overview of Specific Adaptive Immunity, the antibodies involved in humoral immunity often bind pathogens and toxins before they can attach to and invade host cells. Thus, humoral immunity is primarily concerned with fighting pathogens in extracellular spaces. However, pathogens that have already gained entry to host cells are largely protected from the humoral antibody-mediated defenses. Cellular immunity, on the other hand, targets and eliminates intracellular pathogens through the actions of T lymphocytes, or T cells (Figure 11.3.1). T cells also play a more central role in orchestrating the overall adaptive immune response (humoral as well as cellular) along with the cellular defenses of innate immunity.

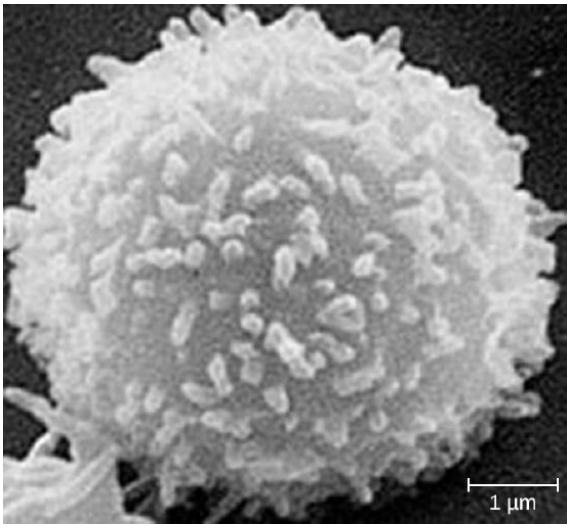


Figure 11.3.1: This scanning electron micrograph shows a T lymphocyte, which is responsible for the cell-mediated immune response. The spike-like membrane structures increase surface area, allowing for greater interaction with other cell types and their signals. (credit: modification of work by NCI)

T Cell Production and Maturation

T cells, like all other white blood cells involved in innate and adaptive immunity, are formed from multipotent hematopoietic stem cells (HSCs) in the bone marrow (see Figure 17.3.1). However, unlike the white blood cells of innate immunity, eventual T cells differentiate first into lymphoid stem cells that then become small, immature lymphocytes, sometimes called lymphoblasts. The first steps of differentiation occur in the red marrow of bones (Figure 11.3.2), after which immature T lymphocytes enter the bloodstream and travel to the thymus for the final steps of maturation (Figure 11.3.3). Once in the thymus, the immature T lymphocytes are referred to as thymocytes.

The maturation of thymocytes within the thymus can be divided into tree critical steps of positive and negative selection, collectively referred to as thymic selection. The first step of thymic selection occurs in the cortex of the thymus and involves the development of a functional T-cell receptor (TCR) that is required for activation by APCs. Thymocytes with defective TCRs are removed by negative selection through the induction of apoptosis (programmed controlled cell death). The second step of thymic selection also occurs in the cortex and involves the positive selection of thymocytes that will interact appropriately with MHC molecules. Thymocytes that can interact appropriately with MHC molecules receive a positive stimulation that moves them further through the process of maturation, whereas thymocytes that do not interact appropriately are not stimulated and are eliminated by apoptosis. The third and final step of thymic selection occurs in both the cortex and medulla and involves negative selection to remove self-reacting thymocytes, those that react to self-antigens, by apoptosis. This final step is sometimes referred to as central

tolerance because it prevents self-reacting T cells from reaching the bloodstream and potentially causing autoimmune disease, which occurs when the immune system attacks healthy “self” cells.

Despite central tolerance, some self-reactive T cells generally escape the thymus and enter the peripheral bloodstream. Therefore, a second line of defense called peripheral tolerance is needed to protect against autoimmune disease. Peripheral tolerance involves mechanisms of anergy and inhibition of self-reactive T cells by regulatory T cells. Anergy refers to a state of nonresponsiveness to antigen stimulation. In the case of self-reactive T cells that escape the thymus, lack of an essential co-stimulatory signal required for activation causes anergy and prevents autoimmune activation. Regulatory T cells participate in peripheral tolerance by inhibiting the activation and function of self-reactive T cells and by secreting anti-inflammatory cytokines.

It is not completely understood what events specifically direct maturation of thymocytes into regulatory T cells. Current theories suggest the critical events may occur during the third step of thymic selection, when most self-reactive T cells are eliminated. Regulatory T cells may receive a unique signal that is below the threshold required to target them for negative selection and apoptosis. Consequently, these cells continue to mature and then exit the thymus, armed to inhibit the activation of self-reactive T cells.

It has been estimated that the three steps of thymic selection eliminate 98% of thymocytes. The remaining 2% that exit the thymus migrate through the bloodstream and lymphatic system to sites of secondary lymphoid organs/tissues, such as the lymph nodes, spleen, and tonsils (Figure **11.3.3**), where they await activation through the presentation of specific antigens by APCs. Until they are activated, they are known as mature naïve T cells.

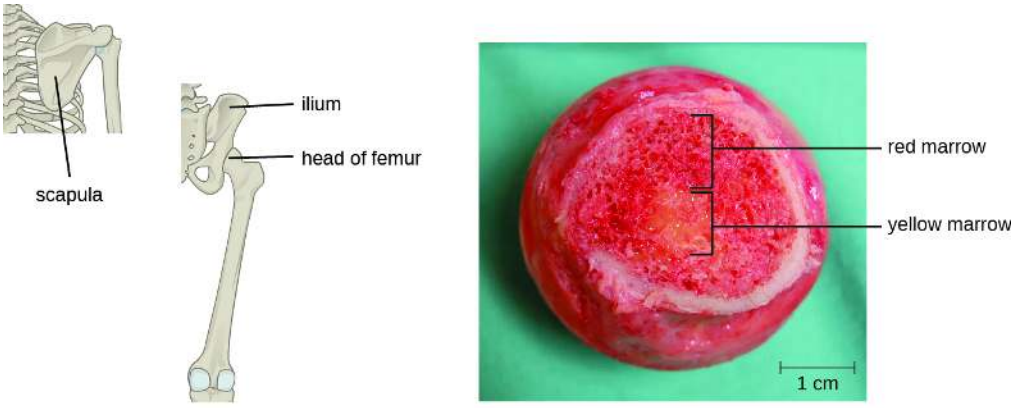


Figure **11.3.2**: (a) Red bone marrow can be found in the head of the femur (thighbone) and is also present in the flat bones of the body, such as the ilium and the scapula. (b) Red bone marrow is the site of production and differentiation of many formed elements of blood, including erythrocytes, leukocytes, and platelets. The yellow bone marrow is populated primarily with adipose cells.

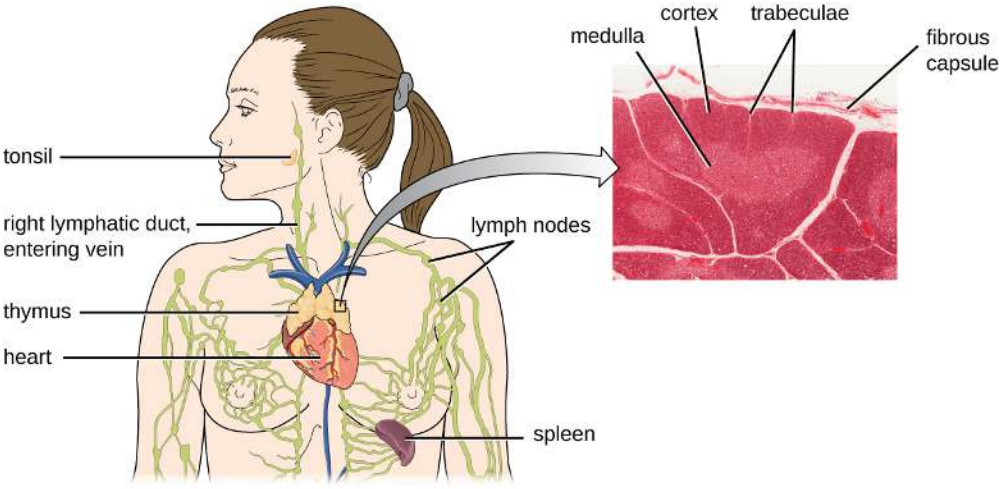


Figure **11.3.3**: The thymus is a bi-lobed, H-shaped glandular organ that is located just above the heart. It is surrounded by a fibrous capsule of connective tissue. The darkly staining cortex and the lighter staining medulla of individual lobules are clearly visible in the light micrograph of the thymus

https://med.libretexts.org/@go/page/77795

of a newborn (top right, LM × 100). (credit micrograph: modification of micrograph provided by the Regents of University of Michigan Medical School © 2012)

? Exercise 11.3.1

1. What anatomical sites are involved in T cell production and maturation?
2. What are the three steps involved in thymic selection?
3. Why are central tolerance and peripheral tolerance important? What do they prevent?

Classes of T Cells

T cells can be categorized into three distinct classes: helper T cells, regulatory T cells, and cytotoxic T cells. These classes are differentiated based on their expression of certain surface molecules, their mode of activation, and their functional roles in adaptive immunity (Table **11.3.1**).

All T cells produce cluster of differentiation (CD) molecules, cell surface glycoproteins that can be used to identify and distinguish between the various types of white blood cells. Although T cells can produce a variety of CD molecules, CD4and CD8 are the two most important used for differentiation of the classes. Helper T cells and regulatory T cells are characterized by the expression of CD4 on their surface, whereas cytotoxic T cells are characterized by the expression of CD8.

Classes of T cells can also be distinguished by the specific MHC molecules and APCs with which they interact for activation. Helper T cells and regulatory T cells can only be activated by APCs presenting antigens associated with MHC II. In contrast, cytotoxic T cells recognize antigens presented in association with MHC I, either by APCs or by nucleated cells infected with an intracellular pathogen.

The different classes of T cells also play different functional roles in the immune system. Helper T cells serve as the central orchestrators that help activate and direct functions of humoral and cellular immunity. In addition, helper T cells enhance the pathogen-killing functions of macrophages and NK cells of innate immunity. In contrast, the primary role of regulatory T cells is to prevent undesirable and potentially damaging immune responses. Their role in peripheral tolerance, for example, protects against autoimmune disorders, as discussed earlier. Finally, cytotoxic T cells are the primary effector cells for cellular immunity. They recognize and target cells that have been infected by intracellular pathogens, destroying infected cells along with the pathogens inside.

Table **11.3.1**: Classes of T Cells

Class	Surface CD Molecules	Activation	Functions
Helper T cells	CD4	APCs presenting antigens associated with MHC II	Orchestrate humoral and cellular immunity Involved in the activation of macrophages and NK cells
Regulatory T cells	CD4	APCs presenting antigens associated with MHC II	Involved in peripheral tolerance and prevention of autoimmune responses
Cytotoxic T cells	CD8	APCs or infected nucleated cells presenting antigens associated with MHC I	Destroy cells infected with intracellular pathogens

? Exercise 11.3.2

1. What are the unique functions of the three classes of T cells?
2. Which T cells can be activated by antigens presented by cells other than APCs?

T-Cell Receptors

For both helper T cells and cytotoxic T cells, activation is a complex process that requires the interactions of multiple molecules and exposure to cytokines. The T-cell receptor (TCR) is involved in the first step of pathogen epitope recognition during the activation process.

The TCR comes from the same receptor family as the antibodies IgD and IgM, the antigen receptors on the B cell membrane surface, and thus shares common structural elements. Similar to antibodies, the TCR has a variable regionand a constant region, and the variable region provides the antigen-binding site (Figure **11.3.4**). However, the structure of TCR is smaller and less complex than the immunoglobulin molecules (Figure 18.1.4). Whereas immunoglobulins have four peptide chains and Y-shaped structures, the TCR consists of just two peptide chains (α and β chains), both of which span the cytoplasmic membrane of the T cell.

TCRs are epitope-specific, and it has been estimated that 25 million T cells with unique epitope-binding TCRs are required to protect an individual against a wide range of microbial pathogens. Because the human genome only contains about 25,000 genes, we know that each specific TCR cannot be encoded by its own set of genes. This raises the question of how such a vast population of T cells with millions of specific TCRs can be achieved. The answer is a process called genetic rearrangement, which occurs in the thymus during the first step of thymic selection.

The genes that code for the variable regions of the TCR are divided into distinct gene segments called variable (V), diversity (D), and joining (J) segments. The genes segments associated with the α chain of the TCR consist 70 or more different V_α segments and 61 different J_α segments. The gene segments associated with the β chain of the TCR consist of 52 different V_β segments, two different D_β segments, and 13 different J_β segments. During the development of the functional TCR in the thymus, genetic rearrangement in a T cell brings together one V_α segment and one J_α segment to code for the variable region of the α chain. Similarly, genetic rearrangement brings one of the V_β segments together with one of the D_β segments and one of theJ_β segments to code for the variable region of the β chain. All the possible combinations of rearrangements between different segments of V, D, and J provide the genetic diversity required to produce millions of TCRs with unique epitope-specific variable regions.

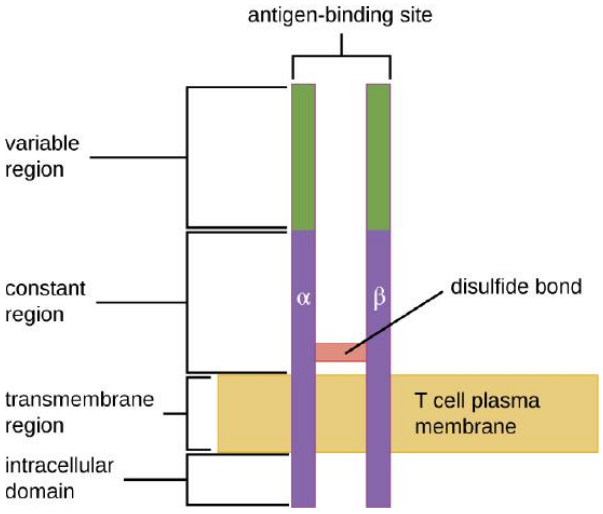


Figure **11.3.4**: A T-cell receptor spans the cytoplasmic membrane and projects variable binding regions into the extracellular space to bind processed antigens associated with MHC I or MHC II molecules.

? Exercise 11.3.3

1. What are the similarities and differences between TCRs and immunoglobulins?
2. What process is used to provide millions of unique TCR binding sites?

Activation and Differentiation of Helper T Cells

Helper T cells can only be activated by APCs presenting processed foreign epitopes in association with MHC II. The first step in the activation process is TCR recognition of the specific foreign epitope presented within the MHC II antigen-binding cleft. The second step involves the interaction of CD4 on the helper T cell with a region of the MHC II molecule separate from the antigen-

binding cleft. This second interaction anchors the MHC II-TCR complex and ensures that the helper T cell is recognizing both the foreign (“nonself”) epitope and “self” antigen of the APC; both recognitions are required for activation of the cell. In the third step, the APC and T cell secrete cytokines that activate the helper T cell. The activated helper T cell then proliferates, dividing by mitosis to produce clonal naïve helper T cells that differentiate into subtypes with different functions (Figure **11.3.5**).

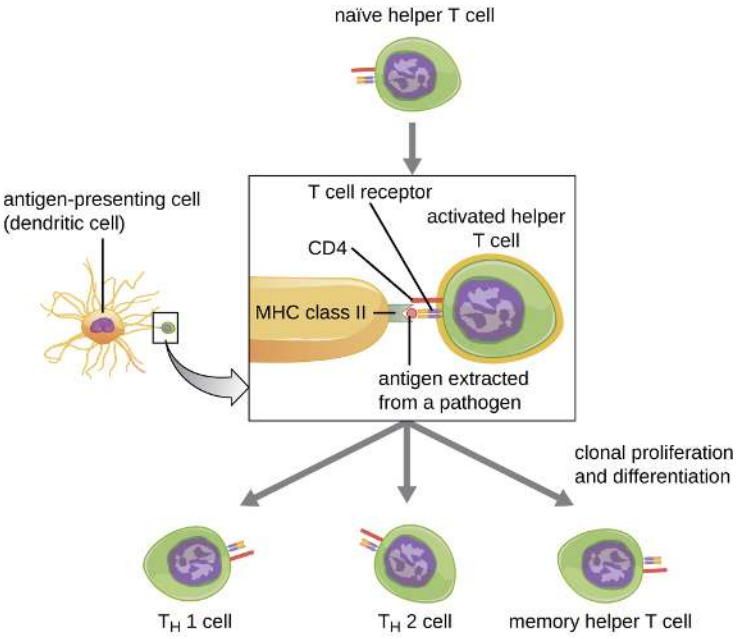


Figure **11.3.5**: This illustration depicts the activation of a naïve (unactivated) helper T cell by an antigen-presenting cell and the subsequent proliferation and differentiation of the activated T cell into different subtypes.

Activated helper T cells can differentiate into one of four distinct subtypes, summarized in Table **11.3.2**. The differentiation process is directed by APC-secreted cytokines. Depending on which APC-secreted cytokines interact with an activated helper T cell, the cell may differentiate into a T helper 1 (T_H1) cell, a T helper 2 (T_H2) cell, or a memory helper T cell. The two types of helper T cells are relatively short-lived effector cells, meaning that they perform various functions of the immediate immune response. In contrast, memory helper T cells are relatively long lived; they are programmed to “remember” a specific antigen or epitope in order to mount a rapid, strong, secondary response to subsequent exposures.

T_H1 cells secrete their own cytokines that are involved in stimulating and orchestrating other cells involved in adaptive and innate immunity. For example, they stimulate cytotoxic T cells, enhancing their killing of infected cells and promoting differentiation into memory cytotoxic T cells. T_H1 cells also stimulate macrophages and neutrophils to become more effective in their killing of intracellular bacteria. They can also stimulate NK cells to become more effective at killing target cells.

T_H2 cells play an important role in orchestrating the humoral immune response through their secretion of cytokines that activate B cells and direct B cell differentiation and antibody production. Various cytokines produced by T_H2 cells orchestrate antibody class switching, which allows B cells to switch between the production of IgM, IgG, IgA, and IgE as needed to carry out specific antibody functions and to provide pathogen-specific humoral immune responses.

A third subtype of helper T cells called T_H17 cells was discovered through observations that immunity to some infections is not associated with T_H1 or T_H2 cells. T_H17 cells and the cytokines they produce appear to be specifically responsible for the body’s defense against chronic mucocutaneous infections. Patients who lack sufficient T_H17 cells in the mucosa (e.g., HIV patients) may be more susceptible to bacteremia and gastrointestinal infections.[1]

Table **11.3.2**: Subtypes of Helper T Cells

Subtype	Functions
T_H1 cells	Stimulate cytotoxic T cells and produce memory cytotoxic T cells
	Stimulate macrophages and neutrophils (PMNs) for more effective intracellular killing of pathogens
	Stimulate NK cells to kill more effectively
T_H2 cells	Stimulate B cell activation and differentiation into plasma cells and memory B cells
	Direct antibody class switching in B cells
T_H17 cells	Stimulate immunity to specific infections such as chronic mucocutaneous infections
Memory helper T cells	"Remember" a specific pathogen and mount a strong, rapid secondary response upon re-exposure

Activation and Differentiation of Cytotoxic T Cells

Cytotoxic T cells (also referred to as cytotoxic T lymphocytes, or CTLs) are activated by APCs in a three-step process similar to that of helper T cells. The key difference is that the activation of cytotoxic T cells involves recognition of an antigen presented with MHC I (as opposed to MHC II) and interaction of CD8 (as opposed to CD4) with the receptor complex. After the successful co-recognition of foreign epitope and self-antigen, the production of cytokines by the APC and the cytotoxic T cell activate clonal proliferation and differentiation. Activated cytotoxic T cells can differentiate into effector cytotoxic T cells that target pathogens for destruction or memory cells that are ready to respond to subsequent exposures.

As noted, proliferation and differentiation of cytotoxic T cells is also stimulated by cytokines secreted from T_H1 cells activated by the same foreign epitope. The co-stimulation that comes from these T_H1 cells is provided by secreted cytokines. Although it is possible for activation of cytotoxic T cells to occur without stimulation from T_H1 cells, the activation is not as effective or long-lasting.

Once activated, cytotoxic T cells serve as the effector cells of cellular immunity, recognizing and kill cells infected with intracellular pathogens through a mechanism very similar to that of NK cells. However, whereas NK cells recognize nonspecific signals of cell stress or abnormality, cytotoxic T cells recognize infected cells through antigen presentation of pathogen-specific epitopes associated with MHC I. Once an infected cell is recognized, the TCR of the cytotoxic T cell binds to the epitope and releases perforin and granzymes that destroy the infected cell (Figure **11.3.6**). Perforin is a protein that creates pores in the target cell, and granzymes are proteases that enter the pores and induce apoptosis. This mechanism of programmed cell death is a controlled and efficient means of destroying and removing infected cells without releasing the pathogens inside to infect neighboring cells, as might occur if the infected cells were simply lysed.

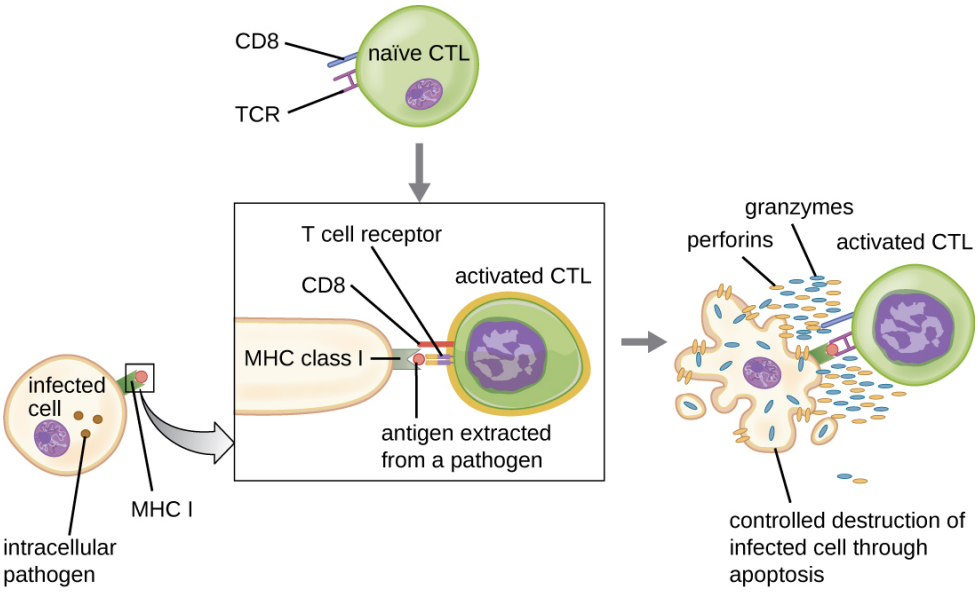


Figure 11.3.6: This figure illustrates the activation of a naïve (unactivated) cytotoxic T cell (CTL) by an antigen-presenting MHC I molecule on an infected body cell. Once activated, the CTL releases perforin and granzymes that invade the infected cell and induce controlled cell death, or apoptosis.

Link to Learning

In this video, you can see a cytotoxic T cell inducing apoptosis in a target cell.

Exercise 11.3.4

1. Compare and contrast the activation of helper T cells and cytotoxic T cells.
2. What are the different functions of helper T cell subtypes?
3. What is the mechanism of CTL-mediated destruction of infected cells?

Superantigens and Unregulated Activation of T Cells

When T cell activation is controlled and regulated, the result is a protective response that is effective in combating infections. However, if T cell activation is unregulated and excessive, the result can be a life-threatening. Certain bacterial and viral pathogens produce toxins known as superantigens (see Virulence Factors of Bacterial and Viral Pathogens) that can trigger such an unregulated response. Known bacterial superantigens include toxic shock syndrome toxin (TSST), staphylococcal enterotoxins, streptococcal pyrogenic toxins, streptococcal superantigen, and the streptococcal mitogenic exotoxin. Viruses known to produce superantigens include Epstein-Barr virus (human herpesvirus 4), cytomegalovirus (human herpesvirus 5), and others.

The mechanism of T cell activation by superantigens involves their simultaneous binding to MHC II molecules of APCs and the variable region of the TCR β chain. This binding occurs outside of the antigen-binding cleft of MHC II, so the superantigen will bridge together and activate MHC II and TCR without specific foreign epitope recognition (Figure 11.3.7). The result is an excessive, uncontrolled release of cytokines, often called a cytokine storm, which stimulates an excessive inflammatory response. This can lead to a dangerous decrease in blood pressure, shock, multi-organ failure, and potentially, death.

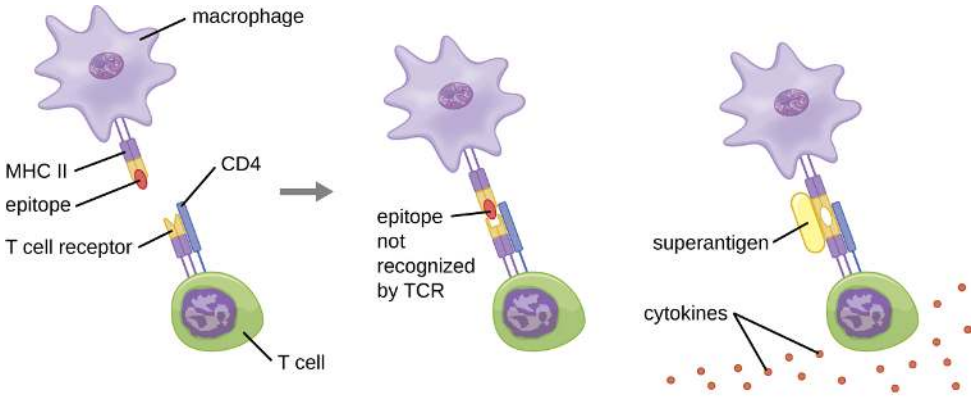


Figure **11.3.7**: (a) The macrophage in this figure is presenting a foreign epitope that does not match the TCR of the T cell. Because the T cell does not recognize the epitope, it is not activated. (b) The macrophage in this figure is presenting a superantigen that is not recognized by the TCR of the T cell, yet the superantigen still is able to bridge and bind the MHC II and TCR molecules. This nonspecific, uncontrolled activation of the T cell results in an excessive release of cytokines that activate other T cells and cause excessive inflammation. (credit: modification of work by "Microbiotic"/YouTube)

? Exercise 11.3.5

1. What are examples of superantigens?
2. How does a superantigen activate a helper T cell?
3. What effect does a superantigen have on a T cell?

Case in Point: Superantigens

Melissa, an otherwise healthy 22-year-old woman, is brought to the emergency room by her concerned boyfriend. She complains of a sudden onset of high fever, vomiting, diarrhea, and muscle aches. In her initial interview, she tells the attending physician that she is on hormonal birth control and also is two days into the menstruation portion of her cycle. She is on no other medications and is not abusing any drugs or alcohol. She is not a smoker. She is not diabetic and does not currently have an infection of any kind to her knowledge.

While waiting in the emergency room, Melissa's blood pressure begins to drop dramatically and her mental state deteriorates to general confusion. The physician believes she is likely suffering from toxic shock syndrome (TSS). TSS is caused by the toxin TSST-1, a superantigen associated with *Staphylococcus aureus*, and improper tampon use is a common cause of infections leading to TSS. The superantigen inappropriately stimulates widespread T cell activation and excessive cytokine release, resulting in a massive and systemic inflammatory response that can be fatal.

Vaginal or cervical swabs may be taken to confirm the presence of the microbe, but these tests are not critical to perform based on Melissa's symptoms and medical history. The physician prescribes rehydration, supportive therapy, and antibiotics to stem the bacterial infection. She also prescribes drugs to increase Melissa's blood pressure. Melissa spends three days in the hospital undergoing treatment; in addition, her kidney function is monitored because of the high risk of kidney failure associated with TSS. After 72 hours, Melissa is well enough to be discharged to continue her recovery at home.

Exercise 11.3.6

In what way would antibiotic therapy help to combat a superantigen?

Clinical Focus: Part 2

Olivia's swollen lymph nodes, abdomen, and spleen suggest a strong immune response to a systemic infection in progress. In addition, little Olivia is reluctant to turn her head and appears to be experiencing severe neck pain. The physician orders a complete blood count, blood culture, and lumbar puncture. The cerebrospinal fluid (CSF) obtained appears cloudy and is

further evaluated by Gram stain assessment and culturing for potential bacterial pathogens. The complete blood count indicates elevated numbers of white blood cells in Olivia's bloodstream. The white blood cell increases are recorded at 28.5 K/µL (normal range: 6.0–17.5 K/µL). The neutrophil percentage was recorded as 60% (normal range: 23–45%). Glucose levels in the CSF were registered at 30 mg/100 mL (normal range: 50–80 mg/100 mL). The WBC count in the CSF was 1,163/mm3 (normal range: 5–20/mm^3).

Exercise 11.3.7

1. Based on these results, do you have a preliminary diagnosis?
2. What is a recommended treatment based on this preliminary diagnosis?

Key Concepts and Summary

- Immature T lymphocytes are produced in the red bone marrow and travel to the thymus for maturation.
- **Thymic selection** is a three-step process of negative and positive selection that determines which T cells will mature and exit the thymus into the peripheral bloodstream.
- **Central tolerance** involves negative selection of self-reactive T cells in the thymus, and **peripheral tolerance**involves **anergy** and **regulatory T cells** that prevent self-reactive immune responses and autoimmunity.
- The **TCR** is similar in structure to immunoglobulins, but less complex. Millions of unique epitope-binding TCRs are encoded through a process of genetic rearrangement of V, D, and J gene segments.
- T cells can be divided into three classes—**helper T cells, cytotoxic T cells,** and **regulatory T cells—**based on their expression of CD4 or CD8, the MHC molecules with which they interact for activation, and their respective functions.
- Activated helper T cells differentiate into **T_H1, T_H2, T_H17**, or **memory T cell subtypes**. Differentiation is directed by the specific cytokines to which they are exposed. T_H1, T_H2, and T_H17 perform different functions related to stimulation of adaptive and innate immune defenses. Memory T cells are long-lived cells that can respond quickly to secondary exposures.
- Once activated, cytotoxic T cells target and kill cells infected with intracellular pathogens. Killing requires recognition of specific pathogen epitopes presented on the cell surface using MHC I molecules. Killing is mediated by **perforin** and **granzymes** that induce apoptosis.
- **Superantigens** are bacterial or viral proteins that cause a nonspecific activation of helper T cells, leading to an excessive release of cytokines (**cytokine storm**) and a systemic, potentially fatal inflammatory response.

Footnotes

1. 1 Blaschitz C., Raffatellu M. "Th17 cytokines and the gut mucosal barrier." J Clin Immunol. 2010 Mar; 30(2):196-203. doi: 10.1007/s10875-010-9368-7.

This page titled 11.3: T Lymphocytes is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **18.3: T Lymphocytes** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

11.4: B Lymphocytes and Antibodies

Learning Objectives

- Describe the production and maturation of B cells
- Compare the structure of B-cell receptors and T-cell receptors
- Compare T-dependent and T-independent activation of B cells
- Compare the primary and secondary antibody responses

Humoral immunity refers to mechanisms of the adaptive immune defenses that are mediated by antibodies secreted by B lymphocytes, or B cells. This section will focus on B cells and discuss their production and maturation, receptors, and mechanisms of activation.

B Cell Production and Maturation

Like T cells, B cells are formed from multipotent hematopoietic stem cells (HSCs) in the bone marrow and follow a pathway through lymphoid stem cell and lymphoblast (see Figure 17.3.1). Unlike T cells, however, lymphoblasts destined to become B cells do not leave the bone marrow and travel to the thymus for maturation. Rather, eventual B cells continue to mature in the bone marrow.

The first step of B cell maturation is an assessment of the functionality of their antigen-binding receptors. This occurs through positive selection for B cells with normal functional receptors. A mechanism of negative selection is then used to eliminate self-reacting B cells and minimize the risk of autoimmunity. Negative selection of self-reacting B cells can involve elimination by apoptosis, editing or modification of the receptors so they are no longer self-reactive, or induction of anergy in the B cell. Immature B cells that pass the selection in the bone marrow then travel to the spleenfor their final stages of maturation. There they become naïve mature B cells, i.e., mature B cells that have not yet been activated.

Exercise 11.4.1

Compare the maturation of B cells with the maturation of T cells.

B-Cell Receptors

Like T cells, B cells possess antigen-specific receptors with diverse specificities. Although they rely on T cells for optimum function, B cells can be activated without help from T cells. B-cell receptors (BCRs) for naïve mature B cells are membrane-bound monomeric forms of IgD and IgM. They have two identical heavy chains and two identical light chains connected by disulfide bonds into a basic “Y” shape (Figure **11.4.1**). The trunk of the Y-shaped molecule, the constant region of the two heavy chains, spans the B cell membrane. The two antigen-binding sites exposed to the exterior of the B cell are involved in the binding of specific pathogen epitopes to initiate the activation process. It is estimated that each naïve mature B cell has upwards of 100,000 BCRs on its membrane, and each of these BCRs has an identical epitope-binding specificity.

In order to be prepared to react to a wide range of microbial epitopes, B cells, like T cells, use genetic rearrangementof hundreds of gene segments to provide the necessary diversity of receptor specificities. The variable region of the BCR heavy chain is made up of V, D, and J segments, similar to the β chain of the TCR. The variable region of the BCR light chain is made up of V and J segments, similar to the α chain of the TCR. Genetic rearrangement of all possible combinations of V-J-D (heavy chain) and V-J (light chain) provides for millions of unique antigen-binding sites for the BCR and for the antibodies secreted after activation.

One important difference between BCRs and TCRs is the way they can interact with antigenic epitopes. Whereas TCRs can only interact with antigenic epitopes that are presented within the antigen-binding cleft of MHC I or MHC II, BCRs do not require antigen presentation with MHC; they can interact with epitopes on free antigens or with epitopesdisplayed on the surface of intact pathogens. Another important difference is that TCRs only recognize protein epitopes, whereas BCRs can recognize epitopes associated with different molecular classes (e.g., proteins, polysaccharides, lipopolysaccharides).

Activation of B cells occurs through different mechanisms depending on the molecular class of the antigen. Activation of a B cell by a protein antigen requires the B cell to function as an APC, presenting the protein epitopes with MHC II to helper T cells.

Because of their dependence on T cells for activation of B cells, protein antigens are classified as T-dependent antigens. In contrast, polysaccharides, lipopolysaccharides, and other nonprotein antigens are considered T-independent antigens because they can activate B cells without antigen processing and presentation to T cells.

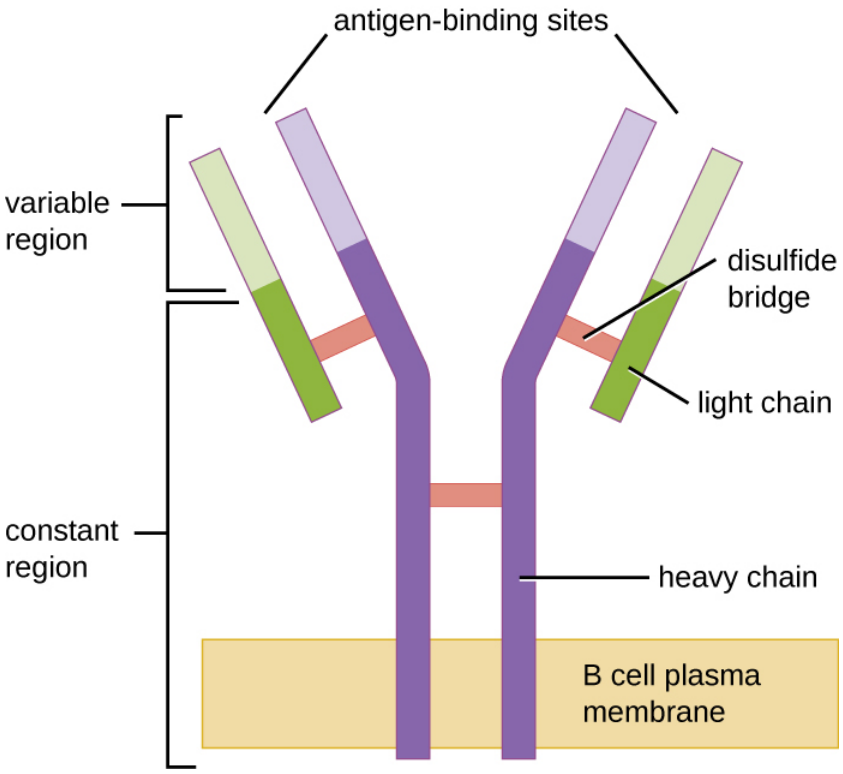


Figure 11.4.1: B-cell receptors are embedded in the membranes of B cells. The variable regions of all of the receptors on a single cell bind the same specific antigen.

? Exercise 11.4.2

1. What types of molecules serve as the BCR?
2. What are the differences between TCRs and BCRs with respect to antigen recognition?
3. Which molecule classes are T-dependent antigens and which are T-independent antigens?

T Cell-Independent Activation of B cells

Activation of B cells without the cooperation of helper T cells is referred to as T cell-independent activation and occurs when BCRs interact with T-independent antigens. T-independent antigens (e.g., polysaccharide capsules, lipopolysaccharide) have repetitive epitope units within their structure, and this repetition allows for the cross-linkageof multiple BCRs, providing the first signal for activation (Figure 11.4.2). Because T cells are not involved, the second signal has to come from other sources, such as interactions of toll-like receptors with PAMPs or interactions with factors from the complement system.

Once a B cell is activated, it undergoes clonal proliferation and daughter cells differentiate into plasma cells. Plasma cells are antibody factories that secrete large quantities of antibodies. After differentiation, the surface BCRs disappear and the plasma cell secretes pentameric IgM molecules that have the same antigen specificity as the BCRs (Figure 11.4.2).

The T cell-independent response is short-lived and does not result in the production of memory B cells. Thus it will not result in a secondary response to subsequent exposures to T-independent antigens.

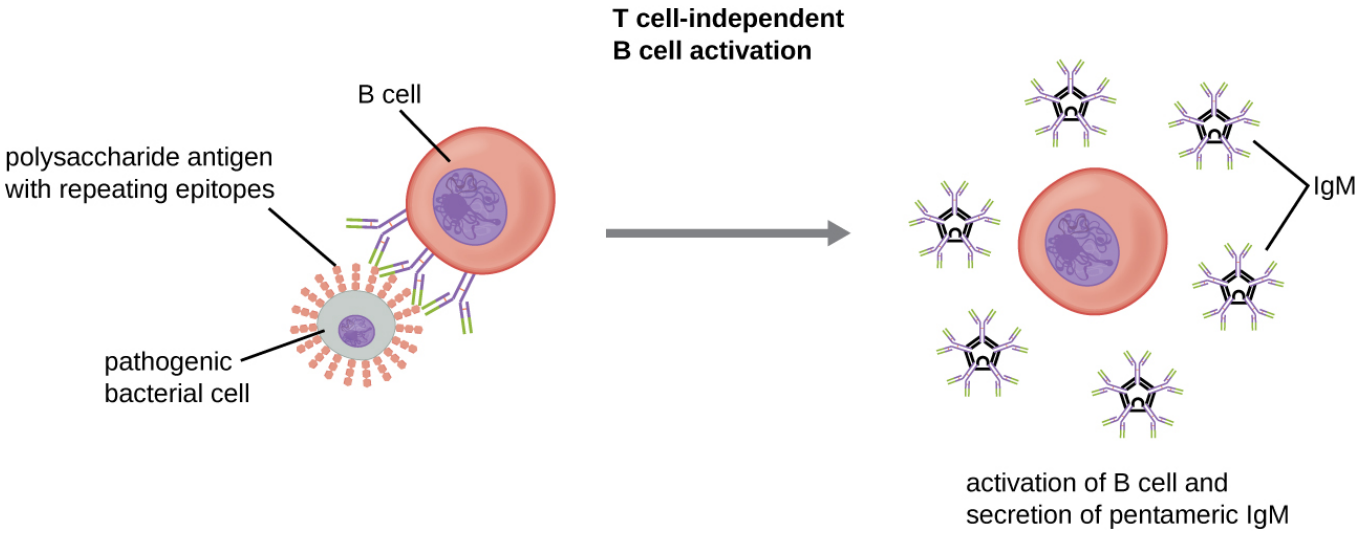


Figure **11.4.2**: T-independent antigens have repeating epitopes that can induce B cell recognition and activation without involvement from T cells. A second signal, such as interaction of TLRs with PAMPs (not shown), is also required for activation of the B cell. Once activated, the B cell proliferates and differentiates into antibody-secreting plasma cells.

? Exercise 11.4.3

1. What are the two signals required for T cell-independent activation of B cells?
2. What is the function of a plasma cell?

T Cell-Dependent Activation of B cells

T cell-dependent activation of B cells is more complex than T cell-independent activation, but the resulting immune response is stronger and develops memory. T cell-dependent activation can occur either in response to free protein antigens or to protein antigens associated with an intact pathogen. Interaction between the BCRs on a naïve mature B cell and a free protein antigen stimulate internalization of the antigen, whereas interaction with antigens associated with an intact pathogen initiates the extraction of the antigen from the pathogen before internalization. Once internalized inside the B cell, the protein antigen is processed and presented with MHC II. The presented antigen is then recognized by helper T cells specific to the same antigen. The TCR of the helper T cell recognizes the foreign antigen, and the T cell's CD4 molecule interacts with MHC II on the B cell. The coordination between B cells and helper T cells that are specific to the same antigen is referred to as linked recognition.

Once activated by linked recognition, T_H2 cells produce and secrete cytokines that activate the B cell and cause proliferation into clonal daughter cells. After several rounds of proliferation, additional cytokines provided by the T_H2 cells stimulate the differentiation of activated B cell clones into memory B cells, which will quickly respond to subsequent exposures to the same protein epitope, and plasma cells that lose their membrane BCRs and initially secrete pentameric IgM (Figure **11.4.3**).

After initial secretion of IgM, cytokines secreted by T_H2 cells stimulate the plasma cells to switch from IgM production to production of IgG, IgA, or IgE. This process, called class switching or isotype switching, allows plasma cellscloned from the same activated B cell to produce a variety of antibody classes with the same epitope specificity. Class switching is accomplished by genetic rearrangement of gene segments encoding the constant region, which determines an antibody's class. The variable region is not changed, so the new class of antibody retains the original epitope specificity.

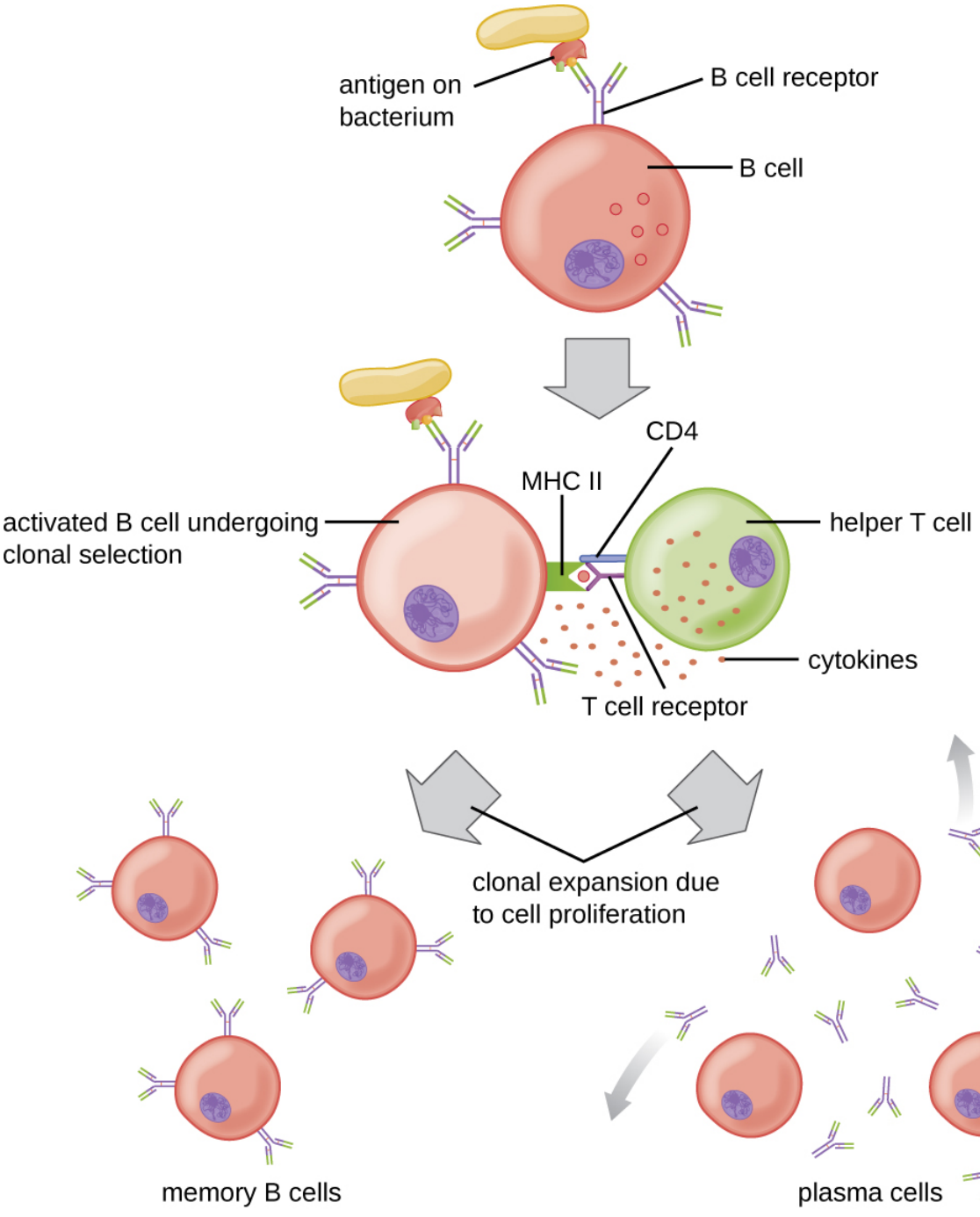


Figure **11.4.3**: In T cell-dependent activation of B cells, the B cell recognizes and internalizes an antigen and presents it to a helper T cell that is specific to the same antigen. The helper T cell interacts with the antigen presented by the B cell, which activates the T cell and stimulates the release of cytokines that then activate the B cell. Activation of the B cell triggers proliferation and differentiation into B cells and plasma cells.

? Exercise 11.4.4

1. What steps are required for T cell-dependent activation of B cells?
2. What is antibody class switching and why is it important?

Primary and Secondary Responses

T cell-dependent activation of B cells plays an important role in both the primary and secondary responses associated with adaptive immunity. With the first exposure to a protein antigen, a T cell-dependent primary antibody responseoccurs. The initial stage of the primary response is a lag period, or latent period, of approximately 10 days, during which no antibody can be detected in serum. This lag period is the time required for all of the steps of the primary response, including naïve mature B cell binding of antigen with BCRs, antigen processing and presentation, helper T cell activation, B cell activation, and clonal proliferation. The end of the lag period is characterized by a rise in IgM levels in the serum, as T_H2 cells stimulate B cell differentiation into plasma cells. IgM levels reach their peak around 14 days after primary antigen exposure; at about this same time, T_H2 stimulates antibody class switching, and IgM levels in serum begin to decline. Meanwhile, levels of IgG increase until they reach a peak about three weeks into the primary response (Figure 11.4.4).

During the primary response, some of the cloned B cells are differentiated into memory B cells programmed to respond to subsequent exposures. This secondary response occurs more quickly and forcefully than the primary response. The lag period is decreased to only a few days and the production of IgG is significantly higher than observed for the primary response (Figure 11.4.4). In addition, the antibodies produced during the secondary response are more effective and bind with higher affinity to the targeted epitopes. Plasma cells produced during secondary responses live longer than those produced during the primary response, so levels of specific antibody remain elevated for a longer period of time.

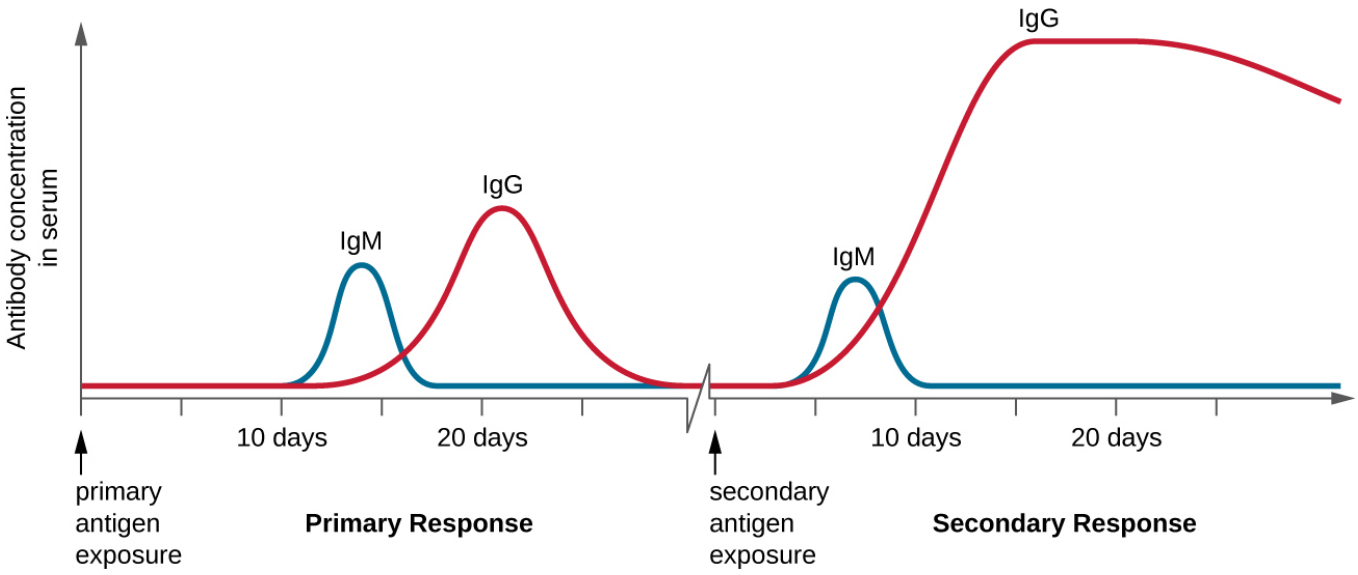


Figure 11.4.4: Compared to the primary response, the secondary antibody response occurs more quickly and produces antibody levels that are higher and more sustained. The secondary response mostly involves IgG.

? Exercise 11.4.5

1. What events occur during the lag period of the primary antibody response?
2. Why do antibody levels remain elevated longer during the secondary antibody response?

Key Concepts and Summary

- **B lymphocytes** or **B cells** produce antibodies involved in humoral immunity. B cells are produced in the bone marrow, where the initial stages of maturation occur, and travel to the spleen for final steps of maturation into naïve mature B cells.
- **B-cell receptors (BCRs)** are membrane-bound monomeric forms of IgD and IgM that bind specific antigen epitopes with their Fab antigen-binding regions. Diversity of antigen binding specificity is created by genetic rearrangement of V, D, and J segments similar to the mechanism used for TCR diversity.
- Protein antigens are called **T-dependent antigens** because they can only activate B cells with the cooperation of helper T cells. Other molecule classes do not require T cell cooperation and are called **T-independent antigens**.

- **T cell-independent activation** of B cells involves cross-linkage of BCRs by repetitive nonprotein antigen epitopes. It is characterized by the production of IgM by **plasma cells** and does not produce memory B cells.
- **T cell-dependent activation** of B cells involves processing and presentation of protein antigens to helper T cells, activation of the B cells by cytokines secreted from activated T_H2 cells, and plasma cells that produce different classes of antibodies as a result of **class switching**. **Memory B cells** are also produced.
- Secondary exposures to T-dependent antigens result in a secondary antibody response initiated by memory B cells. The secondary response develops more quickly and produces higher and more sustained levels of antibody with higher affinity for the specific antigen.

This page titled 11.4: B Lymphocytes and Antibodies is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **18.4: B Lymphocytes and Antibodies** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

12: Hypersensitivities

Learning Objectives

- Identify and compare the distinguishing characteristics, mechanisms, and major examples of type I, II, III, and IV hypersensitivities

Clinical Focus: Part 1

Kerry, a 40-year-old airline pilot, has made an appointment with her primary care physician to discuss a rash that develops whenever she spends time in the sun. As she explains to her physician, it does not seem like sunburn. She is careful not to spend too much time in the sun and she uses sunscreen. Despite these precautions, the rash still appears, manifesting as red, raised patches that get slightly scaly. The rash persists for 7 to 10 days each time, and it seems to largely go away on its own. Lately, the rashes have also begun to appear on her cheeks and above her eyes on either side of her forehead.

Exercise 12.1

1. Is Kerry right to be concerned, or should she simply be more careful about sun exposure?
2. Are there conditions that might be brought on by sun exposure that Kerry's physician should be considering?

In Adaptive Specific Host Defenses, we discussed the mechanisms by which adaptive immune defenses, both humoral and cellular, protect us from infectious diseases. However, these same protective immune defenses can also be responsible for undesirable reactions called hypersensitivity reactions. Hypersensitivity reactions are classified by their immune mechanism.

- Type I hypersensitivity reactions involve immunoglobulin E (IgE) antibody against soluble antigen, triggering mast cell degranulation.
- Type II hypersensitivity reactions involve IgG and IgM antibodies directed against cellular antigens, leading to cell damage mediated by other immune system effectors.
- Type III hypersensitivity reactions involve the interactions of IgG, IgM, and, occasionally, IgA[1] antibodies with antigen to form immune complexes. Accumulation of immune complexes in tissue leads to tissue damage mediated by other immune system effectors.
- Type IV hypersensitivity reactions are T-cell–mediated reactions that can involve tissue damage mediated by activated macrophages and cytotoxic T cells.

Type I Hypersensitivities

When a presensitized individual is exposed to an allergen, it can lead to a rapid immune response that occurs almost immediately. Such a response is called an allergy and is classified as a type I hypersensitivity. Allergens may be seemingly harmless substances such as animal dander, molds, or pollen. Allergens may also be substances considered innately more hazardous, such as insect venom or therapeutic drugs. Food intolerances can also yield allergic reactions as individuals become sensitized to foods such as peanuts or shellfish (Figure **12.1**). Regardless of the allergen, the first exposure activates a primary IgE antibody response that sensitizes an individual to type I hypersensitivity reaction upon subsequent exposure.



(a)



(b)



(c)

Figure 12.1: (a) Allergens in plant pollen, shown here in a colorized electron micrograph, may trigger allergic rhinitis or hay fever in sensitive individuals. (b) Skin rashes are often associated with allergic reactions. (c) Peanuts can be eaten safely by most people but can provoke severe allergic reactions in sensitive individuals.

For susceptible individuals, a first exposure to an allergen activates a strong T_H2 cell response (Figure 12.2). Cytokines interleukin (IL)-4 and IL-13 from the T_H2 cells activate B cells specific to the same allergen, resulting in clonal proliferation, differentiation into plasma cells, and antibody-class switch from production of IgM to production of IgE. The fragment crystallizable (Fc) regions of the IgE antibodies bind to specific receptors on the surface of mast cellsthroughout the body. It is estimated that each mast cell can bind up to 500,000 IgE molecules, with each IgE molecule having two allergen-specific fragment antigen-binding (Fab) sites available for binding allergen on subsequent exposures. By the time this occurs, the allergen is often no longer present and there is no allergic reaction, but the mast cells are primed for a subsequent exposure and the individual is sensitized to the allergen.

On subsequent exposure, allergens bind to multiple IgE molecules on mast cells, cross-linking the IgE molecules. Within minutes, this cross-linking of IgE activates the mast cells and triggers degranulation, a reaction in which the contents of the granules in the mast cell are released into the extracellular environment. Preformed components that are released from granules include histamine, serotonin, and bradykinin (Table 12.1). The activated mast cells also release newly formed lipid mediators (leukotrienes and prostaglandins from membrane arachadonic acid metabolism) and cytokines such as tumor necrosis factor (Table 12.2).

Table 12.1: Selected Preformed Components of Mast Cell Granules

Granule Component	Activity
Heparin	Stimulates the generation of bradykinin, which causes increased vascular permeability, vasodilation, bronchiole constriction, and increased mucus secretion
Histamine	Causes smooth-muscle contraction, increases vascular permeability, increases mucus and tear formation
Serotonin	Increases vascular permeability, causes vasodilation and smooth-muscle contraction

The chemical mediators released by mast cells collectively cause the inflammation and signs and symptoms associated with type I hypersensitivity reactions. Histamine stimulates mucus secretion in nasal passages and tear formation from lacrimal glands, promoting the runny nose and watery eyes of allergies. Interaction of histamine with nerve endings causes itching and sneezing. The vasodilation caused by several of the mediators can result in hives, headaches, angioedema (swelling that often affects the lips, throat, and tongue), and hypotension (low blood pressure). Bronchiole constriction caused by some of the chemical mediators leads to wheezing, dyspnea (difficulty breathing), coughing, and, in more severe cases, cyanosis (bluish color to the skin or mucous membranes). Vomiting can result from stimulation of the vomiting center in the cerebellum by histamine and serotonin. Histamine can also cause relaxation of intestinal smooth muscles and diarrhea.

Table 12.2: Selected Newly Formed Chemical Mediators of Inflammation and Allergic Response

Chemical Mediator	Activity
Leukotriene	Causes smooth-muscle contraction and mucus secretion, increases vascular permeability
Prostaglandin	Causes smooth-muscle contraction and vasodilation
TNF-α (cytokine)	Causes inflammation and stimulates cytokine production by other cell types

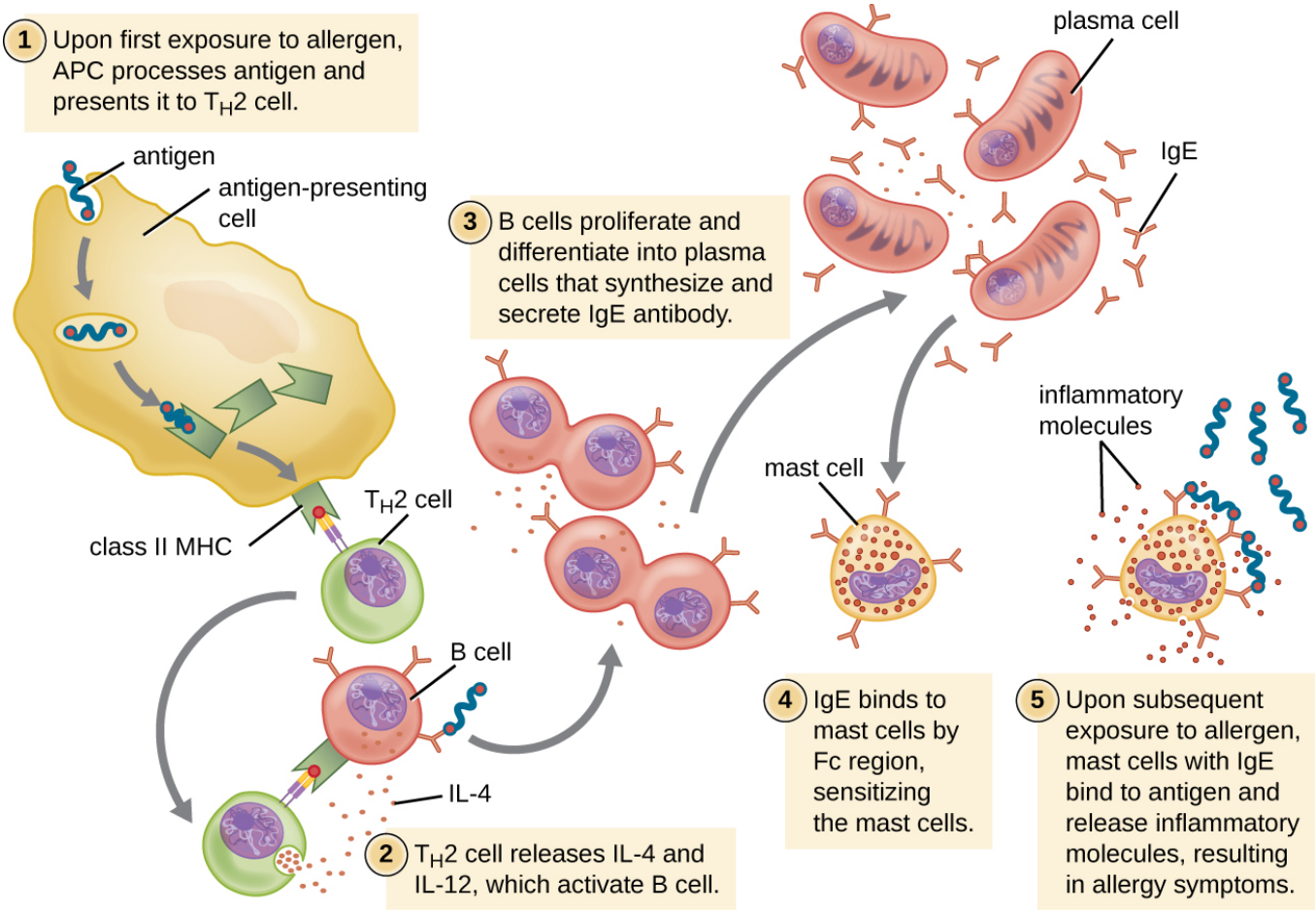


Figure 12.2: On first exposure to an allergen in a susceptible individual, antigen-presenting cells process and present allergen epitopes with major histocompatibility complex (MHC) II to T helper cells. B cells also process and present the same allergen epitope to T_H2 cells, which release cytokines IL-4 and IL-13 to stimulate proliferation and differentiation into IgE-secreting plasma cells. The IgE molecules bind to mast cells with their Fc region, sensitizing the mast cells for activation with subsequent exposure to the allergen. With each subsequent exposure, the allergen cross-links IgE molecules on the mast cells, activating the mast cells and causing the release of preformed chemical mediators from granules (degranulation), as well as newly formed chemical mediators that collectively cause the signs and symptoms of type I hypersensitivity reactions.

Type I hypersensitivity reactions can be either localized or systemic. Localized type I hypersensitivity reactions include hay fever rhinitis, hives, and asthma (Table 12.3). Systemic type I hypersensitivity reactions are referred to as anaphylaxisor anaphylactic shock. Although anaphylaxis shares many symptoms common with the localized type I hypersensitivity reactions, the swelling of the tongue and trachea, blockage of airways, dangerous drop in blood pressure, and development of shock can make anaphylaxis especially severe and life-threatening. In fact, death can occur within minutes of onset of signs and symptoms.

Late-phase reactions in type I hypersensitivities may develop 4–12 hours after the early phase and are mediated by eosinophils, neutrophils, and lymphocytes that have been recruited by chemotactic factors released from mast cells. Activation of these recruited

cells leads to the release of more chemical mediators that cause tissue damage and late-phase symptoms of swelling and redness of the skin, coughing, wheezing, and nasal discharge.

Individuals who possess genes for maladaptive traits, such as intense type I hypersensitivity reactions to otherwise harmless components of the environment, would be expected to suffer reduced reproductive success. With this kind of evolutionary selective pressure, such traits would not be expected to persist in a population. This suggests that type I hypersensitivities may have an adaptive function. There is evidence that the IgE produced during type I hypersensitivity reactions is actually meant to counter helminth infections[2]. Helminths are one of few organisms that possess proteins that are targeted by IgE. In addition, there is evidence that helminth infections at a young age reduce the likelihood of type I hypersensitivities to innocuous substances later in life. Thus it may be that allergies are an unfortunate consequence of strong selection in the mammalian lineage or earlier for a defense against parasitic worms.

Table **12.3**: Type I Hypersensitivities

Common Name	Cause	Signs and Symptoms
Allergy-induced asthma	Inhalation of allergens	Constriction of bronchi, labored breathing, coughing, chills, body aches
Anaphylaxis	Systemic reaction to allergens	Hives, itching, swelling of tongue and throat, nausea, vomiting, low blood pressure, shock
Hay fever	Inhalation of mold or pollen	Runny nose, watery eyes, sneezing
Hives (urticaria)	Food or drug allergens, insect stings	Raised, bumpy skin rash with itching; bumps may converge into large raised areas

? Exercise 12.2

1. What are the cells that cause a type I hypersensitivity reaction?
2. Describe the differences between immediate and late-phase type I hypersensitivity reactions.
3. List the signs and symptoms of anaphylaxis.

The Hygiene Hypothesis

In most modern societies, good hygiene is associated with regular bathing, and good health with cleanliness. But some recent studies suggest that the association between health and clean living may be a faulty one. Some go so far as to suggest that children should be encouraged to play in the dirt—or even eat dirt[3]—for the benefit of their health. This recommendation is based on the so-called hygiene hypothesis, which proposes that childhood exposure to antigens from a diverse range of microbes leads to a better-functioning immune system later in life.

The hygiene hypothesis was first suggested in 1989 by David Strachan[4], who observed an inverse relationship between the number of older children in a family and the incidence of hay fever. Although hay fever in children had increased dramatically during the mid-20th century, incidence was significantly lower in families with more children. Strachan proposed that the lower incidence of allergies in large families could be linked to infections acquired from older siblings, suggesting that these infections made children less susceptible to allergies. Strachan also argued that trends toward smaller families and a greater emphasis on cleanliness in the 20th century had decreased exposure to pathogens and thus led to higher overall rates of allergies, asthma, and other immune disorders.

Other researchers have observed an inverse relationship between the incidence of immune disorders and infectious diseases that are now rare in industrialized countries but still common in less industrialized countries.[5] In developed nations, children under the age of 5 years are not exposed to many of the microbes, molecules, and antigens they almost certainly would have encountered a century ago. The lack of early challenges to the immune system by organisms with which humans and their ancestors evolved may result in failures in immune system functioning later in life.

Type II (Cytotoxic) Hypersensitivities

Immune reactions categorized as type II hypersensitivities, or cytotoxic hypersensitivities, are mediated by IgG and IgM antibodies binding to cell-surface antigens or matrix-associated antigens on basement membranes. These antibodies can either activate complement, resulting in an inflammatory response and lysis of the targeted cells, or they can be involved in antibody-dependent cell-mediated cytotoxicity (ADCC) with cytotoxic T cells.

In some cases, the antigen may be a self-antigen, in which case the reaction would also be described as an autoimmune disease. (Autoimmune diseases are described in Autoimmune Disorders). In other cases, antibodies may bind to naturally occurring, but exogenous, cell-surface molecules such as antigens associated with blood typing found on red blood cells (RBCs). This leads to the coating of the RBCs by antibodies, activation of the complement cascade, and complement-mediated lysis of RBCs, as well as opsonization of RBCs for phagocytosis. Two examples of type II hypersensitivity reactions involving RBCs are hemolytic transfusion reaction (HTR) and hemolytic disease of the newborn (HDN). These type II hypersensitivity reactions, which will be discussed in greater detail, are summarized in Table **12.4**.

Immunohematology is the study of blood and blood-forming tissue in relation to the immune response. Antibody-initiated responses against blood cells are type II hypersensitivities, thus falling into the field of immunohematology. For students first learning about immunohematology, understanding the immunological mechanisms involved is made even more challenging by the complex nomenclature system used to identify different blood-group antigens, often called blood types. The first blood-group antigens either used alphabetical names or were named for the first person known to produce antibodies to the red blood cell antigen (e.g., Kell, Duffy, or Diego). However, in 1980, the International Society of Blood Transfusion (ISBT) Working Party on Terminology created a standard for blood-group terminology in an attempt to more consistently identify newly discovered blood group antigens. New antigens are now given a number and assigned to a blood-group system, collection, or series. However, even with this effort, blood-group nomenclature is still inconsistent.

Table **12.4**: Common Type II Hypersensitivities

Common Name	Cause	Signs and Symptoms
Hemolytic disease of the newborn (HDN)	IgG from mother crosses the placenta, targeting the fetus' RBCs for destruction	Anemia, edema, enlarged liver or spleen, hydrops (fluid in body cavity), leading to death of newborn in severe cases
Hemolytic transfusion reactions (HTR)	IgG and IgM bind to antigens on transfused RBCs, targeting donor RBCs for destruction	Fever, jaundice, hypotension, disseminated intravascular coagulation, possibly leading to kidney failure and death

ABO Blood Group Incompatibility

The recognition that individuals have different blood types was first described by Karl Landsteiner (1868–1943) in the early 1900s, based on his observation that serum from one person could cause a clumping of RBCs from another. These studies led Landsteiner to the identification of four distinct blood types. Subsequent research by other scientists determined that the four blood types were based on the presence or absence of surface glycoproteins "A" and "B," and this provided the foundation for the ABO blood group system that is still in use today (Figure **12.3**). The functions of these antigens are unknown, but some have been associated with normal biochemical functions of the cell. Furthermore, ABO blood types are inherited as alleles (one from each parent), and they display patterns of dominant and codominant inheritance. The alleles for A and B blood types are codominant to each other, and both are dominant over blood type O. Therefore, individuals with genotypes of AA or AO have type A blood and express the A glycoprotein antigen on the surface of their RBCs. People with genotypes of BB or BO have type B blood and express the B glycoprotein antigen on the surface of their RBCs. Those with a genotype of AB have type AB blood and express both A and B glycoprotein antigens on the surface of their RBCs. Finally, individuals with a genotype of OO have type O blood and lack A and B glycoproteins on the surface of their RBCs.

It is important to note that the RBCs of all four ABO blood types share a common protein receptor molecule, and it is the addition of specific carbohydrates to the protein receptors that determines A, B, and AB blood types. The genes that are inherited for the A, B, and AB blood types encode enzymes that add the carbohydrate component to the protein receptor. Individuals with O blood type

still have the protein receptor but lack the enzymes that would add carbohydrates that would make their red blood cell type A, B, or AB.

IgM antibodies in plasma that cross-react with blood group antigens not present on an individual's own RBCs are called isohemagglutinins (Figure **12.3**). Isohemagglutinins are produced within the first few weeks after birth and persist throughout life. These antibodies are produced in response to exposure to environmental antigens from food and microorganisms. A person with type A blood has A antigens on the surface of their RBCs and will produce anti-B antibodies to environmental antigens that resemble the carbohydrate component of B antigens. A person with type B blood has B antigens on the surface of their RBCs and will produce anti-A antibodies to environmental antigens that are similar to the carbohydrate component of A antigens. People with blood type O lack both A and B antigens on their RBCs and, therefore, produce both anti-A and anti-B antibodies. Conversely, people with AB blood type have both A and B antigens on their RBCs and, therefore, lack anti-A and anti-B antibodies.

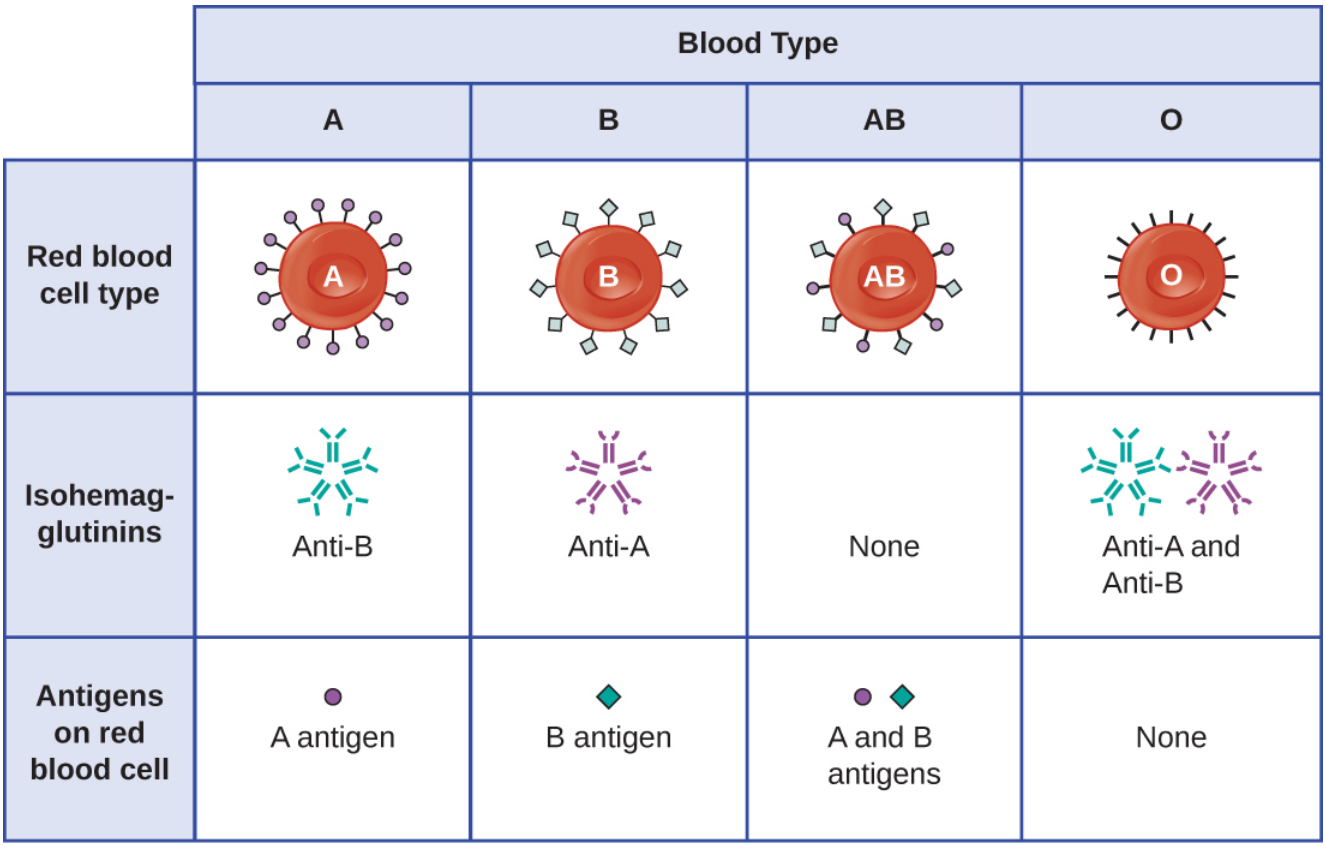


Figure **12.3**: Isohemagglutinins

A patient may require a blood transfusion because they lack sufficient RBCs (anemia) or because they have experienced significant loss of blood volume through trauma or disease. Although the blood transfusion is given to help the patient, it is essential that the patient receive a transfusion with matching ABO blood type. A transfusion with an incompatible ABO blood type may lead to a strong, potentially lethal type II hypersensitivity cytotoxic response called hemolytic transfusion reaction (HTR) (Figure **12.4**).

For instance, if a person with type B blood receives a transfusion of type A blood, their anti-A antibodies will bind to and agglutinate the transfused RBCs. In addition, activation of the classical complement cascade will lead to a strong inflammatory response, and the complement membrane attack complex (MAC) will mediate massive hemolysis of the transfused RBCs. The debris from damaged and destroyed RBCs can occlude blood vessels in the alveoli of the lungs and the glomeruli of the kidneys. Within 1 to 24 hours of an incompatible transfusion, the patient experiences fever, chills, pruritus (itching), urticaria (hives), dyspnea, hemoglobinuria (hemoglobin in the urine), and hypotension (low blood pressure). In the most serious reactions, dangerously low blood pressure can lead to shock, multi-organ failure, and death of the patient.

Hospitals, medical centers, and associated clinical laboratories typically use hemovigilance systems to minimize the risk of HTRs due to clerical error. Hemovigilance systems are procedures that track transfusion information from the donor source and blood

products obtained to the follow-up of recipient patients. Hemovigilance systems used in many countries identify HTRs and their outcomes through mandatory reporting (e.g., to the Food and Drug Administration in the United States), and this information is valuable to help prevent such occurrences in the future. For example, if an HTR is found to be the result of laboratory or clerical error, additional blood products collected from the donor at that time can be located and labeled correctly to avoid additional HTRs. As a result of these measures, HTR-associated deaths in the United States occur in about one per 2 million transfused units.[6]

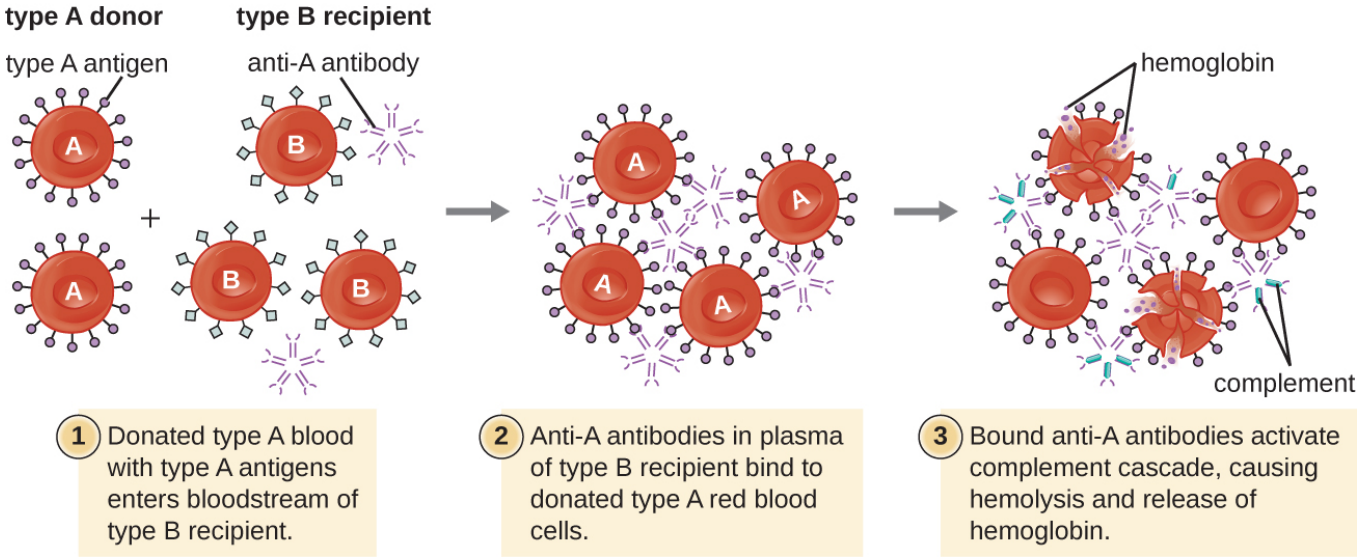


Figure **12.4**: A type II hypersensitivity hemolytic transfusion reaction (HTR) leading to hemolytic anemia. Blood from a type A donor is administered to a patient with type B blood. The anti-A isohemagglutinin IgM antibodies in the recipient bind to and agglutinate the incoming donor type A red blood cells. The bound anti-A antibodies activate the classical complement cascade, resulting in destruction of the donor red blood cells.

Rh Factors

Many different types of erythrocyte antigens have been discovered since the description of the ABO red cell antigens. The second most frequently described RBC antigens are Rh factors, named after the rhesus macaque (*Macaca mulatta*) factors identified by Karl Landsteiner and Alexander Weiner in 1940. The Rh system of RBC antigens is the most complex and immunogenic blood group system, with more than 50 specificities identified to date. Of all the Rh antigens, the one designated Rho (Weiner) or D (Fisher-Race) is the most immunogenic. Cells are classified as Rh positive (Rh+) if the Rho/D antigen is present or as Rh negative (Rh−) if the Rho/D antigen is absent. In contrast to the carbohydrate molecules that distinguish the ABO blood groups and are the targets of IgM isohemagglutinins in HTRs, the Rh factor antigens are proteins. As discussed in B Lymphocytes and Humoral Immunity, protein antigens activate B cells and antibody production through a T-cell–dependent mechanism, and the T_H2 cells stimulate class switching from IgM to other antibody classes. In the case of Rh factor antigens, T_H2 cells stimulate class switching to IgG, and this has important implications for the mechanism of HDN.

Like ABO incompatibilities, blood transfusions from a donor with the wrong Rh factor antigens can cause a type II hypersensitivity HTR. However, in contrast to the IgM isohemagglutinins produced early in life through exposure to environmental antigens, production of anti-Rh factor antibodies requires the exposure of an individual with Rh− blood to Rh+ positive RBCs and activation of a primary antibody response. Although this primary antibody response can cause an HTR in the transfusion patient, the hemolytic reaction would be delayed up to 2 weeks during the extended lag period of a primary antibody response (B Lymphocytes and Humoral Immunity). However, if the patient receives a subsequent transfusion with Rh+ RBCs, a more rapid HTR would occur with anti-Rh factor antibody already present in the blood. Furthermore, the rapid secondary antibody response would provide even more anti-Rh factor antibodies for the HTR.

Rh factor incompatibility between mother and fetus can also cause a type II hypersensitivity hemolytic reaction, referred to as hemolytic disease of the newborn (HDN) (Figure **12.5**). If an Rh− woman carries an Rh+ baby to term, the mother's immune system can be exposed to Rh+ fetal red blood cells. This exposure will usually occur during the last trimester of pregnancy and during the delivery process. If this exposure occurs, the Rh+ fetal RBCs will activate a primary adaptive immune response in the

mother, and anti-Rh factor IgG antibodies will be produced. IgG antibodies are the only class of antibody that can cross the placenta from mother to fetus; however, in most cases, the first Rh+ baby is unaffected by these antibodies because the first exposure typically occurs late enough in the pregnancy that the mother does not have time to mount a sufficient primary antibody response before the baby is born.

If a subsequent pregnancy with an Rh+ fetus occurs, however, the mother's second exposure to the Rh factor antigens causes a strong secondary antibody response that produces larger quantities of anti-Rh factor IgG. These antibodies can cross the placenta from mother to fetus and cause HDN, a potentially lethal condition for the baby (Figure **12.5**).

Prior to the development of techniques for diagnosis and prevention, Rh factor incompatibility was the most common cause of HDN, resulting in thousands of infant deaths each year worldwide.[7] For this reason, the Rh factors of prospective parents are regularly screened, and treatments have been developed to prevent HDN caused by Rh incompatibility. To prevent Rh factor-mediated HDN, human Rho(D) immune globulin (e.g., RhoGAM) is injected intravenously or intramuscularly into the mother during the 28th week of pregnancy and within 72 hours after delivery. Additional doses may be administered after events that may result in transplacental hemorrhage (e.g., umbilical blood sampling, chorionic villus sampling, abdominal trauma, amniocentesis). This treatment is initiated during the first pregnancy with an Rh+ fetus. The anti-Rh antibodies in Rho(D) immune globulin will bind to the Rh factor of any fetal RBCs that gain access to the mother's bloodstream, preventing these Rh+ cells from activating the mother's primary antibody response. Without a primary anti-Rh factor antibody response, the next pregnancy with an Rh+ will have minimal risk of HDN. However, the mother will need to be retreated with Rho(D) immune globulin during that pregnancy to prevent a primary anti-Rh antibody response that could threaten subsequent pregnancies.

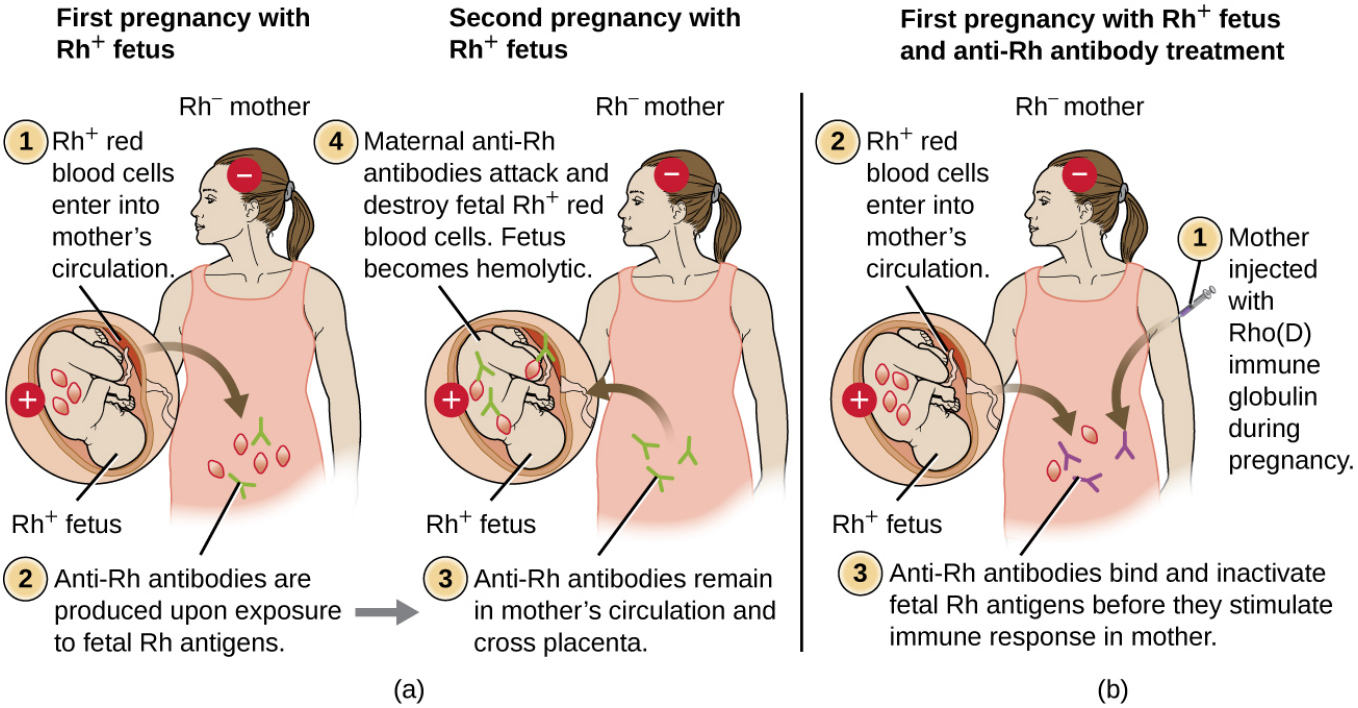


Figure **12.5**: (a) When an Rh− mother has an Rh+ fetus, fetal erythrocytes are introduced into the mother's circulatory system before or during birth, leading to production of anti-Rh IgG antibodies. These antibodies remain in the mother and, if she becomes pregnant with a second Rh+ baby, they can cross the placenta and attach to fetal Rh+ erythrocytes. Complement-mediated hemolysis of fetal erythrocytes results in a lack of sufficient cells for proper oxygenation of the fetus. (b) HDN can be prevented by administering Rho(D) immune globulin during and after each pregnancy with an Rh+ fetus. The immune globulin binds fetal Rh+ RBCs that gain access to the mother's bloodstream, preventing activation of her primary immune response.

Link to Learning

Use this interactive Blood Typing Game to reinforce your knowledge of blood typing.

Exercise 12.3

1. What happens to cells that possess incompatible antigens in a type II hypersensitivity reaction?
2. Describe hemolytic disease of the newborn and explain how it can be prevented.

Clinical Focus: Part 2

Kerry's primary care physician is not sure why Kerry seems to develop rashes after spending time in the sun, so she orders a urinalysis and basic blood tests. The results reveal that Kerry has proteinuria (abnormal protein levels in the urine), hemoglobinuria (excess hemoglobin in the urine), and a low hematocrit (RBC count). These tests suggest that Kerry is suffering from a mild bout of hemolytic anemia. The physician suspects that the problem might be autoimmune, so she refers Kerry to a rheumatologist for additional testing and diagnosis.

Exercise 12.4

Rheumatologists specialize in musculoskeletal diseases such as arthritis, osteoporosis, and joint pain. Why might Kerry's physician refer her to this particular type of specialist even though she is exhibiting none of these symptoms?

Type III Hypersensitivities

Type III hypersensitivities are immune-complex reactions that were first characterized by Nicolas Maurice Arthus (1862–1945) in 1903. To produce antibodies for experimental procedures, Arthus immunized rabbits by injecting them with serum from horses. However, while immunizing rabbits repeatedly with horse serum, Arthus noticed a previously unreported and unexpected localized subcutaneous hemorrhage with edema at the site of injection. This reaction developed within 3 to10 hours after injection. This localized reaction to non-self serum proteins was called an Arthus reaction. An Arthus reaction occurs when soluble antigens bind with IgG in a ratio that results in the accumulation of antigen-antibody aggregates called immune complexes.

A unique characteristic of type III hypersensitivity is antibody excess (primarily IgG), coupled with a relatively low concentration of antigen, resulting in the formation of small immune complexes that deposit on the surface of the epithelial cells lining the inner lumen of small blood vessels or on the surfaces of tissues (Figure 12.6). This immune complex accumulation leads to a cascade of inflammatory events that include the following:

1. IgG binding to antibody receptors on localized mast cells, resulting in mast-cell degranulation
2. Complement activation with production of pro-inflammatory C3a and C5a (see Chemical Defenses)
3. Increased blood-vessel permeability with chemotactic recruitment of neutrophils and macrophages

Because these immune complexes are not an optimal size and are deposited on cell surfaces, they cannot be phagocytosed in the usual way by neutrophils and macrophages, which, in turn, are often described as "frustrated." Although phagocytosis does not occur, neutrophil degranulation results in the release of lysosomal enzymes that cause extracellular destruction of the immune complex, damaging localized cells in the process. Activation of coagulation pathways also occurs, resulting in thrombi (blood clots) that occlude blood vessels and cause ischemia that can lead to vascular necrosis and localized hemorrhage.

Systemic type III hypersensitivity (serum sickness) occurs when immune complexes deposit in various body sites, resulting in a more generalized systemic inflammatory response. These immune complexes involve non-self proteins such as antibodies produced in animals for artificial passive immunity (see Vaccines), certain drugs, or microbial antigens that are continuously released over time during chronic infections (e.g., subacute bacterial endocarditis, chronic viral hepatitis). The mechanisms of serum sickness are similar to those described in localized type III hypersensitivity but involve widespread activation of mast cells, complement, neutrophils, and macrophages, which causes tissue destruction in areas such as the kidneys, joints, and blood vessels. As a result of tissue destruction, symptoms of serum sickness include chills, fever, rash, vasculitis, and arthritis. Development of glomerulonephritis or hepatitis is also possible.

Autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis can also involve damaging type III hypersensitivity reactions when auto-antibodies form immune complexes with self antigens. These conditions are discussed in Autoimmune Disorders.

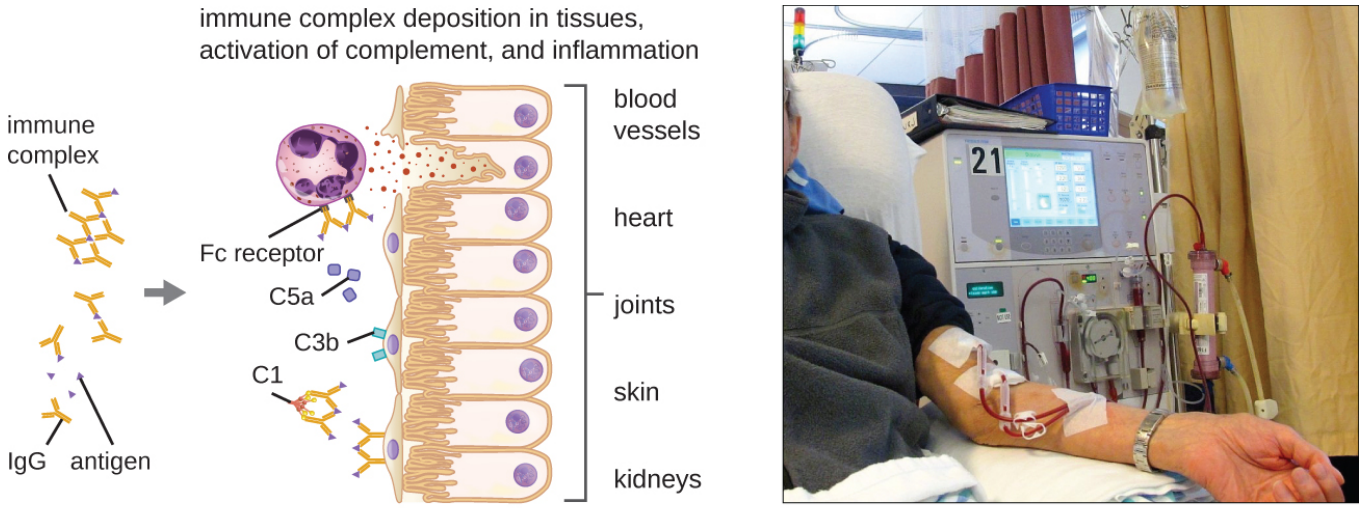


Figure **12.6**: Type III hypersensitivities and the systems they affect. (a) Immune complexes form and deposit in tissue. Complement activation, stimulation of an inflammatory response, and recruitment and activation of neutrophils result in damage to blood vessels, heart tissue, joints, skin, and/or kidneys. (b) If the kidneys are damaged by a type III hypersensitivity reaction, dialysis may be required.

Exercise 12.5

1. Why is antibody excess important in type III hypersensitivity?
2. Describe the differences between the Arthus reaction and serum sickness.

Diphtheria Antitoxin

Antibacterial sera are much less commonly used now than in the past, having been replaced by toxoid vaccines. However, a diphtheria antitoxin produced in horses is one example of such a treatment that is still used in some parts of the world. Although it is not licensed by the FDA for use in the United States, diphtheria antitoxin can be used to treat cases of diphtheria, which are caused by the bacterium *Corynebacterium diphtheriae*. The treatment is not without risks, however. Serum sickness can occur when the patient develops an immune response to non-self horse proteins. Immune complexes are formed between the horse proteins and circulating antibodies when the two exist in certain proportions. These immune complexes can deposit in organs, causing damage such as arthritis, nephritis, rash, and fever. Serum sickness is usually transient with no permanent damage unless the patient is chronically exposed to the antigen, which can then result in irreversible damage to body sites such as joints and kidneys. Over time, phagocytic cells such as macrophages are able to clear the horse serum antigens, which results in improvement of the patient's condition and a decrease in symptoms as the immune response dissipates.

Clinical Focus: Part 3

Kerry does not make it to the rheumatologist. She has a seizure as she is leaving her primary care physician's office. She is quickly rushed to the emergency department, where her primary care physician relates her medical history and recent test results. The emergency department physician calls in the rheumatologist on staff at the hospital for consultation. Based on the symptoms and test results, the rheumatologist suspects that Kerry has lupus and orders a pair of blood tests: an antinuclear antibody test (ANA) to look for antibodies that bind to DNA and another test that looks for antibodies that bind to a self-antigen called the Smith antigen (Sm).

Exercise 12.6

Based on the blood tests ordered, what type of reaction does the rheumatologist suspect is causing Kerry's seizure?

Type IV Hypersensitivities

Type IV hypersensitivities are not mediated by antibodies like the other three types of hypersensitivities. Rather, type IV hypersensitivities are regulated by T cells and involve the action of effector cells. These types of hypersensitivities can be organized into three subcategories based on T-cell subtype, type of antigen, and the resulting effector mechanism (Table **12.5**).

In the first type IV subcategory, CD4 T_H1-mediated reactions are described as delayed-type hypersensitivities (DTH). The sensitization step involves the introduction of antigen into the skin and phagocytosis by local antigen presenting cells (APCs). The APCs activate helper T cells, stimulating clonal proliferation and differentiation into memory T_H1 cells. Upon subsequent exposure to the antigen, these sensitized memory T_H1 cells release cytokines that activate macrophages, and activated macrophages are responsible for much of the tissue damage. Examples of this T_H1-mediated hypersensitivity are observed in tuberculin the Mantoux skin test and contact dermatitis, such as occurs in latex allergy reactions.

In the second type IV subcategory, CD4 T_H2-mediated reactions result in chronic asthma or chronic allergic rhinitis. In these cases, the soluble antigen is first inhaled, resulting in eosinophil recruitment and activation with the release of cytokines and inflammatory mediators.

In the third type IV subcategory, CD8 cytotoxic T lymphocyte (CTL)-mediated reactions are associated with tissue transplant rejection and contact dermatitis (Figure **12.7**). For this form of cell-mediated hypersensitivity, APCs process and present the antigen with MHC I to naïve CD8 T cells. When these naïve CD8 T cells are activated, they proliferate and differentiate into CTLs. Activated T_H1 cells can also enhance the activation of the CTLs. The activated CTLs then target and induce granzyme-mediated apoptosis in cells presenting the same antigen with MHC I. These target cells could be "self" cells that have absorbed the foreign antigen (such as with contact dermatitis due to poison ivy), or they could be transplanted tissue cells displaying foreign antigen from the donor.

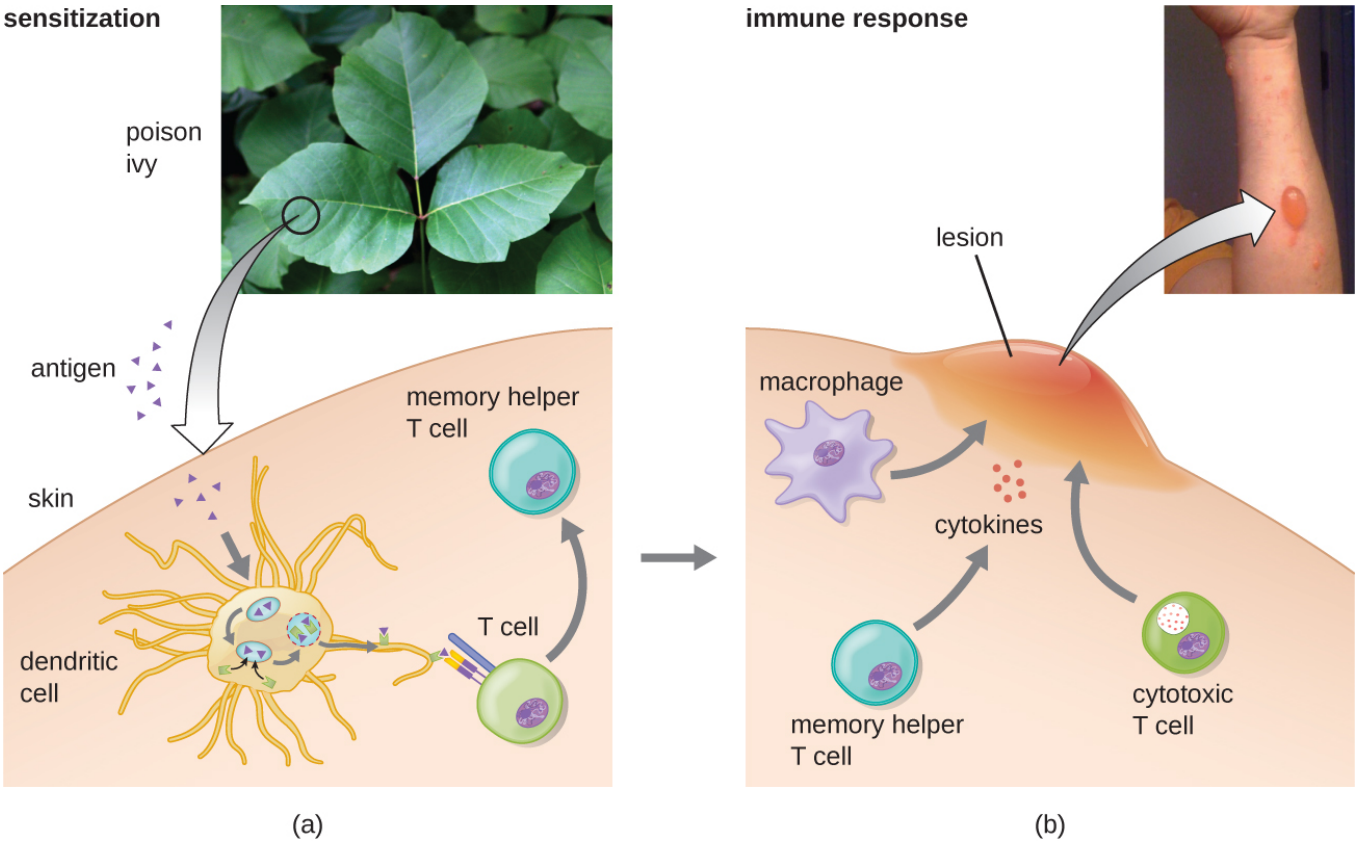


Figure **12.7**: Exposure to hapten antigens in poison ivy can cause contact dermatitis, a type IV hypersensitivity. (a) The first

exposure to poison ivy does not result in a reaction. However, sensitization stimulates helper T cells, leading to production of memory helper T cells that can become reactivated on future exposures. (b) Upon secondary exposure, the memory helper T cells become reactivated, producing inflammatory cytokines that stimulate macrophages and cytotoxic T cells to induce an inflammatory lesion at the exposed site. This lesion, which will persist until the allergen is removed, can inflict significant tissue damage if it continues long enough.

Table **12.5**: Type IV Hypersensitivities

Subcategory	Antigen	Effector Mechanism	Examples
1	Soluble antigen	Activated macrophages damage tissue and promote inflammatory response	Contact dermatitis (e.g., exposure to latex) and delayed-type hypersensitivity (e.g., tuberculin reaction)
2	Soluble antigen	Eosinophil recruitment and activation release cytokines and pro-inflammatory chemicals	Chronic asthma and chronic allergic rhinitis
3	Cell-associated antigen	CTL-mediated cytotoxicity	Contact dermatitis (e.g., contact with poison ivy) and tissue-transplant rejection

Exercise 12.7

1. Describe the three subtypes of type IV hypersensitivity.
2. Explain how T cells contribute to tissue damage in type IV hypersensitivity.

Using Delayed Hypersensitivity to Test for TB

Austrian pediatrician Clemans von Pirquet (1874–1929) first described allergy mechanisms, including type III serum sickness.[9] His interest led to the development of a test for tuberculosis (TB), using the tuberculin antigen, based on earlier work identifying the TB pathogen performed by Robert Koch. Pirquet's method involved scarification, which results in simultaneous multiple punctures, using a device with an array of needles to break the skin numerous times in a small area. The device Pirquet used was similar to the tine testdevice with four needles seen in Figure **12.8**.

The tips of all the needles in the array are coated with tuberculin, a protein extract of TB bacteria, effectively introducing the tuberculin into the skin. One to 3 days later, the area can be examined for a delayed hypersensitivity reaction, signs of which include swelling and redness.

As you can imagine, scarification was not a pleasant experience,[10] and the numerous skin punctures put the patient at risk of developing bacterial infection of the skin. Mantoux modified Pirquet's test to use a single subcutaneous injection of purified tuberculin material. A positive test, which is indicated by a delayed localized swelling at the injection site, does not necessarily mean that the patient is currently infected with active TB. Because type IV (delayed-type) hypersensitivity is mediated by reactivation of memory T cells, such cells may have been created recently (due to an active current infection) or years prior (if a patient had TB and had spontaneously cleared it, or if it had gone into latency). However, the test can be used to confirm infection in cases in which symptoms in the patient or findings on a radiograph suggest its presence.

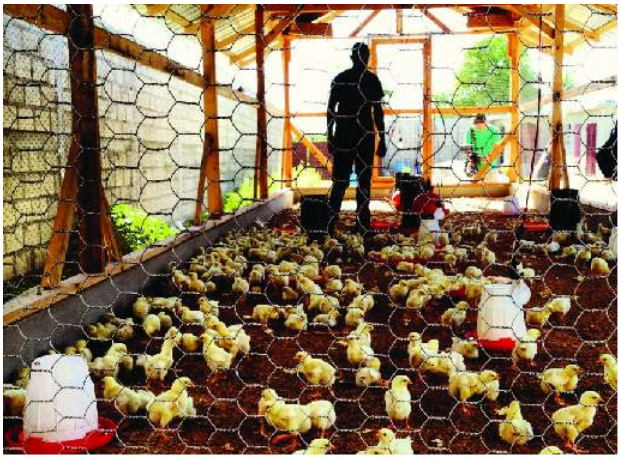


Figure 12.8: The modern version of Pirquet's scarification is the tine test, which uses devices like this to administer tuberculin antigen into the skin, usually on the inside of the forearm. The tine test is considered less reliable than the Mantoux test. (credit: modification of work by the Centers for Disease Control and Prevention)

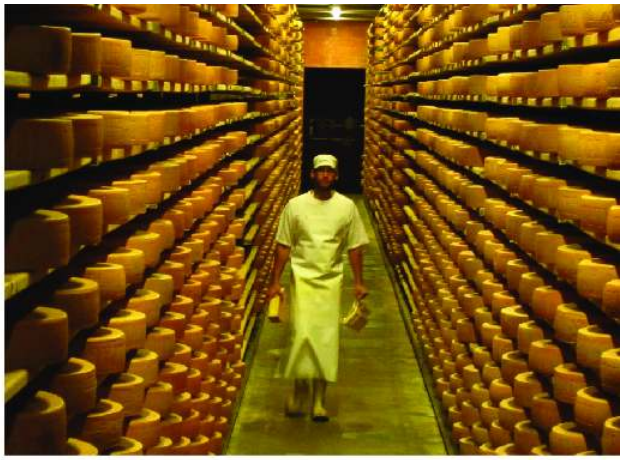
Hypersensitivity Pneumonitis

Some disease caused by hypersensitivities are not caused exclusively by one type. For example, hypersensitivity pneumonitis (HP), which is often an occupational or environmental disease, occurs when the lungs become inflamed due to an allergic reaction to inhaled dust, endospores, bird feathers, bird droppings, molds, or chemicals. HP goes by many different names associated with various forms of exposure (Figure 12.9). HP associated with bird droppings is sometimes called pigeon fancier's lung or poultry worker's lung—both common in bird breeders and handlers. Cheese handler's disease, farmer's lung, sauna takers' disease, and hot-tub lung are other names for HP associated with exposure to molds in various environments.

Pathology associated with HP can be due to both type III (mediated by immune complexes) and type IV (mediated by T_H1 cells and macrophages) hypersensitivities. Repeated exposure to allergens can cause alveolitis due to the formation of immune complexes in the alveolar wall of the lung accompanied by fluid accumulation, and the formation of granulomas and other lesions in the lung as a result of T_H1-mediated macrophage activation. Alveolitis with fluid and granuloma formation results in poor oxygen perfusion in the alveoli, which, in turn, can cause symptoms such as coughing, dyspnea, chills, fever, sweating, myalgias, headache, and nausea. Symptoms may occur as quickly as 2 hours after exposure and can persist for weeks if left untreated.



(a)



(b)

Figure 12.9: Occupational exposure to dust, mold, and other allergens can result in hypersensitivity pneumonitis. (a) People exposed daily to large numbers of birds may be susceptible to poultry worker's lung. (b) Workers in a cheese factory may become sensitized to different types of molds and develop cheese handler's disease. (credit a: modification of work by The Global Orphan Project)

? Exercise 12.8

Explain why hypersensitivity pneumonitis is considered an occupational disease.

Figure 12.10 summarizes the mechanisms and effects of each type of hypersensitivity discussed in this section.

	Hypersensitivity Types and Their Mechanisms			
	Type I	**Type II**	**Type III**	**Type IV**
Immune reactant	IgE	IgG or IgM	IgG and IgM	T cells
Antigen form	Soluble antigen	Cell-bound antigen	Soluble antigen	Soluble or cell-bound antigen
Mechanism of activation	Allergen-specific IgE antibodies bind to mast cells via their Fc receptor. When the specific allergen binds to the IgE, cross-linking of IgE induces degranulation of mast cells.	IgG or IgM antibody binds to cellular antigen, leading to complement activation and cell lysis. IgG can also mediate ADCC with cytotoxic T cells, natural killer cells, macrophages, and neutrophils.	Antigen-antibody complexes are deposited in tissues. Complement activation provides inflammatory mediators and recruits neutrophils. Enzymes released from neutrophils damage tissue.	T_H1 cells secrete cytokines, which activate macrophages and cytotoxic T cells.
Examples of hypersensitivity reactions	Local and systemic anaphylaxis, seasonal hay fever, food allergies, and drug allergies	Red blood cell destruction after transfusion with mismatched blood types or during hemolytic disease of the newborn.	Post-streptococcal glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus	Contact dermatitis, type I diabetes mellitus, and multiple sclerosis

Figure 12.10: Components of the immune system cause four types of hypersensitivities. Notice that types I–III are B-cell/antibody-mediated hypersensitivities, whereas type IV hypersensitivity is exclusively a T-cell phenomenon.

Diagnosis of Hypersensitivities

Diagnosis of type I hypersensitivities is a complex process requiring several diagnostic tests in addition to a well-documented patient history. Serum IgE levels can be measured, but elevated IgE alone does not confirm allergic disease. As part of the process to identify the antigens responsible for a type I reaction allergy, testing through a prick puncture skin test (PPST) or an intradermal test can be performed. PPST is carried out with the introduction of allergens in a series of superficial skin pricks on the patient's back or arms (Figure 12.11). PPSTs are considered to be the most convenient and least expensive way to diagnose allergies, according to the US Joint Council of Allergy and the European Academy of Allergy and Immunology. The second type of testing, the intradermal test, requires injection into the dermis with a small needle. This needle, also known as a tuberculin needle, is attached to a syringe containing a small amount of allergen. Both the PPST and the intradermal tests are observed for 15–20 minutes for a wheal-flare reaction to the allergens. Measurement of any wheal (a raised, itchy bump) and flare (redness) within minutes indicates a type I hypersensitivity, and the larger the wheal-flare reaction, the greater the patient's sensitivity to the allergen.

Type III hypersensitivities can often be misdiagnosed because of their nonspecific inflammatory nature. The symptoms are easily visible, but they may be associated with any of a number of other diseases. A strong, comprehensive patient history is crucial to proper and accurate diagnosis. Tests used to establish the diagnosis of hypersensitivity pneumonitis (resulting from type III

hypersensitivity) include bronchoalveolar lavage (BAL), pulmonary function tests, and high-resolution computed tomography (HRCT).

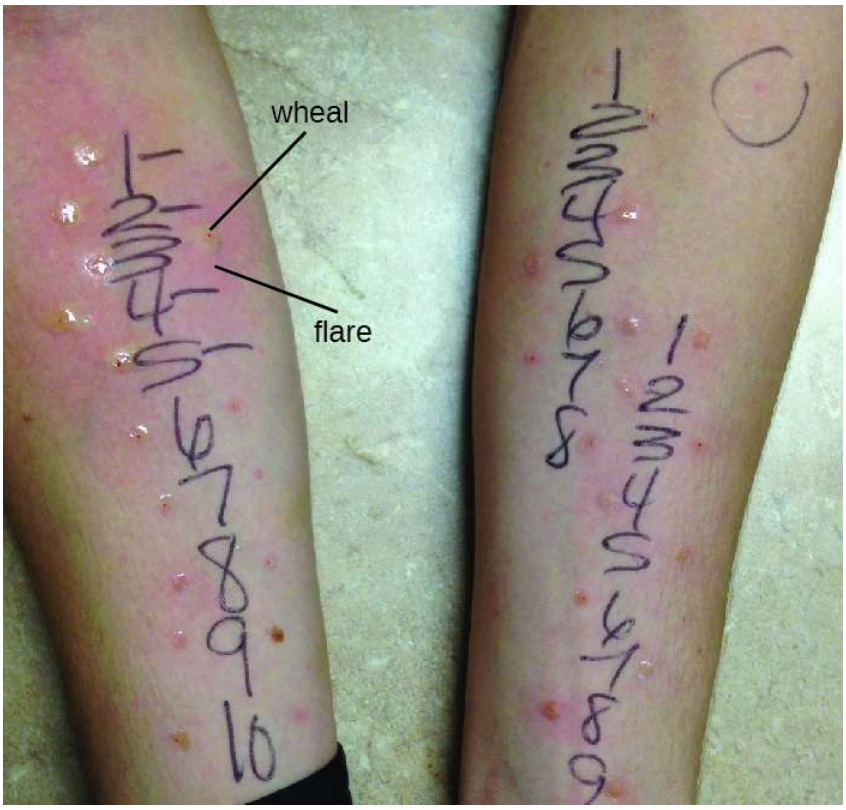


Figure **12.11**: Results of an allergy skin-prick test to test for type I hypersensitivity to a group of potential allergens. A positive result is indicated by a raised area (wheal) and surrounding redness (flare). (credit: modification of work by “OakleyOriginals”/Flickr)

? Exercise 12.9

1. Describe the prick puncture skin test.
2. Explain why type III hypersensitivities can be difficult to diagnose

Treatments of Hypersensitivities

Allergic reactions can be treated in various ways. Prevention of allergic reactions can be achieved by desensitization(hyposensitization) therapy, which can be used to reduce the hypersensitivity reaction through repeated injections of allergens. Extremely dilute concentrations of known allergens (determined from the allergen tests) are injected into the patient at prescribed intervals (e.g., weekly). The quantity of allergen delivered by the shots is slowly increased over a buildup period until an effective dose is determined and that dose is maintained for the duration of treatment, which can last years. Patients are usually encouraged to remain in the doctor’s office for 30 minutes after receiving the injection in case the allergens administered cause a severe systemic reaction. Doctors’ offices that administer desensitization therapy must be prepared to provide resuscitation and drug treatment in the case of such an event.

Desensitization therapy is used for insect sting allergies and environmental allergies. The allergy shots elicit the production of different interleukins and IgG antibody responses instead of IgE. When excess allergen-specific IgG antibodies are produced and bind to the allergen, they can act as blocking antibodies to neutralize the allergen before it can bind IgE on mast cells. There are early studies using oral therapy for desensitization of food allergies that are promising.[1112] These studies involve feeding children who have allergies tiny amounts of the allergen (e.g., peanut flour) or related proteins over time. Many of the subjects show reduced severity of reaction to the food allergen after the therapy.

There are also therapies designed to treat severe allergic reactions. Emergency systemic anaphylaxis is treated initially with an epinephrine injection, which can counteract the drop in blood pressure. Individuals with known severe allergies often carry a self-administering auto-injector that can be used in case of exposure to the allergen (e.g., an insect sting or accidental ingestion of a food that causes a severe reaction). By self-administering an epinephrine shot (or sometimes two), the patient can stem the reaction long enough to seek medical attention. Follow-up treatment generally involves giving the patient antihistamines and slow-acting corticosteroids for several days after the reaction to prevent potential late-phase reactions. However, the effects of antihistamine and corticosteroid treatment are not well studied and are used based on theoretical considerations.

Treatment of milder allergic reactions typically involves antihistamines and other anti-inflammatory drugs. A variety of antihistamine drugs are available, in both prescription and over-the-counter strengths. There are also antileukotriene and antiprostaglandin drugs that can be used in tandem with antihistamine drugs in a combined (and more effective) therapy regime.

Treatments of type III hypersensitivities include preventing further exposure to the antigen and the use of anti-inflammatory drugs. Some conditions can be resolved when exposure to the antigen is prevented. Anti-inflammatory corticosteroid inhalers can also be used to diminish inflammation to allow lung lesions to heal. Systemic corticosteroid treatment, oral or intravenous, is also common for type III hypersensitivities affecting body systems. Treatment of hypersensitivity pneumonitis includes avoiding the allergen, along with the possible addition of prescription steroids such as prednisone to reduce inflammation.

Treatment of type IV hypersensitivities includes antihistamines, anti-inflammatory drugs, analgesics, and, if possible, eliminating further exposure to the antigen.

? Exercise 12.10

1. Describe desensitization therapy.
2. Explain the role of epinephrine in treatment of hypersensitivity reactions.

Key Concepts and Summary

- An **allergy** is an adaptive immune response, sometimes life-threatening, to an **allergen**.
- **Type I hypersensitivity** requires sensitization of mast cells with IgE, involving an initial IgE antibody response and IgE attachment to mast cells. On second exposure to an allergen, cross-linking of IgE molecules on mast cells triggers degranulation and release of preformed and newly formed chemical mediators of inflammation. Type I hypersensitivity may be localized and relatively minor (hives and hay fever) or system-wide and dangerous (systemic **anaphylaxis**).
- **Type II hypersensitivities** result from antibodies binding to antigens on cells and initiating cytotoxic responses. Examples include **hemolytic transfusion reaction** and **hemolytic disease of the newborn**.
- **Type III hypersensitivities** result from formation and accumulation of **immune complexes** in tissues, stimulating damaging inflammatory responses.
- **Type IV hypersensitivities** are not mediated by antibodies, but by helper T-cell activation of macrophages, eosinophils, and cytotoxic T cells.

Footnotes

1. 1 D.S. Strayer et al (eds). *Rubin's Pathology: Clinicopathologic Foundations of Medicine*. 7th ed. 2Philadelphia, PA: Lippincott, Williams & Wilkins, 2014.
2. 2 C.M. Fitzsimmons et al. "Helminth Allergens, Parasite-Specific IgE, and Its Protective Role in Human Immunity." *Frontier in Immunology* 5 (2015):47.
3. 3 S.T. Weiss. "Eat Dirt—The Hygiene Hypothesis and Allergic Diseases." *New England Journal of Medicine* 347 no. 12 (2002):930–931.
4. 4 D.P. Strachan "Hay Fever, Hygiene, and Household Size." *British Medical Journal* 299 no. 6710 (1989):1259.
5. 5 H. Okada et al. "The 'Hygiene Hypothesis' for Autoimmune and Allergic Diseases: An Update." *Clinical & Experimental Immunology* 160 no. 1 (2010):1–9.
6. 6 E.C. Vamvakas, M.A. Blajchman. "Transfusion-Related Mortality: The Ongoing Risks of Allogeneic Blood Transfusion and the Available Strategies for Their Prevention." *Blood* 113 no. 15 (2009):3406–3417.
7. 7 G. Reali. "Forty Years of Anti-D Immunoprophylaxis." *Blood Transfusion* 5 no. 1 (2007):3–6.

8. 8 Centers for Disease Control and Prevention. “Diphtheria Antitoxin.” http://www.cdc.gov/diphtheria/dat.html. Accessed March 25, 2016.
9. 9 B. Huber “100 Jahre Allergie: Clemens von Pirquet–sein Allergiebegriff und das ihm zugrunde liegende Krankheitsverständnis.” *Wiener Klinische Wochenschrift* 118 no. 19–20 (2006):573–579.
10. 10 C.A. Stewart. “The Pirquet Test: Comparison of the Scarification and the Puncture Methods of Application.” *Archives of Pediatrics & Adolescent Medicine* 35 no. 3 (1928):388–391.
11. 11 C.L. Schneider et al. “A Pilot Study of Omalizumab to Facilitate Rapid Oral Desensitization in High-Risk Peanut-Allergic Patients.” *Journal of Allergy and Clinical Immunology* 132 no. 6 (2013):1368–1374.
12. 12 P. Varshney et al. “A Randomized Controlled Study of Peanut Oral Immunotherapy: Clinical Desensitization and Modulation of the Allergic Response.” *Journal of Allergy and Clinical Immunology* 127 no. 3 (2011):654–660.

This page titled 12: Hypersensitivities is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **19.1: Hypersensitivities** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

12.1: Type I (Anaphylactic) Reactions

Learning Objectives

- Describe Type I hypersensitivity reactions

Type I hypersensitivity is also known as immediate or anaphylactic hypersensitivity. Anaphylaxis typically produces many different symptoms over minutes or hours. Symptoms typically include raised bumps on the skin (; hives), itchiness, red face or skin (flushing), or swollen lips.



Figure: **Hives and flushing on the back of a person with anaphylaxis**: Hives and flushing on the back of a person with anaphylaxis

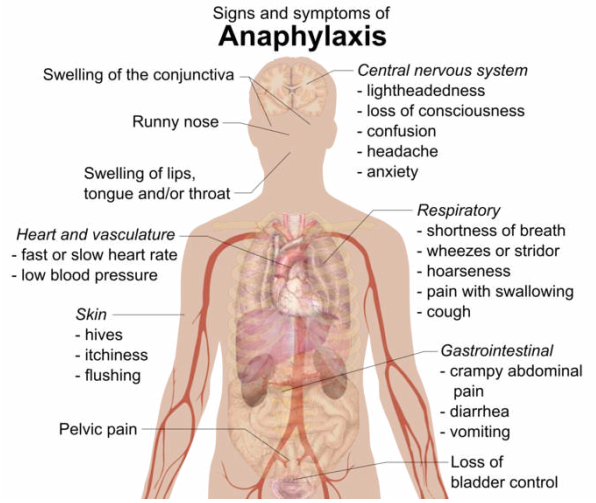


Figure: **Anaphylaxis**: A representation of the signs and symptoms of anaphylaxis that result from an allergic reaction.

Anaphylaxis can be caused by the body's response to almost any foreign substance. Common triggers include venom from insect bites or stings, foods, and medication. Foods are the most common trigger in children and young adults. Medications and insect bites and stings are more common triggers in older adults. Less common causes include physical factors, biological agents (such as semen), latex, hormonal changes, food additives (e.g. monosodium glutamate (MSG) and food coloring), and medications that are applied to the skin (topical medications). Exercise or temperature (either hot or cold) may also trigger anaphylaxis by causing tissue cells known as mast cells to release chemicals that start the allergic reaction.

Anaphylaxis caused by exercise is often also linked to eating certain foods. If anaphylaxis occurs while a person is receiving anesthesia, the most common causes are certain medications that are given to produce paralysis (neuromuscular blocking agents), antibiotics, and latex. Many foods can trigger anaphylaxis, even when the food is eaten for the first time. In Western cultures, the most common causes are eating or being in contact with peanuts, wheat, tree nuts, shellfish, fish, milk, and eggs.

People with atopic diseases such as asthma, eczema, or allergic rhinitis have a high risk of anaphylaxis from food, latex, and radiocontrast agents. These people do not have a higher risk from injectable medications or stings. People who have disorders caused by too many mast cells in their tissues (mastocytosis) or who are wealthier are at increased risk. The longer the time since the last exposure to an agent that caused anaphylaxis, the lower the risk of a new reaction.

Anaphylaxis is a severe allergic reaction that starts suddenly and affects many body systems. It results from the release of inflammatory mediators and cytokines from mast cells and basophils. This release is typically associated with an immune system reaction, but may also be caused by damage to cells that are not related to an immune reaction. When anaphylaxis is caused by an immune response, immunoglobulin E (IgE) binds to the foreign material that starts the allergic reaction (the antigen). The combination of IgE bound to the antigen activates FcεRI receptors on mast cells and basophils. The mast cells and basophils react by releasing inflammatory mediators such as histamine. These mediators increase the contraction of bronchial smooth muscles, cause blood vessels to widen (vasodilation), increase the leakage of fluid from blood vessels, and depress the actions of the heart muscle. There is also an immunologic mechanism that does not rely on IgE, but it is not known if this occurs in humans. When anaphylaxis is not caused by in immune response, the reaction is due to an agent that directly damages mast cells and basophils, causing them to release histamine and other substances that are usually associated with an allergic reaction (degranulation). Agents that can damage these cells include contrast medium for X-rays, opioids, temperature (hot or cold), and vibration.

Key Points

- Common triggers for anaphylaxis include venom from insect bites or stings, foods, and medication.
- People with atopic diseases such as asthma, eczema, or allergic rhinitis have a high risk of anaphylaxis from food, latex, and radiocontrast agents.
- Anaphylaxis is a severe allergic reaction that starts suddenly and affects many body systems due to the release of inflammatory mediators and cytokines from mast cells and basophils.

Key Terms

- **anaphylaxis**: A severe and rapid systemic allergic reaction to an allergen, causing a constriction of the trachea, preventing breathing; anaphylactic shock.
- **hives**: Itchy, swollen, red areas of the skin which can appear quickly in response to an allergen or due to other conditions.
- **mast cells**: A mast cell is a resident cell of several types of tissues and contains many granules rich in histamine and heparin. Mat cells play a role in allergy, anaphylaxis, wound healing and defense against pathogens.

This page titled 12.1: Type I (Anaphylactic) Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **12.4A: Type I (Anaphylactic) Reactions** is licensed CC BY-SA 4.0.

12.2: Diagnosis and Treatment of Allergy

Allergy testing can help confirm or rule out allergies, reducing adverse reactions and limiting unnecessary avoidance and medications.

Learning Objectives

- Describe how the skin prick test and the allergy blood test work to assess the presence of allergen specific antibodies in an individual

Allergy testing can help confirm or rule out allergies, reducing adverse reactions and limiting unnecessary avoidance and medications. Correct diagnosis, counseling, and avoidance advice based on valid allergy test results will help reduce the incidence of symptoms and medications and will improve quality of life. Earlier and more accurate diagnoses save costs due to a reduction in consultations, referrals to secondary care, misdiagnoses, and emergency admissions.

For assessing the presence of allergen-specific IgE antibodies, you can use two different methods: a skin prick test or an allergy blood test. Both methods are recommended by the NIH guidelines, are equally cost-effective, and have similar diagnostic value in terms of sensitivity and specificity. A healthcare provider can use the test results to identify the specific allergic triggers that may be contributing to symptoms.



Figure: **Allergy Skin Testing**: Skin testing on an arm.

Allergies undergo dynamic changes over time. Regular allergy testing for relevant allergens provides information on if and how patient management can be changed in order to improve health and quality of life. Annual testing is often the practice for determining whether allergies to milk, eggs, soy, and wheat have been outgrown. The testing interval is extended to two to three years for allergies to peanuts, tree nuts, fish, and crustacean shellfish. Results of followup testing can guide decision-making regarding whether and when it is safe to introduce or re-introduce allergenic food into the diet.

Skin testing is also known as “puncture testing” and “prick testing” because of the series of tiny punctures or pricks made in the patient’s skin. Small amounts of suspected allergens or their extracts are introduced to sites on the skin marked with pen or dye (the dye should be carefully selected, lest it cause an allergic response itself). Sometimes, the allergens are injected “intradermally” into the patient’s skin with a needle and syringe. Common areas for testing include the inside forearm and the back. If the patient is allergic to the substance, then a visible inflammatory reaction will usually occur within 30 minutes. This response will range from a slight reddening of the skin to a full-blown hive (called “wheal and flare”) similar to a mosquito bite in more sensitive patients. Interpretation of the results of the skin-prick test is normally done by allergists on a scale of severity, with +/- meaning borderline reactivity and 4+ indicating a severe reaction.

In contrast, an allergy blood test is quick and simple and can be performed irrespective of age, skin condition, medication, symptom, disease activity, and pregnancy. In addition, multiple allergens can be detected with a single blood sample. Allergy blood tests are very safe, since the patient is not exposed to any allergens during the testing procedure. The test measures the concentration of specific IgE antibodies in the blood.

Challenge testing is when small amounts of a suspected allergen are introduced to the body orally, through inhalation, or via other routes. Challenge tests are utilized most often with foods or medicines. If the patient experiences significant improvement while avoiding a suspected allergen, she may then be “challenged” by reintroducing it to see if symptoms can be reproduced.

Patch testing is used to help ascertain the cause of skin contact allergy (contact dermatitis). Adhesive patches, usually treated with a number of different commonly allergenic chemicals or skin sensitizers, are applied to the back. The skin is then examined for possible local reactions at least twice, usually 48 hours after application and then again two or three days later.

Traditional treatment and management of allergies consisted of simply avoiding the allergen in question. However, while avoidance of allergens may reduce symptoms and avoid life-threatening anaphylaxis, it is difficult to do for those with allergies to pollen or other airborne allergens. Several antagonistic drugs are used to block the action of allergic mediators or to prevent activation of cells and degranulation processes. These include antihistamines, glucocorticoids, epinephrine (adrenaline), theophylline, and cromolyn sodium.

Desensitization or hyposensitization is a treatment in which the patient is gradually vaccinated with progressively larger doses of the allergen in question. This can either reduce the severity or eliminate hypersensitivity altogether. It relies on the progressive skewing of IgG antibody production to block excessive IgE production seen in atopys. In effect, the person builds up immunity to increasing amounts of the allergen. Studies have demonstrated the long-term efficacy and the preventive effect of immunotherapy in reducing the development of new allergies. A second form of immunotherapy involves the intravenous injection of monoclonal anti-IgE antibodies. These bind to free- and B cell-associated IgE, signaling their destruction.

Key Points

- To assess the presence of allergen -specific IgE antibodies, you can use one of two methods: a skin-prick test or an allergy blood test.
- Challenge testing is when small amounts of a suspected allergen are introduced to the body orally, through inhalation, or via other routes.
- Patch testing is used to help ascertain the cause of skin contact allergy (contact dermatitis).
- Traditional treatment and management of allergies consisted of simply avoiding the allergen in question.
- Several antagonistic drugs are used to block the action of allergic mediators or to prevent activation of cells and degranulation processes.

Key Terms

- **allergen**: a substance that causes an allergic reaction
- **antihistamine**: a drug or substance that counteracts the effects of a histamine. Commonly used to alleviate the symptoms of hay fever and other allergies
- **skin prick test**: Skin-prick testing is also known as “puncture testing” and “prick testing” because of the series of tiny punctures or pricks made in the patient’s skin. Small amounts of suspected allergens or their extracts (pollen, grass, mite proteins, peanut extract, etc.) are introduced to sites on the skin marked with pen or dye.

This page titled 12.2: Diagnosis and Treatment of Allergy is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **12.4B: Diagnosis and Treatment of Allergy** is licensed CC BY-SA 4.0.

12.3: Type II (Cytotoxic) Reactions

Learning Objectives

- Describe Type II hypersensitivity reactions

In type II hypersensitivity (or cytotoxic hypersensitivity), the antibodies produced by the immune response bind to antigens on the patient's own cell surfaces. The antigens recognized in this way may either be intrinsic ("self" antigen, innately part of the patient's cells) or extrinsic (adsorbed onto the cells during exposure to some foreign antigen, possibly as part of infection with a pathogen). These cells are recognized by macrophages or dendritic cells, which act as antigen-presenting cells. This causes a B cell response, wherein antibodies are produced against the foreign antigen.

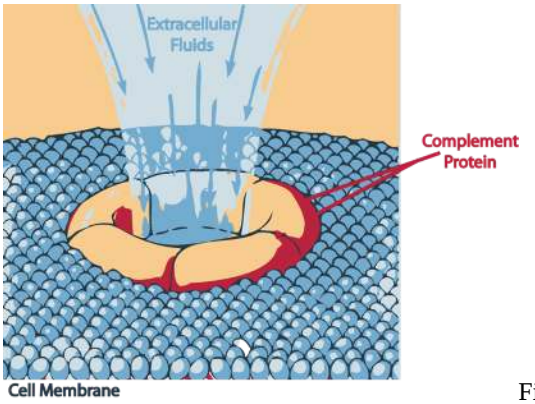


Figure: **Complement death**: A complement protein attacking an invader.

An example of type II hypersensitivity is the reaction to penicillin wherein the drug can bind to red blood cells, causing them to be recognized as different; B cell proliferation will take place and antibodies to the drug are produced. IgG and IgM antibodies bind to these antigens to form complexes that activate the classical pathway of complement activation to eliminate cells presenting foreign antigens (which are usually, but not in this case, pathogens). That is, mediators of acute inflammation are generated at the site and membrane attack complexes cause cell lysis and death. The reaction takes hours to a day. The membrane attack complex (MAC;) is typically formed on the surface of pathogenic bacterial cells as a result of the activation of the alternative pathway and the classical pathway of the complement system, and it is one of the effector proteins of the immune system. The membrane-attack complex (MAC) forms transmembrane channels. These channels disrupt the phospholipid bilayer of target cells, leading to cell lysis and death.

Another form of type II hypersensitivity is called antibody-dependent cell-mediated cytotoxicity (ADCC). Here, cells exhibiting the foreign antigen are tagged with antibodies (IgG or IgM). These tagged cells are then recognised by natural killer (NK) cells and macrophages (recognised via IgG bound (via the Fc region) to the effector cell surface receptor, CD16 (FcγRIII)), which in turn kill these tagged cells.

Autoimmune diseases resemble type II-IV hypersensitivity reactions. They differ from hypersensitivity reactions in that the antigens driving the immune process are self-antigens rather than non-self as in hypersensitivity reactions. Below are some examples of Type II hypersensitivity-like autoimmunity.

Key Points

- The antigens recognized in this way may either be intrinsic ("self" antigen, innately part of the patient's cells) or extrinsic (adsorbed onto the cells during exposure to some foreign antigen, possibly as part of infection with a pathogen).
- Mediators of acute inflammation are generated at the site where a foreign antigen is recognized and membrane attack complexes cause cell lysis and death.
- In antibody -dependent cell-mediated cytotoxicity (ADCC), cells exhibiting the foreign antigen are tagged with antibodies (IgG or IgM) and they are then recognised by natural killer (NK) cells and macrophages which in turn kill these tagged cells.

Key Terms

- **macrophages**: A type of white blood cell that targets foreign material, including bacteria and viruses.
- **dendritic cells**: Dendritic cells are immune cells that function to process antigen material and present it on the surface of other cells of the immune system. They act as messengers between innate and adaptive immunity.
- **cytotoxic hypersensitivity**: In type II hypersensitivity, the antibodies produced by the immune response bind to antigens on the patient's own cell surfaces.

This page titled 12.3: Type II (Cytotoxic) Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **12.4C: Type II (Cytotoxic) Reactions** is licensed CC BY-SA 4.0.

12.4: Type III (Immune Complex) Reactions

Learning Objectives

- Describe Type III hypersensitivity reactions

Type III hypersensitivity occurs when there is little antibody and an excess of antigen, leading to small immune complexes being formed that do not fix complement and are not cleared from the circulation. It is characterized by solvent antigens that are not bound to cell surfaces (which is the case in type II hypersensitivity). When these antigens bind antibodies, immune complexes of different sizes form. Large complexes can be cleared by macrophages but macrophages have difficulty in the disposal of small immune complexes. These immune complexes insert themselves into small blood vessels, joints, and glomeruli, causing symptoms. Unlike the free variant, small immune complex bound to sites of deposition (like blood vessel walls) are far more capable of interacting with complement. These medium-sized complexes, formed in the slight excess of antigen, are viewed as being highly pathogenic.

Such depositions in tissues often induce an inflammatory response, and can cause damage wherever they precipitate. The cause of damage is as a result of the action of cleaved complement anaphylotoxins C3a and C5a, which, respectively, mediate the induction of granule release from mast cells (from which histamine can cause urticaria), and recruitment of inflammatory cells into the tissue (mainly those with lysosomal action, leading to tissue damage through frustrated phagocytosis by polymorphonuclear neutrophils and macrophages).

Immune complex glomerulonephritis, as seen in Henoch-Schönlein purpura is an example of IgA involvement in a nephropathy. The reaction can take hours, days, or even weeks to develop, depending on whether or not there is immunlogic memory of the precipitating antigen. Typically, clinical features emerge a week following initial antigen challenge, when the deposited immune complexes can precipitate an inflammatory response. Because of the nature of the antibody aggregation, tissues that are associated with blood filtration at considerable osmotic and hydrostatic gradient (e.g. sites of urinary and synovial fluid formation, kidney glomeruli and joint tissues respectively) bear the brunt of the damage. Hence, vasculitis, glomerulonephritis and arthritis are commonly-associated conditions as a result of type III hypersensitivity responses. As observed under methods of histopathology, acute necrotizing vasculitis within the affected tissues is observed concomitant to neutrophilic infiltration, along with notable eosinophilic deposition (fibrinoid necrosis).

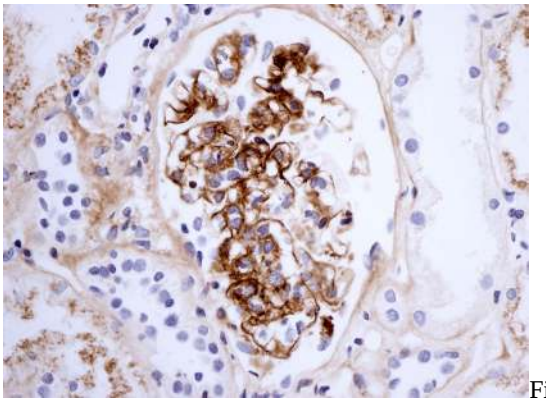


Figure: **Henoch-Schönlein nephritis IgA immunostaining**: Immune Complex Glomerulonephritis, as seen in Henoch-Schönlein purpura; this is an example of IgA involvement in a nephropathy.

Often, immunofluorescence microscopy can be used to visualize the immune complexes. Skin response to a hypersensitivity of this type is referred to as an Arthus reaction, and is characterized by local erythema and some induration. Platelet aggregation, especially in microvasculature, can cause localized clot formation, leading to blotchy hemorrhages. This typifies the response to injection of foreign antigen sufficient to lead to the condition of serum sickness. An immune complex is formed from the integral binding of an antibody to a soluble antigen. The bound antigen acting as a specific epitope, bound to an antibody, is referred to as a singular immune complex. After an antigen-antibody reaction, the immune complexes can be subject to any of a number of responses, including complement deposition, opsonization, phagocytosis, or processing by proteases.

Red blood cells carrying CR1-receptors on their surface may bind C3b-decorated immune complexes and transport them to phagocytes, mostly in liver and spleen, and return back to the general circulation. Immune complexes may themselves cause disease when they are deposited in organs, e.g. in certain forms of vasculitis. This is the third form of hypersensitivity in the Gell-Coombs classification, called Type III hypersensitivity. Immune complex deposition is a prominent feature of several autoimmune diseases, including systemic lupus erythematosus, cryoglobulinemia, rheumatoid arthritis, scleroderma and Sjögren's syndrome.

Key Points

- It is characterized by solvent antigens that are not bound to cell surfaces (which is the case in type II hypersensitivity) but bind antibodies to form immune complexes of different sizes.
- Large complexes can be cleared by macrophages but small immune complexes cannot be cleared and they insert themselves into small blood vessels, joints, and glomeruli, causing symptoms.
- The cause of damage is as a result of the action of cleaved complement anaphylotoxins C3a and C5a, which, mediate the onset of the inflammatory response and eventual tissue damage.

Key Terms

- **glomerulonephritis**: A form of nephritis characterized by inflammation of the glomeruli
- **immune complex**: An immune complex is formed from the integral binding of an antibody to a soluble antigen. The bound antigen acting as a specific epitope, bound to an antibody is referred to as a singular immune complex.
- **Arthus reaction**: The Arthus reaction is a type of local type III hypersensitivity reaction which involves the deposition of antigen/antibody complexes mainly in the vascular walls, serosa (pleura, pericardium, synovium) and glomeruli.

This page titled 12.4: Type III (Immune Complex) Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **12.4D: Type III (Immune Complex) Reactions** is licensed CC BY-SA 4.0.

12.5: Type IV (Delayed Cell-Mediated) Reactions

Learning Objectives

- Describe Type IV cell-mediated reactions and explain why they take two to three days to develop

Cell-mediated immunity is an immune response that does not involve antibodies, but rather involves the activation of phagocytes, natural killer cells (NK), antigen-specific cytotoxic T-lymphocytes, and the release of various cytokines in response to an antigen. Historically, the immune system was separated into two branches: humoral immunity, for which the protective function of immunization could be found in the humor (cell-free bodily fluid or serum) and cellular immunity, for which the protective function of immunization was associated with cells. CD4 cells or helper T cells provide protection against different pathogens. Cytotoxic T cells cause death by apoptosis without using cytokines. Therefore in cell mediated immunity cytokines are not always present.

Cellular immunity protects the body by:

1. activating antigen-specific cytotoxic T-lymphocytes that are able to induce apoptosis in body cells displaying epitopes of foreign antigen on their surface, such as virus-infected cells, cells with intracellular bacteria, and cancer cells displaying tumor antigens

2. activating macrophages and natural killer cells, enabling them to destroy pathogens

3. stimulating cells to secrete a variety of cytokines that influence the function of other cells involved in adaptive immune responses and innate immune responses

Cell-mediated immunity is directed primarily at microbes that survive in phagocytes and microbes that infect non-phagocytic cells. It is most effective in removing virus-infected cells, but also participates in defending against fungi, protozoans, cancers, and intracellular bacteria. It also plays a major role in transplant rejection.

Type IV hypersensitivity is often called delayed type hypersensitivity as the reaction takes two to three days to develop. Unlike the other types, it is not antibody mediated but rather is a type of cell-mediated response. CD4+ helper T cells recognize antigen in a complex with Class 2 major histocompatibility complex. The antigen-presenting cells in this case are macrophages that secrete IL-12, which stimulates the proliferation of further CD4+ Th1 cells. CD4+ T cells secrete IL-2 and interferon gamma, further inducing the release of other Th1 cytokines, thus mediating the immune response. Activated CD8+ T cells destroy target cells on contact, whereas activated macrophages produce hydrolytic enzymes and, on presentation with certain intracellular pathogens, transform into multinucleated giant cells.

A classic example of delayed type IV hypersensitivity is the Mantoux tuberculin test in which skin induration indicates exposure to tuberculosis. Other examples include: temporal arteritis, Hashimoto's thyroiditis, symptoms of leprosy, symptoms of tuberculosis, coeliac disease, graft-versus-host disease and chronic transplant rejection.



Figure: **Mantoux test**: The reaction is read by measuring the diameter of induration (palpable raised, hardened area) across the forearm (perpendicular to the long axis) in millimeters. If there is no induration, the result should be recorded as "0 mm". Erythema (redness) should not be measured. If a person has had a history of a positive tuberculin skin test, or had a recent tuberculin skin test (within one year), another skin test should be used.

 Figure: **Mantoux tuberculin test**: The Mantoux test (also known as the Mantoux screening test, tuberculin sensitivity test, Pirquet test, or PPD test for purified protein derivative) is a diagnostic tool for tuberculosis. A standard dose of tuberculin is injected intradermally (between the layers of dermis) and read 48 to 72 hours later.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: ***CC BY-SA: Attribution-ShareAlike***

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- Anaphylaxis. **Provided by**: Wikipedia. **Located at**: **simple.Wikipedia.org/wiki/Anaphylaxis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- hives. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/hives**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- mast cells. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/mast%20cells**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- anaphylaxis. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/anaphylaxis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Signs and symptoms of anaphylaxis. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...naphylaxis.png**. **License**: ***Public Domain: No Known Copyright***
- BackRed. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:BackRed.JPG**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Allergy. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Allergy**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- skin prick test. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/skin%20prick%20test**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- antihistamine. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/antihistamine**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- allergen. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/allergen**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Signs and symptoms of anaphylaxis. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...naphylaxis.png**. **License**: ***Public Domain: No Known Copyright***
- BackRed. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:BackRed.JPG**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Allergy skin testing. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Al...in_testing.JPG**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Complement membrane attack complex. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Complem...attack_complex**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Type II (cytotoxic) hypersensitivity. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Type_II...persensitivity**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- dendritic cells. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/dendritic%20cells**. **License**: ***CC BY-SA: Attribution-ShareAlike***

- cytotoxic hypersensitivity. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/cytotox...persensitivity**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- macrophages. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/macrophages**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Signs and symptoms of anaphylaxis. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...naphylaxis.png**. **License**: ***Public Domain: No Known Copyright***
- BackRed. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:BackRed.JPG**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Allergy skin testing. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Al...in_testing.JPG**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Complement death. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:C...ment_death.PNG**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Immune complex. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Immune_complex**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Type III hypersensitivity. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Type_II...persensitivity**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- glomerulonephritis. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/glomerulonephritis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Arthus reaction. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Arthus%20reaction**. **License**: *CC BY-SA: Attribution-ShareAlike*
- immune complex. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/immune%20complex**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Signs and symptoms of anaphylaxis. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...naphylaxis.png**. **License**: ***Public Domain: No Known Copyright***
- BackRed. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:BackRed.JPG**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Allergy skin testing. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Al...in_testing.JPG**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Complement death. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:C...ment_death.PNG**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Henoch-Schu00f6nlein nephritis IgA immunostaining. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:He...nostaining.jpg**. **License**: ***CC BY: Attribution***
- type IV hypersensitivity. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/type%20...persensitivity**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Gell-Coombs classification. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Gell-Co...classification**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Type IV hypersensitivity. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Type_IV_hypersensitivity**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Cell-mediated immunity. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Cell-mediated_immunity**. **License**: *CC BY-SA: Attribution-ShareAlike*
- cellular immunity. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/cellular%20immunity**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Signs and symptoms of anaphylaxis. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Signs_and_symptoms_of_anaphylaxis.png**. **License**: ***Public Domain: No Known Copyright***
- BackRed. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:BackRed.JPG**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Allergy skin testing. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Al...in_testing.JPG**. **License**: *CC BY-SA: Attribution-ShareAlike*

- Complement death. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:C...ment_death.PNG**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Henoch-Schu00f6nlein nephritis IgA immunostaining. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:He...nostaining.jpg**. **License**: ***CC BY: Attribution***
- Mantoux test. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Mantoux_test.jpg**. **License**: ***Public Domain: No Known Copyright***
- Mantoux tuberculin skin test. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Mantoux_tuberculin_skin_test.jpg**. **License**: ***Public Domain: No Known Copyright***

Key Points

- Cell-mediated immunity is an immune response that does not involve antibodies but rather involves the activation of phagocytes, natural killer cells (NK), antigen -specific cytotoxic T-lymphocytes, and the release of various cytokines in response to an antigen.
- In type IV hypersensitivity reactions, CD4+ helper T cells recognize antigen in a complex with Class 2 major histocompatibility complex on macrophages (the antigen-presenting cells).
- A classic example of delayed type IV hypersensitivity is the Mantoux tuberculin test in which skin induration indicates exposure to tuberculosis.

Key Terms

- **cellular immunity**: Cellular immunity protects the body by: activating antigen-specific cytotoxic T-lymphocytes, activating macrophages and natural killer cells and stimulating cytokine secretion to stimulate other cells involved in adaptive immune responses and innate immune responses.
- **type IV hypersensitivity**: A cell-mediated immune response that takes two to three days to develop.

This page titled 12.5: Type IV (Delayed Cell-Mediated) Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **12.4E: Type IV (Delayed Cell-Mediated) Reactions** is licensed CC BY-SA 4.0.

12.6: Immunity Disorders- Hypersensitivity

This page titled 12.6: Immunity Disorders- Hypersensitivity is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **12.4: Immunity Disorders- Hypersensitivity** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

CHAPTER OVERVIEW

13: Laboratory Analysis of the Immune Response

Many laboratory tests are designed to confirm a presumptive diagnosis by detecting antibodies specific to a suspected pathogen. Unfortunately, many such tests are time-consuming and expensive. That is now changing, however, with the development of new, miniaturized technologies that are fast and inexpensive. For example, researchers at Columbia University are developing a "lab-on-a-chip" technology that will test a single drop of blood for 15 different infectious diseases, including HIV and syphilis, in a matter of minutes.[1] The blood is pulled through tiny capillaries into reaction chambers where the patient's antibodies mix with reagents. A chip reader that attaches to a cell phone analyzes the results and sends them to the patient's healthcare provider. Currently the device is being field tested in Rwanda to check pregnant women for chronic diseases. Researchers estimate that the chip readers will sell for about $100 and individual chips for $1.[2]

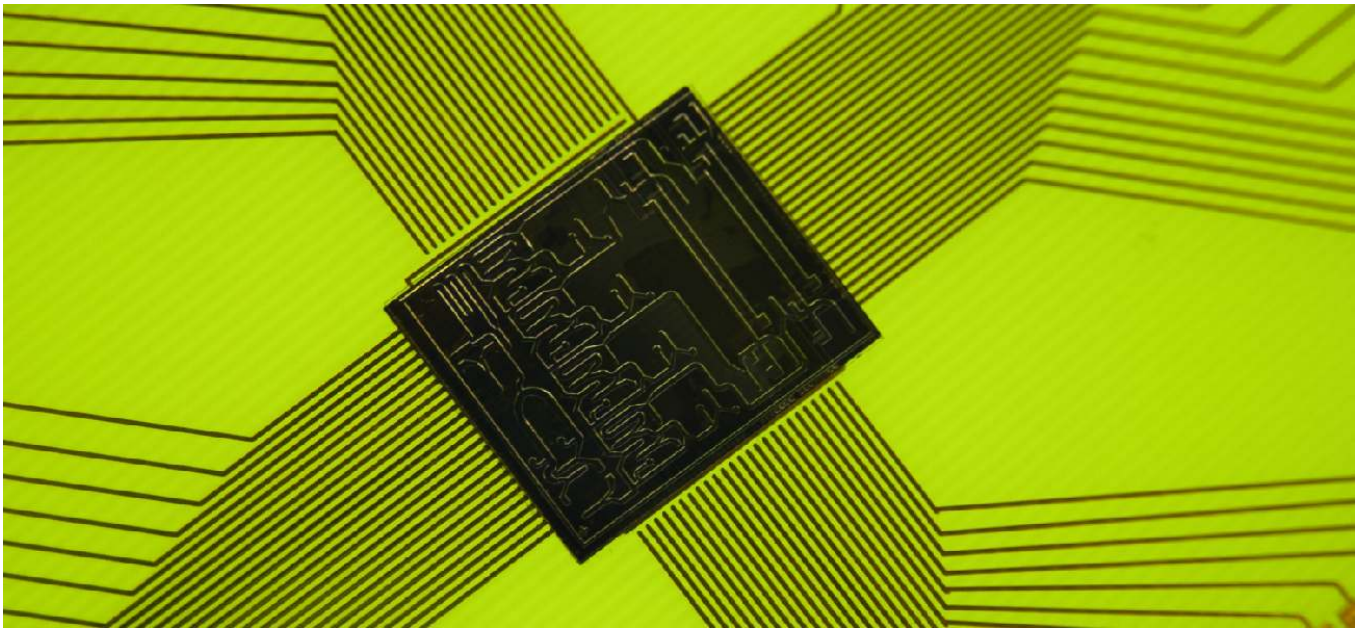


Figure **13.1**: Lab-on-a-chip technology allows immunological assays to be miniaturized so tests can be done rapidly with minimum quantities of expensive reagents. The chips contain tiny flow tubes to allow movement of fluids by capillary action, reactions sites with embedded reagents, and data output through electronic sensors. (credit: modification of work by Maggie Bartlett, NHGRI)

13.1: Practical Applications of Monoclonal and Polyclonal Antibodies

13.2: Detecting Antigen-Antibody Complexes in vitro

13.3: Agglutination Assays

13.4: Enzyme Immunoassays (EIA) and Enzyme-Linked Immunosorbent Assays (ELISA)

13.5: Fluorescent Auto-Antibody Techniques

13.E: Laboratory Analysis of the Immune Response (Exercises)

Footnotes

1. 1 Chin, Curtis D. et al., "Mobile Device for Disease Diagnosis and Data Tracking in Resource-Limited Settings," *Clinical Chemistry* 59, no. 4 (2013): 629-40.
2. 2 Evarts, H., "Fast, Low-Cost Device Uses the Cloud to Speed Up Testing for HIV and More," January 24, 2013. Accessed July 14, 2016. http://engineering.columbia.edu/fast...g-hiv-and-more.

This page titled 13: Laboratory Analysis of the Immune Response is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of

the LibreTexts platform.

13.1: Practical Applications of Monoclonal and Polyclonal Antibodies

Learning Objectives

- Compare the method of development, use, and characteristics of monoclonal and polyclonal antibodies
- Explain the nature of antibody cross-reactivity and why this is less of a problem with monoclonal antibodies

Clinical Focus: Part 1

In an unfortunate incident, a healthcare worker struggling with addiction was caught stealing syringes of painkillers and replacing them with syringes filled with unknown substances. The hospital immediately fired the employee and had him arrested; however, two patients that he had worked with later tested positive for HIV.

While there was no proof that the infections originated from the tainted syringes, the hospital's public health physician took immediate steps to determine whether any other patients had been put at risk. Although the worker had only been employed for a short time, it was determined that he had come into contact with more than 1300 patients. The hospital decided to contact all of these patients and have them tested for HIV.

Exercise 13.1.1

1. Why does the hospital feel it is necessary to test every patient for HIV?
2. What types of tests can be used to determine if a patient has HIV?

In addition to being crucial for our normal immune response, antibodies provide powerful tools for research and diagnostic purposes. The high specificity of antibodies makes them an excellent tool for detecting and quantifying a broad array of targets, from drugs to serum proteins to microorganisms. With *in vitro* assays, antibodies can be used to precipitate soluble antigens, agglutinate (clump) cells, opsonize and kill bacteria with the assistance of complement, and neutralize drugs, toxins, and viruses.

An antibody's specificity results from the antigen-binding site formed within the variable regions—regions of the antibody that have unique patterns of amino acids that can only bind to target antigens with a molecular sequence that provides complementary charges and noncovalent bonds. There are limitations to antibody specificity, however. Some antigens are so chemically similar that cross-reactivity occurs; in other words, antibodies raised against one antigen bind to a chemically similar but different antigen. Consider an antigen that consists of a single protein with multiple epitopes (Figure **13.1.1**). This single protein may stimulate the production of many different antibodies, some of which may bind to chemically identical epitopes on other proteins.

Cross-reactivity is more likely to occur between antibodies and antigens that have low affinity or avidity. Affinity, which can be determined experimentally, is a measure of the binding strength between an antibody's binding site and an epitope, whereas avidity is the total strength of all the interactions in an antibody-antigen complex (which may have more than one bonding site). Avidity is influenced by affinity as well as the structural arrangements of the epitope and the variable regions of the antibody. If an antibody has a high affinity/avidity for a specific antigen, it is less likely to cross-react with an antigen for which it has a lower affinity/avidity.

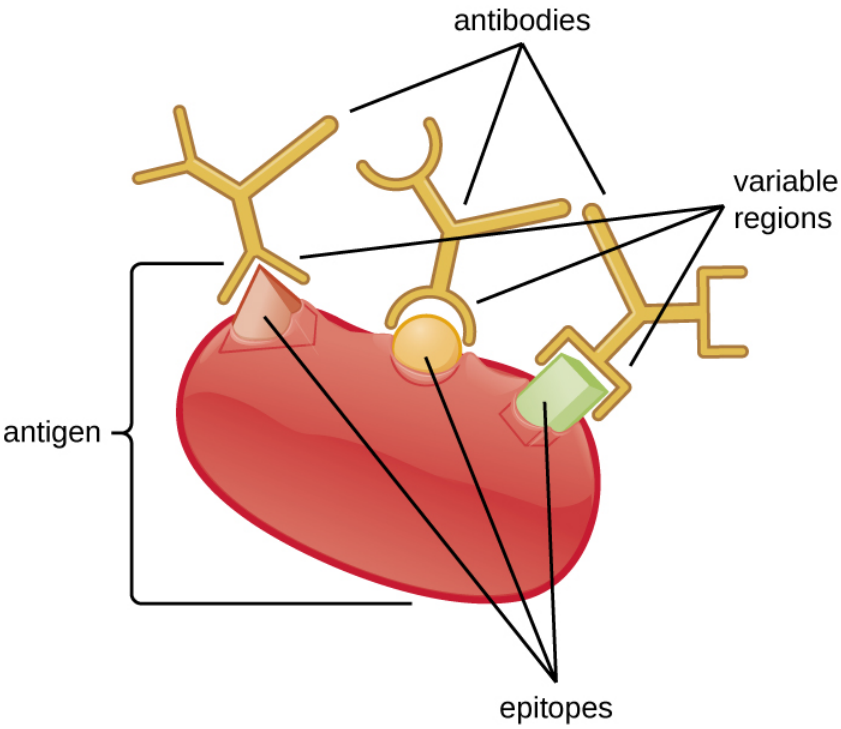


Figure **13.1.1**: An antibody binds to a specific region on an antigen called an epitope. A single antigen can have multiple epitopes for different, specific antibodies.

? Exercise 13.1.2

1. What property makes antibodies useful for research and clinical diagnosis?
2. What is cross-reactivity and why does it occur?

Producing Polyclonal Antibodies

Antibodies used for research and diagnostic purposes are often obtained by injecting a lab animal such as a rabbit or a goat with a specific antigen. Within a few weeks, the animal's immune system will produce high levels of antibodies specific for the antigen. These antibodies can be harvested in an antiserum, which is whole serum collected from an animal following exposure to an antigen. Because most antigens are complex structures with multiple epitopes, they result in the production of multiple antibodies in the lab animal. This so-called polyclonal antibody response is also typical of the response to infection by the human immune system. Antiserum drawn from an animal will thus contain antibodies from multiple clones of B cells, with each B cell responding to a specific epitope on the antigen (Figure **13.1.2**).

Lab animals are usually injected at least twice with antigen when being used to produce antiserum. The second injection will activate memory cells that make class IgG antibodies against the antigen. The memory cells also undergo affinity maturation, resulting in a pool of antibodies with higher average affinity. Affinity maturation occurs because of mutations in the immunoglobulin gene variable regions, resulting in B cells with slightly altered antigen-binding sites. On re-exposure to the antigen, those B cells capable of producing antibody with higher affinity antigen-binding sites will be stimulated to proliferate and produce more antibody than their lower-affinity peers. An adjuvant, which is a chemical that provokes a generalized activation of the immune system that stimulates greater antibody production, is often mixed with the antigen prior to injection.

Antiserum obtained from animals will not only contain antibodies against the antigen artificially introduced in the laboratory, but it will also contain antibodies to any other antigens to which the animal has been exposed during its lifetime. For this reason, antisera must first be "purified" to remove other antibodies before using the antibodies for research or diagnostic assays.

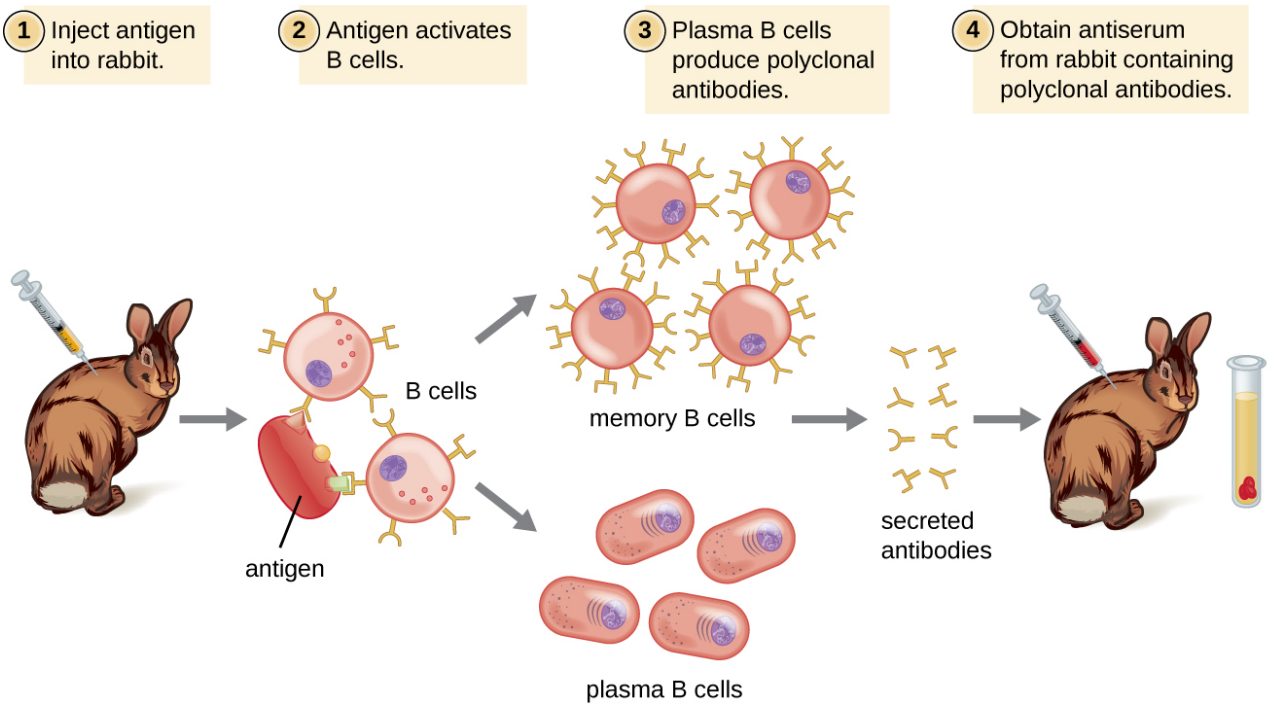


Figure **13.1.2**: This diagram illustrates the process for harvesting polyclonal antibodies produced in response to an antigen.

Clinical Uses of Polyclonal Antisera

Polyclonal antisera are used in many clinical tests that are designed to determine whether a patient is producing antibodies in response to a particular pathogen. While these tests are certainly powerful diagnostic tools, they have their limitations, because they are an indirect means of determining whether a particular pathogen is present. Tests based on a polyclonal response can sometimes lead to a false-positive result—in other words, a test that confirms the presence of an antigen that is, in fact, not present. Antibody-based tests can also result in a false-negative result, which occurs when the test fails to detect an antibody that is, in fact, present.

The accuracy of antibody tests can be described in terms of test sensitivity and test specificity. Test sensitivity is the probability of getting a positive test result when the patient is indeed infected. If a test has high sensitivity, the probability of a false negative is low. Test specificity, on the other hand, is the probability of getting a negative test result when the patient is not infected. If a test has high specificity, the probability of a false positive is low.

False positives often occur due to cross-reactivity, which can occur when epitopes from a different pathogen are similar to those found on the pathogen being tested for. For this reason, antibody-based tests are often used only as screening tests; if the results are positive, other confirmatory tests are used to make sure that the results were not a false positive.

For example, a blood sample from a patient suspected of having hepatitis C can be screened for the virus using antibodies that bind to antigens on hepatitis C virus. If the patient is indeed infected with hepatitis C virus, the antibodies will bind to the antigens, yielding a positive test result. If the patient is not infected with hepatitic C virus, the antibodies will generally not bind to anything and the test should be negative; however, a false positive may occur if the patient has been previously infected by any of a variety of pathogens that elicit antibodies that cross-react with the hepatitis C virus antigens. Antibody tests for hepatitis C have high sensitivity (a low probability of a false negative) but low specificity (a high probability of a false positive). Thus, patients who test positive must have a second, confirmatory test to rule out the possibility of a false positive. The confirmatory test is a more expensive and time-consuming test that directly tests for the presence of hepatitis C viral RNA in the blood. Only after the confirmatory test comes back positive can the patient be definitively diagnosed with a hepatitis C infection. Antibody-based tests can result in a false negative if, for any reason, the patient's immune system has not produced detectable levels of antibodies. For some diseases, it may take several weeks following infection before the immune system produces enough antibodies to cross the detection threshold of the assay. In immunocompromised patients, the immune system may not be capable of producing a detectable level of antibodies.

Another limitation of using antibody production as an indicator of disease is that antibodies in the blood will persist long after the infection has been cleared. Depending on the type of infection, antibodies will be present for many months; sometimes, they may be present for the remainder of the patient's life. Thus, a positive antibody-based test only means that the patient was infected at some point in time; it does not prove that the infection is active.

In addition to their role in diagnosis, polyclonal antisera can activate complement, detect the presence of bacteria in clinical and food industry settings, and perform a wide array of precipitation reactions that can detect and quantify serum proteins, viruses, or other antigens. However, with the many specificities of antibody present in a polyclonal antiserum, there is a significant likelihood that the antiserum will cross-react with antigens to which the individual was never exposed. Therefore, we must always account for the possibility of false-positive results when working with a polyclonal antiserum.

? Exercise 13.1.3

1. What is a false positive and what are some reasons that false positives occur?
2. What is a false negative and what are some reasons that false positives occur?
3. If a patient tests negative on a highly sensitive test, what is the likelihood that the person is infected with the pathogen?

Producing Monoclonal Antibodies

Some types of assays require better antibody specificity and affinity than can be obtained using a polyclonal antiserum. To attain this high specificity, all of the antibodies must bind with high affinity to a single epitope. This high specificity can be provided by monoclonal antibodies (mAbs). Table **13.1.1** compares some of the important characteristics of monoclonal and polyclonal antibodies.

Unlike polyclonal antibodies, which are produced in live animals, monoclonal antibodies are produced *in vitro* using tissue-culture techniques. mAbs are produced by immunizing an animal, often a mouse, multiple times with a specific antigen. B cells from the spleen of the immunized animal are then removed. Since normal B cells are unable to proliferate forever, they are fused with immortal, cancerous B cells called myeloma cells, to yield hybridoma cells. All of the cells are then placed in a selective medium that allows only the hybridomas to grow; unfused myeloma cells cannot grow, and any unfused B cells die off. The hybridomas, which are capable of growing continuously in culture while producing antibodies, are then screened for the desired mAb. Those producing the desired mAb are grown in tissue culture; the culture medium is harvested periodically and mAbs are purified from the medium. This is a very expensive and time-consuming process. It may take weeks of culturing and many liters of media to provide enough mAbs for an experiment or to treat a single patient. mAbs are expensive (Figure **13.1.3**).

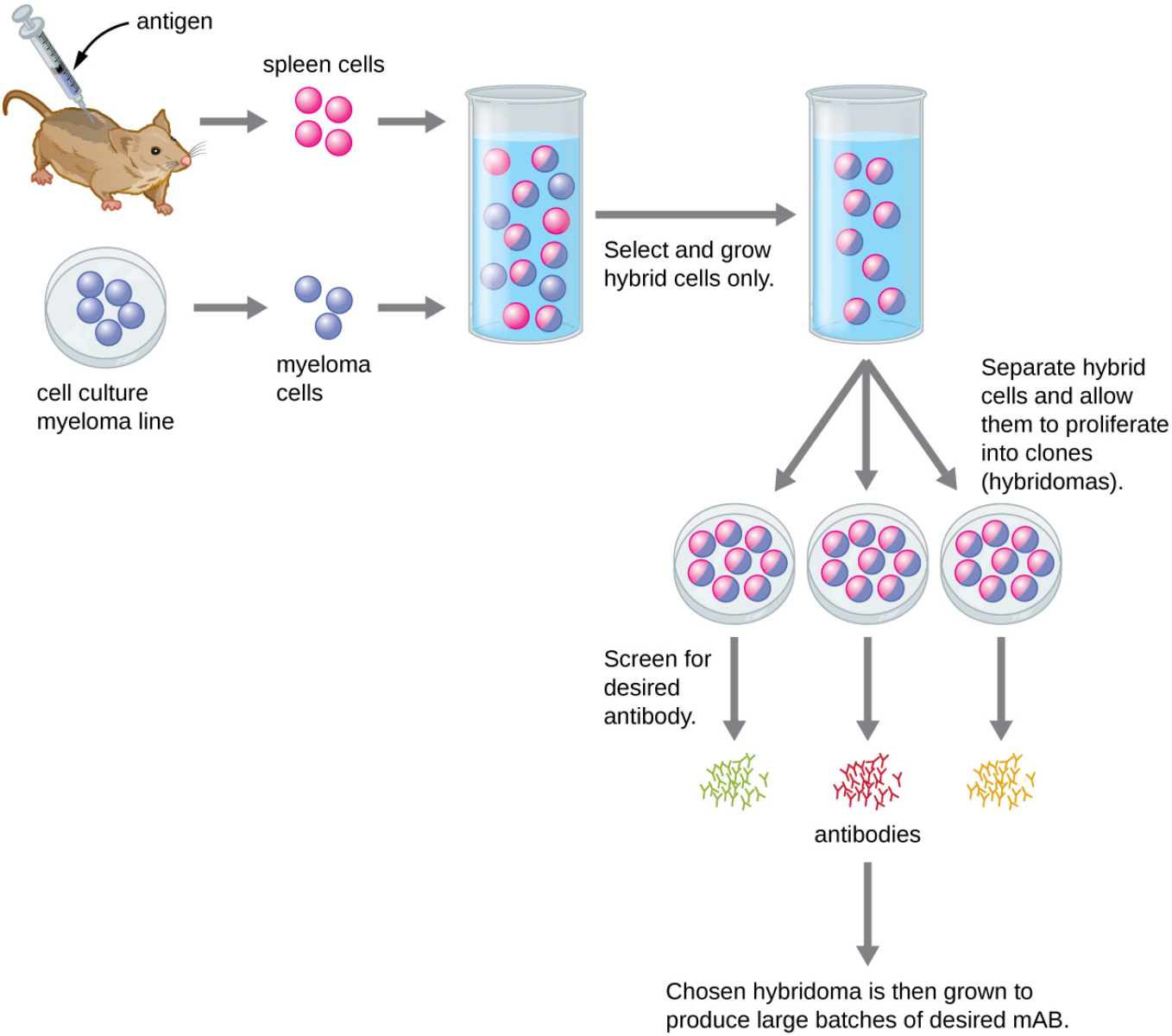


Figure **13.1.3**: Monoclonal antibodies (mAbs) are produced by introducing an antigen to a mouse and then fusing polyclonal B cells from the mouse's spleen to myeloma cells. The resulting hybridoma cells are cultured and continue to produce antibodies to the antigen. Hybridomas producing the desired mAb are then grown in large numbers on a selective medium that is periodically harvested to obtain the desired mAbs.

Table **13.1.1**: Characteristics of Polyclonal and Monoclonal Antibodies

Monoclonal Antibodies	Polyclonal Antibodies
Expensive production	Inexpensive production
Long production time	Rapid production
Large quantities of specific antibodies	Large quantities of nonspecific antibodies
Recognize a single epitope on an antigen	Recognize multiple epitopes on an antigen
Production is continuous and uniform once the hybridoma is made	Different batches vary in composition

Clinical Uses of Monoclonal Antibodies

Since the most common methods for producing monoclonal antibodies use mouse cells, it is necessary to create humanized monoclonal antibodies for human clinical use. Mouse antibodies cannot be injected repeatedly into humans, because the immune system will recognize them as being foreign and will respond to them with neutralizing antibodies. This problem can be minimized by genetically engineering the antibody in the mouse B cell. The variable regions of the mouse light and heavy chain genes are ligated to human constant regions, and the chimeric gene is then transferred into a host cell. This allows production of a mAb that is mostly "human" with only the antigen-binding site being of mouse origin.

Humanized mAbs have been successfully used to treat cancer with minimal side effects. For example, the humanized monoclonal antibody drug Herceptin has been helpful for the treatment of some types of breast cancer. There have also been a few preliminary trials of humanized mAb for the treatment of infectious diseases, but none of these treatments are currently in use. In some cases, mAbs have proven too specific to treat infectious diseases, because they recognize some serovars of a pathogen but not others. Using a cocktail of multiple mAbs that target different strains of the pathogen can address this problem. However, the great cost associated with mAb production is another challenge that has prevented mAbs from becoming practical for use in treating microbial infections.[1]

One promising technology for inexpensive mAbs is the use of genetically engineered plants to produce antibodies (or plantibodies). This technology transforms plant cells into antibody factories rather than relying on tissue culture cells, which are expensive and technically demanding. In some cases, it may even be possible to deliver these antibodies by having patients eat the plants rather than by extracting and injecting the antibodies. For example, in 2013, a research group cloned antibody genes into plants that had the ability to neutralize an important toxin from bacteria that can cause severe gastrointestinal disease.[2] Eating the plants could potentially deliver the antibodies directly to the toxin.

? Exercise 13.1.4

1. How are humanized monoclonal antibodies produced?
2. What does the "monoclonal" of monoclonal antibodies mean?

Using Monoclonal Antibodies to Combat Ebola

During the 2014–2015 Ebola outbreak in West Africa, a few Ebola-infected patients were treated with ZMapp, a drug that had been shown to be effective in trials done in rhesus macaques only a few months before.[3] ZMapp is a combination of three mAbs produced by incorporating the antibody genes into tobacco plants using a viral vector. By using three mAbs, the drug is effective across multiple strains of the virus. Unfortunately, there was only enough ZMapp to treat a tiny number of patients.

While the current technology is not adequate for producing large quantities of ZMapp, it does show that plantibodies—plant-produced mAbs—are feasible for clinical use, potentially cost effective, and worth further development. The last several years have seen an explosion in the number of new mAb-based drugs for the treatment of cancer and infectious diseases; however, the widespread use of such drugs is currently inhibited by their exorbitant cost, especially in underdeveloped parts of the world, where a single dose might cost more than the patient's lifetime income. Developing methods for cloning antibody genes into plants could reduce costs dramatically.

Key Concepts and Summary

- Antibodies bind with high **specificity** to antigens used to challenge the immune system, but they may also show **cross-reactivity** by binding to other antigens that share chemical properties with the original antigen.
- Injection of an antigen into an animal will result in a **polyclonal antibody** response in which different antibodies are produced that react with the various epitopes on the antigen.
- **Polyclonal antisera** are useful for some types of laboratory assays, but other assays require more specificity. Diagnostic tests that use polyclonal antisera are typically only used for screening because of the possibility of **false-positive** and **false-negative** results.
- **Monoclonal antibodies** provide higher specificity than polyclonal antisera because they bind to a single epitope and usually have high **affinity**.

- Monoclonal antibodies are typically produced by culturing antibody-secreting **hybridomas** derived from mice. mAbs are currently used to treat cancer, but their exorbitant cost has prevented them from being used more widely to treat infectious diseases. Still, their potential for laboratory and clinical use is driving the development of new, cost-effective solutions such as **plantibodies**.

Footnotes

1. 1 Saylor, Carolyn, Ekaterina Dadachova and Arturo Casadevall, “Monoclonal Antibody-Based Therapies for Microbial Diseases,” *Vaccine* 27 (2009): G38-G46.
2. 2 Nakanishi, Katsuhiro et al., “Production of Hybrid-IgG/IgA Plantibodies with Neutralizing Activity against Shiga Toxin 1,” *PloS One* 8, no. 11 (2013): e80712.
3. 3 Qiu, Xiangguo et al., “Reversion of Advanced Ebola Virus Disease in Nonhuman Primates with ZMapp,” *Nature* 514 (2014): 47–53.

This page titled 13.1: Practical Applications of Monoclonal and Polyclonal Antibodies is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **20.1: Practical Applications of Monoclonal and Polyclonal Antibodies** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

13.2: Detecting Antigen-Antibody Complexes in vitro

Learning Objectives

- Describe various types of assays used to find antigen-antibody complexes
- Describe the circumstances under which antigen-antibody complexes precipitate out of solution
- Explain how antibodies in patient serum can be used to diagnose disease

Laboratory tests to detect antibodies and antigens outside of the body (e.g., in a test tube) are called *in vitro* assays. When both antibodies and their corresponding antigens are present in a solution, we can often observe a precipitation reaction in which large complexes (lattices) form and settle out of solution. In the next several sections, we will discuss several common *in vitro* assays.

Precipitin Reactions

A visible antigen-antibody complex is called a precipitin, and *in vitro* assays that produce a precipitin are called precipitin reactions. A precipitin reaction typically involves adding soluble antigens to a test tube containing a solution of antibodies. Each antibody has two arms, each of which can bind to an epitope. When an antibody binds to two antigens, the two antigens become bound together by the antibody. A lattice can form as antibodies bind more and more antigens together, resulting in a precipitin (Figure **13.2.1**). Most precipitin tests use a polyclonal antiserum rather than monoclonal antibodies because polyclonal antibodies can bind to multiple epitopes, making lattice formation more likely. Although mAbs may bind some antigens, the binding will occur less often, making it much less likely that a visible precipitin will form.

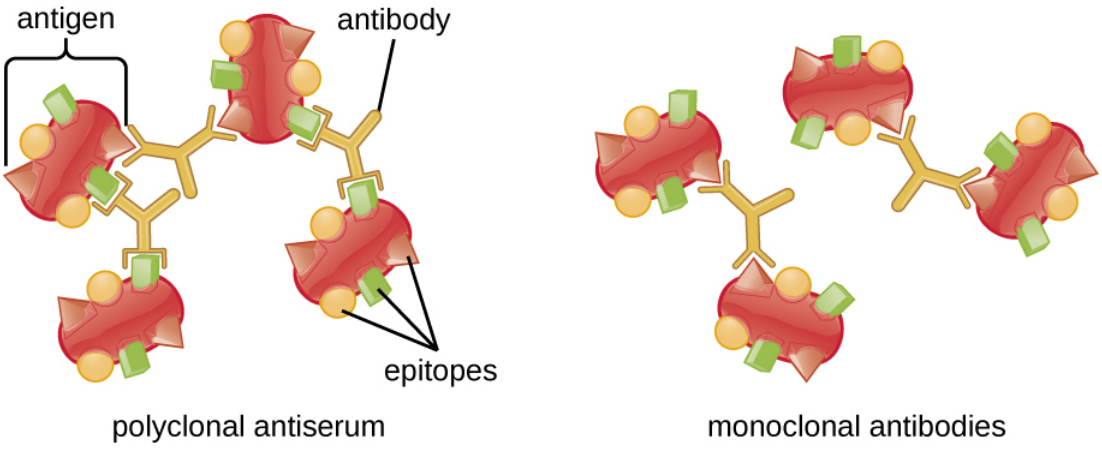


Figure **13.2.1**: Polyclonal antiserum binds to multiple epitopes on an antigen, leading to lattice formation that results in a visible precipitin. Monoclonal antibodies can only bind to a single epitope; therefore, less binding occurs and lattice formation generally does not occur.

The amount of precipitation also depends on several other factors. For example, precipitation is enhanced when the antibodies have a high affinity for the antigen. While most antibodies bind antigen with high affinity, even high-affinity binding uses relatively weak noncovalent bonds, so that individual interactions will often break and new interactions will occur.

In addition, for precipitin formation to be visible, there must be an optimal ratio of antibody to antigen. The optimal ratio is not likely to be a 1:1 antigen-to-antibody ratio; it can vary dramatically, depending on the number of epitopes on the antigen and the class of antibody. Some antigens may have only one or two epitopes recognized by the antiserum, whereas other antigens may have many different epitopes and/or multiple instances of the same epitope on a single antigen molecule.

Figure **13.2.2** illustrates how the ratio of antigen and antibody affects the amount of precipitation. To achieve the optimal ratio, antigen is slowly added to a solution containing antibodies, and the amount of precipitin is determined qualitatively. Initially, there is not enough antigen to produce visible lattice formation; this is called the zone of antibody excess. As more antigen is added, the reaction enters the equivalence zone (or zone of equivalence), where both the optimal antigen-antibody interaction and maximal precipitation occur. If even more antigen were added, the amount of antigen would become excessive and actually cause the amount of precipitation to decline.

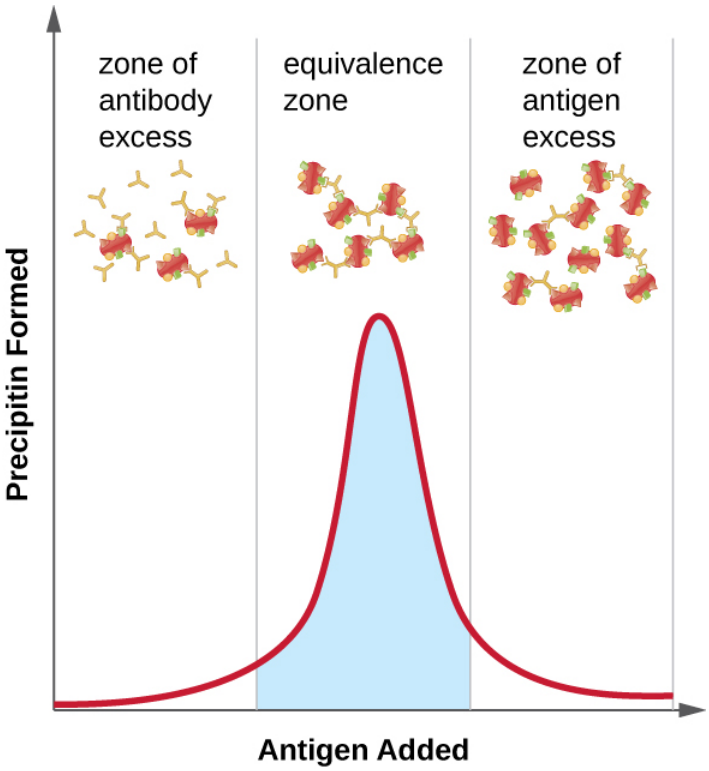


Figure **13.2.2**: As antigen is slowly added to a solution containing a constant amount antibody, the amount of precipitin increases as the antibody-to-antigen ratio approaches the equivalence zone and decreases once the proportion of antigen exceeds the optimal ratio.

? Exercise 13.2.1

1. What is a precipitin?
2. Why do polyclonal antisera produce a better precipitin reaction?

Precipitin Ring Test

A variety of techniques allow us to use precipitin formation to quantify either antigen concentration or the amount of antibody present in an antiserum. One such technique is the precipitin ring test (Figure **13.2.3**), which is used to determine the relative amount of antigen-specific antibody in a sample of serum. To perform this test, a set of test tubes is prepared by adding an antigen solution to the bottom of each tube. Each tube receives the same volume of solution, and the concentration of antigens is constant (e.g., 1 mg/mL). Next, glycerol is added to the antigen solution in each test tube, followed by a serial dilution of the antiserum. The glycerol prevents mixing of the antiserum with the antigen solution, allowing antigen-antibody binding to take place only at the interface of the two solutions. The result is a visible ring of precipitin in the tubes that have an antigen-antibody ratio within the equivalence zone. This highest dilution with a visible ring is used to determine the titer of the antibodies. The titer is the reciprocal of the highest dilution showing a positive result, expressed as a whole number. In Figure **13.2.3**, the titer is 16.

While a measurement of titer does not tell us in absolute terms how much antibody is present, it does give a measure of biological activity, which is often more important than absolute amount. In this example, it would not be useful to know what mass of IgG were present in the antiserum, because there are many different specificities of antibody present; but it is important for us to know how much of the antibody activity in a patient's serum is directed against the antigen of interest (e.g., a particular pathogen or allergen).

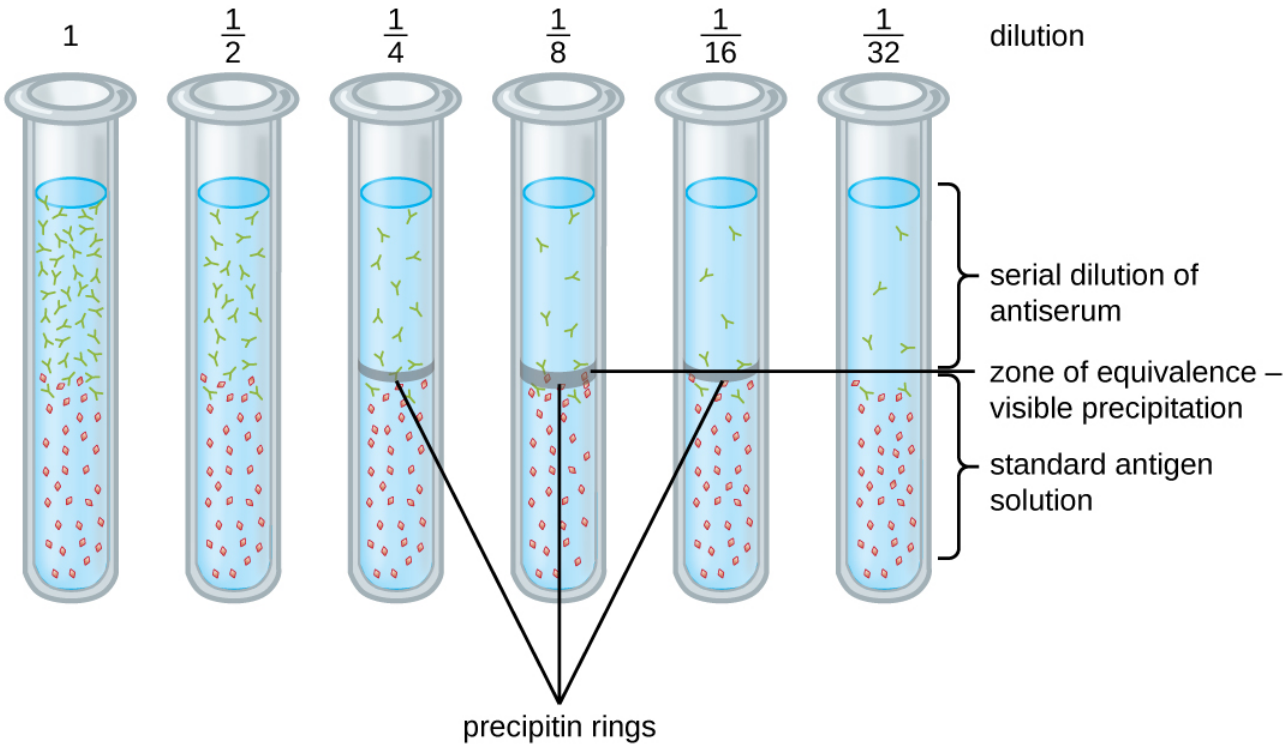


Figure **13.2.3**: A precipitin ring test is performed using a standard antigen solution in the bottom of the tube and a serial dilution of antiserum in the top of the tube. Glycerol prevents the two solutions from mixing so that precipitation only occurs at the interface. A visible ring of precipitation is seen in the 1/4, 1/8, and 1/16 dilutions, indicating that these concentrations are within the equivalence zone. Since 1/16 is the highest dilution in which a precipitin is observed, the titer is the reciprocal, or 16.

Ouchterlony Assay

While the precipitin ring test provides insights into antibody-antigen interactions, it also has some drawbacks. It requires the use of large amounts of serum, and great care must be taken to avoid mixing the solutions and disrupting the ring. Performing a similar test in an agar gel matrix can minimize these problems. This type of assay is variously called double immunodiffusion or the Ouchterlony assay for Orjan Ouchterlony,[1] who first described the technique in 1948.

When agar is highly purified, it produces a clear, colorless gel. Holes are punched in the gel to form wells, and antigen and antisera are added to neighboring wells. Proteins are able to diffuse through the gel, and precipitin arcs form between the wells at the zone of equivalence. Because the precipitin lattice is too large to diffuse through the gel, the arcs are firmly locked in place and easy to see (Figure **13.2.4**).

Although there are now more sensitive and quantitative methods of detecting antibody-antigen interactions, the Ouchterlony test provides a rapid and qualitative way of determining whether an antiserum has antibodies against a particular antigen. The Ouchterlony test is particularly useful when looking for cross-reactivity. We can check an antiserum against a group of closely related antigens and see which combinations form precipitin arcs.

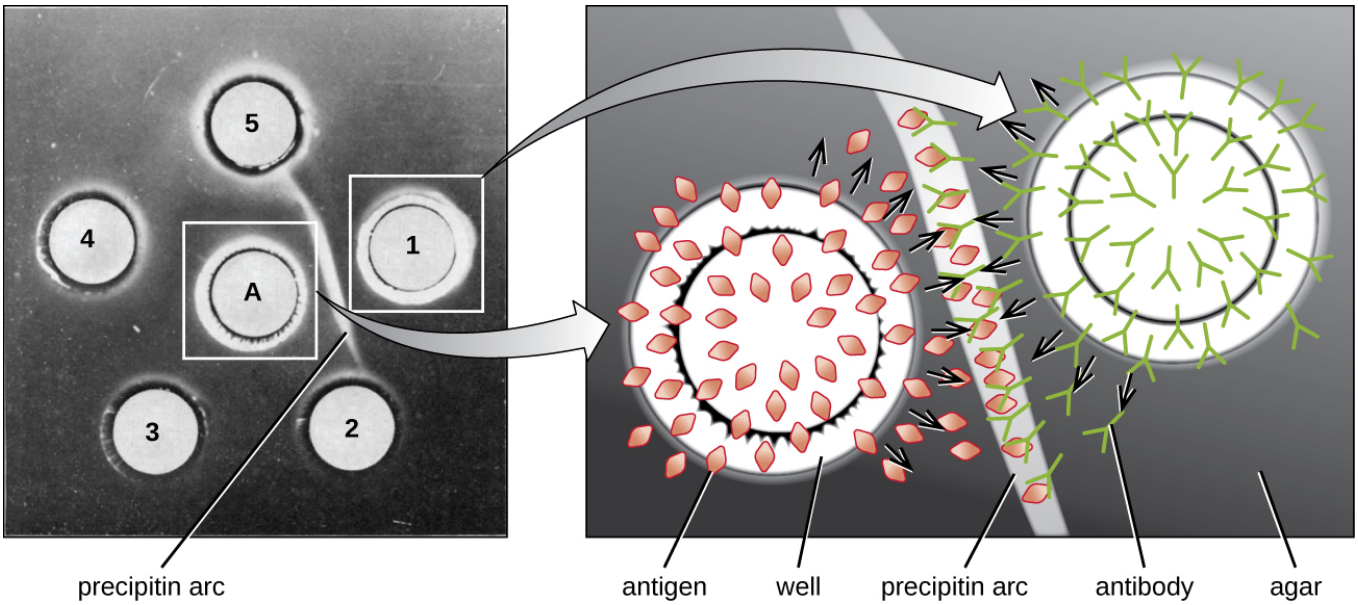


Figure **13.2.4**: The Ouchterlony test places antigen (well A) and antisera (wells 1 through 5) in a gel. The antibodies and antigen diffuse through the gel, causing a precipitin arc to form at the zone of equivalence. In this example, only the antiserum in well 1 contains antibodies to the antigen. The resulting precipitin arc is stable because the lattice is too large to diffuse through the gel. (credit left: modification of work by Higgins PJ, Tong C, Borenfreund E, Okin RS, Bendich A)

Radial Immunodiffusion Assay

The radial immunodiffusion (RID) assay is similar to the Ouchterlony assay but is used to precisely quantify antigen concentration rather than to compare different antigens. In this assay, the antiserum is added to tempered agar (liquid agar at slightly above 45 °C), which is poured into a small petri dish or onto a glass slide and allowed to cool. Wells are cut in the cooled agar, and antigen is then added to the wells and allowed to diffuse. As the antigen and antibody interact, they form a zone of precipitation. The square of the diameter of the zone of precipitation is directly proportional to the concentration of antigen. By measuring the zones of precipitation produced by samples of known concentration (see the outer ring of samples in Figure **13.2.5**), we can prepare a standard curve for determining the concentration of an unknown solution. The RID assay is a also useful test for determining the concentration of many serum proteins such as the C3 and C4 complement proteins, among others.

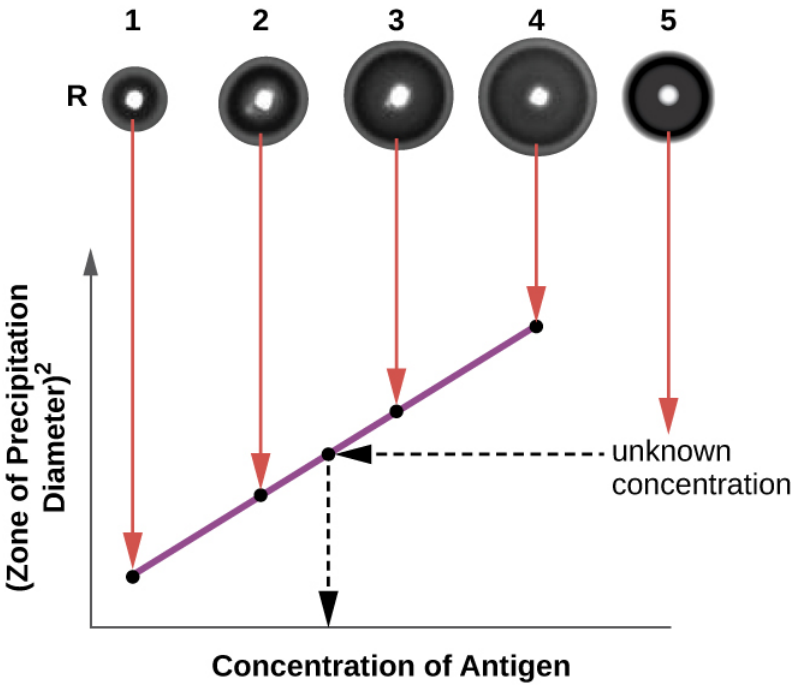


Figure 13.2.5: In this radial immunodiffusion (RID) assay, an antiserum is mixed with the agar before it is cooled, and solutions containing antigen are added to each well in increasing concentrations (wells 1–4). An antigen solution of an unknown concentration is added to well 5. The zones of precipitation are measured and plotted against a standard curve to determine the antigen concentration of the unknown sample. (credit circles: modification of work by Kangwa M, Yelemane V, Polat AN, Gorrepati KD, Grasselli M, Fernández-Lahore M)

? Exercise 13.2.2

1. Why does a precipitin ring form in a precipitin ring test, and what are some reasons why a ring might not form?
2. Compare and contrast the techniques used in an Ouchterlony assay and a radial immunodiffusion assay.

Flocculation Assays

A flocculation assay is similar to a precipitin reaction except that it involves insoluble antigens such as lipids. A flocculant is similar to a precipitin in that there is a visible lattice of antigen and antibody, but because lipids are insoluble in aqueous solution, they cannot precipitate. Instead of precipitation, flocculation (foaming) is observed in the test tube fluid.

Using Flocculation to Test for Syphilis

Syphilis is a sexually transmitted infection that can cause severe, chronic disease in adults. In addition, it is readily passed from infected mothers to their newborns during pregnancy and childbirth, often resulting in stillbirth or serious long-term health problems for the infant. Unfortunately, syphilis can also be difficult to diagnose in expectant mothers, because it is often asymptomatic, especially in women. In addition, the causative agent, the bacterium *Treponema pallidum*, is both difficult to grow on conventional lab media and too small to see using routine microcopy. For these reasons, presumptive diagnoses of syphilis are generally confirmed indirectly in the laboratory using tests that detect antibodies to treponemal antigens.

In 1906, German scientist August von Wassermann (1866–1925) introduced the first test for syphilis that relied on detecting anti-treponemal antibodies in the patient's blood. The antibodies detected in the Wassermann test were antiphospholipid antibodies that are nonspecific to *T. pallidum*. Their presence can assist in the diagnosis of syphilis, but because they are nonspecific, they can also lead to false-positive results in patients with other diseases and autoimmune conditions. The original Wasserman test has been modified over the years to minimize false-positives and is now known as the Venereal Disease Research Lab test, better known by its acronym, the VDRL test.

To perform the VDRL test, patient serum or cerebral spinal fluid is placed on a slide with a mixture of cardiolipin (an antigenic phospholipid found in the mitochondrial membrane of various pathogens), lecithin, and cholesterol. The lecithin and

cholesterol stabilize the reaction and diminish false positives. Anti-treponemal antibodies from an infected patient's serum will bind cardiolipin and form a flocculant. Although the VDRL test is more specific than the original Wassermann assay, false positives may still occur in patients with autoimmune diseases that cause extensive cell damage (e.g., systemic lupus erythematosus).

Neutralization Assay

To cause infection, viruses must bind to receptors on host cells. Antiviral antibodies can neutralize viral infections by coating the virions, blocking the binding (Figure 18.1.6). This activity neutralizes virions and can result in the formation of large antibody-virus complexes (which are readily removed by phagocytosis) or by antibody binding to the virus and blocking its binding to host cell receptors. This neutralization activity is the basis of neutralization assays, sensitive assays used for diagnoses of viral infections.

When viruses infect cells, they often cause damage (cytopathic effects) that may include lysis of the host cells. Cytopathic effects can be visualized by growing host cells in a petri dish, covering the cells with a thin layer of agar, and then adding virus (see Isolation, Culture, and Identification of Viruses). The virus will diffuse very slowly through the agar. A virus will enter a host cell, proliferate (causing cell damage), be released from the dead host cell, and then move to neighboring cells. As more and more cells die, plaques of dead cells will form (Figure **13.2.6**).

During the course of a viral infection, the patient will mount an antibody response to the virus, and we can quantify those antibodies using a plaque reduction assay. To perform the assay, a serial dilution is carried out on a serum sample. Each dilution is then mixed with a standardized amount of the suspect virus. Any virus-specific antibodies in the serum will neutralize some of the virus. The suspensions are then added to host cells in culture to allow any nonneutralized virus to infect the cells and form plaques after several days. The titer is defined as the reciprocal of the highest dilution showing a 50% reduction in plaques. Titer is always expressed as a whole number. For example, if a 1/64 dilution was the highest dilution to show 50% plaque reduction, then the titer is 64.

The presence of antibodies in the patient's serum does not tell us whether the patient is currently infected or was infected in the past. Current infections can be identified by waiting two weeks and testing another serum sample. A four-fold increase in neutralizing titer in this second sample indicates a new infection.

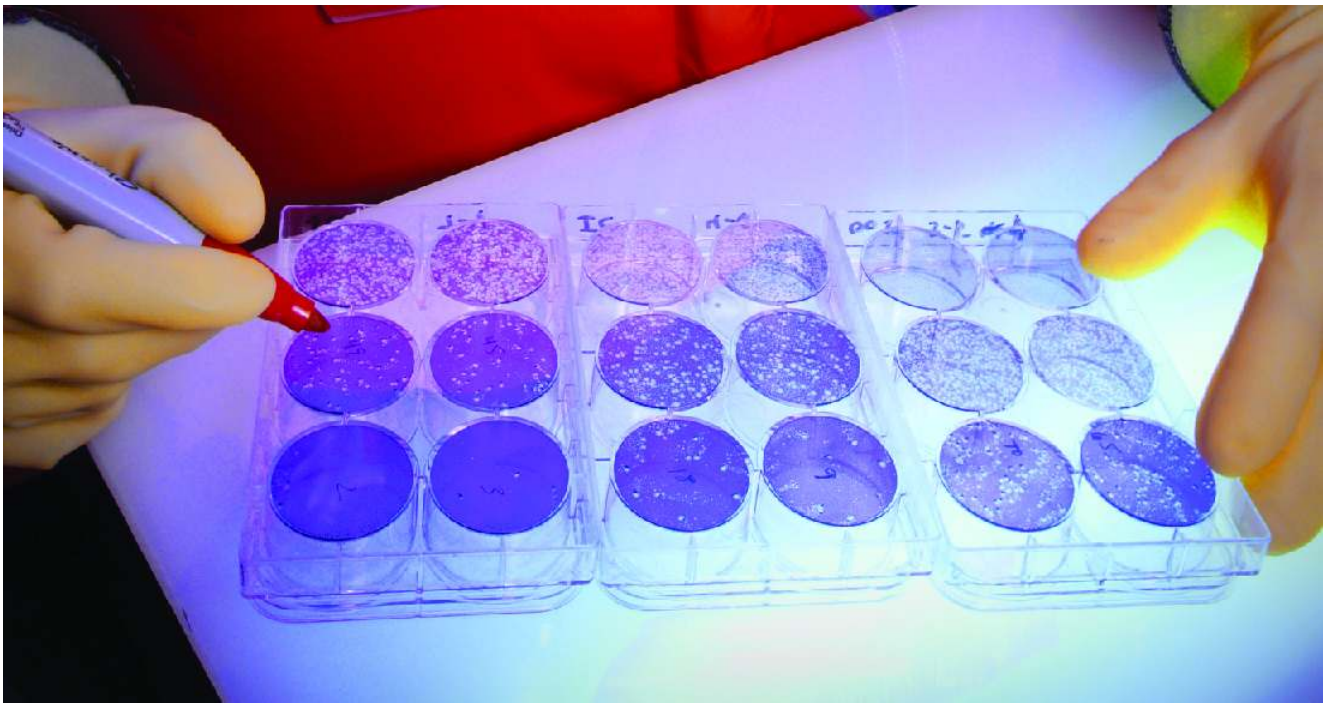


Figure **13.2.6**: In a neutralization assay, antibodies in patient serum neutralize viruses added to the wells, preventing the formation of plaques. In the assay pictured, the wells with numerous plaques (white patches) contain a low concentration of antibodies. The

wells with relatively few plaques have a high concentration of antibodies. (credit: modification of work by Centers for Disease Control and Prevention)

? Exercise 13.2.3

In a neutralization assay, if a patient's serum has high numbers of antiviral antibodies, would you expect to see more or fewer plaques?

Immunoelectrophoresis

When a patient has elevated protein levels in the blood or is losing protein in the urine, a clinician will often order a polyacrylamide gel electrophoresis (PAGE) assay (see Visualizing and Characterizing DNA, RNA, and Protein). This assay compares the relative abundance of the various types of serum proteins. Abnormal protein electrophoresis patterns can be further studied using immunoelectrophoresis (IEP). The IEP begins by running a PAGE. Antisera against selected serum proteins are added to troughs running parallel to the electrophoresis track, forming precipitin arcs similar to those seen in an Ouchterlony assay (Figure **13.2.7**). This allows the identification of abnormal immunoglobulin proteins in the sample.

IEP is particularly useful in the diagnosis of multiple myeloma, a cancer of antibody-secreting cells. Patients with multiple myeloma cannot produce healthy antibodies; instead they produce abnormal antibodies that are monoclonal proteins (M proteins). Thus, patients with multiple myeloma will present with elevated serum protein levels that show a distinct band in the gamma globulin region of a protein electrophoresis gel and a sharp spike (in M protein) on the densitometer scan rather than the normal broad smear (Figure **13.2.7**). When antibodies against the various types of antibody heavy and light chains are used to form precipitin arcs, the M protein will cause distinctly skewed arcs against one class of heavy chain and one class of light chain as seen in Figure **13.2.7**.

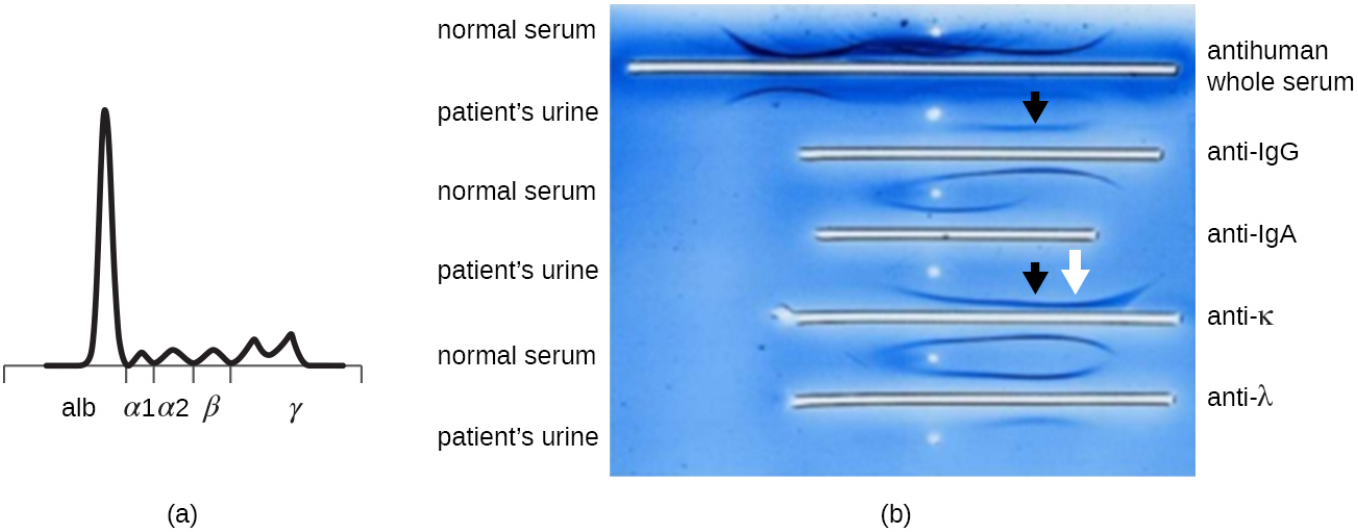


Figure **13.2.7**: (a) This graph shows normal measurements of serum proteins. (b) This photograph shows an immunoelectrophoresis of urine. After electrophoresis, antisera were added to the troughs and the precipitin arcs formed, illustrating the distribution of specific proteins. The skewed arcs (arrows) help to diagnose multiple myeloma. (credit a, b: modification of work by Izawa S, Akimoto T, Ikeuchi H, Kusano E, Nagata D)

Protein Electrophoresis and the Characterization of Immunoglobulin Structure

The advent of electrophoresis ultimately led to researching and understanding the structure of antibodies. When Swedish biochemist Arne Tiselius (1902–1971) published the first protein electrophoresis results in 1937,[2] he could identify the protein albumin (the smallest and most abundant serum protein) by the sharp band it produced in the gel. The other serum proteins could not be resolved in a simple protein electrophoresis, so he named the three broad bands, with many proteins in each band, alpha, beta, and gamma globulins. Two years later, American immunologist Elvin Kabat (1914–2000) traveled to Sweden to work with Tiselius using this new technique and showed that antibodies migrated as gamma globulins.[3] With this new understanding in hand, researchers soon learned that multiple myeloma, because it is a cancer of antibody-secreting cells, could

be tentatively diagnosed by the presence of a large M spike in the gamma-globulin region by protein electrophoresis. Prior to this discovery, studies on immunoglobulin structure had been minimal, because of the difficulty of obtaining pure samples to study. Sera from multiple myeloma patients proved to be an excellent source of highly enriched monoclonal immunoglobulin, providing the raw material for studies over the next 20-plus years that resulted in the elucidation of the structure of immunoglobulin.

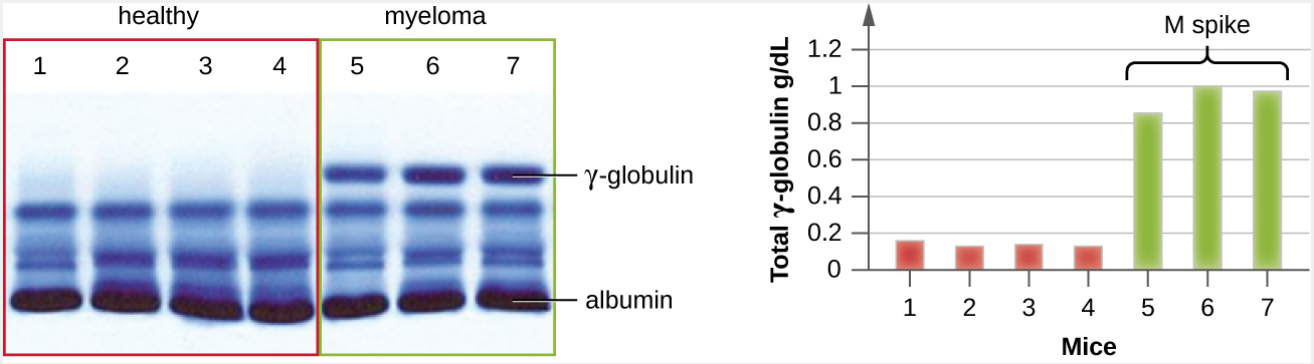


Figure 13.2.8: Electrophoresis patterns of myeloma (right) and normal sera (left). The proteins have been stained; when the density of each band is quantified by densitometry, the data produce the bar graph on the right. Both gels show the expected dense band of albumin at the bottom and an abnormal spike in the gamma-globulin region. (credit: modification of work by Soodgupta D, Hurchla MA, Jiang M, Zheleznyak A, Weilbaecher KN, Anderson CJ, Tomasson MH, Shokeen M)

Exercise 13.2.4

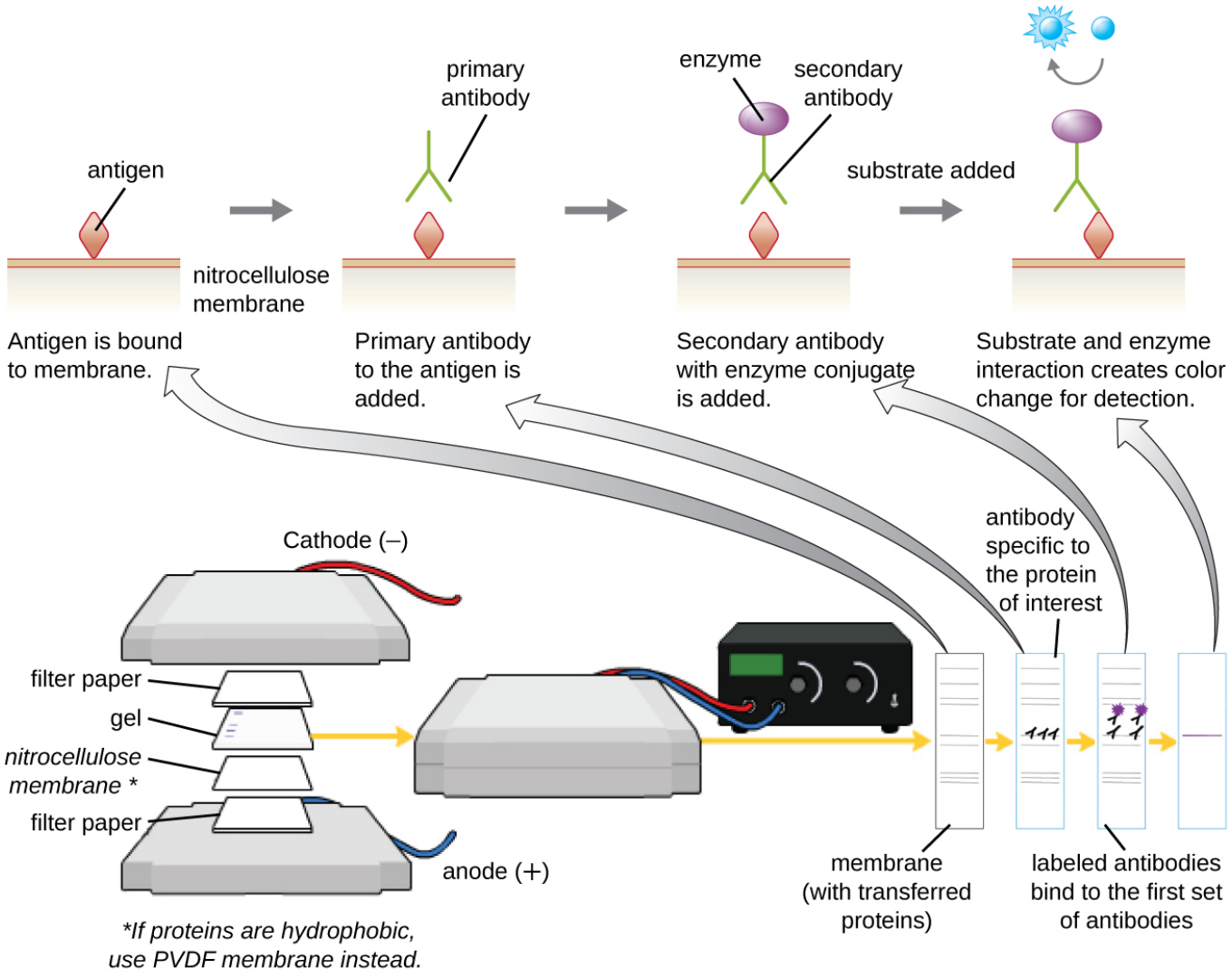
In general, what does an immunoelectrophoresis assay accomplish?

Immunoblot Assay: The Western Blot

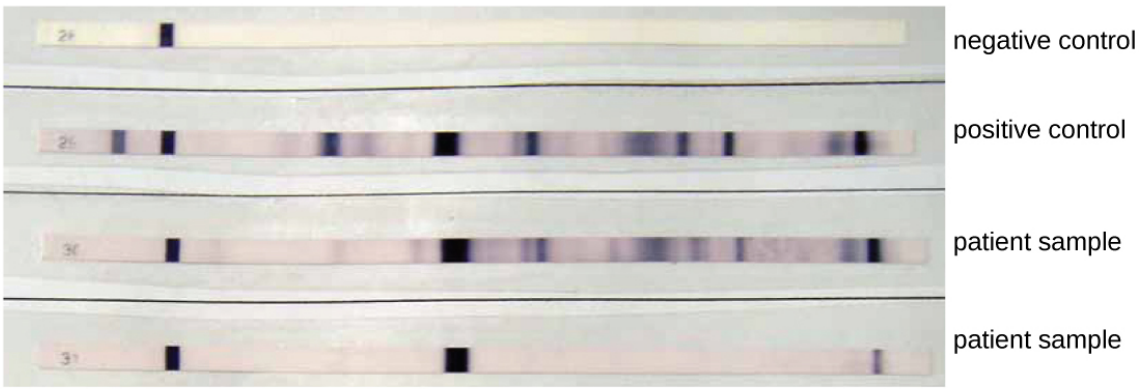
After performing protein gel electrophoresis, specific proteins can be identified in the gel using antibodies. This technique is known as the western blot. Following separation of proteins by PAGE, the protein antigens in the gel are transferred to and immobilized on a nitrocellulose membrane. This membrane can then be exposed to a primary antibody produced to specifically bind to the protein of interest. A second antibody equipped with a molecular beacon will then bind to the first. These secondary antibodies are coupled to another molecule such as an enzyme or a fluorophore (a molecule that fluoresces when excited by light). When using antibodies coupled to enzymes, a chromogenic substrate for the enzyme is added. This substrate is usually colorless but will develop color in the presence of the antibody. The fluorescence or substrate coloring identifies the location of the specific protein in the membrane to which the antibodies are bound (Figure 13.2.9).

Typically, polyclonal antibodies are used for western blot assays. They are more sensitive than mAbs because of their ability to bind to various epitopes of the primary antigen, and the signal from polyclonal antibodies is typically stronger than that from mAbs. Monoclonal antibodies can also be used; however, they are much more expensive to produce and are less sensitive, since they are only able to recognize one specific epitope.

Several variations of the western blot are useful in research. In a southwestern blot, proteins are separated by SDS-PAGE, blotted onto a nitrocellulose membrane, allowed to renature, and then probed with a fluorescently or radioactively labeled DNA probe; the purpose of the southwestern is to identify specific DNA-protein interactions. Far-western blotsare carried out to determine protein-protein interactions between immobilized proteins (separated by SDS-PAGE, blotted onto a nitrocellulose membrane, and allowed to renature) and non-antibody protein probes. The bound non-antibody proteins that interact with the immobilized proteins in a far-western blot may be detected by radiolabeling, fluorescence, or the use of an antibody with an enzymatic molecular beacon.



(a)



(b)

Figure 13.2.9: (a) This diagram summarizes the process of western blotting. Antibodies are used to identify specific bands on the protein gel. (b) A western blot test for antibodies against HIV. The top strip is the negative control; the next strip is the positive control. The bottom two strips are patient serum samples containing antibodies. (credit a: modification of work by "Bensaccount"/Wikimedia Commons)

? Exercise 13.2.5

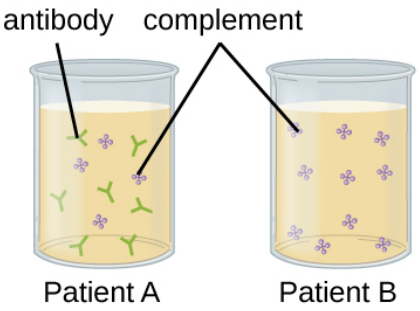
What is the function of the enzyme in the immunoblot assay?

Complement-Mediated Immunoassay

One of the key functions of antibodies is the activation (fixation) of complement. When antibody binds to bacteria, for example, certain complement proteins recognize the bound antibody and activate the complement cascade. In response, other complement proteins bind to the bacteria where some serve as opsonins to increase the efficiency of phagocytosis and others create holes in gram-negative bacterial cell membranes, causing lysis. This lytic activity can be used to detect the presence of antibodies against specific antigens in the serum.

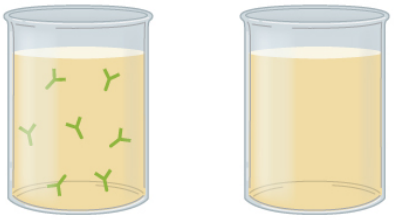
Red blood cells are good indicator cells to use when evaluating complement-mediated cytolysis. Hemolysis of red blood cells releases hemoglobin, which is a brightly colored pigment, and hemolysis of even a small number of red cells will cause the solution to become noticeably pink (Figure **13.2.10**). This characteristic plays a role in the complement fixation test, which allows the detection of antibodies against specific pathogens. The complement fixation test can be used to check for antibodies against pathogens that are difficult to culture in the lab such as fungi, viruses, or the bacteria *Chlamydia*.

To perform the complement fixation test, antigen from a pathogen is added to patient serum. If antibodies to the antigen are present, the antibody will bind the antigen and fix all the available complement. When red blood cells and antibodies against red blood cells are subsequently added to the mix, there will be no complement left to lyse the red cells. Thus, if the solution remains clear, the test is positive. If there are no antipathogen antibodies in the patient's serum, the added antibodies will activate the complement to lyse the red cells, yielding a negative test (Figure **13.2.10**).



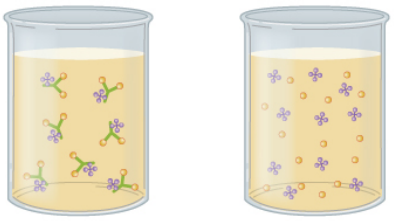
1 Patient A's serum contains antibodies to the suspected antigen. Patient B's serum does not. Both patients have complement, but different amounts.

Heat both samples to destroy complement.



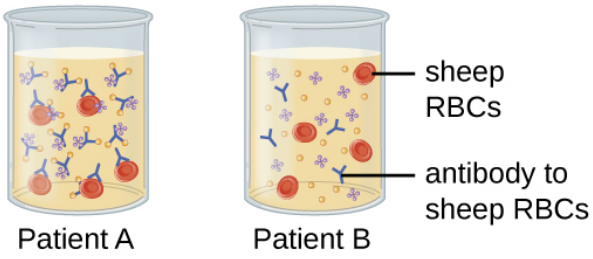
2 Heating the serum destroys all of the complement in the patient's serum. Antibodies remain in Patient A's serum.

Complement and antigen are added.

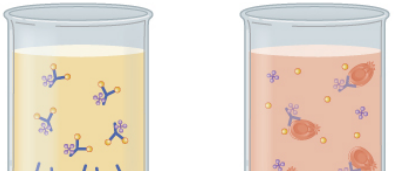


3 An equal amount of complement is then added to the serum for both patients. Antigens are also added. In patient A's serum, antibodies bind to antigens and complement fixation occurs. Patient B's serum lacks antibodies, so complement fixation does not occur.

Sheep RBCs and antibodies against sheep RBCs are added.



4 Sheep RBCs and antibodies to sheep RBCs are added to both samples.



5 In patient A, complement is already fixed and cannot lyse RBCs. The antibodies bind to RBCs and settle to the bottom. In patient B, antibodies bind to RBCs and complement lyses the RBCs. Serum

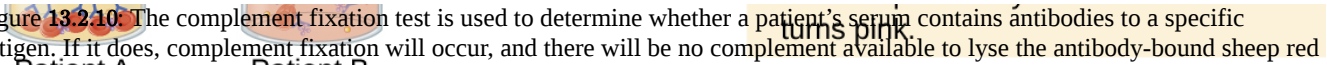


Figure **13.2.10**: The complement fixation test is used to determine whether a patient's serum contains antibodies to a specific antigen. If it does, complement fixation will occur, and there will be no complement available to lyse the antibody-bound sheep red blood cells that are added to the solution in the next step. If the sample does not contain antibodies to the antigen, hemolysis of the sheep blood cells will be observed.

Link to Learning

View this video to see an outline of the steps of the complement fixation test.

Exercise 13.2.6

In a complement fixation test, if the serum turns pink, does the patient have antibodies to the antigen or not? Explain.

Table **13.2.1** summarizes the various types of antibody-antigen assays discussed in this section.

Table **13.2.1**: Mechanisms of Select Antibody-Antigen Assays

Type of Assay	Mechanism	Examples
Precipitation	Antibody binds to soluble antigen, forming a visible precipitin	Precipitin ring test to visualize lattice formation in solution
		Immunoelectrophoresis to examine distribution of antigens following electrophoresis
		Ouchterlony assay to compare diverse antigens
		Radial immunodiffusion assay to quantify antigens
Flocculation	Antibody binds to insoluble molecules in suspension, forming visible aggregates	VDRL test for syphilis
Neutralization	Antibody binds to virus, blocking viral entry into target cells and preventing formation of plaques	Plaque reduction assay for detecting presence of neutralizing antibodies in patient sera
Complement activation	Antibody binds to antigen, inducing complement activation and leaving no complement to lyse red blood cells	Complement fixation test for patient antibodies against hard-to-culture bacteria such as *Chlamydia*

Key Concepts and Summary

- When present in the correct ratio, antibody and antigen will form a **precipitin**, or lattice that precipitates out of solution.
- A **precipitin ring test** can be used to visualize lattice formation in solution. The **Ouchterlony assay** demonstrates lattice formation in a gel. The **radial immunodiffusion** assay is used to quantify antigen by measuring the size of a precipitation zone in a gel infused with antibodies.
- Insoluble antigens in suspension will form **flocculants** when bound by antibodies. This is the basis of the VDRL test for syphilis in which anti-treponemal antibodies bind to cardiolipin in suspension.
- Viral infections can be detected by quantifying virus-neutralizing antibodies in a patient's serum.
- Different antibody classes in plasma or serum are identified by using **immunoelectrophoresis**.
- The presence of specific antigens (e.g., bacterial or viral proteins) in serum can be demonstrated by **western blot** assays, in which the proteins are transferred to a nitrocellulose membrane and identified using labeled antibodies.
- In the complement fixation test, complement is used to detect antibodies against various pathogens.

Footnotes

1. 1 Ouchterlony, Örjan, “In Vitro Method for Testing the Toxin-Producing Capacity of Diphtheria Bacteria,” *Acta Pathologica Microbiologica Scandinavica* 26, no. 4 (1949): 516-24.
2. 2 Tiselius, Arne, “Electrophoresis of Serum Globulin: Electrophoretic Analysis of Normal and Immune Sera,” *Biochemical Journal* 31, no. 9 (1937): 1464.
3. 3 Tiselius, Arne and Elvin A. Kabat. “An Electrophoretic Study of Immune Sera and Purified Antibody Preparations,” *The Journal of Experimental Medicine* 69, no. 1 (1939): 119-31.

This page titled 13.2: Detecting Antigen-Antibody Complexes in vitro is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **20.2: Detecting Antigen-Antibody Complexes in vitro** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

13.3: Agglutination Assays

Learning Objectives

- Compare direct and indirect agglutination
- Identify various uses of hemagglutination in the diagnosis of disease
- Explain how blood types are determined
- Explain the steps used to cross-match blood to be used in a transfusion

In addition to causing precipitation of soluble molecules and flocculation of molecules in suspension, antibodies can also clump together cells or particles (e.g., antigen-coated latex beads) in a process called agglutination (Figure 18.1.8). Agglutination can be used as an indicator of the presence of antibodies against bacteria or red blood cells. Agglutination assays are usually quick and easy to perform on a glass slide or microtiter plate (Figure **13.3.1**). Microtiter plates have an array of wells to hold small volumes of reagents and to observe reactions (e.g., agglutination) either visually or using a specially designed spectrophotometer. The wells come in many different sizes for assays involving different volumes of reagents.

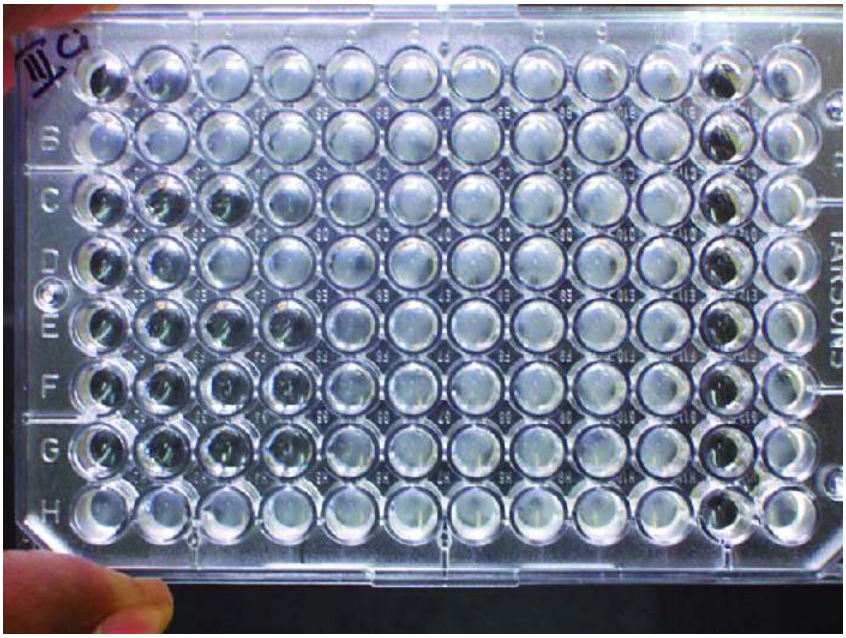


Figure **13.3.1**: Microtiter plates are used for conducting numerous reactions simultaneously in an array of wells. (credit: modification of work by “Microrao”/Wikimedia)

Agglutination of Bacteria and Viruses

The use of agglutination tests to identify streptococcal bacteria was developed in the 1920s by Rebecca Lancefieldworking with her colleagues A.R. Dochez and Oswald Avery.[1] She used antibodies to identify M protein, a virulence factor on streptococci that is necessary for the bacteria’s ability to cause strep throat. Production of antibodies against M protein is crucial in mounting a protective response against the bacteria.

Lancefield used antisera to show that different strains of the same species of streptococci express different versions of M protein, which explains why children can come down with strep throat repeatedly. Lancefield classified beta-hemolytic streptococci into many groups based on antigenic differences in group-specific polysaccharides located in the bacterial cell wall. The strains are called serovars because they are differentiated using antisera. Identifying the serovars present in a disease outbreak is important because some serovars may cause more severe disease than others.

The method developed by Lancefield is a direct agglutination assay, since the bacterial cells themselves agglutinate. A similar strategy is more commonly used today when identifying serovars of bacteria and viruses; however, to improve visualization of the agglutination, the antibodies may be attached to inert latex beads. This technique is called an indirect agglutination assay (or latex

fixation assay), because the agglutination of the beads is a marker for antibody binding to some other antigen (Figure **13.3.2**). Indirect assays can be used to detect the presence of either antibodies or specific antigens.

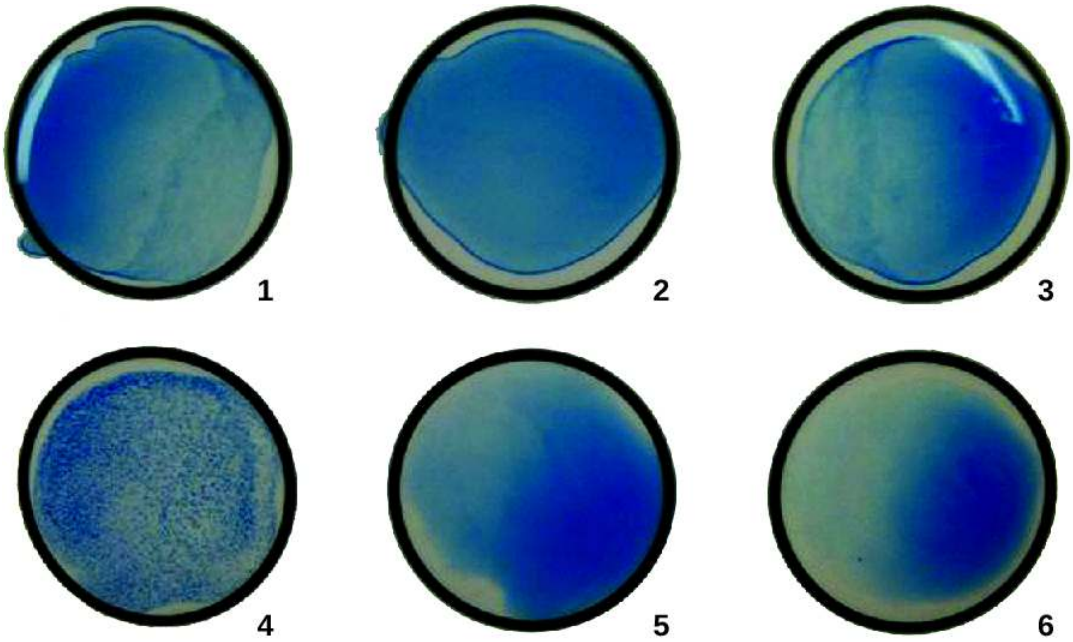


Figure **13.3.2**: Antibodies against six different serovars of Group A strep were attached to latex beads. Each of the six antibody preparations was mixed with bacteria isolated from a patient. The tiny clumps seen in well 4 are indicative of agglutination, which is absent from all other wells. This indicates that the serovar associated with well 4 is present in the patient sample. (credit: modification of work by American Society for Microbiology)

To identify antibodies in a patient's serum, the antigen of interest is attached to latex beads. When mixed with patient serum, the antibodies will bind the antigen, cross-linking the latex beads and causing the beads to agglutinate indirectly; this indicates the presence of the antibody (Figure **13.3.3**). This technique is most often used when looking for IgM antibodies, because their structure provides maximum cross-linking. One widely used example of this assay is a test for rheumatoid factor (RF) to confirm a diagnosis of rheumatoid arthritis. RF is, in fact, the presence of IgM antibodies that bind to the patient's own IgG. RF will agglutinate IgG-coated latex beads.

In the reverse test, soluble antigens can be detected in a patient's serum by attaching specific antibodies (commonly mAbs) to the latex beads and mixing this complex with the serum (Figure **13.3.3**).

Agglutination tests are widely used in underdeveloped countries that may lack appropriate facilities for culturing bacteria. For example, the Widal test, used for the diagnosis of typhoid fever, looks for agglutination of *Salmonella enterica* subspecies *typhi* in patient sera. The Widal test is rapid, inexpensive, and useful for monitoring the extent of an outbreak; however, it is not as accurate as tests that involve culturing of the bacteria. The Widal test frequently produces false positives in patients with previous infections with other subspecies of *Salmonella*, as well as false negatives in patients with hyperproteinemia or immune deficiencies.

In addition, agglutination tests are limited by the fact that patients generally do not produce detectable levels of antibody during the first week (or longer) of an infection. A patient is said to have undergone seroconversion when antibody levels reach the threshold for detection. Typically, seroconversion coincides with the onset of signs and symptoms of disease. However, in an HIV infection, for example, it generally takes 3 weeks for seroconversion to take place, and in some instances, it may take much longer.

Similar to techniques for the precipitin ring test and plaque assays, it is routine to prepare serial two-fold dilutions of the patient's serum and determine the titer of agglutinating antibody present. Since antibody levels change over time in both primary and secondary immune responses, by checking samples over time, changes in antibody titer can be detected. For example, a comparison of the titer during the acute phase of an infection versus the titer from the convalescent phase will distinguish whether an infection

is current or has occurred in the past. It is also possible to monitor how well the patient's immune system is responding to the pathogen.

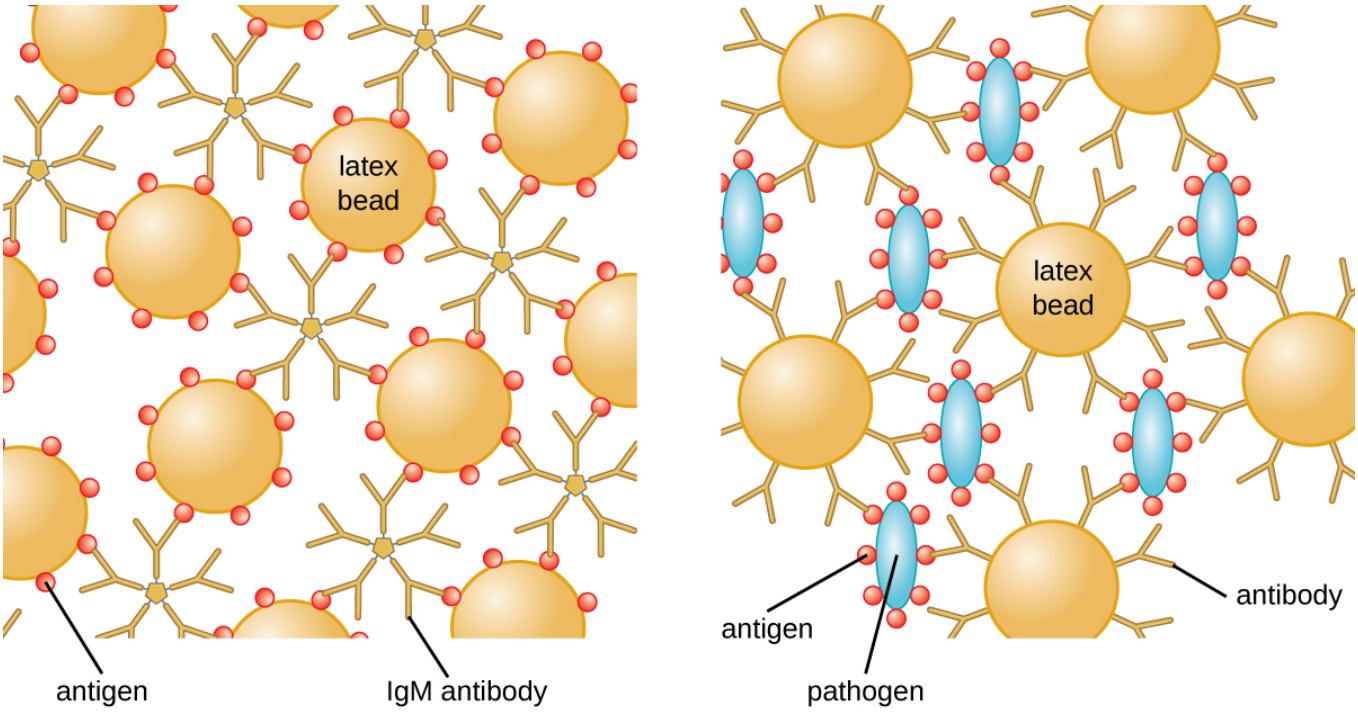


Figure **13.3.3**: (a) Latex beads coated with an antigen will agglutinate when mixed with patient serum if the serum contains IgM antibodies against the antigen. (b) Latex beads coated with antibodies will agglutinate when mixed with patient serum if the serum contains antigens specific to the antibodies.

Link to Learning

Watch this video that demonstrates agglutination reactions with latex beads.

Exercise 13.3.1

1. How is agglutination used to distinguish serovars from each other?
2. In a latex bead assay to test for antibodies in a patient's serum, with what are the beads coated?
3. What has happened when a patient has undergone seroconversion?

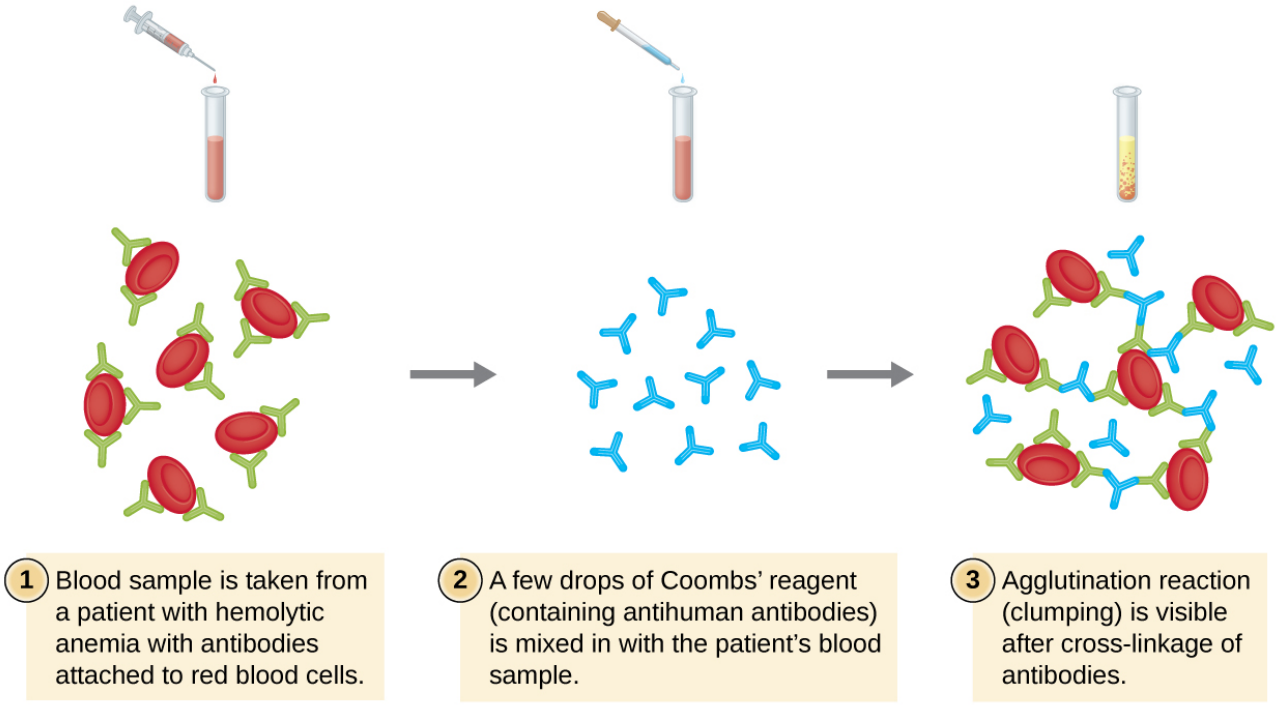
Hemagglutination

Agglutination of red blood cells is called hemagglutination. One common assay that uses hemagglutination is the direct Coombs' test, also called the direct antihuman globulin test (DAT), which generally looks for nonagglutinating antibodies. The test can also detect complement attached to red blood cells.

The Coombs' test is often employed when a newborn has jaundice, yellowing of the skin caused by high blood concentrations of bilirubin, a product of the breakdown of hemoglobin in the blood. The Coombs' test is used to determine whether the child's red blood cells have been bound by the mother's antibodies. These antibodies would activate complement, leading to red blood cell lysis and the subsequent jaundice. Other conditions that can cause positive direct Coombs' tests include hemolytic transfusion reactions, autoimmune hemolytic anemia, infectious mononucleosis (caused by Epstein-Barr virus), syphilis, and *Mycoplasma* pneumonia. A positive direct Coombs' test may also be seen in some cancers and as an allergic reaction to some drugs (e.g., penicillin).

The antibodies bound to red blood cells in these conditions are most often IgG, and because of the orientation of the antigen-binding sites on IgG and the comparatively large size of a red blood cell, it is unlikely that any visible agglutination will occur. However, the presence of IgG bound to red blood cells can be detected by adding Coombs' reagent, an antiserum containing antihuman IgG antibodies (that may be combined with anti-complement) (Figure **13.3.4**). The Coombs' reagent links the IgG attached to neighboring red blood cells and thus promotes agglutination.

There is also an indirect Coombs' test known as the indirect antiglobulin test (IAT). This screens an individual for antibodies against red blood cell antigens (other than the A and B antigens) that are unbound in a patient's serum (Figure **13.3.4**). IAT can be used to screen pregnant women for antibodies that may cause hemolytic disease of the newborn. It can also be used prior to giving blood transfusions. More detail on how the IAT is performed is discussed below.



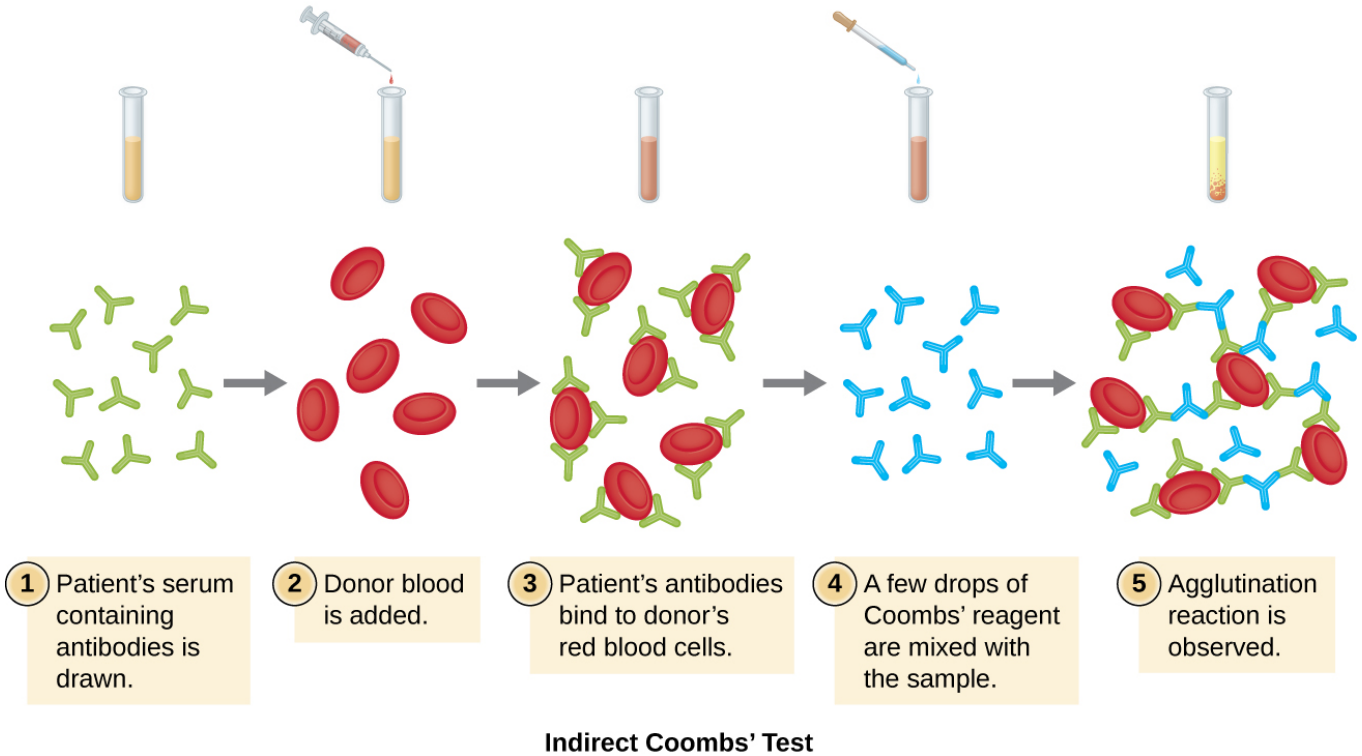


Figure **13.3.4**: The steps in direct and indirect Coombs' tests are shown in the illustration.

Antibodies that bind to red blood cells are not the only cause of hemagglutination. Some viruses also bind to red blood cells, and this binding can cause agglutination when the viruses cross-link the red blood cells. For example, influenza viruses have two different types of viral spikes called neuraminidase (N) and hemagglutinin (H), the latter named for its ability to agglutinate red blood cells (see Viruses). Thus, we can use red blood cells to detect the presence of influenza virus by direct hemagglutination

assays (HA), in which the virus causes visible agglutination of red blood cells. The mumps and rubella viruses can also be detected using HA.

Most frequently, a serial dilution viral agglutination assay is used to measure the titer or estimate the amount of virus produced in cell culture or for vaccine production. A viral titer can be determined using a direct HA by making a serial dilution of the sample containing the virus, starting with a high concentration of sample that is then diluted in a series of wells. The highest dilution producing visible agglutination is the titer. The assay is carried out in a microtiter plate with V- or round-bottomed wells. In the presence of agglutinating viruses, the red blood cells and virus clump together and produce a diffuse mat over the bottom of the well. In the absence of virus, the red blood cells roll or sediment to the bottom of the well and form a dense pellet, which is why flat-bottomed wells cannot be used (Figure **13.3.5**).

A modification of the HA assay can be used to determine the titer of antiviral antibodies. The presence of these antibodies in a patient's serum or in a lab-produced antiserum will neutralize the virus and block it from agglutinating the red cells, making this a viral hemagglutination inhibition assay (HIA). In this assay, patient serum is mixed with a standardized amount of virus. After a short incubation, a standardized amount of red blood cells is added and hemagglutination is observed. The titer of the patient's serum is the highest dilution that blocks agglutination (Figure **13.3.6**).

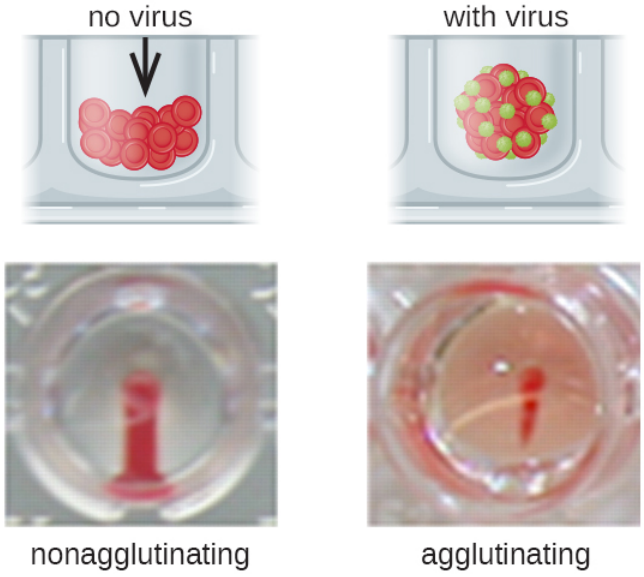
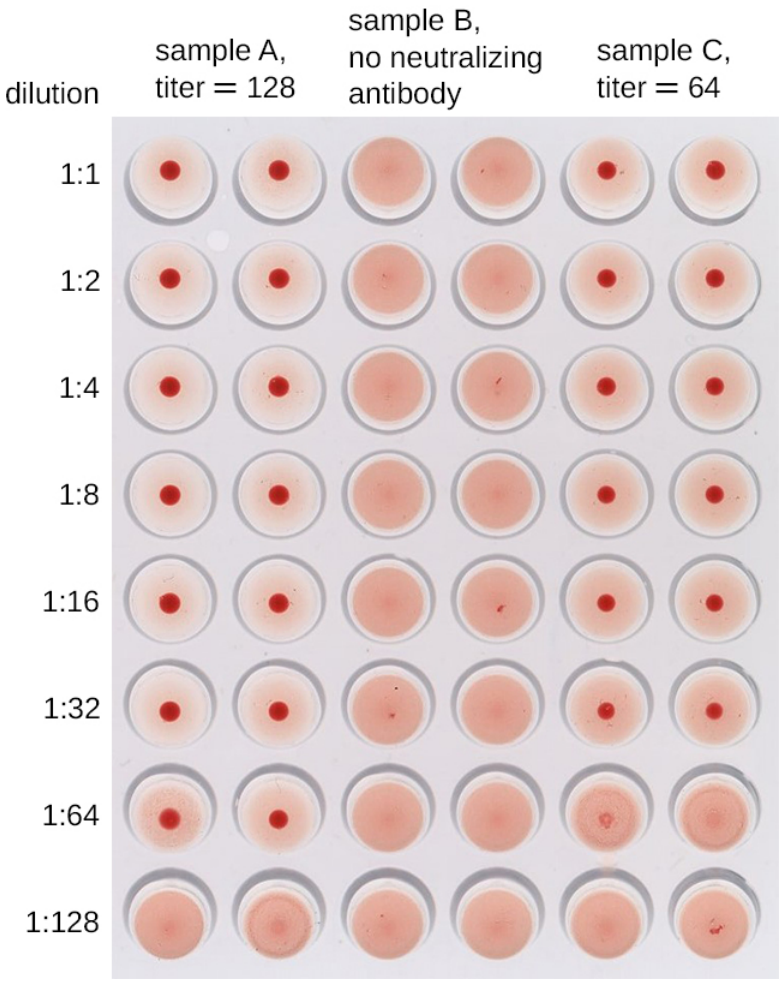


Figure **13.3.5**: A viral suspension is mixed with a standardized amount of red blood cells. No agglutination of red blood cells is visible when the virus is absent, and the cells form a compact pellet at the bottom of the well. In the presence of virus, a diffuse pink precipitate forms in the well. (credit bottom: modification of



work by American Society for Microbiology) Figure **13.3.6**: In this HIA, serum containing antibodies to influenzavirus underwent serial two-fold dilutions in a microtiter plate. Red blood cells were then added to the wells. Agglutination only occurred in those wells where the antibodies were too dilute to neutralize the virus. The highest concentration at which agglutination occurs is the titer of the antibodies in the patient's serum. In the case of this test, Sample A shows a titer of 128, and Sample C shows a titer of 64. (credit: modification of work by Evan Burkala)

? Exercise 13.3.2

1. What is the mechanism by which viruses are detected in a hemagglutination assay?
2. Which hemagglutination result tells us the titer of virus in a sample?

Animals in the Laboratory

Much of what we know today about the human immune system has been learned through research conducted using animals—primarily, mammals—as models. Besides research, mammals are also used for the production of most of the antibodies and other immune system components needed for immunodiagnostics. Vaccines, diagnostics, therapies, and translational medicine in general have all been developed through research with animal models.

Consider some of the common uses of laboratory animals for producing immune system components. Guinea pigs are used as a source of complement, and mice are the primary source of cells for making mAbs. These mAbs can be used in research and for therapeutic purposes. Antisera are raised in a variety of species, including horses, sheep, goats, and rabbits. When producing an antiserum, the animal will usually be injected at least twice, and adjuvants may be used to boost the antibody response. The larger animals used for making antisera will have blood harvested repeatedly over long periods of time, with little harm to the animals, but that is not usually the case for rabbits. Although we can obtain a few milliliters of blood from the ear veins of rabbits, we usually need larger volumes, which results in the deaths of the animals.

We also use animals for the study of disease. The only way to grow *Treponema pallidum* for the study of syphilis is in living animals. Many viruses can be grown in cell culture, but growth in cell culture tells us very little about how the immune system will respond to the virus. When working on a newly discovered disease, we still employ Koch's postulates, which require causing disease in lab animals using pathogens from pure culture as a crucial step in proving that a particular microorganism is the cause of a disease. Studying the proliferation of bacteria and viruses in animal hosts, and how the host immune system responds, has been central to microbiological research for well over 100 years.

While the practice of using laboratory animals is essential to scientific research and medical diagnostics, many people strongly object to the exploitation of animals for human benefit. This ethical argument is not a new one—indeed, one of Charles Darwin's daughters was an active antivivisectionist (vivisection is the practice of cutting or dissecting a live animal to study it). Most scientists acknowledge that there should be limits on the extent to which animals can be exploited for research purposes. Ethical considerations have led the National Institutes of Health (NIH) to develop strict regulations on the types of research that may be performed. These regulations also include guidelines for the humane treatment of lab animals, setting standards for their housing, care, and euthanization. The NIH document "Guide for the Care and Use of Laboratory Animals" makes it clear that the use of animals in research is a privilege granted by society to researchers.

The NIH guidelines are based on the principle of the three R's: replace, refine, and reduce. Researchers should strive to *replace* animal models with nonliving models, *replace* vertebrates with invertebrates whenever possible, or use computer-models when applicable. They should *refine* husbandry and experimental procedures to reduce pain and suffering, and use experimental designs and procedures that *reduce* the number of animals needed to obtain the desired information. To obtain funding, researchers must satisfy NIH reviewers that the research justifies the use of animals and that their use is in accordance with the guidelines.

At the local level, any facility that uses animals and receives federal funding must have an Institutional Animal Care and Use Committee (IACUC) that ensures that the NIH guidelines are being followed. The IACUC must include researchers, administrators, a veterinarian, and at least one person with no ties to the institution, that is, a concerned citizen. This committee also performs inspections of laboratories and protocols. For research involving human subjects, an Institutional Review Board (IRB) ensures that proper guidelines are followed.

Link to Learning

Visit this site to view the NIH Guide for the Care and Use of Laboratory Animals.

Blood Typing and Cross-Matching

In addition to antibodies against bacteria and viruses to which they have previously been exposed, most individuals also carry antibodies against blood types other than their own. There are presently 33 immunologically important blood-type systems, many of which are restricted within various ethnic groups or rarely result in the production of antibodies. The most important and perhaps best known are the ABO and Rh blood groups (see Figure 19.1.3).

When units of blood are being considered for transfusion, pretransfusion blood testing must be performed. For the blood unit, commercially prepared antibodies against the A, B, and Rh antigens are mixed with red blood cells from the units to initially confirm that the blood type on the unit is accurate. Once a unit of blood has been requested for transfusion, it is vitally important to make sure the donor (unit of blood) and recipient (patient) are compatible for these crucial antigens. In addition to confirming the blood type of the unit, the patient's blood type is also confirmed using the same commercially prepared antibodies to A, B, and Rh. For example, as shown in Figure **13.3.7**, if the donor blood is A-positive, it will agglutinate with the anti-A antiserum and with the anti-Rh antiserum. If no agglutination is observed with any of the sera, then the blood type would be O-negative.

Following determination of the blood type, immediately prior to releasing the blood for transfusion, a cross-match is performed in which a small aliquot of the donor red blood cells are mixed with serum from the patient awaiting transfusion. If the patient does have antibodies against the donor red blood cells, hemagglutination will occur. To confirm any negative test results and check for sensitized red blood cells, Coombs' reagent may be added to the mix to facilitate visualization of the antibody-red blood cell interaction.

Under some circumstances, a minor cross-match may be performed as well. In this assay, a small aliquot of donor serum is mixed with patient red blood cells. This allows the detection of agglutinizing antibodies in the donor serum. This test is rarely necessary because transfusions generally use packed red blood cells with most of the plasma removed by centrifugation.

Red blood cells have many other antigens in addition to ABO and Rh. While most people are unlikely to have antibodies against these antigens, women who have had multiple pregnancies or patients who have had multiple transfusions may have them because of repeated exposure. For this reason, an antibody screen test is used to determine if such antibodies are present. Patient serum is checked against commercially prepared, pooled, type O red blood cells that express these antigens. If agglutination occurs, the antigen to which the patient is responding must be identified and determined not to be present in the donor unit.

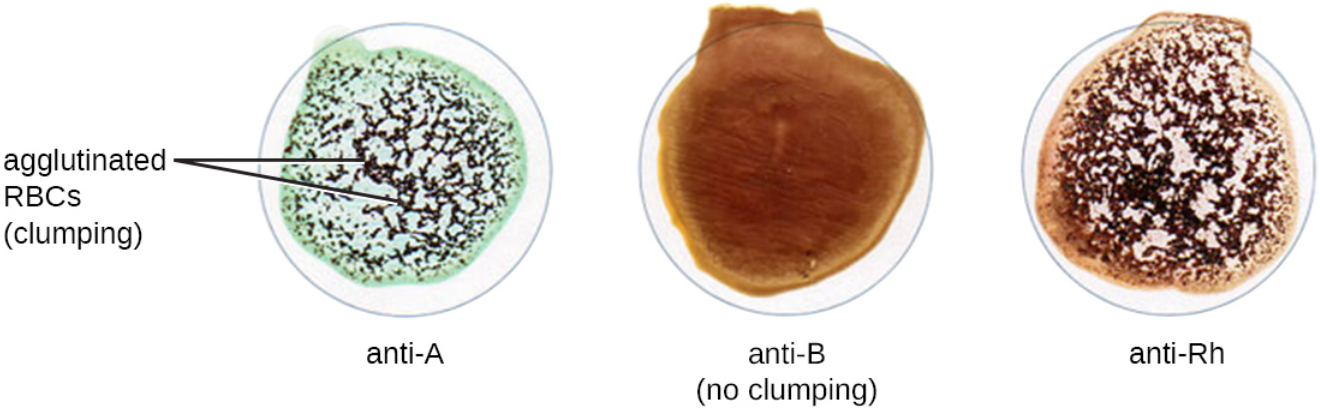


Figure **13.3.7**: This sample of a commercially produced “bedside” card enables quick typing of both a recipient’s and donor’s blood before transfusion. The card contains three reaction sites or wells. One is coated with an anti-A antibody, one with an anti-B antibody, and one with an anti-Rh antibody. Agglutination of red blood cells in a given site indicates a positive identification of the blood antigens: in this case, A and Rh antigens for blood type A-positive.

? Exercise 13.3.3

1. If a patient's blood agglutinates with anti-B serum, what is the patient’s blood type?
2. What is a cross-match assay, and why is it performed?

Table **13.3.1** summarizes the various kinds of agglutination assays discussed in this section.

Table **13.3.1**: Mechanisms of Select Antibody-Antigen Assays

Type of Assay	Mechanism	Example
Agglutination	Direct: Antibody is used to clump bacterial cells or other large structures	Serotyping bacteria
	Indirect: Latex beads are coupled with antigen or antibody to look for antibody or antigen, respectively, in patient serum	Confirming the presence of rheumatoid factor (IgM-binding Ig) in patient serum
Hemagglutination	Direct: Some bacteria and viruses cross-link red blood cells and clump them together	Diagnosing influenza, mumps, and measles
	Direct Coombs' test (DAT): Detects nonagglutinating antibodies or complement proteins on red blood cells *in vivo*	Checking for maternal antibodies binding to neonatal red blood cells
	Indirect Coombs' test (IAT): Screens an individual for antibodies against red blood cell antigens (other than the A and B antigens) that are unbound in a patient's serum *in vitro*	Performing pretransfusion blood testing
	Viral hemagglutination inhibition: Uses antibodies from a patient to inhibit viral agglutination	Diagnosing various viral diseases by the presence of patient antibodies against the virus
	Blood typing and cross-matching: Detects ABO, Rh, and minor antigens in the blood	Matches donor blood to recipient immune requirements

Key Concepts and Summary

- Antibodies can agglutinate cells or large particles into a visible matrix. **Agglutination** tests are often done on cards or in **microtiter plates** that allow multiple reactions to take place side by side using small volumes of reagents.
- Using antisera against certain proteins allows identification of **serovars** within species of bacteria.
- Detecting antibodies against a pathogen can be a powerful tool for diagnosing disease, but there is a period of time before patients go through **seroconversion** and the level of antibodies becomes detectable.
- Agglutination of latex beads in **indirect agglutination assays** can be used to detect the presence of specific antigens or specific antibodies in patient serum.
- The presence of some antibacterial and antiviral antibodies can be confirmed by the use of the direct **Coombs' test**, which uses Coombs' reagent to cross-link antibodies bound to red blood cells and facilitate **hemagglutination**.
- Some viruses and bacteria will bind and agglutinate red blood cells; this interaction is the basis of the **direct hemagglutination assay**, most often used to determine the titer of virus in solution.
- **Neutralization assays** quantify the level of virus-specific antibody by measuring the decrease in hemagglutination observed after mixing patient serum with a standardized amount of virus.
- Hemagglutination assays are also used to screen and **cross-match** donor and recipient blood to ensure that the transfusion recipient does not have antibodies to antigens in the donated blood.

Footnotes

1. 1 Lancefield, Rebecca C., "The Antigenic Complex of *Streptococcus haemoliticus*. I. Demonstration of a Type-Specific Substance in Extracts of *Streptococcus haemolyticus*," *The Journal of Experimental Medicine* 47, no. 1 (1928): 91-103.

This page titled 13.3: Agglutination Assays is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **20.3: Agglutination Assays** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

13.4: Enzyme Immunoassays (EIA) and Enzyme-Linked Immunosorbent Assays (ELISA)

Learning Objectives

- Explain the differences and similarities between EIA, FEIA, and ELISA
- Describe the difference and similarities between immunohistochemistry and immunocytochemistry
- Describe the different purposes of direct and indirect ELISA

Similar to the western blot, enzyme immunoassays (EIAs) use antibodies to detect the presence of antigens. However, EIAs differ from western blots in that the assays are conducted in microtiter plates or *in vivo* rather than on an absorbent membrane. There are many different types of EIAs, but they all involve an antibody molecule whose constant region binds an enzyme, leaving the variable region free to bind its specific antigen. The addition of a substrate for the enzyme allows the antigen to be visualized or quantified (Figure **13.4.1**).

In EIAs, the substrate for the enzyme is most often a chromogen, a colorless molecule that is converted into a colored end product. The most widely used enzymes are alkaline phosphatase and horseradish peroxidase for which appropriate substrates are readily available. In some EIAs, the substrate is a fluorogen, a nonfluorescent molecule that the enzyme converts into a fluorescent form. EIAs that utilize a fluorogen are called fluorescent enzyme immunoassays (FEIAs). Fluorescence can be detected by either a fluorescence microscope or a spectrophotometer.

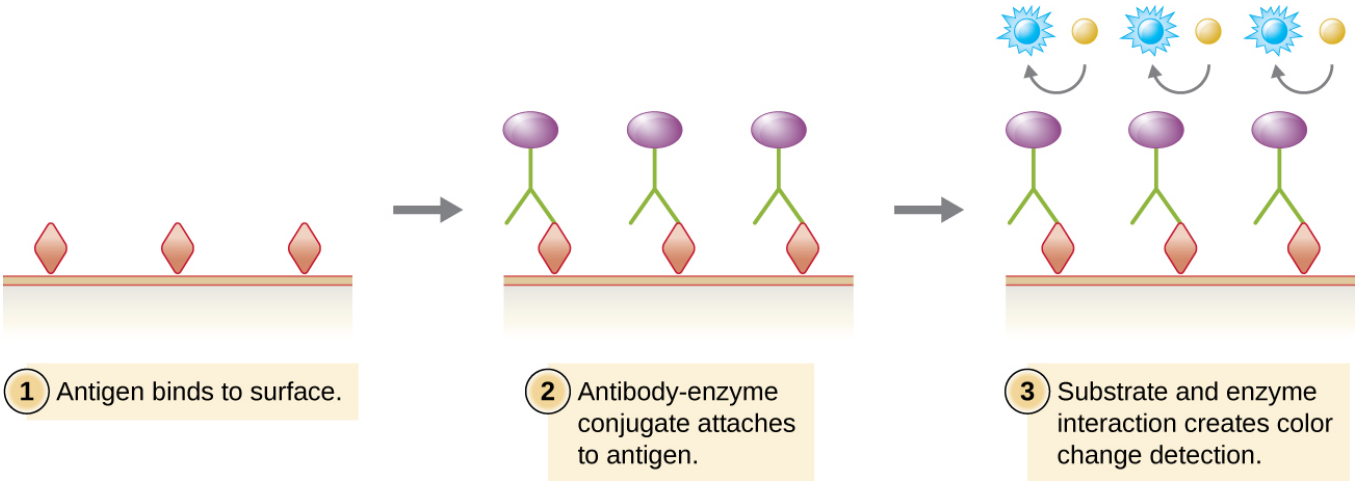


Figure **13.4.1**: Enzyme immunoassays, such as the direct ELISA shown here, use an enzyme-antibody conjugate to deliver a detectable substrate to the site of an antigen. The substrate may be a colorless molecule that is converted into a colored end product or an inactive fluorescent molecule that fluoresces after enzyme activation. (credit: modification of work by "Cavitri"/Wikimedia Commons)

The MMR Titer

The MMR vaccine is a combination vaccine that provides protection against measles, mumps, and rubella (German measles). Most people receive the MMR vaccine as children and thus have antibodies against these diseases. However, for various reasons, even vaccinated individuals may become susceptible to these diseases again later in life. For example, some children may receive only one round of the MMR vaccine instead of the recommended two. In addition, the titer of protective antibodies in an individual's body may begin to decline with age or as the result of some medical conditions.

To determine whether the titer of antibody in an individual's bloodstream is sufficient to provide protection, an MMR titer test can be performed. The test is a simple immunoassay that can be done quickly with a blood sample. The results of the test will indicate whether the individual still has immunity or needs another dose of the MMR vaccine.

Submitting to an MMR titer is often a pre-employment requirement for healthcare workers, especially those who will frequently be in contact with young children or immunocompromised patients. Were a healthcare worker to become infected

with measles, mumps, or rubella, the individual could easily pass these diseases on to susceptible patients, leading to an outbreak. Depending on the results of the MMR titer, healthcare workers might need to be revaccinated prior to beginning work.

Immunostaining

One powerful use of EIA is immunostaining, in which antibody-enzyme conjugates enhance microscopy. Immunohistochemistry (IHC) is used for examining whole tissues. As seen in Figure **13.4.2**, a section of tissue can be stained to visualize the various cell types. In this example, a mAb against CD8 was used to stain CD8 cells in a section of tonsil tissue. It is now possible to count the number of CD8 cells, determine their relative numbers versus the other cell types present, and determine the location of these cells within this tissue. Such data would be useful for studying diseases such as AIDS, in which the normal function of CD8 cells is crucial for slowing disease progression.

Immunocytochemistry (ICC) is another valuable form of immunostaining. While similar to IHC, in ICC, extracellular matrix material is stripped away, and the cell membrane is etched with alcohol to make it permeable to antibodies. This allows antibodies to pass through the cell membrane and bind to specific targets inside the cell. Organelles, cytoskeletal components, and other intracellular structures can be visualized in this way. While some ICC techniques use EIA, the enzyme can be replaced with a fluorescent molecule, making it a fluorescent immunoassay.

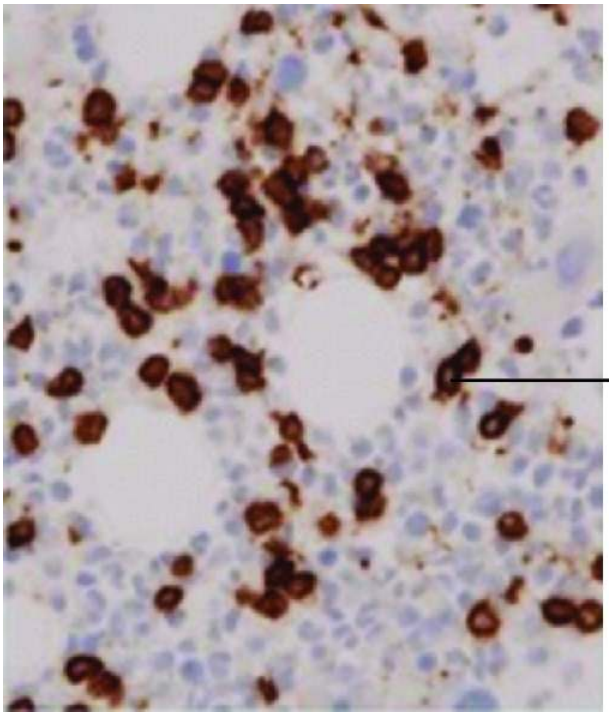


Figure **13.4.2**: Enzyme-linked antibodies against CD8 were used to stain the CD8 cells in this preparation of bone marrow using a chromogen. (credit: modification of work by Yamashita M, Fujii Y, Ozaki K, Urano Y, Iwasa M, Nakamura S, Fujii S, Abe M, Sato Y, Yoshino T)

? Exercise 13.4.1

1. What is the difference between immunohistochemistry and immunocytochemistry?
2. What must be true of the product of the enzymatic reaction used in immunohistochemistry?

Enzyme-linked Immunosorbent Assays (ELISAs)

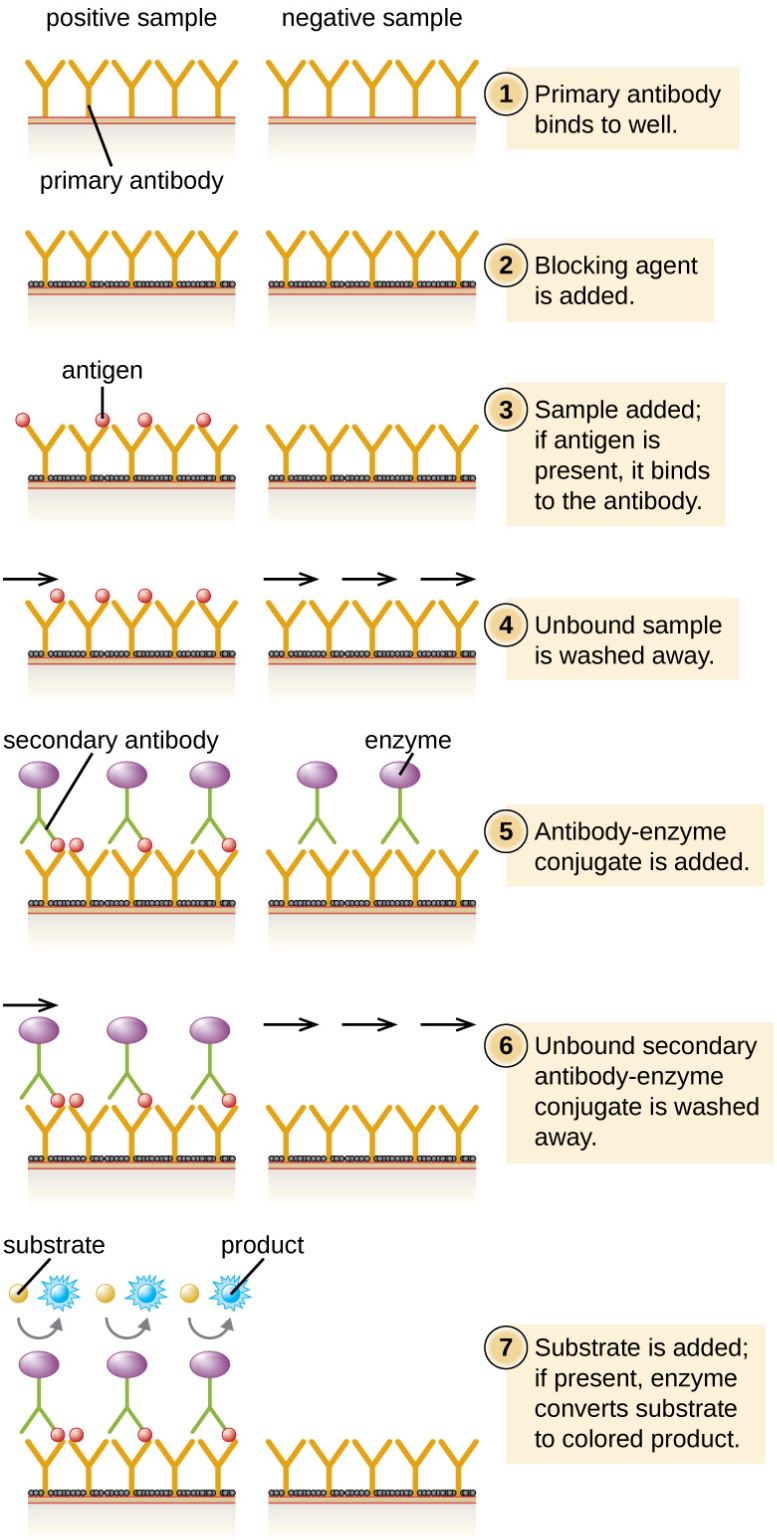
The enzyme-linked immunosorbent assays (ELISAs) are widely used EIAs. In the direct ELISA, antigens are immobilized in the well of a microtiter plate. An antibody that is specific for a particular antigen and is conjugated to an enzyme is added to each well. If the antigen is present, then the antibody will bind. After washing to remove any unbound antibodies, a colorless substrate (chromogen) is added. The presence of the enzyme converts the substrate into a colored end product (Figure **13.4.1**). While this

technique is faster because it only requires the use of one antibody, it has the disadvantage that the signal from a direct ELISA is lower (lower sensitivity).

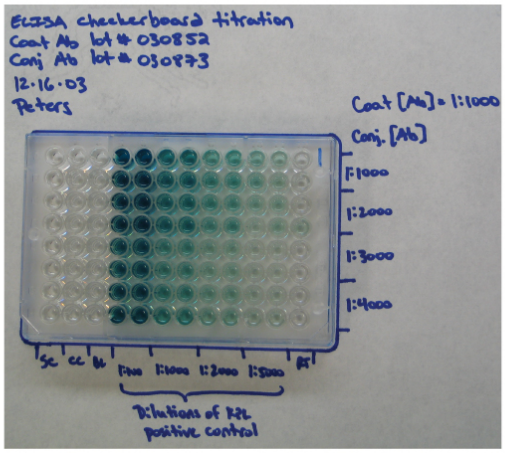
In a sandwich ELISA, the goal is to use antibodies to precisely quantify specific antigen present in a solution, such as antigen from a pathogen, a serum protein, or a hormone from the blood or urine to list just a few examples. The first step of a sandwich ELISA is to add the primary antibody to all the wells of a microtiter plate (Figure **13.4.3**). The antibody sticks to the plastic by hydrophobic interactions. After an appropriate incubation time, any unbound antibody is washed away. Comparable washes are used between each of the subsequent steps to ensure that only specifically bound molecules remain attached to the plate. A blocking protein is then added (e.g., albumin or the milk protein casein) to bind the remaining nonspecific protein-binding sites in the well. Some of the wells will receive known amounts of antigen to allow the construction of a standard curve, and unknown antigen solutions are added to the other wells. The primary antibody captures the antigen and, following a wash, the secondary antibody is added, which is a polyclonal antibody that is conjugated to an enzyme. After a final wash, a colorless substrate (chromogen) is added, and the enzyme converts it into a colored end product. The color intensity of the sample caused by the end product is measured with a spectrophotometer. The amount of color produced (measured as absorbance) is directly proportional to the amount of enzyme, which in turn is directly proportional to the captured antigen. ELISAs are extremely sensitive, allowing antigen to be quantified in the nanogram (10^{-9} g) per mL range.

In an indirect ELISA, we quantify antigen-specific antibody rather than antigen. We can use indirect ELISA to detect antibodies against many types of pathogens, including *Borrelia burgdorferi* (Lyme disease) and HIV. There are three important differences between indirect and direct ELISAs as shown in Figure **13.4.4**. Rather than using antibody to capture antigen, the indirect ELISA starts with attaching known antigen (e.g., peptides from HIV) to the bottom of the microtiter plate wells. After blocking the unbound sites on the plate, patient serum is added; if antibodies are present (primary antibody), they will bind the antigen. After washing away any unbound proteins, the secondary antibody with its conjugated enzyme is directed against the primary antibody (e.g., antihuman immunoglobulin). The secondary antibodyallows us to quantify how much antigen-specific antibody is present in the patient's serum by the intensity of the color produced from the conjugated enzyme-chromogen reaction.

As with several other tests for antibodies discussed in this chapter, there is always concern about cross-reactivity with antibodies directed against some other antigen, which can lead to false-positive results. Thus, we cannot definitively diagnose an HIV infection (or any other type of infection) based on a single indirect ELISA assay. We must confirm any suspected positive test, which is most often done using either an immunoblot that actually identifies the presence of specific peptides from the pathogen or a test to identify the nucleic acids associated with the pathogen, such as reverse transcriptase PCR (RT-PCR) or a nucleic acid antigen test.

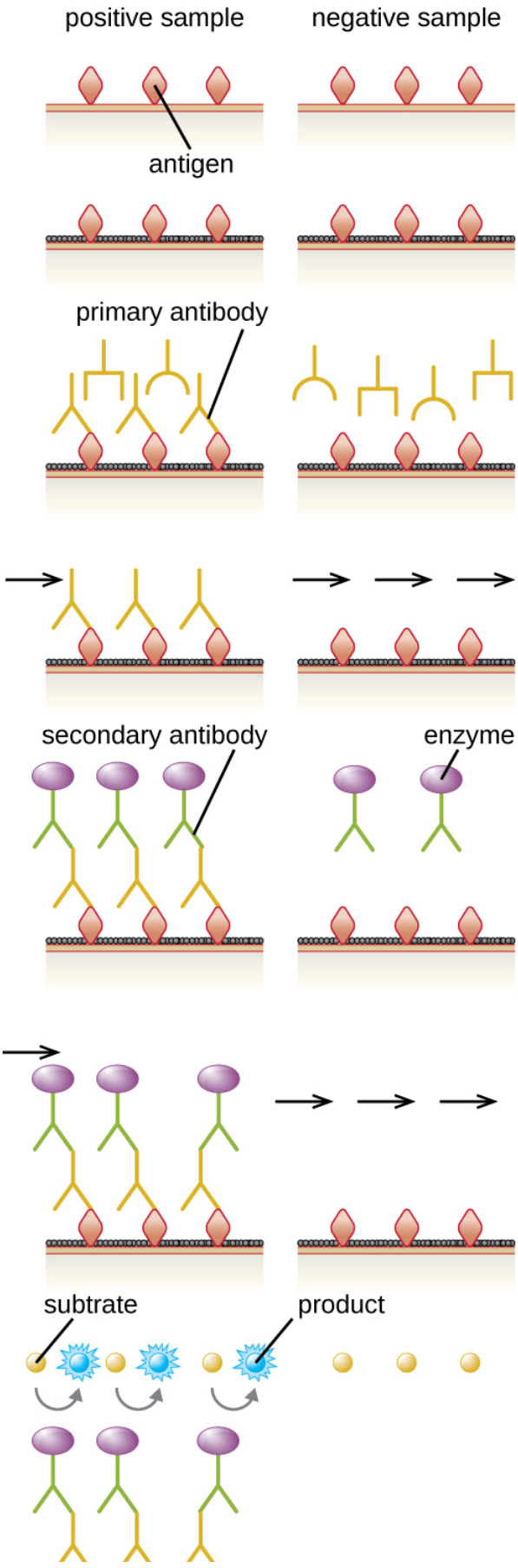


(a)



(b)

Figure 13.4.3: (a) In a sandwich ELISA, a primary antibody is used to first capture an antigen with the primary antibody. A secondary antibody conjugated to an enzyme that also recognizes epitopes on the antigen is added. After the addition of the chromogen, a spectrophotometer measures the absorbance of end product, which is directly proportional to the amount of captured antigen. (b) An ELISA plate shows dilutions of antibodies (left) and antigens (bottom). Higher concentrations result in a darker final color. (credit b: modification of work by U.S. Fish and Wildlife Service Pacific Region)



1. Antigen is bound to well.
2. Blocking agent is added.
3. Sample added; if antibody is present, it binds to the antigen.
4. Unbound sample is washed away.
5. Antihuman enzyme-linked antibody is added.
6. Unbound antihuman antibody is washed away.
7. Substrate is added; if present, enzyme converts substrate to colored product.

used to quantify antigen-specific antibodies in patient serum for disease diagnosis. Antigen from the suspected disease agent is attached to microtiter plates. The primary antibody comes from the patient's serum, which is subsequently bound by the enzyme-conjugated secondary antibody. Measuring the production of end product allows us to detect or quantify the amount of antigen-specific antibody present in the patient's serum.

Figure **13.4.4**: The indirect ELISA is

? Exercise 13.4.2

1. What is the purpose of the secondary antibody in a direct ELISA?
2. What do the direct and indirect ELISAs quantify?

Clinical Focus: Part 2

Although contacting and testing the 1300 patients for HIV would be time consuming and expensive, administrators hoped to minimize the hospital's liability by proactively seeking out and treating potential victims of the rogue employee's crime. Early detection of HIV is important, and prompt treatment can slow the progression of the disease.

There are a variety of screening tests for HIV, but the most widely used is the indirect ELISA. As with other indirect ELISAs, the test works by attaching antigen (in this case, HIV peptides) to a well in a 96-well plate. If the patient is HIV positive, anti-HIV antibodies will bind to the antigen and be identified by the second antibody-enzyme conjugate.

Exercise 13.4.3

1. How accurate is an indirect ELISA test for HIV, and what factors could impact the test's accuracy?
2. Should the hospital use any other tests to confirm the results of the indirect ELISA?

Immunofiltration and Immunochromatographic Assays

For some situations, it may be necessary to detect or quantify antigens or antibodies that are present at very low concentration in solution. Immunofiltration techniques have been developed to make this possible. In immunofiltration, a large volume of fluid is passed through a porous membrane into an absorbent pad. An antigen attached to the porous membrane will capture antibody as it passes; alternatively, we can also attach an antibody to the membrane to capture antigen.

The method of immunofiltration has been adapted in the development of immunochromatographic assays, commonly known as lateral flow tests or strip tests. These tests are quick and easy to perform, making them popular for point-of-care use (i.e., in the doctor's office) or in-home use. One example is the TORCH test that allows doctors to screen pregnant women or newborns for infection by an array of viruses and other pathogens (*Toxoplasma*, other viruses, rubella, cytomegalovirus, herpes simplex). In-home pregnancy tests are another widely used example of a lateral flow test (Figure **13.4.5**). Immunofiltration tests are also popular in developing countries, because they are inexpensive and do not require constant refrigeration of the dried reagents. However, the technology is also built into some sophisticated laboratory equipment.

In lateral flow tests (Figure **13.4.6**), fluids such as urine are applied to an absorbent pad on the test strip. The fluid flows by capillary action and moves through a stripe of beads with antibodies attached to their surfaces. The fluid in the sample actually hydrates the reagents, which are present in a dried state in the stripe. Antibody-coated beads made of latex or tiny gold particles will bind antigens in the test fluid. The antibody-antigen complexes then flow over a second stripe that has immobilized antibody against the antigen; this stripe will retain the beads that have bound antigen. A third control stripe binds any beads. A red color (from gold particles) or blue (from latex beads) developing at the test line indicates a positive test. If the color only develops at the control line, the test is negative.

Like ELISA techniques, lateral flow tests take advantage of antibody sandwiches, providing sensitivity and specificity. While not as quantitative as ELISA, these tests have the advantage of being fast, inexpensive, and not dependent on special equipment. Thus, they can be performed anywhere by anyone. There are some concerns about putting such powerful diagnostic tests into the hands of people who may not understand the tests' limitations, such as the possibility of false-positive results. While home pregnancy tests have become widely accepted, at-home antibody-detection tests for diseases like HIV have raised some concerns in the medical community. Some have questioned whether self-administration of such tests should be allowed in the absence of medical personnel who can explain the test results and order appropriate confirmatory tests. However, with growing numbers of lateral flow

tests becoming available, and the rapid development of lab-on-a-chip technology (Figure 20.1), home medical tests are likely to become even more commonplace in the future.

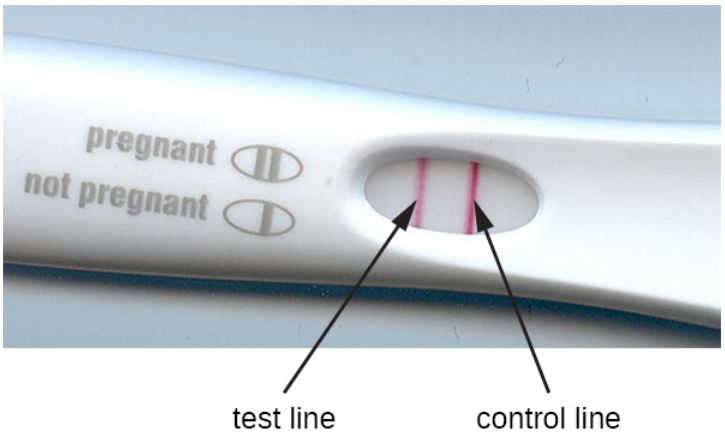


Figure **13.4.5**: A lateral flow test detecting pregnancy-related hormones in urine. The control stripe verifies the validity of the test and the test line determines the presence of pregnancy-related hormones in the urine. (credit: modification of work by Klaus Hoffmeier)

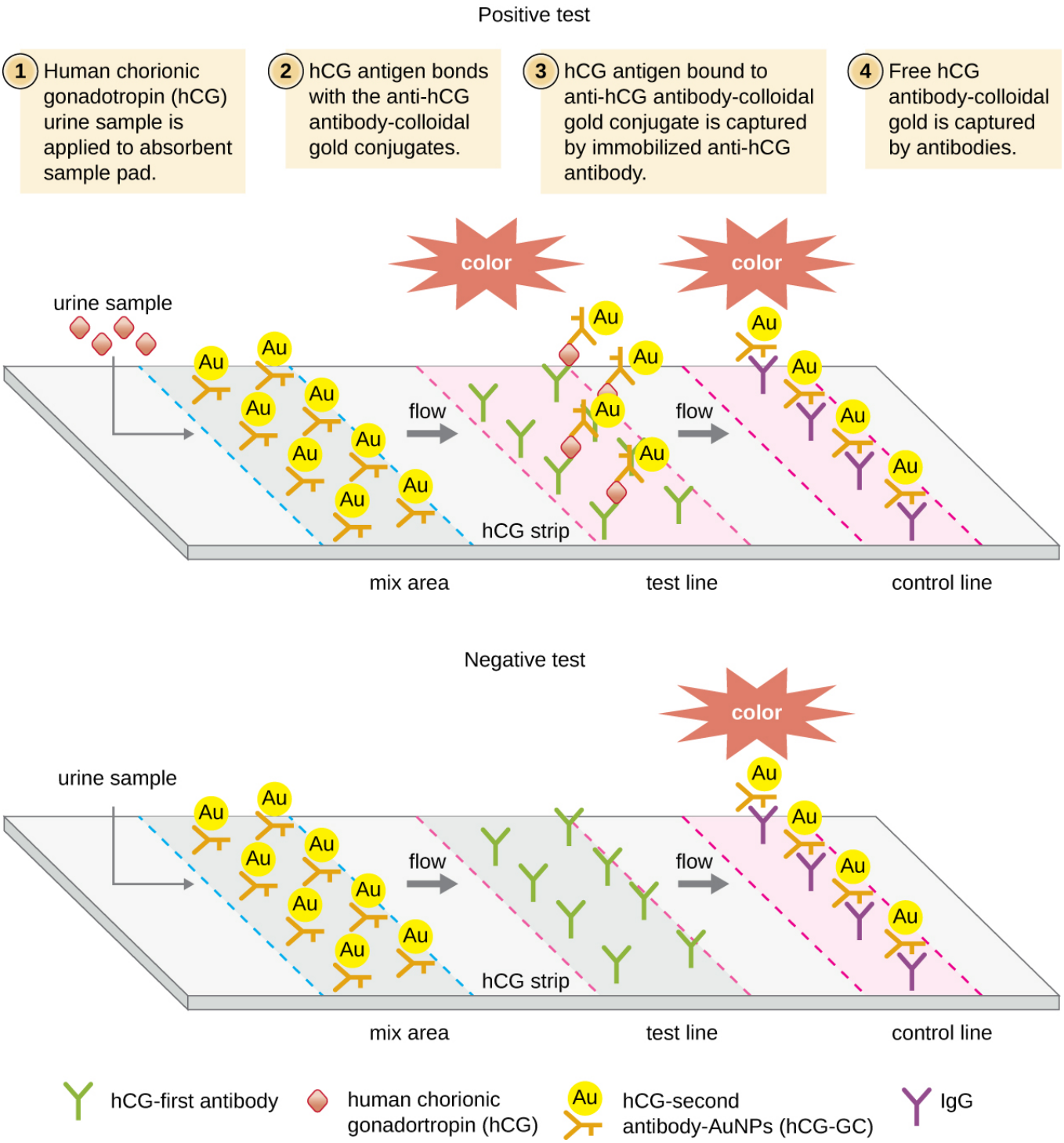


Figure 13.4.6: Immunochromatographic assays, or lateral flow tests, allow the testing of antigen in a dilute solution. As the fluid flows through the test strip, it rehydrates the reagents. Antibodies conjugated to small particles bind the antigen in the first stripe and then flow onto the second stripe where they are bound by a second, fixed antibody. This produces a line of color, depending on the color of the beads. The third, control stripe binds beads as well to indicate that the test is working properly. (credit: modification of work by Yeh CH, Zhao ZQ, Shen PL, Lin YC)

? Exercise 13.4.4

1. What physical process does the lateral flow method require to function?
2. Explain the purpose of the third strip in a lateral flow assay.

Table 13.4.1 compares some of the key mechanisms and examples of some of the EIAs discussed in this section as well as immunoblots, which were discussed in Detecting Antigen-Antibody Complexes.

Table 13.4.1: Immunoblots & Enzyme Immunoassays

Type of Assay	Mechanism	Specific Procedures	Examples
Immunoblots	Uses enzyme-antibody conjugates to identify specific proteins that have been transferred to an absorbent membrane	Western blot: Detects the presence of a particular protein	Detecting the presence of HIV peptides (or peptides from other infectious agents) in patient sera
Immunostaining	Uses enzyme-antibody conjugates to stain specific molecules on or in cells	Immunohistochemistry: Used to stain specific cells in a tissue	Stain for presence of CD8 cells in host tissue
Enzyme-linked immunosorbent assay (ELISA)	Uses enzyme-antibody conjugates to quantify target molecules	Direct ELISA: Uses a single antibody to detect the presence of an antigen	Detection of HIV antigen p24 up to one month after being infected
		Indirect ELISA: Measures the amount of antibody produced against an antigen	Detection of HIV antibodies in serum
Immunochromatographic (lateral flow) assays	Techniques use the capture of flowing, color-labeled antigen-antibody complexes by fixed antibody for disease diagnosis	Sandwich ELISA: Measures the amount of antigen bound by the antibody	Detection of antibodies for various pathogens in patient sera (e.g., rapid strep, malaria dipstick)
			Pregnancy test detecting human chorionic gonadotrophin in urine

Clinical Focus: Part 3

Although the indirect ELISA for HIV is a sensitive assay, there are several complicating considerations. First, if an infected person is tested too soon after becoming infected, the test can yield false-negative results. The seroconversion window is generally about three weeks, but in some cases, it can be more than two months.

In addition to false negatives, false positives can also occur, usually due to previous infections with other viruses that induce cross-reacting antibodies. The false-positive rate depends on the particular brand of test used, but 0.5% is not unusual.[1] Because of the possibility of a false positive, all positive tests are followed up with a confirmatory test. This confirmatory test is often an immunoblot (western blot) in which HIV peptides from the patient's blood are identified using an HIV-specific mAb-enzyme conjugate. A positive western blot would confirm an HIV infection and a negative blot would confirm the absence of HIV despite the positive ELISA.

Unfortunately, western blots for HIV antigens often yield indeterminant results, in which case, they neither confirm nor invalidate the results of the indirect ELISA. In fact, the rate of indeterminants can be 10–49% (which is why, combined with their cost, western blots are not used for screening). Similar to the indirect ELISA, an indeterminant western blot can occur because of cross-reactivity or previous viral infections, vaccinations, or autoimmune diseases.

Exercise 13.4.5

1. Of the 1300 patients being tested, how many false-positive ELISA tests would be expected?
2. Of the false positives, how many indeterminant western blots could be expected?
3. How would the hospital address any cases in which a patient's western blot was indeterminant?

Key Concepts and Summary

- **Enzyme immunoassays (EIA)** are used to visualize and quantify antigens. They use an antibody conjugated to an enzyme to bind the antigen, and the enzyme converts a substrate into an observable end product. The substrate may be either a chromogen or a fluorogen.
- **Immunostaining** is an EIA technique for visualizing cells in a tissue (**immunohistochemistry**) or examining intracellular structures (**immunocytochemistry**).
- **Direct ELISA** is used to quantify an antigen in solution. The primary antibody captures the antigen, and the secondary antibody delivers an enzyme. Production of end product from the chromogenic substrate is directly proportional to the amount of captured antigen.
- **Indirect ELISA** is used to detect antibodies in patient serum by attaching antigen to the well of a microtiter plate, allowing the patient (primary) antibody to bind the antigen and an enzyme-conjugated secondary antibody to detect the primary antibody.
- **Immunofiltration and immunochromatographic assays** are used in **lateral flow tests**, which can be used to diagnose pregnancy and various diseases by detecting color-labeled antigen-antibody complexes in urine or other fluid samples

Footnotes

1. 1 Thomas, Justin G., Victor Jaffe, Judith Shaffer, and Jose Abreu, “HIV Testing: US Recommendations 2014,” *Osteopathic Family Physician* 6, no. 6 (2014).

This page titled 13.4: Enzyme Immunoassays (EIA) and Enzyme-Linked Immunosorbent Assays (ELISA) is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **20.4: Enzyme Immunoassays (EIA) and Enzyme-Linked Immunosorbent Assays (ELISA)** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

13.5: Fluorescent Auto-Antibody Techniques

Learning Objectives

- Describe the benefits of immunofluorescent antibody assays in comparison to nonfluorescent assays
- Compare direct and indirect fluorescent antibody assays
- Explain how a flow cytometer can be used to quantify specific subsets of cells present in a complex mixture of cell types
- Explain how a fluorescence-activated cell sorter can be used to separate unique types of cells

Rapid visualization of bacteria from a clinical sample such as a throat swab or sputum can be achieved through fluorescent antibody (FA) techniques that attach a fluorescent marker (fluorogen) to the constant region of an antibody, resulting in a reporter molecule that is quick to use, easy to see or measure, and able to bind to target markers with high specificity. We can also label cells, allowing us to precisely quantify particular subsets of cells or even purify these subsets for further research.

As with the enzyme assays, FA methods may be direct, in which a labeled mAb binds an antigen, or indirect, in which secondary polyclonal antibodies bind patient antibodies that react to a prepared antigen. Applications of these two methods were demonstrated in Figure 2.3.8. FA methods are also used in automated cell counting and sorting systems to enumerate or segregate labeled subpopulations of cells in a sample.

Direct Fluorescent Antibody Techniques

Direct fluorescent antibody (DFA) tests use a fluorescently labeled mAb to bind and illuminate a target antigen. DFA tests are particularly useful for the rapid diagnosis of bacterial diseases. For example, fluorescence-labeled antibodies against *Streptococcus pyogenes* (group A strep) can be used to obtain a diagnosis of strep throat from a throat swab. The diagnosis is ready in a matter of minutes, and the patient can be started on antibiotics before even leaving the clinic. DFA techniques may also be used to diagnose pneumonia caused by *Mycoplasma pneumoniae* or *Legionella pneumophila* from sputum samples (Figure **13.5.1**). The fluorescent antibodies bind to the bacteria on a microscope slide, allowing ready detection of the bacteria using a fluorescence microscope. Thus, the DFA technique is valuable for visualizing certain bacteria that are difficult to isolate or culture from patient samples.



Figure **13.5.1**: A green fluorescent mAb against *L. pneumophila* is used here to visualize and identify bacteria from a smear of a sample from the respiratory tract of a pneumonia patient. (credit: modification of work by American Society for Microbiology)

? Exercise 13.5.1

In a direct fluorescent antibody test, what does the fluorescent antibody bind to?

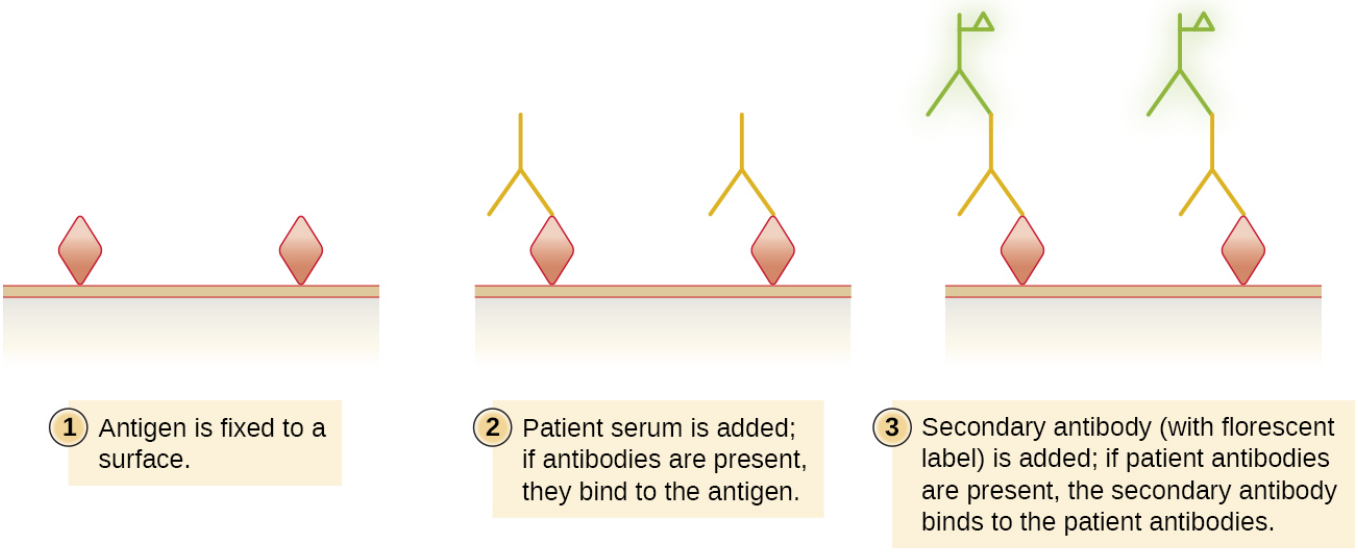
Indirect Fluorescent Antibody Techniques

Indirect fluorescent antibody (IFA) tests (Figure **13.5.2**) are used to look for antibodies in patient serum. For example, an IFA test for the diagnosis of syphilis uses *T. pallidum* cells isolated from a lab animal (the bacteria cannot be grown on lab media) and a smear prepared on a glass slide. Patient serum is spread over the smear and anti-treponemal antibodies, if present, are allowed to bind. The serum is washed off and a secondary antibody added. The secondary antibody is an antihuman immunoglobulin conjugated to a fluorogen. On examination, the *T. pallidum* bacteria will only be visible if they have been bound by the antibodies from the patient's serum.

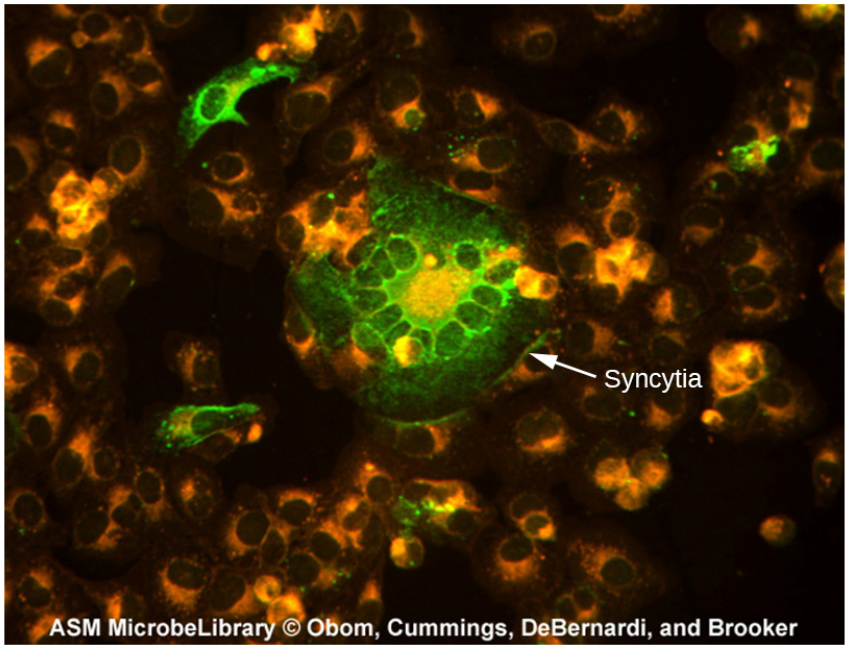
The IFA test for syphilis provides an important complement to the VDRL test discussed in Detecting Antigen-Antibody Complexes. The VDRL is more likely to generate false-positive reactions than the IFA test; however, the VDRL is a better test for determining whether an infection is currently active.

IFA tests are also useful for the diagnosis of autoimmune diseases. For example, systemic lupus erythematosus (SLE) (see Autoimmune Disorders) is characterized by elevated expression levels of antinuclear antibodies (ANA). These autoantibodies can be expressed against a variety of DNA-binding proteins and even against DNA itself. Because autoimmunity is often difficult to diagnose, especially early in disease progression, testing for ANA can be a valuable clue in making a diagnosis and starting appropriate treatment.

The IFA for ANA begins by fixing cells grown in culture to a glass slide and making them permeable to antibody. The slides are then incubated with serial dilutions of serum from the patient. After incubation, the slide is washed to remove unbound proteins, and the fluorescent antibody (antihuman IgG conjugated to a fluorogen) added. After an incubation and wash, the cells can be examined for fluorescence evident around the nucleus (Figure **13.5.3**). The titer of ANA in the serum is determined by the highest dilution showing fluorescence. Because many healthy people express ANA, the American College of Rheumatology recommends that the titer must be at least 1:40 in the presence of symptoms involving two or more organ systems to be considered indicative of SLE.[1]

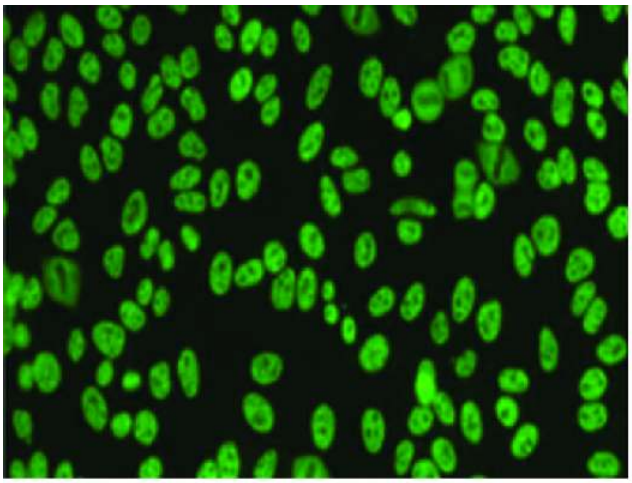


(a)

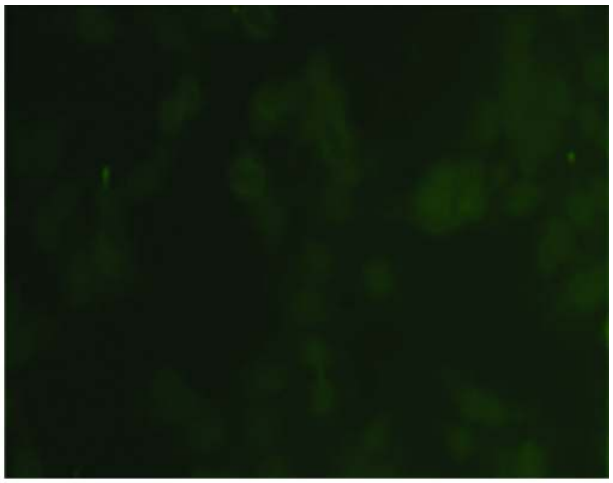


(b)

Figure **13.5.2**: (a) The IFA test is used to detect antigen-specific antibodies by allowing them to bind to antigen fixed to a surface and then illuminating these complexes with a secondary antibody-fluorogen conjugate. (b) In this example of a micrograph of an indirect fluorescent antibody test, a patient's antibodies to the measles virus bind to viral antigens present on inactivated measles-infected cells affixed to a slide. Secondary antibodies bind the patient's antibodies and carry a fluorescent molecule. (credit b: modification of work by American Society for Microbiology)



diseased



healthy control

Figure **13.5.3**: In this test for antinuclear antibodies (ANA), cells are exposed to serum from a patient suspected of making ANA and then to a fluorescent mAb specific for human immunoglobulin. As a control, serum from a healthy patient is also used. Visible fluorescence around the nucleus demonstrates the presence of ANA in the patient's serum. In the healthy control where lower levels of ANA are produced, very faint green is detected. (credit left, right: modification of work by Al-Hussaini AA, Alzahrani MD, Alenizi AS, Suliman NM, Khan MA, Alharbi SA, Chentoufi AA)

? Exercise 13.5.2

1. In an indirect fluorescent antibody test, what does the fluorescent antibody bind to?
2. What is the ANA test looking for?

Flow Cytometry

Fluorescently labeled antibodies can be used to quantify cells of a specific type in a complex mixture using flow cytometry (Figure **13.5.4**), an automated, cell-counting system that detects fluorescing cells as they pass through a narrow tube one cell at a time. For example, in HIV infections, it is important to know the level of CD4 T cells in the patient's blood; if the numbers fall below 500 per µL of blood, the patient becomes more likely to acquire opportunistic infections; below 200 per µL, the patient can no longer mount a useful adaptive immune response at all. The analysis begins by incubating a mixed-cell population (e.g., white blood cells from a donor) with a fluorescently labeled mAb specific for a subpopulation of cells (e.g., anti-CD4). Some experiments look at two cell markers simultaneously by adding a different fluorogen to the appropriate mAb. The cells are then introduced to the flow cytometer through a narrow capillary that forces the cells to pass in single file. A laser is used to activate the fluorogen. The fluorescent light radiates out in all directions, so the fluorescence detector can be positioned at an angle from the incident laser light.

Figure **13.5.4** shows the obscuration bar in front of the forward-scatter detector that prevents laser light from hitting the detector. As a cell passes through the laser bar, the forward-scatter detector detects light scattered around the obscuration bar. The scattered light is transformed into a voltage pulse, and the cytometer counts a cell. The fluorescence from a labeled cell is detected by the side-scatter detectors. The light passes through various dichroic mirrors such that the light emitted from the fluorophore is received by the correct detector.

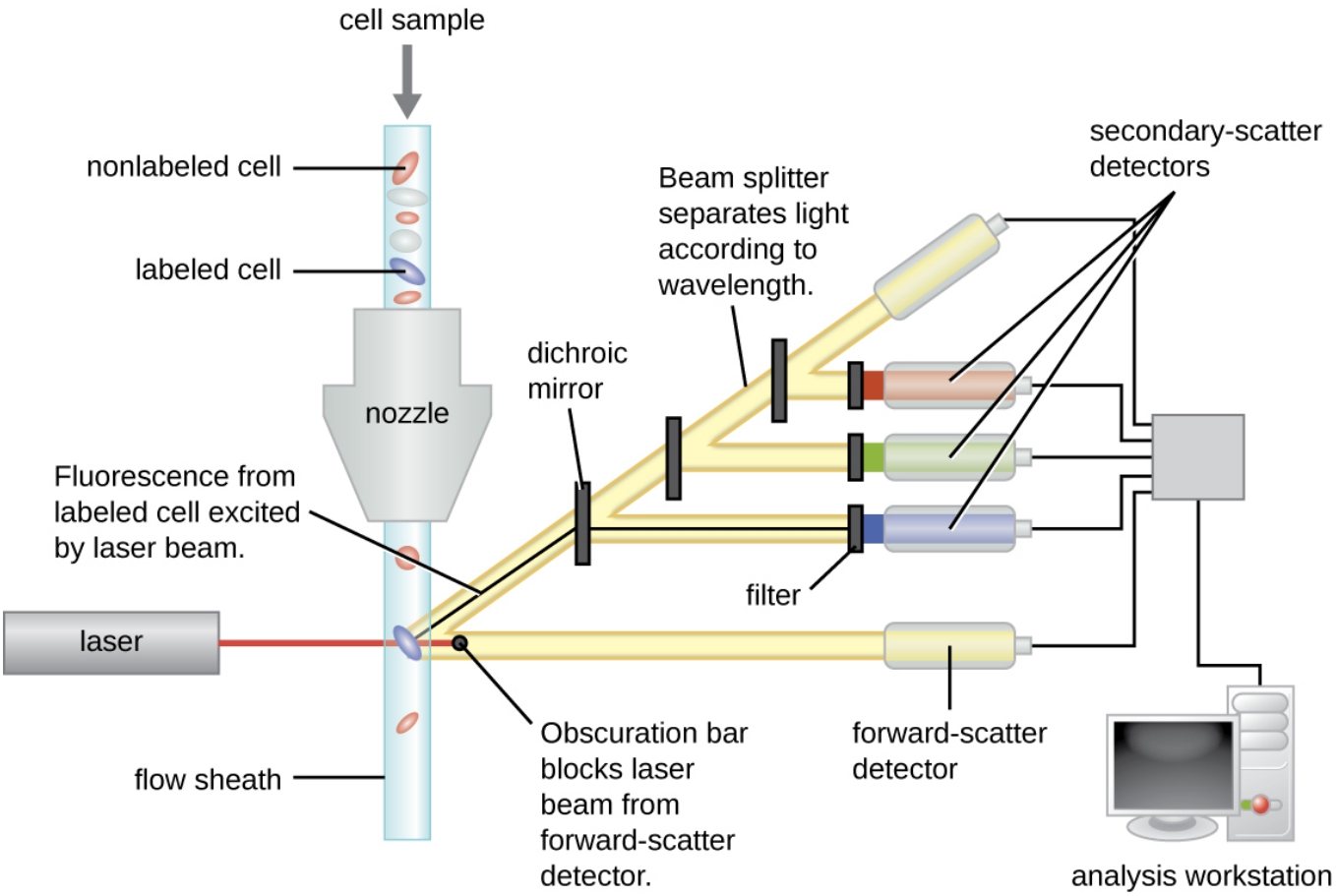


Figure 13.5.4: In flow cytometry, a mixture of fluorescently labeled and unlabeled cells passes through a narrow capillary. A laser excites the fluorogen, and the fluorescence intensity of each cell is measured by a detector. (credit: modification of work by "Kierano"/Wikimedia Commons)

Data are collected from both the forward- and side-scatter detectors. One way these data can be presented is in the form of a histogram. The forward scatter is placed on the *y*-axis (to represent the number of cells), and the side scatter is placed on the *x*-axis (to represent the fluoresence of each cell). The scaling for the *x*-axis is logarithmic, so fluorescence intensity increases by a factor of 10 with each unit increase along the axis. Figure 13.5.5 depicts an example in which a culture of cells is combined with an antibody attached to a fluorophore to detect CD8 cells and then analyzed by flow cytometry. The histogram has two peaks. The peak on the left has lower fluorescence readings, representing the subset of the cell population (approximately 30 cells) that does not fluoresce; hence, they are not bound by antibody and therefore do not express CD8. The peak on the right has higher fluorescence readings, representing the subset of the cell population (approximately 100 cells) that show fluorescence; hence, they are bound by the antibody and therefore do express CD8.

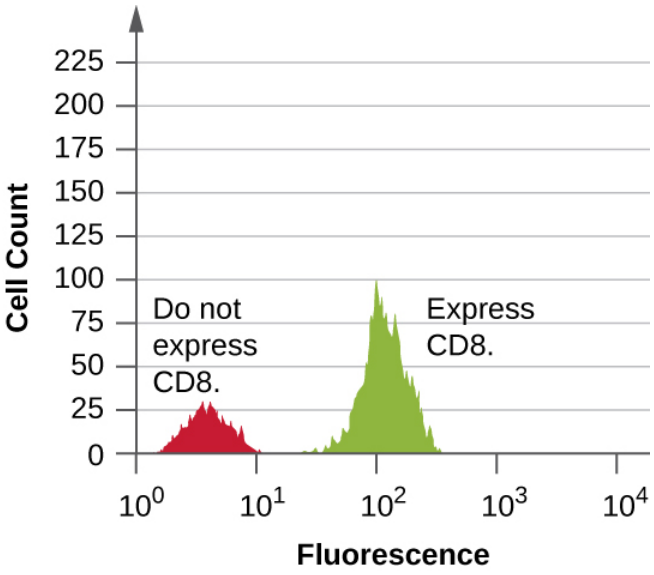


Figure 13.5.5: Flow cytometry data are often compiled as a histogram. In the histogram, the area under each peak is proportional to the number of cells in each population. The *x*-axis is the relative fluorescence expressed by the cells (on a log scale), and the *y*-axis represents the number of cells at a particular level of fluorescence.

? Exercise 13.5.3

1. What is the purpose of the laser in a flow cytometer?
2. In the output from a flow cytometer, the area under the histogram is equivalent to what?

Clinical Focus: Resolution

After notifying all 1300 patients, the hospital begins scheduling HIV screening. Appointments were scheduled a minimum of 3 weeks after the patient's last hospital visit to minimize the risk of false negatives. Because some false positives were anticipated, the public health physician set up a counseling protocol for any patient whose indirect ELISA came back positive.

Of the 1300 patients, eight tested positive using the ELISA. Five of these tests were invalidated by negative western blot tests, but one western blot came back positive, confirming that the patient had indeed contracted HIV. The two remaining western blots came back indeterminate. These individuals had to submit to a third test, a PCR, to confirm the presence or absence of HIV sequences. Luckily, both patients tested negative.

As for the lone patient confirmed to have HIV, the tests cannot prove or disprove any connection to the syringes compromised by the former hospital employee. Even so, the hospital's insurance will fully cover the patient's treatment, which began immediately.

Although we now have drugs that are typically effective at controlling the progression of HIV and AIDS, there is still no cure. If left untreated, or if the drug regimen fails, the patient will experience a gradual decline in the number of CD4 helper T cells, resulting in severe impairment of all adaptive immune functions. Even moderate declines of helper T cell numbers can result in immunodeficiency, leaving the patient susceptible to opportunistic infections. To monitor the status of the patient's helper T cells, the hospital will use flow cytometry. This sensitive test allows physicians to precisely determine the number of helper T cells so they can adjust treatment if the number falls below 500 cells/μL.

Cell Sorting Using Immunofluorescence

The flow cytometer and immunofluorescence can also be modified to sort cells from a single sample into purified subpopulations of cells for research purposes. This modification of the flow cytometer is called a fluorescence-activated cell sorter (FACS). In a FACS, fluorescence by a cell induces the device to put a charge on a droplet of the transporting fluid containing that cell. The charge is specific to the wavelength of the fluorescent light, which allows for differential sorting by those different charges. The

sorting is accomplished by an electrostatic deflector that moves the charged droplet containing the cell into one collecting vessel or another. The process results in highly purified subpopulations of cells.

One limitation of a FACS is that it only works on isolated cells. Thus, the method would work in sorting white blood cells, since they exist as isolated cells. But for cells in a tissue, flow cytometry can only be applied if we can excise the tissue and separate it into single cells (using proteases to cleave cell-cell adhesion molecules) without disrupting cell integrity. This method may be used on tumors, but more often, immunohistochemistry and immunocytochemistry are used to study cells in tissues.

Link to Learning

Watch videos to learn more about how flow cytometry and a FACS work.

Exercise 13.5.4

In fluorescence activated cell sorting, what characteristic of the target cells allows them to be separated?

Table **13.5.1** compares the mechanisms of the fluorescent antibody techniques discussed in this section.

Table **13.5.1**: Fluorescent Antibody Techniques

Type of Assay	Mechanism	Examples
Direct fluorescent antibody (DFA)	Uses fluorogen-antibody conjugates to label bacteria from patient samples	Visualizing *Legionella pneumophila* from a throat swab
Indirect fluorescent antibody (IFA)	Detects disease-specific antibodies in patent serum	Diagnosing syphilis; detecting antinuclear antibodies (ANA) for lupus and other autoimmune diseases
Flow cytometry	Labels cell membranes with fluorogen-antibody conjugate markers excited by a laser; machine counts the cell and records the relative fluorescence	Counting the number of fluorescently labeled CD4 or CD8 cells in a sample
Fluorescence activated cell sorter (FACS)	Form of flow cytometry that both counts cells and physically separates them into pools of high and low fluorescence cells	Sorting cancer cells

Key Concepts and Summary

- **Immunofluorescence** assays use antibody-fluorogen conjugates to illuminate antigens for easy, rapid detection.
- **Direct immunofluorescence** can be used to detect the presence of bacteria in clinical samples such as sputum.
- **Indirect immunofluorescence** detects the presence of antigen-specific antibodies in patient sera. The fluorescent antibody binds to the antigen-specific antibody rather than the antigen.
- The use of indirect immunofluorescence assays to detect **antinuclear antibodies** is an important tool in the diagnosis of several autoimmune diseases.
- **Flow cytometry** uses fluorescent mAbs against cell-membrane proteins to quantify specific subsets of cells in complex mixtures.
- **Fluorescence-activated cell sorters** are an extension of flow cytometry in which fluorescence intensity is used to physically separate cells into high and low fluorescence populations.

Footnotes

1. 1 Gill, James M., ANNA M. Quisel, PETER V. Rocca, and DENE T. Walters. “Diagnosis of systemic lupus erythematosus.” *American family physician* 68, no. 11 (2003): 2179-2186.

This page titled 13.5: Fluorescent Auto-Antibody Techniques is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of

the LibreTexts platform.

- **20.5: Fluorescent Auto-Antibody Techniques** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

13.E: Laboratory Analysis of the Immune Response (Exercises)

20.1: Practical Applications of Monoclonal and Polyclonal Antibodies

In addition to being crucial for our normal immune response, antibodies provide powerful tools for research and diagnostic purposes. The high specificity of antibodies makes them an excellent tool for detecting and quantifying a broad array of targets, from drugs to serum proteins to microorganisms. With in vitro assays, antibodies can be used to precipitate soluble antigens, agglutinate cells, and neutralize drugs, toxins, and viruses.

Multiple Choice

For many uses in the laboratory, polyclonal antibodies work well, but for some types of assays, they lack sufficient _____ because they cross-react with inappropriate antigens.

A. specificity
B. sensitivity
C. accuracy
D. reactivity

Answer

A

How are monoclonal antibodies produced?

A. Antibody-producing B cells from a mouse are fused with myeloma cells and then the cells are grown in tissue culture.
B. A mouse is injected with an antigen and then antibodies are harvested from its serum.
C. They are produced by the human immune system as a natural response to an infection.
D. They are produced by a mouse's immune system as a natural response to an infection.

Answer

A

Fill in the Blank

When we inject an animal with the same antigen a second time a few weeks after the first, _____ takes place, which means the antibodies produced after the second injection will on average bind the antigen more tightly.

Answer

affinity maturation

When using mAbs to treat disease in humans, the mAbs must first be _____ by replacing the mouse constant region DNA with human constant region DNA.

Answer

humanized

If we used normal mouse mAbs to treat human disease, multiple doses would cause the patient to respond with _____ against the mouse antibodies.

Answer

neutralizing antibodies

A polyclonal response to an infection occurs because most antigens have multiple _____,

Answer

epitopes

Short Answer

Describe two reasons why polyclonal antibodies are more likely to exhibit cross-reactivity than monoclonal antibodies.

Critical Thinking

Suppose you were screening produce in a grocery store for the presence of *E. coli* contamination. Would it be better to use a polyclonal anti-*E. coli* antiserum or a mAb against an *E. coli* membrane protein? Explain.

20.2: Detecting Antigen-Antibody Complexes in vitro

Laboratory tests to detect antibodies and antigens outside of the body (e.g., in a test tube) are called *in vitro* assays. When both antibodies and their corresponding antigens are present in a solution, we can often observe a precipitation reaction in which large complexes (lattices) form and settle out of solution.

Multiple Choice

The formation of _____ is a positive result in the VDRL test.

A. flocculant
B. precipitin
C. coagulation
D. a bright pink color

Answer

A

The titer of a virus neutralization test is the highest dilution of patient serum

A. in which there is no detectable viral DNA.
B. in which there is no detectable viral protein.
C. that completely blocks plaque formation.
D. that reduces plaque formation by at least 50%.

Answer

D

In the Ouchterlony assay, we see a sharp precipitin arc form between antigen and antiserum. Why does this arc remain visible for a long time?

A. The antibody molecules are too large to diffuse through the agar.
B. The precipitin lattice is too large to diffuse through the agar.
C. Methanol, added once the arc forms, denatures the protein and blocks diffusion.
D. The antigen molecules are chemically coupled to the gel matrix.

Answer

B

Fill in the Blank

When slowly adding antigen to an antiserum, the amount of precipitin would gradually increase until reaching the _____; addition of more antigen after this point would actually decrease the amount of precipitin.

Answer

equivalence zone or zone of equivalence

The radial immunodiffusion test quantifies antigen by mixing _____ into a gel and then allowing antigen to diffuse out from a well cut in the gel.

Answer

antiserum

Short Answer

Explain why hemolysis in the complement fixation test is a negative test for infection.

What is meant by the term “neutralizing antibodies,” and how can we quantify this effect using the viral neutralization assay?

Critical Thinking

Both IgM and IgG antibodies can be used in precipitation reactions. However, one of these immunoglobulin classes will form precipitates at much lower concentrations than the other. Which class is this, and why is it so much more efficient in this regard?

20.3: Agglutination Assays

In addition to causing precipitation of soluble molecules and flocculation of molecules in suspension, antibodies can also clump together cells or particles (e.g., antigen-coated latex beads) in a process called agglutination. Agglutination can be used as an indicator of the presence of antibodies against bacteria or red blood cells. Agglutination assays are usually quick and easy to perform on a glass slide or microtiter plate.

Multiple Choice

We use antisera to distinguish between various _____ within a species of bacteria.

A. isotypes
B. serovars
C. subspecies
D. lines

Answer

B

When using antisera to characterize bacteria, we will often link the antibodies to _____ to better visualize the agglutination.

A. latex beads
B. red blood cells
C. other bacteria
D. white blood cells

Answer

A

The antibody screening test that is done along with pretransfusion blood typing is used to ensure that the recipient

A. does not have a previously undetected bacterial or viral infection.
B. is not immunocompromised.
C. actually does have the blood type stated in the online chart.
D. is not making antibodies against antigens outside the ABO or Rh systems.

Answer

D

The direct Coombs’ test is designed to detect when people have a disease that causes them to

A. have an excessively high fever.
B. quit making antibodies.
C. make too many red blood cells.
D. produce antibodies that bind to their own red blood cells.

Answer

D

Viral hemagglutination assays only work with certain types of viruses because

A. the virus must be able to cross-link red blood cells directly.
B. the virus must be able to lyse red blood cells.
C. the virus must not be able to lyse red blood cells.
D. other viruses are too dangerous to work with in a clinical lab setting.

Answer

A

Fill in the Blank

In the major cross-match, we mix _____ with the donor red blood cells and look for agglutination.

Answer

patient serum

Coombs' reagent is an antiserum with antibodies that bind to human _____.

Answer

immunoglobulins/antibodies and/or complement

Short Answer

Explain why the titer of a direct hemagglutination assay is the highest dilution that still causes hemagglutination, whereas in the viral hemagglutination inhibition assay, the titer is the highest dilution at which hemagglutination is not observed.

Why would a doctor order a direct Coombs' test when a baby is born with jaundice?

Critical Thinking

When shortages of donated blood occur, O-negative blood may be given to patients, even if they have a different blood type. Why is this the case? If O-negative blood supplies were depleted, what would be the next-best choice for a patient with a different blood type in critical need of a transfusion? Explain your answers.

20.4: Enzyme Immunoassays (EIA) and Enzyme-Linked Immunosorbent Assays (ELISA)

Enzyme immunoassays (EIA) are used to visualize and quantify antigens. They use an antibody conjugated to an enzyme to bind the antigen, and the enzyme converts a substrate into an observable end product. The substrate may be either a chromogen or a fluorogen. Immunostaining is an EIA technique for visualizing cells in a tissue (immunohistochemistry) or examining intracellular structures (immunocytochemistry). Direct ELISA is used to quantify an antigen in solution.

Multiple Choice

In an enzyme immunoassay, the enzyme

A. is bound by the antibody's antigen-binding site.
B. is attached to the well of a microtiter plate.
C. is conjugated to the suspect antigen.
D. is bound to the constant region of the secondary antibody.

Answer

D

When using an EIA to study microtubules or other structures inside a cell, we first chemically fix the cell and then treat the cells with alcohol. What is the purpose of this alcohol treatment?

A. It makes holes in the cell membrane large enough for antibodies to pass.
B. It makes the membrane sticky so antibodies will bind and be taken up by receptor-mediated endocytosis.
C. It removes negative charges from the membrane, which would otherwise repulse the antibodies.
D. It prevents nonspecific binding of the antibodies to the cell membrane.

Answer

A

In a lateral-flow pregnancy test, you see a blue band form on the control line and no band form on the test line. This is probably a _____ test for pregnancy.

A. positive
B. false-positive
C. false-negative
D. negative

Answer

D

When performing an FEIA, the fluorogen replaces the _____ that is used in an EIA.

A. antigen
B. chromogenic substrate
C. enzyme
D. secondary antibody

Answer

B

Fill in the Blank

To detect antibodies against bacteria in the bloodstream using an EIA, we would run a(n) _____, which we would start by attaching antigen from the bacteria to the wells of a microtiter plate.

Answer

indirect ELISA

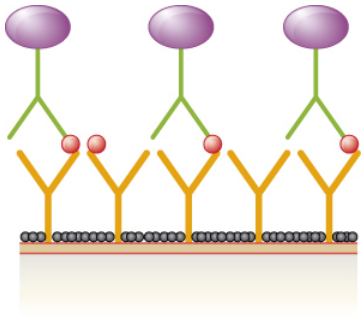
Short Answer

Why is it important in a sandwich ELISA that the antigen has multiple epitopes? And why might it be advantageous to use polyclonal antisera rather than mAb in this assay?

The pregnancy test strip detects the presence of human chorionic gonadotrophin in urine. This hormone is initially produced by the fetus and later by the placenta. Why is the test strip preferred for this test rather than using either a direct or indirect ELISA with their more quantifiable results?

Critical Thinking

Label the primary and secondary antibodies, and discuss why the production of end product will be proportional to the amount of antigen.

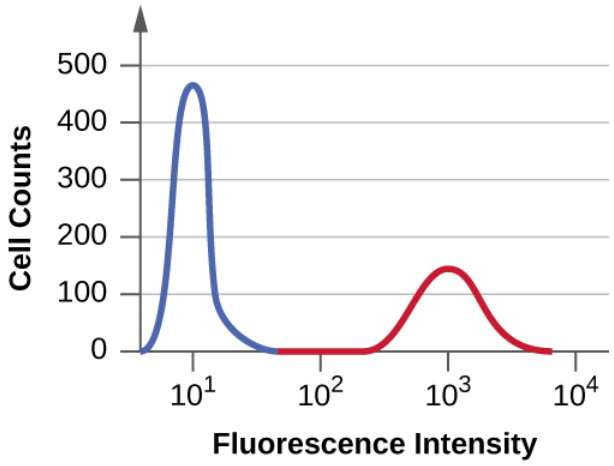


20.5: Fluorescent Auto-Antibody Techniques

Rapid visualization of bacteria from a clinical sample such as a throat swab or sputum can be achieved through fluorescent antibody (FA) techniques that attach a fluorescent marker (fluorogen) to the constant region of an antibody, resulting in a reporter molecule that is quick to use, easy to see or measure, and able to bind to target markers with high specificity. We can also label cells, allowing us to precisely quantify particular subsets of cells or even purify them for further research.

Multiple Choice

Suppose you need to quantify the level of CD8 T cells in the blood of a patient recovering from influenza. You treat a sample of the patient's white blood cells using a fluorescent mAb against CD8, pass the cells through a flow cytometer, and produce the histogram shown below. The area under the peak to the left (blue) is three times greater than the area of the peak on the right (red). What can you determine from these data?



A. There are no detectable CD8 cells.
B. There are three times as many CD4 cells than CD8 cells.
C. There are three times as many CD8 cells than CD4 cells.
D. CD8 cells make up about one-fourth of the total number of cells.

Answer

D

In the data described in the previous question, the average fluorescence intensity of cells in the second (red) peak is about _____ that in the first (blue) peak.

A. three times
B. 100 times
C. one-third
D. 1000 times

Answer

B

In a direct fluorescent antibody test, which of the following would we most likely be looking for using a fluorescently-labeled mAb?

A. bacteria in a patient sample
B. bacteria isolated from a patient and grown on agar plates
C. antiserum from a patient smeared onto a glass slide
D. antiserum from a patient that had bound to antigen-coated beads

Answer

A

Fill in the Blank

In flow cytometry, cell subsets are labeled using a fluorescent antibody to a membrane protein. The fluorogen is activated by a(n) _____ as the cells pass by the detectors.

Answer

laser

Fluorescence in a flow cytometer is measured by a detector set at an angle to the light source. There is also an in-line detector that can detect cell clumps or _____.

Answer

fragments

Critical Thinking

A patient suspected of having syphilis is tested using both the VDRL test and IFA. The IFA test comes back positive, but the VDRL test is negative. What is the most likely reason for these results?

A clinician suspects that a patient with pneumonia may be infected by *Legionella pneumophila*. Briefly describe two reasons why a DFA test might be better for detecting this pathogen than standard bacteriology techniques.

This page titled 13.E: Laboratory Analysis of the Immune Response (Exercises) is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **20.E: Laboratory Analysis of the Immune Response (Exercises)** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

CHAPTER OVERVIEW

14: Immunodeficiencies

14.1: Immunity Disorders- Autoimmune Diseases

14.1A: Immunodeficiency

14.2: Autoimmune Disorders

14.3: Superantigens

14.4: Immunity Disorders- Immunodeficiencies

14.5: Cell-Mediated Autoimmune Reactions

14.6: Immune Complex Autoimmune Reactions

14.7: Cytotoxic Autoimmune Reactions

14.8: Primary Immunodeficiency

14.9: Primary Immunodeficiency Diseases

14.10: Secondary Immunodeficiency

14.11: Secondary Immunodeficiency Diseases

14.12: Immunotherapy for Cancer

14.13: The Roles of Genetics and Gender in Autoimmune Disease

This page titled 14: Immunodeficiencies is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

This page titled 14: Immunodeficiencies is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

14.1: Immunity Disorders- Autoimmune Diseases

This page titled 14.1: Immunity Disorders- Autoimmune Diseases is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **12.5: Immunity Disorders- Autoimmune Diseases** is licensed CC BY-SA 4.0.

14.1A: Immunodeficiency

Learning Objectives

- Explain the problems associated with immunodeficiency

Immunodeficiency

Failures, insufficiencies, or delays at any level of the immune response can allow pathogens or tumor cells to gain a foothold to replicate or proliferate to high enough levels that the immune system becomes overwhelmed, leading to immunodeficiency; it may be acquired or inherited. Immunodeficiency can be acquired as a result of infection with certain pathogens (such as HIV), chemical exposure (including certain medical treatments), malnutrition, or, possibly, by extreme stress. For instance, radiation exposure can destroy populations of lymphocytes, elevating an individual's susceptibility to infections and cancer. Dozens of genetic disorders result in immunodeficiencies, including Severe Combined Immunodeficiency (SCID), bare lymphocyte syndrome, and MHC II deficiencies. Rarely, primary immunodeficiencies that are present from birth may occur. Neutropenia is one form in which the immune system produces a below-average number of neutrophils, the body's most abundant phagocytes. As a result, bacterial infections may go unrestricted in the blood, causing serious complications.

HIV/AIDS

Human immunodeficiency virus infection / acquired immunodeficiency syndrome (HIV/AIDS), is a disease of the human immune system caused by infection with human immunodeficiency virus (HIV). During the initial infection, a person may experience a brief period of influenza-like illness. This is typically followed by a prolonged period without symptoms. As the illness progresses, it interferes more and more with the immune system. The person has a high probability of becoming infected, including from opportunistic infections and tumors that do not usually affect people who have working immune systems.

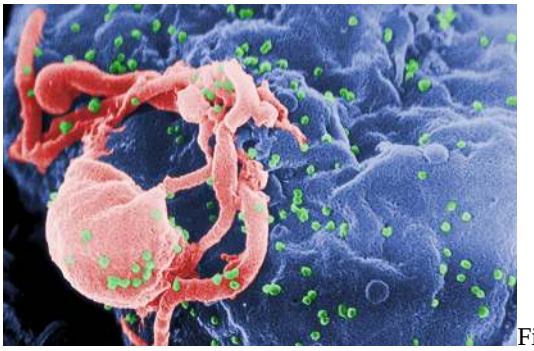


Figure: **Image of HIV: scanning electron micrograph of HIV-1 budding (in green, color added) from cultured lymphocyte**: Multiple round bumps on cell surface represent sites of assembly and budding of HIV. During primary infection, the level of HIV may reach several million virus particles per milliliter of blood.

After the virus enters the body, there is a period of rapid viral replication, leading to an abundance of virus in the peripheral blood. During primary infection, the level of HIV may reach several million virus particles per milliliter of blood. This response is accompanied by a marked drop in the number of circulating CD4+ T cells, cells that are or will become helper T cells. The acute viremia, or spreading of the virus, is almost invariably associated with activation of CD8+ T cells (which kill HIV-infected cells) and, subsequently, with antibody production. The CD8+ T cell response is thought to be important in controlling virus levels, which peak and then decline, as the CD4+ T cell counts recover.

Ultimately, HIV causes AIDS by depleting CD4+ T cells (helper T cells). This weakens the immune system, allowing opportunistic infections. T cells are essential to the immune response; without them, the body cannot fight infections or kill cancerous cells. The mechanism of CD4+ T cell depletion differs in the acute and chronic phases. During the acute phase, HIV-induced cell lysis and killing of infected cells by cytotoxic T cells accounts for CD4+ T cell depletion, although apoptosis (programmed cell death) may also be a factor. During the chronic phase, the consequences of generalized immune activation coupled with the gradual loss of the ability of the immune system to generate new T cells appear to account for the slow decline in CD4+ T cell numbers.

Key Points

- If a pathogen is allowed to proliferate to certain levels, the immune system can become overwhelmed; immunodeficiency occurs when the immune system fails to respond sufficiently to a pathogen.
- Immunodeficiency can be caused by many factors, including certain pathogens, malnutrition, chemical exposure, radiation exposure, or even extreme stress.
- HIV is a virus that causes immunodeficiency by infecting helper T cells, causing cytotoxic T cells to destroy them.

Key Terms

- **phagocyte**: a cell of the immune system, such as a neutrophil, macrophage or dendritic cell, that engulfs and destroys viruses, bacteria, and waste materials
- **lysis**: the disintegration or destruction of cells
- **immunodeficiency**: a depletion in the body's natural immune system, or in some component of it

---

This page titled 14.1A: Immunodeficiency is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **12.5A: Immunodeficiency** is licensed CC BY-SA 4.0.

14.2: Autoimmune Disorders

Learning Objectives

- Explain why autoimmune disorders develop
- Provide a few examples of organ-specific and systemic autoimmune diseases

In 1970, artist Walt Kelly developed a poster promoting Earth Day, featuring a character from *Pogo*, his daily newspaper comic strip. In the poster, Pogo looks out across a litter-strewn forest and says wryly, “We have met the enemy and he is us.” Pogo was not talking about the human immune system, but he very well could have been. Although the immune system protects the body by attacking invading “enemies” (pathogens), in some cases, the immune system can mistakenly identify the body’s own cells as the enemy, resulting in autoimmune disease.

Autoimmune diseases are those in which the body is attacked by its own specific adaptive immune response. In normal, healthy states, the immune system induces tolerance, which is a lack of an anti-self immune response. However, with autoimmunity, there is a loss of immune tolerance, and the mechanisms responsible for autoimmune diseases include type II, III, and IV hypersensitivity reactions. Autoimmune diseases can have a variety of mixed symptoms that flare up and disappear, making diagnosis difficult.

The causes of autoimmune disease are a combination of the individual's genetic makeup and the effect of environmental influences, such as sunlight, infections, medications, and environmental chemicals. However, the vagueness of this list reflects our poor understanding of the etiology of these diseases. Except in a very few specific diseases, the initiation event(s) of most autoimmune states has not been fully characterized.

There are several possible causes for the origin of autoimmune diseases and autoimmunity is likely due to several factors. Evidence now suggests that regulatory T and B cells play an essential role in the maintenance of tolerance and prevention of autoimmune responses. The regulatory T cells are especially important for inhibiting autoreactive T cells that are not eliminated during thymic selection and escape the thymus (see T Lymphocytes and Cellular Immunity). In addition, antigen mimicry between pathogen antigens and our own self antigens can lead to cross-reactivity and autoimmunity. Hidden self-antigens may become exposed because of trauma, drug interactions, or disease states, and trigger an autoimmune response. All of these factors could contribute to autoimmunity. Ultimately, damage to tissues and organs in the autoimmune disease state comes as a result of inflammatory responses that are inappropriate; therefore, treatment often includes immunosuppressive drugs and corticosteroids.

Organ-Specific Autoimmune Diseases

Some autoimmune diseases are considered organ specific, meaning that the immune system targets specific organs or tissues. Examples of organ-specific autoimmune diseases include celiac disease, Graves disease, Hashimoto thyroiditis, type I diabetes mellitus, and Addison disease.

Celiac Disease

Celiac disease is largely a disease of the small intestine, although other organs may be affected. People in their 30s and 40s, and children are most commonly affected, but celiac disease can begin at any age. It results from a reaction to proteins, commonly called gluten, found mainly in wheat, barley, rye, and some other grains. The disease has several genetic causes (predispositions) and poorly understood environmental influences. On exposure to gluten, the body produces various autoantibodies and an inflammatory response. The inflammatory response in the small intestine leads to a reduction in the depth of the microvilli of the mucosa, which hinders absorption and can lead to weight loss and anemia. The disease is also characterized by diarrhea and abdominal pain, symptoms that are often misdiagnosed as irritable bowel syndrome.

Diagnosis of celiac disease is accomplished from serological tests for the presence of primarily IgA antibodies to components of gluten, the transglutinaminase enzyme, and autoantibodies to endomysium, a connective tissue surrounding muscle fibers. Serological tests are typically followed up with endoscopy and biopsy of the duodenal mucosa. Serological screening surveys have found about 1% of individuals in the United Kingdom are positive even though they do not all display symptoms.[1] This early recognition allows for more careful monitoring and prevention of severe disease.

Celiac disease is treated with complete removal of gluten-containing foods from the diet, which results in improved symptoms and reduced risk of complications. Other theoretical approaches include breeding grains that do not contain the immunologically reactive components or developing dietary supplements that contain enzymes that break down the protein components that cause the immune response.[2]

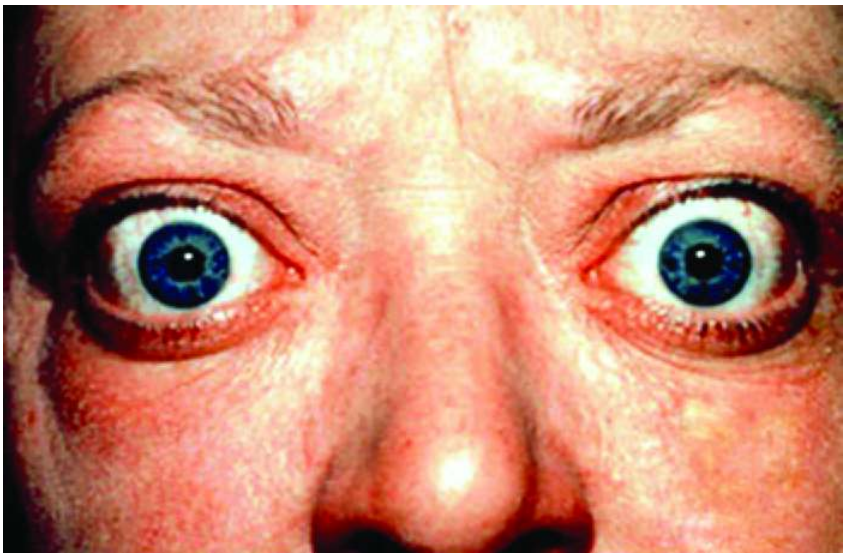
Disorders of the Thyroid

Graves disease is the most common cause of hyperthyroidism in the United States. Symptoms of Graves disease result from the production of thyroid-stimulating immunoglobulin (TSI) also called TSH-receptor antibody. TSI targets and binds to the receptor for thyroid stimulating hormone (TSH), which is naturally produced by the pituitary gland. TSI may cause conflicting symptoms because it may stimulate the thyroid to make too much thyroid hormone or block thyroid hormone production entirely, making diagnosis more difficult. Signs and symptoms of Graves disease include heat intolerance, rapid and irregular heartbeat, weight loss, goiter (a swollen thyroid gland, protruding under the skin of the throat [Figure **14.2.1**]) and exophthalmia (bulging eyes) often referred to as Graves ophthalmopathy (Figure **14.2.2**).



Figure **14.2.1**: Goiter, a hypertrophy of the thyroid, is a symptom of Graves disease and Hashimoto thyroiditis.

The most common cause of hypothyroidism in the United States is Hashimoto thyroiditis, also called chronic lymphocytic thyroiditis. Patients with Hashimoto thyroiditis often develop a spectrum of different diseases because they are more likely to develop additional autoimmune diseases such as Addison disease (discussed later in this section), type 1 diabetes, rheumatoid arthritis, and celiac disease. Hashimoto thyroiditis is a T_H1 cell-mediated disease that occurs when the thyroid gland is attacked by cytotoxic lymphocytes, macrophages, and autoantibodies. This autoimmune response leads to numerous symptoms that include goiter (Figure **14.2.1**), cold intolerance, muscle weakness, painful and stiff joints, depression, and memory loss.


Figure **14.2.2**: Exophthalmia, or Graves ophthalmopathy, is a sign of Graves disease. (credit: modification of work by Jonathan Trobe, University of Michigan Kellogg Eye Center)

Type 1 Diabetes

Juvenile diabetes, or type 1 diabetes mellitus, is usually diagnosed in children and young adults. It is a T-cell-dependent autoimmune disease characterized by the selective destruction of the β cells of the islets of Langerhans in the pancreas by CD4 T_H1-mediated CD8 T cells, anti-β-cell antibodies, and macrophage activity. There is also evidence that viral infections can have either a potentiating or inhibitory role in the development of type 1 diabetes (T1D) mellitus. The destruction of the β cells causes a lack of insulin production by the pancreas. In T1D, β-cell destruction may take place over several years, but symptoms of hyperglycemia, extreme increase in thirst and urination, weight loss, and extreme fatigue usually have a sudden onset, and diagnosis usually does not occur until most β cells have already been destroyed.

Autoimmune Addison Disease

Destruction of the adrenal glands (the glands lying above the kidneys that produce glucocorticoids, mineralocorticoids, and sex steroids) is the cause of Addison disease, also called primary adrenal insufficiency (PAI). Today, up to 80% of Addison disease cases are diagnosed as autoimmune Addison disease (AAD), which is caused by an autoimmune response to adrenal tissues disrupting adrenal function. Disruption of adrenal function causes impaired metabolic processes that require normal steroid hormone levels, causing signs and symptoms throughout the body. There is evidence that both humoral and CD4 T_H1-driven CD8 T-cell–mediated immune mechanisms are directed at the adrenal cortex in AAD. There is also evidence that the autoimmune response is associated with autoimmune destruction of other endocrine glands as well, such as the pancreas and thyroid, conditions collectively referred to as autoimmune polyendocrine syndromes (APS). In up to 80% of patients with AAD, antibodies are produced to three enzymes involved in steroid synthesis: 21-hydroxylase (21-OH), 17α-hydroxylase, and cholesterol side-chain–cleaving enzyme.[3]The most common autoantibody found in AAD is to 21-OH, and antibodies to any of the key enzymes for steroid production are diagnostic for AAD. The adrenal cortex cells are targeted, destroyed, and replaced with fibrous tissue by immune-mediated inflammation. In some patients, at least 90% of the adrenal cortex is destroyed before symptoms become diagnostic.

Symptoms of AAD include weakness, nausea, decreased appetite, weight loss, hyperpigmentation (Figure **14.2.3**), hyperkalemia (elevated blood potassium levels), hyponatremia (decreased blood sodium levels), hypoglycemia(decreased levels of blood sugar), hypotension (decreased blood pressure), anemia, lymphocytosis (decreased levels of white blood cells), and fatigue. Under extreme stress, such as surgery, accidental trauma, or infection, patients with AAD may experience an adrenal crisis that causes the patient to vomit, experience abdominal pain, back or leg cramps, and even severe hypotension leading to shock.



Figure 14.2.3: Hyperpigmentation is a sign of Addison disease. (credit: modification of work by Petros Perros)

? Exercise 14.2.1

1. What are the names of autoimmune diseases that interfere with hormone gland function?
2. Describe how the mechanisms of Graves disease and Hashimoto thyroiditis differ.
3. Name the cells that are destroyed in type 1 diabetes mellitus and describe the result.

Systemic Autoimmune Diseases

Whereas organ-specific autoimmune diseases target specific organs or tissues, systemic autoimmune diseases are more generalized, targeting multiple organs or tissues throughout the body. Examples of systemic autoimmune diseases include multiple sclerosis, myasthenia gravis, psoriasis, rheumatoid arthritis, and systemic lupus erythematosus.

Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune central nervous system disease that affects the brain and spinal cord. Lesions in multiple locations within the central nervous system are a hallmark of multiple sclerosis and are caused by infiltration of immune cells across the blood-brain barrier. The immune cells include T cells that promote inflammation, demyelination, and neuron degeneration, all of which disrupt neuronal signaling. Symptoms of MS include visual disturbances; muscle weakness; difficulty with coordination and balance; sensations such as numbness, prickling, or “pins and needles”; and cognitive and memory problems.

Myasthenia Gravis

Autoantibodies directed against acetylcholine receptors (AChRs) in the synaptic cleft of neuromuscular junctions lead to myasthenia gravis (Figure 14.2.4). Anti-AChR antibodies are high-affinity IgGs and their synthesis requires activated CD4 T cells to interact with and stimulate B cells. Once produced, the anti-AChR antibodies affect neuromuscular transmission by at least three mechanisms:

- Complement binding and activation at the neuromuscular junction
- Accelerated AChR endocytosis of molecules cross-linked by antibodies
- Functional AChR blocking, which prevents normal acetylcholine attachment to, and activation of, AChR

Regardless of the mechanism, the effect of anti-AChR is extreme muscle weakness and potentially death through respiratory arrest in severe cases.

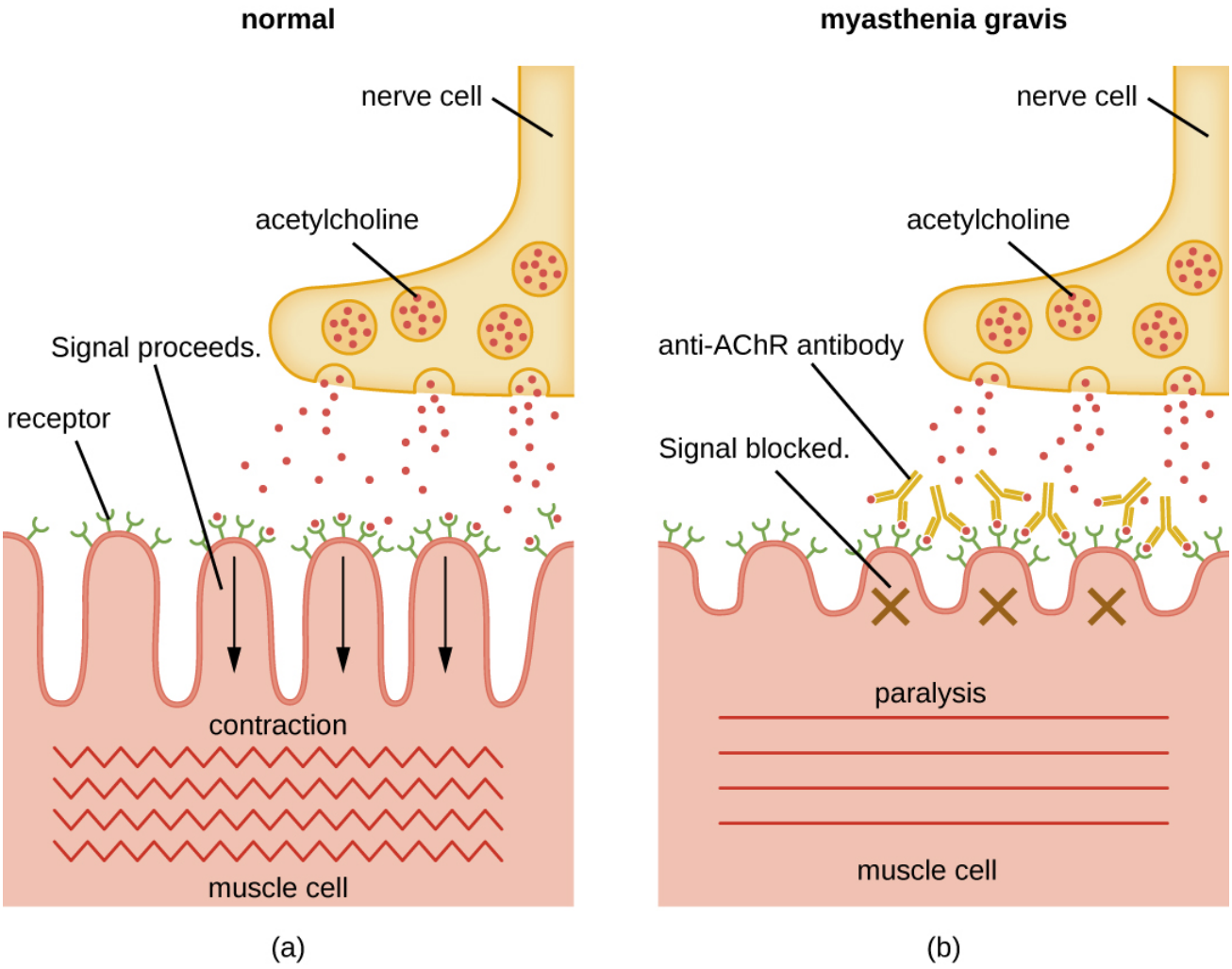


Figure 14.2.4: Myasthenia gravis and impaired muscle contraction. (a) Normal release of the neurotransmitter acetylcholine stimulates muscle contraction. (b) In myasthenia gravis, autoantibodies block the receptors for acetylcholine (AChr) on muscle cells, resulting in paralysis.

Psoriasis

Psoriasis is a skin disease that causes itchy or sore patches of thick, red skin with silvery scales on elbows, knees, scalp, back, face, palms, feet, and sometimes other areas. Some individuals with psoriasis also get a form of arthritis called psoriatic arthritis, in which the joints can become inflamed. Psoriasis results from the complex interplay between keratinocytes, dendritic cells, and T cells, and the cytokines produced by these various cells. In a process called cell turnover, skin cells that grow deep in the skin rise to the surface. Normally, this process takes a month. In psoriasis, as a result of cytokine activation, cell turnover happens in just a few days. The thick inflamed patches of skin that are characteristic of psoriasis develop because the skin cells rise too fast.

Rheumatoid Arthritis

The most common chronic inflammatory joint disease is rheumatoid arthritis (RA) (Figure 14.2.5) and it is still a major medical challenge because of unsolved questions related to the environmental and genetic causes of the disease. RA involves type III hypersensitivity reactions and the activation of CD4 T cells, resulting in chronic release of the inflammatory cytokines IL-1, IL-6, and tumor necrosis factor-α (TNF-α). The activated CD4 T cells also stimulate the production of rheumatoid factor (RF) antibodies and anticyclic citrullinated peptide antibodies (anti-CCP) that form immune complexes. Increased levels of acute-phase proteins, such as C-reactive protein (CRP), are also produced as part of the inflammatory process and participate in complement fixation with the antibodies on the immune complexes. The formation of immune complexes and reaction to the immune factors cause an inflammatory process in joints, particularly in the hands, feet, and legs. Diagnosis of RA is based on elevated levels of RF, anti-CCP, quantitative CRP, and the erythrocyte sedimentation rate (ESR) (modified Westergren). In addition, radiographs, ultrasound,

or magnetic resonance imaging scans can identify joint damage, such as erosions, a loss of bone within the joint, and narrowing of joint space.



Figure 14.2.5: The radiograph (left) and photograph (right) show damage to the hands typical of rheumatoid arthritis. (credit right: modification of work by “handarmdoc”/Flickr)

Systemic Lupus Erythematosus

The damage and pathology of systemic lupus erythematosus (SLE) is caused by type III hypersensitivity reactions. Autoantibodies produced in SLE are directed against nuclear and cytoplasmic proteins. Anti-nuclear antibodies (ANAs) are present in more than 95% of patients with SLE,[4] with additional autoantibodies including anti-double–stranded DNA (ds-DNA) and anti-Sm antibodies (antibodies to small nuclear ribonucleoprotein). Anti-ds-DNA and anti-Sm antibodies are unique to patients with SLE; thus, their presence is included in the classification criteria of SLE. Cellular interaction with autoantibodies leads to nuclear and cellular destruction, with components released after cell death leading to the formation of immune complexes.

Because autoantibodies in SLE can target a wide variety of cells, symptoms of SLE can occur in many body locations. However, the most common symptoms include fatigue, fever with no other cause, hair loss, and a sunlight-sensitive "butterfly" or wolf-mask (lupus) rash that is found in about 50% of people with SLE (Figure **14.2.6**). The rash is most often seen over the cheeks and bridge of the nose, but can be widespread. Other symptoms may appear depending on affected areas. The joints may be affected, leading to arthritis of the fingers, hands, wrists, and knees. Effects on the brain and nervous system can lead to headaches, numbness, tingling, seizures, vision problems, and personality changes. There may also be abdominal pain, nausea, vomiting, arrhythmias, shortness of breath, and blood in the sputum. Effects on the skin can lead to additional areas of skin lesions, and vasoconstriction can cause color changes in the fingers when they are cold (Raynaud phenomenon). Effects on the kidneys can lead to edema in the legs and weight gain. A diagnosis of SLE depends on identification of four of 11 of the most common symptoms and confirmed production of an array of autoantibodies unique to SLE. A positive test for ANAs alone is not diagnostic.

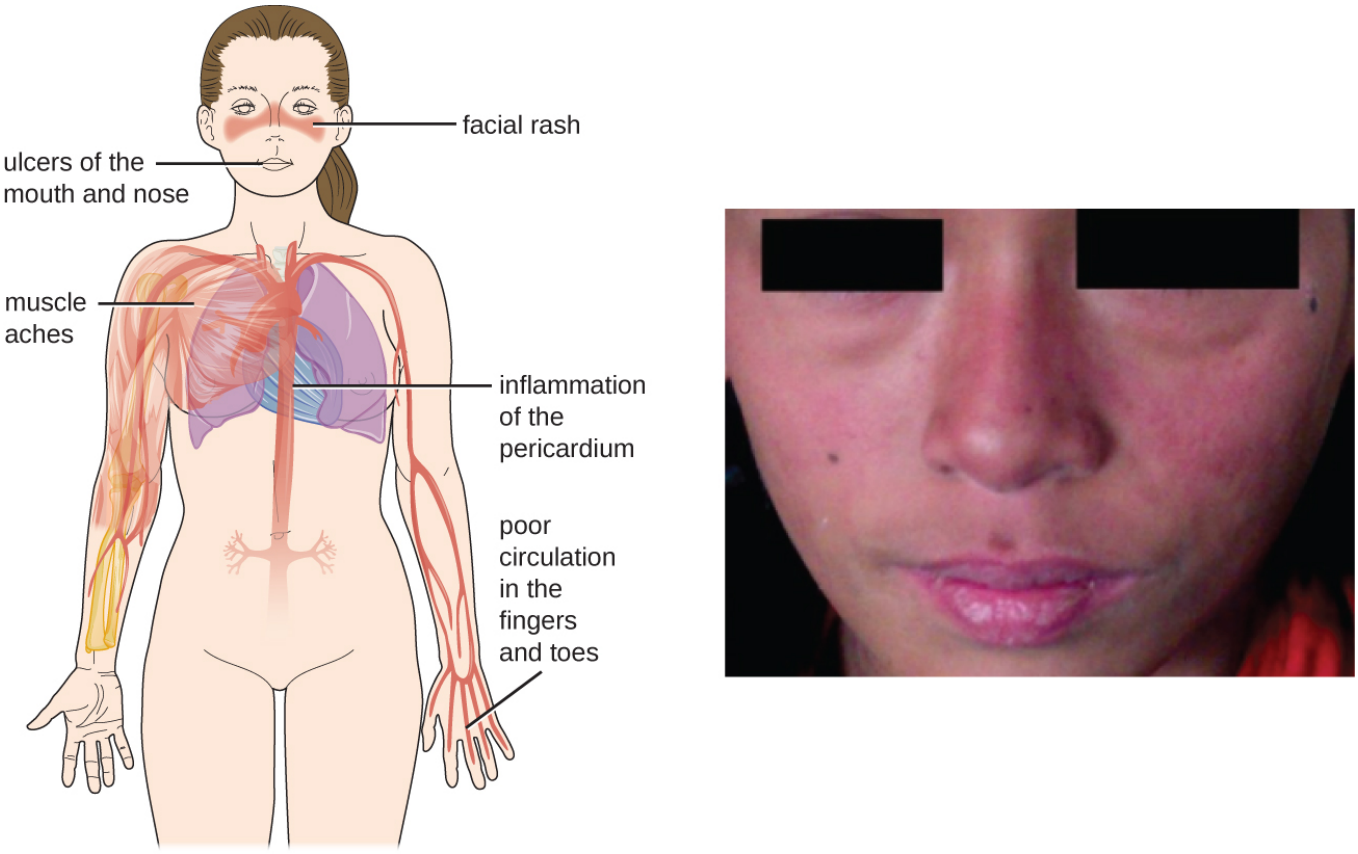


Figure **14.2.6**: (a) Systemic lupus erythematosus is characterized by autoimmunity to the individual's own DNA and/or proteins. (b) This patient is presenting with a butterfly rash, one of the characteristic signs of lupus. (credit a: modification of work by Mikael Häggström; credit b: modification of work by Shrestha D, Dhakal AK, Shiva RK, Shakya A, Shah SC, Shakya H)

? Exercise 14.2.2

1. List the ways antibodies contribute to the pathogenesis of myasthenia gravis.
2. Explain why rheumatoid arthritis is considered a type III hypersensitivity.
3. Describe the symptoms of systemic lupus erythematosus and explain why they affect so many different parts of the body.
4. What is recognized as an antigen in myasthenia gravis?

Table **14.2.1** summarizes the causes, signs, and symptoms of select autoimmune diseases.

Table **14.2.1**: Select Autoimmune Diseases

Disease	Cause	Signs and Symptoms
Addison disease	Destruction of adrenal gland cells by cytotoxic T cells	Weakness, nausea, hypotension, fatigue; adrenal crisis with severe pain in abdomen, lower back, and legs; circulatory system collapse, kidney failure
Celiac disease	Antibodies to gluten become autoantibodies that target cells of the small intestine	Severe diarrhea, abdominal pain, anemia, malnutrition
Diabetes mellitus (type I)	Cytotoxic T-cell destruction of the insulin-producing β cells of the pancreas	Hyperglycemia, extreme increase in thirst and urination, weight loss, extreme fatigue
Graves disease	Autoantibodies target thyroid-stimulating hormone receptors, resulting in overstimulation of the thyroid	Hyperthyroidism with rapid and irregular heartbeat, heat intolerance, weight loss, goiter, exophthalmia
Hashimoto thyroiditis	Thyroid gland is attacked by cytotoxic T cells, lymphocytes, macrophages, and autoantibodies	Thyroiditis with goiter, cold intolerance, muscle weakness, painful and stiff joints, depression, memory loss
Multiple sclerosis (MS)	Cytotoxic T-cell destruction of the myelin sheath surrounding nerve axons in the central nervous system	Visual disturbances, muscle weakness, impaired coordination and balance, numbness, prickling or “pins and needles” sensations, impaired cognitive function and memory
Myasthenia gravis	Autoantibodies directed against acetylcholine receptors within the neuromuscular junction	Extreme muscle weakness eventually leading to fatal respiratory arrest
Psoriasis	Cytokine activation of keratinocytes causes rapid and excessive epidermal cell turnover	Itchy or sore patches of thick, red skin with silvery scales; commonly affects elbows, knees, scalp, back, face, palms, feet
Rheumatoid arthritis	Autoantibodies, immune complexes, complement activation, phagocytes, and T cells damage membranes and bone in joints	Joint inflammation, pain and disfigurement, chronic systemic inflammation
Systemic lupus erythematosus (SLE)	Autoantibodies directed against nuclear and cytoplasmic molecules form immune complexes that deposit in tissues. Phagocytic cells and complement activation cause tissue damage and inflammation	Fatigue, fever, joint pain and swelling, hair loss, anemia, clotting, a sunlight-sensitive "butterfly" rash, skin lesions, photosensitivity, decreased kidney function, memory loss, confusion, depression

Key Concepts and Summary

- **Autoimmune diseases** result from a breakdown in immunological tolerance. The actual induction event(s) for autoimmune states are largely unknown.
- Some autoimmune diseases attack specific organs, whereas others are more systemic.
- Organ-specific autoimmune diseases include **celiac disease**, **Graves disease**, **Hashimoto thyroiditis**, **type I diabetes mellitus,** and **Addison disease**.
- Systemic autoimmune diseases include **multiple sclerosis**, **myasthenia gravis**, **psoriasis**, **rheumatoid arthritis**, and **systemic lupus erythematosus**.
- Treatments for autoimmune diseases generally involve anti-inflammatory and immunosuppressive drugs.

Footnotes

1. 1 D.A. Van Heel, J. West. “Recent Advances in Coeliac Disease.” *Gut* 55 no. 7 (2006):1037—1046.
2. 2 ibid.
3. 3 P. Martorell et al. “Autoimmunity in Addison’s Disease.” *Netherlands Journal of Medicine* 60 no. 7 (2002):269—275.
4. 4 C.C. Mok, C.S. Lau. “Pathogenesis of Systemic Lupus Erythematosus.” *Journal of Clinical Pathology* 56 no. 7 (2003):481—490.

This page titled 14.2: Autoimmune Disorders is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **19.2: Autoimmune Disorders** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

14.3: Superantigens

Learning Objectives

1. Define superantigen.
2. Briefly describe the mechanism by which superantigens cause harm to the body.
3. Name 2 superantigens and give an example of a bacterium that produces each.

As was learned earlier under Bacterial Pathogenicity, superantigens are type I toxins that can trigger a harmful immune response. Exotoxins are toxins, often proteins in nature, secreted from a living bacterium but also released upon bacterial lysis. In addition, some bacteria use a type 3 secretion system or a type 4 secretion system to inject toxins directly into human cells. There are three main types of exotoxins:

1. Superantigens (Type I toxins),
2. Exotoxins that damage host cell membranes (Type II toxins)
3. A-B toxins and other toxin that interfere with host cell function (TypeIII toxins).

We will look at superantigens and their role in hypersensitivity.

Learning Objectives

1. Define superantigen.
2. Briefly describe the mechanism by which superantigens cause harm to the body.
3. Name 2 superantigens and give an example of a bacterium that produces each.

Highlighted Bacterium

1. Read the description of *Streptococcus pyogenes* and match the bacterium with the description of the organism and the infection it causes.

Superantigens are unusual bacterial toxins that interact with exceedingly large numbers of T4-lymphocytes. They bind to the surface of the target cell but do not enter the cell.

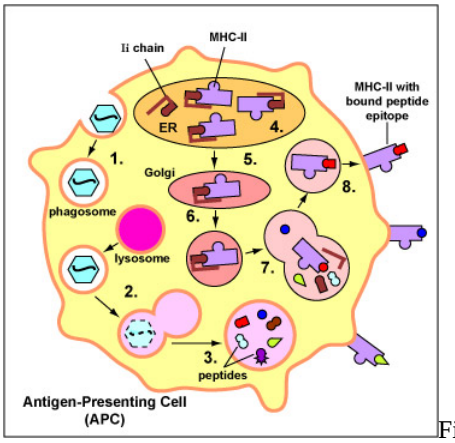


Figure **14.3.1**: Binding of Peptide Epitopes from Exogenous Antigens to MHC-II Molecules. Exogenous antigens are those from outside cells of the body. Examples include bacteria, free viruses, yeasts, protozoa, and toxins. These exogenous antigens enter antigen-presenting cells or APCs (macrophages, dendritic cells, and B-lymphocytes) through phagocytosis. The microbes are engulfed and placed in a phagosome. After lysosomes fuse with the phagosome, protein antigens are degraded by proteases into a series of peptides. These peptides eventually bind to grooves in MHC-II milecules and are transported to the surface of the APC. T4-lymphocytes are then able to recognize peptide/MHC-II complexes by means of their T-cell receptors (TCRs) and CD4 molecules. 1. Exogenous antigens, such as viruses, are engulfed and placed in a phagosome. 2. Lysosomes fuse with the phagosome forming an phagolysosome. 3. Protein antigens are degraded into a series of peptides. 4. MHC-II molecules are synthesized in the endoplasmic reticulum and transported to the Golgi complex. Once assembled, within the endoplasmic reticulum, a protein called the invarient chain (Ii) attaches to the the peptide-binding groove of the MHC-II molecules

and in this way prevents peptides designated for binding to MHC-I molecules within the ER from attaching to the MHC-II. 5&6. The MHC-II molecules with bound Ii chain are now transported to the Golgi complex, and placed in vesicles. 7. The vesicles containing the MHC-II molecules fuse with the peptide-containing phaglysosomes. The Ii chain is removed and the peptides are now free to bind to the grooves of the MHC-II molecules. 8. The MHC-II molecules with bound peptides are transported to the cytoplasmic membrane where they become anchored. Here, the peptide and MHC-II complexes can be recognized by T4-lymphocytes by way of TCRs and CD4 molecules having a complementary shape.

Conventional antigens are engulfed by antigen presenting cells (APCs), degraded into epitopes, bind to the peptide groove of MHC-II molecules, and are put on the surface of the APC(Figure **14.3.1**). Here they are recognized by specific T4-lymphocytes having a TCR with a corresponding shape (Figure **14.3.2**).

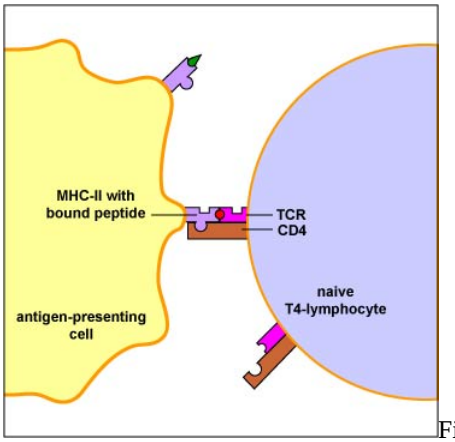


Figure **14.3.2**: Binding of T4-Lymphocytes to Conventional Antigens. Conventional antigens are only recognized by specific T4-lymphocytes having a TCR with a shape that corresponds to a peptide of that antigen bound to MHC-II molecules.

Superantigens, however, bind directly to the outside of MHC-II molecules and activate large numbers of T4-lymphocytes (Figure **14.3.3**). This activation of very large numbers of T4-lymphocytes results in the secretion of excessive amounts of a cytokine called interleukin-2 (IL-2) as well as the activation of self-reactive T-lymphocytes. The normal response to a conventional antigen results in the activation of maybe 1 in 10,000 T-lymphocytes; superantigens can activate as many as 1 in 5 T-lymphocytes.

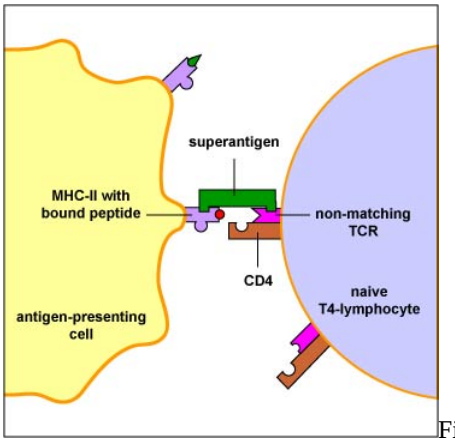


Figure **14.3.3**: Binding of Superantigens. Conventional antigens are only recognized by specific T4-lymphocytes having a TCR with a shape that corresponds to a peptide of that antigen bound to MHC-II molecules. Superantigens, on the other hand, bind directly to the outside of MHC-II molecules and the TCRs and activate many T4-lymphocytes. A specific TCR is not required for activation.

Production of high levels of IL-2 can result in circulation of IL-2 in the blood leading to symptoms such as fever, nausea, vomiting, diarrhea, and malaise. However, excess stimulation of IL-2 secretion can also lead to production of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (IL-1), inflammatory chemokines such as IL-8, and platelet-activating factor (PAF), and can lead to the same endothelial damage, acute respiratory

distress syndrome, disseminated intravascular coagulation, shock, and multiple organ system failure seen above with LPS and other bacterial cell wall factors. Activation of self-reactive T-lymphocytes can also lead to autoimmune attack.

The following are examples of superantigens.

1. Toxic shock syndrome toxin-1 (TSST-1), produced by some strains of *Staphylococcus aureus.* This exotoxin causes toxic shock syndrome (TSS). Excessive cytokine production leads to fever, rash, and shock.
2. Streptococcal pyrogenic exotoxin (Spe), produced by rare invasive strains and scarlet fever strains of *Streptococcus pyogenes* (the group A beta streptococci). *S pyogenes* produces a number of SPEs that are cytotoxic, pyrogenic, enhance the lethal effects of endotoxins, and contribute to cytokine-induced inflammatory damage. SPEs are responsible for causing streptococcal toxic shock syndrome (STSS) whereby excessive cytokine production leads to fever, rash, and triggering the shock cascade. The SPEs also appear to be responsible for inducing necrotizing fasciitis, a disease that can destroy the skin, fat, and tissue covering the muscle (the fascia). SPE B is also a precursor for a cysteine protease that can destroy muscles tissue.

> Read the description of *Streptococcus pyogenes*, and be able to match the bacterium with its description on an exam.

3. Staphylococcal enterotoxins (SE), producedby many strains of *Staphylococcus aureus.* These exotoxins cause staphylococcal food poisoning. Excessive Il-2 production results in fever, nausea, vomiting,and diarrhea. The vomiting may also be due to these toxins stimulating the vagus nerve in the stomach lining that controls vomiting.
4. ETEC enterotoxin, produced by enterotoxogenic *E. coli* (ETEC), one of the most common causes of traveler's diarrhea.

? Exercise: Think-Pair-Share Questions

What is the mechanism by which superantigens ultimately lead to SIRS?

Summary

1. Conventional antigens are only recognized by specific T4-cells having a TCR with a corresponding shape.
2. Superantigens are unusual bacterial toxins that interact with exceedingly large numbers of T4-lymphocytes.
3. Activation of very large numbers of T4-lymphocytes results in the secretion of excessive amounts of a cytokine called interleukin-2 (IL-2).
4. Excess stimulation of IL-2 secretion can also lead to production of inflammatory and can lead to the same endothelial damage, acute respiratory distress syndrome, disseminated intravascular coagulation, shock, and multiple organ system failure seen with PAMP-induced inflammation.
5. Examples of superantigens include toxic shock syndrome toxin-1 (TSST-1), Streptococcal pyrogenic exotoxins (SPE), Staphylococcal enterotoxins (SE), and enterotoxogenic E. coli (ETEC) enterotoxin.

Questions

Study the material in this section and then write out the answers to these questions. Do not just click on the answers and write them out. This will not test your understanding of this tutorial.

1. Define superantigen *(ans)*.
2. Briefly describe the mechanism by which superantigens cause harm to the body. *(ans)*
3. Name 2 superantigens and give an example of a bacterium that produces each.
   A. *(ans)*
   B. *(ans)*
4. Multiple Choice *(ans)*

This page titled 14.3: Superantigens is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **16.6: Superantigens** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.
- **6.2A: Type I Toxins: Superantigens** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

14.4: Immunity Disorders- Immunodeficiencies

This page titled 14.4: Immunity Disorders- Immunodeficiencies is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **12.6: Immunity Disorders- Immunodeficiencies** is licensed CC BY-SA 4.0.

14.5: Cell-Mediated Autoimmune Reactions

Learning Objectives

- Define cell-mediated autoimmunity and describe the mechanisms that are thought to operate in the pathogenesis of autoimmune disease

Several mechanisms are thought to be operative in the pathogenesis of autoimmune diseases, against a backdrop of genetic predisposition and environmental modulation. Four of the important mechanisms are described below.

T Cell Bypass

A normal immune system requires the activation of B cells by T cells before the former can produce antibodies in large quantities. This requirement of a T cell can be bypassed in rare instances, such as infection by organisms producing super-antigens, which are capable of initiating polyclonal activation of B cells, or even of T cells, by directly binding to the β-subunit of T cell receptors in a non-specific fashion.

T Cell to B Cell Discordance

A normal immune response is assumed to involve B and T cell responses to the same antigen, where B cells recognize conformations on the surface of a molecule for B cells, and T cells recognize pre-processed peptide fragments of proteins for T cells. However, there is no evidence that this response is required. All that is required is that a B cell that recognizes antigen X endocytoses processes a protein Y (normally =X) and presents it to a T cell. Roosnek and Lanzavecchia showed that B cells recognizing IgGFc could get help from any T cell that responds to an antigen co-endocytosed with IgG by the B cell as part of an immune complex. In coeliac disease it seems likely that B cells that recognize transglutamine tissue are helped by T cells that recognize gliadin.

Aberrant B Cell Receptor-Mediated Feedback

A feature of human autoimmune disease is that it is largely restricted to a small group of antigens, several of which have known signaling roles in the immune response (for example DNA, C1q, IgGFc, Ro, Con. A receptor, Peanut agglutinin receptor(PNAR)). This fact gave rise to the idea that spontaneous autoimmunity may result when the binding of antibody to certain antigens leads to aberrant signals being fed back to parent B cells through membrane bound ligands. These ligands include B cell receptor (for antigen), IgG Fc receptors, CD21 (which binds complement C3d), Toll-like receptors 9 and 7 (which can bind DNA and nucleoproteins) and PNAR. More indirect aberrant activation of B cells can also be envisaged with autoantibodies to acetyl choline receptor (on thymic myoid cells) and hormone binding proteins. Together with the concept of T cell-B cell discordance, this idea forms the basis of the hypothesis of self-perpetuating autoreactive B cells. Autoreactive B cells in spontaneous autoimmunity are seen as surviving because of subversion both of the T cell help pathway and of the feedback signal through the B cell receptor. This reaction thereby overcomes the negative signals responsible for B cell self-tolerance without necessarily requiring loss of T cell self-tolerance.

Dendritic Cell Apoptosis

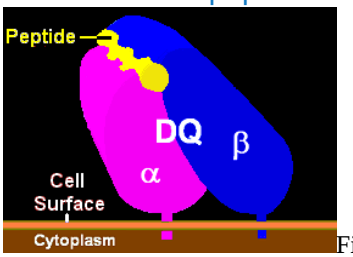


Figure: **MHC Class II, DQ**: HLA-DQ (DQ) is a cell surface receptor type protein found on antigen presenting cells (APC). DQ is an alpha-beta heterodimer of the MHC class II type.

Immune system cells called dendritic cells present antigens to active lymphocytes. Dendritic cells that are defective in apoptosis can lead to inappropriate systemic lymphocyte activation and consequent decline in self-tolerance.

HLA-DQ (DQ) is a cell surface receptor type protein found on antigen presenting cells. DQ is an α heterodimer of the MHC Class II type. The α and β chains are encoded by HLA-DQA1 and HLA-DQB1, respectively. These two loci are adjacent to each other on chromosome 6p21.3. Both the α-chain and β-chain vary greatly. A person often produces two α-chain and two β-chain variants and thus four DQ isoforms.

DQ isoforms can bind to and present foreign and self antigens to T-cells. In this process T-cells are stimulated to grow and can signal B-cells to produce antibodies. DQ therefore is involved in recognizing common self-antigens and presenting those antigens to the immune system in order to develop tolerance from a very young age. When tolerance to self proteins is lost, DQ may become involved in autoimmune disease. Two autoimmune diseases in which HLA-DQ is involved are celiac disease and diabetes mellitus type 1. DQ is one of several antigens involved in rejection of organ transplants. As a variable cell surface receptor on immune cells, these D antigens, originally HL-A4 antigens, are involved in graft versus host disease when lymphoid tissues are transplanted between people.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: ***CC BY-SA: Attribution-ShareAlike***

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- OpenStax College, Biology. October 17, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44831/latest...ol11448/latest. **License**: ***CC BY: Attribution***
- HIV/AIDS. **Provided by**: Wikipedia. **Located at**: http://en.Wikipedia.org/wiki/HIV/AIDS. **License**: ***CC BY-SA: Attribution-ShareAlike***
- immunodeficiency. **Provided by**: Wiktionary. **Located at**: http://en.wiktionary.org/wiki/immunodeficiency. **License**: ***CC BY-SA: Attribution-ShareAlike***
- phagocyte. **Provided by**: Wiktionary. **Located at**: http://en.wiktionary.org/wiki/phagocyte. **License**: ***CC BY-SA: Attribution-ShareAlike***
- lysis. **Provided by**: Wiktionary. **Located at**: http://en.wiktionary.org/wiki/lysis. **License**: *CC BY-SA: Attribution-ShareAlike*
- HIV-budding-Color. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:HI...ding-Color.jpg**. **License**: *CC BY: Attribution*
- Autoimmunity. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Autoimmunity**. **License**: *CC BY-SA: Attribution-ShareAlike*
- autoimmunity. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/autoimmunity**. **License**: *CC BY-SA: Attribution-ShareAlike*
- alloimmunity. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/alloimmunity**. **License**: *CC BY-SA: Attribution-ShareAlike*
- HIV-budding-Color. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:HI...ding-Color.jpg**. **License**: *CC BY: Attribution*
- DR Illustration. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:DR_Illustration.PNG**. **License**: ***Public Domain: No Known Copyright***
- Autoimmunity. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Autoimmunity%23Sex**. **License**: *CC BY-SA: Attribution-ShareAlike*
- alloimmunity. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/alloimmunity**. **License**: *CC BY-SA: Attribution-ShareAlike*
- autoimmunity. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/autoimmunity**. **License**: *CC BY-SA: Attribution-ShareAlike*
- HIV-budding-Color. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:HI...ding-Color.jpg**. **License**: *CC BY: Attribution*
- DR Illustration. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:DR_Illustration.PNG**. **License**: ***Public Domain: No Known Copyright***
- DR Illustration. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:DR_Illustration.PNG**. **License**: ***Public Domain: No Known Copyright***

- Arthus reaction. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Arthus_reaction**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Immune complex. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Immune_complex**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- immune complex. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/immune%20complex**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- epitope. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/epitope**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- HIV-budding-Color. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:HIV-budding-Color.jpg**. **License**: ***CC BY: Attribution***
- DR Illustration. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:DR_Illustration.PNG**. **License**: ***Public Domain: No Known Copyright***
- DR Illustration. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:DR_Illustration.PNG**. **License**: ***Public Domain: No Known Copyright***
- Immune22. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Immune22.gif**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- HLA-DQ. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/HLA-DQ**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Autoimmunity. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Autoimmunity**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- tolerance. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/tolerance**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- autoimmunity. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/autoimmunity**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- HIV-budding-Color. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:HIV-budding-Color.jpg**. **License**: ***CC BY: Attribution***
- DR Illustration. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:DR_Illustration.PNG**. **License**: ***Public Domain: No Known Copyright***
- DR Illustration. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:DR_Illustration.PNG**. **License**: ***Public Domain: No Known Copyright***
- Immune22. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Immune22.gif**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- HLA-DQ. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/HLA-DQ**. **License**: ***Public Domain: No Known Copyright***

Key Points

- Superantigens can bypass the T-cell requirement for B cell activation.
- In some instances such as celiac disease, B cells can be activated to produce antibodies to epitope A by T cells activated by epitope B.
- Autoreactive B cells in spontaneous autoimmunity survive due to subversion both of the T cell help pathway and of the feedback signal through B cell receptor, leading to loss of the negative signals responsible for B cell self- tolerance without necessarily requiring loss of T cell self-tolerance.
- DQ therefore is involved in recognizing common self- antigens and presenting those antigens to the immune system in order to develop tolerance from a very young age.

Key Terms

- **autoimmunity**: The condition where one's immune system attacks one's own tissues, i.e., an autoimmune disorder.
- **tolerance**: The process by which the immune system does not attack an antigen

This page titled 14.5: Cell-Mediated Autoimmune Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **12.5E: Cell-Mediated Autoimmune Reactions** is licensed CC BY-SA 4.0.

14.6: Immune Complex Autoimmune Reactions

Learning Objectives

- Describe how immune complex autoimmune reactions arise

An immune complex is formed from the integral binding of an antibody to a soluble antigen. The bound antigen acting as a specific epitope, bound to an antibody is referred to as a singular immune complex. After an antigen-antibody reaction, the immune complexes can be subject to any of a number of responses, including complement deposition, opsonization, phagocytosis, or processing by proteases. Red blood cells carrying CR1-receptors on their surface may bind C3b-decorated immune complexes and transport them to phagocytes, mostly in liver and spleen, and return back to the general circulation. Immune complexes may cause disease when they are deposited in organs, e.g. in certain forms of vasculitis. This is the third form of hypersensitivity in the Gell-Coombs classification, called Type III hypersensitivity. Immune complex deposition is a prominent feature of several autoimmune diseases, including systemic lupus erythematosus, cryoglobulinemia, rheumatoid arthritis, scleroderma, and Sjögren's syndrome.

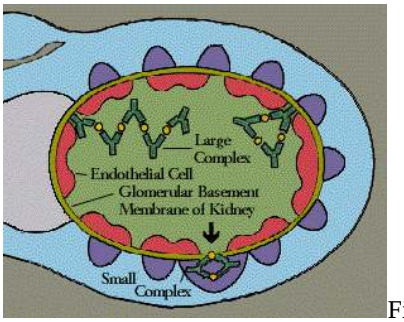


Figure: **Immune Complex Diseases**: An immune complex is formed from the integral binding of an antibody to a soluble antigen. The bound antigen acting as a specific epitope, bound to an antibody is referred to as a singular immune complex.

In immunology, the Arthus reaction is a type of local type III hypersensitivity reaction. Type III hypersensitivity reactions are immune complex-mediated. They involve the deposition of antigen/antibody complexes mainly in the vascular walls, serosa (pleura, pericardium, synovium), and glomeruli. The Arthus reaction involves the in situformation of antigen/antibody complexes after the intradermal injection of an antigen (as seen in passive immunity). If the animal/patient was previously sensitized (has circulating antibody), an Arthus reaction occurs. Typical of most mechanisms of the type III hypersensitivity, Arthus manifests as local vasculitis due to deposition of IgG-based immune complexes in dermal blood vessels. Activation of complement primarily results in cleavage of soluble complement proteins forming C5a and C3a, which activate recruitment of PMNs and local mast cell degranulation (requiring the binding of the immune complex onto FcγRIII), resulting in an inflammatory response. Further aggregation of immune complex-related processes induces a local fibrinoid necrosis with ischemia-aggravating thrombosis in the tissue vessel walls. The end result is a localized area of redness and induration that typically lasts a day or so. Arthus reactions have been infrequently reported after vaccination against diphtheria and tetanus.

Key Points

- After an antigen – antibody reaction, the immune complexes can be subject to any of a number of responses including complement deposition, opsonization, phagocytosis, or processing by proteases.
- Immune complexes may cause disease when they are deposited in organs.
- The Arthus reaction involves the in situ formation of antigen/antibody complexes after the intradermal injection of an antigen (as seen in passive immunity).

Key Terms

- **epitope**: That part of a biomolecule (such as a protein) that is the target of an immune response.
- **immune complex**: An immune complex is formed from the integral binding of an antibody to a soluble antigen. The bound antigen acting as a specific epitope, bound to an antibody is referred to as a singular immune complex.

This page titled 14.6: Immune Complex Autoimmune Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **12.5D: Immune Complex Autoimmune Reactions** is licensed CC BY-SA 4.0.

14.7: Cytotoxic Autoimmune Reactions

Learning Objectives

- Define autoimmunity and describe how it can lead to disease

Autoimmunity is the failure of an organism in recognizing its own constituent parts as self, creating an immune response against its own cells and tissues. Any disease that results from such an aberrant immune response is termed an *autoimmune* disease.

Autoimmunity is often caused by a lack of germ development of a target body and, as such, the immune response acts against its own cells and tissues. Prominent examples include Coeliac disease, diabetes mellitus type 1 (IDDM), Sarcoidosis, systemic lupus erythematosus (SLE), Sjögren's syndrome, Churg-Strauss Syndrome, Hashimoto's thyroiditis, Graves' disease, idiopathic thrombocytopenic purpura, Addison's Disease, rheumatoid arthritis (RA) and allergies.

Autoimmune diseases are very often treated with steroids. The misconception that an individual's immune system is totally incapable of recognizing self antigens is not new. Paul Ehrlich, at the beginning of the twentieth century, proposed the concept of horror autotoxicus, wherein a 'normal' body does not mount an immune response against its own tissues. Thus, any autoimmune response was perceived to be abnormal and postulated to be connected with human disease. Now, it is accepted that autoimmune responses are an integral part of vertebrate immune systems (sometimes termed 'natural autoimmunity'), normally prevented from causing disease by the phenomenon of immunological tolerance to self-antigens.

Autoimmunity should not be confused with *alloimmunity*. Certain individuals are genetically susceptible to developing autoimmune diseases. This susceptibility is associated with multiple genes plus other risk factors. Genetically predisposed individuals do not always develop autoimmune diseases. Three main sets of genes are suspected in many autoimmune diseases: immunoglobulins, T-cell receptors and the major histocompatibility complexes (MHC).

Immunoglobulins and the T-cell receptors are involved in the recognition of antigens and they are inherently variable and susceptible to recombination. These variations enable the immune system to respond to a very wide variety of invaders, but may also give rise to lymphocytes capable of self-reactivity. Scientists such as H. McDevitt, G. Nepom, J. Bell and J. Todd have also provided strong evidence to suggest that certain MHC class II allotypes are strongly correlated with autoimmunity.

For example:

1. HLA DR2 is strongly positively correlated with Systemic Lupus Erythematosus, narcolepsy and multiple sclerosis, and negatively correlated with DM Type 1.

2. HLA DR3 is correlated strongly with Sjögren's syndrome, myasthenia gravis, SLE, and DM Type 1.

3. HLA DR4 is correlated with the genesis of rheumatoid arthritis, Type 1 diabetes mellitus, and pemphigus vulgaris.

Fewer correlations exist with MHC class I molecules. The most notable and consistent is the association between HLA B27 and ankylosing spondylitis. Correlations may exist between polymorphisms within class II MHC promoters and autoimmune disease. The contributions of genes outside the MHC complex remain the subject of research both in animal models of disease (Linda Wicker's extensive genetic studies of diabetes in the NOD mouse), and in patients (Brian Kotzin's linkage analysis of susceptibility to SLE).

A person's sex also seems to have some role in the development of autoimmunity, classifying most autoimmune diseases as sex-related diseases. Nearly 75% of the more than 23.5 million Americans who suffer from autoimmune disease are women, although it is less-frequently acknowledged that millions of men also suffer from these diseases.

According to the American Autoimmune Related Diseases Association (AARDA), autoimmune diseases that develop in men tend to be more severe. A few autoimmune diseases that men are just as or more likely to develop as women, include: ankylosing spondylitis, type 1 diabetes mellitus, Wegener's granulomatosis, Crohn's disease, Primary sclerosing cholangitis and psoriasis.

The reasons for the sex role in autoimmunity are unclear. Women appear to generally mount larger inflammatory responses than men when their immune systems are triggered, increasing the risk of autoimmunity. Similarly, involvement of sex steroids is indicated by the fact that many autoimmune diseases tend to fluctuate in accordance with hormonal changes. Interestingly, a history

of pregnancy also appears to leave a persistent increased risk for autoimmune disease. Indeed, it has been suggested that the slight exchange of cells between mothers and their children during pregnancy may induce autoimmunity. This would tip the gender balance in the direction of the female.

Another theory suggests the female-high tendency to get autoimmunity is due to an imbalanced X chromosome inactivation. The X-inactivation skew theory, proposed by Princeton University's Jeff Stewart, has recently been confirmed experimentally in scleroderma and autoimmune thyroiditis.

Key Points

- Autoimmunity is often caused by a lack of germ development of a target body and, as such, the immune response acts against its own cells and tissues.
- Certain individuals are genetically susceptible to developing autoimmune diseases but genetically predisposed individuals do not always develop an autoimmune disease.
- Three main sets of genes are suspected in many autoimmune diseases: immunoglobulins, T-cell receptors and the major histocompatibility complexes (MHC).
- Women are more likely to develop an autoimmune disease.

Key Terms

- **alloimmunity**: Immunity, obtained from another, against one's own cells.
- **autoimmunity**: The condition where one's immune system attacks one's own tissues, i.e., an autoimmune disorder.

This page titled 14.7: Cytotoxic Autoimmune Reactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **12.5C: Cytotoxic Autoimmune Reactions** is licensed CC BY-SA 4.0.

14.8: Primary Immunodeficiency

Learning Objectives

1. Define primary immunodeficiency.
2. Compare and contrast conventional and novel primary immunodeficiencies.
3. Name four categories of conventional immunodeficiencies and give an example of each.

A primary immunodeficiency is usually an immunodeficiency that one is born with. Until recently, primary immunodeficiencies were defined as a rare recessive genetic defect in the immune responses that involved the development of B-lymphocytes, T-lymphocytes, or both and resulted in multiple, recurrent infections during infancy. Depending on the disorder, the lymphocytes in question were either completely absent, present in very low levels, or present but not functioning normally. These disorders represent the conventional immunodeficiencies.

However, based on our increased understanding of the human genome and immune responses it now appears that there are a multitude of common, less severe primary immunodeficiencies involving just one or more of the huge number of genes involved in the immune responses. These so called novel primary immunodeficiencies involve the decreased ability to combat just a single type of infection or a narrow range of infections. The conventional primary immunodeficiencies were grouped as follows:

Conventional: B-lymphocyte Disorders

In the case of B-lymphocyte disorders, there may be may be greatly decreased humoral immunity but cell-mediated immunity , mediated by T-lymphocytes, remains normal.

1. Agammaglobulinemias: Few if any antibodies are produced and there are reduced B-lymphocyte numbers. The person is very susceptible to recurrent infections by common pyogenic bacteria such as *Staphylococcus aureus, Streptococcus pyogenes, Streptococcus pneumoniae, Neisseria meningitidis,* and *Hemophilus influenzae. These* bacteria have antiphagocytic capsules that are normally eliminated by antibodies through opsonization. Examples include X-linked agammaglobulinemia and Autosomal recessive agammaglobulinemia.

2. Hypogammaglobulinemias /Isotype Defects: Decreased general antibody production or decrease production of a single isotype of antibody. Examples include:

- *IgG2 subclass deficiency:* A person is unable to produce the subclass of IgG called IgG2 but can produce other classes of antibodies. There is increased susceptibility to bacterial infections.
- *Selective IgA deficiency:* A person is unable to make IgA but can produce other classes of antibodies. There is increased susceptibility to bacterial infections and certain protozoan infections.
- *Combined Variable Immunodeficiency* (CVID): Hypogammaglobulinemia with normal or decreased numbers of B-lymphocytes.

More severe forms such as agammaglobulinemia are treated with artificially-acquired passive immunization - periodic injections of large amounts of immune globulin (IG or IVIG).

Conventional: T-lymphocyte Disorders

In the case of T-lymphocyte disorders, there is little or no cell-mediated immunity if the disorder involves T8-lymphocytes and/or T4-lymphocytes. There may also be decreased humoral immunity if there is a disorder involves T4-lymphocytes.

1. MHC Expression Defects

- MHC-I deficiency. Decreased levels of MHC-I production and reduced T8-lymphocyte numbers.
- Bare lymphocyte syndrome. Decreased levels of MHC-II, decreased numbers of T4-lymphocytes, and decreased T4-dependent antibody production by B-lymphocytes.

2. T-Lymphocyte Signaling Defects

- Wiskott-Aldrich syndrome. Defective T-lymphocyte activation and defective leukocyte mobility.
- Proximal TCR signaling defects. Defective cell-mediated immunity and defective T4-dependent antibody production by B-lymphocytes.

3. Familial Hemophagocytic Lymphohistiocytosis

- Perforin deficiencies. Defective CTL and NK cell function; uncontrolled activation of macrophages and CTLs.
- Granule fusion defects. Defective CTL and NK cell function; uncontrolled activation of macrophages and CTLs.
- X-linked lymphoproliferative syndrome. Defective CTL and NK cell function; uncontrolled activation of macrophages and CTLs. Uncontrolled Epstein-Barr virus - induced B-lymphocyte proliferation.

Conventional: Combined B- and T-lymphocyte Disorders (Severe Combined Immunodeficiency Disease or SCID)

Severe combined immunodeficiency disease or SCID affects both humoral immunity and cell-mediated immunity . There is a defect in both B-lymphocytes and T-lymphocytes, or just T-lymphocytes in which case the humoral deficiency is due to the lack of T4-helper lymphocytes.

1. Cytokine-Signaling Defects

- Autosomal recessive SCID. Shows a marked decrease in T-lymphocytes but normal to increased levels of B-lymphocytes. There is reduced antibody levels due to the lack of T4-helper lymphocytes.
- X-linked recessive SCID. Shows a marked decrease in T-lymphocytes but normal to increased levels of B-lymphocytes. There is reduced antibody levels due to the lack of T4-helper lymphocytes.

2. Defects in Nucleotide Salvage Pathways

- PNP deficiency. Shows a progressive decrease in both T-lymphocytes, B-lymphocytes, and NK cells, as well as reduced antibody levels.
- ADA deficiency. Shows a progressive decrease in both T-lymphocytes, B-lymphocytes, and NK cells, as well as reduced antibody levels.

3. Defects in V(D)J Recombination (Combinatorial Diversity)

- RAG1 or RAG2 deficiency. Shows an absence or deficiency of both T-lymphocytes and B-lymphocytes, as well as reduced antibody levels.
- ARTEMIS defects. Shows an absence or deficiency of both T-lymphocytes and B-lymphocytes, as well as reduced antibody levels.

4. Defective Thymus Development

The thymus is needed for the development of T-lymphocytes from stem cells.

- DiGeorge syndrome. Shows decreased levels of T-lymphocytes, normal levels of B-lymphocytes, and reduced antibody levels.
- Defective pre-TCR checkpoint. Shows decreased levels of T-lymphocytes, normal or reduced levels of B-lymphocytes, and reduced antibody levels.

Conventional: Innate Immunity Disorders

- Chronic granulomatous disease. No oxygen-dependant killing pathway in phagocytes. Recurrent intracellular bacterial and fungal infections.
- Leukocyte adhesion deficiencies. Defective leukocyte adhesion, diapedesis , and migration. Recurrent bacterial and fungal infections.

- Chediak-Higashi syndrome. Defective vesicle fusion and lysosomal function in neutrophils, dendritic cells, macrophages and other cells. Recurrent infections by pyogenic bacteria.

Novel Immunodeficiencies

While the rare conventional primary immunodeficiencies mentioned above are still very important, based on our increased understanding of the human genome and immune responses it now appears that there are a multitude of common, less severe primary immunodeficiencies. These so called novel *primary immunodeficiencies* relate to an individual's own unique genetics and can involve one or more of many immunity genes, ranging from any of the huge number of genes conferring protective immunity in general, to individual genes conferring specific immunity to a single pathogen.

It is now thought that almost every person suffers from one form of primary immunodeficiency or another. Unlike the classical primary immunodeficiencies, however, these primary Examples include:

- Disorders of the interleukin-12/interferon-gamma pathway appear to make individuals more susceptible to *Mycobacterium* and *Salmonella* infections.
- Disorders of the TLR-3 pathway makes individuals more susceptible to herpes simplex virus encephalitis.
- Disorders of the toll-interleukin 1 receptor/nuclear factor kappa B pathway makes individuals more susceptible to staphylococcal and pneumococcal infections.
- Disorders of properdin and terminal components of the complement pathways make individuals more susceptible to *Neisseria* infections.
- People with chronic sinusitis that does not respond well to treatment have decreased activity of TLR-9 and produce reduced levels of human beta-defensin 2, as well as mannan-binding lectin needed to initiate the lectin complement pathway.

Summary

1. Immunodeficiency results in an inability to combat certain diseases.
2. A primary immunodeficiency is usually an immunodeficiency that one is born with.
3. Conventional primary immunodeficiencies are rare recessive genetic defect in the immune responses that involved the development of B-lymphocytes, T-lymphocytes, or both and resulted in multiple, recurrent infections during infancy. Depending on the disorder, the lymphocytes in question were either completely absent, present in very low levels, or present but not functioning normally.
4. Conventional primary immunodeficiencies include B-lymphocyte disorders, T-lymphocyte disorders, Severe combined immunodeficiency disease or SCID,and innate immunity disorders.
5. B-lymphocyte disorders may result in greatly decreased humoral immunity but cell-mediated immunity, mediated by T-lymphocytes, remains normal.
6. T-lymphocyte disorders may result in little or no cell-mediated immunity if the disorder involves T8-lymphocytes and/or T4-helper lymphocytes. There may also be decreased humoral immunity if there is a disorder involves T4-helper lymphocytes.
7. Severe combined immunodeficiency disease deficiencies affect both humoral immunity and cell-mediated immunity may result in a defect in both B-lymphocytes and T-lymphocytes, or just T-lymphocytes in which case the humoral deficiency is due to the lack of T4-helper lymphocytes.
8. Innate immunity disorders are due to defects in genes that play a role in innate immune responses.
9. Novel primary immunodeficiencies include a multitude of common, less severe primary immunodeficiencies involving just one or more of the huge number of genes involved in the immune responses resulting in the decreased ability to combat just a single type of infection or a narrow range of infections.

This page titled 14.8: Primary Immunodeficiency is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **15.1: Primary Immunodeficiency** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

14.9: Primary Immunodeficiency Diseases

Learning Objectives

- Describe primary immunodeficiency disorders and explain what treatment options are available

Primary immunodeficiencies are disorders in which a part of the body's immune system is missing or does not function properly. To be considered a primary immunodeficiency, the cause of the immune deficiency must not be secondary in nature (caused by another disease, drug treatment, or environmental exposure to toxins). Most primary immunodeficiencies are genetic disorders; the majority are diagnosed in children under the age of one, although milder forms may not be recognized until adulthood.

Symptoms

The precise symptoms of a primary immunodeficiency depend on the type of defect. Generally, the symptoms and signs that lead to the diagnosis of an immunodeficiency include recurrent or persistent infections, or developmental delay as a result of infection. Particular organ problems; such as diseases involving the skin, heart, facial development and skeletal system; may be present in certain conditions. Others predispose to autoimmune disease, where the immune system attacks the body's own tissues, or tumors (sometimes specific forms of cancer, such as lymphoma). The nature of the infections, as well as the additional features, may provide clues as to the exact nature of the immune defect.

Diagnostic Tests

The basic tests performed when an immunodeficiency is suspected should include a full blood count (including accurate lymphocyte and granulocyte counts) and immunoglobulin levels. Tthe three most important types of antibodies are IgG, IgA and IgM.

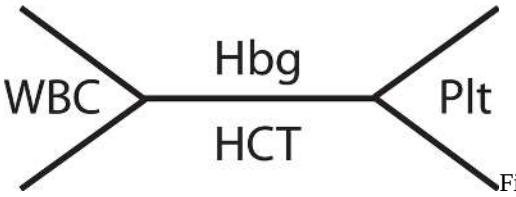


Figure: **Complete Blood Count**: Schematics (also called "fishbones") of shorthand commonly used by clinicians for complete blood count. The shorthand on the right is used more often in the U.S. Hgb=Hemoglobin, WBC=White blood cells, Plt=Platelets, Hct=Hematocrit.

Other tests are performed depending on the suspected disorder:

- Quantification of the different types of mononuclear cells in the blood (lymphocytes and monocytes): different groups of T lymphocytes (dependent on their cell surface markers, e.g. CD4+, CD8+, CD3+, TCRα and TCRγ); groups of B lymphocytes (CD19, CD20, CD21 and Immunoglobulin); natural killer cells and monocytes (CD15+); as well as activation markers (HLA-DR, CD25, CD80 (B cells)
- Tests for T cell function: skin tests for delayed-type hypersensitivity, cell responses to mitogens and allogeneic cells, cytokine production by cells
- Tests for B cell function: antibodies to routine immunizations and commonly acquired infections, quantification of IgG subclasses
- Tests for phagocyte function: reduction of nitro blue tetrazolium chloride, assays of chemotaxis, bactericidal activity

Due to the rarity of many primary immunodeficiencies, many of the above tests are highly specialized and tend to be performed in research laboratories.

Immunodeficiency Disorders

In genetic immunodeficiency disorders, both T lymphocytes and often B lymphocytes—regulators of adaptive immunity—are dysfunctional or decreased in number. The main members are various types of severe combined immunodeficiency (SCID).

In primary antibody deficiencies, one or more isotypes of immunoglobulin are decreased or don't function properly. These proteins, generated by plasma cells, normally bind to pathogens, targeting them for destruction.

A number of syndromes, including the following, escape formal classification but are otherwise recognisable by particular clinical or immunological features:

- Wiskott-Aldrich syndrome
- DNA repair defects not causing isolated SCID; for example ataxia telangiectasia and ataxia-like syndrome
- DiGeorge syndrome (when associated with thymic defects)
- Various immuno-osseous dysplasias (abnormal development of the skeleton with immune problems);for example, cartilage-hair hypoplasia, Schimke syndrome

In certain conditions, including the following, the regulation rather than the intrinsic activity of parts of the immune system is the predominant problem:

- Immunodeficiency with hypopigmentation or albinism; for example, Chediak-Higashi syndrome, Griscelli syndrome type two
- Familial hemophagocytic lymphohistiocytosis; for example, perforin deficiency, MUNC13D deficiency, syntaxin 11 deficiency
- X-linked lymphoproliferative syndrome

Phagocytes are the cells that engulf and ingest pathogens (phagocytosis), and destroy them with chemicals. Monocytes/macrophages as well as granulocytes are capable of this process. In certain conditions, either the number of phagocytes is reduced or their functional capacity is impaired. Several rare conditions are due to defects in the innate immune system, which is a basic line of defense independent of the more advanced lymphocyte-related systems. Many of these conditions are associated with skin problems.

Rather than predisposing for infections, most of the autoinflammatory disorders lead to excessive inflammation. Many manifest themselves as periodic fever syndromes. They may involve various organs directly, as well as predisposing for long-term damage by leading to amyloid deposition.

The complement system is part of the innate as well as the adaptive immune system; it is a group of circulating proteins that can bind pathogens and form a membrane attack complex. Complement deficiencies are the result of a lack of any of these proteins. They may predispose to infections but also to autoimmune conditions.

Treatment

The treatment of primary immunodeficiencies depends foremost on the nature of the abnormality. This may range from immunoglobulin replacement therapy in antibody deficiencies—in the form of intravenous immunoglobulin (IVIG) or subcutaneous immunoglobulin (SCIG)—to hematopoietic stem cell transplantation for SCID and other severe immunodeficiences. SCID can now be treated with a bone marrow transplant. Reduction of exposure to pathogens may be recommended, and in many situations prophylactic antibiotics may be advised.

Key Points

- To be considered a primary immunodeficiency, the cause of the immune deficiency must not be secondary in nature (caused by other disease, drug treatment, or environmental exposure to toxins).
- Most primary immunodeficiencies are genetic disorders; the majority are diagnosed in children under the age of one, although milder forms may not be recognized until adulthood.
- The precise symptoms of a primary immunodeficiency depend on the type of defect but generally include recurrent or persistent infections or developmental delay as a result of infection.

Key Terms

- **genetic disorder**: An illness caused by abnormalities in genes or chromosomes, especially a condition that is present prior to birth. Most genetic disorders are quite rare and affect one person in every several thousands or millions.
- **immunodeficiency**: A depletion in the body’s natural immune system, or in some component of it.

This page titled 14.9: Primary Immunodeficiency Diseases is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **12.6A: Primary Immunodeficiency Diseases** is licensed CC BY-SA 4.0.

14.10: Secondary Immunodeficiency

Learning Objectives

1. State what is meant by secondary immunodeficiency and list four possible contributing factors.
2. Briefly give at least four mechanisms of HIV-induced immunodeficiency.

In the case of secondary immunodeficiency, one is born with normal immune responses but some secondary factor or occurrence causes a decrease in immune responses. Secondary immunodeficiency is induced by factors such as:

- Malnutrition. Inhibits lymphocyte maturation and function.
- Some viruses, e.g., HIV. Depletes T4-lymphocytes.
- Irradiation - exposure to X-rays and gamma rays. Causes a decreased production of lymphocyte precursors in the bone marrow.
- Cytotoxic drugs such as many used in cancer chemotherapy. Causes a decreased production of lymphocyte precursors in the bone marrow.
- Corticosteroids – anti-inflammatory steroids. Damages lymphocytes.
- Leukemias, cancers of the lymphoid system, metastases. Reduces areas for lymphocyte development.
- Aging. Adaptive immunity, especially cell-mediated immunity, tends to diminish with aging.
- Removal of the spleen. Decreased ability to remove microbes that enter the blood.

A secondary immunodeficiency of current notoriety is of course Acquired Immunodeficiency Syndrome or AIDS, a secondary immunodeficiency caused by Human Immunodeficiency Virus (HIV). As we saw in Unit 4, HIV, via its gp120, primarily infects cells with CD4 molecules and chemokine receptors on their surface, namely, T4-lymphocytes, macrophages, and dendritic cells. The median incubation period for AIDS is around 10 years.

During early or acute HIV infection the virus primarily infects and destroys memory T4-lymphocytes which express the chemokine receptor CCR5 and are very abundant in mucosal lymphoid tissues. Here HIV also encounters the dendritic cells located throughout the epithelium of the skin and the mucous membranes where in their immature form called Langerhans cells they are attached by long cytoplasmic processes. The envelope glycoproteins gp41 and gp120 of HIV contain mannose-rich glycans that bind to mannan-binding proteins (pattern recognition receptors; also called lectin receptors) on the dendritic cells.

Upon capturing antigens through pinocytosis and phagocytosis and becoming activated by pro-inflammatory cytokines, the dendritic cells detach from the epithelium, enter lymph vessels, and are carried to regional lymph nodes. By the time they enter the lymph nodes, the dendritic cells have matured and are now able to present antigens of HIV to naive T-lymphocytes located in the the lymph nodes in order to induce adaptive immune responses.

At this point the infection has transitioned from the acute phase to the chronic phase. The chronic phase of HIV infection is characterized by viral dissemination, viremia, and induction of adaptive immune responses. The viremia allows the viruses to spread and infect T4-helper lymphocytes, macrophages, and dendritic cells found in peripheral lymphoid tissues.

During the chronic phase of HIV infection, the lymph nodes and the spleen become sites for continuous viral replication and host cell destruction. During most of this phase, the immune system remains active and competent and there are few clinical symptoms. A steady state-infection generally persists where T4-lymphocyte death and T4-lymphocyte replacement by the body are in equilibrium. In a person infected with HIV, somewhere between one and two billion of these T4-cells die each day as a result of HIV infection and must be replaced by the body's lymphopoietic system in the bone marrow. It is estimated that 10 billion virions are produced and cleared in an infected individual each day. However, the enormous turnover of T4-lymphocytes eventually exhausts the lymphopoietic system and it becomes unable to replace the T4-cells being destroyed. A variety of mechanisms then eventually lead to immunodeficiency.

Mechanisms of HIV-induced immunodeficiency include:

- Direct HIV-induced cytopathic effect on infected T4-lymphocytes. This can occur through:
  - Increased cell permeability as a result of gp41 expression in the host cell membrane and viral release by budding;
  - Inhibition of host cell protein synthesis as a result of viral replication within the infected cell; and
  - Fusion of infected T4-cells with numerous uninfected T4-cells resulting in syncytia formation.

- Killing of HIV-infected T4-cells by cytotoxic T-lymphocytes or CTLs.
- Killing of HIV-infected T4-cells by antibody-dependent cytotoxicity or ADCC.
- Apoptosis of T4-cells as a result of chronic activation by HIV and by cytokines.
- Shedding of gp120 molecules by HIV. This subsequently triggers a series of events that cause the adaptive immune system to become less and less effective, primarily by altering the normal balance of immunoregulatory T_H1 and T_H2 cells in the body.
- Impaired function of HIV infected macrophages and dendritic cells.

To further complicate problems, during the replication of HIV the reverse transcriptase of HIV exhibits a high error rate as it transcribes the RNA genome into DNA. As a result, HIV readily mutates to become more immunoresistant, more drug resistant, and able to change the preferred cell type it is able to infect, e.g., M-tropic to T-tropic as shown in Figure **14.10.2**.

Progression to AIDS is marked by a viral load that progressively increases in number while the immune system weakens as a result of the destruction of increasing numbers of T4-lymphocytes and the inability of the body to continually replace these destroyed cells. The loss of T4-helper lymphocytes leads to a marked decline in cells called cytotoxic T-lymphocytes (CTLs), the primary cells the body's immune responses use to destroy virus-infected cells. Once a person progresses to full-blown AIDS he or she becomes susceptible to a variety of opportunistic infections by:

- bacteria such as *Mycobacterium avium* complex (MAC), *Salmonella*, and *Nocardia*;
- protozoa such as *Cryptosporidium* and *Toxoplasma*;
- viruses such as cytomegalovirus (CMV), herpes simplex viruses types 1 and 2 (HSV-1, HSV-2), and varicella zoster virus (VZV);
- *Candida*, *Cryptococcus*, *Coccidioides*, *Histoplasma*, and *Pneumocystis*.

There is also an increased incidence of tumors, such Epstein-Barr virus-associated B-cell lymphomas, other lymphomas, cervical cancer, and Kaposi’s sarcoma. Wasting syndrome and encephalopathy are also common.

Summary

A secondary immunodeficiency is one in which a person is born with normal immune responses but some secondary factor or occurrence causes a decrease in immune responses. Causes of secondary immunodeficiencies include malnutrition, some viruses such as HIV, irradiation, cytotoxic drugs used in cancer chemotherapy, anti-inflammatory steroids, leukemias, aging, and removal of the spleen. HIV infects and destroys T4-lymphocytes and when the body becomes unable to replace the T4-lymphocytes as fast as they are being destroyed, secondary immunodeficiency results.

This page titled 14.10: Secondary Immunodeficiency is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Gary Kaiser via source content that was edited to the style and standards of the LibreTexts platform.

- **15.2: Secondary Immunodeficiency** by Gary Kaiser is licensed CC BY 4.0. Original source: https://cwoer.ccbcmd.edu/science/microbiology/index_gos.html.

14.11: Secondary Immunodeficiency Diseases

Learning Objectives

- Define immunodeficiency and list the types that occur

Immunodeficiency (or immune deficiency) is a state in which the immune system's ability to fight infectious disease is compromised or entirely absent. Immunodeficiency may also decrease cancer immunosurveillance. Most cases of immunodeficiency are acquired ("secondary") but some people are born with defects in their immune system, or primary immunodeficiency. Transplant patients take medications to suppress their immune system as an anti-rejection measure, as do some patients suffering from an over-active immune system. A person who has an immunodeficiency of any kind is said to be immunocompromised. An immunocompromised person may be particularly vulnerable to opportunistic infections, in addition to normal infections that could affect everyone. Distinction between primary versus secondary immunodeficiencies are based on, respectively, whether the cause originates in the immune system itself or is, in turn, due to insufficiency of a supporting component of it or an external decreasing factor of it.

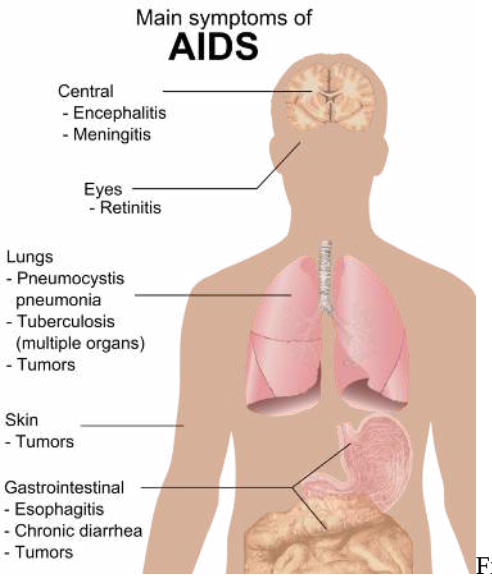


Figure: **Main Symptoms of AIDS**: Acquired immunodeficiency syndrome (AIDS) is defined in terms of either a CD4+ T cell count below 200 cells per µL or the occurrence of specific diseases in association with an HIV infection. In the absence of specific treatment, around half the people infected with HIV develop AIDS within 10 years. The most common initial conditions that alert to the presence of AIDS are pneumocystis pneumonia and cachexia.

Primary Immunodeficiency (PID)

A number of rare diseases feature a heightened susceptibility to infections from childhood onward. Primary Immunodeficiency is also known as "congenital immunodeficiencies. " Many of these disorders are hereditary and are autosomal recessive or X-linked. There are over 80 recognized primary immunodeficiency syndromes; they are generally grouped by the part of the immune system that is malfunctioning, such as lymphocytes or granulocytes. The treatment of primary immunodeficiencies depends on the nature of the defect and may involve antibody infusions, long-term antibiotics, and (in some cases) stem cell transplantation.

Secondary Immunodeficiencies

Secondary immunodeficiencies, also known as acquired immunodeficiencies, can result from various immunosuppressive agents, for example, malnutrition, aging and particular medications (e.g., chemotherapy, disease-modifying antirheumatic drugs, immunosuppressive drugs after organ transplants, glucocorticoids). For medications, the term immunosuppression generally refers to both beneficial and potential adverse effects of decreasing the function of the immune system, while the term immunodeficiency generally refers solely to the adverse effect of increased risk for infection. Many specific diseases directly or indirectly cause immunosuppression. This includes many types of cancer, particularly those of the bone marrow and blood cells (leukemia,

lymphoma, multiple myeloma), and certain chronic infections. Immunodeficiency is also the hallmark of acquired immunodeficiency syndrome (AIDS), caused by the human immunodeficiency virus (HIV). HIV directly infects a small number of T helper cells and also impairs other immune system responses indirectly.

Key Points

- A deficit in the immune system can lead to unusually severe or uncommon recurrent infections.
- Secondary immune deficiencies or acquired deficiencies, more frequent than primary immune deficiencies, are problems of the immune system that are not genetic and which are caused by external factors.
- Secondary immunodeficiency disorders can occur in, for example, malnutrition, aging, many types of cancer (such as leukemia, lymphoma, multiple myeloma), and certain chronic infections such as acquired immunodeficiency syndrome (AIDS).
- Immunosuppression is one form of secondary immunodeficiency performed to prevent the body from rejecting an organ transplant, treating graft-versus-host disease after a bone marrow transplant, or for the treatment of auto-immune diseases, such as rheumatoid arthritis or Crohn's disease.
- A person who is undergoing immunosuppression or whose immune system is weak for other reasons (for example, chemotherapy, HIV, and Lupus), is said to be immunocompromised.

Key Terms

- **immunodeficiency**: A depletion in the body's natural immune system, or in some component of it.
- **immunocompromised**: Having an immune system that has been impaired by disease or treatment.
- **immunosuppressive**: Having the capability to suppress the immune system, capable of immunosuppression.
- **secondary infection**: any infection that arises subsequent to a pre-existing infection; but especially a nosocomial infection

---

This page titled 14.11: Secondary Immunodeficiency Diseases is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **12.6B: Secondary Immunodeficiency Diseases** is licensed CC BY-SA 4.0.

14.12: Immunotherapy for Cancer

Learning Objectives

- Describe the use of immunotherapy in cancer treatment

Cancer immunotherapy is the use of the body's own immune system to reject cancer. The main idea is stimulating the patient's immune system to attack the malignant tumor cells that are responsible for the disease. This can be either through immunization of the patient (e.g., by administering a cancer vaccine such as Dendreon's Provenge), in which case the patient's own immune system is trained to recognize tumor cells as targets to be destroyed, or through the administration of therapeutic antibodies as drugs, in which case the patient's immune system is recruited to destroy tumor cells by the therapeutic antibodies. Cell-based immunotherapy is another major entity of cancer immunotherapy. This involves immune cells such as the natural killer cells (NK cells), lymphokine-activated killer cells (LAK cells), cytotoxic T lymphocytes (CTLs), and dendritic cells (DC). These immune cells are either activated *in vivo* by administering certain cytokines such as interleukins, or they are isolated, enriched, and transfused back into the patient to fight against cancer.

Since the immune system responds to the environmental factors it encounters on the basis of discrimination between self and non-self, many kinds of tumor cells that arise as a result of the onset of cancer are more or less tolerated by the patient's own immune system since the tumor cells are essentially the patient's own cells that are growing, dividing, and spreading without proper regulatory control. In spite of this fact, however, many kinds of tumor cells display unusual antigens that are inappropriate for either the cell type or its environment or that are only normally present during the organism 's development (e.g. fetal antigens). Examples of such antigens include the glycosphingolipid GD2, a disialoganglioside that is normally only expressed at a significant level on the outer surface membranes of neuronal cells, where its exposure to the immune system is limited by the blood-brain barrier.

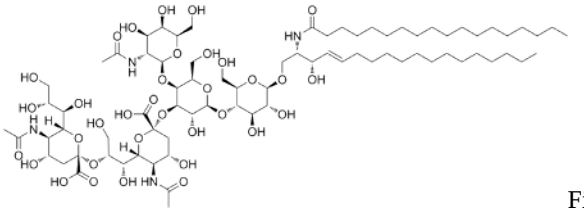


Figure: **Structure of GD2**: GD2 is a disialoganglioside expressed on tumors of neuroectodermal origin, including human neuroblastomas and melanomas, with highly restricted expression on normal tissues, principally to the cerebellum and peripheral nerves in humans. The relatively tumor-specific expression of GD2 makes it a suitable target for immunotherapy with monoclonal antibodies or with artificial T-cell receptors.

GD2 is expressed on the surfaces of a wide range of tumor cells, including neuroblastomas, medulloblastomas, astrocytomas, melanomas, small-cell lung cancer, osteosarcomas, and other soft tissue sarcomas. GD2 is thus a convenient tumor-specific target for immunotherapies.

Adoptive cell-based immunotherapy involves isolating either allogenic or autologous immune cells, enriching them outside the body, and transfusing them back to the patient. The injected immune cells are highly cytotoxic to the cancer cells and so help to fight them.

Antibodies are a key component of the adaptive immune response. They play a central role in both the recognition of foreign antigens and the stimulation of an immune response to them. It is not surprising, therefore, that many immunotherapeutic approaches involve the use of antibodies. The advent of monoclonal antibody technology has made it possible to raise antibodies against specific antigens, such as the unusual antigens that are presented on the surfaces of tumors. A number of therapeutic monoclonal antibodies have been approved for use in humans, such as alemtuzumab, an anti-CD52 humanized IgG1 monoclonal antibody indicated for the treatment of chronic lymphocytic leukemia (CLL). Radioimmunotherapy in turn involves the use of radioactively conjugated murine antibodies against cellular antigens, mostly for treatment of lymphomas.

The development and testing of second-generation immunotherapies is already under way. While antibodies targeted to disease-causing antigens can be effective under certain circumstances, in many cases their efficacy may be limited by other factors. In the case of cancer tumors, the microenvironment is immunosuppressive, allowing even those tumors that present unusual antigens to

survive and flourish in spite of the immune response generated by the cancer patient against his own tumor tissue. Certain members of a group of molecules known as cytokines, such as interleukin-2, also play a key role in modulating the immune response. Cytokines have been tested in conjunction with antibodies in order to generate an even more devastating immune response against the tumor. While the therapeutic administration of such cytokines may cause systemic inflammation, resulting in serious side effects and toxicity, there is a new generation of chimeric molecules consisting of an immune-stimulatory cytokine attached to an antibody that targets a tumor. These chimeric molecules are able to generate a very effective yet localized immune response against the tumor tissue, destroying the cancer-causing cells without the unwanted side effects.

Dermatologists use new creams and injections in the management of benign and malignant skin tumors. Topical immunotherapy utilizes an immune enhancement cream (imiquimod), which is an interferon producer, causing the patient's own killer T cells to destroy warts, actinic keratoses, basal cell carcinoma, squamous cell carcinoma, cutaneous T cell lymphoma, and superficial spreading melanoma. Injection immunotherapy uses mumps, candida, or trichophytin antigen injections to treat warts (HPV-induced tumors).

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: *CC BY-SA: Attribution-ShareAlike*

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- Primary immune deficiency. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Primary_immune_deficiency**. **License**: *CC BY-SA: Attribution-ShareAlike*
- genetic disorder. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/genetic%20disorder**. **License**: *CC BY-SA: Attribution-ShareAlike*
- immunodeficiency. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/immunodeficiency**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Complete blood count CBC diagram. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Complete_blood_count_CBC_diagram.png**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Immune suppression. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Immune_suppression**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Secondary immune deficiency. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Secondary_immune_deficiency%23acquired**. **License**: *CC BY-SA: Attribution-ShareAlike*
- immunocompromised. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/immunocompromised**. **License**: *CC BY-SA: Attribution-ShareAlike*
- immunosuppressive. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/immunosuppressive**. **License**: *CC BY-SA: Attribution-ShareAlike*
- immunodeficiency. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/immunodeficiency**. **License**: *CC BY-SA: Attribution-ShareAlike*
- secondary infection. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/secondary_infection**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Complete blood count CBC diagram. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Complete_blood_count_CBC_diagram.png**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Symptoms of AIDS. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Symptoms_of_AIDS.png**. **License**: ***Public Domain: No Known Copyright***
- Cancer immunotherapy. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Cancer_immunotherapy**. **License**: *CC BY-SA: Attribution-ShareAlike*
- immunotherapy. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/immunotherapy**. **License**: *CC BY-SA: Attribution-ShareAlike*
- allogenic. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/allogenic**. **License**: *CC BY-SA: Attribution-ShareAlike*
- autologous. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/autologous**. **License**: *CC BY-SA: Attribution-ShareAlike*

- Complete blood count CBC diagram. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Complete_blood_count_CBC_diagram.png**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Symptoms of AIDS. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Symptoms_of_AIDS.png**. **License**: ***Public Domain: No Known Copyright***
- GD2 ganglioside. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:GD2_ganglioside.png**. **License**: ***Public Domain: No Known Copyright***

Key Points

- Cancer immunotherapy can involve immunization of the patient with a cancer vaccine, administration of therapeutic antibodies as drugs, or cell-based immunotherapy.
- Vaccines can be raised against antigens that are inappropriate either for the cell type or for its environment.
- Adoptive cell-based immunotherapy involves isolating either allogenic or autologous immune cells, enriching them outside the body, and transfusing them back into the patient.
- Monoclonal antibodies can be raised against unusual antigens that are presented on the surfaces of tumors.

Key Terms

- **immunotherapy**: the treatment of cancer by improving the ability of the host to reject a tumor immunologically
- **allogenic**: genetically distinct, but of the same species
- **autologous**: derived from part of the same individual (i.e., from the recipient rather than the donor)

This page titled 14.12: Immunotherapy for Cancer is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **12.6C: Immunotherapy for Cancer** is licensed CC BY-SA 4.0.

14.13: The Roles of Genetics and Gender in Autoimmune Disease

Learning Objectives

- Define autoimmunity and explain how it gives rise to autoimmune disease

Autoimmunity is the failure of an organism in recognizing its own constituent parts as self, which allows an immune response against its own cells and tissues. Any disease that results from such an aberrant immune response is termed an autoimmune disease. Autoimmunity is often caused by a lack of germ development of a target body and as such the immune response acts against its own cells and tissues. Prominent examples include Coeliac disease, diabetes mellitus type 1 (IDDM), Sarcoidosis, systemic lupus erythematosus (SLE), Sjögren's syndrome, Churg-Strauss Syndrome, Hashimoto's thyroiditis, Graves' disease, idiopathic thrombocytopenic purpura, Addison's Disease, rheumatoid arthritis (RA), and allergies.

Autoimmune diseases are very often treated with steroids. The misconception that an individual's immune system is totally incapable of recognizing self antigens is not new. Paul Ehrlich, at the beginning of the 20th century, proposed the concept of horror autotoxicus, wherein a 'normal' body does not mount an immune response against its own tissues. Therefore, any autoimmune response was perceived to be abnormal and postulated to be connected with human disease. Now, it is accepted that autoimmune responses are an integral part of vertebrate immune systems (sometimes termed 'natural autoimmunity'), normally prevented from causing disease by the phenomenon of immunological tolerance to self-antigens.

Autoimmunity should not be confused with alloimmunity. While a high level of autoimmunity is unhealthy, a low level of autoimmunity may actually be beneficial. First, low-level autoimmunity might aid in the recognition of neoplastic cells by CD8+ T cells, and thus reduce the incidence of cancer. Second, autoimmunity may have a role in allowing a rapid immune response in the early stages of an infection when the availability of foreign antigens limits the response (i.e., when there are few pathogens present).

Certain individuals are genetically susceptible to developing autoimmune diseases. This susceptibility is associated with multiple genes plus other risk factors. However, genetically predisposed individuals do not always develop autoimmune diseases. Three main sets of genes are suspected in many autoimmune diseases. These genes are related to immunoglobulins, T-cell receptors, and the major histocompatibility complexes (MHC). Immunoglobulins and T-cell receptors are involved in the recognition of antigens and they are inherently variable and susceptible to recombination. These variations enable the immune system to respond to a very wide variety of invaders, but may also give rise to lymphocytes capable of self-reactivity. Scientists such as H. McDevitt, G. Nepom, J. Bell, and J. Todd have also provided strong evidence to suggest that certain MHC class II allotypes are strongly correlated with disease. For example:

1. HLA DR2 is strongly positively correlated with Systemic Lupus Erythematosus, narcolepsy and multiple sclerosis, and negatively correlated with DM Type 1.

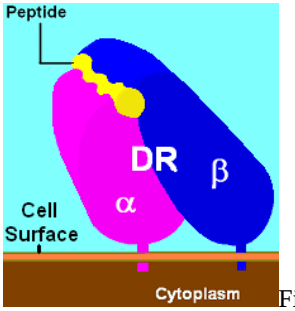


Figure: **MHC Class II, DR**: HLA-DR is a MHC class II cell surface receptor encoded by the human leukocyte antigen complex on chromosome 6 region 6p21.31. The complex of HLA-DR and its ligand, a peptide of 9 amino acids in length or longer, constitutes a ligand for the T-cell receptor (TCR).

2. HLA DR3 is correlated strongly with Sjögren's syndrome, myasthenia gravis, SLE, and DM Type 1.

3. HLA DR4 is correlated with the genesis of rheumatoid arthritis, Type 1 diabetes mellitus, and pemphigus vulgaris.

Fewer correlations exist with MHC class I molecules. The most notable and consistent is the association between HLA B27 and ankylosing spondylitis. Correlations may exist between polymorphisms within class II MHC promoters and autoimmune disease. The contributions of genes outside the MHC complex remain the subject of research, in animal models of disease (Linda Wicker's extensive genetic studies of diabetes in the NOD mouse), and in patients (Brian Kotzin's linkage analysis of susceptibility to SLE).

A person's sex also seems to have some role in the development of autoimmunity, classifying most autoimmune diseases as sex-related diseases. Nearly 75% of the more than 23.5 million Americans who suffer from autoimmune disease are women, although it is less-frequently acknowledged that millions of men also suffer from these diseases. However, autoimmune diseases that develop in men tend to be more severe. A few autoimmune diseases that men are just as or more likely to develop as women, include: ankylosing spondylitis, type 1 diabetes mellitus, Wegener's granulomatosis, and Crohn's disease. The reasons for the sex role in autoimmunity are unclear. However, women appear to generally mount larger inflammatory responses than men when their immune systems are triggered, increasing the risk of autoimmunity. In addition, involvement of sex steroids is indicated by the fact that many autoimmune diseases tend to fluctuate in accordance with hormonal changes, for example, during pregnancy. Interestingly, a history of pregnancy also appears to leave a persistent increased risk for autoimmune disease. Indeed, it has been suggested that the slight exchange of cells between mothers and their children during pregnancy may induce autoimmunity. This would tip the gender balance in the direction of the female. Another theory suggests the female high tendency to get autoimmunity is due to an imbalanced X chromosome inactivation.

Key Points

- Autoimmune diseases are very often treated with steroids which will dampen the immune response.
- Certain individuals are genetically susceptible to developing autoimmune diseases and susceptibility is linked to immunoglobulin, T-cell receptor, and MHC complex genes.
- Women are more likely than men to develop an autoimmune disease, but the severity of the disease is more accentuated in men.

Key Terms

- **autoimmunity**: The condition where one's immune system attacks one's own tissues, i.e., an autoimmune disorder.
- **alloimmunity**: Immunity, obtained from another, against one's own cells.

This page titled 14.13: The Roles of Genetics and Gender in Autoimmune Disease is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **12.5B: The Roles of Genetics and Gender in Autoimmune Disease** is licensed CC BY-SA 4.0.

CHAPTER OVERVIEW

15: Acellular Pathogens

Public health measures in the developed world have dramatically reduced mortality from viral epidemics. But when epidemics do occur, they can spread quickly with global air travel. In 2009, an outbreak of H1N1 influenza spread across various continents. In early 2014, cases of Ebola in Guinea led to a massive epidemic in western Africa. This included the case of an infected man who traveled to the United States, sparking fears the epidemic might spread beyond Africa.

Until the late 1930s and the advent of the electron microscope, no one had seen a virus. Yet treatments for preventing or curing viral infections were used and developed long before that. Historical records suggest that by the 17th century, and perhaps earlier, inoculation (also known as variolation) was being used to prevent the viral disease smallpox in various parts of the world. By the late 18th century, Englishman Edward Jenner was inoculating patients with cowpox to prevent smallpox, a technique he coined *vaccination*.[1]

Today, the structure and genetics of viruses are well defined, yet new discoveries continue to reveal their complexities. In this chapter, we will learn about the structure, classification, and cultivation of viruses, and how they impact their hosts. In addition, we will learn about other infective particles such as viroids and prions.

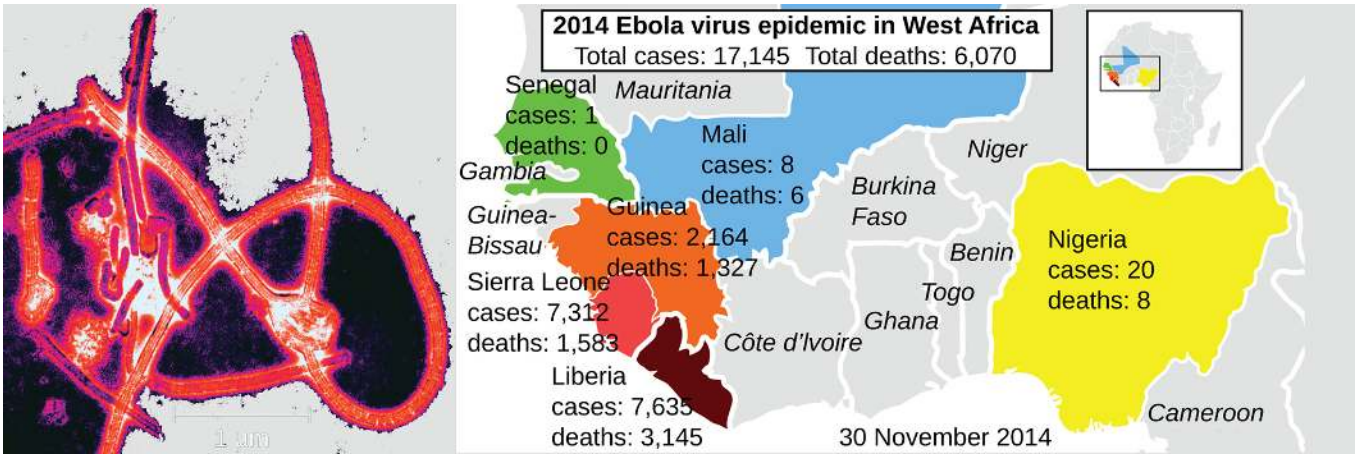


Figure 15.1: The year 2014 saw the first large-scale outbreak of Ebola virus (electron micrograph, left) in human populations in West Africa (right). Such epidemics are now widely reported and documented, but viral epidemics are sure to have plagued human populations since the origin of our species. (credit left: modification of work by Thomas W. Geisbert)

15.1: Viruses

15.2: The Viral Life Cycle

15.3: Isolation, Culture, and Identification of Viruses

15.4: Viroids, Virusoids, and Prions

15.5: Viral Replication

- 15.5A: General Features of Virus Replication
- 15.5B: Steps of Virus Infections
- 15.5C: Tissue Tropism in Animal Viruses
- 15.5D: Animal Viruses
- 15.5E: Plant Virus Life Cycles

15.6: Viral Diversity

- 15.6A: Overview of Bacterial Viruses
- 15.6B: RNA Bacteriophages
- 15.6C: Single-Stranded DNA Bacteriophages

15.6D: Double-Stranded DNA Bacteriophages
15.6E: Mu- A Double-Stranded Transposable DNA Bacteriophage
15.6F: Virulent Bacteriophages and T4
15.6G: Temperate Bacteriophages - Lambda and P1
15.6H: Viruses of Archaea
15.7: Positive-Strand RNA Viruses in Animals
15.7A: Positive-Strand RNA Viruses of Animals
15.7B: Virus Attachment and Genome Entry
15.7C: Viral Replication and Gene Expression
15.7D: Viral Exit
15.8: Retroviruses- Double-Stranded RNA Viruses
15.8A: Double-Stranded RNA Viruses - Retroviruses
15.8B: HIV Attachment and Host Cell Entry
15.8C: Retroviral RNA Genome
15.8D: Replicative Cycle of HIV
15.9: Negative-Strand RNA Viruses in Animals
15.9.1: Negative-Strand RNA Viruses of Animals
15.9.2: Attachment and Entry to the Host Cell
15.9.3: Replicative Cycle of Influenza A
15.10: DNA Viruses in Eukaryotes
15.10.1: Plant DNA Viruses
15.10.2: Replication of Double-Stranded DNA Viruses of Animals
15.10.3: Double-Stranded DNA Viruses - Herpesviruses
15.10.4: Attachment and Entry of Herpes Simplex
15.10.5: Replication of Herpes Simplex Virus
15.10.6: Immunodeficiency
15.10.7: Double-Stranded DNA Viruses - Pox Viruses
15.10.8: Double-Stranded DNA Viruses- Adenoviruses
15.10.9: Retroviruses and Hepadnavirus
15.10.10: Treatment of Animal Viral Infections
15.11: Viruses and Cancer
15.11.1: Cancer Viruses
15.11.2: DNA Oncogenic Viruses
15.11.3: RNA Oncogenic Viruses
15.12: Overview of Viruses
15.12.1: Discovery and Detection of Viruses
15.12.2: Nature of the Virion
15.12.3: Viral Genomes
15.12.4: Host Range
15.12.5: Viral Size
15.13: Structure of Viruses
15.13A: Viral Morphology
15.13B: General Morphology

15.13C: Complex and Asymmetrical Virus Particles
15.14: Classifying Viruses
15.14.1: The International Committee on Taxonomy of Viruses
15.14.2: The Baltimore Virus Classification
15.14.3: Evolution of Viruses
15.14.4: Medical Importance of Viruses
15.15: Culturing Viruses
15.15A: Batch Culture of Bacteriophages
15.15B: Tissue Culture of Animal Viruses
15.15C: Inoculation of Live Animals
15.15D: Viral Identification
15.16: Subviral Entities
15.16A: Defective Viruses
15.16B: Viroids
15.16C: Prions
15.17: Viral Ecology
15.17A: Emergence of Viral Pathogens
15.17B: Viral Roles in Ecosystems

Footnotes

1. 1 S. Riedel “Edward Jenner and the History of Smallpox and Vaccination.” *Baylor University Medical Center Proceedings* 18, no. 1 (January 2005): 21–25.

This page titled 15: Acellular Pathogens is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

15.1: Viruses

Learning Objectives

- Describe the general characteristics of viruses as pathogens
- Describe viral genomes
- Describe the general characteristics of viral life cycles
- Differentiate among bacteriophages, plant viruses, and animal viruses
- Describe the characteristics used to identify viruses as obligate intracellular parasites

Clinical Focus: Part 1

David, a 45-year-old journalist, has just returned to the U.S. from travels in Russia, China, and Africa. He is not feeling well, so he goes to his general practitioner complaining of weakness in his arms and legs, fever, headache, noticeable agitation, and minor discomfort. He thinks it may be related to a dog bite he suffered while interviewing a Chinese farmer. He is experiencing some prickling and itching sensations at the site of the bite wound, but he tells the doctor that the dog seemed healthy and that he had not been concerned until now. The doctor ordered a culture and sensitivity test to rule out bacterial infection of the wound, and the results came back negative for any possible pathogenic bacteria.

Exercise 15.1.1

1. Based on this information, what additional tests should be performed on the patient?
2. What type of treatment should the doctor recommend?

Despite their small size, which prevented them from being seen with light microscopes, the discovery of a filterable component smaller than a bacterium that causes tobacco mosaic disease (TMD) dates back to 1892.[1] At that time, Dmitri Ivanovski, a Russian botanist, discovered the source of TMD by using a porcelain filtering device first invented by Charles Chamberland and Louis Pasteur in Paris in 1884. Porcelain Chamberland filters have a pore size of 0.1 µm, which is small enough to remove all bacteria ≥0.2 µm from any liquids passed through the device. An extract obtained from TMD-infected tobacco plants was made to determine the cause of the disease. Initially, the source of the disease was thought to be bacterial. It was surprising to everyone when Ivanovski, using a Chamberland filter, found that the cause of TMD was not removed after passing the extract through the porcelain filter. So if a bacterium was not the cause of TMD, what could be causing the disease? Ivanovski concluded the cause of TMD must be an extremely small bacterium or bacterial spore. Other scientists, including Martinus Beijerinck, continued investigating the cause of TMD. It was Beijerinck, in 1899, who eventually concluded the causative agent was not a bacterium but, instead, possibly a chemical, like a biological poison we would describe today as a toxin. As a result, the word *virus*, Latin for poison, was used to describe the cause of TMD a few years after Ivanovski's initial discovery. Even though he was not able to see the virus that caused TMD, and did not realize the cause was not a bacterium, Ivanovski is credited as the original discoverer of viruses and a founder of the field of virology.

Today, we can see viruses using electron microscopes (Figure **15.1.1**) and we know much more about them. Viruses are distinct biological entities; however, their evolutionary origin is still a matter of speculation. In terms of taxonomy, they are not included in the tree of life because they are acellular (not consisting of cells). In order to survive and reproduce, viruses must infect a cellular host, making them obligate intracellular parasites. The genome of a virus enters a host cell and directs the production of the viral components, proteins and nucleic acids, needed to form new virus particles called virions. New virions are made in the host cell by assembly of viral components. The new virions transport the viral genome to another host cell to carry out another round of infection. Table **15.1.1** summarizes the properties of viruses.

Table **15.1.1**: Properties of viruses.

Characteristics of Viruses
Infectious, acellular pathogens
Obligate intracellular parasites with host and cell-type specificity
DNA or RNA genome (never both)
Genome is surrounded by a protein capsid and, in some cases, a phospholipid membrane studded with viral glycoproteins
Lack genes for many products needed for successful reproduction, requiring exploitation of host-cell genomes to reproduce

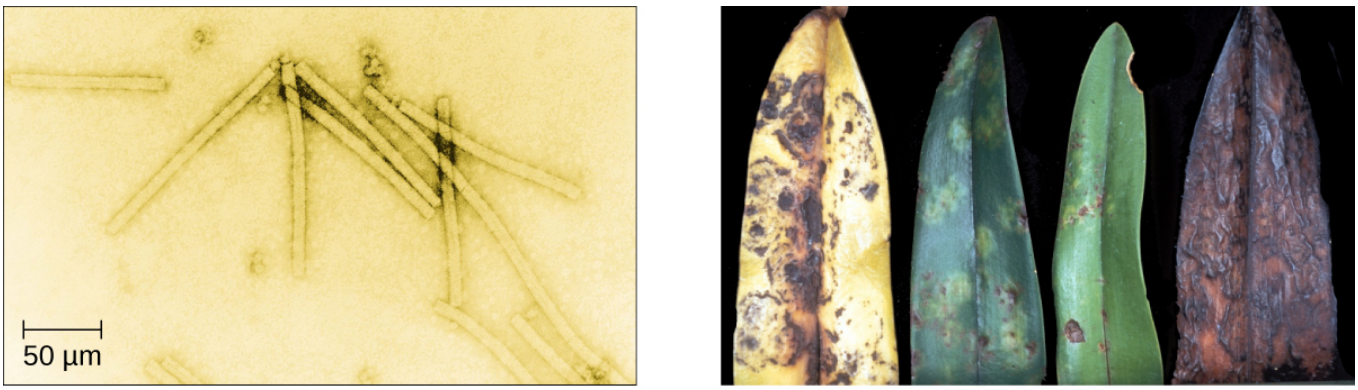


Figure 15.1.1: (a) Tobacco mosaic virus (TMV) viewed with transmission electron microscope. (b) Plants infected with tobacco mosaic disease (TMD), caused by TMV. (credit a: modification of work by USDA Agricultural Research Service—scale-bar data from Matt Russell; credit b: modification of work by USDA Forest Service, Department of Plant Pathology Archive North Carolina State University)

? Exercise 15.1.2

Why was the first virus investigated mistaken for a toxin?

Hosts and Viral Transmission

Viruses can infect every type of host cell, including those of plants, animals, fungi, protists, bacteria, and archaea. Most viruses will only be able to infect the cells of one or a few species of organism. This is called the host range. However, having a wide host range is not common and viruses will typically only infect specific hosts and only specific cell types within those hosts. The viruses that infect bacteria are called bacteriophages, or simply phages. The word *phage* comes from the Greek word for devour. Other viruses are just identified by their host group, such as animal or plant viruses. Once a cell is infected, the effects of the virus can vary depending on the type of virus. Viruses may cause abnormal growth of the cell or cell death, alter the cell's genome, or cause little noticeable effect in the cell.

Viruses can be transmitted through direct contact, indirect contact with fomites, or through a vector: an animal that transmits a pathogen from one host to another. Arthropods such as mosquitoes, ticks, and flies, are typical vectors for viral diseases, and they may act as mechanical vectors or biological vectors. Mechanical transmission occurs when the arthropod carries a viral pathogen on the outside of its body and transmits it to a new host by physical contact. Biological transmission occurs when the arthropod carries the viral pathogen inside its body and transmits it to the new host through biting.

In humans, a wide variety of viruses are capable of causing various infections and diseases. Some of the deadliest emerging pathogens in humans are viruses, yet we have few treatments or drugs to deal with viral infections, making them difficult to eradicate.

Viruses that can be transmitted from an animal host to a human host can cause zoonoses. For example, the avian influenza virus originates in birds, but can cause disease in humans. Reverse zoonoses are caused by infection of an animal by a virus that originated in a human.

Fighting Bacteria With Viruses

The emergence of superbugs, or multidrug resistant bacteria, has become a major challenge for pharmaceutical companies and a serious health-care problem. According to a 2013 report by the US Centers for Disease Control and Prevention (CDC), more than 2 million people are infected with drug-resistant bacteria in the US annually, resulting in at least 23,000 deaths.[2] The continued use and overuse of antibiotics will likely lead to the evolution of even more drug-resistant strains.

One potential solution is the use of phage therapy, a procedure that uses bacteria-killing viruses (bacteriophages) to treat bacterial infections. Phage therapy is not a new idea. The discovery of bacteriophages dates back to the early 20th century, and phage therapy was first used in Europe in 1915 by the English bacteriologist Frederick Twort.[3] However, the subsequent discovery of penicillin and other antibiotics led to the near abandonment of this form of therapy, except in the former Soviet Union and a few countries in Eastern Europe. Interest in phage therapy outside of the countries of the former Soviet Union is only recently re-emerging because of the rise in antibiotic-resistant bacteria.[4]

Phage therapy has some advantages over antibiotics in that phages kill only one specific bacterium, whereas antibiotics kill not only the pathogen but also beneficial bacteria of the normal microbiota. Development of new antibiotics is also expensive for drug companies and for patients, especially for those who live in countries with high poverty rates.

Phages have also been used to prevent food spoilage. In 2006, the US Food and Drug Administration approved the use of a solution containing six bacteriophages that can be sprayed on lunch meats such as bologna, ham, and turkey to kill *Listeria monocytogenes*, a bacterium responsible for listeriosis, a form of food poisoning. Some consumers have concerns about the use of phages on foods, however, especially given the rising popularity of organic products. Foods that have been treated with phages must declare “bacteriophage preparation” in the list of ingredients or include a label declaring that the meat has been “treated with antimicrobial solution to reduce microorganisms.”[5]

Exercise 15.1.3

1. Why do humans not have to be concerned about the presence of bacteriophages in their food?
2. What are three ways that viruses can be transmitted between hosts?

Viral Structures

In general, virions (viral particles) are small and cannot be observed using a regular light microscope. They are much smaller than prokaryotic and eukaryotic cells; this is an adaptation allowing viruses to infect these larger cells (see Figure **15.1.2**). The size of a virion can range from 20 nm for small viruses up to 900 nm for typical, large viruses (see Figure **15.1.3**). Recent discoveries, however, have identified new giant viral species, such as *Pandoravirus salinus* and *Pithovirus sibericum*, with sizes approaching that of a bacterial cell.[6]

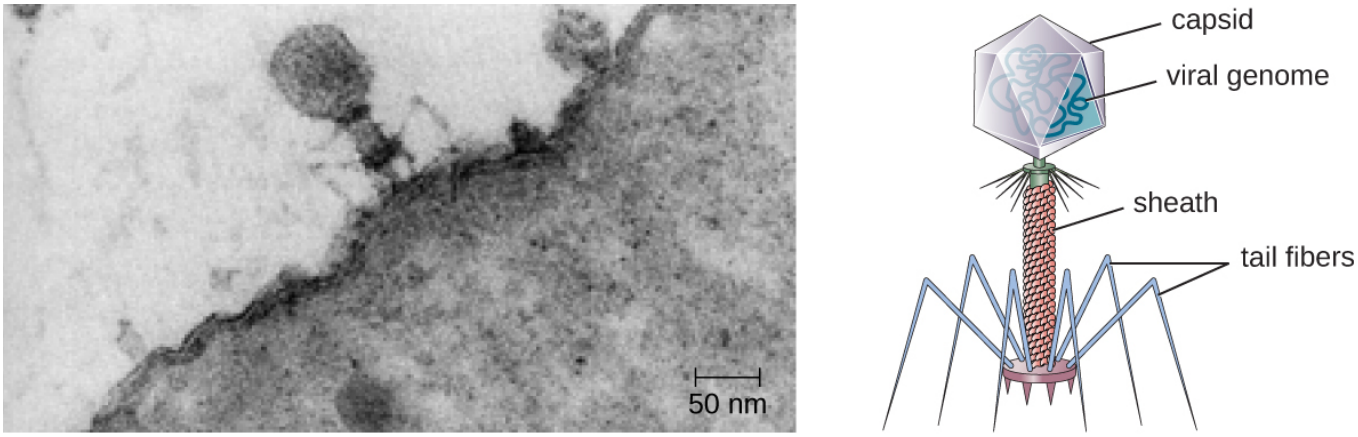


Figure **15.1.2**: (a) In this transmission electron micrograph, a bacteriophage (a virus that infects bacteria) is dwarfed by the bacterial

cell it infects. (b) An illustration of the bacteriophage in the micrograph. (credit a: modification of work by U.S. Department of Energy, Office of Science, LBL, PBD)

In 1935, after the development of the electron microscope, Wendell Stanley was the first scientist to crystallize the structure of the tobacco mosaic virus and discovered that it is composed of RNA and protein. In 1943, he isolated *Influenza B virus*, which contributed to the development of an influenza (flu) vaccine. Stanley's discoveries unlocked the mystery of the nature of viruses that had been puzzling scientists for over 40 years and his contributions to the field of virology led to him being awarded the Nobel Prize in 1946.

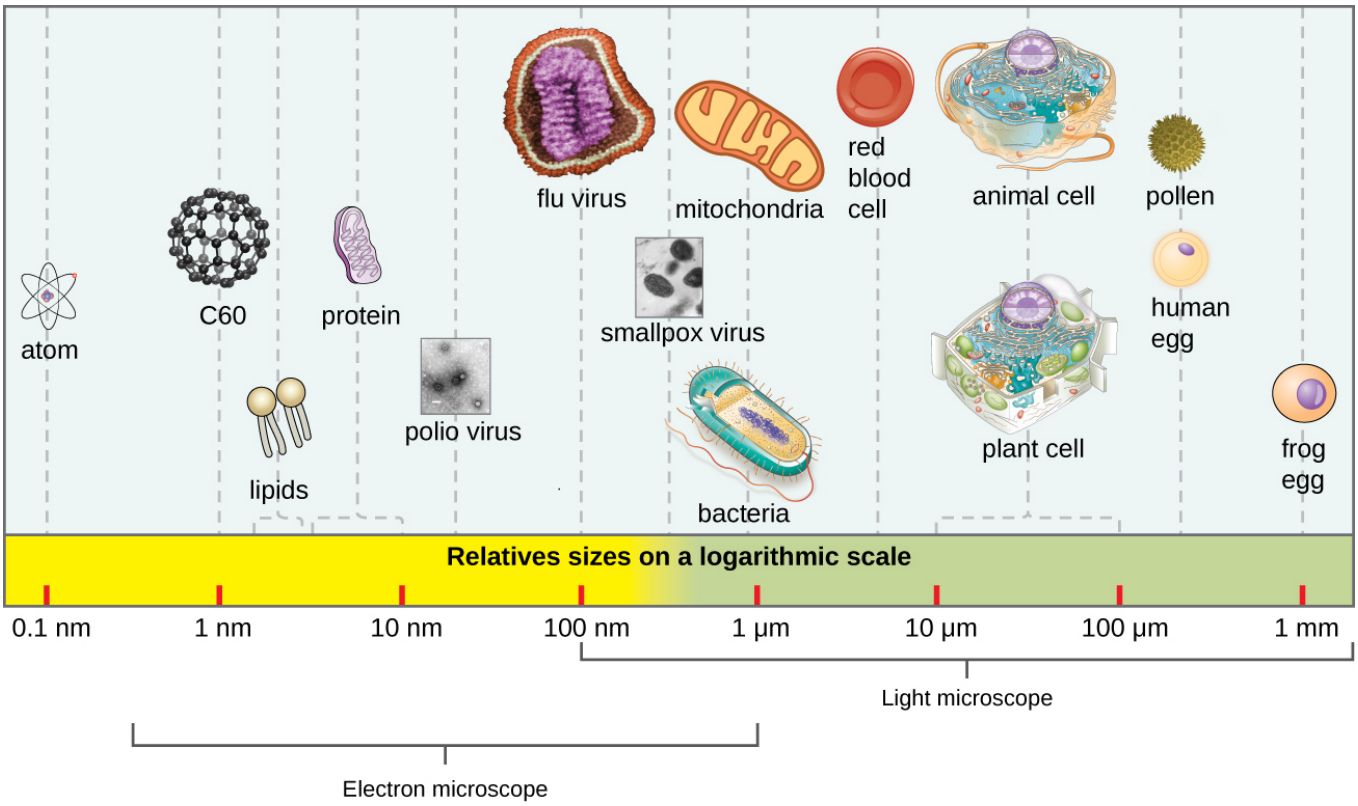


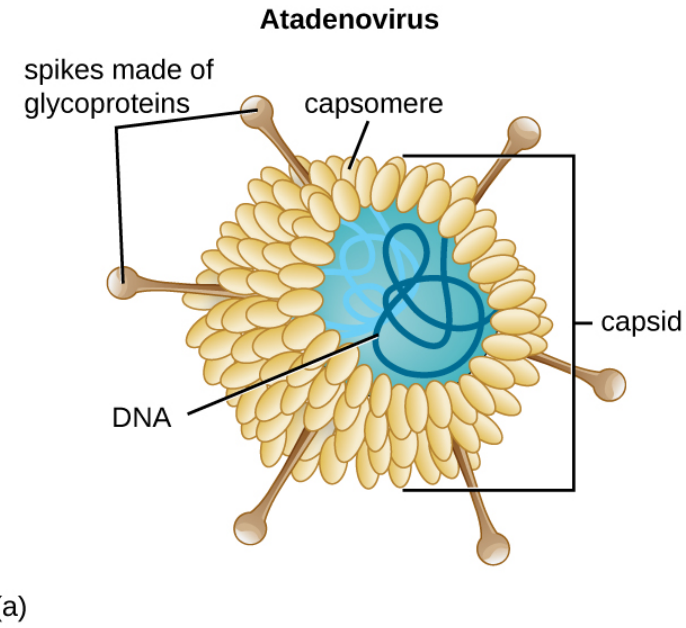
Figure 15.1.3:The size of a virus is small relative to the size of most bacterial and eukaryotic cells and their organelles.

As a result of continuing research into the nature of viruses, we now know they consist of a nucleic acid (either RNA or DNA, but never both) surrounded by a protein coat called a capsid (see Figure 15.1.4). The interior of the capsid is not filled with cytosol, as in a cell, but instead it contains the bare necessities in terms of genome and enzymes needed to direct the synthesis of new virions. Each capsid is composed of protein subunits called capsomeres made of one or more different types of capsomere proteins that interlock to form the closely packed capsid.

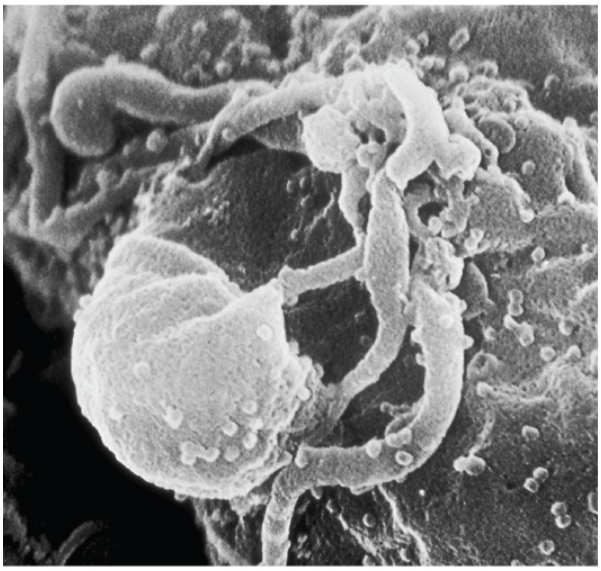
There are two categories of viruses based on general composition. Viruses formed from only a nucleic acid and capsid are called naked viruses or nonenveloped viruses. Viruses formed with a nucleic-acid packed capsid surrounded by a lipid layer are called enveloped viruses (see Figure 15.1.4). The viral envelope is a small portion of phospholipid membrane obtained as the virion buds from a host cell. The viral envelope may either be intracellular or cytoplasmic in origin.

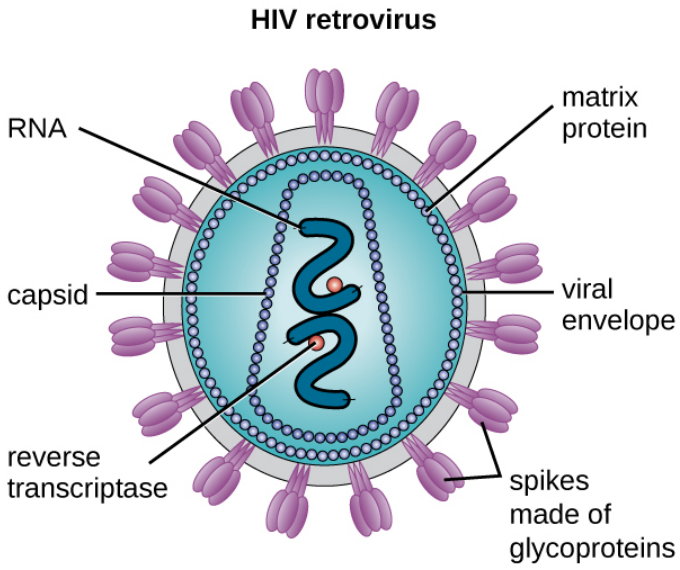
Extending outward and away from the capsid on some naked viruses and enveloped viruses are protein structures called spikes. At the tips of these spikes are structures that allow the virus to attach and enter a cell, like the influenza virus hemagglutinin spikes (H) or enzymes like the neuraminidase (N) influenza virus spikes that allow the virus to detach from the cell surface during release of new virions. Influenza viruses are often identified by their H and N spikes. For example, H1N1 influenza viruses were responsible for the pandemics in 1918 and 2009,[7] H2N2 for the pandemic in 1957, and H3N2 for the pandemic in 1968.





(a)





(b)

Figure 15.1.4: (a) The naked atadenovirus uses spikes made of glycoproteins from its capsid to bind to host cells. (b) The enveloped human immunodeficiency virus uses spikes made of glycoproteins embedded in its envelope to bind to host cells (credit a "micrograph": modification of work by NIAID; credit b "micrograph": modification of work by Centers for Disease Control and Prevention)

Viruses vary in the shape of their capsids, which can be either helical, polyhedral, or complex. A helical capsid forms the shape of tobacco mosaic virus (TMV), a naked helical virus, and Ebola virus, an enveloped helical virus. The capsid is cylindrical or rod shaped, with the genome fitting just inside the length of the capsid. Polyhedral capsids form the shapes of poliovirus and rhinovirus, and consist of a nucleic acid surrounded by a polyhedral (many-sided) capsid in the form of an icosahedron. An icosahedral capsid is a three-dimensional, 20-sided structure with 12 vertices. These capsids somewhat resemble a soccer ball. Both helical and polyhedral viruses can have envelopes. Viral shapes seen in certain types of bacteriophages, such as T4 phage, and poxviruses, like vaccinia virus, may have features of both polyhedral and helical viruses so they are described as a complex viral shape (see Figure 15.1.5). In the bacteriophage complex form, the genome is located within the polyhedral head and the sheath

connects the head to the tail fibers and tail pins that help the virus attach to receptors on the host cell's surface. Poxviruses that have complex shapes are often brick shaped, with intricate surface characteristics not seen in the other categories of capsid.

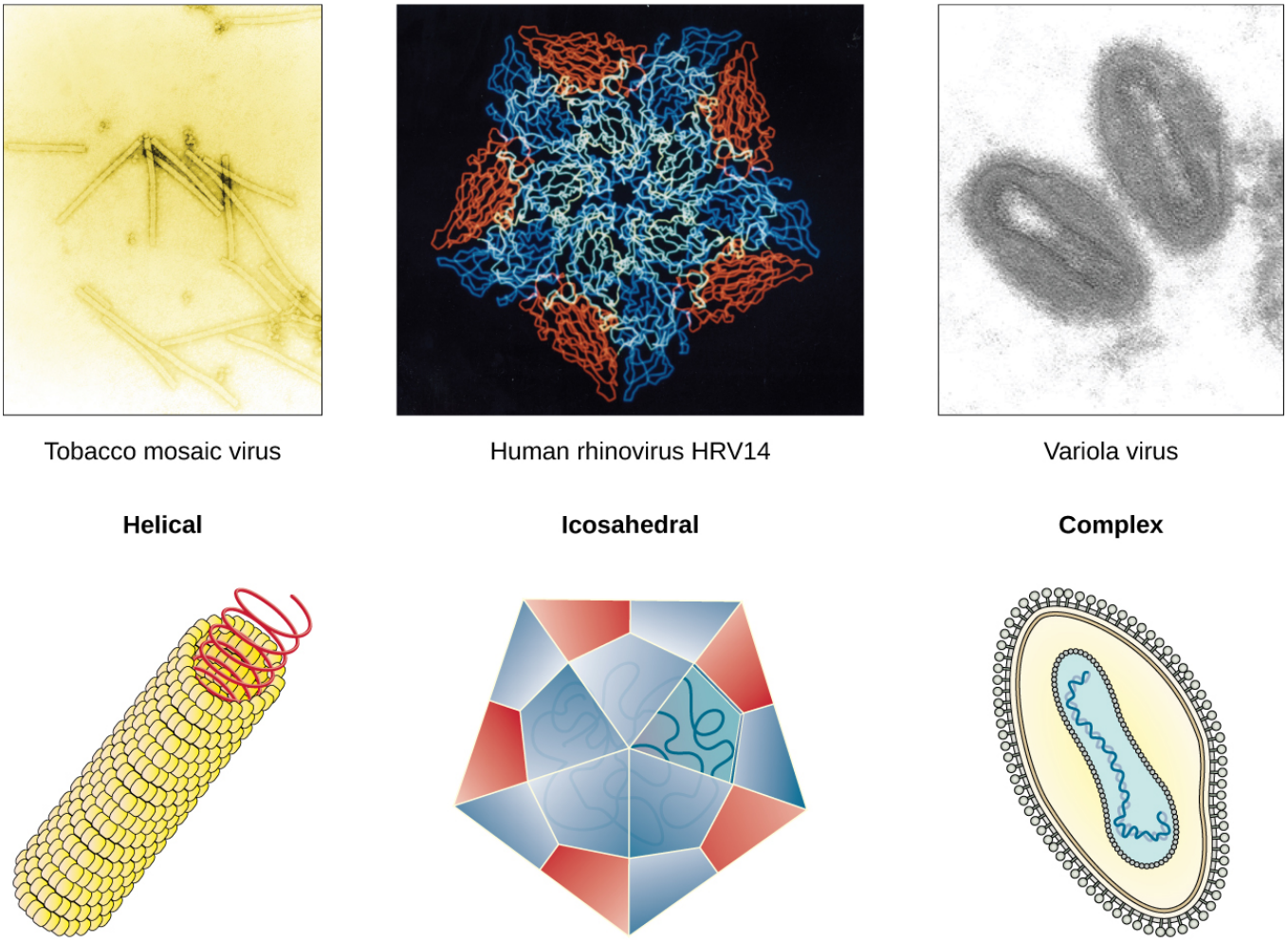


Figure 15.1.5: Viral capsids can be (a) helical, (b) polyhedral, or (c) have a complex shape. (credit a "micrograph": modification of work by USDA ARS; credit b "micrograph": modification of work by U.S. Department of Energy)

? Exercise 15.1.4

Which types of viruses have spikes?

Classification and Taxonomy of Viruses

Although viruses are not classified in the three domains of life, their numbers are great enough to require classification. Since 1971, the International Union of Microbiological Societies Virology Division has given the task of developing, refining, and maintaining a universal virus taxonomy to the International Committee on Taxonomy of Viruses (ICTV). Since viruses can mutate so quickly, it can be difficult to classify them into a genus and a species epithet using the binomial nomenclature system. Thus, the ICTV's viral nomenclature system classifies viruses into families and genera based on viral genetics, chemistry, morphology, and mechanism of multiplication. To date, the ICTV has classified known viruses in seven orders, 96 families, and 350 genera. Viral family names end in *-viridae* (e.g, *Parvoviridae*) and genus names end in *−virus* (e.g., *Parvovirus*). The names of viral orders, families, and genera are all italicized. When referring to a viral species, we often use a genus and species epithet such as *Pandoravirus dulcis* or *Pandoravirus salinus.*

The Baltimore classification system is an alternative to ICTV nomenclature. The Baltimore system classifies viruses according to their genomes (DNA or RNA, single versus double stranded, and mode of replication). This system thus creates seven groups of viruses that have common genetics and biology.

Link to Learning

Explore the latest virus taxonomy at the ICTV website.

Aside from formal systems of nomenclature, viruses are often informally grouped into categories based on chemistry, morphology, or other characteristics they share in common. Categories may include naked or enveloped structure, single-stranded (ss) or double-stranded (ds) DNA or ss or ds RNA genomes, segmented or nonsegmented genomes, and positive-strand (+) or negative-strand (−) RNA. For example, herpes viruses can be classified as a dsDNA enveloped virus; human immunodeficiency virus (HIV) is a +ssRNA enveloped virus, and tobacco mosaic virus is a +ssRNA virus. Other characteristics such as host specificity, tissue specificity, capsid shape, and special genes or enzymes may also be used to describe groups of similar viruses. Table **15.1.2** lists some of the most common viruses that are human pathogens by genome type.

Table **15.1.2**: Common Pathogenic Viruses

Genome	Family	Example Virus	Clinical Features
dsDNA, enveloped	*Poxviridae*	*Orthopoxvirus*	Skin papules, pustules, lesions
	Poxviridae	*Parapoxvirus*	Skin lesions
	Herpesviridae	*Simplexvirus*	Cold sores, genital herpes, sexually transmitted disease
dsDNA, naked	*Adenoviridae*	*Atadenovirus*	Respiratory infection (common cold)
	Papillomaviridae	*Papillomavirus*	Genital warts, cervical, vulvar, or vaginal cancer
	Reoviridae	*Reovirus*	Gastroenteritis severe diarrhea (stomach flu)
ssDNA, naked	*Parvoviridae*	*Adeno-associated dependoparvovirus A*	Respiratory tract infection
	Parvoviridae	*Adeno-associated dependoparvovirus B*	Respiratory tract infection
dsRNA, naked	*Reoviridae*	*Rotavirus*	Gastroenteritis
+ssRNA, naked	*Picornaviridae*	*Enterovirus C*	Poliomyelitis
	Picornaviridae	*Rhinovirus*	Upper respiratory tract infection (common cold)
	Picornaviridae	*Hepatovirus*	Hepatitis
+ssRNA, enveloped	*Togaviridae*	*Alphavirus*	Encephalitis, hemorrhagic fever
	Togaviridae	*Rubivirus*	Rubella
	Retroviridae	*Lentivirus*	Acquired immune deficiency syndrome (AIDS)
−ssRNA, enveloped	*Filoviridae*	*Zaire Ebolavirus*	Hemorrhagic fever
	Orthomyxoviridae	*Influenzavirus A, B, C*	Flu
	Rhabdoviridae	*Lyssavirus*	Rabies

? Exercise 15.1.5

What are the types of virus genomes?

Classification of Viral Diseases

While the ICTV has been tasked with the biological classification of viruses, it has also played an important role in the classification of diseases caused by viruses. To facilitate the tracking of virus-related human diseases, the ICTV has created classifications that link to the International Classification of Diseases (ICD), the standard taxonomy of disease that is maintained and updated by the World Health Organization (WHO). The ICD assigns an alphanumeric code of up to six characters to every type of viral infection, as well as all other types of diseases, medical conditions, and causes of death. This ICD code is used in conjunction with two other coding systems (the Current Procedural Terminology, and the Healthcare Common Procedure Coding System) to categorize patient conditions for treatment and insurance reimbursement.

For example, when a patient seeks treatment for a viral infection, ICD codes are routinely used by clinicians to order laboratory tests and prescribe treatments specific to the virus suspected of causing the illness. This ICD code is then used by medical laboratories to identify tests that must be performed to confirm the diagnosis. The ICD code is used by the health-care management system to verify that all treatments and laboratory work performed are appropriate for the given virus. Medical coders use ICD codes to assign the proper code for procedures performed, and medical billers, in turn, use this information to process claims for reimbursement by insurance companies. Vital-records keepers use ICD codes to record cause of death on death certificates, and epidemiologists used ICD codes to calculate morbidity and mortality statistics.

? Exercise 15.1.6

Identify two locations where you would likely find an ICD code.

Clinical Focus:Part 2

David's doctor was concerned that his symptoms included prickling and itching at the site of the dog bite; these sensations could be early symptoms of rabies. Several tests are available to diagnose rabies in live patients, but no single antemortem test is adequate. The doctor decided to take samples of David's blood, saliva, and skin for testing. The skin sample was taken from the nape of the neck (posterior side of the neck near the hairline). It was about 6-mm long and contained at least 10 hair follicles, including the superficial cutaneous nerve. An immunofluorescent staining technique was used on the skin biopsy specimen to detect rabies antibodies in the cutaneous nerves at the base of the hair follicles. A test was also performed on a serum sample from David's blood to determine whether any antibodies for the rabies virus had been produced.

Meanwhile, the saliva sample was used for reverse transcriptase-polymerase chain reaction (RT-PCR) analysis, a test that can detect the presence of viral nucleic acid (RNA). The blood tests came back positive for the presence of rabies virus antigen, prompting David's doctor to prescribe prophylactic treatment. David is given a series of intramuscular injections of human rabies immunoglobulin along with a series of rabies vaccines.

Exercise 15.1.7

1. Why does the immunofluorescent technique look for rabies antibodies rather than the rabies virus itself?
2. If David has contracted rabies, what is his prognosis?

Summary

- Viruses are generally ultramicroscopic, typically from 20 nm to 900 nm in length. Some large viruses have been found.
- **Virions** are acellular and consist of a nucleic acid, DNA or RNA, but not both, surrounded by a protein **capsid**. There may also be a phospholipid membrane surrounding the capsid.
- Viruses are obligate intracellular parasites.
- Viruses are known to infect various types of cells found in plants, animals, fungi, protists, bacteria, and archaea. Viruses typically have limited **host ranges** and infect specific cell types.
- Viruses may have **helical**, **polyhedral,** or **complex** shapes.
- Classification of viruses is based on morphology, type of nucleic acid, host range, cell specificity, and enzymes carried within the virion.
- Like other diseases, viral diseases are classified using ICD codes.

Footnotes

1. 1 H. Lecoq. "[Discovery of the First Virus, the Tobacco Mosaic Virus: 1892 or 1898?]." *Comptes Rendus de l'Academie des Sciences – Serie III – Sciences de la Vie* 324, no. 10 (2001): 929–933.
2. 2 US Department of Health and Human Services, Centers for Disease Control and Prevention. "Antibiotic Resistance Threats in the United States, 2013." www.cdc.gov/drugresistance/pd...s-2013-508.pdf (accessed September 22, 2015).
3. 3 M. Clokie et al. "Phages in Nature." *Bacteriophage* 1, no. 1 (2011): 31–45.
4. 4 A. Sulakvelidze et al. "Bacteriophage Therapy." *Antimicrobial Agents and Chemotherapy* 45, no. 3 (2001): 649–659.

5. 5 US Food and Drug Administration. “FDA Approval of *Listeria*-specific Bacteriophage Preparation on Ready-to-Eat (RTE) Meat and Poultry Products.” www.fda.gov/food/ingredientsp.../ucm083572.htm (accessed September 22, 2015).
6. 6 N. *Philippe et al. “Pandoraviruses: Amoeba Viruses with Genomes up to 2.5 Mb Reaching that of Parasitic Eukaryotes.” Science 341, no. 6143 (2013): 281–286.*
7. 7 J. Cohen. “What’s Old Is New: 1918 Virus Matches 2009 H1N1 Strain. *Science* 327, no. 5973 (2010): 1563–1564.

This page titled 15.1: Viruses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **6.1: Viruses** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

15.2: The Viral Life Cycle

Learning Objectives

- Describe the lytic and lysogenic life cycles
- Describe the replication process of animal viruses
- Describe unique characteristics of retroviruses and latent viruses
- Discuss human viruses and their virus-host cell interactions
- Explain the process of transduction
- Describe the replication process of plant viruses

All viruses depend on cells for reproduction and metabolic processes. By themselves, viruses do not encode for all of the enzymes necessary for viral replication. But within a host cell, a virus can commandeer cellular machinery to produce more viral particles. Bacteriophages replicate only in the cytoplasm, since prokaryotic cells do not have a nucleus or organelles. In eukaryotic cells, most DNA viruses can replicate inside the nucleus, with an exception observed in the large DNA viruses, such as the poxviruses, that can replicate in the cytoplasm. RNA viruses that infect animal cells often replicate in the cytoplasm.

The Life Cycle of Viruses with Prokaryote Hosts

The life cycle of bacteriophages has been a good model for understanding how viruses affect the cells they infect, since similar processes have been observed for eukaryotic viruses, which can cause immediate death of the cell or establish a latent or chronic infection. Virulent phages typically lead to the death of the cell through cell lysis. **Temperate phages**, on the other hand, can become part of a host chromosome and are replicated with the cell genome until such time as they are induced to make newly assembled viruses, or **progeny viruses**.

The Lytic Cycle

During the lytic cycle of virulent phage, the bacteriophage takes over the cell, reproduces new phages, and destroys the cell. T-even phage is a good example of a well-characterized class of virulent phages. There are five stages in the bacteriophage lytic cycle (see Figure 15.2.1). Attachment is the first stage in the infection process in which the phage interacts with specific bacterial surface receptors (e.g., lipopolysaccharides and OmpC protein on host surfaces). Most phages have a narrow host range and may infect one species of bacteria or one strain within a species. This unique recognition can be exploited for targeted treatment of bacterial infection by phage therapy or for phage typing to identify unique bacterial subspecies or strains. The second stage of infection is entry or penetration. This occurs through contraction of the tail sheath, which acts like a hypodermic needle to inject the viral genome through the cell wall and membrane. The phage head and remaining components remain outside the bacteria.

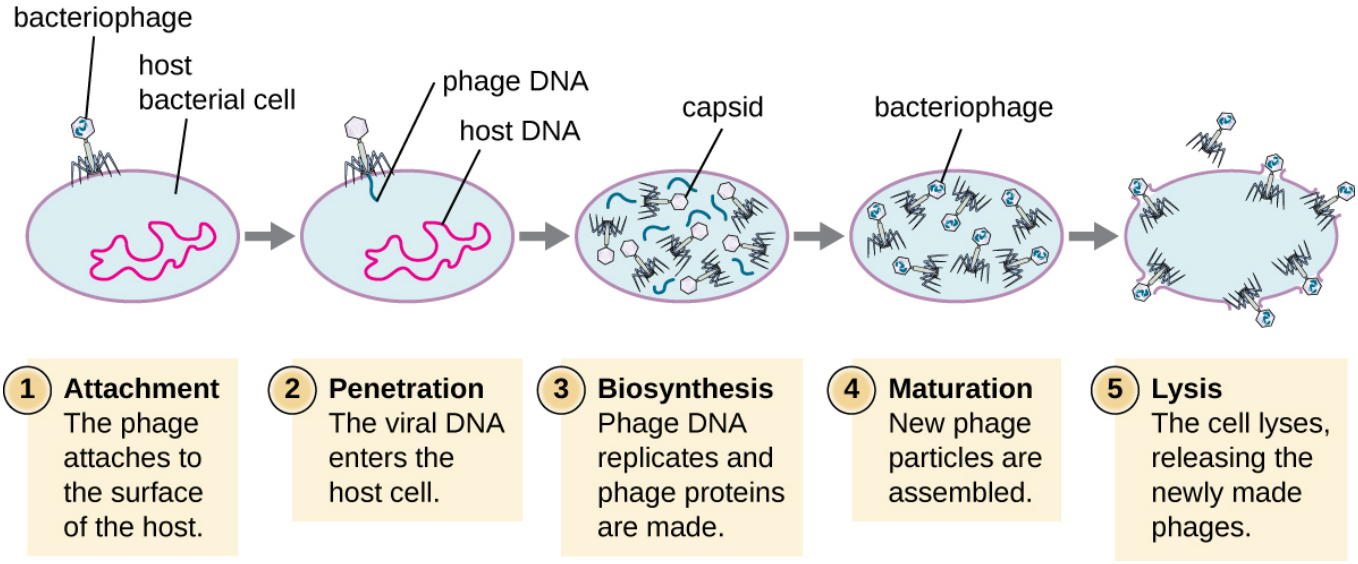


Figure 15.2.1: A virulent phage shows only the lytic cycle pictured here. In the lytic cycle, the phage replicates and lyses the host

cell.

The third stage of infection is biosynthesis of new viral components. After entering the host cell, the virus synthesizes virus-encoded endonucleases to degrade the bacterial chromosome. It then hijacks the host cell to replicate, transcribe, and translate the necessary viral components (capsomeres, sheath, base plates, tail fibers, and viral enzymes) for the assembly of new viruses. Polymerase genes are usually expressed early in the cycle, while capsid and tail proteins are expressed later. During the maturation phase, new virions are created. To liberate free phages, the bacterial cell wall is disrupted by phage proteins such as holin or lysozyme. The final stage is release. Mature viruses burst out of the host cell in a process called lysis and the progeny viruses are liberated into the environment to infect new cells.

The Lysogenic Cycle

In a lysogenic cycle, the phage genome also enters the cell through attachment and penetration. A prime example of a phage with this type of life cycle is the lambda phage. During the lysogenic cycle, instead of killing the host, the phage genome integrates into the bacterial chromosome and becomes part of the host. The integrated phage genome is called a prophage. A bacterial host with a prophage is called a lysogen. The process in which a bacterium is infected by a temperate phage is called lysogeny. It is typical of temperate phages to be latent or inactive within the cell. As the bacterium replicates its chromosome, it also replicates the phage's DNA and passes it on to new daughter cells during reproduction. The presence of the phage may alter the phenotype of the bacterium, since it can bring in extra genes (e.g., toxin genes that can increase bacterial virulence). This change in the host phenotype is called lysogenic conversion or phage conversion. Some bacteria, such as *Vibrio cholerae* and *Clostridium botulinum*, are less virulent in the absence of the prophage. The phages infecting these bacteria carry the toxin genes in their genome and enhance the virulence of the host when the toxin genes are expressed. In the case of *V. cholera*, phage encoded toxin can cause severe diarrhea; in *C. botulinum*, the toxin can cause paralysis. During lysogeny, the prophage will persist in the host chromosome until induction, which results in the excision of the viral genome from the host chromosome. After induction has occurred the temperate phage can proceed through a lytic cycle and then undergo lysogeny in a newly infected cell (see Figure **15.2.2**).

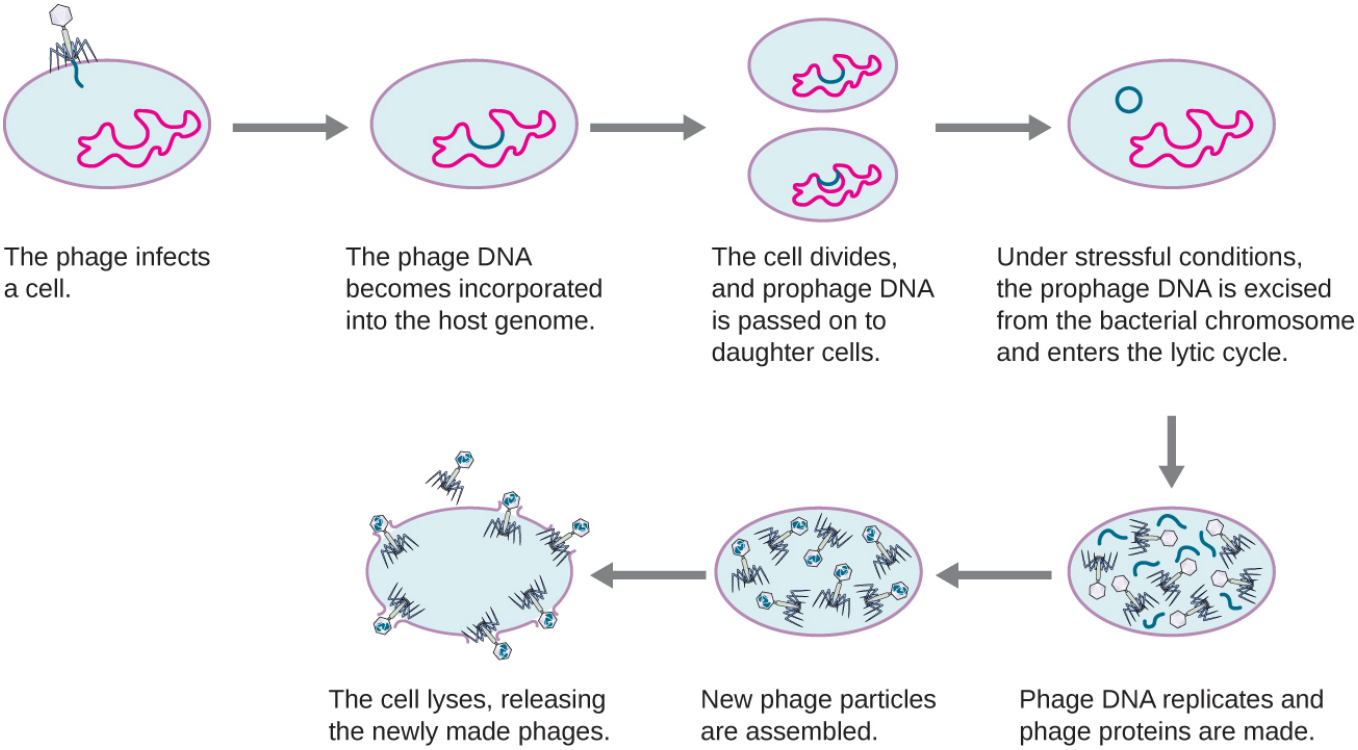


Figure **15.2.2**: A temperate bacteriophage has both lytic and lysogenic cycles. In the lysogenic cycle, phage DNA is incorporated into the host genome, forming a prophage, which is passed on to subsequent generations of cells. Environmental stressors such as starvation or exposure to toxic chemicals may cause the prophage to be excised and enter the lytic cycle.

Link to Learning

This video illustrates the stages of the lysogenic life cycle of a bacteriophage and the transition to a lytic phase.

Exercise 15.2.1

Is a latent phage undetectable in a bacterium?

Transduction

Transduction occurs when a bacteriophage transfers bacterial DNA from one bacterium to another during sequential infections. There are two types of transduction: generalized and specialized transduction. During the lytic cycle of viral replication, the virus hijacks the host cell, degrades the host chromosome, and makes more viral genomes. As it assembles and packages DNA into the phage head, packaging occasionally makes a mistake. Instead of packaging viral DNA, it takes a random piece of host DNA and inserts it into the capsid. Once released, this virion will then inject the former host's DNA into a newly infected host. The asexual transfer of genetic information can allow for DNA recombination to occur, thus providing the new host with new genes (e.g., an antibiotic-resistance gene, or a sugar-metabolizing gene). Generalized transduction occurs when a random piece of bacterial chromosomal DNA is transferred by the phage during the lytic cycle. Specialized transduction occurs at the end of the lysogenic cycle, when the prophage is excised and the bacteriophage enters the lytic cycle. Since the phage is integrated into the host genome, the prophage can replicate as part of the host. However, some conditions (e.g., ultraviolet light exposure or chemical exposure) stimulate the prophage to undergo induction, causing the phage to excise from the genome, enter the lytic cycle, and produce new phages to leave host cells. During the process of excision from the host chromosome, a phage may occasionally remove some bacterial DNA near the site of viral integration. The phage and host DNA from one end or both ends of the integration site are packaged within the capsid and are transferred to the new, infected host. Since the DNA transferred by the phage is not randomly packaged but is instead a specific piece of DNA near the site of integration, this mechanism of gene transfer is referred to as specialized transduction (see Figure 15.2.3). The DNA can then recombine with host chromosome, giving the latter new characteristics. Transduction seems to play an important role in the evolutionary process of bacteria, giving them a mechanism for asexual exchange of genetic information.

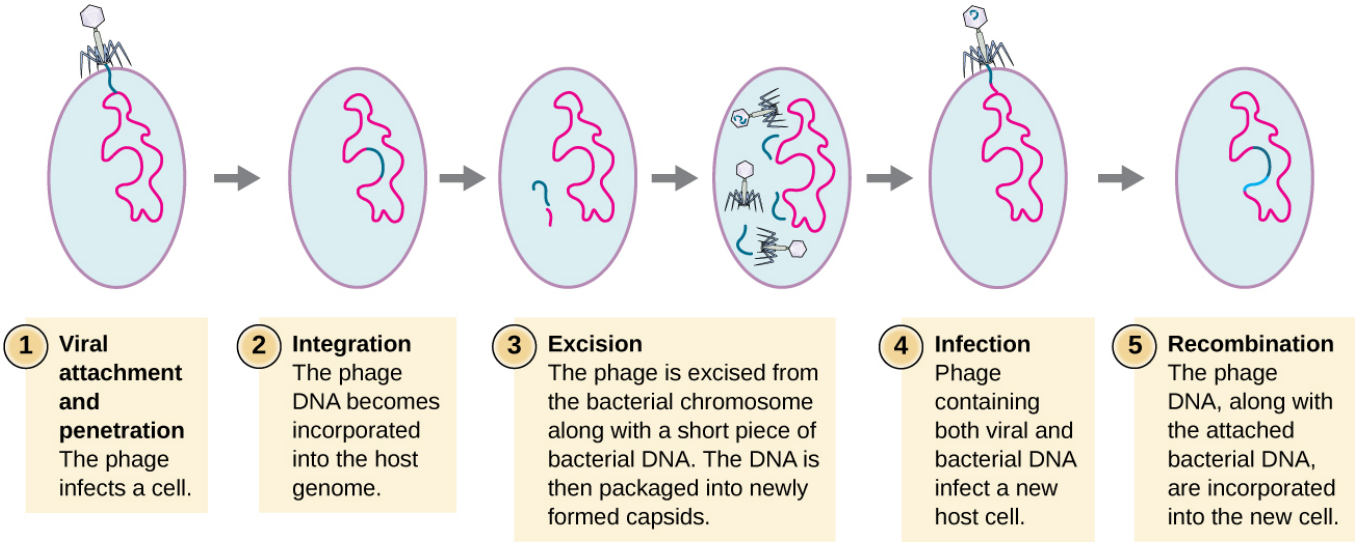


Figure 15.2.3: This flowchart illustrates the mechanism of specialized transduction. An integrated phage excises, bringing with it a piece of the DNA adjacent to its insertion point. On reinfection of a new bacterium, the phage DNA integrates along with the genetic material acquired from the previous host.

Exercise 15.2.2

Which phage life cycle is associated with which forms of transduction?

Life Cycle of Viruses with Animal Hosts

Lytic animal viruses follow similar infection stages to bacteriophages: attachment, penetration, biosynthesis, maturation, and release (see Figure **15.2.4**). However, the mechanisms of penetration, nucleic-acid biosynthesis, and release differ between bacterial and animal viruses. After binding to host receptors, animal viruses enter through endocytosis(engulfment by the host cell) or through membrane fusion (viral envelope with the host cell membrane). Many viruses are host specific, meaning they only infect a certain type of host; and most viruses only infect certain types of cells within tissues. This specificity is called a tissue tropism. Examples of this are demonstrated by the poliovirus, which exhibits tropism for the tissues of the brain and spinal cord, or the influenza virus, which has a primary tropism for the respiratory tract.

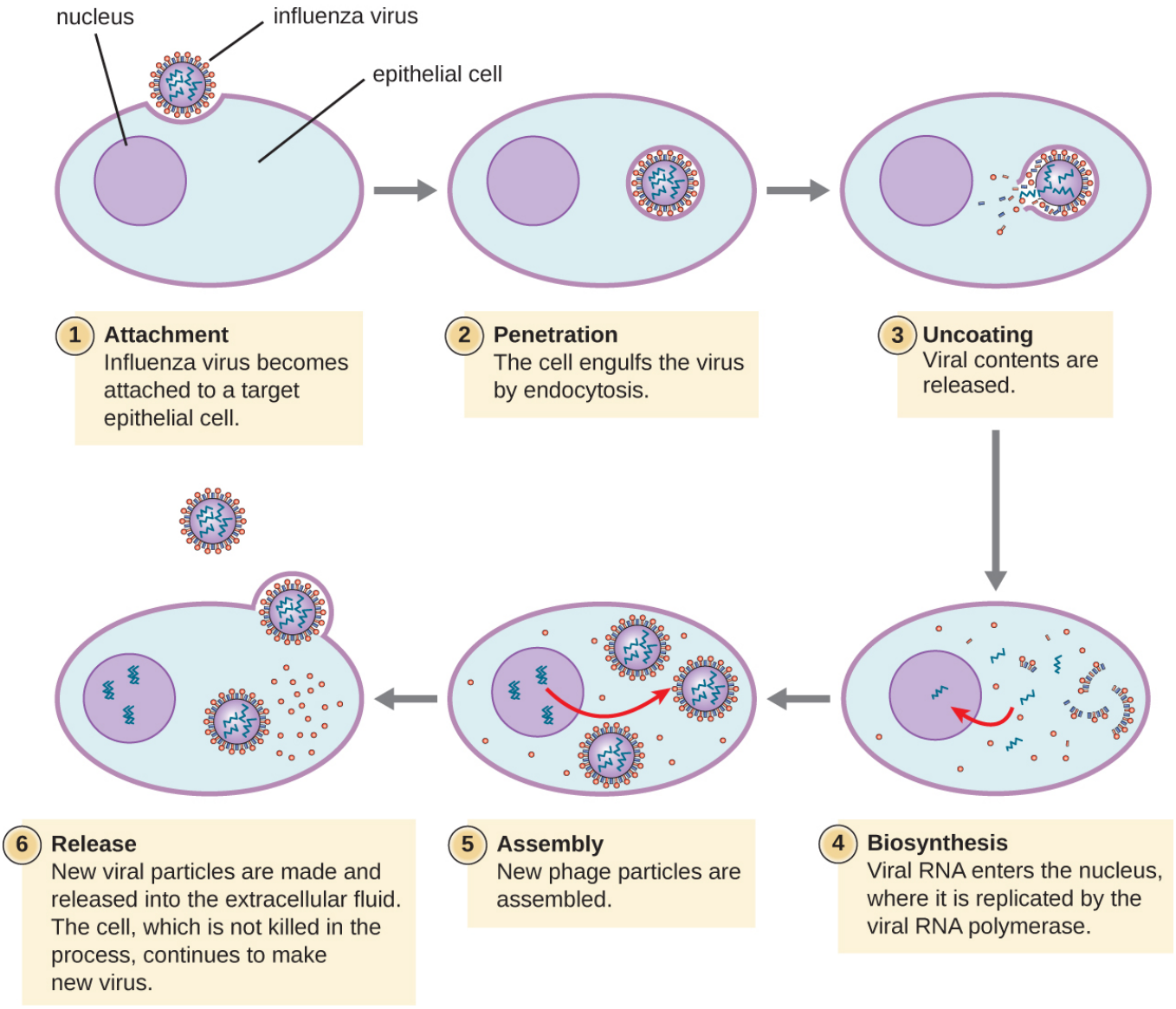


Figure **15.2.4**: In influenza virus infection, viral glycoproteins attach the virus to a host epithelial cell. As a result, the virus is engulfed. Viral RNA and viral proteins are made and assembled into new virions that are released by budding.

Animal viruses do not always express their genes using the normal flow of genetic information—from DNA to RNA to protein. Some viruses have a dsDNA genome like cellular organisms and can follow the normal flow. However, others may have ssDNA, dsRNA, or ssRNA genomes. The nature of the genome determines how the genome is replicated and expressed as viral proteins. If a genome is ssDNA, host enzymes will be used to synthesize a second strand that is complementary to the genome strand, thus producing dsDNA. The dsDNA can now be replicated, transcribed, and translated similar to host DNA.

If the viral genome is RNA, a different mechanism must be used. There are three types of RNA genome: dsRNA, positive (+) single-strand (+ssRNA) or negative (−) single-strand RNA (−ssRNA). If a virus has a +ssRNA genome, it can be translated directly to make viral proteins. Viral genomic +ssRNA acts like cellular mRNA. However, if a virus contains a −ssRNA genome, the host ribosomes cannot translate it until the −ssRNA is replicated into +ssRNA by viral RNA-dependent RNA polymerase (RdRP) (see Figure **15.2.5**). The RdRP is brought in by the virus and can be used to make +ssRNA from the original −ssRNA genome. The RdRP is also an important enzyme for the replication of dsRNA viruses, because it uses the negative strand of the double-stranded genome as a template to create +ssRNA. The newly synthesized +ssRNA copies can then be translated by cellular ribosomes.

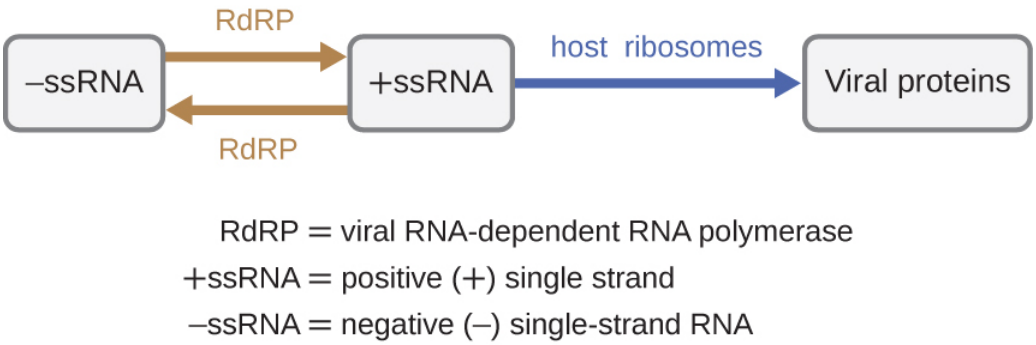


Figure **15.2.5**: RNA viruses can contain +ssRNA that can be directly read by the ribosomes to synthesize viral proteins. Viruses containing −ssRNA must first use the −ssRNA as a template for the synthesis of +ssRNA before viral proteins can be synthesized.

An alternative mechanism for viral nucleic acid synthesis is observed in the retrovirus**es**, which are +ssRNA viruses (see Figure **15.2.6**). Single-stranded RNA viruses such as HIV carry a special enzyme called reverse transcriptase within the capsid that synthesizes a complementary ssDNA (cDNA) copy using the +ssRNA genome as a template. The ssDNA is then made into dsDNA, which can integrate into the host chromosome and become a permanent part of the host. The integrated viral genome is called a provirus. The virus now can remain in the host for a long time to establish a chronic infection. The provirus stage is similar to the prophage stage in a bacterial infection during the lysogenic cycle. However, unlike prophage, the provirus does not undergo excision after splicing into the genome.

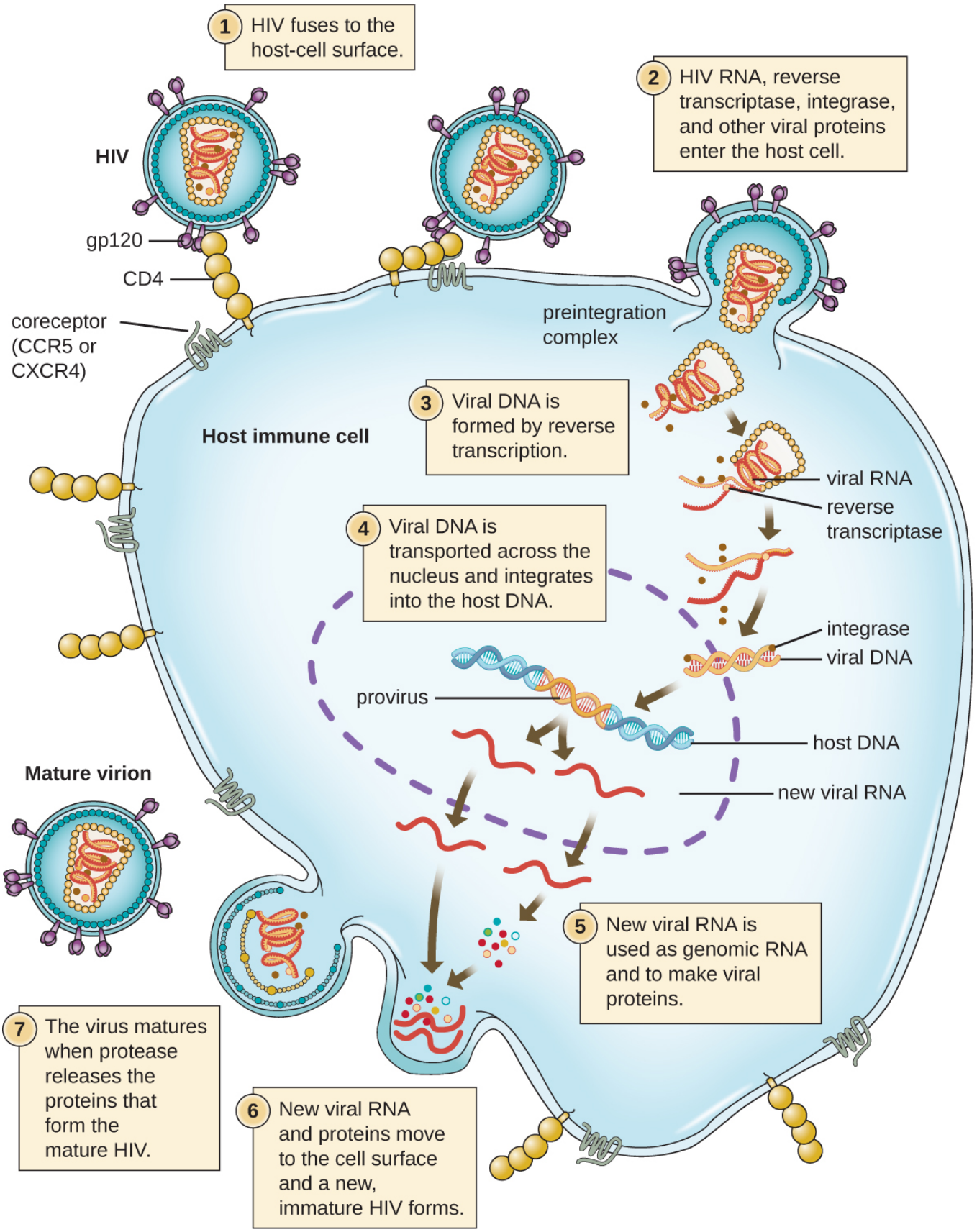


Figure **15.2.6**: HIV, an enveloped, icosahedral retrovirus, attaches to a cell surface receptor of an immune cell and fuses with the

cell membrane. Viral contents are released into the cell, where viral enzymes convert the single-stranded RNA genome into DNA and incorporate it into the host genome. (credit: modification of work by NIAID, NIH)

? Exercise 15.2.3

Is RNA-dependent RNA polymerase made from a viral gene or a host gene?

Persistent Infections

Persistent infection occurs when a virus is not completely cleared from the system of the host but stays in certain tissues or organs of the infected person. The virus may remain silent or undergo productive infection without seriously harming or killing the host. Mechanisms of persistent infection may involve the regulation of the viral or host gene expressions or the alteration of the host immune response. The two primary categories of persistent infections are latent infection and chronic infection. Examples of viruses that cause latent infections include herpes simplex virus (oral and genital herpes), varicella-zoster virus (chickenpox and shingles), and Epstein-Barr virus (mononucleosis). Hepatitis C virus and HIV are two examples of viruses that cause long-term chronic infections.

Latent Infection

Not all animal viruses undergo replication by the lytic cycle. There are viruses that are capable of remaining hidden or dormant inside the cell in a process called latency. These types of viruses are known as latent viruses and may cause latent infections. Viruses capable of latency may initially cause an acute infection before becoming dormant.

For example, the varicella-zoster virus infects many cells throughout the body and causes chickenpox, characterized by a rash of blisters covering the skin. About 10 to 12 days postinfection, the disease resolves and the virus goes dormant, living within nerve-cell ganglia for years. During this time, the virus does not kill the nerve cells or continue replicating. It is not clear why the virus stops replicating within the nerve cells and expresses few viral proteins but, in some cases, typically after many years of dormancy, the virus is reactivated and causes a new disease called shingles (Figure 15.2.7). Whereas chickenpox affects many areas throughout the body, shingles is a nerve cell-specific disease emerging from the ganglia in which the virus was dormant.

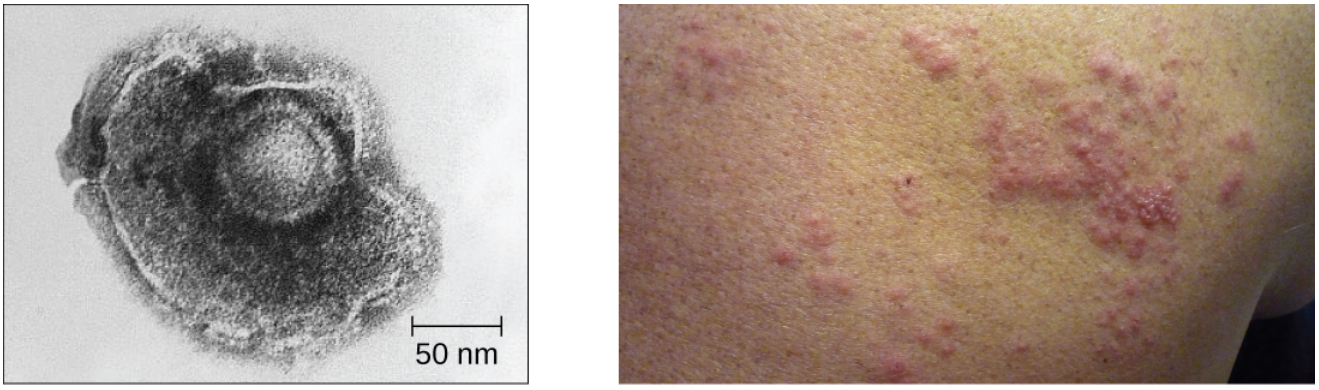


Figure 15.2.7: (a) Varicella-zoster, the virus that causes chickenpox, has an enveloped icosahedral capsid visible in this transmission electron micrograph. Its double-stranded DNA genome becomes incorporated in the host DNA. (b) After a period of latency, the virus can reactivate in the form of shingles, usually manifesting as a painful, localized rash on one side of the body. (credit a: modification of work by Erskine Palmer and B.G. Partin—scale-bar data from Matt Russell; credit b: modification of work by Rosmarie Voegtli)

Latent viruses may remain dormant by existing as circular viral genome molecules outside of the host chromosome. Others become proviruses by integrating into the host genome. During dormancy, viruses do not cause any symptoms of disease and may be difficult to detect. A patient may be unaware that he or she is carrying the virus unless a viral diagnostic test has been performed.

Chronic Infection

A chronic infection is a disease with symptoms that are recurrent or persistent over a long time. Some viral infections can be chronic if the body is unable to eliminate the virus. HIV is an example of a virus that produces a chronic infection, often after a long period of latency. Once a person becomes infected with HIV, the virus can be detected in tissues continuously thereafter, but untreated patients often experience no symptoms for years. However, the virus maintains chronic persistence through several mechanisms that interfere with immune function, including preventing expression of viral antigens on the surface of infected cells, altering immune cells themselves, restricting expression of viral genes, and rapidly changing viral antigens through mutation. Eventually, the damage to the immune system results in progression of the disease leading to acquired immunodeficiency syndrome (AIDS). The various mechanisms that HIV uses to avoid being cleared by the immune system are also used by other chronically infecting viruses, including the hepatitis C virus.

? Exercise 15.2.4

In what two ways can a virus manage to maintain a persistent infection?

Life Cycle of Viruses with Plant Hosts

Plant viruses are more similar to animal viruses than they are to bacteriophages. Plant viruses may be enveloped or non-enveloped. Like many animal viruses, plant viruses can have either a DNA or RNA genome and be single stranded or double stranded. However, most plant viruses do not have a DNA genome; the majority have a +ssRNA genome, which acts like messenger RNA (mRNA). Only a minority of plant viruses have other types of genomes.

Plant viruses may have a narrow or broad host range. For example, the citrus tristeza virus infects only a few plants of the *Citrus* genus, whereas the cucumber mosaic virus infects thousands of plants of various plant families. Most plant viruses are transmitted by contact between plants, or by fungi, nematodes, insects, or other arthropods that act as mechanical vectors. However, some viruses can only be transferred by a specific type of insect vector; for example, a particular virus might be transmitted by aphids but not whiteflies. In some cases, viruses may also enter healthy plants through wounds, as might occur due to pruning or weather damage.

Viruses that infect plants are considered biotrophic parasites, which means that they can establish an infection without killing the host, similar to what is observed in the lysogenic life cycles of bacteriophages. Viral infection can be asymptomatic (latent) or can lead to cell death (lytic infection). The life cycle begins with the penetration of the virus into the host cell. Next, the virus is uncoated within the cytoplasm of the cell when the capsid is removed. Depending on the type of nucleic acid, cellular components are used to replicate the viral genome and synthesize viral proteins for assembly of new virions. To establish a systemic infection, the virus must enter a part of the vascular system of the plant, such as the phloem. The time required for systemic infection may vary from a few days to a few weeks depending on the virus, the plant species, and the environmental conditions. The virus life cycle is complete when it is transmitted from an infected plant to a healthy plant.

? Exercise 15.2.5

What is the structure and genome of a typical plant virus?

Viral Growth Curve

Unlike the growth curve for a bacterial population, the growth curve for a virus population over its life cycle does not follow a sigmoidal curve. During the initial stage, an inoculum of virus causes infection. In the eclipse phase, viruses bind and penetrate the cells with no virions detected in the medium. The chief difference that next appears in the viral growth curve compared to a bacterial growth curve occurs when virions are released from the lysed host cell at the same time. Such an occurrence is called a burst, and the number of virions per bacterium released is described as the burst size. In a one-step multiplication curve for bacteriophage, the host cells lyse, releasing many viral particles to the medium, which leads to a very steep rise in viral titer (the number of virions per unit volume). If no viable host cells remain, the viral particles begin to degrade during the decline of the culture (see Figure **15.2.8**).

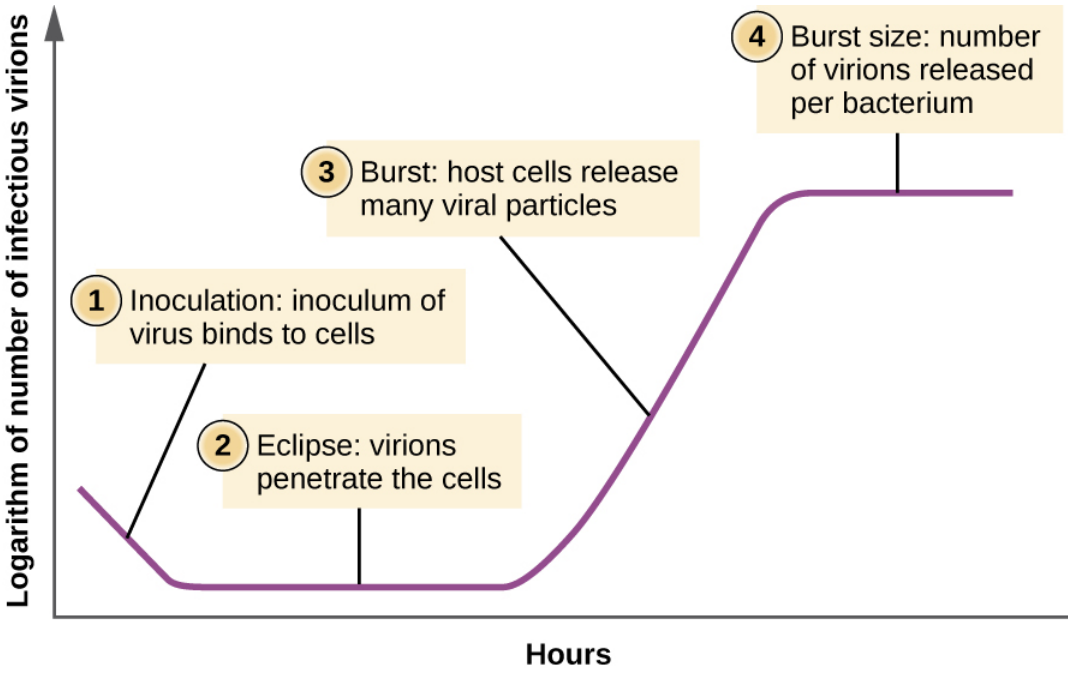


Figure 15.2.8: The one-step multiplication curve for a bacteriophage population follows three steps: 1) inoculation, during which the virions attach to host cells; 2) eclipse, during which entry of the viral genome occurs; and 3) burst, when sufficient numbers of new virions are produced and emerge from the host cell. The burst size is the maximum number of virions produced per bacterium.

? Exercise 15.2.6

What aspect of the life cycle of a virus leads to the sudden increase in the growth curve?

Unregistered Treatments

Ebola is incurable and deadly. The outbreak in West Africa in 2014 was unprecedented, dwarfing other human Ebola epidemics in the level of mortality. Of 24,666 suspected or confirmed cases reported, 10,179 people died.

No approved treatments or vaccines for Ebola are available. While some drugs have shown potential in laboratory studies and animal models, they have not been tested in humans for safety and effectiveness. Not only are these drugs untested or unregistered but they are also in short supply.

Given the great suffering and high mortality rates, it is fair to ask whether unregistered and untested medications are better than none at all. Should such drugs be dispensed and, if so, who should receive them, in light of their extremely limited supplies? Is it ethical to treat untested drugs on patients with Ebola? On the other hand, is it ethical to withhold potentially life-saving drugs from dying patients? Or should the drugs perhaps be reserved for health-care providers working to contain the disease?

In August 2014, two infected US aid workers and a Spanish priest were treated with ZMapp, an unregistered drug that had been tested in monkeys but not in humans. The two American aid workers recovered, but the priest died. Later that month, the WHO released a report on the ethics of treating patients with the drug. Since Ebola is often fatal, the panel reasoned that it is ethical to give the unregistered drugs and unethical to withhold them for safety concerns. This situation is an example of “compassionate use” outside the well-established system of regulation and governance of therapies.

Ebola in the US

On September 24, 2014, Thomas Eric Duncan arrived at the Texas Health Presbyterian Hospital in Dallas complaining of a fever, headache, vomiting, and diarrhea—symptoms commonly observed in patients with the cold or the flu. After examination, an emergency department doctor diagnosed him with sinusitis, prescribed some antibiotics, and sent him home.

Two days later, Duncan returned to the hospital by ambulance. His condition had deteriorated and additional blood tests confirmed that he has been infected with the Ebola virus.

Further investigations revealed that Duncan had just returned from Liberia, one of the countries in the midst of a severe Ebola epidemic. On September 15, nine days before he showed up at the hospital in Dallas, Duncan had helped transport an Ebola-stricken neighbor to a hospital in Liberia. The hospital continued to treat Duncan, but he died several days after being admitted.

The timeline of the Duncan case is indicative of the life cycle of the Ebola virus. The incubation time for Ebola ranges from 2 days to 21 days. Nine days passed between Duncan's exposure to the virus infection and the appearance of his symptoms. This corresponds, in part, to the eclipse period in the growth of the virus population. During the eclipse phase, Duncan would have been unable to transmit the disease to others. However, once an infected individual begins exhibiting symptoms, the disease becomes very contagious. Ebola virus is transmitted through direct contact with droplets of bodily fluids such as saliva, blood, and vomit. Duncan could conceivably have transmitted the disease to others at any time after he began having symptoms, presumably some time before his arrival at the hospital in Dallas. Once a hospital realizes a patient like Duncan is infected with Ebola virus, the patient is immediately quarantined, and public health officials initiate a back trace to identify everyone with whom a patient like Duncan might have interacted during the period in which he was showing symptoms.

Public health officials were able to track down 10 high-risk individuals (family members of Duncan) and 50 low-risk individuals to monitor them for signs of infection. None contracted the disease. However, one of the nurses charged with Duncan's care did become infected. This, along with Duncan's initial misdiagnosis, made it clear that US hospitals needed to provide additional training to medical personnel to prevent a possible Ebola outbreak in the US.

Exercise 15.2.7

1. What types of training can prepare health professionals to contain emerging epidemics like the Ebola outbreak of 2014?
2. What is the difference between a contagious pathogen and an infectious pathogen?



Figure 15.2.9: Researchers working with Ebola virus use layers of defenses against accidental infection, including protective clothing, breathing systems, and negative air-pressure cabinets for bench work. (credit: modification of work by Randal J. Schoepp)

Link to Learning

For additional information about Ebola, please visit the CDC website.

Summary

- Many viruses target specific hosts or tissues. Some may have more than one host.
- Many viruses follow several stages to infect host cells. These stages include **attachment, penetration, uncoating, biosynthesis, maturation,** and **release**.

- Bacteriophages have a **lytic** or **lysogenic cycle**. The lytic cycle leads to the death of the host, whereas the lysogenic cycle leads to integration of phage into the host genome.
- Bacteriophages inject DNA into the host cell, whereas animal viruses enter by endocytosis or membrane fusion.
- Animal viruses can undergo **latency**, similar to lysogeny for a bacteriophage.
- The majority of plant viruses are positive-strand ssRNA and can undergo latency, chronic, or lytic infection, as observed for animal viruses.
- The growth curve of bacteriophage populations is a **one-step multiplication curve** and not a sigmoidal curve, as compared to the bacterial growth curve.
- Bacteriophages transfer genetic information between hosts using either **generalized** or **specialized transduction**.

Footnotes

1. 1 World Health Organization. “WHO Ebola Data and Statistics.” March 18, 2005. http://apps.who.int/gho/data/view.eb...150318?lang=en

---

This page titled 15.2: The Viral Life Cycle is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **6.2: The Viral Life Cycle** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

15.3: Isolation, Culture, and Identification of Viruses

Learning Objectives

- Discuss why viruses were originally described as filterable agents
- Describe the cultivation of viruses and specimen collection and handling
- Compare in vivo and in vitro techniques used to cultivate viruses

At the beginning of this chapter, we described how porcelain Chamberland filters with pores small enough to allow viruses to pass through were used to discover TMV. Today, porcelain filters have been replaced with membrane filters and other devices used to isolate and identify viruses.

Isolation of Viruses

Unlike bacteria, many of which can be grown on an artificial nutrient medium, viruses require a living host cell for replication. Infected host cells (eukaryotic or prokaryotic) can be cultured and grown, and then the growth medium can be harvested as a source of virus. Virions in the liquid medium can be separated from the host cells by either centrifugation or filtration. Filters can physically remove anything present in the solution that is larger than the virions; the viruses can then be collected in the filtrate (Figure 15.3.1).

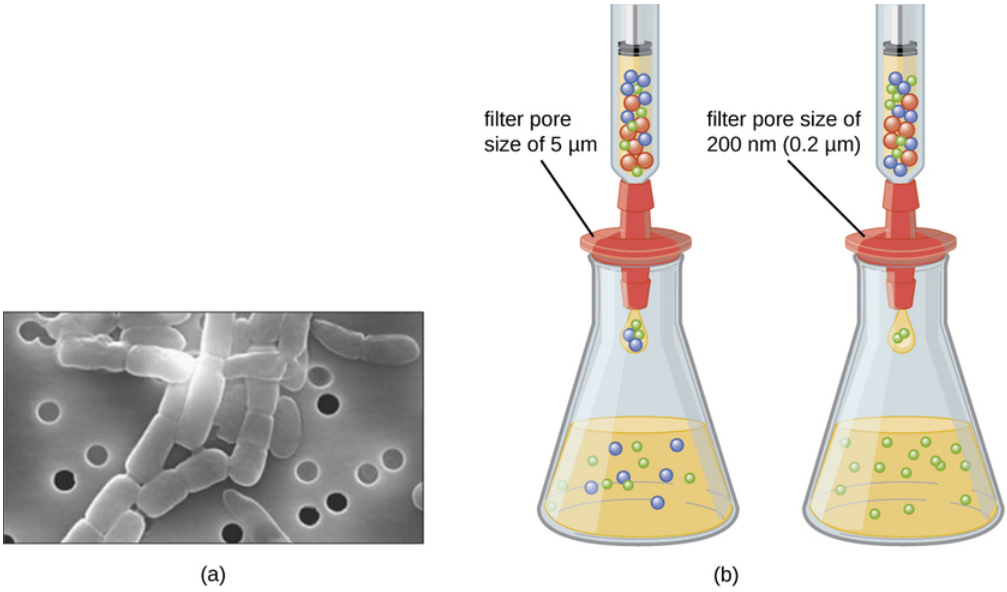


Figure 15.3.1: Membrane filters can be used to remove cells or viruses from a solution. (a) This scanning electron micrograph shows rod-shaped bacterial cells captured on the surface of a membrane filter. Note differences in the comparative size of the membrane pores and bacteria. Viruses will pass through this filter. (b) The size of the pores in the filter determines what is captured on the surface of the filter (animal [red] and bacteria [blue]) and removed from liquid passing through. Note the viruses (green) pass through the finer filter. (credit a: modification of work by U.S. Department of Energy)

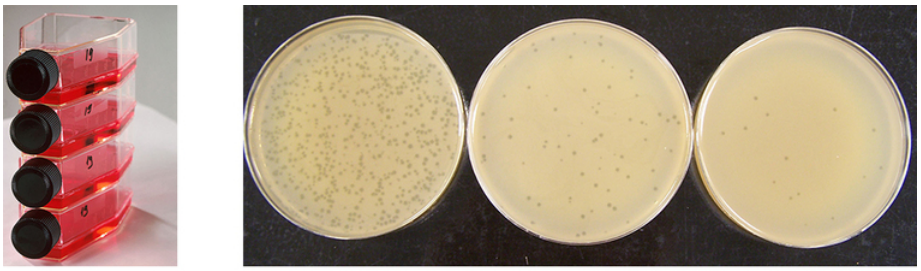
Exercise 15.3.1

What size filter pore is needed to collect a virus?

Cultivation of Viruses

Viruses can be grown in vivo (within a whole living organism, plant, or animal) or in vitro (outside a living organism in cells in an artificial environment, such as a test tube, cell culture flask, or agar plate). Bacteriophages can be grown in the presence of a dense layer of bacteria (also called a bacterial lawn) grown in a 0.7 % soft agar in a Petri dish or flat (horizontal) flask (Figure 15.3.2a). The agar concentration is decreased from the 1.5% usually used in culturing bacteria. The soft 0.7% agar allows the bacteriophages to easily diffuse through the medium. For lytic bacteriophages, lysing of the bacterial hosts can then be readily observed when a

clear zone called a plaque is detected (Figure **15.3.1***b*). As the phage kills the bacteria, many plaques are observed among the cloudy bacterial lawn.

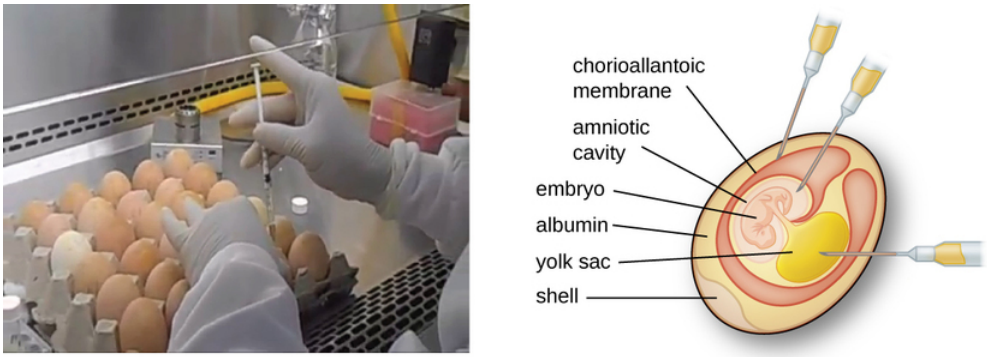


(a) (b)

Figure **15.3.2**: (a) Flasks like this may be used to culture human or animal cells for viral culturing. (b) These plates contain bacteriophage T4 grown on an *Escherichia coli* lawn. Clear plaques are visible where host bacterial cells have been lysed. Viral titers increase on the plates to the left. (credit a: modification of work by National Institutes of Health; credit b: modification of work by American Society for Microbiology)

Animal viruses require cells within a host animal or tissue-culture cells derived from an animal. Animal virus cultivation is important for 1) identification and diagnosis of pathogenic viruses in clinical specimens, 2) production of vaccines, and 3) basic research studies. In vivo host sources can be a developing embryo in an embryonated bird's egg (e.g., chicken, turkey) or a whole animal. For example, most of the influenza vaccine manufactured for annual flu vaccination programs is cultured in hens' eggs.

The embryo or host animal serves as an incubator for viral replication (Figure **15.3.3**). Location within the embryo or host animal is important. Many viruses have a tissue tropism, and must therefore be introduced into a specific site for growth. Within an embryo, target sites include the amniotic cavity, the chorioallantoic membrane, or the yolk sac. Viral infection may damage tissue membranes, producing lesions called pox; disrupt embryonic development; or cause the death of the embryo.



(a) (b)

Figure **15.3.3**: (a) The cells within chicken eggs are used to culture different types of viruses. (b) Viruses can be replicated in various locations within the egg, including the chorioallantoic membrane, the amniotic cavity, and the yolk sac. (credit a: modification of work by "Chung Hoang"/YouTube)

For in vitro studies, various types of cells can be used to support the growth of viruses. A primary cell culture is freshly prepared from animal organs or tissues. Cells are extracted from tissues by mechanical scraping or mincing to release cells or by an enzymatic method using trypsin or collagenase to break up tissue and release single cells into suspension. Because of anchorage-dependence requirements, primary cell cultures require a liquid culture medium in a Petri dish or tissue-culture flask so cells have a solid surface such as glass or plastic for attachment and growth. Primary cultures usually have a limited life span. When cells in a primary culture undergo mitosis and a sufficient density of cells is produced, cells come in contact with other cells. When this cell-to-cell-contact occurs, mitosis is triggered to stop. This is called contact inhibition and it prevents the density of the cells from becoming too high. To prevent contact inhibition, cells from the primary cell culture must be transferred to another vessel with fresh growth medium. This is called a secondary cell culture. Periodically, cell density must be reduced by pouring off some cells and adding fresh medium to provide space and nutrients to maintain cell growth. In contrast to primary cell cultures, continuous cell lines, usually derived from transformed cells or tumors, are often able to be subcultured many times or even grown indefinitely (in which case they are called immortal). Continuous cell lines may not exhibit anchorage dependency (they will grow in

suspension) and may have lost their contact inhibition. As a result, continuous cell lines can grow in piles or lumps resembling small tumor growths (Figure **15.3.4**).

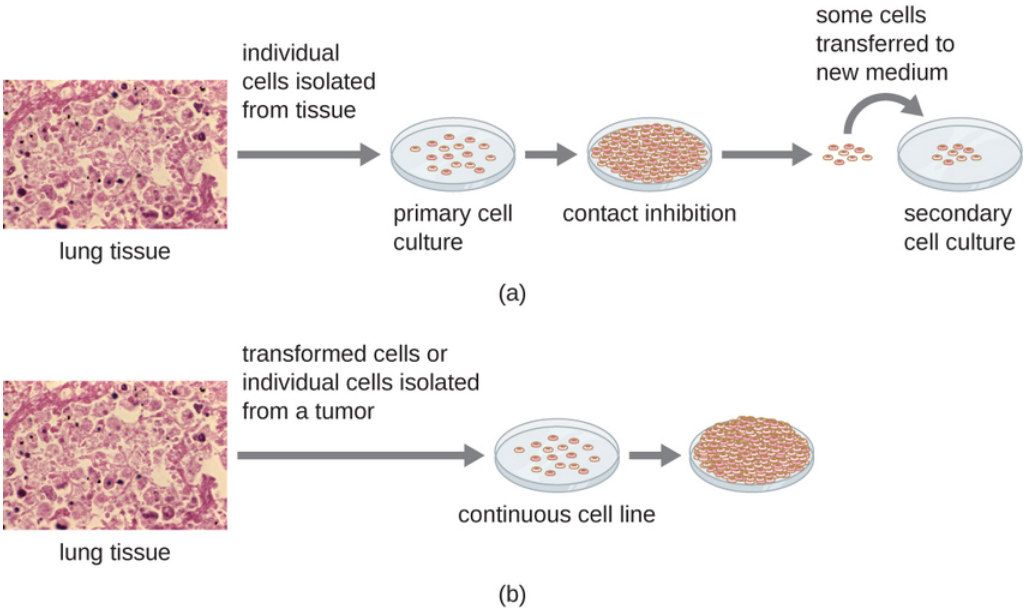


Figure **15.3.4**: Cells for culture are prepared by separating them from their tissue matrix. (a) Primary cell cultures grow attached to the surface of the culture container. Contact inhibition slows the growth of the cells once they become too dense and begin touching each other. At this point, growth can only be sustained by making a secondary culture. (b) Continuous cell cultures are not affected by contact inhibition. They continue to grow regardless of cell density. (credit "micrographs": modification of work by Centers for Disease Control and Prevention)

An example of an immortal cell line is the HeLa cell line, which was originally cultivated from tumor cells obtained from Henrietta Lacks, a patient who died of cervical cancer in 1951. HeLa cells were the first continuous tissue-culture cell line and were used to establish tissue culture as an important technology for research in cell biology, virology, and medicine. Prior to the discovery of HeLa cells, scientists were not able to establish tissue cultures with any reliability or stability. More than six decades later, this cell line is still alive and being used for medical research. See The Immortal Cell Line of Henrietta Lacks to read more about this important cell line and the controversial means by which it was obtained.

? Exercise 15.3.2

What property of cells makes periodic dilutions of primary cell cultures necessary?

The Immortal Cell Line of Henrietta Lacks

In January 1951, Henrietta Lacks, a 30-year-old African American woman from Baltimore, was diagnosed with cervical cancer at John Hopkins Hospital. We now know her cancer was caused by the human papillomavirus (HPV). Cytopathic effects of the virus altered the characteristics of her cells in a process called transformation, which gives the cells the ability to divide continuously. This ability, of course, resulted in a cancerous tumor that eventually killed Mrs. Lacks in October at age 31. Before her death, samples of her cancerous cells were taken without her knowledge or permission. The samples eventually ended up in the possession of Dr. George Gey, a biomedical researcher at Johns Hopkins University. Gey was able to grow some of the cells from Lacks's sample, creating what is known today as the immortal HeLa cell line. These cells have the ability to live and grow indefinitely and, even today, are still widely used in many areas of research.

According to Lacks's husband, neither Henrietta nor the family gave the hospital permission to collect her tissue specimen. Indeed, the family was not aware until 20 years after Lacks's death that her cells were still alive and actively being used for commercial and research purposes. Yet HeLa cells have been pivotal in numerous research discoveries related to polio, cancer, and AIDS, among other diseases. The cells have also been commercialized, although they have never themselves been

patented. Despite this, Henrietta Lacks's estate has never benefited from the use of the cells, although, in 2013, the Lacks family was given control over the publication of the genetic sequence of her cells.

This case raises several bioethical issues surrounding patients' informed consent and the right to know. At the time Lacks's tissues were taken, there were no laws or guidelines about informed consent. Does that mean she was treated fairly at the time? Certainly by today's standards, the answer would be no. Harvesting tissue or organs from a dying patient without consent is not only considered unethical but illegal, regardless of whether such an act could save other patients' lives. Is it ethical, then, for scientists to continue to use Lacks's tissues for research, even though they were obtained illegally by today's standards?

Ethical or not, Lacks's cells are widely used today for so many applications that it is impossible to list them all. Is this a case in which the ends justify the means? Would Lacks be pleased to know about her contribution to science and the millions of people who have benefited? Would she want her family to be compensated for the commercial products that have been developed using her cells? Or would she feel violated and exploited by the researchers who took part of her body without her consent? Because she was never asked, we will never know.

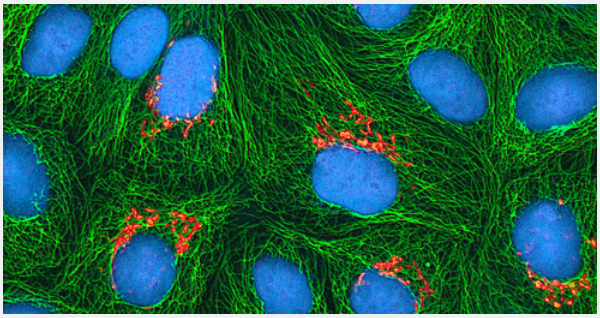


Figure **15.3.5**: A multiphoton fluorescence image of HeLa cells in culture. Various fluorescent stains have been used to show the DNA (cyan), microtubules (green), and Golgi apparatus (orange). (credit: modification of work by National Institutes of Health)

Detection of a Virus

Regardless of the method of cultivation, once a virus has been introduced into a whole host organism, embryo, or tissue-culture cell, a sample can be prepared from the infected host, embryo, or cell line for further analysis under a brightfield, electron, or fluorescent microscope. Cytopathic effects (CPEs) are distinct observable cell abnormalities due to viral infection. CPEs can include loss of adherence to the surface of the container, changes in cell shape from flat to round, shrinkage of the nucleus, vacuoles in the cytoplasm, fusion of cytoplasmic membranes and the formation of multinucleated syncytia, inclusion bodies in the nucleus or cytoplasm, and complete cell lysis (see Figure **15.3.6**).

Further pathological changes include viral disruption of the host genome and altering normal cells into transformed cells, which are the types of cells associated with carcinomas and sarcomas. The type or severity of the CPE depends on the type of virus involved. Figure **15.3.6** lists CPEs for specific viruses.

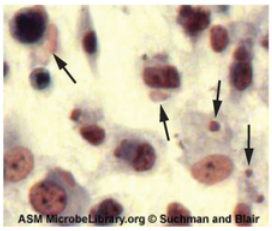
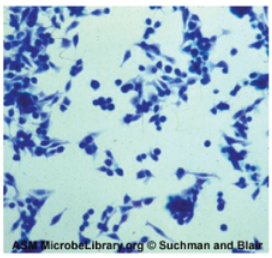
Cytopathic Effects of Specific Viruses		
Virus	**Cytopathic Effect**	**Example**
Paramyxovirus	Syncytium and faint basophilic cytoplasmic inclusion bodies	
Poxvirus	Pink eosinophilic cytoplasmic inclusion bodies (arrows) and cell swelling	
Herpesvirus	Cytoplasmic stranding (arrow) and nuclear inclusion bodies (dashed arrow)	
Adenovirus	Cell enlargement, rounding, and distinctive "grape-like" clusters	

Figure **15.3.6**: (credit "micrographs": modification of work by American Society for Microbiology)

Link to Learning

Watch this video to learn about the effects of viruses on cells.

Hemagglutination Assay

A serological assay is used to detect the presence of certain types of viruses in patient serum. Serum is the straw-colored liquid fraction of blood plasma from which clotting factors have been removed. Serum can be used in a direct assay called a hemagglutination assay to detect specific types of viruses in the patient's sample. Hemagglutination is the agglutination (clumping) together of erythrocytes (red blood cells). Many viruses produce surface proteins or spikes called hemagglutinins that can bind to receptors on the membranes of erythrocytes and cause the cells to agglutinate. Hemagglutination is observable without using the microscope, but this method does not always differentiate between infectious and noninfectious viral particles, since both can agglutinate erythrocytes.

To identify a specific pathogenic virus using hemagglutination, we must use an indirect approach. Proteins called antibodies, generated by the patient's immune system to fight a specific virus, can be used to bind to components such as hemagglutinins that are uniquely associated with specific types of viruses. The binding of the antibodies with the hemagglutinins found on the virus subsequently prevent erythrocytes from directly interacting with the virus. So when erythrocytes are added to the antibody-coated viruses, there is no appearance of agglutination; agglutination has been inhibited. We call these types of indirect assays for virus-specific antibodies hemagglutination inhibition (HAI) assays. HAI can be used to detect the presence of antibodies specific to many types of viruses that may be causing or have caused an infection in a patient even months or years after infection (see Figure 15.3.7). This assay is described in greater detail in Agglutination Assays.

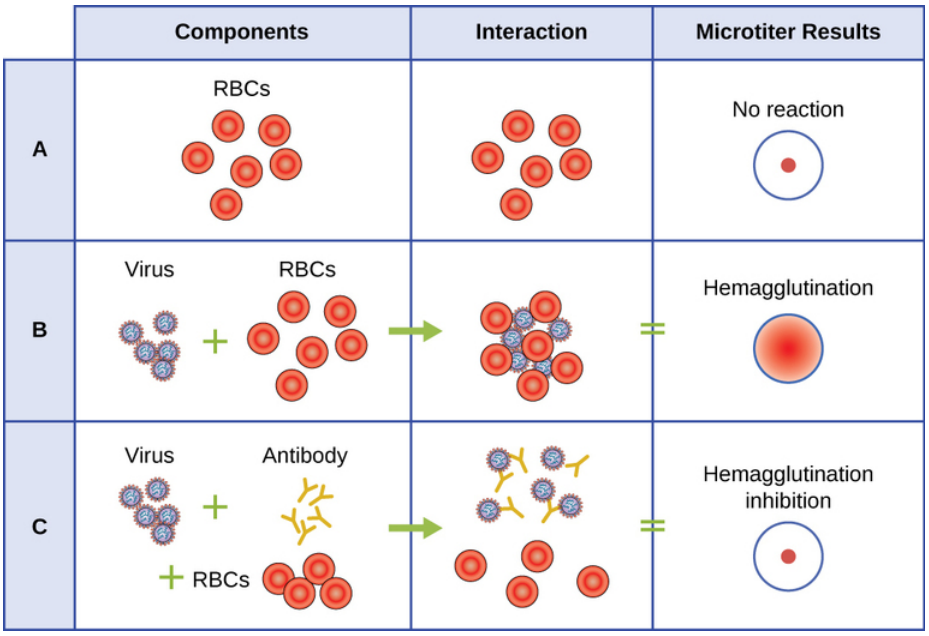


Figure 15.3.7: This chart shows the possible outcomes of a hemagglutination test. Row A: Erythrocytes do not bind together and will sink to the bottom of the well plate; this becomes visible as a red dot in the center of the well. Row B: Many viruses have hemagglutinins that causes agglutination of erythrocytes; the resulting hemagglutination forms a lattice structure that results in red color throughout the well. Row C: Virus-specific antibody, the viruses, and the erythrocytes are added to the well plate. The virus-specific antibodies inhibit agglutination, as can be seen as a red dot in the bottom of the well. (credit: modification of work by Centers for Disease Control and Prevention)

? Exercise 15.3.3

What is the outcome of a positive HIA test?

Nucleic Acid Amplification Test

Nucleic acid amplification tests (NAAT) are used in molecular biology to detect unique nucleic acid sequences of viruses in patient samples. Polymerase chain reaction (PCR) is an NAAT used to detect the presence of viral DNA in a patient's tissue or body fluid sample. PCR is a technique that amplifies (i.e., synthesizes many copies) of a viral DNA segment of interest. Using PCR, short nucleotide sequences called primers bind to specific sequences of viral DNA, enabling identification of the virus.

Reverse transcriptase-PCR (RT-PCR) is an NAAT used to detect the presence of RNA viruses. RT-PCR differs from PCR in that the enzyme reverse transcriptase (RT) is used to make a cDNA from the small amount of viral RNA in the specimen. The cDNA can then be amplified by PCR. Both PCR and RT-PCR are used to detect and confirm the presence of the viral nucleic acid in patient specimens.

HPV Scare

Michelle, a 21-year-old nursing student, came to the university clinic worried that she might have been exposed to a sexually transmitted disease (STD). Her sexual partner had recently developed several bumps on the base of his penis. He had put off going to the doctor, but Michelle suspects they are genital warts caused by HPV. She is especially concerned because she knows that HPV not only causes warts but is a prominent cause of cervical cancer. She and her partner always use condoms for contraception, but she is not confident that this precaution will protect her from HPV.

Michelle's physician finds no physical signs of genital warts or any other STDs, but recommends that Michelle get a Pap smear along with an HPV test. The Pap smear will screen for abnormal cervical cells and the CPEs associated with HPV; the HPV test will test for the presence of the virus. If both tests are negative, Michelle can be more assured that she most likely has not become infected with HPV. However, her doctor suggests it might be wise for Michelle to get vaccinated against HPV to protect herself from possible future exposure.

Exercise 15.3.4

Why does Michelle's physician order two different tests instead of relying on one or the other?

Enzyme Immunoassay

Enzyme immunoassays (EIAs) rely on the ability of antibodies to detect and attach to specific biomolecules called antigens. The detecting antibody attaches to the target antigen with a high degree of specificity in what might be a complex mixture of biomolecules. Also included in this type of assay is a colorless enzyme attached to the detecting antibody. The enzyme acts as a tag on the detecting antibody and can interact with a colorless substrate, leading to the production of a colored end product. EIAs often rely on layers of antibodies to capture and react with antigens, all of which are attached to a membrane filter (see Figure **15.3.8**). EIAs for viral antigens are often used as preliminary screening tests. If the results are positive, further confirmation will require tests with even greater sensitivity, such as a western blot or an NAAT. EIAs are discussed in more detail in EIAs and ELISAs.

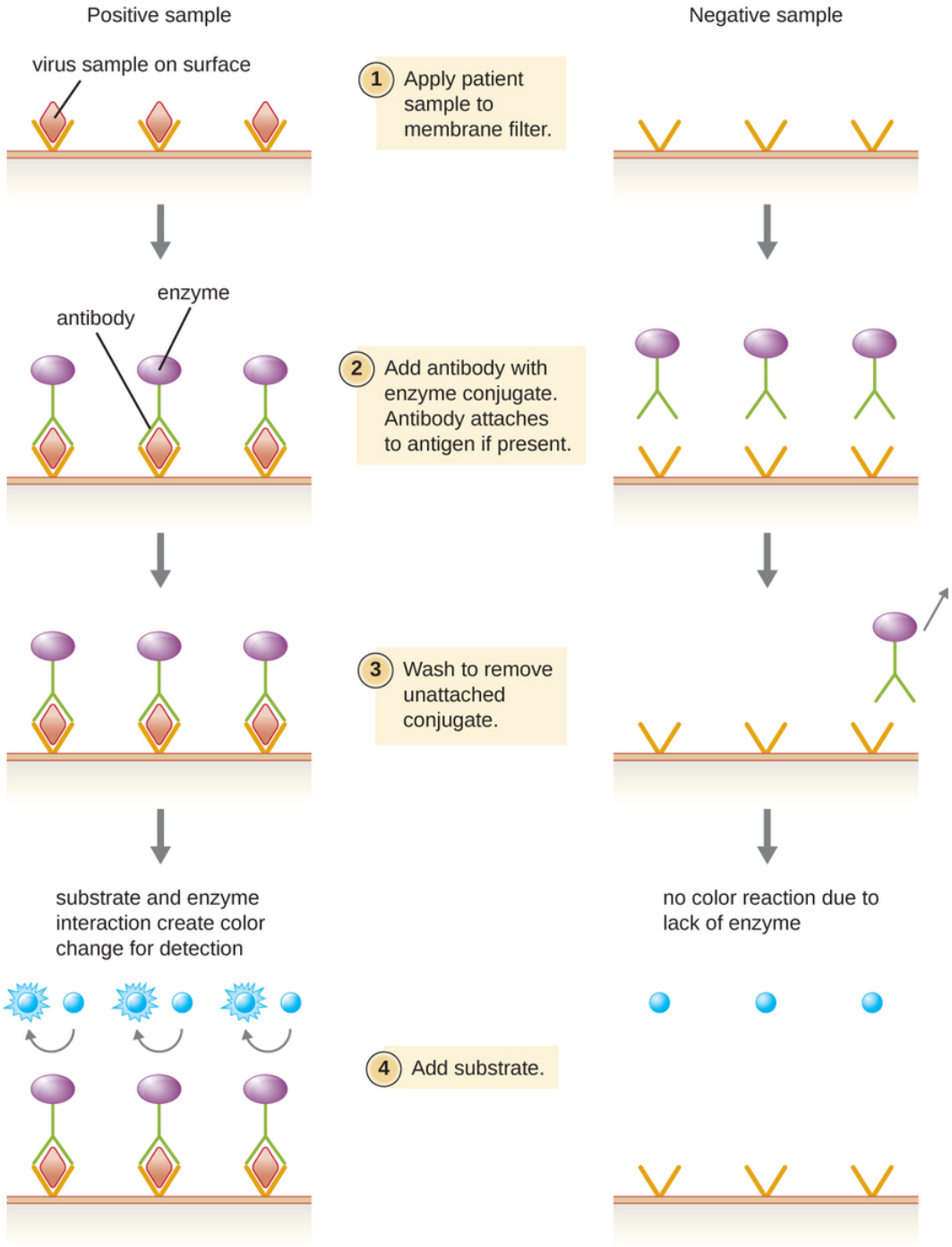


Figure 15.3.8: Similar to rapid, over-the-counter pregnancy tests, EIAs for viral antigens require a few drops of diluted patient serum or plasma applied to a membrane filter. The membrane filter has been previously modified and embedded with antibody to viral antigen and internal controls. Antibody conjugate is added to the filter, with the targeted antibody attached to the antigen (in the case of a positive test). Excess conjugate is washed off the filter. Substrate is added to activate the enzyme-mediated reaction to reveal the color change of a positive test. (credit: modification of work by "Cavitri"/Wikimedia Commons)

? Exercise 15.3.5

What typically indicates a positive EIA test?

Clinical Focus: Part 3

Along with the RT/PCR analysis, David's saliva was also collected for viral cultivation. In general, no single diagnostic test is sufficient for antemortem diagnosis, since the results will depend on the sensitivity of the assay, the quantity of virions present at the time of testing, and the timing of the assay, since release of virions in the saliva can vary. As it turns out, the result was negative for viral cultivation from the saliva. This is not surprising to David's doctor, because one negative result is not an absolute indication of the absence of infection. It may be that the number of virions in the saliva is low at the time of sampling. It is not unusual to repeat the test at intervals to enhance the chance of detecting higher virus loads.

Exercise 15.3.6

Should David's doctor modify his course of treatment based on these test results?

Summary

- Viral cultivation requires the presence of some form of host cell (whole organism, embryo, or cell culture).
- Viruses can be isolated from samples by filtration.
- Viral filtrate is a rich source of released virions.
- Bacteriophages are detected by presence of clear **plaques** on bacterial lawn.
- Animal and plant viruses are detected by **cytopathic effects**, molecular techniques (PCR, RT-PCR), enzyme immunoassays, and serological assays (hemagglutination assay, hemagglutination inhibition assay).

This page titled 15.3: Isolation, Culture, and Identification of Viruses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **6.3: Isolation, Culture, and Identification of Viruses** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

15.4: Viroids, Virusoids, and Prions

Learning Objectives

- Describe viroids and their unique characteristics
- Describe virusoids and their unique characteristics
- Describe prions and their unique characteristics

Research attempts to discover the causative agents of previously uninvestigated diseases have led to the discovery of nonliving disease agents quite different from viruses. These include particles consisting only of RNA or only of protein that, nonetheless, are able to self-propagate at the expense of a host—a key similarity to viruses that allows them to cause disease conditions. To date, these discoveries include viroids, virusoids, and the proteinaceous prions.

Viroids

In 1971, Theodor Diener, a pathologist working at the Agriculture Research Service, discovered an acellular particle that he named a viroid, meaning "virus-like." Viroids consist only of a short strand of circular RNA capable of self-replication. The first viroid discovered was found to cause potato tuber spindle disease, which causes slower sprouting and various deformities in potato plants (see Figure **15.4.1**). Like viruses, potato spindle tuber viroids (PSTVs) take control of the host machinery to replicate their RNA genome. Unlike viruses, viroids do not have a protein coat to protect their genetic information.



Figure **15.4.1**: These potatoes have been infected by the potato spindle tuber viroid (PSTV), which is typically spread when infected knives are used to cut healthy potatoes, which are then planted. (credit: Pamela Roberts, University of Florida Institute of Food and Agricultural Sciences, USDA ARS)

Viroids can result in devastating losses of commercially important agricultural food crops grown in fields and orchards. Since the discovery of PSTV, other viroids have been discovered that cause diseases in plants. Tomato planta macho viroid (TPMVd) infects tomato plants, which causes loss of chlorophyll, disfigured and brittle leaves, and very small tomatoes, resulting in loss of productivity in this field crop. Avocado sunblotch viroid (ASBVd) results in lower yields and poorer-quality fruit. ASBVd is the smallest viroid discovered thus far that infects plants. Peach latent mosaic viroid(PLMVd) can cause necrosis of flower buds and branches, and wounding of ripened fruit, which leads to fungal and bacterial growth in the fruit. PLMVd can also cause similar pathological changes in plums, nectarines, apricots, and cherries, resulting in decreased productivity in these orchards, as well. Viroids, in general, can be dispersed mechanically during crop maintenance or harvesting, vegetative reproduction, and possibly via seeds and insects, resulting in a severe drop in food availability and devastating economic consequences.

Exercise 15.4.1

What is the genome of a viroid made of?

Virusoids

A second type of pathogenic RNA that can infect commercially important agricultural crops are the virusoids, which are subviral particles best described as non–self-replicating ssRNAs. RNA replication of virusoids is similar to that of viroids but, unlike viroids, virusoids require that the cell also be infected with a specific “helper” virus. There are currently only five described types of virusoids and their associated helper viruses. The helper viruses are all from the family of Sobemoviruses. An example of a helper virus is the subterranean clover mottle virus, which has an associated virusoid packaged inside the viral capsid. Once the helper virus enters the host cell, the virusoids are released and can be found free in plant cell cytoplasm, where they possess ribozyme activity. The helper virus undergoes typical viral replication independent of the activity of the virusoid. The virusoid genomes are small, only 220 to 388 nucleotides long. A virusoid genome does not code for any proteins, but instead serves only to replicate virusoid RNA.

Virusoids belong to a larger group of infectious agents called satellite RNAs, which are similar pathogenic RNAs found in animals. Unlike the plant virusoids, satellite RNAs may encode for proteins; however, like plant virusoids, satellite RNAs must coinfect with a helper virus to replicate. One satellite RNA that infects humans and that has been described by some scientists as a virusoid is the hepatitis delta virus (HDV), which, by some reports, is also called hepatitis delta virusoid. Much larger than a plant virusoid, HDV has a circular, ssRNA genome of 1,700 nucleotides and can direct the biosynthesis of HDV-associated proteins. The HDV helper virus is the hepatitis B virus (HBV). Coinfection with HBV and HDV results in more severe pathological changes in the liver during infection, which is how HDV was first discovered.

? Exercise 15.4.2

What is the main difference between a viroid and a virusoid?

Prions

At one time, scientists believed that any infectious particle must contain DNA or RNA. Then, in 1982, Stanley Prusiner, a medical doctor studying scrapie (a fatal, degenerative disease in sheep) discovered that the disease was caused by proteinaceous infectious particles, or prions. Because proteins are acellular and do not contain DNA or RNA, Prusiner’s findings were originally met with resistance and skepticism; however, his research was eventually validated, and he received the Nobel Prize in Physiology or Medicine in 1997.

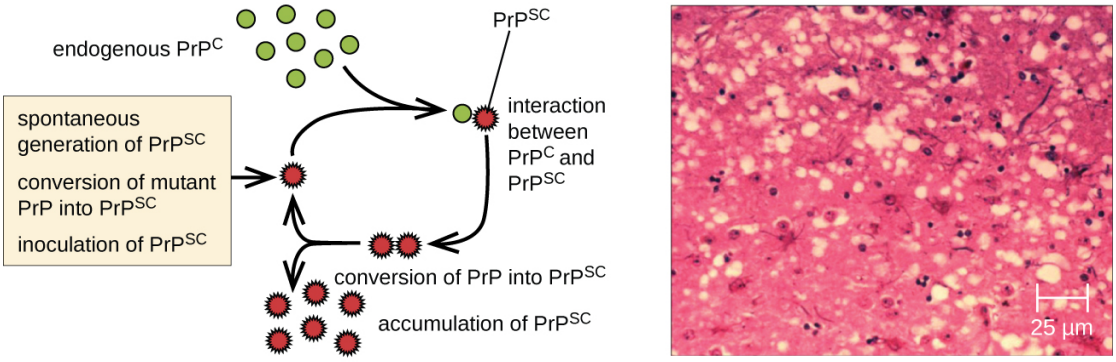


Figure 15.4.2: Endogenous normal prion protein (PrPc) is converted into the disease-causing form (PrPsc) when it encounters this variant form of the protein. PrPsc may arise spontaneously in brain tissue, especially if a mutant form of the protein is present, or it may originate from misfolded prions consumed in food that eventually find their way into brain tissue. (credit b: modification of work by USDA)

A prion is a misfolded rogue form of a normal protein (PrPc) found in the cell. This rogue prion protein (PrPsc), which may be caused by a genetic mutation or occur spontaneously, can be infectious, stimulating other endogenous normal proteins to become misfolded, forming plaques (see Figure 15.4.2). Today, prions are known to cause various forms of transmissible spongiform encephalopathy (TSE) in human and animals. TSE is a rare degenerative disorder that affects the brain and nervous system. The accumulation of rogue proteins causes the brain tissue to become sponge-like, killing brain cells and forming holes in the tissue, leading to brain damage, loss of motor coordination, and dementia (see Figure 15.4.3). Infected individuals are mentally impaired

and become unable to move or speak. There is no cure, and the disease progresses rapidly, eventually leading to death within a few months or years.

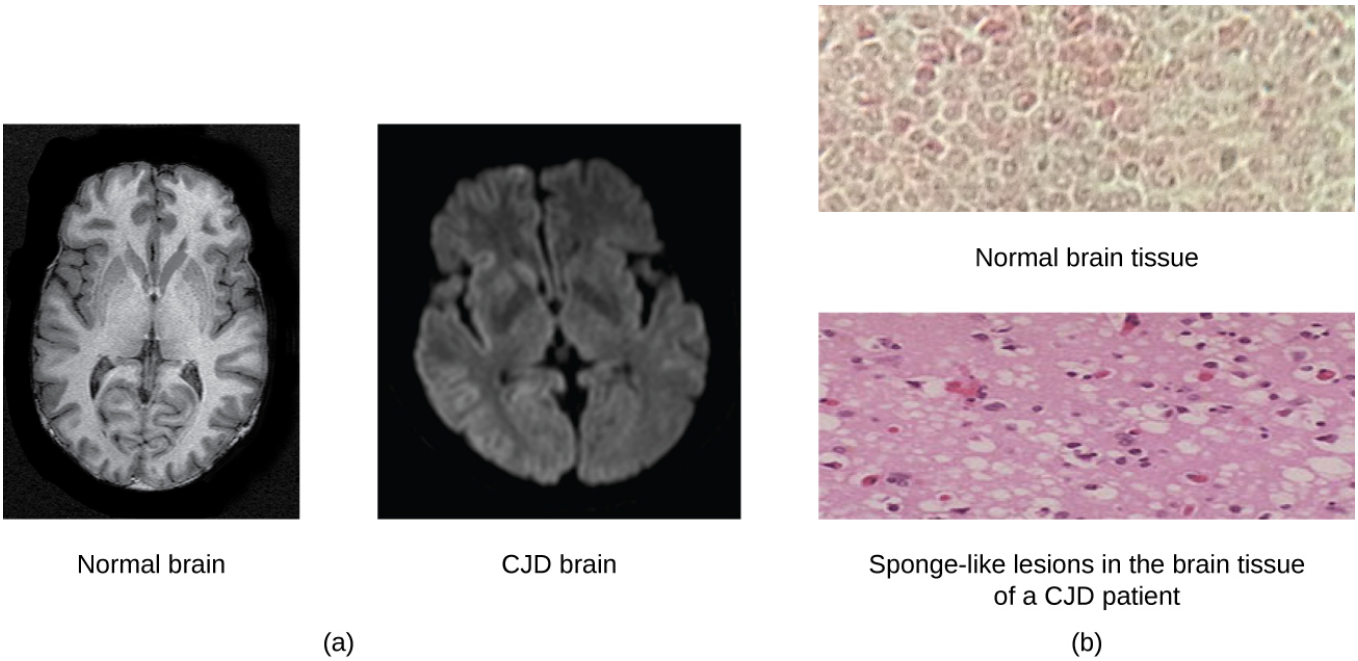


Figure **15.4.3**: Creutzfeldt-Jakob disease (CJD) is a fatal disease that causes degeneration of neural tissue. (a) These brain scans compare a normal brain to one with CJD. (b) Compared to a normal brain, the brain tissue of a CJD patient is full of sponge-like lesions, which result from abnormal formations of prion protein. (credit a (right): modification of work by Dr. Laughlin Dawes; credit b (top): modification of work by Suzanne Wakim; credit b (bottom): modification of work by Centers for Disease Control and Prevention)

TSEs in humans include kuru, fatal familial insomnia, Gerstmann-Straussler-Scheinker disease, and Creutzfeldt-Jakob disease (see Figure **15.4.3**). TSEs in animals include mad cow disease, scrapie (in sheep and goats), and chronic wasting disease (in elk and deer). TSEs can be transmitted between animals and from animals to humans by eating contaminated meat or animal feed. Transmission between humans can occur through heredity (as is often the case with GSS and CJD) or by contact with contaminated tissue, as might occur during a blood transfusion or organ transplant. There is no evidence for transmission via casual contact with an infected person. Table **15.4.1** lists TSEs that affect humans and their modes of transmission.

Table **15.4.1**: Transmissible Spongiform Encephalopathies (TSEs) in Humans

Disease	Mechanism(s) of Transmission[1]
Sporadic CJD (sCJD)	Not known; possibly by alteration of normal prior protein (PrP) to rogue form due to somatic mutation
Variant CJD (vCJD)	Eating contaminated cattle products and by secondary bloodborne transmission
Familial CJD (fCJD)	Mutation in germline PrP gene
Iatrogenic CJD (iCJD)	Contaminated neurosurgical instruments, corneal graft, gonadotrophic hormone, and, secondarily, by blood transfusion
Kuru	Eating infected meat through ritualistic cannibalism
Gerstmann-Straussler-Scheinker disease (GSS)	Mutation in germline PrP gene
Fatal familial insomnia (FFI)	Mutation in germline PrP gene

Prions are extremely difficult to destroy because they are resistant to heat, chemicals, and radiation. Even standard sterilization procedures do not ensure the destruction of these particles. Currently, there is no treatment or cure for TSE disease, and

contaminated meats or infected animals must be handled according to federal guidelines to prevent transmission.

Exercise 15.4.3

Does a prion have a genome?

Clinical Focus: Resolution

A few days later, David's doctor receives the results of the immunofluorescence test on his skin sample. The test is negative for rabies antigen. A second viral antigen test on his saliva sample also comes back negative. Despite these results, the doctor decides to continue David's current course of treatment. Given the positive RT-PCR test, it is best not to rule out a possible rabies infection.

Near the site of the bite, David receives an injection of rabies immunoglobulin, which attaches to and inactivates any rabies virus that may be present in his tissues. Over the next 14 days, he receives a series of four rabies-specific vaccinations in the arm. These vaccines activate David's immune response and help his body recognize and fight the virus. Thankfully, with treatment, David symptoms improve and he makes a full recovery.

Not all rabies cases have such a fortunate outcome. In fact, rabies is usually fatal once the patient starts to exhibit symptoms, and postbite treatments are mainly palliative (i.e., sedation and pain management).

Summary

- Other acellular agents such as **viroids**, **virusoids**, and **prions** also cause diseases. Viroids consist of small, naked ssRNAs that cause diseases in plants. Virusoids are ssRNAs that require other helper viruses to establish an infection. Prions are proteinaceous infectious particles that cause **transmissible spongiform encephalopathies**.
- Prions are extremely resistant to chemicals, heat, and radiation.
- There are no treatments for prion infection.

Footnotes

1. 1 National Institute of Neurological Disorders and Stroke. "Creutzfeldt-Jakob Disease Fact Sheet." http://www.ninds.nih.gov/disorders/cjd/detail_cjd.htm (accessed December 31, 2015).

This page titled 15.4: Viroids, Virusoids, and Prions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **6.4: Viroids, Virusoids, and Prions** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

15.5: Viral Replication

This page titled 15.5: Viral Replication is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.5: Viral Replication** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.5A: General Features of Virus Replication

Learning Objectives

- Outline the features of viral replication

Multiplication Within the Host Cell

Viral replication is the term used indicate the formation of biological viruses during the infection process in the target host cells. Viruses must first penetrate and enter the cell before viral replication can occur. From the perspective of the virus, the purpose of viral replication is to allow reproduction and survival of its kind. By generating abundant copies of its genome and packaging these copies into viruses, the virus is able to continue infecting new hosts.

Replication between viruses is varied and depends on the type of genes involved. Most DNA viruses assemble in the nucleus; most RNA viruses develop solely in cytoplasm. Viral populations do not grow through cell division, because they are acellular. Instead, they hijack the machinery and metabolism of a host cell to produce multiple copies of themselves, and they assemble inside the cell.

The life cycle of viruses differs greatly between species but there are six common basic stages:

Attachment is a specific binding between viral capsid proteins and specific receptors on the host cellular surface. This specificity determines the host range of a virus. For example, HIV can infect only a limited range of human leukocytes. Its surface protein, gp120, specifically interacts only with the CD4 molecule – a chemokine receptor – which is most commonly found on the surface of CD4+ T-Cells. This mechanism has evolved to favor those viruses that infect only cells within which they are capable of replication. Attachment to the receptor can fore the viral envelope protein to undergo either changes that result in the fusion of viral and cellular membranes, or changes of non-enveloped virus surface proteins that allow the virus to enter.

Penetration follows attachment. Virions enter the host cell through receptor-mediated endocytosis or membrane fusion. This is often called *viral entry*. The infection of plant and fungal cells is different from that of animal cells. Plants have a rigid cell wall made of cellulose, and fungi one of chitin, so most viruses can get inside these cells only after trauma to the cell wall. However, nearly all plant viruses (such as tobacco mosaic virus) can also move directly from cell to cell, in the form of single-stranded nucleoprotein complexes, through pores called plasmodesmata. Bacteria, like plants, have strong cell walls that a virus must breach to infect the cell. However, since bacterial cell walls are much less thick than plant cell walls due to their much smaller size, some viruses have evolved mechanisms that inject their genome into the bacterial cell across the cell wall, while the viral capsid remains outside.

Uncoating is a process in which the viral capsid is removed: This may be by degradation by viral or host enzymes or by simple dissociation. In either case the end-result is the release of the viral genomic nucleic acid.

Replication of viruses depends on the multiplication of the genome. This is accomplished through synthesis of viral messenger RNA (mRNA) from “early” genes (with exceptions for positive sense RNA viruses), viral protein synthesis, possible assembly of viral proteins, then viral genome replication mediated by early or regulatory protein expression. This may be followed, for complex viruses with larger genomes, by one or more further rounds of mRNA synthesis: “late” gene expression is, in general, of structural or virion proteins.

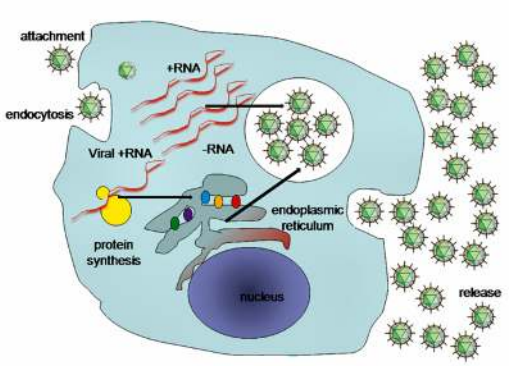


Figure: **Hepatitis C virus**: A simplified diagram of the Hepatitis C virus replication cycle.

Following the structure-mediated self-assembly of the virus particles, some modification of the proteins often occurs. In viruses such as HIV, this modification (sometimes called maturation) occurs after the virus has been released from the host cell.

Viruses can be released from the host cell by lysis, a process that kills the cell by bursting its membrane and cell wall if present. This is a feature of many bacterial and some animal viruses. Some viruses undergo a lysogenic cycle where the viral genome is incorporated by genetic recombination into a specific place in the host's chromosome. The viral genome is then known as a *provirus* or, in the case of bacteriophages a *prophage*. Whenever the host divides, the viral genome is also replicated. The viral genome is mostly silent within the host; however, at some point the provirus or prophage may give rise to active virus, which may lyse the host cells. Enveloped viruses (e.g., HIV) typically are released from the host cell by budding. During this process the virus acquires its envelope, which is a modified piece of the host's plasma or other internal membrane. The genetic material within virus particles, and the method by which the material is replicated, varies considerably between different types of viruses.

Key Points

- Viral populations do not grow through cell division, because they are acellular. Instead, they use the machinery and metabolism of a host cell to produce multiple copies of themselves, and they assemble in the cell.
- The life cycle of viruses differs greatly between species but there are six basic stages in the life cycle of viruses: attachment, penetration (viral entry), uncoating, replication, and lysis.
- Some viruses undergo a lysogenic cycle where the viral genome is incorporated by genetic recombination into a specific place in the host's chromosome.

Key Terms

- **lysis**: The disintegration or destruction of cells
- **leukocyte**: A white blood cell.
- **uncoating**: A process in which the viral capsid of a virus is removed, leading to the release of the viral genomic nucleic acid.
- **attachment**: specific binding between viral capsid proteins and specific receptors on the host cellular surface

---

This page titled 15.5A: General Features of Virus Replication is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.5A: General Features of Virus Replication** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.5B: Steps of Virus Infections

Learning Objectives

- List the steps of viral replication and explain what occurs at each step

Steps of Virus Infections

A virus must use cell processes to replicate. The viral replication cycle can produce dramatic biochemical and structural changes in the host cell, which may cause cell damage. These changes, called cytopathic (causing cell damage) effects, can change cell functions or even destroy the cell. Some infected cells, such as those infected by the common cold virus known as rhinovirus, die through lysis (bursting) or apoptosis (programmed cell death or "cell suicide"), releasing all progeny virions at once. The symptoms of viral diseases result from the immune response to the virus, which attempts to control and eliminate the virus from the body and from cell damage caused by the virus. Many animal viruses, such as HIV (Human Immunodeficiency Virus), leave the infected cells of the immune system by a process known as budding, where virions leave the cell individually. During the budding process, the cell does not undergo lysis and is not immediately killed. However, the damage to the cells that the virus infects may make it impossible for the cells to function normally, even though the cells remain alive for a period of time. Most productive viral infections follow similar steps in the virus replication cycle: attachment, penetration, uncoating, replication, assembly, and release.

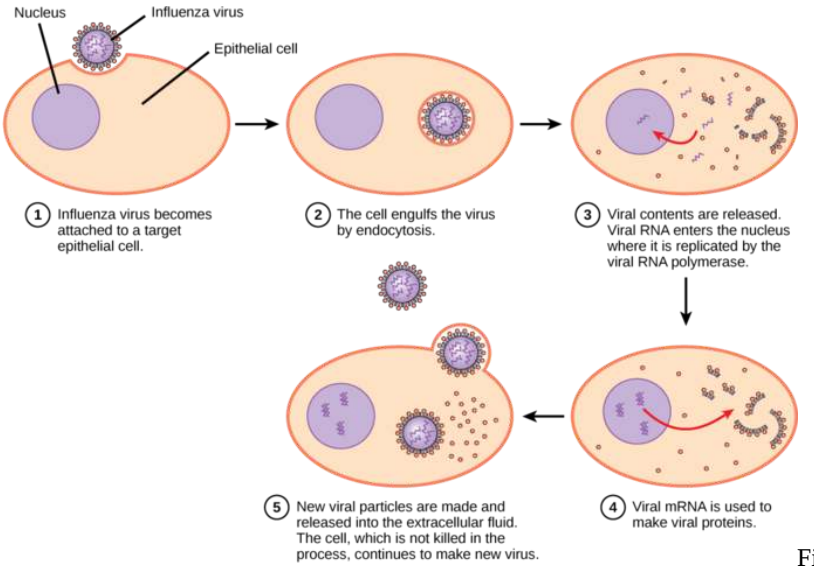


Figure: **Pathway to viral infection**: In influenza virus infection, glycoproteins attach to a host epithelial cell. As a result, the virus is engulfed. RNA and proteins are made and assembled into new virions.

Attachment

A virus attaches to a specific receptor site on the host cell membrane through attachment proteins in the capsid or via glycoproteins embedded in the viral envelope. The specificity of this interaction determines the host (and the cells within the host) that can be infected by a particular virus. This can be illustrated by thinking of several keys and several locks where each key will fit only one specific lock.

Entry

The nucleic acid of bacteriophages enters the host cell naked, leaving the capsid outside the cell. Plant and animal viruses can enter through endocytosis, in which the cell membrane surrounds and engulfs the entire virus. Some enveloped viruses enter the cell when the viral envelope fuses directly with the cell membrane. Once inside the cell, the viral capsid is degraded and the viral nucleic acid is released, which then becomes available for replication and transcription.

Replication and Assembly

The replication mechanism depends on the viral genome. DNA viruses usually use host cell proteins and enzymes to make additional DNA that is transcribed to messenger RNA (mRNA), which is then used to direct protein synthesis. RNA viruses usually use the RNA core as a template for synthesis of viral genomic RNA and mRNA. The viral mRNA directs the host cell to synthesize viral enzymes and capsid proteins, and to assemble new virions. Of course, there are exceptions to this pattern. If a host cell does not provide the enzymes necessary for viral replication, viral genes supply the information to direct synthesis of the missing proteins. Retroviruses, such as HIV, have an RNA genome that must be reverse transcribed into DNA, which then is incorporated into the host cell genome.

To convert RNA into DNA, retroviruses must contain genes that encode the virus-specific enzyme reverse transcriptase, which transcribes an RNA template to DNA. Reverse transcription never occurs in uninfected host cells; the needed enzyme, reverse transcriptase, is only derived from the expression of viral genes within the infected host cells. The fact that HIV produces some of its own enzymes not found in the host has allowed researchers to develop drugs that inhibit these enzymes. These drugs, including the reverse transcriptase inhibitor AZT, inhibit HIV replication by reducing the activity of the enzyme without affecting the host's metabolism. This approach has led to the development of a variety of drugs used to treat HIV and has been effective at reducing the number of infectious virions (copies of viral RNA) in the blood to non-detectable levels in many HIV-infected individuals.

Egress

The last stage of viral replication is the release of the new virions produced in the host organism. They are then able to infect adjacent cells and repeat the replication cycle. As you have learned, some viruses are released when the host cell dies, while other viruses can leave infected cells by budding through the membrane without directly killing the cell.

Key Points

- Viral replication involves six steps: attachment, penetration, uncoating, replication, assembly, and release.
- During attachment and penetration, the virus attaches itself to a host cell and injects its genetic material into it.
- During uncoating, replication, and assembly, the viral DNA or RNA incorporates itself into the host cell's genetic material and induces it to replicate the viral genome.
- During release, the newly-created viruses are released from the host cell, either by causing the cell to break apart, waiting for the cell to die, or by budding off through the cell membrane.

Key Terms

- **virion**: a single individual particle of a virus (the viral equivalent of a cell)
- **glycoprotein**: a protein with covalently-bonded carbohydrates
- **retrovirus**: a virus that has a genome consisting of RNA

This page titled 15.5B: Steps of Virus Infections is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.5B: Steps of Virus Infections** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.5C: Tissue Tropism in Animal Viruses

Learning Objectives

- Explain viral tropism

A tropism is a biological phenomenon, indicating growth or turning movement of a biological organism in response to an environmental stimulus. In tropisms, this response is dependent on the direction of the stimulus (as opposed to nastic movements which are non-directional responses). Viruses and other pathogens also affect what is called “host tropism” or “cell tropism. ” Case tropism refers to the way in which different viruses/pathogens have evolved to preferentially target specific host species or specific cell types within those species.

Host tropism is the name given to a process of tropism that determines which cells can become infected by a given pathogen. Host tropism is determined by the biochemical receptor complexes on cell surfaces that are permissive or non-permissive to the docking or attachment of various viruses.

Various factors determine the ability of a pathogen to infect a particular cell. For example, viruses must bind to specific cell surface receptors to enter a cell. If a cell does not express these receptors then the virus cannot normally infect it. Viral tropism is determined by a combination of susceptibility and permissiveness: a host cell must be both permissive (allow viral entry) and susceptible (possess the receptor complement needed for viral entry) for a virus to establish infection. An example of this is the HIV virus, which exhibits tropism for CD4 related immune cells (e.g. T helper cells, macrophages or dendritic cells). These cells express a CD4 receptor, to which the HIV virus can bind, through the gp120 and gp41 proteins on its surface.

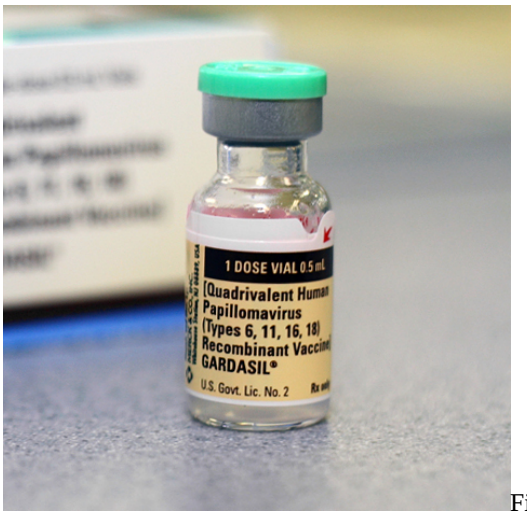


Figure: **Human papillomavirus vaccine**: Gardasil is a human papillomavirus vaccine on the market and it protects against HPV-16 and HPV-18 which cause 70% of cervical cancers, 80% of anal cancers, 60% of vaginal cancers, and 40% of vulvar cancers.

In virology, Tissue tropism is the cells and tissues of a host that support growth of a particular virus or bacteria. Some viruses have a broad tissue tropism and can infect many types of cells and tissues. Other viruses may infect primarily a single tissue.

Factors influencing viral tissue tropism include: 1) the presence of cellular receptors permitting viral entry, 2) availability of transcription factors involved in viral replication, 3) the molecular nature of the viral tropogen, and 4) the cellular receptors are the proteins found on a cell or viral surface.

These receptors are like keys allowing the viral cell to fuse with a cell or attach itself to a cell. The way that these proteins are acquired is through similar process to that of an infection cycle.

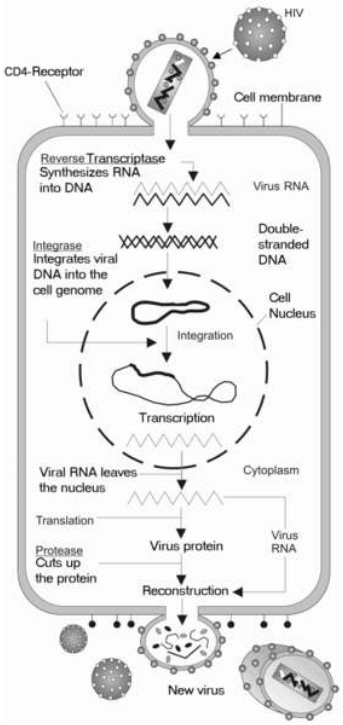


Figure: **HIV life cycle**: HIV has a gp120 which is precisely what the CD4 marker is on the surface of the macrophages and T cells. Therefore, HIV can enter T cells and macrophages.

Key Points

- Viruses must bind to specific cell surface receptors in order to enter a cell.
- If a cell does not express these receptors then the virus cannot normally infect it.
- In virology, Tissue tropism is the cells and tissues of a host which support growth of a particular virus or bacteria. Some viruses have a broad tissue tropism and can infect many types of cells and tissues. Other viruses may infect primarily a single tissue.

Key Terms

- **dendritic cell**: Any cell, having branching processes, that forms part of the mammalian immune system.
- **macrophage**: A white blood cell that phagocytizes necrotic cell debris and foreign material, including viruses, bacteria, and tattoo ink. It presents foreign antigens on MHC II to lymphocytes. Part of the innate immune system.

This page titled 15.5C: Tissue Tropism in Animal Viruses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.5C: Tissue Tropism in Animal Viruses** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.5D: Animal Viruses

Learning Objectives

- Describe various animal viruses and the diseases they cause

Animal Viruses

Animal viruses, unlike the viruses of plants and bacteria, do not have to penetrate a cell wall to gain access to the host cell. Non-enveloped or “naked” animal viruses may enter cells in two different ways. When a protein in the viral capsid binds to its receptor on the host cell, the virus may be taken inside the cell via a vesicle during the normal cell process of receptor-mediated endocytosis. An alternative method of cell penetration used by non-enveloped viruses is for capsid proteins to undergo shape changes after binding to the receptor, creating channels in the host cell membrane. The viral genome is then “injected” into the host cell through these channels in a manner analogous to that used by many bacteriophages. Enveloped viruses also have two ways of entering cells after binding to their receptors: receptor-mediated endocytosis and fusion. Many enveloped viruses enter the cell by receptor-mediated endocytosis in a fashion similar to some non-enveloped viruses. On the other hand, fusion only occurs with enveloped virions. These viruses, which include HIV among others, use special fusion proteins in their envelopes to cause the envelope to fuse with the plasma membrane of the cell, thus releasing the genome and capsid of the virus into the cell cytoplasm.

After making their proteins and copying their genomes, animal viruses complete the assembly of new virions and exit the cell. Using the example of HIV, enveloped animal viruses may bud from the cell membrane as they assemble themselves, taking a piece of the cell’s plasma membrane in the process. On the other hand, non-enveloped viral progeny, such as rhinoviruses, accumulate in infected cells until there is a signal for lysis or apoptosis, and all virions are released together.

Animal viruses are associated with a variety of human diseases. Some of them follow the classic pattern of acute disease, where symptoms worsen for a short period followed by the elimination of the virus from the body by the immune system with eventual recovery from the infection. Examples of acute viral diseases are the common cold and influenza. Other viruses cause long-term chronic infections, such as the virus causing hepatitis C, whereas others, like herpes simplex virus, cause only intermittent symptoms. Still other viruses, such as human herpes viruses 6 and 7, which in some cases can cause the minor childhood disease roseola, often successfully cause productive infections without causing any symptoms at all in the host; these patients have an asymptomatic infection.

In hepatitis C infections, the virus grows and reproduces in liver cells, causing low levels of liver damage. The damage is so low that infected individuals are often unaware that they are infected, with many infections only detected by routine blood work on patients with risk factors such as intravenous drug use. Since many of the symptoms of viral diseases are caused by immune responses, a lack of symptoms is an indication of a weak immune response to the virus. This allows the virus to escape elimination by the immune system and persist in individuals for years, while continuing to produce low levels of progeny virions in what is known as a chronic viral disease. Chronic infection of the liver by this virus leads to a much greater chance of developing liver cancer, sometimes as much as 30 years after the initial infection.

As mentioned, herpes simplex virus can remain in a state of latency in nervous tissue for months, even years. As the virus “hides” in the tissue and makes few if any viral proteins, there is nothing for the immune response to act against; immunity to the virus slowly declines. Under certain conditions, including various types of physical and psychological stress, the latent herpes simplex virus may be reactivated and undergo a lytic replication cycle in the skin, causing the lesions associated with the disease. Once virions are produced in the skin and viral proteins are synthesized, the immune response is again stimulated and resolves the skin lesions in a few days by destroying viruses in the skin. As a result of this type of replicative cycle, appearances of cold sores and genital herpes outbreaks only occur intermittently, even though the viruses remain in the nervous tissue for life. Latent infections are common with other herpes viruses as well, including the varicella-zoster virus that causes chickenpox. After having a chickenpox infection in childhood, the varicella-zoster virus can remain latent for many years and reactivate in adults to cause the painful condition known as “shingles”.

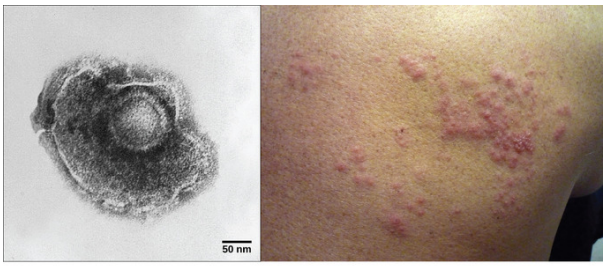


Figure: **Chicken pox virus**: (a) Varicella-zoster, the virus that causes chickenpox, has an enveloped icosahedral capsid visible in this transmission electron micrograph. Its double-stranded DNA genome incorporates into the host DNA and reactivates after latency in the form of (b) shingles, often exhibiting a rash.

Key Points

- Animal viruses may enter a host cell by either receptor -mediated endocytosis or by changing shape and entering the cell through the cell membrane.
- Viruses cause diseases in humans and other animals; they often have to run their course before symptoms disappear.
- Examples of viral animal diseases include hepatitis C, chicken pox, and shingles.

Key Terms

- **receptor-mediated endocytosis**: a process by which cells internalize molecules (endocytosis) by the inward budding of plasma membrane vesicles containing proteins with receptor sites specific to the molecules being internalized

---

This page titled 15.5D: Animal Viruses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.5D: Animal Viruses** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.5E: Plant Virus Life Cycles

Learning Objectives

- Outline plant virus life cycles

Plant viruses are viruses that affect plants. Like all other viruses, plant viruses are obligate intracellular parasites that do not have the molecular machinery to replicate without a host. Plant viruses are pathogenic to higher plants.

There are many types of plant virus, but often they only cause a loss of yield, and it is not economically viable to try to control them. Plant viruses are often spread from plant to plant by organisms (vectors). These are normally insects, but some fungi, nematode worms and single-celled organisms have been shown to be vectors. When control of plant virus infections is considered economical, (for perennial fruits for example), efforts are concentrated on killing the vectors and removing alternate hosts such as weeds. Plant viruses are harmless to humans and other animals because they can only reproduce in living plant cells.

Viral Life Cycle

For the virus to reproduce and thereby establish infection, it must enter cells of the host organism and use those cells' materials. To enter the cells, proteins on the surface of the virus interact with proteins of the cell. Attachment, or adsorption, occurs between the viral particle and the host cell membrane. A hole forms in the cell membrane, then the virus particle or its genetic contents are released into the host cell, where viral reproduction may commence. Next, a virus must take control of the host cell's replication mechanisms. At this stage, a distinction between susceptibility and permissibility of a host cell is made. Permissibility determines the outcome of the infection. After control is established and the environment is set for the virus to begin making copies of itself, replication occurs quickly by the millions. After a virus has made many copies of itself, it usually has exhausted the cell of its resources. The host cell is now no longer useful to the virus, therefore the cell often dies and the newly produced viruses must find a new host. The process by which virus progeny are released to find new hosts, is called shedding. This is the final stage in the viral life cycle. Some viruses can "hide" within a cell, either to evade the host cell defenses or immune system, or simply because it is not in the best interest of the virus to continually replicate. This hiding is deemed latency. During this time, the virus does not produce any progeny, it remains inactive until external stimuli—such as light or stress—prompts it to activate.

Viruses can be spread by direct transfer of sap, and by contact of a wounded plant with a healthy one. Such contact may occur during agricultural practices, when damage is caused by tools or hands, or naturally, when an animal feeds on the plant. Generally Tobacco mosaic virus (TMV), potato viruses, and cucumber mosaic viruses are transmitted via sap.

Tobacco mosaic virus and Cauliflower mosaic virus (CaMV) are frequently used in plant molecular biology. Of special interest is the CaMV 35S promoter, which is a very strong promoter most frequently used in plant transformations.

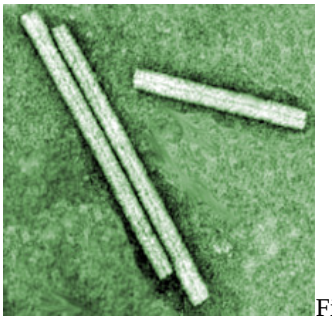


Figure: **Tobacco Mosaic Virus**: Tobacco mosaic virus (TMV) is a positive-sense single stranded RNA virus that infects plants, especially tobacco and other members of the family Solanaceae. The infection causes characteristic patterns (mottling and discoloration) on the leaves (hence the name). TMV was the first virus to be discovered. Although it was known from the late 19th century that an infectious disease was damaging tobacco crops, it was not until 1930 that the infectious agent was determined to be a virus.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: *CC BY-SA: Attribution-ShareAlike*

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- Virus replication cycle. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Virus_replication_cycle%23Replication_cycle**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Viral replication. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Viral_replication**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Viral life cycle. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Viral_life_cycle**. **License**: *CC BY-SA: Attribution-ShareAlike*
- lysis. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/lysis**. **License**: *CC BY-SA: Attribution-ShareAlike*
- uncoating. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/uncoating**. **License**: *CC BY-SA: Attribution-ShareAlike*
- attachment. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/attachment**. **License**: *CC BY-SA: Attribution-ShareAlike*
- leukocyte. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/leukocyte**. **License**: *CC BY-SA: Attribution-ShareAlike*
- HepC replication. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:HepC_replication.png**. **License**: *Public Domain: No Known Copyright*
- OpenStax College, Biology. October 16, 2013. **Provided by**: OpenStax CNX. **Located at**: **http://cnx.org/content/m44597/latest/?collection=col11448/latest**. **License**: *CC BY: Attribution*
- virion. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/virion**. **License**: *CC BY-SA: Attribution-ShareAlike*
- retrovirus. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/retrovirus**. **License**: *CC BY-SA: Attribution-ShareAlike*
- glycoprotein. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/glycoprotein**. **License**: *CC BY-SA: Attribution-ShareAlike*
- HepC replication. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:HepC_replication.png**. **License**: *Public Domain: No Known Copyright*
- OpenStax College, Virus Infections and Hosts. October 16, 2013. **Provided by**: OpenStax CNX. **Located at**: **http://cnx.org/content/m44597/latest/Figure_21_02_01.png**. **License**: *CC BY: Attribution*
- Host tropism. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Host_tropism**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Tissue tropism. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Tissue_tropism**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Tropism. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Tropism**. **License**: *CC BY-SA: Attribution-ShareAlike*
- macrophage. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/macrophage**. **License**: *CC BY-SA: Attribution-ShareAlike*
- dendritic cell. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/dendritic_cell**. **License**: *CC BY-SA: Attribution-ShareAlike*
- HepC replication. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:HepC_replication.png**. **License**: *Public Domain: No Known Copyright*
- OpenStax College, Virus Infections and Hosts. October 16, 2013. **Provided by**: OpenStax CNX. **Located at**: **http://cnx.org/content/m44597/latest/Figure_21_02_01.png**. **License**: *CC BY: Attribution*
- Gardasil vaccine and box new. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Gardasil_vaccine_and_box_new.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- HIV gross cycle only. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:HIV_gross_cycle_only.png**. **License**: *Public Domain: No Known Copyright*
- OpenStax College, Biology. October 16, 2013. **Provided by**: OpenStax CNX. **Located at**: **http://cnx.org/content/m44597/latest/?collection=col11448/latest**. **License**: *CC BY: Attribution*
- receptor-mediated endocytosis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/receptor-mediated%20endocytosis**. **License**: *CC BY-SA: Attribution-ShareAlike*

- HepC replication. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:HepC_replication.png**. **License**: ***Public Domain: No Known Copyright***
- OpenStax College, Virus Infections and Hosts. October 16, 2013. **Provided by**: OpenStax CNX. **Located at**: **http://cnx.org/content/m44597/latest/Figure_21_02_01.png**. **License**: ***CC BY: Attribution***
- Gardasil vaccine and box new. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Gardasil_vaccine_and_box_new.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- HIV gross cycle only. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:HIV_gross_cycle_only.png**. **License**: ***Public Domain: No Known Copyright***
- OpenStax College, Virus Infections and Hosts. October 16, 2013. **Provided by**: OpenStax CNX. **Located at**: **http://cnx.org/content/m44597/latest/Figure_21_02_04ab.jpg**. **License**: ***CC BY: Attribution***
- Introduction to viruses. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Introduction_to_viruses%23Diseases_of_plants**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Plant virus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Plant_virus**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Viral life cycle. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Viral_life_cycle**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- vector. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/vector**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- HepC replication. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:HepC_replication.png**. **License**: ***Public Domain: No Known Copyright***
- OpenStax College, Virus Infections and Hosts. October 16, 2013. **Provided by**: OpenStax CNX. **Located at**: **http://cnx.org/content/m44597/latest/Figure_21_02_01.png**. **License**: ***CC BY: Attribution***
- Gardasil vaccine and box new. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Gardasil_vaccine_and_box_new.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- HIV gross cycle only. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:HIV_gross_cycle_only.png**. **License**: ***Public Domain: No Known Copyright***
- OpenStax College, Virus Infections and Hosts. October 16, 2013. **Provided by**: OpenStax CNX. **Located at**: **http://cnx.org/content/m44597/latest/Figure_21_02_04ab.jpg**. **License**: ***CC BY: Attribution***
- Tobacco mosaic virus (TMV) | Flickr - Photo Sharing!. **Provided by**: Flickr. **Located at**: **www.flickr.com/photos/ajc1/6312327066/**. **License**: ***CC BY-SA: Attribution-ShareAlike***

Key Points

- Plant viruses are harmless to humans and other animals because they can only reproduce in living plant cells.
- For the virus to reproduce and thereby establish infection, it must enter cells of the host organism and use those cells' materials.
- A virus must take control of the host cell's replication mechanisms. At this stage a distinction between susceptibility and permissibility of a host cell is made.
- After control is established and the environment is set for the virus to begin making copies of itself, replication occurs quickly by the millions.

Key Terms

- **vector**: A carrier of a disease-causing agent.

This page titled 15.5E: Plant Virus Life Cycles is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.5E: Plant Virus Life Cycles** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.6: Viral Diversity

This page titled 15.6: Viral Diversity is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.7: Viral Diversity** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.6A: Overview of Bacterial Viruses

Learning Objectives

- Evaluate the complexity of bacteriophages

Bacteriophages

Bacteriophages (phages) are potentially the most numerous “organisms” on Earth. They are among the most common and diverse entities in the biosphere. They are the viruses of bacteria (more generally, of prokaryotes). Phages are obligate intracellular parasites, meaning that they are able to reproduce only while infecting bacteria. Bacteriophages are comprised of proteins that encapsulate a DNA or RNA genome, and may have relatively simple or elaborate structures. Their genomes may encode as few as four genes, and as many as hundreds of genes. Phages replicate within bacteria following the injection of their genome into the cytoplasm.

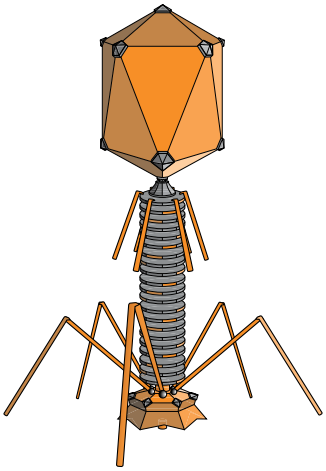


Figure: **Artistic rendering of a T4 bacteriophage**: The structure of a typical myovirus bacteriophage

Phage-ecological interactions are quantitatively vast. Bacteria (along with archaea) are highly diverse, with possibly millions of species. Phage-ecological interactions are also qualitatively diverse. There are huge numbers of environment types, bacterial-host types, and also individual phage types. Bacteriophages occur in over 140 bacterial or archaeal genera. They arose repeatedly in different hosts and there are at least 11 separate lines of descent. Over 5100 bacteriophages have been examined in the electron microscope since 1959. Of these, at least 4950 phages (96%) have tails. Of the tailed phages 61% have long, noncontractile tails (Siphoviridae). Tailed phages appear to be monophyletic and are the oldest known virus group.

Phages are widely distributed in locations populated by bacterial hosts, such as soil or the intestines of animals. One of the densest natural sources for phages and other viruses is sea water, where up to 9×108 virions per milliliter have been found in microbial mats at the surface. Up to 70% of marine bacteria may be infected by phages.

The dsDNA tailed phages, or Caudovirales, account for 95% of all the phages reported in the scientific literature, and possibly make up the majority of phages on the planet. However, other phages occur abundantly in the biosphere, with different virions, genomes and lifestyles. Phages are classified by the International Committee on Taxonomy of Viruses (ICTV) according to morphology and nucleic acid.

Nineteen families are currently recognised that infect bacteria and archaea. Of these, only two families have RNA genomes and only five families are enveloped. Of the viral families with DNA genomes, only two have single-stranded genomes. Eight of the viral families with DNA genomes have circular genomes, while nine have linear genomes. Nine families infect bacteria only, nine infect archaea only, and one (Tectiviridae) infects both bacteria and archaea.

Bacteriophages may have a lytic cycle or a lysogenic cycle, and a few viruses are capable of carrying out both. With lytic phages such as the T4 phage, bacterial cells are broken open (lysed) and destroyed after immediate replication of the virion. As soon as the

cell is destroyed, the phage progeny can find new hosts to infect.

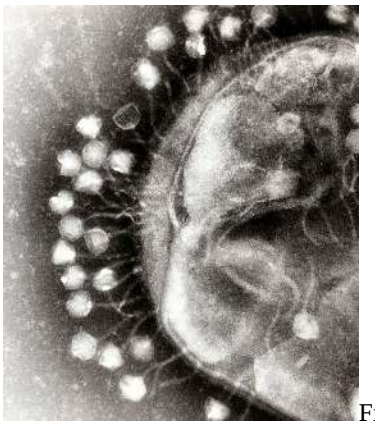


Figure: **Electron micrograph of Bacteriophages**: In this electron micrograph of bacteriophages attached to a bacterial cell, the viruses are the size and shape of coliphage T1.

In contrast, the lysogenic cycle does not result in immediate lysing of the host cell. Those phages able to undergo lysogeny are known as temperate phages. Their viral genome will integrate with host DNA and replicate along with it fairly harmlessly, or may even become established as a plasmid. The virus remains dormant until host conditions deteriorate, perhaps due to depletion of nutrients; then, the endogenous phages (known as prophages) become active. At this point they initiate the reproductive cycle, resulting in lysis of the host cell. As the lysogenic cycle allows the host cell to continue to survive and reproduce, the virus is reproduced in all of the cell's offspring. An example of a bacteriophage known to follow the lysogenic cycle and the lytic cycle is the phage lambda of E. coli.

To enter a host cell, bacteriophages attach to specific receptors on the surface of bacteria, including lipopolysaccharides, teichoic acids, proteins, or even flagella. This specificity means a bacteriophage can infect only certain bacteria bearing receptors to which they can bind, which in turn determines the phage's host range. Host growth conditions also influence the ability of the phage to attach and invade them.

Phages may be released via cell lysis, by extrusion, or, in a few cases, by budding. Lysis, by tailed phages, is achieved by an enzyme called endolysin, which attacks and breaks down the cell wall peptidoglycan. An altogether different phage type, the filamentous phages, make the host cell continually secrete new virus particles. Budding is associated with certain Mycoplasma phages.

Bacteriophage genomes are especially mosaic: the genome of any one phage species appears to be composed of numerous individual modules. These modules may be found in other phage species in different arrangements. Mycobacteriophages – bacteriophages with mycobacterial hosts – have provided excellent examples of this mosaicism. In these mycobacteriophages, genetic assortment may be the result of repeated instances of site-specific recombination and illegitimate recombination (the result of phage genome acquisition of bacterial host genetic sequences).

Key Points

- Phages are obligate intracellular parasites that are able to reproduce only while infecting bacteria. Bacteriophages are comprised of proteins that encapsulate a DNA or RNA genome.
- Bacteriophages occur in over 140 bacterial or archaeal genera. They arose repeatedly in different hosts and there are at least 11 separate lines of descent. Nineteen families are currently recognised that infect bacteria and archaea.
- Phages are widely distributed in locations populated by bacterial hosts, such as soil or the intestines of animals. One of the densest natural sources for phages and other viruses is sea water.
- Bacteriophages may have a lytic cycle or a lysogenic cycle, and a few viruses are capable of carrying out both.
- To enter a host cell, bacteriophages attach to specific receptors on the surface of bacteria. This specificity means a bacteriophage can infect only certain bacteria bearing receptors to which they can bind, which in turn determines the phage's host range.

Key Terms

- **bacteriophage**: A virus that specifically infects bacteria.
- **lysogeny**: the process by which a bacteriophage incorporates its nucleic acids into a host bacterium

---

This page titled 15.6A: Overview of Bacterial Viruses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.7A: Overview of Bacterial Viruses** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.6B: RNA Bacteriophages

Learning Objectives

- Identify differences between bacterial ssRNA and dsRNA viruses

Nineteen families of bacteriophages that infect bacteria and archaea are currently recognized. Of these, only two families have RNA genomes: Cystoviridae (segmented dsRNA) and Leviviridae (linear ssRNA).

The Leviviridae include the genera Allolevivirus (type species: *Enterobacteria phage Qβ*) and Levivirus (type species: *Enterobacteria phage MS2*).

Cystovirus is a genus of dsRNA virus that infect certain Gram-negative bacteria. All cystoviruses are distinguished by their three strands (analogous to chromosomes) of dsRNA, totalling ~14 kb in length, and by their protein and lipid outer layer. No other bacteriophage has any lipid in its outer coat, though the Tectiviridae and the Corticoviridae have lipids within their capsids.

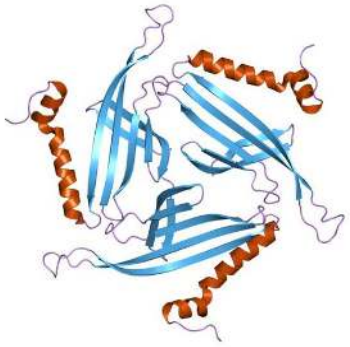


Figure: **Structure of bacteriophage PP7 from Pseudomonas aeruginosa**: Members of this protein family form the capsid of Pseudomonas phage PP7. They adopt a secondary structure consisting of a six-stranded beta sheet and an alpha helix.

Most identified cystoviruses infect Pseudomonas species, but this is likely biased due to the method of screening and enrichment. The type species is *Pseudomonas phage Φ6*, but there are many other members of this family: Φ7, Φ8, Φ9, Φ10, Φ11, Φ12, and Φ13 have been identified and named, but other cystoviruses have also been isolated.

Members of the Cystoviridae appear to be most closely related to the Reoviridae, but also share homology with the Totiviridae. Cystoviruses are the only bacteriophage that are more closely related to viruses of eukaryotes than to other phage.

Bacteriophage Φ6 is a member of the Cystoviridae family. It infects Pseudomonas bacteria (typically plant-pathogenic *P. syringae*). It has a three-part, segmented, double-stranded RNA genome, totalling ~13.5 kb in length. Φ6 and its relatives have a lipid membrane around their nucleocapsid, a rare trait among bacteriophages. It is a lytic phage, though under certain circumstances has been observed to display a delay in lysis that may be described as a “carrier state. ”

Φ6 typically attaches to the Type IV pilus of *P. syringae* with its attachment protein, P3. It is thought that the cell then retracts its pilus, pulling the phage toward the bacterium. Fusion of the viral envelope with the bacterial outer membrane is facilitated by the phage protein, P6. The muralytic (peptidoglycan-digesting) enzyme, P5, then digests a portion of the cell wall, and the nucleocapsid enters the cell coated with the bacterial outer membrane.

RNA-dependent RNA polymerases (RdRPs) are critical components in the life cycle of double-stranded RNA (dsRNA) viruses. However, it is not fully understood how these important enzymes function during viral replication. Expression and characterization of the purified recombinant RdRP of Φ6 is the first direct demonstration of RdRP activity catalyzed by a single protein from a dsRNA virus. The recombinant Φ6 RdRP is highly active in vitro, possesses RNA replication and transcription activities, and is capable of using both homologous and heterologous RNA molecules as templates.

Key Points

- Cystovirus is a genus of dsRNA virus that infect certain Gram-negative bacteria. All cystoviruses are distinguished by their three strands of dsRNA and their protein and lipid outer layer. No other bacteriophage has any lipid in its outer coat.

- RNA -dependent RNA polymerases (RdRPs) are critical components in the life cycle of double-stranded RNA (dsRNA) viruses. However, it is not fully understood how these important enzymes function during viral replication.
- Bacteriophage Φ6 is a member of the Cystoviridae family that infects Pseudomonas bacteria (typically plant-pathogenic P. syringae). It is a lytic phage, though under certain circumstances has been observed to display a delay in lysis that may be described as a “carrier state”.

Key Terms

- **RNA genome**: Like DNA, RNA can carry genetic information. RNA viruses have genomes composed of RNA that encodes a number of proteins.

This page titled 15.6B: RNA Bacteriophages is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.7B: RNA Bacteriophages** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.6C: Single-Stranded DNA Bacteriophages

Learning Objectives

- Illustrate the characteristics and life cycle of ssDNA bacteriophages

Nineteen viral families are currently recognized that infect bacteria and archaea. Of these, only two families have RNA genomes and only five are enveloped. Of the viral families with DNA genomes, only two have single-stranded genomes.

Inoviridae

The Inoviridae are a family of filamentous bacteriophages. The name of the family is derived from the Greek *nos*, meaning "muscle. "

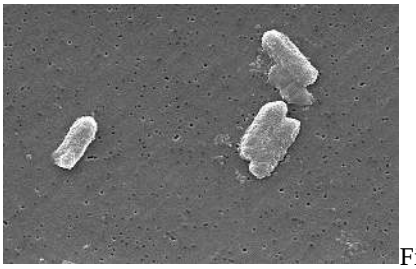


Figure: **Citrobacter freundii**: Citrobacter freundii, one member of the family Enterobacteriaceae. The genus Inovirus infect species of Enterobacteriaceae.

Taxonomy

There are two genera in this family: Inovirus and Plectrovirus. These genera differ in their host range: Plectovirii infect hosts of the class Mollicutes, while Inovirii infect species of the Enterobacteriaceae, Pseudomonadaceae, Spirillaceae, Xanthomonadaceae, Clostridium, and Propionibacterium classes.

Physical and Genomic Properties

Inoviridae are non-enveloped, rod-shaped, and filamentous. The capsid has a helical symmetry, and in general has a length of 85-280 nm or 760-1950 nm and a width of 10-16 nm or 6-8 nm, respectively. These morphological differences depend on the species.

The genomes are non-segmented, circular, positive-sense, single-stranded DNA, 4.4-8.5 kilobases in length. They encode 4 to 11 proteins. Replication of the genome occurs via a dsDNA intermediate and the rolling circle mechanism. Gene transcription is by the host's cellular machinery, as each gene has a specific promoter.

Life Cycle

There are six steps in the life cycle of Inoviridae:

1. Adsorbion to the host via specific receptor(s)
2. Movement of the viral DNA into the host cell
3. Conversion of the single-strand form to a double-stranded intermediate
4. Replication of the viral genome
5. Synthesis of the new virions
6. Release of the new virions from the host

Action in Host

Conversion from single-stranded to double-stranded form is carried out by the host's own DNA polymerase. The host's RNA polymerase binds to the viral genome and syntheses RNA. Some of this RNA is translated and the remainder is used to initiate DNA replication.

Virion release may involve host lysis, but alternatively productive infection may occur by budding from the host membrane. This pattern is typically seen in the Plectivirus genus. A number of exceptions to this life cycle are known. Lysogenic species, which

encode integrases, exist within this family.

Microviridae

The Microviridae are a family of bacteriophages with a single-stranded DNA genome. The name of this family is derived from the Greek *micro*, meaning “small. ” This refers to the size of their genomes, which are among the smallest of the DNA viruses.

Taxonomy

This family is divided into two subfamilies, Gokushovirinae (derived from the Japanese for “very small”) and Microvirinae. These groups differ in their hosts, genome structure, and virion composition.

Gokushoviruses are currently known to infect only obligate intra-cellular parasites. These species are members of the genera Bdellovibrio, Chlamydia, and Spiroplasma. Subfamily Microvirinae are all of the genus Microvirus. All seven such members infect Enterobacteria.

Physical and Genomic Properties

Members of the subfamily Gokushovirus have only two structural proteins: capsid proteins F (Virus Protein 1) and DNA pilot protein H (Virus Protein 2) and do not use scaffolding proteins. They also possess ‘mushroom-like’ protrusions positioned at the three-fold axes of symmetry of their icosahedral capsids. These are formed by large insertion loops within the protein F of gokushoviruses and are absent in the microviruses. They lack both the external scaffolding protein D and the major spike protein G of the species in the genus Microvirus. The genomes of this group tend to be smaller, about 4.5 kb in length. This subfamily includes the genera Bdellomicrovirus, Chlamydiamicrovirus, and Spiromicrovirus.

Microviridae are non-enveloped and round with an icosahedral symmetry. They have a diameter between 25-27 nanometers and lack tails. Each virion has 60 copies each of the F, G, and J proteins and 12 copies of the H protein. Viruses in this family replicate their genomes via a rolling circle mechanism and encode dedicated RCR initiation proteins. Although the majority of species in this family have lytic life cycles, a few may have temperate life cycles.

Life Cycle

There are a number of steps in the life cycle:

1. Adsorbion to the host via specific receptor(s)
2. Movement of the viral DNA into the host cell
3. Conversion of the single-strand form to a double-stranded intermediate, known as the replicative form I
4. Transcription of early genes
5. Replication of the viral genome
6. Late genes are now transcribed by the host’s RNA polymerase
7. Synthesis of the new virions
8. Maturation of the virions in the host cytoplasm
9. Release from the host

Action in Host

Cell lysis is mediated by the phiX174-encoded protein E, which inhibits the peptidoglycan synthesis, leading to the eventual bursting of the infected cell.

Key Points

- The Inoviridae are a family of filamentous bacteriophages. The virons are non-enveloped, rod-shaped, and filamentous. Viron release may involve host lysis, but alternatively productive infection may occur by budding from the host membrane.
- The Microviridae are a family of bacteriophages with a single-stranded DNA genome. Their genomes are among the smallest of the DNA viruses. Although the majority of species in this family have lytic life cycles, a few may have temperate life cycles.
- The Microviridae are divided into two subfamilies, Gokushovirinae and Microvirinae. These groups differ in their hosts, genome structure, and viron composition.

Key Terms

- **microviridae**: The Microviridae are a family of bacteriophages with a single-stranded DNA genome.
- **virion**: A single individual particle of a virus (the viral equivalent of a cell).

This page titled 15.6C: Single-Stranded DNA Bacteriophages is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.7C: Single-Stranded DNA Bacteriophages** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.6D: Double-Stranded DNA Bacteriophages

Learning Objectives

- Describe dsDNA bacteriophages

The Double-Stranded DNA (dsDNA) tailed phages, or Caudovirales, account for 95% of all the phages reported in the scientific literature, and possibly make up the majority of phages on the planet. Nineteen families that infect bacteria and archaea are currently recognized; of these, 15 have double-stranded DNA genomes.

Under the Baltimore classification scheme, the Caudovirales are group I viruses as they have double-stranded DNA (dsDNA) genomes, which can be anywhere from 18,000 base pairs to 500,000 base pairs in length. The virus particles have a distinct shape; each virion has an icosohedral head that contains the viral genome, and is attached to a flexible tail by a connector protein. The order encompasses a wide range of viruses, many of which contain genes of similar nucleotide sequence and function. Some tailed bacteriophage genomes can vary quite significantly in nucleotide sequence, however, even among the same genus. Due to their characteristic structure and possession of potentially homologous genes, it is believed these bacteriophages possess a common origin. There are at least 350 recognized species in this order.

Upon encountering a host bacterium, the tail section of the virion binds to receptors on the cell surface and delivers the DNA into the cell by use of an injectisome-like mechanism (an *injectisome* is a nanomachine that evolved for the delivery of proteins by type III secretion). The tail section of the virus punches a hole through the bacterial cell wall and plasma membrane and the genome passes down the tail into the cell. Once inside, the genes are expressed from transcripts made by the host machinery, using host ribosomes. Typically, the genome is replicated by use of concatemers, in which overlapping segments of DNA are made, and then put together to form the whole genome.

Viral capsid proteins come together to form a precursor prohead, into which the genome enters. Once this has occurred, the prohead undergoes maturation by cleavage of capsid subunits to form an icosohedral phage head with 5-fold symmetry. After the head maturation, the tail is joined in one of two ways: either the tail is constructed separately and joined with the connector, or the tail is constructed directly onto the phage head. The tails consist of helix-based proteins with 6-fold symmetry. After maturation of virus particles, the cell is lysed by lysins, holins, or a combination of the two.

Because the lack of homology between the amino acid and DNA sequences of these viruses precludes these from being used as taxonomic markers (as is common for other organisms), the three families here are defined on the basis of morphology. This classification scheme was originated by Bradley in 1969 and has since been extended. All viruses in this order have icosahedral or oblate heads, but differ in the length and contractile abilities of their tails. The Myoviridae have long tails that are contractile, the Podoviridae have short noncontractile tails, and the Siphoviridae have long non-contractile tails. Siphoviridae constitute the majority of the known tailed viruses.

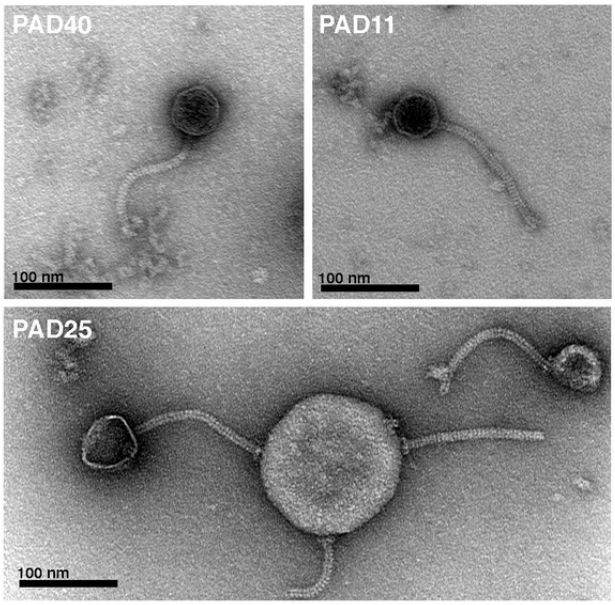


Figure: **Siphovirus phages**: Electron micrographs of bacteriophages from P. acnes. Phages were negatively stained with 0.75% uranyl formate and subjected to transmission electron microscopy. The phages have a head of approximately 55 nm in diameter, loaded with genetic material. Their tails have a size of 150 × 10 nm and are flexible and non-contractile. In the lower micrograph, PAD25 is adhering to bacterial cell debris, and two phages have lost their heads. At the attachment site between the phage and the cell debris, a base plate with attached spikes can be observed. All phages were classified as Siphoviruses based on their morphology.

Key Points

- The Caudovirales are an order of viruses also known as the tailed bacteriophages. The virus particles have a distinct shape; each virion has an icosohedral head that contains the viral genome, and is attached to a flexible tail by a connector protein.
- The order encompasses a wide range of viruses, many of which contain genes of similar nucleotide sequence and function. Some tailed bacteriophage genomes can vary quite significantly in nucleotide sequence, even among the same genus. There are at least 350 recognized species in this order.
- Because of the lack of homology between the amino acid and DNA sequences of these viruses, the three families here are defined based on morphology: the Myoviridae have long contractile tails, the Podoviridae have short noncontractile tails, and the Siphoviridae have long non-contractile tails.

Key Terms

- **Caudovirales**: A taxonomic order within the kingdom Virus—the bacteriophages that have tails.

This page titled 15.6D: Double-Stranded DNA Bacteriophages is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.7D: Double-Stranded DNA Bacteriophages** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.6E: Mu- A Double-Stranded Transposable DNA Bacteriophage

Learning Objectives

- Outline the life cycle of Mu phages

Bacteriophage Mu, or phage Mu, is a temperate bacteriophage, a type of virus that infects bacteria. It belongs to the family Myoviridae, and consists of an icosahedral head, a contractile tail, and six tail fibers.

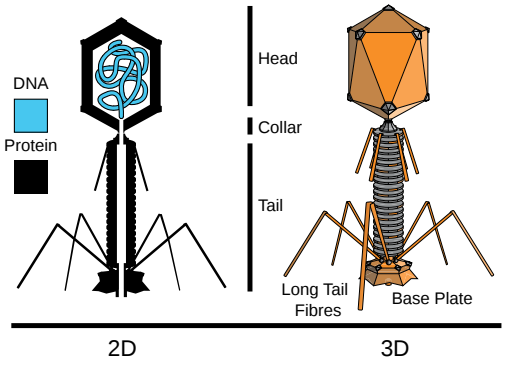


Figure: **Myoviridae**: Structural overview of the T4 phage, from the same family (Myoviridae) as Mu bacteriophage.

All of the known temperate phages employ one of only three different systems for their lysogenic cycle: lambda-like integration/excision, Mu-like transposition, or the plasmid-like partitioning of phage N15.

Mu bacteriophage uses DNA-based transposition to integrate its genome into the genome of the host cell that it is infecting. It can then use transposition to initiate its viral DNA replication. Once the viral DNA is inserted into the bacteria, the Mu's transposase protein/enzyme in the cell recognizes the recombination sites at the ends of the viral DNA (gix-L and gix-R sites) and binds to them, allowing the process of replicating the viral DNA or embedding it into the host genome. A transposable element (TE) is a DNA sequence that can change its relative position (self-transpose) within the genome of a single cell. The mechanism of transposition can be either "copy and paste" or "cut and paste. " Transposition can create phenotypically significant mutations and alter the cell's genome size.

Mu phage transposition is the best known example of replicative transposition. Its transposition mechanism is somewhat similar to a homologous recombination. Replicative transposition is a mechanism of transposition in molecular biology, proposed by James A. Shapiro in 1979, in which the transposable element is duplicated during the reaction, so that the transposing entity is a copy of the original element. In this mechanism, the donor and receptor DNA sequences form a characteristic intermediate "theta" configuration, sometimes called a "Shapiro intermediate. " Replicative transposition is characteristic to retrotransposons and occurs from time to time in class II transposons.

Key Points

- All of the known temperate phages employ one of only three different systems for their lysogenic cycle: lambda-like integration/excision, Mu-like transposition, or the plasmid-like partitioning of phage N15.
- Phage Mu uses DNA -based transposition to integrate its genome into the genome of the host cell that it is infecting. It can then use transposition to initiate its viral DNA replication.
- Mu phage transposition is the best-known example of replicative transposition. Its transposition mechanism is somewhat similar to a homologous recombination.

Key Terms

- **replicative transposition**: A mechanism of transposition in which the transposable element is duplicated during the reaction, so that the transposing entity is a copy of the original element.

This page titled 15.6E: Mu- A Double-Stranded Transposable DNA Bacteriophage is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.7E: Mu- A Double-Stranded Transposable DNA Bacteriophage** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.6F: Virulent Bacteriophages and T4

Learning Objectives

- Summarize how the T4 life cycle serves as a model for viral virulence

Virulence is the degree of pathogenicity within a group or species of parasites as indicated by case fatality rates and/or the ability of the organism to invade the tissues of the host. The pathogenicity of an organism is determined by its virulence factors. Virus virulence factors determine whether an infection will occur and how severe the resulting viral disease symptoms are. Viruses often require receptor proteins on host cells to which they specifically bind. Typically, these host cell proteins are endocytosed and the bound virus then enters the host cell. Virulent viruses such as HIV, which causes AIDS, have mechanisms for evading host defenses.

Some viral virulence factors confer ability to replicate during the defensive inflammation responses of the host such as during virus-induced fever. Many viruses can exist inside a host for long periods during which little damage is done. Extremely virulent strains can eventually evolve by mutation and natural selection within the virus population inside a host. The term “neurovirulent” is used for viruses such as rabies and herpes simplex which can invade the nervous system and cause disease there.

Model organisms of virulent viruses that have been extensively studied include virus T4 and other T-even bacteriophages which infect Escherichia coli and a number of related Bacteria.

The lytic cycle is one of the two cycles of viral reproduction, the other being the lysogenic cycle. The lytic cycle is typically considered the main method of viral replication, since it results in the destruction of the infected cell. A key difference between the lytic and lysogenic phage cycles is that in the lytic phage, the viral DNA exists as a separate molecule within the bacterial cell, and replicates separately from the host bacterial DNA. The location of viral DNA in the lysogenic phage cycle is within the host DNA, therefore in both cases the virus/phage replicates using the host DNA machinery, but in the lytic phage cycle, the phage is a free floating separate molecule to the host DNA.

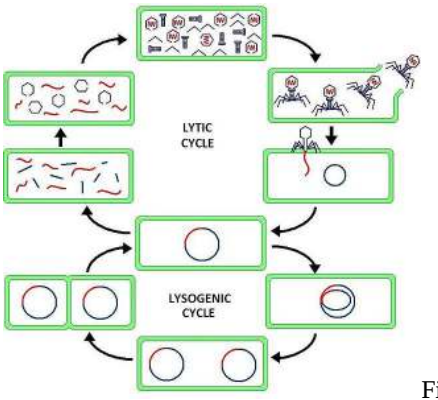


Figure: **Cycles of viral reproduction**: Comparison of the bacteriophage lysogenic and lytic cycles.

The lytic cycle is a six-stage cycle. In the first stage, called “penetration,” the virus injects its own nucleic acids into a host cell. Then the viral acids form a circle in the center of the cell. The cell then mistakenly copies the viral acids instead of its own nucleic acids. Then the viral DNA organize themselves as viruses inside the cell. When the number of viruses inside becomes too much for the cell to hold, the membrane splits and the viruses are free to infect other cells. Some viruses escape the host cell without bursting the cell membrane; instead, they bud off from it by taking a portion of the membrane with them. Because it otherwise is characteristic of the lytic cycle in other steps, it still belongs to this category, although it is sometimes named the Productive Cycle. HIV, influenza and other viruses that infect eukaryotic organisms generally use this method.

T-4 bacteriophage is a bacteriophage that infects E. coli bacteria. Its double-stranded DNA genome is about 169 kbp long and is held in an icosahedral head, also known as a capsid. T4 is a relatively large phage, at approximately 90 nm wide and 200 nm long (most phages range from 25 to 200 nm in length). Its tail fibres allow attachment to a host cell, and the T4’s tail is hollow so that it

can pass its nucleic acid to the cell it is infecting during attachment. T4 is capable of undergoing only a lytic lifecycle and not the lysogenic lifecycle.

The T4 Phage initiates an E. coli infection by recognizing cell surface receptors of the host with its long tail fibers (LTF). A recognition signal is sent through the LTFs to the baseplate. This unravels the short tail fibers (STF) that bind irreversibly to the E. coli cell surface. The baseplate changes conformation and the tail sheath contracts causing GP5 at the end of the tail tube to puncture the outer membrane of the cell. The lysozyme domain of GP5 is activated and degrades the periplasmic peptidoglycan layer. The remaining part of the membrane is degraded and then DNA from the head of the phage can travel through the tail tube and enter the E. coli.

The lytic lifecycle (from entering a bacterium to its destruction) takes approximately 30 minutes (at 37 °C) and consists of:

- Adsorption and penetration (starting immediately)
- Arrest of host gene expression (starting immediately)
- Enzyme synthesis (starting after 5 minutes)
- DNA replication (starting after 10 minutes)
- Formation of new virus particles (starting after 12 minutes)

After the life cycle is complete, the host cell bursts open and ejects the newly built viruses into the environment, destroying the host cell. T4 has a burst size of approximately 100-150 viral particles per infected host. Complementation, deletion, and recombination tests can be used to map out the rII gene locus by using T4. These bacteriophage infect a host cell with their information and then blow up the host cell, thereby propagating themselves.

The T4 phage has some unique features, including:

- Eukaryote-like introns
- High speed DNA copying mechanism, with only 1 error in 300 copies
- Special DNA repair mechanisms
- It infects E. coli O157:H7

Key Points

- Virulence is the degree of pathogenicity within a group or species of parasites as indicated by case fatality rates and/or the ability of the organism to invade the tissues of the host. The pathogenicity of an organism is determined by its virulence factors.
- A key difference between the lytic and lysogenic phage cycles is that in the lytic phage, the viral DNA exists as a separate molecule within the bacterial cell, and replicates separately from the host bacterial DNA.
- The T-4's tail fibres allow attachment to a host cell, and the T4's tail is hollow so that it can pass its nucleic acid to the cell it is infecting during attachment. T4 is capable of undergoing only a lytic lifecycle and not the lysogenic lifecycle.

Key Terms

- **lytic cycle**: The normal process of viral reproduction involving penetration of the cell membrane, nucleic acid synthesis, and lysis of the host cell.
- **virulence**: the degree of pathogenicity within a group or species of parasites as indicated by case fatality rates and/or the ability of the organism to invade the tissues of the host.

This page titled 15.6F: Virulent Bacteriophages and T4 is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.7F: Virulent Bacteriophages and T4** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.6G: Temperate Bacteriophages - Lambda and P1

Learning Objectives

- Evaluate the differences between the temperate phages, P1, and lambda

In virology, temperate refers to the ability of some bacteriophages (notable coliphage λ) to display a lysogenic life cycle. Many (but not all) temperate phages can integrate their genomes into their host bacterium's chromosome, together becoming a lysogen as the phage genome becomes a prophage. A temperate phage is also able to undergo a productive, typically-lytic life cycle, where the prophage is expressed, replicates the phage genome, and produces phage progeny, which then leave the bacterium. With phage the term *virulent* is often used as an antonym to *temperate*, but more strictly a virulent phage is one that has lost its ability to display lysogeny through mutation, rather than a phage lineage with no genetic potential to ever display lysogeny (which more properly would be described as an obligately lytic phage).

P1 is a temperate bacteriophage (phage) that infects *Escherichia coli* and some other bacteria. When undergoing a lysogenic cycle, the phage genome exists as a plasmid in the bacterium, unlike other phages (e.g., the lambda phage) that integrate into the host DNA. P1 has an icosahedral "head" containing the DNA, attached to a contractile tail with six tail fibers.

The virion is similar in structure to the T4 phage, but simpler. It has an icosahedral head containing the genome attached at one vertex to the tail. The tail has a tube surrounded by a contractile sheath, and ends in a base plate with six tail fibers. The tail fibers are involved in attaching to the host and providing specificity.

At around 93Kbp in length, the genome of the P1 phage is moderately large compared to the genomes of others, like T4 (169Kbp), lambda (48Kbp), and Ff (6.4Kbp). In the viral particle it is in the form of a linear double-stranded DNA molecule. Once inserted into the host, it circularizes and replicates as a plasmid.

Temperate phage, such as P1, have the ability to exist within the bacterial cell they infect in two different ways. In lysogeny, P1 can exist within a bacterial cell as a circular DNA, in that it exists by replicating as if it were a plasmid and does not cause cell death. Alternatively, in its lytic phase, P1 can promote cell lysis during growth, resulting in host cell death. During lysogeny, new phage particles are not produced. In contrast, during lytic growth many new phage particles are assembled and released from the cell. By alternating between these two modes of infection, P1 can survive during extreme nutritional conditions that may be imposed upon the bacterial host in which it exists.

A unique feature of phage P1 is that during lysogeny its genome is not incorporated into the bacterial chromosome, as is commonly observed during lysogeny of other bacteriophage. Instead, P1 exists independently within the bacterial cell, much like a plasmid would. P1 replicates as a 90 kilobase (kb) plasmid in the lysogenic state and is partitioned equally into two new daughter cells during normal cell division.

Enterobacteria phage λ (lambda phage, coliphage λ) is a bacterial virus, or bacteriophage, that infects the bacterial species *Escherichia coli*. This virus is temperate and may reside within the genome of its host through lysogeny.

Lambda phage consists of a virus particle including a head (also known as a capsid), a tail, and tail fibers. The head contains the phage's double-stranded circular DNA genome. The phage particle recognizes and binds to its host, *E. coli*, causing DNA in the head of the phage to be ejected through the tail into the cytoplasm of the bacterial cell. Usually, a "lytic cycle" ensues, where the lambda DNA is replicated many times and the genes for head, tail, and lysis proteins are expressed. This leads to assembly of multiple new phage particles within the cell and subsequent cell lysis, releasing the cell contents, including virions that have been assembled, into the environment. However, under certain conditions the phage DNA may integrate itself into the host cell chromosome in the lysogenic pathway. In this state, the λ DNA is called a prophage and stays resident within the host's genome without apparent harm to the host. The host can be termed a lysogen when a prophage is present.

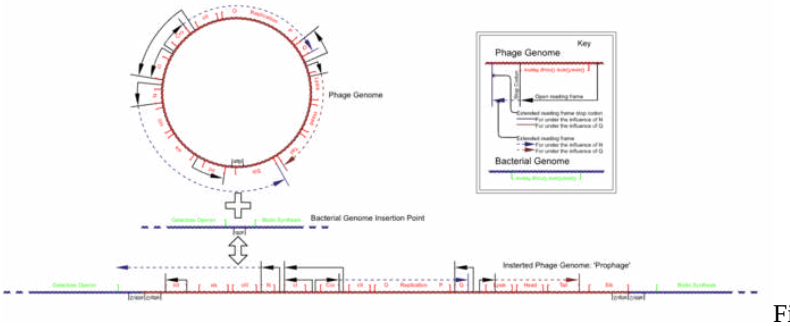


Figure: **Insertion of the bacteriophage lambda**: Schematic representation of the insertion of the bacteriophage lambda. Note how sib is displaced by the recombination event from the N extended PL promoter open reading frame.

The virus particle consists of a head and a tail that can have tail fibers. The head contains 48,490 base pairs of double-stranded, linear DNA, with 12-base single-stranded segments at both 5′ ends. These two single-stranded segments are the “sticky ends” of what is called the cos site. The cos site circularizes the DNA in the host cytoplasm. In its circular form, the phage genome therefore is 48,502 base pairs in length. The prophage exists as a linear section of DNA inserted into the host chromosome.

Key Points

- Many temperate phages can integrate their genomes into their host bacterium ‘s chromosome, together becoming a lysogen as the phage genome becomes a prophage. A temperate phage is also able to undergo a productive, typically-lytic life cycle.
- P1 is a temperate bacteriophage (phage) that infects Escherichia coli and some other bacteria. A unique feature of phage P1 is that during lysogeny its genome is not incorporated into the bacterial chromosome, as is commonly observed during lysogeny of other bacteriophage.
- Enterobacteria phage λ (lambda phage, coliphage λ) is a bacterial virus, or bacteriophage, that infects the bacterial species Escherichia coli.
- With the infection of a bacteria by phage, a lytic cycle usually ensues where the lambda DNA is replicated many times and the genes for head, tail, and lysis proteins are expressed. Under certain conditions the phage DNA may integrate itself into the host cell chromosome in the lysogenic pathway.

Key Terms

- **lytic life cycle**: One of the two cycles of viral reproduction (the other being the lysogenic cycle). The lytic cycle is typically considered the main method of viral replication and it results in the destruction of the infected cell.
- **temperate bacteriophage**: Phages able to undergo lysogeny.

This page titled 15.6G: Temperate Bacteriophages - Lambda and P1 is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.7G: Temperate Bacteriophages - Lambda and P1** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.6H: Viruses of Archaea

Learning Objectives

- Illustrate the typical characteristics of archaea-infecting viruses

A virus infecting archaea was first described in 1974. Several others have been described since then. Most have head-tail morphologies and linear double-stranded DNA genomes. Other morphologies have also been described including spindle shaped, rod shaped, filamentous, icosahedral, and spherical. Additional morphological types may exist.

Archaea can be infected by double-stranded DNA viruses that are unrelated to any other form of virus and have a variety of unusual shapes. These viruses have been studied in the most detail in thermophilics, particularly the orders Sulfolobales and Thermoproteales. Two groups of single-stranded DNA viruses that infect archaea have been recently isolated. One group is exemplified by the Halorubrum pleomorphic virus 1 ("Pleolipoviridae") infecting halophilic archaea and the other one by the Aeropyrum coil-shaped virus.

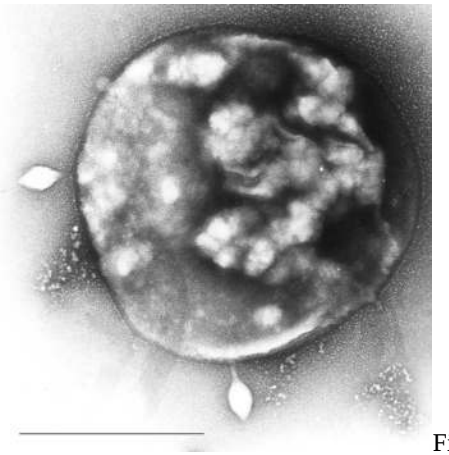


Figure: **Archaeal viral infection**: Cell of Sulfolobus infected by virus STSV1 observed under microscopy. Two spindle-shaped viruses were being released from the host cell. The strain of Sulfolobus and STSV1 (Sulfolobus tengchongensis Spindle-shaped Virus 1) were isolated by Xiaoyu Xiang and his colleagues in an acidic hot spring in Yunnan Province, China. At present, STSV1 is the largest archaeal virus to have been isolated and studied. Its genome sequence has been sequenced.

Double-stranded DNA viruses infecting archaea:

- Bacteriophages (viruses infecting bacteria) belonging to the families Tectiviridae and Corticoviridae have a lipid bilayer membrane inside the icosahedral protein capsid and the membrane surrounds the genome. The crenarchaeal virus Sulfolobus turreted icosahedral virus has a similar structure.
- Species of the order Ligamenvirales and the families Ampullaviridae, Bicaudaviridae, Clavaviridae, Fuselloviridae, Globuloviridae, and Guttaviridae infect hyperthermophilic archaea species of the Crenarchaeota.
- Species of the genus Salterprovirus infect halophilic archaea species of the Euryarchaeota.

Single-stranded DNA viruses infecting archaea:

Although around 50 archaeal viruses are known, all but two have double stranded genomes. The first archaeal ssDNA virus to be isolated is the Halorubrum pleomorphic virus 1, which has a pleomorphic enveloped virion and a circular genome. Defenses against these viruses may involve RNA interference from repetitive DNA sequences that are related to the genes of the viruses.

The second single stranded DNA virus infecting Archaea is Aeropyrum coil-shaped virus (ACV). The genome is circular and with 24,893 nucleotides is currently the largest known ssDNA genome. The viron is nonenveloped, hollow, cylindrical, and formed from a coiling fiber. The morphology and the genome appear to be unique. ACV has been suggested to represent a new viral family tentatively called "Spiraviridae" (from Latin spira, "a coil"). The Aeropyrum coil-shaped virus infects a hyperthermophilic (optimal growth at 90-95°C) host. Notably, the latter virus has the largest currently reported ssDNA genome.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: ***CC BY-SA: Attribution-ShareAlike***

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- Bacteriophage. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Bacteriophage**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Phage ecology. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Phage_ecology**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- DNA viruses. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/DNA_viruses%23Bacteriophage_evolution**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- bacteriophage. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/bacteriophage**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- lysogeny. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/lysogeny**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Phage. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Phage.jpg**. **License**: ***Public Domain: No Known Copyright***
- PhageExterior. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:PhageExterior.svg**. **License**: ***Public Domain: No Known Copyright***
- Bacteriophage. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Bacteriophage**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Pseudomonas phage u03a66. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Pseudomonas_phage_%CE%A66**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Double-stranded RNA viruses. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Double-stranded_RNA_viruses**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Bacteriophage. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Bacteriophage**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Cystoviridae. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Cystoviridae**. **License**: *CC BY-SA: Attribution-ShareAlike*
- RNA genome. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/RNA%20genome**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Phage. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Phage.jpg**. **License**: ***Public Domain: No Known Copyright***
- PhageExterior. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:PhageExterior.svg**. **License**: ***Public Domain: No Known Copyright***
- PDB 1dwn EBI. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:PDB_1dwn_EBI.jpg**. **License**: ***Public Domain: No Known Copyright***
- Bacteriophage. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Bacteriophage**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Microviridae. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Microviridae**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Inoviridae. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Inoviridae**. **License**: *CC BY-SA: Attribution-ShareAlike*
- virion. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/virion**. **License**: *CC BY-SA: Attribution-ShareAlike*
- microviridae. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/microviridae**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Phage. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Phage.jpg**. **License**: ***Public Domain: No Known Copyright***
- PhageExterior. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:PhageExterior.svg**. **License**: ***Public Domain: No Known Copyright***

- PDB 1dwn EBI. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:PDB_1dwn_EBI.jpg**. **License**: ***Public Domain: No Known Copyright***
- Citrobacter freundii. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ci...r_freundii.jpg**. **License**: ***Public Domain: No Known Copyright***
- Bacteriophage. **Provided by**: Wikipedia. **Located at**: **http://en.Wikipedia.org/wiki/Bacteriophage**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Caudovirales. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Caudovirales**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Caudovirales. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/Caudovirales**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Phage. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Phage.jpg**. **License**: ***Public Domain: No Known Copyright***
- PhageExterior. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:PhageExterior.svg**. **License**: ***Public Domain: No Known Copyright***
- PDB 1dwn EBI. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:PDB_1dwn_EBI.jpg**. **License**: ***Public Domain: No Known Copyright***
- Citrobacter freundii. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Citrobacter_freundii.jpg**. **License**: ***Public Domain: No Known Copyright***
- File:Siphovirus.tiff - Wikipedia, the free encyclopedia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/w/index.php?...us.tiff&page=1**. **License**: ***CC BY: Attribution***
- Mu phage. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Mu_phage**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Transposable element. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Transposable_element**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Replicative transposition. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Replicative_transposition**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- DsDNA virus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/DsDNA_v..._dsDNA_viruses**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- replicative transposition. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/replica...0transposition**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Phage. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Phage.jpg**. **License**: ***Public Domain: No Known Copyright***
- PhageExterior. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:PhageExterior.svg**. **License**: ***Public Domain: No Known Copyright***
- PDB 1dwn EBI. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:PDB_1dwn_EBI.jpg**. **License**: ***Public Domain: No Known Copyright***
- Citrobacter freundii. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Citrobacter_freundii.jpg**. **License**: ***Public Domain: No Known Copyright***
- File:Siphovirus.tiff - Wikipedia, the free encyclopedia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/w/index.php?...us.tiff&page=1**. **License**: ***CC BY: Attribution***
- Tevenphage. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Tevenphage.svg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Virulence. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Virulen...rulent_viruses**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Lytic cycle. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Lytic_cycle**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- T4 phage. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/T4_phage**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- virulence. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/virulence**. **License**: ***CC BY-SA: Attribution-ShareAlike***

- lytic cycle. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/lytic_cycle**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Phage. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Phage.jpg**. **License**: ***Public Domain: No Known Copyright***
- PhageExterior. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:PhageExterior.svg**. **License**: ***Public Domain: No Known Copyright***
- PDB 1dwn EBI. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:PDB_1dwn_EBI.jpg**. **License**: ***Public Domain: No Known Copyright***
- Citrobacter freundii. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Citrobacter_freundii.jpg**. **License**: ***Public Domain: No Known Copyright***
- File:Siphovirus.tiff - Wikipedia, the free encyclopedia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/w/index.php?title=File:Siphovirus.tiff&page=1**. **License**: *CC BY: Attribution*
- Tevenphage. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Tevenphage.svg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Phage2. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Phage2.JPG**. **License**: ***Public Domain: No Known Copyright***
- P1 phage. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/P1_phage**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Temperateness (virology). **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Temperateness_(virology)**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Lambda phage. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Lambda_phage**. **License**: *CC BY-SA: Attribution-ShareAlike*
- temperate bacteriophage. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/tempera...0bacteriophage**. **License**: *CC BY-SA: Attribution-ShareAlike*
- lytic life cycle. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/lytic%20life%20cycle**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Phage. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Phage.jpg**. **License**: *Public Domain: No Known Copyright*
- PhageExterior. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:PhageExterior.svg**. **License**: *Public Domain: No Known Copyright*
- PDB 1dwn EBI. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:PDB_1dwn_EBI.jpg**. **License**: *Public Domain: No Known Copyright*
- Citrobacter freundii. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Citrobacter_freundii.jpg**. **License**: *Public Domain: No Known Copyright*
- File:Siphovirus.tiff - Wikipedia, the free encyclopedia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/w/index.php?title=File:Siphovirus.tiff&page=1**. **License**: *CC BY: Attribution*
- Tevenphage. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Tevenphage.svg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Phage2. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Phage2.JPG**. **License**: *Public Domain: No Known Copyright*
- Bacteriophage lambda genome insertion. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ba..._insertion.png**. **License**: *Public Domain: No Known Copyright*
- Archaeal viruses. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Archaeal_viruses**. **License**: *CC BY-SA: Attribution-ShareAlike*
- DNA viruses. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/DNA_viruses**. **License**: *CC BY-SA: Attribution-ShareAlike*
- DNA virus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/DNA%20virus**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Phage. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Phage.jpg**. **License**: *Public Domain: No Known Copyright*

- PhageExterior. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:PhageExterior.svg**. **License**: ***Public Domain: No Known Copyright***
- PDB 1dwn EBI. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:PDB_1dwn_EBI.jpg**. **License**: ***Public Domain: No Known Copyright***
- Citrobacter freundii. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Citrobacter_freundii.jpg**. **License**: ***Public Domain: No Known Copyright***
- File:Siphovirus.tiff - Wikipedia, the free encyclopedia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/w/index.php?title=File:Siphovirus.tiff&page=1**. **License**: ***CC BY: Attribution***
- Tevenphage. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Tevenphage.svg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Phage2. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Phage2.JPG**. **License**: ***Public Domain: No Known Copyright***
- Bacteriophage lambda genome insertion. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ba..._insertion.png**. **License**: ***Public Domain: No Known Copyright***
- RT8-4. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:RT8-4.jpg**. **License**: ***Public Domain: No Known Copyright***

Key Points

- Archaea can be infected by double-stranded DNA viruses that are unrelated to any other form of virus and have a variety of unusual shapes. These viruses have been studied in most detail in thermophilics, particularly the orders Sulfolobales and Thermoproteales.
- Although around 50 archaeal viruses are known, all but two have double stranded genomes; two groups of single-stranded DNA viruses that infect archaea have been recently isolated.
- Defenses against these ssDNA viruses may involve RNA interference from repetitive DNA sequences that are related to the genes of the viruses.

Key Terms

- **DNA virus**: A DNA virus is a virus that has DNA as its genetic material and replicates using a DNA-dependent DNA polymerase. The nucleic acid is usually double-stranded DNA (dsDNA) but may also be single-stranded DNA (ssDNA).

This page titled 15.6H: Viruses of Archaea is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.7H: Viruses of Archaea** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.7: Positive-Strand RNA Viruses in Animals

This page titled 15.7: Positive-Strand RNA Viruses in Animals is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.8: Positive-Strand RNA Viruses in Animals** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.7A: Positive-Strand RNA Viruses of Animals

Positive-Strand RNA Viruses of Animals

Positive strand RNA viruses are the single largest group of RNA viruses with 30 families.

LEARNING OBJECTIVES

Categorize the characteristics of positive-strand viruses

KEY TAKEAWAYS

Key Points

- Nucleic acid is usually single-stranded RNA (ssRNA), but may be double-stranded RNA (dsRNA).
- An RNA virus is a virus that has RNA (ribonucleic acid) as its genetic material.
- Notable human diseases caused by RNA viruses include SARS, influenza, hepatitis C, West Nile fever, and polio.

Key Terms

- **virus**: A submicroscopic infectious organism, now understood to be a non-cellular structure consisting of a core of DNA or RNA surrounded by a protein coat. It requires a living cell to replicate, and often causes disease in the host organism.
- **genetic**: Relating to genetics or genes.
- **RNA**: Ribonucleic acid (RNA) is a ubiquitous family of large biological molecules that performs multiple vital roles in the coding, decoding, regulation, and expression of genes.

Single stranded RNA viruses can be classified according to the sense or polarity of their RNA into negative-sense and positive-sense, or ambisense RNA viruses. Positive-sense viral RNA is similar to mRNA and thus can be immediately translated by the host cell. Negative-sense viral RNA is complementary to mRNA and thus must be converted to positive-sense RNA by an RNA polymerase before translation. As such, purified RNA of a positive-sense virus can directly cause infection though it may be less infectious than the whole virus particle. Purified RNA of a negative-sense virus is not infectious by itself as it needs to be transcribed into positive-sense RNA; each virion can be transcribed to several positive-sense RNAs. Ambisense RNA viruses resemble negative-sense RNA viruses, except they also translate genes from the positive strand. A common viral positive-strand RNA viruses that infect humans are the picornaviruses.

 Figure: **Foot and Mouth Disease**: Foot and Mouth Disease is caused by the Aphthovirus virus which positive-strand RNA virus, of the Picornaviridae family of animal viruses.

A picornavirus is a virus belonging to the family Picornaviridae. Picornaviruses are non-enveloped, positive-stranded RNA viruses with an icosahedral capsid. The genome RNA is unusual because it has a protein on the 5′ end that is used as a primer for transcription by RNA polymerase. The name is derived from pico, meaning small, and RNA, referring to the ribonucleic acid genome, so “picornavirus” literally means small RNA virus. Picornaviruses are separated into a number of genera and include many important pathogens of humans and animals. The diseases they cause are varied, ranging from acute “common-cold”-like illnesses, to poliomyelitis, to chronic infections in livestock. Additional species not belonging to any of the recognized genera continue to be described.

Picornaviruses are separated into a number of genera. Contained within the picornavirus family are many organisms of importance as vertebrate and human pathogens, shown in the table below.Enteroviruses infect the enteric tract, which is reflected in their name. On the other hand, rhinoviruses infect primarily the nose and the throat. Enteroviruses replicate at 37°C, whereas rhinoviruses grow better at 33°C, as this is the lower temperature of the nose. Enteroviruses are stable under acid conditions and thus they are able to

survive exposure to gastric acid. In contrast, rhinoviruses are acid-labile (inactivated or destroyed by low pH conditions) and that is the reason why rhinovirus infections are restricted to the nose and throat.

This page titled 15.7A: Positive-Strand RNA Viruses of Animals is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.8A: Positive-Strand RNA Viruses of Animals** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.7B: Virus Attachment and Genome Entry

Learning Objectives

- Differentiate virus attachment and genome entry

Viral populations do not grow through cell division, because they are acellular. Instead, they use the machinery and metabolism of a host cell to produce multiple copies of themselves, and they assemble in the cell. The life cycle of viruses differs greatly between species, but they all share the same basic life cycle stages.

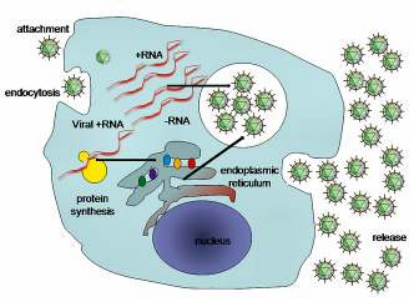


Figure: **A typical virus replication cycle**: There are six basic stages in the life cycle of viruses: attachment, penetration, uncoating, replication, assembly of viral particles, and release.

Attachment is a specific binding between viral capsid proteins and specific receptors on the host cellular surface. This specificity determines the host range of a virus. For example, HIV infects a limited range of human leukocytes. This is because its surface protein, gp120, specifically interacts with the CD4 molecule, a chemokine receptor, which is most commonly found on the surface of CD4+ T-Cells. This mechanism has evolved to favor those viruses that infect only cells in which they are capable of replication. Attachment to the receptor can induce the viral envelope protein to undergo changes that results in the fusion of viral and cellular membranes, or changes of non-enveloped virus surface proteins that allow the virus to enter.

Penetration follows attachment: Virions enter the host cell through receptor-mediated endocytosis or membrane fusion. This is often called “viral entry. ” The infection of plant and fungal cells is different from that of animal cells. Plants have a rigid cell wall made of cellulose, and fungi one of chitin, so most viruses can get inside these cells only after trauma to the cell wall. However, nearly all plant viruses (such as tobacco mosaic virus) can also move directly from cell to cell, in the form of single-stranded nucleoprotein complexes, through pores called “plasmodesmata”. Bacteria, such as plants, have strong cell walls that a virus must breach to infect the cell. However, given that bacterial cell walls are less thick than plant cell walls due to their much smaller size, some viruses have evolved mechanisms that inject their genome into the bacterial cell across the cell wall, while the viral capsid remains outside

Key Points

- Viral entry is the earliest stage of infection in the viral life cycle, as the virus comes into contact with the host cell and introduces viral material into the cell.
- Attachment to the receptor can induce the viral envelope protein to undergo changes that results in the fusion of viral and cellular membranes, or changes of non-enveloped virus surface proteins that allow the virus to enter.
- Virions enter the host cell through receptor-mediated endocytosis or membrane fusion.

Key Terms

- **capsid**: The outer protein shell of a virus.
- **receptors**: In the field of biochemistry, a receptor is a molecule most often found on the surface of a cell, which receives chemical signals originating externally from the cell.
- **virions**: An entire virus particle, consisting of an outer protein shell called a capsid and an inner core of nucleic acid.

This page titled 15.7B: Virus Attachment and Genome Entry is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.8B: Virus Attachment and Genome Entry** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.7C: Viral Replication and Gene Expression

Learning Objectives

- Examine viral gene expression during virus replication

Replication of viruses primarily involves the multiplication of the viral genome. Replication also involves synthesis of viral messenger RNA (mRNA) from “early” genes (with exceptions for positive sense RNA viruses), viral protein synthesis, possible assembly of viral proteins, then viral genome replication mediated by early or regulatory protein expression. This may be followed, for complex viruses with larger genomes, by one or more further rounds of mRNA synthesis: “late” gene expression is, in general, necessary for structural or virion proteins. Viral replication usually takes place in the cytoplasm.

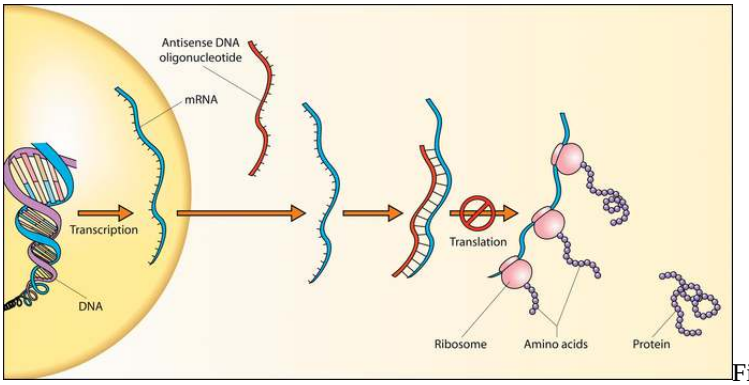


Figure: **DNA to RNA to protein**: Schematic showing how antisense DNA strands can interfere with protein translation.

Viruses that replicate via RNA intermediates need an RNA-dependent RNA- polymerase to replicate their RNA, but animal cells do not seem to possess a suitable enzyme. Therefore, this type of animal RNA virus needs to code for an RNA-dependent RNA polymerase. No viral proteins can be made until viral messenger RNA is available; thus, the nature of the RNA in the virion affects the strategy of the virus: In plus-stranded RNA viruses, the virion (genomic) RNA is the same sense as mRNA and so functions as mRNA. This mRNA can be translated immediately upon infection of the host cell. Examples: poliovirus (picornavirus), togaviruses, and flaviviruses.

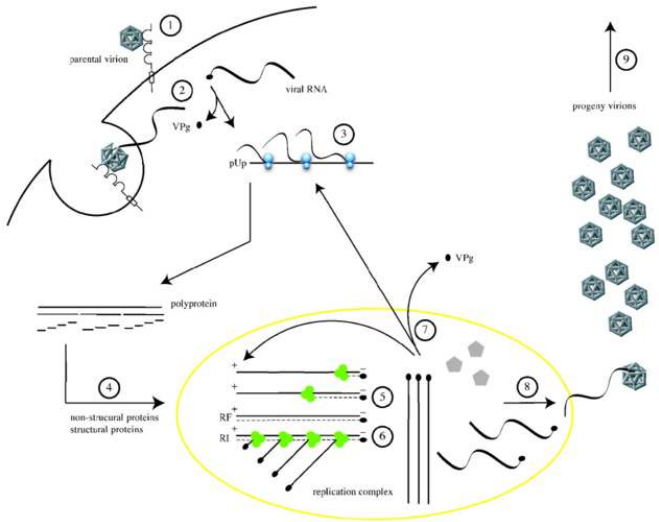


Figure: **The replication cycle of poliovirus**: The cellular life cycle of poliovirus. It is initiated by binding of a poliovirion to the cell surface macromolecule CD155, which functions as the receptor (1). Uncoating of the viral RNA is mediated by receptor-dependent destabilization of the virus capsid (2). Cleavage of the viral protein VPg is performed by a cellular phosphodiesterase, and translation of the viral RNA occurs by a cap-independent (IRES-mediated) mechanism (3). Proteolytic processing of the viral polyprotein yields mature structural and non-structural proteins

(4). The positive-sense RNA serves as template for complementary negative-strand synthesis, thereby producing a double-stranded RNA (replicative form, RF) (5). Initiation of many positive strands from a single negative strand produces the partially single-stranded replicative intermediate (RI) (6). The newly synthesized positive-sense RNA molecules can serve as templates for translation (7) or associate with capsid precursors to undergo encapsidation and induce the maturation cleavage of VP0 (8), which ultimately generates progeny virions. Lysis of the infected cell results in release of infectious progeny virions (9).

RNA viruses are classified into distinct groups depending on their genome and mode of replication (and the numerical groups based on the older Baltimore classification).

Positive-sense ssRNA viruses (Group IV) have their genome directly utilized as if it were mRNA, with host ribosomes translating it into a single protein which is modified by host and viral proteins to form the various proteins needed for replication. One of these includes RNA-dependent RNA polymerase (RNA replicase), which copies the viral RNA to form a double-stranded replicative form, in turn this directs the formation of new virions.

Key Points

- Positive sense, negative sense, double stranded viruses, and retroviruses are RNA viruses with different modes of replication.
- Positive-sense ssRNA viruses (Group IV) have their genome directly utilized as if it were mRNA.
- Replication of viruses involves primarily multiplication of the genome.
- The polarity of single-stranded RNA viruses largely determines the replicative mechanism.

Key Terms

- **genome**: The complete genetic information (either DNA or, in some viruses, RNA) of an organism, typically expressed in the number of basepairs.
- **virus**: A submicroscopic infectious organism, now understood to be a non-cellular structure consisting of a core of DNA or RNA surrounded by a protein coat. It requires a living cell to replicate, and often causes disease in the host organism.
- **replication**: Process by which an object, person, place or idea may be copied mimicked or reproduced.

This page titled 15.7C: Viral Replication and Gene Expression is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.8C: Viral Replication and Gene Expression** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.7D: Viral Exit

Learning Objectives

- Explain how viruses exit host cells

Viral populations do not grow through cell division because they are acellular. Instead, they use the machinery and metabolism of a host cell to produce multiple copies of themselves, and they assemble in the cell. The life cycle of viruses differs between species, but follows the same basic stages.

Viruses can be released from the host cell by lysis, a process that kills the cell by bursting its membrane and cell wall if present. This is a feature of many bacterial and some animal viruses. Some viruses undergo a lysogenic cycle where the viral genome is incorporated by genetic recombination into a specific place in the host's chromosome. The viral genome is then known as a " provirus " or, in the case of bacteriophages a "prophage. " Whenever the host divides, the viral genome is also replicated. The viral genome is mostly silent within the host. However, at some point, the provirus or prophage may give rise to active virus, which may lyse the host cells. Enveloped viruses (e.g., HIV) typically are released from the host cell by budding. During this process the virus acquires its envelope, which is a modified piece of the host's plasma or other, internal membrane.

Viral shedding refers to the successful reproduction, expulsion, and host-cell infection caused by virus progeny. Once replication has been completed and the host cell is exhausted of all resources in making viral progeny, the viruses may begin to leave the cell by several methods.

Different types of virus have varying sites of synthesis and replication. For example, synthesis and replication for DNA viruses occur in the cell's nucleus while it is usually the cytoplasm for RNA viruses. Virus assembly depends on the site of synthesis and such sites are the nucleus, endoplasmic reticulum, and the Golgi apparatus aka Golgi body. Aside from this, assembly also occurs in the viroplasm which is an inclusion body in a cell. When the virus has replicated and multiplied, they would want to leave the infected cell and infect other cells. However, they require an envelope to enclose the DNA as well as to bind with the other healthy cells so that they can infect. The viral envelope is the typical lipid bilayer, derived from the host cell itself and sources usually come from the nuclear membrane, endoplasmic reticulum, Golgi apparatus/body, and plasma membrane. It also depends on where the virus 'bud' off from the host.

Budding is a method which viruses use to exit the cell. "Budding" through the cell envelope, in effect using the cell's membrane for the virus itself is most effective for viruses that need an envelope in the first place. These include enveloped viruses such as HSV, SARS, or smallpox. Prior to budding, the virus may put its own receptor onto the surface of the cell in preparation for the virus to bud through, forming an envelope with the viral receptors already on it. This process will slowly use up the cell membrane and eventually lead to the demise of the cell. This is also how antiviral responses are able to detect virus infected cells.

Other methods for exit would be cell lysis. This method releases the virus from the infected cell by bursting its membrane and this kills the cell as well. Another method is by accumulating the virus particles in vesicles and releasing them via exocytosis. Exocytosis is the process where vesicles containing the virus are secreted/excreted out of the infected cell.

Positive-strand RNA mature virions are infectious. Virions are released following cell lysis. Excess capsids are formed and inclusion bodies may be seen in the cytoplasm.

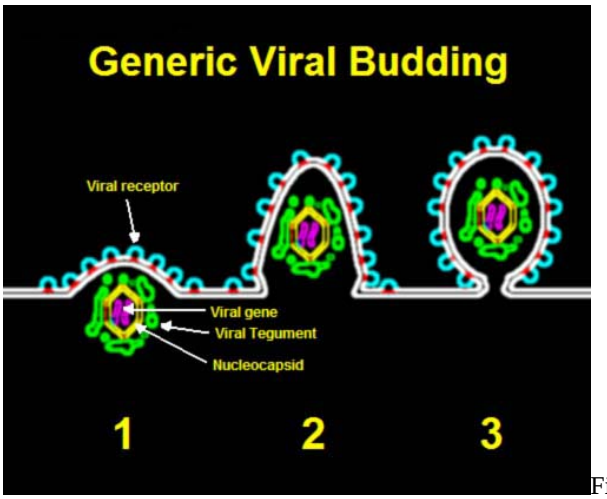


Figure: **Generic Viral Budding**: Viral budding uses the host's cell membrane eventually causing cell death.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: ***CC BY-SA: Attribution-ShareAlike***

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- RNA virus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/RNA_vir...nd_RNA_viruses**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Picornaviruses. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Picornaviruses**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Picornaviruses. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Picornaviruses**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- virus. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/virus**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Boundless. **Provided by**: Boundless Learning. **Located at**: **www.boundless.com//microbiology/definition/rna**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- genetic. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/genetic**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Foot and mouth disease in mouth. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...e_in_mouth.jpg**. **License**: ***Public Domain: No Known Copyright***
- Virus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Virus%2...lication_cycle**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- virions. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/virions**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- receptors. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/receptors**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- capsid. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/capsid**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Foot and mouth disease in mouth. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...e_in_mouth.jpg**. **License**: ***Public Domain: No Known Copyright***
- HepC replication. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:He...eplication.png**. **License**: ***Public Domain: No Known Copyright***
- RNA virus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/RNA_virus**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Virus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Virus%2...lication_cycle**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- genome. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/genome**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- virus. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/virus**. **License**: ***CC BY-SA: Attribution-ShareAlike***

- replication. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/replication**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Foot and mouth disease in mouth. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...e_in_mouth.jpg**. **License**: ***Public Domain: No Known Copyright***
- HepC replication. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:He...eplication.png**. **License**: ***Public Domain: No Known Copyright***
- Poliovirus life cycle. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Po...life_cycle.png**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Sense (molecular biology). **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Sense_(...cular_biology)**. **License**: ***Public Domain: No Known Copyright***
- virions. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/virions**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Virus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Virus%2...lication_cycle**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Viral shedding. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Viral_shedding**. **License**: *CC BY-SA: Attribution-ShareAlike*
- lysogenic. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/lysogenic**. **License**: *CC BY-SA: Attribution-ShareAlike*
- exocytosis. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/exocytosis**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Foot and mouth disease in mouth. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...e_in_mouth.jpg**. **License**: ***Public Domain: No Known Copyright***
- HepC replication. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:He...eplication.png**. **License**: ***Public Domain: No Known Copyright***
- Poliovirus life cycle. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Po...life_cycle.png**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Sense (molecular biology). **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Sense_(molecular_biology)**. **License**: *Public Domain: No Known Copyright*
- Budding of generic virus, pictorial represent. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Budding_of_generic_virus,_pictorial_represent.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*

Key Points

- Once replication has been completed and the host cell is exhausted of all resources in making viral progeny, the viruses may begin to leave the cell by several methods.
- Viral exit methods include budding, exocytosis, and cell lysis.
- Budding through the cell envelope, in effect using the cell's membrane for the virus itself is most effective for viruses that need an envelope.
- This process will slowly use up the cell membrane and eventually lead to the demise of the cell.

Key Terms

- **exocytosis**: The secretion of substances through cellular membranes, either to excrete waste products or as a regulatory function
- **lysogenic**: Of, relating to, or causing lysis.
- **virions**: An entire virus particle, consisting of an outer protein shell called a capsid and an inner core of nucleic acid.

This page titled 15.7D: Viral Exit is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.8D: Viral Exit** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.8: Retroviruses- Double-Stranded RNA Viruses

This page titled 15.8: Retroviruses- Double-Stranded RNA Viruses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.10: Retroviruses- Double-Stranded RNA Viruses** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.8A: Double-Stranded RNA Viruses - Retroviruses

Learning Objectives

- Identify the unique features of retroviruses

A retrovirus is an RNA virus that is duplicated in a host cell using the reverse transcriptase enzyme to produce DNA from its RNA genome. The DNA is then incorporated into the host's genome by an integrase enzyme. The virus thereafter replicates as part of the host cell's DNA. Retroviruses are enveloped viruses that belong to the viral family Retroviridae. A special variant of retroviruses are endogenous retroviruses, which are integrated into the genome of the host and inherited across generations. Endogenous retroviruses are a type of transposon.

The virus itself stores its nucleic acid in the form of an mRNA genome and serves as a means of delivering that genome into cells it targets as an obligate parasite (a parasite that cannot live without its host). That process of delivering the genome into cells constitutes the infection. Once in the host's cell, the RNA strands undergo reverse transcription in the cytoplasm and are integrated into the host's genome, at which point the retroviral DNA is referred to as a provirus. It is difficult to detect the virus until it has infected the host, where the provirus can stay for months, even years, before becoming active and making new infectious viral particles.

In most viruses, DNA is transcribed into RNA, and then RNA is translated into protein. Retroviruses, however, function differently. Their RNA is reverse-transcribed into DNA, which is integrated into the host cell's genome (when it becomes a provirus), and then undergoes the usual transcription and translation processes to express the genes carried by the virus. So, the information contained in a retroviral gene is used to generate the corresponding protein via the sequence: RNA → DNA → RNA → protein. Retroviruses can be pathogens of many different hosts, including humans. A notable retrovirus is Human immunodeficiency virus (HIV), the virus responsible for acquired immunodeficiency syndrome (AIDS). As well as infecting a host, some retroviruses can cause cancer.

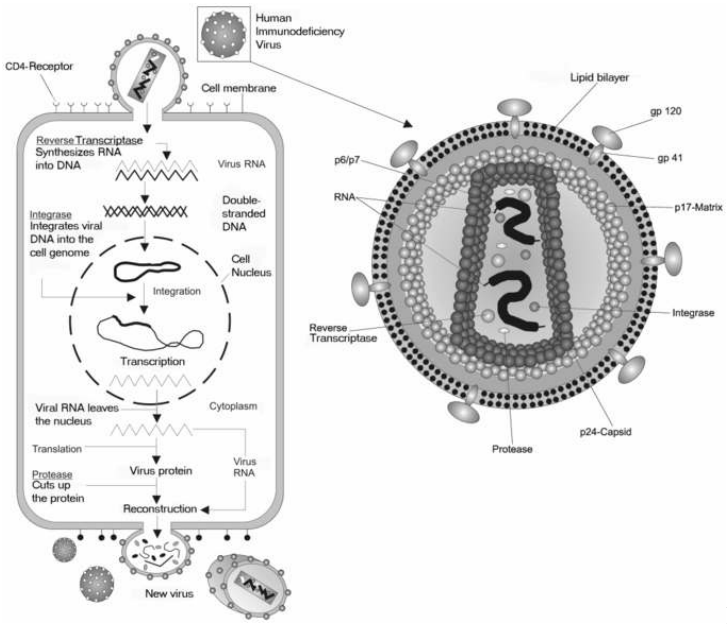


Figure: **HIV viral life cycle**: This diagram depicts the viral life cycle of HIV, from infection, integration into a host genome, reconstruction, and formation of new viral particles. The inset on the left depicts an individual HIV particle.

Finally, retroviruses are proving to be valuable research tools in molecular biology and have been successfully used in gene delivery systems.

Key Points

- In a double stranded RNA form, retroviruses infect a host cell with their genome, and then are reverse transcribed into double stranded DNA, with the DNA then integrated into the home cell genome.
- When integrated into a host genome, a retrovirus is hard to detect and can lay dormant for prolonged periods, having no discernible effect on the host.
- Retroviruses can be human pathogens, and cause many diseases, but have also proven to be invaluable tools when used by molecular biologists.

Key Terms

- **reverse transcriptase**: An enzyme that catalyzes the formation of DNA from RNA; found in retroviruses.
- **transposon**: A segment of DNA that can move to a different position within a genome.
- **integrase**: Any enzyme that integrates viral DNA into that of an infected cell.

This page titled 15.8A: Double-Stranded RNA Viruses - Retroviruses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.10A: Double-Stranded RNA Viruses - Retroviruses** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.8B: HIV Attachment and Host Cell Entry

Learning Objectives

- Define the unique aspects of HIV attachment and host cell entry

HIV entry is the earliest stage of infection in the HIV viral life cycle, occurring when the HIV virus comes into contact with the host cell and introduces viral material into the cell. HIV enters macrophages and CD4-positive T cells (CD4 is a glycoprotein receptor found on cells) by the adsorption of glycoproteins on its surface to receptors on the target cell, followed by fusion of the viral envelope with the cell membrane and the release of the HIV capsid into the cell.

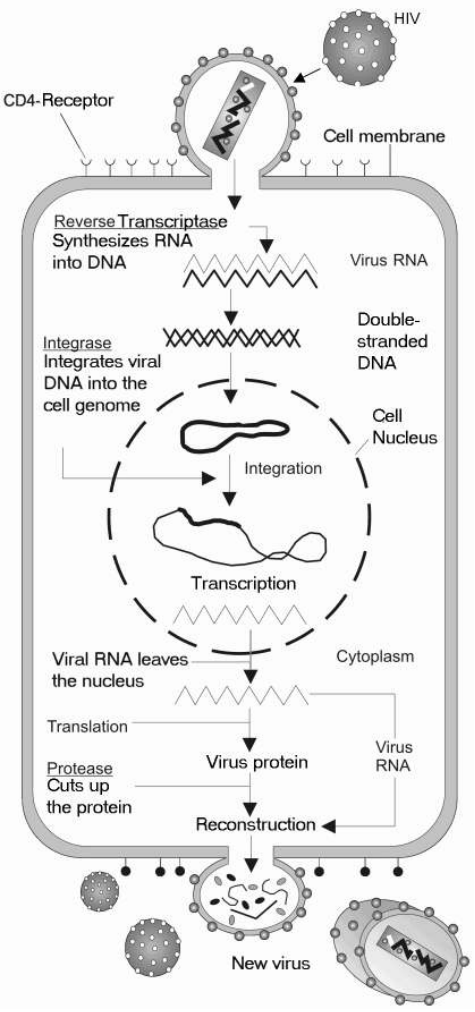


Figure: **HIV Replication**: Steps in the HIV Replication Cycle: Fusion of the HIV cell to the host cell surface.Cell Entry, HIV RNA, reverse transcriptase, integrase, and other viral proteins enter the host cell.Viral DNA is formed by reverse transcription.Viral DNA is transported across the nucleus and integrates into the host DNA.New viral RNA is used as genomic RNA to make viral proteins.New viral RNA and proteins move to cell surface and a new, immature, HIV virus forms.Virus maturation and protease release of individual HIV proteins.

Entry to the cell begins through interaction of the trimeric envelope complex and both CD4 and a chemokine receptor on the host cell on the cell surface. The HIV coat protein, gp120, binds to integrin $\alpha 4\beta 7$, activating LFA-1 (the central integrin involved in the establishment of bridges known as “virological synapses”) which facilitate efficient cell-to-cell spreading of HIV-1.

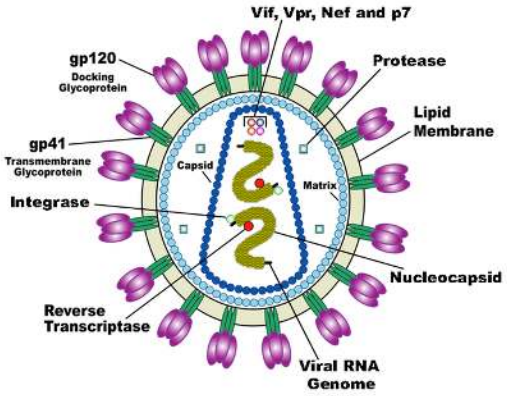


Figure: **Origin of HIV-1 M: An Example of Molecular Clock Application**: The attachment and fusion of HIV virons to host cells are crucial to allowing HIV infection to occur. Shown in purple is gp120 and in green gp41, two proteins crucial in viral docking to host cells.

After attachment, the HIV viron must next fuse with the host cell. The first step in fusion begins after the attachment of the CD4 binding domains of gp120 to CD4. Once gp120 is bound with the CD4 protein, the envelope complex undergoes a structural change, exposing the chemokine binding domains of gp120 and allowing them to interact with the target chemokine receptor. This allows for a more stable two-pronged attachment, which allows the N-terminal fusion peptide gp41 to penetrate the cell membrane. Repeat sequences in gp41, known as HR1 and HR2, then interact, causing the collapse of the extracellular portion of gp41 into a hairpin. This loop structure brings the virus and cell membranes close together, allowing fusion of the membranes and subsequent entry of the viral capsid.

After HIV has bound to the target cell, the HIV RNA and various enzymes (including reverse transcriptase, integrase, ribonuclease, and protease) are injected into the cell. Because HIV attachment is critical for the HIV replication cycle, understanding the specific mechanisms through which HIV attachment occurs has implications for potential treatments of HIV.

Key Points

- HIV proteins bind to specific receptors of host cells, most importantly HIV coat proteins gp41 and gp160.
- After attaching to the host, many of the receptors on both the cell and invading virus bind together for fusion of the virus with its host.
- Because HIV attachment is critical for the HIV replication cycle, understanding the specific mechanisms by which HIV attachment occurs has implications for potential treatments of HIV.

Key Terms

- **glycoprotein**: A protein with covalently bonded carbohydrates.
- **macrophages**: A type of white blood cell that targets foreign material, including bacteria and viruses.
- **capsid**: The outer protein shell of a virus.
- **chemokine**: Any of various cytokines, produced during inflammation, that organize the leukocytes.
- **T cells**: A lymphocyte, from the thymus, that can recognise specific antigens and can activate or deactivate other immune cells.

This page titled 15.8B: HIV Attachment and Host Cell Entry is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.10B: HIV Attachment and Host Cell Entry** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.8C: Retroviral RNA Genome

Learning Objectives

- Discover the features of retroviral genomes

The retroviral while in the viral capsid consists of a dimer RNA. It has a cap at the 5′ end and a poly(A) tail at the 3′ end. The RNA genome also has terminal noncoding regions, which are important in replication, and internal regions that encode virion proteins for gene expression.

The 5′ end includes four regions, which are R, U5, PBS, and L.

- The R region is a short repeated sequence at each end of the genome during the reverse transcription in order to ensure correct end-to-end transfer in growing chain.
- U5, on the other hand, is a short unique sequence between R and PBS.
- PBS (primer binding site) consists of 18 bases complementary to 3′ end of the tRNA primer, which supplies an ‘OH group to initiate reverse transcription.
- The L region is an untranslated leader region that give the signal for packaging of genome RNA.

The 3′ end includes 3 regions, which are PPT (polypurine tract), U3, and R.

- PPT (or PP), polypurine tract is the primer for plus-strand DNA synthesis during reverse transcription.
- U3 is a sequence between PPT and R, which has signal that provirus can use in transcription.
- R is the terminal repeated sequence at 3′ end, the same as the R (i.e., repeat region of the 5′ end).

Inbetween the 5′ and 3′ region is the protein encoding region of the retrovirus, consisting of gag proteins, protease (PR), pol proteins and env proteins. Gag proteins are major components of the viral capsid, which are about 2,000-4,000 copies per virion. Protease is expressed differently in different viruses. It functions in proteolytic cleavages during virion maturation to make mature gag and pol proteins. Pol proteins, such as the reverse transcriptase (RT), are responsible for synthesis of viral DNA and integration into host DNA after infection. Finally, env proteins play a role in association and entry of virion into the host cell. Possessing a functional copy of an env gene is what makes retroviruses distinct from retroelements. The env gene serves three distinct functions: enabling the retrovirus to enter/exit host cells through endosomal membrane trafficking, protection from the extracellular environment via the lipid bilayer, and the ability to enter cells. The ability of the retrovirus to bind to its target host cell using specific cell-surface receptors is given by the surface component (SU) of the env, while the ability of the retrovirus to enter the cell via membrane fusion is imparted by the membrane-anchored trans-membrane component (TM). Thus, the env protein is what enables the retrovirus to be infectious.

Please refer to the figure, in it you see all the elements of a retroviral genome and how they interact to contribute to retroviral reverse transcription and integration.

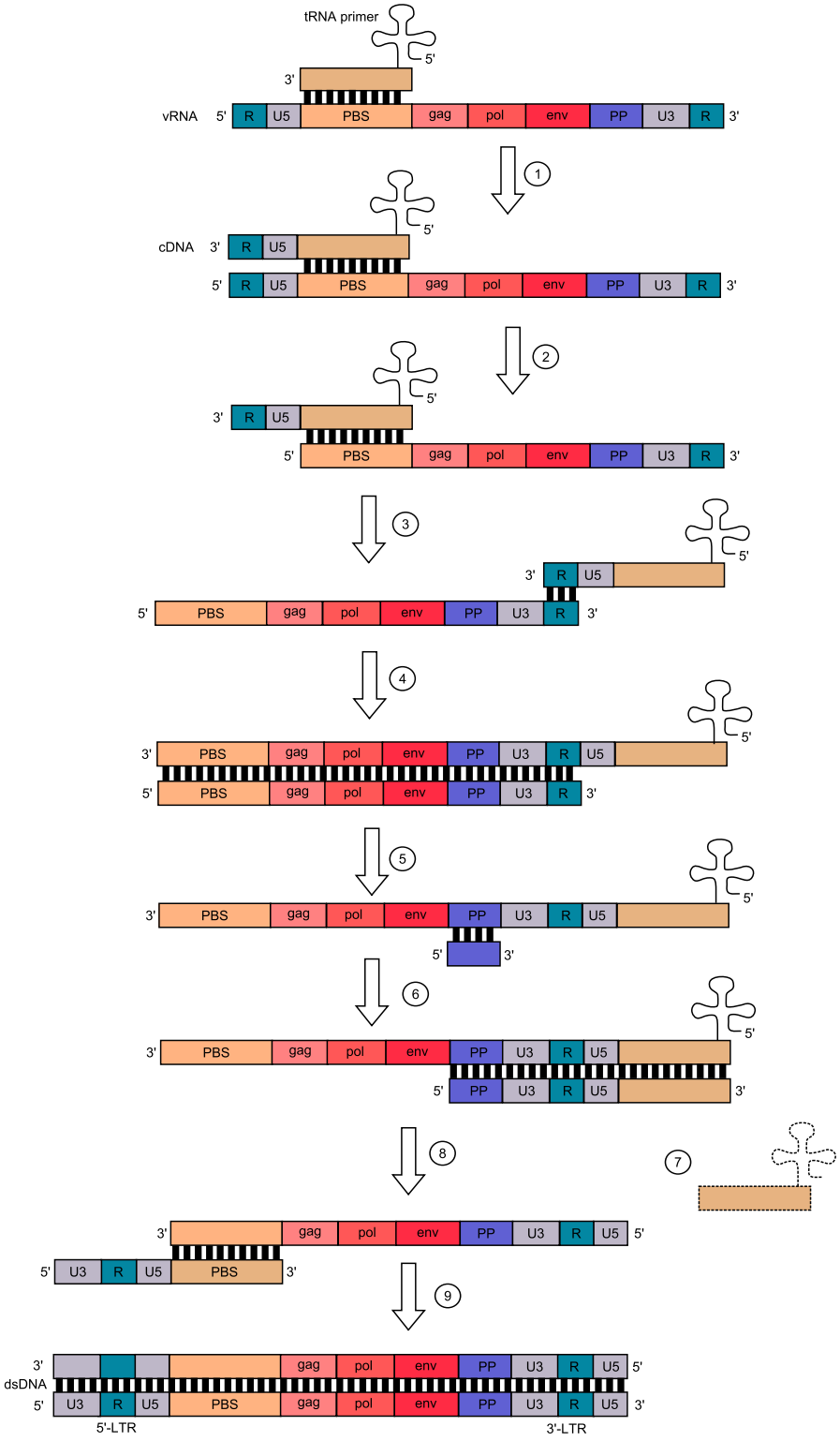


Figure: ***Retroviral genome****: Through the mechanism of reverse transcription by human immunodeficiency virus (HIV), we see what the different genomic elements of a retrovirus are. Reverse transcription occurs in the cytoplasm of host cell. In this process, viral ssRNA is transcribed by the viral reverse transcriptase (RT) into double stranded DNA. Reverse transcription takes place in 5'→3' direction. tRNA ("cloverleaf") hybridizes to PBS and provides -OH group for initiation of reverse transcription. 1) Complementary DNA (cDNA) is formed. 2) Template in RNA:DNA hybrid is degraded by RNase H domain of reverse transcriptase 3) DNA:tRNA is transferred to the 3'-end of the template. 4) First strand synthesis takes place. 5) The rest of viral ssRNA is degraded by RNase H, except for the PP site. 6) Synthesis of second strand of ssDNA is initiated from the 3'-end of the template. tRNA is necessary to synthesis of complementary PBS 7) tRNA is degraded 8) PBS from the second strand hybridizes with the complementary PBS on the first strand. 9) Synthesis of*

https://med.libretexts.org/@go/page/77883

both strands is completed by the DNA Polmerase function of reverse transcriptase. Both dsDNA ends have U3-R-U5 sequences, so called long terminal repeat sequences (3'LTR and 5'LTR, respectively). LTRs mediate integration of the retroviral DNA into another region of the host genome.Key: U3 – promoter region, U5 – recognition site for viral integrase; PBS – primer binding site; PP – polypurine section (polypurine tract); gag, pol, and env. Colors mark complementary sequences.

Key Points

- The ends of a retrovirus, both the 5′ and 3′, contain many elements needed for the retroviral life cycle, including the regions referred to as R, U5, PBS, PPT, and U3.
- In between the 5′ and 3′ ends is the protein coding region which includes the gag, pol, and env encoding regions.
- Key to the unique attributes of a retrovirus is the pol region, which encodes a reverse trancriptase (RT), RT is the enzyme which takes the RNA form of the retrovirus genome and converts into DNA, the DNA form of which can integrate into the host genome.

Key Terms

- **protease**: An enzyme that cuts or cleaves proteins.
- **capsid**: The outer protein shell of a virus.

This page titled 15.8C: Retroviral RNA Genome is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.10C: Retroviral RNA Genome** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.8D: Replicative Cycle of HIV

Learning Objectives

- Compare and contrast HIV replication to other viruses

Human immunodeficiency virus (HIV) is a lentivirus (a member of the retrovirus family) that causes acquired immunodeficiency syndrome (AIDS). AIDS is a condition in humans in which progressive failure of the immune system allows life-threatening opportunistic infections and cancers to thrive. HIV can infect dendritic cells (DCs). DCs are one of the first cells encountered by the virus during sexual transmission. They are currently thought to play an important role by transmitting HIV to T-cells when the virus is captured in the mucosa by DCs. HIV enters macrophages and T cells by the adsorption of glycoproteins on its surface to receptors on the target cell. This is followed by fusion of the viral envelope with the cell membrane and the release of the HIV capsid into the cell.

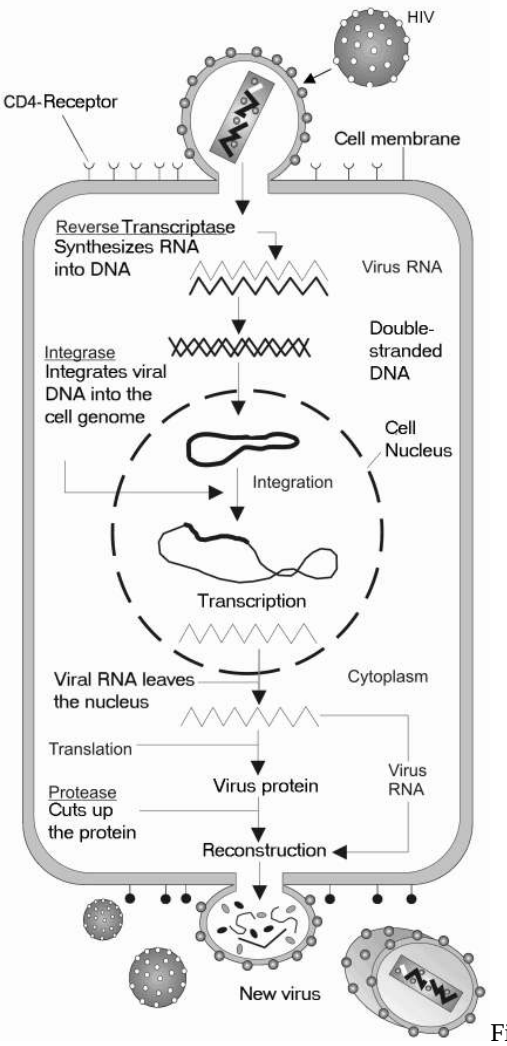


Figure: ***HIV Replication****: Steps in the HIV Replication Cycle: Fusion of the HIV cell to the host cell surface.Cell Entry, HIV RNA, reverse transcriptase, integrase, and other viral proteins enter the host cell.Viral DNA is formed by reverse transcription.Viral DNA is transported across the nucleus and integrates into the host DNA.New viral RNA is used as genomic RNA to make viral proteins.New viral RNA and proteins move to cell surface and a new, immature, HIV virus forms.Virus maturation and protease release of individual HIV proteins.*

Shortly after the viral capsid enters the cell, an enzyme called reverse transcriptase liberates the single-stranded (+)RNA genome from the attached viral proteins and copies it into a complementary DNA (cDNA) molecule. The process of reverse transcription is extremely error-prone, and the resulting mutations may cause drug resistance or allow the virus to evade the body's immune

system. The reverse transcriptase also has ribonuclease activity that degrades the viral RNA during the synthesis of cDNA, as well as DNA-dependent DNA polymerase activity that creates a sense DNA from the antisense cDNA. Together, the cDNA and its complement form a double-stranded viral DNA that is then transported into the cell nucleus.

This integrated viral DNA may then lie dormant, in the latent stage of HIV infection. To actively produce the virus, certain cellular transcription factors need to be present. The most important of these is NF-κB (NF kappa B), which is upregulated when T-cells become activated. This means that those cells most likely to be killed by HIV are those currently fighting infection. During viral replication, the integrated DNA provirus is transcribed into mRNA, which is then spliced into smaller pieces. These small pieces are exported from the nucleus into the cytoplasm, where they are translated into the regulatory proteins Tat (which encourages new virus production) and Rev.

As the newly produced Rev protein accumulates in the nucleus, it binds to viral mRNAs and allows unspliced RNAs to leave the nucleus, where they are otherwise retained until spliced. At this stage, the structural proteins Gag and Env are produced from the full-length mRNA. The full-length RNA is actually the virus genome; it binds to the Gag protein and is packaged into new virus particles. The final step of the viral cycle, assembly of new HIV-1 virions, begins at the plasma membrane of the host cell. The Env polyprotein goes through the endoplasmic reticulum and is transported to the Golgi complex. There, it is cleaved by HIV protease and processed into the two HIV envelope glycoproteins, gp41 and gp120. These are transported to the plasma membrane of the host cell where gp41 anchors gp120 to the membrane of the infected cell. The Gag (p55) and Gag-Pol (p160) polyproteins also associate with the inner surface of the plasma membrane along with the HIV genomic RNA as the forming virion begins to bud from the host cell.

Maturation occurs either in the forming bud or in the immature virion after it buds from the host cell. During maturation, HIV proteases cleave the polyproteins into individual functional HIV proteins. This cleavage step can be inhibited by protease inhibitors. The various structural components then assemble to produce a mature HIV virion. The mature virion is then able to infect another cell.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: *CC BY-SA: Attribution-ShareAlike*

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- Retrovirus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Retrovirus**. **License**: *CC BY-SA: Attribution-ShareAlike*
- integrase. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/integrase**. **License**: *CC BY-SA: Attribution-ShareAlike*
- transposon. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/transposon**. **License**: *CC BY-SA: Attribution-ShareAlike*
- reverse transcriptase. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/reverse_transcriptase**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Hiv gross. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...:Hiv_gross.png**. **License**: *CC BY-SA: Attribution-ShareAlike*
- HIV. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/HIV**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Viral entry. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Viral_entry**. **License**: *CC BY-SA: Attribution-ShareAlike*
- glycoprotein. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/glycoprotein**. **License**: *CC BY-SA: Attribution-ShareAlike*
- macrophages. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/macrophages**. **License**: *CC BY-SA: Attribution-ShareAlike*
- capsid. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/capsid**. **License**: *CC BY-SA: Attribution-ShareAlike*
- chemokine. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/chemokine**. **License**: *CC BY-SA: Attribution-ShareAlike*
- T cells. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/T_cells**. **License**: *CC BY-SA: Attribution-ShareAlike*

- Hiv gross. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...:Hiv_gross.png**. **License**: *CC BY-SA: Attribution-ShareAlike*
- HIV Virion-en. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:HIV_Virion-en.png**. **License**: *Public Domain: No Known Copyright*
- HIV gross cycle only. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:HIV_gross_cycle_only.png**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Retrovirus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Retrovirus**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Retrovirus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Retrovirus**. **License**: *CC BY-SA: Attribution-ShareAlike*
- protease. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/protease**. **License**: *CC BY-SA: Attribution-ShareAlike*
- capsid. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/capsid**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Hiv gross. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...:Hiv_gross.png**. **License**: *CC BY-SA: Attribution-ShareAlike*
- HIV Virion-en. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:HIV_Virion-en.png**. **License**: *Public Domain: No Known Copyright*
- HIV gross cycle only. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:HIV_gross_cycle_only.png**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Reverse transcription. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Reverse_transcription.svg**. **License**: *CC BY: Attribution*
- HIV. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/HIV%23cite_note-Chan2-35**. **License**: *CC BY-SA: Attribution-ShareAlike*
- HIV. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/HIV**. **License**: *CC BY-SA: Attribution-ShareAlike*
- provirus. **Provided by**: Wiktionary. **Located at**: **http://en.wiktionary.org/wiki/provirus**. **License**: *CC BY-SA: Attribution-ShareAlike*
- reverse transcriptase. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/reverse_transcriptase**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Hiv gross. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...:Hiv_gross.png**. **License**: *CC BY-SA: Attribution-ShareAlike*
- HIV Virion-en. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:HIV_Virion-en.png**. **License**: *Public Domain: No Known Copyright*
- HIV gross cycle only. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:HIV_gross_cycle_only.png**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Reverse transcription. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Reverse_transcription.svg**. **License**: *CC BY: Attribution*
- HIV gross cycle only. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:HIV_gross_cycle_only.png**. **License**: *CC BY-SA: Attribution-ShareAlike*

Key Points

- First the HIV viron binds to host cell, after binding the virus and cell fuse, which releases the various enzymes HIV needs to reverse transcribe and integrate into the host genome.
- The reverse transcription of HIV viral RNA to DNA is error prone, causing HIV to have a high mutation rate. This makes it difficult to design treatments against HIV.
- The HIV provirus can stay dormant in the host genome for years. It may become active when the host T cell is itself activated by fighting an infection that the body is facing.
- Understanding the HIV life cycle will help in providing effective treatments against HIV.

Key Terms

- **provirus**: A virus genome, such as HIV, that integrates itself into the DNA of a host cell so as to be passively replicated along with the host genome.
- **reverse transcriptase**: An enzyme that catalyzes the formation of DNA from RNA; found in retroviruses.

This page titled 15.8D: Replicative Cycle of HIV is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.10D: Replicative Cycle of HIV** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.9: Negative-Strand RNA Viruses in Animals

This page titled 15.9: Negative-Strand RNA Viruses in Animals is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.9: Negative-Strand RNA Viruses in Animals** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.9.1: Negative-Strand RNA Viruses of Animals

Learning Objectives

- Explain the mechanism of genome replication in negative-strand RNA viruses

The study of animal viruses is important from a veterinary viewpoint, but many animal viruses are also important from a human medical perspective. The emergence of the SARS virus or Ebola Zaire virus in the human population, coming from an animal source, highlights the importance of animals in bearing infectious agents. In addition, research into animal viruses has made an important contribution to our understanding of viruses in general, including their replication, molecular biology, evolution, and interaction with the host. Animal RNA viruses can be classified according to the sense or polarity of their RNA into negative-sense, positive-sense, or ambisense RNA viruses.



Figure: **Rabies**: Note the salivia dripping from the dog's mouth, a typical sign of a rabies infection. The infection of domestic animals with rabies was common until the 1960s; now most instances of rabies-infected animals are found in the wild.

The RNA found in a negative-sense virus is not infectious by itself, as it needs to be transcribed into positive-sense RNA. The complementary plus-sense mRNA must be made before proteins can be translated from the viral genome. This RNA negative-strand to positive-strand copying is carried out by an RNA-dependent RNA-polymerase. Each virion that has one negative-strand copy can be transcribed to several positive-sense RNAs. There are several different types of negative-strand RNA viruses that infect animals; two families will be discussed here in further detail.

Rhabdoviruses are a diverse family of single-stranded, negative-sense RNA viruses that can successfully utilize a myriad of ecological niches, ranging from plants and insects, to fish and mammals. This virus family includes pathogens —the rabies virus, vesicular stomatitis virus, potato yellow dwarf virus, etc.—that are of tremendous public health, veterinary, and agricultural significance. Due to the relative simplicity of their genomes and morphology, in recent years rhabdoviruses have become powerful model systems for studying molecular virology.

Paramyxoviruses are a diverse family of non-segmented negative-strand RNA viruses that include many highly pathogenic viruses affecting humans, animals, and birds. In recent years the advent of reverse genetics has led to a greater understanding of their genomics, molecular biology, and viral pathogenesis. Paramyxoviruses cause a range of diseases in animal species: canine distemper virus (dogs), phocine distemper virus (seals), cetacean morbillivirus (dolphins and porpoises), Newcastle disease virus (birds), and rinderpest virus (cattle). Some paramyxoviruses, such as the henipaviruses, are zoonotic pathogens, occurring naturally in an animal host, but also able to infect humans.

Key Points

- Negative-strand RNA viruses can infect animals, but in several cases they can go from animals into humans, such as the SARS virus of the Ebola Zaire virus.
- The viron RNA is negative sense (complementary to mRNA and cannot encode proteins), which means it must be replciated over to mRNA before protein production can begin. This is carried out by an RNA-dependent RNA-polymerase.

- Negative-strand viruses can be found in many niches of Earth and are responsible for many common and very deleterious diseases of animals.

Key Terms

- **SARS**: The SARS coronavirus, sometimes shortened to SARS-CoV, is the virus that causes severe acute respiratory syndrome (SARS).
- **RNA-dependent RNA-polymerase**: (RdRP, or RNA replicase) An enzyme that catalyzes the replication of RNA from an RNA template. This is in contrast to a typical DNA-dependent RNA polymerase, which catalyzes the transcription of RNA from a DNA template.

This page titled 15.9.1: Negative-Strand RNA Viruses of Animals is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.9A: Negative-Strand RNA Viruses of Animals** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.9.2: Attachment and Entry to the Host Cell

Learning Objectives

- Explain the role of hemagglutinin in the attachment and entry processes of influenza virus

One of the best understood examples of virus entry into the host cell is the influenza viral infection. The glycoprotein responsible for attachment on the surface of an influenza viral particle is hemagglutinin (HA). HA is an antigenic glycoprotein. It is responsible for binding the virus to the cell that is being infected. HA proteins bind to cells with sialic acid on the membranes, such as cells in the upper respiratory tract or erythrocytes.

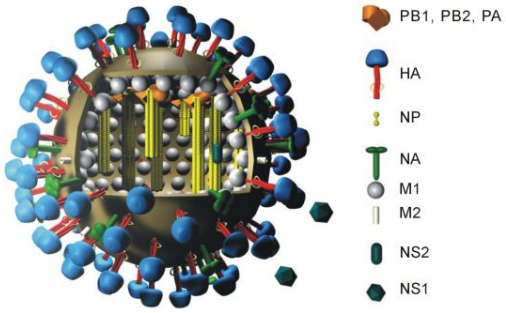


Figure: **Swine influenza**: A depiction of the different structures present on and in an influenza virus. Of special note is HA (hemagglutinin), the glycoprotein critical for influenza attachment and entry into host cells.

HA has two functions. First, it allows the recognition of target vertebrate cells, accomplished through the binding of these cells' sialic acid-containing receptors. Second, once bound, it facilitates the entry of the viral genome into the target cells by causing the fusion of the host endosomal membrane with the viral membrane. HA binds to the monosaccharide sialic acid that is present on the surface of its target cells, which causes the viral particles to stick to the cell's surface. The cell membrane then engulfs the virus and the portion of the membrane that encloses it pinches off to form a new membrane-bound compartment within the cell called an endosome, which contains the engulfed virus. The cell then attempts to begin digesting the contents of the endosome by acidifying its interior and transforming it into a lysosome.

However, as soon as the pH within the endosome drops to about 6.0, the original folded structure of the HA molecule becomes unstable, causing it to partially unfold and release a very hydrophobic portion of its peptide chain that was previously hidden within the protein. This so-called "fusion peptide" acts like a molecular grappling hook by inserting itself into the endosomal membrane and locking on. Then, when the rest of the HA molecule refolds into a new structure (which is more stable at the lower pH), it "retracts the grappling hook" and pulls the endosomal membrane right up next to the virus particle's own membrane, causing the two to fuse together. Once this has happened, the contents of the virus, including its RNA genome, are free to pour out into the cell's cytoplasm.

Key Points

- A glycoprotein on the surface of a virus recognizes a receptor on a host, beginning the attachment process.
- After attachment, the influenza virus is brought into the host cell through an endosome. The low pH of the endosome breaks down the viral capsid and releases the viral contents into the cell.
- A well-described example of this is the influenza virus that relies on hemagglutinin, the glycoprotein that allows the influenza virus to attach to target cells, in this case cells in the human respiratory pathway.

Key Terms

- **endosome**: An endocytic vacuole through which molecules are internalized during endocytosis pass, en route to lysosomes.
- **glycoprotein**: A protein with covalently bonded carbohydrates.
- **sialic**: Of or pertaining to sialic acid or its derivatives.

This page titled 15.9.2: Attachment and Entry to the Host Cell is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.9B: Attachment and Entry to the Host Cell** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.9.3: Replicative Cycle of Influenza A

Learning Objectives

- Contrast the roles of hemagglutinin and neuraminidase throughout the major stages of the replicative cycle of influenza A virus

Influenza A follows the typical life cycle of most influenza viruses. The infection and replication is a multi-step process:

- Binding to and entering the cell
- Delivering the genome to a site where it can produce new copies of viral proteins and RNA
- Assembling these components into new viral particles
- Exiting the host cell

Influenza viruses bind through hemagglutinin onto sialic acid sugars on the surfaces of epithelial cells, typically in the nose, throat, and lungs of mammals, and the intestines of birds (Step 1 in infection figure). After the hemagglutinin is cleaved by a protease, the cell imports the virus by endocytosis.

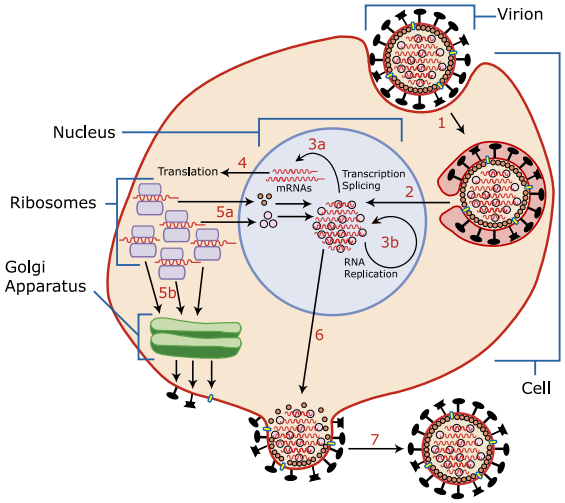


Figure: ***Influenza replication cycle****: Host invasion and replication cycle of an influenza virus. Step 1: Binding Step 2: Entry Step 3: Complex formation and transcription Step 4: Translation Step 5: Secretion Step 6: Assembly Step 7: Release*

The intracellular details are still being worked out. It is known that virions converge to the microtubule organizing center, interact with acidic endosomes, and finally enter the target endosomes for genome release. Once inside the cell, the acidic conditions in the endosome cause two events to happen:

1. The hemagglutinin protein fuses the viral envelope with the vacuole's membrane.
2. The M2 ion channel allows protons to move through the viral envelope and acidify the core of the virus, which causes the core to dissemble and release the viral RNA and core proteins.

The viral RNA (vRNA) molecules, accessory proteins, and RNA-dependent RNA polymerase are then released into the cytoplasm (Step 2 in figure). These core proteins and vRNA form a complex that is transported into the cell nucleus, where the RNA-dependent RNA polymerase begins transcribing complementary positive-sense vRNA (Steps 3a and b in figure).

The vRNA either enters into the cytoplasm and translated (Step 4) or remains in the nucleus. Newly synthesized viral proteins are either secreted through the Golgi apparatus onto the cell surface (in the case of neuraminidase and hemagglutinin, Step 5b) or transported back into the nucleus to bind vRNA and form new viral genome particles (Step 5a).

Other viral proteins have multiple actions in the host cell—including degrading cellular mRNA and using the released nucleotides for vRNA synthesis, and also inhibiting translation of host-cell mRNAs.

Negative-sense vRNAs that form the genomes of future viruses, RNA-dependent RNA polymerase, and other viral proteins are assembled into a virion. Hemagglutinin and neuraminidase molecules cluster into a bulge in the cell membrane. The vRNA and viral core proteins leave the nucleus and enter this membrane protrusion (Step 6). The mature virus buds off from the cell in a sphere of the host phospholipid membrane, acquiring hemagglutinin and neuraminidase with this membrane coat (Step 7). As before, the viruses adhere to the cell through hemagglutinin; the mature viruses detach once their neuraminidase has cleaved sialic acid residues from the host cell. Drugs that inhibit neuraminidase, such as oseltamivir, therefore prevent the release of new infectious viruses and halt viral replication. After the release of new influenza viruses, the host cell dies.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: *CC BY-SA: Attribution-ShareAlike*

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- Animal virology. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Animal_virology**. **License**: *CC BY-SA: Attribution-ShareAlike*
- RNA virus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/RNA_virus%23Single-stranded_RNA_viruses_and_RNA_Sense**. **License**: *CC BY-SA: Attribution-ShareAlike*
- RNA-dependent RNA polymerase. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/RNA-dependent_RNA_polymerase**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Animal virology. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Animal_virology**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Sars virus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Sars_virus**. **License**: *CC BY-SA: Attribution-ShareAlike*
- RNA virus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/RNA_virus%23Single-stranded_RNA_viruses_and_RNA_Sense**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Animal virology. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Animal_virology**. **License**: *CC BY-SA: Attribution-ShareAlike*
- RNA-dependent RNA-polymerase. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/RNA-dep...RNA-polymerase**. **License**: *CC BY-SA: Attribution-ShareAlike*
- SARS. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/SARS**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Rabid dog. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Rabid_dog.jpg**. **License**: *Public Domain: No Known Copyright*
- Hemagglutinin (influenza). **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Hemagglutinin_(influenza)**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Hemagglutinin (influenza). **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Hemagglutinin_(influenza)**. **License**: *CC BY-SA: Attribution-ShareAlike*
- endosome. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/endosome**. **License**: *CC BY-SA: Attribution-ShareAlike*
- glycoprotein. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/glycoprotein**. **License**: *CC BY-SA: Attribution-ShareAlike*
- sialic. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/sialic**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Rabid dog. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Rabid_dog.jpg**. **License**: *Public Domain: No Known Copyright*
- Flu und legende color c. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Flu_und_legende_color_c.jpg**. **License**: *Public Domain: No Known Copyright*
- Influenza. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Influenza%23Replication**. **License**: *CC BY-SA: Attribution-ShareAlike*
- hemagglutinin. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/hemagglutinin**. **License**: *CC BY-SA: Attribution-ShareAlike*
- sialic. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/sialic**. **License**: *CC BY-SA: Attribution-ShareAlike*

- neuraminidase. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/neuraminidase**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Rabid dog. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Rabid_dog.jpg**. **License**: ***Public Domain: No Known Copyright***
- Flu und legende color c. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Flu_und_legende_color_c.jpg**. **License**: ***Public Domain: No Known Copyright***
- Virus Replication large. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Virus_Replication_large.svg**. **License**: ***CC BY-SA: Attribution-ShareAlike***

Key Points

- A component of the viral coat, hemagglutinin, binds to the surface of target cells. After binding, the virus fuses and is imported by endocytosis.
- Once the vRNA is released into the cytoplasm, it is transported into the nucleus where it is transcribed. The resulting vRNAs are then transported into the cytoplasm and new viral particles are made.
- The endosome ‘s acidic environment breaks down the viron coat, releasing the vRNA. The acidic environment also promotes the release of the vRNA to proteins that are bound to it.
- Once new viral particles are made in the host cell and bud off, the host cell dies.

Key Terms

- **neuraminidase**: An antigenic enzyme, found on the surfaces of viruses, that catalyzes the hydrolysis of terminal acylneuraminic residues from oligosaccharides, glycoproteins, and glycolipids.
- **hemagglutinin**: An antigenic glycoprotein that causes agglutination of red blood cells.
- **sialic**: Of or pertaining to sialic acid or its derivatives.

This page titled 15.9.3: Replicative Cycle of Influenza A is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.9C: Replicative Cycle of Influenza A** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.10: DNA Viruses in Eukaryotes

This page titled 15.10: DNA Viruses in Eukaryotes is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.11: DNA Viruses in Eukaryotes** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.10.1: Plant DNA Viruses

Learning Objectives

- Differentiate between ssDNA and dsDNA plant viruses

A DNA virus is a virus with DNA as its genetic material and replicates using a DNA-dependent DNA polymerase. DNA viruses belong to either Group I (double-stranded DNA; dsDNA) or Group II (single-stranded DNA; ssDNA) of the Baltimore classification system for viruses. Single-stranded DNA is usually expanded to double-stranded in infected cells.

DNA viruses are relatively rare in plants. Seventeen percent of plant viruses are ssDNA, while dsDNA viruses infect only lower plants, such as eukaryotic algae. The rarity of dsDNA plant viruses is notable when compared to other taxonomic kingdoms; a quarter of animal viruses and three quarters of bacterial viruses are dsDNA.

Plant viruses are transmitted through a variety of different methods, and generally require breach of protective barriers. Viruses can be spread by direct transfer of sap by contact of a wounded plant with a healthy one, most commonly resulting from agricultural practices, as by damage caused by tools or hands. More often, viruses are spread through vector intermediaries such as insects, nematodes, or protozoa which pick up viruses by feeding on infected plants, and then spread the virus to healthy plants.

Viral transmission from generation to generation occurs in about 20% of plant viruses. When viruses are transmitted by seeds, the seed is infected in the generative cells and the virus is maintained in the germ cells, or occasionally in the seed coat. Little is known about the mechanisms involved in the transmission of plant viruses via seeds, though environment is known to play a key role.

Single-Stranded DNA Viruses



Figure: **Geminiviruses**: Drawing of geminiviruses, characterized by elongated, geminate capsids with two incomplete T=1 icosahedra joined at the missing vertex.

The *Geminiviridae* and *Nanoviridae* are the two families of ssDNA viruses known to infect plants. *Geminiviridae* is the largest known family of single-stranded DNA viruses. It contains a wide range of plant viruses including bean golden mosaic virus, beet curly top virus, maize streak virus, and tomato pseudo-curly top virus, which together are responsible for a significant amount of crop damage worldwide. The genome can either be a single component between 2500-3100 nucleotides, or, in the case of some begomoviruses, two similar-sized components each between 2600 and 2800 nucleotides. They have elongated, geminate capsids with two incomplete T=1 icosahedra joined at the missing vertex. The capsids range in size from 18-20 nm in diameter with a length of about 30 nm. Begomoviruses possess two component genomes separated into two different particles, both of which must usually be transmitted together to initiate a new infection within a suitable host cell. Like many viruses, geminivirus genomes encode only a few proteins, and are therefore dependent on host cell factors for replication. Geminiviruses replication occurs within the nucleus of an infected plant cell via a rolling circle mechanism, similar to that seen in bacteriophages, such as M13, and many plasmids. The resulting ssDNA is packaged into germinate particles in the nucleus. It is not clear if these particles can then leave the nucleus and be transmitted to surrounding cells as virions, or whether ssDNA is trafficked from cell to cell via the plasmodesmata. These viruses tend to be introduced into and initially infect differentiated plant cells, via the piercing mouthparts of the vector insect: however, these cells generally lack the host enzymes necessary for DNA replication, making it difficult for the virus to replicate. To overcome this block geminiviruses can induce plant cells to reenter the cell cycle from a quiescent state so that viral replication can occur.

The *Nanoviridae* are a family of single-stranded DNA viruses that infect plants. Their name is derived from the Greek word 'nano' (dwarf) because of their small genome and their stunting effect on infected plants.

 Figure: **Maize Streak Virus**: The black-faced leafhopper (Graminella nigrifrons) transmits both maize fine streak virus and maize chlorotic dwarf virus.

Virions of this family have a capsid and are non-enveloped. The capsid is icosahedral with diameter of 18-20 nm. The genome is composed of 6 to 11 segments of single-stranded circular DNA each ~1 kb in length, with the exact number of segments varying depending on the genus. The segments each encode a single protein. There is a putative stem loop structure in the non-coding region of each segment which has a conserved 9-nucleotide sequence at its apex. Each member has up to 4 segments encoding replication proteins of ~33 kDa. The other segments encode products of 10-20 kDa in size and include a coat protein of ~19 kDa and a protein with a retinoblastoma binding motif.

Double-Stranded DNA Viruses

Double-stranded DNA viruses of plants are rare, and only infect lower plants, such as algae. These viruses (family *Phycodnaviridae*) are huge dsDNA viruses with genomes ranging from 160 to 560 kb with up to 600 protein-encoding genes, making them distinctly different from viruses infecting higher plants. They are found in aqueous environments throughout the world and play dynamic, albeit largely undocumented, roles in regulating algal communities such as the termination of massive algal blooms commonly referred to as red and brown tides.

Key Points

- DNA viruses are relatively rare in plants, compared to their RNA counterparts.
- Like most viruses, the genomes of most single stranded DNA viruses are small, encoding only a few proteins, and are therefore dependent on host cell factors for replication.
- Double stranded DNA viruses only infect lower species of plants, such as algae. These viruses are huge dsDNA viruses with genomes ranging from 160 to 560 kb with up to 600 protein-encoding genes, making them distinctly different from viruses infecting higher plants.
- Plant viruses are generally spread through vectors, such as insects, but can also be passed from generation to generation.

Key Terms

- **Baltimore Classification System**: The Baltimore classification, developed by David Baltimore, is a virus classification system that groups viruses into families, depending on their type of genome (DNA, RNA, single-stranded (ss), double-stranded (ds), etc.) and their method of replication.
- **plasmodesmata**: Plasmodesmata (singular: plasmodesma) are microscopic channels which traverse the cell walls of plant cells and some algal cells, enabling transport and communication between them.
- **capsid**: The outer protein shell of a virus.

This page titled 15.10.1: Plant DNA Viruses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.11A: Plant DNA Viruses** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.10.2: Replication of Double-Stranded DNA Viruses of Animals

Learning Objectives

- Differentiate the ways which different classes of dsDNA viruses replicate

Viral replication is the formation of biological viruses during the infection process in the target host cells. Viruses must first get into the cell before viral replication can occur. From the perspective of the virus, the purpose of viral replication is to allow production and survival of its kind. By generating abundant copies of its genome and packaging these copies into viruses, the virus is able to continue infecting new hosts. Replication between viruses is greatly varied and depends on the type of genes involved in them. Most DNA viruses assemble in the nucleus while most RNA viruses develop solely in cytoplasm.

Double-stranded DNA viruses usually must enter the host nucleus before they are able to replicate. Some of these viruses require host cell polymerases to replicate their genome, while others, such as adenoviruses or herpes viruses, encode their own replication factors. However, in either cases, replication of the viral genome is highly dependent on a cellular state permissive to DNA replication and, thus, on the cell cycle. The virus may induce the cell to forcefully undergo cell division, which may lead to transformation of the cell and, ultimately, cancer. An example of a family within this classification is the Adenoviridae.

Polyomaviruses, adenoviruses, and herpesviruses are all nuclear-replicating DNA viruses, each with their own specific approaches to replication. There is only one well-studied example in which a double-stranded DNA virus does not replicate within the nucleus. This is the Poxvirus family, which comprises highly pathogenic viruses that infect vertebrates.

Polyomaviruses

Polyomaviridae is a family of viruses whose natural hosts are primarily mammals and birds. Most of these viruses, such as BK virus and JC virus, are very common and typically asymptomatic in most human populations studied. However, some polyomaviruses are associated with human disease, particularly in immunocompromised individuals. Some members of the family are oncoviruses, meaning they can cause tumors; they often persist as latent infections in a host without causing disease, but may produce tumors in a host of a different species, or in individuals with ineffective immune systems. The name polyoma refers to the viruses' ability to produce multiple (poly-) tumors (-oma).

Replication

Prior to genome replication, the processes of viral attachment, entry and uncoating occur. Polyomavirus virions are subsequently endocytosed and transported first to the endoplasmic reticulum where a conformational change occurs; then by an unknown mechanism the virus is exported to the nucleus. Polyomaviruses replicate in the nucleus of the host.

Adenoviruses

Adenoviruses (members of the family Adenoviridae) are medium-sized (90–100 nm), nonenveloped (without an outer lipid bilayer) viruses with an icosahedral nucleocapsid containing a double stranded DNA genome.

Adenoviruses represent the largest nonenveloped viruses. They are able to be transported through the endosome (i.e., envelope fusion is not necessary). The virion also has a unique "spike" or fiber associated with each penton base of the capsid that aids in attachment to the host cell via the receptor on the surface of the host cell.

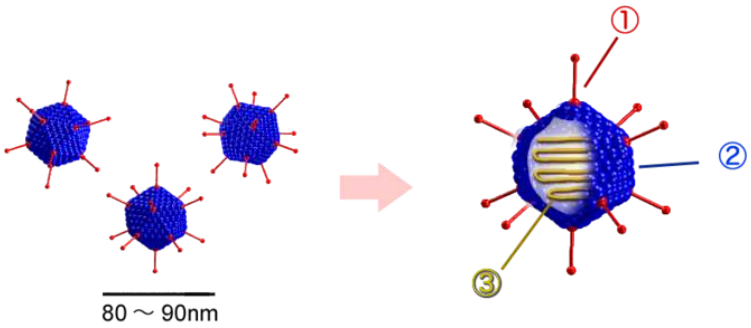


Figure: **Adenovirus structure**: Adenoviruses are non-enveloped (i.e., they have no external lipid bilayer) and are icosahedral (i.e., shaped like a polyhedron with 20 faces). They have fibers at their vertices that help them attach to host cells.

Replication

Adenoviruses possess a linear dsDNA genome and are able to replicate in the nucleus of vertebrate cells using the host's replication machinery.

Once the virus has successfully gained entry into the host cell, the endosome acidifies, which alters virus topology by causing capsid components to disband, which in turn destroys the endosome and allows the virion entry into the cytoplasm. It is transported to the nuclear pore, disassembles, and is released into the nucleus. At this point viral gene expression can occur and new virus particles can be generated.

Herpesviruses

Herpesviridae is a large family of DNA viruses that cause diseases in animals, including humans. The members of this family are also known as herpesviruses. The family name is derived from the Greek word herpein ("to creep"), referring to the latent, recurring infections typical of this group of viruses. Herpesviridae can cause latent or lytic infections.

At least five species of Herpesviridae – HSV-1 and HSV-2 (both of which can cause orolabial herpes and genital herpes), Varicella zoster virus (which causes chicken-pox and shingles), Epstein-Barr virus (which causes mononucleosis), and Cytomegalovirus – are extremely widespread among humans. More than 90% of adults have been infected with at least one of these, and a latent form of the virus remains in most people. In total, there are 8 herpesvirus types that infect humans: herpes simplex viruses 1 and 2, varicella-zoster virus, EBV (Epstein-Barr virus), human cytomegalovirus, human herpesvirus 6, human herpesvirus 7, and Kaposi's sarcoma-associated herpesvirus. There are more than 130 herpesviruses, and some are from mammals, birds, fish, reptiles, amphibians, and molluscs.

Replication

All herpesviruses are nuclear-replicating—the viral DNA is transcribed to mRNA within the infected cell's nucleus. Infection is initiated when a viral particle contacts a cell with specific types of receptor molecules on the cell surface. Following binding of viral envelope glycoproteins to cell membrane receptors, the virion is internalized and dismantled, allowing viral DNA to migrate to the cell nucleus. Within the nucleus, replication of viral DNA and transcription of viral genes occurs.

Poxviruses

Poxviridae is a family of viruses. Human, vertebrates, and arthropods serve as natural hosts. There are currently 69 species in this family, divided among 28 genera, which are divided into two subfamilies. Diseases associated with this family include smallpox.

Poxviridae viral particles (virions) are generally enveloped (external enveloped virion- EEV), though the intracellular mature virion (IMV) form of the virus, which contains different envelope, is also infectious. The virion is exceptionally large—around 200 nm in diameter and 300 nm in length.

Replication

The replication of poxvirus is unusual for a virus with double-stranded DNA genome (dsDNA) because it occurs in the cytoplasm, although this is typical of other large DNA viruses. Poxvirus encodes its own machinery for genome transcription, a DNA dependent RNA polymerase, which makes replication in the cytoplasm possible. Most dsDNA viruses require the host cell's DNA-dependent RNA polymerase to perform transcription. These host DNA are found in the nucleus, and therefore most dsDNA viruses carry out a part of their infection cycle within the host cell's nucleus.

Key Points

- From the perspective of the virus, the purpose of viral replication is to allow production and survival of its kind.
- Most double-stranded DNA viruses replicate within the host cell nucleus, including polyomaviruses, adenoviruses, and herpesviruses—poxviruses, however, replicate in the cytoplasm.
- Adenoviruses and herpes viruses encode their own replication factors.

Key Terms

- **Okazaki fragments**: Okazaki fragments are short, newly synthesized DNA fragments that are formed on the lagging template strand during DNA replication.
- **polymerase**: Any of various enzymes that catalyze the formation of polymers of DNA or RNA using an existing strand of DNA or RNA as a template.

This page titled 15.10.2: Replication of Double-Stranded DNA Viruses of Animals is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.11B: Replication of Double-Stranded DNA Viruses of Animals** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.10.3: Double-Stranded DNA Viruses - Herpesviruses

Learning Objectives

- Recognize the attributes of herpes viruses

Herpesviridae is a large family of DNA viruses that cause diseases in animals, including humans. The members of this family are also known as herpes viruses. The family name is derived from the Greek word *herpein* ("to creep"), referring to the latent, recurring infections typical of this group of viruses.

Animal herpes viruses all share some common properties. The structure of these viruses consists of a relatively large double-stranded, linear DNA genome encased within an icosahedral protein cage called the capsid, which is wrapped in a lipid bilayer called the envelope. The envelope is joined to the capsid by means of a tegument. This complete particle is known as the virion. HSV-1 and HSV-2 each contain at least 74 genes within their genomes, although speculation over gene crowding allows as many as 84 unique protein-coding genes by 94 putative pen reading frames. These genes encode a variety of proteins involved in forming the capsid, tegument and envelope of the virus, as well as controlling the replication and infectivity of the virus.

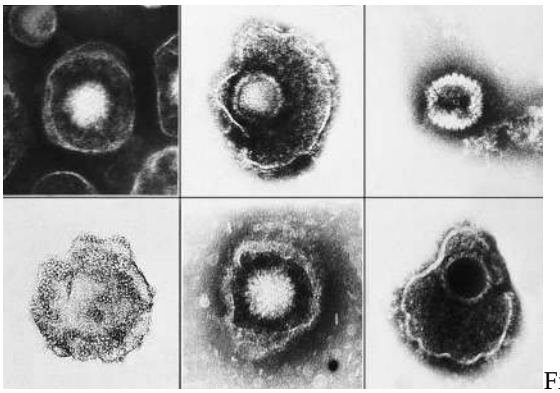


Figure: **Herpesviridae**: Various viruses from the Herpesviridae family seen using an electron micrograph Amongst these members is varicella-zoster (Chickenpox), and herpes simplex type 1 and 2 (HSV-1, HSV-2).

Types of herpes viruses

There are nine distinct herpes viruses which cause disease in humans:

- HHV-1 Herpes simplex virus-1 (HSV-1)
- HHV-2 Herpes simplex virus-2 (HSV-2)
- HHV-3 Varicella zoster virus (VZV)
- HHV-4 Epstein-Barr virus (EBV)
- HHV-5 Cytomegalovirus (CMV)
- HHV-6A/B Roseolovirus, Herpes lymphotropic virus
- HHV-7 Pityriasis Rosea
- HHV-8 Kaposi's sarcoma-associated herpesvirus

Of particular interest include HSV-1 and HSV-2, which cause oral and/or genital herpes, HSV-3 which causes chickenpox and shingles, and HHV-5 which causes mononucleosis-like symptoms, and HHV-8 which causes a Kaposi's sarcoma, a cancer of the lymphatic epithelium.

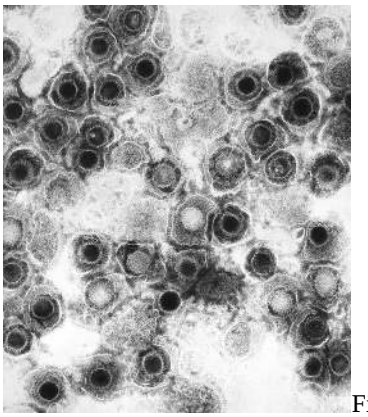


Figure: **Herpes Simplex Virions**: This negatively-stained transmission electron micrograph (TEM) revealed the presence of numerous herpes simplex virions, members of the Herpesviridae family. There are two strains of the herpes simplex virus, HSV-1, which is responsible for cold sores, and HSV-2, which is responsible for genital herpes. At the core of its icosahedral proteinaceous capsid, the HSV contains a double-stranded DNA linear genome.

Infection is caused through close contact with an infected individual. Infection is initiated when a viral particle comes in contact with the target cell specific to the individual herpes virus. Viral glycoproteins bind cell surface receptors molecules on the cell surface, followed by virion internalization and disassembly. Viral DNA then migrates to the cell nucleus where replication of viral DNA and transcription of viral genes occurs.

During symptomatic infection, infected cells transcribe lytic viral genes. In some host cells, a small number of viral genes termed *latency-associated transcripts* accumulate instead. In this fashion, the virus can persist in the cell (and thus the host) indefinitely. While primary infection is often accompanied by a self-limited period of clinical illness, long-term latency is symptom-free.

Reactivation of latent viruses

This has been implicated in a number of diseases (e.g. Shingles, Pityriasis Rosea). Following activation, transcription of viral genes transitions from latency-associated transcripts to multiple lytic genes; these lead to enhanced replication and virus production. Often, lytic activation leads to cell death. Clinically, lytic activation is often accompanied by emergence of non-specific symptoms such as low grade fever, headache, sore throat, malaise, and rash, as well as clinical signs such as swollen or tender lymph nodes, and immunological findings such as reduced levels of natural killer cells.

There is no method to eradicate the herpes virus from the body, but antiviral medications, such as *acyclovir*, can reduce the frequency, duration, and severity of outbreaks. Analgesics such as *ibuprofen* and *acetaminophen* can reduce pain and fever. Topical anesthetic treatments such as *prilocaine*, *lidocaine*, *benzocaine* or *tetracaine* can also relieve itching and pain.

Key Points

- Herpesviridae is a large family of DNA viruses that cause diseases in animals, including humans.
- The structure of herpes viruses consists of a relatively large double-stranded, linear DNA genome encased within an icosahedral protein cage called the capsid, which is wrapped in a lipid bilayer called the envelope.
- Notable herpes viruses include herpes simplex viruses 1 and 2, Varicella zoster virus (the causative agent of shingles and chicken pox), cytomegalovirus, and Kaposi's sarcoma virus.
- There is no method to eradicate herpes virus from the body, but antiviral medications, such as acyclovir, can reduce the frequency, duration, and severity of outbreaks.

Key Terms

- **tegument**: A natural covering of the body or of a bodily organ.
- **capsid**: The outer protein shell of a virus.
- **virion**: A single individual particle of a virus (the viral equivalent of a cell).

This page titled 15.10.3: Double-Stranded DNA Viruses - Herpesviruses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.11C: Double-Stranded DNA Viruses - Herpesviruses** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.10.4: Attachment and Entry of Herpes Simplex

Learning Objectives

- Illustrate HSV attachment to host cells

Herpes simplex viruses 1 and 2 (HSV-1 and HSV-2) are two members of the herpes virus family, *Herpesviridae*, that infect humans. Both HSV-1 (which produces most cold sores) and HSV-2 (which produces most genital herpes) are ubiquitous and contagious. They can be spread when an infected person is producing and shedding the virus.

The sequential stages of HSV entry are analogous to those of other viruses. At first, complementary receptors on the virus and the cell surface bring the viral and cell membranes into close proximity. In an intermediate state, the two membranes begin to merge, forming a hemifusion state. Finally, a stable entry pore is formed through which the viral envelope contents are introduced to the host cell.

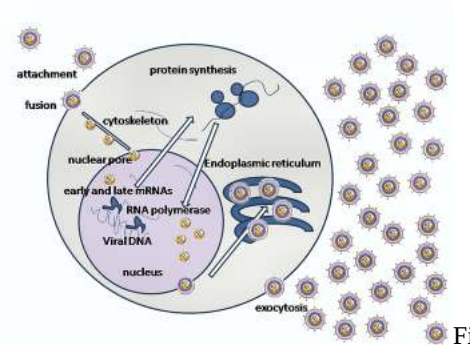


Figure: **Virus replication**: Herpes simplex virus attaches to host cell surface receptors using glycoproteins. Following attachment, the viral envelope fuses with the host cell membrane and the viral capsid gains entry into the cell.

The genome encodes for 11 different glycoproteins, four of which, gB, gC, gD and gH, are involved in viral attachment. Initial interactions occur when viral envelope glycoprotein C (gC) binds to a cell surface particle called heparan sulfate. A second glycoprotein, glycoprotein D (gD), binds specifically to at least one of three known entry receptors. These include herpesvirus entry mediator (HVEM), nectin-1 and 3-O sulfated heparan sulfate. The receptor provides a strong, fixed attachment to the host cell. These interactions bring the membrane surfaces into mutual proximity and allow for other glycoproteins embedded in the viral envelope to interact with other cell surface molecules. Once bound to the HVEM, gD changes its conformation and interacts with viral glycoproteins H (gH) and L (gL), which form a complex. The interaction of these membrane proteins results in the hemifusion state. Afterward, gB interaction with the gH/gL complex creates an entry pore for the viral capsid. Glycoprotein B interacts with glycosaminoglycans on the surface of the host cell.

Key Points

- The genome encodes for 11 different glycoproteins, four of which, gB, gC, gD and gH, are involved in viral attachment.
- The sequential stages of HSV entry are analogous to those of other viruses.
- First, complementary viral and cell surface receptors bring the viral and host cell membranes into close proximity. Next, the two membranes begin to merge, forming a hemifusion state. Finally, a stable entry pore is formed through which the viral envelope contents are introduced to the host cell.

Key Terms

- **glycoprotein**: A protein with covalently bonded carbohydrates.
- **hemifusion**: Partial fusion, or the first stage in full fusion.
- **heparan sulfate**: A polysaccharide found, associated with protein, in all animal tissue; it has a regulatory function in several biological activities.

This page titled 15.10.4: Attachment and Entry of Herpes Simplex is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.11E: Attachment and Entry of Herpes Simplex** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.10.5: Replication of Herpes Simplex Virus

Learning Objectives

- List the treatments we have to combat viruses

The study of animal viruses is important from a veterinary viewpoint. Many animal viruses are also important from a human medical perspective. The emergence of the SARS virus in the human population, coming from an animal source, highlights the importance of animals in bearing infectious agents. Avian influenza viruses can directly infect humans. In addition research into animal viruses has made an important contribution to our understanding of viruses in general, their replication, molecular biology, evolution, and interaction with the host.

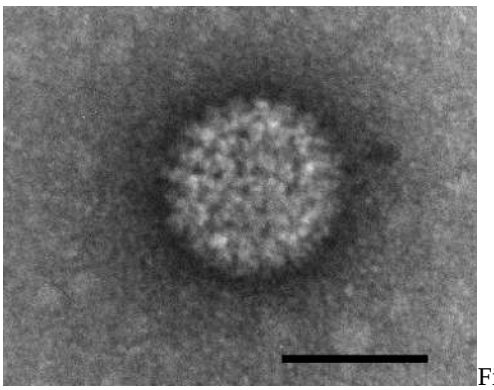


Figure: **TEM of the Bluetongue virus**: Bluetongue virus (BTV), a member of Orbivirus genus within the Reoviridae family causes serious disease in livestock (sheep, goat, cattle).

Rhabdoviruses are a diverse family of single stranded, negative sense RNA viruses that can successfully utilize a myriad of ecological niches, ranging from plants and insects, to fish and mammals. This virus family includes pathogens such as rabies virus, vesicular stomatitis virus, and potato yellow dwarf virus that are of tremendous public health, veterinary, and agricultural significance. Due to the relative simplicity of their genomes and morphology, in recent years rhabdoviruses have become powerful model systems for studying molecular virology.

Foot and mouth disease virus (FMDV) is the prototypic member of the Aphthovirus genus in the Picornaviridae family. This picornavirus is the etiological agent of an acute systemic vesicular disease that affects cattle worldwide, foot-and-mouth disease. FMDV is a highly variable and transmissible virus. It enters the body through inhalation. Soon after infection, the single stranded positive RNA that constitutes the viral genome is efficiently translated using a cap-independent mechanism driven by the internal ribosome entry site element (IRES). This process occurs concomitantly with the inhibition of cellular protein synthesis, caused by the expression of viral proteases. In depth knowledge of the molecular basis of the viral cycle is needed to control viral pathogenesis and disease spreading.

Pestiviruses account for important diseases in animals such as Classical swine fever (CSF) and Bovine viral diarrhea / Mucosal disease (BVD/MD). The molecular biology of pestiviruses shares many similarities and peculiarities with the human hepaciviruses. Genome organization and translation strategy are highly similar for the members of both genera. One hallmark of pestiviruses is their unique strategy to establish persistent infection during pregnancy.

Coronavirus (CoV) genome replication takes place in the cytoplasm in a membrane-protected microenvironment, and starts with the translation of the genome to produce the viral replicase.

The first line of defense against viral infections is usually antiviral vaccines, which prime the body’s immune system against specific pathogens. Vaccines traditionally consist of an attenuated (weakened or killed) version of the virus, although many vaccines now target specific immunogenic targets unique to a particular pathogen. Both viral and cellular proteins are required for replication and transcription. CoVs initiate translation by cap-dependent and cap-independent mechanisms. Cell macromolecular synthesis may be controlled after CoV infection by locating some virus proteins in the host cell nucleus. Infection by different coronaviruses cause in the host alteration in the transcription and translation patterns, in the cell cycle, the cytoskeleton, apoptosis

and coagulation pathways, inflammation, and immune and stress responses. The balance between genes up- and down-regulated could explain the pathogenesis caused by these viruses.

Antiviral drugs are a class of medication used specifically for treating viral infections. Like antibiotics for bacteria, antiviral drugs are usually specific for a particular virus. Unlike most antibiotics, antiviral drugs do not destroy their target pathogen; instead they inhibit their development.

In addition to targeting viral infections directly, some therapeutics work by enhancing the immune responses necessary for viral clearance. One of the best-known of this class of drugs are interferons, which inhibit viral synthesis in infected cells. Interferons (IFNs) play pivotal roles in shaping the immune responses in mammals and are particularly important for the control of viral infections, cell growth, and immune regulation. These proteins rapidly induce an “anti-viral state” in cells that surround infected cells. In order to survive, viruses have evolved multiple strategies to evade the anti-viral effects of IFNs. Elucidating the molecular and cellular biology of the virus-interferon interaction is key to understanding issues such as viral pathogenesis, latency, and the development of novel antivirals.


Figure: **Pediatric polio vaccination in India by a Stop Transmission of Polio (STOP) teams (2002)**: Vaccinations are the best defense against a wide range of viruses, but they are not effective in treating active infections.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: ***CC BY-SA: Attribution-ShareAlike***

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- Baltimore classification. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Baltimore_classification**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Nanoviridae. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Nanoviridae**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- DNA virus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/DNA_virus**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Plant virus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Plant_virus**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- MicrobiologyBytesplants Archives u00bb MicrobiologyBytes. **Provided by**: Microbiology Bytes. **Located at**: **www.microbiologybytes.com/blog/tag/plants/**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Geminiviridae. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Geminiviridae**. **License**: ***CC BY-SA: Attribution-ShareAlike***

- DNA virus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/DNA_virus**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Plant virus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Plant_v..._plant_viruses**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Baltimore Classification System. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Baltimo...ation%20System**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- plasmodesmata. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/plasmodesmata**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- capsid. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/capsid**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Leafhopper. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Leafhopper.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Geminiviruses drawing. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ge...es_drawing.png**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Viral replication. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Viral_replication**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Adenoviridae. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Adenoviridae**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Polyomaviridae. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Polyomaviridae**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Poxviridae. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Poxviridae**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Herpesviridae. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Herpesviridae**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- polymerase. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/polymerase**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Okazaki fragments. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Okazaki%20fragments**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Leafhopper. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Leafhopper.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Geminiviruses drawing. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ge...es_drawing.png**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Adenovirus_structure.png. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/F..._structure.png**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Herpes simplex virus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Herpes_...iral_structure**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Herpesviridae. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Herpesviridae**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Varicella zoster virus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Varicella_zoster_virus**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Herpes simplex. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Herpes_simplex**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- capsid. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/capsid**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- virion. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/virion**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- tegument. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/tegument**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Leafhopper. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Leafhopper.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Geminiviruses drawing. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ge...es_drawing.png**. **License**: ***CC BY-SA: Attribution-ShareAlike***

- Adenovirus_structure.png. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/F..._structure.png**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Herpesviridae_EM_PHIL_2171_lores.jpg. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/F...2171_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- Herpes simplex virions, TEM. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...rions,_TEM.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Herpes simplex virus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Herpes_simplex_virus**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Herpes simplex virus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Herpes_simplex_virus**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- glycoprotein. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/glycoprotein**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- hemifusion. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/hemifusion**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- heparan sulfate. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/heparan_sulfate**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Leafhopper. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Leafhopper.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Geminiviruses drawing. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ge...es_drawing.png**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Adenovirus_structure.png. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/F..._structure.png**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Herpesviridae_EM_PHIL_2171_lores.jpg. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/F...2171_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- Herpes simplex virions, TEM. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...rions,_TEM.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- **Provided by**: Wikimedia. **Located at**: **upload.wikimedia.org/wikipedi...eplication.png**. **License**: ***Public Domain: No Known Copyright***
- Herpes simplex virus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Herpes_simplex_virus**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- nucleocapsid. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/nucleocapsid**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Leafhopper. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Leafhopper.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Geminiviruses drawing. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ge...es_drawing.png**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Adenovirus_structure.png. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/F..._structure.png**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Herpesviridae_EM_PHIL_2171_lores.jpg. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/F...2171_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- Herpes simplex virions, TEM. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...rions,_TEM.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- **Provided by**: Wikimedia. **Located at**: **upload.wikimedia.org/wikipedi...eplication.png**. **License**: ***Public Domain: No Known Copyright***
- HSV_replication.png. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:H...eplication.png**. **License**: ***Public Domain: No Known Copyright***
- PDB_16vp_EBI.jpg. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/F...B_16vp_EBI.jpg**. **License**: ***Public Domain: No Known Copyright***
- OpenStax College, Biology. October 17, 2013. **Provided by**: OpenStax CNX. **Located at**: **http://cnx.org/content/m44831/latest...ol11448/latest**. **License**: ***CC BY: Attribution***

- HIV/AIDS. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/HIV/AIDS**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- immunodeficiency. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/immunodeficiency**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- phagocyte. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/phagocyte**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- lysis. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/lysis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Leafhopper. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Leafhopper.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Geminiviruses drawing. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ge...es_drawing.png**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Adenovirus_structure.png. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/F..._structure.png**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Herpesviridae_EM_PHIL_2171_lores.jpg. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/F...2171_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- Herpes simplex virions, TEM. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...rions,_TEM.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- **Provided by**: Wikimedia. **Located at**: **upload.wikimedia.org/wikipedi...eplication.png**. **License**: ***Public Domain: No Known Copyright***
- HSV_replication.png. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:H...eplication.png**. **License**: ***Public Domain: No Known Copyright***
- PDB_16vp_EBI.jpg. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/F...B_16vp_EBI.jpg**. **License**: ***Public Domain: No Known Copyright***
- HIV-budding-Color. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:HI...ding-Color.jpg**. **License**: ***CC BY: Attribution***
- MicrobiologyBytes u00bb Blog Archive Lipid Membranes in Poxvirus Replication u00bb MicrobiologyBytes. **Provided by**: Microbiology Bytes. **Located at**: **www.microbiologybytes.com/blo...s-replication/**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Smallpox. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Smallpox**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Pox virus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Pox_virus**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- recombinant. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/recombinant**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- lipoprotein. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/lipoprotein**. **License**: ***CC BY-SA: Attribution-ShareAlike***

- Leafhopper. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Leafhopper.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Geminiviruses drawing. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ge...es_drawing.png**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Adenovirus_structure.png. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/F..._structure.png**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Herpesviridae_EM_PHIL_2171_lores.jpg. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/F...2171_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- Herpes simplex virions, TEM. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...rions,_TEM.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- **Provided by**: Wikimedia. **Located at**: **upload.wikimedia.org/wikipedi...eplication.png**. **License**: ***Public Domain: No Known Copyright***
- HSV_replication.png. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:H...eplication.png**. **License**: ***Public Domain: No Known Copyright***

- PDB_16vp_EBI.jpg. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/F...B_16vp_EBI.jpg**. **License**: ***Public Domain: No Known Copyright***
- HIV-budding-Color. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:HI...ding-Color.jpg**. **License**: ***CC BY: Attribution***
- Child with Smallpox Bangladesh. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ch...Bangladesh.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- capsid. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/capsid**. **License**: *CC BY-SA: Attribution-ShareAlike*
- recombinant DNA. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/recombinant_DNA**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Adenovirus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Adenovirus**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Adenovirus infection. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Adenovirus_infection**. **License**: *CC BY-SA: Attribution-ShareAlike*
- endosome. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/endosome**. **License**: *CC BY-SA: Attribution-ShareAlike*
- integrin. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/integrin**. **License**: *CC BY-SA: Attribution-ShareAlike*
- penton. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/penton**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Leafhopper. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Leafhopper.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Geminiviruses drawing. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ge...es_drawing.png**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Adenovirus_structure.png. **Provided by**: Wikimedia. **Located at**: **https://commons.wikimedia.org/wiki/F..._structure.png**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Herpesviridae_EM_PHIL_2171_lores.jpg. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/F...2171_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- Herpes simplex virions, TEM. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...rions,_TEM.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- **Provided by**: Wikimedia. **Located at**: **upload.wikimedia.org/wikipedi...eplication.png**. **License**: ***Public Domain: No Known Copyright***
- HSV_replication.png. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:H...eplication.png**. **License**: ***Public Domain: No Known Copyright***
- PDB_16vp_EBI.jpg. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/F...B_16vp_EBI.jpg**. **License**: ***Public Domain: No Known Copyright***
- HIV-budding-Color. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:HI...ding-Color.jpg**. **License**: ***CC BY: Attribution***
- Child with Smallpox Bangladesh. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ch...Bangladesh.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Adenovirus structure. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ad..._structure.png**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Virus classification. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Virus_c...classification**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Baltimore classification. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Baltimore_classification**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Hepadnavirus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Hepadnavirus**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Retrovirus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Retrovirus**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Hepadnaviridae. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Hepadnaviridae**. **License**: *CC BY-SA: Attribution-ShareAlike*

- episome. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/episome**. **License**: *CC BY-SA: Attribution-ShareAlike*
- endogenous. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/endogenous**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Leafhopper. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Leafhopper.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Geminiviruses drawing. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ge...es_drawing.png**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Adenovirus_structure.png. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Adenovirus_structure.png**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Herpesviridae_EM_PHIL_2171_lores.jpg. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Herpesviridae_EM_PHIL_2171_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- Herpes simplex virions, TEM. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...rions,_TEM.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- **Provided by**: Wikimedia. **Located at**: **upload.wikimedia.org/wikipedi...eplication.png**. **License**: ***Public Domain: No Known Copyright***
- HSV_replication.png. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:HSV_replication.png**. **License**: ***Public Domain: No Known Copyright***
- PDB_16vp_EBI.jpg. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:PDB_16vp_EBI.jpg**. **License**: ***Public Domain: No Known Copyright***
- HIV-budding-Color. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:HI...ding-Color.jpg**. **License**: ***CC BY: Attribution***
- Child with Smallpox Bangladesh. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ch...Bangladesh.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Adenovirus structure. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ad..._structure.png**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Hepatitis B virus 01. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...B_virus_01.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Antiviral drug. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Antiviral_drug**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Animal virus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Animal_virus**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Hepadnavirus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Hepadnavirus**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Zidovudine. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Zidovudine**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Acyclovir. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Acyclovir**. **License**: *CC BY-SA: Attribution-ShareAlike*
- foot and mouth disease. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/foot%20...outh%20disease**. **License**: *CC BY-SA: Attribution-ShareAlike*
- interferon. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/interferon**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Leafhopper. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Leafhopper.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Geminiviruses drawing. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Geminiviruses_drawing.png**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Adenovirus_structure.png. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Adenovirus_structure.png**. **License**: *CC BY-SA: Attribution-ShareAlike*

- Herpesviridae_EM_PHIL_2171_lores.jpg. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Herpesviridae_EM_PHIL_2171_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- Herpes simplex virions, TEM. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Herpes_simplex_virions,_TEM.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- **Provided by**: Wikimedia. **Located at**: **upload.wikimedia.org/Wikipedia/en/3/35/HSV_replication.png**. **License**: ***Public Domain: No Known Copyright***
- HSV_replication.png. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:HSV_replication.png**. **License**: ***Public Domain: No Known Copyright***
- PDB_16vp_EBI.jpg. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:PDB_16vp_EBI.jpg**. **License**: ***Public Domain: No Known Copyright***
- HIV-budding-Color. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:HI...ding-Color.jpg**. **License**: *CC BY: Attribution*
- Child with Smallpox Bangladesh. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ch...Bangladesh.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Adenovirus structure. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ad..._structure.png**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Hepatitis B virus 01. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...B_virus_01.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- 417px-Vaccination-polio-india.jpg. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/F...olio-india.jpg**. **License**: ***Public Domain: No Known Copyright***
- Bluetongue virus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Bl...ngue_virus.gif**. **License**: ***Public Domain: No Known Copyright***

Key Points

- Vaccines prime the body's immune system against specific pathogens, but are not effective for treating an infection.
- Many animal viruses are also important from a human medical perspective. The emergence of the SARS virus in the human population, coming from an animal source, highlights the importance of animals in bearing infectious agents. Avian influenza viruses can directly infect humans.
- Immune therapy using immunomodulatory factors, such as interferons, is effective for treatment of hepatitis B and C.
- Immune therapy using immunomodulatory factors, such as interferons, is effective for treatment of hepatitis B and C.

Key Terms

- **foot and mouth disease**: A highly variable and transmissible viral disease. The virus enters the body through inhalation and affects cattle worldwide.
- **interferon**: Any of a group of glycoproteins, produced by the immune system, that prevent viral replication in infected cells.

This page titled 15.10.5: Replication of Herpes Simplex Virus is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.11E: Replication of Herpes Simplex Virus** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.10.6: Immunodeficiency

Learning Objectives

- Explain the problems associated with immunodeficiency

Immunodeficiency

Failures, insufficiencies, or delays at any level of the immune response can allow pathogens or tumor cells to gain a foothold to replicate or proliferate to high enough levels that the immune system becomes overwhelmed, leading to immunodeficiency; it may be acquired or inherited. Immunodeficiency can be acquired as a result of infection with certain pathogens (such as HIV), chemical exposure (including certain medical treatments), malnutrition, or, possibly, by extreme stress. For instance, radiation exposure can destroy populations of lymphocytes, elevating an individual's susceptibility to infections and cancer. Dozens of genetic disorders result in immunodeficiencies, including Severe Combined Immunodeficiency (SCID), bare lymphocyte syndrome, and MHC II deficiencies. Rarely, primary immunodeficiencies that are present from birth may occur. Neutropenia is one form in which the immune system produces a below-average number of neutrophils, the body's most abundant phagocytes. As a result, bacterial infections may go unrestricted in the blood, causing serious complications.

HIV/AIDS

Human immunodeficiency virus infection / acquired immunodeficiency syndrome (HIV/AIDS), is a disease of the human immune system caused by infection with human immunodeficiency virus (HIV). During the initial infection, a person may experience a brief period of influenza-like illness. This is typically followed by a prolonged period without symptoms. As the illness progresses, it interferes more and more with the immune system. The person has a high probability of becoming infected, including from opportunistic infections and tumors that do not usually affect people who have working immune systems.

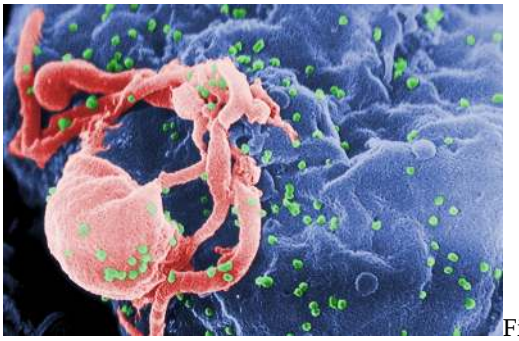


Figure: **Image of HIV: scanning electron micrograph of HIV-1 budding (in green, color added) from cultured lymphocyte**: Multiple round bumps on cell surface represent sites of assembly and budding of HIV. During primary infection, the level of HIV may reach several million virus particles per milliliter of blood.

After the virus enters the body, there is a period of rapid viral replication, leading to an abundance of virus in the peripheral blood. During primary infection, the level of HIV may reach several million virus particles per milliliter of blood. This response is accompanied by a marked drop in the number of circulating CD4+ T cells, cells that are or will become helper T cells. The acute viremia, or spreading of the virus, is almost invariably associated with activation of CD8+ T cells (which kill HIV-infected cells) and, subsequently, with antibody production. The CD8+ T cell response is thought to be important in controlling virus levels, which peak and then decline, as the CD4+ T cell counts recover.

Ultimately, HIV causes AIDS by depleting CD4+ T cells (helper T cells). This weakens the immune system, allowing opportunistic infections. T cells are essential to the immune response; without them, the body cannot fight infections or kill cancerous cells. The mechanism of CD4+ T cell depletion differs in the acute and chronic phases. During the acute phase, HIV-induced cell lysis and killing of infected cells by cytotoxic T cells accounts for CD4+ T cell depletion, although apoptosis (programmed cell death) may also be a factor. During the chronic phase, the consequences of generalized immune activation coupled with the gradual loss of the ability of the immune system to generate new T cells appear to account for the slow decline in CD4+ T cell numbers.

Key Points

- If a pathogen is allowed to proliferate to certain levels, the immune system can become overwhelmed; immunodeficiency occurs when the immune system fails to respond sufficiently to a pathogen.
- Immunodeficiency can be caused by many factors, including certain pathogens, malnutrition, chemical exposure, radiation exposure, or even extreme stress.
- HIV is a virus that causes immunodeficiency by infecting helper T cells, causing cytotoxic T cells to destroy them.

Key Terms

- **phagocyte**: a cell of the immune system, such as a neutrophil, macrophage or dendritic cell, that engulfs and destroys viruses, bacteria, and waste materials
- **lysis**: the disintegration or destruction of cells
- **immunodeficiency**: a depletion in the body's natural immune system, or in some component of it

---

This page titled 15.10.6: Immunodeficiency is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.11F: Immunodeficiency** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.10.7: Double-Stranded DNA Viruses - Pox Viruses

Learning Objectives

- Examine pox viruses for their relevance to human disease and research

The poxviruses are a family of large, complex, enveloped DNA viruses that infect a variety of vertebrate and invertebrate hosts. Poxviruses are of significance both medically and scientifically due to their wide distribution, pathogenicity, and cytoplasmic replicative life cycle. Several prominent members, including variola virus (causative agent of smallpox), molluscum contagiosum virus (cause of a common skin infection of young children and immunosuppressed adults) and monkeypox virus (agent of a smallpox-like disease in parts of Africa), are of considerable concern for public health and biodefense.

The most famous of the poxviruses was smallpox. Smallpox was an infectious disease unique to humans, caused by either of two virus variants, Variola major and Variola minor. The disease is also known by the Latin names Variola or Variola vera, which is a derivative of the Latin varius, meaning “spotted,” or varus, meaning “pimple. ” The term “smallpox” was first used in Britain in the 15th century to distinguish variola from the “great pox” (syphilis). The last naturally occurring case of smallpox (Variola minor) was diagnosed on October 26, 1977. After vaccination campaigns throughout the 19th and 20thcenturies, the World Health Organization (WHO) certified the eradication of smallpox in 1979. Smallpox is one of two infectious diseases to have been eradicated, the other being rinderpest, which was declared eradicated in 2011.

The prototypic and most studied poxvirus, vaccinia virus (VACV), serves as an effective smallpox vaccine, a platform for recombinant vaccines against other pathogens, and an efficient gene expression vector for basic research. Along its approximate 195-kbp double-stranded DNA genome, VACV encodes approximately 200 proteins, ranging in function from viral RNA and DNA synthesis and virion assembly to modulation of host immune defenses.

The most abundant and simplest infectious form of the poxvirus particle, the mature virion (MV), consists of the viral DNA genome encased in a proteinaceous core and an outer lipoprotein membrane with approximately 60 and 25 associated viral proteins, respectively. Following attachment to cell surfaces and fusion with the plasma or endosomal membrane, poxvirus replication is initiated by entry of the viral core into the cytoplasm, where all subsequent steps of the life cycle take place. Poxvirus cores harbor the viral DNA-dependent RNA polymerase and transcription factors necessary for expression of early genes, which constitute nearly half of the viral genome and encode proteins needed for DNA replication and intermediate gene transcription, as well as a large number of immunomodulators.

Poxviruses exhibit a temporally-regulated gene expression program, i.e., expression of early genes encoding DNA replication and intermediate transcription factors triggers the expression of intermediate genes encoding late gene specific transcription factors. Late gene products primarily consist of structural proteins needed for progeny virion assembly, as well as those enzymes destined for incorporation into progeny virions, and used for early gene expression during the next round of infection. Assembly of the MV involves more than 80 viral gene products. In addition, during transit through the cytoplasm, a subset of progeny MVs acquires two additional membrane bilayers, one of which is lost during exocytosis of the particle, to yield the less abundant enveloped virion (EV). Thus, an EV is essentially an MV with an additional membrane in which at least six unique proteins are associated. EVs are antigenically distinct from MVs and are important for efficient virus dissemination in the infected host and protection against immune defenses. In contrast, MVs are released upon cell lysis and may be important for animal-to-animal transmission.

 Figure: **Girl infected with smallpox. Bangladesh, 1973.**: In ordinary type smallpox the bumps are filled with a thick, opaque fluid and often have a depression or dimple in the center. This is a major distinguishing characteristic of smallpox.

Key Points

- The most famous of the poxviruses was smallpox. Smallpox is one of two infectious diseases to have been eradicated, the other being rinderpest, which was declared eradicated in 2011.
- The most abundant and simplest infectious form of the poxvirus particle, the mature virion, consists of the viral DNA genome encased in a proteinaceous core and an outer lipoprotein membrane.
- Poxviruses exhibit a temporally-regulated gene expression program: early, intermediate, and late genes drive DNA replication followed by expression of structural proteins necessary for progeny virion assembly.

Key Terms

- **recombinant**: This term refers to something formed by combining existing elements in a new combination. Thus, the phrase recombinant DNA refers to an organism created in the lab by adding DNA from another species.
- **lipoprotein**: Any of a large group of complexes of protein and lipid with many biochemical functions.

This page titled 15.10.7: Double-Stranded DNA Viruses - Pox Viruses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.11G: Double-Stranded DNA Viruses - Pox Viruses** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.10.8: Double-Stranded DNA Viruses- Adenoviruses

Learning Objectives

- Define the characteristics of adenoviruses

Adenoviruses are medium-sized (90–100 nm), non-enveloped, icosahedral viruses composed of a nucleocapsid and a linear, double-stranded DNA (dsDNA) genome. There are 57 described serotypes in humans, which are responsible for 5–10% of upper respiratory infections in children, and many infections in adults as well.

Diversity

Viruses of the family *Adenoviridae* infect vertebrates, including humans. Among human-tropic viruses classification can be complex; there are 57 accepted human adenovirus types (HAdV-1 to 57) in seven species (Human adenovirus A to G). Different species/serotypes are associated with different conditions:

- respiratory disease (mainly species HAdV-B and C)
- conjunctivitis (HAdV-B and D)
- gastroenteritis (HAdV-F types 40, 41, HAdV-G type 52)

In addition to human viruses, *Adenoviridae* can be divided into five genera: *Mastadenovirus*, *Aviadenovirus*, *Atadenovirus*, *Siadenovirus*, and *Ichtadenovirus*.

Genome

Structurally, adenoviruses represent the largest non-enveloped viruses. They possess non-segmented dsDNA genomes between 26 and 45 Kbp, significantly larger than other dsDNA viruses. The virion also has unique “spike” or fiber associated with each penton base of the capsid that aids in attachment to the host cell via host cell surface receptors.

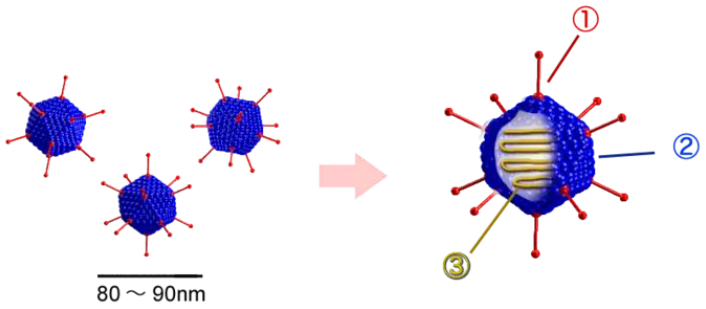


Figure: **Adenovirus Structure**: 1) Penton capsomeres 2) Hexon capsomeres 3) Viral genome (linear dsDNA)

Viral Entry and Replication

Entry of adenoviruses into the host cell involves two sets of interactions between the virus and the host cell. First, entry into the host cell is initiated by the knob domain of the fiber protein binding to a host cell receptor, either CD46 for the group B human adenovirus serotypes, or the coxsackievirus adenovirus receptor for all other serotypes. Next, a specialized motif in the penton base protein interacts with αv integrin, stimulating internalization of the adenovirus via clathrin-coated pits, resulting in entry of the virion into the host cell within an endosome.

Following internalization, the endosome acidifies, which alters virus topology, causing capsid components to disassociate. These changes, as well as the toxic nature of the pentons, result in the release of the virion into the cytoplasm. With the help of cellular microtubules, the virus is transported to the nuclear pore complex, where viral gene expression can occur.

The adenovirus life cycle is separated by the DNA replication process into two phases: an early and a late phase. In both, a primary transcript that is alternatively spliced to generate monocistronic mRNAs compatible with the host’s ribosome is generated, allowing for the products to be translated.

The early genes are responsible for expressing mainly non-structural, regulatory proteins. The goal of these proteins is threefold: to alter the expression of host proteins necessary for DNA synthesis; to activate other viral genes (such as the virus-encoded DNA polymerase); and to avoid premature death of the infected cell by the host-immune defenses (blockage of apoptosis, blockage of interferon activity, and blockage of MHC class I translocation and expression).

The late phase of the adenovirus lifecycle is focused on producing sufficient quantities of structural protein to pack all the genetic material produced by DNA replication. Once the viral components have successfully been replicated, the virus is assembled into its protein shells and released from the cell as a result of virally induced cell lysis.

Transmission

Adenoviruses are unusually stable to chemical or physical agents and adverse pH conditions, allowing for prolonged survival outside of the body and water. Adenoviruses are spread primarily via respiratory droplets; however, they can also be spread by fecal routes.

Humans infected with adenoviruses display a wide range of responses, from no symptoms at all to the severe infections typical of Adenovirus serotype 14. In the past, U.S. military recruits were vaccinated against two serotypes of adenoviruses, with a corresponding decrease in illnesses caused by those serotypes. Although the vaccine is no longer manufactured for civilians, military personnel can receive the vaccine as of 2014.

Infections

Viral transmission occurs primarily through expectorate, but can also be transmitted via contact with infected objects. Most adenovirus infections affect the upper respiratory tract. These often show up as conjunctivitis, tonsillitis, ear infection, or croup. Adenoviruses, types 40 and 41 can also cause gastroenteritis. A combination of conjunctivitis and tonsillitis is particularly common with adenovirus infections. Some children (especially small ones) can develop adenovirus bronchiolitis or pneumonia, both of which can be severe.

Utilization in Treatment of Unrelated Diseases

Adenovirus is used as a vehicle to administer targeted therapy in the form of recombinant DNA or protein. Specific modifications on fiber proteins are used to target Adenovirus to certain cell types; a major effort is made to limit hepatotoxicity and prevent multiple organ failure. Adenovirus dodecahedron serves as a potent delivery platform for foreign antigens to human myeloid dendritic cells (MDC), and is efficiently presented by MDC to M1-specific CD8+ T lymphocytes.

Key Points

- Adenoviruses are medium-sized (90–100 nm), non-enveloped, icosahedral viruses composed of a nucleocapsid and a linear double-stranded DNA (dsDNA) genome.
- There are 57 described serotypes in humans, which are responsible for 5–10% of upper respiratory infections in children, and many infections in adults as well.
- Adenoviruses bind cell surface receptors on host cells, resulting in entry of the virion into the host cell within an endosome.
- The adenovirus life cycle is separated by the DNA replication process into two phases: an early and a late phase. Early genes are responsible for expressing mainly non-structural, regulatory proteins, while late genes produce structural protein necessary for viral replication.

Key Terms

- **endosome**: An endocytic vacuole through which molecules are internalized during endocytosis pass, en route to lysosomes.
- **recombinant DNA**: DNA that has been engineered by splicing together fragments of DNA from multiple species and introduced into the cells of a host.
- **integrin**: Any of many heterodimeric transmembrane proteins that function as receptors in communication between cells.
- **penton**: A pentagonal capsomere of an adenovirus capsid.
- **capsid**: A capsid is the protein shell of a virus.

This page titled 15.10.8: Double-Stranded DNA Viruses- Adenoviruses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.11H: Double-Stranded DNA Viruses- Adenoviruses** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.10.9: Retroviruses and Hepadnavirus

Learning Objectives

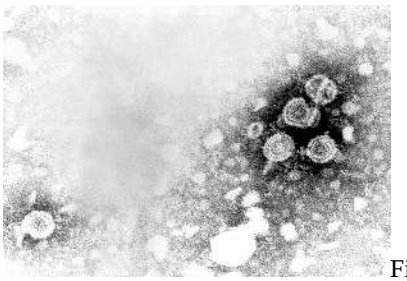
- Differentiate between retroviruses and hepadnaviruses

A well-studied family of this class of viruses includes the retroviruses. One defining feature is the use of reverse transcriptase to convert the positive-sense RNA into DNA. Instead of using the RNA for templates of proteins, they use DNA to create the templates, which is spliced into the host genome using integrase. Replication can then commence with the help of the host cell's polymerases. A well-studied example of this includes HIV.

A special variant of retroviruses are endogenous retroviruses, which are integrated into the genome of the host and inherited across generations.

The virus itself stores its nucleic acid in the form of a +mRNA (including the 5'cap and 3'PolyA inside the virion) genome. This then serves as a means of delivery of that genome into cells it targets as an obligate parasite, and constitutes the infection. Once in the host's cell, the RNA strands undergo reverse transcription in the cytoplasm and are integrated into the host's genome, at which point the retroviral DNA is referred to as a provirus. It is difficult to detect the virus until it has infected the host.

In most viruses, DNA is transcribed into RNA, and then RNA is translated into protein. However, retroviruses function differently – their RNA is reverse-transcribed into DNA, which is integrated into the host cell's genome (when it becomes a provirus), and then undergoes the usual transcription and translational processes to express the genes carried by the virus. So, the information contained in a retroviral gene is used to generate the corresponding protein via the sequence: RNA → DNA → RNA → protein. This extends the fundamental process identified by Francis Crick, in which the sequence is: DNA → RNA → protein. Retroviruses are proving to be valuable research tools in molecular biology and have been used successfully in gene delivery systems.


Figure: **Hepatitis B Virus**: TEM micrograph showing hepatitis B virions.

Hepadnaviruses are a family of viruses which can cause liver infections in humans and animals. There are two recognized genera:

- Genus *Orthohepadnavirus* ; type species: *Hepatitis B virus*
- Genus *Avihepadnavirus* ; type species: *Duck hepatitis B virus*

Hepadnaviruses have very small genomes of partially double-stranded, partially single stranded circular DNA. The genome consists of two uneven strands of DNA. One has a negative-sense orientation, and the other, shorter, strand has a positive-sense orientation.Hepadnaviruses replicate through an RNA intermediate (which they transcribe back into cDNA using reverse transcriptase). The reverse transcriptase becomes covalently linked to a short 3- or 4-nucleotide primer. Most hepadnaviruses will only replicate in specific hosts, and this makes experiments using in vitro methods very difficult.

HBV infection is initiated through viral attachment to an unknown cell surface receptor. The virally encoded DNA polymerase acts upon the DNA, leaving it fully double-stranded.

Key Points

- Retrovirus RNA serves as a template for reverse transcriptase and is copied into DNA.
- Hepadnaviruses are a family of viruses which can cause liver infections in humans and animals.

Key Terms

- **endogenous**: produced, originating or growing from within
- **episome**: A segment of DNA that can exist and replicate either autonomously in the cytoplasm or as part of achromosome, mainly found in bacteria.

This page titled 15.10.9: Retroviruses and Hepadnavirus is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.11I: Retroviruses and Hepadnavirus** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.10.10: Treatment of Animal Viral Infections

This page titled 15.10.10: Treatment of Animal Viral Infections is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

15.11: Viruses and Cancer

This page titled 15.11: Viruses and Cancer is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.12: Viruses and Cancer** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.11.1: Cancer Viruses

Learning Objectives

- Illustrate how cancer viruses turn normal cells into tumor cells

Worldwide, cancer viruses are estimated to cause 15-20% of all cancers in humans. Most viral infections, however, do not lead to tumor formation; several factors influence the progression from viral infection to cancer development. These factors include host's genetic makeup, mutation occurrence, exposure to cancer causing agents, and immune impairment.

Viruses typically initiate cancer development by suppressing the host's immune system, causing inflammation over a long period of time, or by altering host genes. Cancer cells have characteristics that differ from normal cells, such as acquiring the ability to grow uncontrollably. This can result from having control of their own growth signals, losing sensitivity to anti-growth signals, and losing the ability to undergo apoptosis, or programmed cell death.

Cancer cells don't experience biological aging, and maintain their ability to undergo cell division and growth. Transformation occurs when a virus infects and genetically alters a cell. The infected cell is regulated by the viral genes and has the ability to undergo abnormal new growth. Scientists have been able to discern some commonality among viruses that cause tumors. The tumor viruses or oncoviruses change cells by integrating their genetic material with the host cell's DNA. Unlike the integration seen in prophages, this is a permanent insertion; the genetic material is never removed.

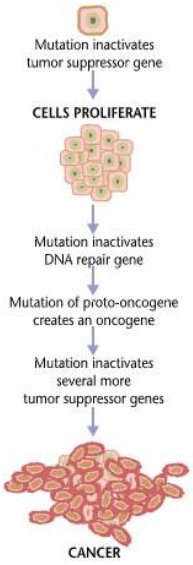


Figure: **Mutations Leading to Increased Cell Division**: Cancer is caused by a series of mutations. Viral infections contribute to the process through genetic alteration.

The insertion mechanism can differ depending on whether the nucleic acid in the virus is DNA or RNA. In DNA viruses, the genetic material can be directly inserted into the host's DNA. RNA viruses must first transcribe RNA to DNA and then insert the genetic material into the host cell's DNA.

Key Points

- A direct oncogenic viral mechanism involves either the insertion of additional viral oncogenic genes into the host cell, or the enhancement of already existing oncogenic genes in the genome.
- Tumor viruses come in a variety of forms. Viruses with a DNA genome, such as adenovirus, and viruses with an RNA genome, like the Hepatitis C virus (HCV), can cause cancers. Retroviruses having both DNA and RNA genomes (Human T-lymphotropic virus and hepatitis B virus) can also cause cancers.
- Viruses can become carcinogenic when they integrate into the host cell genome as part of a biological accident, such as polyomaviruses and papillomaviruses.

Key Terms

- **oncogenic**: Tending to cause the formation of tumors.
- **transformation**: The alteration of a bacterial cell caused by the transfer of DNA from another, especially if pathogenic.

This page titled 15.11.1: Cancer Viruses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.12A: Cancer Viruses** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.11.2: DNA Oncogenic Viruses

Learning Objectives

- Outline DNA oncogenic viruses

There are two classes of cancer viruses: DNA and RNA viruses. Several viruses have been linked to certain types of cancer in humans. These viruses have varying ways of reproduction and represent several different virus families.

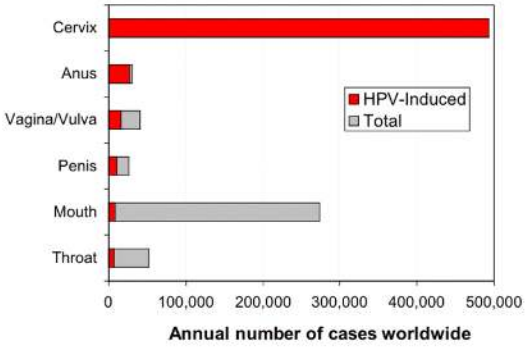


Figure: **Virus Causing Cervical Cancer**: Human papilloma virus is strongly linked to the development of cervical cancer among other types of cancers.

DNA Oncogenic Viruses include the following:

- The Epstein-Barr virus has been linked to Burkitt's lymphoma. This virus infects B cells of the immune system and epithelial cells.
- The hepatitis B virus has been linked to liver cancer in people with chronic infections.
- Human papilloma viruses have been linked to cervical cancer. They also cause warts and benign papillomas.
- Human herpes virus-8 has been linked to the development of Kaposi sarcoma. Kaposi sarcoma causes patches of abnormal tissue to develop in various area of the body including under the skin, in the lining of the mouth, nose, and throat or in other organs.

DNA tumor viruses have two life-styles. In permissive cells, all parts of the viral genome are expressed. This leads to viral replication, cell lysis and cell death. In cells that are non-permissive for replication, viral DNA is usually, but not always, integrated into the cell chromosomes at random sites. Only part of the viral genome is expressed. These are the early control functions of the virus. Viral structural proteins are not made, and no progeny virus is released.

The first DNA tumor viruses to be discovered were rabbit fibroma virus and Shope papilloma virus, both discovered by Richard Shope in the 1930s. Papillomas are benign growths, such as warts, of epithelial cells. They were discovered by making a filtered extract of a tumor from a wild rabbit and injecting the filtrate into another rabbit in which a benign papilloma grew. However, when the filtrate was injected into a domestic rabbit, the result was a carcinoma, a malignant growth. A seminal observation was that it was no longer possible to isolate infectious virus from the malignant growth because the virus had become integrated into the chromosomes of the malignant cells.

Key Points

- Both DNA and RNA viruses have been shown to be capable of causing cancer in humans.
- Epstein-Barr virus, human papilloma virus, hepatitis B virus, and human herpes virus-8 are the four DNA viruses that are capable of causing the development of human cancers.
- The presence of viral gene products in tumor cells that require them to maintain their unchecked proliferation, can provide important targets for directed therapies that specifically can distinguish tumor cells from normal cells.

Key Terms

- **oncogenic**: Tending to cause the formation of tumors.

This page titled 15.11.2: DNA Oncogenic Viruses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.12B: DNA Oncogenic Viruses** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.11.3: RNA Oncogenic Viruses

Learning Objectives

- Classify the viruses with oncogenic properties

There are two classes of cancer viruses: DNA and RNA viruses. Several viruses have been linked to certain types of cancer in humans. These viruses have varying ways of reproduction and represent several different virus families. Specifically, RNA viruses have RNA as their genetic material and can be either single-stranded RNA (ssRNA) or double-stranded (dsRNA). RNA viruses are classified based on the Baltimore classification system and do not take into account viruses with DNA intermediates in their life cycle. Viruses which contain RNA for their genetic material but do include DNA intermediates in their life cycle are called "retroviruses. " There are numerous RNA oncogenic viruses that have been linked to various cancer types. These various oncogenic viruses include:

1. Human T lymphotrophic virus type 1 (HTLV-I), a retrovirus, has been linked to T-cell leukemia. 2. The hepatitis C virus has been linked to liver cancer in people with chronic infections.

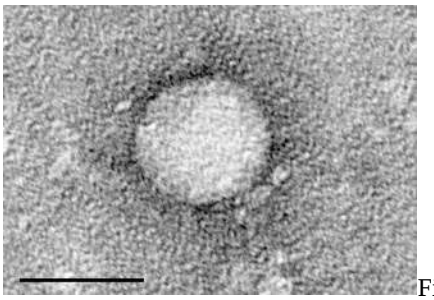


Figure: **Electron micrograph of Hepatitis C**: Hepatitis C viral infections have been linked to the development of liver cancer.

2. Hepatitis viruses includes hepatitis B and hepatitis C have been linked to hepatocellular carcinoma.

3. Human papillomaviruses (HPV) have been linked to cancer of the cervix, anus, penis, vagina/vulva, and some cancers of the head and neck.

4. Kaposi's sarcoma-associated herpesvirus (HHV-8) has been linked to Kaposi's sarcoma and primary effusion lymphoma.

5. Epstein-Barr virus (EBV) has been linked to Burkitt's lymphoma, Hodgkin's lymphoma, post-transplantation lymphoproliferative disease, and nasopharyngeal carcinoma.

RNA Retroviruses

Retroviruses are different from DNA tumor viruses in that their genome is RNA, but they are similar to many DNA tumor viruses in that the genome is integrated into host genome. Since RNA makes up the genome of the mature virus particle, it must be copied to DNA prior to integration into the host cell chromosome. This lifestyle goes against the central dogma of molecular biology in which that DNA is copied into RNA. The outer envelope comes from the host cell plasma membrane. Coat proteins (surface antigens) are encoded by env (envelope) gene and are glycosylated. One primary gene product is made, but this is cleaved so that there are more than one surface glycoprotein in the mature virus (cleavage is by host enzyme in the Golgi apparatus). The primary protein (before cleavage) is made on ribosomes attached to the endoplasmic reticulum and is a transmembrane (type 1) protein. Inside the membrane is an icosahedral capsid containing proteins encoded by the gag gene (group-specific AntiGen). Gag-encoded proteins also coat the genomic RNA. Again, there is one primary gene product. This is cleaved by a virally-encoded protease (from the pol gene). There are two molecules of genomic RNA per virus particle with a 5′ cap and a 3′ poly A sequence. Thus, the virus is diploid. The RNA is plus sense (same sense as mRNA). About 10 copies of reverse transcriptase are present within the mature virus, these are encoded by the pol gene. Pol gene codes for several functions (again, as with gag and env, a polyprotein is made that is then cut up).

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: ***CC BY-SA: Attribution-ShareAlike***

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- Oncovirus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Oncovirus**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- oncogenic. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/oncogenic**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- transformation. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/transformation**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Carcinogenesis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Carcinogenesis**. **License**: ***Public Domain: No Known Copyright***
- Oncovirus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Oncovirus**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- oncogenic. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/oncogenic**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Carcinogenesis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Carcinogenesis**. **License**: ***Public Domain: No Known Copyright***
- Cases of HPV cancers graph. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ca...cers_graph.png**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- RNA viruses. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/RNA_viruses**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Oncovirus. **Provided by**: Wikipedia. **Located at**: **http://en.Wikipedia.org/wiki/Oncovirus**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Oncovirus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Oncovirus%23RNA_viruses**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- oncogenic. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/oncogenic**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- hepatocellular. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/hepatocellular**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Carcinogenesis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Carcinogenesis**. **License**: ***Public Domain: No Known Copyright***
- Cases of HPV cancers graph. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ca...cers_graph.png**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- HCV EM picture 2. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:HC..._picture_2.png**. **License**: ***CC BY-SA: Attribution-ShareAlike***

Key Points

- Both DNA and RNA viruses have been shown to be capable of causing cancer in humans.
- Human T lymphotrophic virus type 1 and hepatitis C viruses are the two RNA viruses that contribute to human cancers.
- Hepatitis C virus is an enveloped RNA virus capable of causing acute and chronic hepatitis in humans by infecting liver cells. It is estimated 3% of the world's population are carriers. Chronic infection with hepatitis C virus results in cirrhosis, which in turn can lead to liver cancer.

Key Terms

- **oncogenic**: Tending to cause the formation of tumors.
- **hepatocellular**: Of or pertaining to the cells of the liver

This page titled 15.11.3: RNA Oncogenic Viruses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.12C: RNA Oncogenic Viruses** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.12: Overview of Viruses

This page titled 15.12: Overview of Viruses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.1: Overview of Viruses** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.12.1: Discovery and Detection of Viruses

Learning Objectives

- Describe how viruses were first discovered and how they are detected

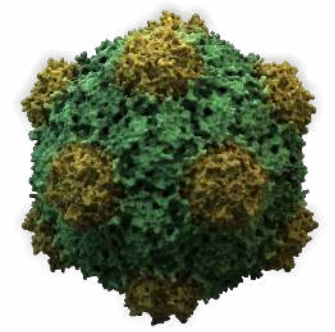


Figure: **The structure of the icosahedral cowpea mosaic virus**: In the past, viruses were classified by the type of nucleic acid they contained, DNA or RNA, and whether they had single- or double-stranded nucleic acid.

Discovery and Detection

Viruses were first discovered after the development of a porcelain filter, called the Chamberland-Pasteur filter, which could remove all bacteria visible in the microscope from any liquid sample. In 1886, Adolph Meyer demonstrated that a disease of tobacco plants, tobacco mosaic disease, could be transferred from a diseased plant to a healthy one via liquid plant extracts. In 1892, Dmitri Ivanowski showed that this disease could be transmitted in this way even after the Chamberland-Pasteur filter had removed all viable bacteria from the extract. Still, it was many years before it was proven that these “filterable” infectious agents were not simply very small bacteria, but were a new type of tiny, disease-causing particle.

Virions, single virus particles, are very small, about 20–250 nanometers in diameter. These individual virus particles are the infectious form of a virus outside the host cell. Unlike bacteria (which are about 100 times larger), we cannot see viruses with a light microscope, with the exception of some large virions of the poxvirus family. It was not until the development of the electron microscope in the late 1930s that scientists got their first good view of the structure of the tobacco mosaic virus (TMV) and other viruses. The surface structure of virions can be observed by both scanning and transmission electron microscopy, whereas the internal structures of the virus can only be observed in images from a transmission electron microscope. The use of these technologies has enabled the discovery of many viruses of all types of living organisms. They were initially grouped by shared morphology. Later, groups of viruses were classified by the type of nucleic acid they contained, DNA or RNA, and whether their nucleic acid was single- or double-stranded. More recently, molecular analysis of viral replicative cycles has further refined their classification.

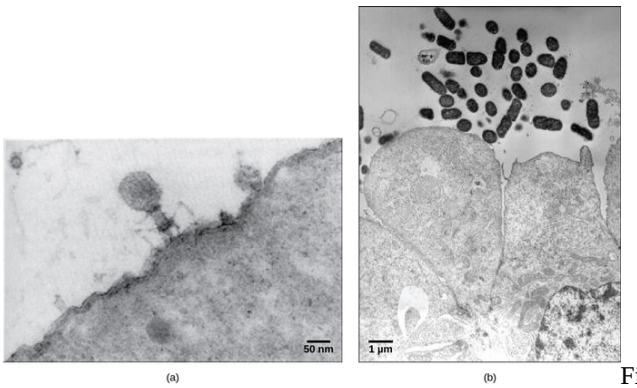


Figure: **Examples of transmission electron micrographs of viruses**: In these transmission electron micrographs, (a) a virus is dwarfed by the bacterial cell it infects, while (b) these E. coli cells are dwarfed by cultured colon cells.

Key Points

- Virions, single virus particles, are 20–250 nanometers in diameter.
- In the past, viruses were classified by the type of nucleic acid they contained, DNA or RNA, and whether they had single- or double-stranded nucleic acid.
- Molecular analysis of viral replicative cycles is now more routinely used to classify viruses.

Key Terms

- **virus**: a submicroscopic infectious organism, now understood to be a non-cellular structure consisting of a core of DNA or RNA surrounded by a protein coat
- **virion**: a single individual particle of a virus (the viral equivalent of a cell)

This page titled 15.12.1: Discovery and Detection of Viruses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.1A: Discovery and Detection of Viruses** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.12.2: Nature of the Virion

Learning Objectives

- Illustrate the attributes of a virion

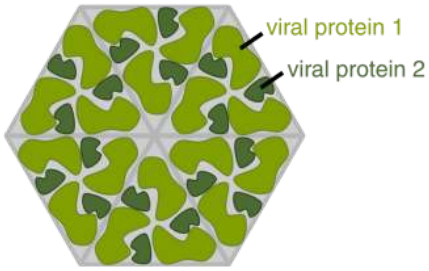


Figure: **Virion capsid**: Structure of a capsid and the organization of molecules that constitute it.

A virion is an entire virus particle consisting of an outer protein shell called a *capsid* and an inner core of nucleic acid (either ribonucleic or deoxyribonucleic acid—RNA or DNA). The core confers infectivity, and the capsid provides specificity to the virus. In some virions the capsid is further enveloped by a fatty membrane, in which case the virion can be inactivated by exposure to fat solvents such as ether and chloroform. Many virions are spheroidal—actually icosahedral (the capsid having 20 triangular faces)—with regularly arranged units called capsomeres, two to five or more along each side. The nucleic acid is densely coiled within. Other virions have a capsid consisting of an irregular number of surface spikes, with the nucleic acid loosely coiled within. Virions of most plant viruses are rod-shaped; the capsid is a naked cylinder (lacking a fatty membrane) within which lies a straight or helical rod of nucleic acid.

Virion capsids are formed from identical protein subunits called capsomeres. Viruses can have a lipid “envelope” derived from the host cell membrane. The capsid is made from proteins encoded by the viral genome and its shape serves as the basis for morphological distinction. Virally coded protein subunits will self-assemble to form a capsid, in general requiring the presence of the virus genome. Complex viruses code for proteins that assist in the construction of their capsid. Proteins associated with nucleic acid are known as nucleoproteins, and the association of viral capsid proteins with viral nucleic acid is called a nucleocapsid. The capsid and entire virus structure can be mechanically (physically) probed through atomic force microscopy.

Key Points

- The virion shell or capsid protects the interior core that includes the genome and other proteins. After the virion binds to the surface of a specific host cell, its DNA or RNA is injected into the host cell and viral replication occurs, resulting in the spread of the infection to other host cells.
- A virion is the infectious particle that is designed for transmitting the nucleic acid genome among hosts or host cells.
- Virions are produced in the cytoplasm of complex viral ‘factories,’ the virus.

Key Terms

- **capsid**: The outer protein shell of a virus.

This page titled 15.12.2: Nature of the Virion is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.1B: Nature of the Virion** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.12.3: Viral Genomes

Learning Objectives

- Generalize the features of viral genomes

Viral diseases have an enormous impact on human health worldwide. Genomic technologies are providing infectious disease researchers an unprecedented capability to study at a genetic level the viruses that cause disease and their interactions with infected hosts. An enormous variety of genomic structures can be seen among viral species; as a group, they contain more structural genomic diversity than plants, animals, archaea, or bacteria. There are millions of different types of viruses, although only about 5,000 of them have been described in detail.

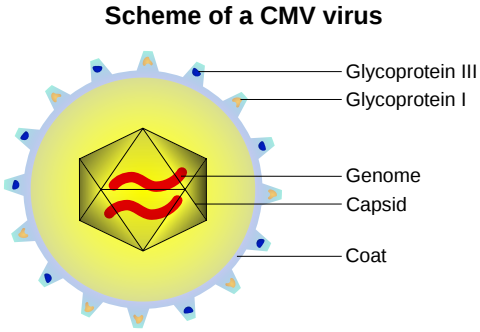


Figure: ***Diagram of a virus****: The location of the genome inside the virus.*

A virus has either DNA or RNA genes and is called a DNA virus or a RNA virus, respectively. The vast majority of viruses have RNA genomes. Plant viruses tend to have single-stranded RNA genomes and bacteriophages tend to have double-stranded DNA genomes. Viral genomes are circular, as in the polyomaviruses, or linear, as in the adenoviruses. The type of nucleic acid is irrelevant to the shape of the genome. Among RNA viruses and certain DNA viruses, the genome is often divided up into separate parts, in which case it is called segmented. For RNA viruses, each segment often codes for only one protein, and they are usually found together in one capsid. However, all segments are not required to be in the same virion for the virus to be infectious, as demonstrated by the brome mosaic virus and several other plant viruses.

A viral genome, irrespective of nucleic acid type, is almost always either single-stranded or double-stranded. Single-stranded genomes consist of an unpaired nucleic acid, analogous to one-half of a ladder split down the middle. Double-stranded genomes consist of two complementary paired nucleic acids, analogous to a ladder. The virus particles of some virus families, such as those belonging to the Hepadnaviridae, contain a genome that is partially double-stranded and partially single-stranded.

Key Points

- In modern molecular biology and genetics, the genome is the entirety of an organism ‘s hereditary information. It is encoded either in DNA or, for many types of virus, in RNA.
- A virus has either DNA or RNA genes and is called a DNA virus or a RNA virus.
- The genome includes both the genes and the non-coding sequences of the DNA/RNA.

Key Terms

- **genome**: The complete genetic information (either DNA or, in some viruses, RNA) of an organism, typically expressed in the number of basepairs.

This page titled 15.12.3: Viral Genomes is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.1C: Viral Genomes** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.12.4: Host Range

Learning Objectives

- Explain factors that limit viral host range

Factors Limiting Viral Infection

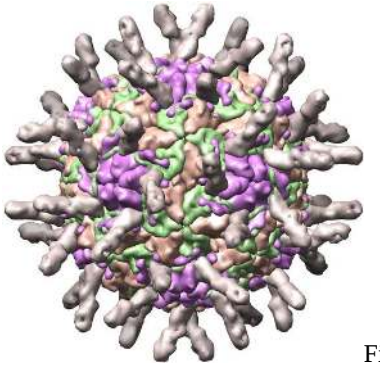


Figure: **ICAM-1**: structure of ICAM-1 molecule that enables viruses to bind to host's cell membrane.

A host is an organism that harbors a parasite or a mutual or commensal symbiont, typically providing nourishment and shelter. Resistance to and recovery from viral infections depend on the interactions that occur between the virus and the host. The defenses mounted by the host may act directly on the virus or indirectly on virus replication by altering or killing the infected cell. Non-specific host defenses function early in an encounter with a virus to prevent or limit infection, while the specific host defenses function after infection in recovery to provide immunity for subsequent challenges.

The host defense mechanisms involved in a particular viral infection will vary depending on the virus, dose, and portal of entry. The host has many barriers against infection that are inherent in the organism. These represent the first line of defense, which functions to prevent or limit infection Examples of natural barriers include but are not limited to skin, the expression of surface receptors such as CD4, complement receptors, glycophorin, intercelullar adhesion molecule 1 (ICAM-1), mucus, a ciliated epithelium, low pH, and humoral and cellular components.

The host range of the virus will depend upon the presence of the receptors described above. If a host lacks the receptor for a virus, or if the host cell lacks some component necessary for the replication of a virus, the host will inherently be resistant to that virus. For example, mice lack the receptors for polio viruses and thus are resistant to polio virus. Similarly, humans are inherently resistant to plant and many animal viruses.

Key Points

- The host range or host specificity of a parasite is the collection of hosts that an organism can use as a partner.
- The host range is usually a function of an inability of the virus to successfully adsorb and/or enter cells because of an incompatibility between virus capsid proteins (or virus envelope proteins) and the host receptor molecule.
- The host range is also a function of an incompatibility between the biochemistry of the virus and the biochemistry of the host. For closely related hosts, the biochemical differences can be quite subtle.

Key Terms

- **surface receptor**: Cell surface receptors (membrane receptors, transmembrane receptors) are specialized integral membrane proteins that take part in communication between the cell and the outside world.
- **commensal**: A term for a form of symbiosis in which one organism derives a benefit while the other is unaffected

This page titled 15.12.4: Host Range is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

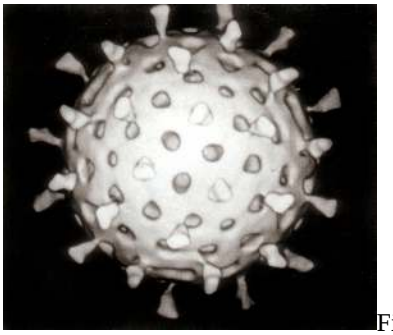
- **9.1D: Host Range** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.12.5: Viral Size

Learning Objectives

- Recognize the cause and effect of different sizes of viruses

A virus is an infectious agent of small size and simple composition that can multiply only in living cells of animals, plants, or bacteria. They range in size from about 20 to 400 nanometres in diameter (1 nanometre = 10^{-9} meters). By contrast, the smallest bacteria are about 400 nanometres in size. A virus consists of a single- or double-stranded nucleic acid and at least one protein surrounded by a protein shell, called a capsid; some viruses also have an outer envelope composed of fatty materials (lipids) and proteins. The nucleic acid carries the virus's genome —its collection of genes—and may consist of either deoxyribonucleic acid (DNA) or ribonucleic acid (RNA). The protein capsid provides protection for the nucleic acid and may contain enzymes that enable the virus to enter its appropriate host cell.


Figure: **Viral structure**: Rotavirus particles measure 76.5 nm in diameter and are not enveloped.

There exists a strong association between viral geometry and features of viral disease outbreaks. The amount and arrangement of the proteins and nucleic acid of viruses determine their size and shape. The protein and nucleic acid constituents have properties unique for each class of virus; when assembled, they determine the size and shape of the virus for that specific class.

Only the largest and most complex viruses can be seen under the light microscope at the highest resolution. Any determination of the size of a virus also must take into account its shape, since different classes of viruses have distinctive shapes. Shapes of viruses are predominantly of two kinds: rods, or filaments, so called because of the linear array of the nucleic acid and the protein subunits; and spheres, which are actually 20-sided (icosahedral) polygons. Most plant viruses are small and are either filaments or polygons, as are many bacterial viruses. The larger and more-complex bacteriophages contain double-stranded DNA as their genetic information and combine both filamentous and polygonal shapes. The classic T4 bacteriophage is composed of a polygonal head, which contains the DNA genome, and a special-function rod-shaped tail of long fibres. Structures such as these are unique to the bacteriophages.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: *CC BY-SA: Attribution-ShareAlike*

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- OpenStax College, Biology. October 16, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44595/latest/?collection=col11448/latest. **License**: *CC BY: Attribution*
- virus. **Provided by**: Wiktionary. **Located at**: http://en.wiktionary.org/wiki/virus. **License**: *CC BY-SA: Attribution-ShareAlike*
- virion. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/virion**. **License**: *CC BY-SA: Attribution-ShareAlike*
- OpenStax College, Viral Evolution, Morphology, and Classification. October 16, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44595/latest/Figure_21_01_01ab.jpg. **License**: *CC BY: Attribution*
- CowpeaMosaicVirus3D. **Provided by**: Wikimedia Commons. **Located at**: **en.Wikipedia.org/wiki/File:CowpeaMosaicVirus3D.png**. **License**: *CC BY-SA: Attribution-ShareAlike*

- Virus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Virus**. **License**: *CC BY-SA: Attribution-ShareAlike*
- capsid. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/capsid**. **License**: *CC BY-SA: Attribution-ShareAlike*
- OpenStax College, Viral Evolution, Morphology, and Classification. October 16, 2013. **Provided by**: OpenStax CNX. **Located at**: **http://cnx.org/content/m44595/latest/Figure_21_01_01ab.jpg**. **License**: *CC BY: Attribution*
- CowpeaMosaicVirus3D. **Provided by**: Wikimedia Commons. **Located at**: **en.Wikipedia.org/wiki/File:CowpeaMosaicVirus3D.png**. **License**: *CC BY-SA: Attribution-ShareAlike*
- File:Hexon.svg - Wikipedia, the free encyclopedia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/w/index.php?title=File:Hexon.svg&page=1**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Virus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Virus**. **License**: *CC BY-SA: Attribution-ShareAlike*
- genome. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/genome**. **License**: *CC BY-SA: Attribution-ShareAlike*
- OpenStax College, Viral Evolution, Morphology, and Classification. October 16, 2013. **Provided by**: OpenStax CNX. **Located at**: **http://cnx.org/content/m44595/latest/Figure_21_01_01ab.jpg**. **License**: *CC BY: Attribution*
- CowpeaMosaicVirus3D. **Provided by**: Wikimedia Commons. **Located at**: **en.Wikipedia.org/wiki/File:CowpeaMosaicVirus3D.png**. **License**: *CC BY-SA: Attribution-ShareAlike*
- File:Hexon.svg - Wikipedia, the free encyclopedia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/w/index.php?title=File:Hexon.svg&page=1**. **License**: *CC BY-SA: Attribution-ShareAlike*
- CMVschema. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:CMVschema.svg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Host range. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Host_range**. **License**: *CC BY-SA: Attribution-ShareAlike*
- surface receptor. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/surface%20receptor**. **License**: *CC BY-SA: Attribution-ShareAlike*
- commensal. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/commensal**. **License**: *CC BY-SA: Attribution-ShareAlike*
- OpenStax College, Viral Evolution, Morphology, and Classification. October 16, 2013. **Provided by**: OpenStax CNX. **Located at**: **http://cnx.org/content/m44595/latest/Figure_21_01_01ab.jpg**. **License**: *CC BY: Attribution*
- CowpeaMosaicVirus3D. **Provided by**: Wikimedia Commons. **Located at**: **en.Wikipedia.org/wiki/File:CowpeaMosaicVirus3D.png**. **License**: *CC BY-SA: Attribution-ShareAlike*
- File:Hexon.svg - Wikipedia, the free encyclopedia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/w/index.php?title=File:Hexon.svg&page=1**. **License**: *CC BY-SA: Attribution-ShareAlike*
- CMVschema. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:CMVschema.svg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- PBB Protein ICAM1 image. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:PBB_Protein_ICAM1_image.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Virus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Virus**. **License**: *CC BY-SA: Attribution-ShareAlike*
- bacteriophage. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/bacteriophage**. **License**: *CC BY-SA: Attribution-ShareAlike*
- OpenStax College, Viral Evolution, Morphology, and Classification. October 16, 2013. **Provided by**: OpenStax CNX. **Located at**: **http://cnx.org/content/m44595/latest/Figure_21_01_01ab.jpg**. **License**: *CC BY: Attribution*
- CowpeaMosaicVirus3D. **Provided by**: Wikimedia Commons. **Located at**: **en.Wikipedia.org/wiki/File:CowpeaMosaicVirus3D.png**. **License**: *CC BY-SA: Attribution-ShareAlike*
- File:Hexon.svg - Wikipedia, the free encyclopedia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/w/index.php?title=File:Hexon.svg&page=1**. **License**: *CC BY-SA: Attribution-ShareAlike*
- CMVschema. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:CMVschema.svg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- PBB Protein ICAM1 image. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:PBB_Protein_ICAM1_image.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Rotavirus Reconstruction. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Rotavirus_Reconstruction.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*

Key Points

- The size and shape of a virus helps us understand its class and components.
- Viruses also exist in different shapes that include helical, polyhedral, enveloped, and complex.
- Proteins and nucleic acid of viruses determine their size and shape.

Key Terms

- **bacteriophage**: A virus that specifically infects bacteria.

This page titled 15.12.5: Viral Size is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.1E: Viral Size** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.13: Structure of Viruses

This page titled 15.13: Structure of Viruses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.2: Structure of Viruses** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.13A: Viral Morphology

Learning Objectives

- Describe the relationship between the viral genome, capsid, and envelope

Viral Morphology

Viruses are acellular, meaning they are biological entities that do not have a cellular structure. Therefore, they lack most of the components of cells, such as organelles, ribosomes, and the plasma membrane. A virion consists of a nucleic acid core, an outer protein coating or capsid, and sometimes an outer envelope made of protein and phospholipid membranes derived from the host cell. The capsid is made up of protein subunits called capsomeres. Viruses may also contain additional proteins, such as enzymes. The most obvious difference between members of viral families is their morphology, which is quite diverse. An interesting feature of viral complexity is that host and virion complexity are uncorrelated. Some of the most intricate virion structures are observed in bacteriophages, viruses that infect the simplest living organisms: bacteria.

Morphology

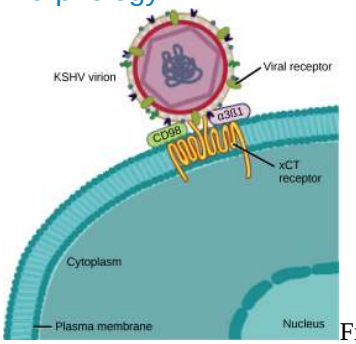


Figure: **Example of a virus attaching to its host cell**: The KSHV virus binds the xCT receptor on the surface of human cells. This attachment allows for later penetration of the cell membrane and replication inside the cell.

Viruses come in many shapes and sizes, but these are consistent and distinct for each viral family. In general, the shapes of viruses are classified into four groups: filamentous, isometric (or icosahedral), enveloped, and head and tail. Filamentous viruses are long and cylindrical. Many plant viruses are filamentous, including TMV (tobacco mosaic virus). Isometric viruses have shapes that are roughly spherical, such as poliovirus or herpesviruses. Enveloped viruses have membranes surrounding capsids. Animal viruses, such as HIV, are frequently enveloped. Head and tail viruses infect bacteria. They have a head that is similar to icosahedral viruses and a tail shape like filamentous viruses.

Many viruses use some sort of glycoprotein to attach to their host cells via molecules on the cell called viral receptors. For these viruses, attachment is a requirement for later penetration of the cell membrane, allowing them to complete their replication inside the cell. The receptors that viruses use are molecules that are normally found on cell surfaces and have their own physiological functions. Viruses have simply evolved to make use of these molecules for their own replication.

Overall, the shape of the virion and the presence or absence of an envelope tell us little about what disease the virus may cause or what species it might infect, but they are still useful means to begin viral classification. Among the most complex virions known, the T4 bacteriophage, which infects the *Escherichia coli* bacterium, has a tail structure that the virus uses to attach to host cells and a head structure that houses its DNA. Adenovirus, a non-enveloped animal virus that causes respiratory illnesses in humans, uses glycoprotein spikes protruding from its capsomeres to attach to host cells. Non-enveloped viruses also include those that cause polio (poliovirus), plantar warts (papillomavirus), and hepatitis A (hepatitis A virus).

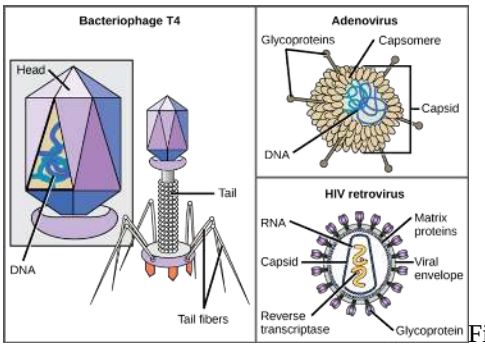


Figure: **Examples of virus shapes**: Viruses can be either complex in shape or relatively simple. This figure shows three relatively-complex virions: the bacteriophage T4, with its DNA-containing head group and tail fibers that attach to host cells; adenovirus, which uses spikes from its capsid to bind to host cells; and HIV, which uses glycoproteins embedded in its envelope to bind to host cells.

Enveloped virions like HIV consist of nucleic acid and capsid proteins surrounded by a phospholipid bilayer envelope and its associated proteins. Glycoproteins embedded in the viral envelope are used to attach to host cells. Other envelope proteins include the matrix proteins that stabilize the envelope and often play a role in the assembly of progeny virions. Chicken pox, influenza, and mumps are examples of diseases caused by viruses with envelopes. Because of the fragility of the envelope, non-enveloped viruses are more resistant to changes in temperature, pH, and some disinfectants than are enveloped viruses.

Types of Nucleic Acid

Unlike nearly all living organisms that use DNA as their genetic material, viruses may use either DNA or RNA. The virus core contains the genome or total genetic content of the virus. Viral genomes tend to be small, containing only those genes that encode proteins that the virus cannot obtain from the host cell. This genetic material may be single- or double-stranded. It may also be linear or circular. While most viruses contain a single nucleic acid, others have genomes that have several, called segments.

In DNA viruses, the viral DNA directs the host cell's replication proteins to synthesize new copies of the viral genome and to transcribe and translate that genome into viral proteins. DNA viruses cause human diseases, such as chickenpox, hepatitis B, and some venereal diseases, like herpes and genital warts.

RNA viruses contain only RNA as their genetic material. To replicate their genomes in the host cell, the RNA viruses encode enzymes that can replicate RNA into DNA, which cannot be done by the host cell. These RNA polymerase enzymes are more likely to make copying errors than DNA polymerases and, therefore, often make mistakes during transcription. For this reason, mutations in RNA viruses occur more frequently than in DNA viruses. This causes them to change and adapt more rapidly to their host. Human diseases caused by RNA viruses include hepatitis C, measles, and rabies.

Key Points

- Viruses are classified into four groups based on shape: filamentous, isometric (or icosahedral), enveloped, and head and tail.
- Many viruses attach to their host cells to facilitate penetration of the cell membrane, allowing their replication inside the cell.
- Non-enveloped viruses can be more resistant to changes in temperature, pH, and some disinfectants than are enveloped viruses.
- The virus core contains the small single- or double-stranded genome that encodes the proteins that the virus cannot get from the host cell.

Key Terms

- **capsid**: the outer protein shell of a virus
- **envelope**: an enclosing structure or cover, such as a membrane
- **filamentous**: Having the form of threads or filaments
- **isometric**: of, or being a geometric system of three equal axes lying at right angles to each other (especially in crystallography)

This page titled 15.13A: Viral Morphology is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.2A: Viral Morphology** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.13B: General Morphology

Learning Objectives

- Distinguish between the 5 main morphological virus types

Viruses display a wide diversity of shapes and sizes, called morphologies. In general, there are five main morphological virus types:

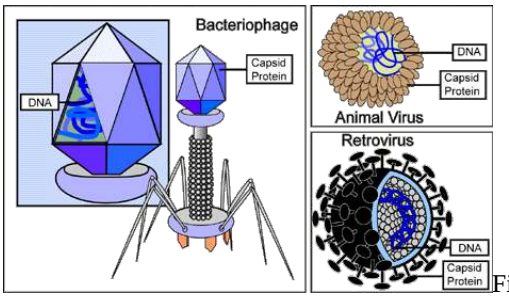


Figure: **Viral structure**: An outline of the structures of some common viral types.

1. Helical – These viruses are composed of a single type of capsomer stacked around a central axis to form a helical structure, which may have a central cavity, or hollow tube.
2. Icosahedral – Most animal viruses are icosahedral or near-spherical with icosahedral symmetry.
3. Prolate – This is an isosahedron elongated along one axis and is a common arrangement of the heads of bacteriophages.
4. Envelope – Some species of virus envelop themselves in a modified form of one of the cell membranes, either the outer membrane surrounding an infected host cell or internal membranes such as nuclear membrane or endoplasmic reticulum, thus gaining an outer lipid bilayer known as a viral envelope.
5. Complex – These viruses possess a capsid that is neither purely helical nor purely icosahedral, and that may possess extra structures such as protein tails or a complex outer wall.

A complete virus particle, known as a virion, consists of nucleic acid surrounded by a protective coat of protein called a capsid. These are formed from identical protein subunits called capsomeres. Viruses can have a lipid “envelope” derived from the host cell membrane. The capsid is made from proteins encoded by the viral genome and its shape serves as the basis for morphological distinction. Virally coded protein subunits will self-assemble to form a capsid, in general requiring the presence of the virus genome. Complex viruses code for proteins that assist in the construction of their capsid. Proteins associated with nucleic acid are known as nucleoproteins, and the association of viral capsid proteins with viral nucleic acid is called a nucleocapsid. The capsid and entire virus structure can be mechanically (physically) probed through atomic force microscopy.

viruses are much smaller than bacteria. Most viruses that have been studied have a diameter between 20 and 300 nanometers. Some filoviruses have a total length of up to 1400 nm; their diameters are only about 80 nm. Most viruses, such as virions, cannot be seen with an optical microscope, so scanning and transmission electron microscopes are used to visualize them.

To increase the contrast between viruses and the background, electron-dense “stains” are used. These are solutions of salts of heavy metals, such as tungsten, that scatter the electrons from regions covered with the stain. When virions are coated with stain (positive staining), fine detail is obscured. Negative staining overcomes this problem by staining the background only.

Key Points

- Viruses are very small and to reliably visualize them, stains and electron microscopy are needed.
- Each virus is a nucleic acid (RNA or DNA) surrounded by a coating, referred to as an envelope or capsid.
- Viruses encode capsid proteins which encase the nucleic acid. Sometimes, viral proteins combine with host proteins to make the envelope.
- The shape of a viral coat has implications on how a virus infects a host.

Key Terms

- **capsomere**: Any of the individual protein subunits of a viral capsid
- **capsid**: The outer protein shell of a virus.
- **icosahedral**: of, relating to, or having the shape of an icosahedron

---

This page titled 15.13B: General Morphology is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.2B: General Morphology** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.13C: Complex and Asymmetrical Virus Particles

Learning Objectives

- Break down the differences between complex and asymmetrical viruses

Viruses have many structural shapes, often falling into certain categories. While some have symmetrical shapes, viruses with asymmetrical structures are referred to as “complex. ” These viruses possess a capsid that is neither purely helical nor purely icosahedral, and may possess extra structures such as protein tails or a complex outer walls.

Some bacteriophages, such as Enterobacteria phage T4, have a complex structure consisting of an icosahedral head bound to a helical tail, which may have a hexagonal base plate with protruding protein tail fibers. This tail structure acts like a molecular syringe, attaching to the bacterial host and then injecting the viral genome into the cell.

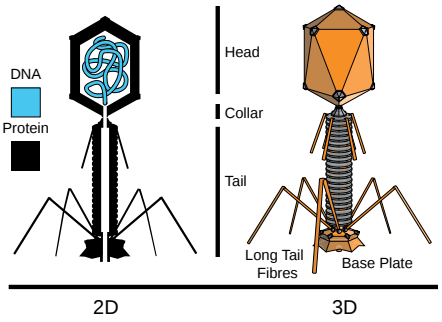


Figure: **T4 Bacteriophage**: T4 is a bacteriophage that infects E. coli and is referred to as a complex virus. Although it has an icosahedral head, its tail makes it asymmetrical, or complex in terms of structure.

The poxviruses are large, complex viruses that have an unusual morphology. The viral genome is associated with proteins within a central disk structure known as a nucleoid. The nucleoid is surrounded by a membrane and two lateral bodies of unknown function. The virus has an outer envelope with a thick layer of protein studded over its surface. The whole virion is slightly pleiomorphic, ranging from ovoid to brick shape.

Mimivirus is the largest characterized virus, with a capsid diameter of 400 nm. Protein filaments measuring 100 nm project from the surface. The capsid appears hexagonal under an electron microscope, therefore the capsid is probably icosahedral. In 2011, researchers discovered a larger virus on the ocean floor off the coast of Las Cruces, Chile. Provisionally named *Megavirus chilensis*, it can be seen with a basic optical microscope.

Some viruses that infect archaea have complex structures unrelated to any other form of virus. These include a wide variety of unusual shapes, ranging from spindle-shaped structures, to viruses that resemble hooked rods, teardrops, or even bottles. Other archaeal viruses resemble the tailed bacteriophages, and can have multiple tail structures.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: ***CC BY-SA: Attribution-ShareAlike***

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- OpenStax College, Biology. October 16, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44595/latest...ol11448/latest. **License**: ***CC BY: Attribution***
- isometric. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/isometric. **License**: ***CC BY-SA: Attribution-ShareAlike***
- capsid. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/capsid. **License**: ***CC BY-SA: Attribution-ShareAlike***
- envelope. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/envelope. **License**: ***CC BY-SA: Attribution-ShareAlike***
- filamentous. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/filamentous. **License**: ***CC BY-SA: Attribution-ShareAlike***

- OpenStax College, Viral Evolution, Morphology, and Classification. October 16, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44595/latest...e_21_01_02.jpg. **License**: *CC BY: Attribution*
- OpenStax College, Viral Evolution, Morphology, and Classification. October 16, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44595/latest...e_21_01_03.png. **License**: *CC BY: Attribution*
- Virus. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Virus. **License**: *CC BY-SA: Attribution-ShareAlike*
- Virus. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Virus. **License**: *CC BY-SA: Attribution-ShareAlike*
- capsomere. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/capsomere. **License**: *CC BY-SA: Attribution-ShareAlike*
- capsid. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/capsid. **License**: *CC BY-SA: Attribution-ShareAlike*
- icosahedral. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/icosahedral. **License**: *CC BY-SA: Attribution-ShareAlike*
- OpenStax College, Viral Evolution, Morphology, and Classification. October 16, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44595/latest...e_21_01_02.jpg. **License**: *CC BY: Attribution*
- OpenStax College, Viral Evolution, Morphology, and Classification. October 16, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44595/latest...e_21_01_03.png. **License**: *CC BY: Attribution*
- Virus-types. **Provided by**: Wikimedia. **Located at**: commons.wikimedia.org/wiki/Fi...irus-types.png. **License**: ***Public Domain: No Known Copyright***
- Virus. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Virus. **License**: *CC BY-SA: Attribution-ShareAlike*
- capsid. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/capsid. **License**: *CC BY-SA: Attribution-ShareAlike*
- poxvirus. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/poxvirus. **License**: *CC BY-SA: Attribution-ShareAlike*
- OpenStax College, Viral Evolution, Morphology, and Classification. October 16, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44595/latest/Figure_21_01_02.jpg. **License**: *CC BY: Attribution*
- OpenStax College, Viral Evolution, Morphology, and Classification. October 16, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44595/latest/Figure_21_01_03.png. **License**: *CC BY: Attribution*
- Virus-types. **Provided by**: Wikimedia. **Located at**: commons.wikimedia.org/wiki/File:Virus-types.png. **License**: *Public Domain: No Known Copyright*
- Tevenphage. **Provided by**: Wikimedia. **Located at**: commons.wikimedia.org/wiki/File:Tevenphage.svg. **License**: *CC BY-SA: Attribution-ShareAlike*

Key Points

- Viruses can be structurally very different.
- Some complex viruses are large enough to be visible with a light microscope.
- The viruses of archaea are unique compared to other viruses.

Key Terms

- **capsid**: The outer protein shell of a virus.
- **poxvirus**: Any of the group of DNA viruses belonging to the family Poxviridae, which cause pox diseases in vertebrates.

This page titled 15.13C: Complex and Asymmetrical Virus Particles is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.2C: Complex and Asymmetrical Virus Particles** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.14: Classifying Viruses

This page titled 15.14: Classifying Viruses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.3: Classifying Viruses** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.14.1: The International Committee on Taxonomy of Viruses

Learning Objectives

- Describe the purpose and objectives of the International Committee on Taxonomy of Viruses

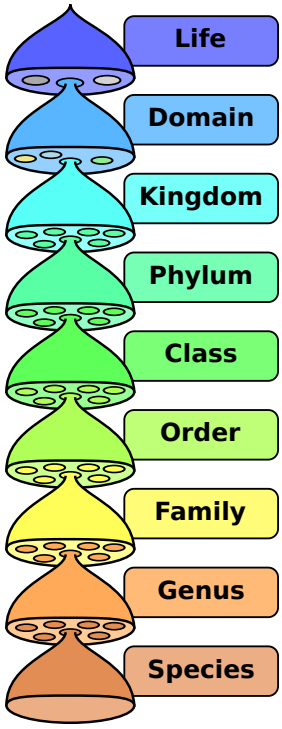


Figure: **Microbial taxonomy**: Taxonomic ranks

The International Committee on Taxonomy of Viruses (ICTV) is a committee which authorizes and organizes the taxonomic classification of viruses. They have developed a universal taxonomic scheme for viruses and aim to describe all the viruses of living organisms. Members of the committee are considered to be world experts on viruses. The committee formed from and is governed by the Virology Division of the International Union of Microbiological Societies. Detailed work such as delimiting the boundaries of species within a family is typically done by study groups, which consist of experts in the families. The committee also operates an authoritative database (ICTVdB) containing taxonomic information for 1,950 virus species, as of 2005. It is open to the public and is searchable by several different means.

The official objectives of the ICTV are:

1. To develop an internationally agreed upon taxonomy for viruses.
2. To develop internationally agreed upon names for virus taxa, including species and subviral agents.
3. To communicate taxonomic decisions to all users of virus names, in particular the international community of virologists, by publications and via the Internet.
4. To maintain an index of virus names.
5. To maintain an ICTV database on the Internet, that records the data that characterize each named viral taxon, together with the common names of each taxon in all major languages.

Proposals for new names, name changes, and the establishment and taxonomic placement of taxa are handled by the Executive Committee of the ICTV in the form of proposals. All relevant ICTV subcommittees and study groups are consulted prior to a decision being made. The name of a taxon has no status until it has been approved by ICTV, and names will only be accepted if they are linked to approved hierarchical taxa. If no suitable name is proposed for a taxon, the taxon may be approved and the name be left undecided until the adoption of an acceptable international name, when one is proposed to and accepted by ICTV. Names must not convey a meaning for the taxon which would seem to either exclude viruses which are rightfully members of that taxa, exclude members which might one day belong to that taxa, or include viruses which are members of different taxa.

Key Points

- Only a small part of the total diversity of viruses has been studied. Analyses of samples from humans found that about 20% of the virus sequences recovered have not been seen before.
- A large majority of sequences of viral samples from the environment, such as from seawater and ocean sediments, are completely novel.
- The general taxonomic structure is as follows: Order (-virales); Family (-viridae); Subfamily (-virinae); Genus (-virus); Species (-virus).

Key Terms

- **taxonomy**: the academic discipline of defining groups of biological organisms on the basis of shared characteristics and giving names to those groups. Each group is given a rank and groups of a given rank can be aggregated to form a super group of higher rank and thus create a hierarchical classification.

This page titled 15.14.1: The International Committee on Taxonomy of Viruses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.3A: The International Committee on Taxonomy of Viruses** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.14.2: The Baltimore Virus Classification

Learning Objectives

- List the characteristics of viruses that are useful for Baltimore classification

Virus classification is the process of naming viruses and placing them into a taxonomic system. Much like the classification systems used for cellular organisms, virus classification is the subject of ongoing debate and proposals. This is mainly due to the pseudo-living nature of viruses, which is to say they are non-living particles with some chemical characteristics similar to those of life. As such, they do not fit neatly into the established biological classification system in place for cellular organisms.

Baltimore classification (first defined in 1971) is a classification system that places viruses into one of seven groups depending on a combination of their nucleic acid (DNA or RNA), strandedness (single-stranded or double-stranded), Sense, and method of replication. Named after David Baltimore, a Nobel Prize-winning biologist, these groups are designated by Roman numerals and discriminate viruses depending on their mode of replication and genome type. Other classifications are determined by the disease caused by the virus or its morphology, neither of which are satisfactory due to different viruses either causing the same disease or looking very similar. In addition, viral structures are often difficult to determine under the microscope.

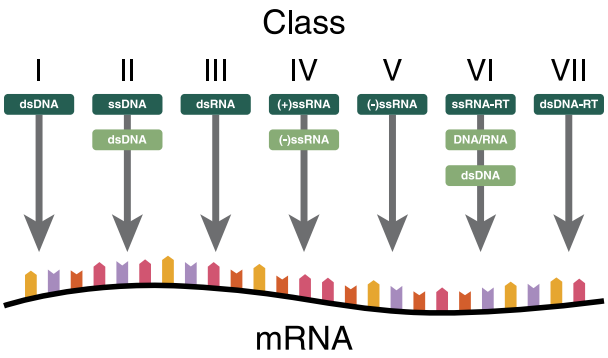


Figure: **Viral classes**: Baltimore classification of viruses

Classifying viruses according to their genome means that those in a given category will all behave in a similar fashion, offering some indication of how to proceed with further research. Viruses can be placed in one of the seven following groups:

1. I: dsDNA viruses (e.g. Adenoviruses, Herpesviruses, Poxviruses)
2. II: ssDNA viruses (+)sense DNA (e.g. Parvoviruses)
3. III: dsRNA viruses (e.g. Reoviruses)
4. IV: (+)ssRNA viruses (+)sense RNA (e.g. Picornaviruses, Togaviruses)
5. V: (−)ssRNA viruses (−)sense RNA (e.g. Orthomyxoviruses, Rhabdoviruses)
6. VI: ssRNA-RT viruses (+)sense RNA with DNA intermediate in life-cycle (e.g. Retroviruses)
7. VII: dsDNA-RT viruses (e.g. Hepadnaviruses)

Key Points

- Viral genome ‘s nucleic acid (DNA or RNA), strandedness (single-stranded or double-stranded), Sense, and method of replication determine its class.
- Other classifications are determined by the disease caused by the virus or its morphology.
- Viruses can be placed in one of the seven groups.

Key Terms

- **genome**: The complete genetic information (either DNA or, in some viruses, RNA) of an organism, typically expressed in the number of basepairs.

This page titled 15.14.2: The Baltimore Virus Classification is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.3B: The Baltimore Virus Classification** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.14.3: Evolution of Viruses

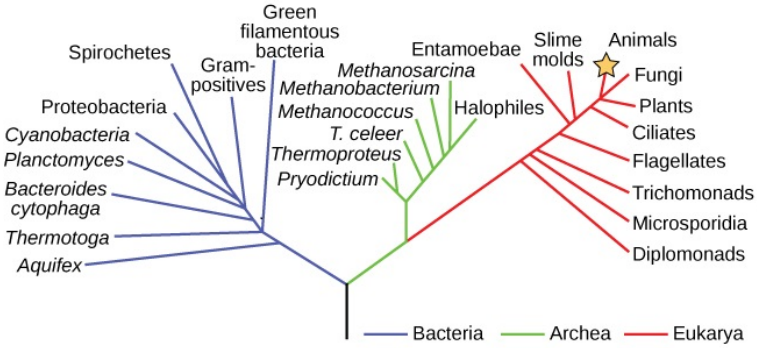
Learning Objectives

- Describe the difficulties in determining the origin of viruses

Evolution of Viruses

Although biologists have accumulated a significant amount of knowledge about how present-day viruses evolve, much less is known about how viruses originated in the first place. When exploring the evolutionary history of most organisms, scientists can look at fossil records and similar historic evidence. However, viruses do not fossilize, so researchers must conjecture by investigating how today's viruses evolve and by using biochemical and genetic information to create speculative virus histories.

While most findings agree that viruses don't have a single common ancestor, scholars have yet to find one hypothesis about virus origins that is fully accepted in the field. One possible hypothesis, called devolution or the regressive hypothesis, proposes to explain the origin of viruses by suggesting that viruses evolved from free-living cells. However, many components of how this process might have occurred are a mystery. A second hypothesis (called escapist or the progressive hypothesis) accounts for viruses having either an RNA or a DNA genome and suggests that viruses originated from RNA and DNA molecules that escaped from a host cell. A third hypothesis posits a system of self-replication similar to that of other self-replicating molecules, probably evolving alongside the cells they rely on as hosts; studies of some plant pathogens support this hypothesis.



(a) Rooted phylogenetic tree

Figure: **Common ancestor tree of life**: This phylogenetic tree of the three domains of life (Bacteria, Archaea, and Eukarya) attempts to identify when various species diverged from a common ancestor. Finding a common ancestor for viruses has proven to be far more difficult, especially since they do not fossilize.

As technology advances, scientists may develop and refine further hypotheses to explain the origin of viruses. The emerging field called virus molecular systematics attempts to do just that through comparisons of sequenced genetic material. These researchers hope to one day better understand the origin of viruses, a discovery that could lead to advances in the treatments for the ailments they produce.

Key Points

- Scientists agree that viruses don't have a single common ancestor, but have yet to agree on a single hypothesis about virus origins.
- The devolution or the regressive hypothesis suggests that viruses evolved from free-living cells.
- The escapist or the progressive hypothesis suggests that viruses originated from RNA and DNA molecules that escaped from a host cell.
- The self-replicating hypothesis posits a system of self-replication that most probably involves evolution alongside the host cells.

Key Terms

- **self-replicating**: able to generate a copy of itself
- **devolution**: degeneration (as opposed to evolution)

This page titled 15.14.3: Evolution of Viruses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.3C: Evolution of Viruses** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.14.4: Medical Importance of Viruses

Learning Objectives

- Describe the fundamental characteristics of viruses

Viruses are extremely diverse and have evolved to infect nearly all life forms. Amid this diversity, viruses with similar genome organizations exhibit major conserved themes in their replication strategies. Once inside a cell, all viruses must uncoat, replicate, and transcribe their genomes, and then repackage their genomes into viral progeny that are released from cells. RNA viruses in particular must coordinate the switch between plus and minus strand synthesis and between replication and transcription while protecting their genomes from cellular nucleases. Because of the conserved nature of a virus ‘s intracellular life cycle, fundamental advances in our understanding of replication have come from viruses that infect both animal and non-animal hosts.

The devastating effects of viral diseases such as AIDs, smallpox, polio, influenza, diarrhea, and hepatitis are well known, and studies of viral pathogens are easily justified from a world health perspective. Sobering examples of emerging viral diseases have occurred. Among these are the sudden emergence of the coronavirus that causes severe acute respiratory syndrome (SARS), the continued transmission of an avian influenza virus to humans (“bird flu”), and the isolation of poliovirus vaccine -wild type recombinants that have hampered poliovirus eradication efforts. In addition, the threat of bioterrorism became a reality on U.S. soil, creating an obligation for scientists to respond with aggressive countermeasures. Vaccination remains the preferred strategy for controlling viral diseases because the intimate association of viruses with the host cellular machinery complicates the development of safe drugs. However, certain viruses have proven difficult targets for vaccines, and antiviral drugs provide the only option for controlling disease.

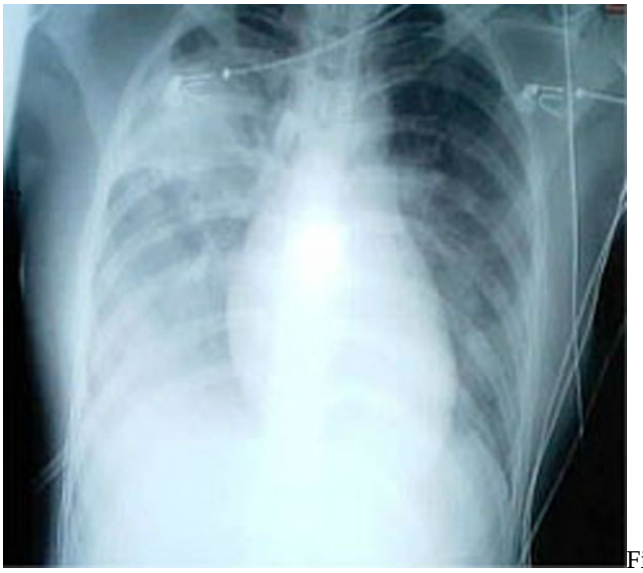


Figure: **Medical importance of SARS**: A chest x-ray showing increased opacity in both lungs, indicative of pneumonia, in a patient with SARS.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: ***CC BY-SA: Attribution-ShareAlike***

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- International Committee on Taxonomy of Viruses. **Provided by**: Wikipedia. **Located at**: http://en.Wikipedia.org/wiki/Interna...omy_of_Viruses. **License**: ***CC BY-SA: Attribution-ShareAlike***
- taxonomy. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/taxonomy**. **License**: ***CC BY-SA: Attribution-ShareAlike***

- Biological classification L Pengo vflip. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Bi...engo_vflip.svg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Virus classification. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Virus_classification**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- genome. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/genome**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Biological classification L Pengo vflip. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Bi...engo_vflip.svg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- File:VirusBaltimoreClassification.svg - Wikipedia, the free encyclopedia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/w/index.php?...ion.svg&page=1**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- OpenStax College, Biology. October 16, 2013. **Provided by**: OpenStax CNX. **Located at**: **http://cnx.org/content/m44595/latest...ol11448/latest**. **License**: ***CC BY: Attribution***
- devolution. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/devolution**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- self-replicating. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/self-replicating**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Biological classification L Pengo vflip. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Bi...engo_vflip.svg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- File:VirusBaltimoreClassification.svg - Wikipedia, the free encyclopedia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/w/index.php?...ion.svg&page=1**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- OpenStax College, Organizing Life on Earth. November 9, 2013. **Provided by**: OpenStax CNX. **Located at**: **http://cnx.org/content/m44588/latest/#fig-ch20_01_01**. **License**: ***CC BY: Attribution***
- Severe acute respiratory syndrome. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Severe_...atory_syndrome**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Poliovirus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Poliovirus**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- vaccination. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/vaccination**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- eradication. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/eradication**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Biological classification L Pengo vflip. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Bi...engo_vflip.svg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- File:VirusBaltimoreClassification.svg - Wikipedia, the free encyclopedia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/w/index.php?...ion.svg&page=1**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- OpenStax College, Organizing Life on Earth. November 9, 2013. **Provided by**: OpenStax CNX. **Located at**: **http://cnx.org/content/m44588/latest/#fig-ch20_01_01**. **License**: ***CC BY: Attribution***
- SARS xray. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:SARS_xray.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***

Key Points

- Viruses multiply by taking control of the host cell's genetic material and regulating the synthesis and assembly of new viruses.
- Viruses are able to infect a host cell and cause acute diseases or alter its genetic material to cause chronic diseases such as cancer.
- Most viral infections can resolve in weeks but others are the cause of more serious, debilitating and sometimes fatal diseases.

Key Terms

- **vaccination**: inoculation with a vaccine in order to protect a particular disease or strain of disease.
- **eradication**: the act of plucking up by the roots; a rooting out; extirpation; utter destruction.

This page titled 15.14.4: Medical Importance of Viruses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.3D: Medical Importance of Viruses** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.15: Culturing Viruses

This page titled 15.15: Culturing Viruses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.4: Culturing Viruses** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.15A: Batch Culture of Bacteriophages

Learning Objectives

- Define the reasons for, and ways to batch culture bacteriophages

Strategies of Replication

Virus or phage cultures require host cells in which to multiply. For bacteriophages, cultures are grown by infecting bacterial cells. The phage can then be isolated from the resulting plaques in a lawn of bacteria on a plate.

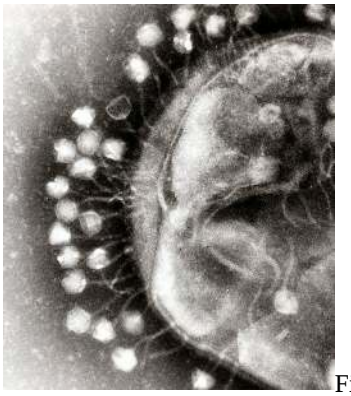


Figure: **Bacteriophages infecting a bacteria**: Virus or phage cultures require host cells in which to multiply. For bacteriophages, cultures are grown by infecting bacterial cells. The phage can then be isolated from the resulting plaques in a lawn of bacteria on a plate.

A bacteriophage is any one of a number of viruses that infect bacteria. They do this by injecting genetic material, which they carry enclosed in an outer protein capsid, into a host bacterial cell. The genetic material can be ssRNA, dsRNA, ssDNA, or dsDNA ('ss-' or 'ds-' prefix denotes single-strand or double-strand), along with either circular or linear arrangements.

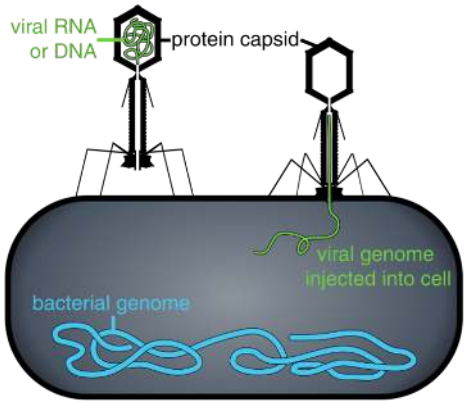


Figure: **Bacteriophage**: Diagram of how some bacteriophages infect bacterial cells.

To enter a host cell, bacteriophages attach to specific receptors on the surface of bacteria, including lipopolysaccharides, teichoic acids, proteins, or even flagella. This specificity means a bacteriophage can infect only those bacteria bearing receptors to which they can bind, which in turn determines the phage's host range. Host growth conditions also influence the ability of the phage to attach and invade them. As phage virions do not move independently, they must rely on random encounters with the right receptors when in solution within blood, lymphatic circulation, irrigation, soil water, or other environments..

Phages may be released via cell lysis, by extrusion, or, in a few cases, by budding. Lysis, by tailed phages, is achieved by an enzyme called endolysin, which attacks and breaks down the cell wall peptidoglycan. An altogether different phage type, the filamentous phages, make the host cell continually secrete new virus particles. Released virions are described as free, and, unless defective, are capable of infecting a new bacterium. Budding is associated with certain Mycoplasma phages. In contrast to virion release, phages displaying a lysogenic cycle do not kill the host but, rather, become long-term residents as prophage.

Key Points

- A bacteriophage is a type of virus that infects bacteria. It does so by injecting genetic material – either DNA or RNA – which it carries enclosed in an outer protein capsid.
- To enter a host cell, bacteriophages attach to specific receptors on the surface of bacteria, including lipopolysaccharides, teichoic acids, proteins, or even flagella.
- Phage virions do not move independently, they must rely on random encounters with the right receptors when in solution (blood, lymphatic circulation, irrigation, soil water, etc.).

Key Terms

- **bacteriophage**: A virus that specifically infects bacteria.

This page titled 15.15A: Batch Culture of Bacteriophages is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.4A: Batch Culture of Bacteriophages** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.15B: Tissue Culture of Animal Viruses

Learning Objectives

- Discover the use of, and reasons for, culturing animal viruses in host cells

Cell culture is the complex process by which cells are grown under controlled conditions, generally outside of their natural environment. In practice, the term “cell culture” now refers to the culturing of cells derived from multi-cellular eukaryotes, especially animal cells. However, there are also cultures of plants, fungi, and microbes, including viruses, bacteria, and protists. The historical development and methods of cell culture are closely interrelated to those of tissue culture and organ culture. Animal cell culture became a common laboratory technique in the mid-1900’s, but the concept of maintaining live cell lines separated from their original tissue source was discovered in the 19th century.

Viruses are obligate intracellular parasites that require living cells in order to replicate. Cultured cells, eggs, and laboratory animals may be used for virus isolation. Although embroyonated eggs and laboratory animals are very useful for the isolation of certain viruses, cell cultures are the sole system for virus isolation in most laboratories. The development of methods for cultivating animal cells has been essential to the progress of animal virology. To prepare cell cultures, tissue fragments are first dissociated, usually with the aid of trypsin or collagenase. The cell suspension is then placed in a flat-bottomed glass or plastic container (petri dish, a flask, a bottle, test tube) together with a suitable liquid medium. e.g. Eagle’s, and an animal serum. After a variable lag, the cells will attach and spread on the bottom of the container and then start dividing, giving rise to a primary culture. Attachment to a solid support is essential for the growth of normal cells.



Figure: **Cytopathic effect**: Viral cytopathic effect of herpes simplex virus.

Cell cultures vary greatly in their susceptibility to different viruses. It is of utmost importance that the most sensitive cell cultures are used for a particular suspected virus. Specimens for cell culture should be transported to the laboratory as soon as possible upon being taken. Swabs should be put in a vial containing virus transport medium. Bodily fluids and tissues should be placed in a sterile container. Upon receipt, the specimen is inoculated into several different types of cell culture depending on the nature of the specimen and the clinical presentation. The maintenance media should be changed after one hour or the next morning. The inoculated tubes should be incubated at 35-37ºC in a rotating drum. Rotation is optimal for the isolation of respiratory viruses and result in an earlier appearance of the cytopathic effects (CPE) for many viruses. If stationary tubes are used, it is critical that the culture tubes be positioned so that the cell monolayer is bathed in nutrient medium.

Key Points

- Tissue culture is a useful method for cultivating clinical samples suspected of harboring a virus. This method helps with the detection, identification, and characterization of viruses in the laboratory.
- Tissue culture of animal viruses involves growing animal cells in flasks using various broth media and then infecting these cells with virus.
- Transfection can be carried out using calcium phosphate, by electroporation, or by mixing a cationic lipid with the material to produce liposomes, which fuse with the cell membrane and deposit their cargo inside.
- Cytopathic effect is a non-lytic damage that viruses cause to cells. These vary in their manifestation and damaging effect.

Key Terms

- **cell culture**: The complex process by which cells are grown under controlled conditions, generally outside of their natural environment.

- **cytopathic effect**: Refers to degenerative changes in cells, especially in tissue culture, and may be associated with the multiplication of certain viruses.

This page titled 15.15B: Tissue Culture of Animal Viruses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.4B: Tissue Culture of Animal Viruses** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.15C: Inoculation of Live Animals

Learning Objectives

- Describe live animal innoculation

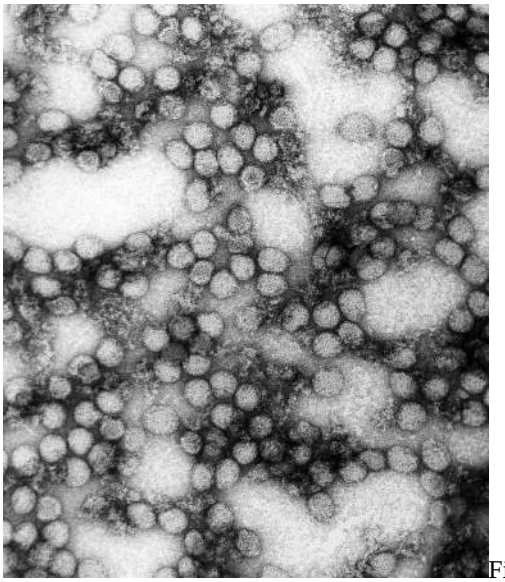


Figure: **Yellow fever virus**: A micrograph of the yellow fever virus.

Viruses are obligate intracellular parasites and cannot grow on inanimate media. They need living cells for replication, which can be provided by inoculation in live animals among other methods used to culture viruses (cell culture or inoculation of embryonated eggs). Inoculation of human volunteers was the only known method of cultivation of viruses and understanding viral disease. In 1900, Reed and his colleagues used human volunteers for their work on yellow fever. Due to serious risk involved, human volunteers are recruited only when no other method is available and the virus is relatively harmless. Smallpox was likely the first disease people tried to prevent by purposely inoculating themselves with other infections and was the first disease for which a vaccine was produced. Today, studying viruses via the inoculation of humans would require a stringent study of ethical practices by an institutional review board.

In the past few decades, animal inoculation has been employed for virus isolation. The laboratory animals used include monkeys, rabbits, guinea pigs, rats, hamsters, and mice. The choice of animals and route of inoculation (intracerebral, intraperitoneal, subcutaneous, intradermal, or intraocular) depends largely on the type of virus to be isolated. Handling of animals and inoculation into various routes requires special experience and training. In addition to virus isolation, animal inoculation can also be used to observe pathogenesis, immune response, epidemiology, and oncogenesis. Growth of the virus in inoculated animals may be indicated by visible lesions, disease, or death. Sometimes, serial passage into animals may be required to obtain visible evidence of viral growth. Animal inoculation has several disadvantages as immunity may interfere with viral growth, and the animal may harbor latent viruses.

Key Points

- Live inoculation was first used on human volunteers for the study of yellow fever virus.
- Animals of choice for cultivating viruses include monkeys, rabbits, guinea pigs, rats, hamsters, and mice.
- Live animal inoculation requires an experienced personnel to perform various inoculation techniques.

Key Terms

- **latent**: Existing or present but concealed or inactive.
- **oncogenesis**: The formation and development of tumors
- **inoculation**: The introduction of an antigenic substance or vaccine into the body to produce immunity to a specific disease.

This page titled 15.15C: Inoculation of Live Animals is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.4C: Inoculation of Live Animals** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.15D: Viral Identification

Learning Objectives

- Compare the replication of DNA, RNA, and reverse transcribing viruses

Replication of Viruses

The genetic material within virus particles and the method by which the material is replicated vary considerably between different types of viruses.

TYPES

DNA viruses: The genome replication of most DNA viruses takes place in the cell's nucleus. If the cell has the appropriate receptor on its surface, these viruses sometimes enter the cell by direct fusion with the cell membrane (e.g., herpesviruses) or, more usually, by receptor-mediated endocytosis. Most DNA viruses are entirely dependent on the host cell's DNA and RNA synthesizing machinery and RNA processing machinery; however, viruses with larger genomes may encode much of this machinery themselves. In eukaryotes the viral genome must cross the cell's nuclear membrane to access this machinery, while in bacteria it need only enter the cell.

RNA viruses: Replication usually takes place in the cytoplasm. RNA viruses can be placed into four different groups, depending on their modes of replication. The polarity of single-stranded RNA viruses largely determines the replicative mechanism, depending on whether or not it can be used directly by ribosomes to make proteins. The other major criterion is whether the genetic material is single-stranded or double-stranded. All RNA viruses use their own RNA replicase enzymes to create copies of their genomes.

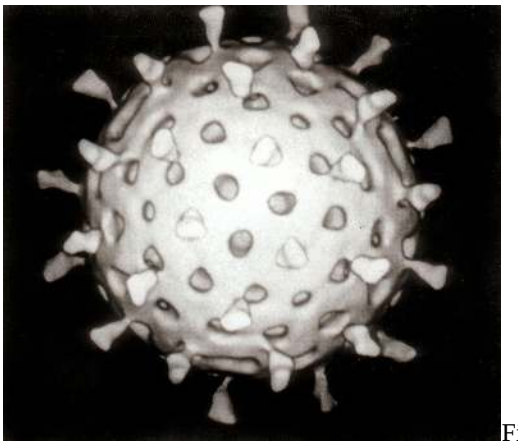


Figure: **Computer assisted reconstruction of a rotavirus particle**: An example of Baltimore Virus classification I: dsDNA virusesII: ssDNA virusesIII: dsRNA virusesIV: (+)ssRNA virusesV: (−)ssRNA virusesVI: ssRNA-RT virusesVII: dsDNA-RT viruses

Reverse transcribing viruses: These have ssRNA (Retroviridae, Metaviridae, Pseudoviridae) or dsDNA (Caulimoviridae, and Hepadnaviridae) in their particles. Reverse transcribing viruses with RNA genomes (retroviruses), use a DNA intermediate to replicate, whereas those with DNA genomes (pararetroviruses) use an RNA intermediate during genome replication. Both types use a reverse transcriptase, or RNA-dependent DNA polymerase enzyme, to carry out the nucleic acid conversion. Retroviruses integrate the DNA produced by reverse transcription into the host genome as a provirus as a part of the replication process. Pararetroviruses do not, although integrated genome copies, usually of plant pararetroviruses, can give rise to infectious virus. They are susceptible to antiviral drugs that inhibit the reverse transcriptase enzyme, e.g. zidovudine and lamivudine. An example of the first type is HIV, which is a retrovirus. Examples of the second type are the Hepadnaviridae, which includes Hepatitis B virus.

The *Baltimore classification* developed by David Baltimore is a virus classification system that groups viruses into families, depending on their type of genome (DNA, RNA, single-stranded (ss), double-stranded (ds), etc.) and their method of replication. Classifying viruses according to their genome means that those in a given category will all behave in much the same way, which offers some indication of how to proceed with further research.

In summary:

- I: dsDNA viruses (e.g. Adenoviruses, Herpesviruses, Poxviruses)
- II: ssDNA viruses (+)sense DNA (e.g. Parvoviruses)
- III: dsRNA viruses (e.g. Reoviruses)IV: (+)ssRNA viruses (+)sense RNA (e.g. Picornaviruses, Togaviruses)V: (−)ssRNA viruses (−)sense RNA (e.g. Orthomyxoviruses, Rhabdoviruses)
- VI: ssRNA-RT viruses (+)sense RNA with DNA intermediate in life-cycle (e.g. Retroviruses)
- VII: dsDNA-RT viruses (e.g. Hepadnaviruses)

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: *CC BY-SA: Attribution-ShareAlike*

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- Microbiological culture. **Provided by**: Wikipedia. **Located at**: http://en.Wikipedia.org/wiki/Microbiological_culture. **License**: *CC BY-SA: Attribution-ShareAlike*
- Bacteriophage. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Bacteriophage. **License**: *CC BY-SA: Attribution-ShareAlike*
- Bacteriophage. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Bacteriophage. **License**: *CC BY-SA: Attribution-ShareAlike*
- bacteriophage. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/bacteriophage. **License**: *CC BY-SA: Attribution-ShareAlike*
- File:Phage injecting its genome into bacteria.svg - Wikimedia Commons. **Provided by**: Wikimedia. **Located at**: commons.wikimedia.org/w/index.php?title=File:Phage_injecting_its_genome_into_bacteria.svg&page=1. **License**: *CC BY-SA: Attribution-ShareAlike*
- **Provided by**: Wikimedia. **Located at**: upload.wikimedia.org/Wikipedia/commons/5/52/Phage.jpg. **License**: *Public Domain: No Known Copyright*
- Cell culture. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Cell_culture. **License**: *CC BY-SA: Attribution-ShareAlike*
- Viral culture. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Viral_culture. **License**: *CC BY-SA: Attribution-ShareAlike*
- cell culture. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/cell%20culture. **License**: *CC BY-SA: Attribution-ShareAlike*
- cytopathic effect. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/cytopathic%20effect. **License**: *CC BY-SA: Attribution-ShareAlike*
- File:Phage injecting its genome into bacteria.svg - Wikimedia Commons. **Provided by**: Wikimedia. **Located at**: commons.wikimedia.org/w/index.php?title=File:Phage_injecting_its_genome_into_bacteria.svg&page=1. **License**: *CC BY-SA: Attribution-ShareAlike*
- **Provided by**: Wikimedia. **Located at**: upload.wikimedia.org/Wikipedia/commons/5/52/Phage.jpg. **License**: *Public Domain: No Known Copyright*
- Herpes simplex virus pap test. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:Herpes_simplex_virus_pap_test.jpg. **License**: *CC BY-SA: Attribution-ShareAlike*
- Viral culture. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Viral_culture. **License**: *CC BY-SA: Attribution-ShareAlike*
- Inoculation. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Inoculation. **License**: *CC BY-SA: Attribution-ShareAlike*
- oncogenesis. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/oncogenesis. **License**: *CC BY-SA: Attribution-ShareAlike*
- inoculation. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/inoculation. **License**: *CC BY-SA: Attribution-ShareAlike*
- latent. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/latent. **License**: *CC BY-SA: Attribution-ShareAlike*

- File:Phage injecting its genome into bacteria.svg - Wikimedia Commons. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/w/index.php?title=File:Phage_injecting_its_genome_into_bacteria.svg&page=1**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- **Provided by**: Wikimedia. **Located at**: **upload.wikimedia.org/Wikipedia/commons/5/52/Phage.jpg**. **License**: ***Public Domain: No Known Copyright***
- Herpes simplex virus pap test. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Herpes_simplex_virus_pap_test.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- YellowFeverVirus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:YellowFeverVirus.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Virus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Virus**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Baltimore classification. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Baltimore_classification**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- genome. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/genome**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- File:Phage injecting its genome into bacteria.svg - Wikimedia Commons. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/w/index.php?title=File:Phage_injecting_its_genome_into_bacteria.svg&page=1**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- **Provided by**: Wikimedia. **Located at**: **upload.wikimedia.org/Wikipedia/commons/5/52/Phage.jpg**. **License**: ***Public Domain: No Known Copyright***
- Herpes simplex virus pap test. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Herpes_simplex_virus_pap_test.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- YellowFeverVirus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:YellowFeverVirus.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Rotavirus Reconstruction. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Rotavirus_Reconstruction.jpg**. **License**: ***Public Domain: No Known Copyright***

Key Points

- The genome replication of most DNA viruses takes place in the cell's nucleus.
- RNA viruses can be placed into four different groups depending on their modes of replication.
- Reverse transcribing viruses have ssRNA (Retroviridae, Metaviridae, Pseudoviridae) or dsDNA (Caulimoviridae, and Hepadnaviridae) in their particles.

Key Terms

- **genome**: The complete genetic information (either DNA or, in some viruses, RNA) of an organism, typically expressed in the number of basepairs.

This page titled 15.15D: Viral Identification is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.4D: Viral Identification** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.16: Subviral Entities

This page titled 15.16: Subviral Entities is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.6: Subviral Entities** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.16A: Defective Viruses

Learning Objectives

- Distinguish between defective viruses, satellite viruses, and helper viruses

Virologists also study subviral particles, infectious entities notably smaller and simpler than viruses:

- viroids (naked circular RNA molecules infecting plants)
- satellites (nucleic acid molecules with or without a capsid that require a helper virus for infection and reproduction)
- prions (proteins that can exist in a pathological conformation that induces other prion molecules to assume that same conformation)

Not all viruses can reproduce in a host cell by themselves. Since viruses are so small, the size of their genome is limited. For example, some viruses have coded instructions for only making a few different proteins for the viruses' capsid. On the other hand, the human genome codes for over 30,000 different proteins. Therefore, the lack of coded instructions causes some viruses to need the presence of other viruses to help them reproduce themselves. Such viruses are called replication defective.

Satellites depend on co-infection of a host cell with a helper virus for productive multiplication. Their nucleic acids have substantially distinct nucleotide sequences from either their helper virus or host. When a satellite subviral agent encodes the coat protein in which it is encapsulated, it is then called a satellite virus. Satellite viral particles should not be confused with satellite DNA.

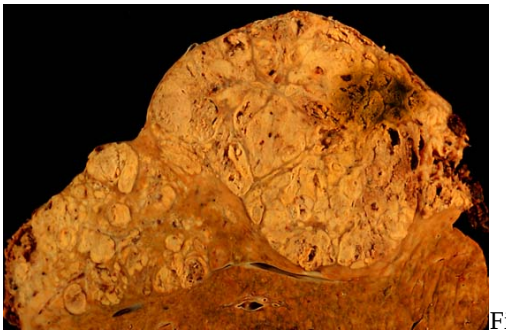


Figure: ***Hepatocellular Carcinoma****: Cirrhosis leading to hepatocellular carcinoma (autopsy specimen). The photo shows a view of a longitudinal slice taken through the full length of the liver.*

The hepatitis delta virus of humans has an RNA genome similar to viroids, but has a protein coat derived from hepatitis B virus and cannot produce one of its own. Therefore, it is a defective virus and cannot replicate without the help of hepatitis B virus. In similar manner, the sputnik virophage is dependent on mimivirus, which infects the protozoan Acanthamoeba castellanii. These viruses that are dependent on the presence of other virus species in the host cell are called satellites. They may represent evolutionary intermediates of viroids and viruses.

Hepatitis D, also referred to as hepatitis D virus (HDV) and classified as Hepatitis delta virus, is a disease caused by a small circular enveloped RNA virus. It is one of five known hepatitis viruses: A, B, C, D, and E. HDV is considered to be a subviral satellite because it can only propagate in the presence of the hepatitis B virus (HBV). Transmission of HDV can occur either via simultaneous infection with HBV (coinfection) or superimposed on chronic hepatitis B or hepatitis B carrier state (superinfection). Both superinfection and coinfection with HDV results in more severe complications compared to infection with HBV alone. These complications include a greater likelihood of experiencing liver failure in acute infections and a rapid progression to liver cirrhosis, with an increased chance of developing liver cancer in chronic infections. In combination with hepatitis B virus, hepatitis D has the highest mortality rate of all the hepatitis infections of 20%.

Key Points

- Not all viruses can reproduce in a host cell by themselves. Since viruses are so small, the size of their genome is limited. The lack of coded instructions causes some viruses to need the presence of other viruses to help them reproduce themselves. Such viruses are called replication defective.

- A satellite is a subviral agent composed of nucleic acid that depends on the co- infection of a host cell with a helper or master virus for its multiplication. When a satellite encodes the coat protein in which its nucleic acid is encapsidated it is referred to as a satellite virus.
- These viruses that are dependent on the presence of other virus species in the host cell are called satellites and may represent evolutionary intermediates of viroids and viruses.

Key Terms

- **Helper virus**: A helper virus is a virus used when producing copies of a helper dependent viral vector which does not have the ability to replicate on its own. The helper virus is used to coinfect cells alongside the viral vector and provides the necessary enzymes for replication of the genome of the viral vector.
- **Satellite**: A subviral agent composed of nucleic acid that depends on the co-infection of a host cell with a helper or master virus for its multiplication.

This page titled 15.16A: Defective Viruses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.6A: Defective Viruses** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.16B: Viroids

Learning Objectives

- Relate the structure and replication of a viroid to its ability to cause diseases in plants

Viroids are plant pathogens that consist of a short stretch (a few hundred nucleobases) of highly complementary, circular, single-stranded RNA without the protein coat that is typical for viruses. In comparison, the genome of the smallest known viruses capable of causing an infection by themselves is around 2 kilobases in size. The human pathogen Hepatitis D virus is similar to viroids. Viroids are extremely small in size, ranging from 246 to 467 nucleotide (nt) long genome and consisting of fewer than 10,000 atoms. Viroids were discovered and given this name by Theodor Otto Diener, a plant pathologist at the Agricultural Research Service in Maryland, in 1971.

Viroid RNA does not code for any protein. The replication mechanism involves RNA polymerase II, an enzyme normally associated with synthesis of messenger RNA from DNA, which instead catalyzes “rolling circle” synthesis of new RNA using the viroid’s RNA as template. Some viroids are ribozymes, having catalytic properties which allow self-cleavage and ligation of unit-size genomes from larger replication intermediates. The first viroid to be identified was the potato spindle tuber viroid (PSTVd). Some 33 species have been identified.



Figure: ***Putative secondary structure of the potato spindle tuber viroid.****: black – secondary structure of the viroid red – GAAAC sequence common to all viroids yellow – central conservative sequence blue – nucleotide numbers*

There has long been confusion over how viroids are able to induce symptoms in plants without encoding any protein products within their sequences. Evidence now suggests that RNA silencing is involved in the process. First, changes to the viroid genome can dramatically alter its virulence. This reflects the fact that any siRNAs produced would have less complementary base pairing with target messenger RNA. Secondly, siRNAs corresponding to sequences from viroid genomes have been isolated from infected plants. Finally, transgenic expression of the noninfectious hpRNA of potato spindle tuber viroid develops all the corresponding viroid like symptoms. This evidence indicates that when viroids replicate via a double stranded intermediate RNA, they are targeted by a dicer enzyme and cleaved into siRNAs that are then loaded onto the RNA-induced silencing complex. The viroid siRNAs actually contain sequences capable of complementary base pairing with the plant’s own messenger RNAs and induction of degradation or inhibition of translation is what causes the classic viroid symptoms.

Virusoids are circular single-stranded RNAs dependent on plant viruses for replication and encapsidation. The genome of virusoids consists of several hundred nucleotides and only encodes structural proteins. Virusoids are similar to viroids in size, structure, and means of replication. Virusoids, while being studied in virology, are not considered as viruses but as subviral particles. Since they depend on helper viruses, they are classified as satellites.

The Pospiviroidae are a family of viroids, including the first viroid to be discovered, PSTVd. Their secondary structure is key to their biological activity. The classification of this family is based on differences in the conserved central region sequence. Pospiviroidae replication occurs in an asymmetric fashion via host cell RNA polymerase, RNase, and RNA ligase.

The Avsunviroidae are a family of viroids. At present three members are known. They consist of RNA genomes between 246-375 nucleotides in length. They are single stranded covalent circles and have intramolecular base pairing. All members lack a central conserved region. Replication occurs in the chloroplasts of plant cells. Key features of replication include no helper virus required and no proteins are encoded for. Unlike the other family of viroids, Pospiviroidae, Avsunviroidae are thought to replicate via a symmetrical rolling mechanism. It is thought the positive RNA strand acts as a template to form negative strands with the help of an enzyme thought to be RNA polymerase II. The negative RNA strands are then cleaved by ribozyme activity and circularizes. A second rolling circle mechanism forms a positive strand which is also cleaved by ribozyme activity and then ligated to become circular. The site of replication is unknown, but it is thought to be in the chloroplast and in the presence of Mg2+ ions.

Avocado sunblotch viroid (ASBV) is an important disease affecting avocado trees. Infections result in lower yields and poorer quality fruit. ASBV is the smallest known viroid that infects plants and is transmitted by pollen and infected seeds or budwood. Trees infected with the viroid often show no symptoms other than a reduction in yield. However, they are still carriers and can pass

the disease onto other plants. Symptoms in more serious infections include depressed longitudinal streaks of yellow in the fruit. The fruit may also become red or white in color. Symptoms in the leaf are uncommon, but include bleached veins and petioles. Rectangular cracking patterns also occur in the bark of older branches. Infected but symptomless trees have a higher concentration of viroid particles than those showing symptoms. Symptomless trees also represent a greater danger in terms of spread of the viroid.

Key Points

- Viroid RNA does not code for any protein. The replication mechanism involves RNA polymerase II, an enzyme normally associated with synthesis of messenger RNA from DNA, which instead catalyzes “rolling circle” synthesis of new RNA using the viroid’s RNA as template.
- The first viroid to be identified was potato spindle tuber viroid (PSTVd). Some 33 species have been identified.
- There has long been confusion over how viroids are able to induce symptoms in plants without encoding any protein products within their sequences. Evidence now suggests that RNA silencing is involved in the process.
- Virusoids are circular single-stranded RNAs dependent on plant viruses for replication and encapsidation. Since they depend on helper viruses, they are classified as satellites.

Key Terms

- **Virusoid**: Circular single-stranded RNAs dependent on plant viruses for replication and encapsidation. The genome of virusoids consist of several hundred nucleotides and only encodes structural proteins.
- **viroid**: plant pathogens, of the order Viroidales, that consist of just a short section of RNA but without the protein coat typical of viruses

---

This page titled 15.16B: Viroids is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.6B: Viroids** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.16C: Prions

Learning Objectives

- Compare the protein-only hypothesis of prion diseases with the virion hypothesis, as well as the heterodimer model and the fibril model of prion replication

A prion is an infectious agent composed of protein in a misfolded form. This is the central idea of the Prion Hypothesis, which remains debated. This is in contrast to all other known infectious agents (virus /bacteria/fungus/parasite) which must contain nucleic acids (either DNA, RNA, or both). The word *prion*, coined in 1982 by Stanley B. Prusiner, is derived from the words protein and infection. Prions are responsible for the transmissible spongiform encephalopathies in a variety of mammals, including bovine spongiform encephalopathy (BSE, also known as “mad cow disease”) in cattle and Creutzfeldt–Jakob disease (CJD) in humans. All known prion diseases affect the structure of the brain or other neural tissue, are currently untreatable and universally fatal.

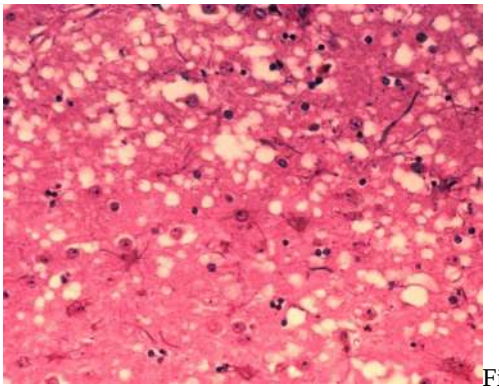


Figure: ***Prion-affected tissue****: This micrograph of brain tissue reveals the cytoarchitectural histopathologic changes found in bovine spongiform encephalopathy. The presence of vacuoles, i.e. microscopic “holes” in the gray matter, gives the brain of BSE-affected cows a sponge-like appearance when tissue sections are examined in the lab.*

Prions propagate by transmitting a misfolded protein state. When a prion enters a healthy organism, it induces existing, properly folded proteins to convert into the disease-associated prion form; it acts as a template to guide the misfolding of more proteins into prion form. These newly-formed prions can then go on to convert more proteins themselves; triggering a chain reaction. All known prions induce the formation of an amyloid fold, in which the protein polymerises into an aggregate consisting of tightly-packed beta sheets. Amyloid aggregates are fibrils, growing at their ends, and replicating when breakage causes two growing ends to become four growing ends.

The incubation period of prion diseases is determined by the exponential growth rate associated with prion replication, which is a balance between the linear growth and the breakage of aggregates. Propagation of the prion depends on the presence of normally-folded protein in which the prion can induce misfolding; animals which do not express the normal form of the prion protein cannot develop nor transmit the disease.

All known mammalian prion diseases are caused by the so-called prion protein, PrP. The endogenous, properly-folded form is denoted PrPC (for Common or Cellular) while the disease-linked, misfolded form is denoted PrPSc (for Scrapie, after one of the diseases first linked to prions and neurodegeneration.) The precise structure of the prion is not known, though they can be formed by combining PrPC, polyadenylic acid, and lipids in a Protein Misfolding Cyclic Amplification (PMCA) reaction.

Proteins showing prion-type behavior are also found in some fungi, which has been useful in helping to understand mammalian prions. Fungal prions do not appear to cause disease in their hosts.

The first hypothesis that tried to explain how prions replicate in a protein-only manner was the heterodimer model. This model assumed that a single PrPSc molecule binds to a single PrPC molecule and catalyzes its conversion into PrPSc. The two PrPSc molecules then come apart and can go on to convert more PrPC. However, a model of prion replication must explain both how prions propagate, and why their spontaneous appearance is so rare. Manfred Eigen showed that the heterodimer model requires

PrPSc to be an extraordinarily effective catalyst, increasing the rate of the conversion reaction by a factor of around 10^{15}. This problem does not arise if PrPSc exists only in aggregated forms such as amyloid, where cooperativity may act as a barrier to spontaneous conversion. What is more, despite considerable effort, infectious monomeric PrPSc has never been isolated.

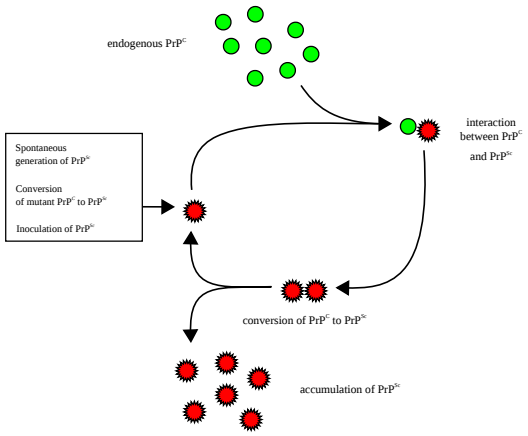


Figure: ***Diagram demonstrating how prion numbers increase****: Heterodimer model of prion propagation.*

An alternative model assumes that PrPSc exists only as fibrils, and that fibril ends bind PrPC and convert it into PrPSc. If this were all, then the quantity of prions would increase linearly, forming ever longer fibrils. But exponential growth of both PrPSc and of the quantity of infectious particles is observed during prion disease. This can be explained by taking into account fibril breakage. A mathematical solution for the exponential growth rate resulting from the combination of fibril growth and fibril breakage has been found.

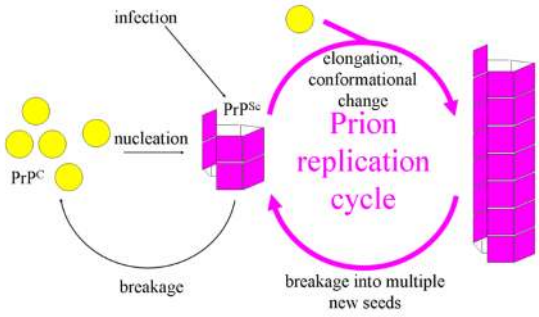


Figure: **The Fibril Model**: Illustrating prion propagation.

The protein-only hypothesis has been criticised by those who feel that the simplest explanation of the evidence to date is viral. For more than a decade, Yale University neuropathologist Laura Manuelidis has been proposing that prion diseases are caused instead by an unidentified slow virus. In January 2007, she and her colleagues published an article reporting to have found a virus in 10%, or less, of their scrapie-infected cells in culture.

The virion hypothesis states that TSEs are caused by a replicable informational molecule (likely to be a nucleic acid) bound to PrP. Many TSEs, including scrapie and BSE, show strains with specific and distinct biological properties, a feature which supporters of the virion hypothesis feel is not explained by prions.

Recent studies propagating TSE infectivity in cell-free reactions and in purified component chemical reactions strongly suggest against TSE's viral nature. Using a similar defined recipe of multiple components (PrP, POPG lipid, RNA), Jiyan Ma and colleagues generated infectious prions from recombinant PrP expressed from E. coli, casting further doubt on this hypothesis.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: *CC BY-SA: Attribution-ShareAlike*

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- Subviral agent. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Subviral_agent%23Subviral_agents**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Virology. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Virology**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Hepatitis delta virus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Hepatitis_delta_virus%23Virology**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Virus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Virus**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Satellite (biology). **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Satellite_(biology)**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Defective interfering particle. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Defective_interfering_particle**. **License**: *CC BY-SA: Attribution-ShareAlike*
- General Biology/Classification of Living Things/Viruses. **Provided by**: Wikibooks. **Located at**: **en.wikibooks.org/wiki/General_Biology/Classification_of_Living_Things/Viruses**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Helper virus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Helper%20virus**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Satellite. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Satellite**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Hepatocellular carcinoma 1. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Hepatocellular_carcinoma_1.jpg**. **License**: *Public Domain: No Known Copyright*
- Avsunviroidae. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Avsunviroidae**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Pospiviroidae. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Pospiviroidae**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Avocado sunblotch viroid. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Avocado_sunblotch_viroid**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Viroid. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Viroid**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Virusoid. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Virusoid**. **License**: *CC BY-SA: Attribution-ShareAlike*
- viroid. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/viroid**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Virusoid. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Virusoid**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Hepatocellular carcinoma 1. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Hepatocellular_carcinoma_1.jpg**. **License**: *Public Domain: No Known Copyright*
- PSTviroid. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:PSTviroid.png?uselang=he**. **License**: *Public Domain: No Known Copyright*
- Prion. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Prion**. **License**: *CC BY-SA: Attribution-ShareAlike*
- prion. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/prion**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Amyloid. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Amyloid**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Creutzfeldt. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Creutzfeldt?Jakob+disease**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Hepatocellular carcinoma 1. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Hepatocellular_carcinoma_1.jpg**. **License**: *Public Domain: No Known Copyright*
- PSTviroid. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:PSTviroid.png?uselang=he**. **License**: *Public Domain: No Known Copyright*
- Histology bse. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Histology_bse.jpg**. **License**: *Public Domain: No Known Copyright*

- Prion propagation. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Prion_propagation.svg**. **License**: ***CC BY: Attribution***
- Prion replication. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Pr...eplication.png**. **License**: ***CC BY-SA: Attribution-ShareAlike***

Key Points

- Prions are responsible for the transmissible spongiform encephalopathies in a variety of mammals, including bovine spongiform encephalopathy and Creutzfeldt–Jakob disease in humans. All known prion diseases affect the structure of neural tissue, are currently untreatable and universally fatal.
- Prions propagate by transmitting a misfolded protein state. When a prion enters a healthy organism, it induces existing, properly-folded proteins to convert into the disease-associated, prion form; it then acts as a template to guide the misfolding of more proteins into prion form.
- All known mammalian prion diseases are caused by the so-called prion protein, PrP. The endogenous, properly folded, form is denoted PrPC while the disease-linked, misfolded form is denoted PrPSc.The precise structure of the prion is not known.
- The first hypothesis to explain how prions replicate in a protein-only manner was the heterodimer model, which assumed that a single PrPSc molecule binds to a single PrPC molecule and catalyzes its conversion into PrPSc. The two PrPSc molecules then come apart and can go on to convert more PrPC.
- An alternative model assumes that PrPSc exists only as fibrils and that fibril ends bind PrPC and convert it into PrPSc. The exponential growth of both PrPSc and of the quantity of infectious particles observed during prion disease can be explained by taking fibril breakage into account.
- The protein-only hypothesis has been criticised by those who feel that the simplest explanation of the evidence to date is viral. However, recent studies propagating TSE infectivity in cell-free reactions and in purified component chemical reactions strongly suggest against TSE's viral nature.

Key Terms

- **Amyloid**: Insoluble fibrous protein aggregates sharing specific structural traits. They arise from at least 18 inappropriately folded versions of proteins and polypeptides present naturally in the body. These misfolded structures alter their proper configuration such that they erroneously interact with one another or other cell components forming insoluble fibrils. They have been associated with the pathology of more than 20 serious human diseases in that, abnormal accumulation of amyloid fibrils in organs may lead to amyloidosis, and may play a role in various neurodegenerative disorders.
- **Creutzfeldt–Jakob disease**: A degenerative neurological disorder (brain disease) that is incurable and invariably fatal. In CJD, the brain tissue develops holes and takes on a sponge-like texture, due to a type of infectious protein called a prion.
- **prion**: A self-propagating misfolded conformer of a protein that is responsible for a number of diseases that affect the brain and other neural tissue.

This page titled 15.16C: Prions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.6C: Prions** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.17: Viral Ecology

This page titled 15.17: Viral Ecology is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.13: Viral Ecology** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.17A: Emergence of Viral Pathogens

Learning Objectives

- Demonstrate the ways a virus can go from benign to pathogenic

Humans or other potential viral hosts are constantly exposed to viruses, yet most viral exposure has no effect. However, many viruses that were once benign later become pathogens through a genetic change, which can occur by different mechanisms. One common evolutionary process whereby viral genes change over time is called genetic drift, where individual bases in the DNA or RNA mutate to other bases. Most of these point mutations are “silent”—they do not change the protein that the gene encodes—but others can confer evolutionary advantages such as resistance to antiviral drugs.

The transformation of viruses from benign to pathogenic occurs via two additional processes more specific to viruses. Viral genomes are constantly mutating, producing new forms of these antigens. If one of these new forms of an antigen is sufficiently different from the old antigen, it will no longer bind to the receptors and viruses with these new antigens can evade immunity to the original strain of the virus. When such a change occurs, people who have had the illness in the past will lose their immunity to the new strain and vaccines against the original virus will also become less effective. Two processes drive the antigens to change: antigenic drift and antigenic shift (antigenic drift being the more common).

Antigenic drift is a mechanism for variation by viruses that involves the accumulation of mutations within the antibody -binding sites so that the resulting viruses cannot be inhibited as well by antibodies against previous strains, making it easier for them to spread throughout a partially immune population. Antigenic drift occurs in both influenza A and influenza B viruses. The rate of antigenic drift is dependent on two characteristics: the duration of the epidemic and the strength of host immunity. A longer epidemic allows for selection pressure to continue over an extended period of time and stronger host immune responses increase selection pressure for the development of novel antigens.

Alternatively, the change can occur by antigenic shift. Antigenic shift is a specific case of reassortment or viral shift that confers a phenotypic change; it is the process by which two or more different strains of a virus, or strains of two or more different viruses, combine to form a new subtype having a mixture of the surface antigens of the two or more original strains. The term is often applied specifically to influenza, as that is the best-known example, but the process also occurs with other viruses, such as the visna virus in sheep. When this happens with influenza viruses, pandemics might result.

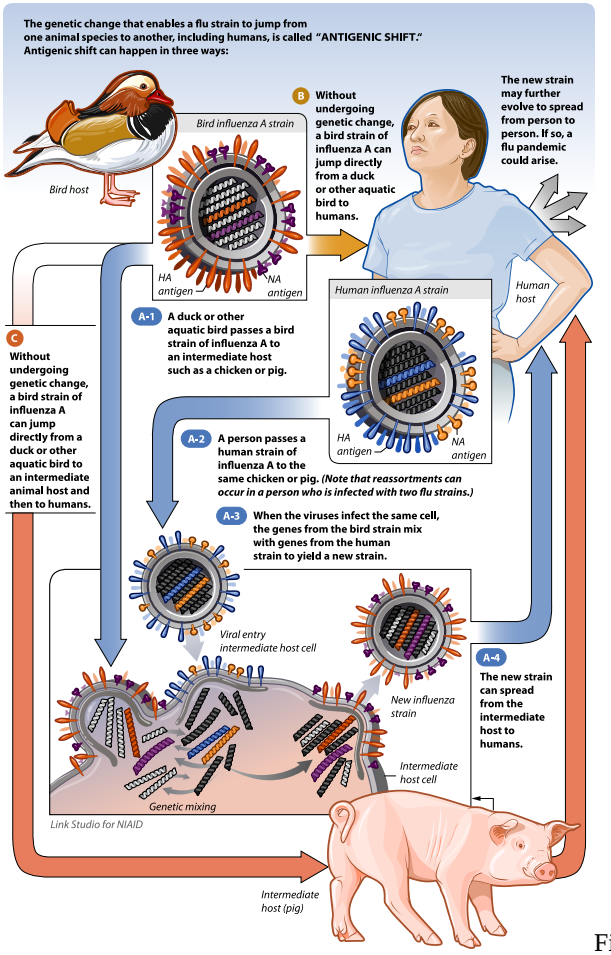


Figure: ***Pathogen emergence by antigenic shift****: This figure describes in detail how a virus that cannot infect a human can gain the ability to infect a human.*

Antigenic shift occurs only in influenza A because it infects more than just humans. Affected species include other mammals and birds, giving influenza A the opportunity for a major reorganization of surface antigens. Influenza B and C principally infect humans, minimizing the chance that a reassortment will change its phenotype drastically.

For example, if a pig was infected with a human influenza virus and an avian influenza virus at the same time, an antigenic shift could occur, producing a new virus that had most of the genes from the human virus, but a hemagglutinin or neuraminidase from the avian virus. The resulting new virus would likely be able to infect humans and spread from person to person, but it would have surface proteins (hemagglutinin and/or neuraminidase) not previously seen in influenza viruses that infect humans, and therefore most people would have little or no immune protection. If this new virus causes illness in people and can be transmitted easily from person to person, an influenza pandemic can occur. The most recent 2009 H1N1 outbreak was a result of an antigenic shift and reassortment between human, avian, and swine viruses.

Key Points

- For a virus to become pathogenic, genetic changes must occur. These changes occur via mutations, antigenic shift, or antigenic drift.
- Antigenic drift is the natural mutation over time of known strains, thus small changes may cause a harmless virus to become dangerous.
- Antigenic shift is a specific case of reassortment or viral shift that confers a phenotypic change. It is the process by which two or more different strains of a virus, or strains of two or more different viruses, combine to form a new subtype that can be more pathogenic than the original strains.
- Antigenic shift is a major driving force behind viruses inhabiting new niches and is responsible for some of the more aggressive human viruses.

Key Terms

- **antigenic shift**: A specific case of reassortment or viral shift that confers a phenotypic change; it is the process by which two or more different strains of a virus, or strains of two or more different viruses, combine to form a new subtype having a mixture of the surface antigens of the two or more original strains.
- **antigenic drift**: A mechanism for variation by viruses that involves the accumulation of mutations within the antibody-binding sites so that the resulting viruses cannot be inhibited as well by antibodies against previous strains, making it easier for them to spread throughout a partially immune population.

This page titled 15.17A: Emergence of Viral Pathogens is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.13A: Emergence of Viral Pathogens** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

15.17B: Viral Roles in Ecosystems

Learning Objectives

- Show the roles viruses play on ecosystems

Metagenomics is a relatively recent field of study that tries to understand the diversity—especially microbial—of the world around us. Through these studies it is now known that the number of viral particles and number of different viral species in almost every environment on Earth is immense. It is largely believed that viruses by species are the most numerous of any biological entity on earth. This is typified by the role of viruses in marine ecology. A teaspoon of seawater contains about one million viruses.

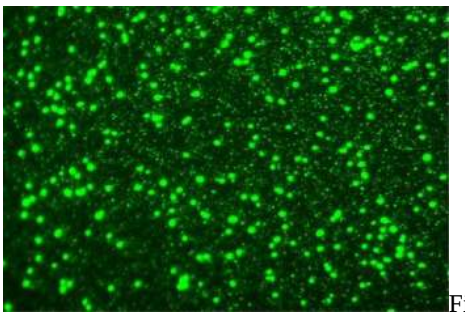


Figure: ***Viral diversity in seawater****: The large green dots are bacteria while the smaller green dots are viral particles. This represents a fraction of the viral diversity seen in teaspoon of marine water.*

Viruses are essential to the regulation of saltwater and freshwater ecosystems. Most of these viruses are bacteriophages, which are harmless to plants and animals. They infect and destroy the bacteria in aquatic microbial communities, comprising the most important mechanism of recycling carbon in the marine environment. The organic molecules released from the bacterial cells by the viruses stimulate fresh bacterial and algal growth.

Microorganisms constitute more than 90% of the biomass in the sea. It is estimated that viruses kill approximately 20% of this biomass each day, and that there are 15 times as many viruses in the oceans as there are bacteria and archaea. Viruses are the main agents responsible for the rapid destruction of harmful algal blooms, which often kill other marine life. The number of viruses in the oceans decreases further offshore and deeper into the water, where there are fewer host organisms. The effects of marine viruses are far-reaching; by increasing the amount of photosynthesis in the oceans, viruses are indirectly responsible for reducing the amount of carbon dioxide in the atmosphere by approximately 3 gigatonnes of carbon per year. Like any organism, marine mammals are susceptible to viral infections. In 1988 and 2002, thousands of harbor seals were killed in Europe by the phocine distemper virus. Many other viruses, including caliciviruses, herpesviruses, adenoviruses, and parvoviruses, circulate in marine mammal populations.

As mentioned, marine viruses are mostly bacteriophages, or phages. Phages are obligate intracellular parasites, meaning that they are able to reproduce only while infecting bacteria. Phages therefore are found only within environments that contain bacteria. Most environments contain bacteria, including our own bodies (called normal flora). Often these bacteria are found in large numbers. As a consequence, phages are found almost everywhere. As a rule of thumb, many phage biologists expect that phage population densities will exceed bacterial densities by a ratio of 10:1 or more (VBR or virus-to-bacterium ratio).

Estimates of bacterial numbers on Earth reach approximately 10^{30}; consequently, there is an expectation that 10^{31} or more individual virus (mostly phage) particles exist, making phages the most numerous category of “organisms” on our planet. Bacteria (along with archaea) appear to be highly diverse and there are possibly millions of species. Phage-ecological interactions therefore are quantitatively vast, with huge numbers of interactions. Phage-ecological interactions are also qualitatively diverse: there are huge numbers of environment types, bacterial-host types, and also individual phage types.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: ***CC BY-SA: Attribution-ShareAlike***

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- Virus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Virus**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Antigenic shift. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Antigenic_shift**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Antigenic drift. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Antigenic_drift**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Antigenic shift. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Antigenic_shift**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- antigenic shift. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/antigenic%20shift**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- antigenic drift. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/antigenic%20drift**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- AntigenicShift HiRes vector. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...Res_vector.svg**. **License**: ***Public Domain: No Known Copyright***
- Virus. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Virus**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Phage ecology. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Phage_ecology**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Boundless. **Provided by**: Boundless Learning. **Located at**: **www.boundless.com//biology/de...n/metagenomics**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- intracellular. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/intracellular**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- ecological. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/ecological**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- AntigenicShift HiRes vector. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...Res_vector.svg**. **License**: ***Public Domain: No Known Copyright***
- Seawater small life. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...small_life.png**. **License**: ***CC BY: Attribution***

Key Points

- The diversity and numbers of different viruses is incredible.
- In the world's oceans, 90% of the biomass is microbial, with viruses turning over 20% of that daily. Without the turnover of biomass driven by viruses, many sources of food would not be present for other organisms.
- As bacteria are incredibly diverse, then the viruses that infect them, phages, are even more diverse. As bacteria inhabit almost every niche of the earth, so do viruses.

Key Terms

- **ecological**: Relating to ecology, the interrelationships of organisms and their environment.
- **metagenomics**: The study of genomes recovered from environmental samples; especially the differentiation of genomes from multiple organisms or individuals, either in a symbiotic relationship, or at a crime scene.
- **intracellular**: Inside or within a cell.

This page titled 15.17B: Viral Roles in Ecosystems is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **9.13B: Viral Roles in Ecosystems** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

CHAPTER OVERVIEW

16: The Eukaryotes of Microbiology

Although bacteria and viruses account for a large number of the infectious diseases that afflict humans, many serious illnesses are caused by eukaryotic organisms. One example is malaria, which is caused by *Plasmodium*, a eukaryotic organism transmitted through mosquito bites. Malaria is a major cause of morbidity (illness) and mortality (death) that threatens 3.4 billion people worldwide.[1] In severe cases, organ failure and blood or metabolic abnormalities contribute to medical emergencies and sometimes death. Even after initial recovery, relapses may occur years later. In countries where malaria is endemic, the disease represents a major public health challenge that can place a tremendous strain on developing economies.

Worldwide, major efforts are underway to reduce malaria infections. Efforts include the distribution of insecticide-treated bed nets and the spraying of pesticides. Researchers are also making progress in their efforts to develop effective vaccines.[2] The President's Malaria Initiative, started in 2005, supports prevention and treatment. The Bill and Melinda Gates Foundation has a large initiative to eliminate malaria. Despite these efforts, malaria continues to cause long-term morbidity (such as intellectual disabilities in children) and mortality (especially in children younger than 5 years), so we still have far to go.

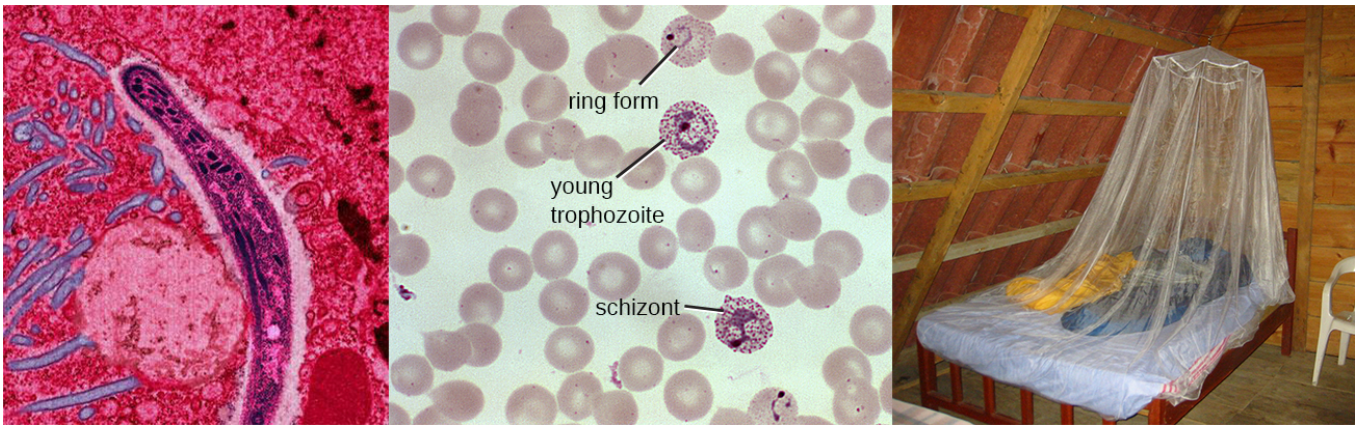


Figure 16.1: Malaria is a disease caused by a eukaryotic parasite transmitted to humans by mosquitos. Micrographs (left and center) show a sporozoite life stage, trophozoites, and a schizont in a blood smear. On the right is depicted a primary defense against mosquito-borne illnesses like malaria—mosquito netting. (credit left: modification of work by Ute Frevert; credit middle: modification of work by Centers for Disease Control and Prevention; credit right: modification of work by Tjeerd Wiersma)

16.1: Unicellular Eukaryotic Microorganisms
16.2: Parasitic Helminths
16.3: Fungi
16.4: Algae
16.5: Lichens
16.E: The Eukaryotes of Microbiology (Exercises)

Footnotes

1. 1 Centers for Disease Control and Prevention. "Impact of Malaria." September 22, 2015. http://www.cdc.gov/malaria/malaria_w...de/impact.html. Accessed January 18, 2016.
2. 2 RTS, S Clinical Trials Partnership. "Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial." The Lancet 23 April 2015. DOI: http://dx.doi.org/10.1016/S0140-6736(15)60721-8.

This page titled 16: The Eukaryotes of Microbiology is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

16.1: Unicellular Eukaryotic Microorganisms

Learning Objectives

- Summarize the general characteristics of unicellular eukaryotic parasites
- Describe the general life cycles and modes of reproduction in unicellular eukaryotic parasites
- Identify challenges associated with classifying unicellular eukaryotes
- Explain the taxonomic scheme used for unicellular eukaryotes
- Give examples of infections caused by unicellular eukaryotes

Clinical Focus: Part 1

Upon arriving home from school, 7-year-old Sarah complains that a large spot on her arm will not stop itching. She keeps scratching at it, drawing the attention of her parents. Looking more closely, they see that it is a red circular spot with a raised red edge (Figure **16.1.1**). The next day, Sarah's parents take her to their doctor, who examines the spot using a Wood's lamp. A Wood's lamp produces ultraviolet light that causes the spot on Sarah's arm to fluoresce, which confirms what the doctor already suspected: Sarah has a case of ringworm.

Sarah's mother is mortified to hear that her daughter has a "worm." How could this happen?

Exercise 16.1.1

What are some likely ways that Sarah might have contracted ringworm?



Figure **16.1.1**: Ringworm presents as a raised, red ring on the skin. (credit: Centers for Disease Control and Prevention)

Eukaryotic microbes are an extraordinarily diverse group, including species with a wide range of life cycles, morphological specializations, and nutritional needs. Although more diseases are caused by viruses and bacteria than by microscopic eukaryotes, these eukaryotes are responsible for some diseases of great public health importance. For example, the protozoal disease malaria was responsible for 584,000 deaths worldwide (primarily children in Africa) in 2013, according to the World Health Organization (WHO). The protist parasite *Giardia* causes a diarrheal illness (giardiasis) that is easily transmitted through contaminated water supplies. In the United States, *Giardia* is the most common human intestinal parasite (Figure **16.1.2**). Although it may seem surprising, parasitic worms are included within the study of microbiology because identification depends on observation of microscopic adult worms or eggs. Even in developed countries, these worms are important parasites of humans and of domestic animals. There are fewer fungal pathogens, but these are important causes of illness, as well. On the other hand, fungi have been important in producing antimicrobial substances such as penicillin. In this chapter, we will examine characteristics of protists, worms, and fungi while considering their roles in causing disease.

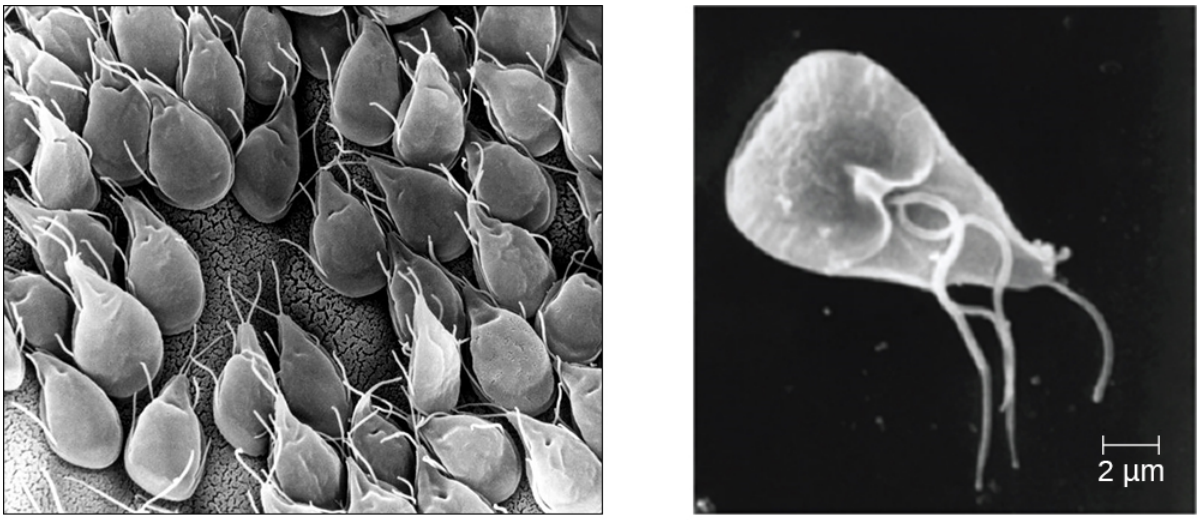


Figure **16.1.2**: (a) A scanning electron micrograph shows many *Giardia* parasites in the trophozoite, or feeding stage, in a gerbil intestine. (b) An individual trophozoite of *G. lamblia*, visualized here in a scanning electron micrograph. This waterborne protist causes severe diarrhea when ingested. (credit a, b: modification of work by Centers for Disease Control and Prevention)

Characteristics of Protists

The word *protist* is a historical term that is now used informally to refer to a diverse group of microscopic eukaryotic organisms. It is not considered a formal taxonomic term because the organisms it describes do not have a shared evolutionary origin. Historically, the protists were informally grouped into the “animal-like” protozoans, the “plant-like” algae, and the “fungus-like” protists such as water molds. These three groups of protists differ greatly in terms of their basic characteristics. For example, algae are photosynthetic organisms that can be unicellular or multicellular. Protozoa, on the other hand, are nonphotosynthetic, motile organisms that are always unicellular. Other informal terms may also be used to describe various groups of protists. For example, microorganisms that drift or float in water, moved by currents, are referred to as plankton. Types of plankton include zooplankton, which are motile and nonphotosynthetic, and phytoplankton, which are photosynthetic.

Protozoans inhabit a wide variety of habitats, both aquatic and terrestrial. Many are free-living, while others are parasitic, carrying out a life cycle within a host or hosts and potentially causing illness. There are also beneficial symbionts that provide metabolic services to their hosts. During the feeding and growth part of their life cycle, they are called trophozoites; these feed on small particulate food sources such as bacteria. While some types of protozoa exist exclusively in the trophozoite form, others can develop from trophozoite to an encapsulated cyst stage when environmental conditions are too harsh for the trophozoite. A cyst is a cell with a protective wall, and the process by which a trophozoite becomes a cyst is called encystment. When conditions become more favorable, these cysts are triggered by environmental cues to become active again through excystment.

One protozoan genus capable of encystment is *Eimeria*, which includes some human and animal pathogens. Figure **16.1.3** illustrates the life cycle of *Eimeria*.

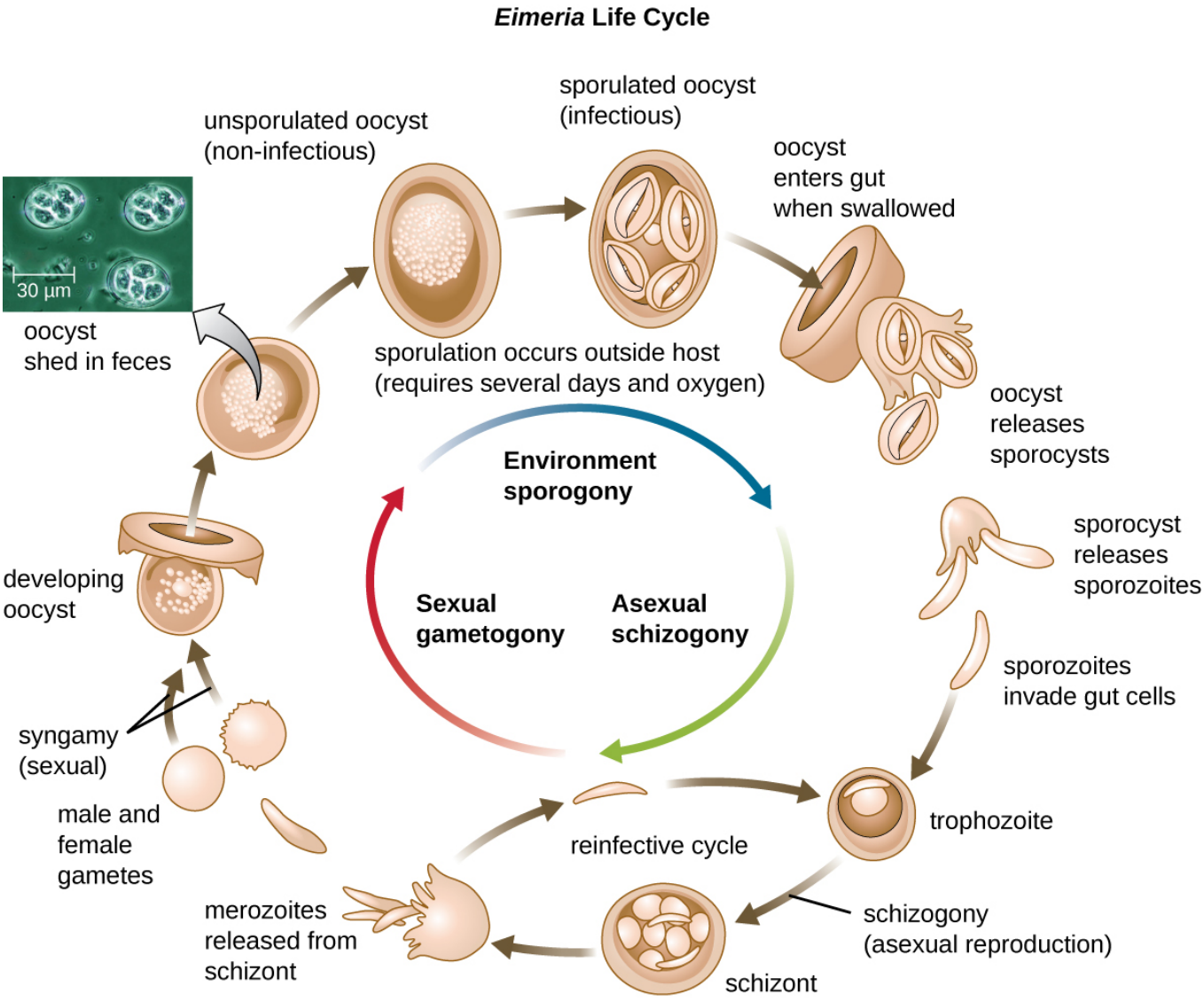


Figure **16.1.3**: In the sexual/asexual life cycle of Eimeria, oocysts (inset) are shed in feces and may cause disease when ingested by a new host. (credit "life cycle," "micrograph": modification of work by USDA)

Protozoans have a variety of reproductive mechanisms. Some protozoans reproduce asexually and others reproduce sexually; still others are capable of both sexual and asexual reproduction. In protozoans, asexual reproduction occurs by binary fission, budding, or schizogony. In schizogony, the nucleus of a cell divides multiple times before the cell divides into many smaller cells. The products of schizogony are called merozoites and they are stored in structures known as schizonts. Protozoans may also reproduce sexually, which increases genetic diversity and can lead to complex life cycles. Protozoans can produce haploid gametes that fuse through syngamy. However, they can also exchange genetic material by joining to exchange DNA in a process called conjugation. This is a different process than the conjugation that occurs in bacteria. The term protist conjugation refers to a true form of eukaryotic sexual reproduction between two cells of different mating types. It is found in ciliates, a group of protozoans, and is described later in this subsection.

All protozoans have a plasma membrane, or plasmalemma, and some have bands of protein just inside the membrane that add rigidity, forming a structure called the pellicle. Some protists, including protozoans, have distinct layers of cytoplasm under the membrane. In these protists, the outer gel layer (with microfilaments of actin) is called the ectoplasm. Inside this layer is a sol (fluid) region of cytoplasm called the endoplasm. These structures contribute to complex cell shapes in some protozoans, whereas others (such as amoebas) have more flexible shapes (Figure **16.1.4**).

Different groups of protozoans have specialized feeding structures. They may have a specialized structure for taking in food through phagocytosis, called a cytostome, and a specialized structure for the exocytosis of wastes called a cytoproct. Oral grooves leading to cytostomes are lined with hair-like cilia to sweep in food particles. Protozoans are heterotrophic. Protozoans that are holozoic ingest whole food particles through phagocytosis. Forms that are saprozoic ingest small, soluble food molecules.

Many protists have whip-like flagella or hair-like cilia made of microtubules that can be used for locomotion (Figure **16.1.4**). Other protists use cytoplasmic extensions known as pseudopodia ("false feet") to attach the cell to a surface; they then allow cytoplasm to flow into the extension, thus moving themselves forward.

Protozoans have a variety of unique organelles and sometimes lack organelles found in other cells. Some have contractile vacuoles, organelles that can be used to move water out of the cell for osmotic regulation (salt and water balance) (Figure **16.1.4**). Mitochondria may be absent in parasites or altered to kinetoplastids (modified mitochondria) or hydrogenosomes (see Unique Characteristics of Eukaryotic Cells for more discussion of these structures).

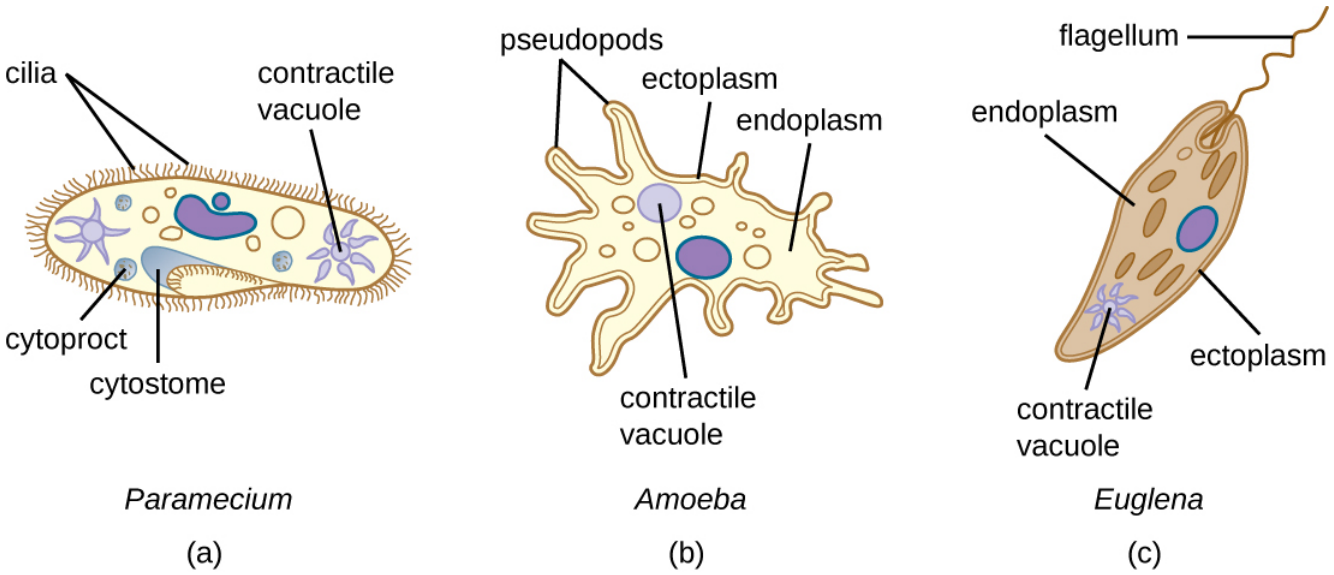


Figure **16.1.4**: (a) *Paramecium* spp. have hair-like appendages called cilia for locomotion. (b) *Amoeba* spp. use lobe-like pseudopodia to anchor the cell to a solid surface and pull forward. (c) *Euglena* spp. use a whip-like structure called a flagellum to propel the cell.

? Exercise 16.1.2

What is the sequence of events in reproduction by schizogony and what are the cells produced called?

Taxonomy of Protists

The protists are a polyphyletic group, meaning they lack a shared evolutionary origin. Since the current taxonomy is based on evolutionary history (as determined by biochemistry, morphology, and genetics), protists are scattered across many different taxonomic groups within the domain Eukarya. Eukarya is currently divided into six supergroups that are further divided into subgroups, as illustrated in (Figure **16.1.5**). In this section, we will primarily be concerned with the supergroups Amoebozoa, Excavata, and Chromalveolata; these supergroups include many protozoans of clinical significance. The supergroups Opisthokonta and Rhizaria also include some protozoans, but few of clinical significance. In addition to protozoans, Opisthokonta also includes animals and fungi, some of which we will discuss in Parasitic Helminths and Fungi. Some examples of the Archaeplastida will be discussed in Algae. Figure **16.1.6** and Figure **16.1.7** summarize the characteristics of each supergroup and subgroup and list representatives of each.

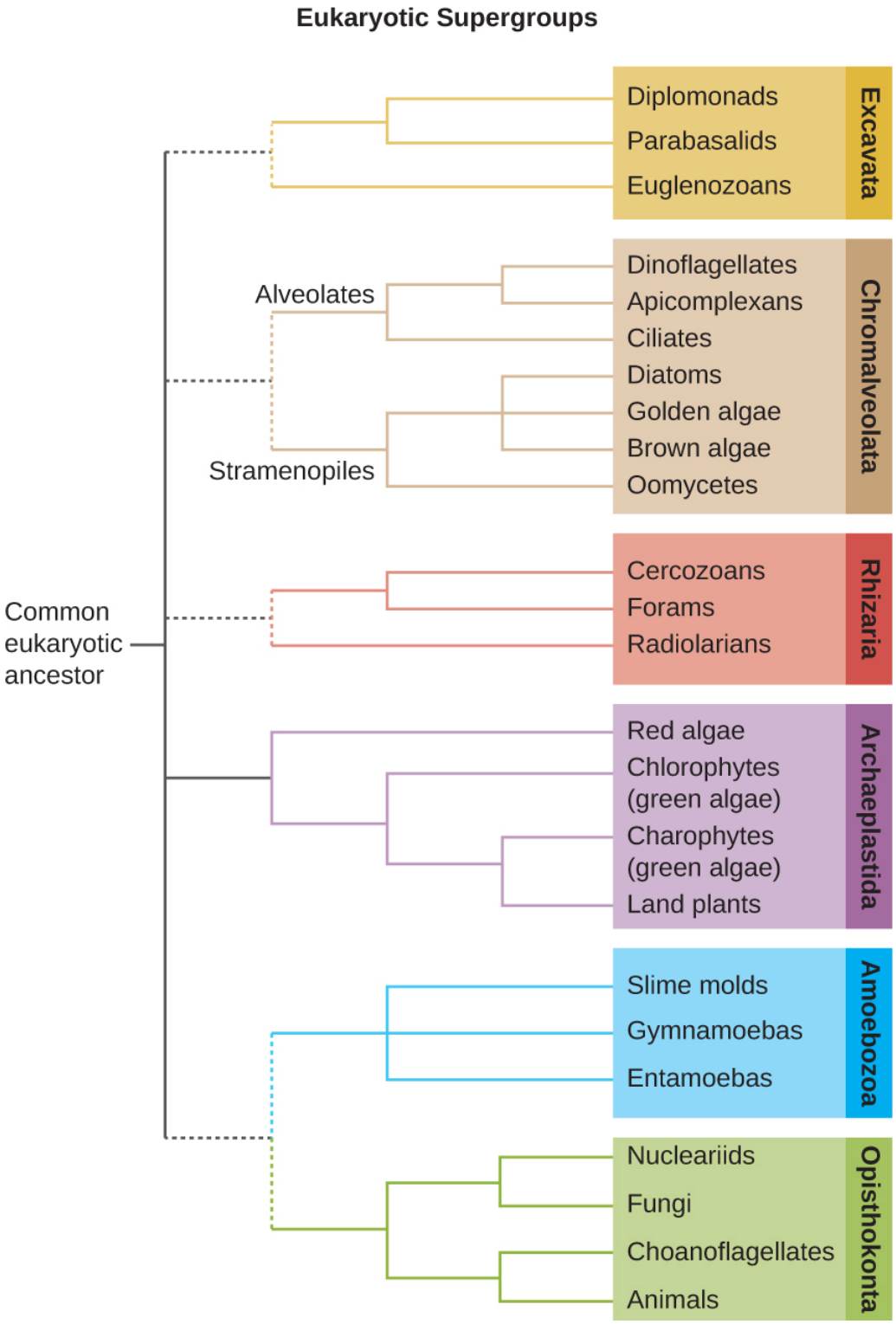


Figure 16.1.5: This tree shows a proposed classification of the domain Eukarya based on evolutionary relationships. Currently, the domain Eukarya is divided into six supergroups. Within each supergroup are multiple kingdoms. Dotted lines indicate suggested evolutionary relationships that remain under debate.

The Eukaryote Supergroups and Some Examples				
Supergroup	**Subgroups**	**Distinguishing Features**	**Examples**	**Clinical Notes**
Excavata	Fornicata	Form cysts Pair of equal nuclei No mitochondria Often parasitic Four free flagella	*Giardia lamblia*	Giardiasis
	Parabasalids	No mitochondria Four free flagella One attached flagellum No cysts Parasitic or symbiotic Basal bodies Kinetoplastids	*Trichomonas*	Trichomoniasis
	Euglenozoans	Photosynthetic or heterotrophic Flagella	*Euglena*	N/a
			Trypanosoma	African sleeping sickness, Chagas disease
			Leishmania	Leishmaniasis
Chromalveolata	Dinoflagellates	Cellulose theca Two dissimilar flagella	*Gonyaulax*	Red tides
			Alexandrium	Paralytic shellfish poisoning
			Pfiesteria	Harmful algal blooms
	Apicomplexans	Intracellular parasite Apical organelles	*Plasmodium*	Malaria
			Cryptosporidium	Cryptosporidiosis
			Theileria (Babesia)	Babesiosis
			Toxoplasma	Toxoplasmosis
	Ciliates	Cilia	*Balantidium*	Balantidiasis
			Paramecium	N/a
			Stentor	N/a
	Öomycetes/ peronosporomy-cetes	“Water molds” Generally diploid Cellulose cell walls	*Phytophthora*	Diseases in crops

Figure 16.1.6

The Eukaryote Supergroups and Some Examples (continued)				
Supergroup	**Subgroups**	**Distinguishing Features**	**Examples**	**Clinical Notes**
Rhizaria	Foraminifera	Amoeboid Threadlike pseudopodia Calcium carbonate shells	*Astrolonche*	N/a
	Radiolaria	Amoeboid Threadlike pseudopodia Silica shells	*Actinomma*	N/a
	Cercozoa	Amoeboid Threadlike pseudopodia Complex shells Parasitic forms	*Spongospora subterranea*	Powdery scab (potato disease)
			Plasmodiophora brassicae	Cabbage clubroot
Archaeplastida	Red algae	Chlorophyll *a* Phycoerythrin Phycocyanin Floridean starch Agar in cell walls	*Gelidium*	Source of agar
			Gracilaria	Source of agar
	Chlorophytes	Chlorophyll *a* Chlorophyll *b* Cellulose cell walls Starch storage	*Acetabularia*	N/a
			Ulva	N/a
Amoebozoa	Slime molds	Plasmodial and cellular forms	*Dictyostelium*	N/a
	Entamoebas	Trophozoites Form cysts	*Entamoeba*	Amoebiasis
			Naegleria	Primary amoebic meningoencephalitis
			Acanthamoeba	Keratitis, granulomatous amoebic encephalitis
Opisthokonta	Fungi	Chitin cell walls Unicellular or multicellular Often hyphae	Zygomycetes	Zygomycosis
			Ascomycetes	Candidiasis
			Basidiomycetes	Cryptococcosis
			Microsporidia	Microsporidiosis
	Animals	Multicellular heterotrophs No cell walls	Nematoda	Trichinosis; hookworm and pinworm infections
			Trematoda	Schistosomiasis
			Cestoda	Tapeworm infections

Figure 16.1.7

? Exercise 16.1.3

Which supergroups contain the clinically significant protists?

Amoebozoa

The supergroup Amoebozoa includes protozoans that use amoeboid movement. Actin microfilaments produce pseudopodia, into which the remainder of the protoplasm flows, thereby moving the organism. The genus *Entamoeba*includes commensal or parasitic

species, including the medically important *E. histolytica*, which is transmitted by cysts in feces and is the primary cause of amoebic dysentery. The notorious “brain-eating amoeba,” *Naegleria fowleri*, is also classified within the Amoebozoa. This deadly parasite is found in warm, fresh water and causes primary amoebic meningoencephalitis (PAM). Another member of this group is *Acanthamoeba*, which can cause keratitis (corneal inflammation) and blindness.

The Eumycetozoa are an unusual group of organisms called slime molds, which have previously been classified as animals, fungi, and plants (Figure 16.1.8). Slime molds can be divided into two types: cellular slime molds and plasmodial slime molds. The cellular slime molds exist as individual amoeboid cells that periodically aggregate into a mobile slug. The aggregate then forms a fruiting body that produces haploid spores. Plasmodial slime molds exist as large, multinucleate amoeboid cells that form reproductive stalks to produce spores that divide into gametes. One cellular slime mold, *Dictyostelium discoideum*, has been an important study organism for understanding cell differentiation, because it has both single-celled and multicelled life stages, with the cells showing some degree of differentiation in the multicelled form. Figure 16.1.9and Figure 16.1.10 illustrate the life cycles of cellular and plasmodial slime molds, respectively.



(a) (b)

Figure 16.1.8: (a) The cellular slime mold *Dictyostelium discoideum* can be grown on agar in a Petri dish. In this image, individual amoeboid cells (visible as small spheres) are streaming together to form an aggregation that is beginning to rise in the upper right corner of the image. The primitively multicellular aggregation consists of individual cells that each have their own nucleus. (b) *Fuligo septica* is a plasmodial slime mold. This brightly colored organism consists of a large cell with many nuclei.

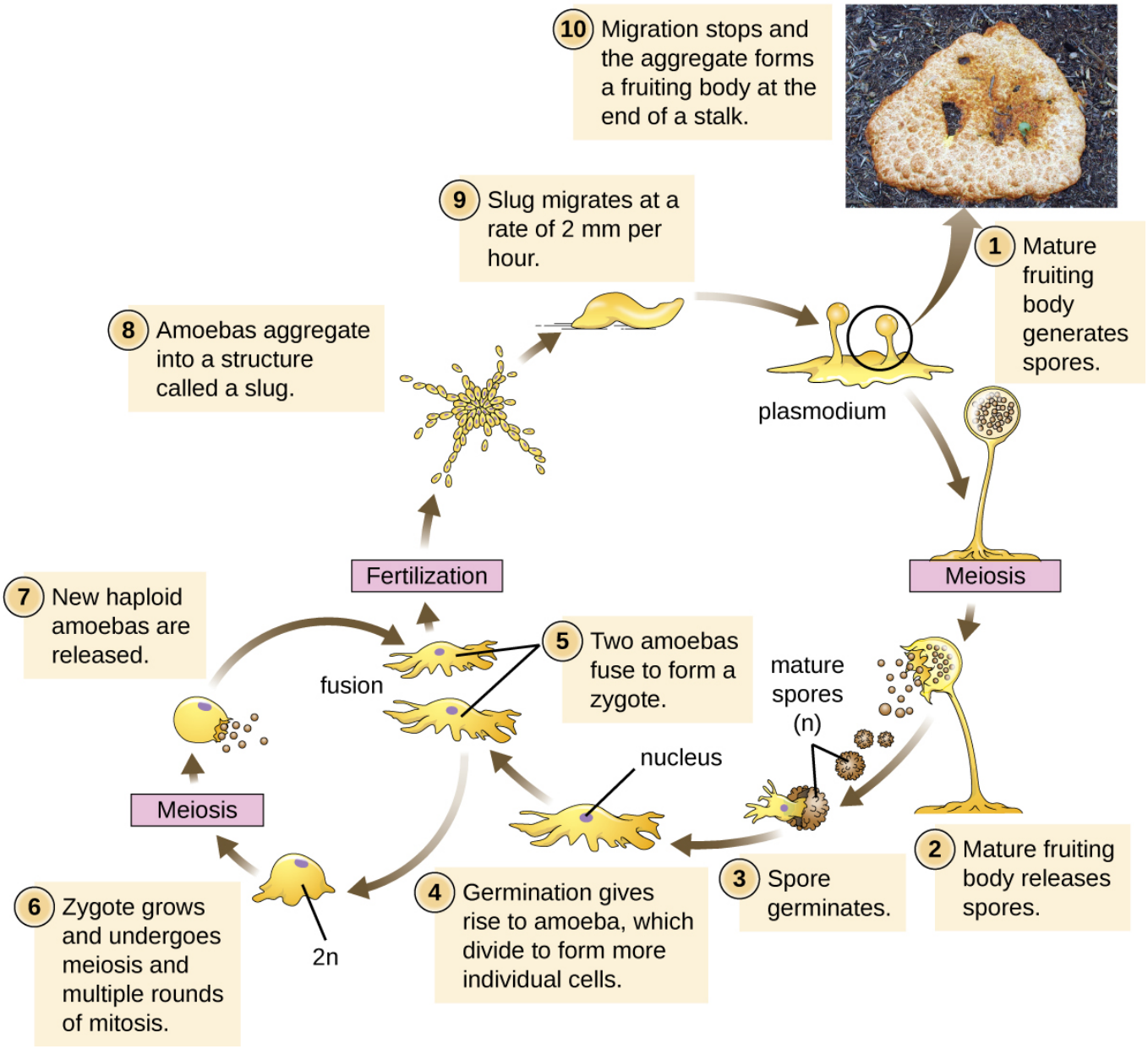


Figure **16.1.9**: The life cycle of the cellular slime mold *Dictyostelium discoideum* primarily involves individual amoebas but includes the formation of a multinucleate plasmodium formed from a uninucleate zygote (the result of the fusion of two individual amoeboid cells). The plasmodium is able to move and forms a fruiting body that generates haploid spores. (credit "photo": modification of work by "thatredhead4"/Flickr)

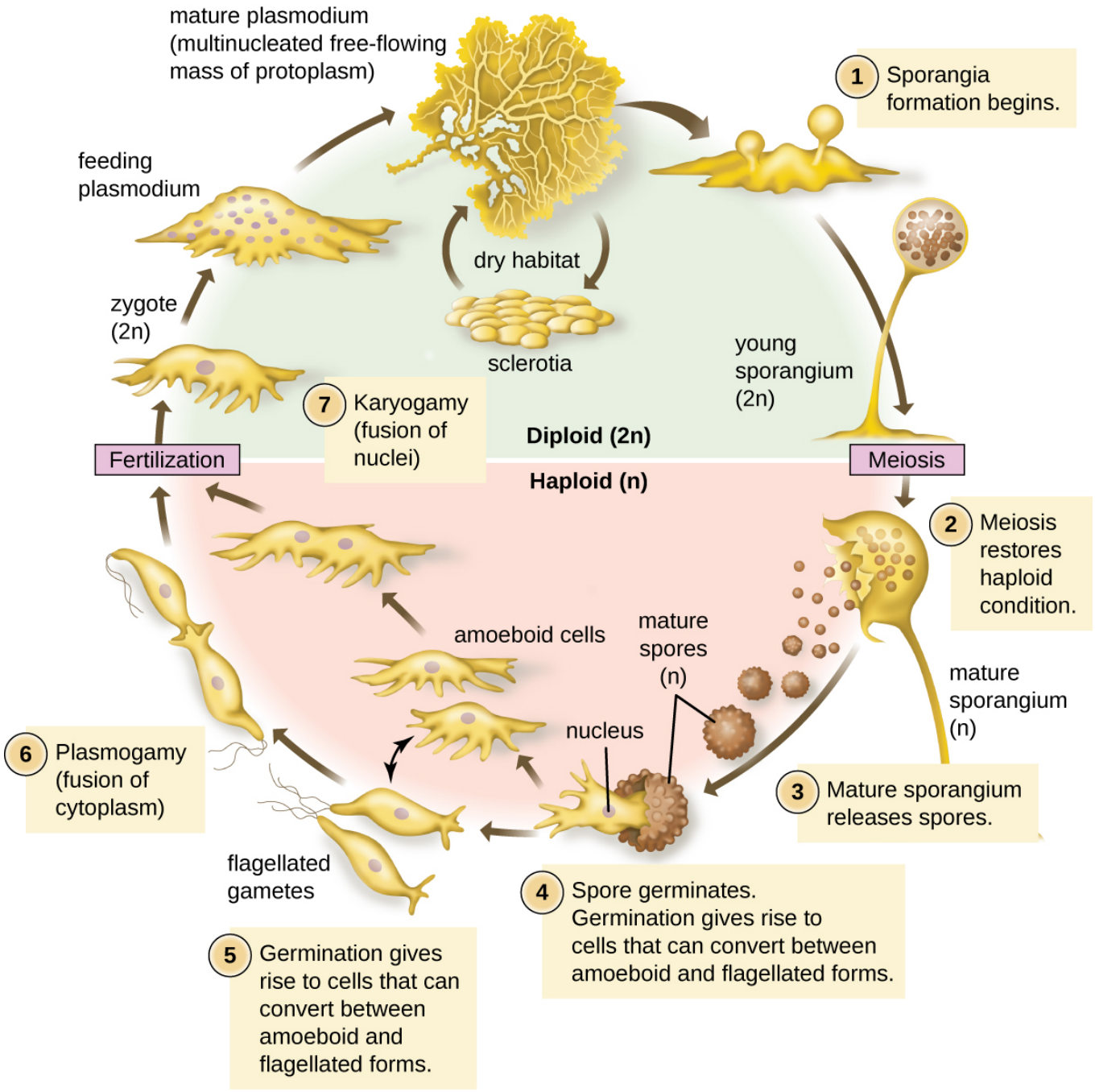


Figure 16.1.1: Plasmodial slime molds exist as large multinucleate amoeboid cells that form reproductive stalks to produce spores that divide into gametes.

Chromalveolata

The supergroup Chromalveolata is united by similar origins of its members' plastids and includes the apicomplexans, ciliates, diatoms, and dinoflagellates, among other groups (we will cover the diatoms and dinoflagellates in Algae). The apicomplexans are intra- or extracellular parasites that have an apical complex at one end of the cell. The apical complex is a concentration of organelles, vacuoles, and microtubules that allows the parasite to enter host cells (Figure 16.1.11). Apicomplexans have complex life cycles that include an infective sporozoite that undergoes schizogony to make many merozoites (see the example in Figure 16.1.3). Many are capable of infecting a variety of animal cells, from insects to livestock to humans, and their life cycles often depend on transmission between multiple hosts. The genus *Plasmodium* is an example of this group.



Figure **16.1.11**: (a) Apicomplexans are parasitic protists. They have a characteristic apical complex that enables them to infect host cells. (b) A colorized electron microscope image of a *Plasmodium* sporozoite. (credit b: modification of work by Ute Frevert)

Other apicomplexans are also medically important. *Cryptosporidium parvum* causes intestinal symptoms and can cause epidemic diarrhea when the cysts contaminate drinking water. *Theileria (Babesia) microti*, transmitted by the tick *Ixodes scapularis*, causes recurring fever that can be fatal and is becoming a common transfusion-transmitted pathogen in the United States (*Theileria* and *Babesia* are closely related genera and there is some debate about the best classification). Finally, *Toxoplasma gondii* causes toxoplasmosis and can be transmitted from cat feces, unwashed fruit and vegetables, or from undercooked meat. Because toxoplasmosis can be associated with serious birth defects, pregnant women need to be aware of this risk and use caution if they are exposed to the feces of potentially infected cats. A national survey found the frequency of individuals with antibodies for toxoplasmosis (and thus who presumably have a current latent infection) in the United States to be 11%. Rates are much higher in other countries, including some developed countries.[1] There is also evidence and a good deal of theorizing that the parasite may be responsible for altering infected humans' behavior and personality traits.[2]

The ciliates (Ciliaphora), also within the Chromalveolata, are a large, very diverse group characterized by the presence of cilia on their cell surface. Although the cilia may be used for locomotion, they are often used for feeding, as well, and some forms are nonmotile. *Balantidium coli* (Figure **16.1.12**) is the only parasitic ciliate that affects humans by causing intestinal illness, although it rarely causes serious medical issues except in the immunocompromised (those having a weakened immune system). Perhaps the most familiar ciliate is *Paramecium*, a motile organism with a clearly visible cytostomeand cytoproct that is often studied in biology laboratories (Figure **16.1.13**). Another ciliate, *Stentor*, is sessile and uses its cilia for feeding (Figure **16.1.14**). Generally, these organisms have a micronucleus that is diploid, somatic, and used for sexual reproduction by conjugation. They also have a macronucleus that is derived from the micronucleus; the macronucleus becomes polyploid (multiple sets of duplicate chromosomes), and has a reduced set of metabolic genes.

Ciliates are able to reproduce through conjugation, in which two cells attach to each other. In each cell, the diploid micronuclei undergo meiosis, producing eight haploid nuclei each. Then, all but one of the haploid micronuclei and the macronucleus disintegrate; the remaining (haploid) micronucleus undergoes mitosis. The two cells then exchange one micronucleus each, which fuses with the remaining micronucleus present to form a new, genetically different, diploid micronucleus. The diploid micronucleus undergoes two mitotic divisions, so each cell has four micronuclei, and two of the four combine to form a new macronucleus. The chromosomes in the macronucleus then replicate repeatedly, the macronucleus reaches its polyploid state, and the two cells separate. The two cells are now genetically different from each other and from their previous versions.



Figure 16.1.12: This specimen of the ciliate *Balantidium coli* is a trophozoite form isolated from the gut of a primate. *B. coli* is the only ciliate capable of parasitizing humans. (credit: modification of work by Kouassi RYW, McGraw SW, Yao PK, Abou-Bacar A, Brunet J, Pesson B, Bonfoh B, N'goran EK & Candolfi E)

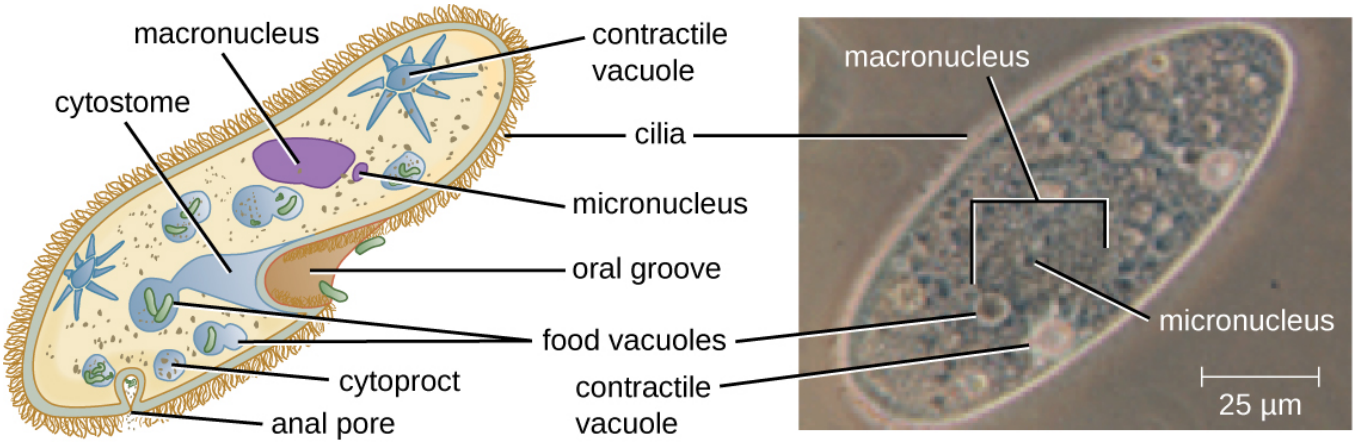


Figure 16.1.13: Paramecium has a primitive mouth (called an oral groove) to ingest food, and an anal pore to excrete it. Contractile vacuoles allow the organism to excrete excess water. Cilia enable the organism to move.

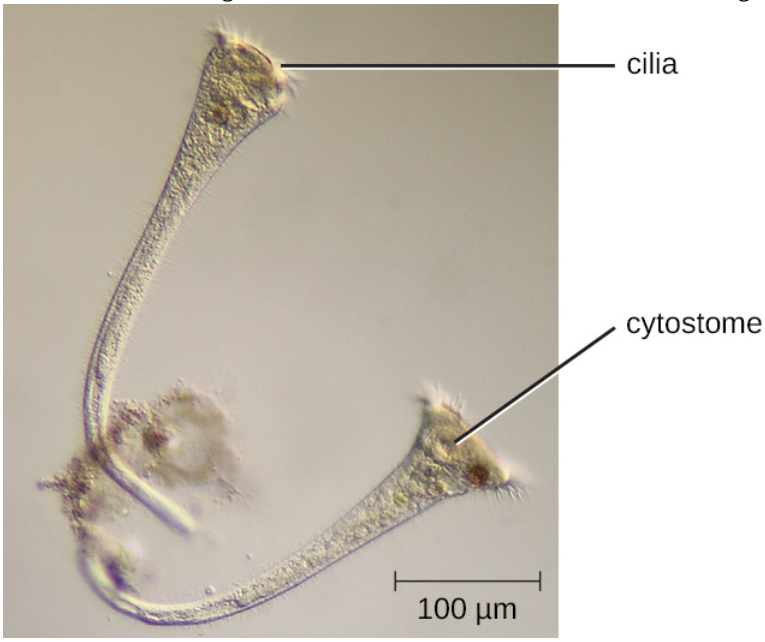


Figure 16.1.14: This differential interference contrast micrograph (magnification: ×65) of *Stentor roeselie* shows cilia present on the margins of the structure surrounding the cytostome; the cilia move food particles. (credit: modification of work by "picturepest"/Flickr)

Öomycetes have similarities to fungi and were once classified with them. They are also called water molds. However, they differ from fungi in several important ways. Öomycetes have cell walls of cellulose (unlike the chitinous cell walls of fungi) and they are generally diploid, whereas the dominant life forms of fungi are typically haploid. *Phytophthora*, the plant pathogen found in the soil that caused the Irish potato famine, is classified within this group (Figure **16.1.15**).



Figure **16.1.15**: A saprobic oomycete, or water mold, engulfs a dead insect. (credit: modification of work by Thomas Bresson)

Link to Learning

This video shows the feeding of *Stentor*.

Excavata

The third and final supergroup to be considered in this section is the Excavata, which includes primitive eukaryotes and many parasites with limited metabolic abilities. These organisms have complex cell shapes and structures, often including a depression on the surface of the cell called an excavate. The group Excavata includes the subgroups Fornicata, Parabasalia, and Euglenozoa. The Fornicata lack mitochondria but have flagella. This group includes *Giardia lamblia* (also known as *G. intestinalis* or *G. duodenalis)*, a widespread pathogen that causes diarrheal illness and can be spread through cysts from feces that contaminate water supplies (Figure **16.1.2**). Parabasalia are frequent animal endosymbionts; they live in the guts of animals like termites and cockroaches. They have basal bodies and modified mitochondria (kinetoplastids). They also have a large, complex cell structure with an undulating membrane and often have many flagella. The trichomonads (a subgroup of the Parabasalia) include pathogens such as *Trichomonas vaginalis*, which causes the human sexually transmitted disease trichomoniasis. Trichomoniasis often does not cause symptoms in men, but men are able to transmit the infection. In women, it causes vaginal discomfort and discharge and may cause complications in pregnancy if left untreated.

The Euglenozoa are common in the environment and include photosynthetic and nonphotosynthetic species. Members of the genus *Euglena* are typically not pathogenic. Their cells have two flagella, a pellicle, a stigma (eyespot) to sense light, and chloroplasts for photosynthesis (Figure **16.1.16**). The pellicle of *Euglena* is made of a series of protein bands surrounding the cell; it supports the cell membrane and gives the cell shape.

The Euglenozoa also include the trypanosomes, which are parasitic pathogens. The genus *Trypanosoma* includes *T. brucei*, which causes African trypanosomiasis (African sleeping sickness and *T. cruzi*, which causes American trypanosomiasis (Chagas disease). These tropical diseases are spread by insect bites. In African sleeping sickness, *T. brucei* colonizes the blood and the brain after being transmitted via the bite of a tsetse fly (*Glossina* spp.) (Figure **16.1.17**). The early symptoms include confusion, difficulty sleeping, and lack of coordination. Left untreated, it is fatal.

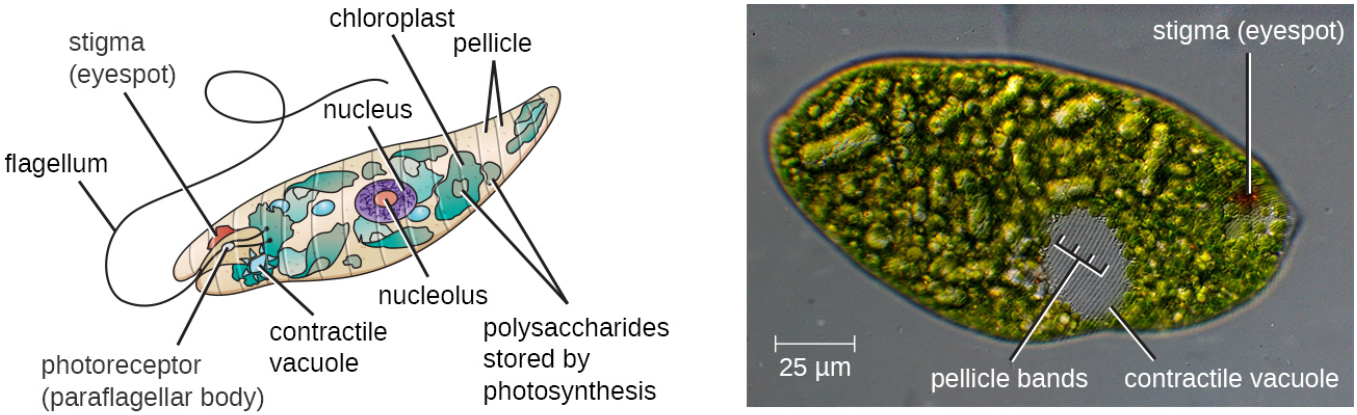


Figure 16.1.16: (a) This illustration of a *Euglena* shows the characteristic structures, such as the stigma and flagellum. (b) The pellicle, under the cell membrane, gives the cell its distinctive shape and is visible in this image as delicate parallel striations over the surface of the entire cell (especially visible over the grey contractile vacuole). (credit a: modification of work by Claudio Miklos; credit b: modification of work by David Shykind)

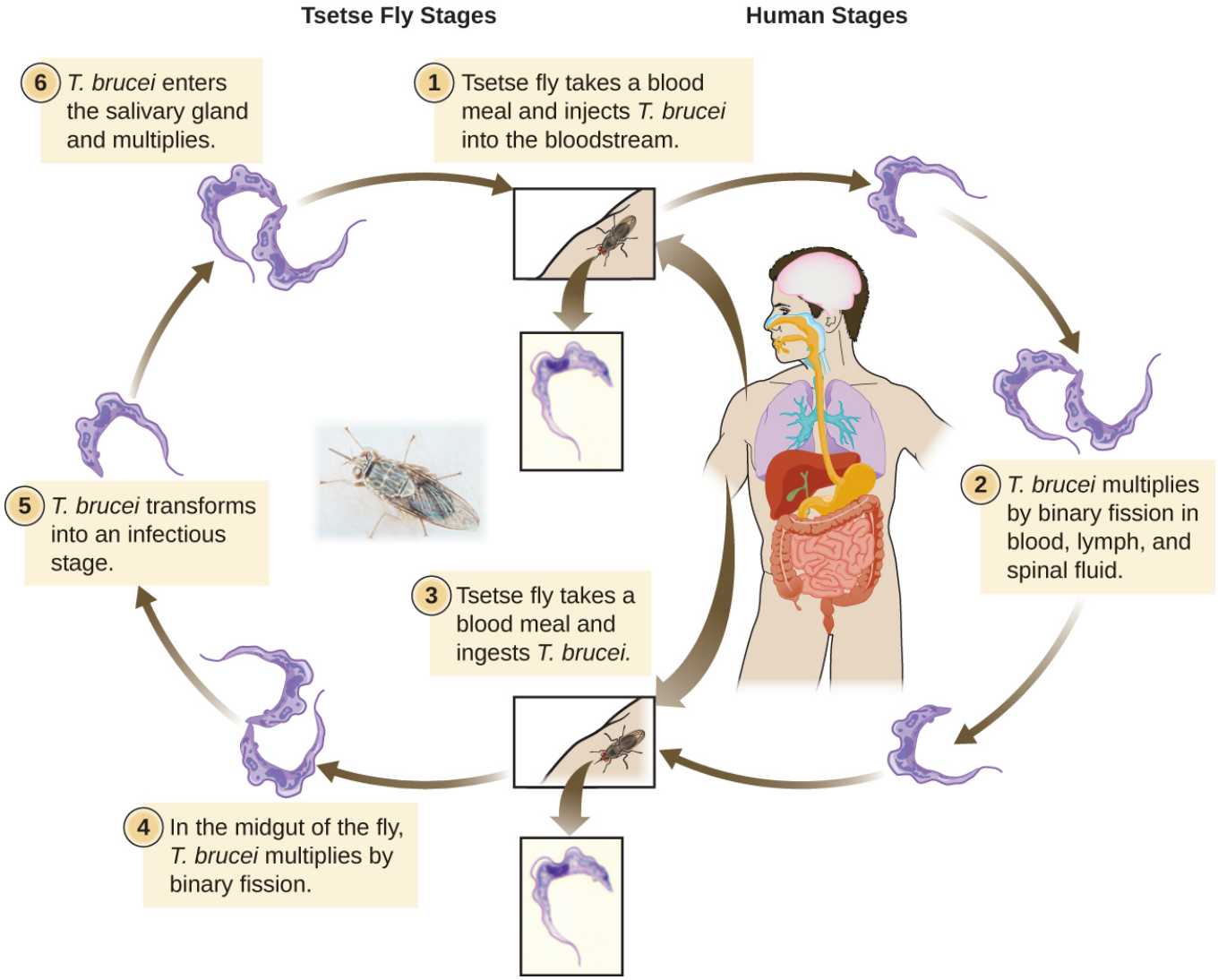


Figure 16.1.17: Trypanosoma brucei, the causative agent of African trypanosomiasis, spends part of its life cycle in the tsetse fly and part in humans. (credit "illustration": modification of work by Centers for Disease Control and Prevention; credit "photo": DPDx/Centers for Disease Control and Prevention)

Chagas' disease originated and is most common in Latin America. The disease is transmitted by *Triatoma* spp., insects often called "kissing bugs," and affects either the heart tissue or tissues of the digestive system. Untreated cases can eventually lead to heart failure or significant digestive or neurological disorders.

The genus *Leishmania* includes trypanosomes that cause disfiguring skin disease and sometimes systemic illness as well.

Neglected Parasites

The Centers for Disease Control and Prevention (CDC) is responsible for identifying public health priorities in the United States and developing strategies to address areas of concern. As part of this mandate, the CDC has officially identified five parasitic diseases it considers to have been neglected (i.e., not adequately studied). These neglected parasitic infections (NPIs) include toxoplasmosis, Chagas disease, toxocariasis (a nematode infection transmitted primarily by infected dogs), cysticercosis (a disease caused by a tissue infection of the tapeworm *Taenia solium*), and trichomoniasis (a sexually transmitted disease caused by the parabasalid *Trichomonas vaginalis*).

The decision to name these specific diseases as NPIs means that the CDC will devote resources toward improving awareness and developing better diagnostic testing and treatment through studies of available data. The CDC may also advise on treatment of these diseases and assist in the distribution of medications that might otherwise be difficult to obtain.3

Of course, the CDC does not have unlimited resources, so by prioritizing these five diseases, it is effectively deprioritizing others. Given that many Americans have never heard of many of these NPIs, it is fair to ask what criteria the CDC used in prioritizing diseases. According to the CDC, the factors considered were the number of people infected, the severity of the illness, and whether the illness can be treated or prevented. Although several of these NPIs may seem to be more common outside the United States, the CDC argues that many cases in the United States likely go undiagnosed and untreated because so little is known about these diseases.4

What criteria should be considered when prioritizing diseases for purposes of funding or research? Are those identified by the CDC reasonable? What other factors could be considered? Should government agencies like the CDC have the same criteria as private pharmaceutical research labs? What are the ethical implications of deprioritizing other potentially neglected parasitic diseases such as leishmaniasis?

Key Concepts and Summary

- **Protists** are a diverse, **polyphyletic** group of eukaryotic organisms.
- Protists may be unicellular or multicellular. They vary in how they get their nutrition, morphology, method of locomotion, and mode of reproduction.
- Important structures of protists include **contractile vacuoles**, cilia, flagella, **pellicles**, and pseudopodia; some lack organelles such as mitochondria.
- Taxonomy of protists is changing rapidly as relationships are reassessed using newer techniques.
- The protists include important pathogens and parasites.

Footnotes

1. 1 J. Flegr et al. "Toxoplasmosis—A Global Threat. Correlation of Latent Toxoplasmosis With Specific Disease Burden in a Set of 88 Countries." *PloS ONE* 9 no. 3 (2014):e90203.
2. 2 J. Flegr. "Effects of Toxoplasma on Human Behavior." *Schizophrenia Bull* 33, no. 3 (2007):757–760.
3. 3 Centers for Disease Control and Prevention. "Neglected Parasitic Infections (NPIs) in the United States." http://www.cdc.gov/parasites/npi/. Last updated July 10, 2014.
4. 4 Centers for Disease Control and Prevention. "Fact Sheet: Neglected Parasitic Infections in the United States." www.cdc.gov/parasites/resourc..._factsheet.pdf

This page titled 16.1: Unicellular Eukaryotic Microorganisms is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **5.1: Unicellular Eukaryotic Microorganisms** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

16.2: Parasitic Helminths

Learning Objectives

- Explain why we include the study of parasitic worms within the discipline of microbiology
- Compare the basic morphology of the major groups of parasitic helminthes
- Describe the characteristics of parasitic nematodes, and give an example of infective eggs and infective larvae
- Describe the characteristics of parasitic trematodes and cestodes, and give examples of each
- Identify examples of the primary causes of infections due to nematodes, trematodes, and cestodes
- Classify parasitic worms according to major groups

Parasitic helminths are animals that are often included within the study of microbiology because many species of these worms are identified by their microscopic eggs and larvae. There are two major groups of parasitic helminths: the roundworms (Nematoda) and flatworms (Platyhelminthes). Of the many species that exist in these groups, about half are parasitic and some are important human pathogens. As animals, they are multicellular and have organ systems. However, the parasitic species often have limited digestive tracts, nervous systems, and locomotor abilities. Parasitic forms may have complex reproductive cycles with several different life stages and more than one type of host. Some are monoecious, having both male and female reproductive organs in a single individual, while others are dioecious, each having either male or female reproductive organs.

Nematoda (Roundworms)

Phylum Nematoda (the roundworms) is a diverse group containing more than 15,000 species, of which several are important human parasites (Figure **16.2.1**). These unsegmented worms have a full digestive system even when parasitic. Some are common intestinal parasites, and their eggs can sometimes be identified in feces or around the anus of infected individuals. *Ascaris lumbricoides* is the largest nematode intestinal parasite found in humans; females may reach lengths greater than 1 meter. *A. lumbricoides* is also very widespread, even in developed nations, although it is now a relatively uncommon problem in the United States. It may cause symptoms ranging from relatively mild (such as a cough and mild abdominal pain) to severe (such as intestinal blockage and impaired growth).

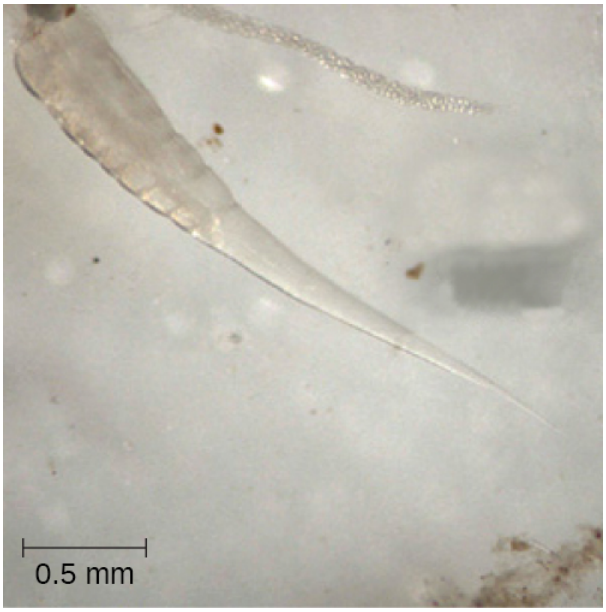


Figure **16.2.1**: A micrograph of the nematode *Enterobius vermicularis*, also known as the pinworm. (credit: modification of work by Centers for Disease Control and Prevention)

Of all nematode infections in the United States, pinworm (caused by *Enterobius vermicularis*) is the most common. Pinworm causes sleeplessness and itching around the anus, where the female worms lay their eggs during the night. *Toxocara canis* and *T. cati* are nematodes found in dogs and cats, respectively, that can be transmitted to humans, causing toxocariasis. Antibodies to these parasites have been found in approximately 13.9% of the U.S. population, suggesting that exposure is common.[1] Infection can

cause larval migrans, which can result in vision loss and eye inflammation, or fever, fatigue, coughing, and abdominal pain, depending on whether the organism infects the eye or the viscera. Another common nematode infection is hookworm, which is caused by *Necator americanus* (the New World or North American hookworm) and *Ancylostoma duodenale* (the Old World hookworm). Symptoms of hookworm infection can include abdominal pain, diarrhea, loss of appetite, weight loss, fatigue, and anemia.

Trichinellosis, also called trichinosis, caused by *Trichinella spiralis*, is contracted by consuming undercooked meat, which releases the larvae and allows them to encyst in muscles. Infection can cause fever, muscle pains, and digestive system problems; severe infections can lead to lack of coordination, breathing and heart problems, and even death. Finally, heartworm in dogs and other animals is caused by the nematode *Dirofilaria immitis*, which is transmitted by mosquitoes. Symptoms include fatigue and cough; when left untreated, death may result.

Clinical Focus: Part 2

The physician explains to Sarah's mother that ringworm can be transferred between people through touch. "It's common in school children, because they often come in close contact with each other, but anyone can become infected," he adds. "Because you can transfer it through objects, locker rooms and public pools are also a potential source of infection. It's very common among wrestlers and athletes in other contact sports."

Looking very uncomfortable, Sarah says to her mother "I want this worm out of me."

The doctor laughs and says, "Sarah, you're in luck because ringworm is just a name; it is not an actual worm. You have nothing wriggling around under your skin."

"Then what is it?" asks Sarah.

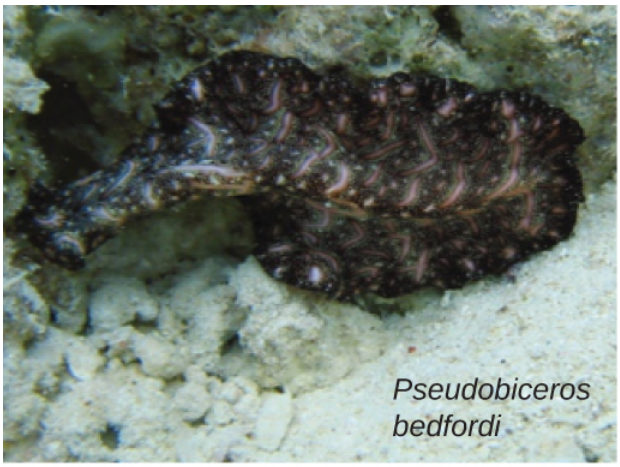
Exercise 16.2.1

1. What type of pathogen causes ringworm?
2. What is the most common nematode infection in the United States?

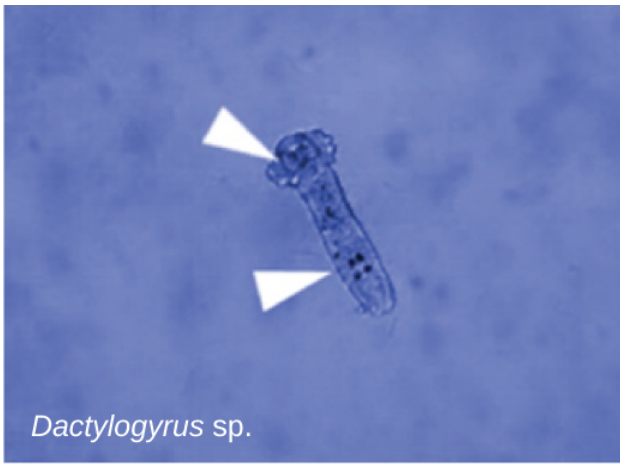
Platyhelminths (Flatworms)

Phylum Platyhelminthes (the platyhelminths) are flatworms. This group includes the flukes, tapeworms, and the turbellarians, which include planarians. The flukes and tapeworms are medically important parasites (Figure **16.2.2**).

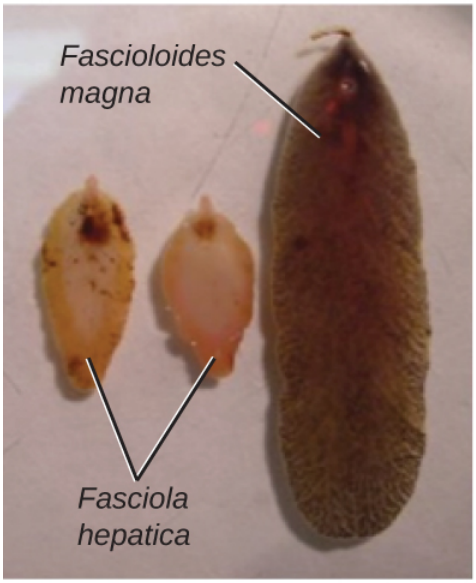
The flukes (trematodes) are nonsegmented flatworms that have an oral sucker (Figure **16.2.3**) (and sometimes a second ventral sucker) and attach to the inner walls of intestines, lungs, large blood vessels, or the liver. Trematodes have complex life cycles, often with multiple hosts. Several important examples are the liver flukes (*Clonorchis* and *Opisthorchis*), the intestinal fluke (*Fasciolopsis buski*), and the oriental lung fluke (*Paragonimus westermani*). Schistosomiasis is a serious parasitic disease, considered second in the scale of its impact on human populations only to malaria. The parasites *Schistosoma mansoni*, *S. haematobium*, and *S. japonicum*, which are found in freshwater snails, are responsible for schistosomiasis (Figure **16.2.4**). Immature forms burrow through the skin into the blood. They migrate to the lungs, then to the liver and, later, other organs. Symptoms include anemia, malnutrition, fever, abdominal pain, fluid buildup, and sometimes death.



(a) Class Turbellaria



(b) Class Monogenea



(c) Class Trematoda



(d) Class Cestoda

Figure **16.2.2**: Phylum Platyhelminthes is divided into four classes. (a) Class Turbellaria includes the Bedford's flatworm (*Pseudobiceros bedfordi*), which is about 8–10 cm long. (b) The parasitic class Monogenea includes *Dactylogyrus* spp. Worms in this genus are commonly called gill flukes. The specimen pictured here is about 0.2 mm long and has two anchors, indicated by arrows, that it uses to latch onto the gills of host fish. (c) The Trematoda class includes the common liver fluke *Fasciola hepatica* and the giant liver fluke *Fascioloides magna* (right). The *F. magna* specimen shown here is about 7 cm long. (d) Class Cestoda includes tapeworms such as *Taenia saginata*, which infects both cattle and humans and can reach lengths of 4–10 meters; the specimen shown here is about 4 meters long. (credit c: modification of work by "Flukeman"/Wikimedia Commons)

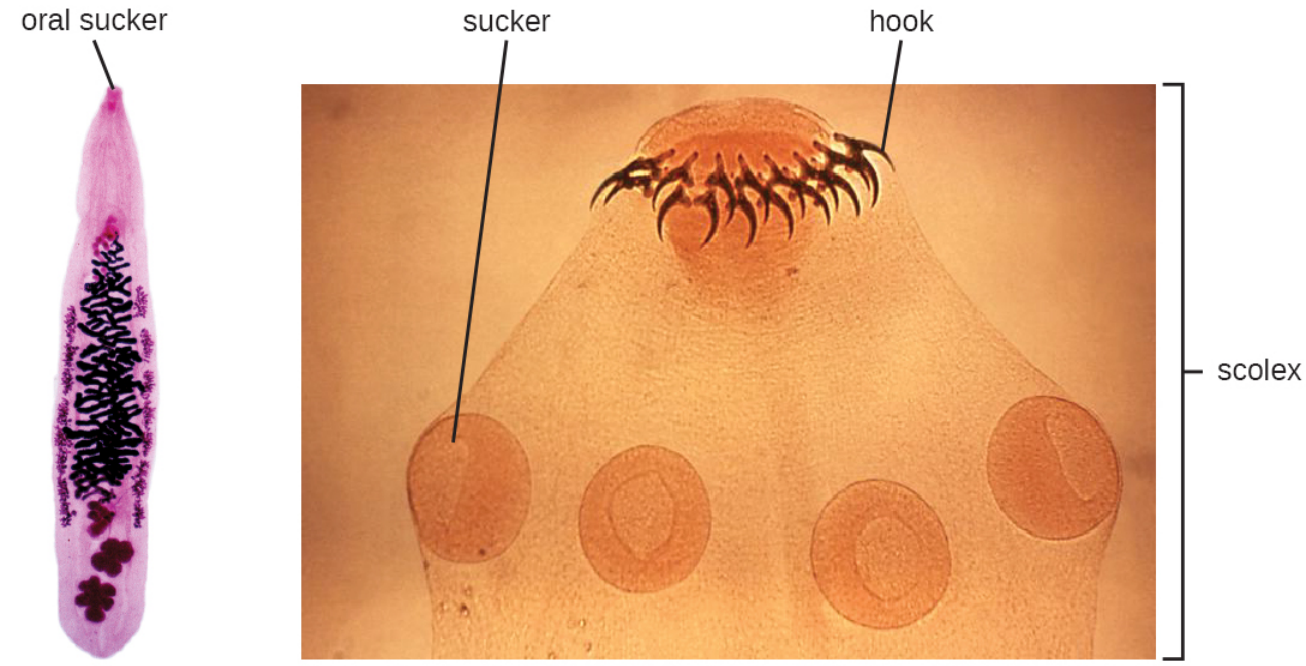


Figure **16.2.3**: (a) The oral sucker is visible on the anterior end of this liver fluke, *Opisthorchis viverrini*. (b) This micrograph shows the scolex of the cestode *Taenia solium*, also known as the pork tapeworm. The visible suckers and hooks allow the worm to attach itself to the inner wall of the intestine. (credit a: modification of work by Sripa B, Kaewkes S, Sithithaworn P, Mairiang E, Laha T, and Smout M; credit b: modification of work by Centers for Disease Control and Prevention)

The other medically important group of platyhelminths are commonly known as tapeworms (cestodes) and are segmented flatworms that may have suckers or hooks at the scolex (head region) (Figure **16.2.3**). Tapeworms use these suckers or hooks to attach to the wall of the small intestine. The body of the worm is made up of segments called proglottid**s** that contain reproductive structures; these detach when the gametes are fertilized, releasing gravid proglottids with eggs. Tapeworms often have an intermediate host that consumes the eggs, which then hatch into a larval form called an oncosphere. The oncosphere migrates to a particular tissue or organ in the intermediate host, where it forms cysticerci. After being eaten by the definitive host, the cysticerci develop into adult tapeworms in the host's digestive system (Figure **16.2.5**). *Taenia saginata* (the beef tapeworm) and *T. solium* (the pork tapeworm) enter humans through ingestion of undercooked, contaminated meat. The adult worms develop and reside in the intestine, but the larval stage may migrate and be found in other body locations such as skeletal and smooth muscle. The beef tapeworm is relatively benign, although it can cause digestive problems and, occasionally, allergic reactions. The pork tapeworm can cause more serious problems when the larvae leave the intestine and colonize other tissues, including those of the central nervous system. *Diphylobothrium latum* is the largest human tapeworm and can be ingested in undercooked fish. It can grow to a length of 15 meters. *Echinococcus granulosus*, the dog tapeworm, can parasitize humans and uses dogs as an important host.

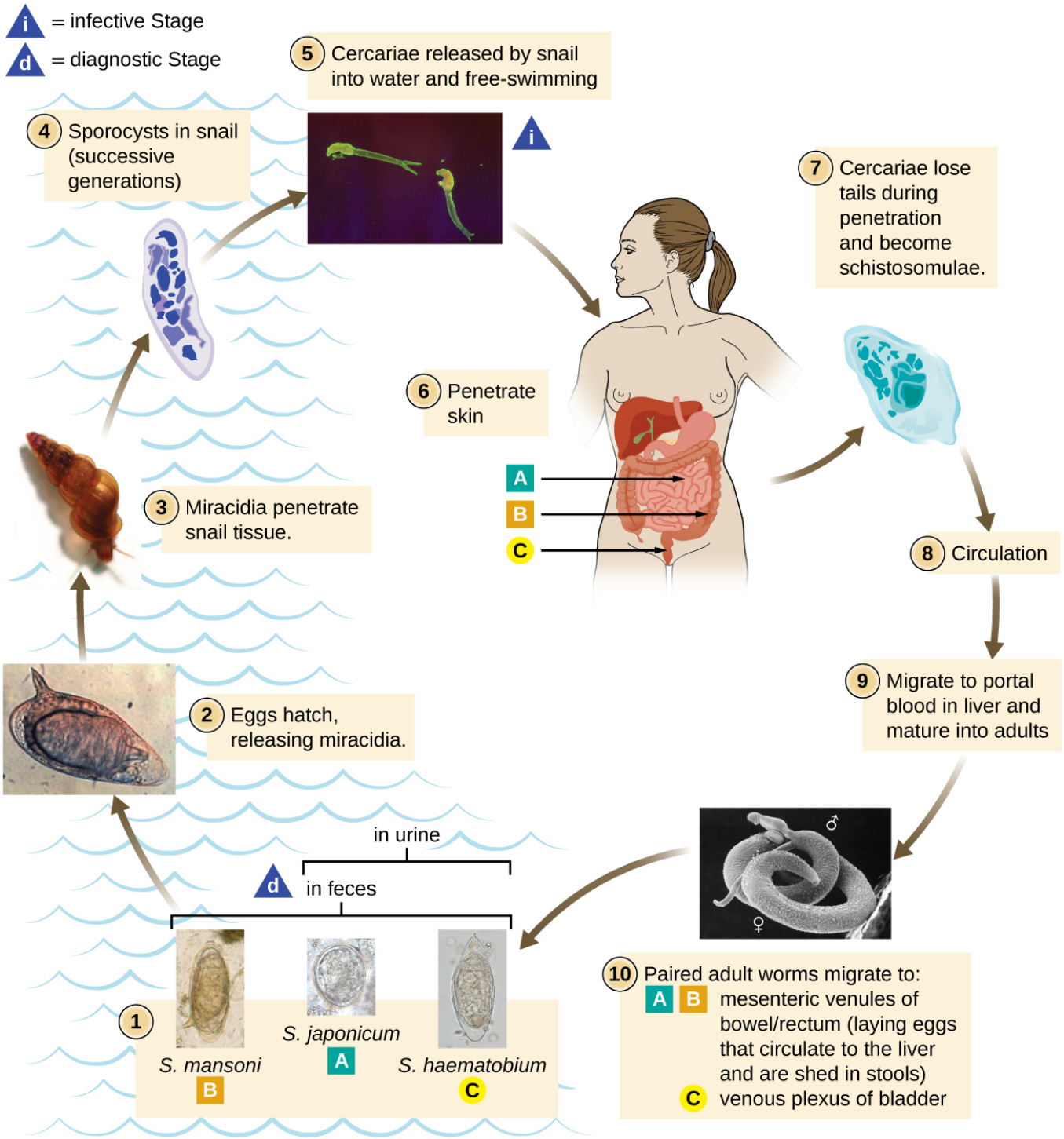


Figure 16.2.4: The life cycle of *Schistosoma* spp. includes several species of water snails, which serve as secondary hosts. The parasite is transmitted to humans through contact with contaminated water and takes up residence in the veins of the digestive system. Eggs escape the host in the urine or feces and infect a snail to complete the life cycle. (credit "illustration": modification of work by Centers for Disease Control and Prevention; credit "step 3 photo": modification of work by Fred A. Lewis, Yung-san Liang, Nithya Raghavan & Matty Knight)

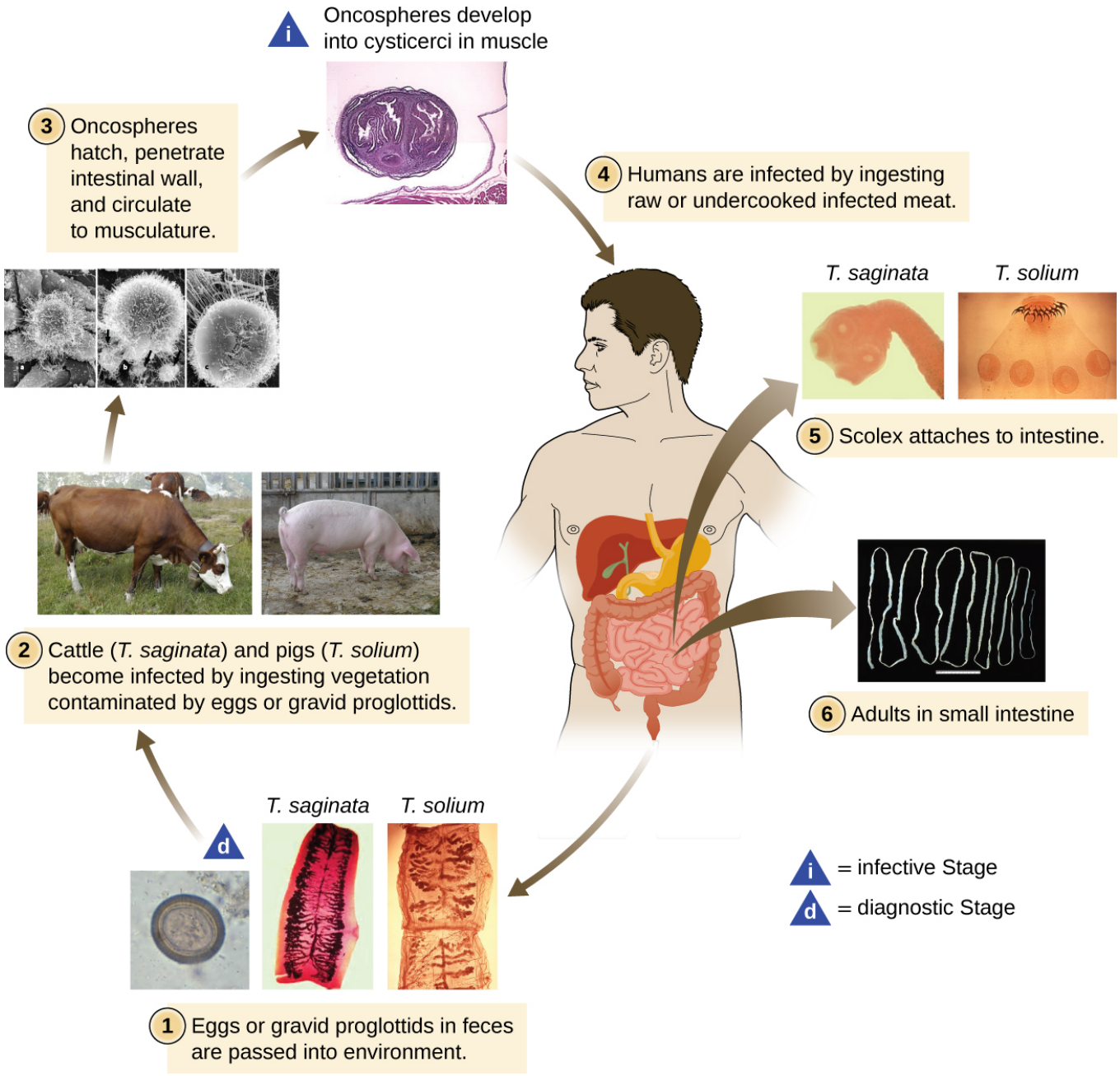


Figure **16.2.5**: Life cycle of a tapeworm. (credit "illustration": modification of work by Centers for Disease Control and Prevention; credit "step 3 micrographs": modification of work by American Society for Microbiology)

? Exercise 16.2.2

What group of medically important flatworms is segmented and what group is unsegmented?

Food for Worms?

For residents of temperate, developed countries, it may be difficult to imagine just how common helminth infections are in the human population. In fact, they are quite common and even occur frequently in the United States. Worldwide, approximately 807–1,221 million people are infected with *Ascaris lumbricoides* (perhaps one-sixth of the human population) and far more are infected if all nematode species are considered.[2] Rates of infection are relatively high even in industrialized nations. Approximately 604–795 million people are infected with whipworm (*Trichuris*) worldwide (*Trichuris* can also

infect dogs), and 576–740 million people are infected with hookworm (*Necator americanus* and *Ancylostoma duodenale*).[3] *Toxocara,* a nematode parasite of dogs and cats, is also able to infect humans. It is widespread in the United States, with about 10,000 symptomatic cases annually. However, one study found 14% of the population (more than 40 million Americans) was seropositive, meaning they had been exposed to the parasite at one time. More than 200 million people have schistosomiasis worldwide. Most of the World Health Organization (WHO) neglected tropical diseases are helminths. In some cases, helminths may cause subclinical illnesses, meaning the symptoms are so mild that that they go unnoticed. In other cases, the effects may be more severe or chronic, leading to fluid accumulation and organ damage. With so many people affected, these parasites constitute a major global public health concern.

Eradicating the Guinea Worm

Dracunculiasis, or Guinea worm disease, is caused by a nematode called *Dracunculus medinensis*. When people consume contaminated water, water fleas (small crustaceans) containing the nematode larvae may be ingested. These larvae migrate out of the intestine, mate, and move through the body until females eventually emerge (generally through the feet). While Guinea worm disease is rarely fatal, it is extremely painful and can be accompanied by secondary infections and edema (Figure **16.2.6**).



Figure **16.2.6**: The Guinea worm can be removed from a leg vein of an infected person by gradually winding it around a stick, like this matchstick. (credit: Centers for Disease Control and Prevention)

An eradication campaign led by WHO, the CDC, the United Nations Children's Fund (UNICEF), and the Carter Center (founded by former U.S. president Jimmy Carter) has been extremely successful in reducing cases of dracunculiasis. This has been possible because diagnosis is straightforward, there is an inexpensive method of control, there is no animal reservoir, the water fleas are not airborne (they are restricted to still water), the disease is geographically limited, and there has been a commitment from the governments involved. Additionally, no vaccines or medication are required for treatment and prevention. In 1986, 3.5 million people were estimated to be affected. After the eradication campaign, which included helping people in affected areas learn to filter water with cloth, only four countries continue to report the disease (Chad, Mali, South Sudan, and Ethiopia) with a total of 126 cases reported to WHO in 2014.

Key Concepts and Summary

- Helminth parasites are included within the study of microbiology because they are often identified by looking for microscopic eggs and larvae.
- The two major groups of helminth parasites are the roundworms (Nematoda) and the flatworms (Platyhelminthes).
- Nematodes are common intestinal parasites often transmitted through undercooked foods, although they are also found in other environments.
- Platyhelminths include **tapeworms** and **flukes**, which are often transmitted through undercooked meat.

Footnotes

1. 1 Won K, Kruszon-Moran D, Schantz P, Jones J. "National seroprevalence and risk factors for zoonotic Toxocara spp. infection." In: Abstracts of the 56th American Society of Tropical Medicine and Hygiene; Philadelphia, Pennsylvania; 2007

Nov 4-8.
2. 2 Fenwick, A. “The global burden of neglected tropical diseases.” *Public health* 126 no.3 (Mar 2012): 233–6.
3. 3 de Silva, N., et. al. (2003). “Soil-transmitted helminth infections: updating the global picture”. *Trends in Parasitology* 19 (December 2003): 547–51.
4. 4 World Health Organization. “South Sudan Reports Zero Cases of Guinea-Worm Disease for Seventh Consecutive Month.” 2016. http://www.who.int/dracunculiasis/no...ive_months/en/. Accessed May 2, 2016.

This page titled 16.2: Parasitic Helminths is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **5.2: Parasitic Helminths** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

16.3: Fungi

Learning Objectives

- Explain why the study of fungi such as yeast and molds is within the discipline of microbiology
- Describe the unique characteristics of fungi
- Describe examples of asexual and sexual reproduction of fungi
- Compare the major groups of fungi in this chapter, and give examples of each
- Identify examples of the primary causes of infections due to yeasts and molds
- Identify examples of toxin-producing fungi
- Classify fungal organisms according to major groups

The fungi comprise a diverse group of organisms that are heterotrophic and typically saprozoic. In addition to the well-known macroscopic fungi (such as mushrooms and molds), many unicellular yeasts and spores of macroscopic fungi are microscopic. For this reason, fungi are included within the field of microbiology.

Fungi are important to humans in a variety of ways. Both microscopic and macroscopic fungi have medical relevance, with some pathogenic species that can cause mycoses (illnesses caused by fungi). Some pathogenic fungi are opportunistic, meaning that they mainly cause infections when the host's immune defenses are compromised and do not normally cause illness in healthy individuals. Fungi are important in other ways. They act as decomposers in the environment, and they are critical for the production of certain foods such as cheeses. Fungi are also major sources of antibiotics, such as penicillin from the fungus *Penicillium*.

Characteristics of Fungi

Fungi have well-defined characteristics that set them apart from other organisms. Most multicellular fungal bodies, commonly called molds, are made up of filaments called hyphae. Hyphae can form a tangled network called a mycelium and form the thallus (body) of fleshy fungi. Hyphae that have walls between the cells are called septate hyphae; hyphae that lack walls and cell membranes between the cells are called nonseptate or coenocytic hyphae). (Figure **16.3.1**).

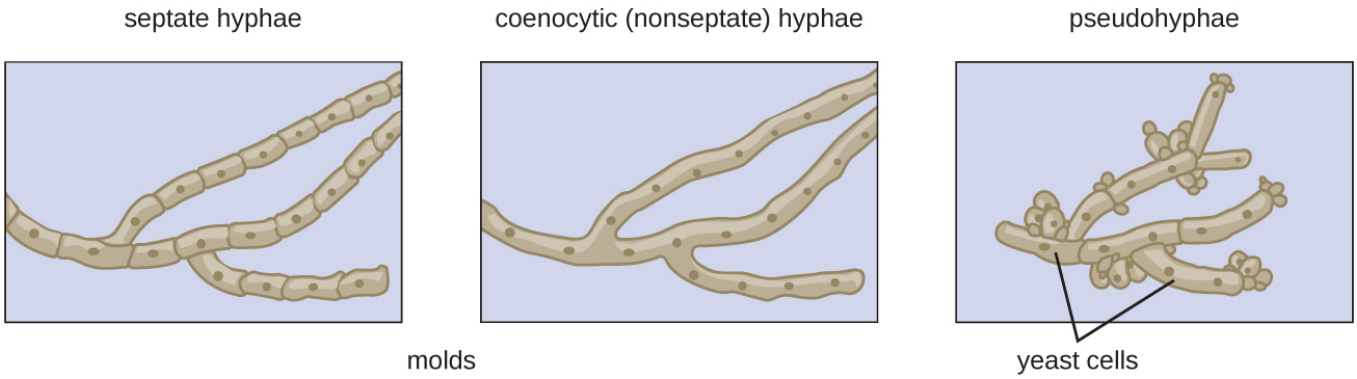


Figure **16.3.1**: Multicellular fungi (molds) form hyphae, which may be septate or nonseptate. Unicellular fungi (yeasts) cells form pseudohyphae from individual yeast cells.

In contrast to molds, yeasts are unicellular fungi. The budding yeasts reproduce asexually by budding off a smaller daughter cell; the resulting cells may sometimes stick together as a short chain or pseudohypha (Figure **16.3.1**). *Candida albicans* is a common yeast that forms pseudohyphae; it is associated with various infections in humans, including vaginal yeast infections, oral thrush, and candidiasis of the skin.

Some fungi are dimorphic, having more than one appearance during their life cycle. These dimorphic fungi may be able to appear as yeasts or molds, which can be important for infectivity. They are capable of changing their appearance in response to environmental changes such as nutrient availability or fluctuations in temperature, growing as a mold, for example, at 25 °C (77 °F), and as yeast cells at 37 °C (98.6 °F). This ability helps dimorphic fungi to survive in diverse environments. *Histoplasma capsulatum*, the pathogen that causes histoplasmosis, a lung infection, is an example of a dimorphic fungus (Figure **16.3.2**).

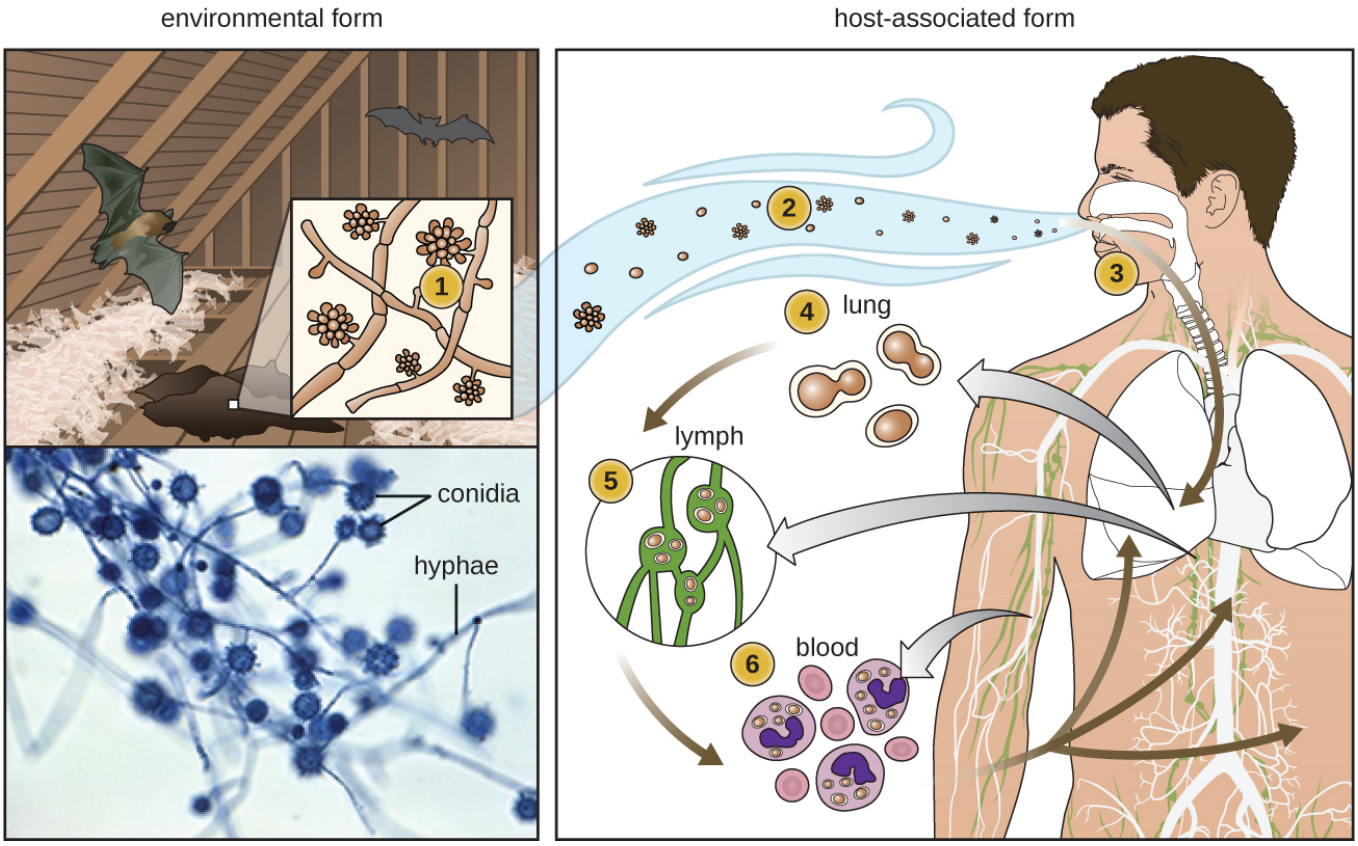


Figure **16.3.2**: Histoplasma capsulatum is a dimorphic fungus that grows in soil exposed to bird feces or bat feces (guano) (top left). It can change forms to survive at different temperatures. In the outdoors, it typically grows as a mycelium (as shown in the micrograph, bottom left), but when the spores are inhaled (right), it responds to the high internal temperature of the body (37 °C [98.6 °F]) by turning into a yeast that can multiply in the lungs, causing the chronic lung disease histoplasmosis. (credit: modification of work by Centers for Disease Control and Prevention)

There are notable unique features in fungal cell walls and membranes. Fungal cell walls contain chitin, as opposed to the cellulose found in the cell walls of plants and many protists. Additionally, whereas animals have cholesterol in their cell membranes, fungal cell membranes have different sterols called ergosterols. Ergosterols are often exploited as targets for antifungal drugs.

Fungal life cycles are unique and complex. Fungi reproduce sexually either through cross- or self-fertilization. Haploid fungi form hyphae that have gametes at the tips. Two different mating types (represented as "+ type" and "– type") are involved. The cytoplasms of the + and – type gametes fuse (in an event called plasmogamy), producing a cell with two distinct nuclei (a dikaryotic cell). Later, the nuclei fuse (in an event called karyogamy) to create a diploid zygote. The zygote undergoes meiosis to form spores that germinate to start the haploid stage, which eventually creates more haploid mycelia (Figure **16.3.3**). Depending on the taxonomic group, these sexually produced spores are known as zygospores (in Zygomycota), ascospores (in Ascomycota), or basidiospores (in Basidiomycota) (Figure **16.3.4**).

Fungi may also exhibit asexual reproduction by mitosis, mitosis with budding, fragmentation of hyphae, and formation of asexual spores by mitosis. These spores are specialized cells that, depending on the organism, may have unique characteristics for survival, reproduction, and dispersal. Fungi exhibit several types of asexual spores and these can be important in classification.

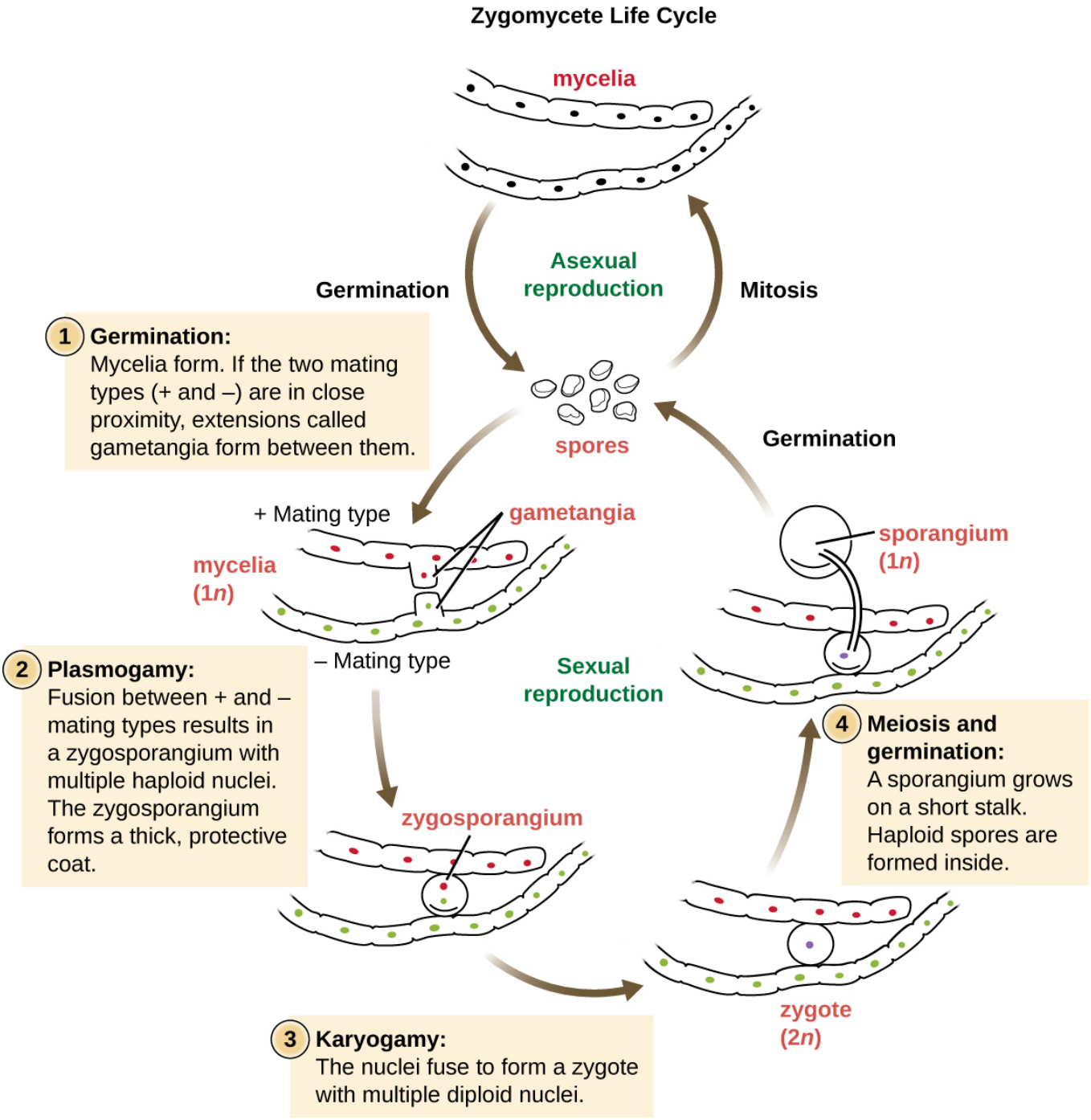


Figure **16.3.3**: Zygomycetes have sexual and asexual life cycles. In the sexual life cycle, + and – mating types conjugate to form a zygosporangium.

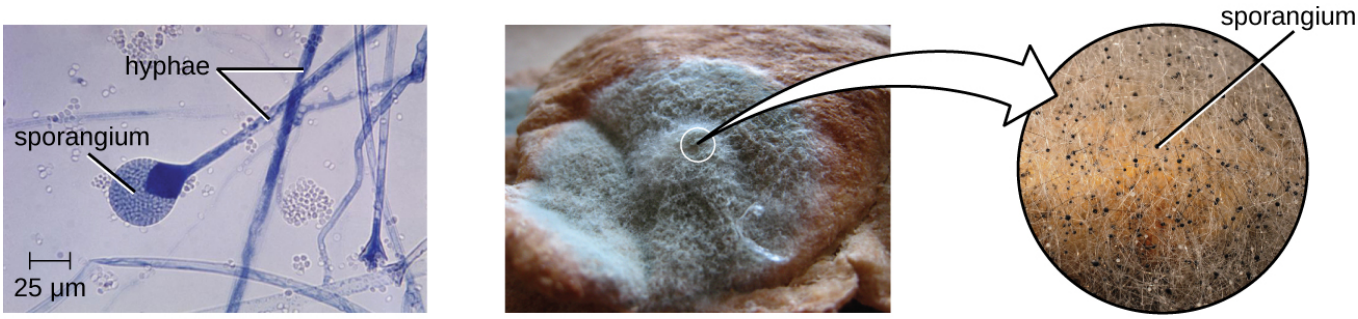


Figure **16.3.4**: These images show asexually produced spores. (a) This brightfield micrograph shows the release of spores from a sporangium at the end of a hypha called a sporangiophore. The organism is a *Mucor* sp. fungus, a mold often found indoors. (b) Sporangia grow at the ends of stalks, which appear as the white fuzz seen on this bread mold, *Rhizopus stolonifer*. The tips of bread mold are the dark, spore-containing sporangia. (credit a: modification of work by Centers for Disease Control and Prevention; credit b right: modification of work by "Andrew"/Flickr)

? Exercise 16.3.1

Is a dimorphic fungus a yeast or a mold? Explain.

Fungal Diversity

The fungi are very diverse, comprising seven major groups. Not all of the seven groups contain pathogens. Some of these groups are generally associated with plants and include plant pathogens. For example, Urediniomycetes and Ustilagomycetes include the plant rusts and smuts, respectively. These form reddish or dark masses, respectively, on plants as rusts (red) or smuts (dark). Some species have substantial economic impact because of their ability to reduce crop yields. Glomeromycota includes the mycorrhizal fungi, important symbionts with plant roots that can promote plant growth by acting like an extended root system. The Glomeromycota are obligate symbionts, meaning that they can only survive when associated with plant roots; the fungi receive carbohydrates from the plant and the plant benefits from the increased ability to take up nutrients and minerals from the soil. The Chytridiomycetes (chytrids) are small fungi, but are extremely ecologically important. Chytrids are generally aquatic and have flagellated, motile gametes; specific types are implicated in amphibian declines around the world. Because of their medical importance, we will focus on Zygomycota, Ascomycota, Basidiomycota, and Microsporidia. Figure **16.3.9** summarizes the characteristics of these medically important groups of fungi.

The Zygomycota (zygomycetes) are mainly saprophytes with coenocytic hyphae and haploid nuclei. They use sporangiospores for asexual reproduction. The group name comes from the zygospores that they use for sexual reproduction (Figure **16.3.3**), which have hard walls formed from the fusion of reproductive cells from two individuals. Zygomycetes are important for food science and as crop pathogens. One example is *Rhizopus stolonifer* (Figure **16.3.4**), an important bread mold that also causes rice seedling blight. *Mucor* is a genus of fungi that can potentially cause necrotizing infections in humans, although most species are intolerant of temperatures found in mammalian bodies (Figure **16.3.4**).

The Ascomycota include fungi that are used as food (edible mushrooms, morels, and truffles), others that are common causes of food spoilage (bread molds and plant pathogens), and still others that are human pathogens. Ascomycota may have septate hyphae and cup-shaped fruiting bodies called ascocarps. Some genera of Ascomycota use sexually produced ascospores as well as asexual spores called conidia, but sexual phases have not been discovered or described for others. Some produce an ascus containing ascospores within an ascocarp (Figure **16.3.5**).

Examples of the Ascomycota include several bread molds and minor pathogens, as well as species capable of causing more serious mycoses. Species in the genus *Aspergillus* are important causes of allergy and infection, and are useful in research and in the production of certain fermented alcoholic beverages such as Japanese *sake*. The fungus *Aspergillus flavus*, a contaminant of nuts and stored grains, produces an aflatoxin that is both a toxin and the most potent known natural carcinogen. *Neurospora crassa* is of particular use in genetics research because the spores produced by meiosis are kept inside the ascus in a row that reflects the cell

divisions that produced them, giving a direct view of segregation and assortment of genes (Figure **16.3.6**). *Penicillium* produces the antibiotic penicillin (Figure **16.3.5**).

Many species of ascomycetes are medically important. A large number of species in the genera *Trichophyton*, *Microsporum*, and *Epidermophyton* are dermatophytes, pathogenic fungi capable of causing skin infections such as athlete's foot, jock itch, and ringworm. *Blastomyces dermatitidis* is a dimorphic fungus that can cause blastomycosis, a respiratory infection that, if left untreated, can become disseminated to other body sites, sometimes leading to death. Another important respiratory pathogen is the dimorphic fungus *Histoplasma capsulatum* (Figure **16.3.2**), which is associated with birds and bats in the Ohio and Mississippi river valleys. *Coccidioides immitis* causes the serious lung disease Valley fever. *Candida albicans*, the most common cause of vaginal and other yeast infections, is also an ascomycete fungus; it is a part of the normal microbiota of the skin, intestine, genital tract, and ear (Figure **16.3.5**). Ascomycetes also cause plant diseases, including ergot infections, Dutch elm disease, and powdery mildews.

Saccharomyces yeasts, including the baker's yeast *S. cerevisiae*, are unicellular ascomycetes with haploid and diploid stages (Figure **16.3.7**). This and other *Saccharomyces* species are used for brewing beer.

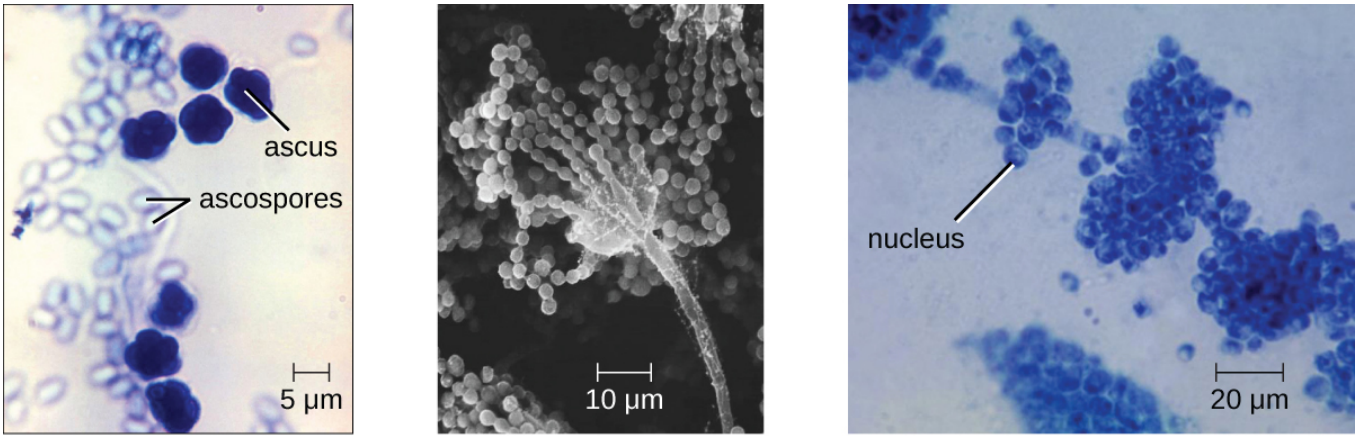


Figure **16.3.5**: (a) This brightfield micrograph shows ascospores being released from asci in the fungus *Talaromyces flavus* var. *flavus*. (b) This electron micrograph shows the conidia (spores) borne on the conidiophore of *Aspergillus*, a type of toxic fungus found mostly in soil and plants. (c) This brightfield micrograph shows the yeast *Candida albicans*, the causative agent of candidiasis and thrush. (credit a, b, c: modification of work by Centers for Disease Control and Prevention)

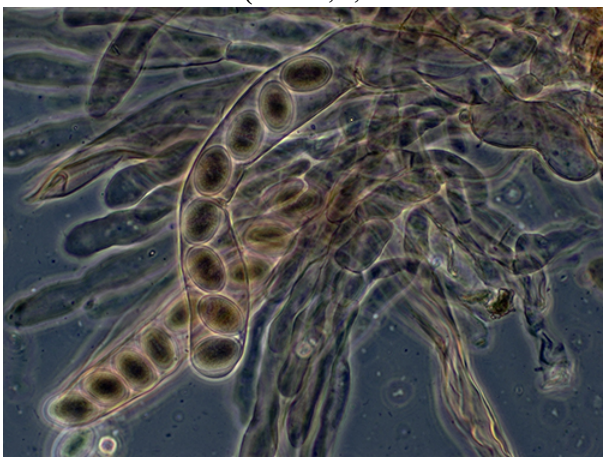


Figure **16.3.6**: These ascospores, lined up within an ascus, are produced sexually. (credit: Peter G. Werner)

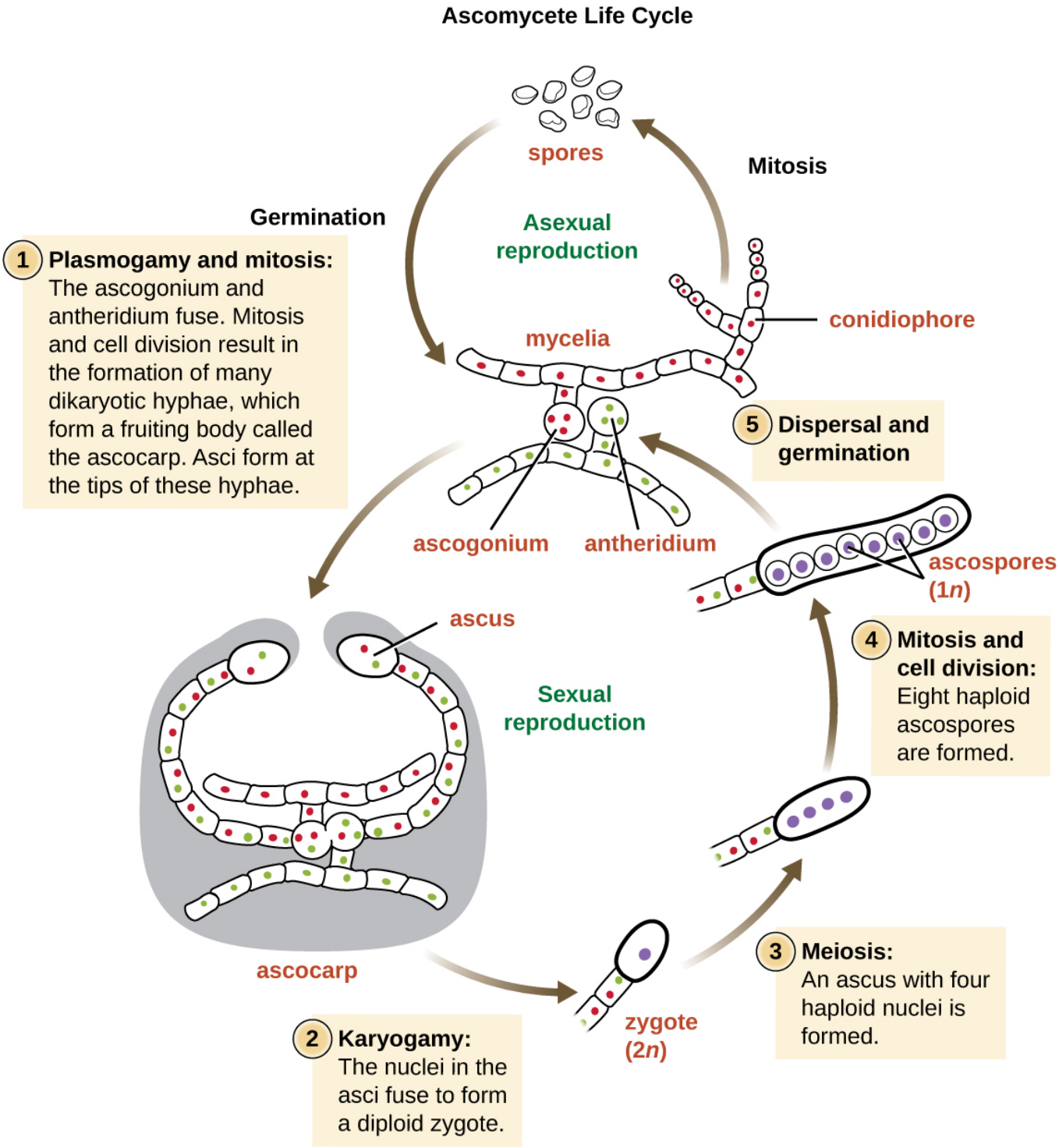


Figure **16.3.7**: The life cycle of an ascomycete is characterized by the production of asci during the sexual phase. The haploid phase is the predominant phase of the life cycle.

The Basidiomycota (basidiomycetes) are fungi that have basidia (club-shaped structures) that produce basidiospores(spores produced through budding) within fruiting bodies called basidiocarps (Figure **16.3.8**). They are important as decomposers and as food. This group includes rusts, stinkhorns, puffballs, and mushrooms. Several species are of particular importance. *Cryptococcus neoformans*, a fungus commonly found as a yeast in the environment, can cause serious lung infections when inhaled by individuals with weakened immune systems. The edible meadow mushroom, *Agricus campestris*, is a basidiomycete, as is the

poisonous mushroom *Amanita phalloides*, known as the death cap. The deadly toxins produced by *A. phalloides* have been used to study transcription.

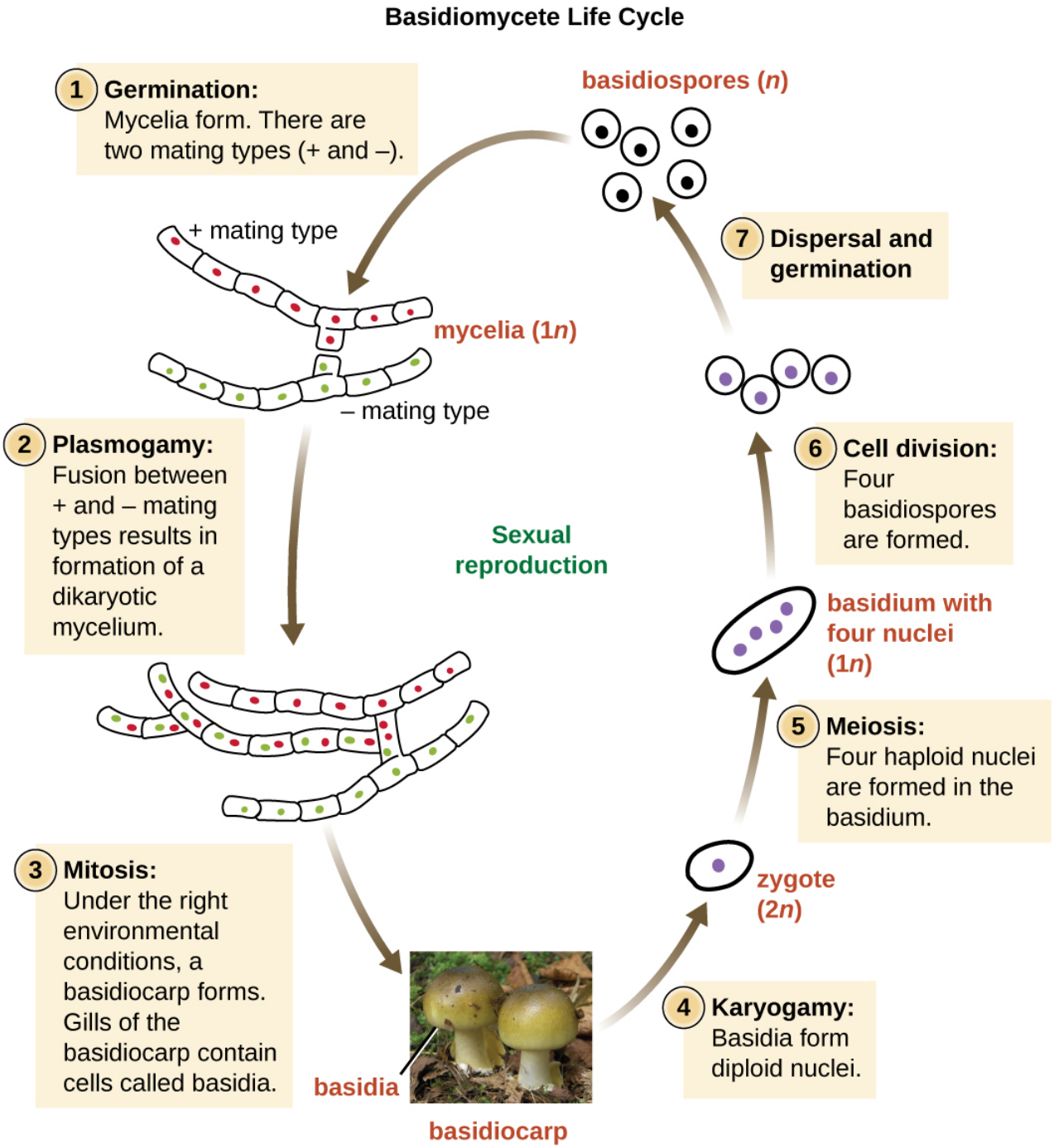
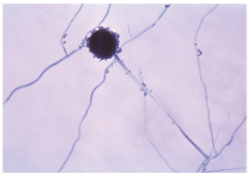
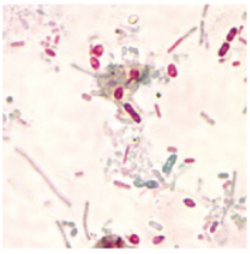
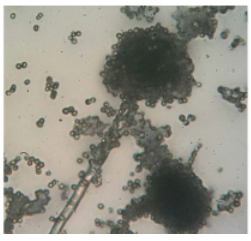


Figure 16.3.8: The life cycle of a basidiomycete alternates a haploid generation with a prolonged stage in which two nuclei (dikaryon) are present in the hyphae.

Finally, the Microsporidia are unicellular fungi that are obligate intracellular parasites. They lack mitochondria, peroxisomes, and centrioles, but their spores release a unique polar tubule that pierces the host cell membrane to allow the fungus to gain entry into the cell. A number of microsporidia are human pathogens, and infections with microsporidia are called microsporidiosis. One pathogenic species is *Enterocystozoan bieneusi*, which can cause symptoms such as diarrhea, cholecystitis (inflammation of the gall bladder), and in rare cases, respiratory illness.

Select Groups of Fungi				
Group	**Characteristics**	**Examples**	**Medically Important Species**	**Image**
Ascomycota	Septate hyphae Ascus with ascospores in ascocarp Conidiospores	Cup fungi Edible mushrooms Morels Truffles *Neurospora* *Penicillium*	*Aspergillus* spp. *Trichophyton* spp. *Microsporum* spp. *Epidermophyton* spp. *Blastomyces dermititidis* *Histoplasma capsulatum*	 *Aspergillus niger*
Basidiomycota	Basidia produce basidiospores in a basidiocarp	Club fungi Rusts Stinkhorns Puffballs Mushrooms *Cryptococcus neoformans* *Amanita phalloides*	*Crytococcus neoformans*	 *Amanita phalloides*
Microsporidia	Lack mitochondria, perioxisomes, centrioles Spores produce a polar tube	*Entero-cystozoan bieneusi*	*Enterocystozoan bieneusi*	 Microsporidia (unidentified)
Zygomycota	Mainly saprophytes Coenocytic hyphae Haploid nuclei Zygospores	*Rhizopus stolonifera*	*Mucor* spp.	

https://med.libretexts.org/@go/page/77939

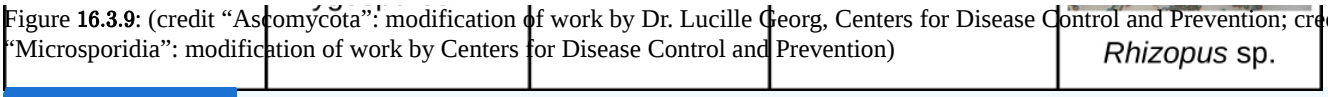


Figure **16.3.9**: (credit "Ascomycota": modification of work by Dr. Lucille Georg, Centers for Disease Control and Prevention; credit "Microsporidia": modification of work by Centers for Disease Control and Prevention)

? Exercise 16.3.2

Which group of fungi appears to be associated with the greatest number of human diseases?

Eukaryotic Pathogens in Eukaryotic Hosts

When we think about antimicrobial medications, antibiotics such as penicillin often come to mind. Penicillin and related antibiotics interfere with the synthesis of peptidoglycan cell walls, which effectively targets bacterial cells. These antibiotics are useful because humans (like all eukaryotes) do not have peptidoglycan cell walls.

Developing medications that are effective against eukaryotic cells but not harmful to human cells is more difficult. Despite huge morphological differences, the cells of humans, fungi, and protists are similar in terms of their ribosomes, cytoskeletons, and cell membranes. As a result, it is more challenging to develop medications that target protozoans and fungi in the same way that antibiotics target prokaryotes.

Fungicides have relatively limited modes of action. Because fungi have ergosterols(instead of cholesterol) in their cell membranes, the different enzymes involved in sterol production can be a target of some medications. The azole and morpholine fungicidesinterfere with the synthesis of membrane sterols. These are used widely in agriculture (fenpropimorph) and clinically (e.g., miconazole). Some antifungal medications target the chitin cell walls of fungi. Despite the success of these compounds in targeting fungi, antifungal medications for systemic infections still tend to have more toxic side effects than antibiotics for bacteria.

Clinical Focus: Part 3

Sarah is relieved the ringworm is not an actual worm, but wants to know what it really is. The physician explains that ringworm is a fungus. He tells her that she will not see mushrooms popping out of her skin, because this fungus is more like the invisible part of a mushroom that hides in the soil. He reassures her that they are going to get the fungus out of her too.

The doctor cleans and then carefully scrapes the lesion to place a specimen on a slide. By looking at it under a microscope, the physician is able to confirm that a fungal infection is responsible for Sarah's lesion. In Figure **16.3.10**, it is possible to see macro- and microconidia in *Trichophyton rubrum*. Cell walls are also visible. Even if the pathogen resembled a helminth under the microscope, the presence of cell walls would rule out the possibility because animal cells lack cell walls.

The doctor prescribes an antifungal cream for Sarah's mother to apply to the ringworm. Sarah's mother asks, "What should we do if it doesn't go away?"

? Exercise 16.3.3

Can all forms of ringworm be treated with the same antifungal medication?

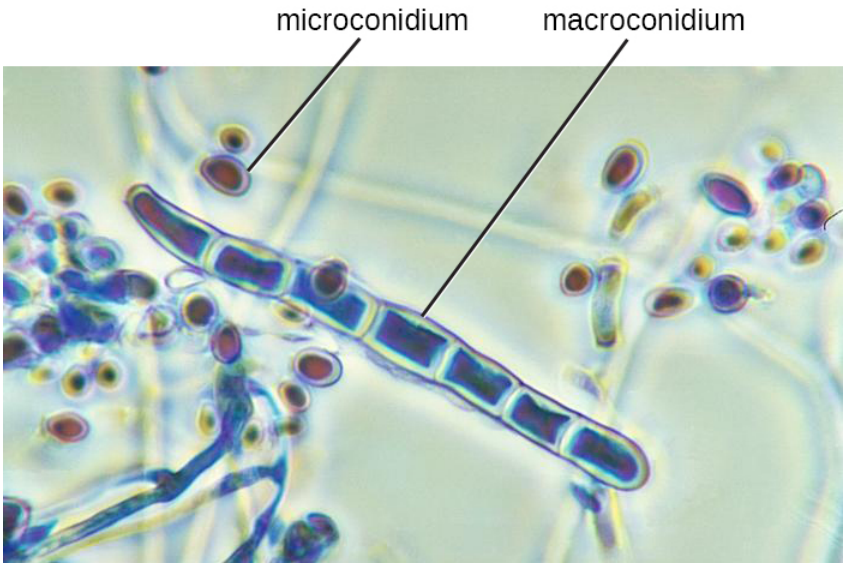


Figure **16.3.10**: This micrograph shows hyphae (macroconidium) and microconidia of *Trichophyton rubrum*, a dermatophyte responsible for fungal infections of the skin. (credit: modification of work by Centers for Disease Control and Prevention)

Key Concepts and Summary

- The fungi include diverse saprotrophic eukaryotic organisms with chitin cell walls
- Fungi can be unicellular or multicellular; some (like yeast) and fungal spores are microscopic, whereas some are large and conspicuous
- Reproductive types are important in distinguishing fungal groups
- Medically important species exist in the four fungal groups Zygomycota, Ascomycota, Basidiomycota, and Microsporidia
- Members of Zygomycota, Ascomycota, and Basidiomycota produce deadly toxins
- Important differences in fungal cells, such as ergosterols in fungal membranes, can be targets for antifungal medications, but similarities between human and fungal cells make it difficult to find targets for medications and these medications often have toxic adverse effects

---

This page titled 16.3: Fungi is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **5.3: Fungi** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

16.4: Algae

Learning Objectives

- Explain why algae are included within the discipline of microbiology
- Describe the unique characteristics of algae
- Identify examples of toxin-producing algae
- Compare the major groups of algae in this chapter, and give examples of each
- Classify algal organisms according to major groups

The algae are autotrophic protists that can be unicellular or multicellular. These organisms are found in the supergroups Chromalveolata (dinoflagellates, diatoms, golden algae, and brown algae) and Archaeplastida (red algae and green algae). They are important ecologically and environmentally because they are responsible for the production of approximately 70% of the oxygen and organic matter in aquatic environments. Some types of algae, even those that are microscopic, are regularly eaten by humans and other animals. Additionally, algae are the source for agar, agarose, and carrageenan, solidifying agents used in laboratories and in food production. Although algae are typically not pathogenic, some produce toxins. Harmful algal blooms, which occur when algae grow quickly and produce dense populations, can produce high concentrations of toxins that impair liver and nervous-system function in aquatic animals and humans.

Like protozoans, algae often have complex cell structures. For instance, algal cells can have one or more chloroplasts that contain structures called pyrenoids to synthesize and store starch. The chloroplasts themselves differ in their number of membranes, indicative of secondary or rare tertiary endosymbiotic events. Primary chloroplasts have two membranes—one from the original cyanobacteria that the ancestral eukaryotic cell engulfed, and one from the plasma membrane of the engulfing cell. Chloroplasts in some lineages appear to have resulted from secondary endosymbiosis, in which another cell engulfed a green or red algal cell that already had a primary chloroplast within it. The engulfing cell destroyed everything except the chloroplast and possibly the cell membrane of its original cell, leaving three or four membranes around the chloroplast. Different algal groups have different pigments, which are reflected in common names such as red algae, brown algae, and green algae.

Some algae, the seaweeds, are macroscopic and may be confused with plants. Seaweeds can be red, brown, or green, depending on their photosynthetic pigments. Green algae, in particular, share some important similarities with land plants; however, there are also important distinctions. For example, seaweeds do not have true tissues or organs like plants do. Additionally, seaweeds do not have a waxy cuticle to prevent desiccation. Algae can also be confused with cyanobacteria, photosynthetic bacteria that bear a resemblance to algae; however, cyanobacteria are prokaryotes (see Nonproteobacteria Gram-negative Bacteria and Phototrophic Bacteria).

Algae have a variety of life cycles. Reproduction may be asexual by mitosis or sexual using gametes.

Algal Diversity

Although the algae and protozoa were formerly separated taxonomically, they are now mixed into supergroups. The algae are classified within the Chromalveolata and the Archaeplastida. Although the Euglenozoa (within the supergroup Excavata) include photosynthetic organisms, these are not considered algae because they feed and are motile.

The dinoflagellates and stramenopiles fall within the Chromalveolata. The dinoflagellates are mostly marine organisms and are an important component of plankton. They have a variety of nutritional types and may be phototrophic, heterotrophic, or mixotrophic. Those that are photosynthetic use chlorophyll *a*, chlorophyll c_2, and other photosynthetic pigments (Figure 16.4.1). They generally have two flagella, causing them to whirl (in fact, the name dinoflagellate comes from the Greek word for “whirl”: *dini*). Some have cellulose plates forming a hard outer covering, or theca, as armor. Additionally, some dinoflagellates produce neurotoxins that can cause paralysis in humans or fish. Exposure can occur through contact with water containing the dinoflagellate toxins or by feeding on organisms that have eaten dinoflagellates.

When a population of dinoflagellates becomes particularly dense, a red tide (a type of harmful algal bloom) can occur. Red tides cause harm to marine life and to humans who consume contaminated marine life. Major toxin producers include *Gonyaulax* and *Alexandrium*, both of which cause paralytic shellfish poisoning. Another species, *Pfiesteria piscicida*, is known as a fish killer

because, at certain parts of its life cycle, it can produce toxins harmful to fish and it appears to be responsible for a suite of symptoms, including memory loss and confusion, in humans exposed to water containing the species.

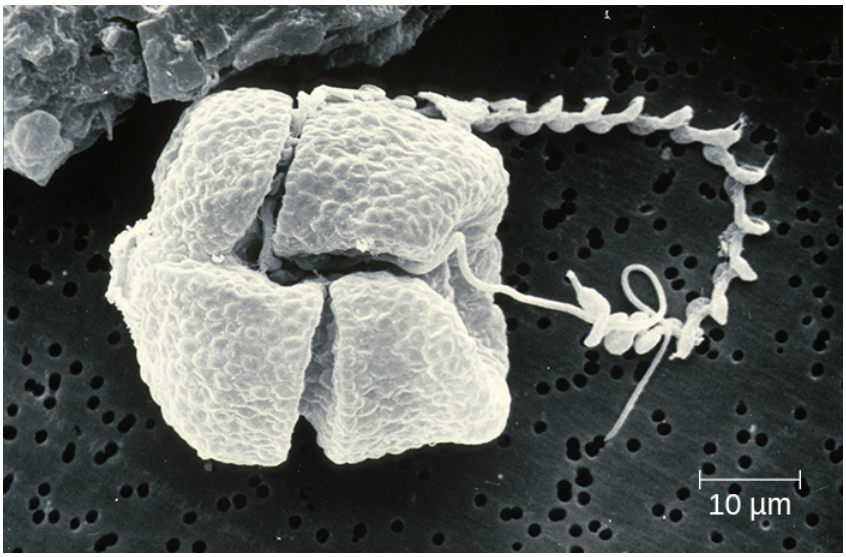


Figure **16.4.1**: The dinoflagellates exhibit great diversity in shape. Many are encased in cellulose armor and have two flagella that fit in grooves between the plates. Movement of these two perpendicular flagella causes a spinning motion. (credit: modification of work by CSIRO)

The stramenopiles include the golden algae (Chrysophyta), the brown algae (Phaeophyta), and the diatoms(Bacillariophyta). Stramenopiles have chlorophyll *a*, chlorophyll c_1/c_2, and fucoxanthin as photosynthetic pigments. Their storage carbohydrate is chrysolaminarin. While some lack cell walls, others have scales. Diatoms have flagella and frustules, which are outer cell walls of crystallized silica; their fossilized remains are used to produce diatomaceous earth, which has a range of uses such as filtration and insulation. Additionally, diatoms can reproduce sexually or asexually. One diatom genus, *Pseudo-nitzschia*, is known to be associated with harmful algal blooms.

Brown algae (Phaeophyta) are multicellular marine seaweeds. Some can be extremely large, such as the giant kelp (*Laminaria*). They have leaf-like blades, stalks, and structures called holdfasts that are used to attach to substrate. However, these are not true leaves, stems, or roots (Figure **16.4.2**). Their photosynthetic pigments are chlorophyll *a*, chlorophyll *c*, *β*-carotene, and fucoxanthine. They use laminarin as a storage carbohydrate.

The Archaeplastids include the green algae (Chlorophyta), the red algae (Rhodophyta), another group of green algae (Charophyta), and the land plants. The Charaphyta are the most similar to land plants because they share a mechanism of cell division and an important biochemical pathway, among other traits that the other groups do not have. Like land plants, the Charophyta and Chlorophyta have chlorophyll *a* and chlorophyll *b* as photosynthetic pigments, cellulose cell walls, and starch as a carbohydrate storage molecule. *Chlamydomonas* is a green alga that has a single large chloroplast, two flagella, and a stigma (eyespot); it is important in molecular biology research (Figure **16.4.3**).

Chlorella is a nonmotile, large, unicellular alga, and *Acetabularia* is an even larger unicellular green alga. The size of these organisms challenges the idea that all cells are small, and they have been used in genetics research since Joachim Hämmerling (1901–1980) began to work with them in 1943. *Volvox* is a colonial, unicellular alga (Figure **16.4.3**). A larger, multicellular green alga is *Ulva*, also known as the sea lettuce because of its large, edible, green blades. The range of life forms within the Chlorophyta —from unicellular to various levels of coloniality to multicellular forms—has been a useful research model for understanding the evolution of multicellularity. The red algae are mainly multicellular but include some unicellular forms. They have rigid cell walls containing agar or carrageenan, which are useful as food solidifying agents and as a solidifier added to growth media for microbes.

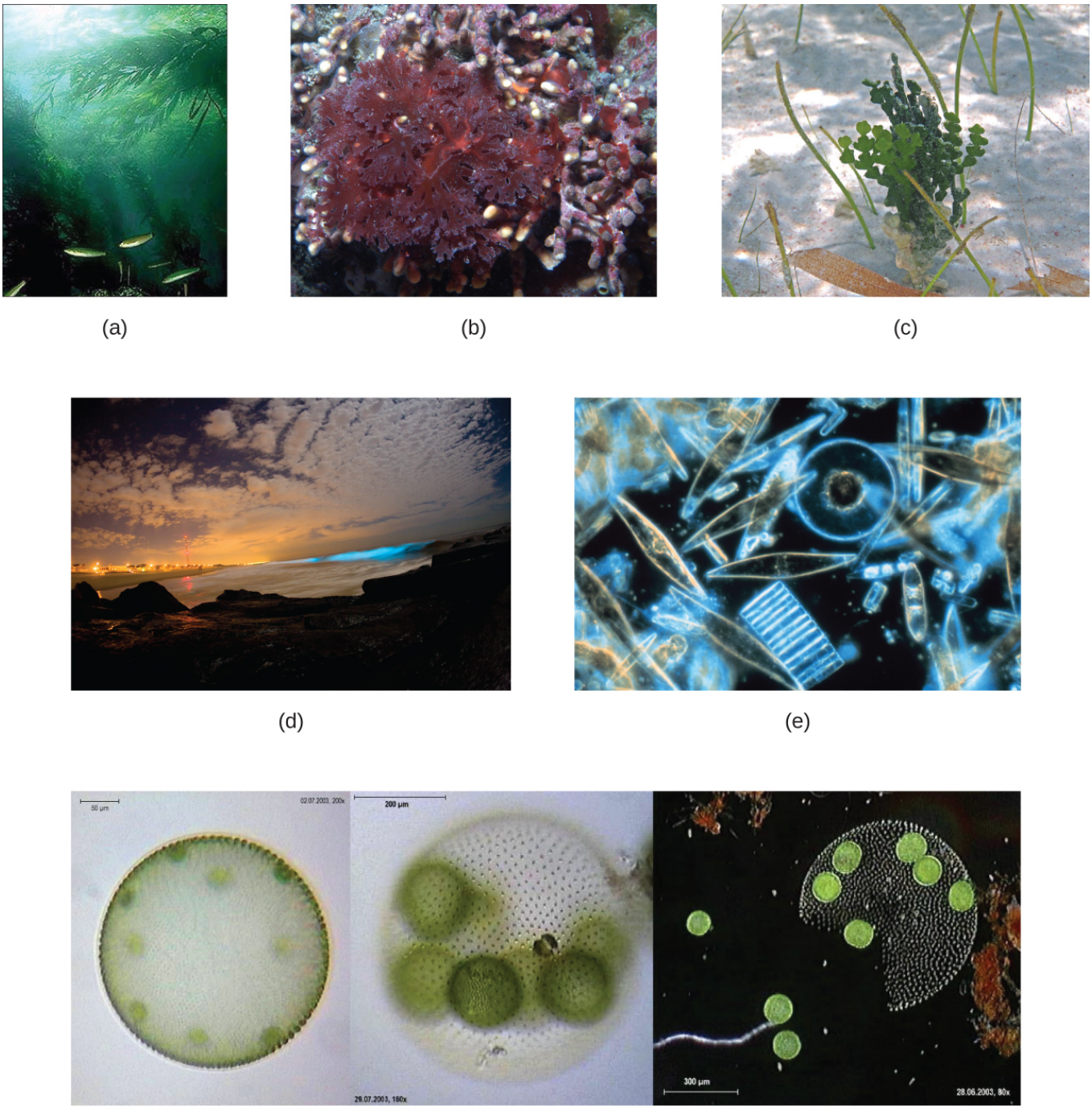


Figure **16.4.2**: (a) These large multicellular kelps are members of the brown algae. Note the “leaves” and “stems” that make them appear similar to green plants. (b) This is a species of red algae that is also multicellular. (c) The green alga *Halimeda incrassata*, shown here growing on the sea floor in shallow water, appears to have plant-like structures, but is not a true plant. (d) Bioluminesence, visible in the cresting wave in this picture, is a phenomenon of certain dinoflagellates. (e) Diatoms (pictured in this micrograph) produce silicaceous tests (skeletons) that form diatomaceous earths. (f) Colonial green algae, like volvox in these three micrographs, exhibit simple cooperative associations of cells. (credit a, e: modification of work by NOAA; credit b: modification of work by Ed Bierman; credit c: modification of work by James St. John; credit d: modification of work by “catalano82”/Flickr; credit f: modification of work by Dr. Ralf Wagner)

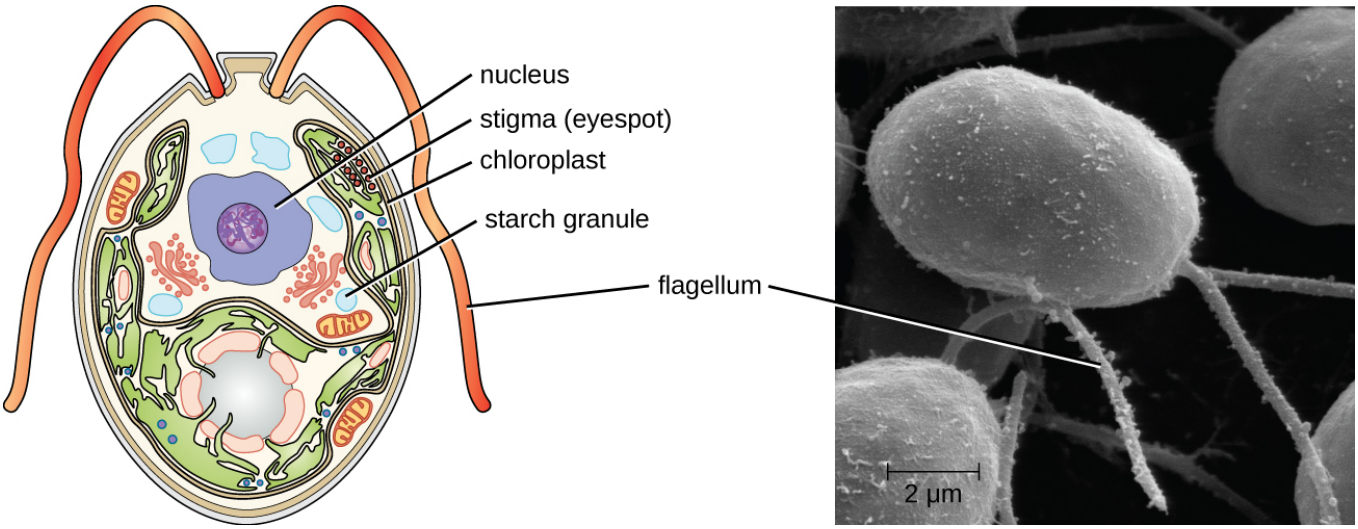


Figure **16.4.3**: Chlamydomonas is a unicellular green alga.

? Exercise 16.4.1

Which groups of algae are associated with harmful algal blooms?

Key Concepts and Summary

- Algae are a diverse group of photosynthetic eukaryotic protists.
- Algae may be unicellular or multicellular.
- Large, multicellular algae are called seaweeds but are not plants and lack plant-like tissues and organs.
- Although algae have little pathogenicity, they may be associated with toxic **algal blooms** that can harm aquatic wildlife and contaminate seafood with toxins that cause paralysis.
- Algae are important for producing **agar**, which is used as a solidifying agent in microbiological media, and **carrageenan**, which is used as a solidifying agent.

This page titled 16.4: Algae is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **5.4: Algae** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

16.5: Lichens

Learning Objectives

- Explain why lichens are included in the study of microbiology
- Describe the unique characteristics of a lichen and the role of each partner in the symbiotic relationship of a lichen
- Describe ways in which lichens are beneficial to the environment

No one has to worry about getting sick from a lichen infection, but lichens are interesting from a microbiological perspective and they are an important component of most terrestrial ecosystems. Lichens provide opportunities for study of close relationships between unrelated microorganisms. Lichens contribute to soil production by breaking down rock, and they are early colonizers in soilless environments such as lava flows. The cyanobacteria in some lichens can fix nitrogen and act as a nitrogen source in some environments. Lichens are also important soil stabilizers in some desert environments and they are an important winter food source for caribou and reindeer. Finally, lichens produce compounds that have antibacterial effects, and further research may discover compounds that are medically useful to humans.

Characteristics

A lichen is a combination of two organisms, a green alga or cyanobacterium and an ascomycete fungus, living in a symbiotic relationship. Whereas algae normally grow only in aquatic or extremely moist environments, lichens can potentially be found on almost any surface (especially rocks) or as epiphytes (meaning that they grow on other plants).

In some ways, the symbiotic relationship between lichens and algae seems like a mutualism (a relationship in which both organisms benefit). The fungus can obtain photosynthates from the algae or cyanobacterium and the algae or cyanobacterium can grow in a drier environment than it could otherwise tolerate. However, most scientists consider this symbiotic relationship to be a controlled parasitism (a relationship in which one organism benefits and the other is harmed) because the photosynthetic organism grows less well than it would without the fungus. It is important to note that such symbiotic interactions fall along a continuum between conflict and cooperation.

Lichens are slow growing and can live for centuries. They have been used in foods and to extract chemicals as dyes or antimicrobial substances. Some are very sensitive to pollution and have been used as environmental indicators.

Lichens have a body called a thallus, an outer, tightly packed fungal layer called a cortex, and an inner, loosely packed fungal layer called a medulla (Figure **16.5.1**). Lichens use hyphal bundles called rhizines to attach to the substrate.

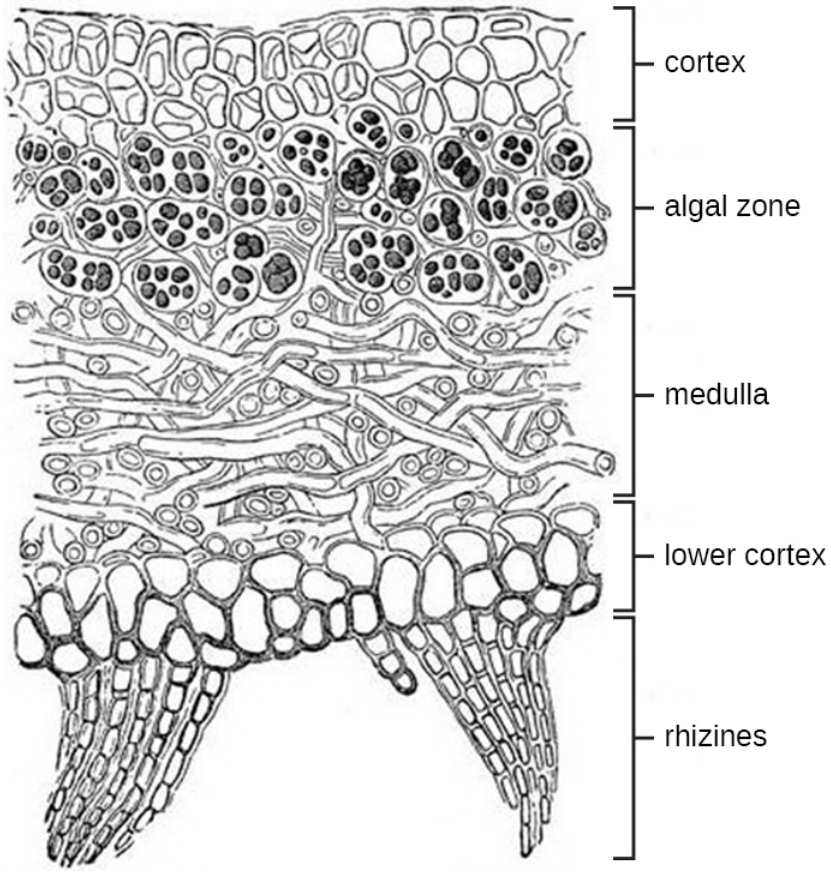


Figure **16.5.1**: This cross-section of a lichen thallus shows its various components. The upper cortex of fungal hyphae provides protection. Photosynthesis occurs in the algal zone. The medulla consists of fungal hyphae. The lower cortex also provides protection. The rhizines anchor the thallus to the substrate.

Lichen Diversity

Lichens are classified as fungi and the fungal partners belong to the Ascomycota and Basidiomycota. Lichens can also be grouped into types based on their morphology. There are three major types of lichens, although other types exist as well. Lichens that are tightly attached to the substrate, giving them a crusty appearance, are called crustose lichens. Those that have leaf-like lobes are foliose lichens; they may only be attached at one point in the growth form, and they also have a second cortex below the medulla. Finally, fruticose lichens have rounded structures and an overall branched appearance. Figure **16.5.2** shows an example of each of the forms of lichens.



Figure **16.5.2**: Examples of the three types of lichens are shown here. (a) This is a crustose lichen found mostly on marine rocks,

Caloplaca marina. (b) This is a foliose lichen, *Flavoparmelia caperata*. (c) This is a fruticose lichen, *Letharia vulpina*, which is sufficiently poisonous that it was once used to make arrowheads. (credit b, c: modification of work by Jason Hollinger)

Exercise 16.5.1

1. What types of organisms are found in lichens?
2. What are the three growth forms of lichens?

Clinical Focus: Resolution

Sarah's mother asks the doctor what she should do if the cream prescribed for Sarah's ringworm does not work. The doctor explains that ringworm is a general term for a condition caused by multiple species. The first step is to take a scraping for examination under the microscope, which the doctor has already done. He explains that he has identified the infection as a fungus, and that the antifungal cream works against the most common fungi associated with ringworm. However, the cream may not work against some species of fungus. If the cream is not working after a couple of weeks, Sarah should come in for another visit, at which time the doctor will take steps to identify the species of the fungus.

Positive identification of dermatophytes requires culturing. For this purpose, Sabouraud's agar may be used. In the case of Sarah's infection, which cleared up within 2 weeks of treatment, the culture would have a granular texture and would appear pale pink on top and red underneath. These features suggest that the fungus is *Trichophyton rubrum*, a common cause of ringworm.

Key Concepts and Summary

- **Lichens** are a symbiotic association between a fungus and an algae or a cyanobacterium
- The symbiotic association found in lichens is currently considered to be a controlled **parasitism**, in which the fungus benefits and the algae or cyanobacterium is harmed
- Lichens are slow growing and can live for centuries in a variety of habitats
- Lichens are environmentally important, helping to create soil, providing food, and acting as indicators of air pollution

This page titled 16.5: Lichens is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **5.5: Lichens** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

16.E: The Eukaryotes of Microbiology (Exercises)

5.1: Unicellular Eukaryotic Microorganisms

Protists are a diverse, polyphyletic group of eukaryotic organisms. Protists may be unicellular or multicellular. They vary in how they get their nutrition, morphology, method of locomotion, and mode of reproduction. Important structures of protists include contractile vacuoles, cilia, flagella, pellicles, and pseudopodia; some lack organelles such as mitochondria. Taxonomy of protists is changing rapidly as relationships are reassessed using newer techniques.

Multiple Choice

Which genus includes the causative agent for malaria?

A. *Euglena*
B. *Paramecium*
C. *Plasmodium*
D. *Trypanosoma*

Answer

C

Which protist is a concern because of its ability to contaminate water supplies and cause diarrheal illness?

A. *Plasmodium vivax*
B. *Toxoplasma gondii*
C. *Giardia lamblia*
D. *Trichomonas vaginalis*

Answer

C

Fill in the Blank

The plasma membrane of a protist is called the _____.

Answer

plasmalemma

Animals belong to the same supergroup as the kingdom _____.

Answer

Fungi

Short Answer

What are kinetoplastids?

Aside from a risk of birth defects, what other effect might a toxoplasmosis infection have?

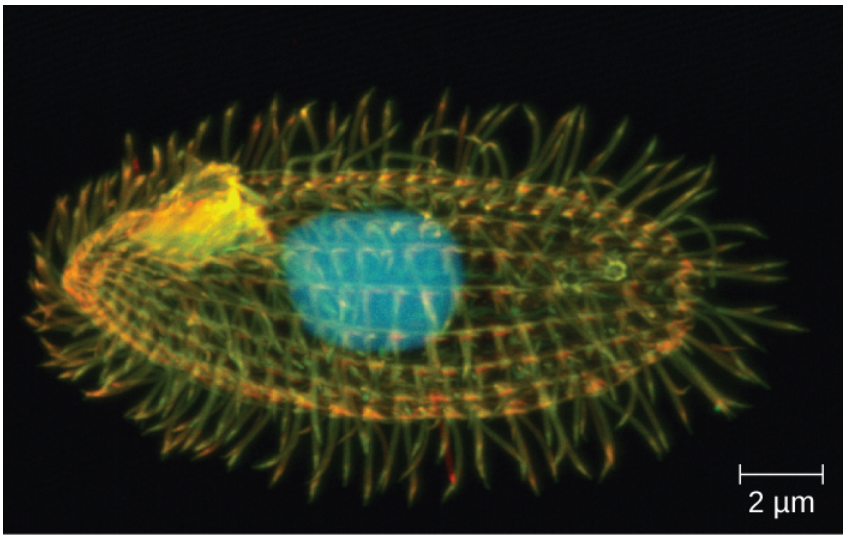
What is the function of the ciliate macronucleus?

Critical Thinking

The protist shown has which of the following?

A. pseudopodia
B. flagella
C. a shell

D. cilia



(credit: modification of work by Richard Robinson)

Protist taxonomy has changed greatly in recent years as relationships have been re-examined using newer approaches. How do newer approaches differ from older approaches?

What characteristics might make you think a protist could be pathogenic? Are certain nutritional characteristics, methods of locomotion, or morphological differences likely to be associated with the ability to cause disease?

5.2: Parasitic Helminths

Helminth parasites are included within the study of microbiology because they are often identified by looking for microscopic eggs and larvae. The two major groups of helminth parasites are the roundworms (Nematoda) and the flatworms (Platyhelminthes). Nematodes are common intestinal parasites often transmitted through undercooked foods, although they are also found in other environments. Platyhelminths include tapeworms and flukes, which are often transmitted through undercooked meat.

Multiple Choice

A fluke is classified within which of the following?

A. Nematoda
B. Rotifera
C. Platyhelminthes
D. Annelida

Answer

C

A nonsegmented worm is found during a routine colonoscopy of an individual who reported having abdominal cramps, nausea, and vomiting. This worm is likely which of the following?

A. nematode
B. fluke
C. trematode
D. annelid

Answer

A

A segmented worm has male and female reproductive organs in each segment. Some use hooks to attach to the intestinal wall. Which type of worm is this?

A. fluke
B. nematode
C. cestode
D. annelid

Answer

C

Fill in the Blank

Flukes are in class _____.

Answer

Trematoda

A species of worm in which there are distinct male and female individuals is described as _____.

Answer

dioecious

Short Answer

What is the best defense against tapeworm infection?

Critical Thinking

Given the life cycle of the *Schistosoma* parasite, suggest a method of prevention of the disease.

5.3: Fungi

The fungi include diverse saprotrophic eukaryotic organisms with chitin cell walls. Fungi can be unicellular or multicellular; some (like yeast) and fungal spores are microscopic, whereas some are large and conspicuous. Reproductive types are important in distinguishing fungal groups. Medically important species exist in the four fungal groups Zygomycota, Ascomycota, Basidiomycota, and Microsporidia.

Multiple Choice

Mushrooms are a type of which of the following?

A. conidia
B. ascus
C. polar tubule
D. basidiocarp

Answer

D

Which of the following is the most common cause of human yeast infections?

A. *Candida albicans*
B. *Blastomyces dermatitidis*
C. *Cryptococcus neoformans*
D. *Aspergillus fumigatus*

Answer

A

Which of the following is an ascomycete fungus associated with bat droppings that can cause a respiratory infection if inhaled?

A. *Candida albicans*
B. *Histoplasma capsulatum*
C. *Rhizopus stolonifera*
D. *Trichophyton rubrum*

Answer

B

Fill in the Blank

Nonseptate hyphae are also called _____.

Answer

coenocytic

Unicellular fungi are called _____.

Answer

yeasts

Some fungi have proven medically useful because they can be used to produce _____.

Answer

antibiotics

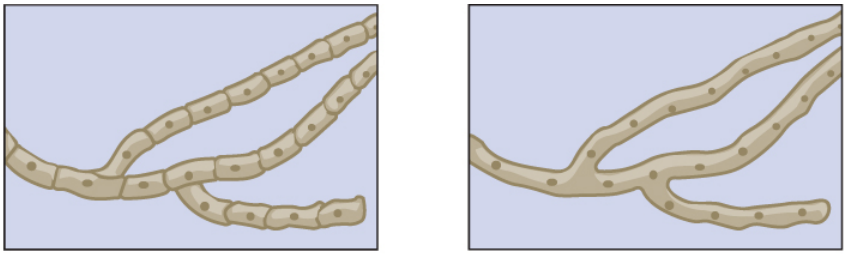
Short Answer

Which genera of fungi are common dermatophytes (fungi that cause skin infections)?

What is a dikaryotic cell?

Critical Thinking

Which of the drawings shows septate hyphae?



A B

Explain the benefit of research into the pathways involved in the synthesis of chitin in fungi.

5.4: Algae

Algae are a diverse group of photosynthetic eukaryotic protists. Algae may be unicellular or multicellular. Large, multicellular algae are called seaweeds but are not plants and lack plant-like tissues and organs. Although algae have little pathogenicity, they may be associated with toxic algal blooms that can harm aquatic wildlife and contaminate seafood with toxins that cause paralysis.

Multiple Choice

Which polysaccharide found in red algal cell walls is a useful solidifying agent?

A. chitin
B. cellulose
C. phycoerythrin
D. agar

Answer

D

Which is the term for the hard outer covering of some dinoflagellates?

A. theca
B. thallus
C. mycelium
D. shell

Answer

A

Which protists are associated with red tides?

A. red algae
B. brown algae
C. dinoflagellates
D. green algae

Answer

C

Fill in the Blank

Structures in chloroplasts used to synthesize and store starch are called _____.

Answer

pyrenoids

Algae with chloroplasts with three or four membranes are a result of _____ _____.

Answer

secondary endosymbiosis

Short Answer

What is a distinctive feature of diatoms?

Why are algae not considered parasitic?

Which groups contain the multicellular algae?

5.5: Lichens

Lichens are a symbiotic association between a fungus and an algae or a cyanobacterium. The symbiotic association found in lichens is currently considered to be a controlled parasitism, in which the fungus benefits and the algae or cyanobacterium is harmed. Lichens are slow growing and can live for centuries in a variety of habitats. Lichens are environmentally important, helping to create soil, providing food, and acting as indicators of air pollution.

Multiple Choice

You encounter a lichen with leafy structures. Which term describes this lichen?

A. crustose
B. foliose
C. fruticose
D. agarose

Answer

B

Which of the following is the term for the outer layer of a lichen?

A. the cortex
B. the medulla
C. the thallus
D. the theca

Answer

A

The fungus in a lichen is which of the following?

A. a basidiomycete
B. an ascomycete
C. a zygomycete
D. an apicomplexan

Answer

B

Short Answer

What are three ways that lichens are environmentally valuable?

This page titled 16.E: The Eukaryotes of Microbiology (Exercises) is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **5.E: The Eukaryotes of Microbiology (Exercises)** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

CHAPTER OVERVIEW

17: Systemic Infections

17.1: Respiratory System Infections

17.1.1: Anatomy and Normal Microbiota of the Respiratory Tract

17.1.2: Bacterial Infections of the Respiratory Tract

17.1.3: Viral Infections of the Respiratory Tract

17.1.4: Respiratory Mycoses

17.1.E: Respiratory System Infections (Exercises)

17.2: Urogenital System Infections

17.2.1: Anatomy and Normal Microbiota of the Urogenital Tract

17.2.2: Bacterial Infections of the Urinary System

17.2.3: Bacterial Infections of the Reproductive System

17.2.4: Viral Infections of the Reproductive System

17.2.5: Fungal Infections of the Reproductive System

17.2.6: Protozoan Infections of the Reproductive System

17.2.E: Urogenital System Infections (Exercises)

17.3: Digestive System Infections

17.3.1: Anatomy and Normal Microbiota of the Digestive System

17.3.2: Microbial Diseases of the Mouth and Oral Cavity

17.3.3: Bacterial Infections of the Gastrointestinal Tract

17.3.4: Viral Infections of the Gastrointestinal Tract

17.3.5: Protozoan Infections of the Gastrointestinal Tract

17.3.6: Helminthic Infections of the Gastrointestinal Tract

17.3.E: Digestive System Infections (Exercises)

17.4: Circulatory and Lymphatic System Infections

17.4.1: Anatomy of the Circulatory and Lymphatic Systems

17.4.2: Bacterial Infections of the Circulatory and Lymphatic Systems

17.4.3: Viral Infections of the Circulatory and Lymphatic Systems

17.4.4: Parasitic Infections of the Circulatory and Lymphatic Systems

17.4.E: Circulatory and Lymphatic System Infections (Exercises)

17.5: Nervous System Infections

17.5.1: Anatomy of the Nervous System

17.5.2: Bacterial Diseases of the Nervous System

17.5.3: Acellular Pathogenic Diseases of the Nervous System

17.5.4: Neuromycoses and Parasitic Diseases of the Nervous System

17.5.E: Nervous System Infections (Exercises)

17.6: Fungal Diseases of the Respiratory System

17.6.1: Histoplasmosis

17.6.2: Coccidiomycosis

17.6.3: Pneumocystis Pneumonia

17.6.4: Blastomycosis

17.6.5: Other Fungi Involved in Respiratory Disease
17.7: Fungal and Protozoan Diseases of the Digestive System
17.7.1: Ergot Poisoning
17.7.2: Aflatoxin Poisoning
17.7.3: Giardiasis
17.7.4: Cryptosporidiosis
17.7.5: Cyclospora Diarrheal Infection
17.7.6: Amoebic Dysentery (Amoebiasis)
17.7.7: Legionellosis
17.8: Helminthic Diseases of the Digestive System
17.8.1: Tapeworms
17.8.2: Hydatid Disease
17.8.3: Nematodes
17.9: Fungal and Protozoan Diseases of the Reproductive System
17.9.1: Vulvovaginal Candidiasis
17.9.2: Trichomoniasis
17.9.3: The TORCH Panel of Tests
17.10: Fungal Skin and Nail Diseases
17.11: Parasitic Skin Diseases
17.12: Other Infectious Eye Diseases
17.13: Fungal, Protozoan, Prion, and Other Diseases of the Nervous System
17.13.1: Cryptococcosis
17.13.2: African Trypanosomiasis
17.13.3: Amoebic Meningoencephalitis
17.13.4: Bovine Spongiform Encephalopathy
17.13.5: Variant Creutzfeldt-Jakob Disease
17.13.6: Chronic Fatigue Syndrome

This page titled 17: Systemic Infections is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

SECTION OVERVIEW

17.1: Respiratory System Infections

The respiratory tract is one of the main portals of entry into the human body for microbial pathogens. On average, a human takes about 20,000 breaths each day. This roughly corresponds to 10,000 liters, or 10 cubic meters, of air. Suspended within this volume of air are millions of microbes of terrestrial, animal, and human origin—including many potential pathogens. A few of these pathogens will cause relatively mild infections like sore throats and colds. Others, however, are less benign. According to the World Health Organization, respiratory tract infections such as tuberculosis, influenza, and pneumonia were responsible for more than 4 million deaths worldwide in 2012.[1]

At one time, it was thought that antimicrobial drugs and preventive vaccines might hold respiratory infections in check in the developed world, but recent developments suggest otherwise. The rise of multiple-antibiotic resistance in organisms like *Mycobacterium tuberculosis* has rendered many of our modern drugs ineffective. In addition, there has been a recent resurgence in diseases like whooping cough and measles, once-common childhood illnesses made rare by effective vaccines. Despite advances in medicine and public health programs, it is likely that respiratory pathogens will remain formidable adversaries for the foreseeable future.



Figure **17.1.1**: Aerosols produced by sneezing, coughing, or even just speaking are an important mechanism for respiratory pathogen transmission. Simple actions, like covering your mouth when coughing or sneezing, can reduce the spread of these microbes. (credit: modification of work by Centers for Disease Control and Prevention)

17.1.1: Anatomy and Normal Microbiota of the Respiratory Tract

17.1.2: Bacterial Infections of the Respiratory Tract

17.1.3: Viral Infections of the Respiratory Tract

17.1.4: Respiratory Mycoses

17.1.E: Respiratory System Infections (Exercises)

Footnotes

1. 1 World Health Organization. “The Top Ten Causes of Death.” May 2014. http://www.who.int/mediacentre/factsheets/fs310/en/

This page titled 17.1: Respiratory System Infections is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

17.1.1: Anatomy and Normal Microbiota of the Respiratory Tract

Learning Objectives

- Describe the major anatomical features of the upper and lower respiratory tract
- Describe the normal microbiota of the upper and lower respiratory tracts
- Explain how microorganisms overcome defenses of upper and lower respiratory-tract membranes to cause infection
- Explain how microbes and the respiratory system interact and modify each other in healthy individuals and during an infection

Clinical Focus: Part 1

John, a 65-year-old man with asthma and type 2 diabetes, works as a sales associate at a local home improvement store. Recently, he began to feel quite ill and made an appointment with his family physician. At the clinic, John reported experiencing headache, chest pain, coughing, and shortness of breath. Over the past day, he had also experienced some nausea and diarrhea. A nurse took his temperature and found that he was running a fever of 40 °C (104 °F).

John suggested that he must have a case of influenza (flu), and regretted that he had put off getting his flu vaccine this year. After listening to John's breathing through a stethoscope, the physician ordered a chest radiography and collected blood, urine, and sputum samples.

Exercise 17.1.1.1

Based on this information, what factors may have contributed to John's illness?

The primary function of the respiratory tract is to exchange gases (oxygen and carbon dioxide) for metabolism. However, inhalation and exhalation (particularly when forceful) can also serve as a vehicle of transmission for pathogens between individuals.

Anatomy of the Upper Respiratory System

The respiratory system can be conceptually divided into upper and lower regions at the point of the epiglottis, the structure that seals off the lower respiratory system from the pharynx during swallowing (Figure 17.1.1.1). The upper respiratory system is in direct contact with the external environment. The nares (or nostrils) are the external openings of the nose that lead back into the nasal cavity, a large air-filled space behind the nares. These anatomical sites constitute the primary opening and first section of the respiratory tract, respectively. The nasal cavity is lined with hairs that trap large particles, like dust and pollen, and prevent their access to deeper tissues. The nasal cavity is also lined with a mucous membrane and Bowman's glands that produce mucus to help trap particles and microorganisms for removal. The nasal cavity is connected to several other air-filled spaces. The sinuses, a set of four, paired small cavities in the skull, communicate with the nasal cavity through a series of small openings. The nasopharynx is part of the upper throat extending from the posterior nasal cavity. The nasopharynx carries air inhaled through the nose. The middle ear is connected to the nasopharynx through the eustachian tube. The middle ear is separated from the outer ear by the tympanic membrane, or ear drum. And finally, the lacrimal glands drain to the nasal cavity through the nasolacrimal ducts (tear ducts). The open connections between these sites allow microorganisms to move from the nasal cavity to the sinuses, middle ears (and back), and down into the lower respiratory tract from the nasopharynx.

The oral cavity is a secondary opening for the respiratory tract. The oral and nasal cavities connect through the fauces to the pharynx, or throat. The pharynx can be divided into three regions: the nasopharynx, the oropharynx, and the laryngopharynx. Air inhaled through the mouth does not pass through the nasopharynx; it proceeds first through the oropharynx and then through the laryngopharynx. The palatine tonsils, which consist of lymphoid tissue, are located within the oropharynx. The laryngopharynx, the last portion of the pharynx, connects to the larynx, which contains the vocal fold (Figure 17.1.1.1).

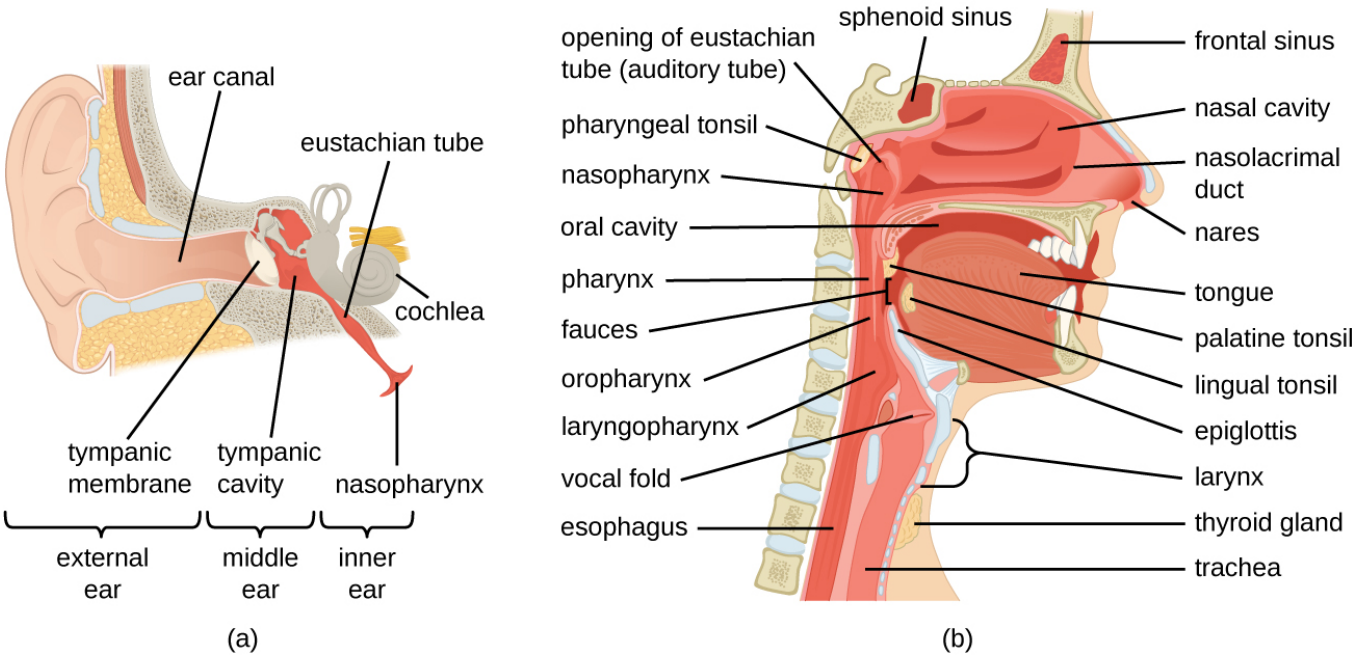


Figure **17.1.1.1**: (a) The ear is connected to the upper respiratory tract by the eustachian tube, which opens to the nasopharynx. (b) The structures of the upper respiratory tract.

? Exercise 17.1.1.2

1. Identify the sequence of anatomical structures through which microbes would pass on their way from the nares to the larynx.
2. What two anatomical points do the eustachian tubes connect?

Anatomy of the Lower Respiratory System

The lower respiratory system begins below the epiglottis in the larynx or voice box (Figure **17.1.1.2**). The trachea, or windpipe, is a cartilaginous tube extending from the larynx that provides an unobstructed path for air to reach the lungs. The trachea bifurcates into the left and right bronchi as it reaches the lungs. These paths branch repeatedly to form smaller and more extensive networks of tubes, the bronchioles. The terminal bronchioles formed in this tree-like network end in cul-de-sacs called the alveoli. These structures are surrounded by capillary networks and are the site of gas exchange in the respiratory system. Human lungs contain on the order of 400,000,000 alveoli. The outer surface of the lungs is protected with a double-layered pleural membrane. This structure protects the lungs and provides lubrication to permit the lungs to move easily during respiration.

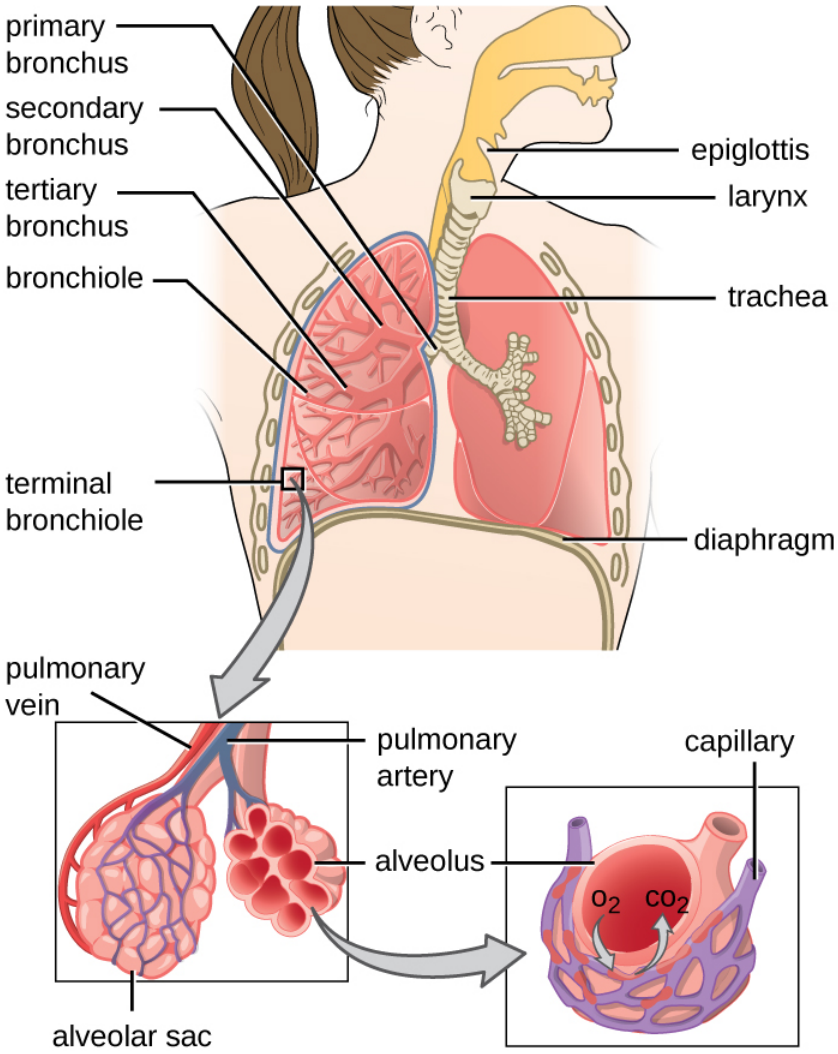


Figure 17.1.1.2: The structures of the lower respiratory tract are identified in this illustration. (credit: modification of work by National Cancer Institute)

Defenses of the Respiratory System

The inner lining of the respiratory system consists of mucous membranes (Figure **17.1.1.3**) and is protected by multiple immune defenses. The goblet cells within the respiratory epithelium secrete a layer of sticky mucus. The viscosity and acidity of this secretion inhibits microbial attachment to the underlying cells. In addition, the respiratory tract contains ciliated epithelial cells. The beating cilia dislodge and propel the mucus, and any trapped microbes, upward to the epiglottis, where they will be swallowed. Elimination of microbes in this manner is referred to as the mucociliary escalator effect and is an important mechanism that prevents inhaled microorganisms from migrating further into the lower respiratory tract.

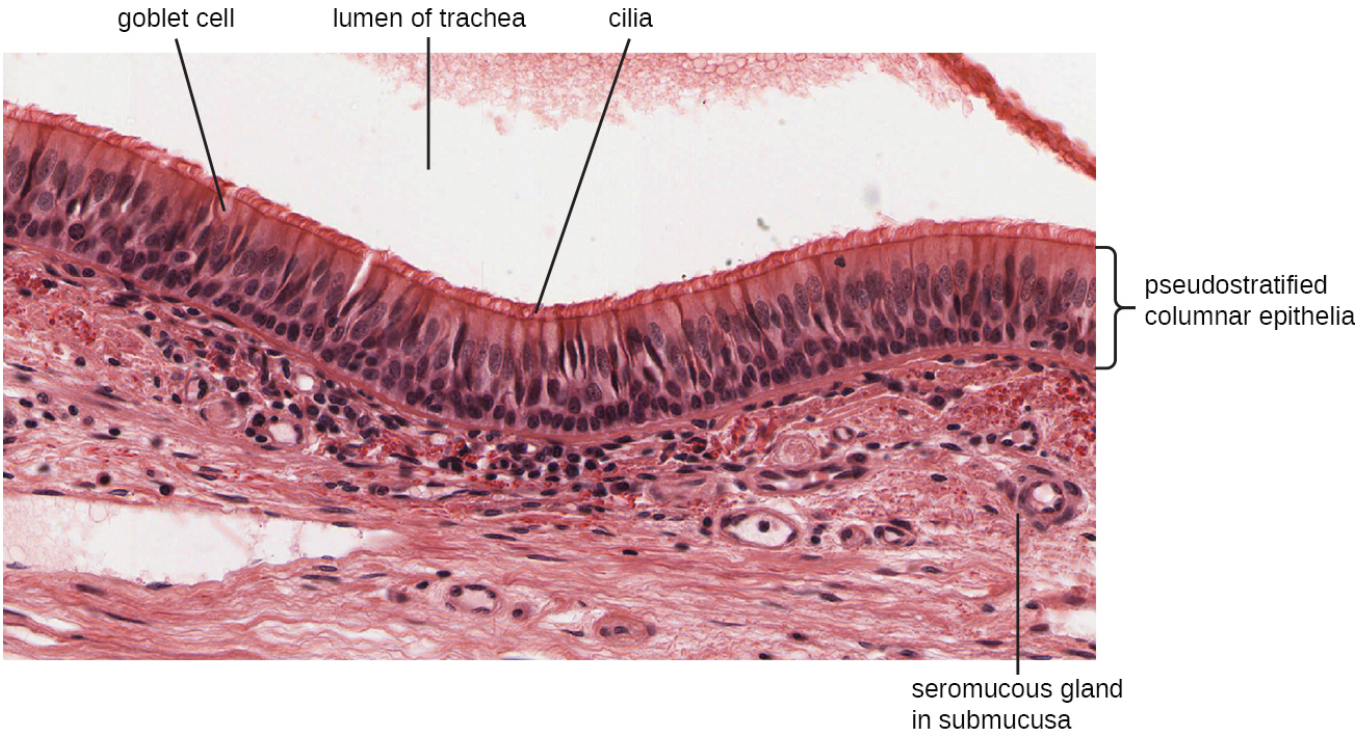


Figure **17.1.1.3**: This micrograph shows the structure of the mucous membrane of the respiratory tract. (credit: modification of micrograph provided by the Regents of University of Michigan Medical School © 2012)

The upper respiratory system is under constant surveillance by mucosa-associated lymphoid tissue (MALT), including the adenoids and tonsils. Other mucosal defenses include secreted antibodies (IgA), lysozyme, surfactant, and antimicrobial peptides called defensins. Meanwhile, the lower respiratory tract is protected by alveolar macrophages. These phagocytes efficiently kill any microbes that manage to evade the other defenses. The combined action of these factors renders the lower respiratory tract nearly devoid of colonized microbes.

? Exercise 17.1.1.3

1. Identify the sequence of anatomical structures through which microbes would pass on their way from the larynx to the alveoli.
2. Name some defenses of the respiratory system that protect against microbial infection.

Normal Microbiota of the Respiratory System

The upper respiratory tract contains an abundant and diverse microbiota. The nasal passages and sinuses are primarily colonized by members of the Firmicutes, Actinobacteria, and Proteobacteria. The most common bacteria identified include *Staphylococcus epidermidis*, viridans group streptococci (VGS), *Corynebacterium* spp. (diphtheroids), *Propionibacterium* spp., and *Haemophilus* spp. The oropharynx includes many of the same isolates as the nose and sinuses, with the addition of variable numbers of bacteria like species of *Prevotella*, *Fusobacterium*, *Moraxella*, and *Eikenella*, as well as some *Candida* fungal isolates. In addition, many healthy humans asymptomatically carry potential pathogens in the upper respiratory tract. As much as 20% of the population carry *Staphylococcus aureus* in their nostrils.[1] The pharynx, too, can be colonized with pathogenic strains of *Streptococcus*, *Haemophilus*, and *Neisseria*.

The lower respiratory tract, by contrast, is scantily populated with microbes. Of the organisms identified in the lower respiratory tract, species of *Pseudomonas*, *Streptococcus*, *Prevotella*, *Fusobacterium*, and *Veillonella* are the most common. It is not clear at this time if these small populations of bacteria constitute a normal microbiota or if they are transients.

Many members of the respiratory system's normal microbiota are opportunistic pathogens. To proliferate and cause host damage, they first must overcome the immune defenses of respiratory tissues. Many mucosal pathogens produce virulence factors such as adhesins that mediate attachment to host epithelial cells, or polysaccharide capsules that allow microbes to evade phagocytosis. The

endotoxins of gram-negative bacteria can stimulate a strong inflammatory response that damages respiratory cells. Other pathogens produce exotoxins, and still others have the ability to survive within the host cells. Once an infection of the respiratory tract is established, it tends to impair the mucociliary escalator, limiting the body's ability to expel the invading microbes, thus making it easier for pathogens to multiply and spread.

Vaccines have been developed for many of the most serious bacterial and viral pathogens. Several of the most important respiratory pathogens and their vaccines, if available, are summarized in Table **17.1.1.1**. Components of these vaccines will be explained later in the chapter.

Table **17.1.1.1**: Some Important Respiratory Diseases and Vaccines

Disease	Pathogen	Available Vaccine(s)[2]
Chickenpox/shingles	Varicella-zoster virus	Varicella (chickenpox) vaccine, herpes zoster (shingles) vaccine
Common cold	Rhinovirus	None
Diphtheria	*Corynebacterium diphtheriae*	DtaP, Tdap, DT,Td, DTP
Epiglottitis, otitis media	*Haemophilus influenzae*	Hib
Influenza	Influenza viruses	Inactivated, FluMist
Measles	Measles virus	MMR
Pertussis	*Bordetella pertussis*	DTaP, Tdap
Pneumonia	*Streptococcus pneumoniae*	Pneumococcal conjugate vaccine (PCV13), pneumococcal polysaccharide vaccine (PPSV23)
Rubella (German measles)	Rubella virus	MMR
Severe acute respiratory syndrome (SARS)	SARS-associated coronavirus (SARS-CoV)	None
Tuberculosis	*Mycobacterium tuberculosis*	BCG

? Exercise 17.1.1.4

1. What are some pathogenic bacteria that are part of the normal microbiota of the respiratory tract?
2. What virulence factors are used by pathogens to overcome the immune protection of the respiratory tract?

Signs and Symptoms of Respiratory Infection

Microbial diseases of the respiratory system typically result in an acute inflammatory response. These infections can be grouped by the location affected and have names ending in "itis", which literally means *inflammation of*. For instance, rhinitis is an inflammation of the nasal cavities, often characteristic of the common cold. Rhinitis may also be associated with hay fever allergies or other irritants. Inflammation of the sinuses is called sinusitis inflammation of the ear is called otitis. Otitis media is an inflammation of the middle ear. A variety of microbes can cause pharyngitis, commonly known as a sore throat. An inflammation of the larynx is called laryngitis. The resulting inflammation may interfere with vocal cord function, causing voice loss. When tonsils are inflamed, it is called tonsillitis. Chronic cases of tonsillitis may be treated surgically with tonsillectomy. More rarely, the epiglottis can be infected, a condition called epiglottitis. In the lower respiratory system, the inflammation of the bronchial tubes results in bronchitis. Most serious of all is pneumonia, in which the alveoli in the lungs are infected and become inflamed. Pus and edema accumulate and fill the alveoli with fluids (called consolidations). This reduces the lungs' ability to exchange gases and often results in a productive cough expelling phlegm and mucus. Cases of pneumonia can range from mild to life-threatening, and remain an important cause of mortality in the very young and very old.

? Exercise 17.1.1.5

Describe the typical symptoms of rhinitis, sinusitis, pharyngitis, and laryngitis.

Smoking-Associated Pneumonia

Camila is a 22-year-old student who has been a chronic smoker for 5 years. Recently, she developed a persistent cough that has not responded to over-the-counter treatments. Her doctor ordered a chest radiograph to investigate. The radiological results were consistent with pneumonia. In addition, *Streptococcus pneumoniae* was isolated from Camila's sputum.

Smokers are at a greater risk of developing pneumonia than the general population. Several components of tobacco smoke have been demonstrated to impair the lungs' immune defenses. These effects include disrupting the function of the ciliated epithelial cells, inhibiting phagocytosis, and blocking the action of antimicrobial peptides. Together, these lead to a dysfunction of the mucociliary escalator effect. The organisms trapped in the mucus are therefore able to colonize the lungs and cause infections rather than being expelled or swallowed.

Key Concepts and Summary

- The respiratory tract is divided into upper and lower regions at the **epiglottis**.
- Air enters the upper respiratory tract through the **nasal cavity** and mouth, which both lead to the **pharynx**. The lower respiratory tract extends from the **larynx** into the **trachea** before branching into the **bronchi**, which divide further to form the **bronchioles**, which terminate in **alveoli**, where gas exchange occurs.
- The upper respiratory tract is colonized by an extensive and diverse normal microbiota, many of which are potential pathogens. Few microbial inhabitants have been found in the lower respiratory tract, and these may be transients.
- Members of the normal microbiota may cause opportunistic infections, using a variety of strategies to overcome the innate nonspecific defenses (including the mucociliary escalator) and adaptive specific defenses of the respiratory system.
- Effective vaccines are available for many common respiratory pathogens, both bacterial and viral.
- Most respiratory infections result in inflammation of the infected tissues; these conditions are given names ending in *-itis*, such as **rhinitis**, **sinusitis**, **otitis**, **pharyngitis**, and **bronchitis**.

Footnotes

1. 1 J. Kluytmans et al. "Nasal Carriage of *Staphylococcus aureus*: Epidemiology, Underlying Mechanisms, and Associated Risks." *Clinical Microbiology Reviews* 10 no. 3 (1997):505–520.
2. 2 Full names of vaccines listed in table: *Haemophilus influenzae* type B (Hib); Diphtheria, tetanus, and acellular pertussis (DtaP); tetanus, diphtheria, and acellular pertussis (Tdap); diphtheria and tetanus (DT); tetanus and diphtheria (Td); diphtheria, pertussis, and tetanus (DTP); Bacillus Calmette-Guérin; Measles, mumps, rubella (MMR)

This page titled 17.1.1: Anatomy and Normal Microbiota of the Respiratory Tract is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **22.1: Anatomy and Normal Microbiota of the Respiratory Tract** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

17.1.2: Bacterial Infections of the Respiratory Tract

Learning Objectives

- Identify the most common bacteria that can cause infections of the upper and lower respiratory tract
- Compare the major characteristics of specific bacterial diseases of the respiratory tract

The respiratory tract can be infected by a variety of bacteria, both gram positive and gram negative. Although the diseases that they cause may range from mild to severe, in most cases, the microbes remain localized within the respiratory system. Fortunately, most of these infections also respond well to antibiotic therapy.

Streptococcal Infections

A common upper respiratory infection, streptococcal pharyngitis (strep throat) is caused by *Streptococcus pyogenes*. This gram-positive bacterium appears as chains of cocci, as seen in Figure 17.1.2.1. Rebecca Lancefieldserologically classified streptococci in the 1930s using carbohydrate antigens from the bacterial cell walls. *S. pyogenes* is the sole member of the Lancefield group A streptococci and is often referred to as GAS, or group A strep.

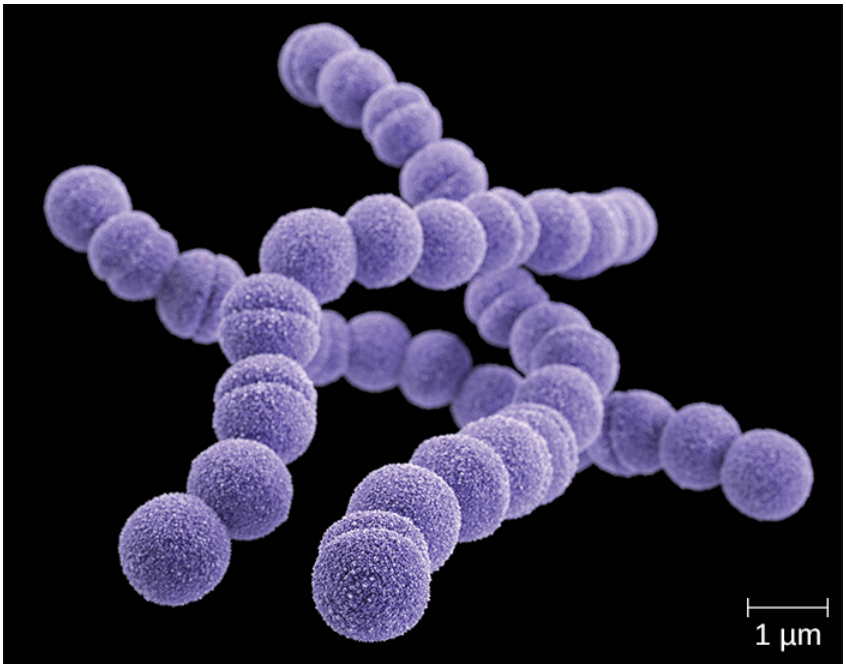


Figure 17.1.2.1: This scanning electron micrograph of *Streptococcus pyogenes* shows the characteristic cellular phenotype resembling chains of cocci. (credit: modification of work by U.S. Centers for Disease Control and Prevention - Medical Illustrator)

Similar to streptococcal infections of the skin, the mucosal membranes of the pharynx are damaged by the release of a variety of exoenzymes and exotoxins by this extracellular pathogen. Many strains of *S. pyogenes* can degrade connective tissues by using hyaluronidase, collagenase and streptokinase. Streptokinase activates plasmin, which leads to degradation of fibrin and, in turn, dissolution of blood clots, which assists in the spread of the pathogen. Released toxins include streptolysins that can destroy red and white blood cells. The classic signs of streptococcal pharyngitis are a fever higher than 38 °C (100.4 °F); intense pharyngeal pain; erythema associated with pharyngeal inflammation; and swollen, dark-red palatine tonsils, often dotted with patches of pus; and petechiae (microcapillary hemorrhages) on the soft or hard palate (roof of the mouth) (Figure 17.1.2.2). The submandibular lymph nodes beneath the angle of the jaw are also often swollen during strep throat.

Some strains of group A streptococci produce erythrogenic toxin. This exotoxin is encoded by a temperate bacteriophage (bacterial virus) and is an example of phage conversion (see The Viral Life Cycle). The toxin attacks the plasma membranes of capillary endothelial cells and leads to scarlet fever (or scarlatina), a disseminated fine red rash on the skin, and strawberry tongue, a red rash

on the tongue (Figure 17.1.2.2). Severe cases may even lead to streptococcal toxic shock syndrome (STSS), which results from massive superantigen production that leads to septic shock and death.

S. pyogenes can be easily spread by direct contact or droplet transmission through coughing and sneezing. The disease can be diagnosed quickly using a rapid enzyme immunoassay for the group A antigen. However, due to a significant rate of false-negative results (up to 30%[1]), culture identification is still the gold standard to confirm pharyngitis due to *S. pyogenes*. *S. pyogenes* can be identified as a catalase-negative, beta hemolytic bacterium that is susceptible to 0.04 units of bacitracin. Antibiotic resistance is limited for this bacterium, so most β-lactams remain effective; oral amoxicillin and intramuscular penicillin G are those most commonly prescribed.

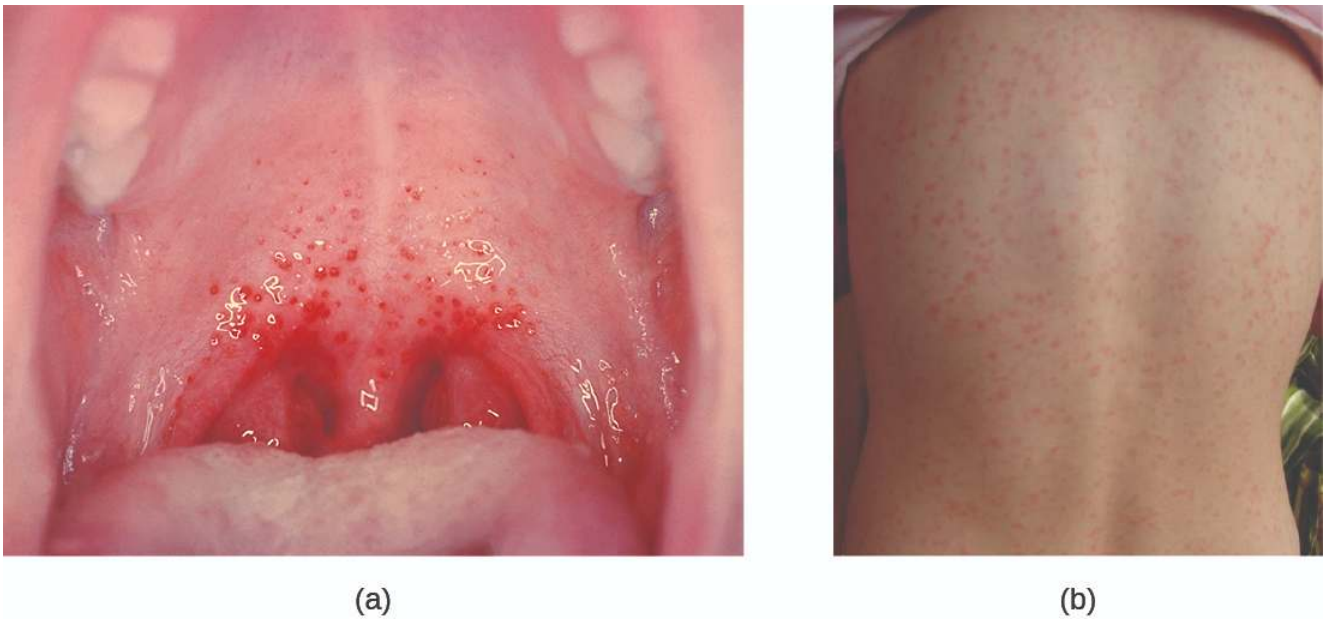


Figure 17.1.2.2: Streptococcal infections of the respiratory tract may cause localized pharyngitis or systemic signs and symptoms. (a) The characteristic appearance of strep throat: bright red arches of inflammation with the presence of dark-red spots (petechiae). (b) Scarlet fever presents as a rash on the skin. (credit a: modification of work by Centers for Disease Control and Prevention; credit b: modification of work by Alicia Williams)

Sequelae of *S. pyogenes* Infections

One reason strep throat infections are aggressively treated with antibiotics is because they can lead to serious sequelae, later clinical consequences of a primary infection. It is estimated that 1%–3% of untreated *S. pyogenes* infections can be followed by nonsuppurative (without the production of pus) sequelae that develop 1–3 weeks after the acute infection has resolved. Two such sequelae are acute rheumatic fever and acute glomerulonephritis.

Acute rheumatic fever can follow pharyngitis caused by specific rheumatogenic strains of *S. pyogenes* (strains 1, 3, 5, 6, and 18). Although the exact mechanism responsible for this sequela remains unclear, molecular mimicry between the M protein of rheumatogenic strains of *S. pyogenes* and heart tissue is thought to initiate the autoimmune attack. The most serious and lethal clinical manifestation of rheumatic fever is damage to and inflammation of the heart (carditis). Acute glomerulonephritis also results from an immune response to streptococcal antigens following pharyngitis and cutaneous infections. Acute glomerulonephritis develops within 6–10 days after pharyngitis, but can take up to 21 days after a cutaneous infection. Similar to acute rheumatic fever, there are strong associations between specific nephritogenic strains of *S. pyogenes* and acute glomerulonephritis, and evidence suggests a role for antigen mimicry and autoimmunity. However, the primary mechanism of acute glomerulonephritis appears to be the formation of immune complexes between *S. pyogenes* antigens and antibodies, and their deposition between endothelial cells of the glomeruli of kidney. Inflammatory response against the immune complexes leads to damage and inflammation of the glomeruli (glomerulonephritis).

? Exercise 17.1.2.1

1. What are the symptoms of strep throat?
2. What is erythrogenic toxin and what effect does it have?
3. What are the causes of rheumatic fever and acute glomerulonephritis?

Acute Otitis Media

An infection of the middle ear is called acute otitis media (AOM), but often it is simply referred to as an earache. The condition is most common between ages 3 months and 3 years. In the United States, AOM is the second-leading cause of visits to pediatricians by children younger than age 5 years, and it is the leading indication for antibiotic prescription.[2]

AOM is characterized by the formation and accumulation of pus in the middle ear. Unable to drain, the pus builds up, resulting in moderate to severe bulging of the tympanic membrane and otalgia (ear pain). Inflammation resulting from the infection leads to swelling of the eustachian tubes, and may also lead to fever, nausea, vomiting, and diarrhea, particularly in infants. Infants and toddlers who cannot yet speak may exhibit nonverbal signs suggesting AOM, such as holding, tugging, or rubbing of the ear, as well as uncharacteristic crying or distress in response to the pain.

AOM can be caused by a variety of bacteria. Among neonates, *S. pneumoniae* is the most common cause of AOM, but *Escherichia coli*, *Enterococcus* spp., and group B *Streptococcus* species can also be involved. In older infants and children younger than 14 years old, the most common bacterial causes are *S. pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*. Among *S. pneumoniae* infections, encapsulated strains are frequent causes of AOM. By contrast, the strains of *H. influenzae* and *M. cattarhalis* that are responsible for AOM do not possess a capsule. Rather than direct tissue damage by these pathogens, bacterial components such as lipopolysaccharide (LPS) in gram-negative pathogens induce an inflammatory response that causes swelling, pus, and tissue damage within the middle ear (Figure **17.1.2.3**).

Any blockage of the eustachian tubes, with or without infection, can cause fluid to become trapped and accumulate in the middle ear. This is referred to as otitis media with effusion (OME). The accumulated fluid offers an excellent reservoir for microbial growth and, consequently, secondary bacterial infections often ensue. This can lead to recurring and chronic earaches, which are especially common in young children. The higher incidence in children can be attributed to many factors. Children have more upper respiratory infections, in general, and their eustachian tubes are also shorter and drain at a shallower angle. Young children also tend to spend more time lying down than adults, which facilitates drainage from the nasopharynx through the eustachian tube and into the middle ear. Bottle feeding while lying down enhances this risk because the sucking action on the bottle causes negative pressure to build up within the eustachian tube, promoting the movement of fluid and bacteria from the nasopharynx.

Diagnosis is typically made based on clinical signs and symptoms, without laboratory testing to determine the specific causative agent. Antibiotics are frequently prescribed for the treatment of AOM. High-dose amoxicillin is the first-line drug, but with increasing resistance concerns, macrolides and cephalosporins may also be used. The pneumococcal conjugate vaccine (PCV13) contains serotypes that are important causes of AOM, and vaccination has been shown to decrease the incidence of AOM. Vaccination against influenza has also been shown to decrease the risk for AOM, likely because viral infections like influenza predispose patients to secondary infections with *S. pneumoniae*. Although there is a conjugate vaccine available for the invasive serotype B of *H. influenzae*, this vaccine does not impact the incidence of *H. influenzae* AOM. Because unencapsulated strains of *H. influenzae* and *M. catarrhalis* are involved in AOM, vaccines against bacterial cellular factors other than capsules will need to be developed.

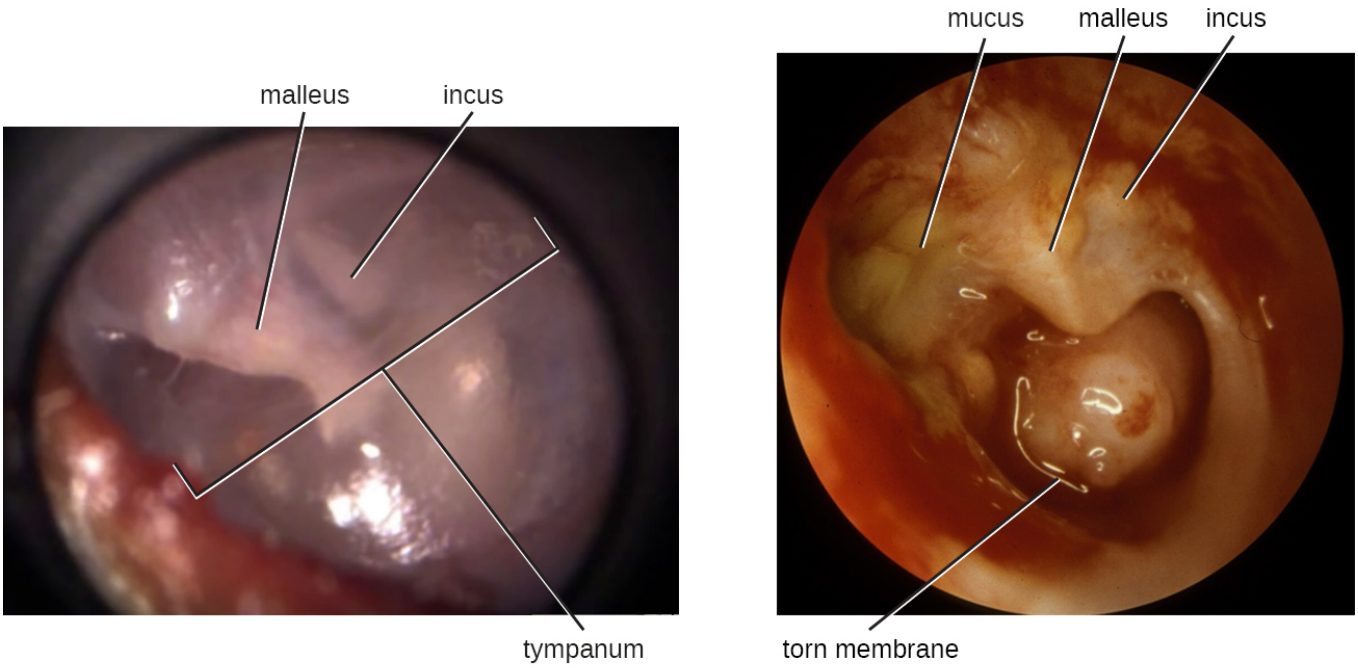


Figure **17.1.2.3**: (a) A healthy tympanic membrane; the middle ear bones can be seen behind the membrane. (b) An ear with chronic inflammation that has resulted in a torn membrane, erosion of the inner ear bones, and mucus buildup. (credit a: modification of work by "DrER.tv"/YouTube; credit b: modification of work by Li Mg, Hotez PJ, Vrabec JT, Donovan DT)

Bacterial Rhinosinusitis

The microbial community of the nasopharynx is extremely diverse and harbors many opportunistic pathogens, so it is perhaps not surprising that infections leading to rhinitis and sinusitis have many possible causes. These conditions often occur as secondary infections after a viral infection, which effectively compromises the immune defenses and allows the opportunistic bacteria to establish themselves. Bacterial sinusitis involves infection and inflammation within the paranasal sinuses. Because bacterial sinusitis rarely occurs without rhinitis, the preferred term is rhinosinusitis. The most common causes of bacterial rhinosinusitis are similar to those for AOM, including *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*.

? Exercise 17.1.2.2

1. What are the usual causative agents of acute otitis media?
2. What factors facilitate acute otitis media with effusion in young children?
3. What factor often triggers bacterial rhinosinusitis?

Diphtheria

The causative agent of diphtheria, *Corynebacterium diphtheriae*, is a club-shaped, gram-positive rod that belongs to the phylum Actinobacteria. Diphtheroids are common members of the normal nasopharyngeal microbiota. However, some strains of *C. diphtheriae* become pathogenic because of the presence of a temperate bacteriophage-encoded protein—the diphtheria toxin. Diphtheria is typically a respiratory infection of the oropharynx but can also cause impetigo-like lesions on the skin. Although the disease can affect people of all ages, it tends to be most severe in those younger than 5 years or older than 40 years. Like strep throat, diphtheria is commonly transmitted in the droplets and aerosols produced by coughing. After colonizing the throat, the bacterium remains in the oral cavity and begins producing the diphtheria toxin. This protein is an A-B toxin that blocks host-cell protein synthesis by inactivating elongation factor (EF)-2 (see Virulence Factors of Bacterial and Viral Pathogens). The toxin's action leads to the death of the host cells and an inflammatory response. An accumulation of grayish exudate consisting of dead host cells, pus, red blood cells, fibrin, and infectious bacteria results in the formation of a pseudomembrane. The pseudomembrane can cover mucous membranes of the nasal cavity, tonsils, pharynx, and larynx (Figure **17.1.2.4**). This is a classic sign of diphtheria.

As the disease progresses, the pseudomembrane can enlarge to obstruct the fauces of the pharynx or trachea and can lead to suffocation and death. Sometimes, intubation, the placement of a breathing tube in the trachea, is required in advanced infections. If the diphtheria toxin spreads throughout the body, it can damage other tissues as well. This can include myocarditis (heart damage) and nerve damage that may impair breathing.

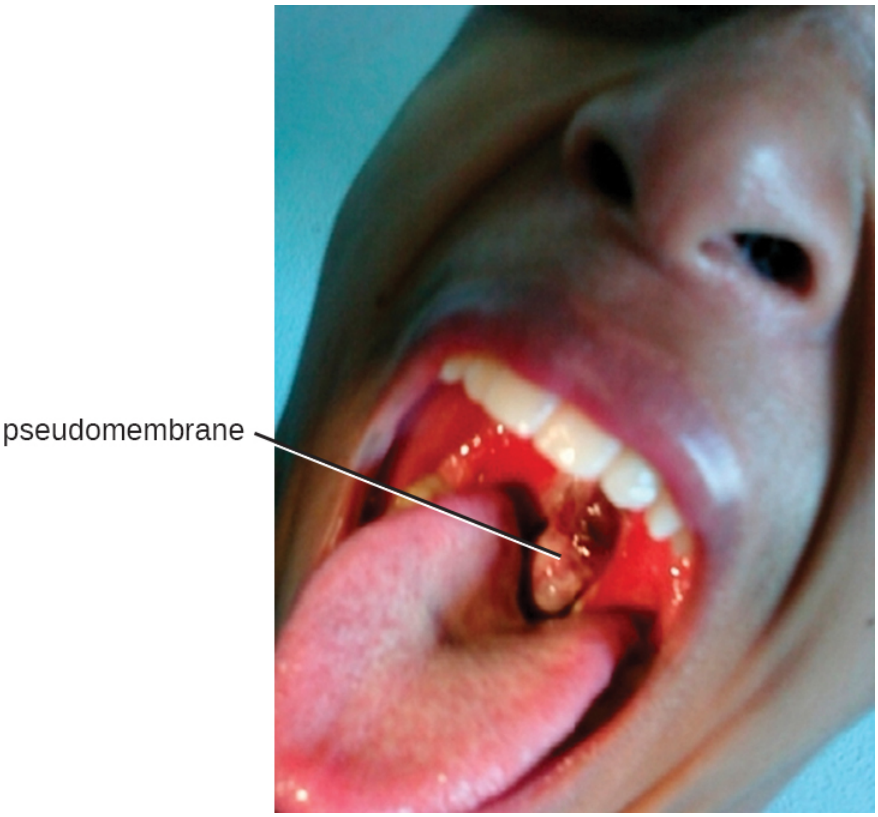


Figure 17.1.2.4: The pseudomembrane in a patient with diphtheria presents as a leathery gray patch consisting of dead cells, pus, fibrin, red blood cells, and infectious microbes. (credit: modification of work by Putnong N, Agustin G, Pasubillo M, Miyagi K, Dimaano EM)

The presumptive diagnosis of diphtheria is primarily based on the clinical symptoms (i.e., the pseudomembrane) and vaccination history, and is typically confirmed by identifying bacterial cultures obtained from throat swabs. The diphtheria toxin itself can be directly detected in vitro using polymerase chain reaction (PCR)-based, direct detection systems for the diphtheria *tox* gene, and immunological techniques like radial immunodiffusion or Elek's immunodiffusion test.

Broad-spectrum antibiotics like penicillin and erythromycin tend to effectively control *C. diphtheriae* infections. Regrettably, they have no effect against preformed toxins. If toxin production has already occurred in the patient, antitoxins (preformed antibodies against the toxin) are administered. Although this is effective in neutralizing the toxin, the antitoxins may lead to serum sickness because they are produced in horses (see Hypersensitivities).

Widespread vaccination efforts have reduced the occurrence of diphtheria worldwide. There are currently four combination toxoid vaccines available that provide protection against diphtheria and other diseases: DTaP, Tdap, DT, and Td. In all cases, the letters "d," "t," and "p" stand for diphtheria, tetanus, and pertussis, respectively; the "a" stands for acellular. If capitalized, the letters indicate a full-strength dose; lowercase letters indicate reduced dosages. According to current recommendations, children should receive five doses of the DTaP vaccine in their youth and a Td booster every 10 years. Children with adverse reactions to the pertussis vaccine may be given the DT vaccine in place of the DTaP.

? Exercise 17.1.2.3

1. What effect does diphtheria toxin have?
2. What is the pseudomembrane composed of?

Bacterial Pneumonia

Pneumonia is a general term for infections of the lungs that lead to inflammation and accumulation of fluids and white blood cells in the alveoli. Pneumonia can be caused by bacteria, viruses, fungi, and other organisms, although the vast majority of pneumonias are bacterial in origin. Bacterial pneumonia is a prevalent, potentially serious infection; it caused more 50,000 deaths in the United States in 2014.[3] As the alveoli fill with fluids and white blood cells (consolidation), air exchange becomes impaired and patients experience respiratory distress (Figure **17.1.2.5**). In addition, pneumonia can lead to pleurisy, an infection of the pleural membrane surrounding the lungs, which can make breathing very painful. Although many different bacteria can cause pneumonia under the right circumstances, three bacterial species cause most clinical cases: *Streptococcus pneumoniae*, *H. influenzae*, and *Mycoplasma pneumoniae*. In addition to these, we will also examine some of the less common causes of pneumonia.

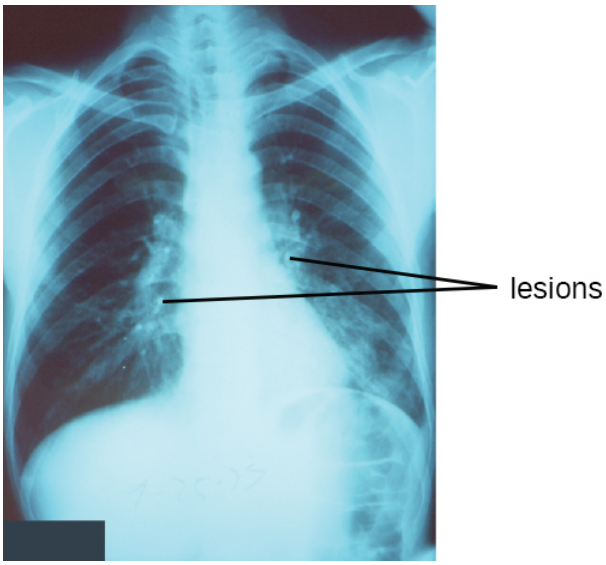
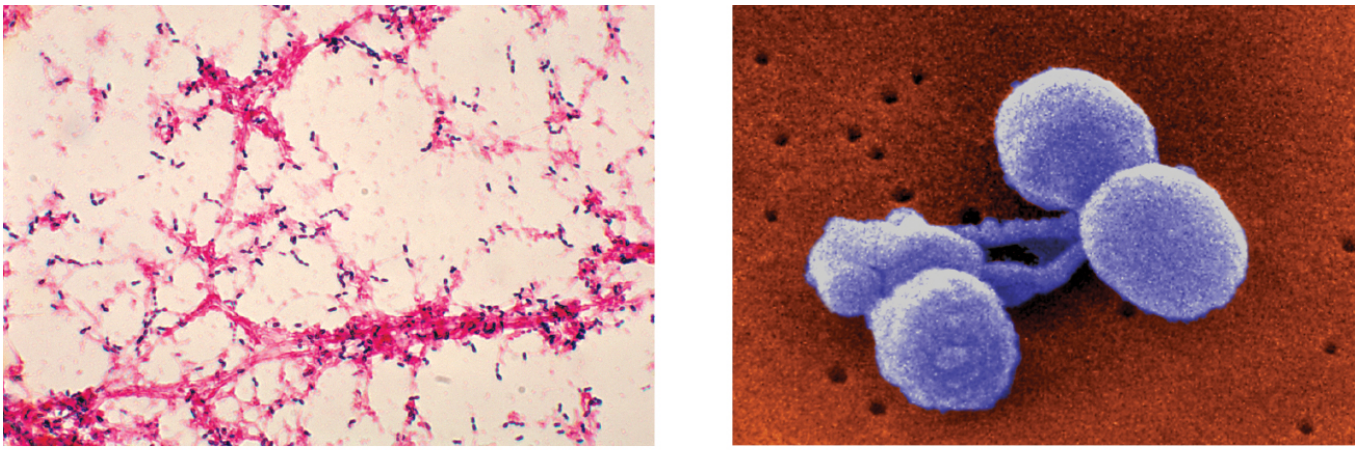


Figure **17.1.2.5**: A chest radiograph of a patient with pneumonia shows the consolidations (lesions) present as opaque patches. (credit: modification of work by Centers for Disease Control and Prevention)

Pneumococcal Pneumonia

The most common cause of community-acquired bacterial pneumonia is *Streptococcus pneumoniae*. This gram-positive, alpha hemolytic streptococcus is commonly found as part of the normal microbiota of the human respiratory tract. The cells tend to be somewhat lancet-shaped and typically appear as pairs (Figure **17.1.2.6**). The pneumococci initially colonize the bronchioles of the lungs. Eventually, the infection spreads to the alveoli, where the microbe's polysaccharide capsule interferes with phagocytic clearance. Other virulence factors include autolysins like Lyt A, which degrade the microbial cell wall, resulting in cell lysis and the release of cytoplasmic virulence factors. One of these factors, pneumolysin O, is important in disease progression; this pore-forming protein damages host cells, promotes bacterial adherence, and enhances pro-inflammatory cytokine production. The resulting inflammatory response causes the alveoli to fill with exudate rich in neutrophils and red blood cells. As a consequence, infected individuals develop a productive cough with bloody sputum.



(a) (b)

Figure **17.1.2.6**: (a) This micrograph of *Streptococcus pneumoniae* grown from a blood culture shows the characteristic lancet-shaped diplococcal morphology. (b) A colorized scanning electron micrograph of *S. pneumoniae*. (credit a: modification of work by Centers for Disease Control and Prevention; credit b: modification of work by Janice Carr, Centers for Disease Control and Prevention)

Pneumococci can be presumptively identified by their distinctive gram-positive, lancet-shaped cell morphology and diplococcal arrangement. In blood agar cultures, the organism demonstrates alpha hemolytic colonies that are autolytic after 24 to 48 hours. In addition, *S. pneumoniae* is extremely sensitive to optochin and colonies are rapidly destroyed by the addition of 10% solution of sodium deoxycholate. All clinical pneumococcal isolates are serotyped using the quellung reaction with typing antisera produced by the CDC. Positive quellung reactions are considered definitive identification of pneumococci.

Antibiotics remain the mainstay treatment for pneumococci. β-Lactams like penicillin are the first-line drugs, but resistance to β-lactams is a growing problem. When β-lactam resistance is a concern, macrolides and fluoroquinolones may be prescribed. However, *S. pneumoniae* resistance to macrolides and fluoroquinolones is increasing as well, limiting the therapeutic options for some infections. There are currently two pneumococcal vaccines available: pneumococcal conjugate vaccine (PCV13) and pneumococcal polysaccharide vaccine (PPSV23). These are generally given to the most vulnerable populations of individuals: children younger than 2 years and adults older than 65 years.

Haemophilus Pneumonia

Encapsulated strains of *Haemophilus influenzae* are known for causing meningitis, but nonencapsulated strains are important causes of pneumonia. This small, gram-negative coccobacillus is found in the pharynx of the majority of healthy children; however, *Haemophilus* pneumonia is primarily seen in the elderly. Like other pathogens that cause pneumonia, *H. influenzae* is spread by droplets and aerosols produced by coughing. A fastidious organism, *H. influenzae* will only grow on media with available factor X (hemin) and factor V (NAD), like chocolate agar (Figure **17.1.2.7**). Serotyping must be performed to confirm identity of *H. influenzae* isolates.

Infections of the alveoli by *H. influenzae* result in inflammation and accumulation of fluids. Increasing resistance to β-lactams, macrolides, and tetracyclines presents challenges for the treatment of *Haemophilus* pneumonia. Resistance to the fluoroquinolones is rare among isolates of *H. influenzae* but has been observed. As discussed for AOM, a vaccine directed against nonencapsulated *H. influenzae*, if developed, would provide protection against pneumonia caused by this pathogen.

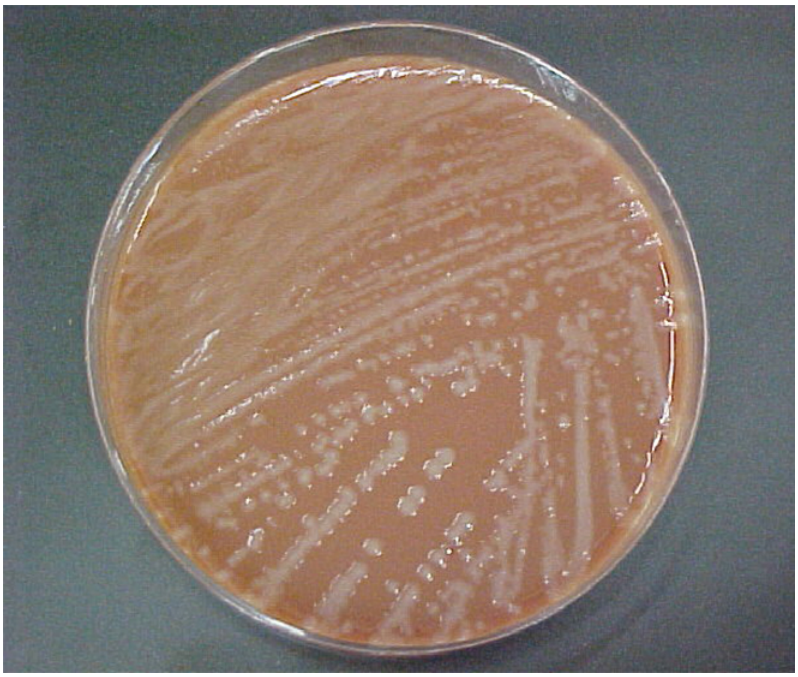


Figure **17.1.2.7**: Culture of *Haemophilus influenzae* on a chocolate agar plate. (credit: modification of work by Centers for Disease Control and Prevention)

Why Me?

Tracy is a 6-year old who developed a serious cough that would not seem to go away. After 2 weeks, her parents became concerned and took her to the pediatrician, who suspected a case of bacterial pneumonia. Tests confirmed that the cause was *Haemophilus influenzae*. Fortunately, Tracy responded well to antibiotic treatment and eventually made a full recovery.

Because there had been several other cases of bacterial pneumonia at Tracy's elementary school, local health officials urged parents to have their children screened. Of the children who were screened, it was discovered that greater than 50% carried *H. influenzae* in their nasal cavities, yet all but two of them were asymptomatic.

Why is it that some individuals become seriously ill from bacterial infections that seem to have little or no effect on others? The pathogenicity of an organism—its ability to cause host damage—is not solely a property of the microorganism. Rather, it is the product of a complex relationship between the microbe's virulence factors and the immune defenses of the individual. Preexisting conditions and environmental factors such as exposure to secondhand smoke can make some individuals more susceptible to infection by producing conditions favorable to microbial growth or compromising the immune system. In addition, individuals may have genetically determined immune factors that protect them—or not—from particular strains of pathogens. The interactions between these host factors and the pathogenicity factors produced by the microorganism ultimately determine the outcome of the infection. A clearer understanding of these interactions may allow for better identification of at-risk individuals and prophylactic interventions in the future.

Mycoplasma Pneumonia (Walking Pneumonia)

Primary atypical pneumonia is caused by *Mycoplasma pneumoniae*. This bacterium is not part of the respiratory tract's normal microbiota and can cause epidemic disease outbreaks. Also known as walking pneumonia, *mycoplasma*pneumonia infections are common in crowded environments like college campuses and military bases. It is spread by aerosols formed when coughing or sneezing. The disease is often mild, with a low fever and persistent cough. These bacteria, which do not have cell walls, use a specialized attachment organelle to bind to ciliated cells. In the process, epithelial cells are damaged and the proper function of the cilia is hindered (Figure **17.1.2.8**).

Mycoplasma grow very slowly when cultured. Therefore, penicillin and thallium acetate are added to agar to prevent the overgrowth by faster-growing potential contaminants. Since *M. pneumoniae* does not have a cell wall, it is resistant to these substances. Without a cell wall, the microbial cells appear pleomorphic. *M. pneumoniae* infections tend to be self-limiting but may

also respond well to macrolide antibiotic therapy. β-lactams, which target cell wall synthesis, are not indicated for treatment of infections with this pathogen.

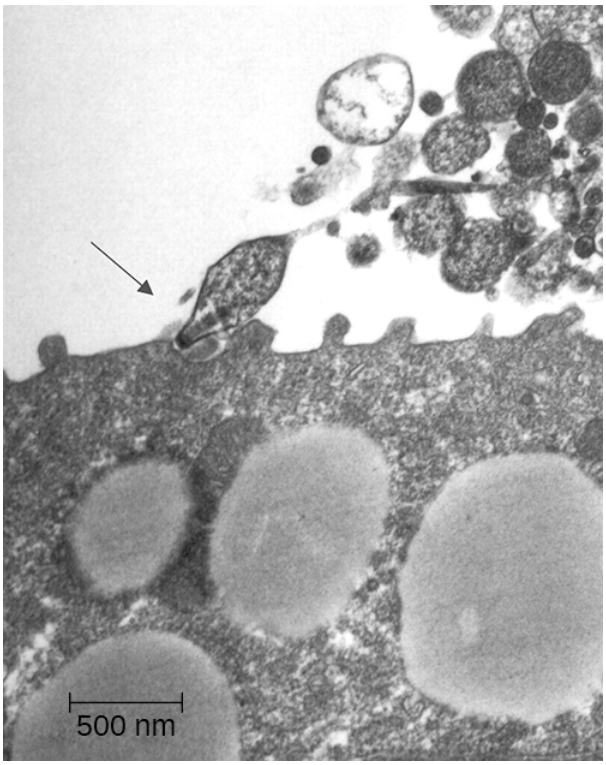


Figure 17.1.2.8: The micrograph shows *Mycoplasma pneumoniae* using their specialized receptors to attach to epithelial cells in the trachea of an infected hamster. (credit: modification of work by American Society for Microbiology)

Chlamydial Pneumonias and Psittacosis

Chlamydial pneumonia can be caused by three different species of bacteria: *Chlamydophila pneumoniae* (formerly known as *Chlamydia pneumoniae*), *Chlamydophila psittaci* (formerly known as *Chlamydia psittaci*), and *Chlamydia trachomatis*. All three are obligate intracellular pathogens and cause mild to severe pneumonia and bronchitis. Of the three, *Chlamydophila pneumoniae* is the most common and is transmitted via respiratory droplets or aerosols. *C. psittaci* causes psittacosis, a zoonotic disease that primarily affects domesticated birds such as parakeets, turkeys, and ducks, but can be transmitted from birds to humans. Psittacosis is a relatively rare infection and is typically found in people who work with birds. *Chlamydia trachomatis*, the causative agent of the sexually transmitted disease chlamydia, can cause pneumonia in infants when the infection is passed from mother to baby during birth.

Diagnosis of chlamydia by culturing tends to be difficult and slow. Because they are intracellular pathogens, they require multiple passages through tissue culture. Recently, a variety of PCR- and serologically based tests have been developed to enable easier identification of these pathogens. Tetracycline and macrolide antibiotics are typically prescribed for treatment.

Health Care-Associated Pneumonia

A variety of opportunistic bacteria that do not typically cause respiratory disease in healthy individuals are common causes of health care-associated pneumonia. These include *Klebsiella pneumoniae*, *Staphylococcus aureus*, and proteobacteria such as species of *Escherichia*, *Proteus*, and *Serratia*. Patients at risk include the elderly, those who have other preexisting lung conditions, and those who are immunocompromised. In addition, patients receiving supportive therapies such as intubation, antibiotics, and immunomodulatory drugs may also be at risk because these interventions disrupt the mucociliary escalator and other pulmonary defenses. Invasive medical devices such as catheters, medical implants, and ventilators can also introduce opportunistic pneumonia-causing pathogens into the body.[4]

Pneumonia caused by *K. pneumoniae* is characterized by lung necrosis and “currant jelly sputum,” so named because it consists of clumps of blood, mucus, and debris from the thick polysaccharide capsule produced by the bacterium. *K. pneumoniae* is often

multidrug resistant. Aminoglycoside and cephalosporin are often prescribed but are not always effective. *Klebsiella* pneumonia is frequently fatal even when treated.

Pseudomonas Pneumonia

Pseudomonas aeruginosa is another opportunistic pathogen that can cause serious cases of bacterial pneumonia in patients with cystic fibrosis (CF) and hospitalized patients assisted with artificial ventilators. This bacterium is extremely antibiotic resistant and can produce a variety of exotoxins. Ventilator-associated pneumonia with *P. aeruginosa* is caused by contaminated equipment that causes the pathogen to be aspirated into the lungs. In patients with CF, a genetic defect in the cystic fibrosis transmembrane receptor (CFTR) leads to the accumulation of excess dried mucus in the lungs. This decreases the effectiveness of the defensins and inhibits the mucociliary escalator. *P. aeruginosa* is known to infect more than half of all patients with CF. It adapts to the conditions in the patient's lungs and begins to produce alginate, a viscous exopolysaccharide that inhibits the mucociliary escalator. Lung damage from the chronic inflammatory response that ensues is the leading cause of mortality in patients with CF.[5]

? Exercise 17.1.2.4

1. What three pathogens are responsible for the most prevalent types of bacterial pneumonia?
2. Which cause of pneumonia is most likely to affect young people?
3. In what contexts does *Pseudomonas aeruginosa* cause pneumonia?

Clinical Focus: Part 2

John's chest radiograph revealed an extensive consolidation in the right lung, and his sputum cultures revealed the presence of a gram-negative rod. His physician prescribed a course of the antibiotic clarithromycin. He also ordered the rapid influenza diagnostic tests (RIDTs) for type A and B influenza to rule out a possible underlying viral infection. Despite antibiotic therapy, John's condition continued to deteriorate, so he was admitted to the hospital.

Exercise 17.1.2.5

What are some possible causes of pneumonia that would not have responded to the prescribed antibiotic?

Tuberculosis

Tuberculosis (TB) is one of the deadliest infectious diseases in human history. Although tuberculosis infection rates in the United States are extremely low, the CDC estimates that about one-third of the world's population is infected with *Mycobacterium tuberculosis*, the causal organism of TB, with 9.6 million new TB cases and 1.5 million deaths worldwide in 2014.[6]

M. tuberculosis is an acid-fast, high G + C, gram-positive, nonspore-forming rod. Its cell wall is rich in waxy mycolic acids, which make the cells impervious to polar molecules. It also causes these organisms to grow slowly. *M. tuberculosis* causes a chronic granulomatous disease that can infect any area of the body, although it is typically associated with the lungs. *M. tuberculosis* is spread by inhalation of respiratory droplets or aerosols from an infected person. The infectious dose of *M. tuberculosis* is only 10 cells.[7]

After inhalation, the bacteria enter the alveoli (Figure **17.1.2.9**). The cells are phagocytized by macrophages but can survive and multiply within these phagocytes because of the protection by the waxy mycolic acid in their cell walls. If not eliminated by macrophages, the infection can progress, causing an inflammatory response and an accumulation of neutrophils and macrophages in the area. Several weeks or months may pass before an immunological response is mounted by T cells and B cells. Eventually, the lesions in the alveoli become walled off, forming small round lesions called tubercles. Bacteria continue to be released into the center of the tubercles and the chronic immune response results in tissue damage and induction of apoptosis (programmed host-cell death) in a process called liquefaction. This creates a caseous center, or air pocket, where the aerobic *M. tuberculosis* can grow and multiply. Tubercles may eventually rupture and bacterial cells can invade pulmonary capillaries; from there, bacteria can spread through the bloodstream to other organs, a condition known as miliary tuberculosis. The rupture of tubercles also facilitates transmission of the bacteria to other individuals via droplet aerosols that exit the body in coughs. Because these droplets can be

very small and stay aloft for a long time, special precautions are necessary when caring for patients with TB, such as the use of face masks and negative-pressure ventilation and filtering systems.

Eventually, most lesions heal to form calcified Ghon complexes. These structures are visible on chest radiographs and are a useful diagnostic feature. But even after the disease has apparently ended, viable bacteria remain sequestered in these locations. Release of these organisms at a later time can produce reactivation tuberculosis (or secondary TB). This is mainly observed in people with alcoholism, the elderly, or in otherwise immunocompromised individuals (Figure **17.1.2.9**).

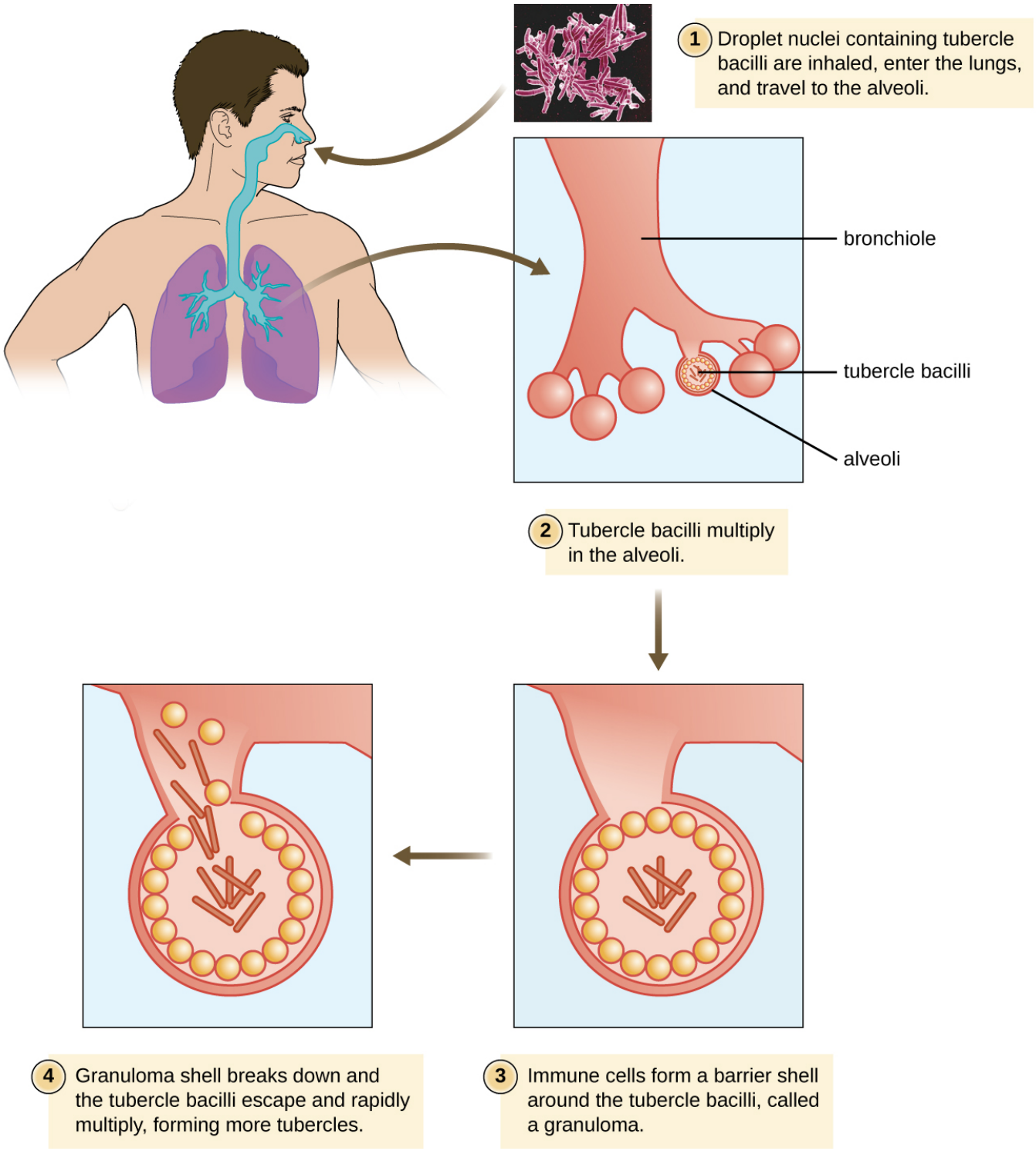


Figure **17.1.2.9**: In the infectious cycle of tuberculosis, the immune response of most infected individuals (approximately 90%) results in the formation of tubercles in which the infection is walled off.[8] The remainder will suffer progressive primary

tuberculosis. The sequestered bacteria may be reactivated to form secondary tuberculosis in immunocompromised patients at a later time. (credit: modification of work by Centers for Disease Control and Prevention)

Because TB is a chronic disease, chemotherapeutic treatments often continue for months or years. Multidrug resistant (MDR-TB) and extensively drug-resistant (XDR-TB) strains of *M. tuberculosis* are a growing clinical concern. These strains can arise due to misuse or mismanagement of antibiotic therapies. Therefore, it is imperative that proper multidrug protocols are used to treat these infections. Common antibiotics included in these mixtures are isoniazid, rifampin, ethambutol, and pyrazinamide.

A TB vaccine is available that is based on the so-called bacillus Calmette-Guérin (BCG) strain of *M. bovis* commonly found in cattle. In the United States, the BCG vaccine is only given to health-care workers and members of the military who are at risk of exposure to active cases of TB. It is used more broadly worldwide. Many individuals born in other countries have been vaccinated with BCG strain. BCG is used in many countries with a high prevalence of TB, to prevent childhood tuberculous meningitis and miliary disease.

The Mantoux tuberculin skin test (Figure **17.1.2.10**) is regularly used in the United States to screen for potential TB exposure (see Hypersensitivities). However, prior vaccinations with the BCG vaccine can cause false-positive results. Chest radiographs to detect Ghon complex formation are required, therefore, to confirm exposure.



(a) (b)

Figure **17.1.2.10**: (a) The Mantoux skin test for tuberculosis involves injecting the subject with tuberculin protein derivative. The injection should initially produce a raised wheal. (b) The test should be read in 48–72 hours. A positive result is indicated by redness, swelling, or hardness; the size of the responding region is measured to determine the final result. (credit a, b: modification of work by Centers for Disease Control and Prevention)

? Exercise 17.1.2.6

1. What characteristic of *Mycobacterium tuberculosis* allows it to evade the immune response?
2. What happens to cause miliary tuberculosis?
3. Explain the limitations of the Mantoux tuberculin skin test.

Pertussis (Whooping Cough)

The causative agent of pertussis, commonly called whooping cough, is *Bordetella pertussis*, a gram-negative coccobacillus. The disease is characterized by mucus accumulation in the lungs that leads to a long period of severe coughing. Sometimes, following a bout of coughing, a sound resembling a “whoop” is produced as air is inhaled through the inflamed and restricted airway—hence the name whooping cough. Although adults can be infected, the symptoms of this disease are most pronounced in infants and children. Pertussis is highly communicable through droplet transmission, so the uncontrollable coughing produced is an efficient means of transmitting the disease in a susceptible population.

Following inhalation, *B. pertussis* specifically attaches to epithelial cells using an adhesin, filamentous hemagglutinin. The bacteria then grow at the site of infection and cause disease symptoms through the production of exotoxins. One of the main virulence factors of this organism is an A-B exotoxin called the pertussis toxin (PT). When PT enters the host cells, it increases the cyclic adenosine monophosphate (cAMP) levels and disrupts cellular signaling. PT is known to enhance inflammatory responses

involving histamine and serotonin. In addition to PT, *B. pertussis* produces a tracheal cytotoxin that damages ciliated epithelial cells and results in accumulation of mucus in the lungs. The mucus can support the colonization and growth of other microbes and, as a consequence, secondary infections are common. Together, the effects of these factors produce the cough that characterizes this infection.

A pertussis infection can be divided into three distinct stages. The initial infection, termed the catarrhal stage, is relatively mild and unremarkable. The signs and symptoms may include nasal congestion, a runny nose, sneezing, and a low-grade fever. This, however, is the stage in which *B. pertussis* is most infectious. In the paroxysmal stage, mucus accumulation leads to uncontrollable coughing spasms that can last for several minutes and frequently induce vomiting. The paroxysmal stage can last for several weeks. A long convalescence stage follows the paroxysmal stage, during which time patients experience a chronic cough that can last for up to several months. In fact, the disease is sometimes called the 100-day cough.

In infants, coughing can be forceful enough to cause fractures to the ribs, and prolonged infections can lead to death. The CDC reported 20 pertussis-related deaths in 2012,[9] but that number had declined to five by 2015.[10]

During the first 2 weeks of infection, laboratory diagnosis is best performed by culturing the organism directly from a nasopharyngeal (NP) specimen collected from the posterior nasopharynx. The NP specimen is streaked onto Bordet-Gengou medium. The specimens must be transported to the laboratory as quickly as possible, even if transport media are used. Transport times of longer than 24 hours reduce the viability of *B. pertussis* significantly.

Within the first month of infection, *B. pertussis* can be diagnosed using PCR techniques. During the later stages of infection, pertussis-specific antibodies can be immunologically detected using an enzyme-linked immunosorbent assay (ELISA).

Pertussis is generally a self-limiting disease. Antibiotic therapy with erythromycin or tetracycline is only effective at the very earliest stages of disease. Antibiotics given later in the infection, and prophylactically to uninfected individuals, reduce the rate of transmission. Active vaccination is a better approach to control this disease. The DPT vaccine was once in common use in the United States. In that vaccine, the P component consisted of killed whole-cell *B. pertussis* preparations. Because of some adverse effects, that preparation has now been superseded by the DTaP and Tdap vaccines. In both of these new vaccines, the “aP” component is a pertussis toxoid.

Widespread vaccination has greatly reduced the number of reported cases and prevented large epidemics of pertussis. Recently, however, pertussis has begun to reemerge as a childhood disease in some states because of declining vaccination rates and an increasing population of susceptible children.

? Exercise 17.1.2.7

1. What accounts for the mucus production in a pertussis infection?
2. What are the signs and symptoms associated with the three stages of pertussis?
3. Why is pertussis becoming more common in the United States?

Legionnaires Disease

An atypical pneumonia called Legionnaires disease (also known as legionellosis) is caused by an aerobic gram-negative bacillus, *Legionella pneumophila*. This bacterium infects free-living amoebae that inhabit moist environments, and infections typically occur from human-made reservoirs such as air-conditioning cooling towers, humidifiers, misting systems, and fountains. Aerosols from these reservoirs can lead to infections of susceptible individuals, especially those suffering from chronic heart or lung disease or other conditions that weaken the immune system.

When *L. pneumophila* bacteria enter the alveoli, they are phagocytized by resident macrophages. However, *L. pneumophila* uses a secretion system to insert proteins in the endosomal membrane of the macrophage; these proteins prevent lysosomal fusion, allowing *L. pneumophila* to continue to proliferate within the phagosome. The resulting respiratory disease can range from mild to severe pneumonia, depending on the status of the host’s immune defenses. Although this disease primarily affects the lungs, it can also cause fever, nausea, vomiting, confusion, and other neurological effects.

Diagnosis of Legionnaires disease is somewhat complicated. *L. pneumophila* is a fastidious bacterium and is difficult to culture. In addition, since the bacterial cells are not efficiently stained with the Gram stain, other staining techniques, such as the Warthin-

Starry silver-precipitate procedure, must be used to visualize this pathogen. A rapid diagnostic test has been developed that detects the presence of *Legionella* antigen in a patient's urine; results take less than 1 hour, and the test has high selectivity and specificity (greater than 90%). Unfortunately, the test only works for one serotype of *L. pneumophila* (type 1, the serotype responsible for most infections). Consequently, isolation and identification of *L. pneumophila* from sputum remains the defining test for diagnosis.

Once diagnosed, Legionnaire disease can be effectively treated with fluoroquinolone and macrolide antibiotics. However, the disease is sometimes fatal; about 10% of patients die of complications.[11] There is currently no vaccine available.

? Exercise 17.1.2.8

- Why is Legionnaires disease associated with air-conditioning systems?
- How does *Legionella pneumophila* circumvent the immune system?

Q Fever

The zoonotic disease Q fever is caused by a rickettsia, *Coxiella burnetii*. The primary reservoirs for this bacterium are domesticated livestock such as cattle, sheep, and goats. The bacterium may be transmitted by ticks or through exposure to the urine, feces, milk, or amniotic fluid of an infected animal. In humans, the primary route of infection is through inhalation of contaminated farmyard aerosols. It is, therefore, largely an occupational disease of farmers. Humans are acutely sensitive to *C. burnetii*—the infective dose is estimated to be just a few cells.[12] In addition, the organism is hardy and can survive in a dry environment for an extended time. Symptoms associated with acute Q fever include high fever, headache, coughing, pneumonia, and general malaise. In a small number of patients (less than 5%[13]), the condition may become chronic, often leading to endocarditis, which may be fatal.

Diagnosing rickettsial infection by cultivation in the laboratory is both difficult and hazardous because of the easy aerosolization of the bacteria, so PCR and ELISA are commonly used. Doxycycline is the first-line drug to treat acute Q fever. In chronic Q fever, doxycycline is often paired with hydroxychloroquine.

Bacterial Diseases of the Respiratory Tract

Numerous pathogens can cause infections of the respiratory tract. Many of these infections produce similar signs and symptoms, but appropriate treatment depends on accurate diagnosis through laboratory testing. The tables in Figure **17.1.2.11** and Figure **17.1.2.12** summarize the most important bacterial respiratory infections, with the latter focusing specifically on forms of bacterial pneumonia.

Bacterial Infections of the Respiratory Tract						
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Diagnostic Tests**	**Antimicrobial Drugs**	**Vaccine**
Acute otitis media (AOM)	*Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis, others*	Earache, possible effusion; may cause fever, nausea, vomiting, diarrhea	Often a secondary infection; bacteria from respiratory tract become trapped in eustachian tube, cause infection	None	Cephalosporins, fluoroquinolones	None
Diphtheria	*Corynebacterium diphtheriae*	Pseudomembrane on throat, possibly leading to suffocation and death	Inhalation of respiratory droplets or aerosols from infected person	Identification of bacteria in throat swabs; PCR to detect diphtheria toxin in vitro	Erythromycin, penicillin, antitoxin produced in horses	DtaP, Tdap, DT, Td, DTP
Legionnaires disease	*Legionella pneumophila*	Cough, fever, muscle aches, headaches, nausea, vomiting, confusion; sometimes fatal	Inhalation of aerosols from contaminated water reservoirs	Isolation, using Warthin-Starry procedure, of bacteria in sputum	Fluoroquinolones, macrolides	None
Pertussis (whooping cough)	*Bordetella pertussis*	Severe coughing with “whoop” sound; chronic cough lasting several months; can be fatal in infants	Inhalation of respiratory droplets from infected person	Direct culture of throat swab, PCR, ELISA	Macrolides	DTaP, Tdap
Q fever	*Coxiella burnetii*	High fever, coughing, pneumonia, malaise; in chronic cases, potentially fatal endocarditis	Inhalation of aerosols of urine, feces, milk, or amniotic fluid of infected cattle, sheep, goats	PCR, ELISA	Doxycycline, hydroxychloroquine	None
Streptococcal pharyngitis, scarlet fever	*Streptococcus pyogenes*	Fever, sore throat, inflammation of pharynx and tonsils, petechiae, swollen lymph nodes; skin rash (scarlet fever), strawberry tongue	Direct contact, inhalation of respiratory droplets or aerosols from infected person	Direct culture of throat swab, rapid enzyme immunoassay	β-lactams	None
Tuberculosis	*Mycobacterium tuberculosis*	Formation of tubercles in lungs; rupture of tubercles, leading to chronic, bloody cough; healed tubercles (Ghon complexes) visible in radiographs; can be fatal	Inhalation of respiratory droplets or aerosols from infected person	Mantoux tuberculin skin test with chest radiograph to identify Ghon complexes	Isoniazid, rifampin, ethambutol, pyrazinamide	BCG

Figure **17.1.2.11**: Bacterial infections of the respiratory tract

Bacterial Causes of Pneumonia						
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Diagnostic Tests**	**Antimicrobial Drugs**	**Vaccine**
Chlamydial pneumonia	*Chlamydophila pneumoniae, C. psittaci, Chlamydia trachomatis*	Bronchitis; mild to severe respiratory distress	Inhalation of respiratory droplets or aerosols from infected person (*C. pneumoniae*); exposure to infected bird (*C. psittaci*); exposure in the birth canal (*Chlamydia trachomatis*)	Tissue culture, PCR	Tetracycline, macrolides	None
Haemophilus pneumonia	*Haemophilus influenzae*	Cough, fever or low body temperature, chills, chest pain, headache, fatigue	Inhalation of respiratory droplets or aerosols from infected person or asymptomatic carrier	Culture on chocolate agar, serotyping of blood or cerebrospinal fluid samples	Cephalosporins, fluoroquinolones	Hib
Klebsiella pneumonia	*Klebsiella pneumoniae,* others	Lung necrosis, "currant jelly" sputum; often fatal	Health care associated; bacteria introduced via contaminated ventilators, intubation, or other medical equipment	Culture, PCR	Multidrug resistant; antibiotic susceptibility testing necessary	None
Mycoplasma pneumonia (walking pneumonia)	*Mycoplasma pneumoniae*	Low fever, persistent cough	Inhalation of respiratory droplets or aerosols from infected person	Culture with penicillin, thallium acetate	Macrolides	None
Pneumococcal pneumonia	*Streptococcus pneumoniae*	Productive cough, bloody sputum, fever, chills, chest pain, respiratory distress	Direct contact with respiratory secretions	Gram stain, blood agar culture with optichin and sodium deoxycholate, quellung reaction	β-lactams, macrolides, fluoroquinolones	Pneumococcal conjugate vaccine (PCV13), pneumococcal polysaccharide vaccine (PPSV23)
Pseudomonas pneumonia	*Pseudomonas aeruginosa*	Viscous fluid and chronic inflammation of lungs; often fatal	Health care associated; bacteria introduced via contaminated ventilators; also frequently affects patients with cystic fibrosis	Culture from sputum or other body fluid	Multidrug resistant; antibiotic susceptibility testing necessary	None

Figure **17.1.2.12**: Bacterial causes of pneumonia

Key Concepts and Summary

- A wide variety of bacteria can cause respiratory diseases; most are treatable with antibiotics or preventable with vaccines.
- *Streptococcus pyogenes* causes **strep throat**, an infection of the pharynx that also causes high fever and can lead to **scarlet fever**, **acute rheumatic fever**, and **acute glomerulonephritis**.
- **Acute otitis media** is an infection of the middle ear that may be caused by several bacteria, including *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. The infection can block the eustachian tubes, leading to **otitis media with effusion**.
- **Diphtheria**, caused by *Corynebacterium diphtheriae*, is now a rare disease because of widespread vaccination. The bacteria produce exotoxins that kill cells in the pharynx, leading to the formation of a **pseudomembrane**; and damage other parts of the body.
- **Bacterial pneumonia** results from infections that cause inflammation and fluid accumulation in the alveoli. It is most commonly caused by *S. pneumoniae* or *H. influenzae*. The former is commonly multidrug resistant.
- ***Mycoplasma* pneumonia** results from infection by *Mycoplasma pneumoniae*; it can spread quickly, but the disease is mild and self-limiting.
- **Chlamydial pneumonia** can be caused by three pathogens that are obligate intracellular parasites. *Chlamydophila pneumoniae* is typically transmitted from an infected person, whereas *C. psittaci* is typically transmitted from an infected bird. *Chlamydia trachomatis*, may cause pneumonia in infants.
- Several other bacteria can cause pneumonia in immunocompromised individuals and those with cystic fibrosis.
- **Tuberculosis** is caused by *Mycobacterium tuberculosis*. Infection leads to the production of protective **tubercles** in the alveoli and calcified **Ghon complexes** that can harbor the bacteria for a long time. Antibiotic-resistant forms are common and treatment is typically long term.
- **Pertussis** is caused by *Bordetella pertussis*. Mucus accumulation in the lungs leads to prolonged severe coughing episodes (whooping cough) that facilitate transmission. Despite an available vaccine, outbreaks are still common.
- **Legionnaires disease** is caused by infection from environmental reservoirs of the *Legionella pneumophila* bacterium. The bacterium is endocytic within macrophages and infection can lead to pneumonia, particularly among immunocompromised individuals.
- **Q fever** is caused by *Coxiella burnetii*, whose primary hosts are domesticated mammals (zoonotic disease). It causes pneumonia primarily in farm workers and can lead to serious complications, such as endocarditis.

Footnotes

1. 1 WL Lean et al. “Rapid Diagnostic Tests for Group A Streptococcal Pharyngitis: A Meta-Analysis.” *Pediatrics* 134, no. 4 (2014):771–781.
2. 2 G. Worrall. “Acute Otitis Media.” *Canadian Family Physician* 53 no. 12 (2007):2147–2148.
3. 3 KD Kochanek et al. “Deaths: Final Data for 2014.” *National Vital Statistics Reports* 65 no 4 (2016).
4. 4 SM Koenig et al. “Ventilator-Associated Pneumonia: Diagnosis, Treatment, and Prevention.” *Clinical Microbiology Reviews* 19 no. 4 (2006):637–657.
5. 5 R. Sordé et al. “Management of Refractory *Pseudomonas aeruginosa* Infection in Cystic Fibrosis.” *Infection and Drug Resistance* 4 (2011):31–41.
6. 6 Centers for Disease Control and Prevention. “Tuberculosis (TB). Data and Statistics.” http://www.cdc.gov/tb/statistics/default.htm
7. 7 D. Saini et al. “Ultra-Low Dose of *Mycobacterium tuberculosis* Aerosol Creates Partial Infection in Mice.” *Tuberculosis* 92 no. 2 (2012):160–165.
8. 8 G. Kaplan et al. “*Mycobacterium tuberculosis* Growth at the Cavity Surface: A Microenvironment with Failed Immunity.” *Infection and Immunity* 71 no.12 (2003):7099–7108.
9. 9 Centers for Disease Control and Prevention. “2012 Final Pertussis Surveillance Report.” 2015. http://www.cdc.gov/pertussis/downloa...eport-2012.pdf. Accessed July 6, 2016.
10. 10 Centers for Disease Control and Prevention. “2015 Provisional Pertussis Surveillance Report.” 2016. http://www.cdc.gov/pertussis/downloa...rovisional.pdf. Accessed July 6, 2016.
11. 11 Centers for Disease Control and Prevention. “*Legionella* (Legionnaires’ Disease and Pontiac Fever: Diagnosis, Treatment, and Complications).” http://www.cdc.gov/legionella/about/diagnosis.html. Accessed Sept 14, 2016.

12. 12 WD Tigertt et al. “Airborne Q Fever.” *Bacteriological Reviews* 25 no. 3 (1961):285–293.
13. 13 Centers for Disease Control and Prevention. “Q fever. Symptoms, Diagnosis, and Treatment.” 2013. http://www.cdc.gov/qfever/symptoms/index.html. Accessed July 6, 2016.

This page titled 17.1.2: Bacterial Infections of the Respiratory Tract is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **22.2: Bacterial Infections of the Respiratory Tract** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

17.1.3: Viral Infections of the Respiratory Tract

Learning Objectives

- Identify the most common viruses that can cause infections of the upper and lower respiratory tract
- Compare the major characteristics of specific viral diseases of the respiratory tract

Viruses are the most frequent cause of respiratory tract infections. Unlike the bacterial pathogens, we have few effective therapies to combat viral respiratory infections. Fortunately, many of these diseases are mild and self-limiting. A few respiratory infections manifest their primary symptoms at other locations in the body.

The Common Cold

The common cold is a generic term for a variety of mild viral infections of the nasal cavity. More than 200 different viruses are known to cause the common cold. The most common groups of cold viruses include rhinoviruses, coronaviruses, and adenoviruses. These infections are widely disseminated in the human population and are transmitted through direct contact and droplet transmission. Coughing and sneezing efficiently produce infectious aerosols, and rhinoviruses are known to persist on environmental surfaces for up to a week.[1]

Viral contact with the nasal mucosa or eyes can lead to infection. Rhinoviruses tend to replicate best between 33 °C (91.4 °F) and 35 °C (95 °F), somewhat below normal body temperature (37 °C [98.6 °F]). As a consequence, they tend to infect the cooler tissues of the nasal cavities. Colds are marked by an irritation of the mucosa that leads to an inflammatory response. This produces common signs and symptoms such as nasal excess nasal secretions (runny nose), congestion, sore throat, coughing, and sneezing. The absence of high fever is typically used to differentiate common colds from other viral infections, like influenza. Some colds may progress to cause otitis media, pharyngitis, or laryngitis, and patients may also experience headaches and body aches. The disease, however, is self-limiting and typically resolves within 1–2 weeks.

There are no effective antiviral treatments for the common cold and antibacterial drugs should not be prescribed unless secondary bacterial infections have been established. Many of the viruses that cause colds are related, so immunity develops throughout life. Given the number of viruses that cause colds, however, individuals are never likely to develop immunity to all causes of the common cold.

Exercise 17.1.3.1

1. How are colds transmitted?
2. What is responsible for the symptoms of a cold?

Clinical Focus: Part 3

Since antibiotic treatment had proven ineffective, John's doctor suspects that a viral or fungal pathogen may be the culprit behind John's case of pneumonia. Another possibility is that John could have an antibiotic-resistant bacterial infection that will require a different antibiotic or combination of antibiotics to clear.

The RIDT tests both came back negative for type A and type B influenza. However, the diagnostic laboratory identified the sputum isolate as *Legionella pneumophila*. The doctor ordered tests of John's urine and, on the second day after his admission, results of an enzyme immunoassay (EIA) were positive for the *Legionella* antigen. John's doctor added levofloxacin to his antibiotic therapy and continued to monitor him. The doctor also began to ask John where he had been over the past 10 to 14 days.

Exercise 17.1.3.2

1. Do negative RIDT results absolutely rule out influenza virus as the etiologic agent? Why or why not?
2. What is John's prognosis?

Influenza

Commonly known as the flu, influenza is a common viral disease of the lower respiratory system caused by an orthomyxovirus. Influenza is pervasive worldwide and causes 3,000–50,000 deaths each year in the United States. The annual mortality rate can vary greatly depending on the virulence of the strain(s) responsible for seasonal epidemics. [2]

Influenza infections are most typically characterized by fever, chills, and body aches. This is followed by symptoms similar to the common cold that may last a week or more. Table **17.1.3.1** compares the signs and symptoms of influenza and the common cold.

Table **17.1.3.1**: Comparing the Common Cold and Influenza

Sign/Symptom	Common Cold	Influenza
Fever	Low (37.2 °C [99 °F])	High (39 °C [102.2 °F])
Headache	Common	Common
Aches and pains	Mild	Severe
Fatigue	Slight	Severe
Nasal congestion	Common	Rare
Sneezing	Common	Rare

In general, influenza is self-limiting. However, serious cases can lead to pneumonia and other complications that can be fatal. Such cases are more common in the very young and the elderly; however, certain strains of influenza virus (like the 1918–1919 variant discussed later in this chapter) are more lethal to young adults than to the very young or old. Strains that affect young adults are believed to involve a cytokine storm—a positive feedback loop that forms between cytokine production and leukocytes. This cytokine storm produces an acute inflammatory response that leads to rapid fluid accumulation in the lungs, culminating in pulmonary failure. In such cases, the ability to mount a vigorous immune response is actually detrimental to the patient. The very young and very old are less susceptible to this effect because their immune systems are less robust.

A complication of influenza that occurs primarily in children and teenagers is Reye syndrome. This sequela causes swelling in the liver and brain, and may progress to neurological damage, coma, or death. Reye syndrome may follow other viral infections, like chickenpox, and has been associated with the use of aspirin. For this reason, the CDC and other agencies recommend that aspirin and products containing aspirin never be used to treat viral illnesses in children younger than age 19 years.[3]

The influenza virus is primarily transmitted by direct contact and inhalation of aerosols. The RNA genome of this virus exists as seven or eight segments, each coated with ribonucleoprotein and encoding one or two specific viral proteins. The influenza virus is surrounded by a lipid membrane envelope, and two of the main antigens of the influenza virus are the spike proteins hemagglutinin (H) and neuraminidase (N), as shown in Figure **17.1.3.1**. These spike proteins play important roles in the viral infectious cycle.

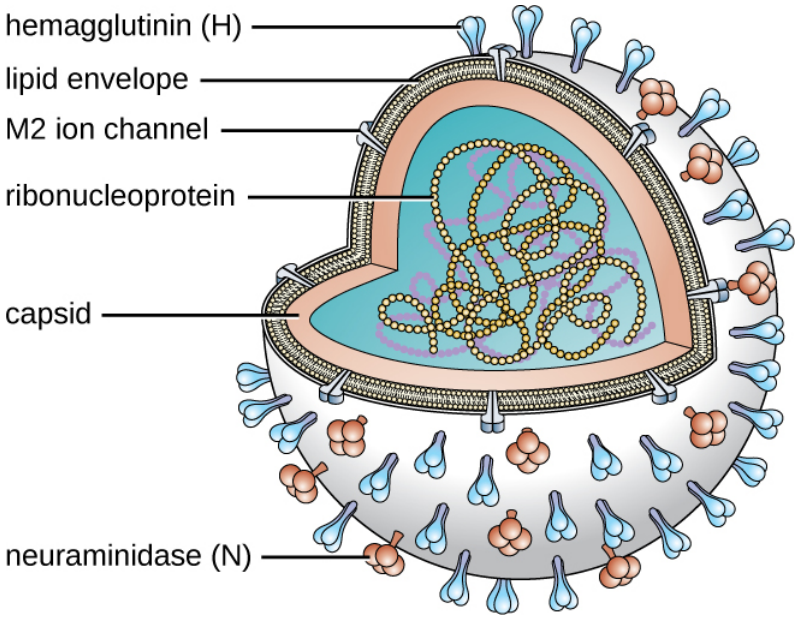


Figure **17.1.3.1**: The illustration shows the structure of an influenza virus. The viral envelope is studded with copies of the proteins neuraminidase and hemagglutinin, and surrounds the individual seven or eight RNA genome segments. (credit: modification of work by Dan Higgins, Centers for Disease Control and Prevention)

Following inhalation, the influenza virus uses the hemagglutinin protein to bind to sialic acid receptors on host respiratory epithelial cells. This facilitates endocytosis of the viral particle. Once inside the host cell, the negative strand viral RNA is replicated by the viral RNA polymerase to form mRNA, which is translated by the host to produce viral proteins. Additional viral RNA molecules are transcribed to produce viral genomic RNA, which assemble with viral proteins to form mature virions. Release of the virions from the host cell is facilitated by viral neuraminidase, which cleaves sialic-acid receptors to allow progeny viruses to make a clean exit when budding from an infected cell.

There are three genetically related influenza viruses, called A, B, and C. The influenza A viruses have different subtypes based on the structure of their hemagglutinin and neuraminidase proteins. There are currently 18 known subtypes of hemagglutinin and 11 known subtypes of neuraminidase. Influenza viruses are serologically characterized by the type of H and N proteins that they possess. Of the nearly 200 different combinations of H and N, only a few, such as the H1N1 strain, are associated with human disease. The influenza viruses A, B, and C make up three of the five major groups of orthomyxoviruses. The differences between the three types of influenza are summarized in Table **17.1.3.2**. The most virulent group is the influenza A viruses, which cause seasonal pandemics of influenza each year. Influenza A virus can infect a variety of animals, including pigs, horses, pigs, and even whales and dolphins. Influenza B virus is less virulent and is sometimes associated with epidemic outbreaks. Influenza C virus generally produces the mildest disease symptoms and is rarely connected with epidemics. Neither influenza B virus nor influenza C virus has significant animal reservoirs.

Table **17.1.3.2**: The Three Major Groups of Influenza Viruses

	Influenza A virus	Influenza B virus	Influenza C virus
Severity	Severe	Moderate	Mild
Animal reservoir	Yes	No	No
Genome segments	8	8	7
Population spread	Epidemic and pandemic	Epidemic	Sporadic
Antigenic variation	Shift/drift	Drift	Drift

Influenza virus infections elicit a strong immune response, particularly to the hemagglutinin protein, which would protect the individual if they encountered the same virus. Unfortunately, the antigenic properties of the virus change relatively rapidly, so new

strains are evolving that immune systems previously challenged by influenza virus cannot recognize. When an influenza virus gains a new hemagglutinin or neuraminidase type, it is able to evade the host's immune response and be successfully transmitted, often leading to an epidemic.

There are two mechanisms by which these evolutionary changes may occur. The mechanisms of antigen drift and antigenic shift for influenza virus have been described in Virulence Factors of Bacterial and Viral Pathogens. Of these two genetic processes, it is viruses produced by antigenic shift that have the potential to be extremely virulent because individuals previously infected by other strains are unlikely to produce any protective immune response against these novel variants.

The most lethal influenza pandemic in recorded history occurred from 1918 through 1919. Near the end of World War I, an antigenic shift involving the recombination of avian and human viruses is thought to have produced a new H1N1 virus. This strain rapidly spread worldwide and is commonly claimed to have killed as many as 40 million to 50 million people—more than double the number killed in the war. Although referred to as the Spanish flu, this disease is thought to have originated in the United States. Regardless of its source, the conditions of World War I greatly contributed to the spread of this disease. Crowding, poor sanitation, and rapid mobilization of large numbers of personnel and animals facilitated the dissemination of the new virus once it appeared.

Several of the most important influenza pandemics of modern times have been associated with antigenic shifts. A few of these are summarized in Table **17.1.3.3**.

Table **17.1.3.3**: Historical Influenza Outbreaks[4 5 6]

Years	Common Name	Serotype	Estimated Number of Deaths
1918–1919	Spanish flu	H1N1	20,000,000–40,000,000
1957–1958	Asian flu	N2N2	1,000,000–2,000,000
1968–1969	Hong Kong flu	H3N2	1,000,000–3,000,000
2009–2010	Swine flu	H1N1/09	152,000–575,000

Laboratory diagnosis of influenza is typically performed using a variety of RIDTs. These tests are inoculated by point-of-care personnel and give results within 15–20 minutes. Unfortunately, these tests have variable sensitivity and commonly yield false-negative results. Other tests include hemagglutination of erythrocytes (due to hemagglutinin action) or complement fixation. Patient serum antibodies against influenza viruses can also be detected in blood samples. Because influenza is self-limiting disease, diagnosis through these more time-consuming and expensive methods is not typically used.

Three drugs that inhibit influenza neuraminidase activity are available: inhaled zanamivir, oral oseltamivir, and intravenous peramivir. If taken at the onset of symptoms, these drugs can shorten the course of the disease. These drugs are thought to impair the ability of the virus to efficiently exit infected host cells. A more effective means of controlling influenza outbreaks, though, is vaccination. Every year, new influenza vaccines are developed to be effective against the strains expected to be predominant. This is determined in February by a review of the dominant strains around the world from a network of reporting sites; their reports are used to generate a recommendation for the vaccine combination for the following winter in the northern hemisphere. In September, a similar recommendation is made for the winter in the southern hemisphere.[7] These recommendations are used by vaccine manufacturers to formulate each year's vaccine. In most cases, three or four viruses are selected—the two most prevalent influenza A strains and one or two influenza B strains. The chosen strains are typically cultivated in eggs and used to produce either an inactivated or a live attenuated vaccine (e.g., FluMist). For individuals 18 years or older with an allergy to egg products, a recombinant egg-free trivalent vaccine is available. Most of the influenza vaccines over the past decade have had an effectiveness of about 50%.[8]

Flu Pandemic

During the spring of 2013, a new strain of H7N9 influenza was reported in China. A total of 132 people were infected. Of those infected, 44 (33%) died. A genetic analysis of the virus suggested that this strain arose from the reassortment of three different influenza viruses: a domestic duck H7N3 virus, a wild bird H7N9 virus, and a domestic poultry H9N2 virus. The virus was detected in the Chinese domestic bird flocks and contact with this reservoir is thought to have been the primary source of

infection. This strain of influenza was not able to spread from person to person. Therefore, the disease did not become a global problem. This case does, though, illustrate the potential threat that influenza still represents. If a strain like the H7N9 virus were to undergo another antigenic shift, it could become more communicable in the human population. With a mortality rate of 33%, such a pandemic would be disastrous. For this reason, organizations like the World Health Organization and the Centers for Disease Control and Prevention keep all known influenza outbreaks under constant surveillance.

Exercise 17.1.3.3

1. Compare the severity of the three types of influenza viruses.
2. Why must new influenza vaccines be developed each year?

Viral Pneumonia

Viruses cause fewer cases of pneumonia than bacteria; however, several viruses can lead to pneumonia in children and the elderly. The most common sources of viral pneumonia are adenoviruses, influenza viruses, parainfluenza viruses, and respiratory syncytial viruses. The signs and symptoms produced by these viruses can range from mild cold-like symptoms to severe cases of pneumonia, depending on the virulence of the virus strain and the strength of the host defenses of the infected individual. Occasionally, infections can result in otitis media.

Respiratory syncytial virus (RSV) infections are fairly common in infants; most people have been infected by the age of 2 years. During infection, a viral surface protein causes host cells to fuse and form multinucleated giant cells called syncytia. There are no specific antiviral therapies or vaccines available for viral pneumonia. In adults, these infections are self-limiting, resemble the common cold, and tend to resolve uneventfully within 1 or 2 weeks. Infections in infants, however, can be life-threatening. RSV is highly contagious and can be spread through respiratory droplets from coughing and sneezing. RSV can also survive for a long time on environmental surfaces and, thus, be transmitted indirectly via fomites.

Exercise 17.1.3.4

1. Who is most likely to contract viral pneumonia?
2. What is the recommended treatment for viral pneumonia?

SARS and MERS

Severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) are two acute respiratory infections caused by coronaviruses. In both cases, these are thought to be zoonotic infections. Bats and civet cats are thought to have been the reservoirs for SARS; camels seem to be the reservoir for MERS.

SARS originated in southern China in the winter of 2002 and rapidly spread to 37 countries. Within about 1 year, more than 8,000 people experienced influenza-like symptoms and nearly 800 people died. The rapid spread and severity of these infections caused grave concern at the time. However, the outbreak was controlled in 2003 and no further cases of SARS have been recorded since 2004.[9] Signs and symptoms of SARS include high fever, headache, body aches, and cough, and most patients will develop pneumonia.

MERS was first reported in Saudi Arabia in 2013. Although some infected individuals will be asymptomatic or have mild cold-like symptoms, most will develop a high fever, aches, cough and a severe respiratory infection that can progress to pneumonia. As of 2015, over 1,300 people in 27 countries have been infected. About 500 people have died. There are no specific treatments for either MERS or SARS. In addition, no vaccines are currently available. Several recombinant vaccines, however, are being developed.

Exercise 17.1.3.5

1. What is the cause of SARS?
2. What are the signs and symptoms of MERS?

Viral Respiratory Diseases Causing Skin Rashes

Measles, rubella (German measles), and chickenpox are three important viral diseases often associated with skin rashes. However, their symptoms are systemic, and because their portal of entry is the respiratory tract, they can be considered respiratory infections.

Measles (Rubeola)

The measles virus (MeV) causes the highly contagious disease measles, also known as rubeola, which is a major cause of childhood mortality worldwide. Although vaccination efforts have greatly reduced the incidence of measles in much of the world, epidemics are still common in unvaccinated populations in certain countries.[10]

The measles virus is a single-stranded, negative-strand RNA virus and, like the influenza virus, it possesses an envelope with spikes of embedded hemagglutinin. The infection is spread by direct contact with infectious secretions or inhalation of airborne droplets spread by breathing, coughing, or sneezing. Measles is initially characterized by a high fever, conjunctivitis, and a sore throat. The virus then moves systemically through the bloodstream and causes a characteristic rash. The measles rash initially forms on the face and later spreads to the extremities. The red, raised macular rash will eventually become confluent and can last for several days. At the same time, extremely high fevers (higher than 40.6 °C [105 °F]) can occur. Another diagnostic sign of measles infections is Koplik's spots, white spots that form on the inner lining of inflamed cheek tissues (Figure **17.1.3.2**).

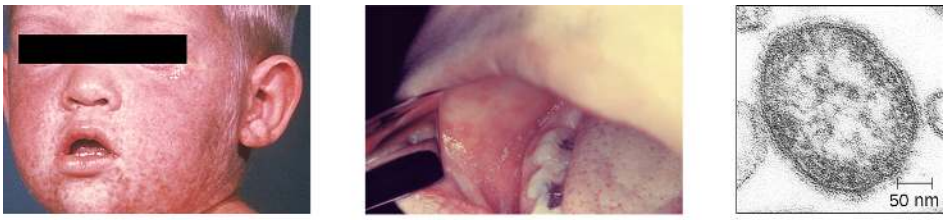


Figure **17.1.3.2**: (a) Measles typically presents as a raised macular rash that begins on the face and spreads to the extremities. (b) Koplik's spots on the oral mucosa are also characteristic of measles. (c) A thin-section transmission electron micrograph of a measles virion. (credit a, b, c: modification of work by Centers for Disease Control and Prevention)

Although measles is usually self-limiting, it can lead to pneumonia, encephalitis, and death. In addition, the inhibition of immune system cells by the measles virus predisposes patients to secondary infections. In severe infections with highly virulent strains, measles fatality rates can be as high as 10% to 15%. There were more than 145,000 measles deaths (mostly young children) worldwide in 2013.[11]

The preliminary diagnosis of measles is typically based on the appearance of the rash and Koplik's spots. Hemagglutination inhibition tests and serological tests may be used to confirm measles infections in low-prevalence settings.

There are no effective treatments for measles. Vaccination is widespread in developed countries as part of the measles, mumps, and rubella (MMR) vaccine. As a result, there are typically fewer than 200 cases of measles in the United States annually.[12] When it is seen, it is often associated with children who have not been vaccinated.

Preventable Measles Outbreaks

In December 2014, a measles epidemic began at Disneyland in southern California. Within just 4 months, this outbreak affected 134 people in 24 states.[13] Characterization of the virus suggests that an unidentified infected individual brought the disease to the United States from the Philippines, where a similar virus had sickened more than 58,000 people and killed 110.[14] Measles is highly communicable, and its spread at Disneyland may have been facilitated by the low vaccination rate in some communities in California.[15]

Several factors could conceivably lead to a strong comeback of measles in the U.S. Measles is still an epidemic disease in many locations worldwide. Air travel enables infected individuals to rapidly translocate these infections globally. Compounding this problem, low vaccination rates in some local areas in the United States (such as in Amish communities) provide populations of susceptible hosts for the virus to establish itself. Finally, measles has been a low-prevalence infection in the U.S. for some time. As a consequence, physicians are not as likely to recognize the initial symptoms and make accurate

diagnoses. Until vaccination rates become high enough to ensure herd immunity, measles is likely to be an ongoing problem in the United States.

Rubella (German Measles)

Rubella, or the German measles, is a relatively mild viral disease that produces a rash somewhat like that caused by the measles, even though the two diseases are unrelated. The rubella virus is an enveloped RNA virus that can be found in the respiratory tract. It is transmitted from person to person in aerosols produced by coughing or sneezing. Nearly half of all infected people remain asymptomatic. However, the virus is shed and spread by asymptomatic carriers. Like rubeola, rubella begins with a facial rash that spreads to the extremities (Figure **17.1.3.3**). However, the rash is less intense, shorter lived (2–3 days), not associated with Koplik's spots, and the resulting fever is lower (101 °F [38.3 °C]).

Congenital rubella syndrome is the most severe clinical complication of the German measles. This occurs if a woman is infected with rubella during pregnancy. The rubella virus is teratogenic, meaning it can cause developmental defects if it crosses the placenta during pregnancy. There is a very high incidence of stillbirth, spontaneous abortion, or congenital birth defects if the mother is infected before 11 weeks of pregnancy and 35% if she is infected between weeks 13–16; after this time the incidence is low.[16] For this reason, prenatal screening for rubella is commonly practiced in the United States. Postnatal infections are usually self-limiting and rarely cause severe complications.

Like measles, the preliminary diagnosis of rubella is based on the patient's history, vaccination records, and the appearance of the rash. The diagnosis can be confirmed by hemagglutinin inhibition assays and a variety of other immunological techniques. There are no antiviral therapies for rubella, but an effective vaccine (MMR) is widely available. Vaccination efforts have essentially eliminated rubella in the United States; fewer than a dozen cases are reported in a typical year.

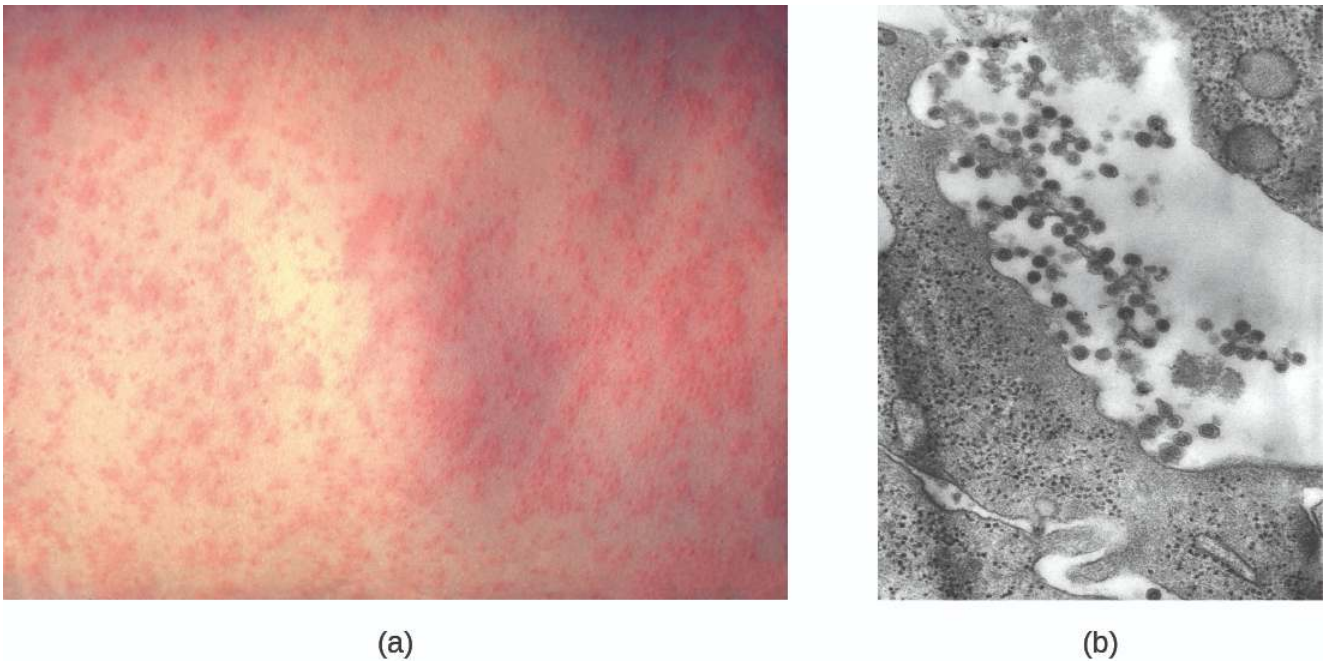


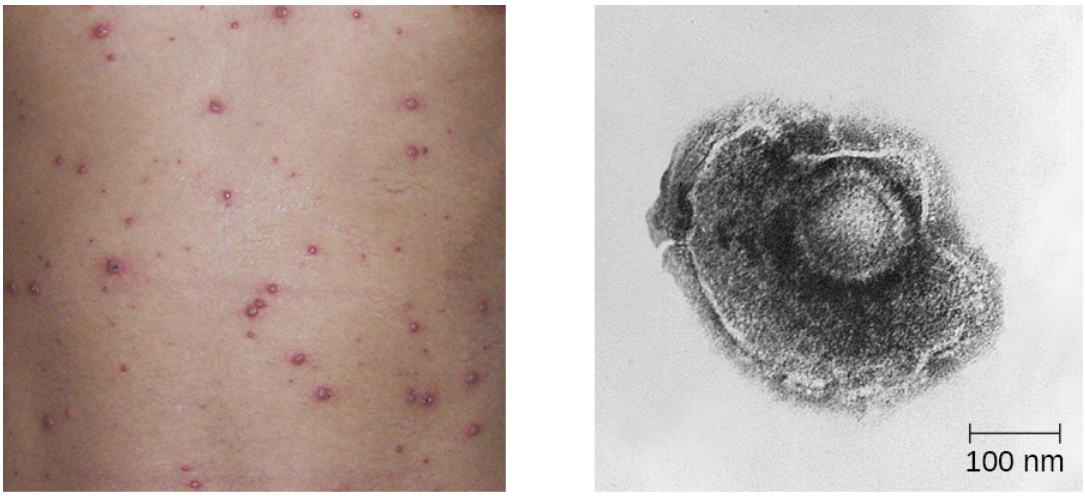
Figure **17.1.3.3**: (a) This photograph shows the appearance of the German measles (rubella) rash. Note that this is less intense than the rash of measles and the lesions are not confluent. (b) This transmission electron micrograph shows rubella virus virions just budding from a host cell. (credit a, b: modification of work by Centers for Disease Control and Prevention)

Chickenpox and Shingles

Chickenpox, also known as varicella, was once a common viral childhood disease. The causative agent of chickenpox, the varicella-zoster virus, is a member of the herpesvirus family. In children, the disease is mild and self-limiting, and is easily transmitted by direct contact or inhalation of material from the skin lesions. In adults, however, chickenpox infections can be much more severe and can lead to pneumonia and birth defects in the case of infected pregnant women. Reye syndrome, mentioned earlier in this chapter, is also a serious complication associated with chickenpox, generally in children.

Once infected, most individuals acquire a lifetime immunity to future chickenpox outbreaks. For this reason, parents once held “chickenpox parties” for their children. At these events, uninfected children were intentionally exposed to an infected individual so they would contract the disease earlier in life, when the incidence of complications is very low, rather than risk a more severe infection later.

After the initial viral exposure, chickenpox has an incubation period of about 2 weeks. The initial infection of the respiratory tract leads to viremia and eventually produces fever and chills. A pustular rash then develops on the face, progresses to the trunk, and then the extremities, although most form on the trunk (Figure **17.1.3.4**). Eventually, the lesions burst and form a crusty scab. Individuals with chickenpox are infectious from about 2 days before the outbreak of the rash until all the lesions have scabbed over.



(a) (b)

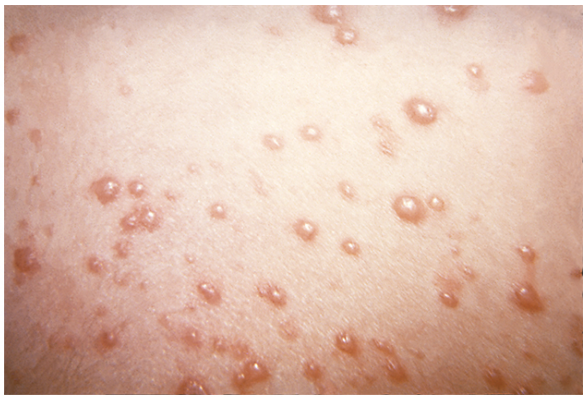
Figure **17.1.3.4**: (a) The characteristic appearance of the pustular chickenpox rash is concentrated on the trunk region. (b) This transmission electron micrograph shows a viroid of human herpesvirus 3, the virus that causes chickenpox in children and shingles when it is reactivated in adults. (credit b: modification of work by Centers for Disease Control and Prevention)

Like other herpesviruses, the varicella-zoster virus can become dormant in nerve cells. While the pustular vesicles are developing, the virus moves along sensory nerves to the dorsal ganglia in the spinal cord. Once there, the varicella-zoster virus can remain latent for decades. These dormant viruses may be reactivated later in life by a variety of stimuli, including stress, aging, and immunosuppression. Once reactivated, the virus moves along sensory nerves to the skin of the face or trunk. This results in the production of the painful lesions in a condition known as shingles (Figure **17.1.3.5**). These symptoms generally last for 2–6 weeks, and may recur more than once. Postherpetic neuralgia, pain signals sent from damaged nerves long after the other symptoms have subsided, is also possible. In addition, the virus can spread to other organs in immunocompromised individuals. A person with shingles lesions can transmit the virus to a nonimmune contact, and the newly infected individual would develop chickenpox as the primary infection. Shingles cannot be transmitted from one person to another.

The primary diagnosis of chickenpox in children is mainly based on the presentation of a pustular rash of the trunk. Serological and PCR-based tests are available to confirm the initial diagnosis. Treatment for chickenpox infections in children is usually not required. In patients with shingles, acyclovir treatment can often reduce the severity and length of symptoms, and diminish the risk of postherpetic neuralgia. An effective vaccine is now available for chickenpox. A vaccine is also available for adults older than 60 years who were infected with chickenpox in their youth. This vaccine reduces the likelihood of a shingles outbreak by boosting the immune defenses that are keeping the latent infection in check and preventing reactivation.



(a)



(b)

Figure 17.1.3.5: (a) An individual suffering from shingles. (b) The rash is formed because of the reactivation of a varicella-zoster infection that was initially contracted in childhood. (credit a: modification of work by National Institute of Allergy and Infectious Diseases (NIAID); credit b: modification of work by Centers for Disease Control and Prevention)

? Exercise 17.1.3.6

1. Why does measles often lead to secondary infections?
2. What signs or symptoms would distinguish rubella and measles?
3. Why can chickenpox lead to shingles later in life?

Smallpox Stockpiles

Smallpox has probably killed more humans than any other infectious disease, with the possible exception of tuberculosis. This disease, caused by the variola major virus, is transmitted by inhalation of viral particles shed from lesions in the throat. The smallpox virus spreads systemically in the bloodstream and produces a pustular skin rash. Historical epidemics of smallpox had fatality rates of 50% or greater in susceptible populations. Concerted worldwide vaccination efforts eradicated smallpox from the general population in 1977. This was the first microbial disease in history to be eradicated, a feat made possible by the fact that the only reservoir for the smallpox virus is infected humans.

Although the virus is no longer present in the wild, laboratory samples of the virus still exist in the United States and Russia.[17] The question is, why do these samples still exist? Some claim that these stocks should be maintained for research purposes. Should the smallpox virus ever reappear, they say, we would need access to such stocks for development of vaccines and treatments. Concerns about a re-emergence of the virus are not totally unfounded. Although there are no living reservoirs of the virus, there is always the possibility that smallpox could re-emerge from mummified human bodies or human remains preserved in permafrost. It is also possible that there are as-yet undiscovered samples of the virus in other locations around the world. An example of such "lost" samples was discovered in a drawer in a Food and Drug Administration lab in Maryland.[18] If an outbreak from such a source were to occur, it could lead to uncontrolled epidemics, since the population is largely unvaccinated now.

Critics of this argument, including many research scientists and the World Health Organization, claim that there is no longer any rational argument for keeping the samples. They view the “re-emergence scenarios” as a thinly veiled pretense for harboring biological weapons. These scenarios, they say, are less probable than an intentional reintroduction of the virus from militarized stocks by humans. Furthermore, they point out that if we needed to research smallpox in the future, we could rebuild the virus from its DNA sequence.

What do you think? Are there legitimate arguments for maintaining stockpiles of smallpox, or should all forms of this deadly disease be eradicated?

Viral Infections of the Respiratory Tract

Many viruses are capable of entering and causing disease in the respiratory system, and a number are able to spread beyond the respiratory system to cause systemic infections. Most of these infections are highly contagious and, with a few exceptions, antimicrobial drugs are not effective for treatment. Although some of these infections are self-limiting, others can have serious or fatal complications. Effective vaccines have been developed for several of these diseases, as summarized in Figure **17.1.3.6**.

Viral Infections of the Respiratory Tract

Disease	Pathogen	Signs and Symptoms	Transmission	Vaccine
Chickenpox (varicella)	Varicella-zoster virus	In children, fever, chills, pustular rash of lesions that burst and form crusty scabs; in adults, more severe symptoms and complications (e.g., pneumonia)	Highly contagious via contact with aerosols, particles, or droplets from infected individual's blisters or respiratory secretions	Varicella (chickenpox) vaccine
Common cold	Rhinoviruses, adenoviruses, coronaviruses, others	Runny nose, congestion, sore throat, sneezing, headaches and muscle aches; may lead to otitis media, pharyngitis, laryngitis	Highly contagious via contact with respiratory secretions or inhalation of droplets or aerosols	None
Influenza	Influenza viruses A, B, C	Fever, chills, headaches, body aches, fatigue; may lead to pneumonia or complications such as Reye syndrome. Highly virulent strains may cause lethal complications	Highly contagious between humans via contact with respiratory secretions or inhalation of droplets or aerosols. Influenza A virus can be transmitted from animal reservoirs.	Vaccines developed yearly against most prevalent strains
Measles	Measles virus (MeV)	High fever, conjunctivitis, sore throat, macular rash becoming confluent, Koplik's spots on oral mucosa; in severe cases, can lead to fatal pneumonia or encephalitis, especially in children	Highly contagious via contact with respiratory secretions, skin rash, or eye secretions of infected individual	MMR
MERS	Middle East respiratory syndrome coronavirus (MERS-CoV)	Fever, cough, shortness of breath; in some cases, complications such as pneumonia and kidney failure; can be fatal	Contact with respiratory secretions or inhalation of droplets or aerosols	None
Rubella (German measles)	Rubella virus	Facial rash spreading to extremities, followed by low-grade fever, headache, conjunctivitis, cough, runny nose, swollen lymph nodes; congenital rubella may cause birth defects, miscarriage, or stillbirth	Contagious via inhalation of droplets or aerosols from infected person or asymptomatic carrier; transplacental infection from mother to fetus	MMR
SARS	SARS-associated coronavirus (SARS-CoV)	High fever, headache, body aches, dry cough, pneumonia; can be fatal	Contact with respiratory secretions or inhalation of droplets or aerosols	None
Shingles	Varicella-zoster virus	Painful lesions on face or trunk lasting several weeks; may cause postherpetic neuralgia (chronic pain) or spread to organs in severe cases	Nontransmissible; occurs when dormant virus is reactivated, generally many years after initial chicken-pox infection	Herpes zoster (shingles) vaccine
Viral pneumonia	Adenoviruses, influenza viruses, parainfluenza viruses, respiratory syncytial viruses,others	From mild cold-like symptoms to severe pneumonia; in infants, RSV infections may be life-threatening	Highly contagious via contact with respiratory secretions or inhalation of droplets or aerosols	None

Figure **17.1.3.6**: Viral infections of respiratory tract

Key Concepts and Summary

- Viruses cause respiratory tract infections more frequently than bacteria, and most viral infections lead to mild symptoms.

- The **common cold** can be caused by more than 200 viruses, typically rhinoviruses, coronaviruses, and adenoviruses, transmitted by direct contact, aerosols, or environmental surfaces.
- Due to its ability to rapidly mutate through **antigenic drift** and **antigenic shift**, **influenza** remains an important threat to human health. Two new influenza vaccines are developed annually.
- Several viral infections, including **respiratory syncytial virus** infections, which frequently occur in the very young, can begin with mild symptoms before progressing to viral pneumonia.
- **SARS** and **MERS** are acute respiratory infections caused by coronaviruses, and both appear to originate in animals. SARS has not been seen in the human population since 2004 but had a high mortality rate during its outbreak. MERS also has a high mortality rate and continues to appear in human populations.
- **Measles**, **rubella**, and **chickenpox** are highly contagious, systemic infections that gain entry through the respiratory system and cause rashes and fevers. Vaccines are available for all three. Measles is the most severe of the three and is responsible for significant mortality around the world. Chickenpox typically causes mild infections in children but the virus can reactivate to cause painful cases of **shingles** later in life.

Footnotes

1. 1 AG L'Huillier et al. "Survival of Rhinoviruses on Human Fingers." *Clinical Microbiology and Infection* 21, no. 4 (2015):381–385.
2. 2 Centers for Disease Control and Prevention. "Estimating Seasonal Influenza-Associated Deaths in the United States: CDC Study Confirms Variability of Flu." 2016. https://www.cdc.gov/flu/about/burden/preliminary-in-season-estimates.htm. Accessed July 6, 2016.
3. 3 ED Belay et al. "Reye's Syndrome in the United States From 1981 Through 1997." *New England Journal of Medicine* 340 no. 18 (1999):1377–1382.
4. 4 CE Mills et al. "Transmissibility of 1918 Pandemic Influenza." *Nature* 432, no. 7019 (2004):904–906.
5. 5 E. Tognotti. "Influenza Pandemics: A Historical Retrospect." *Journal of Infection in Developing Countries* 3, no. 5 (2009):331–334.
6. 6 FS Dawood et al. "Estimated Global Mortality Associated with the First 12 Months of 2009 Pandemic Influenza A H1N1 Virus Circulation: A Modelling Study." *The Lancet Infectious Diseases* 12, no. 9 (2012):687–695.
7. 7 World Health Organization. "WHO Report on Global Surveillance of Epidemic-Prone Infectious Diseases." 2000. http://www.who.int/csr/resources/pub.../Influenza.pdf. Accessed July 6, 2016.
8. 8 Centers of Disease Control and Prevention. "Vaccine Effectiveness - How Well Does the Flu Vaccine Work?" 2016. http://www.cdc.gov/flu/about/qa/vaccineeffect.htm. Accessed July 6, 2016.
9. 9 Y. Huang. "The SARS Epidemic and Its Aftermath in China: A Political Perspective." In *Learning from SARS: Preparing for the Next Disease Outbreak*. Edited by S. Knobler et al. Washington, DC: National Academies Press; 2004. Available at: www.ncbi.nlm.nih.gov/books/NBK92479/
10. 10 Centers for Disease Control and Prevention. "Global Health - Measles, Rubella, and CRS, Eliminating Measles, Rubella & Congenital Rubella Syndrome (CRS) Worldwide." 2015. http://www.cdc.gov/globalhealth/measles/. Accessed July 7, 2016.
11. 11 World Health Organization. "Measles Factsheet." 2016. http://www.who.int/mediacentre/factsheets/fs286/en/. Accessed July 7, 2016.
12. 12 Centers for Disease Control and Prevention. "Measles Cases and Outbreaks." 2016. http://www.cdc.gov/measles/cases-outbreaks.html. Accessed July 7, 2016.
13. 13 Ibid.
14. 14 World Health Organization. "Measles-Rubella Bulletin." Manila, Philippines; Expanded Programme on Immunization Regional Office for the Western Pacific World Health Organization; 9 no. 1 (2015). http://www.wpro.who.int/immunization...vol9issue1.pdf
15. 15 M. Bloch et al. "Vaccination Rates for Every Kindergartener in California." *The New York Times* February 6, 2015. http://www.nytimes.com/interactive/2...-map.html?_r=1. Accessed July 7, 2016.
16. 16 E. Miller et al. "Consequences of Confirmed Maternal Rubella at Successive Stages of Pregnancy." *The Lancet* 320, no. 8302 (1982):781–784.
17. 17 Centers for Disease Control and Prevention. "CDC Media Statement on Newly Discovered Smallpox Specimens." July 8, 2014. http://www.cdc.gov/media/releases/2014/s0708-nih.html. Accessed on July 7, 2016.

18. 18 Ibid.

This page titled 17.1.3: Viral Infections of the Respiratory Tract is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **22.3: Viral Infections of the Respiratory Tract** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

17.1.4: Respiratory Mycoses

Learning Objectives

- Identify the most common fungi that can cause infections of the respiratory tract
- Compare the major characteristics of specific fungal diseases of the respiratory tract

Fungal pathogens are ubiquitous in the environment. Serological studies have demonstrated that most people have been exposed to fungal respiratory pathogens during their lives. Yet symptomatic infections by these microbes are rare in healthy individuals. This demonstrates the efficacy of the defenses of our respiratory system. In this section, we will examine some of the fungi that can cause respiratory infections.

Histoplasmosis

Histoplasmosis is a fungal disease of the respiratory system and most commonly occurs in the Mississippi Valley of the United States and in parts of Central and South America, Africa, Asia, and Australia. The causative agent, *Histoplasma capsulatum*, is a dimorphic fungus. This microbe grows as a filamentous mold in the environment but occurs as a budding yeast during human infections. The primary reservoir for this pathogen is soil, particularly in locations rich in bat or bird feces.

Histoplasmosis is acquired by inhaling microconidial spores in the air; this disease is not transmitted from human to human. The incidence of histoplasmosis exposure is high in endemic areas, with 60%–90% of the population having anti-*Histoplasma* antibodies, depending on location;[1] however, relatively few individuals exposed to the fungus actually experience symptoms. Those most likely to be affected are the very young, the elderly, and immunocompromised people.

In many ways, the course of this disease is similar to that of tuberculosis. Following inhalation, the spores enter the lungs and are phagocytized by alveolar macrophages. The fungal cells then survive and multiply within these phagocytes (see Figure 5.3.2). Focal infections cause the formation of granulomatous lesions, which can lead to calcifications that resemble the Ghon complexes of tuberculosis, even in asymptomatic cases. Also like tuberculosis, histoplasmosis can become chronic and reactivation can occur, along with dissemination to other areas of the body (e.g., the liver or spleen).

Signs and symptoms of pulmonary histoplasmosis include fever, headache, and weakness with some chest discomfort. The initial diagnosis is often based on chest radiographs and cultures grown on fungal selective media like Sabouraud's dextrose agar. Direct fluorescence antibody staining and Giemsa staining can also be used to detect this pathogen. In addition, serological tests including a complement fixation assay and histoplasmin sensitivity can be used to confirm the diagnosis. In most cases, these infections are self-limiting and antifungal therapy is not required. However, in disseminated disease, the antifungal agents amphotericin B and ketoconazole are effective; itraconazole may be effective in immunocompromised patients, in whom the disease can be more serious.

Exercise 17.1.4.1

1. In what environments is one more likely to be infected with histoplasmosis?
2. Identify at least two similarities between histoplasmosis and tuberculosis.

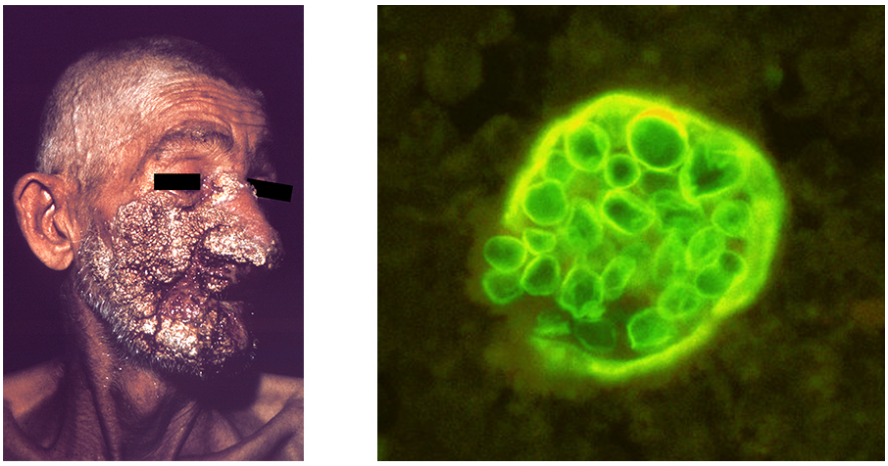
Coccidioidomycosis

Infection by the dimorphic fungus *Coccidioides immitis* causes coccidioidomycosis. Because the microbe is endemic to the San Joaquin Valley of California, the disease is sometimes referred to as Valley fever. A related species that causes similar infections is found in semi-arid and arid regions of the southwestern United States, Mexico, and Central and South America.[2]

Like histoplasmosis, coccidioidomycosis is acquired by inhaling fungal spores—in this case, arthrospores formed by hyphal fragmentation. Once in the body, the fungus differentiates into spherules that are filled with endospores. Most *C. immitis* infections are asymptomatic and self-limiting. However, the infection can be very serious for immunocompromised patients. The endospores may be transported in the blood, disseminating the infection and leading to the formation of granulomatous lesions on the face and

nose (Figure 17.1.4.1). In severe cases, other major organs can become infected, leading to serious complications such as fatal meningitis.

Coccidioidomycosis can be diagnosed by culturing clinical samples. *C. immitis* readily grows on laboratory fungal media, such as Sabouraud's dextrose agar, at 35 °C (95 °F). Culturing the fungus, however, is rather dangerous. *C. immitis* is one of the most infectious fungal pathogens known and is capable of causing laboratory-acquired infections. Indeed, until 2012, this organism was considered a “select agent” of bioterrorism and classified as a BSL-3 microbe. Serological tests for antibody production are more often used for diagnosis. Although mild cases generally do not require intervention, disseminated infections can be treated with intravenous antifungal drugs like amphotericin B.



(a) (b)

Figure 17.1.4.1: (a) This patient has extensive facial lesions due to a disseminated *Coccidioides* infection. (b) This fluorescent micrograph depicts a spherule of *C. immitis* containing endospores. (credit a, b: modification of work by Centers for Disease Control and Prevention)

Clinical Focus: Resolution

John’s negative RIDT tests do not rule out influenza, since false-negative results are common, but the *Legionella* infection still must be treated with antibiotic therapy and is the more serious condition. John's prognosis is good, provided the physician can find an antibiotic therapy to which the infection responds.

While John was undergoing treatment, three of the employees from the home improvement store also reported to the clinic with very similar symptoms. All three were older than 55 years and had *Legionella* antigen in their urine; *L. pneumophila* was also isolated from their sputum. A team from the health department was sent to the home improvement store to identify a probable source for these infections. Their investigation revealed that about 3 weeks earlier, the store's air conditioning system, which was located where the employees ate lunch, had been undergoing maintenance. *L. pneumophila* was isolated from the cooling coils of the air conditioning system and intracellular *L. pneumophila* was observed in amoebae in samples of condensed water from the cooling coils as well (Figure 17.1.4.2). The amoebae provide protection for the *Legionella* bacteria and are known to enhance their pathogenicity.

In the wake of the infections, the store ordered a comprehensive cleaning of the air conditioning system and implemented a regular maintenance program to prevent the growth of biofilms within the cooling tower. They also reviewed practices at their other facilities.

After a month of rest at home, John recovered from his infection enough to return to work, as did the other three employees of the store. However, John experienced lethargy and joint pain for more than a year after his treatment.

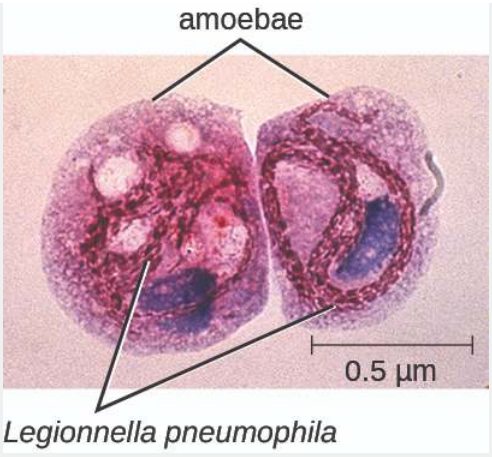
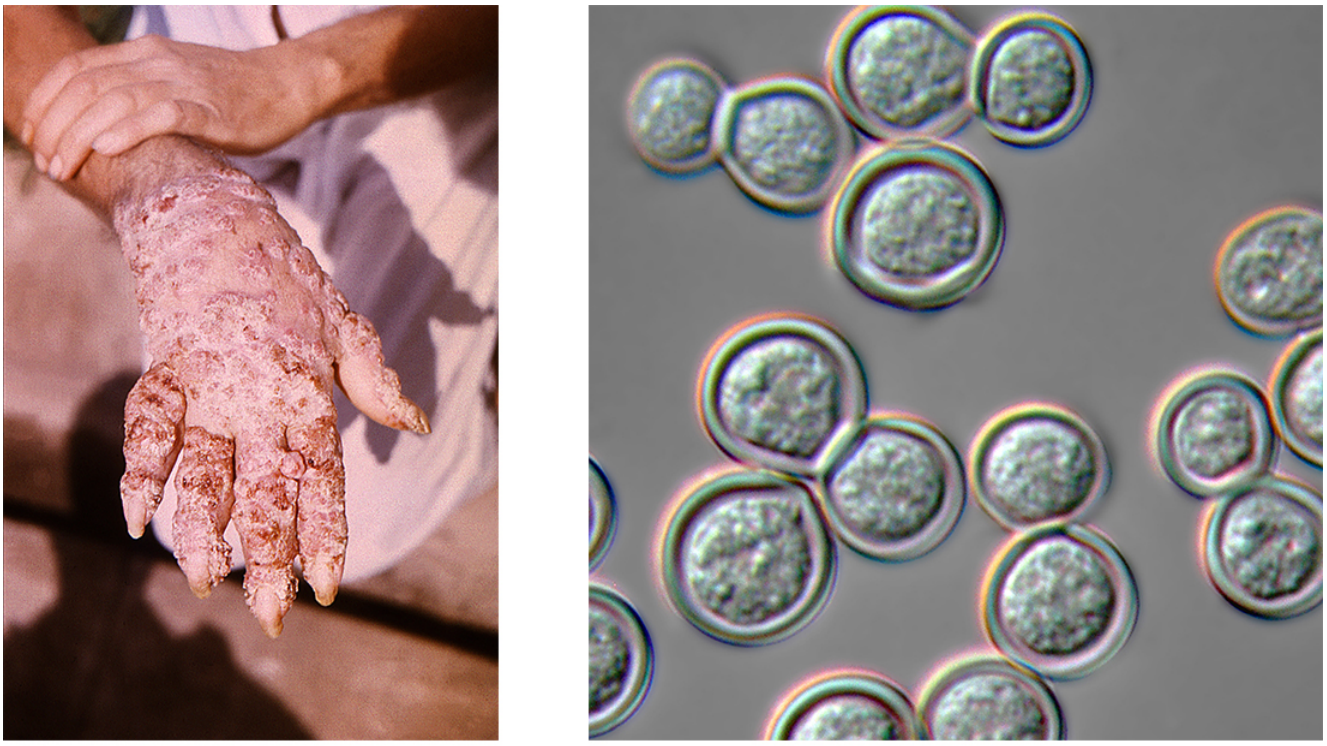


Figure **17.1.4.2**: Legionella pneumophila (red intracellular rods) infecting amoebae from a contaminated water sample. (credit: modification of work by Centers for Disease Control and Prevention)

Blastomycosis

Blastomycosis is a rare disease caused by another dimorphic fungus, *Blastomyces dermatitidis*. Like *Histoplasma* and *Coccidioides*, *Blastomyces* uses the soil as a reservoir, and fungal spores can be inhaled from disturbed soil. The pulmonary form of blastomycosis generally causes mild flu-like symptoms and is self-limiting. It can, however, become disseminated in immunocompromised people, leading to chronic cutaneous disease with subcutaneous lesions on the face and hands (Figure **17.1.4.3**). These skin lesions eventually become crusty and discolored and can result in deforming scars. Systemic blastomycosis is rare, but if left untreated, it is always fatal.

Preliminary diagnosis of pulmonary blastomycosis can be made by observing the characteristic budding yeast forms in sputum samples. Commercially available urine antigen tests are now also available. Additional confirmatory tests include serological assays such as immunodiffusion tests or EIA. Most cases of blastomycosis respond well to amphotericin Bor ketoconazole treatments.



(a) (b)

Figure **17.1.4.3**: (a) These skin lesions are the result of disseminated cutaneous blastomycosis. (b) A differential interference

contrast micrograph of *B. dermatitidis* yeast cultured on blood agar. (credit a: modification of work by Centers for Disease Control and Prevention)

Mucormycosis

A variety of fungi in the order Mucorales cause mucormycosis, a rare fungal disease. These include bread molds, like *Rhizopus* and *Mucor*; the most commonly associated species is *Rhizopus arrhizus (oryzae)* (see Figure 5.3.4). These fungi can colonize many different tissues in immunocompromised patients, but often infect the skin, sinuses, or the lungs.

Although most people are regularly exposed to the causative agents of mucormycosis, infections in healthy individuals are rare. Exposure to spores from the environment typically occurs through inhalation, but the spores can also infect the skin through a wound or the gastrointestinal tract if ingested. Respiratory mucormycosis primarily affects immunocompromised individuals, such as patients with cancer or those who have had a transplant.[4]

After the spores are inhaled, the fungi grow by extending hyphae into the host's tissues. Infections can occur in both the upper and lower respiratory tracts. Rhinocerebral mucormycosis is an infection of the sinuses and brain; symptoms include headache, fever, facial swelling, congestion, and tissue necrosis causing black lesions in the oral cavity. Pulmonary mucormycosis is an infection of the lungs; symptoms include fever, cough, chest pain, and shortness of breath. In severe cases, infections may become disseminated and involve the central nervous system, leading to coma and death.[5]

Diagnosing mucormycosis can be challenging. Currently, there are no serological or PCR-based tests available to identify these infections. Tissue biopsy specimens must be examined for the presence of the fungal pathogens. The causative agents, however, are often difficult to distinguish from other filamentous fungi. Infections are typically treated by the intravenous administration of amphotericin B, and superficial infections are removed by surgical debridement. Since the patients are often immunocompromised, viral and bacterial secondary infections commonly develop. Mortality rates vary depending on the site of the infection, the causative fungus, and other factors, but a recent study found an overall mortality rate of 54%.[6]

? Exercise 17.1.4.2

1. Compare the modes of transmission for coccidioidomycosis, blastomycosis, and mucormycosis.
2. In general, which are more serious: the pulmonary or disseminated forms of these infections?

Aspergillosis

Aspergillus is a common filamentous fungus found in soils and organic debris. Nearly everyone has been exposed to this mold, yet very few people become sick. In immunocompromised patients, however, *Aspergillus* may become established and cause aspergillosis. Inhalation of spores can lead to asthma-like allergic reactions. The symptoms commonly include shortness of breath, wheezing, coughing, runny nose, and headaches. Fungal balls, or aspergilloma, can form when hyphal colonies collect in the lungs (Figure **17.1.4.4**). The fungal hyphae can invade the host tissues, leading to pulmonary hemorrhage and a bloody cough. In severe cases, the disease may progress to a disseminated form that is often fatal. Death most often results from pneumonia or brain hemorrhages.

Laboratory diagnosis typically requires chest radiographs and a microscopic examination of tissue and respiratory fluid samples. Serological tests are available to identify *Aspergillus* antigens. In addition, a skin test can be performed to determine if the patient has been exposed to the fungus. This test is similar to the Mantoux tuberculin skin test used for tuberculosis. Aspergillosis is treated with intravenous antifungal agents, including itraconazole and voriconazole. Allergic symptoms can be managed with corticosteroids because these drugs suppress the immune system and reduce inflammation. However, in disseminated infections, corticosteroids must be discontinued to allow a protective immune response to occur.

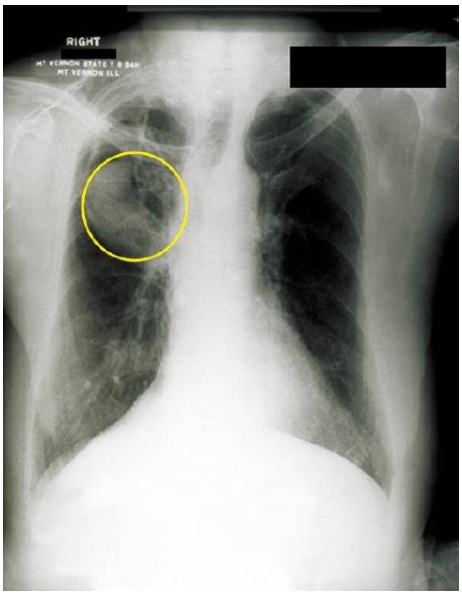
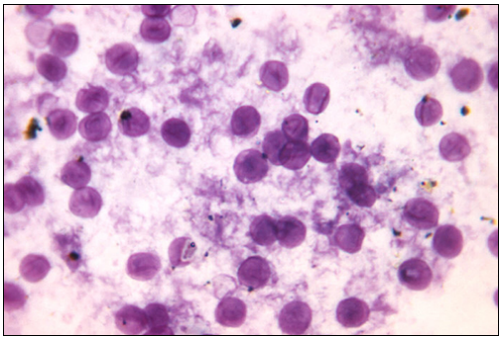


Figure 17.1.4.4: A fungal ball can be observed in the upper lobe of the right lung in this chest radiograph of a patient with aspergilloma. (credit: modification of work by Centers for Disease Control and Prevention)

Pneumocystis Pneumonia

A type of pneumonia called *Pneumocystis* pneumonia (PCP) is caused by *Pneumocystis jirovecii*. Once thought to be a protozoan, this organism was formerly named *P. carinii* but it has been reclassified as a fungus and renamed based on biochemical and genetic analyses. *Pneumocystis* is a leading cause of pneumonia in patients with acquired immunodeficiency syndrome (AIDS) and can be seen in other compromised patients and premature infants. Respiratory infection leads to fever, cough, and shortness of breath. Diagnosis of these infections can be difficult. The organism is typically identified by microscopic examination of tissue and fluid samples from the lungs (Figure 17.1.4.5). A PCR-based test is available to detect *P. jirovecii* in asymptomatic patients with AIDS. The best treatment for these infections is the combination drug trimethoprim-sulfamethoxazole (TMP/SMZ). These sulfa drugs often have adverse effects, but the benefits outweigh these risks. Left untreated, PCP infections are often fatal.


Figure 17.1.4.5: A light micrograph of a smear containing *Pneumocystis jirovecii* (dark purple cells) obtained from human lung tissue and stained with toluidine blue. (credit: Centers for Disease Control and Prevention)

Cryptococcosis

Infection by the encapsulated yeast *Cryptococcus neoformans* causes cryptococcosis. This fungus is ubiquitous in the soil and can be isolated from bird feces. Immunocompromised people are infected by inhaling basidiospores found in aerosols. The thick polysaccharide capsule surrounding these microbes enables them to avoid clearance by the alveolar macrophage. Initial symptoms of infection include fever, fatigue, and a dry cough. In immunocompromised patients, pulmonary infections often disseminate to the brain. The resulting meningitis produces headaches, sensitivity to light, and confusion. Left untreated, such infections are often fatal.

Cryptococcus infections are often diagnosed based on microscopic examination of lung tissues or cerebrospinal fluids. India ink preparations (Figure 17.1.4.6) can be used to visualize the extensive capsules that surround the yeast cells. Serological tests are also

available to confirm the diagnosis. Amphotericin B, in combination with flucytosine, is typically used for the initial treatment of pulmonary infections. Amphotericin B is a broad-spectrum antifungal drug that targets fungal cell membranes. It can also adversely impact host cells and produce side effects. For this reason, clinicians must carefully balance the risks and benefits of treatments in these patients. Because it is difficult to eradicate cryptococcal infections, patients usually need to take fluconazole for up to 6 months after treatment with amphotericin B and flucytosine to clear the fungus. Cryptococcal infections are more common in immunocompromised people, such as those with AIDS. These patients typically require life-long suppressive therapy to control this fungal infection.

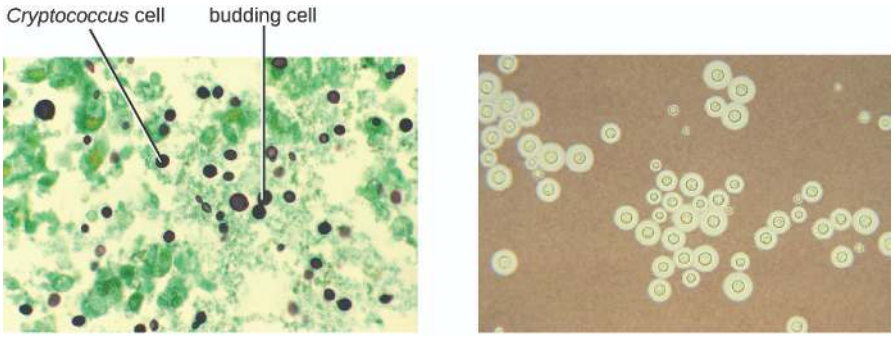


Figure **17.1.4.6**: (a) The micrograph shows stained budding *Cryptococcus* yeast cells from the lungs of a patient with AIDS. (b) The large capsule of *Cryptococcus neoformans* is visible in this negative stain micrograph. (credit a, b: modification of work by Centers for Disease Control and Prevention)

? Exercise 17.1.4.3

1. What populations are most at risk for developing *Pneumocystis* pneumonia or cryptococcosis?
2. Why are these infections fatal if left untreated?

Fungal Diseases of the Respiratory Tract

Most respiratory mycoses are caused by fungi that inhabit the environment. Such infections are generally transmitted via inhalation of fungal spores and cannot be transmitted between humans. In addition, healthy people are generally not susceptible to infection even when exposed; the fungi are only virulent enough to establish infection in patients with HIV, AIDS, or another condition that compromises the immune defenses. Figure **17.1.4.7** summarizes the features of important respiratory mycoses.

Fungal Infections of the Respiratory Tract				
Disease	**Pathogen**	**Signs and Symptoms**	**Diagnostic Tests**	**Antimicrobial Drugs**
Aspergillosis	*Aspergillus fumigatus*	Shortness of breath, wheezing, coughing, runny nose, headaches; formation of aspergillomas causing severe pneumonia and pulmonary or brain hemorrhages; can be fatal	Chest radiograph, skin test, microscopic observation of sputum samples	Itraconazole, voriconazole
Blastomycosis	*Blastomyces dermatitidis*	Fever, chills, cough, headache, fatigue, chest pain, body aches; in disseminated infections, chronic, crusted lesions on face and hands with permanent scarring; can be fatal	Microscopic observation of sputum samples; urine antigen test; EIA	Amphotericin B, ketoconazole
Coccidioidomycosis (Valley fever)	*Coccidioides immitis*	Granulomatous lesions on face and nose; may spread to organs or brain, causing fatal meningitis	Culture (in BSL-3 lab only), serological antibody tests	Amphotericin B
Cryptococcosis	*Cryptococcus neoformans*	Fever, cough, shortness of breath; can cause fatal meningitis if disseminated to brain	Microscopic examination of lung tissue or cerebrospinal fluid	Amphotericin B, fluconazole, flucytosine
Histoplasmosis	*Histoplasma capsulatum*	Fever, headache, weakness, chest pain, lesions on lungs	Chest radiograph, culture, direct fluorescence antibody staining, complement fixation assay, histoplasmin sensitivity test	Amphotericin B, ketoconazole, itraconazole
Mucormycosis	*Rhizopus arrhizus*, other *Rhizopus* spp., *Mucor* spp.	Headache, fever, facial swelling, congestion, black lesions in oral cavity, cough, chest pain, shortness of breath; often fatal	Microscopic examination of tissue biopsy specimens	Amphotericin B
Pneumocystis pneumonia (PCP)	*Pneumocystis jirovecii*	Fever, cough, shortness of breath; can be fatal if untreated	Microscopic examination of lung tissue and fluid, PCR	Trimethoprim-sulfamethoxazole

Figure **17.1.4.7**: Fungal infections of the respiratory tract.

Key Concepts and Summary

- Fungal pathogens rarely cause respiratory disease in healthy individuals, but inhalation of fungal spores can cause severe pneumonia and systemic infections in immunocompromised patients.
- Antifungal drugs like amphotericin B can control most fungal respiratory infections.
- **Histoplasmosis** is caused by a mold that grows in soil rich in bird or bat droppings. Few exposed individuals become sick, but vulnerable individuals are susceptible. The yeast-like infectious cells grow inside phagocytes.
- **Coccidioidomycosis** is also acquired from soil and, in some individuals, will cause lesions on the face. Extreme cases may infect other organs, causing death.
- **Blastomycosis**, a rare disease caused by a soil fungus, typically produces a mild lung infection but can become disseminated in the immunocompromised. Systemic cases are fatal if untreated.
- **Mucormycosis** is a rare disease, caused by fungi of the order Mucorales. It primarily affects immunocompromised people. Infection involves growth of the hyphae into infected tissues and can lead to death in some cases.
- **Aspergillosis**, caused by the common soil fungus *Aspergillus*, infects immunocompromised people. Hyphal balls may impede lung function and hyphal growth into tissues can cause damage. Disseminated forms can lead to death.
- ***Pneumocystis* pneumonia** is caused by the fungus *P. jirovecii*. The disease is found in patients with AIDS and other immunocompromised individuals. Sulfa drug treatments have side effects, but untreated cases may be fatal.
- **Cryptococcosis** is caused by *Cryptococcus neoformans*. Lung infections may move to the brain, causing meningitis, which can be fatal.

Footnotes

1. 1 NE Manos et al. “Geographic Variation in the Prevalence of Histoplasmin Sensitivity.” *Dis Chest* 29, no. 6 (1956):649–668.
2. 2 DR Hospenthal. “Coccioidomycosis.” Medscape. 2015. http://emedicine.medscape.com/article/215978-overview. Accessed July 7, 2016.
3. 3 HY Lau and NJ Ashbolt. “The Role of Biofilms and Protozoa in *Legionella* Pathogenesis: Implications for Drinking Water.” *Journal of Applied Microbiology* 107 no. 2 (2009):368–378.
4. 4 Centers for Disease Control and Prevention. “Fungal Diseases. Definition of Mucormycosis.” 2015 http://www.cdc.gov/fungal/diseases/m...efinition.html. Accessed July 7, 2016.
5. 5 Centers for Disease Control and Prevention. “Fungal Diseases. Symptoms of Mucormycosis.” 2015 http://www.cdc.gov/fungal/diseases/m.../symptoms.html. Accessed July 7, 2016.
6. 6 MM Roden et al. “Epidemiology and Outcome of Zygomycosis: A Review of 929 Reported Cases.” *Clinical Infectious Diseases* 41 no. 5 (2005):634–653.

This page titled 17.1.4: Respiratory Mycoses is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **22.4: Respiratory Mycoses** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

17.1.E: Respiratory System Infections (Exercises)

22.1: Anatomy and Normal Microbiota of the Respiratory Tract

The upper respiratory tract is colonized by an extensive and diverse normal microbiota, many of which are potential pathogens. Few microbial inhabitants have been found in the lower respiratory tract, and these may be transients. Members of the normal microbiota may cause opportunistic infections, using a variety of strategies to overcome the innate nonspecific defenses (including the mucociliary escalator) and adaptive specific defenses of the respiratory system.

Multiple Choice

Which of the following is not directly connected to the nasopharynx?

A. middle ear
B. oropharynx
C. lacrimal glands
D. nasal cavity

Answer

C

What type of cells produce the mucus for the mucous membranes?

A. goblet cells
B. macrophages
C. phagocytes
D. ciliated epithelial cells

Answer

A

Which of these correctly orders the structures through which air passes during inhalation?

A. pharynx → trachea → larynx → bronchi
B. pharynx → larynx → trachea → bronchi
C. larynx → pharynx → bronchi → trachea
D. larynx → pharynx → trachea → bronchi

Answer

B

The _____ separates the upper and lower respiratory tract.

A. bronchi
B. larynx
C. epiglottis
D. palatine tonsil

Answer

C

Which microbial virulence factor is most important for attachment to host respiratory tissues?

A. adhesins
B. lipopolysaccharide
C. hyaluronidase

D. capsules

Answer

A

Fill in the Blank

Unattached microbes are moved from the lungs to the epiglottis by the _____ effect.

Answer

mucociliary escalator

Many bacterial pathogens produce _____ to evade phagocytosis.

Answer

capsules

The main type of antibody in the mucous membrane defenses is _____.

Answer

IgA

_____ results from an inflammation of the “voice box.”

Answer

Laryngitis

_____ phagocytize potential pathogens in the lower lung.

Answer

Alveolar macrophages

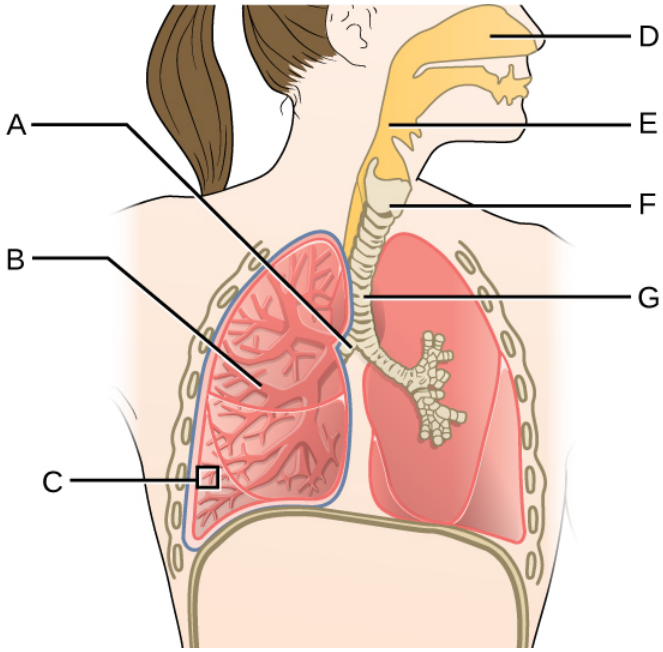
Short Answer

Explain why the lower respiratory tract is essentially sterile.

Explain why pneumonia is often a life-threatening disease.

Critical Thinking

Name each of the structures of the respiratory tract shown, and state whether each has a relatively large or small normal microbiota.



(credit: modification of work by National Cancer Institute)

Cystic fibrosis causes, among other things, excess mucus to be formed in the lungs. The mucus is very dry and caked, unlike the moist, more-fluid mucus of normal lungs. What effect do you think that has on the lung's defenses?

Why do you think smokers are more likely to suffer from respiratory tract infections?

22.2: Bacterial Infections of the Respiratory Tract

The respiratory tract can be infected by a variety of bacteria, both gram positive and gram negative. Although the diseases that they cause may range from mild to severe, in most cases, the microbes remain localized within the respiratory system. Fortunately, most of these infections also respond well to antibiotic therapy.

Multiple Choice

Which of the following does not involve a bacterial exotoxin?

A. diphtheria
B. whooping cough
C. scarlet fever
D. Q fever

Answer

D

What disease is caused by *Coxiella burnetii*?

A. Q fever
B. tuberculosis
C. diphtheria
D. walking pneumonia

Answer

A

In which stage of pertussis is the characteristic whooping sound made?

A. convalescence
B. catarrhal
C. paroxysmal
D. prodromal

Answer

C

What is the causative agent of Q fever?

A. *Coxiella burnetii*
B. *Chlamydophila psittaci*
C. *Mycoplasma pneumoniae*
D. *Streptococcus pyogenes*

Answer

A

Which of these microbes causes “walking pneumonia”?

A. *Klebsiella pneumoniae*
B. *Streptococcus pneumoniae*
C. *Mycoplasma pneumoniae*
D. *Chlamydophila pneumoniae*

Answer

C

Fill in the Blank

Calcified lesions called _____ form in the lungs of patients with TB.

Answer

Ghon complexes

An inflammation of the middle ear is called _____.

Answer

otitis media

The _____ is used to serologically identify *Streptococcus pneumoniae* isolates.

Answer

quellung reaction

_____ is a zoonotic infection that can be contracted by people who handle birds.

Answer

Psittacosis

The main virulence factor involved in scarlet fever is the _____.

Answer

erythrogenic toxin

Short Answer

Name three bacteria that commonly cause pneumonia. Which is the most common cause?

How does smoking make an individual more susceptible to infections?

How does the diphtheria pathogen form a pseudomembrane?

Critical Thinking

Why might β-lactam antibiotics be ineffective against *Mycoplasma pneumoniae* infections?

Why is proper antibiotic therapy especially important for patients with tuberculosis?

22.3: Viral Infections of the Respiratory Tract

Viruses cause respiratory tract infections more frequently than bacteria, and most viral infections lead to mild symptoms. The common cold can be caused by more than 200 viruses, typically rhinoviruses, coronaviruses, and adenoviruses, transmitted by direct contact, aerosols, or environmental surfaces. Due to its ability to rapidly mutate through antigenic drift and antigenic shift, influenza remains an important threat to human health. Two new influenza vaccines are developed annually.

Multiple Choice

Which of the following viruses is not commonly associated with the common cold?

A. coronavirus
B. adenovirus
C. rhinovirus
D. varicella-zoster virus

Answer

D

Which of the following viral diseases has been eliminated from the general population worldwide?

A. smallpox
B. measles
C. German measles
D. influenza

Answer

A

What term refers to multinucleated cells that form when many host cells fuse together during infections?

A. Ghon elements
B. Reye syndrome
C. Koplik’s spots
D. syncytia

Answer

D

Which of the following diseases is not associated with coronavirus infections?

A. Middle East respiratory syndrome
B. German measles
C. the common cold
D. severe acute respiratory syndrome

Answer

B

Which of these viruses is responsible for causing shingles?

A. rubella virus
B. measles virus
C. varicella-zoster virus
D. variola major virus

Answer

C

Fill in the Blank

The _____ virus is responsible for causing German measles.

Answer

rubella

A(n) _____ is an uncontrolled positive feedback loop between cytokines and leucocytes.

Answer

cytokine storm

In cases of shingles, the antiviral drug _____ may be prescribed.

Answer

acyclovir

The slow accumulation of genetic changes to an influenza virus over time is referred to as _____.

Answer

antigenic drift

The _____ vaccine is effective in controlling both measles and rubella.

Answer

MMR

Short Answer

Since we all have experienced many colds in our lifetime, why are we not resistant to future infections?

Critical Thinking

What role does the common cold have in the rise of antibiotic-resistant strains of bacteria in the United States?

Why is it highly unlikely that influenza A virus will ever be eradicated, like the smallpox virus?

22.4: Respiratory Mycoses

Fungal pathogens are ubiquitous in the environment. Serological studies have demonstrated that most people have been exposed to fungal respiratory pathogens during their lives. Yet symptomatic infections by these microbes are rare in healthy individuals. This demonstrates the efficacy of the defenses of our respiratory system. In this section, we examine some of the fungi that can cause respiratory infections.

Multiple Choice

Which of these infections is also referred to as Valley fever?

A. histoplasmosis
B. coccidioidomycosis
C. blastomycosis
D. aspergillosis

Answer

B

Which of the following is not caused by a dimorphic fungus?

A. histoplasmosis
B. coccidioidomycosis
C. blastomycosis
D. aspergillosis

Answer

D

Which of the following is caused by infections by bread molds?

A. mucormycosis
B. coccidioidomycosis
C. cryptococcosis
D. *Pneumocystis* pneumonia

Answer

A

In the United States, most histoplasmosis cases occur

A. in the Pacific northwest.
B. in the desert southwest.
C. in the Mississippi river valley.
D. in Colorado river valley.

Answer

C

Which of the following infections can be diagnosed using a skin test similar to the tuberculin test?

A. histoplasmosis
B. cryptococcosis
C. blastomycosis
D. aspergillosis

Answer

D

Fill in the Blank

In coccidioidomycosis, _____ containing many endospores form in the lungs.

Answer

spherules

In cryptococcosis, the main fungal virulence factor is the _____, which helps the pathogen avoid phagocytosis.

Answer

capsule

In some mycoses, fungal balls called _____ form in the lungs

Answer

aspergillomas

Most US cases of coccidioidomycosis occur in _____.

Answer

the desert southwest

Coccidioidomycosis may develop when *Coccidioides immitis* _____ are inhaled.

Answer

arthrospores

Short Answer

Which pulmonary fungal infection is most likely to be confused with tuberculosis? How can we discriminate between these two types of infection?

Compare and contrast aspergillosis and mucormycosis.

Critical Thinking

Why are fungal pulmonary infections rarely transmissible from person to person?

This page titled 17.1.E: Respiratory System Infections (Exercises) is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **22.E: Respiratory System Infections (Exercises)** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

SECTION OVERVIEW

17.2: Urogenital System Infections

The urogenital system is a combination of the urinary tract and reproductive system. Because both systems are open to the external environment, they are prone to infections. Some infections are introduced from outside, whereas others result from imbalances in the microbiota of the urogenital tract.

Urinary tract infections (UTIs) are one the most common bacterial infections worldwide, affecting over 100 million people each year. During 2007 in the United States, doctor office visits for UTIs exceeded 10 million, and an additional 2–3 million emergency department visits were attributed to UTIs. Sexually transmitted infections (STIs) also primarily affect the urogenital system and are an important cause of patient morbidity. The Centers for Disease Control and Prevention (CDC) estimates that there are approximately 20 million new cases of reportable STIs annually in the United States, half of which occur in people aged 15–24 years old. When STIs spread to the reproductive organs, they can be associated with severe morbidity and loss of fertility.

Because males and females have different urogenital anatomy, urogenital infections may affect males and females differently. In this chapter, we will discuss the various microbes that cause urogenital disease and the factors that contribute to their pathogenicity.

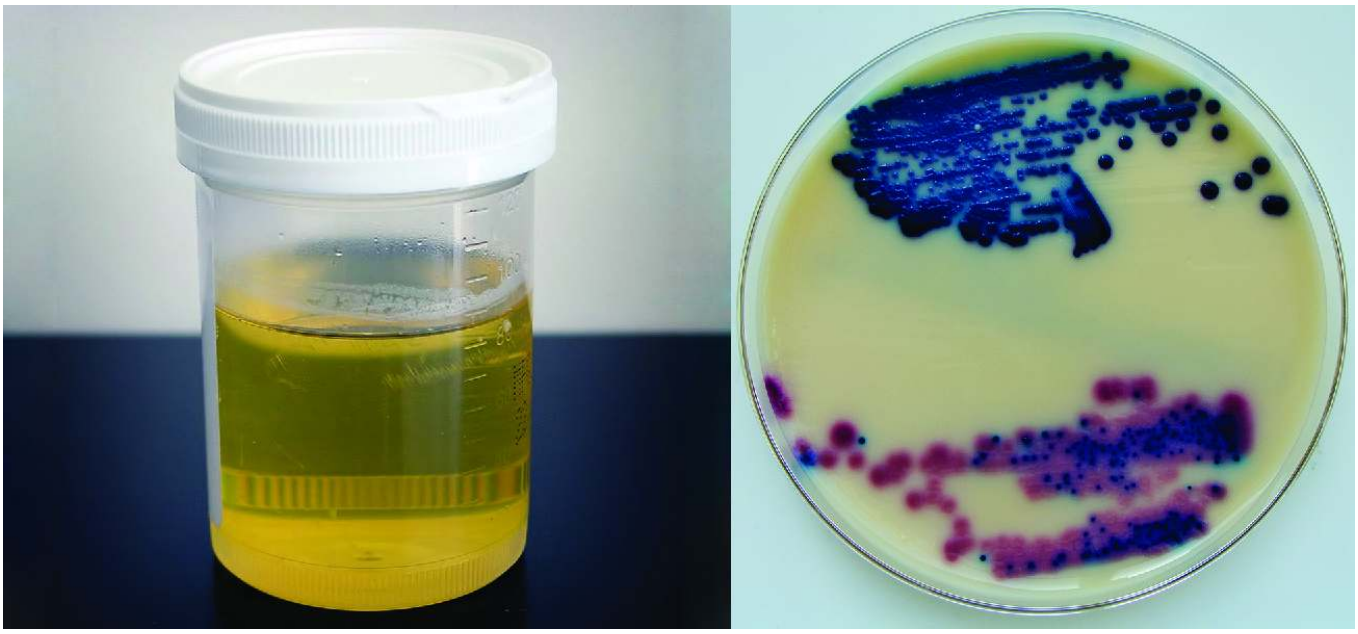


Figure **17.2.1**: Many pathogens that cause infections of the urogenital system can be detected in urine samples (left). The top sample in the culture (right) was prepared from the urine of a patient with a urinary tract infection. (credit b: modification of work by Nathan Reading)

17.2.1: Anatomy and Normal Microbiota of the Urogenital Tract

17.2.2: Bacterial Infections of the Urinary System

17.2.3: Bacterial Infections of the Reproductive System

17.2.4: Viral Infections of the Reproductive System

17.2.5: Fungal Infections of the Reproductive System

17.2.6: Protozoan Infections of the Reproductive System

17.2.E: Urogenital System Infections (Exercises)

This page titled 17.2: Urogenital System Infections is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

17.2.1: Anatomy and Normal Microbiota of the Urogenital Tract

Learning Objectives

- Compare the anatomy, function, and normal microbiota associated with the male and female urogenital systems
- Explain how microorganisms, in general, overcome the defenses of the urogenital system to cause infection
- Name, describe, and differentiate between general signs and symptoms associated with infections of the urogenital tract

Clinical Focus: Part 1

Nadia is a newly married 26-year-old graduate student in economics. Recently she has been experiencing an unusual vaginal discharge, as well as some itching and discomfort. Since she is due for her annual physical exam, she makes an appointment with her doctor hoping that her symptoms can be quickly treated. However, she worries that she may have some sort of sexually transmitted infection (STI). Although she is now in a monogamous relationship, she is not fully certain of her spouse's sexual history and she is reluctant to ask him about it.

At her checkup, Nadia describes her symptoms to her primary care physician and, somewhat awkwardly, explains why she thinks she might have an STI. Nadia's doctor reassures her that she regularly sees patients with similar concerns and encourages her to be fully transparent about her symptoms because some STIs can have serious complications if left untreated. After some further questioning, the doctor takes samples of Nadia's blood, urine, and vaginal discharge to be sent to the lab for testing.

Exercise 17.2.1.1

1. What are some possible causes of Nadia's symptoms?
2. Why does the doctor take so many different samples?

The urinary system filters blood, excretes wastes, and maintains an appropriate electrolyte and water balance. The reproductive system is responsible for the production of gametes and participates in conception and, in females, development of offspring. Due to their proximity and overlap, these systems are often studied together and referred to as the urogenital system (or genitourinary system).

Anatomy of the Urinary Tract

The basic structures of the urinary tract are common in males and females. However, there are unique locations for these structures in females and males, and there is a significant amount of overlap between the urinary and genital structures in males. Figure 17.2.1.1 illustrates the urinary anatomy common to females and males.

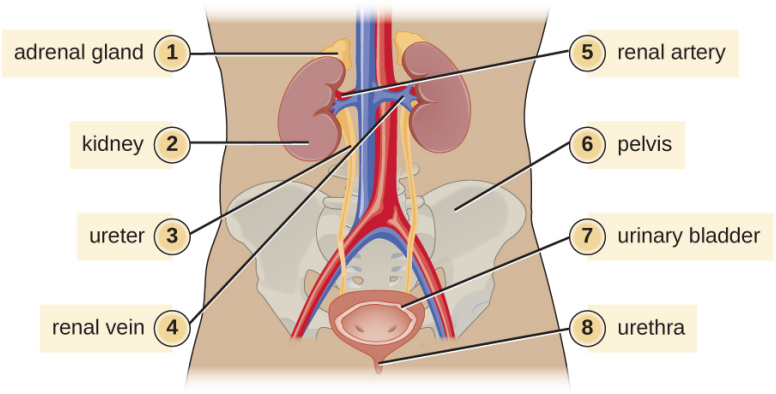


Figure 17.2.1.1: These structures of the human urinary system are present in both males and females.

The kidneys carry out the urinary system's primary functions of filtering the blood and maintaining water and electrolyte balance. The kidneys are composed of millions of filtration units called nephrons. Each nephron is in intimate contact with blood through a

specialized capillary bed called the glomerulus (plural *glomeruli*). Fluids, electrolytes, and molecules from the blood pass from the glomerulus into the nephron, creating the filtrate that becomes urine (Figure **17.2.1.2**). Urine that collects in each kidney empties through a ureter and drains to the urinary bladder, which stores urine. Urine is released from the bladder to the urethra, which transports it to be excreted from the body through the urinary meatus, the opening of the urethra.

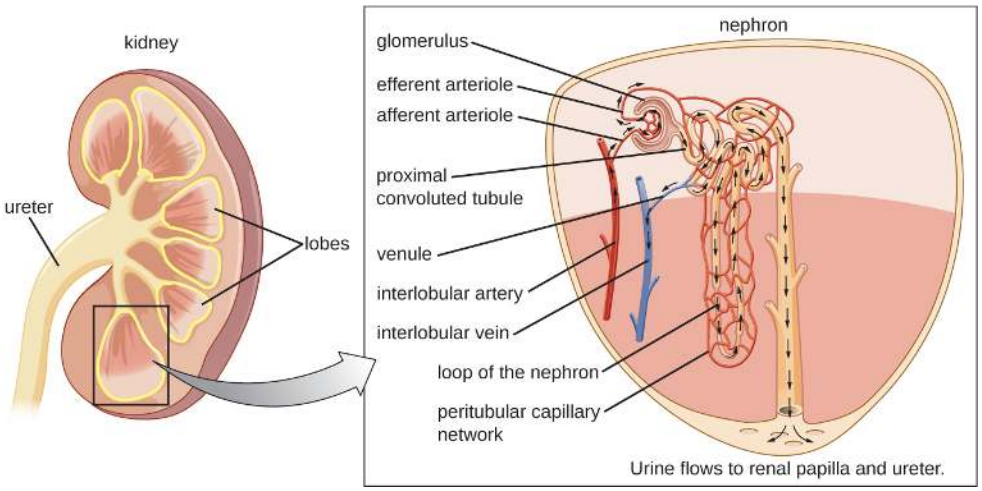


Figure **17.2.1.2**: The kidney contains several lobes, each of which contains millions of nephrons. The nephron is the functional unit of the kidney, filtering the blood and removing water and dissolved compounds. The filtrate first enters the glomerulus and then enters the proximal convoluted tubule. As it passes through the tubule, the filtrate is further modified by osmosis and active transport until it reaches the larger ducts as urine.

Anatomy of the Reproductive System

The male reproductive system (Figure **17.2.1.3**) is located in close proximity to the urinary system, and the urethra is part of both systems. The testes are responsible for the production of sperm. The epididymis is a coiled tube that collects sperm from the testes and passes it on to the vas deferens. The epididymis is also the site of sperm maturation after they leave the testes. The seminal vesicles and prostate are accessory glands that produce fluid that supports sperm. During ejaculation, the vas deferens releases this mixture of fluid and sperm, called semen, into the urethra, which extends to the end of the penis.

The female reproductive system is located near the urinary system (Figure **17.2.1.3**). The external genitalia (vulva) in females open to the vagina, a muscular passageway that connects to the cervix. The cervix is the lower part of the uterus (the organ where a fertilized egg will implant and develop). The cervix is a common site of infection, especially for viruses that may lead to cervical cancer. The uterus leads to the fallopian tubes and eventually to the ovaries. Ovaries are the site of ova (egg) production, as well as the site of estrogen and progesterone production that are involved in maturation and maintenance of reproductive organs, preparation of the uterus for pregnancy, and regulation of the menstrual cycle.

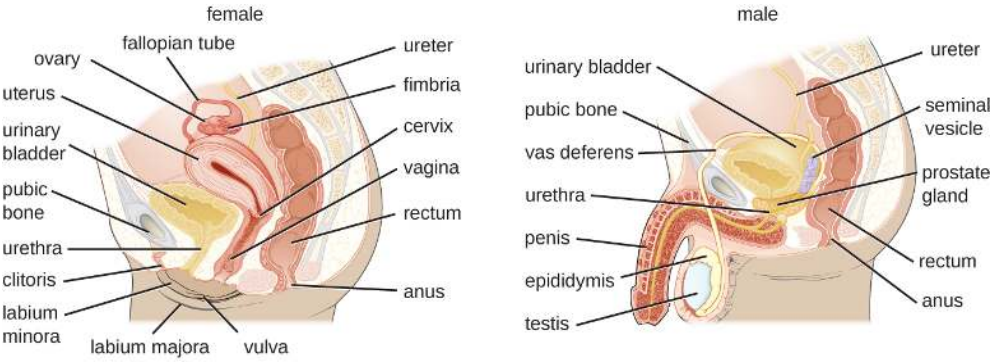


Figure **17.2.1.3**: The female reproductive system is located in close proximity to the urinary system. In males, the urethra is shared by the reproductive and urinary systems.

? Exercise 17.2.1.2

1. What are the major structures of the urinary system, starting where urine is formed?
2. What structure in males is shared by the reproductive and the urinary systems?

Normal Microbiota of the Urogenital System

The normal microbiota of different body sites provides an important nonspecific defense against infectious diseases (see Physical Defenses), and the urogenital tract is no exception. In both men and women, however, the kidneys are sterile. Although urine does contain some antibacterial components, bacteria will grow in urine left out at room temperature. Therefore, it is primarily the flushing action that keeps the ureters and bladder free of microbes.

Below the bladder, the normal microbiota of the male urogenital system is found primarily within the distal urethra and includes bacterial species that are commonly associated with the skin microbiota. In women, the normal microbiota is found within the distal one third of the urethra and the vagina. The normal microbiota of the vagina becomes established shortly after birth and is a complex and dynamic population of bacteria that fluctuates in response to environmental changes. Members of the vaginal microbiota play an important role in the nonspecific defense against vaginal infections and sexually transmitted infections by occupying cellular binding sites and competing for nutrients. In addition, the production of lactic acid by members of the microbiota provides an acidic environment within the vagina that also serves as a defense against infections. For the majority of women, the lactic-acid–producing bacteria in the vagina are dominated by a variety of species of *Lactobacillus*. For women who lack sufficient lactobacilli in their vagina, lactic acid production comes primarily from other species of bacteria such as *Leptotrichia* spp., *Megasphaera* spp., and *Atopobium vaginae*. *Lactobacillus* spp. use glycogen from vaginal epithelial cells for metabolism and production of lactic acid. This process is tightly regulated by the hormone estrogen. Increased levels of estrogen correlate with increased levels of vaginal glycogen, increased production of lactic acid, and a lower vaginal pH. Therefore, decreases in estrogen during the menstrual cycle and with menopause are associated with decreased levels of vaginal glycogen and lactic acid, and a higher pH. In addition to producing lactic acid, *Lactobacillus* spp. also contribute to the defenses against infectious disease through their production of hydrogen peroxide and bacteriocins (antibacterial peptides).

? Exercise 17.2.1.3

What factors affect the microbiota of the female reproductive tract?

General Signs and Symptoms of Urogenital Infections

Infections of the urinary tract most commonly cause inflammation of the bladder (cystitis) or of the urethra (urethritis). Urethritis can be associated with cystitis, but can also be caused by sexually transmitted infections. Symptoms of urethritis in men include burning sensation while urinating, discharge from the penis, and blood in the semen or the urine. In women, urethritis is associated with painful and frequent urination, vaginal discharge, fever, chills, and abdominal pain. The symptoms of cystitis are similar to those of urethritis. When urethritis is caused by a sexually transmitted pathogen, additional symptoms involving the genitalia can occur. These can include painful vesicles (blisters), warts, and ulcers. Ureteritis, a rare infection of the ureter, can also occur with cystitis. These infections can be acute or chronic.

Pyelonephritis and glomerulonephritis are infections of the kidney that are potentially serious. Pyelonephritis is an infection of one or both of the kidneys and may develop from a lower urinary tract infection; the upper urinary tract, including the ureters, is often affected. Signs and symptoms of pyelonephritis include fever, chills, nausea, vomiting, lower back pain, and frequent painful urination. Pyelonephritis usually only becomes chronic in individuals who have malformations in or damage to the kidneys.

Glomerulonephritis is an inflammation of the glomeruli of the nephrons. Symptoms include excessive protein and blood in urine, increased blood pressure, and fluid retention leading to edema of face, hands, and feet. Glomerulonephritis may be an acute infection or it can become chronic.

Infections occurring within the reproductive structures of males include epididymitis, orchitis, and prostatitis. Bacterial infections may cause inflammation of the epididymis, called epididymitis. This inflammation causes pain in the scrotum, testicles, and groin; swelling, redness, and warm skin in these areas may also be observed. Inflammation of the testicle, called orchitis, is usually caused by a bacterial infection spreading from the epididymis, but it can also be a complication of mumps, a viral disease. The

symptoms are similar to those of epididymitis, and it is not uncommon for them both to occur together, in which case the condition is called epididymo-orchitis. Inflammation of the prostate gland, called prostatitis, can result from a bacterial infection. The signs and symptoms of prostatitis include fever, chills, and pain in the bladder, testicles, and penis. Patients may also experience burning during urination, difficulty emptying the bladder, and painful ejaculation.

Because of its proximity to the exterior, the vagina is a common site for infections in women. The general term for any inflammation of the vagina is vaginitis. Vaginitis often develops as a result of an overgrowth of bacteria or fungi that normally reside in the vaginal microbiota, although it can also result from infections by transient pathogens. Bacterial infections of the vagina are called bacterial vaginosis, whereas fungal infections (typically involving *Candida* spp.) are called yeast infections. Dynamic changes affecting the normal microbiota, acid production, and pH variations can be involved in the initiation of the microbial overgrowth and the development of vaginitis. Although some individuals may have no symptoms, vaginosis and vaginitis can be associated with discharge, odor, itching, and burning.

Pelvic inflammatory disease (PID) is an infection of the female reproductive organs including the uterus, cervix, fallopian tubes, and ovaries. The two most common pathogens are the sexually transmitted bacterial pathogens *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. Inflammation of the fallopian tubes, called salpingitis, is the most serious form of PID. Symptoms of PID can vary between women and include pain in the lower abdomen, vaginal discharge, fever, chills, nausea, diarrhea, vomiting, and painful urination.

? Exercise 17.2.1.4

1. What conditions can result from infections affecting the urinary system?
2. What are some common causes of vaginitis in women?

General Causes and Modes of Transmission of Urogenital Infections

Hormonal changes, particularly shifts in estrogen in women due to pregnancy or menopause, can increase susceptibility to urogenital infections. As discussed earlier, estrogen plays an important role in regulating the availability of glycogen and subsequent production of lactic acid by *Lactobacillus* species. Low levels of estrogen are associated with an increased vaginal pH and an increased risk of bacterial vaginosis and yeast infections. Estrogen also plays a role in maintaining the elasticity, strength, and thickness of the vaginal wall, and keeps the vaginal wall lubricated, reducing dryness. Low levels of estrogen are associated with thinning of the vaginal wall. This thinning increases the risk of tears and abrasions, which compromise the protective barrier and increase susceptibility to pathogens.

Another common cause of urogenital infections in females is fecal contamination that occurs because of the close proximity of the anus and the urethra. *Escherichia coli*, an important member of the digestive tract microbiota, is the most common cause of urinary tract infections (urethritis and cystitis) in women; it generally causes infection when it is introduced to the urethra in fecal matter. Good hygiene can reduce the risk of urinary tract infections by this route. In men, urinary tract infections are more commonly associated with other conditions, such as an enlarged prostate, kidney stones, or placement of a urinary catheter. All of these conditions impair the normal emptying of the bladder, which serves to flush out microbes capable of causing infection.

Infections that are transmitted between individuals through sexual contact are called sexually transmitted infections(STIs) or sexually transmitted diseases (STDs). (The CDC prefers the term STD, but WHO prefers STI,[1] which encompasses infections that result in disease as well as those that are subclinical or asymptomatic.) STIs often affect the external genitalia and skin, where microbes are easily transferred through physical contact. Lymph nodes in the genital region may also become swollen as a result of infection. However, many STIs have systemic effects as well, causing symptoms that range from mild (e.g., general malaise) to severe (e.g., liver damage or serious immunosuppression).

? Exercise 17.2.1.5

1. What role does *Lactobacillus* play in the health of the female reproductive system?
2. Why do urinary tract infections have different causes in males and females?

Key Concepts and Summary

- The urinary system is responsible for filtering the blood, excreting wastes, and helping to regulate electrolyte and water balance.
- The urinary system includes the **kidneys, ureters**, **urinary bladder**, and **urethra**; the bladder and urethra are the most common sites of infection.
- Common sites of infection in the male reproductive system include the urethra, as well as the testes, **prostate** and **epididymis**.
- The most common sites of infection in the female reproductive system are the **vulva, vagina**, **cervix,** and **fallopian tubes**.
- Infections of the urogenital tract can occur through colonization from the external environment, alterations in microbiota due to hormonal or other physiological and environmental changes, fecal contamination, and sexual transmission (STIs).

Footnotes

1. 1 World Health Organization. “Guidelines for the Management of Sexually Transmitted Infections.” World Health Organization, 2003. http://www.who.int/hiv/pub/sti/en/ST...elines2003.pdf.

This page titled 17.2.1: Anatomy and Normal Microbiota of the Urogenital Tract is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **23.1: Anatomy and Normal Microbiota of the Urogenital Tract** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

17.2.2: Bacterial Infections of the Urinary System

Learning Objectives

- Identify the most common bacterial pathogens that can cause urinary tract infections
- Compare the major characteristics of specific bacterial diseases affecting the urinary tract

Urinary tract infections (UTIs) include infections of the urethra, bladder, and kidneys, and are common causes of urethritis, cystitis, pyelonephritis, and glomerulonephritis. Bacteria are the most common causes of UTIs, especially in the urethra and bladder.

Cystitis

Cystitis is most often caused by a bacterial infection of the bladder, but it can also occur as a reaction to certain treatments or irritants such as radiation treatment, hygiene sprays, or spermicides. Common symptoms of cystitis include dysuria (urination accompanied by burning, discomfort, or pain), pyuria (pus in the urine), hematuria (blood in the urine), and bladder pain.

In women, bladder infections are more common because the urethra is short and located in close proximity to the anus, which can result in infections of the urinary tract by fecal bacteria. Bladder infections are also more common in the elderly because the bladder may not empty fully, causing urine to pool; the elderly may also have weaker immune systems that make them more vulnerable to infection. Conditions such as prostatitis in men or kidney stones in both men and women can impact proper drainage of urine and increase risk of bladder infections. Catheterization can also increase the risk of bladder infection (see Case in Point: Cystitis in the Elderly).

Gram-negative bacteria such as *Escherichia coli* (most commonly), *Proteus vulgaris*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* cause most bladder infections. Gram-positive pathogens associated with cystitis include the coagulase-negative *Staphylococcus saprophyticus*, *Enterococcus faecalis*, and *Streptococcus agalactiae*. Routine manual urinalysis using a urine dipstick or test strip can be used for rapid screening of infection. These test strips (Figure **17.2.2.1**) are either held in a urine stream or dipped in a sample of urine to test for the presence of nitrites, leukocyte esterase, protein, or blood that can indicate an active bacterial infection. The presence of nitrite may indicate the presence of *E. coli* or *K. pneumonia;* these bacteria produce nitrate reductase, which converts nitrate to nitrite. The leukocyte esterase (LE) test detects the presence of neutrophils as an indication of active infection.

Low specificity, sensitivity, or both, associated with these rapid screening tests require that care be taken in interpretation of results and in their use in diagnosis of urinary tract infections. Therefore, positive LE or nitrite results are followed by a urine culture to confirm a bladder infection. Urine culture is generally accomplished using blood agar and MacConkey agar, and it is important to culture a clean catch of urine to minimize contamination with normal microbiota of the penis and vagina. A clean catch of urine is accomplished by first washing the labia and urethral opening of female patients or the penis of male patients. The patient then releases a small amount of urine into the toilet bowl before stopping the flow of urine. Finally, the patient resumes urination, this time filling the container used to collect the specimen.

Bacterial cystitis is commonly treated with fluoroquinolones, nitrofurantoin, cephalosporins, or a combination of trimethoprim and sulfamethoxazole. Pain medications may provide relief for patients with dysuria. Treatment is more difficult in elderly patients, who experience a higher rate of complications such as sepsis and kidney infections.



Figure 17.2.2.1: A urine dipstick is compared against a color key to determine levels of various chemicals, proteins, or cells in the urine. Abnormal levels may indicate an infection. (credit: modification of work by Suzanne Wakim)

Case in Point: Cystitis in the Elderly

Robert, an 81-year-old widower with early onset Alzheimer's, was recently moved to a nursing home because he was having difficulty living on his own. Within a few weeks of his arrival, he developed a fever and began to experience pain associated with urination. He also began having episodes of confusion and delirium. The doctor assigned to examine Robert read his file and noticed that Robert was treated for prostatitis several years earlier. When he asked Robert how often he had been urinating, Robert explained that he had been trying not to drink too much so that he didn't have to walk to the restroom.

All of this evidence suggests that Robert likely has a urinary tract infection. Robert's age means that his immune system has probably begun to weaken, and his previous prostate condition may be making it difficult for him to empty his bladder. In addition, Robert's avoidance of fluids has led to dehydration and infrequent urination, which may have allowed an infection to establish itself in his urinary tract. The fever and dysuria are common signs of a UTI in patients of all ages, and UTIs in elderly patients are often accompanied by a notable decline in mental function.

Physical challenges often discourage elderly individuals from urinating as frequently as they would otherwise. In addition, neurological conditions that disproportionately affect the elderly (e.g., Alzheimer's and Parkinson's disease) may also reduce their ability to empty their bladders. Robert's doctor noted that he was having difficulty navigating his new home and recommended that he be given more assistance and that his fluid intake be monitored. The doctor also took a urine sample and ordered a laboratory culture to confirm the identity of the causative agent.

Exercise 17.2.2.1

1. Why is it important to identify the causative agent in a UTI?
2. Should the doctor prescribe a broad-spectrum or narrow-spectrum antibiotic to treat Robert's UTI? Why?

Kidney Infections (Pyelonephritis and Glomerulonephritis)

Pyelonephritis, an inflammation of the kidney, can be caused by bacteria that have spread from other parts of the urinary tract (such as the bladder). In addition, pyelonephritis can develop from bacteria that travel through the bloodstream to the kidney. When the

infection spreads from the lower urinary tract, the causative agents are typically fecal bacteria such as *E. coli*. Common signs and symptoms include back pain (due to the location of the kidneys), fever, and nausea or vomiting. Gross hematuria (visible blood in the urine) occurs in 30–40% of women but is rare in men.[1] The infection can become serious, potentially leading to bacteremia and systemic effects that can become life-threatening. Scarring of the kidney can occur and persist after the infection has cleared, which may lead to dysfunction.

Diagnosis of pyelonephritis is made using microscopic examination of urine, culture of urine, testing for leukocyte esterase and nitrite levels, and examination of the urine for blood or protein. It is also important to use blood cultures to evaluate the spread of the pathogen into the bloodstream. Imaging of the kidneys may be performed in high-risk patients with diabetes or immunosuppression, the elderly, patients with previous renal damage, or to rule out an obstruction in the kidney. Pyelonephritis can be treated with either oral or intravenous antibiotics, including penicillins, cephalosporins, vancomycin, fluoroquinolones, carbapenems, and aminoglycosides.

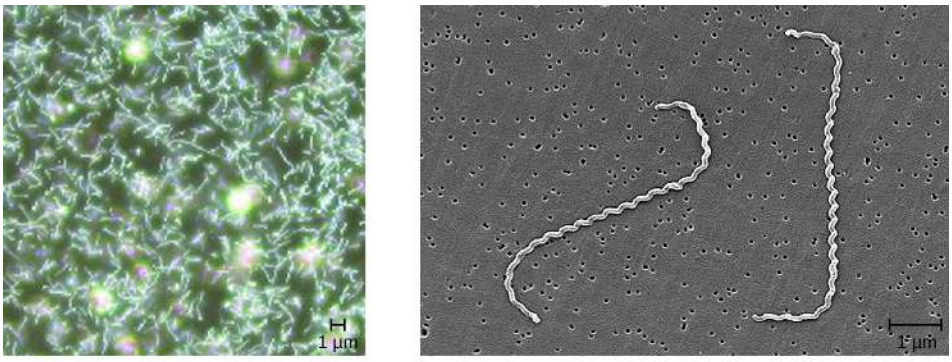
Glomerulonephritis occurs when the glomeruli of the nephrons are damaged from inflammation. Whereas pyelonephritis is usually acute, glomerulonephritis may be acute or chronic. The most well-characterized mechanism of glomerulonephritis is the post-streptococcal sequelae associated with *Streptococcus pyogenes* throat and skin infections. Although *S. pyogenes* does not directly infect the glomeruli of the kidney, immune complexes that form in blood between *S. pyogenes* antigens and antibodies lodge in the capillary endothelial cell junctions of the glomeruli and trigger a damaging inflammatory response. Glomerulonephritis can also occur in patients with bacterial endocarditis(infection and inflammation of heart tissue); however, it is currently unknown whether glomerulonephritis associated with endocarditis is also immune-mediated.

Leptospirosis

Leptospira are generally harmless spirochetes that are commonly found in the soil. However, some pathogenic species can cause an infection called leptospirosis in the kidneys and other organs (Figure **17.2.2.2**). Leptospirosis can produce fever, headache, chills, vomiting, diarrhea, and rash with severe muscular pain. If the disease continues to progress, infection of the kidney, meninges, or liver may occur and may lead to organ failure or meningitis. When the kidney and liver become seriously infected, it is called Weil's disease. Pulmonary hemorrhagic syndrome can also develop in the lungs, and jaundice may occur.

Leptospira spp. are found widely in animals such as dogs, horses, cattle, pigs, and rodents, and are excreted in their urine. Humans generally become infected by coming in contact with contaminated soil or water, often while swimming or during flooding; infection can also occur through contact with body fluids containing the bacteria. The bacteria may enter the body through mucous membranes, skin injuries, or by ingestion. The mechanism of pathogenicity is not well understood.

Leptospirosis is extremely rare in the United States, although it is endemic in Hawaii; 50% of all cases in the United States come from Hawaii.[2] It is more common in tropical than in temperate climates, and individuals who work with animals or animal products are most at risk. The bacteria can also be cultivated in specialized media, with growth observed in broth in a few days to four weeks; however, diagnosis of leptospirosis is generally made using faster methods, such as detection of antibodies to *Leptospira* spp. in patient samples using serologic testing. Polymerase chain reaction (PCR), enzyme-linked immunosorbent assay (ELISA), slide agglutination, and indirect immunofluorescence tests may all be used for diagnosis. Treatment for leptospirosis involves broad-spectrum antibiotics such as penicillin and doxycycline. For more serious cases of leptospirosis, antibiotics may be given intravenously.



(a) (b)

Figure 17.2.2.2: (a) Dark field view of *Leptospira* sp. (b) A scanning electron micrograph of *Leptospira interrogans*, a pathogenic species, shows the distinctive spirochete morphology of this genus. (credit b: modification of work by Janice Carr, Centers for Disease Control and Prevention)

? Exercise 17.2.2.2

- What is the most common cause of a kidney infection?
- What are the most common symptoms of a kidney infection?

Nongonococcal Urethritis (NGU)

There are two main categories of bacterial urethritis: gonorrheal and nongonococcal. Gonorrheal urethritis is caused by *Neisseria gonorrhoeae* and is associated with gonorrhea, a common STI. This cause of urethritis will be discussed in Bacterial Infections of the Reproductive System. The term nongonococcal urethritis (NGU) refers to inflammation of the urethra that is unrelated to *N. gonorrhoeae*. In women, NGU is often asymptomatic. In men, NGU is typically a mild disease, but can lead to purulent discharge and dysuria. Because the symptoms are often mild or nonexistent, most infected individuals do not know that they are infected, yet they are carriers of the disease. Asymptomatic patients also have no reason to seek treatment, and although not common, untreated NGU can spread to the reproductive organs, causing pelvic inflammatory disease and salpingitis in women and epididymitis and prostatitis in men. Important bacterial pathogens that cause nongonococcal urethritis include *Chlamydia trachomatis*, *Mycoplasma genitalium*, *Ureaplasma urealyticum*, and *Mycoplasma hominis*.

C. trachomatis is a difficult-to-stain, gram-negative bacterium with an ovoid shape. An intracellular pathogen, *C. trachomatis* causes the most frequently reported STI in the United States, chlamydia. Although most persons infected with *C. trachomatis* are asymptomatic, some patients can present with NGU. *C. trachomatis* can also cause non-urogenital infections such as the ocular disease trachoma (see Bacterial Infections of the Skin and Eyes). The life cycle of *C. trachomatis* is illustrated in Figure 4.2.2.

C. trachomatis has multiple possible virulence factors that are currently being studied to evaluate their roles in causing disease. These include polymorphic outer-membrane autotransporter proteins, stress response proteins, and type III secretion effectors. The type III secretion effectors have been identified in gram-negative pathogens, including *C. trachomatis*. This virulence factor is an assembly of more than 20 proteins that form what is called an injectisome for the transfer of other effector proteins that target the infected host cells. The outer-membrane autotransporter proteins are also an effective mechanism of delivering virulence factors involved in colonization, disease progression, and immune system evasion.

Other species associated with NGU include *Mycoplasma genitalium*, *Ureaplasma urealyticum*, and *Mycoplasma hominis*. These bacteria are commonly found in the normal microbiota of healthy individuals, who may acquire them during birth or through sexual contact, but they can sometimes cause infections leading to urethritis (in males and females) or vaginitis and cervicitis (in females).

M. genitalium is a more common cause of urethritis in most settings than *N. gonorrhoeae*, although it is less common than *C. trachomatis*. It is responsible for approximately 30% of recurrent or persistent infections, 20–25% of nonchlamydial NGU cases, and 15%–20% of NGU cases. *M. genitalium* attaches to epithelial cells and has substantial antigenic variation that helps it evade host immune responses. It has lipid-associated membrane proteins that are involved in causing inflammation.

Several possible virulence factors have been implicated in the pathogenesis of *U. urealyticum* (Figure 17.2.2.3). These include the ureaplasma proteins phospholipase A, phospholipase C, multiple banded antigen (MBA), urease, and immunoglobulin α protease.

The phospholipases are virulence factors that damage the cytoplasmic membrane of target cells. The immunoglobulin α protease is an important defense against antibodies. It can generate hydrogen peroxide, which may adversely affect host cell membranes through the production of reactive oxygen species.

Treatments differ for gonorrheal and nongonococcal urethritis. However, *N. gonorrhoeae* and *C. trachomatis* are often simultaneously present, which is an important consideration for treatment. NGU is most commonly treated using tetracyclines (such as doxycycline) and azithromycin; erythromycin is an alternative option. Tetracyclines and fluoroquinolones are most commonly used to treat *U. urealyticum*, but resistance to tetracyclines is becoming an increasing problem.[3] While tetracyclines have been the treatment of choice for *M. hominis*, increasing resistance means that other options must be used. Clindamycin and fluoroquinolones are alternatives. *M. genitalium* is generally susceptible to doxycycline, azithromycin, and moxifloxacin. Like other mycoplasma, *M. genitalium* does not have a cell wall and therefore β-lactams (including penicillins and cephalosporins) are not effective treatments.

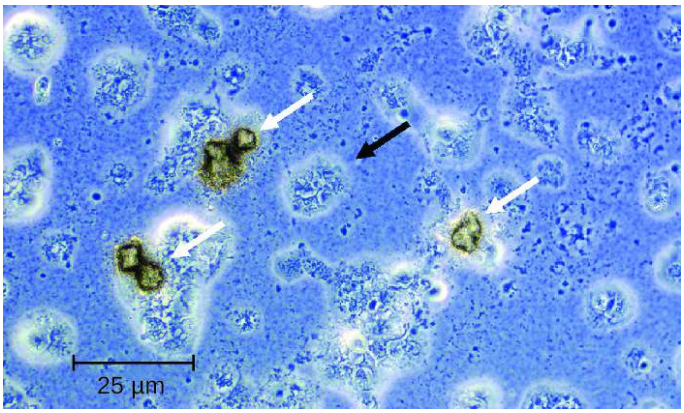


Figure **17.2.2.3**: Ureaplasma urealyticum microcolonies (white arrows) on agar surface after anaerobic incubation, visualized using phase contrast microscopy (800×). The black arrow indicates cellular debris. (credit: modification of work by American Society for Microbiology)

? Exercise 17.2.2.3

1. What are the three most common causes of urethritis?
2. What three members of the normal microbiota can cause urethritis?

Bacterial Infections of the Urinary Tract

Urinary tract infections can cause inflammation of the urethra (urethritis), bladder (cystitis), and kidneys (pyelonephritis), and can sometimes spread to other body systems through the bloodstream. Figure **17.2.2.4** captures the most important features of various types of UTIs.

Bacterial Infections of the Urinary Tract					
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Diagnostic Tests**	**Antimicrobial Drugs**
Cystitis	*Escherichia coli, Enterococcus faecalis, Streptococcus agalactiae, Klebsiella pneumoniae, Staphylococcus saprophyticus,* others	Dysuria, pyuria, hematuria, and bladder pain; most common in females due to the shorter urethra and abundant normal vaginal microbiota	Nontransmisible; opportunistic infections occur when fecal bacteria are introduced to urinary tract or when normal urination or immune function is impaired	Urine dipstick, urine culture for confirmation	Fluoroquinolones, nitrofurantoin, cephalosprins, trimethoprim, sulfamethoxazole
Leptospirosis	*Leptospira* spp.	Fever, headache, chills, vomiting, diarrhea, rash, muscular pain; in disseminated infections, may cause jaundice, pulmonary hemorrhaging, meningitis	From animals to humans via contact with urine or body fluids	PCR, ELISA, slide agglutination, indirect immunofluorescence	Doxycycline, amoxicillin, ampicillin, erythromycin, penicillin
Nongonococcal urethritis (NGU)	*Chlamydia trachomatis, Mycoplasma genitalium, Mycoplasma hominis, Ureaplasma urealyticum*	Mild or asymptomatic; may cause purulent discharge and dysuria	Transmitted sexually or from mother to neonate during birth	Urethral swabs and urine culture, PCR, NAAT	Azithromycin, doxycycline, erythromycin, fluoroquinolones
Pyelonephritis, glomerulonephritis	*E. coli, Proteus* spp., *Klebsiella* spp., *Streptococcus pyogenes,* others	Back pain, fever, nausea, vomiting, blood in urine; possible scarring of the kidneys and impaired kidney function; severe infections may lead to sepsis and death	Nontransmissible; infection spreads to kidneys from urinary tract or through bloodstream	Urinalysis, urine culture, radioimaging of kidneys	Penicillins, cephalosprins, fluoroquinolones, aminoglycosides, others

Figure 17.2.2.4: Bacterial infections of the Urinary tract.

Key Concepts and Summary

- Bacterial **cystitis** is commonly caused by fecal bacteria such as *E. coli.*
- Pyelonephritis is a serious kidney infection that is often caused by bacteria that travel from infections elsewhere in the urinary tract and may cause systemic complications.
- **Leptospirosis** is a bacterial infection of the kidney that can be transmitted by exposure to infected animal urine, especially in contaminated water. It is more common in tropical than in temperate climates.
- **Nongonococcal urethritis (NGU)** is commonly caused by *C. trachomatis*, *M. genitalium*, *Ureaplasma urealyticum*, and *M. hominis.*
- Diagnosis and treatment for bacterial urinary tract infections varies. Urinalysis (e.g., for leukocyte esterase levels, nitrite levels, microscopic evaluation, and culture of urine) is an important component in most cases. Broad-spectrum antibiotics are typically used.

Footnotes

1. 1 Tibor Fulop. “Acute Pyelonephritis” *Medscape*, 2015. http://emedicine.medscape.com/article/245559-overview.
2. 2 Centers for Disease Control and Prevention. “Leptospirosis.” 2015. http://www.cdc.gov/leptospirosis/health_care_workers.
3. 3 Ken B Waites. “Ureaplasma Infection Medication.” *Medscape*, 2015. emedicine.medscape.com/articl...470-medication.

This page titled 17.2.2: Bacterial Infections of the Urinary System is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **23.2: Bacterial Infections of the Urinary System** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

17.2.3: Bacterial Infections of the Reproductive System

Learning Objectives

- Identify the most common bacterial pathogens that can cause infections of the reproductive system
- Compare the major characteristics of specific bacterial diseases affecting the reproductive system

In addition to infections of the urinary tract, bacteria commonly infect the reproductive tract. As with the urinary tract, parts of the reproductive system closest to the external environment are the most likely sites of infection. Often, the same microbes are capable of causing urinary tract and reproductive tract infections.

Bacterial Vaginitis and Vaginosis

Inflammation of the vagina is called vaginitis, often caused by a bacterial infection. It is also possible to have an imbalance in the normal vaginal microbiota without inflammation called bacterial vaginosis (BV). Vaginosis may be asymptomatic or may cause mild symptoms such as a thin, white-to-yellow, homogeneous vaginal discharge, burning, odor, and itching. The major causative agent is *Gardnerella vaginalis*, a gram-variable to gram-negative pleomorphic bacterium. Other causative agents include anaerobic species such as members of the genera *Bacteroides* and *Fusobacterium*. Additionally, ureaplasma and mycoplasma may be involved. The disease is usually self-limiting, although antibiotic treatment is recommended if symptoms develop.

G. vaginalis appears to be more virulent than other vaginal bacterial species potentially associated with BV. Like *Lactobacillus* spp., *G. vaginalis* is part of the normal vaginal microbiota, but when the population of *Lactobacillus* spp. decreases and the vaginal pH increases, *G. vaginalis* flourishes, causing vaginosis by attaching to vaginal epithelial cells and forming a thick protective biofilm. *G. vaginalis* also produces a cytotoxin called vaginolysin that lyses vaginal epithelial cells and red blood cells.Since *G. vaginalis* can also be isolated from healthy women, the “gold standard” for the diagnosis of BV is direct examination of vaginal secretions and not the culture of *G. vaginalis*. Diagnosis of bacterial vaginosis from vaginal secretions can be accurately made in three ways. The first is to use a DNA probe. The second method is to assay for sialidase activity (sialidase is an enzyme produced by *G. vaginalis* and other bacteria associated with vaginosis, including *Bacteroides* spp., *Prevotella* spp., and *Mobiluncus* spp.). The third method is to assess gram-stained vaginal smears for microscopic morphology and relative numbers and types of bacteria, squamous epithelial cells, and leukocytes. By examining slides prepared from vaginal swabs, it is possible to distinguish lactobacilli (long, gram-positive rods) from other gram-negative species responsible for BV. A shift in predominance from gram-positive bacilli to gram-negative coccobacilli can indicate BV. Additionally, the slide may contain so-called clue cells, which are epithelial cells that appear to have a granular or stippled appearance due to bacterial cells attached to their surface (Figure 17.2.3.1).

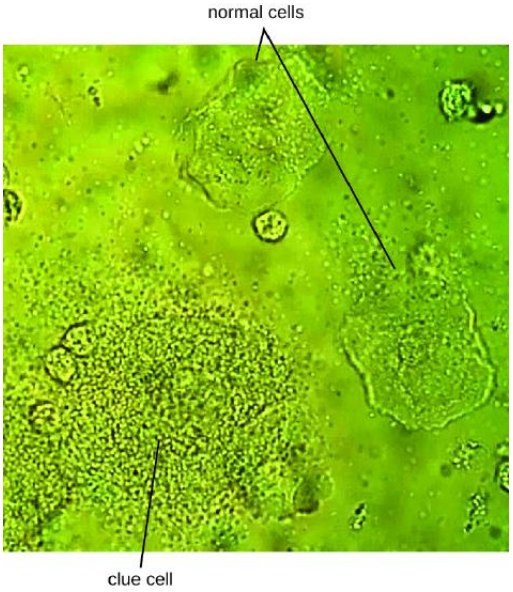


Figure 17.2.3.1: In this vaginal smear, the cell at the lower left is a clue cell with a unique appearance caused by the presence of bacteria on the cell. The cell on the right is a normal cell.

Presumptive diagnosis of bacterial vaginosis can involve an assessment of clinical symptoms and evaluation of vaginal fluids using Amsel's diagnostic criteria which include 3 out of 4 of the following characteristics:

1. white to yellow discharge;
2. a fishy odor, most noticeable when 10% KOH is added;
3. pH greater than 4.5;
4. the presence of clue cells.

Treatment is often unnecessary because the infection often clears on its own. However, in some cases, antibiotics such as topical or oral clindamycin or metronidazole may be prescribed. Alternative treatments include oral tinidazole or clindamycin ovules (vaginal suppositories).

Exercise 17.2.3.1

1. Explain the difference between vaginosis and vaginitis.
2. What organisms are responsible for vaginosis and what organisms typically hold it at bay?

Clinical Focus: Part 2

There is no catch-all test for STIs, so several tests, in addition to a physical exam, are necessary to diagnose an infection. Nadia tries to relax in the exam room while she waits for the doctor to return, but she is nervous about the results.

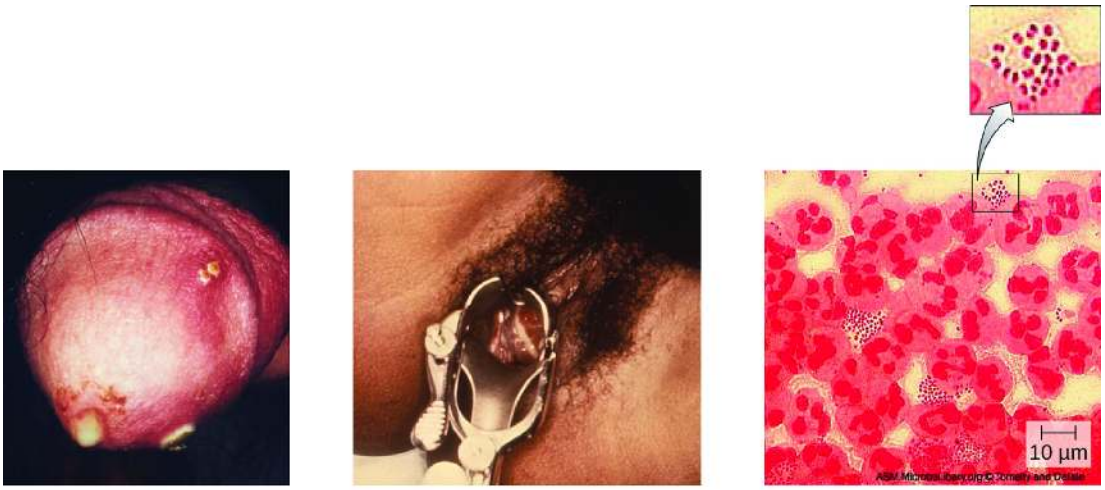
When the doctor finally returns, she has some unexpected news: Nadia is pregnant. Surprised and excited, Nadia wants to know if the pregnancy explains her unusual symptoms. The doctor explains that the irritation that Nadia is experiencing is vaginitis, which can be caused by several types of microorganisms. One possibility is bacterial vaginosis, which develops when there is an imbalance in the bacteria in the vagina, as often occurs during pregnancy. Vaginosis can increase the risk of preterm birth and low birth weight, and a few studies have also shown that it can cause second-trimester miscarriage; however, the condition can be treated. To check for it, the doctor has asked the lab to perform a Gram stain on Nadia's sample.

Exercise 17.2.3.2

- What result would you expect from the Gram stain if Nadia has bacterial vaginosis?
- What is the relationship between pregnancy, estrogen levels, and development of bacterial vaginosis?

Gonorrhea

Also known as the clap, gonorrhea is a common sexually transmitted disease of the reproductive system that is especially prevalent in individuals between the ages of 15 and 24. It is caused by *Neisseria gonorrhoeae*, often called gonococcus or GC, which have fimbriae that allow the cells to attach to epithelial cells. It also has a type of lipopolysaccharide endotoxin called lipooligosaccharide as part of the outer membrane structure that enhances its pathogenicity. In addition to causing urethritis, *N. gonorrhoeae* can infect other body tissues such as the skin, meninges, pharynx, and conjunctiva.



(a) (b) (c)

Figure 17.2.3.2: (a) Clinical photograph of gonococcal discharge from penis. The lesions on the skin could indicate co-infection with another STI. (b) Purulent discharge originating from the cervix and accumulating in the vagina of a patient with gonorrhea. (c) A micrograph of urethral discharge shows gram-negative diplococci (paired cells) both inside and outside the leukocytes (large cells with lobed nuclei). These results could be used to diagnose gonorrhea in a male patient, but female vaginal samples may contain other *Neisseria* spp. even if the patient is not infected with *N. gonorrhoeae*. (credit a, b: modification of work by Centers for Disease Control and Prevention; credit c: modification of work by American Society for Microbiology)

Many infected individuals (both men and women) are asymptomatic carriers of gonorrhea. When symptoms do occur, they manifest differently in males and females. Males may develop pain and burning during urination and discharge from the penis that may be yellow, green, or white (Figure 17.2.3.2). Less commonly, the testicles may become swollen or tender. Over time, these symptoms can increase and spread. In some cases, chronic infection develops. The disease can also develop in the rectum, causing symptoms such as discharge, soreness, bleeding, itching, and pain (especially in association with bowel movements).

Women may develop pelvic pain, discharge from the vagina, intermenstrual bleeding (i.e., bleeding not associated with normal menstruation), and pain or irritation associated with urination. As with men, the infection can become chronic. In women, however, chronic infection can cause increases in menstrual flow. Rectal infection can also occur, with the symptoms previously described for men. Infections that spread to the endometrium and fallopian tubes can cause pelvic inflammatory disease (PID), characterized by pain in the lower abdominal region, dysuria, vaginal discharge, and fever. PID can also lead to infertility through scarring and blockage of the fallopian tubes (salpingitis); it may also increase the risk of a life-threatening ectopic pregnancy, which occurs when a fertilized egg begins developing somewhere other than the uterus (e.g., in the fallopian tube or ovary).

When a gonorrhea infection disseminates throughout the body, serious complications can develop. The infection may spread through the blood (bacteremia) and affect organs throughout the body, including the heart (gonorrheal endocarditis), joints (gonorrheal arthritis), and meninges encasing the brain (meningitis).

Urethritis caused by *N. gonorrhoeae* can be difficult to treat due to antibiotic resistance (see Micro Connections below). Some strains have developed resistance to the fluoroquinolones, so cephalosporins are often a first choice for treatment. Because co-infection with *C. trachomatis* is common, the CDC recommends treating with a combination regimen of ceftriaxone and azithromycin. Treatment of sexual partners is also recommended to avoid reinfection and spread of infection to others.[1]

? Exercise 17.2.3.3

1. What are some of the serious consequences of a gonorrhea infection?
2. What organism commonly coinfects with *N. gonorrhoeae*?

Antibiotic Resistance in *Neisseria*

Antibiotic resistance in many pathogens is steadily increasing, causing serious concern throughout the public health community. Increased resistance has been especially notable in some species, such as *Neisseria gonorrhoeae*. The CDC

monitors the spread of antibiotic resistance in *N. gonorrhoeae*, which it classifies as an urgent threat, and makes recommendations for treatment. So far, *N. gonorrhoeae* has shown resistance to cefixime (a cephalosporin), ceftriaxone (another cephalosporin), azithromycin, and tetracycline. Resistance to tetracycline is the most common, and was seen in 188,600 cases of gonorrhea in 2011 (out of a total 820,000 cases). In 2011, some 246,000 cases of gonorrhea involved strains of *N. gonorrhoeae* that were resistant to at least one antibiotic.[2] These resistance genes are spread by plasmids, and a single bacterium may be resistant to multiple antibiotics. The CDC currently recommends treatment with two medications, ceftriaxone and azithromycin, to attempt to slow the spread of resistance. If resistance to cephalosporins increases, it will be extremely difficult to control the spread of *N. gonorrhoeae*.

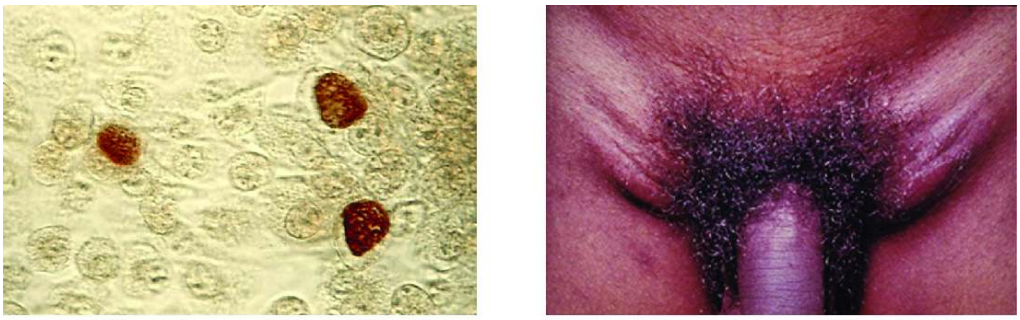
Chlamydia

Chlamydia trachomatis is the causative agent of the STI chlamydia (Figure **17.2.3.3**). While many *Chlamydia* infections are asymptomatic, chlamydia is a major cause of nongonococcal urethritis (NGU) and may also cause epididymitis and orchitis in men. In women, chlamydia infections can cause urethritis, salpingitis, and PID. In addition, chlamydial infections may be associated with an increased risk of cervical cancer.

Because chlamydia is widespread, often asymptomatic, and has the potential to cause substantial complications, routine screening is recommended for sexually active women who are under age 25, at high risk (i.e., not in a monogamous relationship), or beginning prenatal care.

Certain serovars of *C. trachomatis* can cause an infection of the lymphatic system in the groin known as lymphogranuloma venereum. This condition is commonly found in tropical regions and can also co-occur in conjunction with human immunodeficiency virus (HIV) infection. After the microbes invade the lymphatic system, buboes (large lymph nodes, see Figure **17.2.3.3**) form and can burst, releasing pus through the skin. The male genitals can become greatly enlarged and in women the rectum may become narrow.

Urogenital infections caused by *C. trachomatis* can be treated using azithromycin or doxycycline (the recommended regimen from the CDC). Erythromycin, levofloxacin, and ofloxacin are alternatives.



(a) (b)

Figure **17.2.3.3**: (a) *Chlamydia trachomatis* inclusion bodies within McCoy cell monolayers. Inclusion bodies are distinguished by their brown color. (b) Lymphogranuloma venereum infection can cause swollen lymph nodes in the groin called buboes. (credit a: modification of work by Centers for Disease Control and Prevention; credit b: modification of work by Herbert L. Fred and Hendrik A. van Dijk)

? Exercise 17.2.3.4

Compare the signs and symptoms of chlamydia infection in men and women.

Syphilis

Syphilis is spread through direct physical (generally sexual) contact, and is caused by the gram-negative spirochete *Treponema pallidum*. *T. pallidum* has a relatively simple genome and lacks lipopolysaccharide endotoxin characteristic of gram-negative bacteria. However, it does contain lipoproteins that trigger an immune response in the host, causing tissue damage that may enhance the pathogen's ability to disseminate while evading the host immune system.

After entering the body, *T. pallidum* moves rapidly into the bloodstream and other tissues. If not treated effectively, syphilis progresses through three distinct stages: primary, secondary, and tertiary. Primary syphilis appears as a single lesion on the cervix, penis, or anus within 10 to 90 days of transmission. Such lesions contain many *T. pallidum* cells and are highly infectious. The lesion, called a hard chancre, is initially hard and painless, but it soon develops into an ulcerated sore (Figure **17.2.3.4**). Localized lymph node swelling may occur as well. In some cases, these symptoms may be relatively mild, and the lesion may heal on its own within two to six weeks. Because the lesions are painless and often occur in hidden locations (e.g., the cervix or anus), infected individuals sometimes do not notice them.

The secondary stage generally develops once the primary chancre has healed or begun to heal. Secondary syphilis is characterized by a rash that affects the skin and mucous membranes of the mouth, vagina, or anus. The rash often begins on the palms or the soles of the feet and spreads to the trunk and the limbs (Figure **17.2.3.4**). The rash may take many forms, such as macular or papular. On mucous membranes, it may manifest as mucus patches or white, wartlike lesions called condylomata lata. The rash may be accompanied by malaise, fever, and swelling of lymph nodes. Individuals are highly contagious in the secondary stage, which lasts two to six weeks and is recurrent in about 25% of cases.

After the secondary phase, syphilis can enter a latent phase, in which there are no symptoms but microbial levels remain high. Blood tests can still detect the disease during latency. The latent phase can persist for years.

Tertiary syphilis, which may occur 10 to 20 years after infection, produces the most severe symptoms and can be fatal. Granulomatous lesions called gummas may develop in a variety of locations, including mucous membranes, bones, and internal organs (Figure **17.2.3.4**). Gummas can be large and destructive, potentially causing massive tissue damage. The most deadly lesions are those of the cardiovascular system (cardiovascular syphilis) and the central nervous system (neurosyphilis). Cardiovascular syphilis can result in a fatal aortic aneurysm (rupture of the aorta) or coronary stenosis (a blockage of the coronary artery). Damage to the central nervous system can cause dementia, personality changes, seizures, general paralysis, speech impairment, loss of vision and hearing, and loss of bowel and bladder control.



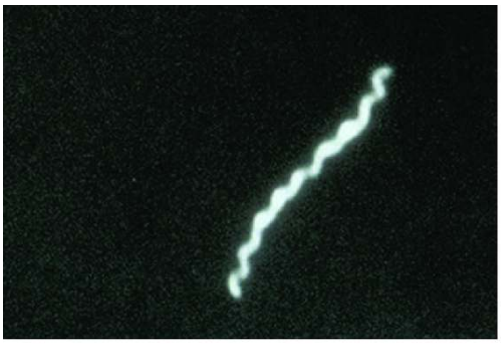
(a) (b) (c)

Figure **17.2.3.4**: (a) This ulcerated sore is a hard chancre caused by syphilis. (b) This individual has a secondary syphilis rash on the hands. (c) Tertiary syphilis produces lesions called gummas, such as this one located on the nose. (credit a, b, c: modification of work by Centers for Disease Control and Prevention)

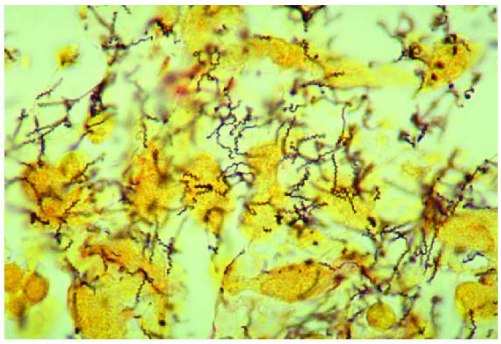
The recommended methods for diagnosing early syphilis are darkfield or brightfield (silver stain) microscopy of tissue or exudate from lesions to detect *T. pallidum* (Figure **17.2.3.5**). If these methods are not available, two types of serologic tests (treponemal and nontreponemal) can be used for a presumptive diagnosis once the spirochete has spread in the body. Nontreponemal serologic tests include the Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin(RPR) tests. These are similar screening tests that detect nonspecific antibodies (those for lipid antigens produced during infection) rather than those produced against the spirochete. Treponemal serologic tests measure antibodies directed against *T. pallidum* antigens using particle agglutination (*T. pallidum* passive particle agglutination or TP-PA), immunofluorescence (the fluorescent *T. pallidum* antibody absorption or FTA-ABS), various enzyme reactions (enzyme immunoassays or EIAs) and chemiluminescence immunoassays (CIA). Confirmatory testing, rather than screening, must be done using treponemal rather than nontreponemal tests because only the former tests for antibodies to spirochete antigens. Both treponemal and nontreponemal tests should be used (as opposed to just one) since both tests have limitations than can result in false positives or false negatives.

Neurosyphilis cannot be diagnosed using a single test. With or without clinical signs, it is generally necessary to assess a variety of factors, including reactive serologic test results, cerebrospinal fluid cell count abnormalities, cerebrospinal fluid protein abnormalities, or reactive VDRL-CSF (the VDRL test of cerebrospinal fluid). The VDRL-CSF is highly specific, but not sufficiently sensitive for conclusive diagnosis.

The recommended treatment for syphilis is parenteral penicillin G (especially long-acting benzathine penicillin, although the exact choice depends on the stage of disease). Other options include tetracycline and doxycycline.



(a)



(b)

Figure 17.2.3.5: (a) Darkfield micrograph of *Treponema pallidum*. (b) Silver stain micrograph of the same species. (credit a, b: modification of work by Centers for Disease Control and Prevention)

Congenital Syphilis

Congenital syphilis is passed by mother to fetus when untreated primary or secondary syphilis is present. In many cases, infection may lead to miscarriage or stillbirth. Children born with congenital syphilis show symptoms of secondary syphilis and may develop mucus patches that deform the nose. In infants, gummas can cause significant tissue damage to organs and teeth. Many other complications may develop, such as osteochondritis, anemia, blindness, bone deformations, neurosyphilis, and cardiovascular lesions. Because congenital syphilis poses such a risk to the fetus, expectant mothers are screened for syphilis infection during the first trimester of pregnancy as part of the TORCH panel of prenatal tests.

? Exercise 17.2.3.5

1. What aspect of tertiary syphilis can lead to death?
2. How do treponemal serologic tests detect an infection?

Chancroid

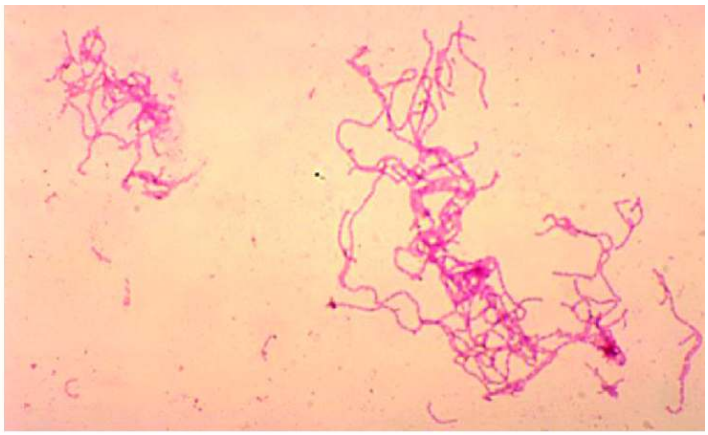
The sexually transmitted infection chancroid is caused by the gram-negative rod *Haemophilus ducreyi*. It is characterized by soft chancres (Figure 17.2.3.6) on the genitals or other areas associated with sexual contact, such as the mouth and anus. Unlike the hard chancres associated with syphilis, soft chancres develop into painful, open sores that may bleed or produce fluid that is highly contagious. In addition to causing chancres, the bacteria can invade the lymph nodes, potentially leading to pus discharge through the skin from lymph nodes in the groin. Like other genital lesions, soft chancres are of particular concern because they compromise the protective barriers of the skin or mucous membranes, making individuals more susceptible to HIV and other sexually transmitted diseases.

Several virulence factors have been associated with *H. ducreyi*, including lipooligosaccharides, protective outer membrane proteins, antiphagocytic proteins, secretory proteins, and collagen-specific adhesin NcaA. The collagen-specific adhesion NcaA plays an important role in initial cellular attachment and colonization. Outer membrane proteins DsrA and DltA have been shown to provide protection from serum-mediated killing by antibodies and complement.

H. ducreyi is difficult to culture; thus, diagnosis is generally based on clinical observation of genital ulcers and tests that rule out other diseases with similar ulcers, such as syphilis and genital herpes. PCR tests for *H. ducreyi* have been developed in some laboratories, but as of 2015 none had been cleared by the US Food and Drug Administration (FDA).[3] Recommended treatments for chancroid include antibiotics such as azithromycin, ciprofloxacin, erythromycin and ceftriaxone. Resistance to ciprofloxacin and erythromycin has been reported.[4]



(a)



(b)

Figure **17.2.3.6**: (a) A soft chancre on the penis of a man with chancroid. (b) Chancroid is caused by the gram-negative bacterium *Haemophilus ducreyi*, seen here in a gram-stained culture of rabbit blood. (credit a, b: modification of work by Centers for Disease Control and Prevention)

? Exercise 17.2.3.6

1. What is the key difference between chancroid lesions and those associated with syphilis?
2. Why is it difficult to definitively diagnose chancroid?

Bacterial Reproductive Tract Infections

Many bacterial infections affecting the reproductive system are transmitted through sexual contact, but some can be transmitted by other means. In the United States, gonorrhea and chlamydia are common illnesses with incidences of about 350,000 and 1.44 million, respectively, in 2014. Syphilis is a rarer disease with an incidence of 20,000 in 2014. Chancroid is exceedingly rare in the United States with only six cases in 2014 and a median of 10 cases per year for the years 2010–2014.[5] Figure **17.2.3.7** summarizes bacterial infections of the reproductive tract.

Bacterial Infections of the Reproductive Tract					
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Diagnostic Tests**	**Antimicrobial Drugs**
Bacterial vaginosis (BV)	*Gardnerella vaginalis*, *Bacteroides* spp., *Fusobacterium* spp., others	Often asymptomatic; vaginal discharge, burning, odor, or itching	Opportunistic infection caused by imbalance of normal vaginal microbiota	Vaginal smear	Clindamycin, metronidazole, tinidazole
Chancroid	*Haemophilus ducreyi*	Soft, painful chancres on genitals, mouth, or anus; swollen lymph nodes; pus discharge	Sexual contact or contact with open lesions or discharge	Observation of clinical symptoms and negative tests for syphilis and herpes	Azithromycin, ceftriaxone, erythromycin, ciprofloxacin
Chlamydia	*Chlamydia trachomatis*	Often asymptomatic; in men, urethritis, epididymitis, orchitis; in women, urethritis, vaginal discharge or bleeding, pelvic inflammatory disease, salpingitis, increased risk of cervical cancer	Sexual contact or from mother to neonate during birth	NAAT, urine sample, vaginal swab, culture	Azithromycin, doxycycline, erythromycin, ofloxacin, or levofloxacin
Gonorrhea	*Neisseria gonorrhoeae*	Urethritis, dysuria, penile or vaginal discharge, rectal pain and bleeding; in females, pelvic pain, intermenstrual bleeding, pelvic inflammatory disease, salpingitis, increased risk of infertility or ectopic pregnancy; in disseminated infections, arthritis, endocarditis, meningitis	Sexual contact	Urine sample or culture, NAAT, PCR, ELISA	Ceftriaxone, azithromycin
Syphilis	*Treponema pallidum*	Primary: hard chancre; Secondary: rash, cutaneous lesions, condylomata, malaise, fever, swollen lymph nodes; Tertiary: gummas, cardiovascular syphilis, neurosyphilis, possibly fatal	Sexual contact or from mother to neonate during birth	Darkfield or brightfield silver stain examination of lesion tissue or exudate, treponemal and non-treponemal serological testing, VDRL-CSF for neurosyphilis, prenatal TORCH panel	Penicillin G, tetracycline, doxycycline

Figure **17.2.3.7**: Bacterial infections of the Reproductive tract.

Key Concepts and Summary

- **Bacterial vaginosis** is caused by an imbalance in the vaginal microbiota, with a decrease in lactobacilli and an increase in vaginal pH. *G. vaginalis* is the most common cause of bacterial vaginosis, which is associated with vaginal discharge, odor, burning, and itching.
- **Gonorrhea** is caused by *N. gonorrhoeae*, which can cause infection of the reproductive and urinary tracts and is associated with symptoms of urethritis. If left untreated, it can progress to epididymitis, salpingitis, and pelvic inflammatory disease and enter the bloodstream to infect other sites in the body.
- **Chlamydia** is the most commonly reported STI and is caused by *C. trachomatis*. Most infections are asymptomatic, and infections that are not treated can spread to involve the epididymis of men and cause salpingitis and pelvic inflammatory disease in women.
- **Syphilis** is caused by *T. pallidum* and has three stages, primary, secondary, and tertiary. Primary syphilis is associated with a painless hard chancre lesion on genitalia. Secondary syphilis is associated with skin and mucous membrane lesions. Tertiary

syphilis is the most serious and life-threatening, and can involve serious nervous system damage.

- **Chancroid** is an infection of the reproductive tract caused by *H. ducreyi* that results in the development of characteristic **soft chancres**.

Footnotes

1. 1 Centers for Disease Control and Prevention. “2015 Sexually Transmitted Diseases Treatment Guidelines: Gonococcal Infections,” 2015. http://www.cdc.gov/std/tg2015/gonorrhea.htm.
2. 2 Centers for Disease Control and Prevention. “Antibiotic Resistance Threats in the United States, 2013,” 2013. http://www.cdc.gov/drugresistance/pd...s-2013-508.pdf.
3. 3 Centers for Disease Control and Prevention. “2015 Sexually Transmitted Diseases Treatment Guidelines: Chancroid,” 2015. http://www.cdc.gov/std/tg2015/chancroid.htm.
4. 4 Ibid.
5. 5 Centers for Disease Control and Prevention. “2014 Sexually Transmitted Disease Surveillance,” 2015. http://www.cdc.gov/std/stats14/default.htm.

This page titled 17.2.3: Bacterial Infections of the Reproductive System is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **23.3: Bacterial Infections of the Reproductive System** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

17.2.4: Viral Infections of the Reproductive System

Learning Objectives

- Identify the most common viruses that cause infections of the reproductive system
- Compare the major characteristics of specific viral diseases affecting the reproductive system

Several viruses can cause serious problems for the human reproductive system. Most of these viral infections are incurable, increasing the risk of persistent sexual transmission. In addition, such viral infections are very common in the United States. For example, human papillomavirus (HPV) is the most common STI in the country, with an estimated prevalence of 79.1 million infections in 2008; herpes simplex virus 2 (HSV-2) is the next most prevalent STI at 24.1 million infections.[1] In this section, we will examine these and other major viral infections of the reproductive system.

Genital Herpes

Genital herpes is a common condition caused by the herpes simplex virus (Figure **17.2.4.1**), an enveloped, double-stranded DNA virus that is classified into two distinct types. Herpes simplex virus has several virulence factors, including infected cell protein (ICP) 34.5, which helps in replication and inhibits the maturation of dendritic cells as a mechanism of avoiding elimination by the immune system. In addition, surface glycoproteins on the viral envelope promote the coating of herpes simplex virus with antibodies and complement factors, allowing the virus to appear as “self” and prevent immune system activation and elimination.

There are two herpes simplex virus types. While herpes simplex virus type 1 (HSV-1) is generally associated with oral lesions like cold sores or fever blisters (see Viral Infections of the Skin and Eyes), herpes simplex virus type 2 (HSV-2)is usually associated with genital herpes. However, both viruses can infect either location as well as other parts of the body. Oral-genital contact can spread either virus from the mouth to the genital region or vice versa.

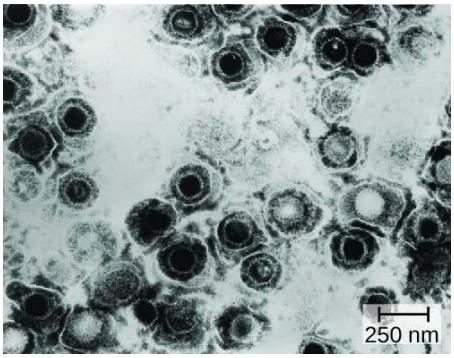


Figure **17.2.4.1**: Virions of the herpes simplex virus are shown here in this transmission electron micrograph. (credit: modification of work by Centers for Disease Control and Prevention)

Many infected individuals do not develop symptoms, and thus do not realize that they carry the virus. However, in some infected individuals, fever, chills, malaise, swollen lymph nodes, and pain precede the development of fluid-filled vesicles that may be irritating and uncomfortable. When these vesicles burst, they release infectious fluid and allow transmission of HSV. In addition, open herpes lesions can increase the risk of spreading or acquiring HIV.

In men, the herpes lesions typically develop on the penis and may be accompanied by a watery discharge. In women, the vesicles develop most commonly on the vulva, but may also develop on the vagina or cervix (Figure **17.2.4.2**). The symptoms are typically mild, although the lesions may be irritating or accompanied by urinary discomfort. Use of condoms may not always be an effective means of preventing transmission of genital herpes since the lesions can occur on areas other than the genitals.

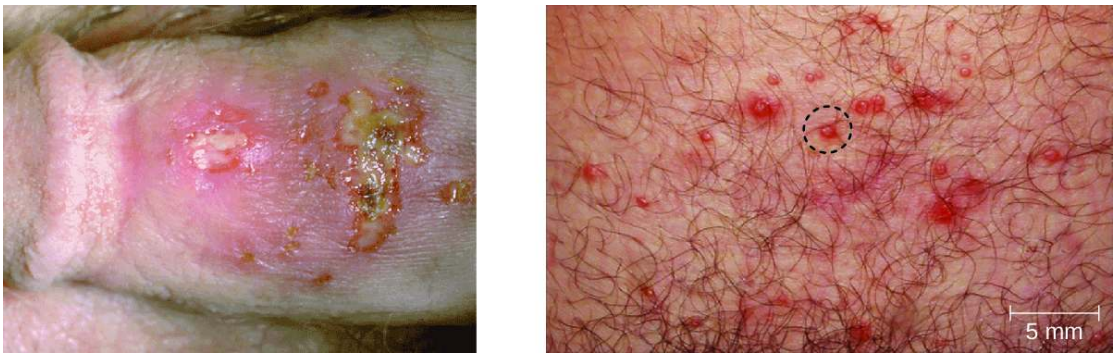


Figure 17.2.4.2: Genital herpes is typically characterized by lesions on the genitals (left), but lesions can also appear elsewhere on the skin or mucous membranes (right). The lesions can be large and painful or small and easily overlooked. (credit b: modification of work by Schiffer JT, Swan D, Al Sallaq R, Magaret A, Johnston C, Mark KE, Selke S, Ocbamichael N, Kuntz S, Zhu J, Robinson B, Huang ML, Jerome KR, Wald A, and Corey)

Herpes simplex viruses can cause recurrent infections because the virus can become latent and then be reactivated. This occurs more commonly with HSV-2 than with HSV-1.[2] The virus moves down peripheral nerves, typically sensory neurons, to ganglia in the spine (either the trigeminal ganglion or the lumbar-sacral ganglia) and becomes latent. Reactivation can later occur, causing the formation of new vesicles. HSV-2 most effectively reactivates from the lumbar-sacral ganglia. Not everyone infected with HSV-2 experiences reactivations, which are typically associated with stressful conditions, and the frequency of reactivation varies throughout life and among individuals. Between outbreaks or when there are no obvious vesicles, the virus can still be transmitted.

Virologic and serologic techniques are used for diagnosis. The virus may be cultured from lesions. The immunostaining methods that are used to detect virus from cultures generally require less expertise than methods based on cytopathic effect (CPE), as well as being a less expensive option. However, PCR or other DNA amplification methods may be preferred because they provide the most rapid results without waiting for culture amplification. PCR is also best for detecting systemic infections. Serologic techniques are also useful in some circumstances, such as when symptoms persist but PCR testing is negative.

While there is no cure or vaccine for HSV-2 infections, antiviral medications are available that manage the infection by keeping the virus in its dormant or latent phase, reducing signs and symptoms. If the medication is discontinued, then the condition returns to its original severity. The recommended medications, which may be taken at the start of an outbreak or daily as a method of prophylaxis, are acyclovir, famciclovir, and valacyclovir.

Neonatal Herpes

Herpes infections in newborns, referred to as neonatal herpes, are generally transmitted from the mother to the neonate during childbirth, when the child is exposed to pathogens in the birth canal. Infections can occur regardless of whether lesions are present in the birth canal. In most cases, the infection of the newborn is limited to skin, mucous membranes, and eyes, and outcomes are good. However, sometimes the virus becomes disseminated and spreads to the central nervous system, resulting in motor function deficits or death.

In some cases, infections can occur before birth when the virus crosses the placenta. This can cause serious complications in fetal development and may result in spontaneous abortion or severe disabilities if the fetus survives. The condition is most serious when the mother is infected with HSV for the first time during pregnancy. Thus, expectant mothers are screened for HSV infection during the first trimester of pregnancy as part of the TORCH panel of prenatal tests (see How Pathogens Cause Disease). Systemic acyclovir treatment is recommended to treat newborns with neonatal herpes.

? Exercise 17.2.4.1

1. Why are latent herpes virus infections still of clinical concern?
2. How is neonatal herpes contracted?

Human Papillomas

Warts of all types are caused by a variety of strains of human papillomavirus (HPV) (see Viral Infections of the Skin and Eyes). Condylomata acuminata, more commonly called genital warts or venereal warts (Figure **17.2.4.3**), are an extremely prevalent STI caused by certain strains of HPV. Condylomata are irregular, soft, pink growths that are found on external genitalia or the anus.



Figure **17.2.4.3**: Genital warts may occur around the anus (left) or genitalia (right). (credit left, right: modification of work by Centers for Disease Control and Prevention)

HPV is a small, non-enveloped virus with a circular double-stranded DNA genome. Researchers have identified over 200 different strains (called types) of HPV, with approximately 40 causing STIs. While some types of HPV cause genital warts, HPV infection is often asymptomatic and self-limiting. However, genital HPV infection often co-occurs with other STIs like syphilis or gonorrhea. Additionally, some forms of HPV (not the same ones associated with genital warts) are associated with cervical cancers. At least 14 oncogenic (cancer-causing) HPV types are known to have a causal association with cervical cancers. Examples of oncogenic HPV are types 16 and 18, which are associated with 70% of cervical cancers.[3] Oncogenic HPV types can also cause oropharyngeal cancer, anal cancer, vaginal cancer, vulvar cancer, and penile cancer. Most of these cancers are caused by HPV type 16. HPV virulence factors include proteins (E6 and E7) that are capable of inactivating tumor suppressor proteins, leading to uncontrolled cell division and the development of cancer.

HPV cannot be cultured, so molecular tests are the primary method used to detect HPV. While routine HPV screening is not recommended for men, it is included in guidelines for women. An initial screening for HPV at age 30, conducted at the same time as a Pap test, is recommended. If the tests are negative, then further HPV testing is recommended every five years. More frequent testing may be needed in some cases. The protocols used to collect, transport, and store samples vary based on both the type of HPV testing and the purpose of the testing. This should be determined in individual cases in consultation with the laboratory that will perform the testing.

Because HPV testing is often conducted concurrently with Pap testing, the most common approach uses a single sample collection within one vial for both. This approach uses liquid-based cytology (LBC). The samples are then used for Pap smear cytology as well as HPV testing and genotyping. HPV can be recognized in Pap smears by the presence of cells called koilocytes (called koilocytosis or koilocytotic atypia). Koilocytes have a hyperchromatic atypical nucleus that stains darkly and a high ratio of nuclear material to cytoplasm. There is a distinct clear appearance around the nucleus called a perinuclear halo (Figure **17.2.4.4**).

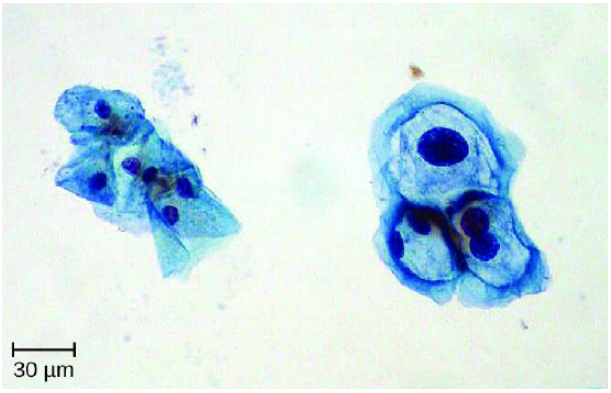


Figure **17.2.4.4**: In this image, the cervical cells on the left are normal and those on the right show enlarged nuclei and hyperchromasia (darkly stained nuclei) typical of HPV-infected koilocytes. (credit: modification of work by Ed Uthman)

Most HPV infections resolve spontaneously; however, various therapies are used to treat and remove warts. Topical medications such as imiquimod (which stimulates the production of interferon), podofilox, or sinecatechins, may be effective. Warts can also be removed using cryotherapy or surgery, but these approaches are less effective for genital warts than for other types of warts. Electrocauterization and carbon dioxide laser therapy are also used for wart removal.

Regular Pap testing can detect abnormal cells that might progress to cervical cancer, followed by biopsy and appropriate treatment. Vaccines for some of the high risk HPV types are now available. Gardasil vaccine includes types 6, 11, 16 and 18 (types 6 and 11 are associated with 90% of genital wart infections and types 16 and 18 are associated with 70% of cervical cancers). Gardasil 9 vaccinates against the previous four types and an additional five high-risk types (31, 33, 45, 52, and 58). Cervarix vaccine includes just HPV types 16 and 18. Vaccination is the most effective way to prevent infection with oncogenic HPV, but it is important to note that not all oncogenic HPV types are covered by the available vaccines. It is recommended for both boys and girls prior to sexual activity (usually between the ages of nine and fifteen).

? Exercise 17.2.4.2

1. What is diagnostic of an HPV infection in a Pap smear?
2. What is the motivation for HPV vaccination?

Secret STIs

Few people who have an STI (or think they may have one) are eager to share that information publicly. In fact, many patients are even uncomfortable discussing the symptoms privately with their doctors. Unfortunately, the social stigma associated with STIs makes it harder for infected individuals to seek the treatment they need and creates the false perception that STIs are rare. In reality, STIs are quite common, but it is difficult to determine exactly *how* common.

A recent study on the effects of HPV vaccination found a baseline HPV prevalence of 26.8% for women between the ages of 14 and 59. Among women aged 20–24, the prevalence was 44.8%; in other words, almost half of the women in this age bracket had a current infection.[4] According to the CDC, HSV-2 infection was estimated to have a prevalence of 15.5% in younger individuals (14–49 years of age) in 2007–2010, down from 20.3% in the same age group in 1988–1994. However, the CDC estimates that 87.4% of infected individuals in this age group have not been diagnosed by a physician.[5]

Another complicating factor is that many STIs can be asymptomatic or have long periods of latency. For example, the CDC estimates that among women ages 14–49 in the United States, about 2.3 million (3.1%) are infected with the sexually transmitted protozoan *Trichomonas* (see Protozoan Infections of the Urogenital System); however, in a study of infected women, 85% of those diagnosed with the infection were asymptomatic.[6]

Even when patients are treated for symptomatic STIs, it can be difficult to obtain accurate data on the number of cases. Whereas STIs like chlamydia, gonorrhea, and syphilis are notifiable diseases—meaning each diagnosis must be reported by healthcare providers to the CDC—other STIs are not notifiable (e.g., genital herpes, genital warts, and trichomoniasis).

Between the social taboos, the inconsistency of symptoms, and the lack of mandatory reporting, it can be difficult to estimate the true prevalence of STIs—but it is safe to say they are much more prevalent than most people think.

Viral Reproductive Tract Infections

Figure **17.2.4.5** summarizes the most important features of viral diseases affecting the human reproductive tract.

Viral Infections of the Reproductive Tract

Disease	Pathogen	Signs and Symptoms	Transmission	Diagnostic Tests	Antimicrobial Drugs/Vaccines
Cervical cancer	HPV types 16, 18, and others	Development of cancer in cervix (or elsewhere)	Direct contact, including sexual	Pap smear	Gardasil vaccine, Cervarix vaccine
Genital herpes	Herpes simplex virus (HSV-1 or HSV-2)	Recurring outbreaks of skin vesicles on genitalia and elsewhere; asymptomatic in many individuals	Sexual contact or contact with open lesions	Viral culture, PCR, ELISA	Acyclovir, famciclovir, valacyclovir
Human papillomas	Human papilloma-virus (HPV) (various strains)	Genital warts or warts in other areas	Direct contact, including sexual	Pap smear	Imiquimod, podofilox, sinecatechins
Neonatal herpes	Herpes simplex virus (HSV-1 or HSV-2)	Vesicles on the skin, mucous membranes, eyes; in disseminated infections, motor impairment and possible death of fetus or newborn	Exposure to pathogens in the birth canal; transplacental infection in some cases	Viral culture or PCR	Acyclovir

Figure **17.2.4.5**: Viral infections of the Reproductive tract.

Key Concepts and Summary

- **Genital herpes** is usually caused by **HSV-2** (although HSV-1 can also be responsible) and may cause the development of infectious, potentially recurrent vesicles.
- **Neonatal herpes** can occur in babies born to infected mothers and can cause symptoms that range from relatively mild (more common) to severe.
- **Human papillomaviruses** are the most common sexually transmitted viruses and include strains that cause **genital warts** as well as strains that cause **cervical cancer**.

Footnotes

1. 1 Catherine Lindsey Satterwhite, Elizabeth Torrone, Elissa Meites, Eileen F. Dunne, Reena Mahajan, M. Cheryl Bañez Ocfemia, John Su, Fujie Xu, and Hillard Weinstock. “Sexually Transmitted Infections Among US Women and Men: Prevalence and Incidence Estimates, 2008.” *Sexually Transmitted Diseases* 40, no. 3 (2013): 187–193.
2. 2 Centers for Disease Control and Prevention. “2015 Sexually Transmitted Disease Treatment Guidelines: Genital Herpes,” 2015. http://www.cdc.gov/std/tg2015/herpes.htm.
3. 3 Lauren Thaxton and Alan G. Waxman. “Cervical Cancer Prevention: Immunization and Screening 2015.” *Medical Clinics of North America* 99, no. 3 (2015): 469–477.
4. 4 Eileen F. Dunne, Elizabeth R. Unger, Maya Sternberg, Geraldine McQuillan, David C. Swan, Sonya S. Patel, and Lauri E. Markowitz. “Prevalence of HPV Infection Among Females in the United States.” *Journal of the American Medical Association*

297, no. 8 (2007): 813–819.
5. 5 Centers for Disease Control and Prevention. “Genital Herpes - CDC Fact Sheet,” 2015. www.cdc.gov/std/herpes/stdfac...s-detailed.htm.
6. 6 Centers for Disease Control and Prevention. “Trichomoniasis Statistics,” 2015. http://www.cdc.gov/std/trichomonas/stats.htm.

This page titled 17.2.4: Viral Infections of the Reproductive System is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **23.4: Viral Infections of the Reproductive System** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

17.2.5: Fungal Infections of the Reproductive System

Learning Objectives

- Summarize the important characteristics of vaginal candidiasis

Only one major fungal pathogen affects the urogenital system. *Candida* is a genus of fungi capable of existing in a yeast form or as a multicellular fungus. *Candida* spp. are commonly found in the normal, healthy microbiota of the skin, gastrointestinal tract, respiratory system, and female urogenital tract (Figure **17.2.5.1**). They can be pathogenic due to their ability to adhere to and invade host cells, form biofilms, secrete hydrolases (e.g., proteases, phospholipases, and lipases) that assist in their spread through tissues, and change their phenotypes to protect themselves from the immune system. However, they typically only cause disease in the female reproductive tract under conditions that compromise the host's defenses. While there are at least 20 *Candida* species of clinical importance, *C. albicans* is the species most commonly responsible for fungal vaginitis.

As discussed earlier, lactobacilli in the vagina inhibit the growth of other organisms, including bacteria and *Candida*, but disruptions can allow *Candida* to increase in numbers. Typical disruptions include antibiotic therapy, illness (especially diabetes), pregnancy, and the presence of transient microbes. Immunosuppression can also play a role, and the severe immunosuppression associated with HIV infection often allows *Candida* to thrive. This can cause genital or vaginal candidiasis, a condition characterized by vaginitis and commonly known as a yeast infection. When a yeast infection develops, inflammation occurs along with symptoms of pruritus (itching), a thick white or yellow discharge, and odor.

Other forms of candidiasis include cutaneous candidiasis (see Mycoses of the Skin) and oral thrush (see Microbial Diseases of the Mouth and Oral Cavity). Although *Candida* spp. are found in the normal microbiota, *Candida* spp. may also be transmitted between individuals. Sexual contact is a common mode of transmission, although candidiasis is not considered an STI.

Diagnosis of vaginal candidiasis can be made using microscopic evaluation of vaginal secretions to determine whether there is an excess of *Candida*. Culturing approaches are less useful because *Candida* is part of the normal microbiota and will regularly appear. It is also easy to contaminate samples with *Candida* because it is so common, so care must be taken to handle clinical material appropriately. Samples can be refrigerated if there is a delay in handling. *Candida* is a dimorphic fungus, so it does not only exist in a yeast form; cultivation can be used to identify chlamydospores and pseudohyphae, which develop from germ tubes (Figure **17.2.5.2**). The presence of the germ tube can be used in a diagnostic test in which cultured yeast cells are combined with rabbit serum and observed after a few hours for the presence of germ tubes. Molecular tests are also available if needed. The Affirm VPII Microbial Identification Test, for instance, tests simultaneously for the vaginal microbes *C. albicans*, *G. vaginalis* (see Bacterial Infections of the Urinary System), and *Trichomonas vaginalis* (see Protozoan Infections of the Urogenital System).

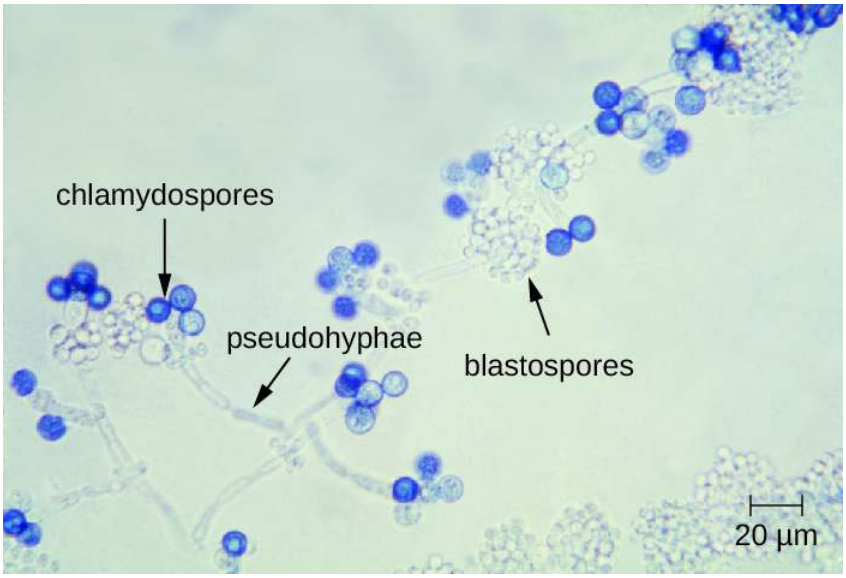


Figure **17.2.5.1**: Candida blastospores (asexual spores that result from budding) and chlamydospores (resting spores produced through asexual reproduction) are visible in this

micrograph. (credit: modification of work by Centers for Disease Control and Prevention)

Topical antifungal medications for vaginal candidiasis include butoconazole, miconazole, clotrimazole, tioconazole, and nystatin. Oral treatment with fluconazole can be used. There are often no clear precipitating factors for infection, so prevention is difficult.

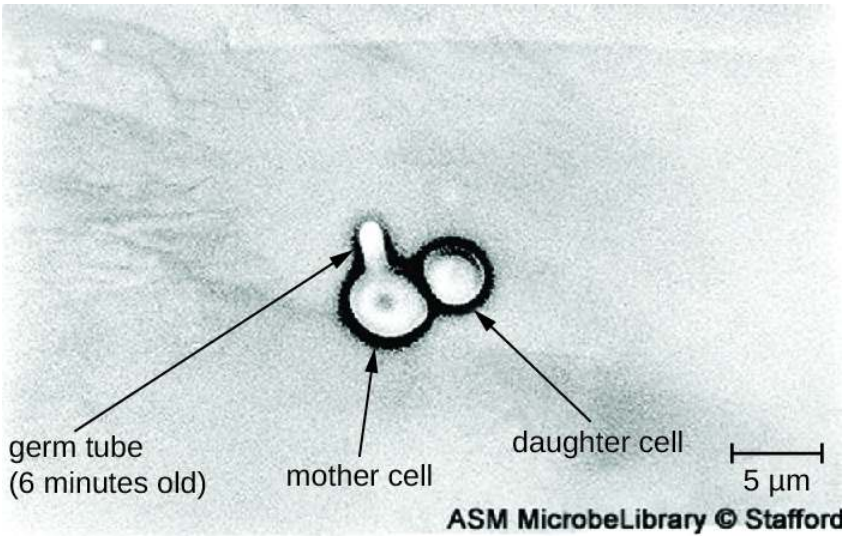


Figure 17.2.5.2: Candida can produce germ tubes, like the one in this micrograph, that develop into hyphae. (credit: modification of work by American Society for Microbiology)

? Exercise 17.2.5.1

1. What factors can lead to candidiasis?
2. How is candidiasis typically diagnosed?

Clinical Focus: Part 3

The Gram stain of Nadia's vaginal smear showed that the concentration of lactobacilli relative to other species in Nadia's vaginal sample was abnormally low. However, there were no clue cells visible, which suggests that the infection is not bacterial vaginosis. But a wet-mount slide showed an overgrowth of yeast cells, suggesting that the problem is candidiasis, or a yeast infection (Figure 17.2.5.3). This, Nadia's doctor assures her, is good news. Candidiasis is common during pregnancy and easily treatable.

Exercise 17.2.5.2

Knowing that the problem is candidiasis, what treatments might the doctor suggest?

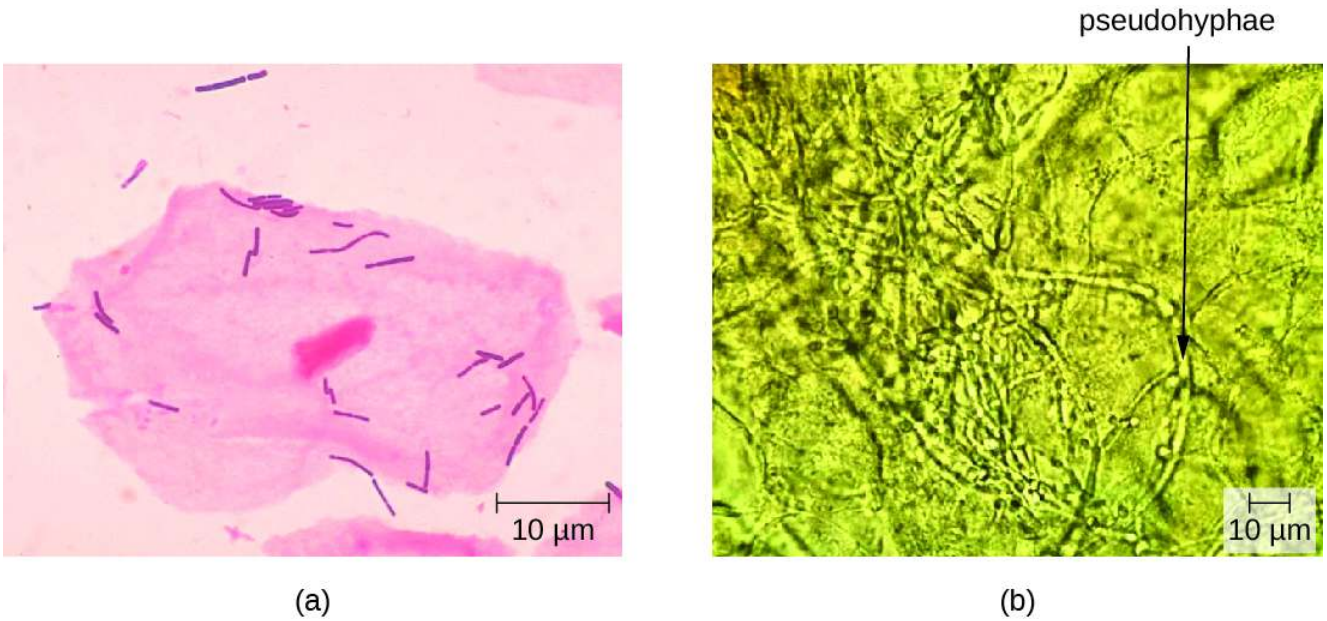


Figure **17.2.5.3**: (a) Lactobacilli are visible as gram-positive rods on and around this squamous epithelial cell. (b) This wet mount prepared with KOH shows *Candida albicans* pseudohyphae and squamous epithelial cells in a vaginal sample from a patient with candidiasis. (credit a: modification of work by Centers for Disease Control and Prevention; credit b: modification of work by Mikael Häggström)

Key Concepts and Summary

- *Candida* spp. are typically present in the normal microbiota in the body, including the skin, respiratory tract, gastrointestinal tract, and female urogenital system.
- Disruptions in the normal vaginal microbiota can lead to an overgrowth of *Candida*, causing vaginal **candidiasis**.
- Vaginal candidiasis can be treated with topical or oral fungicides. Prevention is difficult.

This page titled 17.2.5: Fungal Infections of the Reproductive System is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **23.5: Fungal Infections of the Reproductive System** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

17.2.6: Protozoan Infections of the Reproductive System

Learning Objectives

- Identify the most common protozoan pathogen that causes infections of the reproductive system
- Summarize the important characteristics of trichomoniasis

Only one major protozoan species causes infections in the urogenital system. Trichomoniasis, or “trich,” is the most common nonviral STI and is caused by a flagellated protozoan *Trichomonas vaginalis*. *T. vaginalis* has an undulating membrane and, generally, an amoeboid shape when attached to cells in the vagina. In culture, it has an oval shape.

T. vaginalis is commonly found in the normal microbiota of the vagina. As with other vaginal pathogens, it can cause vaginitis when there is disruption to the normal microbiota. It is found only as a trophozoite and does not form cysts. *T. vaginalis* can adhere to cells using adhesins such as lipoglycans; it also has other cell-surface virulence factors, including tetraspanins that are involved in cell adhesion, motility, and tissue invasion. In addition, *T. vaginalis* is capable of phagocytosing other microbes of the normal microbiota, contributing to the development of an imbalance that is favorable to infection.

Both men and women can develop trichomoniasis. Men are generally asymptomatic, and although women are more likely to develop symptoms, they are often asymptomatic as well. When symptoms do occur, they are characteristic of urethritis. Men experience itching, irritation, discharge from the penis, and burning after urination or ejaculation. Women experience dysuria; itching, burning, redness, and soreness of the genitalia; and vaginal discharge. The infection may also spread to the cervix. Infection increases the risk of transmitting or acquiring HIV and is associated with pregnancy complications such as preterm birth.

Microscopic evaluation of wet mounts is an inexpensive and convenient method of diagnosis, but the sensitivity of this method is low (Figure **17.2.6.1**). Nucleic acid amplification testing (NAAT) is preferred due to its high sensitivity. Using wet mounts and then NAAT for those who initially test negative is one option to improve sensitivity. Samples may be obtained for NAAT using urine, vaginal, or endocervical specimens for women and with urine and urethral swabs for men. It is also possible to use other methods such as the OSOM *Trichomonas* Rapid Test (an immunochromatographic test that detects antigen) and a DNA probe test for multiple species associated with vaginitis (the Affirm VPII Microbial Identification Test discussed in section 23.5).[1] *T. vaginalis* is sometimes detected on a Pap test, but this is not considered diagnostic due to high rates of false positives and negatives. The recommended treatment for trichomoniasis is oral metronidazole or tinidazole. Sexual partners should be treated as well.

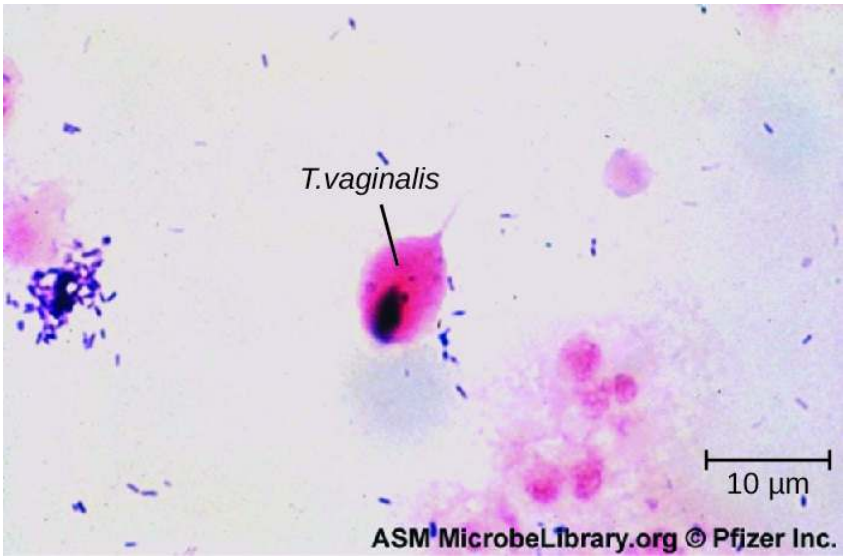


Figure **17.2.6.1**: Trichomonas vaginalis is visible in this Gram stained specimen. (credit: modification of work by American Society for Microbiology)

? Exercise 17.2.6.1

What are the symptoms of trichomoniasis?

STIs and Privacy

For many STIs, it is common to contact and treat sexual partners of the patient. This is especially important when a new illness has appeared, as when HIV became more prevalent in the 1980s. But to contact sexual partners, it is necessary to obtain their personal information from the patient. This raises difficult questions. In some cases, providing the information may be embarrassing or difficult for the patient, even though withholding such information could put their sexual partner(s) at risk.

Legal considerations further complicate such situations. The Health Insurance Portability and Accountability Act (HIPPA), passed into law in 1996, sets the standards for the protection of patient information. It requires businesses that use health information, such as insurance companies and healthcare providers, to maintain strict confidentiality of patient records. Contacting a patient's sexual partners may therefore violate the patient's privacy rights if the patient's diagnosis is revealed as a result.

From an ethical standpoint, which is more important: the patient's privacy rights or the sexual partner's right to know that they may be at risk of a sexually transmitted disease? Does the answer depend on the severity of the disease or are the rules universal? Suppose the physician knows the identity of the sexual partner but the patient does not want that individual to be contacted. Would it be a violation of HIPPA rules to contact the individual without the patient's consent?

Questions related to patient privacy become even more complicated when dealing with patients who are minors. Adolescents may be reluctant to discuss their sexual behavior or health with a health professional, especially if they believe that healthcare professionals will tell their parents. This leaves many teens at risk of having an untreated infection or of lacking the information to protect themselves and their partners. On the other hand, parents may feel that they have a right to know what is going on with their child. How should physicians handle this? Should parents always be told even if the adolescent wants confidentiality? Does this affect how the physician should handle notifying a sexual partner?

Clinical Focus: Resolution

Vaginal candidiasis is generally treated using topical antifungal medications such as butoconazole, miconazole, clotrimazole, ticonozole, nystatin, or oral fluconazole. However, it is important to be careful in selecting a treatment for use during pregnancy. Nadia's doctor recommended treatment with topical clotrimazole. This drug is classified as a category B drug by the FDA for use in pregnancy, and there appears to be no evidence of harm, at least in the second or third trimesters of pregnancy. Based on Nadia's particular situation, her doctor thought that it was suitable for very short-term use even though she was still in the first trimester. After a seven-day course of treatment, Nadia's yeast infection cleared. She continued with a normal pregnancy and delivered a healthy baby eight months later.

Higher levels of hormones during pregnancy can shift the typical microbiota composition and balance in the vagina, leading to high rates of infections such as candidiasis or vaginosis. Topical treatment has an 80–90% success rate, with only a small number of cases resulting in recurrent or persistent infections. Longer term or intermittent treatment is usually effective in these cases.

Fungal and Protozoan Reproductive Tract Infections

Figure **17.2.6.2** summarizes the most important features of candidiasis and trichomoniasis.

Fungal and Protozoan Infections of the Reproductive Tract					
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Diagnostic Tests**	**Antimicrobial Drugs**
Trichomoniasis	*Trichomonas vaginalis*	Urethritis, vaginal or penile discharge; redness or soreness of female genitalia	Sexual contact	Wet mounts, NAAT of urine or vaginal samples; OSOM Trichomonas Rapid Test, Affirm VPII Microbial Identification Test	Metronidazole, tinidazole
Vaginal candidiasis (yeast infection)	*Candida* spp., especially *C. albicans*	Dysuria; vaginal burning, itching, discharge	Transmissible by sexual contact, but typically only causes opportunistic infections after immunosuppression or disruption of vaginal microbiota	Culture, Affirm VPII Microbial Identification Test	Fluconazole, miconazole, clotrimazole, tioconazole, nystatin

Figure **17.2.6.2**: Fungal and Protozoan infections of the reproductive tract.

Link to Learning

Take an online quiz for a review of sexually transmitted infections.

Key Concepts and Summary

- **Trichomoniasis** is a common STI caused by *Trichomonas vaginalis*.
- *T. vaginalis* is common at low levels in the normal microbiota.
- Trichomoniasis is often asymptomatic. When symptoms develop, trichomoniasis causes urinary discomfort, irritation, itching, burning, discharge from the penis (in men), and vaginal discharge (in women).
- Trichomoniasis is treated with the antiflagellate drugs tinidazole and metronidazole.

Footnotes

1. 1 Association of Public Health Laboratories. “Advances in Laboratory Detection of *Trichomonas vaginalis*,” 2013. http://www.aphl.org/AboutAPHL/public...-vaginalis.pdf.

This page titled 17.2.6: Protozoan Infections of the Reproductive System is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **23.6: Protozoan Infections of the Reproductive System** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

17.2.E: Urogenital System Infections (Exercises)

23.1: Anatomy and Normal Microbiota of the Urogenital Tract

The urinary system is responsible for filtering the blood, excreting wastes, and helping to regulate electrolyte and water balance. The urinary system includes the kidneys, ureters, urinary bladder, and urethra; the bladder and urethra are the most common sites of infection. Common sites of infection in the male reproductive system include the urethra, as well as the testes, prostate and epididymis. The common sites of infection in females are the vulva, vagina, cervix, and fallopian tubes.

Multiple Choice

When it first leaves the kidney, urine flows through

A. the urinary bladder.
B. the urethra.
C. the ureter.
D. the glomeruli.

Answer

C

What part of the male urogenital tract is shared by the urinary and reproductive systems?

A. the prostate gland
B. the seminal vesicles
C. the vas deferens
D. the urethra

Answer

D

Fill in the Blank

The genus of bacteria found in the vagina that is important in maintaining a healthy environment, including an acidic pH, is _____.

Answer

Lactobacillus

Short Answer

When the microbial balance of the vagina is disrupted, leading to overgrowth of resident bacteria without necessarily causing inflammation, the condition is called _____.

Answer

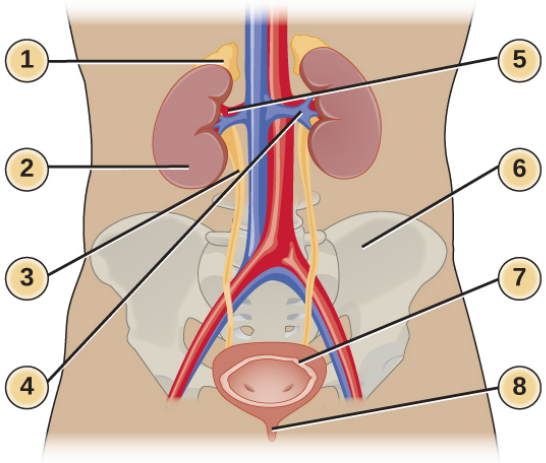
vaginosis

Explain the difference between a sexually transmitted infection and a sexually transmitted disease.

Answer

An STI is a broader term, including colonization by organisms that may not necessarily cause disease.

In the figure shown here, where would cystitis occur?



Critical Thinking

Epidemiological data show that the use of antibiotics is often followed by cases of vaginosis or vaginitis in women. Can you explain this finding?

23.2: Bacterial Infections of the Urinary System

Urinary tract infections (UTIs) include infections of the urethra, bladder, and kidneys, and are common causes of urethritis, cystitis, pyelonephritis, and glomerulonephritis. Bacteria are the most common causes of UTIs, especially in the urethra and bladder. Bacterial cystitis is commonly caused by fecal bacteria such as *E. coli*. Pyelonephritis is a serious kidney infection that is often caused by bacteria that travel from infections elsewhere in the urinary tract.

Multiple Choice

Which species is not associated with NGU?

A. *Neisseria gonorrhoeae*
B. *Mycoplasma hominis*
C. *Chlamydia trachomatis*
D. *Mycoplasma genitalium*

Answer

A

A strain of bacteria associated with a bladder infection shows gram-negative rods. What species is most likely to be the causative agent?

A. *Mycoplasma hominis*
B. *Escherichia coli*
C. *Neisseria gonorrhoeae*
D. *Chlamydia trachomatis*

Answer

B

Fill in the Blank

Pyelonephritis is a potentially severe infection of the _____.

Answer

kidneys

Short Answer

What is pyuria?

Critical Thinking

What are some factors that would increase an individual’s risk of contracting leptospirosis?

23.3: Bacterial Infections of the Reproductive System

In addition to infections of the urinary tract, bacteria commonly infect the reproductive tract. As with the urinary tract, parts of the reproductive system closest to the external environment are the most likely sites of infection. Often, the same microbes are capable of causing urinary tract and reproductive tract infections. Bacterial vaginosis, Chlamydia, Gonorrhea, and Chancroid are diseases caused by bacteria.

Multiple Choice

Treponemal and non-treponemal serological testing can be used to test for

A. vaginosis.
B. chlamydia.
C. syphilis.
D. gonorrhea.

Answer

C

Lymphogranuloma venereum is caused by serovars of

A. *Neisseria gonorrhoeae*.
B. *Chlamydia trachomatis*.
C. *Treponema pallidum*.
D. *Haemophilis ducreyi*.

Answer

B

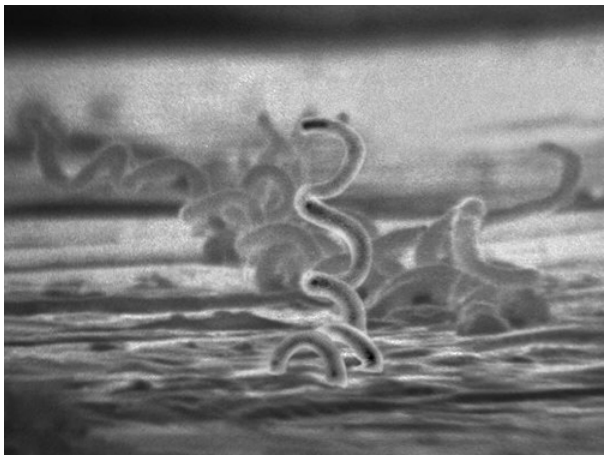
The latent stage of syphilis, which may last for years, can occur between

A. the secondary and tertiary stages.
B. the primary and secondary stages.
C. initial infection and the primary stage.
D. any of the three stages.

Answer

A

Based on its shape, which microbe is this?



(credit: modification of work by Centers for Disease Control and Prevention)

A. *Neisseria gonorrhoeae*
B. *Chlamydia trachomatis*
C. *Treponema pallidum*
D. *Haemophilis ducreyi*

Answer

C

Fill in the Blank

Soft chancres on the genitals are characteristic of the sexually transmitted disease known as _____.

Answer

chancroid

Short Answer

Compare gonococcal and nongonoccocal urethritis with respect to their symptoms and the pathogens that cause each disease.

Critical Thinking

Chlamydia is often asymptomatic. Why might it be important for an individual to know if he or she were infected?

Why does the CDC recommend a two-drug treatment regimen to cover both *C. trachomatis* and *N. gonorrhoeae* if testing to distinguish between the two is not available? Additionally, how does the two-drug treatment regimen address antibiotic resistance?

23.4: Viral Infections of the Reproductive System

Genital herpes is usually caused by HSV-2 (although HSV-1 can also be responsible) and may cause the development of infectious, potentially recurrent vesicles. Neonatal herpes can occur in babies born to infected mothers and can cause symptoms that range from relatively mild (more common) to severe. Human papillomaviruses are the most common sexually transmitted viruses and include strains that cause genital warts as well as strains that cause cervical cancer.

Multiple Choice

Genital herpes is most commonly caused by

A. herpes simplex virus 1.
B. varicella-zoster virus.
C. herpes simplex virus 2.
D. cytomegalovirus.

Answer

C

Koilocytes are characteristic of

A. cells infected with human papillomavirus
B. cells infected with herpes simplex virus 2
C. cells infected with all forms of herpesviruses
D. cervical cancer cells

Answer

A

Fill in the Blank

Condylomata are _____.

Answer

warts

Short Answer

Is it true that human papillomaviruses can always be detected by the presence of genital warts?

How is neonatal herpes transmitted?

Critical Thinking

Recently, studies have shown a reduction in the prevalence of some strains of HPV in younger women. What might be the reason for this?

23.5: Fungal Infections of the Reproductive System

Candida spp. are typically present in the normal microbiota in the body, including the skin, respiratory tract, gastrointestinal tract, and female urogenital system. Disruptions in the normal vaginal microbiota can lead to an overgrowth of *Candida*, causing vaginal candidiasis. Vaginal candidiasis can be treated with topical or oral fungicides. Prevention is difficult.

Multiple Choice

Which oral medication is recommended as an initial topical treatment for genital yeast infections?

A. penicillin
B. acyclovir
C. fluconazole
D. miconazole

Answer

D

Fill in the Blank

The most common *Candida* species associated with yeast infections is _____.

Answer

C. albicans

23.6: Protozoan Infections of the Reproductive System

Trichomoniasis is a common STI caused by *Trichomonas vaginalis*. *T. vaginalis* is common at low levels in the normal microbiota. Trichomoniasis is often asymptomatic. When symptoms develop, trichomoniasis causes urinary discomfort, irritation, itching, burning, discharge from the penis (in men), and vaginal discharge (in women). Trichomoniasis is treated with the antiflagellate drugs tinidazole and metronidazole.

Multiple Choice

What is the only common infection of the reproductive tract caused by a protozoan?

A. gonorrhea
B. chlamydia
C. trichomoniasis
D. candidiasis

Answer

C

Which test is preferred for detecting *T. vaginalis* because of its high sensitivity?

A. NAAT
B. wet mounts
C. Pap tests
D. all of the above are equally good

Answer

A

Fill in the Blank

Trichomoniasis is caused by _____.

Answer

Trichomonas vaginalis

Short Answer

Name three organisms (a bacterium, a fungus, and a protozoan) that are associated with vaginitis.

This page titled 17.2.E: Urogenital System Infections (Exercises) is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **23.E: Urogenital System Infections (Exercises)** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

SECTION OVERVIEW

17.3: Digestive System Infections

Gastrointestinal (GI) diseases are so common that, unfortunately, most people have had first-hand experience with the unpleasant symptoms, such as diarrhea, vomiting, and abdominal discomfort. The causes of gastrointestinal illness can vary widely, but such diseases can be grouped into two categories: those caused by infection (the growth of a pathogen in the GI tract) or intoxication (the presence of a microbial toxin in the GI tract).

Foodborne pathogens like *Escherichia coli* O157:H7 are among the most common sources of gastrointestinal disease. Contaminated food and water have always posed a health risk for humans, but in today's global economy, outbreaks can occur on a much larger scale. *E. coli* O157:H7 is a potentially deadly strain of *E. coli* with a history of contaminating meat and produce that are not properly processed. The source of an *E. coli* O157:H7 outbreak can be difficult to trace, especially if the contaminated food is processed in a foreign country. Once the source is identified, authorities may issue recalls of the contaminated food products, but by then there are typically numerous cases of food poisoning, some of them fatal.

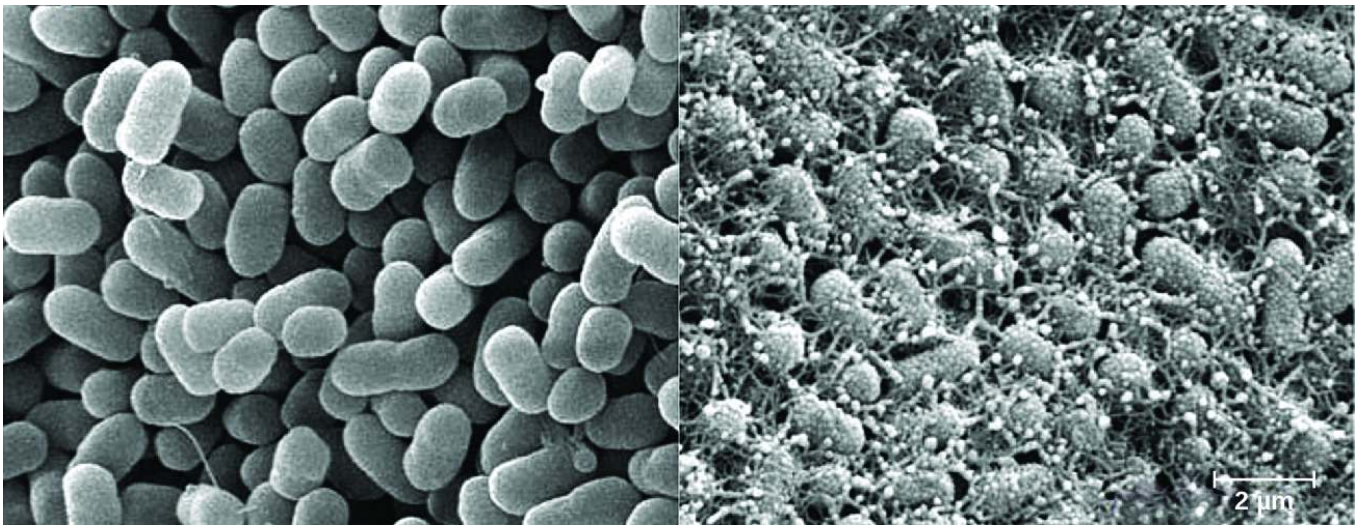


Figure **17.3.1**: *E. coli* O157:H7 causes serious foodborne illness. Curli fibers (adhesive surface fibers that are part of the extracellular matrix) help these bacteria adhere to surfaces and form biofilms. Pictured are two groups of cells, curli non-producing cells (left) and curli producing cells (right). (credit left, right: modification of work by USDA)

17.3.1: Anatomy and Normal Microbiota of the Digestive System

17.3.2: Microbial Diseases of the Mouth and Oral Cavity

17.3.3: Bacterial Infections of the Gastrointestinal Tract

17.3.4: Viral Infections of the Gastrointestinal Tract

17.3.5: Protozoan Infections of the Gastrointestinal Tract

17.3.6: Helminthic Infections of the Gastrointestinal Tract

17.3.E: Digestive System Infections (Exercises)

This page titled 17.3: Digestive System Infections is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

17.3.1: Anatomy and Normal Microbiota of the Digestive System

Learning Objectives

- Describe the major anatomical features of the human digestive system
- Describe the normal microbiota of various regions in the human digestive system
- Explain how microorganisms overcome the defenses of the digestive tract to cause infection or intoxication
- Describe general signs and symptoms associated with infections of the digestive system

Clinical Focus: Part 1

After a morning of playing outside, four-year-old Carli ran inside for lunch. After taking a bite of her fried egg, she pushed it away and whined, “It’s too slimy, Mommy. I don’t want any more.” But her mother, in no mood for games, curtly replied that if she wanted to go back outside she had better finish her lunch. Reluctantly, Carli complied, trying hard not to gag as she choked down the runny egg.

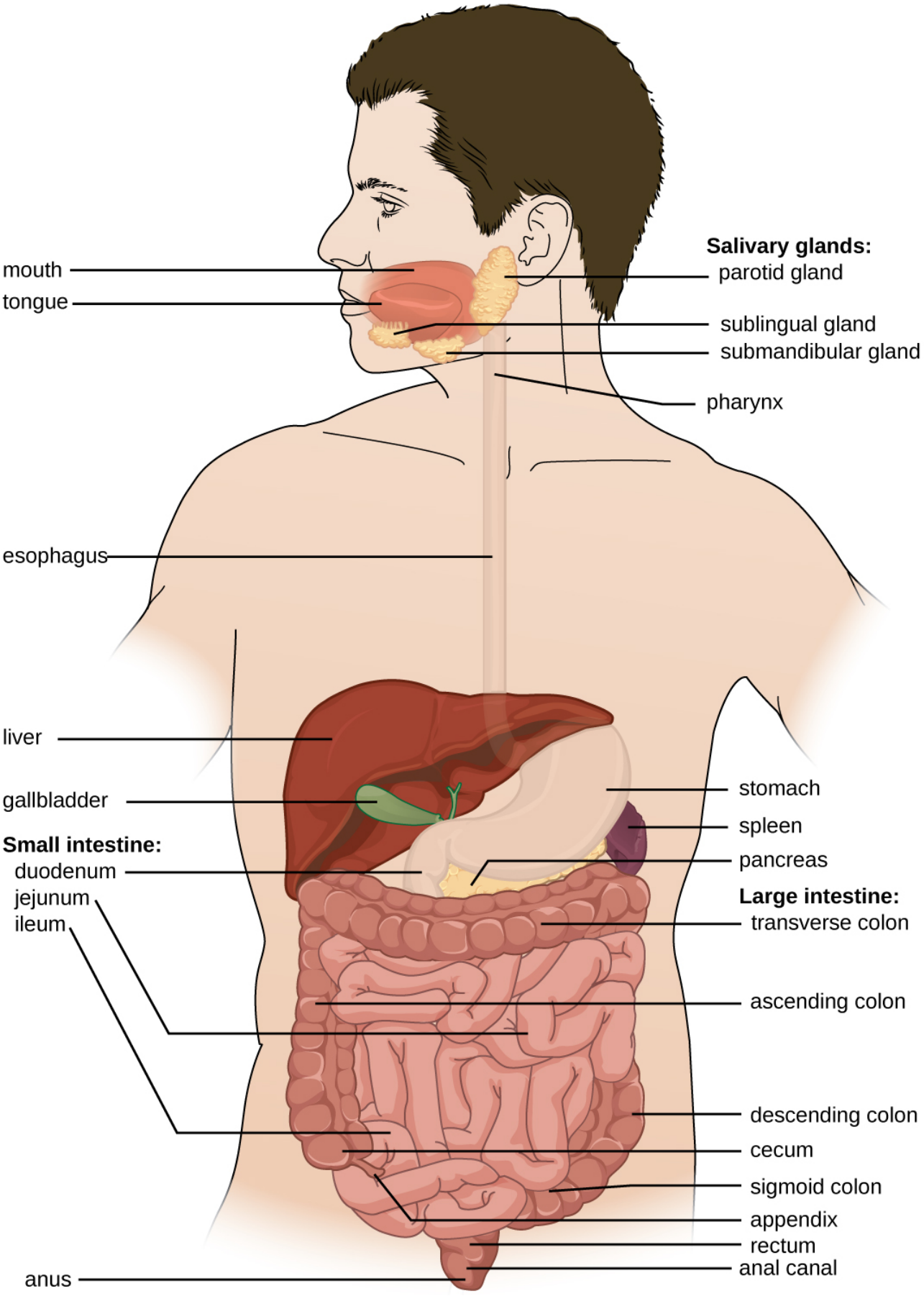
That night, Carli woke up feeling nauseated. She cried for her parents and then began to vomit. Her parents tried to comfort her, but she continued to vomit all night and began to have diarrhea and run a fever. By the morning, her parents were very worried. They rushed her to the emergency room.

Exercise 17.3.1.1

What could have caused Carli’s signs and symptoms?

The human digestive system, or the gastrointestinal (GI) tract, begins with the mouth and ends with the anus. The parts of the mouth include the teeth, the gums, the tongue, the oral vestibule (the space between the gums, lips, and teeth), and the oral cavity proper (the space behind the teeth and gums). Other parts of the GI tract are the pharynx, esophagus, stomach, small intestine, large intestine, rectum, and anus (Figure 17.3.1.1). Accessory digestive organs include the salivary glands, liver, gallbladder, spleen, and pancreas.

The digestive system contains normal microbiota, including archaea, bacteria, fungi, protists, and even viruses. Because this microbiota is important for normal functioning of the digestive system, alterations to the microbiota by antibiotics or diet can be harmful. Additionally, the introduction of pathogens to the GI tract can cause infections and diseases. In this section, we will review the microbiota found in a healthy digestive tract and the general signs and symptoms associated with oral and GI infections.



https://med.libretexts.org/@go/page/77958

Figure 17.3.1.1: The digestive system, or the gastrointestinal tract, includes all of the organs associated with the digestion of food.

Anatomy and Normal Microbiota of the Oral Cavity

Food enters the digestive tract through the mouth, where mechanical digestion (by chewing) and chemical digestion (by enzymes in saliva) begin. Within the mouth are the tongue, teeth, and salivary glands, including the parotid, sublingual, and submandibular glands (Figure 17.3.1.2). The salivary glands produce saliva, which lubricates food and contains digestive enzymes.

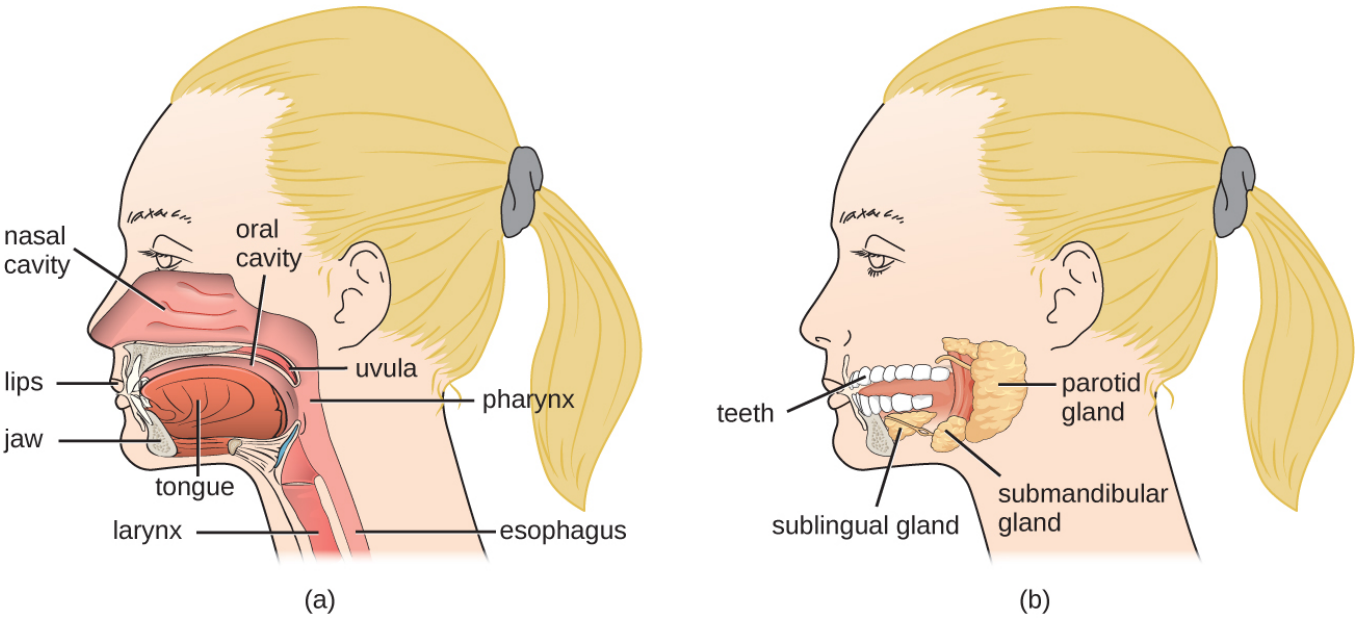


Figure 17.3.1.2: (a) When food enters the mouth, digestion begins. (b) Salivary glands are accessory digestive organs. (credit: modification of work by National Cancer Institute)

The structure of a tooth (Figure 17.3.1.3) begins with the visible outer surface, called the crown, which has to be extremely hard to withstand the force of biting and chewing. The crown is covered with enamel, which is the hardest material in the body. Underneath the crown, a layer of relatively hard dentin extends into the root of the tooth around the innermost pulp cavity, which includes the pulp chamber at the top of the tooth and pulp canal, or root canal, located in the root. The pulp that fills the pulp cavity is rich in blood vessels, lymphatic vessels, connective tissue, and nerves. The root of the tooth and some of the crown are covered with cementum, which works with the periodontal ligament to anchor the tooth in place in the jaw bone. The soft tissues surrounding the teeth and bones are called gums, or gingiva. The gingival space or gingival crevice is located between the gums and teeth.

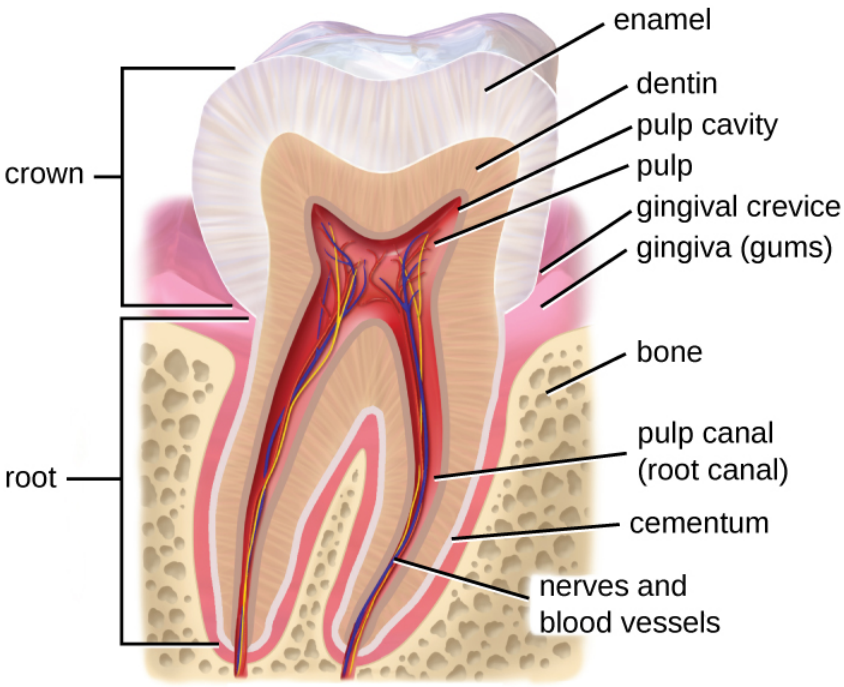


Figure **17.3.1.3**: The tooth has a visible crown with an outer layer of enamel, a layer of dentin, and an inner pulp. The root, hidden by the gums, contains the pulp canal (root canal). (credit: modification of work by Bruce Blaus)

Microbes such as bacteria and archaea are abundant in the mouth and coat all of the surfaces of the oral cavity. However, different structures, such as the teeth or cheeks, host unique communities of both aerobic and anaerobic microbes. Some factors appear to work against making the mouth hospitable to certain microbes. For example, chewing allows microbes to mix better with saliva so they can be swallowed or spit out more easily. Saliva also contains enzymes, including lysozyme, which can damage microbial cells. Recall that lysozyme is part of the first line of defense in the innate immune system and cleaves the β-(1,4) glycosidic linkages between N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM) in bacterial peptidoglycan (see Chemical Defenses). Additionally, fluids containing immunoglobulins and phagocytic cells are produced in the gingival spaces. Despite all of these chemical and mechanical activities, the mouth supports a large microbial community.

? Exercise 17.3.1.2

What factors make the mouth inhospitable for certain microbes?

Anatomy and Normal Microbiota of the GI Tract

As food leaves the oral cavity, it travels through the pharynx, or the back of the throat, and moves into the esophagus, which carries the food from the pharynx to the stomach without adding any additional digestive enzymes. The stomach produces mucus to protect its lining, as well as digestive enzymes and acid to break down food. Partially digested food then leaves the stomach through the pyloric sphincter, reaching the first part of the small intestine called the duodenum. Pancreatic juice, which includes enzymes and bicarbonate ions, is released into the small intestine to neutralize the acidic material from the stomach and to assist in digestion. Bile, produced by the liver but stored in the gallbladder, is also released into the small intestine to emulsify fats so that they can travel in the watery environment of the small intestine. Digestion continues in the small intestine, where the majority of nutrients contained in the food are absorbed. Simple columnar epithelial cells called enterocytes line the lumen surface of the small intestinal folds called villi. Each enterocyte has smaller microvilli (cytoplasmic membrane extensions) on the cellular apical surface that increase the surface area to allow more absorption of nutrients to occur (Figure **17.3.1.4**).

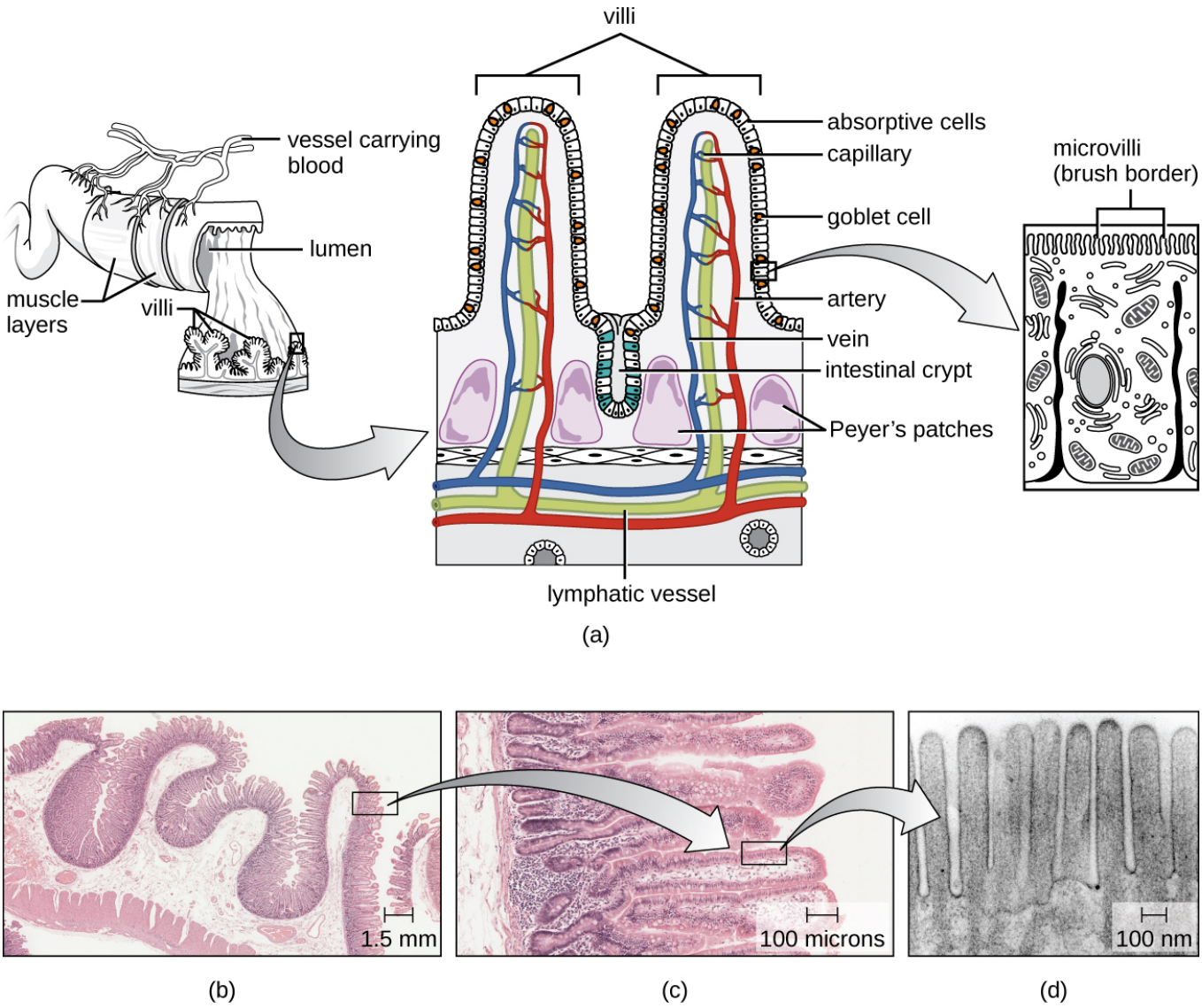


Figure **17.3.1.4**: (a) The structure of the wall of the small intestine allows for the majority of nutrient absorption in the body. (b) Villi are folds in the surface of the small intestine. Microvilli are cytoplasmic extensions on individual cells that increase the surface area for absorption. (c) A light micrograph shows the shape of the villi. (d) An electron micrograph shows the shape of the microvilli. (credit b, c, d: Modification of micrographs provided by the Regents of University of Michigan Medical School © 2012)

Digested food leaves the small intestine and moves into the large intestine, or colon, where there is a more diverse microbiota. Near this junction, there is a small pouch in the large intestine called the cecum, which attaches to the appendix. Further digestion occurs throughout the colon and water is reabsorbed, then waste is excreted through the rectum, the last section of the colon, and out of the body through the anus (Figure **17.3.1.1**).

The environment of most of the GI tract is harsh, which serves two purposes: digestion and immunity. The stomach is an extremely acidic environment (pH 1.5–3.5) due to the gastric juices that break down food and kill many ingested microbes; this helps prevent infection from pathogens. The environment in the small intestine is less harsh and is able to support microbial communities. Microorganisms present in the small intestine can include lactobacilli, diptherioids and the fungus *Candida*. On the other hand, the large intestine (colon) contains a diverse and abundant microbiota that is important for normal function. These microbes include *Bacteriodetes* (especially the genera *Bacteroides* and *Prevotella*) and *Firmicutes* (especially members of the genus *Clostridium*). Methanogenic archaea and some fungi are also present, among many other species of bacteria. These microbes all aid in digestion and contribute to the production of feces, the waste excreted from the digestive tract, and flatus, the gas produced from microbial fermentation of undigested food. They can also produce valuable nutrients. For example, lactic acid bacteria such as bifidobacteria

can synthesize vitamins, such as vitamin B12, folate, and riboflavin, that humans cannot synthesize themselves. *E. coli* found in the intestine can also break down food and help the body produce vitamin K, which is important for blood coagulation.

The GI tract has several other methods of reducing the risk of infection by pathogens. Small aggregates of underlying lymphoid tissue in the ileum, called Peyer's patches (Figure **17.3.1.4**), detect pathogens in the intestines via microfold (M) cells, which transfer antigens from the lumen of the intestine to the lymphocytes on Peyer's patches to induce an immune response. The Peyer's patches then secrete IgA and other pathogen-specific antibodies into the intestinal lumen to help keep intestinal microbes at safe levels. Goblet cells, which are modified simple columnar epithelial cells, also line the GI tract (Figure **17.3.1.5**). Goblet cells secrete a gel-forming mucin, which is the major component of mucus. The production of a protective layer of mucus helps reduce the risk of pathogens reaching deeper tissues.

The constant movement of materials through the gastrointestinal tract also helps to move transient pathogens out of the body. In fact, feces are composed of approximately 25% microbes, 25% sloughed epithelial cells, 25% mucus, and 25% digested or undigested food. Finally, the normal microbiota provides an additional barrier to infection via a variety of mechanisms. For example, these organisms outcompete potential pathogens for space and nutrients within the intestine. This is known as competitive exclusion. Members of the microbiota may also secrete protein toxins known as bacteriocins that are able to bind to specific receptors on the surface of susceptible bacteria.

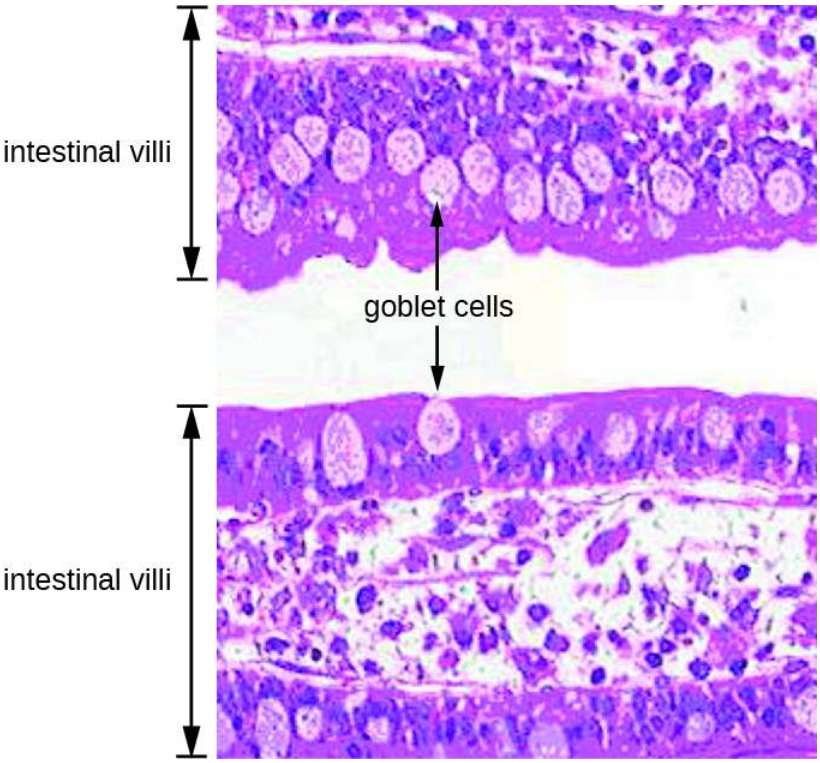


Figure **17.3.1.5**: A magnified image of intestinal villi in the GI tract shows goblet cells. These cells are important in producing a protective layer of mucus.

? Exercise 17.3.1.3

Compare and contrast the microbiota of the small and large intestines.

General Signs and Symptoms of Oral and GI Disease

Despite numerous defense mechanisms that protect against infection, all parts of the digestive tract can become sites of infection or intoxication. The term food poisoning is sometimes used as a catch-all for GI infections and intoxications, but not all forms of GI disease originate with foodborne pathogens or toxins.

In the mouth, fermentation by anaerobic microbes produces acids that damage the teeth and gums. This can lead to tooth decay, cavities, and periodontal disease, a condition characterized by chronic inflammation and erosion of the gums. Additionally, some

pathogens can cause infections of the mucosa, glands, and other structures in the mouth, resulting in inflammation, sores, cankers, and other lesions. An open sore in the mouth or GI tract is typically called an ulcer.

Infections and intoxications of the lower GI tract often produce symptoms such as nausea, vomiting, diarrhea, aches, and fever. In some cases, vomiting and diarrhea may cause severe dehydration and other complications that can become serious or fatal. Various clinical terms are used to describe gastrointestinal symptoms. For example, gastritis is an inflammation of the stomach lining that results in swelling and enteritis refers to inflammation of the intestinal mucosa. When the inflammation involves both the stomach lining and the intestinal lining, the condition is called gastroenteritis. Inflammation of the liver is called hepatitis. Inflammation of the colon, called colitis, commonly occurs in cases of food intoxication. Because an inflamed colon does not reabsorb water as effectively as it normally does, stools become watery, causing diarrhea. Damage to the epithelial cells of the colon can also cause bleeding and excess mucus to appear in watery stools, a condition called dysentery.

? Exercise 17.3.1.4

List possible causes and signs and symptoms of food poisoning.

Key Concepts and Summary

- The digestive tract, consisting of the oral cavity, pharynx, esophagus, stomach, small intestine, and large intestine, has a normal microbiota that is important for health.
- The constant movement of materials through the gastrointestinal canal, the protective layer of mucus, the normal microbiota, and the harsh chemical environment in the stomach and small intestine help to prevent colonization by pathogens.
- Infections or microbial toxins in the oral cavity can cause **tooth decay**, **periodontal disease**, and various types of **ulcers**.
- Infections and intoxications of the gastrointestinal tract can cause general symptoms such as nausea, vomiting, diarrhea, and fever. Localized inflammation of the GI tract can result in **gastritis**, **enteritis**, **gastroenteritis**, **hepatitis**, or **colitis**, and damage to epithelial cells of the colon can lead to **dysentery**.
- **Foodborne illness** refers to infections or intoxications that originate with pathogens or toxins ingested in contaminated food or water.

This page titled 17.3.1: Anatomy and Normal Microbiota of the Digestive System is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **24.1: Anatomy and Normal Microbiota of the Digestive System** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

17.3.2: Microbial Diseases of the Mouth and Oral Cavity

Learning Objectives

- Explain the role of microbial activity in diseases of the mouth and oral cavity
- Compare the major characteristics of specific oral diseases and infections

Despite the presence of saliva and the mechanical forces of chewing and eating, some microbes thrive in the mouth. These microbes can cause damage to the teeth and can cause infections that have the potential to spread beyond the mouth and sometimes throughout the body.

Dental Caries

Cavities of the teeth, known clinically as dental caries, are microbial lesions that cause damage to the teeth. Over time, the lesion can grow through the outer enamel layer to infect the underlying dentin or even the innermost pulp. If dental caries are not treated, the infection can become an abscess that spreads to the deeper tissues of the teeth, near the roots, or to the bloodstream.

Tooth decay results from the metabolic activity of microbes that live on the teeth. A layer of proteins and carbohydrates forms when clean teeth come into contact with saliva. Microbes are attracted to this food source and form a biofilmcalled plaque. The most important cariogenic species in these biofilms is *Streptococcus mutans*. When sucrose, a disaccharide sugar from food, is broken down by bacteria in the mouth, glucose and fructose are produced. The glucose is used to make dextran, which is part of the extracellular matrix of the biofilm. Fructose is fermented, producing organic acids such as lactic acid. These acids dissolve the minerals of the tooth, including enamel, even though it is the hardest material in the body. The acids work even more quickly on exposed dentin (Figure **17.3.2.1**). Over time, the plaque biofilm can become thick and eventually calcify. When a heavy plaque deposit becomes hardened in this way, it is called tartar or dental calculus (Figure **17.3.2.2**). These substantial plaque biofilms can include a variety of bacterial species, including *Streptococcus* and *Actinomyces* species.

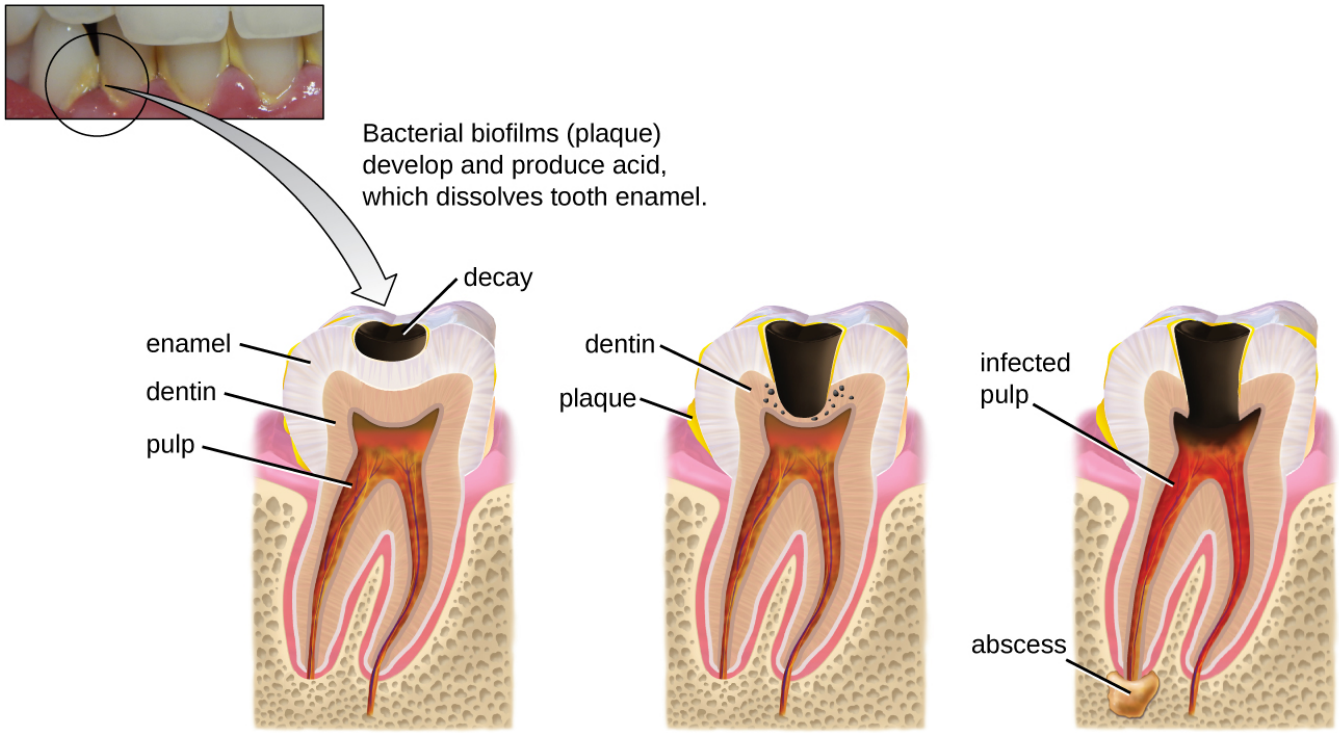


Figure **17.3.2.1**: Tooth decay occurs in stages. When bacterial biofilms (plaque) develop on teeth, the acids produced gradually dissolve the enamel, followed by the dentin. Eventually, if left untreated, the lesion may reach the pulp and cause an abscess. (credit: modification of work by “BruceBlaus”/Wikimedia Commons)

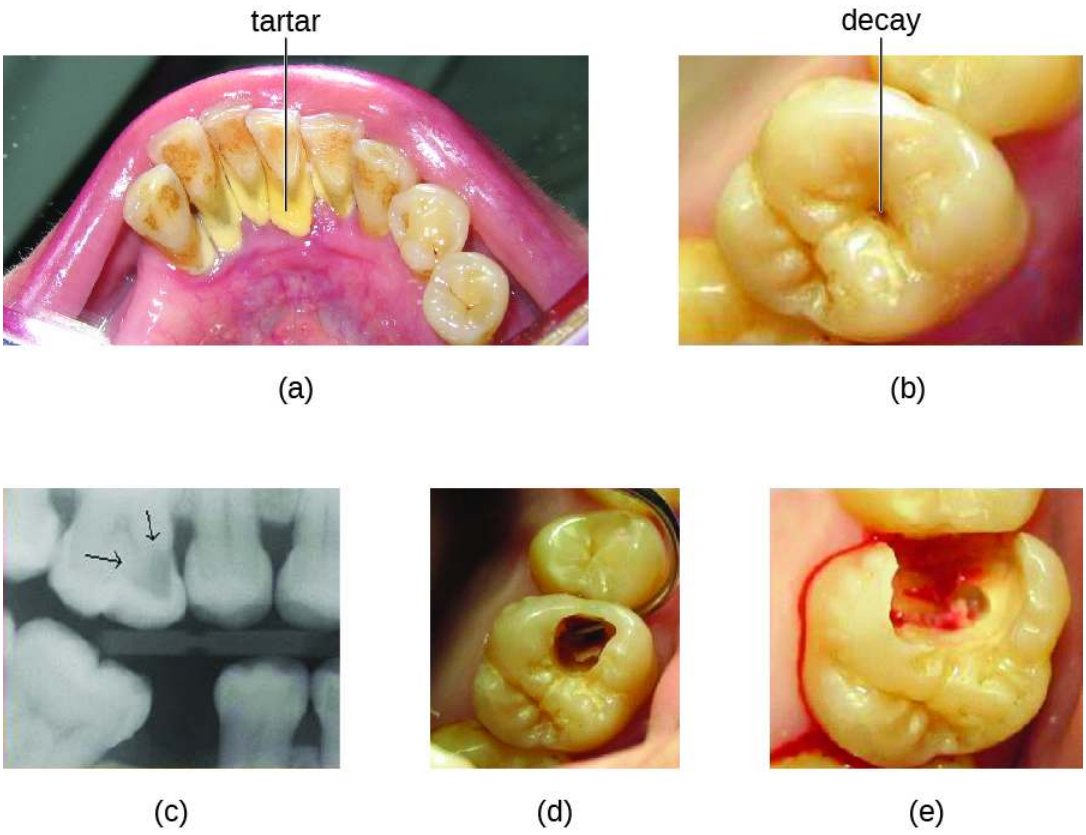


Figure **17.3.2.2**: (a) Tartar (dental calculus) is visible at the bases of these teeth. The darker deposits higher on the crowns are staining. (b) This tooth shows only a small amount of visible decay. (c) An X-ray of the same tooth shows that there is a dark area representing more decay inside the tooth. (d) Removal of a portion of the crown reveals the area of damage. (e) All of the cavity must be removed before filling. (credit: modification of work by "DRosenbach"/Wikimedia Commons)

Some tooth decay is visible from the outside, but it is not always possible to see all decay or the extent of the decay. X-ray imaging is used to produce radiographs that can be studied to look for deeper decay and damage to the root or bone (Figure **17.3.2.2**). If not detected, the decay can reach the pulp or even spread to the bloodstream. Painful abscesses can develop.

To prevent tooth decay, prophylactic treatment and good hygiene are important. Regular tooth brushing and flossing physically removes microbes and combats microbial growth and biofilm formation. Toothpaste contains fluoride, which becomes incorporated into the hydroxyapatite of tooth enamel, protecting it against acidity caused by fermentation of mouth microbiota. Fluoride is also bacteriostatic, thus slowing enamel degradation. Antiseptic mouthwashes commonly contain plant-derived phenolics like thymol and eucalyptol and/or heavy metals like zinc chloride (see Using Chemicals to Control Microorganisms). Phenolics tend to be stable and persistent on surfaces, and they act through denaturing proteins and disrupting membranes.

Regular dental cleanings allow for the detection of decay at early stages and the removal of tartar. They may also help to draw attention to other concerns, such as damage to the enamel from acidic drinks. Reducing sugar consumption may help prevent damage that results from the microbial fermentation of sugars. Additionally, sugarless candies or gum with sugar alcohols (such as xylitol) can reduce the production of acids because these are fermented to nonacidic compounds (although excess consumption may lead to gastrointestinal distress). Fluoride treatment or ingesting fluoridated water strengthens the minerals in teeth and reduces the incidence of dental caries.

If caries develop, prompt treatment prevents worsening. Smaller areas of decay can be drilled to remove affected tissue and then filled. If the pulp is affected, then a root canal may be needed to completely remove the infected tissues to avoid continued spread of the infection, which could lead to painful abscesses.

? Exercise 17.3.2.1

1. Name some ways that microbes contribute to tooth decay.
2. What is the most important cariogenic species of bacteria?

Periodontal Disease

In addition to damage to the teeth themselves, the surrounding structures can be affected by microbes. Periodontal disease is the result of infections that lead to inflammation and tissue damage in the structures surrounding the teeth. The progression from mild to severe periodontal disease is generally reversible and preventable with good oral hygiene.

Inflammation of the gums that can lead to irritation and bleeding is called gingivitis. When plaque accumulates on the teeth, bacteria colonize the gingival space. As this space becomes increasingly blocked, the environment becomes anaerobic. This allows a wide variety of microbes to colonize, including *Porphyromonas*, *Streptococcus*, and *Actinomyces*. The bacterial products, which include lipopolysaccharide (LPS), proteases, lipoteichoic acids, and others, cause inflammation and gum damage (Figure **17.3.2.3**). It is possible that methanogenic archaeans (including *Methanobrevibacter oralis* and other *Methanobrevibacter* species) also contribute to disease progression as some species have been identified in patients with periodontal disease, but this has proven difficult to study.[123] Gingivitis is diagnosed by visual inspection, including measuring pockets in the gums, and X-rays, and is usually treated using good dental hygiene and professional dental cleaning, with antibiotics reserved for severe cases.



Figure **17.3.2.3**: Redness and irritation of the gums are evidence of gingivitis.

Over time, chronic gingivitis can develop into the more serious condition of periodontitis (Figure **17.3.2.4**). When this happens, the gums recede and expose parts of the tooth below the crown. This newly exposed area is relatively unprotected, so bacteria can grow on it and spread underneath the enamel of the crown and cause cavities. Bacteria in the gingival space can also erode the cementum, which helps to hold the teeth in place. If not treated, erosion of cementum can lead to the movement or loss of teeth. The bones of the jaw can even erode if the infection spreads. This condition can be associated with bleeding and halitosis (bad breath). Cleaning and appropriate dental hygiene may be sufficient to treat periodontitis. However, in cases of severe periodontitis, an antibiotic may be given. Antibiotics may be given in pill form or applied directly to the gum (local treatment). Antibiotics given can include tetracycline, doxycycline, macrolides or β-lactams. Because periodontitis can be caused by a mix of microbes, a combination of antibiotics may be given.

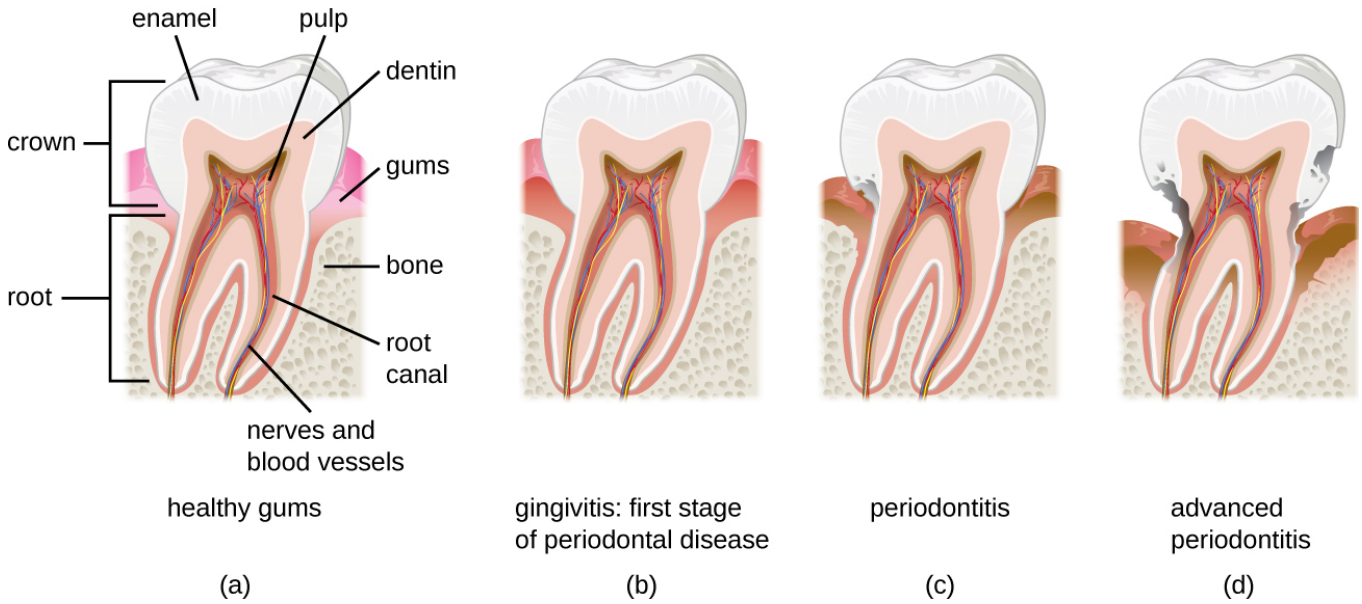


Figure **17.3.2.4**: (a) Healthy gums hold the teeth firmly and do not bleed. (b) Gingivitis is the first stage of periodontal disease. Microbial infection causes gums to become inflamed and irritated, with occasional bleeding. (c) In periodontitis, gums recede and expose parts of the tooth normally covered. (d) In advanced periodontitis, the infection spreads to ligaments and bone tissue supporting the teeth. Tooth loss may occur, or teeth may need to be surgically removed. (credit: modification of work by "BruceBlaus"/Wikimedia Commons)

Trench Mouth

When certain bacteria, such as *Prevotella intermedia*, *Fusobacterium* species, and *Treponema vicentii*, are involved and periodontal disease progresses, acute necrotizing ulcerative gingivitis or trench mouth, also called Vincent's disease, can develop. This is severe periodontitis characterized by erosion of the gums, ulcers, substantial pain with chewing, and halitosis (Figure **17.3.2.5**) that can be diagnosed by visual examination and X-rays. In countries with good medical and dental care, it is most common in individuals with weakened immune systems, such as patients with AIDS. In addition to cleaning and pain medication, patients may be prescribed antibiotics such as amoxicillin, amoxicillin clavulanate, clindamycin, or doxycycline.



Figure 17.3.2.5: These inflamed, eroded gums are an example of a mild case of acute necrotizing ulcerative gingivitis, also known as trench mouth. (credit: modification of work by Centers for Disease Control and Prevention)

? Exercise 17.3.2.2

How does gingivitis progress to periodontitis?

Healthy Mouth, Healthy Body

Good oral health promotes good overall health, and the reverse is also true. Poor oral health can lead to difficulty eating, which can cause malnutrition. Painful or loose teeth can also cause a person to avoid certain foods or eat less. Malnutrition due to dental problems is of greatest concern for the elderly, for whom it can worsen other health conditions and contribute to mortality. Individuals who have serious illnesses, especially AIDS, are also at increased risk of malnutrition from dental problems.

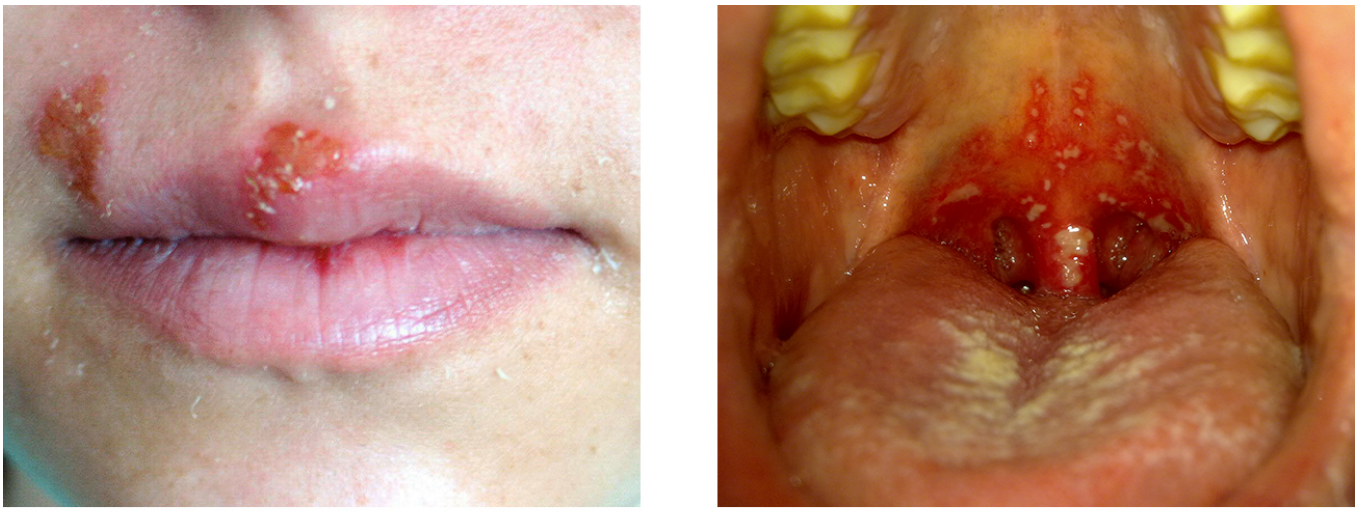
Additionally, poor oral health can contribute to the development of disease. Increased bacterial growth in the mouth can cause inflammation and infection in other parts of the body. For example, *Streptococcus* in the mouth, the main contributor to biofilms on teeth, tartar, and dental caries, can spread throughout the body when there is damage to the tissues inside the mouth, as can happen during dental work. *S. mutans* produces a surface adhesin known as P1, which binds to salivary agglutinin on the surface of the tooth. P1 can also bind to extracellular matrix proteins including fibronectin and collagen. When *Streptococcus* enters the bloodstream as a result of tooth brushing or dental cleaning, it causes inflammation that can lead to the accumulation of plaque in the arteries and contribute to the development of atherosclerosis, a condition associated with cardiovascular disease, heart attack, and stroke. In some cases, bacteria that spread through the blood vessels can lodge in the heart and cause endocarditis (an example of a focal infection).

Oral Infections

As noted earlier, normal oral microbiota can cause dental and periodontal infections. However, there are number of other infections that can manifest in the oral cavity when other microbes are present.

Herpetic Gingivostomatitis

As described in Viral Infections of the Skin and Eyes, infections by herpes simplex virus type 1 (HSV-1) frequently manifest as oral herpes, also called acute herpes labialis and characterized by cold sores on the lips, mouth, or gums. HSV-1 can also cause acute herpetic gingivostomatitis, a condition that results in ulcers of the mucous membranes inside the mouth (Figure **17.3.2.6**). Herpetic gingivostomatitis is normally self-limiting except in immunocompromised patients. Like oral herpes, the infection is generally diagnosed through clinical examination, but cultures or biopsies may be obtained if other signs or symptoms suggest the possibility of a different causative agent. If treatment is needed, mouthwashes or antiviral medications such as acyclovir, famciclovir, or valacyclovir may be used.



(a) (b)

Figure **17.3.2.6**: (a) This cold sore is caused by infection with herpes simplex virus type 1 (HSV-1). (b) HSV-1 can also cause acute herpetic gingivostomatitis. (credit b: modification of work by Klaus D. Peter)

Oral Thrush

The yeast *Candida* is part of the normal human microbiota, but overgrowths, especially of *Candida albicans*, can lead to infections in several parts of the body. When *Candida* infection develops in the oral cavity, it is called oral thrush. Oral thrush is most common in infants because they do not yet have well developed immune systems and have not acquired the robust normal microbiota that keeps *Candida* in check in adults. Oral thrush is also common in immunodeficient patients and is a common infection in patients with AIDS.

Oral thrush is characterized by the appearance of white patches and pseudomembranes in the mouth (Figure **17.3.2.7**) and can be associated with bleeding. The infection may be treated topically with nystatin or clotrimazole oral suspensions, although systemic treatment is sometimes needed. In serious cases, systemic azoles such as fluconazole or itraconazole (for strains resistant to fluconazole), may be used. Amphotericin B can also be used if the infection is severe or if the *Candida* species is azole-resistant.



Figure **17.3.2.7**: Overgrowth of *Candida* in the mouth is called thrush. It often appears as white patches. (credit: modification of work by Centers for Disease Control and Prevention)

Mumps

The viral disease mumps is an infection of the parotid glands, the largest of the three pairs of salivary glands (Figure 24.1.2). The causative agent is mumps virus (MuV), a paramyxovirus with an envelope that has hemagglutinin and neuraminidase spikes. A fusion protein located on the surface of the envelope helps to fuse the viral envelope to the host cell plasma membrane.

Mumps virus is transmitted through respiratory droplets or through contact with contaminated saliva, making it quite contagious so that it can lead easily to epidemics. It causes fever, muscle pain, headache, pain with chewing, loss of appetite, fatigue, and weakness. There is swelling of the salivary glands and associated pain (Figure **17.3.2.8**). The virus can enter the bloodstream (viremia), allowing it to spread to the organs and the central nervous system. The infection ranges from subclinical cases to cases with serious complications, such as encephalitis, meningitis, and deafness. Inflammation of the pancreas, testes, ovaries, and breasts may also occur and cause permanent damage to those organs; despite these complications, a mumps infection rarely cause sterility.

Mumps can be recognized based on clinical signs and symptoms, and a diagnosis can be confirmed with laboratory testing. The virus can be identified using culture or molecular techniques such as RT-PCR. Serologic tests are also available, especially enzyme immunoassays that detect antibodies. There is no specific treatment for mumps, so supportive therapies are used. The most effective way to avoid infection is through vaccination. Although mumps used to be a common childhood disease, it is now rare in the United States due to vaccination with the measles, mumps, and rubella (MMR) vaccine.



Figure 17.3.2.8: This child shows the characteristic parotid swelling associated with mumps. (credit: modification of work by Centers for Disease Control and Prevention)

? Exercise 17.3.2.3

Compare and contrast the signs and symptoms of herpetic gingivostomatitis, oral thrush, and mumps.

Oral Infections

Infections of the mouth and oral cavity can be caused by a variety of pathogens, including bacteria, viruses, and fungi. Many of these infections only affect the mouth, but some can spread and become systemic infections. Figure **17.3.2.9** summarizes the main characteristics of common oral infections.

Oral Infections					
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Diagnostic Tests**	**Antimicrobial Drugs**
Dental caries	*Streptococcus mutans*	Discoloration, softening, cavities in teeth	Non-transmissible; caused by bacteria of the normal oral microbiota	Visual examinations, X-rays	Oral antiseptics (e.g., Listerine)
Gingivitis and periodontitis	*Porphyromonas, Streptococcus, Actinomyces*	Inflammation and erosion of gums, bleeding, halitosis; erosion of cementum, leading to tooth loss in advanced infections	Non-transmissible; caused by bacteria of the normal oral microbiota	Visual examination, X-rays, measuring pockets in gums	Tetracycline, doxycycline, macrolides or beta-lactams. Mixture of antibiotics may be given.
Herpetic gingivostomatitis	Herpes simplex virus type 1 (HSV-1)	Lesions in mucous membranes of mouth	Contact with saliva or lesions of an infected person	Culture or biopsy	Acyclovir, famcyclovir, valacyclovir
Mumps	Mumps virus (a paramyxovirus)	Swelling of parotid glands, fever, headache, muscle pain, weakness, fatigue, loss of appetite, pain while chewing; in serious cases, encephalitis, meningitis, and inflammation of testes, ovaries, and breasts	Contact with saliva or respiratory droplets of an infected person	Virus culture or serologic tests for antibodies, enzyme immunoassay, RT-PCR	None for treatment; MMR vaccine for prevention
Oral thrush	*Candida albicans*, other *Candida* spp.	White patches and pseudomembranes in mouth, may cause bleeding	Non-transmissible; caused by overgrowth of *Candida* spp. in the normal oral microbiota; primarily affects infants and the immuno-compromised	Microscopic analysis of oral samples	Clotrimazole, nystatin, fluconazole, or itraconazole; amphotericin B in severe cases
Trench mouth (acute necrotizing ulcerative gingivitis)	*Prevotella intermedia Fusobacterium* species, *Treponema vincentii,* others	Erosion of gums, ulcers, substantial pain with chewing, halitosis	Non-transmissible; caused by members of the normal oral microbiota	Visual examinations, X-rays	Amoxicillin, amoxicillin clavulanate, clindamycin, or doxycylcine

Figure **17.3.2.9**: Oral infections.

Key Concepts and Summary

- **Dental caries**, **tartar**, and **gingivitis** are caused by overgrowth of oral bacteria, usually *Streptococcus* and *Actinomyces* species, as a result of insufficient dental hygiene.
- Gingivitis can worsen, allowing *Porphyromonas*, *Streptococcus*, and *Actinomyces* species to spread and cause **periodontitis**. When *Prevotella intermedia*, *Fusobacterium* species, and *Treponema vicentii* are involved, it can lead to **acute necrotizing**

ulcerative gingivitis.

- The herpes simplex virus type 1 can cause lesions of the mouth and throat called **herpetic gingivostomatitis.**
- Other infections of the mouth include **oral thrush**, a fungal infection caused by overgrowth of *Candida* yeast, and **mumps**, a viral infection of the salivary glands caused by the mumps virus, a paramyxovirus.

Footnotes

1. 1 Hans-Peter Horz and Georg Conrads. "Methanogenic *Archaea* and Oral Infections—Ways to Unravel the Black Box." *Journal of Oral Microbiology* 3(2011). doi: 10.3402/jom.v3i0.5940.
2. 2 Hiroshi Maeda, Kimito Hirai, Junji Mineshiba, Tadashi Yamamoto, Susumu Kokeguchi, and Shogo Takashiba. "Medical Microbiological Approach to Archaea in Oral Infectious Diseases." *Japanese Dental Science Review* 49: 2, p. 72–78.
3. 3 Paul W. Lepp, Mary M. Brinig, Cleber C. Ouverney, Katherine Palm, Gary C. Armitage, and David A. Relman. "Methanogenic *Archaea* and Human Periodontal Disease." *Proceedings of the National Academy of Sciences of the United States of America* 101 (2003): 16, pp. 6176–6181. doi: 10.1073/pnas.0308766101.

This page titled 17.3.2: Microbial Diseases of the Mouth and Oral Cavity is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **24.2: Microbial Diseases of the Mouth and Oral Cavity** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

17.3.3: Bacterial Infections of the Gastrointestinal Tract

Learning Objectives

- Identify the most common bacteria that can cause infections of the GI tract
- Compare the major characteristics of specific bacterial diseases affecting the GI tract

A wide range of gastrointestinal diseases are caused by bacterial contamination of food. Recall that foodborne diseasecan arise from either infection or intoxication. In both cases, bacterial toxins are typically responsible for producing disease signs and symptoms. The distinction lies in where the toxins are produced. In an infection, the microbial agent is ingested, colonizes the gut, and then produces toxins that damage host cells. In an intoxication, bacteria produce toxins in the food before it is ingested. In either case, the toxins cause damage to the cells lining the gastrointestinal tract, typically the colon. This leads to the common signs and symptoms of diarrhea or watery stool and abdominal cramps, or the more severe dysentery. Symptoms of foodborne diseases also often include nausea and vomiting, which are mechanisms the body uses to expel the toxic materials.

Most bacterial gastrointestinal illness is short-lived and self-limiting; however, loss of fluids due to severe diarrheal illness can lead to dehydration that can, in some cases, be fatal without proper treatment. Oral rehydration therapy with electrolyte solutions is an essential aspect of treatment for most patients with GI disease, especially in children and infants.

Staphylococcal Food Poisoning

Staphylococcal food poisoning is one form of food intoxication. When *Staphylococcus aureus* grows in food, it may produce enterotoxins that, when ingested, can cause symptoms such as nausea, diarrhea, cramping, and vomiting within one to six hours. In some severe cases, it may cause headache, dehydration, and changes in blood pressure and heart rate. Signs and symptoms resolve within 24 to 48 hours. *S. aureus* is often associated with a variety of raw or undercooked and cooked foods including meat (e.g., canned meat, ham, and sausages) and dairy products (e.g., cheeses, milk, and butter). It is also commonly found on hands and can be transmitted to prepared foods through poor hygiene, including poor handwashing and the use of contaminated food preparation surfaces, such as cutting boards. The greatest risk is for food left at a temperature below 60 °C (140 °F), which allows the bacteria to grow. Cooked foods should generally be reheated to at least 60 °C (140 °F) for safety and most raw meats should be cooked to even higher internal temperatures (Figure 17.3.3.1).

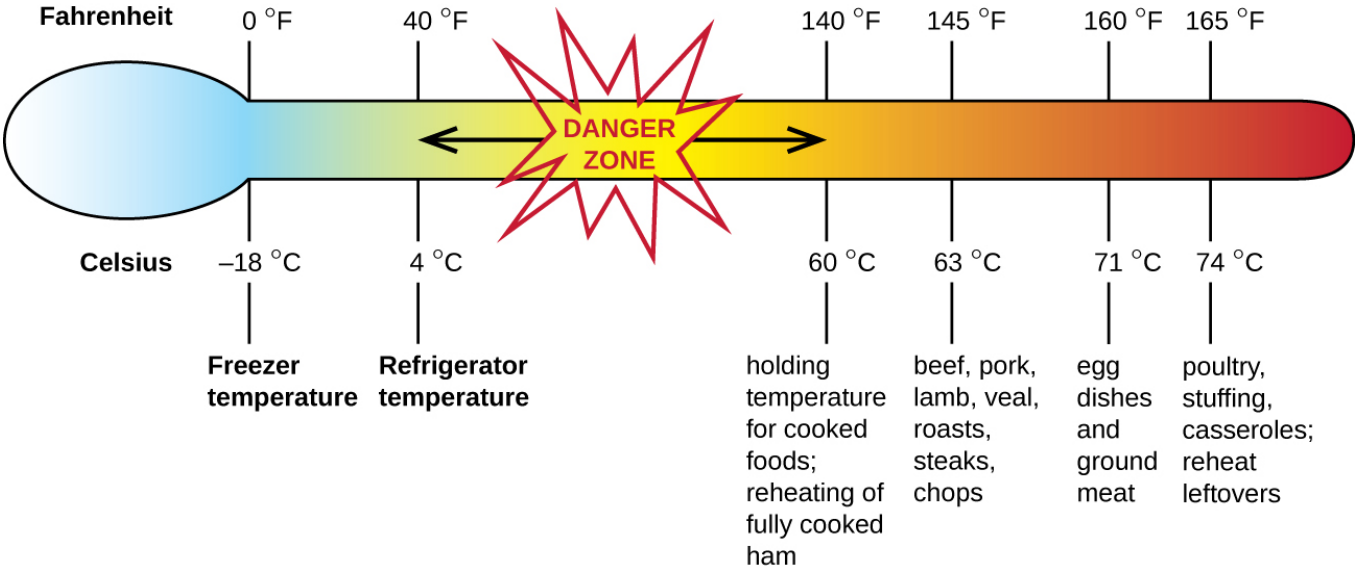


Figure 17.3.3.1: This figure indicates safe internal temperatures associated with the refrigeration, cooking, and reheating of different foods. Temperatures above refrigeration and below the minimum cooking temperature may allow for microbial growth, increasing the likelihood of foodborne disease. (credit: modification of work by USDA)

There are at least 21 *Staphylococcal* enterotoxins and *Staphylococcal* enterotoxin-like toxins that can cause food intoxication. The enterotoxins are proteins that are resistant to low pH, allowing them to pass through the stomach. They are heat stable and are not

destroyed by boiling at 100 °C. Even though the bacterium itself may be killed, the enterotoxins alone can cause vomiting and diarrhea, although the mechanisms are not fully understood. At least some of the symptoms may be caused by the enterotoxin functioning as a superantigen and provoking a strong immune response by activating T cell proliferation.

The rapid onset of signs and symptoms helps to diagnose this foodborne illness. Because the bacterium does not need to be present for the toxin to cause symptoms, diagnosis is confirmed by identifying the toxin in a food sample or in biological specimens (feces or vomitus) from the patient. Serological techniques, including ELISA, can also be used to identify the toxin in food samples.

The condition generally resolves relatively quickly, within 24 hours, without treatment. In some cases, supportive treatment in a hospital may be needed.

? Exercise 17.3.3.1

How can *S. aureus* cause food intoxication?

Shigellosis (Bacillary Dysentery)

When gastrointestinal illness is associated with the rod-shaped, gram-negative bacterium *Shigella*, it is called bacillary dysentery, or shigellosis. Infections can be caused by *S. dysenteriae*, *S. flexneri*, *S. boydii*, and/or *S. sonnei* that colonize the GI tract. Shigellosis can be spread from hand to mouth or through contaminated food and water. Most commonly, it is transmitted through the fecal-oral route.

Shigella bacteria invade intestinal epithelial cells. When taken into a phagosome, they can escape and then live within the cytoplasm of the cell or move to adjacent cells. As the organisms multiply, the epithelium and structures with M cells of the Peyer's patches in the intestine may become ulcerated and cause loss of fluid. Stomach cramps, fever, and watery diarrhea that may also contain pus, mucus, and/or blood often develop. More severe cases may result in ulceration of the mucosa, dehydration, and rectal bleeding. Additionally, patients may later develop hemolytic uremic syndrome (HUS), a serious condition in which damaged blood cells build up in the kidneys and may cause kidney failure, or reactive arthritis, a condition in which arthritis develops in multiple joints following infection. Patients may also develop chronic post-infection irritable bowel syndrome (IBS).

S. dysenteriae type 1 is able to produce Shiga toxin, which targets the endothelial cells of small blood vessels in the small and large intestine by binding to a glycosphingolipid. Once inside the endothelial cells, the toxin targets the large ribosomal subunit, thus affecting protein synthesis of these cells. Hemorrhaging and lesions in the colon can result. The toxin can target the kidney's glomerulus, the blood vessels where filtration of blood in the kidney begins, thus resulting in HUS.

Stool samples, which should be processed promptly, are analyzed using serological or molecular techniques. One common method is to perform immunoassays for *S. dysenteriae*. (Other methods that can be used to identify *Shigella* include API test strips, Enterotube systems, or PCR testing. The presence of white blood cells and blood in fecal samples occurs in about 70% of patients[1] (Figure **17.3.3.2**). Severe cases may require antibiotics such as ciprofloxacin and azithromycin, but these must be carefully prescribed because resistance is increasingly common.

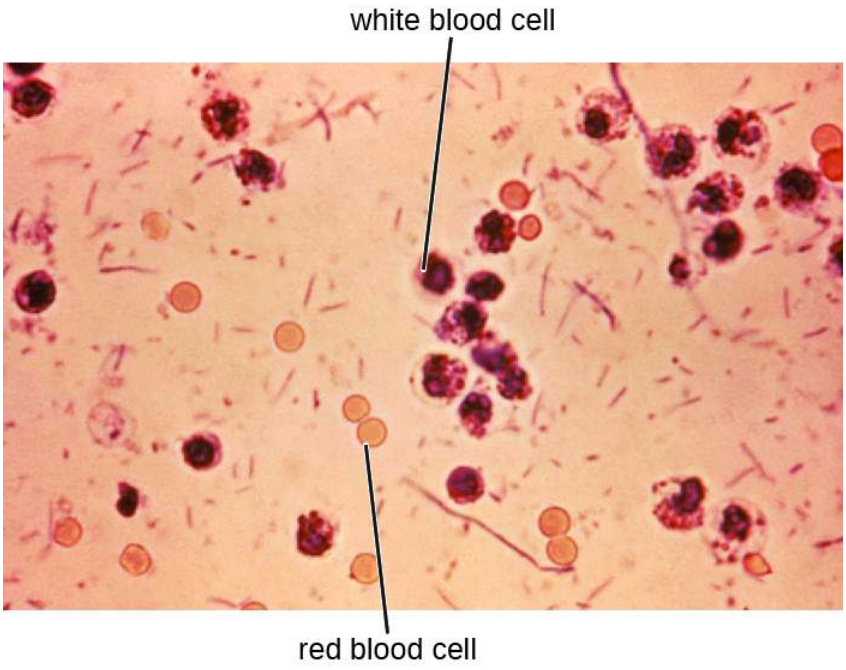


Figure 17.3.3.2: Red and white blood cells can be seen in this micrograph of a stool sample from a patient with shigellosis.

? Exercise 17.3.3.2

Compare and contrast *Shigella* infections and intoxications.

Salmonellosis

Salmonella gastroenteritis, also called salmonellosis, is caused by the rod-shaped, gram-negative bacterium *Salmonella*. Two species, *S. enterica* and *S. bongori*, cause disease in humans, but *S. enterica* is the most common. The most common serotypes of *S. enterica* are Enteritidis and Typhi. We will discuss typhoid fever caused by serotypes Typhi and Paratyphi A separately. Here, we will focus on salmonellosis caused by other serotypes.

Salmonella is a part of the normal intestinal microbiota of many individuals. However, salmonellosis is caused by exogenous agents, and infection can occur depending on the serotype, size of the inoculum, and overall health of the host. Infection is caused by ingestion of contaminated food, handling of eggshells, or exposure to certain animals. *Salmonella* is part of poultry's microbiota, so exposure to raw eggs and raw poultry can increase the risk of infection. Handwashing and cooking foods thoroughly greatly reduce the risk of transmission. *Salmonella* bacteria can survive freezing for extended periods but cannot survive high temperatures.

Once the bacteria are ingested, they multiply within the intestines and penetrate the epithelial mucosal cells via M cells where they continue to grow (Figure 17.3.3.3). They trigger inflammatory processes and the hypersecretion of fluids. Once inside the body, they can persist inside the phagosomes of macrophages. *Salmonella* can cross the epithelial cell membrane and enter the bloodstream and lymphatic system. Some strains of *Salmonella* also produce an enterotoxin that can cause an intoxication.

Infected individuals develop fever, nausea, abdominal cramps, vomiting, headache, and diarrhea. These signs and symptoms generally last a few days to a week. According to the Centers for Disease Control and Prevention (CDC), there are 1,000,000 cases annually, with 380 deaths each year.[2] However, because the disease is usually self-limiting, many cases are not reported to doctors and the overall incidence may be underreported. Diagnosis involves culture followed by serotyping and DNA fingerprinting if needed. Positive results are reported to the CDC. When an unusual serotype is detected, samples are sent to the CDC for further analysis. Serotyping is important for determining treatment. Oral rehydration therapy is commonly used. Antibiotics are only recommended for serious cases. When antibiotics are needed, as in immunocompromised patients, fluoroquinolones, third-generation cephalosporins, and ampicillin are recommended. Antibiotic resistance is a serious concern.



Figure **17.3.3.3**: Salmonella entering an intestinal epithelial cell by reorganizing the host cell's cytoskeleton via the trigger mechanism. (credit: modification of work by National Institutes for Health)

Typhoid Fever

Certain serotypes of *S. enterica*, primarily serotype Typhi (*S. typhi*) but also Paratyphi, cause a more severe type of salmonellosis called typhoid fever. This serious illness, which has an untreated mortality rate of 10%, causes high fever, body aches, headache, nausea, lethargy, and a possible rash.

Some individuals carry *S. typhi* without presenting signs or symptoms (known as asymptomatic carriers) and continually shed them through their feces. These carriers often have the bacteria in the gallbladder or intestinal epithelium. Individuals consuming food or water contaminated with these feces can become infected.

S. typhi penetrate the intestinal mucosa, grow within the macrophages, and are transported through the body, most notably to the liver and gallbladder. Eventually, the macrophages lyse, releasing *S. typhi* into the bloodstream and lymphatic system. Mortality can result from ulceration and perforation of the intestine. A wide range of complications, such as pneumonia and jaundice, can occur with disseminated disease.

S. typhi have *Salmonella* pathogenicity islands (SPIs) that contain the genes for many of their virulence factors. Two examples of important typhoid toxins are the Vi antigen, which encodes for capsule production, and chimeric A2B5 toxin, which causes many of the signs and symptoms of the acute phase of typhoid fever.

Clinical examination and culture are used to make the diagnosis. The bacteria can be cultured from feces, urine, blood, or bone marrow. Serology, including ELISA, is used to identify the most pathogenic strains, but confirmation with DNA testing or culture is needed. A PCR test can also be used, but is not widely available.

The recommended antibiotic treatment involves fluoroquinolones, ceftriaxone, and azithromycin. Individuals must be extremely careful to avoid infecting others during treatment. Typhoid fever can be prevented through vaccination for individuals traveling to parts of the world where it is common.

? Exercise 17.3.3.3

Why is serotyping particularly important in *Salmonella* infections and typhoid fever?

Typhoid Mary

Mary Mallon was an Irish immigrant who worked as a cook in New York in the early 20th century. Over seven years, from 1900 to 1907, Mallon worked for a number of different households, unknowingly spreading illness to the people who lived in each one. In 1906, one family hired George Soper, an expert in typhoid fever epidemics, to determine the cause of the illnesses in their household. Eventually, Soper tracked Mallon down and directly linked 22 cases of typhoid fever to her. He discovered that Mallon was a carrier for typhoid but was immune to it herself. Although active carriers had been recognized before, this was the first time that an asymptomatic carrier of infection had been identified.

Because she herself had never been ill, Mallon found it difficult to believe she could be the source of the illness. She fled from Soper and the authorities because she did not want to be quarantined or forced to give up her profession, which was relatively well paid for someone with her background. However, Mallon was eventually caught and kept in an isolation facility in the Bronx, where she remained until 1910, when the New York health department released her under the condition that she never again work with food. Unfortunately, Mallon did not comply, and she soon began working as a cook again. After new cases began to appear that resulted in the death of two individuals, the authorities tracked her down again and returned her to isolation, where she remained for 23 more years until her death in 1938. Epidemiologists were able to trace 51 cases of typhoid fever and three deaths directly to Mallon, who is unflatteringly remembered as "Typhoid Mary."

The Typhoid Mary case has direct correlations in the health-care industry. Consider Kaci Hickox, an American nurse who treated Ebola patients in West Africa during the 2014 epidemic. After returning to the United States, Hickox was quarantined against her will for three days and later found not to have Ebola. Hickox vehemently opposed the quarantine. In an editorial published in the British newspaper *The Guardian*,[3] Hickox argued that quarantining asymptomatic health-care workers who had not tested positive for a disease would not only prevent such individuals from practicing their profession, but discourage others from volunteering to work in disease-ridden areas where health-care workers are desperately needed.

What is the responsibility of an individual like Mary Mallon to change her behavior to protect others? What happens when an individual believes that she is not a risk, but others believe that she is? How would you react if you were in Mallon's shoes and were placed in a quarantine you did not believe was necessary, at the expense of your own freedom and possibly your career? Would it matter if you were definitely infected or not?

E. coli Infections

The gram-negative rod *Escherichia coli* is a common member of the normal microbiota of the colon. Although the vast majority of *E. coli* strains are helpful commensal bacteria, some can be pathogenic and may cause dangerous diarrheal disease. The pathogenic strains have additional virulence factors such as type 1 fimbriae that promote colonization of the colon or may produce toxins (see Virulence Factors of Bacterial and Viral Pathogens). These virulence factors are acquired through horizontal gene transfer.

Extraintestinal disease can result if the bacteria spread from the gastrointestinal tract. Although these bacteria can be spread from person to person, they are often acquired through contaminated food or water. There are six recognized pathogenic groups of *E. coli*, but we will focus here on the four that are most commonly transmitted through food and water.

Enterotoxigenic *E. coli* (ETEC), also known as traveler's diarrhea, causes diarrheal illness and is common in less developed countries. In Mexico, ETEC infection is called Montezuma's Revenge. Following ingestion of contaminated food or water, infected individuals develop a watery diarrhea, abdominal cramps, malaise (a feeling of being unwell), and a low fever. ETEC produces a heat-stable enterotoxin similar to cholera toxin, and adhesins called colonization factors that help the bacteria to attach to the intestinal wall. Some strains of ETEC also produce heat-labile toxins. The disease is usually relatively mild and self-limiting. Diagnosis involves culturing and PCR. If needed, antibiotic treatment with fluoroquinolones, doxycycline, rifaximin, and trimethoprim-sulfamethoxazole (TMP/SMZ) may shorten infection duration. However, antibiotic resistance is a problem.

Enteroinvasive *E. coli* (EIEC) is very similar to shigellosis, including its pathogenesis of intracellular invasion into intestinal epithelial tissue. This bacterium carries a large plasmid that is involved in epithelial cell penetration. The illness is usually self-limiting, with symptoms including watery diarrhea, chills, cramps, malaise, fever, and dysentery. Culturing and PCR testing can be used for diagnosis. Antibiotic treatment is not recommended, so supportive therapy is used if needed.

Enteropathogenic *E. coli* (EPEC) can cause a potentially fatal diarrhea, especially in infants and those in less developed countries. Fever, vomiting, and diarrhea can lead to severe dehydration. These *E. coli* inject a protein (Tir) that attaches to the surface of the intestinal epithelial cells and triggers rearrangement of host cell actin from microvilli to pedestals. Tir also happens to be the receptor for Intimin, a surface protein produced by EPEC, thereby allowing *E. coli* to "sit" on the pedestal. The genes necessary for this pedestal formation are encoded on the locus for enterocyte effacement (LEE) pathogenicity island. As with ETEC, diagnosis involves culturing and PCR. Treatment is similar to that for ETEC.

The most dangerous strains are enterohemorrhagic *E. coli* (EHEC), which are the strains capable of causing epidemics. In particular, the strain O157:H7 has been responsible for several recent outbreaks. Recall that the O and H refer to surface antigens that contribute to pathogenicity and trigger a host immune response ("O" refers to the O-side chain of the lipopolysaccharide and the "H" refers to the flagella). Similar to EPEC, EHEC also forms pedestals. EHEC also produces a Shiga-like toxin. Because the genome of this bacterium has been sequenced, it is known that the Shiga toxin genes were most likely acquired through transduction (horizontal gene transfer). The Shiga toxin genes originated from *Shigella dysenteriae*. Prophage from a bacteriophage that previously infected *Shigella* integrated into the chromosome of *E. coli*. The Shiga-like toxin is often called verotoxin.

EHEC can cause disease ranging from relatively mild to life-threatening. Symptoms include bloody diarrhea with severe cramping, but no fever. Although it is often self-limiting, it can lead to hemorrhagic colitis and profuse bleeding. One possible complication is HUS. Diagnosis involves culture, often using MacConkey with sorbitol agar to differentiate between *E. coli* O157:H7, which does not ferment sorbitol, and other less virulent strains of *E. coli* that can ferment sorbitol.

Serological typing or PCR testing also can be used, as well as genetic testing for Shiga toxin. To distinguish EPEC from EHEC, because they both form pedestals on intestinal epithelial cells, it is necessary to test for genes encoding for both the Shiga-like toxin and for the LEE. Both EPEC and EHEC have LEE, but EPEC lacks the gene for Shiga toxin. Antibiotic therapy is not recommended and may worsen HUS because of the toxins released when the bacteria are killed, so supportive therapies must be used. Table **17.3.3.1** summarizes the characteristics of the four most common pathogenic groups.

Table **17.3.3.1**: Some Pathogenic Groups of E. coli

Group	Virulence Factors and Genes	Signs and Symptoms	Diagnostic Tests	Treatment
Enterotoxigenic *E. coli* (ETEC)	Heat stable enterotoxin similar to cholera toxin	Relatively mild, watery diarrhea	Culturing, PCR	Self-limiting; if needed, fluoroquinolones, doxycycline, rifaximin, TMP/SMZ; antibiotic resistance is a problem
Enteroinvasive *E. coli* (EIEC)	*Inv* (invasive plasmid) genes	Relatively mild, watery diarrhea; dysentery or inflammatory colitis may occur	Culturing, PCR; testing for *inv* gene; additional assays to distinguish from *Shigella*	Supportive therapy only; antibiotics not recommended
Enteropathogenic *E. coli* (EPEC)	Locus of enterocyte effacement (LEE) pathogenicity island	Severe fever, vomiting, nonbloody diarrhea, dehydration; potentially fatal	Culturing, PCR; detection of LEE lacking Shiga-like toxin genes	Self-limiting; if needed, fluoroquinolones, doxycycline, rifaximin (TMP/SMZ); antibiotic resistance is a problem
Enterohemorrhagic *E. coli* (EHEC)	Verotoxin	May be mild or very severe; bloody diarrhea; may result in HUS	Culturing; plate on MacConkey agar with sorbitol agar as it does not ferment sorbitol; PCR detection of LEE containing Shiga-like toxin genes	Antibiotics are not recommended due to the risk of HUS

? Exercise 17.3.3.4

Compare and contrast the virulence factors and signs and symptoms of infections with the four main *E. coli* groups.

Cholera and Other Vibrios

The gastrointestinal disease cholera is a serious infection often associated with poor sanitation, especially following natural disasters, because it is spread through contaminated water and food that has not been heated to temperatures high enough to kill the bacteria. It is caused by *Vibrio cholerae* serotype O1, a gram-negative, flagellated bacterium in the shape of a curved rod (vibrio). According to the CDC, cholera causes an estimated 3 to 5 million cases and 100,000 deaths each year.[4]

Because *V. cholerae* is killed by stomach acid, relatively large doses are needed for a few microbial cells to survive to reach the intestines and cause infection. The motile cells travel through the mucous layer of the intestines, where they attach to epithelial cells and release cholera enterotoxin. The toxin is an A-B toxin with activity through adenylate cyclase (see Virulence Factors of Bacterial and Viral Pathogens). Within the intestinal cell, cyclic AMP (cAMP) levels increase, which activates a chloride channel and results in the release of ions into the intestinal lumen. This increase in osmotic pressure in the lumen leads to water also entering the lumen. As the water and electrolytes leave the body, it causes rapid dehydration and electrolyte imbalance. Diarrhea is so profuse that it is often called “rice water stool,” and patients are placed on cots with a hole in them to monitor the fluid loss (Figure **17.3.3.4**).

Cholera is diagnosed by taking a stool sample and culturing for *Vibrio*. The bacteria are oxidase positive and show non-lactose fermentation on MacConkey agar. Gram-negative lactose fermenters will produce red colonies while non-fermenters will produce white/colorless colonies. Gram-positive bacteria will not grow on MacConkey. Lactose fermentation is commonly used for pathogen identification because the normal microbiota generally ferments lactose while pathogens do not. *V. cholerae* may also be cultured on thiosulfate citrate bile salts sucrose (TCBS) agar, a selective and differential media for *Vibrio* spp., which produce a distinct yellow colony.

Cholera may be self-limiting and treatment involves rehydration and electrolyte replenishment. Although antibiotics are not typically needed, they can be used for severe or disseminated disease. Tetracyclines are recommended, but doxycycline, erythromycin, orfloxacin, ciprofloxacin, and TMP/SMZ may be used. Recent evidence suggests that azithromycin is also a good first-line antibiotic. Good sanitation—including appropriate sewage treatment, clean supplies for cooking, and purified drinking water—is important to prevent infection (Figure **17.3.3.4**)



(a) (b) (c)

Figure **17.3.3.4**: (a) Outbreaks of cholera often occur in areas with poor sanitation or after natural disasters that compromise sanitation infrastructure. (b) At a cholera treatment center in Haiti, patients are receiving intravenous fluids to combat the dehydrating effects of this disease. They often lie on a cot with a hole in it and a bucket underneath to allow for monitoring of fluid loss. (c) This scanning electron micrograph shows *Vibrio cholera*. (credit a, b: modification of work by Centers for Disease Control and Prevention; credit c: modification of work by Janice Carr, Centers for Disease Control and Prevention)

V. cholera is not the only *Vibrio* species that can cause disease. *V. parahemolyticus* is associated with consumption of contaminated seafood and causes gastrointestinal illness with signs and symptoms such as watery diarrhea, nausea, fever, chills, and abdominal cramps. The bacteria produce a heat-stable hemolysin, leading to dysentery and possible disseminated disease. It also sometimes causes wound infections. *V. parahemolyticus* is diagnosed using cultures from blood, stool, or a wound. As with *V. cholera*,

selective medium (especially TCBS agar) works well. Tetracycline and ciprofloxacin can be used to treat severe cases, but antibiotics generally are not needed.

Vibrio vulnificus is found in warm seawater and, unlike *V. cholerae*, is not associated with poor sanitary conditions. The bacteria can be found in raw seafood, and ingestion causes gastrointestinal illness. It can also be acquired by individuals with open skin wounds who are exposed to water with high concentrations of the pathogen. In some cases, the infection spreads to the bloodstream and causes septicemia. Skin infection can lead to edema, ecchymosis (discoloration of skin due to bleeding), and abscesses. Patients with underlying disease have a high fatality rate of about 50%. It is of particular concern for individuals with chronic liver disease or who are otherwise immunodeficient because a healthy immune system can often prevent infection from developing. *V. vulnificus* is diagnosed by culturing for the pathogen from stool samples, blood samples, or skin abscesses. Adult patients are treated with doxycycline combined with a third generation cephalosporin or with fluoroquinolones, and children are treated with TMP/SMZ.

Two other vibrios, *Aeromonas hydrophila* and *Plesiomonas shigelloides*, are also associated with marine environments and raw seafood; they can also cause gastroenteritis. Like *V. vulnificus*, *A. hydrophila* is more often associated with infections in wounds, generally those acquired in water. In some cases, it can also cause septicemia. Other species of *Aeromonas* can cause illness. *P. shigelloides* is sometimes associated with more serious systemic infections if ingested in contaminated food or water. Culture can be used to diagnose *A. hydrophila* and *P. shigelloides* infections, for which antibiotic therapy is generally not needed. When necessary, tetracycline and ciprofloxacin, among other antibiotics, may be used for treatment of *A. hydrophila*, and fluoroquinolones and trimethoprim are the effective treatments for *P. shigelloides*.

? Exercise 17.3.3.5

How does *V. cholera* infection cause rapid dehydration?

Campylobacter jejuni Gastroenteritis

Campylobacter is a genus of gram-negative, spiral or curved bacteria. They may have one or two flagella. *Campylobacter jejuni* gastroenteritis, a form of campylobacteriosis, is a widespread illness that is caused by *Campylobacter jejuni*. The primary route of transmission is through poultry that becomes contaminated during slaughter. Handling of the raw chicken in turn contaminates cooking surfaces, utensils, and other foods. Unpasteurized milk or contaminated water are also potential vehicles of transmission. In most cases, the illness is self-limiting and includes fever, diarrhea, cramps, vomiting, and sometimes dysentery. More serious signs and symptoms, such as bacteremia, meningitis, pancreatitis, cholecystitis, and hepatitis, sometimes occur. It has also been associated with autoimmune conditions such as Guillain-Barré syndrome, a neurological disease that occurs after some infections and results in temporary paralysis. HUS following infection can also occur. The virulence in many strains is the result of hemolysin production and the presence of *Campylobacter* cytolethal distending toxin (CDT), a powerful deoxyribonuclease (DNase) that irreversibly damages host cell DNA.

Diagnosis involves culture under special conditions, such as elevated temperature, low oxygen tension, and often medium supplemented with antimicrobial agents. These bacteria should be cultured on selective medium (such as Campy CV, charcoal selective medium, or cefaperazone charcoal deoxycholate agar) and incubated under microaerophilic conditions for at least 72 hours at 42 °C. Antibiotic treatment is not usually needed, but erythromycin or ciprofloxacin may be used.

Peptic Ulcers

The gram-negative bacterium *Helicobacter pylori* is able to tolerate the acidic environment of the human stomach and has been shown to be a major cause of peptic ulcers, which are ulcers of the stomach or duodenum. The bacterium is also associated with increased risk of stomach cancer (Figure **17.3.3.5**). According to the CDC, approximately two-thirds of the population is infected with *H. pylori*, but less than 20% have a risk of developing ulcers or stomach cancer. *H. pylori* is found in approximately 80% of stomach ulcers and in over 90% of duodenal ulcers.[5]

H. pylori colonizes epithelial cells in the stomach using pili for adhesion. These bacteria produce urease, which stimulates an immune response and creates ammonia that neutralizes stomach acids to provide a more hospitable microenvironment. The infection damages the cells of the stomach lining, including those that normally produce the protective mucus that serves as a barrier between the tissue and stomach acid. As a result, inflammation (gastritis) occurs and ulcers may slowly develop. Ulcer

formation can also be caused by toxin activity. It has been reported that 50% of clinical isolates of *H. pylori* have detectable levels of exotoxin activity *in vitro*.[6] This toxin, VacA, induces vacuole formation in host cells. VacA has no primary sequence homology with other bacterial toxins, and in a mouse model, there is a correlation between the presence of the toxin gene, the activity of the toxin, and gastric epithelial tissue damage.

Signs and symptoms include nausea, lack of appetite, bloating, burping, and weight loss. Bleeding ulcers may produce dark stools. If no treatment is provided, the ulcers can become deeper, more tissues can be involved, and stomach perforation can occur. Because perforation allows digestive enzymes and acid to leak into the body, it is a very serious condition.

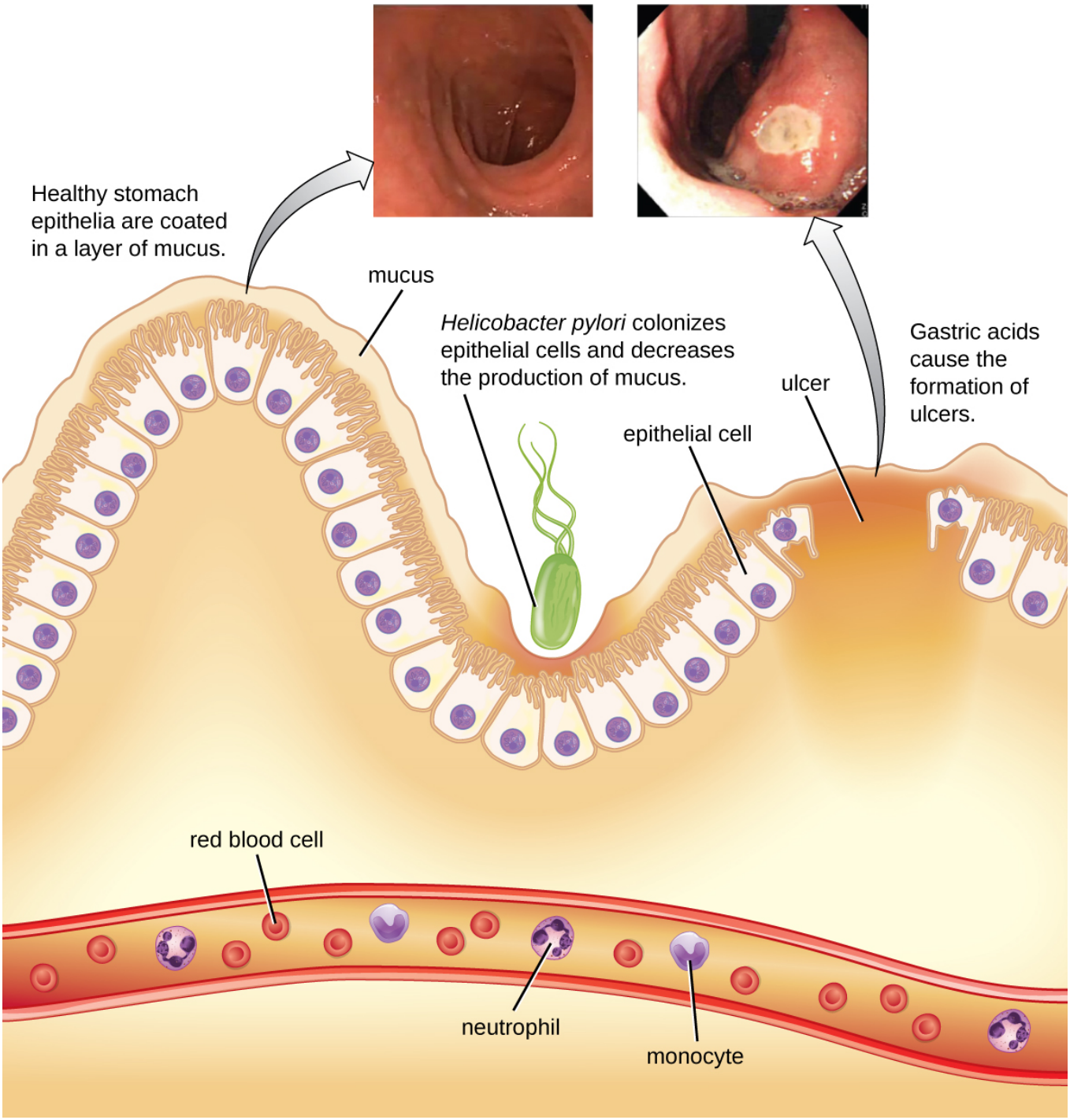


Figure **17.3.3.5**: Helicobacter infection decreases mucus production and causes peptic ulcers. (credit top left photo: modification of work by "Santhosh Thomas"/YouTube; credit top right photo: modification of work by Moriya M, Uehara A, Okumura T, Miyamoto M, and Kohgo Y)

To diagnose *H. pylori* infection, multiple methods are available. In a breath test, the patient swallows radiolabeled urea. If *H. pylori* is present, the bacteria will produce urease to break down the urea. This reaction produces radiolabeled carbon dioxide that can be detected in the patient's breath. Blood testing can also be used to detect antibodies to *H. pylori*. The bacteria themselves can be detected using either a stool test or a stomach wall biopsy.

Antibiotics can be used to treat the infection. However, unique to *H. pylori*, the recommendation from the US Food and Drug Administration is to use a triple therapy. The current protocols are 10 days of treatment with omeprazole, amoxicillin, and clarithromycin (OAC); 14 days of treatment with bismuth subsalicylate, metronidazole, and tetracycline (BMT); or 10 or 14 days of treatment with lansoprazole, amoxicillin, and clarithromycin (LAC). Omeprazole, bismuth subsalicylate, and lansoprazole are not antibiotics but are instead used to decrease acid levels because *H. pylori* prefers acidic environments.

Although treatment is often valuable, there are also risks to *H. pylori* eradication. Infection with *H. pylori* may actually protect against some cancers, such as esophageal adenocarcinoma and gastroesophageal reflux disease.[78]

? Exercise 17.3.3.6

How does *H. pylori* cause peptic ulcers?

Clostridium perfringens Gastroenteritis

Clostridium perfringens gastroenteritis is a generally mild foodborne disease that is associated with undercooked meats and other foods. *C. perfringens* is a gram-positive, rod-shaped, endospore-forming anaerobic bacterium that is tolerant of high and low temperatures. At high temperatures, the bacteria can form endospores that will germinate rapidly in foods or within the intestine. Food poisoning by type A strains is common. This strain always produces an enterotoxin, sometimes also present in other strains, that causes the clinical symptoms of cramps and diarrhea. A more severe form of the illness, called pig-bel or enteritis necroticans, causes hemorrhaging, pain, vomiting, and bloating. Gangrene of the intestines may result. This form has a high mortality rate but is rare in the United States.

Diagnosis involves detecting the *C. perfringens* toxin in stool samples using either molecular biology techniques (PCR detection of the toxin gene) or immunology techniques (ELISA). The bacteria itself may also be detected in foods or in fecal samples. Treatment includes rehydration therapy, electrolyte replacement, and intravenous fluids. Antibiotics are not recommended because they can damage the balance of the microbiota in the gut, and there are concerns about antibiotic resistance. The illness can be prevented through proper handling and cooking of foods, including prompt refrigeration at sufficiently low temperatures and cooking food to a sufficiently high temperature.

Clostridium difficile

Clostridium difficile is a gram-positive rod that can be a commensal bacterium as part of the normal microbiota of healthy individuals. When the normal microbiota is disrupted by long-term antibiotic use, it can allow the overgrowth of this bacterium, resulting in antibiotic-associated diarrhea caused by *C. difficile*. Antibiotic-associated diarrhea can also be considered a nosocomial disease. Patients at the greatest risk of *C. difficile* infection are those who are immunocompromised, have been in health-care settings for extended periods, are older, have recently taken antibiotics, have had gastrointestinal procedures done, or use proton pump inhibitors, which reduce stomach acidity and allow proliferation of *C. difficile*. Because this species can form endospores, it can survive for extended periods of time in the environment under harsh conditions and is a considerable concern in health-care settings.

This bacterium produces two toxins, *Clostridium difficile* toxin A (TcdA) and *Clostridium difficile* toxin B (TcdB). These toxins inactivate small GTP-binding proteins, resulting in actin condensation and cell rounding, followed by cell death. Infections begin with focal necrosis, then ulceration with exudate, and can progress to pseudomembranous colitis, which involves inflammation of the colon and the development of a pseudomembrane of fibrin containing dead epithelial cells and leukocytes (Figure **17.3.3.6**). Watery diarrhea, dehydration, fever, loss of appetite, and abdominal pain can result. Perforation of the colon can occur, leading to septicemia, shock, and death. *C. difficile* is also associated with necrotizing enterocolitis in premature babies and neutropenic enterocolitis associated with cancer therapies.

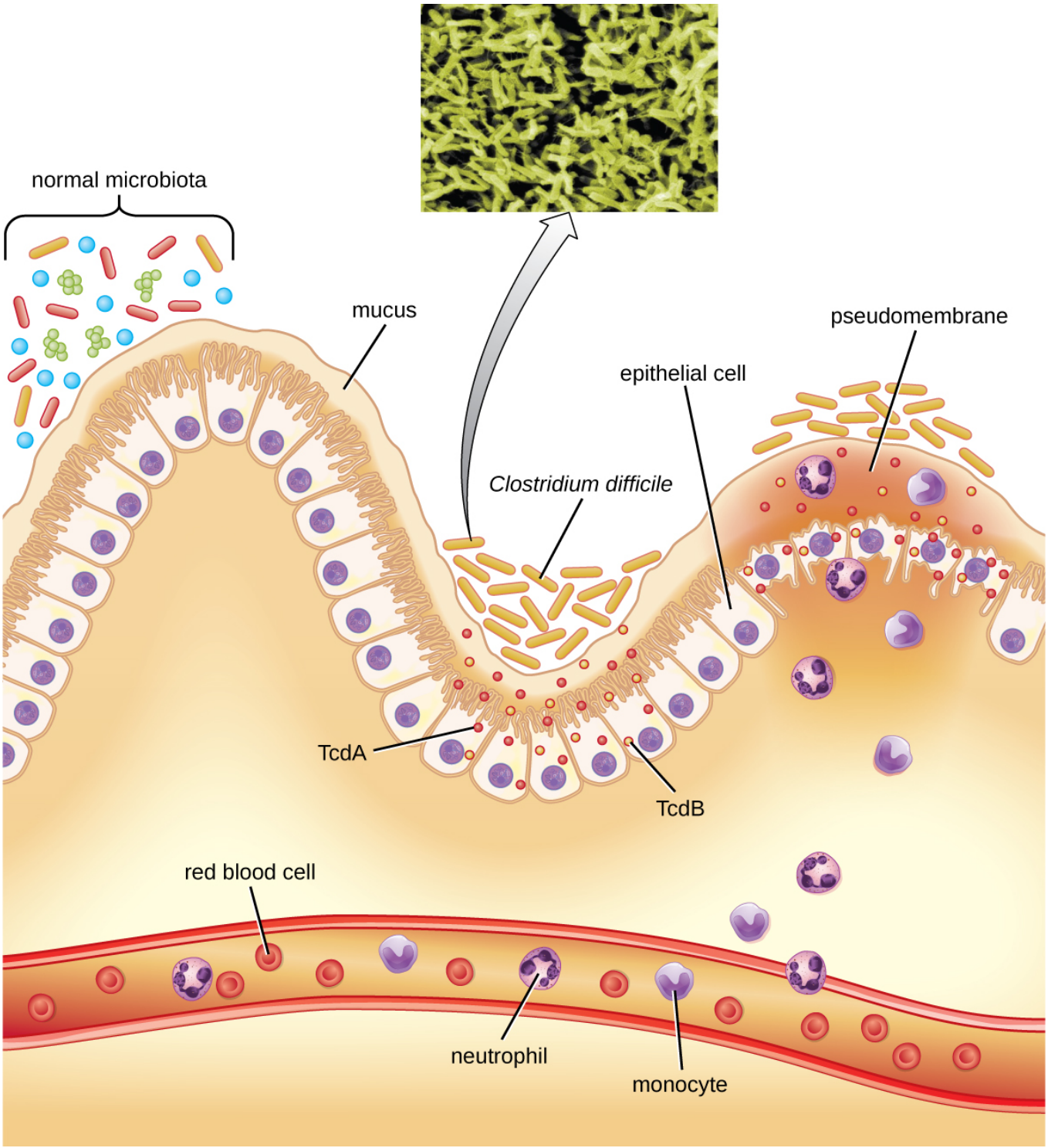


Figure **17.3.3.6**: Clostridium difficile is able to colonize the mucous membrane of the colon when the normal microbiota is disrupted. The toxins TcdA and TcdB trigger an immune response, with neutrophils and monocytes migrating from the bloodstream to the site of infection. Over time, inflammation and dead cells contribute to the development of a pseudomembrane. (credit micrograph: modification of work by Janice Carr, Centers for Disease Control and Prevention)

Diagnosis is made by considering the patient history (such as exposure to antibiotics), clinical presentation, imaging, endoscopy, lab tests, and other available data. Detecting the toxin in stool samples is used to confirm diagnosis. Although culture is preferred, it is rarely practical in clinical practice because the bacterium is an obligate anaerobe. Nucleic acid amplification tests, including PCR, are considered preferable to ELISA testing for molecular analysis.

The first step of conventional treatment is to stop antibiotic use, and then to provide supportive therapy with electrolyte replacement and fluids. Metronidazole is the preferred treatment if the *C. difficile* diagnosis has been confirmed. Vancomycin can also be used, but it should be reserved for patients for whom metronidazole was ineffective or who meet other criteria (e.g., under 10 years of age, pregnant, or allergic to metronidazole).

A newer approach to treatment, known as a fecal transplant, focuses on restoring the microbiota of the gut in order to combat the infection. In this procedure, a healthy individual donates a stool sample, which is mixed with saline and transplanted to the recipient via colonoscopy, endoscopy, sigmoidoscopy, or enema. It has been reported that this procedure has greater than 90% success in resolving *C. difficile* infections.[9]

? Exercise 17.3.3.7

How does antibiotic use lead to *C. difficile* infections?

Foodborne Illness Due to *Bacillus cereus*

Bacillus cereus, commonly found in soil, is a gram-positive endospore-forming bacterium that can sometimes cause foodborne illness. *B. cereus* endospores can survive cooking and produce enterotoxins in food after it has been heated; illnesses often occur after eating rice and other prepared foods left at room temperature for too long. The signs and symptoms appear within a few hours of ingestion and include nausea, pain, and abdominal cramps. *B. cereus* produces two toxins: one causing diarrhea, and the other causing vomiting. More severe signs and symptoms can sometimes develop.

Diagnosis can be accomplished by isolating bacteria from stool samples or vomitus and uneaten infected food. Treatment involves rehydration and supportive therapy. Antibiotics are not typically needed, as the illness is usually relatively mild and is due to toxin activity.

Foodborne Illness Due to *Yersinia*

The genus *Yersinia* is best known for *Yersinia pestis*, a gram-negative rod that causes the plague. However, *Y. enterocolitica* and *Y. pseudotuberculosis* can cause gastroenteritis. The infection is generally transmitted through the fecal-oral route, with ingestion of food or water that has been contaminated by feces. Intoxication can also result because of the activity of its endotoxin and exotoxins (enterotoxin and cytotoxin necrotizing factor). The illness is normally relatively mild and self-limiting. However, severe diarrhea and dysentery can develop in infants. In adults, the infection can spread and cause complications such as reactive arthritis, thyroid disorders, endocarditis, glomerulonephritis, eye inflammation, and/or erythema nodosum. Bacteremia may develop in rare cases.

Diagnosis is generally made by detecting the bacteria in stool samples. Samples may also be obtained from other tissues or body fluids. Treatment is usually supportive, including rehydration, without antibiotics. If bacteremia or other systemic disease is present, then antibiotics such as fluoroquinolones, aminoglycosides, doxycycline, and trimethoprim-sulfamethoxazole may be used. Recovery can take up to two weeks.

? Exercise 17.3.3.8

Compare and contrast foodborne illnesses due to *B. cereus* and *Yersinia*.

Bacterial Infections of the Gastrointestinal Tract

Bacterial infections of the gastrointestinal tract generally occur when bacteria or bacterial toxins are ingested in contaminated food or water. Toxins and other virulence factors can produce gastrointestinal inflammation and general symptoms such as diarrhea and vomiting. Bacterial GI infections can vary widely in terms of severity and treatment. Some can be treated with antibiotics, but in other cases antibiotics may be ineffective in combating toxins or even counterproductive if they compromise the GI microbiota. Figure **17.3.3.7** and Figure **17.3.3.8** the key features of common bacterial GI infections.

Bacterial Infections of the GI Tract					
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Diagnostic Tests**	**Antimicrobial Drugs**
Bacillus cereus infection	*Bacillus cereus*	Nausea, pain, abdominal cramps, diarrhea, or vomiting	Ingestion of contaminated rice or meat, even after cooking	Testing stool sample, vomitus, or uneaten food for presence of bacteria	None
Campylobacter jejuni gastroenteritis	*Campylobacter jejuni*	Fever, diarrhea, cramps, vomiting, and sometimes dysentery; sometimes more severe organ or autoimmune effects	Ingestion of unpasteurized milk, under-cooked chicken, or contaminated water	Culture on selective medium with elevated temperature and low oxygen concentration	Generally none; erythromycin or ciprofloxacin if necessary
Cholera	*Vibrio cholerae*	Severe diarrhea and fluid loss, potentially leading to shock, renal failure, and death	Ingestion of contaminated water or food	Culture on selective medium (TCBS agar); distinguished as oxidase positive with fermentative metabolisms	Generally none; tetracyclines, azithromycin, others if necessary
Clostridium difficile infection	*Clostridium difficile*	Pseudomem-branous colitis, watery diarrhea, fever, abdominal pain, loss of appe-tite, dehydration; in severe cases, perforation of the colon, septicemia, shock, and death	Overgrowth of *C. difficile* in the normal microbiota due to antibiotic use; hospital-acquired infections in immunocompro-mised patients	Detection of toxin in stool, nucleic acid amplification tests (e.g., PCR)	Discontinuation of previous antibiotic treatment; metronidazole or vancomycin
Clostridium perfringens gastroenteritis	*Clostridium perfringens* (especially type A)	Mild cramps and diarrhea in most cases; in rare cases, hemor-rhaging, vomiting, intestinal gangrene, and death	Ingestion of undercooked meats containing *C. perfringens* endospores	Detection of toxin or bacteria in stool or uneaten food	None
E. coli infection	ETEC, EPEC, EIEC, EHEC	Watery diarrhea, dysentery, cramps, malaise, fever, chills, dehydration; in EHEC, possible severe compli-cations such as hematolytic uremic syndrome	Ingestion of contaminated food or water	Tissue culture, immunochemi-cal assays, PCR, gene probes	Not recommended for EIEC and EHEC; fluoroquinolones, doxycycline, rifaximin, and TMP/SMZ possible for ETEC and EPEC

Figure **17.3.3.7**: Bacterial infections of the GI tract.

Bacterial Infections of the GI Tract (continued)					
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Diagnostic Tests**	**Antimicrobial Drugs**
Peptic ulcers	*Helicobacter pylori*	Nausea, bloating, burping, lack of appetite, weight loss, perforation of stomach, blood in stools	Normal flora, can also be acquired via saliva; fecal-oral route via contaminated food and water	Breath test, detection of antibodies in blood, detection of bacteria in stool sample or stomach biopsy	Amoxicillin, clarithromycin metronidazole, tetracycline, lansoprazole; antacids may also be given in combination with antibiotics
Salmonellosis	*Salmonella enterica,* serotype Enteritides	Fever, nausea, vomiting, abdominal cramps, headache, diarrhea; can be fatal in infants	Ingestion of contaminated food, handling of eggshells or contaminated animals	Culturing, serotyping and DNA fingerprinting	Not generally recommended; fluoroquinolones, ampicillin, others for immunocompromised patients
Shigella dysentery	*Shigella dysenteriae, S. flexneri, S. boydii,* and *S. sonnei*	Abdominal cramps, fever, diarrhea, dysentery; possible complications: reactive arthritis and hemolytic uremic syndrome	Fecal-oral route via contaminated food and water	Testing of stool samples for presence of blood and leukocytes; culturing, PCR, immunoassay for *S. dysenteriae*	Ciprofloxacin, azithromycin
Staphylococcal food poisoning	*Staphylococcus aureus*	Rapid-onset nausea, diarrhea, vomiting lasting 24–48 hours; possible dehydration and change in blood pressure and heart rate	Ingestion of raw or undercooked meat or dairy products conta-minated with staphylococcal enterotoxins	ELISA to detect enterotoxins in uneaten food, stool, or vomitus	None
Typhoid fever	*S. entrica*, subtypes Typhi or Paratyphi	Aches, headaches, nausea, lethargy, diarrhea or constipation, possible rash; lethal perforation of intestine can occur	Fecal-oral route; may be spread by asymptomatic carriers	Culture of blood, stool, or bone marrow, serologic tests; PCR tests when available	Fluoroquinolones, ceftriaxone, azithromycin; preventive vaccine available
Yersinia infection	*Yersinia enterocolitica, Y. pseudo-tuberculosis*	Generally mild diarrhea and abdominal cramps; in some cases, bacteremia can occur, leading to severe complications	Fecal-oral route, typically via contaminated food or water	Testing stool samples, tissues, body fluids	Generally none; fluoroquinolones, aminoglycosides, others for systemic infections

Figure **17.3.3.8**: Bacterial infections of the GI tract (continued).

Clinical Focus: Part 2

At the hospital, Carli's doctor began to think about possible causes of her severe gastrointestinal distress. One possibility was food poisoning, but no one else in her family was sick. The doctor asked about what Carli had eaten the previous day; her mother mentioned that she'd had eggs for lunch, and that they may have been a little undercooked. The doctor took a sample of Carli's stool and sent it for laboratory testing as part of her workup. She suspected that Carli could have a case of bacterial or viral gastroenteritis, but she needed to know the cause in order to prescribe an appropriate treatment.

In the laboratory, technicians microscopically identified gram-negative bacilli in Carli's stool sample. They also established a pure culture of the bacteria and analyzed it for antigens. This testing showed that the causative agent was *Salmonella*.

Exercise 17.3.3.9

What should the doctor do now to treat Carli?

Key Concepts and Summary

- Major causes of gastrointestinal illness include *Salmonella* spp., *Staphylococcus* spp., *Helicobacter pylori*, *Clostridium perfringens*, *Clostridium difficile*, *Bacillus cereus*, and *Yersinia* bacteria.
- *C. difficile* is an important cause of hospital acquired infection.
- *Vibrio cholerae* causes **cholera**, which can be a severe diarrheal illness.
- Different strains of *E. coli*, including **ETEC**, **EPEC**, **EIEC**, and **EHEC**, cause different illnesses with varying degrees of severity.
- *H. pylori* is associated with **peptic ulcers**.
- *Salmonella enterica* serotypes can cause **typhoid fever**, a more severe illness than **salmonellosis**.
- Rehydration and other supportive therapies are often used as general treatments.
- Careful antibiotic use is required to reduce the risk of causing *C. difficile* infections and when treating antibiotic-resistant infections.

Footnotes

1. 1 Jaya Sureshbabu. "Shigella Infection Workup." *Medscape*. Updated Jun 28, 2016. http://emedicine.medscape.com/article/968773-workup.
2. 2 Centers for Disease Control and Prevention. *Salmonella*. Updated August 25, 2016. https://www.cdc.gov/salmonella.
3. 3 Kaci Hickox. "Stop Calling Me the 'Ebola Nurse.'" *The Guardian*. November 17, 2014. www.theguardian.com/commentis...se-kaci-hickox.
4. 4 Centers for Disease Control and Prevention. *Cholera—Vibrio cholerae Infection*. Updated November 6, 2014. http://www.cdc.gov/cholera/general. Accessed Sept 14, 2016.
5. 5 Centers for Disease Control and Prevention. "*Helicobacter pylori*: Fact Sheet for Health Care Providers." Updated July 1998. www.cdc.gov/ulcer/files/hpfacts.pdf.
6. 6 T. L. Cover. "The Vacuolating Cytotoxin of *Helicobacter pylori*." *Molecular Microbiology* 20 (1996) 2: pp. 241–246. http://www.ncbi.nlm.nih.gov/pubmed/8733223.
7. 7 Martin J. Blaser. "Disappearing Microbiota: *Helicobacter pylori* Protection against Esophageal Adenocarcinoma." *Cancer Prevention Research* 1 (2008) 5: pp. 308–311. http://cancerpreventionresearch.aacr....full.pdf+html.
8. 8 Ivan F. N. Hung and Benjamin C. Y. Wong. "Assessing the Risks and Benefits of Treating *Helicobacter pylori* Infection." *Therapeutic Advances in Gastroenterology* 2 (2009) 3: pp, 141–147. doi: 10.1177/1756283X08100279.
9. 9 Faith Rohlke and Neil Stollman. "Fecal Microbiota Transplantation in Relapsing *Clostridium difficile* Infection," *Therapeutic Advances in Gastroenterology* 5 (2012) 6: 403–420. doi: 10.1177/1756283X12453637.

This page titled 17.3.3: Bacterial Infections of the Gastrointestinal Tract is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **24.3: Bacterial Infections of the Gastrointestinal Tract** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

https://med.libretexts.org/@go/page/77960

17.3.4: Viral Infections of the Gastrointestinal Tract

Learning Objectives

- Identify the most common viruses that can cause infections of the GI tract
- Compare the major characteristics of specific viral diseases affecting the GI tract and liver

In the developing world, acute viral gastroenteritis is devastating and a leading cause of death for children.[1] Worldwide, diarrhea is the second leading cause of mortality for children under age five, and 70% of childhood gastroenteritis is viral.[2] As discussed, there are a number of bacteria responsible for diarrhea, but viruses can also cause diarrhea. *E. coli* and rotavirus are the most common causative agents in the developing world. In this section, we will discuss rotaviruses and other, less common viruses that can also cause gastrointestinal illnesses.

Gastroenteritis Caused by Rotaviruses

Rotaviruses are double-stranded RNA viruses in the family Reoviridae. They are responsible for common diarrheal illness, although prevention through vaccination is becoming more common. The virus is primarily spread by the fecal-oral route (Figure 17.3.4.1).

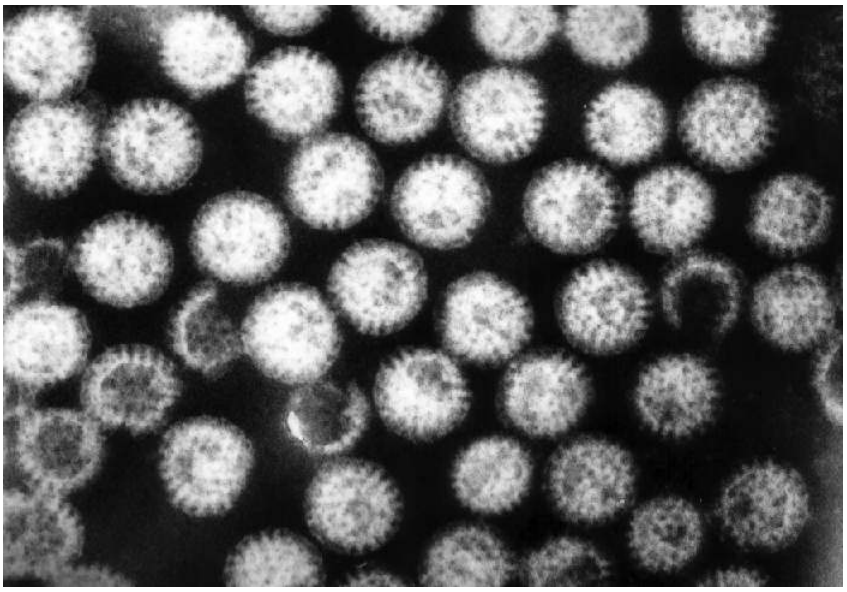


Figure 17.3.4.1: Rotaviruses in a fecal sample are visualized using electron microscopy. (credit: Dr. Graham Beards)

These viruses are widespread in children, especially in day-care centers. The CDC estimates that 95% of children in the United States have had at least one rotavirus infection by the time they reach age five.[3] Due to the memory of the body's immune system, adults who come into contact with rotavirus will not contract the infection or, if they do, are asymptomatic. The elderly, however, are vulnerable to rotavirus infection due to weakening of the immune system with age, so infections can spread through nursing homes and similar facilities. In these cases, the infection may be transmitted from a family member who may have subclinical or clinical disease. The virus can also be transmitted from contaminated surfaces, on which it can survive for some time.

Infected individuals exhibit fever, vomiting, and diarrhea. The virus can survive in the stomach following a meal, but is normally found in the small intestines, particularly the epithelial cells on the villi. Infection can cause food intolerance, especially with respect to lactose. The illness generally appears after an incubation period of about two days and lasts for approximately one week (three to eight days). Without supportive treatment, the illness can cause severe fluid loss, dehydration, and even death. Even with milder illness, repeated infections can potentially lead to malnutrition, especially in developing countries, where rotavirus infection is common due to poor sanitation and lack of access to clean drinking water. Patients (especially children) who are malnourished after an episode of diarrhea are more susceptible to future diarrheal illness, increasing their risk of death from rotavirus infection.

The most common clinical tool for diagnosis is enzyme immunoassay, which detects the virus from fecal samples. Latex agglutination assays are also used. Additionally, the virus can be detected using electron microscopy and RT-PCR.

Treatment is supportive with oral rehydration therapy. Preventive vaccination is also available. In the United States, rotavirus vaccines are part of the standard vaccine schedule and administration follows the guidelines of the World Health Organization (WHO). The WHO recommends that all infants worldwide receive the rotavirus vaccine, the first dose between six and 15 weeks of age and the second before 32 weeks.[4]

Gastroenteritis Caused by Noroviruses

Noroviruses, commonly identified as Norwalk viruses, are caliciviruses. Several strains can cause gastroenteritis. There are millions of cases a year, predominately in infants, young children, and the elderly. These viruses are easily transmitted and highly contagious. They are known for causing widespread infections in groups of people in confined spaces, such as on cruise ships. The viruses can be transmitted through direct contact, through touching contaminated surfaces, and through contaminated food. Because the virus is not killed by disinfectants used at standard concentrations for killing bacteria, the risk of transmission remains high, even after cleaning.

The signs and symptoms of norovirus infection are similar to those for rotavirus, with watery diarrhea, mild cramps, and fever. Additionally, these viruses sometimes cause projectile vomiting. The illness is usually relatively mild, develops 12 to 48 hours after exposure, and clears within a couple of days without treatment. However, dehydration may occur.

Norovirus can be detected using PCR or enzyme immunoassay (EIA) testing. RT-qPCR is the preferred approach as EIA is insufficiently sensitive. If EIA is used for rapid testing, diagnosis should be confirmed using PCR. No medications are available, but the illness is usually self-limiting. Rehydration therapy and electrolyte replacement may be used. Good hygiene, hand washing, and careful food preparation reduce the risk of infection.

Gastroenteritis Caused by Astroviruses

Astroviruses are single-stranded RNA viruses (family Astroviridae) that can cause severe gastroenteritis, especially in infants and children. Signs and symptoms include diarrhea, nausea, vomiting, fever, abdominal pain, headache, and malaise. The viruses are transmitted through the fecal-oral route (contaminated food or water). For diagnosis, stool samples are analyzed. Testing may involve enzyme immunoassays and immune electron microscopy. Treatment involves supportive rehydration and electrolyte replacement if needed.

? Exercise 17.3.4.1

Why are rotaviruses, noroviruses, and astroviruses more common in children?

Viral Infections of the Gastrointestinal Tract

A number of viruses can cause gastroenteritis, characterized by inflammation of the GI tract and other signs and symptoms with a range of severities. As with bacterial GI infections, some cases can be relatively mild and self-limiting, while others can become serious and require intensive treatment. Antimicrobial drugs are generally not used to treat viral gastroenteritis; generally, these illnesses can be treated effectively with rehydration therapy to replace fluids lost in bouts of diarrhea and vomiting. Because most viral causes of gastroenteritis are quite contagious, the best preventive measures involve avoiding and/or isolating infected individuals and limiting transmission through good hygiene and sanitation.

Viral Causes of Gastroenteritis					
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Diagnostic Tests**	**Vaccine**
Astrovirus gastroenteritis	Astroviru-ses	Fever, headache, abdominal pain, malaise, diarrhea, vomiting	Fecal-oral route, contaminated food or water	Enzyme immunoassays, immune electron microscopy	None
Norovirus gastroenteritis	Noroviruses	Fever, diarrhea, projectile vomiting, dehydration; generally self-limiting within two days	Highly contagious via direct contact or contact with contaminated food or fomites	Rapid enzyme immunoassay confirmed with RT-qPCR	None
Rotavirus gastroenteritis	Rotaviruses	Fever, diarrhea, vomiting, severe dehydration; recurring infections can lead to malnutrition and death	Fecal-oral route; children and elderly most susceptible	Enzyme immunoassay of stool sample, latex agglutination assays, RT-PCR	Preventive vaccine recommended for infants

Figure **17.3.4.2**: Viral causes of Gastroenteritis.

Hepatitis

Hepatitis is a general term meaning inflammation of the liver, which can have a variety of causes. In some cases, the cause is viral infection. There are five main hepatitis viruses that are clinically significant: hepatitisviruses A (HAV), B (HBV), C (HCV), D, (HDV) and E (HEV) (Figure **17.3.4.3**). Note that other viruses, such as Epstein-Barr virus (EBV), yellow fever, and cytomegalovirus (CMV) can also cause hepatitis and are discussed in Viral Infections of the Circulatory and Lymphatic Systems.

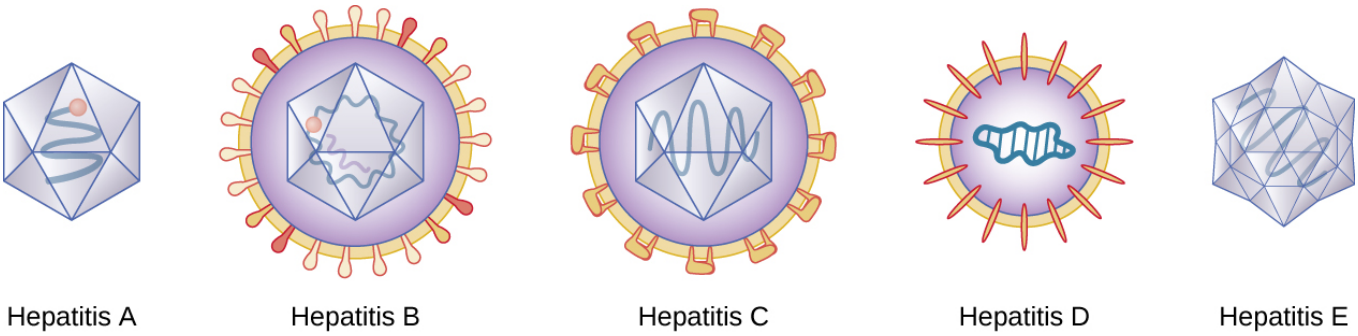


Figure **17.3.4.3**: Five main types of viruses cause hepatitis. HAV is a non-enveloped ssRNA(+) virus and is a member of the picornavirus family (Baltimore Group IV). HBV is a dsDNA enveloped virus, replicates using reverse transcriptase, and is a member of the hepadnavirus family (Baltimore Group VII). HCV is an enveloped ssRNA(+) virus and is a member of the flavivirus family (Baltimore Group IV). HDV is an enveloped ssRNA(–) that is circular (Baltimore Group V). This virus can only propagate in the presence of HBV. HEV is a non-enveloped ssRNA(+) virus and a member of the hepeviridae family (Baltimore Group IV).

Although the five hepatitis viruses differ, they can cause some similar signs and symptoms because they all have an affinity for hepatocytes (liver cells). HAV and HEV can be contracted through ingestion while HBV, HCV, and HDV are transmitted by parenteral contact. It is possible for individuals to become long term or chronic carriers of hepatitis viruses.

The virus enters the blood (viremia), spreading to the spleen, the kidneys, and the liver. During viral replication, the virus infects hepatocytes. The inflammation is caused by the hepatocytes replicating and releasing more hepatitis virus. Signs and symptoms include malaise, anorexia, loss of appetite, dark urine, pain in the upper right quadrant of the abdomen, vomiting, nausea, diarrhea, joint pain, and gray stool. Additionally, when the liver is diseased or injured, it is unable to break down hemoglobin effectively, and

bilirubin can build up in the body, giving the skin and mucous membranes a yellowish color, a condition called jaundice (Figure **17.3.4.4**). In severe cases, death from liver necrosis may occur.

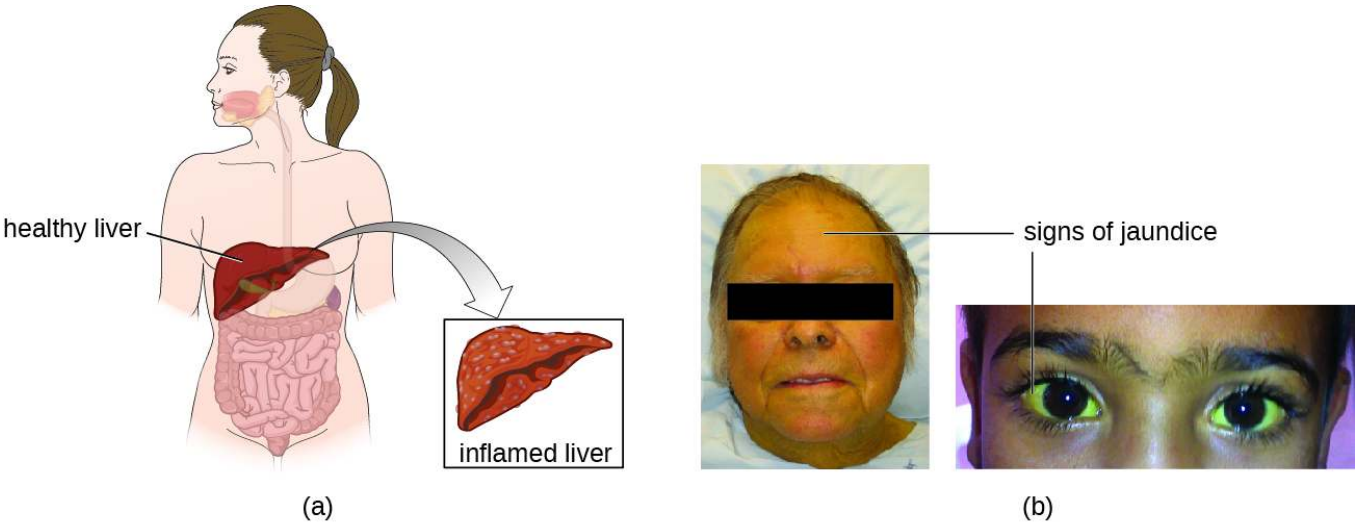


Figure **17.3.4.4**: (a) Hepatitis is inflammation of the liver resulting from a variety of root causes. It can cause jaundice. (b) Jaundice is characterized by yellowing of the skin, mucous membranes, and sclera of the eyes. (credit b left: modification of work by James Heilman, MD; credit b right: modification of work by "Sab3el3eish"/Wikimedia Commons)

Despite having many similarities, each of the hepatitis viruses has its own unique characteristics. HAV is generally transmitted through the fecal-oral route, close personal contact, or exposure to contaminated water or food. Hepatitis A can develop after an incubation period of 15 to 50 days (the mean is 30). It is normally mild or even asymptomatic and is usually self-limiting within weeks to months. A more severe form, fulminant hepatitis, rarely occurs but has a high fatality rate of 70–80%. Vaccination is available and is recommended especially for children (between ages one and two), those traveling to countries with higher risk, those with liver disease and certain other conditions, and drug users.

Although HBV is associated with similar signs and symptoms, transmission and outcomes differ. This virus has a mean incubation period of 120 days and is generally associated with exposure to infectious blood or body fluids such as semen or saliva. Exposure can occur through skin puncture, across the placenta, or through mucosal contact, but it is not spread through casual contact such as hugging, hand holding, sneezing, or coughing, or even through breastfeeding or kissing. Risk of infection is greatest for those who use intravenous drugs or who have sexual contact with an infected individual. Health-care workers are also at risk from needle sticks and other injuries when treating infected patients. The infection can become chronic and may progress to cirrhosis or liver failure. It is also associated with liver cancer. Chronic infections are associated with the highest mortality rates and are more common in infants. Approximately 90% of infected infants become chronic carriers, compared with only 6–10% of infected adults.[5] Vaccination is available and is recommended for children as part of the standard vaccination schedule (one dose at birth and the second by 18 months of age) and for adults at greater risk (e.g., those with certain diseases, intravenous drug users, and those who have sex with multiple partners). Health-care agencies are required to offer the HBV vaccine to all workers who have occupational exposure to blood and/or other infectious materials.

HCV is often undiagnosed and therefore may be more widespread than is documented. It has a mean incubation period of 45 days and is transmitted through contact with infected blood. Although some cases are asymptomatic and/or resolve spontaneously, 75%–85% of infected individuals become chronic carriers. Nearly all cases result from parenteral transmission often associated with IV drug use or transfusions. The risk is greatest for individuals with past or current history of intravenous drug use or who have had sexual contact with infected individuals. It has also been spread through contaminated blood products and can even be transmitted through contaminated personal products such as toothbrushes and razors. New medications have recently been developed that show great effectiveness in treating HCV and that are tailored to the specific genotype causing the infection.

HDV is uncommon in the United States and only occurs in individuals who are already infected with HBV, which it requires for replication. Therefore, vaccination against HBV is also protective against HDV infection. HDV is transmitted through contact with infected blood.

HEV infections are also rare in the United States but many individuals have a positive antibody titer for HEV. The virus is most commonly spread by the fecal-oral route through food and/or water contamination, or person-to-person contact, depending on the genotype of the virus, which varies by location. There are four genotypes that differ somewhat in their mode of transmission, distribution, and other factors (for example, two are zoonotic and two are not, and only one causes chronic infection). Genotypes three and four are only transmitted through food, while genotypes one and two are also transmitted through water and fecal-oral routes. Genotype one is the only type transmitted person-to-person and is the most common cause of HEV outbreaks. Consumption of undercooked meat, especially deer or pork, and shellfish can lead to infection. Genotypes three and four are zoonoses, so they can be transmitted from infected animals that are consumed. Pregnant women are at particular risk. This disease is usually self-limiting within two weeks and does not appear to cause chronic infection.

General laboratory testing for hepatitis begins with blood testing to examine liver function (Figure **17.3.4.5**). When the liver is not functioning normally, the blood will contain elevated levels of alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), direct bilirubin, total bilirubin, serum albumin, serum total protein, and calculated globulin, albumin/globulin (A/G) ratio. Some of these are included in a complete metabolic panel (CMP), which may first suggest a possible liver problem and indicate the need for more comprehensive testing. A hepatitis virus serological test panel can be used to detect antibodies for hepatitis viruses A, B, C, and sometimes D. Additionally, other immunological and genomic tests are available.

Specific treatments other than supportive therapy, rest, and fluids are often not available for hepatitis virus infection, except for HCV, which is often self-limited. Immunoglobulins can be used prophylactically following possible exposure. Medications are also used, including interferon alpha 2b and antivirals (e.g., lamivudine, entecavir, adefovir, and telbivudine) for chronic infections. Hepatitis C can be treated with interferon (as monotherapy or combined with other treatments), protease inhibitors, and other antivirals (e.g., the polymerase inhibitor sofosbuvir). Combination treatments are commonly used. Antiviral and immunosuppressive medications may be used for chronic cases of HEV. In severe cases, liver transplants may be necessary. Additionally, vaccines are available to prevent infection with HAV and HBV. The HAV vaccine is also protective against HEV. The HBV vaccine is also protective against HDV. There is no vaccine against HCV.

Link to Learning

Learn more information about hepatitis virus infections.

Exercise 17.3.4.2

Why do the five different hepatitis viruses all cause similar signs and symptoms?

Preventing HBV Transmission in Health-Care Settings

Hepatitis B was once a leading on-the-job hazard for health-care workers. Many health-care workers over the years have become infected, some developing cirrhosis and liver cancer. In 1982, the CDC recommended that health-care workers be vaccinated against HBV, and rates of infection have declined since then. Even though vaccination is now common, it is not always effective and not all individuals are vaccinated. Therefore, there is still a small risk for infection, especially for health-care workers working with individuals who have chronic infections, such as drug addicts, and for those with higher risk of needle sticks, such as phlebotomists. Dentists are also at risk.

Health-care workers need to take appropriate precautions to prevent infection by HBV and other illnesses. Blood is the greatest risk, but other body fluids can also transmit infection. Damaged skin, as occurs with eczema or psoriasis, can also allow transmission. Avoiding contact with body fluids, especially blood, by wearing gloves and face protection and using disposable syringes and needles reduce the risk of infection. Washing exposed skin with soap and water is recommended. Antiseptics may also be used, but may not help. Post-exposure treatment, including treatment with hepatitis B immunoglobulin (HBIG) and vaccination, may be used in the event of exposure to the virus from an infected patient. Detailed protocols are available for managing these situations. The virus can remain infective for up to seven days when on surfaces, even if no blood or other fluids are visible, so it is important to consider the best choices for disinfecting and sterilizing equipment that could potentially transmit the virus. The CDC recommends a solution of 10% bleach to disinfect surfaces.[6] Finally, testing blood products is important to reduce the risk of transmission during transfusions and similar procedures.

Viral Hepatitis

Hepatitis involves inflammation of the liver that typically manifests with signs and symptoms such as jaundice, nausea, vomiting, joint pain, gray stool, and loss of appetite. However, the severity and duration of the disease can vary greatly depending on the causative agent. Some infections may be completely asymptomatic, whereas others may be life threatening. The five different viruses capable of causing hepatitis are compared in Figure **17.3.4.5**. For the sake of comparison, this table presents only the unique aspects of each form of viral hepatitis, not the commonalities.

Viral Forms of Hepatitis					
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Antimicrobial Drugs**	**Vaccine**
Hepatitis A	Hepatitisvirus A (HAV)	Usually asymptomatic or mild and self-limiting within one to two weeks to a few months, sometimes longer but not, chronic; in rare cases leads to serious or fatal fulminant hepatitis	Contaminated food, water, objects, and person to person	None	Vaccine recommended for one year olds and high-risk adults
Hepatitis B	Hepatitisvirus B (HBV)	Similar to Hepatitis A, but may progress to cirrhosis and liver failure; associated with liver cancer	Contact with infected body fluids (blood, semen, saliva), e.g., via IV drug use, sexual transmission, health-care workers treating infected patients	Interferon, entecavir, tenofovir, lamivudine, adefovir	Vaccine recommended for infants and high-risk adults
Hepatitis C	Hepatitisvirus C (HCV)	Often asymptomatic, with 75%–85% chronic carriers; may progress to cirrhosis and liver failure; associated with liver cancer	Contact with infected body fluids, e.g., via IV drug use, transfusions, sexual transmission	Depends on geno-type and on whether cirrhosis is present; interferons, new treatment such as simeprevir plus sofosbuvir, ombitasvir/ paritaprevir/ritonavir and dasabuvir	None available
Hepatitis D	Hepatitisvirus D (HDV)	Similar to hepatitis B; usually self-limiting within one to two weeks but can become chronic or fulminant in rare cases	Contact with infected blood; infections can only occur in patients already infected with hepatitis B	None	Hepatitis B vaccine protects against HDV
Hepatitis E	Hepatitisvirus E (HEV)	Generally asymptomatic or mild and self-limiting; typically does not cause chronic disease	Fecal-oral route, often in contaminated water or undercooked meat; most common in developing countries	Supportive treatment; usually self-limiting, but some strains can become chronic; antiviral and immunosuppressive possible for chronic cases	Vaccine available in China only

Figure **17.3.4.5**: Viral forms of Hepatitis.

Key Concepts and Summary

- Common viral causes of gastroenteritis include rotaviruses, noroviruses, and astroviruses.
- Hepatitis may be caused by several unrelated viruses: hepatitis viruses A, B, C, D, and E.
- The hepatitis viruses differ in their modes of transmission, treatment, and potential for chronic infection.

Footnotes

1. 1 Caleb K. King, Roger Glass, Joseph S. Bresee, Christopher Duggan. “Managing Acute Gastroenteritis Among Children: Oral Rehydration, Maintenance, and Nutritional Therapy.” *MMWR* 52 (2003) RR16: pp. 1–16. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5216a1.htm.
2. 2 Elizabeth Jane Elliott. “Acute Gastroenteritis in Children.” *British Medical Journal* 334 (2007) 7583: 35–40, doi: 10.1136/bmj.39036.406169.80; S. Ramani and G. Kang. “Viruses Causing Diarrhoea in the Developing World.” *Current Opinions in Infectious Diseases* 22 (2009) 5: pp. 477–482. doi: 10.1097/QCO.0b013e328330662f; Michael Vincent F Tablang. “Viral Gastroenteritis.” *Medscape*. http://emedicine.medscape.com/article/176515-overview.
3. 3 Centers for Disease Control and Prevention. “Rotavirus,” *The Pink Book.* Updated September 8, 2015. http://www.cdc.gov/vaccines/pubs/pinkbook/rota.html.
4. 4 World Health Organization. “Rotavirus.” *Immunization, Vaccines, and Biologicals.* Updated April 21, 2010. www.who.int/immunization/topics/rotavirus/en/.
5. 5 Centers for Disease Control and Prevention. “The ABCs of Hepatitis.” Updated 2016. http://www.cdc.gov/hepatitis/resourc...s/abctable.pdf.
6. 6 Centers for Disease Control and Prevention. “Hepatitis B FAQs for Health Professionals.” Updated August 4, 2016. http://www.cdc.gov/hepatitis/HBV/HBVfaq.htm.

This page titled 17.3.4: Viral Infections of the Gastrointestinal Tract is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **24.4: Viral Infections of the Gastrointestinal Tract** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

17.3.5: Protozoan Infections of the Gastrointestinal Tract

Learning Objectives

- Identify the most common protozoans that can cause infections of the GI tract
- Compare the major characteristics of specific protozoan diseases affecting the GI tract

Like other microbes, protozoa are abundant in natural microbiota but can also be associated with significant illness. Gastrointestinal diseases caused by protozoa are generally associated with exposure to contaminated food and water, meaning that those without access to good sanitation are at greatest risk. Even in developed countries, infections can occur and these microbes have sometimes caused significant outbreaks from contamination of public water supplies.

Giardiasis

Also called backpacker's diarrhea or beaver fever, giardiasis is a common disease in the United States caused by the flagellated protist *Giardia lamblia*, also known as *Giardia intestinalis* or *Giardia duodenalis* (Figure 1.3.5). To establish infection, *G. lamblia* uses a large adhesive disk to attach to the intestinal mucosa. The disk is comprised of microtubules. During adhesion, the flagella of *G. lamblia* move in a manner that draws fluid out from under the disk, resulting in an area of lower pressure that promotes its adhesion to the intestinal epithelial cells. Due to its attachment, *Giardia* also blocks absorption of nutrients, including fats.

Transmission occurs through contaminated food or water or directly from person to person. Children in day-care centers are at risk due to their tendency to put items into their mouths that may be contaminated. Large outbreaks may occur if a public water supply becomes contaminated. *Giardia* have a resistant cyst stage in their life cycle that is able to survive cold temperatures and the chlorination treatment typically used for drinking water in municipal reservoirs. As a result, municipal water must be filtered to trap and remove these cysts. Once consumed by the host, *Giardia* develops into the active tropozoite.

Infected individuals may be asymptomatic or have gastrointestinal signs and symptoms, sometimes accompanied by weight loss. Common symptoms, which appear one to three weeks after exposure, include diarrhea, nausea, stomach cramps, gas, greasy stool (because fat absorption is being blocked), and possible dehydration. The parasite remains in the colon and does not cause systemic infection. Signs and symptoms generally clear within two to six weeks. Chronic infections may develop and are often resistant to treatment. These are associated with weight loss, episodic diarrhea, and malabsorption syndrome due to the blocked nutrient absorption.

Diagnosis may be made using observation under the microscope. A stool ova and parasite (O&P) exam involves direct examination of a stool sample for the presence of cysts and trophozoites; it can be used to distinguish common parasitic intestinal infections. ELISA and other immunoassay tests, including commercial direct fluorescence antibody kits, are also used. The most common treatments use metronidazole as the first-line choice, followed by tinidazole. If the infection becomes chronic, the parasites may become resistant to medications.

Cryptosporidiosis

Another protozoan intestinal illness is cryptosporidiosis, which is usually caused by *Cryptosporidium parvum* or *C. hominis*. (Figure **17.3.5.1**) These pathogens are commonly found in animals and can be spread in feces from mice, birds, and farm animals. Contaminated water and food are most commonly responsible for transmission. The protozoan can also be transmitted through human contact with infected animals or their feces.

In the United States, outbreaks of cryptosporidiosis generally occur through contamination of the public water supply or contaminated water at water parks, swimming pools, and day-care centers. The risk is greatest in areas with poor sanitation, making the disease more common in developing countries.

Signs and symptoms include watery diarrhea, nausea, vomiting, cramps, fever, dehydration, and weight loss. The illness is generally self-limiting within a month. However, immunocompromised patients, such as those with HIV/AIDS, are at particular risk of severe illness or death.

Diagnosis involves direct examination of stool samples, often over multiple days. As with giardiasis, a stool O&P exam may be helpful. Acid fast staining is often used. Enzyme immunoassays and molecular analysis (PCR) are available.

The first line of treatment is typically oral rehydration therapy. Medications are sometimes used to treat the diarrhea. The broad-range anti-parasitic drug nitazoxanide can be used to treat cryptosporidiosis. Other anti-parasitic drugs that can be used include azithromycin and paromomycin.

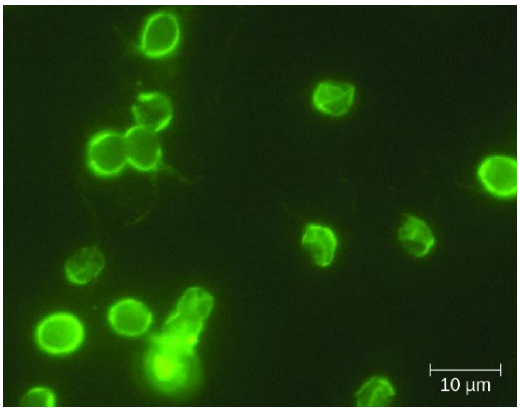


Figure 17.3.5.1: Immunofluorescent staining allows for visualization of *Cryptosporidium* spp. (credit: modification of work by EPA/H.D.A. Lindquist)

Amoebiasis (Amebiasis)

The protozoan parasite *Entamoeba histolytica* causes amoebiasis, which is known as amoebic dysentery in severe cases. *E. histolytica* is generally transmitted through water or food that has fecal contamination. The disease is most widespread in the developing world and is one of the leading causes of mortality from parasitic disease worldwide. Disease can be caused by as few as 10 cysts being transmitted.

Signs and symptoms range from nonexistent to mild diarrhea to severe amoebic dysentery. Severe infection causes the abdomen to become distended and may be associated with fever. The parasite may live in the colon without causing signs or symptoms or may invade the mucosa to cause colitis. In some cases, the disease spreads to the spleen, brain, genitourinary tract, or lungs. In particular, it may spread to the liver and cause an abscess. When a liver abscess develops, fever, nausea, liver tenderness, weight loss, and pain in the right abdominal quadrant may occur. Chronic infection may occur and is associated with intermittent diarrhea, mucus, pain, flatulence, and weight loss.

Direct examination of fecal specimens may be used for diagnosis. As with cryptosporidiosis, samples are often examined on multiple days. A stool O&P exam of fecal or biopsy specimens may be helpful. Immunoassay, serology, biopsy, molecular, and antibody detection tests are available. Enzyme immunoassay may not distinguish current from past illness. Magnetic resonance imaging (MRI) can be used to detect any liver abscesses. The first line of treatment is metronidazole or tinidazole, followed by diloxanide furoate, iodoquinol, or paromomycin to eliminate the cysts that remain.

Cyclosporiasis

The intestinal disease cyclosporiasis is caused by the protozoan *Cyclospora cayetanensis*. It is endemic to tropical and subtropical regions and therefore uncommon in the United States, although there have been outbreaks associated with contaminated produce imported from regions where the protozoan is more common. This protist is transmitted through contaminated food and water and reaches the lining of the small intestine, where it causes infection. Signs and symptoms begin within seven to ten days after ingestion. Based on limited data, it appears to be seasonal in ways that differ regionally and that are poorly understood.

Some individuals do not develop signs or symptoms. Those who do may exhibit explosive and watery diarrhea, fever, nausea, vomiting, cramps, loss of appetite, fatigue, and bloating. These symptoms may last for months without treatment. Trimethoprim-sulfamethoxazole is the recommended treatment. Microscopic examination is used for diagnosis. A stool O&P examination may be helpful. The oocysts have a distinctive blue halo when viewed using ultraviolet fluorescence microscopy (Figure 17.3.5.2).

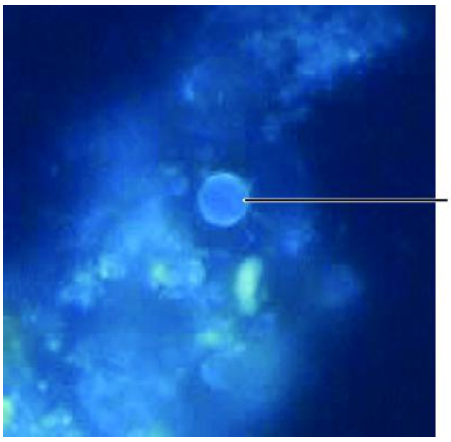


Figure 17.3.5.2: Cyclospora cayetanensis are autofluorescent under ultraviolet light. (credit: modification of work by Centers for Disease Control and Prevention)

? Exercise 17.3.5.1

Which protozoan GI infections are common in the United States?

Protozoan Gastrointestinal Infections

Protozoan GI infections are generally transmitted through contaminated food or water, triggering diarrhea and vomiting that can lead to dehydration. Rehydration therapy is an important aspect of treatment, but most protozoan GI infections can also be treated with drugs that target protozoans.

Protozoan Infections of the GI Tract

Disease	Pathogen	Signs and Symptoms	Transmission	Diagnostic Tests	Antimicrobial Drugs
Amoebiasis (amoebic dysentery)	*Entamoeba histolytica*	From mild diarrhea to severe dysentery and colitis; may cause abscess on the liver	Fecal-oral route; ingestion of cysts from fecally contaminated water, food, or hands	Stool O&P exam, enzyme immunoassay	Metronidazole, tinidazole, diloxanide furoate, iodoquinol, paromomycin
Cryptosporidiosis	*Cryptosporidium parvum, Cryptosporidium hominis*	Watery diarrhea, nausea, vomiting, cramps, fever, dehydration, and weight loss	Contact with feces of infected mice, birds, farm animals; ingestion of contaminated food or water; exposure to contaminated water while swimming or bathing	Stool O&P exam, enzyme immunoassay, PCR	Nitazoxanide, azithromycin, and paromomycin
Cyclosporiasis	*Cyclospora cayetanensis*	Explosive diarrhea, fever, nausea, vomiting, cramps, loss of appetite, fatigue, bloating	Ingestion of contaminated food or water	Stool O&P exam using ultraviolet fluorescence microscopy	Trimethoprim-sulfmethoxazole
Giardiasis	*Giardia lamblia*	Diarrhea, nausea, stomach cramps, gas, greasy stool, dehydration if severe; sometimes malabsorption syndrome	Contact with infected individual or contaminated fomites; ingestion of contaminated food or water	Stool O&P exam; ELISA, direct fluorescence antibody assays	Metronidazole, tinidazole

Figure 17.3.5.3: Protozoan infections of the GI tract.

Key Concepts and Summary

- **Giardiasis**, **cryptosporidiosis**, **amoebiasis**, and **cyclosporiasis** are intestinal infections caused by protozoans.
- Protozoan intestinal infections are commonly transmitted through contaminated food and water.
- Treatment varies depending on the causative agent, so proper diagnosis is important.
- Microscopic examination of stool or biopsy specimens is often used in diagnosis, in combination with other approaches.

Footnotes

1. 1 Centers for Disease Control and Prevention. “Cyclosporiasis FAQs for Health Professionals.” Updated June 13, 2014. http://www.cdc.gov/parasites/cyclosp...s/hp-faqs.html.

This page titled 17.3.5: Protozoan Infections of the Gastrointestinal Tract is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **24.5: Protozoan Infections of the Gastrointestinal Tract** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

17.3.6: Helminthic Infections of the Gastrointestinal Tract

Learning Objectives

- Identify the most common helminths that cause infections of the GI tract
- Compare the major characteristics of specific helminthic diseases affecting GI tract

Helminths are widespread intestinal parasites. These parasites can be divided into three common groups: round-bodied worms also described as nematodes, flat-bodied worms that are segmented (also described as cestodes), and flat-bodied worms that are non-segmented (also described as trematodes). The nematodes include roundworms, pinworms, hookworms, and whipworms. Cestodes include beef, pork, and fish tapeworms. Trematodes are collectively called flukes and more uniquely identified with the body site where the adult flukes are located. Although infection can have serious consequences, many of these parasites are so well adapted to the human host that there is little obvious disease.

Ascariasis

Infections caused by the large nematode roundworm *Ascaris lumbricoides*, a soil-transmitted helminth, are called ascariasis. Over 800 million to 1 billion people are estimated to be infected worldwide.[1] Infections are most common in warmer climates and at warmer times of year. At present, infections are uncommon in the United States. The eggs of the worms are transmitted through contaminated food and water. This may happen if food is grown in contaminated soil, including when manure is used as fertilizer.

When an individual consumes embryonated eggs (those with a developing embryo), the eggs travel to the intestine and the larvae are able to hatch. *Ascaris* is able to produce proteases that allow for penetration and degradation of host tissue. The juvenile worms can then enter the circulatory system and migrate to the lungs where they enter the alveoli (air sacs). From here they crawl to the pharynx and then follow the gut lumen to return to the small intestine, where they mature into adult roundworms. Females in the host will produce and release eggs that leave the host via feces. In some cases, the worms can block ducts such as those of the pancreas or gallbladder.

The infection is commonly asymptomatic. When signs and symptoms are present, they include shortness of breath, cough, nausea, diarrhea, blood in the stool, abdominal pain, weight loss, and fatigue. The roundworms may be visible in the stool. In severe cases, children with substantial infections may experience intestinal blockage.

The eggs can be identified by microscopic examination of the stool (Figure **17.3.6.1**). In some cases, the worms themselves may be identified if coughed up or excreted in stool. They can also sometimes be identified by X-rays, ultrasounds, or MRIs.

Ascariasis is self-limiting, but can last one to two years because the worms can inhibit the body's inflammatory response through glycan gimmickry (see Virulence Factors of Eukaryotic Pathogens). The first line of treatment is mebendazole or albendazole. In some severe cases, surgery may be required.



(a) (b) (c)

Figure **17.3.6.1**: (a) Adult *Ascaris lumbricoides* roundworms can cause intestinal blockage. (b) This mass of *A. lumbricoides* worms was excreted by a child. (c) A micrograph of a fertilized egg of *A. lumbricoides*. Fertilized eggs can be distinguished from unfertilized eggs because they are round rather than elongated and have a thicker cell wall. (credit a: modification of work by South African Medical Research Council; credit b: modification of work by James Gathany, Centers for Disease Control and Prevention; credit c: modification of work by Centers for Disease Control and Prevention)

? Exercise 17.3.6.1

Describe the route by which *A. lumbricoides* reaches the host's intestines as an adult worm.

Hookworm

Two species of nematode worms are associated with hookworm infection. Both species are found in the Americas, Africa, and Asia. *Necator americanus* is found predominantly in the United States and Australia. Another species, *Ancylostoma doudenale*, is found in southern Europe, North Africa, the Middle East, and Asia. The eggs of these species develop into larvae in soil contaminated by dog or cat feces. These larvae can penetrate the skin. After traveling through the venous circulation, they reach the lungs. When they are coughed up, they are then swallowed and can enter the intestine and develop into mature adults. At this stage, they attach to the wall of the intestine, where they feed on blood and can potentially cause anemia. Signs and symptoms include cough, an itchy rash, loss of appetite, abdominal pain, and diarrhea. In children, hookworms can affect physical and cognitive growth.

Some hookworm species, such as *Ancylostoma braziliense* that is commonly found in animals such as cats and dogs, can penetrate human skin and migrate, causing cutaneous larva migrans, a skin disease caused by the larvae of hookworms. As they move across the skin, in the subcutaneous tissue, pruritic tracks appear (Figure **17.3.6.2**).



(a) (b) (c)

Figure **17.3.6.2**: (a) This animal hookworm, *Ancylostoma caninum*, is attached to the intestinal wall. (b) The tracks of hookworms are visible in this individual with cutaneous larva migrans. (c) This micrograph shows the microscopic egg of a hookworm. (credit a, c: modification of work by Centers for Disease Control and Prevention).

The infection is diagnosed using microscopic examination of the stool, allowing for observation of eggs in the feces. Medications such as albendazole, mebendazole, and pyrantel pamoate are used as needed to treat systemic infection. In addition to systemic medication for symptoms associated with cutaneous larva migrans, topical thiabendazole is applied to the affected areas.

Strongyloidiasis

Strongyloidiasis is generally caused by *Strongyloides stercoralis*, a soil-transmitted helminth with both free-living and parasitic forms. In the parasitic form, the larvae of these nematodes generally penetrate the body through the skin, especially through bare feet, although transmission through organ transplantation or at facilities like day-care centers can also occur. When excreted in the stool, larvae can become free-living adults rather than developing into the parasitic form. These free-living worms reproduce, laying eggs that hatch into larvae that can develop into the parasitic form. In the parasitic life cycle, infective larvae enter the skin, generally through the feet. The larvae reach the circulatory system, which allows them to travel to the alveolar spaces of the lungs. They are transported to the pharynx where, like many other helminths, the infected patient coughs them up and swallows them again so that they return to the intestine. Once they reach the intestine, females live in the epithelium and produce eggs that develop asexually, unlike the free-living forms, which use sexual reproduction. The larvae may be excreted in the stool or can reinfect the host by entering the tissue of the intestines and skin around the anus, which can lead to chronic infections.

The condition is generally asymptomatic, although severe symptoms can develop after treatment with corticosteroids for asthma or chronic obstructive pulmonary disease, or following other forms of immunosuppression. When the immune system is suppressed, the rate of autoinfection increases, and huge amounts of larvae migrate to organs throughout the body.

Signs and symptoms are generally nonspecific. The condition can cause a rash at the site of skin entry, cough (dry or with blood), fever, nausea, difficulty breathing, bloating, pain, heartburn, and, rarely, arthritis, or cardiac or kidney complications. Disseminated strongyloidiasis or hyperinfection is a life-threatening form of the disease that can occur, usually following immunosuppression such as that caused by glucocorticoid treatment (most commonly), with other immunosuppressive medications, with HIV infection, or with malnutrition.

As with other helminths, direct examination of the stool is important in diagnosis. Ideally, this should be continued over seven days. Serological testing, including antigen testing, is also available. These can be limited by cross-reactions with other similar parasites and by the inability to distinguish current from resolved infection. Ivermectin is the preferred treatment, with albendazole as a secondary option.

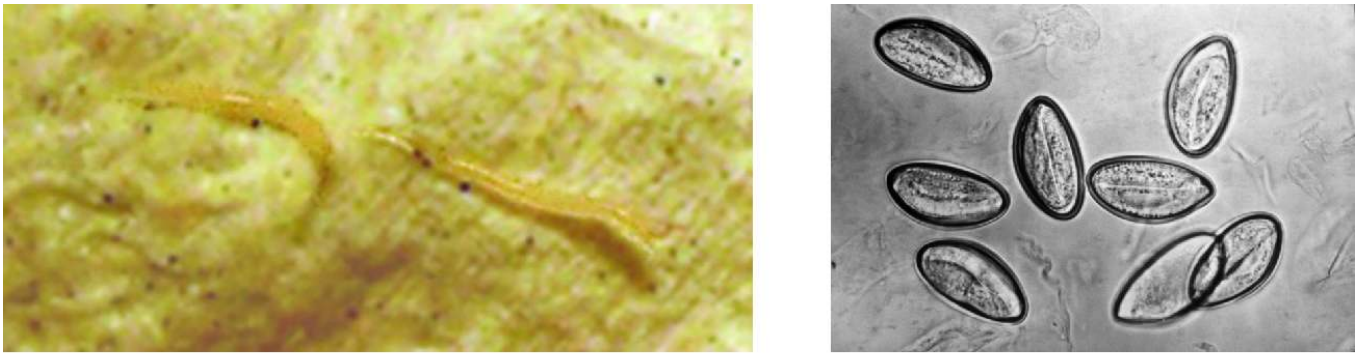
? Exercise 17.3.6.2

How does an acute infection of *S. stercoralis* become chronic?

Pinworms (Enterobiasis)

Enterobius vermicularis, commonly called pinworms, are tiny (2–13 mm) nematodes that cause enterobiasis. Of all helminthic infections, enterobiasis is the most common in the United States, affecting as many as one-third of American children.[2] Although the signs and symptoms are generally mild, patients may experience abdominal pain and insomnia from itching of the perianal region, which frequently occurs at night when worms leave the anus to lay eggs. The itching contributes to transmission, as the disease is transmitted through the fecal-oral route. When an infected individual scratches the anal area, eggs may get under the fingernails and later be deposited near the individual's mouth, causing reinfection, or on fomites, where they can be transferred to new hosts. After being ingested, the larvae hatch within the small intestine and then take up residence in the colon and develop into adults. From the colon, the female adult exits the body at night to lay eggs (Figure **17.3.6.3**).

Infection is diagnosed in any of three ways. First, because the worms emerge at night to lay eggs, it is possible to inspect the perianal region for worms while an individual is asleep. An alternative is to use transparent tape to remove eggs from the area around the anus first thing in the morning for three days to yield eggs for microscopic examination. Finally, it may be possible to detect eggs through examination of samples from under the fingernails, where eggs may lodge due to scratching. Once diagnosis has been made, mebendazole, albendazole, and pyrantel pamoate are effective for treatment.



(a) (b)

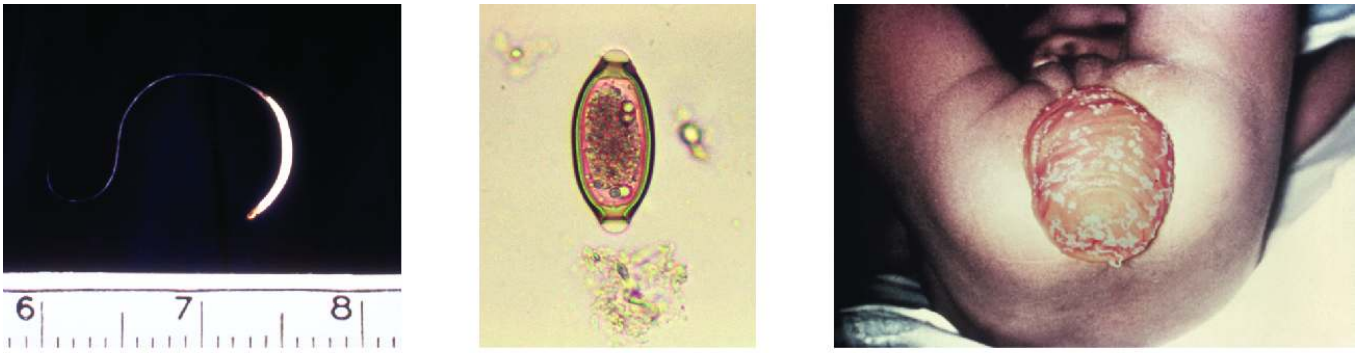
Figure **17.3.6.3**: (a) *E. vermicularis* are tiny nematodes commonly called pinworms. (b) This micrograph shows pinworm eggs.

Trichuriasis

The nematode whipworm *Trichuris trichiura* is a parasite that is transmitted by ingestion from soil-contaminated hands or food and causes trichuriasis. Infection is most common in warm environments, especially when there is poor sanitation and greater risk of fecal contamination of soil, or when food is grown in soil using manure as a fertilizer. The signs and symptoms may be minimal or nonexistent. When a substantial infection develops, signs and symptoms include painful, frequent diarrhea that may contain mucus and blood. It is possible for the infection to cause rectal prolapse, a condition in which a portion of the rectum becomes detached from the inside of the body and protrudes from the anus (Figure **17.3.6.4**). Severely infected children may experience reduced growth and their cognitive development may be affected.

When fertilized eggs are ingested, they travel to the intestine and the larvae emerge, taking up residence in the walls of the colon and cecum. They attach themselves with part of their bodies embedded in the mucosa. The larvae mature and live in the cecum and ascending colon. After 60 to 70 days, females begin to lay 3000 to 20,000 eggs per day.

Diagnosis involves examination of the feces for the presence of eggs. It may be necessary to use concentration techniques and to collect specimens on multiple days. Following diagnosis, the infection may be treated with mebendazole, albendazole, or ivermectin.



(a) (b) (c)

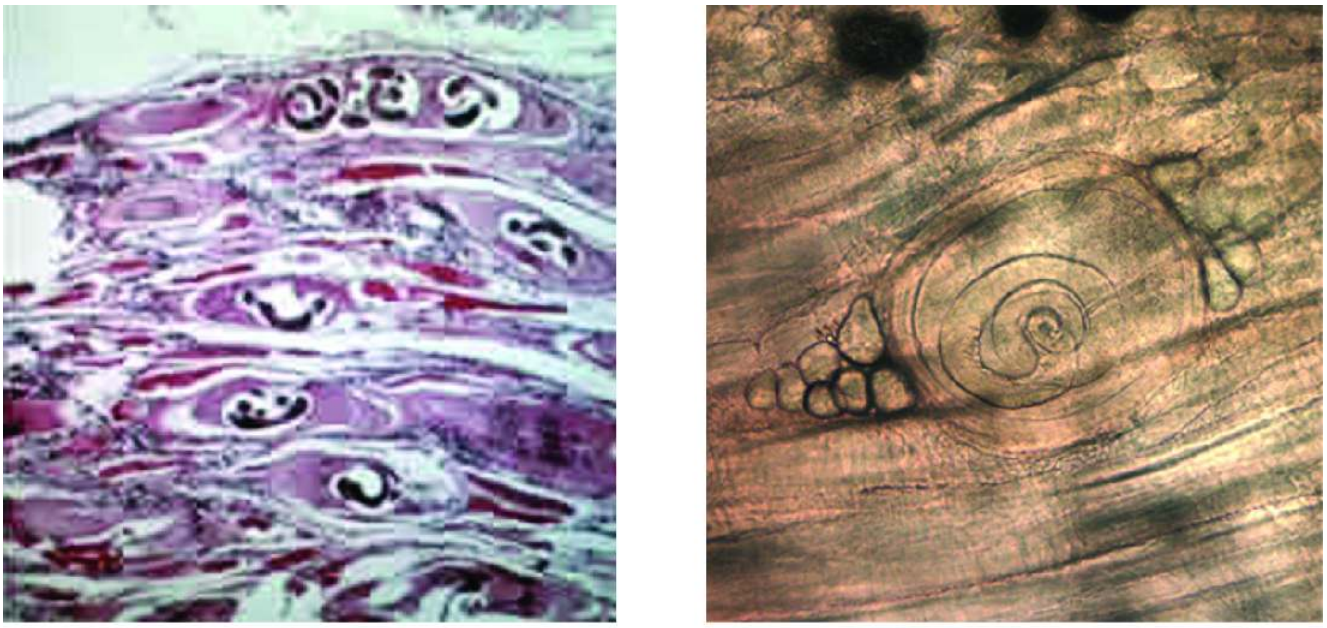
Figure 17.3.6.4: (a) This adult female *Trichuris* whipworm is a soil-transmitted parasite. (b) *Trichuris trichiura* eggs are ingested and travel to the intestines where the larvae emerge and take up residence. (c) Rectal prolapse is a condition that can result from whipworm infections. It occurs when the rectum loses its attachment to the internal body structure and protrudes from the anus. (credit a, b, c: modification of work by Centers for Disease Control and Prevention)

Trichinosis

Trichinosis (trichenellosis) develops following consumption of food that contains *Trichinella spiralis* (most commonly) or other *Trichinella* species. These microscopic nematode worms are most commonly transmitted in meat, especially pork, that has not been cooked thoroughly. *T. spiralis* larvae in meat emerge from cysts when exposed to acid and pepsin in the stomach. They develop into mature adults within the large intestine. The larvae produced in the large intestine are able to migrate into the muscles mechanically via the stylet of the parasite, forming cysts. Muscle proteins are reduced in abundance or undetectable in cells that contain *Trichinella* (nurse cells). Animals that ingest the cysts from other animals can later develop infection (Figure 17.3.6.5).

Although infection may be asymptomatic, symptomatic infections begin within a day or two of consuming the nematodes. Abdominal symptoms arise first and can include diarrhea, constipation, and abdominal pain. Other possible symptoms include headache, light sensitivity, muscle pain, fever, cough, chills, and conjunctivitis. More severe symptoms affecting motor coordination, breathing, and the heart sometimes occur. It may take months for the symptoms to resolve, and the condition is occasionally fatal. Mild cases may be mistaken for influenza or similar conditions.

Infection is diagnosed using clinical history, muscle biopsy to look for larvae, and serological testing, including immunoassays. Enzyme immunoassay is the most common test. It is difficult to effectively treat larvae that have formed cysts in the muscle, although medications may help. It is best to begin treatment as soon as possible because medications such as mebendazole and albendazole are effective in killing only the adult worms in the intestine. Steroids may be used to reduce inflammation if larvae are in the muscles.



(a) (b)

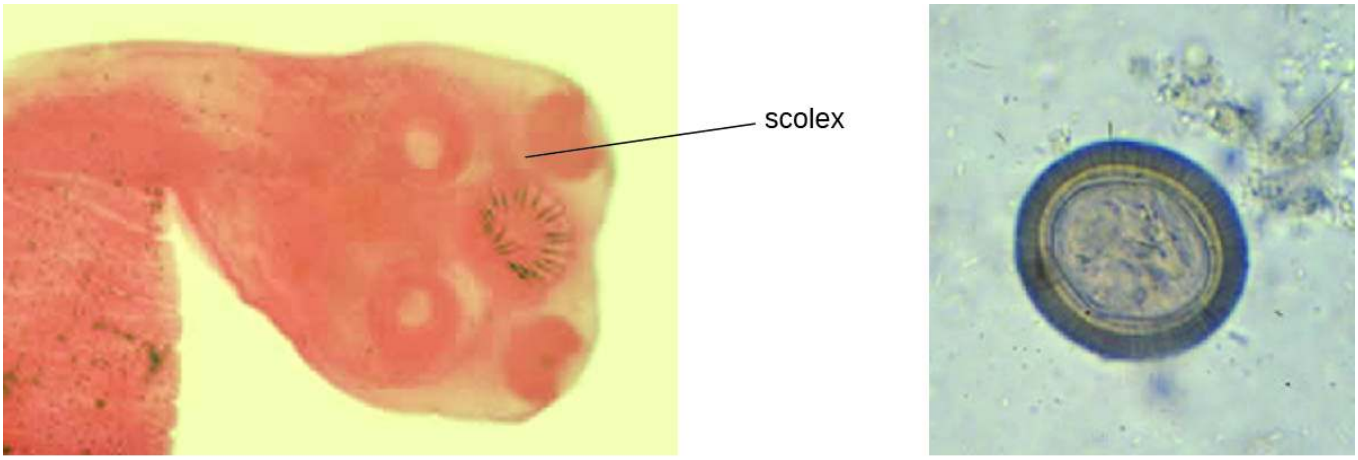
Figure **17.3.6.5**: (a) This image shows larvae of *T. spiralis* within muscle. (b) In meat, the larvae have a characteristic coiled appearance, as seen in this partially digested larva in bear meat. (credit a, b: modification of work by Centers for Disease Control and Prevention)

? Exercise 17.3.6.3

Compare and contrast the transmissions of pinworms and whipworms.

Tapeworms (Taeniasis)

Taeniasis is a tapeworm infection, generally caused by pork (*Taenia solium*), beef (*Taenia saginata*), and Asian (*Taenia asiatica*) tapeworms found in undercooked meat. Consumption of raw or undercooked fish, including contaminated sushi, can also result in infection from the fish tapeworm (*Diphyllobothrium latum*). Tapeworms are flatworms (cestodes) with multiple body segments and a head called a scolex that attaches to the intestinal wall. Tapeworms can become quite large, reaching 4 to 8 meters long (Figure **17.3.6.6**). Figure 5.2.5 illustrates the life cycle of a tapeworm.



(a) (b)

Figure **17.3.6.6**: (a) An adult tapeworm uses the scolex to attach to the intestinal wall. (b) The egg of a pork tapeworm (*Taenia solium*) is visible in this micrograph. (credit a, b: modification of work by Centers for Disease Control and Prevention)

Tapeworms attached to the intestinal wall produce eggs that are excreted in feces. After ingestion by animals, the eggs hatch and the larvae emerge. They may take up residence in the intestine, but can sometimes move to other tissues, especially muscle or brain tissue. When *T. solium* larvae form cysts in tissue, the condition is called cysticercosis. This occurs through ingestion of eggs via the fecal-oral route, not through consumption of undercooked meat. It can develop in the muscles, eye (ophthalmic cysticercosis), or brain (neurocysticercosis).

Infections may be asymptomatic or they may cause mild gastrointestinal symptoms such as epigastric discomfort, nausea, diarrhea, flatulence, or hunger pains. It is also common to find visible tapeworm segments passed in the stool. In cases of cysticercosis, symptoms differ depending upon where the cysts become established. Neurocysticercosis can have severe, life-threatening consequences and is associated with headaches and seizures because of the presence of the tapeworm larvae encysted in the brain. Cysts in muscles may be asymptomatic, or they may be painful.

To diagnose these conditions, microscopic analysis of stool samples from three separate days is generally recommended. Eggs or body segments, called proglottids, may be visible in these samples. Molecular methods have been developed but are not yet widely available. Imaging, such as CT and MRI, may be used to detect cysts. Praziquantel or niclosamide are used for treatment.

What's in Your Sushi Roll?

As foods that contain raw fish, such as sushi and sashimi, continue to increase in popularity throughout the world, so does the risk of parasitic infections carried by raw or undercooked fish. *Diphyllobothrium* species, known as fish tapeworms, is one of the main culprits. Evidence suggests that undercooked salmon caused an increase in *Diphyllobothrium* infections in British Columbia in the 1970s and early 1980s. In the years since, the number of reported cases in the United States and Canada has been low, but it is likely that cases are underreported because the causative agent is not easily recognized.[3]

Another illness transmitted in undercooked fish is herring worm disease, or anisakiasis, in which nematodes attach to the epithelium of the esophagus, stomach, or small intestine. Cases have increased around the world as raw fish consumption has increased.[4]

Although the message may be unpopular with sushi lovers, fish should be frozen or cooked before eating. The extremely low and high temperatures associated with freezing and cooking kill worms and larvae contained in the meat, thereby preventing infection. Ingesting fresh, raw sushi may make for a delightful meal, but it also entails some risk.

Hydatid Disease

Another cestode, *Echinococcus granulosus*, causes a serious infection known as hydatid disease (cystic echinococcosis). *E. granulosus* is found in dogs (the definitive host), as well as several intermediate hosts (sheep, pigs, goats, cattle). The cestodes are transmitted through eggs in the feces from infected animals, which can be an occupational hazard for individuals who work in agriculture.

Once ingested, *E. granulosus* eggs hatch in the small intestine and release the larvae. The larvae invade the intestinal wall to gain access to the circulatory system. They form hydatid cysts in internal organs, especially in the lungs and liver, that grow slowly and are often undetected until they become large. If the cysts burst, a severe allergic reaction (anaphylaxis) may occur.

Cysts present in the liver can cause enlargement of the liver, nausea, vomiting, right epigastric pain, pain in the right upper quadrant, and possible allergic signs and symptoms. Cysts in the lungs can lead to alveolar disease. Abdominal pain, weight loss, pain, and malaise may occur, and inflammatory processes develop.

E. granulosus can be detected through imaging (ultrasonography, CT, MRI) that shows the cysts. Serologic tests, including ELISA and indirect hemagglutinin tests, are used. Cystic disease is most effectively treated with surgery to remove cysts, but other treatments are also available, including chemotherapy with anti-helminthic drugs (albendazoleor mebendazole).

Exercise 17.3.6.4

Describe the risks of the cysts associated with taeniasis and hydatid disease.

Flukes

Flukes are flatworms that have a leaflike appearance. They are a type of trematode worm, and multiple species are associated with disease in humans. The most common are liver flukes and intestinal flukes (Figure **17.3.6.7**).

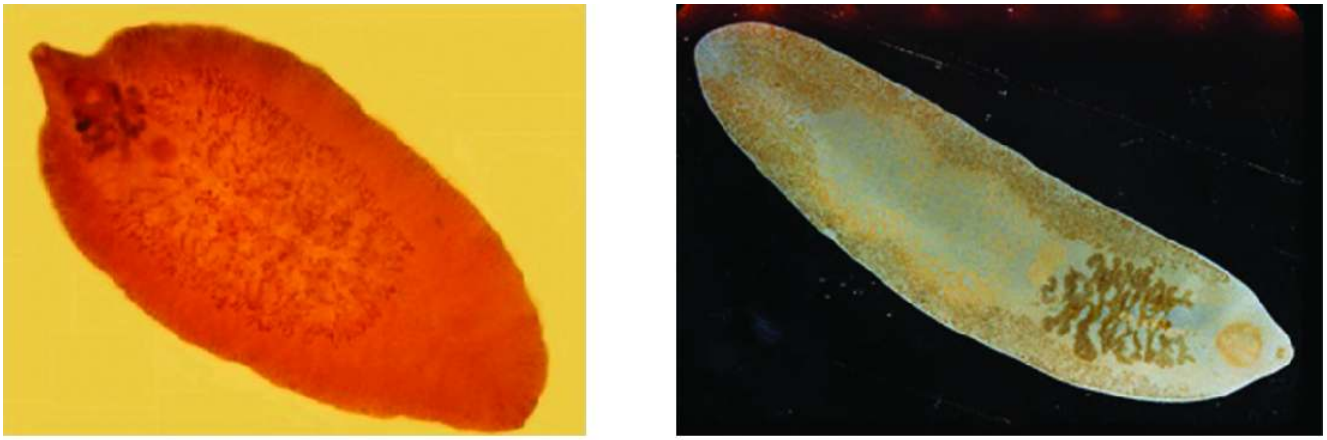


Figure **17.3.6.7**: (a) A liver fluke infects the bile ducts. (b) An intestinal fluke infects the intestines. (credit a: modification of work by Shafiei R, Sarkari B, Sadjjadi SM, Mowlavi GR, and Moshfe A; credit b: modification of work by Georgia Division of Public Health)

Liver Flukes

The liver flukes are several species of trematodes that cause disease by interfering with the bile duct. Fascioliasis is caused by *Fasciola hepatica* and *Fasciola gigantica* in contaminated raw or undercooked aquatic plants (e.g., watercress). In *Fasciola* infection, adult flukes develop in the bile duct and release eggs into the feces. Clonochiasis is caused by *Clonorchis sinensis* in contaminated freshwater fish. Other flukes, such as *Opisthorchis viverrini* (found in fish) and *Opisthorchis felineus* (found in freshwater snails), also cause infections. Liver flukes spend part of their life cycle in freshwater snails, which serve as an intermediate host. Humans are typically infected after eating aquatic plants contaminated by the infective larvae after they have left the snail. Once they reach the human intestine, they migrate back to the bile duct, where they mature. The life cycle is similar for the other infectious liver flukes (see Figure 5.2.4).

When *Fasciola* flukes cause acute infection, signs and symptoms include nausea, vomiting, abdominal pain, rash, fever, malaise, and breathing difficulties. If the infection becomes chronic, with adult flukes living in the bile duct, then cholangitis, cirrhosis, pancreatitis, cholecystitis, and gallstones may develop. Symptoms are similar for infections by other liver flukes. Cholangiocarcinoma can occur from *C. sinensis* infection. The *Opisthorchis* species can also be associated with cancer development.

Diagnosis is accomplished using patient history and examination of samples from feces or other samples (such as vomitus). Because the eggs may appear similar, immunoassay techniques are available that can help distinguish species. The preferred treatment for fascioliasis is triclabendazole. *C. sinensis* and *Opisthorchis* spp. infections are treated with praziquantel or albendazole.

Intestinal Flukes

The intestinal flukes are trematodes that develop in the intestines. Many, such as *Fasciolopsis buski*, which causes fasciolopsiasis, are closely related to liver flukes. Intestinal flukes are ingested from contaminated aquatic plants that have not been properly cooked. When the cysts are consumed, the larvae emerge in the duodenum and develop into adults while attached to the intestinal epithelium. The eggs are released in stool.

Intestinal fluke infection is often asymptomatic, but some cases may involve mild diarrhea and abdominal pain. More severe symptoms such as vomiting, nausea, allergic reactions, and anemia can sometimes occur, and high parasite loads may sometimes lead to intestinal obstructions.

Diagnosis is the same as with liver flukes: examination of feces or other samples and immunoassay. Praziquantel is used to treat infections caused by intestinal flukes.

Exercise 17.3.6.5

How are flukes transmitted?

Helminthic Gastrointestinal Infections

Numerous helminths are capable of colonizing the GI tract. Many such infections are asymptomatic, but others may cause signs and symptoms ranging from mild GI stress to severe systemic infection. Helminths have complex and unique life cycles that dictate their specific modes of transmission. Most helminthic infections can be treated with medications.

Common Helminthic Infections of the GI Tract					
Disease	**Causative Agent(s)**	**Mode of Transmission**	**Laboratory Tests**	**Symptoms**	**Treatments**
Ascariasis	*Ascaris lumbricoides*	Eggs in fecally contaminated food or water	Microscopic examination of the stool, imaging	Shortness of breath, cough, nausea, diarrhea, blood in stool, abdominal pain, weight loss, fatigue	Self-limiting within 1 to 2 years; albendazole and mebendazole if needed
Hookworm	*Necator americanus, Ancyclostoma doudenale*	Larvae in soil contaminated by dog or cat feces penetrate skin	Microscopic examination of stool (may require a concentration procedure)	Cough, itchy rash, loss of appetite, abdominal pain, diarrhea; in children, may affect physical and cognitive growth	Albendazole and mebendazole; pyrantel pamoatemay if needed
Strongyloidiasis	*Strongyloides stercoralis*	Soil-dwelling larvae penetrate the skin, usually bare feet	Microscopic examination of stool over several days (ideally at least 7); some serologic testing available	Often asymptomatic; cough (sometimes bloody), skin rash, abdominal pain, and diarrhea; in immunosuppressed patients, may become disseminated, causing serious and potentially fatal complications	Ivermectin (preferred), albendazole
Enterobiasis (pinworm)	*Enterobius vermicularis*	Fecal–oral route	Observation of eggs or worms from anal area; examination of samples under fingernails	Itching around the anus, abdominal pain, insomnia, irritation of female genital tract	Mebendazole, albendazole, pyrantel pamoate
Trichiuriasis (whipworm)	*Trichuris trichiura*	Fecal contamination or fertilization in soil	Microscopic examination of stool	Abdominal pain, anemia, diarrhea that may be bloody	Albendazole, mebendazole, ivermectin if needed
Trichinosis	*Trichinella spiralis*	Eating raw or undercooked pork or other meat of infected animal	Clinical history, muscle biopsy, serological testing, enzyme immunoassay	Diarrhea, constipation, abdominal pain, headache, cough, chills, light sensitivity, muscle pain, fever, conjunctivitis; in severe cases may affect motor coordination, breathing, heart function	Albendazole, mebendazole if needed
Taeniasis and cysticercosis	*Taenia solium, T. saginata, T. asiatica, Diphyllobo-thrium latum*	Eating raw or undercooked beef or pork from infected animal	Observation of worm segments or microscopic eggs in stool samples	Asymptomatic or mild GI distress; cysts in muscle, eye, or brain (cysticercosis); brain cysts can cause headaches, seizures, or death	Praziquantel or niclosamide
Cystic echinococcosis (hydatid disease)	*Echinococcus granulosus* (cystic)	Exposure to eggs in feces of infected dogs or livestock	Imaging; serological testing including ELISA and indirect hemagglutinin test	Cysts in lungs, liver, and other organs causing nausea, GI distress, and weight loss; severe anaphylaxis or death if cysts burst	Surgical removal or aspiration of cysts or chemotherapy with albendazole or mebenazole
Liver fluke infections	*Fasciola hepatica, F. gigantica, Clonorchis sinensis, Opisthorchis viverrini, O. felineus*	Eating raw or undercooked aquatic plants (*Fasciola* spp.) or freshwater fish (*Clonorchis* spp.) contaminated with eggs or cysts	Microscopic examination of eggs in stool or other samples; immunoassays	Fever, malaise, anemia, abdominal symptoms, transaminitis; cholangitis, cirrhosis, pancreatitis, cholecystitis, gall stones in chronic phase	Triclabendazole (preferred) for *Fasciola* spp.; praziquantel and albendazole for *C. sinensis* and *Opisthorchis* spp.
Fasciolopiasis (intestinal fluke)	*Fasciola buski*	Eating raw or undercooked aquatic plants containing cysts	Microscopic examination of eggs in stool or other samples; immunoassays	Diarrhea, abdominal pain; in severe cases, vomiting, nausea, intestinal obstruction, anemia, allergic reactions	Praziquantel

Figure 17.3.6.8: Helminthic infections of the GI tract.

Helminthic Infections of the GI Tract (continued)					
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Diagnostic Tests**	**Antimicrobial Drugs**
Strongyloidiasis	*Strongyloides stercoralis*	Often asymptomatic; cough (sometimes bloody), skin rash, abdominal pain, diarrhea; in immunosuppressed patients, may become disseminated, causing serious and potentially fatal complications	Soil-dwelling larvae penetrate the skin, usually bare feet	Microscopic observation of larvae in stool; serological testing for antigens	Ivermectin, albendazole
Tapeworms (taeniasis)	*Taenia solium, T. saginata, T. asiatica, Diphyllobothrium latum*	Asymptomatic or mild GI distress; cysts in muscle, eye, or brain (cysticercosis); brain cysts can cause headaches, seizures, or death	Ingestion of raw or undercooked pork or beef from infected animal	Observation of worm segments or microscopic eggs in stool; CT or MRI to detect cysts	Praziquantel, niclosamide
Trichinosis	*Trichinella spiralis,* other *Trichinella* spp.	Diarrhea, constipation, abdominal pain, headache, cough, chills, light sensitivity, muscle pain, fever, conjunctivitis; in severe cases may affect motor coordination, breathing, heart function	Ingestion of raw or undercooked pork or other meat of infected animal	Observation of cysts in muscle biopsy, enzyme immunoassay	Albendazole, mebendazole
Whipworm (trichuriasis)	*Trichuris trichiura*	Abdominal pain, anemia, diarrhea (possibly bloody), rectal prolapse	Ingestion of eggs in fecally contaminated food	Microscopic observation of eggs in stool	Albendazole, mebendazole, ivermectin

Figure **17.3.6.9**: Helminthic infections of the GI tract (continued).

Clinical Focus: Resolution

Carli's doctor explained that she had bacterial gastroenteritis caused by *Salmonella* bacteria. The source of these bacteria was likely the undercooked egg. Had the egg been fully cooked, the high temperature would have been sufficient to kill any *Salmonella* in or on the egg. In this case, enough bacteria survived to cause an infection once the egg was eaten.

Carli's signs and symptoms continued to worsen. Her fever became higher, her vomiting and diarrhea continued, and she began to become dehydrated. She felt thirsty all the time and had continual abdominal cramps. Carli's doctor treated her with intravenous fluids to help with her dehydration, but did not prescribe antibiotics. Carli's parents were confused because they thought a bacterial infection should always be treated with antibiotics.

The doctor explained that the worst medical problem for Carli was dehydration. Except in the most vulnerable and sick patients, such as those with HIV/AIDS, antibiotics do not reduce recovery time or improve outcomes in *Salmonella* infections. In fact, antibiotics can actually delay the natural excretion of bacteria from the body. Rehydration therapy replenishes lost fluids, diminishing the effects of dehydration and improving the patient's condition while the infection resolves.

After two days of rehydration therapy, Carli's signs and symptoms began to fade. She was still somewhat thirsty, but the amount of urine she passed became larger and the color lighter. She stopped vomiting. Her fever was gone, and so was the

diarrhea. At that point, stool analysis found very few *Salmonella* bacteria. In one week, Carli was discharged as fully recovered.

Key Concepts and Summary

- Helminths often cause intestinal infections after transmission to humans through exposure to contaminated soil, water, or food. Signs and symptoms are often mild, but severe complications may develop in some cases.
- *Ascaris lumbricoides* eggs are transmitted through contaminated food or water and hatch in the intestine. Juvenile larvae travel to the lungs and then to the pharynx, where they are swallowed and returned to the intestines to mature. These nematode roundworms cause **ascariasis**.
- *Necator americanus* and *Ancylostoma doudenale* cause **hookworm infection** when larvae penetrate the skin from soil contaminated by dog or cat feces. They travel to the lungs and are then swallowed to mature in the intestines.
- *Strongyloides stercoralis* are transmitted from soil through the skin to the lungs and then to the intestine where they cause **strongyloidiasis**.
- *Enterobius vermicularis* are nematode pinworms transmitted by the fecal-oral route. After ingestion, they travel to the colon where they cause **enterobiasis**.
- *Trichuris trichiura* can be transmitted through soil or fecal contamination and cause **trichuriasis**. After ingestion, the eggs travel to the intestine where the larvae emerge and mature, attaching to the walls of the colon and cecum.
- *Trichinella* spp. is transmitted through undercooked meat. Larvae in the meat emerge from cysts and mature in the large intestine. They can migrate to the muscles and form new cysts, causing **trichinosis**.
- *Taenia* spp. and *Diphyllobothrium latum* are tapeworms transmitted through undercooked food or the fecal-oral route. *Taenia* infections cause **taeniasis**. Tapeworms use their scolex to attach to the intestinal wall. Larvae may also move to muscle or brain tissue.
- *Echinococcus granulosus* is a cestode transmitted through eggs in the feces of infected animals, especially dogs. After ingestion, eggs hatch in the small intestine, and the larvae invade the intestinal wall and travel through the circulatory system to form dangerous cysts in internal organs, causing **hydatid disease**.
- Flukes are transmitted through aquatic plants or fish. **Liver flukes** cause disease by interfering with the bile duct. **Intestinal flukes** develop in the intestines, where they attach to the intestinal epithelium.

Footnotes

1. 1 Centers for Disease Control and Prevention. “Parasites–Ascariasis.” Updated May 24, 2016. http://www.cdc.gov/parasites/ascariasis/index.html.
2. 2 “Roundworms.” *University of Maryland Medical Center Medical Reference Guide*. Last reviewed December 9, 2014. https://umm.edu/health/medical/altme...ion/roundworms.
3. 3 Nancy Craig. “Fish Tapeworm and Sushi.” *Canadian Family Physician* 58 (2012) 6: pp. 654–658. www.ncbi.nlm.nih.gov/pmc/articles/PMC3374688/.
4. 4 Centers for Disease Control and Prevention. “Anisakiasis FAQs.” Updated November 12, 2012. http://www.cdc.gov/parasites/anisakiasis/faqs.html.

This page titled 17.3.6: Helminthic Infections of the Gastrointestinal Tract is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **24.6: Helminthic Infections of the Gastrointestinal Tract** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

17.3.E: Digestive System Infections (Exercises)

24.1: Anatomy and Normal Microbiota of the Digestive System

The human digestive system, or the gastrointestinal (GI) tract, begins with the mouth and ends with the anus. The parts of the mouth include the teeth, the gums, the tongue, the oral vestibule (the space between the gums, lips, and teeth), and the oral cavity proper (the space behind the teeth and gums). Other parts of the GI tract are the pharynx, esophagus, stomach, small intestine, large intestine, rectum, and anus.

Multiple Choice

Which of the following is NOT a way the normal microbiota of the intestine helps to prevent infection?

A. It produces acids that lower the pH of the stomach.
B. It speeds up the process by which microbes are flushed from the digestive tract.
C. It consumes food and occupies space, outcompeting potential pathogens.
D. It generates large quantities of oxygen that kill anaerobic pathogens.

Answer

D

What types of microbes live in the intestines?

A. Diverse species of bacteria, archaea, and fungi, especially *Bacteroides* and *Firmicutes* bacteria
B. A narrow range of bacteria, especially *Firmicutes*
C. A narrow range of bacteria and fungi, especially *Bacteroides*
D. Archaea and fungi only

Answer

A

Fill in the Blank

The part of the gastrointestinal tract with the largest natural microbiota is the _____.

Answer

Large intestine or colon

Short Answer

How does the diarrhea caused by dysentery differ from other types of diarrhea?

24.2: Microbial Diseases of the Mouth and Oral Cavity

Despite the presence of saliva and the mechanical forces of chewing and eating, some microbes thrive in the mouth. These microbes can cause damage to the teeth and can cause infections that have the potential to spread beyond the mouth and sometimes throughout the body.

Multiple Choice

What pathogen is the most important contributor to biofilms in plaque?

A. *Staphylococcus aureus*
B. *Streptococcus mutans*
C. *Escherichia coli*
D. *Clostridium difficile*

Answer

B

What type of organism causes thrush?

A. a bacterium
B. a virus
C. a fungus
D. a protozoan

Answer

C

In mumps, what glands swell to produce the disease's characteristic appearance?

A. the sublingual glands
B. the gastric glands
C. the parotid glands
D. the submandibular glands

Answer

C

Which of the following is true of HSV-1?

A. It causes oral thrush in immunocompromised patients.
B. Infection is generally self-limiting.
C. It is a bacterium.
D. It is usually treated with amoxicillin.

Answer

B

Fill in the Blank

When plaque becomes heavy and hardened, it is called dental calculus or _____.

Answer

tartar

Short Answer

Why do sugary foods promote dental caries?

24.3: Bacterial Infections of the Gastrointestinal Tract

Major causes of gastrointestinal illness include *Salmonella* spp., *Staphylococcus* spp., *Helicobacter pylori*, *Clostridium perfringens*, *Clostridium difficile*, *Bacillus cereus*, and *Yersinia* bacteria. *C. difficile* is an important cause of hospital acquired infection. *Vibrio cholerae* causes cholera, which can be a severe diarrheal illness. Different strains of *E. coli*, including ETEC, EPEC, EIEC, and EHEC, cause different illnesses with varying degrees of severity.

Multiple Choice

Which type of *E. coli* infection can be severe with life-threatening consequences such as hemolytic uremic syndrome?

A. ETEC
B. EPEC
C. EHEC
D. EIEC

Answer

C

Which species of *Shigella* has a type that produces Shiga toxin?

A. *S. boydii*
B. *S. flexneri*
C. *S. dysenteriae*
D. *S. sonnei*

Answer

C

Which type of bacterium produces an A-B toxin?

A. *Salmonella*
B. *Vibrio cholera*
C. ETEC
D. *Shigella dysenteriae*

Answer

B

Fill in the Blank

Antibiotic associated pseudomembranous colitis is caused by _____.

Answer

Clostridium difficile

Critical Thinking

Why does use of antibiotics and/or proton pump inhibitors contribute to the development of *C. difficile* infections?

Why did scientists initially think it was unlikely that a bacterium caused peptic ulcers?

Does it makes a difference in treatment to know if a particular illness is caused by a bacterium (an infection) or a toxin (an intoxication)?

24.4: Viral Infections of the Gastrointestinal Tract

Common viral causes of gastroenteritis include rotaviruses, noroviruses, and astroviruses. Hepatitis may be caused by several unrelated viruses: hepatitis viruses A, B, C, D, and E. The hepatitis viruses differ in their modes of transmission, treatment, and potential for chronic infection.

Multiple Choice

Which form of hepatitisvirus can only infect an individual who is already infected with another hepatitisvirus?

A. HDV
B. HAV
C. HBV
D. HEV

Answer

A

Which cause of viral gastroenteritis commonly causes projectile vomiting?

A. hepatitisvirus
B. Astroviruses
C. Rotavirus
D. Noroviruses

Answer

D

Fill in the Blank

Jaundice results from a buildup of _____.

Answer

bilirubin

Short Answer

Which forms of viral hepatitis are transmitted through the fecal-oral route?

Critical Thinking

Based on what you know about HBV, what are some ways that its transmission could be reduced in a health-care setting?

24.5: Protozoan Infections of the Gastrointestinal Tract

Like other microbes, protozoa are abundant in natural microbiota but can also be associated with significant illness. Gastrointestinal diseases caused by protozoa are generally associated with exposure to contaminated food and water, meaning that those without access to good sanitation are at greatest risk. Even in developed countries, infections can occur and these microbes have sometimes caused significant outbreaks from contamination of public water supplies.

Multiple Choice

Which protozoan is associated with the ability to cause severe dysentery?

A. *Giardia lamblia*
B. *Cryptosporidium hominis*
C. *Cyclospora cayetanesis*
D. *Entamoeba histolytica*

Answer

D

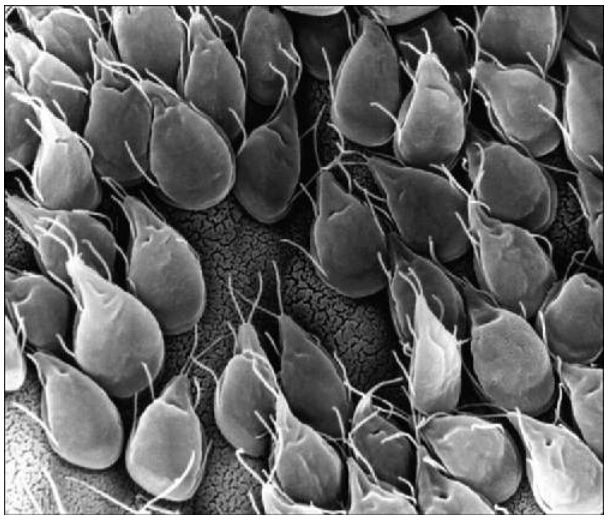
Which protozoan has a unique appearance, with a blue halo, when viewed using ultraviolet fluorescence microscopy?

A. *Giardia lamblia*
B. *Cryptosporidium hominis*
C. *Cyclospora cayetanesis*
D. *Entamoeba histolytica*

Answer

C

The micrograph shows protozoans attached to the intestinal wall of a gerbil. Based on what you know about protozoan intestinal parasites, what is it?



(credit: Dr. Stan Erlandsen, Centers for Disease Control and Prevention)

A. *Giardia lamblia*
B. *Cryptosporidium hominis*
C. *Cyclospora cayetanesis*
D. *Entamoeba histolytica*

Fill in the Blank

Chronic _____ infections cause the unique sign of disease of greasy stool and are often resistant to treatment.

Answer

giardia

Short Answer

What is an O&P exam?

24.6: Helminthic Infections of the Gastrointestinal Tract

Helminths are widespread intestinal parasites. These parasites can be divided into three common groups: round-bodied worms also described as nematodes, flat-bodied worms that are segmented (also described as cestodes), and flat-bodied worms that are non-segmented (also described as trematodes). The nematodes include roundworms, pinworms, hookworms, and whipworms. Many of these parasites are so well adapted to the human host that there is little obvious disease.

Multiple Choice

What is another name for *Trichuris trichiura*?

A. pinworm
B. whipworm
C. hookworm
D. ascariasis

Answer

B

Which type of helminth infection can be diagnosed using tape?

A. pinworm
B. whipworm

C. hookworm
D. tapeworm

Answer

A

Fill in the Blank

Liver flukes are often found in the _____ duct.

Answer

bile

Short Answer

Why does the coughing up of worms play an important part in the life cycle of some helminths, such as the roundworm *Ascaris lumbricoides*?

Critical Thinking

Cases of strongyloidiasis are often more severe in patients who are using corticosteroids to treat another disorder. Explain why this might occur.

This page titled 17.3.E: Digestive System Infections (Exercises) is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **24.E: Digestive System Infections (Exercises)** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

SECTION OVERVIEW

17.4: Circulatory and Lymphatic System Infections

Yellow fever was once common in the southeastern US, with annual outbreaks of more than 25,000 infections in New Orleans in the mid-1800s.[1] In the early 20th century, efforts to eradicate the virus that causes yellow fever were successful thanks to vaccination programs and effective control (mainly through the insecticide dichlorodiphenyltrichloroethane [DDT]) of *Aedes aegypti*, the mosquito that serves as a vector. Today, the virus has been largely eradicated in North America.

Elsewhere, efforts to contain yellow fever have been less successful. Despite mass vaccination campaigns in some regions, the risk for yellow fever epidemics is rising in dense urban cities in Africa and South America.[2] In an increasingly globalized society, yellow fever could easily make a comeback in North America, where *A. aegypti* is still present. If these mosquitoes were exposed to infected individuals, new outbreaks would be possible.

Like yellow fever, many of the circulatory and lymphatic diseases discussed in this chapter are emerging or re-emerging worldwide. Despite medical advances, diseases like malaria, Ebola, and others could become endemic in the US given the right circumstances.



Figure 17.4.1: Yellow fever is a viral hemorrhagic disease that can cause liver damage, resulting in jaundice (left) as well as serious and sometimes fatal complications. The virus that causes yellow fever is transmitted through the bite of a biological vector, the *Aedes aegypti* mosquito (right). (credit left: modification of work by Centers for Disease Control and Prevention; credit right: modification of work by James Gathany, Centers for Disease Control and Prevention)

17.4.1: Anatomy of the Circulatory and Lymphatic Systems

17.4.2: Bacterial Infections of the Circulatory and Lymphatic Systems

17.4.3: Viral Infections of the Circulatory and Lymphatic Systems

17.4.4: Parasitic Infections of the Circulatory and Lymphatic Systems

17.4.E: Circulatory and Lymphatic System Infections (Exercises)

Footnotes

1. 1 Centers for Disease Control and Prevention. “The History of Yellow Fever.” http://www.cdc.gov/travel-training/local/HistoryEpidemiologyandVaccination/page27568.html
2. 2 C.L. Gardner, K.D. Ryman. “Yellow Fever: A Reemerging Threat.” *Clinical Laboratory Medicine* 30 no. 1 (2010):237–260.

This page titled 17.4: Circulatory and Lymphatic System Infections is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

17.4.1: Anatomy of the Circulatory and Lymphatic Systems

Learning Objectives

- Describe the major anatomical features of the circulatory and lymphatic systems
- Explain why the circulatory and lymphatic systems lack normal microbiota
- Explain how microorganisms overcome defenses of the circulatory and lymphatic systems to cause infection
- Describe general signs and symptoms of disease associated with infections of the circulatory and lymphatic systems

Clinical Focus: Part 1

Barbara is a 43-year-old patient who has been diagnosed with metastatic inflammatory breast cancer. To facilitate her ongoing chemotherapy, her physician implanted a port attached to a central venous catheter. At a recent checkup, she reported feeling restless and complained that the site of the catheter had become uncomfortable. After removing the dressing, the physician observed that the surgical site appeared red and was warm to the touch, suggesting a localized infection. Barbara was also running a fever of 38.2 °C (100.8 °F). Her physician treated the affected area with a topical antiseptic and applied a fresh dressing. She also prescribed a course of the antibiotic oxacillin.

Exercise 17.4.1.1

1. Based on this information, what factors likely contributed to Barbara's condition?
2. What is the most likely source of the microbes involved?

The circulatory and lymphatic systems are networks of vessels and a pump that transport blood and lymph, respectively, throughout the body. When these systems are infected with a microorganism, the network of vessels can facilitate the rapid dissemination of the microorganism to other regions of the body, sometimes with serious results. In this section, we will examine some of the key anatomical features of the circulatory and lymphatic systems, as well as general signs and symptoms of infection.

The Circulatory System

The circulatory (or cardiovascular) system is a closed network of organs and vessels that moves blood around the body (Figure 17.4.1.1). The primary purposes of the circulatory system are to deliver nutrients, immune factors, and oxygen to tissues and to carry away waste products for elimination. The heart is a four-chambered pump that propels the blood throughout the body. Deoxygenated blood enters the right atrium through the superior vena cava and the inferior vena cava after returning from the body. The blood next passes through the tricuspid valve to enter the right ventricle. When the heart contracts, the blood from the right ventricle is pumped through the pulmonary arteries to the lungs. There, the blood is oxygenated at the alveoli and returns to the heart through the pulmonary veins. The oxygenated blood is received at the left atrium and proceeds through the mitral valve to the left ventricle. When the heart contracts, the oxygenated blood is pumped throughout the body via a series of thick-walled vessels called arteries. The first and largest artery is called the aorta. The arteries sequentially branch and decrease in size (and are called arterioles) until they end in a network of smaller vessels called capillaries. The capillary beds are located in the interstitial spaces within tissues and release nutrients, immune factors, and oxygen to those tissues. The capillaries connect to a series of vessels called venules, which increase in size to form the veins. The veins join together into larger vessels as they transfer blood back to the heart. The largest veins, the superior and inferior vena cava, return the blood to the right atrium.

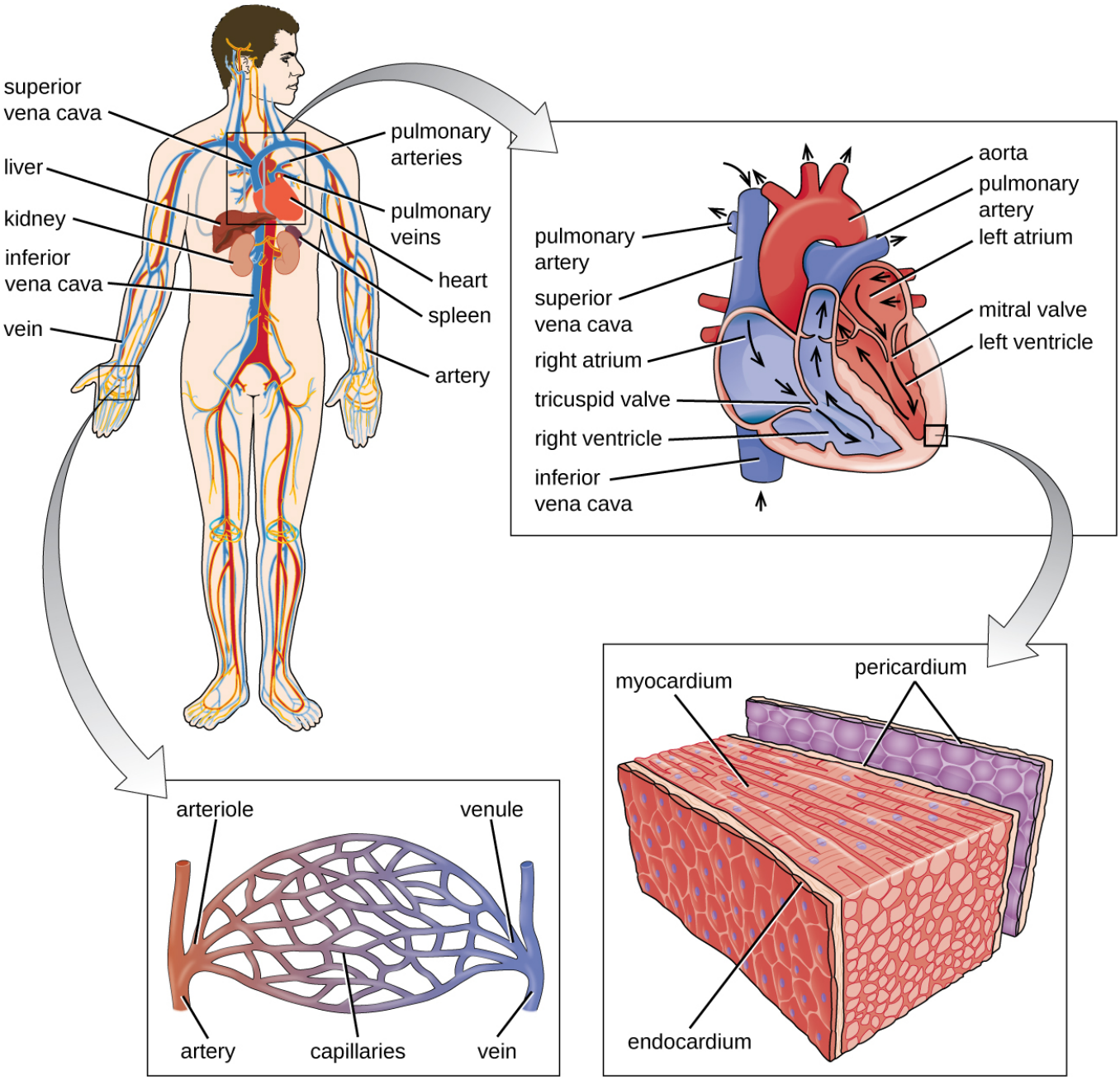


Figure 17.4.1.1: The major components of the human circulatory system include the heart, arteries, veins, and capillaries. This network delivers blood to the body's organs and tissues. (credit top left: modification of work by Mariana Ruiz Villareal; credit bottom right: modification of work by Bruce Blaus)

Other organs play important roles in the circulatory system as well. The kidneys filter the blood, removing waste products and eliminating them in the urine. The liver also filters the blood and removes damaged or defective red blood cells. The spleen filters and stores blood, removes damaged red blood cells, and is a reservoir for immune factors. All of these filtering structures serve as sites for entrapment of microorganisms and help maintain an environment free of microorganisms in the blood.

The Lymphatic System

The lymphatic system is also a network of vessels that run throughout the body (Figure 17.4.1.2). However, these vessels do not form a full circulating system and are not pressurized by the heart. Rather, the lymphatic system is an open system with the fluid moving in one direction from the extremities toward two drainage points into veins just above the heart. Lymphatic fluids move more slowly than blood because they are not pressurized. Small lymph capillaries interact with blood capillaries in the interstitial

spaces in tissues. Fluids from the tissues enter the lymph capillaries and are drained away (Figure **17.4.1.3**). These fluids, termed lymph, also contain large numbers of white blood cells.

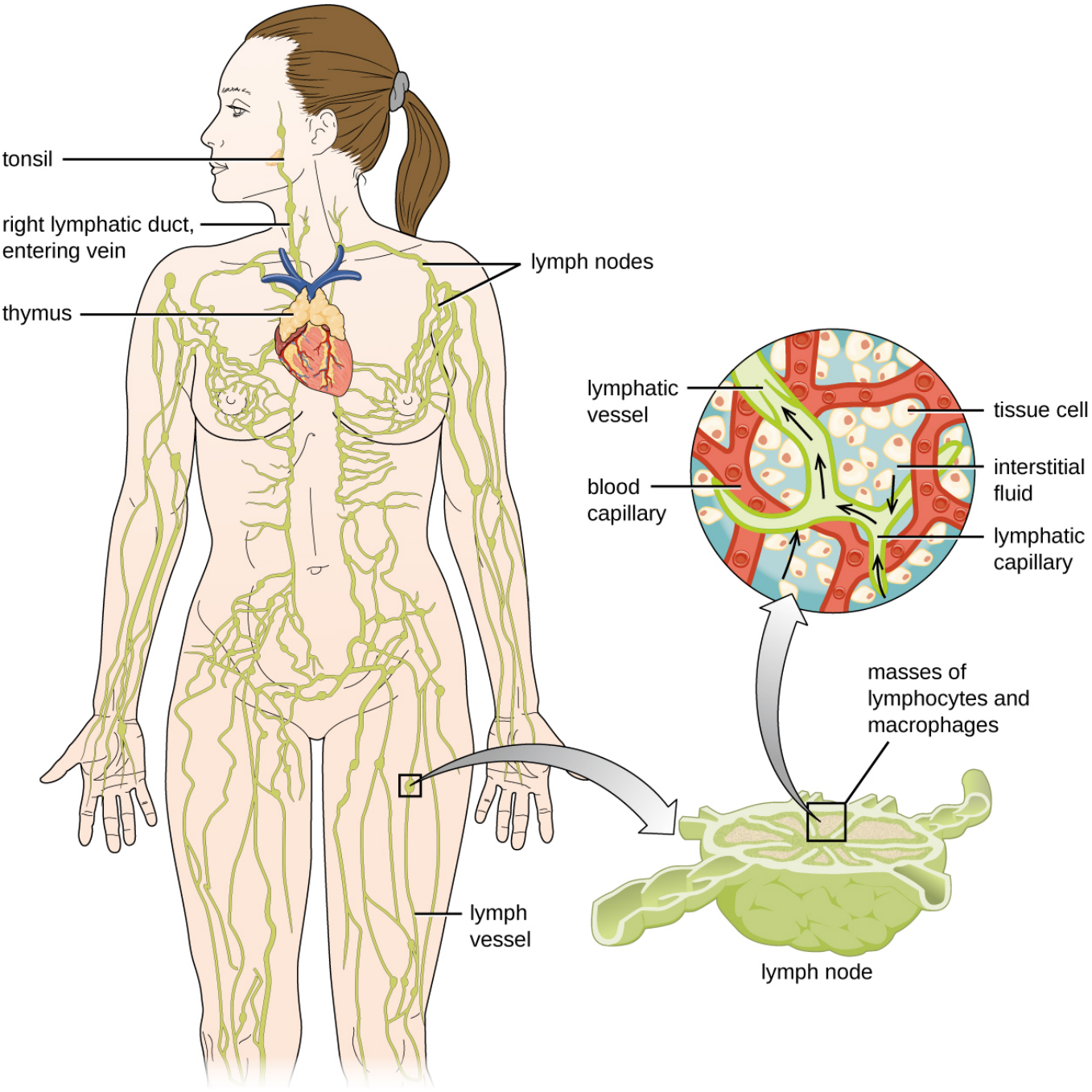


Figure **17.4.1.2**: The essential components of the human lymphatic system drain fluid away from tissues.

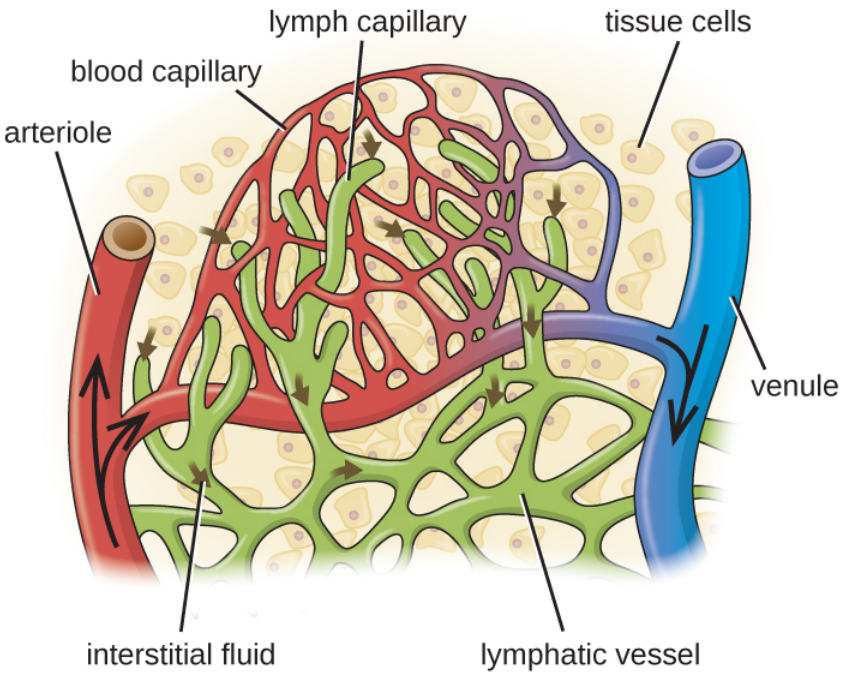


Figure **17.4.1.3**: Blood enters the capillaries from an arteriole (red) and leaves through venules (blue). Interstitial fluids may drain into the lymph capillaries (green) and proceed to lymph nodes. (credit: modification of work by National Cancer Institute, National Institutes of Health)

The lymphatic system contains two types of lymphoid tissues. The primary lymphoid tissue includes bone marrow and the thymus. Bone marrow contains the hematopoietic stem cells (HSC) that differentiate and mature into the various types of blood cells and lymphocytes (see Figure 17.3.1). The secondary lymphoid tissues include the spleen, lymph nodes, and several areas of diffuse lymphoid tissues underlying epithelial membranes. The spleen, an encapsulated structure, filters blood and captures pathogens and antigens that pass into it (Figure **17.4.1.4**). The spleen contains specialized macrophages and dendritic cells that are crucial for antigen presentation, a mechanism critical for activation of T lymphocytes and B lymphocytes (see Major Histocompatibility Complexes and Antigen-Presenting Cells). Lymph nodes are bean-shaped organs situated throughout the body. These structures contain areas called germinal centers that are rich in B and T lymphocytes. The lymph nodes also contain macrophages and dendritic cells for antigen presentation. Lymph from nearby tissues enters the lymph node through afferent lymphatic vessels and encounters these lymphocytes as it passes through; the lymph exits the lymph node through the efferent lymphatic vessels (Figure **17.4.1.4**).

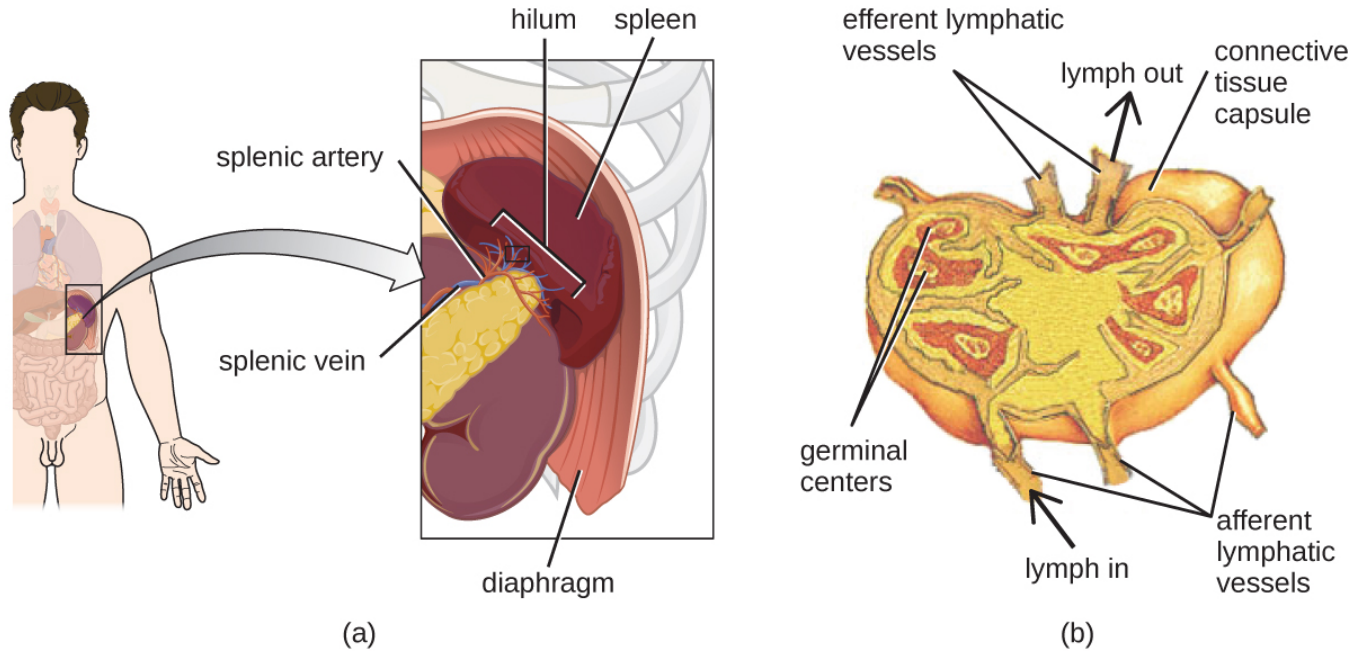


Figure 17.4.1.4: (a) The spleen is a lymphatic organ located in the upper left quadrant of the abdomen near the stomach and left kidney. It contains numerous phagocytes and lymphocytes that combat and prevent circulatory infections by killing and removing pathogens from the blood. (b) Lymph nodes are masses of lymphatic tissue located along the larger lymph vessels. They contain numerous lymphocytes that kill and remove pathogens from lymphatic fluid that drains from surrounding tissues.

Link to Learning

The lymphatic system filters fluids that have accumulated in tissues before they are returned to the blood. A brief overview of this process is provided at this website.

Exercise 17.4.1.2

What is the main function of the lymphatic system?

Infections of the Circulatory System

Under normal circumstances, the circulatory system and the blood should be sterile; the circulatory system has no normal microbiota. Because the system is closed, there are no easy portals of entry into the circulatory system for microbes. Those that are able to breach the body's physical barriers and enter the bloodstream encounter a host of circulating immune defenses, such as antibodies, complement proteins, phagocytes, and other immune cells. Microbes often gain access to the circulatory system through a break in the skin (e.g., wounds, needles, intravenous catheters, insect bites) or spread to the circulatory system from infections in other body sites. For example, microorganisms causing pneumonia or renal infection may enter the local circulation of the lung or kidney and spread from there throughout the circulatory network.

If microbes in the bloodstream are not quickly eliminated, they can spread rapidly throughout the body, leading to serious, even life-threatening infections. Various terms are used to describe conditions involving microbes in the circulatory system. The term bacteremia refers to bacteria in the blood. If bacteria are reproducing in the blood as they spread, this condition is called septicemia. The presence of viruses in the blood is called viremia. Microbial toxins can also be spread through the circulatory system, causing a condition termed toxemia.

Microbes and microbial toxins in the blood can trigger an inflammatory response so severe that the inflammation damages host tissues and organs more than the infection itself. This counterproductive immune response is called systemic inflammatory response syndrome (SIRS), and it can lead to the life-threatening condition known as sepsis. Sepsis is characterized by the production of excess cytokines that leads to classic signs of inflammation such as fever, vasodilation, and edema (see Inflammation and Fever). In a patient with sepsis, the inflammatory response becomes dysregulated and disproportionate to the threat of

infection. Critical organs such as the heart, lungs, liver, and kidneys become dysfunctional, resulting in increased heart and respiratory rates, and disorientation. If not treated promptly and effectively, patients with sepsis can go into shock and die.

Certain infections can cause inflammation in the heart and blood vessels. Inflammation of the endocardium, the inner lining of the heart, is called endocarditis and can result in damage to the heart valves severe enough to require surgical replacement. Inflammation of the pericardium, the sac surrounding the heart, is called pericarditis. The term myocarditis refers to the inflammation of the heart's muscle tissue. Pericarditis and myocarditis can cause fluid to accumulate around the heart, resulting in congestive heart failure. Inflammation of blood vessels is called vasculitis. Although somewhat rare, vasculitis can cause blood vessels to become damaged and rupture; as blood is released, small red or purple spots called petechiae appear on the skin. If the damage of tissues or blood vessels is severe, it can result in reduced blood flow to the surrounding tissues. This condition is called ischemia, and it can be very serious. In severe cases, the affected tissues can die and become necrotic; these situations may require surgical debridement or amputation.

? Exercise 17.4.1.3

1. Why does the circulatory system have no normal microbiota?
2. Explain why the presence of microbes in the circulatory system can lead to serious consequences.

Infections of the Lymphatic System

Like the circulatory system, the lymphatic system does not have a normal microbiota, and the large numbers of immune cells typically eliminate transient microbes before they can establish an infection. Only microbes with an array of virulence factors are able to overcome these defenses and establish infection in the lymphatic system. However, when a localized infection begins to spread, the lymphatic system is often the first place the invading microbes can be detected.

Infections in the lymphatic system also trigger an inflammatory response. Inflammation of lymphatic vessels, called lymphangitis, can produce visible red streaks under the skin. Inflammation in the lymph nodes can cause them to swell. A swollen lymph node is referred to as a bubo, and the condition is referred to as lymphadenitis.

Key Concepts and Summary

- The **circulatory system** moves blood throughout the body and has no normal microbiota.
- The **lymphatic system** moves fluids from the interstitial spaces of tissues toward the circulatory system and filters the lymph. It also has no normal microbiota.
- The circulatory and lymphatic systems are home to many components of the host immune defenses.
- Infections of the circulatory system may occur after a break in the skin barrier or they may enter the bloodstream at the site of a localized infection. Pathogens or toxins in the bloodstream can spread rapidly throughout the body and can provoke systemic and sometimes fatal inflammatory responses such as **SIRS**, **sepsis**, and **endocarditis**.
- Infections of the lymphatic system can cause **lymphangitis** and **lymphadenitis**.

This page titled 17.4.1: Anatomy of the Circulatory and Lymphatic Systems is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **25.1: Anatomy of the Circulatory and Lymphatic Systems** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

17.4.2: Bacterial Infections of the Circulatory and Lymphatic Systems

Learning Objectives

- Identify and compare bacteria that most commonly cause infections of the circulatory and lymphatic systems
- Compare the major characteristics of specific bacterial diseases affecting the circulatory and lymphatic systems

Bacteria can enter the circulatory and lymphatic systems through acute infections or breaches of the skin barrier or mucosa. Breaches may occur through fairly common occurrences, such as insect bites or small wounds. Even the act of tooth brushing, which can cause small ruptures in the gums, may introduce bacteria into the circulatory system. In most cases, the bacteremia that results from such common exposures is transient and remains below the threshold of detection. In severe cases, bacteremia can lead to septicemia with dangerous complications such as toxemia, sepsis, and septic shock. In these situations, it is often the immune response to the infection that results in the clinical signs and symptoms rather than the microbes themselves.

Bacterial Sepsis, Septic and Toxic Shock

At low concentrations, pro-inflammatory cytokines such as interleukin 1 (IL-1) and tumor necrosis factor-α (TNF-α) play important roles in the host's immune defenses. When they circulate systemically in larger amounts, however, the resulting immune response can be life threatening. IL-1 induces vasodilation (widening of blood vessels) and reduces the tight junctions between vascular endothelial cells, leading to widespread edema. As fluids move out of circulation into tissues, blood pressure begins to drop. If left unchecked, the blood pressure can fall below the level necessary to maintain proper kidney and respiratory functions, a condition known as septic shock. In addition, the excessive release of cytokines during the inflammatory response can lead to the formation of blood clots. The loss of blood pressure and occurrence of blood clots can result in multiple organ failure and death.

Bacteria are the most common pathogens associated with the development of sepsis, and septic shock.[1] The most common infection associated with sepsis is bacterial pneumonia (see Bacterial Infections of the Respiratory Tract), accounting for about half of all cases, followed by intra-abdominal infections (Bacterial Infections of the Gastrointestinal Tract) and urinary tract infections (Bacterial Infections of the Urinary System).[2] Infections associated with superficial wounds, animal bites, and indwelling catheters may also lead to sepsis and septic shock.

These initially minor, localized infections can be caused by a wide range of different bacteria, including *Staphylococcus*, *Streptococcus*, *Pseudomonas*, *Pasteurella*, *Acinetobacter*, and members of the Enterobacteriaceae. However, if left untreated, infections by these gram-positive and gram-negative pathogens can potentially progress to sepsis, shock, and death.

Toxic Shock Syndrome and Streptococcal Toxic Shock-Like Syndrome

Toxemia associated with infections caused by *Staphylococcus aureus* can cause staphylococcal toxic shock syndrome (TSS). Some strains of *S. aureus* produce a superantigen called toxic shock syndrome toxin-1 (TSST-1). TSS may occur as a complication of other localized or systemic infections such as pneumonia, osteomyelitis, sinusitis, and skin wounds (surgical, traumatic, or burns). Those at highest risk for staphylococcal TSS are women with preexisting *S. aureus* colonization of the vagina who leave tampons, contraceptive sponges, diaphragms, or other devices in the vagina for longer than the recommended time.

Staphylococcal TSS is characterized by sudden onset of vomiting, diarrhea, myalgia, body temperature higher than 38.9 °C (102.0 °F), and rapid-onset hypotension with a systolic blood pressure less than 90 mm Hg for adults; a diffuse erythematous rash that leads to peeling and shedding skin 1 to 2 weeks after onset; and additional involvement of three or more organ systems.[3] The mortality rate associated with staphylococcal TSS is less than 3% of cases.

Diagnosis of staphylococcal TSS is based on clinical signs, symptoms, serologic tests to confirm bacterial species, and the detection of toxin production from staphylococcal isolates. Cultures of skin and blood are often negative; less than 5% are positive in cases of staphylococcal TSS. Treatment for staphylococcal TSS includes decontamination, debridement, vasopressors to elevate blood pressure, and antibiotic therapy with clindamycin plus vancomycin or daptomycin pending susceptibility results.

A syndrome with signs and symptoms similar to staphylococcal TSS can be caused by *Streptococcus pyogenes*. This condition, called streptococcal toxic shock-like syndrome (STSS), is characterized by more severe pathophysiology than staphylococcal TSS,[4] with about 50% of patients developing *S. pyogenes* bacteremia and necrotizing fasciitis. In contrast to staphylococcal TSS, STSS is

more likely to cause acute respiratory distress syndrome (ARDS), a rapidly progressive disease characterized by fluid accumulation in the lungs that inhibits breathing and causes hypoxemia (low oxygen levels in the blood). STSS is associated with a higher mortality rate (20%–60%), even with aggressive therapy. STSS usually develops in patients with a streptococcal soft-tissue infection such as bacterial cellulitis, necrotizing fasciitis, pyomyositis (pus formation in muscle caused by infection), a recent influenza A infection, or chickenpox.

? Exercise 17.4.2.1

How can large amounts of pro-inflammatory cytokines lead to septic shock?

Clinical Focus: Part 2

Despite oxacillin therapy, Barbara's condition continued to worsen over the next several days. Her fever increased to 40.1 °C (104.2 °F) and she began to experience chills, rapid breathing, and confusion. Her doctor suspected bacteremia by a drug-resistant bacterium and admitted Barbara to the hospital. Cultures of the surgical site and blood revealed *Staphylococcus aureus*. Antibiotic susceptibility testing confirmed that the isolate was methicillin-resistant *S. aureus* (MRSA). In response, Barbara's doctor changed her antibiotic therapy to vancomycin and arranged to have the port and venous catheter removed.

Exercise 17.4.2.2

1. Why did Barbara's infection not respond to oxacillin therapy?
2. Why did the physician have the port and catheter removed?
3. Based on the signs and symptoms described, what are some possible diagnoses for Barbara's condition?

Puerperal Sepsis

A type of sepsis called puerperal sepsis, also known as puerperal infection, puerperal fever, or childbed fever, is a nosocomial infection associated with the period of puerperium—the time following childbirth during which the mother's reproductive system returns to a nonpregnant state. Such infections may originate in the genital tract, breast, urinary tract, or a surgical wound. Initially the infection may be limited to the uterus or other local site of infection, but it can quickly spread, resulting in peritonitis, septicemia, and death. Before the 19th century work of Ignaz Semmelweis and the widespread acceptance of germ theory (see Modern Foundations of Cell Theory), puerperal sepsis was a major cause of mortality among new mothers in the first few days following childbirth.

Puerperal sepsis is often associated with *Streptococcus pyogenes*, but numerous other bacteria can also be responsible. Examples include gram-positive bacterial (e.g. *Streptococcus* spp., *Staphylococcus* spp., and *Enterococcus* spp.), gram-negative bacteria (e.g. *Chlamydia* spp., *Escherichia coli*, *Klebsiella* spp., and *Proteus* spp.), as well as anaerobes such as *Peptostreptococcus* spp., *Bacteroides* spp., and *Clostridium* spp. In cases caused by *S. pyogenes*, the bacteria attach to host tissues using M protein and produce a carbohydrate capsule to avoid phagocytosis. *S. pyogenes* also produces a variety of exotoxins, like streptococcal pyrogenic exotoxins A and B, that are associated with virulence and may function as superantigens.

Diagnosis of puerperal fever is based on the timing and extent of fever and isolation, and identification of the etiologic agent in blood, wound, or urine specimens. Because there are numerous possible causes, antimicrobial susceptibility testing must be used to determine the best antibiotic for treatment. Nosocomial incidence of puerperal fever can be greatly reduced through the use of antiseptics during delivery and strict adherence to handwashing protocols by doctors, midwives, and nurses.

Infectious Arthritis

Also called septic arthritis, infectious arthritis can be either an acute or a chronic condition. Infectious arthritis is characterized by inflammation of joint tissues and is most often caused by bacterial pathogens. Most cases of acute infectious arthritis are secondary to bacteremia, with a rapid onset of moderate to severe joint pain and swelling that limits the motion of the affected joint. In adults and young children, the infective pathogen is most often introduced directly through injury, such as a wound or a surgical site, and brought to the joint through the circulatory system. Acute infections may also occur after joint replacement surgery. Acute

infectious arthritis often occurs in patients with an immune system impaired by other viral and bacterial infections. *S. aureus* is the most common cause of acute septic arthritis in the general population of adults and young children. *Neisseria gonorrhoeae* is an important cause of acute infectious arthritis in sexually active individuals.

Chronic infectious arthritis is responsible for 5% of all infectious arthritis cases and is more likely to occur in patients with other illnesses or conditions. Patients at risk include those who have an HIV infection, a bacterial or fungal infection, prosthetic joints, rheumatoid arthritis (RA), or who are undergoing immunosuppressive chemotherapy. Onset is often in a single joint; there may be little or no pain, aching pain that may be mild, gradual swelling, mild warmth, and minimal or no redness of the joint area.

Diagnosis of infectious arthritis requires the aspiration of a small quantity of synovial fluid from the afflicted joint. Direct microscopic evaluation, culture, antimicrobial susceptibility testing, and polymerase chain reaction (PCR) analyses of the synovial fluid are used to identify the potential pathogen. Typical treatment includes administration of appropriate antimicrobial drugs based on antimicrobial susceptibility testing. For nondrug-resistant bacterial strains, β-lactams such as oxacillin and cefazolin are often prescribed for staphylococcal infections. Third-generation cephalosporins (e.g., ceftriaxone) are used for increasingly prevalent β-lactam-resistant *Neisseria* infections. Infections by *Mycobacterium* spp. or fungi are treated with appropriate long-term antimicrobial therapy. Even with treatment, the prognosis is often poor for those infected. About 40% of patients with nongonnococcal infectious arthritis will suffer permanent joint damage and mortality rates range from 5% to 20%.[5] Mortality rates are higher among the elderly.[6]

Osteomyelitis

Osteomyelitis is an inflammation of bone tissues most commonly caused by infection. These infections can either be acute or chronic and can involve a variety of different bacteria. The most common causative agent of osteomyelitis is *S. aureus*. However, *M. tuberculosis*, *Pseudomonas aeruginosa*, *Streptococcus pyogenes*, *S. agalactiae*, species in the Enterobacteriaceae, and other microorganisms can also cause osteomyelitis, depending on which bones are involved. In adults, bacteria usually gain direct access to the bone tissues through trauma or a surgical procedure involving prosthetic joints. In children, the bacteria are often introduced from the bloodstream, possibly spreading from focal infections. The long bones, such as the femur, are more commonly affected in children because of the more extensive vascularization of bones in the young.[7]

The signs and symptoms of osteomyelitis include fever, localized pain, swelling due to edema, and ulcers in soft tissues near the site of infection. The resulting inflammation can lead to tissue damage and bone loss. In addition, the infection may spread to joints, resulting in infectious arthritis, or disseminate into the blood, resulting in sepsis and thrombosis(formation of blood clots). Like septic arthritis, osteomyelitis is usually diagnosed using a combination of radiography, imaging, and identification of bacteria from blood cultures, or from bone cultures if blood cultures are negative. Parenteral antibiotic therapy is typically used to treat osteomyelitis. Because of the number of different possible etiologic agents, however, a variety of drugs might be used. Broad-spectrum antibacterial drugs such as nafcillin, oxacillin, or cephalosporin are typically prescribed for acute osteomyelitis, and ampicillin and piperacillin/tazobactam for chronic osteomyelitis. In cases of antibiotic resistance, vancomycin treatment is sometimes required to control the infection. In serious cases, surgery to remove the site of infection may be required. Other forms of treatment include hyperbaric oxygen therapy (see Using Physical Methods to Control Microorganisms) and implantation of antibiotic beads or pumps.

? Exercise 17.4.2.3

What bacterium the most common cause of both septic arthritis and osteomyelitis?

Rheumatic Fever

Infections with *S. pyogenes* have a variety of manifestations and complications generally called sequelae. As mentioned, the bacterium can cause suppurative infections like puerperal fever. However, this microbe can also cause nonsuppurative sequelae in the form of acute rheumatic fever (ARF), which can lead to rheumatic heart disease, thus impacting the circulatory system. Rheumatic fever occurs primarily in children a minimum of 2–3 weeks after an episode of untreated or inadequately treated pharyngitis (see Bacterial Infections of the Respiratory Tract). At one time, rheumatic fever was a major killer of children in the US; today, however, it is rare in the US because of early diagnosis and treatment of streptococcal pharyngitis with antibiotics. In

parts of the world where diagnosis and treatment are not readily available, acute rheumatic fever and rheumatic heart disease are still major causes of mortality in children.[8]

Rheumatic fever is characterized by a variety of diagnostic signs and symptoms caused by nonsuppurative, immune-mediated damage resulting from a cross-reaction between patient antibodies to bacterial surface proteins and similar proteins found on cardiac, neuronal, and synovial tissues. Damage to the nervous tissue or joints, which leads to joint pain and swelling, is reversible. However, damage to heart valves can be irreversible and is worsened by repeated episodes of acute rheumatic fever, particularly during the first 3–5 years after the first rheumatic fever attack. The inflammation of the heart valves caused by cross-reacting antibodies leads to scarring and stiffness of the valve leaflets. This, in turn, produces a characteristic heart murmur. Patients who have previously developed rheumatic fever and who subsequently develop recurrent pharyngitis due to *S. pyogenes* are at high risk for a recurrent attacks of rheumatic fever.

The American Heart Association recommends[9] a treatment regimen consisting of benzathine benzylpenicillin every 3 or 4 weeks, depending on the patient's risk for reinfection. Additional prophylactic antibiotic treatment may be recommended depending on the age of the patient and risk for reinfection.

Bacterial Endocarditis and Pericarditis

The endocardium is a tissue layer that lines the muscles and valves of the heart. This tissue can become infected by a variety of bacteria, including gram-positive cocci such as *Staphylococcus aureus*, viridans streptococci, and *Enterococcus faecalis*, and the gram-negative so-called HACEK bacilli: *Haemophilus* spp., *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*. The resulting inflammation is called endocarditis, which can be described as either acute or subacute. Causative agents typically enter the bloodstream during accidental or intentional breaches in the normal barrier defenses (e.g., dental procedures, body piercings, catheterization, wounds). Individuals with preexisting heart damage, prosthetic valves and other cardiac devices, and those with a history of rheumatic fever have a higher risk for endocarditis. This disease can rapidly destroy the heart valves and, if untreated, lead to death in just a few days.

In subacute bacterial endocarditis, heart valve damage occurs slowly over a period of months. During this time, blood clots form in the heart, and these protect the bacteria from phagocytes. These patches of tissue-associated bacteria are called vegetations. The resulting damage to the heart, in part resulting from the immune response causing fibrosis of heart valves, can necessitate heart valve replacement (Figure **17.4.2.1**). Outward signs of subacute endocarditis may include a fever.

Diagnosis of infective endocarditis is determined using the combination of blood cultures, echocardiogram, and clinical symptoms. In both acute and subacute endocarditis, treatment typically involves relatively high doses of intravenous antibiotics as determined by antimicrobial susceptibility testing. Acute endocarditis is often treated with a combination of ampicillin, nafcillin, and gentamicin for synergistic coverage of *Staphylococcus* spp. and *Streptococcus* spp. Prosthetic-valve endocarditis is often treated with a combination of vancomycin, rifampin, and gentamicin. Rifampin is necessary to treat individuals with infection of prosthetic valves or other foreign bodies because rifampin can penetrate the biofilm of most of the pathogens that infect these devices.

Staphylcoccus spp. and *Streptococcus* spp. can also infect and cause inflammation in the tissues surrounding the heart, a condition called acute pericarditis. Pericarditis is marked by chest pain, difficulty breathing, and a dry cough. In most cases, pericarditis is self-limiting and clinical intervention is not necessary. Diagnosis is made with the aid of a chest radiograph, electrocardiogram, echocardiogram, aspirate of pericardial fluid, or biopsy of pericardium. Antibacterial medications may be prescribed for infections associated with pericarditis; however, pericarditis can also be caused other pathogens, including viruses (e.g., echovirus, influenza virus), fungi (e.g., *Histoplasma* spp., *Coccidioides* spp.), and eukaryotic parasites (e.g., *Toxoplasma* spp.).

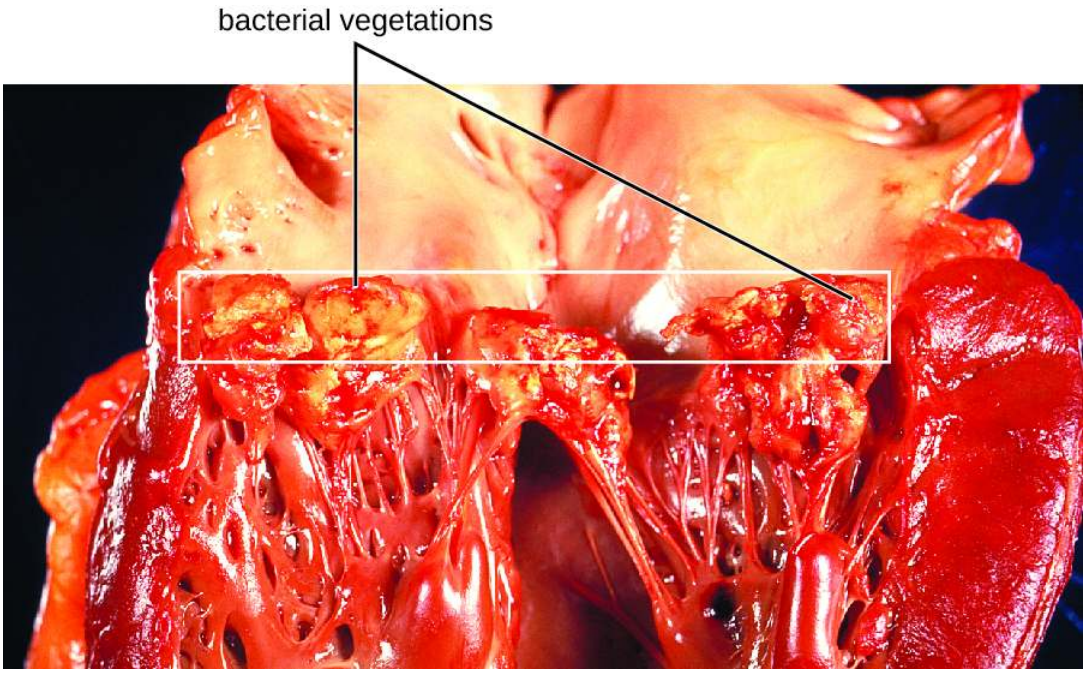


Figure 17.4.2.1: The heart of an individual who had subacute bacterial endocarditis of the mitral valve. Bacterial vegetations are visible on the valve tissues. (credit: modification of work by Centers for Disease Control and Prevention)

? Exercise 17.4.2.4

Compare acute and subacute bacterial endocarditis.

Gas Gangrene

Traumatic injuries or certain medical conditions, such as diabetes, can cause damage to blood vessels that interrupts blood flow to a region of the body. When blood flow is interrupted, tissues begin to die, creating an anaerobic environment in which anaerobic bacteria can thrive. This condition is called ischemia. Endospores of the anaerobic bacterium *Clostridium perfringens* (along with a number of other *Clostridium* spp. from the gut) can readily germinate in ischemic tissues and colonize the anaerobic tissues.

The resulting infection, called gas gangrene, is characterized by rapidly spreading myonecrosis (death of muscle tissue). The patient experiences a sudden onset of excruciating pain at the infection site and the rapid development of a foul-smelling wound containing gas bubbles and a thin, yellowish discharge tinged with a small amount of blood. As the infection progresses, edema and cutaneous blisters containing bluish-purple fluid form. The infected tissue becomes liquefied and begins sloughing off. The margin between necrotic and healthy tissue often advances several inches per hour even with antibiotic therapy. Septic shock and organ failure frequently accompany gas gangrene; when patients develop sepsis, the mortality rate is greater than 50%.

α-Toxin and theta (θ) toxin are the major virulence factors of *C. perfringens* implicated in gas gangrene. α-Toxin is a lipase responsible for breaking down cell membranes; it also causes the formation of thrombi (blood clots) in blood vessels, contributing to the spread of ischemia. θ-Toxin forms pores in the patient's cell membranes, causing cell lysis. The gas associated with gas gangrene is produced by *Clostridium*'s fermentation of butyric acid, which produces hydrogen and carbon dioxide that are released as the bacteria multiply, forming pockets of gas in tissues (Figure **17.4.2.2**).

Gas gangrene is initially diagnosed based on the presence of the clinical signs and symptoms described earlier in this section. Diagnosis can be confirmed through Gram stain and anaerobic cultivation of wound exudate (drainage) and tissue samples on blood agar. Treatment typically involves surgical debridement of any necrotic tissue; advanced cases may require amputation. Surgeons may also use vacuum-assisted closure (VAC), a surgical technique in which vacuum-assisted drainage is used to remove blood or serous fluid from a wound or surgical site to speed recovery. The most common antibiotic treatments include penicillin G and clindamycin. Some cases are also treated with hyperbaric oxygen therapy because *Clostridium* spp. are incapable of surviving in oxygen-rich environments.



Figure **17.4.2.2**: (a) In this image of a patient with gas gangrene, note the bluish-purple discoloration around the bicep and the irregular margin of the discolored tissue indicating the spread of infection. (b) A radiograph of the arm shows a darkening in the tissue, which indicates the presence of gas. (credit a, b: modification of work by Aggelidakis J, Lasithiotakis K, Topalidou A, Koutroumpas J, Kouvidis G, and Katonis P)

Tularemia

Infection with the gram-negative bacterium *Francisella tularensis* causes tularemia (or rabbit fever), a zoonotic infection in humans. *F. tularensis* is a facultative intracellular parasite that primarily causes illness in rabbits, although a wide variety of domesticated animals are also susceptible to infection. Humans can be infected through ingestion of contaminated meat or, more typically, handling of infected animal tissues (e.g., skinning an infected rabbit). Tularemia can also be transmitted by the bites of infected arthropods, including the dog tick (*Dermacentor variabilis*), the lone star tick (*Amblyomma americanum*), the wood tick (*Dermacentor andersoni*), and deer flies (*Chrysops* spp.). Although the disease is not directly communicable between humans, exposure to aerosols of *F. tularensis* can result in life-threatening infections. *F. tularensis* is highly contagious, with an infectious dose of as few as 10 bacterial cells. In addition, pulmonary infections have a 30%–60% fatality rate if untreated.[10] For these reasons, *F. tularensis* is currently classified and must be handled as a biosafety level-3 (BSL-3) organism and as a potential biological warfare agent.

Following introduction through a break in the skin, the bacteria initially move to the lymph nodes, where they are ingested by phagocytes. After escaping from the phagosome, the bacteria grow and multiply intracellularly in the cytoplasm of phagocytes. They can later become disseminated through the blood to other organs such as the liver, lungs, and spleen, where they produce masses of tissue called granulomas (Figure **17.4.2.3**). After an incubation period of about 3 days, skin lesions develop at the site of infection. Other signs and symptoms include fever, chills, headache, and swollen and painful lymph nodes.



Figure **17.4.2.3**: (a) A skin lesion appears at the site of infection on the hand of an individual infected with *Francisella tularensis*.

(b) A scanning electron micrograph shows the coccobacilli cells (blue) of *F. tularensis*. (credit a: modification of work by Centers for Disease Control and Prevention; credit b: modification of work by NIAID)

A direct diagnosis of tularemia is challenging because it is so contagious. Once a presumptive diagnosis of tularemia is made, special handling is required to collect and process patients' specimens to prevent the infection of health-care workers. Specimens suspected of containing *F. tularensis* can only be handled by BSL-2 or BSL-3 laboratories registered with the Federal Select Agent Program, and individuals handling the specimen must wear protective equipment and use a class II biological safety cabinet.

Tularemia is relatively rare in the US, and its signs and symptoms are similar to a variety of other infections that may need to be ruled out before a diagnosis can be made. Direct fluorescent-antibody (DFA) microscopic examination using antibodies specific for *F. tularensis* can rapidly confirm the presence of this pathogen. Culturing this microbe is difficult because of its requirement for the amino acid cysteine, which must be supplied as an extra nutrient in culturing media. Serological tests are available to detect an immune response against the bacterial pathogen. In patients with suspected infection, acute- and convalescent-phase serum samples are required to confirm an active infection. PCR-based tests can also be used for clinical identification of direct specimens from body fluids or tissues as well as cultured specimens. In most cases, diagnosis is based on clinical findings and likely incidents of exposure to the bacterium. The antibiotics streptomycin, gentamycin, doxycycline, and ciprofloxacin are effective in treating tularemia.

Brucellosis

Species in the genus *Brucella* are gram-negative facultative intracellular pathogens that appear as coccobacilli. Several species cause zoonotic infections in animals and humans, four of which have significant human pathogenicity: *B. abortus* from cattle and buffalo, *B. canis* from dogs, *B. suis* from swine, and *B. melitensis* from goats, sheep, and camels. Infections by these pathogens are called brucellosis, also known as undulant fever, "Mediterranean fever," or "Malta fever." Vaccination of animals has made brucellosis a rare disease in the US, but it is still common in the Mediterranean, south and central Asia, Central and South America, and the Caribbean. Human infections are primarily associated with the ingestion of meat or unpasteurized dairy products from infected animals. Infection can also occur through inhalation of bacteria in aerosols when handling animal products, or through direct contact with skin wounds. In the US, most cases of brucellosis are found in individuals with extensive exposure to potentially infected animals (e.g., slaughterhouse workers, veterinarians).

Two important virulence factors produced by *Brucella* spp. are urease, which allows ingested bacteria to avoid destruction by stomach acid, and lipopolysaccharide (LPS), which allows the bacteria to survive within phagocytes. After gaining entry to tissues, the bacteria are phagocytized by host neutrophils and macrophages. The bacteria then escape from the phagosome and grow within the cytoplasm of the cell. Bacteria phagocytized by macrophages are disseminated throughout the body. This results in the formation of granulomas within many body sites, including bone, liver, spleen, lung, genitourinary tract, brain, heart, eye, and skin. Acute infections can result in undulant (relapsing) fever, but untreated infections develop into chronic disease that usually manifests as acute febrile illness (fever of 40–41 °C [104–105.8 °F]) with recurring flu-like signs and symptoms.

Brucella is only reliably found in the blood during the acute fever stage; it is difficult to diagnose by cultivation. In addition, *Brucella* is considered a BSL-3 pathogen and is hazardous to handle in the clinical laboratory without protective clothing and at least a class II biological safety cabinet. Agglutination tests are most often used for serodiagnosis. In addition, enzyme-linked immunosorbent assays (ELISAs) are available to determine exposure to the organism. The antibiotics doxycycline or ciprofloxacin are typically prescribed in combination with rifampin; gentamicin, streptomycin, and trimethoprim-sulfamethoxazole (TMP-SMZ) are also effective against *Brucella* infections and can be used if needed.

? Exercise 17.4.2.5

Compare the pathogenesis of tularemia and brucellosis.

Cat-Scratch Disease

The zoonosis cat-scratch disease (CSD) (or cat-scratch fever) is a bacterial infection that can be introduced to the lymph nodes when a human is bitten or scratched by a cat. It is caused by the facultative intracellular gram-negative bacterium *Bartonella henselae*. Cats can become infected from flea feces containing *B. henselae* that they ingest while grooming. Humans become

infected when flea feces or cat saliva (from claws or licking) containing *B. henselae* are introduced at the site of a bite or scratch. Once introduced into a wound, *B. henselae* infects red blood cells.

B. henselae invasion of red blood cells is facilitated by adhesins associated with outer membrane proteins and a secretion system that mediates transport of virulence factors into the host cell. Evidence of infection is indicated if a small nodule with pus forms in the location of the scratch 1 to 3 weeks after the initial injury. The bacteria then migrate to the nearest lymph nodes, where they cause swelling and pain. Signs and symptoms may also include fever, chills, and fatigue. Most infections are mild and tend to be self-limiting. However, immunocompromised patients may develop bacillary angiomatosis (BA), characterized by the proliferation of blood vessels, resulting in the formation of tumor-like masses in the skin and internal organs; or bacillary peliosis (BP), characterized by multiple cyst-like, blood-filled cavities in the liver and spleen. Most cases of CSD can be prevented by keeping cats free of fleas and promptly cleaning a cat scratch with soap and warm water.

The diagnosis of CSD is difficult because the bacterium does not grow readily in the laboratory. When necessary, immunofluorescence, serological tests, PCR, and gene sequencing can be performed to identify the bacterial species. Given the limited nature of these infections, antibiotics are not normally prescribed. For immunocompromised patients, rifampin, azithromycin, ciprofloxacin, gentamicin (intramuscularly), or TMP-SMZ are generally the most effective options.

Rat-Bite Fever

The zoonotic infection rat-bite fever can be caused by two different gram-negative bacteria: *Streptobacillus moniliformis*, which is more common in North America, and *Spirillum minor*, which is more common in Asia. Because of modern sanitation efforts, rat bites are rare in the US. However, contact with fomites, food, or water contaminated by rat feces or body fluids can also cause infections. Signs and symptoms of rat-bite fever include fever, vomiting, myalgia (muscle pain), arthralgia (joint pain), and a maculopapular rash on the hands and feet. An ulcer may also form at the site of a bite, along with some swelling of nearby lymph nodes. In most cases, the infection is self-limiting. Little is known about the virulence factors that contribute to these signs and symptoms of disease.

Cell culture, MALDI-TOF mass spectrometry, PCR, or ELISA can be used in the identification of *Streptobacillus moniliformis*. The diagnosis *Spirillum minor* may be confirmed by direct microscopic observation of the pathogens in blood using Giemsa or Wright stains, or darkfield microscopy. Serological tests can be used to detect a host immune response to the pathogens after about 10 days. The most commonly used antibiotics to treat these infections are penicillin or doxycycline.

Plague

The gram-negative bacillus *Yersinia pestis* causes the zoonotic infection plague. This bacterium causes acute febrile disease in animals, usually rodents or other small mammals, and humans. The disease is associated with a high mortality rate if left untreated. Historically, *Y. pestis* has been responsible for several devastating pandemics, resulting in millions of deaths (see Micro Connections: The History of the Plague). There are three forms of plague: bubonic plague (the most common form, accounting for about 80% of cases), pneumonic plague, and septicemic plague. These forms are differentiated by the mode of transmission and the initial site of infection. Figure **17.4.2.4** illustrates these various modes of transmission and infection between animals and humans.

In bubonic plague, *Y. pestis* is transferred by the bite of infected fleas. Since most flea bites occur on the legs and ankles, *Y. pestis* is often introduced into the tissues and blood circulation in the lower extremities. After a 2- to 6-day incubation period, patients experience an abrupt onset fever (39.5–41 °C [103.1–105.8 °F]), headache, hypotension, and chills. The pathogen localizes in lymph nodes, where it causes inflammation, swelling, and hemorrhaging that results in purple buboes (Figure **17.4.2.5**). Buboes often form in lymph nodes of the groin first because these are the nodes associated with the lower limbs; eventually, through circulation in the blood and lymph, lymph nodes throughout the body become infected and form buboes. The average mortality rate for bubonic plague is about 55% if untreated and about 10% with antibiotic treatment.

Septicemic plague occurs when *Y. pestis* is directly introduced into the bloodstream through a cut or wound and circulates through the body. The incubation period for septicemic plague is 1 to 3 days, after which patients develop fever, chills, extreme weakness, abdominal pain, and shock. Disseminated intravascular coagulation (DIC) can also occur, resulting in the formation of thrombi that obstruct blood vessels and promote ischemia and necrosis in surrounding tissues (Figure **17.4.2.5**). Necrosis occurs most commonly in extremities such as fingers and toes, which become blackened. Septicemic plague can quickly lead to death, with a mortality rate near 100% when it is untreated. Even with antibiotic treatment, the mortality rate is about 50%.

Pneumonic plague occurs when *Y. pestis* causes an infection of the lungs. This can occur through inhalation of aerosolized droplets from an infected individual or when the infection spreads to the lungs from elsewhere in the body in patients with bubonic or septicemic plague. After an incubation period of 1 to 3 days, signs and symptoms include fever, headache, weakness, and a rapidly developing pneumonia with shortness of breath, chest pain, and cough producing bloody or watery mucus. The pneumonia may result in rapid respiratory failure and shock. Pneumonic plague is the only form of plague that can be spread from person to person by infectious aerosol droplet. If untreated, the mortality rate is near 100%; with antibiotic treatment, the mortality rate is about 50%.

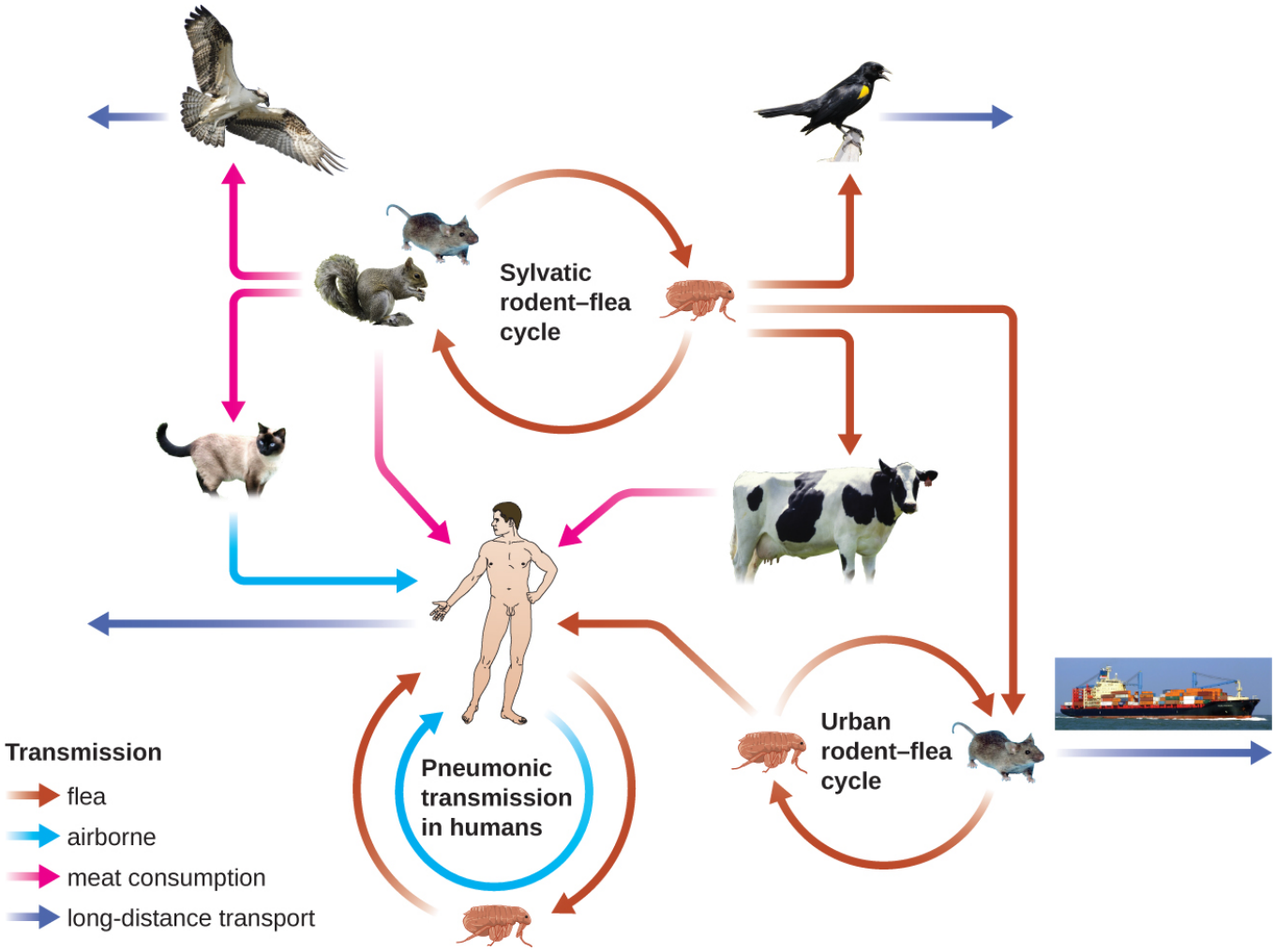


Figure 17.4.2.4: Yersinia pestis, the causative agent of plague, has numerous modes of transmission. The modes are divided into two ecological classes: urban and sylvatic (i.e., forest or rural). The urban cycle primarily involves transmission from infected urban mammals (rats) to humans by flea vectors (brown arrows). The disease may travel between urban centers (purple arrow) if infected rats find their way onto ships or trains. The sylvatic cycle involves mammals more common in nonurban environments. Sylvatic birds and mammals (including humans) may become infected after eating infected mammals (pink arrows) or by flea vectors. Pneumonic transmission occurs between humans or between humans and infected animals through the inhalation of *Y. pestis* in aerosols. (credit “diagram”: modification of work by Stenseth NC, Atshabar BB, Begon M, Belmain SR, Bertherat E, Carniel E, Gage KL, Leirs H, and Rahalison L; credit “cat”: modification of work by “KaCey97078”/Flickr)



(a)



(b)

Figure **17.4.2.5**: (a) *Yersinia pestis* infection can cause inflamed and swollen lymph nodes (buboes), like these in the groin of an infected patient. (b) Septicemic plague caused necrotic toes in this patient. Vascular damage at the extremities causes ischemia and tissue death. (credit a: modification of work by American Society for Microbiology; credit b: modification of work by Centers for Disease Control and Prevention)

The high mortality rate for the plague is, in part, a consequence of it being unusually well equipped with virulence factors. To date, there are at least 15 different major virulence factors that have been identified from *Y. pestis* and, of these, eight are involved with adherence to host cells. In addition, the F1 component of the *Y. pestis* capsule is a virulence factor that allows the bacterium to avoid phagocytosis. F1 is produced in large quantities during mammalian infection and is the most immunogenic component.[11] Successful use of virulence factors allows the bacilli to disseminate from the area of the bite to regional lymph nodes and eventually the entire blood and lymphatic systems.

Culturing and direct microscopic examination of a sample of fluid from a bubo, blood, or sputum is the best way to identify *Y. pestis* and confirm a presumptive diagnosis of plague. Specimens may be stained using either a Gram, Giemsa, Wright, or Wayson's staining technique (Figure **17.4.2.6**). The bacteria show a characteristic bipolar staining pattern, resembling safety pins, that facilitates presumptive identification. Direct fluorescent antibody tests (rapid test of outer-membrane antigens) and serological tests like ELISA can be used to confirm the diagnosis. The confirmatory method for identifying *Y. pestis* isolates in the US is bacteriophage lysis.

Prompt antibiotic therapy can resolve most cases of bubonic plague, but septicemic and pneumonic plague are more difficult to treat because of their shorter incubation stages. Survival often depends on an early and accurate diagnosis and an appropriate choice of antibiotic therapy. In the US, the most common antibiotics used to treat patients with plague are gentamicin, fluoroquinolones, streptomycin, levofloxacin, ciprofloxacin, and doxycycline.

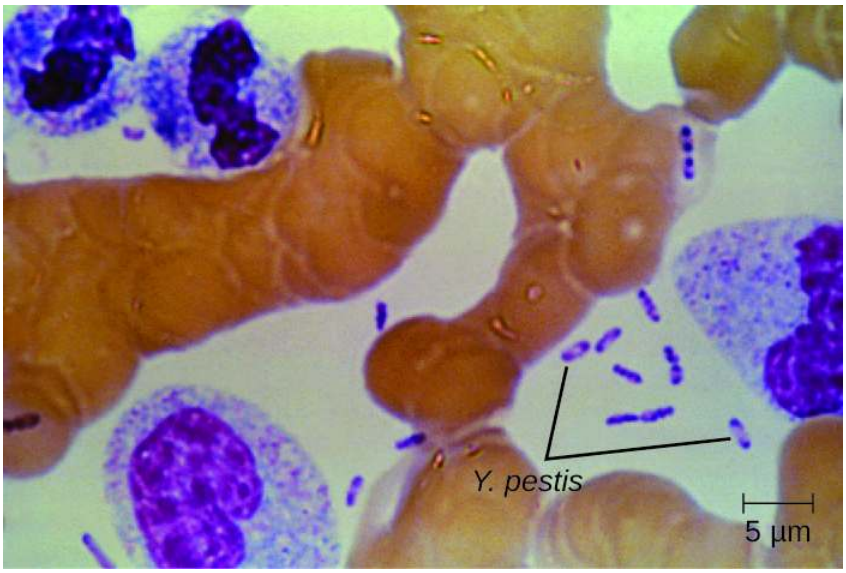


Figure **17.4.2.6**: This Wright's stain of a blood sample from a patient with plague shows the characteristic "safety pin" appearance of *Yersinia pestis*. (credit: modification of work by Centers for Disease Control and Prevention)

? Exercise 17.4.2.6

Compare bubonic plague, septicemic plague, and pneumonic plague.

Micro Connections: The History of the Plague

The first recorded pandemic of plague, the Justinian plague, occurred in the sixth century CE. It is thought to have originated in central Africa and spread to the Mediterranean through trade routes. At its peak, more than 5,000 people died per day in Constantinople alone. Ultimately, one-third of that city's population succumbed to plague.[12] The impact of this outbreak probably contributed to the later fall of Emperor Justinian.

The second major pandemic, dubbed the Black Death, occurred during the 14th century. This time, the infections are thought to have originated somewhere in Asia before being transported to Europe by trade, soldiers, and war refugees. This outbreak killed an estimated one-quarter of the population of Europe (25 million, primarily in major cities). In addition, at least another 25 million are thought to have been killed in Asia and Africa.[13] This second pandemic, associated with strain *Yersinia pestis* biovar Medievalis, cycled for another 300 years in Europe and Great Britain, and was called the Great Plague in the 1660s.

The most recent pandemic occurred in the 1890s with *Yersinia pestis* biovar Orientalis. This outbreak originated in the Yunnan province of China and spread worldwide through trade. It is at this time that plague made its way to the US. The etiologic agent of plague was discovered by Alexandre Yersin (1863–1943) during this outbreak as well. The overall number of deaths was lower than in prior outbreaks, perhaps because of improved sanitation and medical support.[14] Most of the deaths attributed to this final pandemic occurred in India.

Link to Learning

Visit this link to see an article describing how similar the genome of the Black Death bacterium is to today's strains of bubonic plague.

Zoonotic Febrile Diseases

A wide variety of zoonotic febrile diseases (diseases that cause fever) are caused by pathogenic bacteria that require arthropod vectors. These pathogens are either obligate intracellular species of *Anaplasma*, *Bartonella*, *Ehrlichia*, *Orientia*, and *Rickettsia*, or spirochetes in the genus *Borrelia*. Isolation and identification of pathogens in this group are best performed in BSL-3 laboratories because of the low infective dose associated with the diseases.

Anaplasmosis

The zoonotic tickborne disease human granulocytic anaplasmosis (HGA) is caused by the obligate intracellular pathogen *Anaplasma phagocytophilum*. HGA is endemic primarily in the central and northeastern US and in countries in Europe and Asia.

HGA is usually a mild febrile disease that causes flu-like symptoms in immunocompetent patients; however, symptoms are severe enough to require hospitalization in at least 50% of infections and, of those patients, less than 1% will die of HGA.[15] Small mammals such as white-footed mice, chipmunks, and voles have been identified as reservoirs of *A. phagocytophilum*, which is transmitted by the bite of an *Ixodes* tick. Five major virulence factors[16] have been reported in *Anaplasma*; three are adherence factors and two are factors that allow the pathogen to avoid the human immune response. Diagnostic approaches include locating intracellular microcolonies of *Anaplasma* through microscopic examination of neutrophils or eosinophils stained with Giemsa or Wright stain, PCR for detection of *A. phagocytophilum*, and serological tests to detect antibody titers against the pathogens. The primary antibiotic used for treatment is doxycycline.

Ehrlichiosis

Human monocytotropic ehrlichiosis (HME) is a zoonotic tickborne disease caused by the BSL-2, obligate intracellular pathogen *Ehrlichia chaffeensis*. Currently, the geographic distribution of HME is primarily the eastern half of the US, with a few cases reported in the West, which corresponds with the known geographic distribution of the primary vector, the lone star tick (*Amblyomma americanum*). Symptoms of HME are similar to the flu-like symptoms observed in anaplasmosis, but a rash is more common, with 60% of children and less than 30% of adults developing petechial, macula, and maculopapular rashes.[17] Virulence factors allow *E. chaffeensis* to adhere to and infect monocytes, forming intracellular microcolonies in monocytes that are diagnostic for the HME. Diagnosis of HME can be confirmed with PCR and serologic tests. The first-line treatment for adults and children of all ages with HME is doxycycline.

Epidemic Typhus

The disease epidemic typhus is caused by *Rickettsia prowazekii* and is transmitted by body lice, *Pediculus humanus*. Flying squirrels are animal reservoirs of *R. prowazekii* in North America and can also be sources of lice capable of transmitting the pathogen. Epidemic typhus is characterized by a high fever and body aches that last for about 2 weeks. A rash develops on the abdomen and chest and radiates to the extremities. Severe cases can result in death from shock or damage to heart and brain tissues. Infected humans are an important reservoir for this bacterium because *R. prowazekii* is the only *Rickettsia* that can establish a chronic carrier state in humans.

Epidemic typhus has played an important role in human history, causing large outbreaks with high mortality rates during times of war or adversity. During World War I, epidemic typhus killed more than 3 million people on the Eastern front.[18]With the advent of effective insecticides and improved personal hygiene, epidemic typhus is now quite rare in the US. In the developing world, however, epidemics can lead to mortality rates of up to 40% in the absence of treatment.[19] In recent years, most outbreaks have taken place in Burundi, Ethiopia, and Rwanda. For example, an outbreak in Burundi refugee camps in 1997 resulted in 45,000 illnesses in a population of about 760,000 people.[20]

A rapid diagnosis is difficult because of the similarity of the primary symptoms with those of many other diseases. Molecular and immunohistochemical diagnostic tests are the most useful methods for establishing a diagnosis during the acute stage of illness when therapeutic decisions are critical. PCR to detect distinctive genes from *R. prowazekii* can be used to confirm the diagnosis of epidemic typhus, along with immunofluorescent staining of tissue biopsy specimens. Serology is usually used to identify rickettsial infections. However, adequate antibody titers take up to 10 days to develop. Antibiotic therapy is typically begun before the diagnosis is complete. The most common drugs used to treat patients with epidemic typhus are doxycycline or chloramphenicol.

Murine (Endemic) Typhus

Murine typhus (also known as endemic typhus) is caused by *Rickettsia typhi* and is transmitted by the bite of the rat flea, *Xenopsylla cheopis*, with infected rats as the main reservoir. Clinical signs and symptoms of murine typhusinclude a rash and chills accompanied by headache and fever that last about 12 days. Some patients also exhibit a cough and pneumonia-like symptoms. Severe illness can develop in immunocompromised patients, with seizures, coma, and renal and respiratory failure.

Clinical diagnosis of murine typhus can be confirmed from a biopsy specimen from the rash. Diagnostic tests include indirect immunofluorescent antibody (IFA) staining, PCR for *R. typhi*, and acute and convalescent serologic testing. Primary treatment is doxycycline, with chloramphenicol as the second choice.

Rocky Mountain Spotted Fever

The disease Rocky Mountain spotted fever (RMSF) is caused by *Rickettsia rickettsii* and is transmitted by the bite of a hard-bodied tick such as the American dog tick (*Dermacentor variabilis*), Rocky Mountain wood tick (*D. andersoni*), or brown dog tick (*Rhipicephalus sanguineus*).

This disease is endemic in North and South America and its incidence is coincident with the arthropod vector range. Despite its name, most cases in the US do not occur in the Rocky Mountain region but in the Southeast; North Carolina, Oklahoma, Arkansas, Tennessee, and Missouri account for greater than 60% of all cases.[21] The map in Figure **17.4.2.7** shows the distribution of prevalence in the US in 2010.

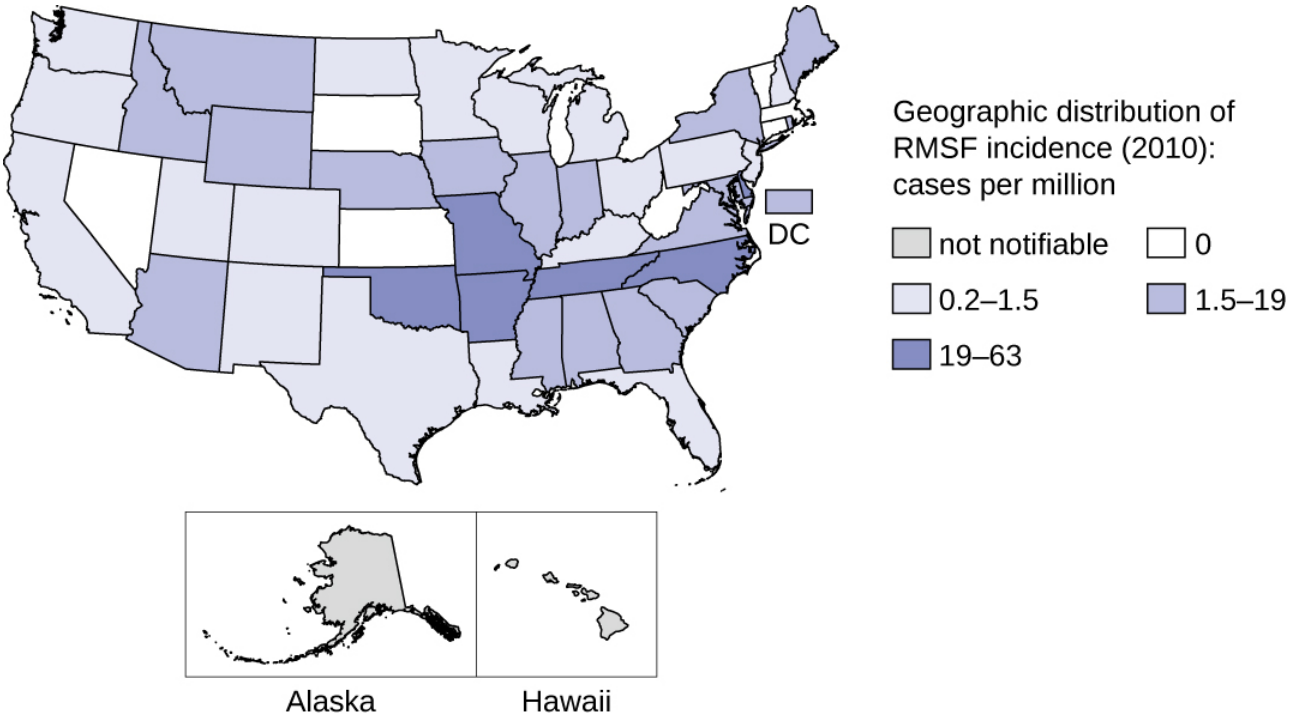


Figure **17.4.2.7**: In the US, Rocky Mountain spotted fever is most prevalent in the southeastern states. (credit: modification of work by Centers for Disease Control and Prevention)

Signs and symptoms of RMSF include a high fever, headache, body aches, nausea, and vomiting. A petechial rash(similar in appearance to measles) begins on the hands and wrists, and spreads to the trunk, face, and extremities (Figure **17.4.2.8**). If untreated, RMSF is a serious illness that can be fatal in the first 8 days even in otherwise healthy patients. Ideally, treatment should begin before petechiae develop, because this is a sign of progression to severe disease; however, the rash usually does not appear until day 6 or later after onset of symptoms and only occurs in 35%–60% of patients with the infection. Increased vascular permeability associated with petechiae formation can result in fatality rates of 3% or greater, even in the presence of clinical support. Most deaths are due to hypotension and cardiac arrest or from ischemia following blood coagulation.

Diagnosis can be challenging because the disease mimics several other diseases that are more prevalent. The diagnosis of RMSF is made based on symptoms, fluorescent antibody staining of a biopsy specimen from the rash, PCR for *Rickettsia rickettsii*, and acute and convalescent serologic testing. Primary treatment is doxycycline, with chloramphenicol as the second choice.



Figure **17.4.2.8**: Rocky Mountain spotted fever causes a petechial rash. Unlike epidemic or murine typhus, the rash begins at the hands and wrists and then spreads to the trunk. (credit: modification of work by Centers for Disease Control and Prevention)

Lyme Disease

Lyme disease is caused by the spirochete *Borrelia burgdorferi* that is transmitted by the bite of a hard-bodied, black-legged *Ixodes* tick. *I. scapularis* is the biological vector transmitting *B. burgdorferi* in the eastern and north-central US and *I. pacificus* transmits *B. burgdorferi* in the western US (Figure **17.4.2.10**). Different species of *Ixodes* ticks are responsible for *B. burgdorferi* transmission in Asia and Europe. In the US, Lyme disease is the most commonly reported vectorborne illness. In 2014, it was the fifth most common Nationally Notifiable disease.[22]

Ixodes ticks have complex life cycles and deer, mice, and even birds can act as reservoirs. Over 2 years, the ticks pass through four developmental stages and require a blood meal from a host at each stage. In the spring, tick eggs hatch into six-legged larvae. These larvae do not carry *B. burgdorferi* initially. They may acquire the spirochete when they take their first blood meal (typically from a mouse). The larvae then overwinter and molt into eight-legged nymphs in the following spring. Nymphs take blood meals primarily from small rodents, but may also feed on humans, burrowing into the skin. The feeding period can last several days to a week, and it typically takes 24 hours for an infected nymph to transmit enough *B. burgdorferi* to cause infection in a human host. Nymphs ultimately mature into male and female adult ticks, which tend to feed on larger animals like deer or, occasionally, humans. The adults then mate and produce eggs to continue the cycle (Figure **17.4.2.9**).

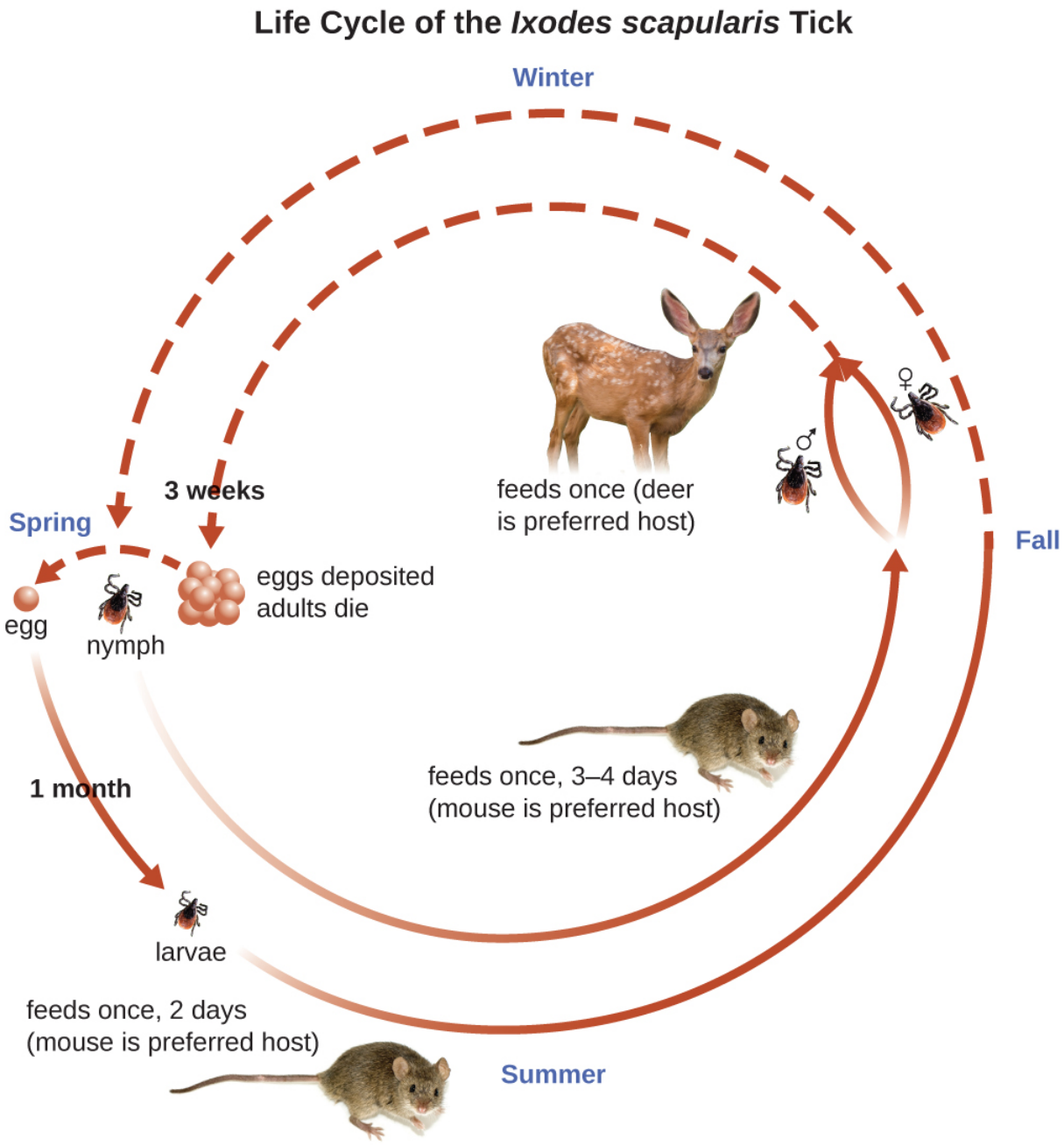


Figure **17.4.2.9**: This image shows the 2-year life cycle of the black-legged tick, the biological vector of Lyme disease. (credit “mouse”: modification of work by George Shuklin)

The symptoms of Lyme disease follow three stages: early localized, early disseminated, and late stage. During the early-localized stage, approximately 70%–80%[23] of cases may be characterized by a bull's-eye rash, called erythema migrans, at the site of the initial tick bite. The rash forms 3 to 30 days after the tick bite (7 days is the average) and may also be warm to the touch (Figure **17.4.2.10**).[24] This diagnostic sign is often overlooked if the tick bite occurs on the scalp or another less visible location. Other early symptoms include flu-like symptoms such as malaise, headache, fever, and muscle stiffness. If the patient goes untreated, the second early-disseminated stage of the disease occurs days to weeks later. The symptoms at this stage may include severe headache, neck stiffness, facial paralysis, arthritis, and carditis. The late-stage manifestations of the disease may occur years after exposure. Chronic inflammation causes damage that can eventually cause severe arthritis, meningitis, encephalitis, and altered mental states. The disease may be fatal if untreated.

A presumptive diagnosis of Lyme disease can be made based solely on the presence of a bull’s-eye rash at the site of infection, if it is present, in addition to other associated symptoms (Figure **17.4.2.10**). In addition, indirect immunofluorescent antibody (IFA)

labeling can be used to visualize bacteria from blood or skin biopsy specimens. Serological tests like ELISA can also be used to detect serum antibodies produced in response to infection. During the early stage of infection (about 30 days), antibacterial drugs such as amoxicillin and doxycycline are effective. In the later stages, penicillin G, chloramphenicol, or ceftriaxone can be given intravenously.

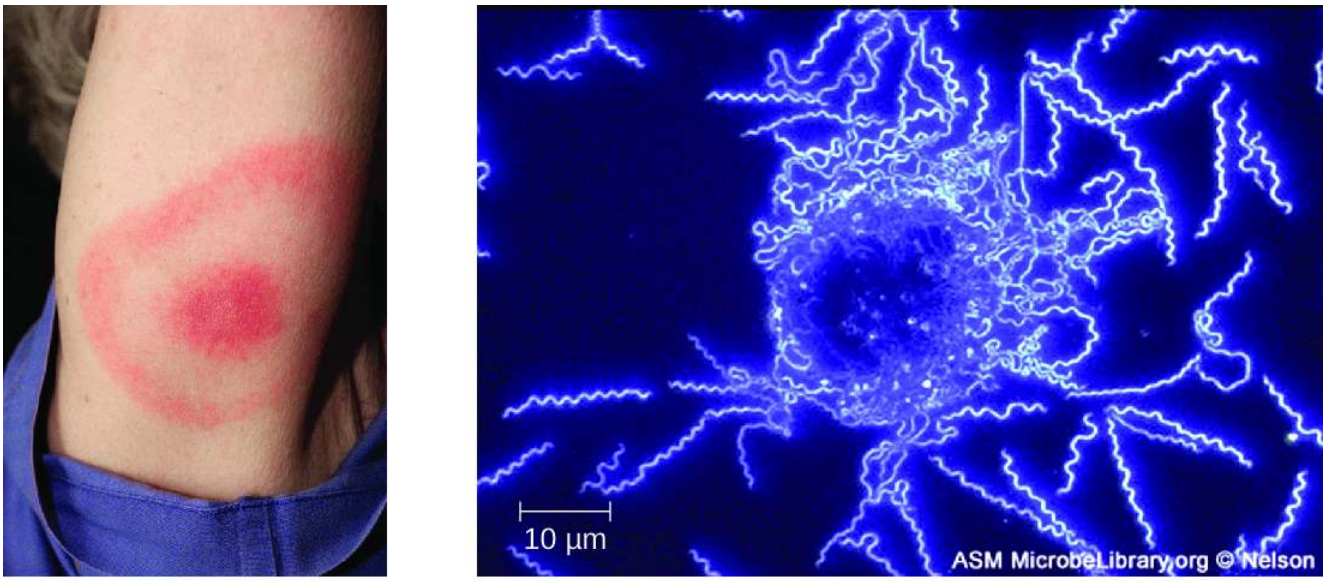


Figure **17.4.2.10**: (a) A characteristic bull's eye rash of Lyme disease forms at the site of a tick bite. (b) A darkfield micrograph shows *Borrelia burgdorferi*, the causative agent of Lyme disease. (credit a: modification of work by Centers for Disease Control and Prevention; credit b: modification of work by American Society for Microbiology)

Relapsing Fever

Borrelia spp. also can cause relapsing fever. Two of the most common species are *B. recurrentis*, which causes epidemics of louseborne relapsing fever, and *B. hermsii*, which causes tickborne relapsing fevers. These *Borrelia* species are transmitted by the body louse *Pediculus humanus* and the soft-bodied tick *Ornithodoros hermsi*, respectively. Lice acquire the spirochetes from human reservoirs, whereas ticks acquire them from rodent reservoirs. Spirochetes infect humans when *Borrelia* in the vector's saliva or excreta enter the skin rapidly as the vector bites.

In both louse- and tickborne relapsing fevers, bacteremia usually occurs after the initial exposure, leading to a sudden high fever (39–43 °C [102.2–109.4 °F) typically accompanied by headache and muscle aches. After about 3 days, these symptoms typically subside, only to return again after about a week. After another 3 days, the symptoms subside again but return a week later, and this cycle may repeat several times unless it is disrupted by antibiotic treatment. Immune evasion through bacterial antigenic variation is responsible for the cyclical nature of the symptoms in these diseases.

The diagnosis of relapsing fever can be made by observation of spirochetes in blood, using darkfield microscopy (Figure **17.4.2.11**). For louseborne relapsing fever, doxycycline or erythromycin are the first-line antibiotics. For tickborne relapsing fever, tetracycline or erythromycin are the first-line antibiotics.

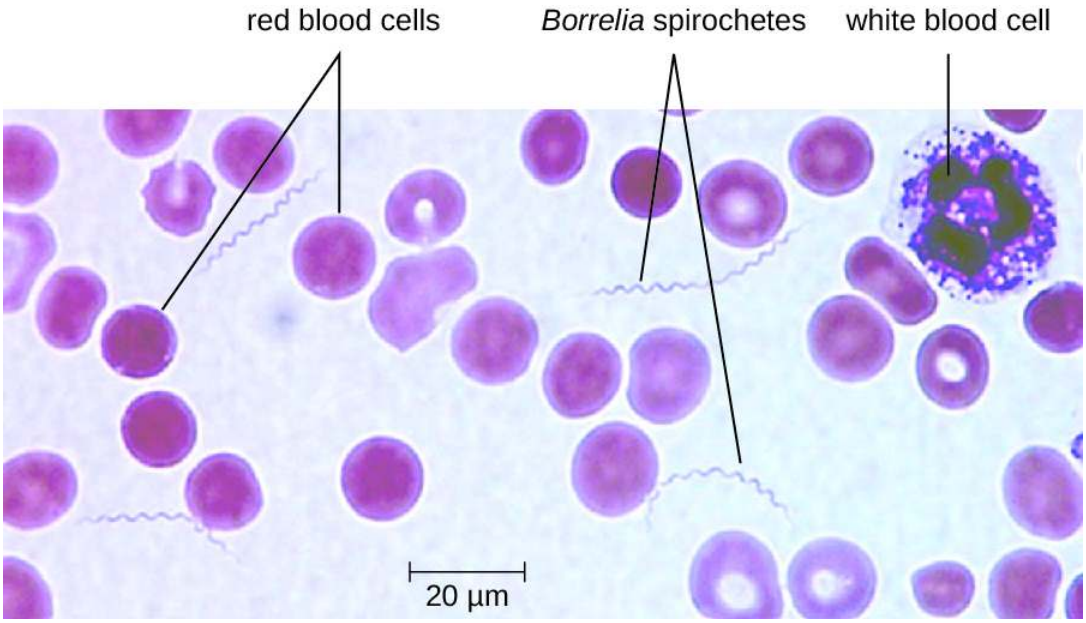


Figure **17.4.2.11**: A peripheral blood smear from a patient with tickborne relapsing fever. *Borrelia* appears as thin spirochetes among the larger red blood cells. (credit: modification of work by Centers for Disease Control and Prevention)

Trench Fever

The louseborne disease trench fever was first characterized as a specific disease during World War I, when approximately 1 million soldiers were infected. Today, it is primarily limited to areas of the developing world where poor sanitation and hygiene lead to infestations of lice (e.g., overpopulated urban areas and refugee camps). Trench fever is caused by the gram-negative bacterium *Bartonella quintana*, which is transmitted when feces from infected body lice, *Pediculus humanus* var *corporis*, are rubbed into the louse bite, abraded skin, or the conjunctiva. The symptoms typically follow a 5-day course marked by a high fever, body aches, conjunctivitis, ocular pain, severe headaches, and severe bone pain in the shins, neck, and back. Diagnosis can be made using blood cultures; serological tests like ELISA can be used to detect antibody titers to the pathogen and PCR can also be used. The first-line antibiotics are doxycycline, macrolide antibiotics, and ceftriaxone.

? Exercise 17.4.2.7

1. What is the vector associated with epidemic typhus?
2. Describe the life cycle of the deer tick and how it spreads Lyme disease.

Tick Tips

Many of the diseases covered in this chapter involve arthropod vectors. Of these, ticks are probably the most commonly encountered in the US. Adult ticks have eight legs and two body segments, the cephalothorax and the head (Figure **17.4.2.12**). They typically range from 2 mm to 4 mm in length, and feed on the blood of the host by attaching themselves to the skin.



Figure **17.4.2.12**: (a) This black-legged tick, also known as the deer tick, has not yet attached to the skin. (b) A notched tick extractor can be used for removal. (c) To remove an attached tick with fine-tipped tweezers, pull gently on the mouth parts until the tick releases its hold on the skin. Avoid squeezing the tick's body, because this could release pathogens and thus increase the risk of contracting Lyme disease. (credit a: modification of work by Jerry Kirkhart; credit c: modification of work by Centers for Disease Control and Prevention)

Unattached ticks should be removed and eliminated as soon as they are discovered. When removing a tick that has already attached itself, keep the following guidelines in mind to reduce the chances of exposure to pathogens:

- Use blunt tweezers to gently pull near the site of attachment until the tick releases its hold on the skin.
- Avoid crushing the tick's body and do not handle the tick with bare fingers. This could release bacterial pathogens and actually increase your exposure. The tick can be killed by drowning in water or alcohol, or frozen if it may be needed later for identification and analysis.
- Disinfect the area thoroughly by swabbing with an antiseptic such as isopropanol.
- Monitor the site of the bite for rashes or other signs of infection.

Many ill-advised home remedies for tick removal have become popular in recent years, propagated by social media and pseudojournalism. Health professionals should discourage patients from resorting to any of the following methods, which are NOT recommended:

- using chemicals (e.g., petroleum jelly or fingernail polish) to dislodge an attached tick, because it can cause the tick to release fluid, which can increase the chance of infection
- using hot objects (matches or cigarette butts) to dislodge an attached tick
- squeezing the tick's body with fingers or tweezers

Bacterial Infections of the Circulatory and Lymphatic Systems

Although the circulatory system is a closed system, bacteria can enter the bloodstream through several routes. Wounds, animal bites, or other breaks in the skin and mucous membranes can result in the rapid dissemination of bacterial pathogens throughout the body. Localized infections may also spread to the bloodstream, causing serious and often fatal systemic infections. Figure **17.4.2.13** and Figure **17.4.2.14** summarize the major characteristics of bacterial infections of the circulatory and lymphatic systems.

Bacterial Infections of the Circulatory and Lymphatic Systems					
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Diagnostic Tests**	**Antimicrobial Drugs**
Anaplasmosis (HGA)	*Anaplasma phagocytophilum*	Fever, flu-like symptoms	From small-mammal reservoirs via tick vector	Blood smear, PCR	Doxycycline
Brucellosis	*Brucella melitensis, B. abortus, B. canis, B. suis*	Granuloma, undulating fever, chronic flu-like symptoms	Direct contact with infected livestock or animals	Agglutination tests, ELISA	Doxycycline, rifampin
Cat-scratch disease	*Bartonella henselae*	Lymph-node swelling and pain, fever, chills, fatigue	Bite or scratch from domestic cats	Immunofluorescence, serological tests, PCR	None for immunocompetent patients
Ehrlichiosis (HME)	*Ehrlichia chaffeensis*	Flu-like symptoms, rash	Lone star tick vector	Serologic tests, PCR	Doxycycline
Endocarditis/ pericarditis	*SStaphylococcus* spp., *Streptococcus spp., Enterococcus spp., HACEK* bacilli	Chest pain, difficulty breathing, dry cough, fever; potentially fatal damage to heart valves	Pathogens introduced to bloodstream via contaminated catheters, dental procedures, piercings, or wounds	Echocardiogram, blood culture	Ampicillin, nafcillin, gentamicin, others; based on susceptibility testing
Epidemic typhus	*Rickettsia prowazekii*	High fever, body aches, rash; potentially fatal damage to heart and brain	From rodent reservoir via body louse vector	PCR, immunofluorescence	Doxycycline, chloramphenicol
Gas gangrene	*Clostridium perfringens,* other *Clostridium* spp.	Rapidly spreading myonecrosis, edema, yellowish and then purple discharge from wound, pockets of gas in tissues, septic shock and death	Germination of endospores in ischemic tissues, typically due to injury or chronic disease (e.g., diabetes)	Wound culture	Penicillin G, clindamycin, metronidazole
Infectious arthritis (septic arthritis)	*Staphylococcus aureus, Neisseria gonorrhoeae*	Joint pain and swelling, limited range of motion	Infection spreads to joint via circulatory system from wound or surgical site	Synovial fluid culture	Oxacillin, cefazolin, cephtriaxone
Lyme disease	*Borrelia burgdorferi*	Early localized: bull's eye rash, malaise, headache, fever, muscle stiffness; early disseminated: stiff neck, facial paralysis, arthritis, carditis; late-stage: arthritis, meningitis, possibly fatal	From deer, rodent, bird reservoirs via tick vector	IFA, serology, and ELISA	Amoxicillin, doxycycline, penicillin G, chloramphenicol, ceftriaxone
Murine (endemic) typhus	*Rickettsia typhi*	Low-grade fever, rash, headache, cough	From rodents or between humans via rat flea vector	Biopsy, IFA, PCR	Doxycycline, chloramphenicol
Osteomyelitis	*Staphylococcus aureus, Streptococcus pyogenes,* others	Inflammation of bone tissue, leading to fever, localized pain, edema, ulcers, bone loss	Pathogens introduced through trauma, prosthetic joint replacement, or from other infected body site via bloodstream	Radiograph of affected bone, culture of bone biopsy specimen	Cephalosporin, penicillins, others

Figure **17.4.2.13**: Bacterial infections of Circulatory and Lymphatic systems.

Bacterial Infections of the Circulatory and Lymphatic Systems (continued)					
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Diagnostic Tests**	**Antimicrobial Drugs**
Plague	*Yersinia pestis*	Bubonic: buboes, fever, internal hemorrhaging; septicemic: fever, abdominal pain, shock, DIC, necrosis in extremities; pneumonic: acute pneumonia, respiratory failure, shock. All forms have high mortality rates.	Transmitted from mammal reservoirs via flea vectors or consumption of infected animal; transmission of pneumonic plague between humans via respiratory aerosols	Culture of bacteria from lymph, blood, or sputum samples; DFA, ELISA	Gentamycin, fluoroquinolones, others
Puerperal sepsis	*Streptococcus pyogenes,* many others	Rapid-onset fever, shock, and death	Pathogens introduced during or immediately following childbirth	Wound, urine,or blood culture	As determined by susceptibility testing
Rat-bite fever	*Streptobacillus moniliformis, Spirillum minor*	Fever, muscle and joint pain, rash, ulcer	Bite from infected rat or exposure to rat feces or body fluids in contaminated food or water	Observation of the organism from samples and antibody tests	Penicillin
Relapsing fever	*Borrelia recurrentis, B. hermsii,* other *Borrelia* spp.	Recurring fever, headache, muscle aches	From rodent or human reservoir via body louse or tick vector	Darkfield microscopy	Doxycycline, tetracycline, erythromycin
Rheumatic fever	*Streptococcus pyogenes*	Joint pain and swelling, inflammation and scarring of heart valves, heart murmur	Sequela of streptococcal pharyngitis	Serology, electrocardiogram, echocardiogram	Benzathine benzylpenicillin
Rocky Mountain spotted fever	*Rickettsia rickettsii*	High fever, headache, body aches, nausea and vomiting, petechial rash; potentially fatal hypotension and ischemia due to blood coagulation	From rodent reservoir via tick vectors	Biopsy, serology, PCR	Doxycycline, chloramphenicol
Toxic shock syndrome (TSS)	*Staphylococcus aureus*	Sudden high fever, vomiting, diarrhea, hypotension, death	Pathogens from localized infection spread to bloodstream; pathogens introduced on tampons or other intravaginal products	Serology, toxin identification from isolates	Clindamycin, vancomycin
Toxic shock-like syndrome (STSS)	*Streptococcus pyogenes*	Sudden high fever, vomiting, diarrhea, acute respiratory distress syndrome (ARDS), hypoxemia, necrotizing fasciitis, death	Sequela of streptococcal skin or soft-tissue infection	Serology, blood culture, urinalysis	Penicillin, cephalosporin
Trench fever	*Bartonella quintana*	High fever, conjunctivitis, ocular pain, headaches, severe pain in bones of shins, neck, and back	Between humans via body louse vector	Blood culture, ELISA, PCR	Doxycycline, macrolide antibiotics, ceftriaxone
Tularemia (rabbit fever)	*Francisella tularensis*	Skin lesions, fever, chills, headache, buboes	Eating or handling infected rabbit; transmission from infected animal via tick or fly vector; aerosol transmission (in laboratory or as bioweapon)	DFA	Streptomycin, gentamycin, others

Figure **17.4.2.14**: Bacterial infections of Circulatory and Lymphatic systems (continued).

Key Concepts and Summary

- Bacterial infections of the circulatory system are almost universally serious. Left untreated, most have high mortality rates.
- Bacterial pathogens usually require a breach in the immune defenses to colonize the circulatory system. Most often, this involves a wound or the bite of an arthropod vector, but it can also occur in hospital settings and result in nosocomial infections.
- **Sepsis** from both gram-negative and gram-positive bacteria**, puerperal fever, rheumatic fever, endocarditis, gas gangrene, osteomyelitis,** and **toxic shock syndrome** are typically a result of injury or introduction of bacteria by medical or surgical intervention.
- **Tularemia, brucellosis, cat-scratch fever, rat-bite fever,** and **bubonic plague** are zoonotic diseases transmitted by biological vectors
- **Ehrlichiosis, anaplasmosis, endemic** and **murine typhus, Rocky Mountain spotted fever, Lyme disease, relapsing fever,** and **trench fever** are transmitted by arthropod vectors.
- Because their symptoms are so similar to those of other diseases, many bacterial infections of the circulatory system are difficult to diagnose.
- Standard antibiotic therapies are effective for the treatment of most bacterial infections of the circulatory system, unless the bacterium is resistant, in which case synergistic treatment may be required.
- The systemic immune response to a bacteremia, which involves the release of excessive amounts of cytokines, can sometimes be more damaging to the host than the infection itself.

Footnotes

1. 1 S.P. LaRosa. “Sepsis.” 2010. http://www.clevelandclinicmeded.com/...isease/sepsis/.
2. 2 D.C. Angus, T. Van der Poll. “Severe Sepsis and Septic Shock.” *New England Journal of Medicine* 369, no. 9 (2013):840–851.
3. 3 Centers for Disease Control and Prevention. “Toxic Shock Syndrome (Other Than Streptococcal) (TSS) 2011 Case Definition.” https://wwwn.cdc.gov/nndss/condition...finition/2011/. Accessed July 25, 2016.
4. 4 Centers for Disease Control and Prevention. “Streptococcal Toxic Shock Syndrome (STSS) (*Streptococcus pyogenes*) 2010 Case Definition.” https://wwwn.cdc.gov/nndss/condition...finition/2010/. Accessed July 25, 2016.
5. 5 M.E. Shirtliff, Mader JT. “Acute Septic Arthritis.” *Clinical Microbiology Reviews* 15 no. 4 (2002):527–544.
6. 6 J.R. Maneiro et al. “Predictors of Treatment Failure and Mortality in Native Septic Arthritis.” *Clinical Rheumatology* 34, no. 11 (2015):1961–1967.
7. 7 M. Vazquez. “Osteomyelitis in Children.” *Current Opinion in Pediatrics* 14, no. 1 (2002):112–115.
8. 8 A. Beaudoin et al. “Acute Rheumatic Fever and Rheumatic Heart Disease Among Children—American Samoa, 2011–2012.” *Morbidity and Mortality Weekly Report* 64 no. 20 (2015):555–558.
9. 9 M.A. Gerber et al. “Prevention of Rheumatic Fever and Diagnosis and Treatment of Acute Streptococcal Pharyngitis: A Scientific Statement From the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on Functional Genomics and Translational Biology, and the Interdisciplinary Council on Quality of Care and Outcomes Research: Endorsed by the American Academy of Pediatrics.” *Circulation* 119, no. 11 (2009):1541–1551.
10. 10 World Health Organization. “WHO Guidelines on Tularaemia.” 2007. http://www.cdc.gov/tularemia/resources/whotularemiamanual.pdf. Accessed July 26, 2016.
11. 11 MOH Key Laboratory of Systems Biology of Pathogens. “Virulence Factors of Pathogenic Bacteria, *Yersinia*.” http://www.mgc.ac.cn/cgi-bin/VFs/gen...Genus=Yersinia. Accessed September 9, 2016.
12. 12 Rosen, William. Justinian’s Flea: Plague, Empire, and the Birth of Europe. Viking Adult; pg 3; ISBN 978-0-670-03855-8.
13. 13 Benedictow, Ole J. 2004. The Black Death 1346-1353: The Complete History. Woodbridge: Boydell Press.
14. 14 Centers for Disease Control and Prevention. “Plague: History.” http://www.cdc.gov/plague/history/. Accessed September 15, 2016.
15. 15 J.S. Bakken et al. “Diagnosis and Management of Tickborne Rickettsial Diseases: Rocky Mountain Spotted Fever, Ehrlichioses, and Anaplasmosis–United States. A Practical Guide for Physicians and Other Health Care and Public Health Professionals.” *MMWR Recommendations and Reports* 55 no. RR04 (2006):1–27.
16. 16 MOH Key Laboratory of Systems Biology of Pathogens, “Virulence Factors of Pathogenic Bacteria, Anaplasma” 2016. http://www.mgc.ac.cn/cgi-bin/VFs/jsif/main.cgi. Accessed July, 26, 2016.

17. 17 Centers for Disease Control and Prevention. “Ehrlichiosis, Symptoms, Diagnosis, and Treatment.” 2016. https://www.cdc.gov/ehrlichiosis/symptoms/index.html. Accessed July 29, 2016.
18. 18 Drali, R., Brouqui, P. and Raoult, D. “Typhus in World War I.” *Microbiology Today* 41 (2014) 2:58–61.
19. 19 Centers for Disease Control and Prevention. *CDC Health Information for International Travel 2014: The Yellow Book*. Oxford University Press, 2013. http://wwwnc.cdc.gov/travel/yellowbook/2016/infectious-diseases-related-to-travel/rickettsial-spotted-typhus-fevers-related-infections-anaplasmosis-ehrlichiosis. Accessed July 26, 2016.
20. 20 World Health Organization. “Typhus.” 1997. www.who.int/mediacentre/factsheets/fs162/en/. Accessed July 26, 2016.
21. 21 Centers for Disease Control and Prevention. “Rocky Mountain Spotted Fever (RMSF): Statistics and Epidemiology.” http://www.cdc.gov/rmsf/stats/index.html. Accessed Sept 16, 2016.
22. 22 Centers for Disease Control and Prevention. “Lyme Disease. Data and Statistics.” 2015. http://www.cdc.gov/lyme/stats/index.html. Accessed July 26, 2016.
23. 23 Centers for Disease Control and Prevention. “Signs and Symptoms of Untreated Lyme Disease.” 2015. http://www.cdc.gov/lyme/signs_symptoms/index.html. Accessed July 27, 2016.
24. 24 Centers for Disease Control and Prevention. “Ticks. Symptoms of Tickborne Illness.” 2015. http://www.cdc.gov/ticks/symptoms.html. Accessed July 27, 2016.

This page titled 17.4.2: Bacterial Infections of the Circulatory and Lymphatic Systems is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **25.2: Bacterial Infections of the Circulatory and Lymphatic Systems** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

17.4.3: Viral Infections of the Circulatory and Lymphatic Systems

Learning Objectives

- Identify common viral pathogens that cause infections of the circulatory and lymphatic systems
- Compare the major characteristics of specific viral diseases affecting the circulatory and lymphatic systems

Viral pathogens of the circulatory system vary tremendously both in their virulence and distribution worldwide. Some of these pathogens are practically global in their distribution. Fortunately, the most ubiquitous viruses tend to produce the mildest forms of disease. In the majority of cases, those infected remain asymptomatic. On the other hand, other viruses are associated with life-threatening diseases that have impacted human history.

Infectious Mononucleosis and Burkitt Lymphoma

Human herpesvirus 4, also known as Epstein-Barr virus (EBV), has been associated with a variety of human diseases, such as mononucleosis and Burkitt lymphoma. Exposure to the human herpesvirus 4 (HHV-4) is widespread and nearly all people have been exposed at some time in their childhood, as evidenced by serological tests on populations. The virus primarily resides within B lymphocytes and, like all herpes viruses, can remain dormant in a latent state for a long time.

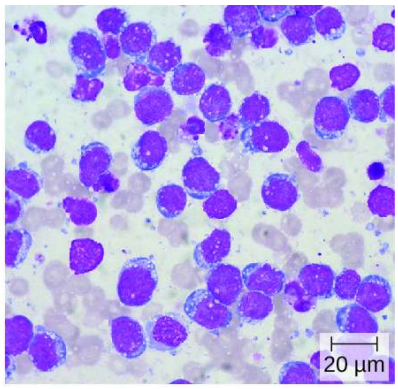
When uninfected young adults are exposed to EBV, they may experience infectious mononucleosis. The virus is mainly spread through contact with body fluids (e.g., saliva, blood, and semen). The main symptoms include pharyngitis, fever, fatigue, and lymph node swelling. Abdominal pain may also occur as a result of spleen and liver enlargement in the second or third week of infection. The disease typically is self-limiting after about a month. The main symptom, extreme fatigue, can continue for several months, however. Complications in immunocompetent patients are rare but can include jaundice, anemia, and possible rupture of the spleen caused by enlargement.

In patients with malaria or HIV, Epstein-Barr virus can lead to a fast-growing malignant cancer known as Burkitt lymphoma (Figure **17.4.3.1**). This condition is a form of non-Hodgkin lymphoma that produces solid tumors chiefly consisting of aberrant B cells. Burkitt lymphoma is more common in Africa, where prevalence of HIV and malaria is high, and it more frequently afflicts children. Repeated episodes of viremia caused by reactivation of the virus are common in immunocompromised individuals. In some patients with AIDS, EBV may induce the formation of malignant B-cell lymphomas or oral hairy leukoplakia. Immunodeficiency-associated Burkitt lymphoma primarily occurs in patients with HIV. HIV infection, similar to malaria, leads to polyclonal B-cell activation and permits poorly controlled proliferation of EBV^+ B cells, leading to the formation of lymphomas.

Infectious mononucleosis is typically diagnosed based on the initial clinical symptoms and a test for antibodies to EBV-associated antigens. Because the disease is self-limiting, antiviral treatments are rare for mononucleosis. Cases of Burkitt lymphoma are diagnosed from a biopsy specimen from a lymph node or tissue from a suspected tumor. Staging of the cancer includes computed tomography (CT) scans of the chest, abdomen, pelvis, and cytologic and histologic evaluation of biopsy specimens. Because the tumors grow so rapidly, staging studies must be expedited and treatment must be initiated promptly. An intensive alternating regimen of cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, etoposide, and cytarabine (CODOX-M/IVAC) plus rituximab results in a cure rate greater than 90% for children and adults.



(a)



(b)

Figure **17.4.3.1**: (a) Burkitt lymphoma can cause large tumors. (b) Characteristic irregularly shaped abnormal lymphocytes (large purple cells) with vacuoles (white spots) from a fine-needle aspirate of a tumor from a patient with Burkitt lymphoma. (credit a: modification of work by Bi CF, Tang Y, Zhang WY, Zhao S, Wang XQ, Yang QP, Li GD, and Liu WP; credit b: modification of work by Ed Uthman)

Cytomegalovirus Infections

Also known as cytomegalovirus (CMV), human herpesvirus 5 (HHV-5) is a virus with high infection rates in the human population. It is currently estimated that 50% of people in the US have been infected by the time they reach adulthood.[1]CMV is the major cause of non-Epstein-Barr infectious mononucleosis in the general human population. It is also an important pathogen in immunocompromised hosts, including patients with AIDS, neonates, and transplant recipients. However, the vast majority of CMV infections are asymptomatic. In adults, if symptoms do occur, they typically include fever, fatigue, swollen glands, and pharyngitis.

CMV can be transmitted between individuals through contact with body fluids such as saliva or urine. Common modes of transmission include sexual contact, nursing, blood transfusions, and organ transplants. In addition, pregnant women with active infections frequently pass this virus to their fetus, resulting in congenital CMV infections, which occur in approximately one in every 150 infants in US.[2] Infants can also be infected during passage through the birth canal or through breast milk and saliva from the mother.

Perinatal infections tend to be milder but can occasionally cause lung, spleen, or liver damage. Serious symptoms in newborns include growth retardation, jaundice, deafness, blindness, and mental retardation if the virus crosses the placenta during the embryonic state when the body systems are developing in utero. However, a majority (approximately 80%) of infected infants will never have symptoms or experience long-term problems.[3] Diagnosis of CMV infection during pregnancy is usually achieved by serology; CMV is the “C” in prenatal TORCH screening.

Many patients receiving blood transfusions and nearly all those receiving kidney transplants ultimately become infected with CMV. Approximately 60% of transplant recipients will have CMV infection and more than 20% will develop symptomatic disease.[4] These infections may result from CMV-contaminated tissues but also may be a consequence of immunosuppression required for transplantation causing reactivation of prior CMV infections. The resulting viremia can lead to fever and leukopenia, a decrease in the number of white blood cells in the bloodstream. Serious consequences may include liver damage, transplant rejection, and death. For similar reasons, many patients with AIDS develop active CMV infections that can manifest as encephalitis or progressive retinitis leading to blindness.[5]

Diagnosis of a localized CMV infection can be achieved through direct microscopic evaluation of tissue specimens stained with routine stains (e.g., Wright-Giemsa, hematoxylin and eosin, Papanicolaou) and immunohistochemical stains. Cells infected by CMV produce characteristic inclusions with an "owl's eye" appearance; this sign is less sensitive than molecular methods like PCR but more predictive of localized disease (Figure **17.4.3.2**). For more severe CMV infection, tests such as enzyme immunoassay (EIA), indirect immunofluorescence antibody (IFA) tests, and PCR, which are based on detection of CMV antigen or DNA, have a higher sensitivity and can determine viral load. Cultivation of the virus from saliva or urine is still the method for detecting CMV in newborn babies up to 3 weeks old. Ganciclovir, valganciclovir, foscarnet, and cidofovir are the first-line antiviral drugs for serious CMV infections.

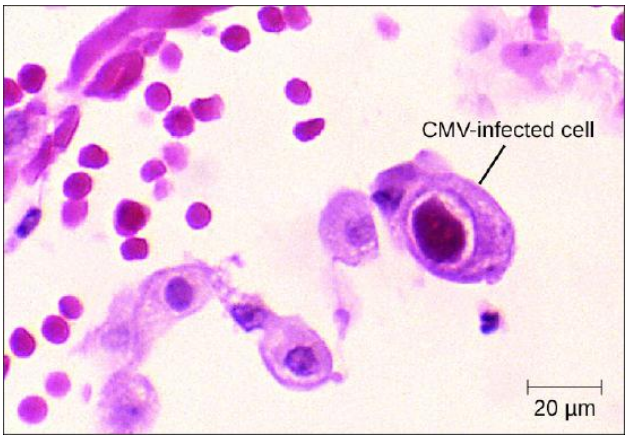


Figure 17.4.3.2: Cells infected with CMV become enlarged and have a characteristic “owl’s eye” nucleus. This micrograph shows kidney cells from a patient with CMV. (credit: modification of work by Centers for Disease Control and Prevention)

? Exercise 17.4.3.1

Compare the diseases caused by HHV-4 and HHV-5.

Arthropod-Borne Viral Diseases

There are a number of arthropod-borne viruses, or arboviruses, that can cause human disease. Among these are several important hemorrhagic fevers transmitted by mosquitoes. We will discuss three that pose serious threats: yellow fever, chikungunya fever, and dengue fever.

Yellow Fever

Yellow fever was once common in the US and caused several serious outbreaks between 1700 and 1900.[6] Through vector control efforts, however, this disease has been eliminated in the US. Currently, yellow fever occurs primarily in tropical and subtropical areas in South America and Africa. It is caused by the yellow fever virus of the genus *Flavivirus* (named for the Latin word *flavus* meaning *yellow*), which is transmitted to humans by mosquito vectors. Sylvatic yellow fever occurs in tropical jungle regions of Africa and Central and South America, where the virus can be transmitted from infected monkeys to humans by the mosquitoes *Aedes africanus* or *Haemagogus* spp. In urban areas, the *Aedes aegypti* mosquito is mostly responsible for transmitting the virus between humans.

Most individuals infected with yellow fever virus have no illness or only mild disease. Onset of milder symptoms is sudden, with dizziness, fever of 39–40 °C (102–104 °F), chills, headache, and myalgias. As symptoms worsen, the face becomes flushed, and nausea, vomiting, constipation, severe fatigue, restlessness, and irritability are common. Mild disease may resolve after 1 to 3 days. However, approximately 15% of cases progress to develop moderate to severe yellow fever disease.[7]

In moderate or severe disease, the fever falls suddenly 2 to 5 days after onset, but recurs several hours or days later. Symptoms of jaundice, petechial rash, mucosal hemorrhages, oliguria (scant urine), epigastric tenderness with bloody vomit, confusion, and apathy also often occur for approximately 7 days of moderate to severe disease. After more than a week, patients may have a rapid recovery and no sequelae.

In its most severe form, called malignant yellow fever, symptoms include delirium, bleeding, seizures, shock, coma, and multiple organ failure; in some cases, death occurs. Patients with malignant yellow fever also become severely immunocompromised, and even those in recovery may become susceptible to bacterial superinfections and pneumonia. Of the 15% of patients who develop moderate or severe disease, up to half may die.

Diagnosis of yellow fever is often based on clinical signs and symptoms and, if applicable, the patient’s travel history, but infection can be confirmed by culture, serologic tests, and PCR. There are no effective treatments for patients with yellow fever. Whenever possible, patients with yellow fever should be hospitalized for close observation and given supportive care. Prevention is the best method of controlling yellow fever. Use of mosquito netting, window screens, insect repellents, and insecticides are all effective methods of reducing exposure to mosquito vectors. An effective vaccine is also available, but in the US, it is only administered to

those traveling to areas with endemic yellow fever. In West Africa, the World Health Organization (WHO) launched a Yellow Fever Initiative in 2006 and, since that time, significant progress has been made in combating yellow fever. More than 105 million people have been vaccinated, and no outbreaks of yellow fever were reported in West Africa in 2015.

Yellow Fever: Altering the Course of History

Yellow fever originated in Africa and is still most prevalent there today. This disease is thought to have been translocated to the Americas by the slave trade in the 16th century.[8] Since that time, yellow fever has been associated with many severe outbreaks, some of which had important impacts upon historic events.

Yellow fever virus was once an important cause of disease in the US. In the summer of 1793, there was a serious outbreak in Philadelphia (then the US capitol). It is estimated that 5,000 people (10% of the city's population) died. All of the government officials, including George Washington, fled the city in the face of this epidemic. The disease only abated when autumn frosts killed the mosquito vector population.

In 1802, Napoleon Bonaparte sent an army of 40,000 to Hispaniola to suppress a slave revolution. This was seen by many as a part of a plan to use the Louisiana Territory as a granary as he reestablished France as a global power. Yellow fever, however, decimated his army and they were forced to withdraw. Abandoning his aspirations in the New World, Napoleon sold the Louisiana Territory to the US for $15 million in 1803.

The most famous historic event associated with yellow fever is probably the construction of the Panama Canal. The French began work on the canal in the early 1880s. However, engineering problems, malaria, and yellow fever forced them to abandon the project. The US took over the task in 1904 and opened the canal a decade later. During those 10 years, yellow fever was a constant adversary. In the first few years of work, greater than 80% of the American workers in Panama were hospitalized with yellow fever. It was the work of Carlos Finlay and Walter Reed that turned the tide. Taken together, their work demonstrated that the disease was transmitted by mosquitoes. Vector control measures succeeded in reducing both yellow fever and malaria rates and contributed to the ultimate success of the project.

Dengue Fever

The disease dengue fever, also known as breakbone fever, is caused by four serotypes of dengue virus called dengue 1–4. These are *Flavivirus* species that are transmitted to humans by *A. aegypti* or *A. albopictus* mosquitoes. The disease is distributed worldwide but is predominantly located in tropical regions. The WHO estimates that 50 million to 100 million infections occur yearly, including 500,000 dengue hemorrhagic fever (DHF) cases and 22,000 deaths, most among children.[9] Dengue fever is primarily a self-limiting disease characterized by abrupt onset of high fever up to 40 °C (104 °F), intense headaches, rash, slight nose or gum bleeding, and extreme muscle, joint, and bone pain, causing patients to feel as if their bones are breaking, which is the reason this disease is also referred to as breakbone fever. As the body temperature returns to normal, in some patients, signs of dengue hemorrhagic fever may develop that include drowsiness, irritability, severe abdominal pain, severe nose or gum bleeding, persistent vomiting, vomiting blood, and black tarry stools, as the disease progresses to DHF or dengue shock syndrome (DSS). Patients who develop DHF experience circulatory system failure caused by increased blood vessel permeability. Patients with dengue fever can also develop DSS from vascular collapse because of the severe drop in blood pressure. Patients who develop DHF or DSS are at greater risk for death without prompt appropriate supportive treatment. About 30% of patients with severe hemorrhagic disease with poor supportive treatment die, but mortality can be less than 1% with experienced support.[10]

Diagnostic tests for dengue fever include serologic testing, ELISA, and reverse transcriptase-polymerase chain reaction (RT-PCR) of blood. There are no specific treatments for dengue fever, nor is there a vaccine. Instead, supportive clinical care is provided to treat the symptoms of the disease. The best way to limit the impact of this viral pathogen is vector control.

Chikungunya Fever

The arboviral disease chikungunya fever is caused by chikungunya virus (CHIKV), which is transmitted to humans by *A. aegypti* and *A. albopictus* mosquitoes. Until 2013, the disease had not been reported outside of Africa, Asia, and a few European countries; however, CHIKV has now spread to mosquito populations in North and South America. Chikungunya fever is characterized by high fever, joint pain, rash, and blisters, with joint pain persisting for several months. These infections are typically self-limiting and rarely fatal.

The diagnostic approach for chikungunya fever is similar to that for dengue fever. Viruses can be cultured directly from patient serum during early infections. IFA, EIA, ELISA, PCR, and RT-PCR are available to detect CHIKV antigens and patient antibody response to the infection. There are no specific treatments for this disease except to manage symptoms with fluids, analgesics, and bed rest. As with most arboviruses, the best strategy for combating the disease is vector control.

Link to Learning

Use this interactive map to explore the global distribution of dengue.

Exercise 17.4.3.2

1. Name three arboviral diseases and explain why they are so named.
2. What is the best method for controlling outbreaks of arboviral diseases?

Ebola Virus Disease

The Ebola virus disease (EVD) is a highly contagious disease caused by species of *Ebolavirus*, a BSL-4 filovirus (Figure **17.4.3.3**). Transmission to humans occurs through direct contact with body fluids (e.g., blood, saliva, sweat, urine, feces, or vomit), and indirect contact by contaminated fomites. Infected patients can easily transmit Ebola virus to others if appropriate containment and use of personal protective equipment is not available or used. Handling and working with patients with EVD is extremely hazardous to the general population and health-care workers. In almost every EVD outbreak there have been Ebola infections among health-care workers. This ease of Ebola virus transmission was recently demonstrated in the Ebola epidemic in Guinea, Liberia, and Sierra Leone in 2014, in which more than 28,000 people in 10 countries were infected and more than 11,000 died.[11]

After infection, the initial symptoms of Ebola are unremarkable: fever, severe headache, myalgia, cough, chest pain, and pharyngitis. As the disease progresses, patients experience abdominal pain, diarrhea, and vomiting. Hemorrhaging begins after about 3 days, with bleeding occurring in the gastrointestinal tract, skin, and many other sites. This often leads to delirium, stupor, and coma, accompanied by shock, multiple organ failure, and death. The mortality rates of EVD often range from 50% to 90%.

The initial diagnosis of Ebola is difficult because the early symptoms are so similar to those of many other illnesses. It is possible to directly detect the virus from patient samples within a few days after symptoms begin, using antigen-capture ELISA, immunoglobulin M (IgM) ELISA, PCR, and virus isolation. There are currently no effective, approved treatments for Ebola other than supportive care and proper isolation techniques to contain its spread.

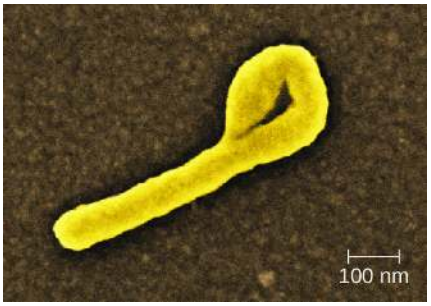


Figure **17.4.3.3**: An Ebola virus particle viewed with electron microscopy. These filamentous viruses often exhibit looped or hooked ends. (credit: modification of work by Centers for Disease Control and Prevention)

Exercise 17.4.3.3

How is Ebola transmitted?

Hantavirus

The genus *Hantavirus* consists of at least four serogroups with nine viruses causing two major clinical (sometimes overlapping) syndromes: hantavirus pulmonary syndrome (HPS) in North America and hemorrhagic fever with renal syndrome (HFRS) in other continents. Hantaviruses are found throughout the world in wild rodents that shed the virus in their urine and feces. Transmission

occurs between rodents and to humans through inhalation of aerosols of the rodent urine and feces. Hantaviruses associated with outbreaks in the US and Canada are transmitted by the deer mouse, white-footed mouse, or cotton rat.

HPS begins as a nonspecific flu-like illness with headache, fever, myalgia, nausea, vomiting, diarrhea, and abdominal pain. Patients rapidly develop pulmonary edema and hypotension resulting in pneumonia, shock, and death, with a mortality rate of up to 50%.[12] This virus can also cause HFRS, which has not been reported in the US. The initial symptoms of this condition include high fever, headache, chills, nausea, inflammation or redness of the eyes, or a rash. Later symptoms are hemorrhaging, hypotension, kidney failure, shock, and death. The mortality rate of HFRS can be as high as 15%.[13]

ELISA, Western blot, rapid immunoblot strip assay (RIBA), and RT-PCR detect host antibodies or viral proteins produced during infection. Immunohistological staining may also be used to detect the presence of viral antigens. There are no clinical treatments other than general supportive care available for HPS infections. Patients with HFRS can be treated with ribavirin.[14]

? Exercise 17.4.3.4

Compare the two Hantavirus diseases discussed in this section.

Human Immunodeficiency Virus

Human T-lymphotropic viruses (HTLV), also called human immunodeficiency viruses (HIV) are retroviruses that are the causative agent of acquired immune deficiency syndrome (AIDS). There are two main variants of human immunodeficiency virus (HIV). HIV-1 (Figure **17.4.3.4**) occurs in human populations worldwide, whereas HIV-2 is concentrated in West Africa. Currently, the most affected region in the world is sub-Saharan Africa, with an estimated 25.6 million people living with HIV in 2015.[15] Sub-Saharan Africa also accounts for two-thirds of the global total of new HIV infections (Figure **17.4.3.5**).[16]

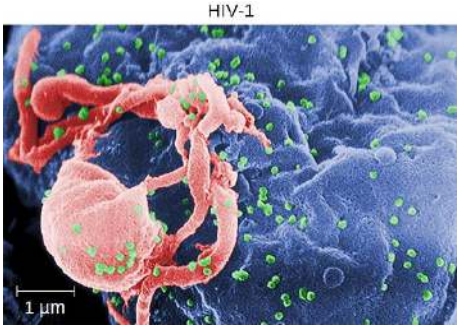


Figure **17.4.3.4**: This micrograph shows HIV particles (green) budding from a lymphocyte (top right). (credit: modification of work by Centers for Disease Control and Prevention)

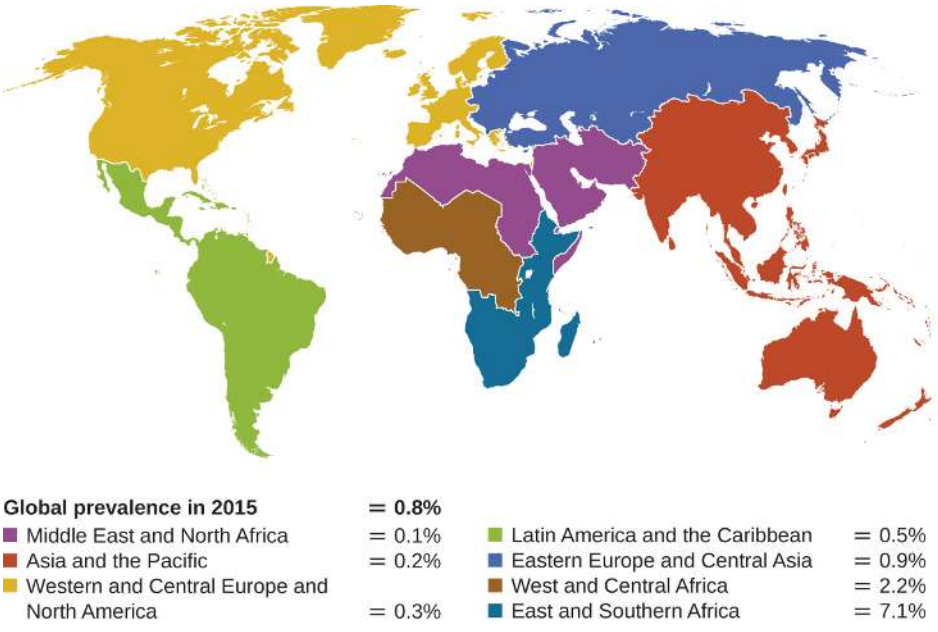


Figure **17.4.3.5**: This map shows the prevalence of HIV worldwide in 2015 among adults ages 15–49 years.

HIV is spread through direct contact with body fluids. Casual contact and insect vectors are not sufficient for disease transmission; common modes of transmission include sexual contact and sharing of needles by intravenous (IV) drug users. It generally takes many years before the effects of an HIV infection are detected. HIV infections are not dormant during this period: virions are continually produced, and the immune system continually attempts to clear the viral infection, while the virus persistently infects additional CD4 T cells. Over time, the CD4 T-cell population is devastated, ultimately leading to AIDS.

When people are infected with HIV, their disease progresses through three stages based on CD4 T-cell counts and the presence of clinical symptoms (Figure **17.4.3.6**).

- **Stage 1: Acute HIV infection.** Two to 4 weeks after infection with HIV, patients may experience a flu-like illness, which can last for a few weeks. Patients with acute HIV infection have more than 500 cells/μL CD4 T cells and a large amount of virus in their blood. Patients are very contagious during this stage. To confirm acute infection, either a fourth-generation antibody-antigen test or a nucleic acid test (NAT) must be performed.
- **Stage 2: Clinical latency.** During this period, HIV enters a period of dormancy. Patients have between 200 and 499 cells/μL CD4 T cells; HIV is still active but reproduces at low levels, and patients may not experience any symptoms of illness. For patients who are not taking medicine to treat HIV, this period can last a decade or longer. For patients receiving antiretroviral therapy, the stage may last for several decades, and those with low levels of the virus in their blood are much less likely to transmit HIV than those who are not virally suppressed. Near the end of the latent stage, the patient's viral load starts to increase and the CD4 T-cell count begins to decrease, leading to the development of symptoms and increased susceptibility to opportunistic infections.
- **Stage 3: Acquired immunodeficiency syndrome (AIDS).** Patients are diagnosed with AIDS when their CD4 T-cell count drops below 200 cells/μL or when they develop certain opportunistic illnesses. During this stage, the immune system becomes severely damaged by HIV. Common symptoms of AIDS include chills, fever, sweats, swollen lymph glands, weakness, and weight loss; in addition, patients often develop rare cancers such as Kaposi's sarcoma and opportunistic infections such as *Pneumocystis* pneumonia, tuberculosis, cryptosporidiosis, and toxoplasmosis. This is a fatal progression that, in the terminal stages, includes wasting syndrome and dementia complex. Patients with AIDS have a high viral load and are highly infectious; they typically survive about 3 years without treatment.

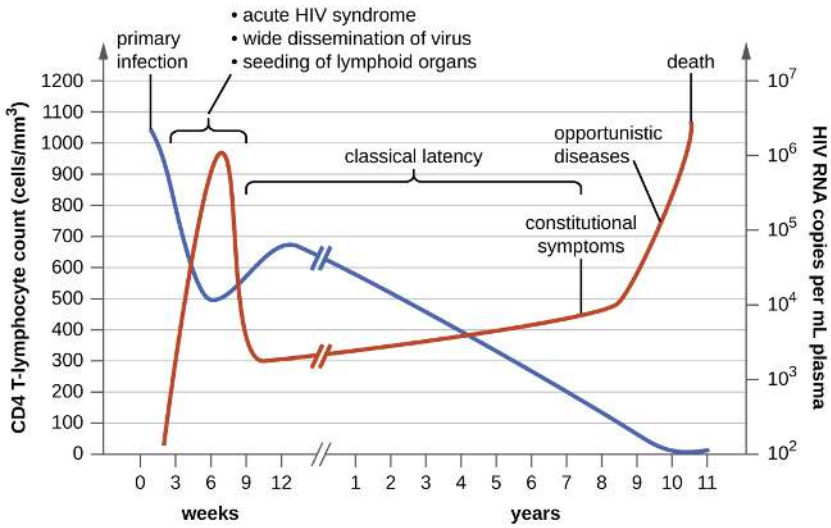


Figure **17.4.3.6**: This graph shows the clinical progression of CD4 T cells (blue line), clinical symptoms, and viral RNA (red line) during an HIV infection. (credit: modification of work by Kogan M, and Rappaport J)

The initial diagnosis of HIV is performed using a serological test for antibody production against the pathogen. Positive test results are confirmed by Western blot or PCR tests. It can take weeks or months for the body to produce antibodies in response to an infection. There are fourth-generation tests that detect HIV antibodies and HIV antigens that are present even before the body begins producing antibodies. Nucleic acid tests (NATs) are a third type of test that is relatively expensive and uncommon; NAT can detect HIV in blood and determine the viral load.

As a consequence of provirus formation, it is currently not possible to eliminate HIV from an infected patient's body. Elimination by specific antibodies is ineffective because the virus mutates rapidly—a result of the error-prone reverse transcriptase and the inability to correct errors. Antiviral treatments, however, can greatly extend life expectancy. To combat the problem of drug resistance, combinations of antiretroviral drugs called antiretroviral therapy (ART), sometimes called highly active ART or combined ART, are used. There are several different targets for antiviral drug action (and a growing list of drugs for each of these targets). One class of drugs inhibits HIV entry; other classes inhibit reverse transcriptase by blocking viral RNA-dependent and DNA-dependent DNA polymerase activity; and still others inhibit one of the three HIV enzymes needed to replicate inside human cells.

? Exercise 17.4.3.5

Why is it not yet possible to cure HIV infections?

HIV, AIDS, and Education

When the first outbreaks of AIDS in the US occurred in the early 1980s, very little was known about the disease or its origins. Erroneously, the disease quickly became stigmatized as one associated with what became identified as at-risk behaviors such as sexual promiscuity, homosexuality, and IV drug use, even though mounting evidence indicated the disease was also contracted through transfusion of blood and blood products or by fetuses of infected mothers. In the mid-1980s, scientists elucidated the identity of the virus, its mode of transmission, and mechanisms of pathogenesis. Campaigns were undertaken to educate the public about how HIV spreads to stem infection rates and encourage behavioral changes that reduced the risk for infection. Approaches to this campaign, however, emphasized very different strategies. Some groups favored educational programs that emphasized sexual abstinence, monogamy, heterosexuality, and "just say no to drugs." Other groups placed an emphasis on "safe sex" in sex education programs and advocated social services programs that passed out free condoms to anyone, including sexually active minors, and provided needle exchange programs for IV drug users.

These are clear examples of the intersection between disease and cultural values. As a future health professional, what is your responsibility in terms of educating patients about behaviors that put them at risk for HIV or other diseases while possibly setting your own personal opinions aside? You will no doubt encounter patients whose cultural and moral values differ from

your own. Is it ethical for you to promote your own moral agenda to your patients? How can you advocate for practical disease prevention while still respecting the personal views of your patients?

Viral Diseases of the Circulatory and Lymphatic Systems

Many viruses are able to cause systemic, difficult-to-treat infections because of their ability to replicate within the host. Some of the more common viruses that affect the circulatory system are summarized in Figure **17.4.3.7**.

Viral Diseases of the Circulatory and Lymphatic Systems

Disease	Pathogen	Signs and Symptoms	Transmission	Diagnostic Tests	Antimicrobial Drugs
AIDS/HIV infection	Human immunodeficiency virus (HIV)	Flu-like symptoms during acute stage, followed by long period of clinical latency; final stage (AIDS) includes fever, weight loss, wasting syndrome, dementia, and opportunistic secondary infections leading to death	Contact with body fluids (e.g., sexual contact, use of contaminated needles)	Serological tests for antibodies and/or HIV antigens; nucleic acid test (NAT) for presence of virus	Antiretroviral therapy (ART) using various combinations of drugs
Burkitt lymphoma	Epstein-Barr virus (human herpesvirus-4 [HHV-4])	Rapid formation of malignant B-cell tumors, oral hairy leukoplakia; fatal if not promptly treated	Contact with body fluids (e.g., saliva, blood, semen); primarily affects patients immunocompromised by HIV or malaria	CT scans, tumor biopsy	Intensive alternating chemotherapy regimen
Chikungunya fever	Chikungunya virus	Fever, rash, joint pain	Transmitted between humans by *Aedes aegypti* and *A. albopictus* vectors	Viral culture, IFA, EIA, ELISA, PCR, RT-PCR	None
Cytomegalovirus infection	Cytomegalovirus (HHV-5)	Usually asymptomatic but may cause non-Epstein-Barr mononucleosis in adults; may cause developmental issues in developing fetus; in transplant recipients, may cause fever, transplant rejection, death	Contact with body fluids, blood transfusions, organ transplants; infected mothers can transmit virus to fetus transplacentally or to newborn in breastmilk, saliva	Histology, culture, EIA, IFA, PCR	Ganciclovir, valganciclovir, foscarnet, cidofovir
Dengue fever (breakbone fever)	Dengue fever viruses 1–4	Fever, headache, extreme bone and joint pain, abdominal pain, vomiting, hemorrhaging; can be fatal	Transmitted between humans by *A. aegypti* and *A. albopictus* vectors	Serologic testing, ELISA, and PCR	None
Ebola virus disease (EVD)	Ebola virus	Fever, headache, joint pain, diarrhea, vomiting, hemorrhaging in gastrointestinal tract, organ failure; often fatal	Contact with body fluids (e.g., blood, saliva, sweat, urine, feces, vomit); highly contagious	ELISA, IgM ELISA, PCR, virus isolation	None
Hantavirus pulmonary syndrome (HPS)	Hantavirus	Initial flu-like symptoms followed by pulmonary edema and hypotension leading to pneumonia and shock; can be fatal	Inhalation of dried feces, urine from infected mouse or rat	ELISA, Western blot, RIBA, RT-PCR	None
Hemorrhagic fever with renal syndrome	Hantavirus	Fever, headache, nausea, rash, or eye inflammation, followed by hemorrhaging and kidney failure; can be fatal	Inhalation of dried feces, urine from infected mouse or rat	ELISA, Western blot, RIBA, RT-PCR	None
Infectious mononucleosis	Epstein-Barr virus (HHV-4), cytomegalovirus (HHV-5)	Pharyngitis, fever, extreme fatigue; swelling of lymph nodes, spleen, and liver	Contact with body fluids (e.g., saliva, blood, semen)	Tests for antibodies to various EBV-associated antigens	None
Yellow fever	Yellow fever virus	Dizziness, fever, chills, headache, myalgia, nausea, vomiting, constipation, fatigue; moderate to severe cases may include jaundice, rash, mucosal hemorrhaging, seizures, shock, and death	From monkeys to humans or between humans via *Aedes* or *Haemagogus* mosquito vectors	Culture, serology, PCR	None for treatment; preventive vaccine available

Figure **17.4.3.7**: Viral diseases of the Circulatory and Lymphatic systems.

Key Concepts and Summary

- Human herpesviruses such **Epstein-Barr virus** (HHV-4) and **cytomegalovirus** (HHV-5) are widely distributed. The former is associated with infectious mononucleosis and Burkitt lymphoma, and the latter can cause serious congenital infections as well as serious disease in immunocompromised adults.

- Arboviral diseases such as y**ellow fever, dengue fever,** and **chikungunya fever** are characterized by high fevers and vascular damage that can often be fatal. **Ebola virus disease** is a highly contagious and often fatal infection spread through contact with bodily fluids.
- Although there is a vaccine available for yellow fever, treatments for patients with yellow fever, dengue, chikungunya fever, and Ebola virus disease are limited to supportive therapies.
- Patients infected with **human immunodeficiency virus (HIV)** progress through three stages of disease, culminating in **AIDS**. **Antiretroviral therapy (ART)** uses various combinations of drugs to suppress viral loads, extending the period of latency and reducing the likelihood of transmission.
- Vector control and animal reservoir control remain the best defenses against most viruses that cause diseases of the circulatory system.

Footnotes

1. 1 Centers for Disease Control and Prevention. “Cytomegalovirus (CMV) and Congenital CMV Infection: About CMV.” 2016. www.cdc.gov/cmv/transmission.html. Accessed July 28, 2016.
2. 2 Centers for Disease Control and Prevention. “Cytomegalovirus (CMV) and Congenital CMV Infection: Babies Born with CMV (Congenital CMV Infection).” 2016. http://www.cdc.gov/cmv/congenital-infection.html. Accessed July 28, 2016.
3. 3 ibid.
4. 4 E. Cordero et al. “Cytomegalovirus Disease in Kidney Transplant Recipients: Incidence, Clinical Profile, and Risk Factors.” *Transplantation Proceedings* 44 no. 3 (2012):694–700.
5. 5 L.M. Mofenson et al. “Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children: Recommendations From CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics.” *MMWR Recommendations and Reports* 58 no. RR-11 (2009):1–166.
6. 6 Centers for Disease Control and Prevention. “History Timeline Transcript.” www.cdc.gov/travel-training/l...Transcript.pdf. Accessed July 28, 2016.
7. 7 Centers for Disease Control and Prevention. “Yellow Fever, Symptoms and Treatment.” 2015 http://www.cdc.gov/yellowfever/symptoms/index.html. Accessed July 28, 2016.
8. 8 J.T. Cathey, J.S. Marr. “Yellow fever, Asia and the East African Slave Trade.” *Transactions of the Royal Society of Tropical Medicine and Hygiene* 108, no. 5 (2014):252–257.
9. 9 Centers for Disease Control and Prevention. “Dengue, Epidemiology.” 2014. http://www.cdc.gov/dengue/epidemiology/index.html. Accessed July 28, 2016.
10. 10 C.R. Pringle “Dengue.” MSD Manual: Consumer Version. www.msdmanuals.com/home/infe...ections/dengue. 2016. Accessed Sept 15, 2016.
11. 11 HealthMap. “2014 Ebola Outbreaks.” http://www.healthmap.org/ebola/#timeline. Accessed July 28, 2016.
12. 12 World Health Organization. “Hantavirus Diseases.” 2016. www.who.int/ith/diseases/hantavirus/en/. Accessed July 28, 2016.
13. 13 ibid.
14. 14 Centers for Disease Control and Prevention. “Hantavirus: Treatment.” 2012. www.cdc.gov/hantavirus/techni...treatment.html. Accessed July 28, 2016.
15. 15 World Health Organization. “HIV/AIDS: Fact Sheet.” 2016. http://www.who.int/mediacentre/factsheets/fs360/en/. Accessed July 28, 2016.
16. 16 ibid.

This page titled 17.4.3: Viral Infections of the Circulatory and Lymphatic Systems is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **25.3: Viral Infections of the Circulatory and Lymphatic Systems** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

17.4.4: Parasitic Infections of the Circulatory and Lymphatic Systems

Learning Objectives

- Identify common parasites that cause infections of the circulatory and lymphatic systems
- Compare the major characteristics of specific parasitic diseases affecting the circulatory and lymphatic systems

Some protozoa and parasitic flukes are also capable of causing infections of the human circulatory system. Although these infections are rare in the US, they continue to cause widespread suffering in the developing world today. Fungal infections of the circulatory system are very rare. Therefore, they are not discussed in this chapter.

Malaria

Despite more than a century of intense research and clinical advancements, malaria remains one of the most important infectious diseases in the world today. Its widespread distribution places more than half of the world's population in jeopardy. In 2015, the WHO estimated there were about 214 million cases of malaria worldwide, resulting in about 438,000 deaths; about 88% of cases and 91% of deaths occurred in Africa.[1] Although malaria is not currently a major threat in the US, the possibility of its reintroduction is a concern. Malaria is caused by several protozoan parasites in the genus *Plasmodium*: *P. falciparum*, *P. knowlesi*, *P. malariae*, *P. ovale*, and *P. vivax*. *Plasmodium* primarily infect red blood cells and are transmitted through the bite of *Anopheles* mosquitoes.

Currently, *P. falciparum* is the most common and most lethal cause of malaria, often called falciparum malaria. Falciparum malaria is widespread in highly populated regions of Africa and Asia, putting many people at risk for the most severe form of the disease.

The classic signs and symptoms of malaria are cycles of extreme fever and chills. The sudden, violent symptoms of malaria start with malaise, abrupt chills, and fever (39–41° C [102.2–105.8 °F]), rapid and faint pulse, polyuria, headache, myalgia, nausea, and vomiting. After 2 to 6 hours of these symptoms, the fever falls, and profuse sweating occurs for 2 to 3 hours, followed by extreme fatigue. These symptoms are a result of *Plasmodium* emerging from red blood cells synchronously, leading to simultaneous rupture of a large number of red blood cells, resulting in damage to the spleen, liver, lymph nodes, and bone marrow. The organ damage resulting from hemolysis causes patients to develop sludge blood (i.e., blood in which the red blood cells agglutinate into clumps) that can lead to lack of oxygen, necrosis of blood vessels, organ failure, and death.

In established infections, malarial cycles of fever and chills typically occur every 2 days in the disease described as tertian malaria, which is caused by *P. vivax* and *P. ovale*. The cycles occur every 3 days in the disease described as quartan malaria, which is caused by *P. malariae*. These intervals may vary among cases.

Plasmodium has a complex life cycle that includes several developmental stages alternately produced in mosquitoes and humans (Figure **17.4.4.1**). When an infected mosquito takes a blood meal, sporozoites in the mosquito salivary gland are injected into the host's blood. These parasites circulate to the liver, where they develop into schizonts. The schizonts then undergo schizogony, resulting in the release of many merozoites at once. The merozoites move to the bloodstream and infect red blood cells. Inside red blood cells, merozoites develop into trophozoites that produce more merozoites. The synchronous release of merozoites from red blood cells in the evening leads to the symptoms of malaria.

In addition, some trophozoites alternatively develop into male and female gametocytes. The gametocytes are taken up when the mosquito takes a blood meal from an infected individual. Sexual sporogony occurs in the gut of the mosquito. The gametocytes fuse to form zygotes in the insect gut. The zygotes become motile and elongate into an ookinete. This form penetrates the midgut wall and develops into an oocyst. Finally, the oocyst releases new sporozoites that migrate to the mosquito salivary glands to complete the life cycle.

Diagnosis of malaria is by microscopic observation of developmental forms of *Plasmodium* in blood smears and rapid EIA assays that detect *Plasmodium* antigens or enzymes (Figure **17.4.4.2**). Drugs such as chloroquine, atovaquone , artemether, and lumefantrine may be prescribed for both acute and prophylactic therapy, although some *Plasmodium* spp. have shown resistance to antimalarial drugs. Use of insecticides and insecticide-treated bed nets can limit the spread of malaria. Despite efforts to develop a vaccine for malaria, none is currently available.

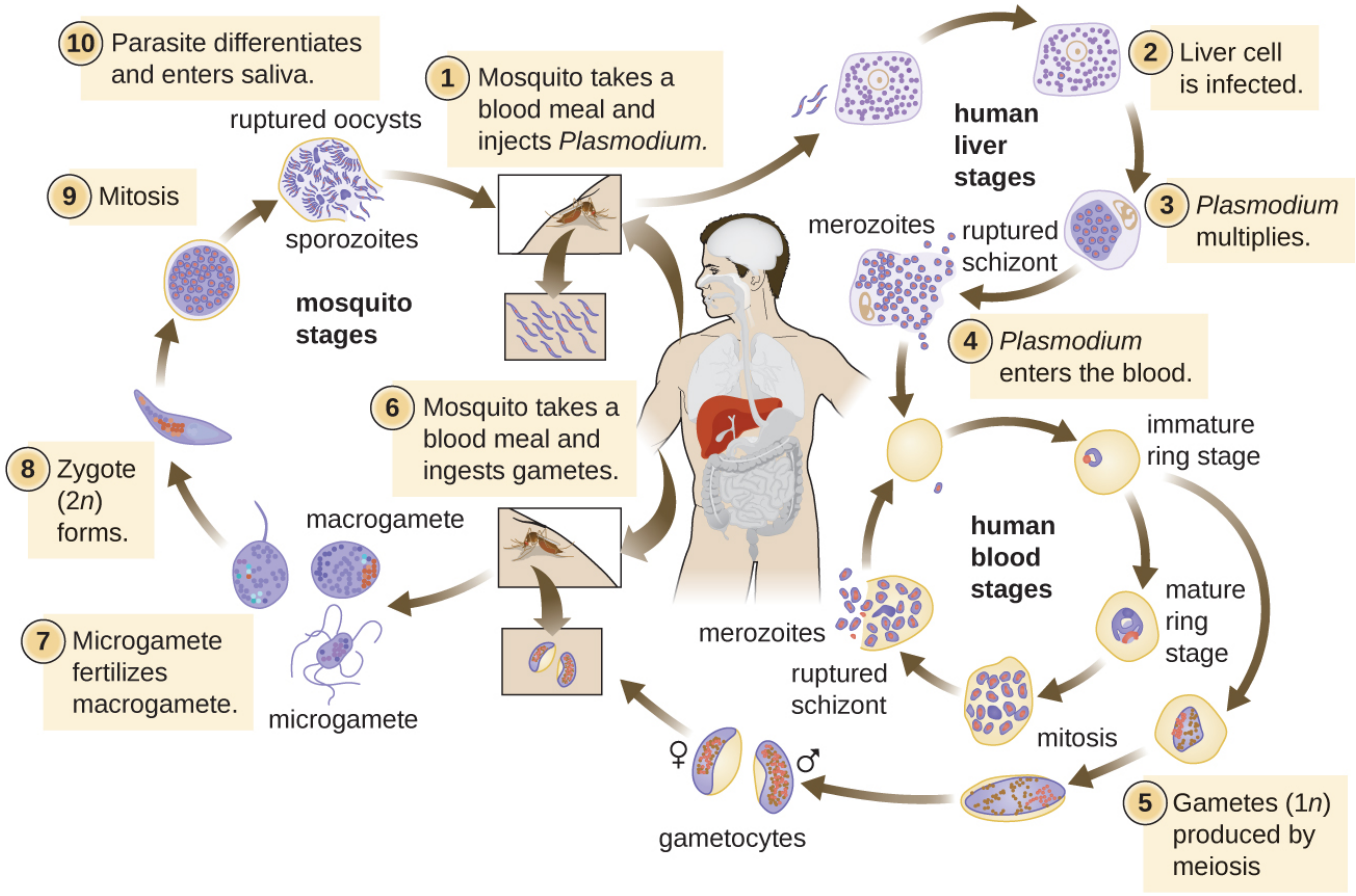


Figure 17.4.4.1: The life cycle of *Plasmodium*. (credit: modification of work by Centers for Disease Control and Prevention)

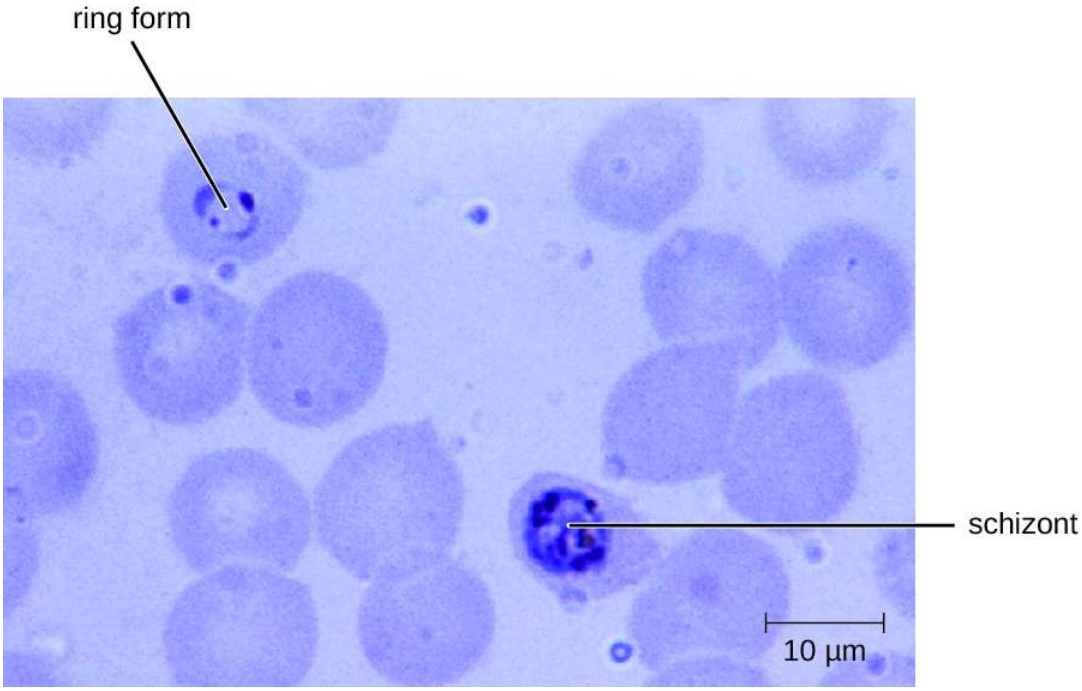


Figure 17.4.4.2: A blood smear (human blood stage) shows an early trophozoite in a delicate ring form (upper left) and an early stage schizont form (center) of *Plasmodium falciparum* from a patient with malaria. (credit: modification of work by Centers for Disease Control and Prevention)

Link to Learning

The Nothing But Nets campaign, an initiative of the United Nations Foundation, has partnered with the Bill and Melinda Gates Foundation to make mosquito bed nets available in developing countries in Africa. Visit their website to learn more about their efforts to prevent malaria.

Exercise 17.4.4.1

Why is malaria one of the most important infectious diseases?

Toxoplasmosis

The disease toxoplasmosis is caused by the protozoan *Toxoplasma gondii*. *T. gondii* is found in a wide variety of birds and mammals,[2] and human infections are common. The Centers for Disease Control and Prevention (CDC) estimates that 22.5% of the population 12 years and older has been infected with *T. gondii*; but immunocompetent individuals are typically asymptomatic, however.[3] Domestic cats are the only known definitive hosts for the sexual stages of *T. gondii* and, thus, are the main reservoirs of infection. Infected cats shed *T. gondii* oocysts in their feces, and these oocysts typically spread to humans through contact with fecal matter on cats' bodies, in litter boxes, or in garden beds where outdoor cats defecate.

T. gondii has a complex life cycle that involves multiple hosts. The *T. gondii* life cycle begins when unsporulated oocysts are shed in the cat's feces. These oocysts take 1–5 days to sporulate in the environment and become infective. Intermediate hosts in nature include birds and rodents, which become infected after ingesting soil, water, or plant material contaminated with the infective oocysts. Once ingested, the oocysts transform into tachyzoites that localize in the bird or rodent neural and muscle tissue, where they develop into tissue cysts. Cats may become infected after consuming birds and rodents harboring tissue cysts. Cats and other animals may also become infected directly by ingestion of sporulated oocysts in the environment. Interestingly, *Toxoplasma* infection appears to be able to modify the host's behavior. Mice infected by *Toxoplasma* lose their fear of cat pheromones. As a result, they become easier prey for cats, facilitating the transmission of the parasite to the cat definitive host[4] (Figure **17.4.4.3**).

Toxoplasma infections in humans are extremely common, but most infected people are asymptomatic or have subclinical symptoms. Some studies suggest that the parasite may be able to influence the personality and psychomotor performance of infected humans, similar to the way it modifies behavior in other mammals.[5] When symptoms do occur, they tend to be mild and similar to those of mononucleosis. However, asymptomatic toxoplasmosis can become problematic in certain situations. Cysts can lodge in a variety of human tissues and lie dormant for years. Reactivation of these quiescent infections can occur in immunocompromised patients following transplantation, cancer therapy, or the development of an immune disorder such as AIDS. In patients with AIDS who have toxoplasmosis, the immune system cannot combat the growth of *T. gondii* in body tissues; as a result, these cysts can cause encephalitis, retinitis, pneumonitis, cognitive disorders, and seizures that can eventually be fatal.

Toxoplasmosis can also pose a risk during pregnancy because tachyzoites can cross the placenta and cause serious infections in the developing fetus. The extent of fetal damage resulting from toxoplasmosis depends on the severity of maternal disease, the damage to the placenta, the gestational age of the fetus when infected, and the virulence of the organism. Congenital toxoplasmosis often leads to fetal loss or premature birth and can result in damage to the central nervous system, manifesting as mental retardation, deafness, or blindness. Consequently, pregnant women are advised by the CDC to take particular care in preparing meat, gardening, and caring for pet cats.[6] Diagnosis of toxoplasmosis infection during pregnancy is usually achieved by serology including TORCH testing (the "T" in TORCH stands for toxoplasmosis). Diagnosis of congenital infections can also be achieved by detecting *T. gondii* DNA in amniotic fluid, using molecular methods such as PCR.

In adults, diagnosis of toxoplasmosis can include observation of tissue cysts in tissue specimens. Tissue cysts may be observed in Giemsa- or Wright-stained biopsy specimens, and CT, magnetic resonance imaging, and lumbar puncture can also be used to confirm infection (Figure **17.4.4.4**).

Preventing infection is the best first-line defense against toxoplasmosis. Preventive measures include washing hands thoroughly after handling raw meat, soil, or cat litter, and avoiding consumption of vegetables possibly contaminated with cat feces. All meat should be cooked to an internal temperature of 73.9–76.7 °C (165–170 °F).

Most immunocompetent patients do not require clinical intervention for *Toxoplasma* infections. However, neonates, pregnant women, and immunocompromised patients can be treated with pyrimethamine and sulfadiazine—except during the first trimester of pregnancy, because these drugs can cause birth defects. Spiramycin has been used safely to reduce transmission in pregnant women with primary infection during the first trimester because it does not cross the placenta.

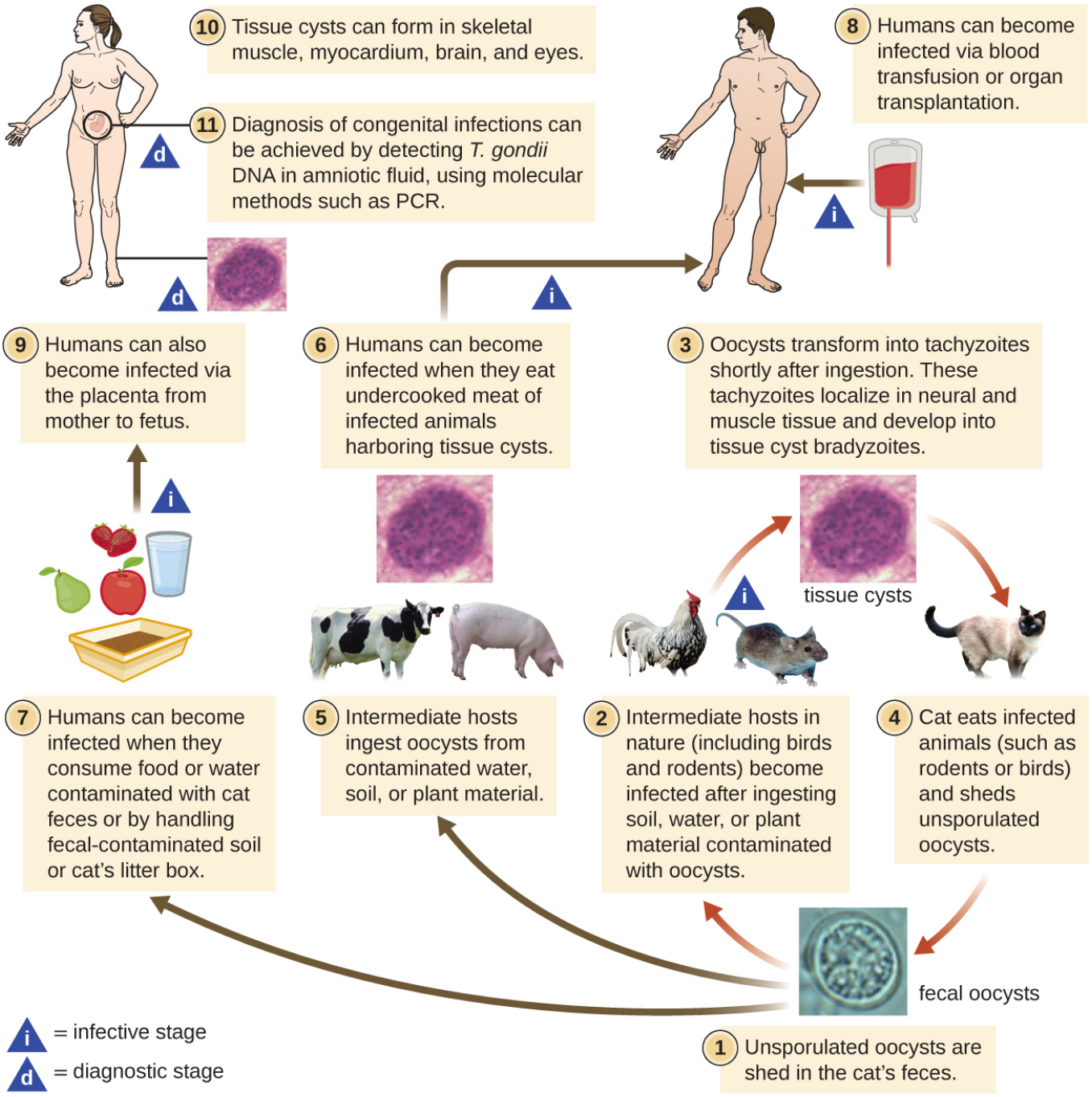


Figure **17.4.4.3**: The infectious cycle of *Toxoplasma gondii*. (credit: "diagram": modification of work by Centers for Disease Control and Prevention; credit "cat": modification of work by "KaCey97078"/Flickr)

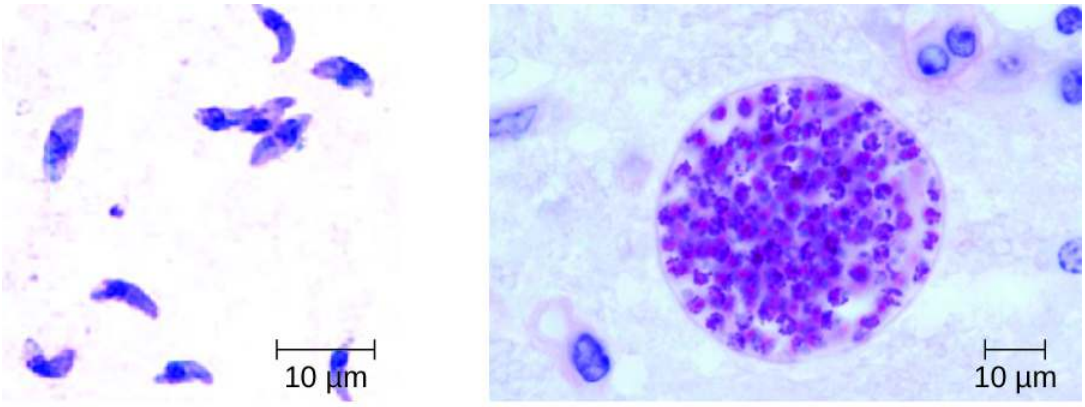


Figure 17.4.4.4: (a) Giemsa-stained *Toxoplasma gondii* tachyzoites from a smear of peritoneal fluid obtained from a mouse inoculated with *T. gondii*. Tachyzoites are typically crescent shaped with a prominent, centrally placed nucleus. (b) Microscopic cyst containing *T. gondii* from mouse brain tissue. Thousands of resting parasites (stained red) are contained in a thin parasite cyst wall. (credit a: modification of work by Centers for Disease Control and Prevention; credit b: modification of work by USDA)

? Exercise 17.4.4.2

How does *T. gondii* infect humans?

Babesiosis

Babesiosis is a rare zoonotic infectious disease caused by *Babesia* spp. These parasitic protozoans infect various wild and domestic animals and can be transmitted to humans by black-legged *Ixodes* ticks. In humans, *Babesia* infect red blood cells and replicate inside the cell until it ruptures. The *Babesia* released from the ruptured red blood cell continue the growth cycle by invading other red blood cells. Patients may be asymptomatic, but those who do have symptoms often initially experience malaise, fatigue, chills, fever, headache, myalgia, and arthralgia. In rare cases, particularly in asplenic (absence of the spleen) patients, the elderly, and patients with AIDS, babesiosis may resemble falciparum malaria, with high fever, hemolytic anemia, hemoglobinuria (hemoglobin or blood in urine), jaundice, and renal failure, and the infection can be fatal. Previously acquired asymptomatic Babesia infection may become symptomatic if a splenectomy is performed.

Diagnosis is based mainly on the microscopic observation of parasites in blood smears (Figure 17.4.4.5). Serologic and antibody detection by IFA can also be performed and PCR-based tests are available. Many people do not require clinical intervention for Babesia infections, however, serious infections can be cleared with a combination of atovaquone and azithromycin or a combination of clindamycin and quinine.

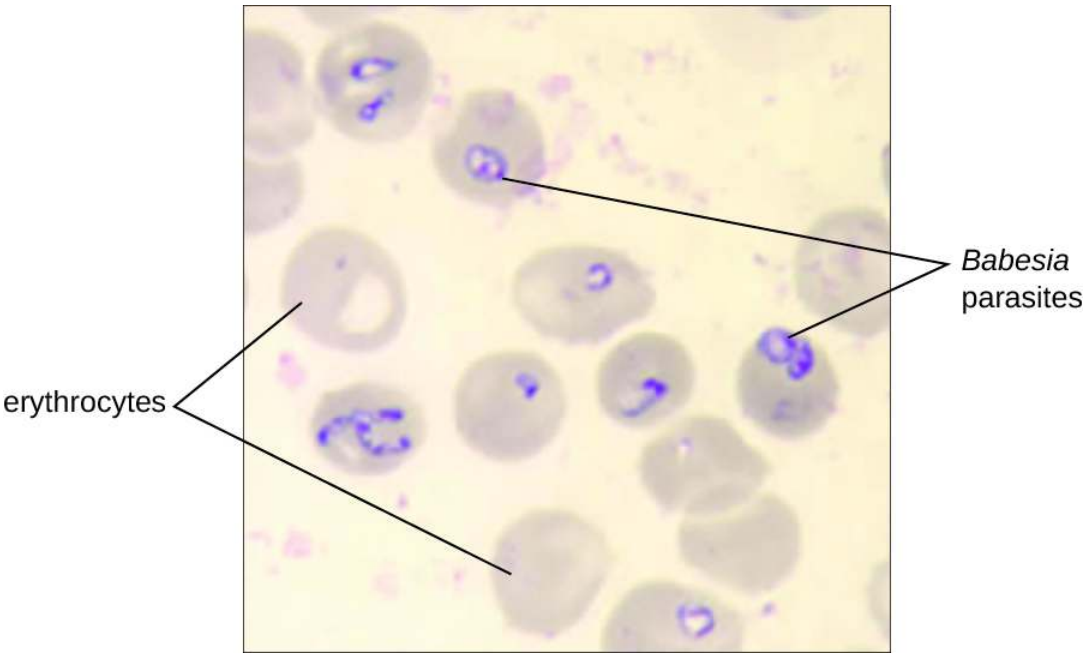


Figure 17.4.4.5: In this blood smear from a patient with babesiosis, *Babesia* parasites can be observed in the red blood cells. (credit: modification of work by Centers for Disease Control and Prevention)

Chagas Disease

Also called American trypanosomiasis, Chagas disease is a zoonosis classified as a neglected tropical disease(NTD). It is caused by the flagellated protozoan *Trypanosoma cruzi* and is most commonly transmitted to animals and people through the feces of triatomine bugs. The triatomine bug is nicknamed the kissing bug because it frequently bites humans on the face or around the eyes; the insect often defecates near the bite and the infected fecal matter may be rubbed into the bite wound by the bitten individual (Figure 17.4.4.6). The bite itself is painless and, initially, many people show no signs of the disease. Alternative modes of transmission include contaminated blood transfusions, organ transplants from infected donors, and congenital transmission from mother to fetus.

Chagas disease is endemic throughout much of Mexico, Central America, and South America, where, according to WHO, an estimated 6 million to 7 million people are infected.[7] Currently, Chagas disease is not endemic in the US, even though triatomine bugs are found in the southern half of the country.

Triatomine bugs typically are active at night, when they take blood meals by biting the faces and lips of people or animals as they sleep and often defecate near the site of the bite. Infection occurs when the host rubs the feces into their eyes, mouth, the bite wound, or another break in the skin. The protozoan then enters the blood and invades tissues of the heart and central nervous system, as well as macrophages and monocytes. Nonhuman reservoirs of *T. cruzi* parasites include wild animals and domesticated animals such as dogs and cats, which also act as reservoirs of the pathogen.[8]

There are three phases of Chagas disease: acute, intermediate, and chronic. These phases can be either asymptomatic or life-threatening depending on the immunocompetence status of the patient.

In acute phase disease, symptoms include fever, headache, myalgia, rash, vomiting, diarrhea, and enlarged spleen, liver, and lymph nodes. In addition, a localized nodule called a chagoma may form at the portal of entry, and swelling of the eyelids or the side of the face, called Romaña's sign, may occur near the bite wound. Symptoms of the acute phase may resolve spontaneously, but if untreated, the infection can persist in tissues, causing irreversible damage to the heart or brain. In rare cases, young children may die of myocarditis or meningoencephalitis during the acute phase of Chagas disease.

Following the acute phase is a prolonged intermediate phase during which few or no parasites are found in the blood and most people are asymptomatic. Many patients will remain asymptomatic for life; however, decades after exposure, an estimated 20%–30% of infected people will develop chronic disease that can be debilitating and sometimes life threatening. In the chronic phase, patients may develop painful swelling of the colon, leading to severe twisting, constipation, and bowel obstruction; painful

swelling of the esophagus, leading to dysphagia and malnutrition; and flaccid cardiomegaly (enlargement of the heart), which can lead to heart failure and sudden death.

Diagnosis can be confirmed through several different tests, including direct microscopic observation of trypanosomes in the blood, IFA, EIAs, PCR, and culturing in artificial media. In endemic regions, xenodiagnoses may be used; this method involves allowing uninfected kissing bugs to feed on the patient and then examining their feces for the presence of *T. cruzi*.

The medications nifurtimox and benznidazole are effective treatments during the acute phase of Chagas disease. The efficacy of these drugs is much lower when the disease is in the chronic phase. Avoiding exposure to the pathogen through vector control is the most effective method of limiting this disease.

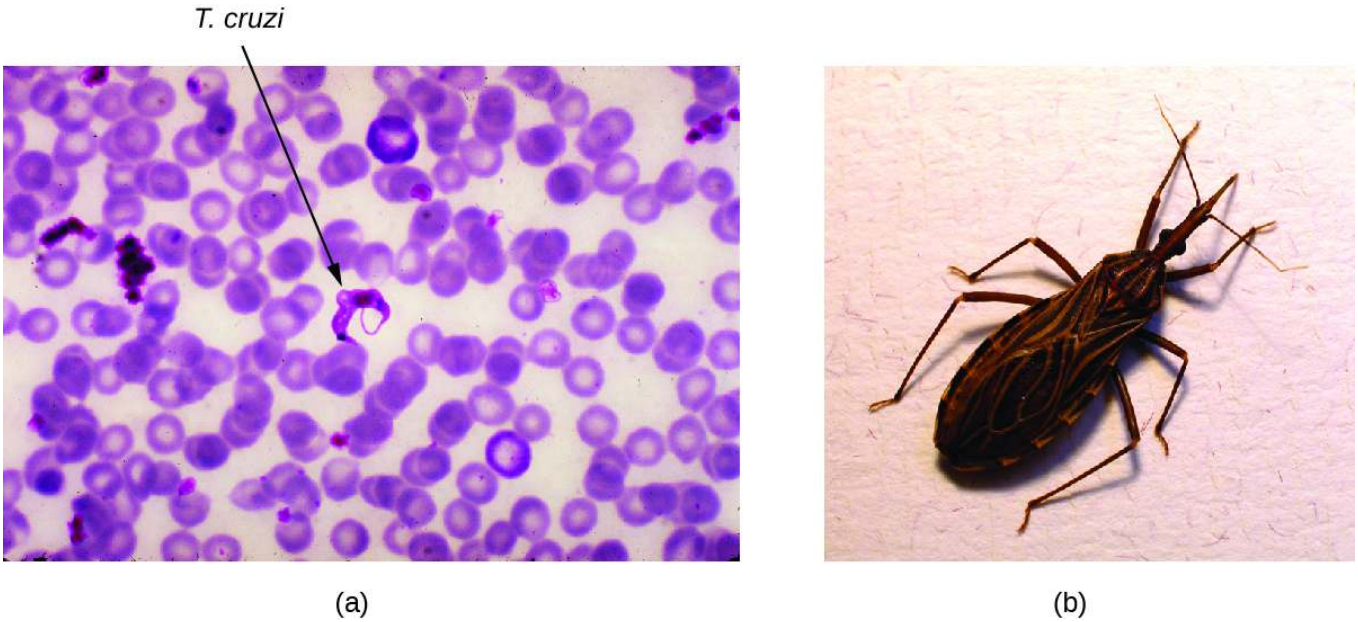


Figure **17.4.4.6**: (a) *Trypanosoma cruzi* protozoan in a blood smear from a patient with Chagas disease. (b) The triatomine bug (also known as the kissing bug or assassin bug) is the vector of Chagas disease. (credit a: modification of work by Centers for Disease Control and Prevention; credit b: modification of work by Erwin Huebner)

? Exercise 17.4.4.3

How do kissing bugs infect humans with *Trypanosoma cruzi*?

Leishmaniasis

Although it is classified as an NTD, leishmaniasis is relatively widespread in tropical and subtropical regions, affecting people in more than 90 countries. It is caused by approximately 20 different species of *Leishmania*, protozoan parasites that are transmitted by sand fly vectors such as *Phlebotomus* spp. and *Lutzomyia* spp. Dogs, cats, sheep, horses, cattle rodents, and humans can all serve as reservoirs.

The *Leishmania* protozoan is phagocytosed by macrophages but uses virulence factors to avoid destruction within the phagolysosome. The virulence factors inhibit the phagolysosome enzymes that would otherwise destroy the parasite. The parasite reproduces within the macrophage, lyses it, and the progeny infect new macrophages (see Micro Connections: When Phagocytosis Fails).

The three major clinical forms of leishmaniasis are cutaneous (oriental sore, Delhi boil, Aleppo boil), visceral (kala-azar, Dumdum fever), and mucosal (espundia). The most common form of disease is cutaneous leishmaniasis, which is characterized by the formation of sores at the site of the insect bite that may start out as papules or nodules before becoming large ulcers (Figure **17.4.4.7**).

It may take visceral leishmaniasis months and sometimes years to develop, leading to enlargement of the lymph nodes, liver, spleen, and bone marrow. The damage to these body sites triggers fever, weight loss, and swelling of the spleen and liver. It also

causes a decrease in the number of red blood cells (anemia), white blood cells (leukopenia), and platelets (thrombocytopenia), causing the patient to become immunocompromised and more susceptible to fatal infections of the lungs and gastrointestinal tract.

The mucosal form of leishmaniasis is one of the less common forms of the disease. It causes a lesion similar to the cutaneous form but mucosal leishmaniasis is associated with mucous membranes of the mouth, nares, or pharynx, and can be destructive and disfiguring. Mucosal leishmaniasis occurs less frequently when the original cutaneous (skin) infection is promptly treated.

Definitive diagnosis of leishmaniasis is made by visualizing organisms in Giemsa-stained smears, by isolating *Leishmania* protozoans in cultures, or by PCR-based assays of aspirates from infected tissues. Specific DNA probes or analysis of cultured parasites can help to distinguish *Leishmania* species that are causing simple cutaneous leishmaniasis from those capable of causing mucosal leishmaniasis.

Cutaneous leishmaniasis is usually not treated. The lesions will resolve after weeks (or several months), but may result in scarring. Recurrence rates are low for this disease. More serious infections can be treated with stibogluconate(antimony gluconate), amphotericin B, and miltefosine.

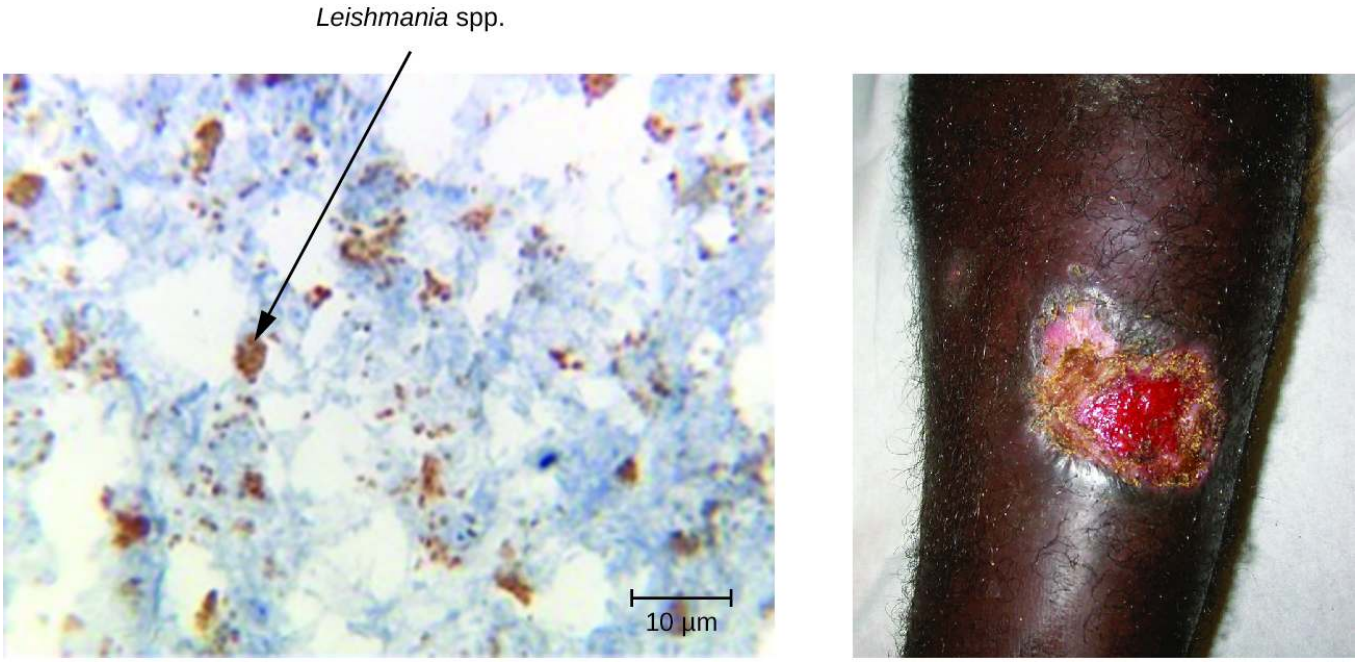


Figure **17.4.4.7**: (a) A micrograph of a tissue sample from a patient with localized cutaneous leishmaniasis. Parasitic *Leishmania mexicana* (black arrow) are visible in and around the host cells. (b) Large skin ulcers are associated with cutaneous leishmaniasis. (credit a: modification of work by Fernández-Figueroa EA, Rangel-Escareño C, Espinosa-Mateos V, Carrillo-Sánchez K, Salaiza-Suazo N, Carrada-Figueroa G, March-Mifsut S, and Becker I; credit b: modification of work by Jean Fortunet)

? Exercise 17.4.4.4

Compare the mucosal and cutaneous forms of leishmaniasis.

Schistosomiasis

Schistosomiasis (bilharzia) is an NTD caused by blood flukes in the genus *Schistosoma* that are native to the Caribbean, South America, Middle East, Asia, and Africa. Most human schistosomiasis cases are caused by *Schistosoma mansoni*, *S. haematobium*, or *S. japonicum*. *Schistosoma* are the only trematodes that invade through the skin; all other trematodes infect by ingestion. WHO estimates that at least 258 million people required preventive treatment for schistosomiasis in 2014.[9]

Infected human hosts shed *Schistosoma* eggs in urine and feces, which can contaminate freshwater habitats of snails that serve as intermediate hosts. The eggs hatch in the water, releasing miracidia, an intermediate growth stage of the *Schistosoma* that infect the snails. The miracidia mature and multiply inside the snails, transforming into cercariae that leave the snail and enter the water,

where they can penetrate the skin of swimmers and bathers. The cercariae migrate through human tissue and enter the bloodstream, where they mature into adult male and female worms that mate and release fertilized eggs. The eggs travel through the bloodstream and penetrate various body sites, including the bladder or intestine, from which they are excreted in urine or stool to start the life cycle over again (Figure 5.2.4).

A few days after infection, patients may develop a rash or itchy skin associated with the site of cercariae penetration. Within 1–2 months of infection, symptoms may develop, including fever, chills, cough, and myalgia, as eggs that are not excreted circulate through the body. After years of infection, the eggs become lodged in tissues and trigger inflammation and scarring that can damage the liver, central nervous system, intestine, spleen, lungs, and bladder. This may cause abdominal pain, enlargement of the liver, blood in the urine or stool, and problems passing urine. Increased risk for bladder cancer is also associated with chronic *Schistosoma* infection. In addition, children who are repeatedly infected can develop malnutrition, anemia, and learning difficulties.

Diagnosis of schistosomiasis is made by the microscopic observation of eggs in feces or urine, intestine or bladder tissue specimens, or serologic tests. The drug praziquantel is effective for the treatment of all schistosome infections. Improving wastewater management and educating at-risk populations to limit exposure to contaminated water can help control the spread of the disease.

Cercarial Dermatitis

The cercaria of some species of *Schistosoma* can only transform into adult worms and complete their life cycle in animal hosts such as migratory birds and mammals. The cercaria of these worms are still capable of penetrating human skin, but they are unable to establish a productive infection in human tissue. Still, the presence of the cercaria in small blood vessels triggers an immune response, resulting in itchy raised bumps called cercarial dermatitis (also known as swimmer’s itch or clam digger's itch). Although it is uncomfortable, cercarial dermatitis is typically self-limiting and rarely serious. Antihistamines and antipruritics can be used to limit inflammation and itching, respectively.

? Exercise 17.4.4.5

How do schistosome infections in humans occur?

Common Eukaryotic Pathogens of the Human Circulatory System

Protozoan and helminthic infections are prevalent in the developing world. A few of the more important parasitic infections are summarized in Figure 17.4.4.8.

Parasitic Diseases of the Circulatory and Lymphatic Systems					
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Diagnostic Tests**	**Antimicrobial Drugs**
Protozoa					
Babesiosis	*Babesia* spp.	Malaise, chills, fever, headache, myalgia, arthralgia	From animals to humans via *Ixodes* tick vectors	Blood smear, serology, IFA, and PCR	Atovaquone and azithromycin or clindamycin and quinine
Chagas disease	*Trypanosoma cruzi*	Fever, headache, body aches, swollen lymph nodes; potentially fatal	Between humans or from animal reservoirs via triatomine (kissing bug) vector	Blood smear, IFA, EIA, PCR, xenodiagnosis	Nifurtimox, benznidazole
Leishmaniasis	*Leishmania* spp.	Ulcer; enlargement of the lymph nodes, liver, spleen, and other organs	Between humans or from animal reservoirs via sand fly (*Phlebotomus* spp., *Lutzomyia* spp.) vectors	Blood smear, culture, PCR, DNA probe, biopsy	Stibogluconate, amphotericin B.
Malaria	*Plasmodium vivax, P. malariae, P. falciparum, P. ovale, P. knowlesi*	Extreme fever, chills, myalgia, nausea, and vomiting, possibly leading to organ failure and death	Between humans via *Anopheles* mosquito vectors	Blood smear, EIA	Chloroquine, atovaquone, artemether, and lumefantrine
Toxoplasmosis	*Toxoplasma gondii*	Tissue cysts; in pregnant women, birth defects or miscarriage	Contact with feces of infected cat; eating contaminated vegetables or undercooked meat of infected animal	Serological tests, direct detection of pathogen in tissue sections	Sulfadiazine, pyrimethamine, spiramycin
Helminths					
Schistosomiasis	*Schistosoma* spp.	Rash, fever, chills, myalgia; chronic inflammation and scarring of liver, spleen, and other organs where cysts develop	Snail hosts release cercaria into freshwater; cercaria burrow into skin of swimmers and bathers	Eggs in stool or urine, tissue biopsy, serological testing	Praziquantel

Figure **17.4.4.8**: Parasitic diseases of the Circulatory and Lymphatic systems.

Clinical Focus: Resolution

Despite continued antibiotic treatment and the removal of the venous catheter, Barbara's condition further declined. She began to show signs of shock and her blood pressure dropped to 77/50 mmHg. Anti-inflammatory drugs and drotrecogin-α were administered to combat sepsis. However, by the seventh day of hospitalization, Barbara experienced hepatic and renal failure and died.

Staphylococcus aureus most likely formed a biofilm on the surface of Barbara's catheter. From there, the bacteria were chronically shed into her circulation and produced the initial clinical symptoms. The chemotherapeutic therapies failed in large part because of the drug-resistant MRSA isolate. Virulence factors like leukocidin and hemolysins also interfered with her immune response. Barbara's ultimate decline may have been a consequence of the production of enterotoxins and toxic shock syndrome toxin (TSST), which can initiate toxic shock.

Venous catheters are common life-saving interventions for many patients requiring long-term administration of medication or fluids. However, they are also common sites of bloodstream infections. The World Health Organization estimates that there are up to 80,000 catheter-related bloodstream infections each year in the US, resulting in about 20,000 deaths.[10]

Key Concepts and Summary

- **Malaria** is a protozoan parasite that remains an important cause of death primarily in the tropics. Several species in the genus *Plasmodium* are responsible for malaria and all are transmitted by *Anopheles* mosquitoes. *Plasmodium* infects and destroys human red blood cells, leading to organ damage, anemia, blood vessel necrosis, and death. Malaria can be treated with various antimalarial drugs and prevented through vector control.
- **Toxoplasmosis** is a widespread protozoal infection that can cause serious infections in the immunocompromised and in developing fetuses. Domestic cats are the definitive host.
- Babesiosis is a generally asymptomatic infection of red blood cells that can causes malaria-like symptoms in elderly, immunocompromised, or asplenic patients.
- **Chagas disease** is a tropical disease transmitted by triatomine bugs. The trypanosome infects heart, neural tissues, monocytes, and phagocytes, often remaining latent for many years before causing serious and sometimes fatal damage to the digestive system and heart.
- **Leishmaniasis** is caused by the protozoan *Leishmania* and is transmitted by sand flies. Symptoms are generally mild, but serious cases may cause organ damage, anemia, and loss of immune competence.
- **Schistosomiasis** is caused by a fluke transmitted by snails. The fluke moves throughout the body in the blood stream and chronically infects various tissues, leading to organ damage.

Footnotes

1. 1 World Health Organization. "World Malaria Report 2015: Summary." 2015. http://www.who.int/malaria/publicati...015/report/en/. Accessed July 28, 2016.
2. 2 A.M. Tenter et al.. "*Toxoplasma gondii*: From Animals to Humans." *International Journal for Parasitology* 30 no. 12-13 (2000):1217–1258.
3. 3 Centers for Disease Control and Prevention. "Parasites - Toxoplasmosis (Toxoplasma Infection). Epidemiology & Risk Factors." 2015 http://www.cdc.gov/parasites/toxoplasmosis/epi.html. Accessed July 28, 2016.
4. 4 J. Flegr. "Effects of *Toxoplasma* on Human Behavior." *Schizophrenia Bulletin* 33, no. 3 (2007):757–760.
5. 5 Ibid
6. 6 Centers for Disease Control and Prevention. "Parasites - Toxoplasmosis (Toxoplasma infection). Toxoplasmosis Frequently Asked Questions (FAQs)." 2013. http://www.cdc.gov/parasites/toxopla...info/faqs.html. Accessed July 28, 2016.
7. 7 World Health Organization. "Chagas disease (American trypanosomiasis). Fact Sheet." 2016. http://www.who.int/mediacentre/factsheets/fs340/en/. Accessed July 29, 2016.
8. 8 C.E. Reisenman et al. "Infection of Kissing Bugs With *Trypanosoma cruzi*, Tucson, Arizona, USA." *Emerging Infectious Diseases* 16 no. 3 (2010):400–405.
9. 9 World Health Organization. "Schistosomiasis. Fact Sheet." 2016. http://www.who.int/mediacentre/factsheets/fs115/en/. Accessed July 29, 2016.

10. 10 World Health Organization. “Patient Safety, Preventing Bloodstream Infections From Central Line Venous Catheters.” 2016. www.who.int/patientsafety/imp...tation/bsi/en/. Accessed July 29, 2016.

This page titled 17.4.4: Parasitic Infections of the Circulatory and Lymphatic Systems is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **25.4: Parasitic Infections of the Circulatory and Lymphatic Systems** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

17.4.E: Circulatory and Lymphatic System Infections (Exercises)

25.1: Anatomy of the Circulatory and Lymphatic Systems

The circulatory and lymphatic systems are networks of vessels and a pump that transport blood and lymph, respectively, throughout the body. When these systems are infected with a microorganism, the network of vessels can facilitate the rapid dissemination of the microorganism to other regions of the body, sometimes with serious results. In this section, we examine some of the key anatomical features of the circulatory and lymphatic systems, as well as general signs and symptoms of infection.

Multiple Choice

Which term refers to an inflammation of the blood vessels?

A. lymphangitis
B. endocarditis
C. pericarditis
D. vasculitis

Answer

D

Which of the following is located in the interstitial spaces within tissues and releases nutrients, immune factors, and oxygen to those tissues?

A. lymphatics
B. arterioles
C. capillaries
D. veins

Answer

C

Which of these conditions results in the formation of a bubo?

A. lymphangitis
B. lymphadenitis
C. ischemia
D. vasculitis

Answer

B

Which of the following is where most microbes are filtered out of the fluids that accumulate in the body tissues?

A. spleen
B. lymph nodes
C. pericardium
D. blood capillaries

Answer

B

Fill in the Blank

Vasculitis can cause blood to leak from damaged vessels, forming purple spots called _____.

Answer

petechiae

The lymph reenters the vascular circulation at _____.

Answer

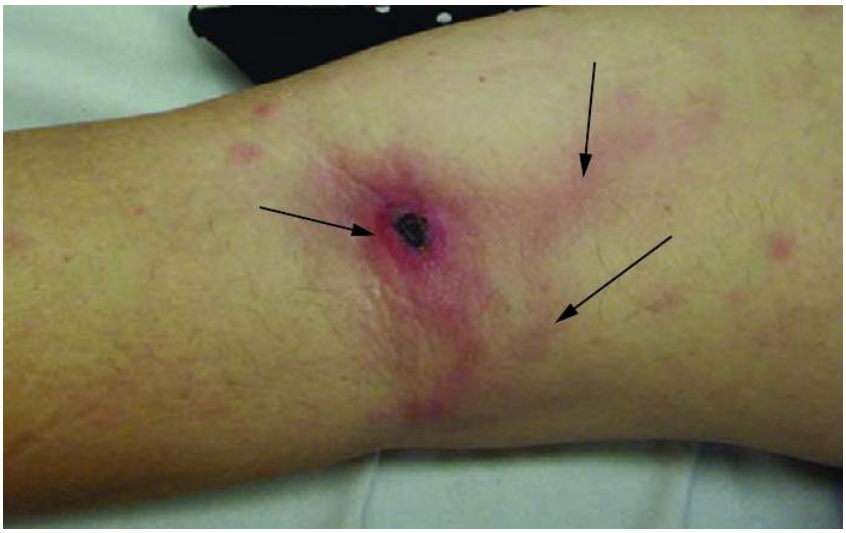
the subclavian veins

Short Answer

How do lymph nodes help to maintain a microbial-free circulatory and lymphatic system?

Critical Thinking

What term refers to the red streaks seen on this patient's skin? What is likely causing this condition?



(credit: modification of work by Centers for Disease Control and Prevention)

Why would septicemia be considered a more serious condition than bacteremia?

25.2: Bacterial Infections of the Circulatory and Lymphatic Systems

Bacterial infections of the circulatory system are almost universally serious. Left untreated, most have high mortality rates. Bacterial pathogens usually require a breach in the immune defenses to colonize the circulatory system. Most often, this involves a wound or the bite of an arthropod vector, but it can also occur in hospital settings and result in nosocomial infections.

Multiple Choice

Which of the following diseases is caused by a spirochete?

A. tularemia
B. relapsing fever
C. rheumatic fever
D. Rocky Mountain spotted fever

Answer

B

Which of the following diseases is transmitted by body lice?

A. tularemia
B. bubonic plague
C. murine typhus

D. epidemic typhus

Answer

D

What disease is most associated with *Clostridium perfringens*?

A. endocarditis
B. osteomyelitis
C. gas gangrene
D. rat bite fever

Answer

C

Which bacterial pathogen causes plague?

A. *Yersinia pestis*
B. *Bacillus moniliformis*
C. *Bartonella quintana*
D. *Rickettsia rickettsii*

Answer

A

Fill in the Blank

Lyme disease is characterized by a(n) _____ that forms at the site of infection.

Answer

bull’s eye-rash

_____ refers to a loss of blood pressure resulting from a system-wide infection.

Answer

Septic shock

Short Answer

What are the three forms of plague and how are they contracted?

Compare epidemic and murine typhus.

Critical Thinking

Why are most vascular pathogens poorly communicable from person to person?

How have human behaviors contributed to the spread or control of arthropod-borne vascular diseases?

25.3: Viral Infections of the Circulatory and Lymphatic Systems

Viral pathogens of the circulatory system vary tremendously both in their virulence and distribution worldwide. Some of these pathogens are practically global in their distribution. Fortunately, the most ubiquitous viruses tend to produce the mildest forms of disease. In the majority of cases, those infected remain asymptomatic. On the other hand, other viruses are associated with life-threatening diseases that have impacted human history.

Multiple Choice

Which of the following viruses is most widespread in the human population?

A. human immunodeficiency virus
B. Ebola virus
C. Epstein-Barr virus
D. hantavirus

Answer

C

Which of these viruses is spread through mouse urine or feces?

A. Epstein-Barr
B. hantavirus
C. human immunodeficiency virus
D. cytomegalovirus

Answer

B

A patient at a clinic has tested positive for HIV. Her blood contained 700/µL CD4 T cells and she does not have any apparent illness. Her infection is in which stage?

A. 1
B. 2
C. 3

Answer

A

Fill in the Blank

_____ is a cancer that forms in patients with HHV-4 and malaria coinfections.

Answer

Burkitt lymphoma

_____ are transmitted by vectors such as ticks or mosquitoes.

Answer

Arboviruses

Infectious mononucleosis is caused by _____ infections.

Answer

Epstein-Barr virus

Short Answer

Describe the progression of an HIV infection over time with regard to the number of circulating viruses, host antibodies, and CD4 T cells.

Describe the general types of diagnostic tests used to diagnose patients infected with HIV.

Identify the general categories of drugs used in ART used to treat patients infected with HIV.

Critical Thinking

Which is a bigger threat to the US population, Ebola or yellow fever? Why?

25.4: Parasitic Infections of the Circulatory and Lymphatic Systems

Some protozoa and parasitic flukes are also capable of causing infections of the human circulatory system. Although these infections are rare in the US, they continue to cause widespread suffering in the developing world today. Malaria, toxoplasmosis, babesiosis, Chagas disease, leishmaniasis, and schistosomiasis are discussed in this section.

Multiple Choice

Which of the following diseases is caused by a helminth?

A. leishmaniasis
B. malaria
C. Chagas disease
D. schistosomiasis

Answer

D

Which of these is the most common form of leishmaniasis?

A. cutaneous
B. mucosal
C. visceral
D. intestinal

Answer

A

Which of the following is a causative agent of malaria?

A. *Trypanosoma cruzi*
B. *Toxoplasma gondii*
C. *Plasmodium falciparum*
D. *Schistosoma mansoni*

Answer

C

Which of the following diseases does not involve an arthropod vector?

A. schistosomiasis
B. malaria
C. Chagas disease
D. babesiosis

Answer

A

Fill in the Blank

The _____ mosquito is the biological vector for malaria.

Answer

Anopheles

The kissing bug is the biological vector for _____.

Answer

Chagas disease

Cercarial dermatitis is also known as _____.

Answer

swimmer’s itch

Short Answer

Describe main cause of *Plasmodium falciparum* infection symptoms.

Why should pregnant women avoid cleaning their cat’s litter box or do so with protective gloves?

Critical Thinking

What measures can be taken to reduce the likelihood of malaria reemerging in the US?

This page titled 17.4.E: Circulatory and Lymphatic System Infections (Exercises) is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **25.E: Circulatory and Lymphatic System Infections (Exercises)** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

SECTION OVERVIEW

17.5: Nervous System Infections

Few diseases inspire the kind of fear that rabies does. The name is derived from the Latin word for “madness” or “fury,” most likely because animals infected with rabies may behave with uncharacteristic rage and aggression. And while the thought of being attacked by a rabid animal is terrifying enough, the disease itself is even more frightful. Once symptoms appear, the disease is almost always fatal, even when treated.



Figure **17.5.1**: This dog is exhibiting the restlessness and aggression associated with rabies, a neurological disease that frequently affects mammals and can be transmitted to humans. (credit: modification of work by the Centers for Disease Control and Prevention)

Rabies is an example of a neurological disease caused by an acellular pathogen. The rabies virus enters nervous tissue shortly after transmission and makes its way to the central nervous system, where its presence leads to changes in behavior and motor function. Well-known symptoms associated with rabid animals include foaming at the mouth, hydrophobia (fear of water), and unusually aggressive behavior. Rabies claims tens of thousands of human lives worldwide, mainly in Africa and Asia. Most human cases result from dog bites, although many mammal species can become infected and transmit the disease. Human infection rates are low in the United States and many other countries as a result of control measures in animal populations. However, rabies is not the only disease with serious or fatal neurological effects. In this chapter, we examine the important microbial diseases of the nervous system.

17.5.1: Anatomy of the Nervous System

17.5.2: Bacterial Diseases of the Nervous System

17.5.3: Acellular Pathogenic Diseases of the Nervous System

17.5.4: Neuromycoses and Parasitic Diseases of the Nervous System

17.5.E: Nervous System Infections (Exercises)

This page titled 17.5: Nervous System Infections is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

17.5.1: Anatomy of the Nervous System

Learning Objectives

- Describe the major anatomical features of the nervous system
- Explain why there is no normal microbiota of the nervous system
- Explain how microorganisms overcome defenses of the nervous system to cause infection
- Identify and describe general symptoms associated with various infections of the nervous system

Clinical Focus: Part 1

David is a 35-year-old carpenter from New Jersey. A year ago, he was diagnosed with Crohn's disease, a chronic inflammatory bowel disease that has no known cause. He has been taking a prescription corticosteroid to manage the condition, and the drug has been highly effective in keeping his symptoms at bay. However, David recently fell ill and decided to visit his primary care physician. His symptoms included a fever, a persistent cough, and shortness of breath. His physician ordered a chest X-ray, which revealed consolidation of the right lung. The doctor prescribed a course of levofloxacin and told David to come back in a week if he did not feel better.

Exercise 17.5.1.1

1. What type of drug is levofloxacin?
2. What type of microbes would this drug be effective against?
3. What type of infection is consistent with David's symptoms?

The human nervous system can be divided into two interacting subsystems: the peripheral nervous system (PNS) and the central nervous system (CNS). The CNS consists of the brain and spinal cord. The peripheral nervous system is an extensive network of nerves connecting the CNS to the muscles and sensory structures. The relationship of these systems is illustrated in Figure 17.5.1.1.

The Central Nervous System

The brain is the most complex and sensitive organ in the body. It is responsible for all functions of the body, including serving as the coordinating center for all sensations, mobility, emotions, and intellect. Protection for the brain is provided by the bones of the skull, which in turn are covered by the scalp, as shown in Figure 17.5.1.2. The scalp is composed of an outer layer of skin, which is loosely attached to the aponeurosis, a flat, broad tendon layer that anchors the superficial layers of the skin. The periosteum, below the aponeurosis, firmly encases the bones of the skull and provides protection, nutrition to the bone, and the capacity for bone repair. Below the boney layer of the skull are three layers of membranes called meninges that surround the brain. The relative positions of these meninges are shown in Figure 17.5.1.2. The meningeal layer closest to the bones of the skull is called the dura mater (literally meaning *tough mother*). Below the dura mater lies the arachnoid mater (literally *spider-like mother*). The innermost meningeal layer is a delicate membrane called the pia mater (literally *tender mother*). Unlike the other meningeal layers, the pia mater firmly adheres to the convoluted surface of the brain. Between the arachnoid mater and pia mater is the subarachnoid space. The subarachnoid space within this region is filled with cerebrospinal fluid (CSF). This watery fluid is produced by cells of the choroid plexus—areas in each ventricle of the brain that consist of cuboidal epithelial cells surrounding dense capillary beds. The CSF serves to deliver nutrients and remove waste from neural tissues.

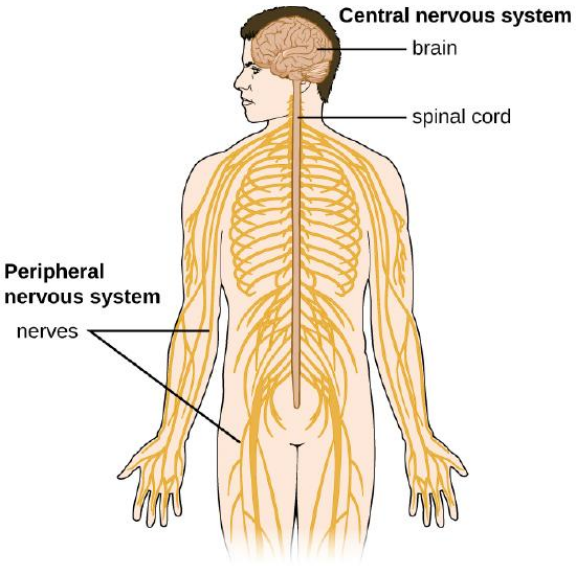


Figure 17.5.1.1: The essential components of the human nervous system are shown in this illustration. The central nervous system (CNS) consists of the brain and spinal cord. It connects to the peripheral nervous system (PNS), a network of nerves that extends throughout the body.

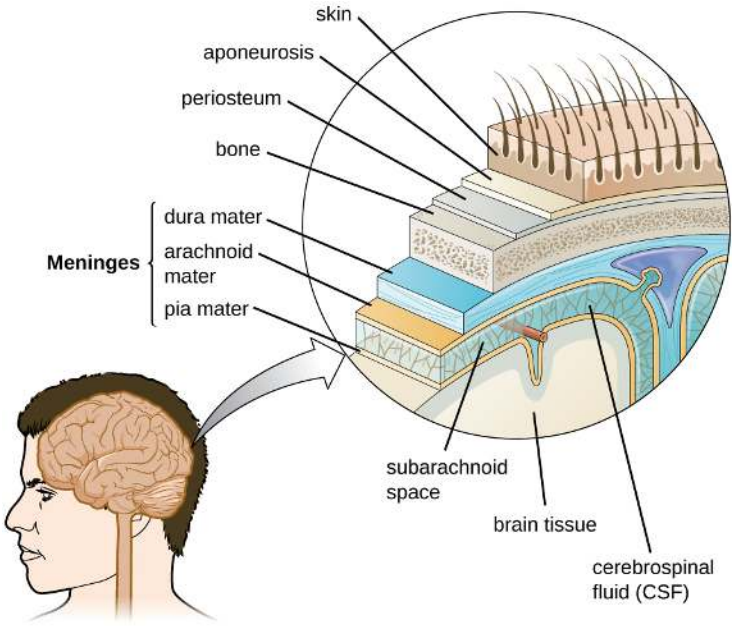


Figure 17.5.1.2: The layers of tissue surrounding the human brain include three meningeal membranes: the dura mater, arachnoid mater, and pia mater. (credit: modification of work by National Institutes of Health)

The Blood-Brain Barrier

The tissues of the CNS have extra protection in that they are not exposed to blood or the immune system in the same way as other tissues. The blood vessels that supply the brain with nutrients and other chemical substances lie on top of the pia mater. The capillaries associated with these blood vessels in the brain are less permeable than those in other locations in the body. The capillary endothelial cells form tight junctions that control the transfer of blood components to the brain. In addition, cranial capillaries have far fewer fenestra (pore-like structures that are sealed by a membrane) and pinocytotic vesicles than other capillaries. As a result, materials in the circulatory system have a very limited ability to interact with the CNS directly. This phenomenon is referred to as the blood-brain barrier.

The blood-brain barrier protects the cerebrospinal fluid from contamination, and can be quite effective at excluding potential microbial pathogens. As a consequence of these defenses, there is no normal microbiota in the cerebrospinal fluid. The blood-brain barrier also inhibits the movement of many drugs into the brain, particularly compounds that are not lipid soluble. This has

profound ramifications for treatments involving infections of the CNS, because it is difficult for drugs to cross the blood-brain barrier to interact with pathogens that cause infections.

The spinal cord also has protective structures similar to those surrounding the brain. Within the bones of the vertebrae are meninges of dura mater (sometimes called the dural sheath), arachnoid mater, pia mater, and a blood-spinal cord barrier that controls the transfer of blood components from blood vessels associated with the spinal cord.

To cause an infection in the CNS, pathogens must successfully breach the blood-brain barrier or blood-spinal cord barrier. Various pathogens employ different virulence factors and mechanisms to achieve this, but they can generally be grouped into four categories: intercellular (also called paracellular), transcellular, leukocyte facilitated, and nonhematogenous. Intercellular entry involves the use of microbial virulence factors, toxins, or inflammation-mediated processes to pass between the cells of the blood-brain barrier. In transcellular entry, the pathogen passes through the cells of the blood-brain barrier using virulence factors that allow it to adhere to and trigger uptake by vacuole- or receptor-mediated mechanisms. Leukocyte-facilitated entry is a Trojan-horse mechanism that occurs when a pathogen infects peripheral blood leukocytes to directly enter the CNS. Nonhematogenous entry allows pathogens to enter the brain without encountering the blood-brain barrier; it occurs when pathogens travel along either the olfactory or trigeminal cranial nerves that lead directly into the CNS.

Link to Learning

View this video about the blood-brain barrier

Exercise 17.5.1.2

What is the primary function of the blood-brain barrier?

The Peripheral Nervous System

The PNS is formed of the nerves that connect organs, limbs, and other anatomic structures of the body to the brain and spinal cord. Unlike the brain and spinal cord, the PNS is not protected by bone, meninges, or a blood barrier, and, as a consequence, the nerves of the PNS are much more susceptible to injury and infection. Microbial damage to peripheral nerves can lead to tingling or numbness known as neuropathy. These symptoms can also be produced by trauma and noninfectious causes such as drugs or chronic diseases like diabetes.

The Cells of the Nervous System

Tissues of the PNS and CNS are formed of cells called glial cells (neuroglial cells) and neurons (nerve cells). Glial cells assist in the organization of neurons, provide a scaffold for some aspects of neuronal function, and aid in recovery from neural injury.

Neurons are specialized cells found throughout the nervous system that transmit signals through the nervous system using electrochemical processes. The basic structure of a neuron is shown in Figure **17.5.1.3**. The cell body (or soma) is the metabolic center of the neuron and contains the nucleus and most of the cell's organelles. The many finely branched extensions from the soma are called dendrites. The soma also produces an elongated extension, called the axon, which is responsible for the transmission of electrochemical signals through elaborate ion transport processes. Axons of some types of neurons can extend up to one meter in length in the human body. To facilitate electrochemical signal transmission, some neurons have a myelin sheath surrounding the axon. Myelin, formed from the cell membranes of glial cells like the Schwann cells in the PNS and oligodendrocytes in the CNS, surrounds and insulates the axon, significantly increasing the speed of electrochemical signal transmission along the axon. The end of an axon forms numerous branches that end in bulbs called synaptic terminals. Neurons form junctions with other cells, such as another neuron, with which they exchange signals. The junctions, which are actually gaps between neurons, are referred to as synapses. At each synapse, there is a presynaptic neuron and a postsynaptic neuron (or other cell). The synaptic terminals of the axon of the presynaptic terminal form the synapse with the dendrites, soma, or sometimes the axon of the postsynaptic neuron, or a part of another type of cell such as a muscle cell. The synaptic terminals contain vesicles filled with chemicals called neurotransmitters. When the electrochemical signal moving down the axon reaches the synapse, the vesicles fuse with the membrane, and neurotransmitters are released, which diffuse across the synapse and bind to receptors on the membrane of the

postsynaptic cell, potentially initiating a response in that cell. That response in the postsynaptic cell might include further propagation of an electrochemical signal to transmit information or contraction of a muscle fiber.

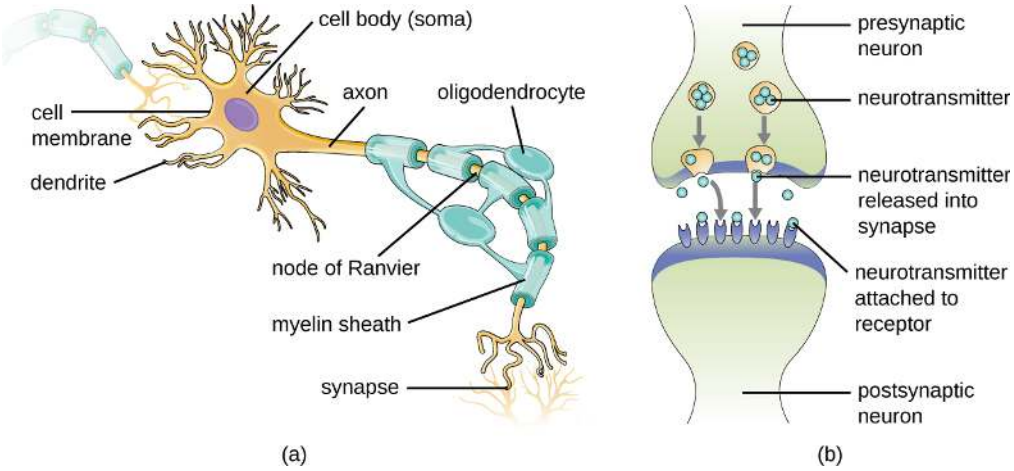


Figure **17.5.1.3**: (a) A myelinated neuron is associated with oligodendrocytes. Oligodendrocytes are a type of glial cell that forms the myelin sheath in the CNS that insulates the axon so that electrochemical nerve impulses are transferred more efficiently. (b) A synapse consists of the axonal end of the presynaptic neuron (top) that releases neurotransmitters that cross the synaptic space (or cleft) and bind to receptors on dendrites of the postsynaptic neuron (bottom).

? Exercise 17.5.1.3

1. What cells are associated with neurons, and what is their function?
2. What is the structure and function of a synapse?

Meningitis and Encephalitis

Although the skull provides the brain with an excellent defense, it can also become problematic during infections. Any swelling of the brain or meninges that results from inflammation can cause intracranial pressure, leading to severe damage of the brain tissues, which have limited space to expand within the inflexible bones of the skull. The term meningitis is used to describe an inflammation of the meninges. Typical symptoms can include severe headache, fever, photophobia (increased sensitivity to light), stiff neck, convulsions, and confusion. An inflammation of brain tissue is called encephalitis, and patients exhibit signs and symptoms similar to those of meningitis in addition to lethargy, seizures, and personality changes. When inflammation affects both the meninges and the brain tissue, the condition is called meningoencephalitis. All three forms of inflammation are serious and can lead to blindness, deafness, coma, and death.

Meningitis and encephalitis can be caused by many different types of microbial pathogens. However, these conditions can also arise from noninfectious causes such as head trauma, some cancers, and certain drugs that trigger inflammation. To determine whether the inflammation is caused by a pathogen, a lumbar puncture is performed to obtain a sample of CSF. If the CSF contains increased levels of white blood cells and abnormal glucose and protein levels, this indicates that the inflammation is a response to an infectioninflinin.

? Exercise 17.5.1.4

1. What are the two types of inflammation that can impact the CNS?
2. Why do both forms of inflammation have such serious consequences?

Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) is a rare condition that can be preceded by a viral or bacterial infection that results in an autoimmune reaction against myelinated nerve cells. The destruction of the myelin sheath around these neurons results in a loss of sensation and function. The first symptoms of this condition are tingling and weakness in the affected tissues. The symptoms intensify over a period of several weeks and can culminate in complete paralysis. Severe cases can be life-

threatening. Infections by several different microbial pathogens, including *Campylobacter jejuni* (the most common risk factor), cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, *Mycoplasma pneumoniae*,[1] and Zika virus[2] have been identified as triggers for GBS. Anti-myelin antibodies from patients with GBS have been demonstrated to also recognize *C. jejuni*. It is possible that cross-reactive antibodies, antibodies that react with similar antigenic sites on different proteins, might be formed during an infection and may lead to this autoimmune response.

GBS is solely identified by the appearance of clinical symptoms. There are no other diagnostic tests available. Fortunately, most cases spontaneously resolve within a few months with few permanent effects, as there is no available vaccine. GBS can be treated by plasmapheresis. In this procedure, the patient's plasma is filtered from their blood, removing autoantibodies.

Key Concepts and Summary

- The nervous system consists of two subsystems: the **central nervous system** and **peripheral nervous system**.
- The skull and three **meninges** (the **dura mater**, **arachnoid mater**, and **pia mater**) protect the brain.
- Tissues of the PNS and CNS are formed of cells called **glial cells** and **neurons**.
- Since the **blood-brain barrier** excludes most microbes, there is no normal microbiota in the CNS.
- Some pathogens have specific virulence factors that allow them to breach the blood-brain barrier. Inflammation of the brain or **meninges** caused by infection is called **encephalitis** or **meningitis**, respectively. These conditions can lead to blindness, deafness, coma, and death.

Footnotes

1. Yuki, Nobuhiro and Hans-Peter Hartung, "Guillain–Barré Syndrome," *New England Journal of Medicine* 366, no. 24 (2012): 2294-304.
2. Cao-Lormeau, Van-Mai, Alexandre Blake, Sandrine Mons, Stéphane Lastère, Claudine Roche, Jessica Vanhomwegen, Timothée Dub et al., "Guillain-Barré Syndrome Outbreak Associated with Zika Virus Infection in French Polynesia: A Case-Control Study," *The Lancet* 387, no. 10027 (2016): 1531-9.

This page titled 17.5.1: Anatomy of the Nervous System is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **26.1: Anatomy of the Nervous System** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

17.5.2: Bacterial Diseases of the Nervous System

Learning Objectives

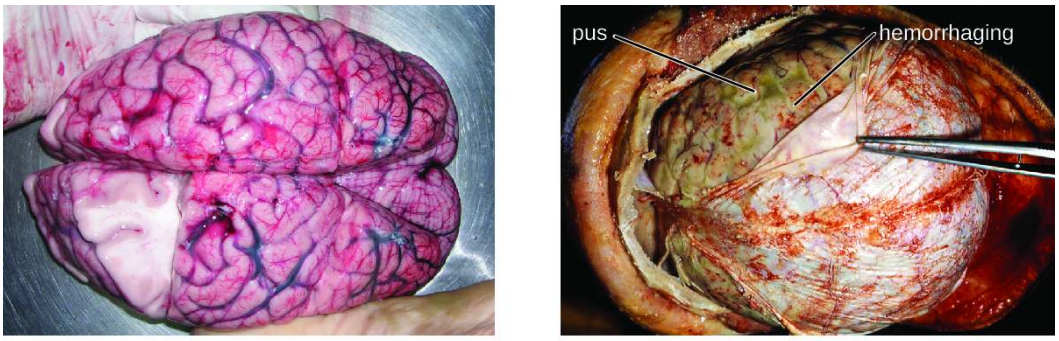
- Identify the most common bacteria that can cause infections of the nervous system
- Compare the major characteristics of specific bacterial diseases affecting the nervous system

Bacterial infections that affect the nervous system are serious and can be life-threatening. Fortunately, there are only a few bacterial species commonly associated with neurological infections.

Bacterial Meningitis

Bacterial meningitis is one of the most serious forms of meningitis. Bacteria that cause meningitis often gain access to the CNS through the bloodstream after trauma or as a result of the action of bacterial toxins. Bacteria may also spread from structures in the upper respiratory tract, such as the oropharynx, nasopharynx, sinuses, and middle ear. Patients with head wounds or cochlear implants (an electronic device placed in the inner ear) are also at risk for developing meningitis.

Many of the bacteria that can cause meningitis are commonly found in healthy people. The most common causes of non-neonatal bacterial meningitis are *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*. All three of these bacterial pathogens are spread from person to person by respiratory secretions. Each can colonize and cross through the mucous membranes of the oropharynx and nasopharynx, and enter the blood. Once in the blood, these pathogens can disseminate throughout the body and are capable of both establishing an infection and triggering inflammation in any body site, including the meninges (Figure 17.5.2.1). Without appropriate systemic antibacterial therapy, the case-fatality rate can be as high as 70%, and 20% of those survivors may be left with irreversible nerve damage or tissue destruction, resulting in hearing loss, neurologic disability, or loss of a limb. Mortality rates are much lower (as low as 15%) in populations where appropriate therapeutic drugs and preventive vaccines are available.[1]



(a) (b)

Figure 17.5.2.1: (a) A normal human brain removed during an autopsy. (b) The brain of a patient who died from bacterial meningitis. Note the pus under the dura mater (being retracted by the forceps) and the red hemorrhagic foci on the meninges. (credit b: modification of work by the Centers for Disease Control and Prevention)

A variety of other bacteria, including *Listeria monocytogenes* and *Escherichia coli*, are also capable of causing meningitis. These bacteria cause infections of the arachnoid mater and CSF after spreading through the circulation in blood or by spreading from an infection of the sinuses or nasopharynx. *Streptococcus agalactiae*, commonly found in the microbiota of the vagina and gastrointestinal tract, can also cause bacterial meningitis in newborns after transmission from the mother either before or during birth.

The profound inflammation caused by these microbes can result in early symptoms that include severe headache, fever, confusion, nausea, vomiting, photophobia, and stiff neck. Systemic inflammatory responses associated with some types of bacterial meningitis can lead to hemorrhaging and purpuric lesions on skin, followed by even more severe conditions that include shock, convulsions, coma, and death—in some cases, in the span of just a few hours.

Diagnosis of bacterial meningitis is best confirmed by analysis of CSF obtained by a lumbar puncture. Abnormal levels of polymorphonuclear neutrophils (PMNs) (> 10 PMNs/mm^3), glucose (< 45 mg/dL), and protein (> 45 mg/dL) in the CSF are

suggestive of bacterial meningitis.[2] Characteristics of specific forms of bacterial meningitis are detailed in the subsections that follow.

Meningococcal Meningitis

Meningococcal meningitis is a serious infection caused by the gram-negative coccus *N. meningitidis*. In some cases, death can occur within a few hours of the onset of symptoms. Nonfatal cases can result in irreversible nerve damage, resulting in hearing loss and brain damage, or amputation of extremities because of tissue necrosis.

Meningococcal meningitis can infect people of any age, but its prevalence is highest among infants, adolescents, and young adults.[3] Meningococcal meningitis was once the most common cause of meningitis epidemics in human populations. This is still the case in a swath of sub-Saharan Africa known as the meningitis belt, but meningococcal meningitis epidemics have become rare in most other regions, thanks to meningococcal vaccines. However, outbreaks can still occur in communities, schools, colleges, prisons, and other populations where people are in close direct contact.

N. meningitidis has a high affinity for mucosal membranes in the oropharynx and nasopharynx. Contact with respiratory secretions containing *N. meningitidis* is an effective mode of transmission. The pathogenicity of *N. meningitidis* is enhanced by virulence factors that contribute to the rapid progression of the disease. These include lipooligosaccharide (LOS) endotoxin, type IV pili for attachment to host tissues, and polysaccharide capsules that help the cells avoid phagocytosis and complement-mediated killing. Additional virulence factors include IgA protease(which breaks down IgA antibodies), the invasion factors Opa, Opc, and porin (which facilitate transcellular entry through the blood-brain barrier), iron-uptake factors (which strip heme units from hemoglobin in host cells and use them for growth), and stress proteins that protect bacteria from reactive oxygen molecules.

A unique sign of meningococcal meningitis is the formation of a petechial rash on the skin or mucous membranes, characterized by tiny, red, flat, hemorrhagic lesions. This rash, which appears soon after disease onset, is a response to LOS endotoxin and adherence virulence factors that disrupt the endothelial cells of capillaries and small veins in the skin. The blood vessel disruption triggers the formation of tiny blood clots, causing blood to leak into the surrounding tissue. As the infection progresses, the levels of virulence factors increase, and the hemorrhagic lesions can increase in size as blood continues to leak into tissues. Lesions larger than 1.0 cm usually occur in patients developing shock, as virulence factors cause increased hemorrhage and clot formation. Sepsis, as a result of systemic damage from meningococcal virulence factors, can lead to rapid multiple organ failure, shock, disseminated intravascular coagulation, and death.

Because meningococcoal meningitis progresses so rapidly, a greater variety of clinical specimens are required for the timely detection of *N. meningitidis*. Required specimens can include blood, CSF, naso- and oropharyngeal swabs, urethral and endocervical swabs, petechial aspirates, and biopsies. Safety protocols for handling and transport of specimens suspected of containing *N. meningitidis* should always be followed, since cases of fatal meningococcal disease have occurred in healthcare workers exposed to droplets or aerosols from patient specimens. Prompt presumptive diagnosis of meningococcal meningitis can occur when CSF is directly evaluated by Gram stain, revealing extra- and intracellular gram-negative diplococci with a distinctive coffee-bean microscopic morphology associated with PMNs (Figure **17.5.2.2**). Identification can also be made directly from CSF using latex agglutination and immunochromatographic rapid diagnostic tests specific for *N. meningitidis*. Species identification can also be performed using DNA sequence-based typing schemes for hypervariable outer membrane proteins of *N. meningitidis*, which has replaced sero(sub)typing.

Meningococcal infections can be treated with antibiotic therapy, and third-generation cephalosporins are most often employed. However, because outcomes can be negative even with treatment, preventive vaccination is the best form of treatment. In 2010, countries in Africa's meningitis belt began using a new serogroup A meningococcal conjugate vaccine. This program has dramatically reduced the number of cases of meningococcal meningitis by conferring individual and herd immunity.

Twelve different capsular serotypes of *N. meningitidis* are known to exist. Serotypes A, B, C, W, X, and Y are the most prevalent worldwide. The CDC recommends that children between 11–12 years of age be vaccinated with a single dose of a quadrivalent vaccine that protects against serotypes A, C, W, and Y, with a booster at age 16.[4] An additional booster or injections of serogroup B meningococcal vaccine may be given to individuals in high-risk settings (such as epidemic outbreaks on college campuses).

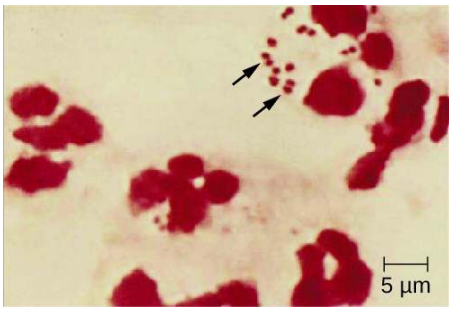


Figure 17.5.2.2: N. meningitidis (arrows) associated with neutrophils (the larger stained cells) in a gram-stained CSF sample. (credit: modification of work by the Centers for Disease Control and Prevention)

Meningitis on Campus

College students living in dorms or communal housing are at increased risk for contracting epidemic meningitis. From 2011 to 2015, there have been at least nine meningococcal outbreaks on college campuses in the United States. These incidents involved a total of 43 students (of whom four died).[5] In spite of rapid diagnosis and aggressive antimicrobial treatment, several of the survivors suffered from amputations or serious neurological problems.

Prophylactic vaccination of first-year college students living in dorms is recommended by the CDC, and insurance companies now cover meningococcal vaccination for students in college dorms. Some colleges have mandated vaccination with meningococcal conjugate vaccine for certain students entering college (Figure 17.5.2.3).


Figure 17.5.2.3: To prevent campus outbreaks, some colleges now require students to be vaccinated against meningogoccal meningitis. (credit: modification of work by James Gathany, Centers for Disease Control and Prevention)

Pneumococcal Meningitis

Pneumococcal meningitis is caused by the encapsulated gram-positive bacterium *S. pneumoniae* (pneumococcus, also called strep pneumo). This organism is commonly found in the microbiota of the pharynx of 30–70% of young children, depending on the sampling method, while *S. pneumoniae* can be found in fewer than 5% of healthy adults. Although it is often present without disease symptoms, this microbe can cross the blood-brain barrier in susceptible individuals. In some cases, it may also result in septicemia. Since the introduction of the Hib vaccine, *S. pneumoniae* has become the leading cause of meningitis in humans aged 2 months through adulthood.

S. pneumoniae can be identified in CSF samples using gram-stained specimens, latex agglutination, and immunochromatographic RDT specific for *S. pneumoniae*. In gram-stained samples, *S. pneumoniae* appears as gram-positive, lancet-shaped diplococci (Figure 17.5.2.4). Identification of *S. pneumoniae* can also be achieved using cultures of CSF and blood, and at least 93 distinct serotypes can be identified based on the quellung reaction to unique capsular polysaccharides. PCR and RT-PCR assays are also available to confirm identification.

Major virulence factors produced by *S. pneumoniae* include PI-1 pilin for adherence to host cells (pneumococcal adherence) and virulence factor B (PavB) for attachment to cells of the respiratory tract; choline-binding proteins(cbpA) that bind to epithelial cells

and interfere with immune factors IgA and C3; and the cytoplasmic bacterial toxin pneumolysin that triggers an inflammatory response.

With the emergence of drug-resistant strains of *S. pneumoniae*, pneumococcal meningitis is typically treated with broad-spectrum antibiotics, such as levofloxacin, cefotaxime, penicillin, or other β-lactam antibiotics. The two available pneumococcal vaccines are described in Bacterial Infections of the Respiratory Tract.

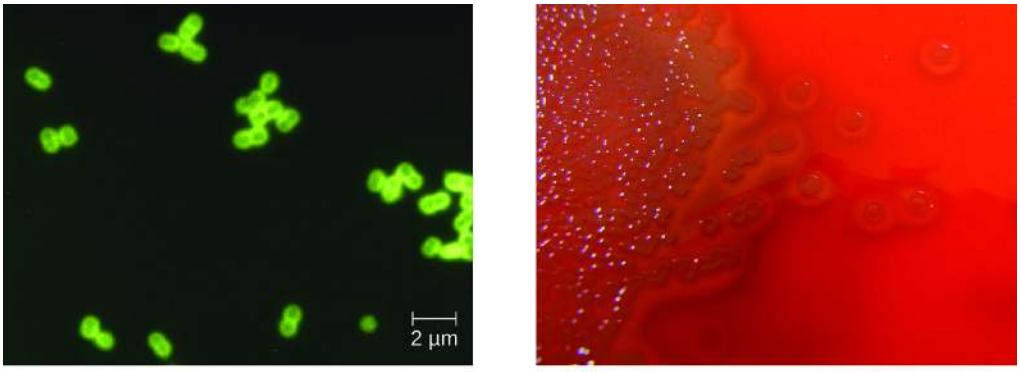


Figure **17.5.2.4**: (a) Digitally colorized fluorescent antibody stained micrograph of *Streptococcus pneumoniae* in CSF. (b) *S. pneumoniae* growing on blood agar. (credit a: modification of work by the Centers for Disease Control and Prevention; credit b: modification of work by Nathan Reading)

Haemophilus influenzae Type b

Meningitis due to *H. influenzae* serotype b (Hib), an encapsulated pleomorphic gram-negative coccobacilli, is now uncommon in most countries, because of the use of the effective Hib vaccine. Without the use of the Hib vaccine, *H. influenzae* can be the primary cause of meningitis in children 2 months thru 5 years of age. *H. influenzae* can be found in the throats of healthy individuals, including infants and young children. By five years of age, most children have developed immunity to this microbe. Infants older than 2 months of age, however, do not produce a sufficient protective antibody response and are susceptible to serious disease. The intracranial pressure caused by this infection leads to a 5% mortality rate and 20% incidence of deafness or brain damage in survivors.[6]

H. influenzae produces at least 16 different virulence factors, including LOS, which triggers inflammation, and *Haemophilus* adhesion and penetration factor (Hap), which aids in attachment and invasion into respiratory epithelial cells. The bacterium also has a polysaccharide capsule that helps it avoid phagocytosis, as well as factors such as IgA1 protease and P2 protein that allow it to evade antibodies secreted from mucous membranes. In addition, factors such as hemoglobin-binding protein (Hgp) and transferrin-binding protein (Tbp) acquire iron from hemoglobin and transferrin, respectively, for bacterial growth.

Preliminary diagnosis of *H. influenzae* infections can be made by direct PCR and a smear of CSF. Stained smears will reveal intracellular and extracellular PMNs with small, pleomorphic, gram-negative coccobacilli or filamentous forms that are characteristic of *H. influenzae*. Initial confirmation of this genus can be based on its fastidious growth on chocolate agar. Identification is confirmed with requirements for exogenous biochemical growth cofactors NAD and heme (by MALDI-TOF), latex agglutination, and RT-PCR.

Meningitis caused by *H. influenzae* is usually treated with doxycycline, fluoroquinolones, second- and third-generation cephalosporins, and carbapenems. The best means of preventing *H. influenza* infection is with the use of the Hib polysaccharide conjugate vaccine. It is recommended that all children receive this vaccine at 2, 4, and 6 months of age, with a final booster dose at 12 to 15 months of age.[7]

Neonatal Meningitis

S. agalactiae, Group B streptococcus (GBS), is an encapsulated gram-positive bacterium that is the most common cause of neonatal meningitis, a term that refers to meningitis occurring in babies up to 3 months of age.[8] *S. agalactiae* can also cause meningitis in people of all ages and can be found in the urogenital and gastrointestinal microbiota of about 10–30% of humans.

Neonatal infection occurs as either early onset or late-onset disease. Early onset disease is defined as occurring in infants up to 7 days old. The infant initially becomes infected by *S. agalactiae* during childbirth, when the bacteria may be transferred from the mother's vagina. Incidence of early onset neonatal meningitis can be greatly reduced by giving intravenous antibiotics to the mother during labor.

Late-onset neonatal meningitis occurs in infants between 1 week and 3 months of age. Infants born to mothers with *S. agalactiae* in the urogenital tract have a higher risk of late-onset menigitis, but late-onset infections can be transmitted from sources other than the mother; often, the source of infection is unknown. Infants who are born prematurely (before 37 weeks of pregnancy) or to mothers who develop a fever also have a greater risk of contracting late-onset neonatal meningitis.

Signs and symptoms of early onset disease include temperature instability, apnea (cessation of breathing), bradycardia(slow heart rate), hypotension, difficulty feeding, irritability, and limpness. When asleep, the baby may be difficult to wake up. Symptoms of late-onset disease are more likely to include seizures, bulging fontanel (soft spot), stiff neck, hemiparesis (weakness on one side of the body), and opisthotonos (rigid body with arched back and head thrown backward).

S. agalactiae produces at least 12 virulence factors that include FbsA that attaches to host cell surface proteins, PI-1 pilithat promotes the invasion of human endothelial cells, a polysaccharide capsule that prevents the activation of the alternative complement pathway and inhibits phagocytosis, and the toxin CAMP factor, which forms pores in host cell membranes and binds to IgG and IgM antibodies.

Diagnosis of neonatal meningitis is often, but not uniformly, confirmed by positive results from cultures of CSF or blood. Tests include routine culture, antigen detection by enzyme immunoassay, serotyping of different capsule types, PCR, and RT-PCR. It is typically treated with β-lactam antibiotics such as intravenous penicillin or ampicillin plus gentamicin. Even with treatment, roughly 10% mortality is seen in infected neonates.[9]

? Exercise 17.5.2.1

1. Which groups are most vulnerable to each of the bacterial meningitis diseases?
2. For which of the bacterial meningitis diseases are there vaccines presently available?
3. Which organism can cause epidemic meningitis?

Clostridium-Associated Diseases

Species in the genus *Clostridium* are gram-positive, endospore-forming rods that are obligate anaerobes. Endospores of *Clostridium* spp. are widespread in nature, commonly found in soil, water, feces, sewage, and marine sediments. *Clostridium* spp. produce more types of protein exotoxins than any other bacterial genus, including two exotoxins with protease activity that are the most potent known biological toxins: botulinum neurotoxin (BoNT) and tetanus neurotoxin (TeNT). These two toxins have lethal doses of 0.2–10 ng per kg body weight.

BoNT can be produced by unique strains of *C. butyricum*, and *C. baratii*; however, it is primarily associated with *C. botulinum* and the condition of botulism. TeNT, which causes tetanus, is only produced by *C. tetani*. These powerful neural exotoxins are the primary virulence factors for these pathogens. The mode of action for these toxins was described in Virulence Factors of Bacterial and Viral Pathogens and illustrated in Figure 15.3.7.

Diagnosis of tetanus or botulism typically involves bioassays that detect the presence of BoNT and TeNT in fecal specimens, blood (serum), or suspect foods. In addition, both *C. botulinum* and *C. tetani* can be isolated and cultured using commercially available media for anaerobes. ELISA and RT-PCR tests are also available.

Tetanus

Tetanus is a noncommunicable disease characterized by uncontrollable muscle spasms (contractions) caused by the action of TeNT. It generally occurs when *C. tetani* infects a wound and produces TeNT, which rapidly binds to neural tissue, resulting in an intoxication (poisoning) of neurons. Depending on the site and extent of infection, cases of tetanus can be described as localized, cephalic, or generalized. Generalized tetanus that occurs in a newborn is called neonatal tetanus.

Localized tetanus occurs when TeNT only affects the muscle groups close to the injury site. There is no CNS involvement, and the symptoms are usually mild, with localized muscle spasms caused by a dysfunction in the surrounding neurons. Individuals with

partial immunity—especially previously vaccinated individuals who neglect to get the recommended booster shots—are most likely to develop localized tetanus as a result of *C. tetani* infecting a puncture wound.

Cephalic tetanus is a rare, localized form of tetanus generally associated with wounds on the head or face. In rare cases, it has occurred in cases of otitis media (middle ear infection). Cephalic tetanus often results in patients seeing double images, because of the spasms affecting the muscles that control eye movement.

Both localized and cephalic tetanus may progress to generalized tetanus—a much more serious condition—if TeNT is able to spread further into body tissues. In generalized tetanus, TeNT enters neurons of the PNS. From there, TeNT travels from the site of the wound, usually on an extremity of the body, retrograde (back up) to inhibitory neurons in the CNS. There, it prevents the release of gamma aminobutyric acid (GABA), the neurotransmitter responsible for muscle relaxation. The resulting muscle spasms often first occur in the jaw muscles, leading to the characteristic symptom of lockjaw (inability to open the mouth). As the toxin progressively continues to block neurotransmitter release, other muscles become involved, resulting in uncontrollable, sudden muscle spasms that are powerful enough to cause tendons to rupture and bones to fracture. Spasms in the muscles in the neck, back, and legs may cause the body to form a rigid, stiff arch, a posture called opisthotonos (Figure **17.5.2.5**). Spasms in the larynx, diaphragm, and muscles of the chest restrict the patient's ability to swallow and breathe, eventually leading to death by asphyxiation (insufficient supply of oxygen).

Neonatal tetanus typically occurs when the stump of the umbilical cord is contaminated with spores of *C. tetani* after delivery. Although this condition is rare in the United States, neonatal tetanus is a major cause of infant mortality in countries that lack maternal immunization for tetanus and where birth often occurs in unsanitary conditions. At the end of the first week of life, infected infants become irritable, feed poorly, and develop rigidity with spasms. Neonatal tetanus has a very poor prognosis with a mortality rate of 70%–100%.[10]

Treatment for patients with tetanus includes assisted breathing through the use of a ventilator, wound debridement, fluid balance, and antibiotic therapy with metronidazole or penicillin to halt the growth of *C. tetani*. In addition, patients are treated with TeNT antitoxin, preferably in the form of human immunoglobulin to neutralize nonfixed toxin and benzodiazepines to enhance the effect of GABA for muscle relaxation and anxiety.

A tetanus toxoid (TT) vaccine is available for protection and prevention of tetanus. It is the T component of vaccines such as DTaP, Tdap, and Td. The CDC recommends children receive doses of the DTaP vaccine at 2, 4, 6, and 15–18 months of age and another at 4–6 years of age. One dose of Td is recommended for adolescents and adults as a TT booster every 10 years.[11]



Figure **17.5.2.5**: A tetanus patient exhibiting the rigid body posture known as opisthotonos. (credit: Centers for Disease Control and Prevention)

Botulism

Botulism is a rare but frequently fatal illness caused by intoxication by BoNT. It can occur either as the result of an infection by *C. botulinum*, in which case the bacteria produce BoNT *in vivo*, or as the result of a direct introduction of BoNT into tissues.

Infection and production of BoNT *in vivo* can result in wound botulism, infant botulism, and adult intestinal toxemia. Wound botulism typically occurs when *C. botulinum* is introduced directly into a wound after a traumatic injury, deep puncture wound, or injection site. Infant botulism, which occurs in infants younger than 1 year of age, and adult intestinal toxemia, which occurs in

immunocompromised adults, results from ingesting *C. botulinum* endospores in food. The endospores germinate in the body, resulting in the production of BoNT in the intestinal tract.

Intoxications occur when BoNT is produced outside the body and then introduced directly into the body through food (foodborne botulism), air (inhalation botulism), or a clinical procedure (iatrogenic botulism). Foodborne botulism, the most common of these forms, occurs when BoNT is produced in contaminated food and then ingested along with the food (recall Case in Point: A Streak of Bad Potluck). Inhalation botulism is rare because BoNT is unstable as an aerosol and does not occur in nature; however, it can be produced in the laboratory and was used (unsuccessfully) as a bioweapon by terrorists in Japan in the 1990s. A few cases of accidental inhalation botulism have also occurred. Iatrogenic botulism is also rare; it is associated with injections of BoNT used for cosmetic purposes (see Micro Connections: Medicinal Uses of Botulinum Toxin).

When BoNT enters the bloodstream in the gastrointestinal tract, wound, or lungs, it is transferred to the neuromuscular junctions of motor neurons where it binds irreversibly to presynaptic membranes and prevents the release of acetylcholine from the presynaptic terminal of motor neurons into the neuromuscular junction. The consequence of preventing acetylcholine release is the loss of muscle activity, leading to muscle relaxation and eventually paralysis.

If BoNT is absorbed through the gastrointestinal tract, early symptoms of botulism include blurred vision, drooping eyelids, difficulty swallowing, abdominal cramps, nausea, vomiting, constipation, or possibly diarrhea. This is followed by progressive flaccid paralysis, a gradual weakening and loss of control over the muscles. A patient's experience can be particularly terrifying, because hearing remains normal, consciousness is not lost, and he or she is fully aware of the progression of his or her condition. In infants, notable signs of botulism include weak cry, decreased ability to suckle, and hypotonia (limpness of head or body). Eventually, botulism ends in death from respiratory failure caused by the progressive paralysis of the muscles of the upper airway, diaphragm, and chest.

Botulism is treated with an antitoxin specific for BoNT. If administered in time, the antitoxin stops the progression of paralysis but does not reverse it. Once the antitoxin has been administered, the patient will slowly regain neurological function, but this may take several weeks or months, depending on the severity of the case. During recovery, patients generally must remain hospitalized and receive breathing assistance through a ventilator.

? Exercise 17.5.2.2

1. How frequently should the tetanus vaccination be updated in adults?
2. What are the most common causes of botulism?
3. Why is botulism not treated with an antibiotic?

Medicinal Uses of Botulinum Toxin

Although it is the most toxic biological material known to man, botulinum toxin is often intentionally injected into people to treat other conditions. Type A botulinum toxin is used cosmetically to reduce wrinkles. The injection of minute quantities of this toxin into the face causes the relaxation of facial muscles, thereby giving the skin a smoother appearance. Eyelid twitching and crossed eyes can also be treated with botulinum toxin injections. Other uses of this toxin include the treatment of hyperhidrosis (excessive sweating). In fact, botulinum toxin can be used to moderate the effects of several other apparently nonmicrobial diseases involving inappropriate nerve function. Such diseases include cerebral palsy, multiple sclerosis, and Parkinson's disease. Each of these diseases is characterized by a loss of control over muscle contractions; treatment with botulinum toxin serves to relax contracted muscles.

Listeriosis

Listeria monocytogenes is a nonencapsulated, nonsporulating, gram-positive rod and a foodborne pathogen that causes listeriosis. At-risk groups include pregnant women, neonates, the elderly, and the immunocompromised (recall the Clinical Focus case studies in Microbial Growth and Microbial Mechanisms of Pathogenicity). Listeriosis leads to meningitis in about 20% of cases, particularly neonates and patients over the age of 60. The CDC identifies listeriosis as the third leading cause of death due to

foodborne illness, with overall mortality rates reaching 16%.[12] In pregnant women, listeriosis can cause also cause spontaneous abortion in pregnant women because of the pathogen's unique ability to cross the placenta.

L. monocytogenes is generally introduced into food items by contamination with soil or animal manure used as fertilizer. Foods commonly associated with listeriosis include fresh fruits and vegetables, frozen vegetables, processed meats, soft cheeses, and raw milk.[13] Unlike most other foodborne pathogens, *Listeria* is able to grow at temperatures between 0 °C and 50 °C, and can therefore continue to grow, even in refrigerated foods.

Ingestion of contaminated food leads initially to infection of the gastrointestinal tract. However, *L. monocytogenes* produces several unique virulence factors that allow it to cross the intestinal barrier and spread to other body systems. Surface proteins called internalins (InlA and InlB) help *L. monocytogenes* invade nonphagocytic cells and tissues, penetrating the intestinal wall and becoming disseminating through the circulatory and lymphatic systems. Internalins also enable *L. monocytogenes* to breach other important barriers, including the blood-brain barrier and the placenta. Within tissues, *L. monocytogenes* uses other proteins called listeriolysin O and ActA to facilitate intercellular movement, allowing the infection to spread from cell to cell (Figure **17.5.2.6**).

L. monocytogenes is usually identified by cultivation of samples from a normally sterile site (e.g., blood or CSF). Recovery of viable organisms can be enhanced using cold enrichment by incubating samples in a broth at 4 °C for a week or more. Distinguishing types and subtypes of *L. monocytogenes*—an important step for diagnosis and epidemiology—is typically done using pulsed-field gel electrophoresis. Identification can also be achieved using chemiluminescence DNA probe assays and MALDI-TOF.

Treatment for listeriosis involves antibiotic therapy, most commonly with ampicillin and gentamicin. There is no vaccine available.

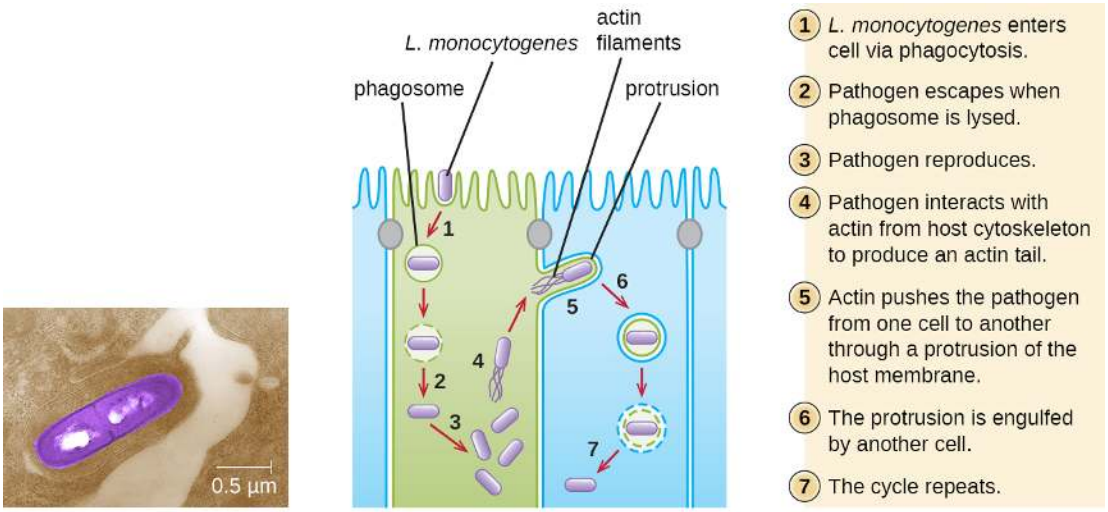


Figure **17.5.2.6**: (a) An electron micrograph of *Listeria monocytogenes* infecting a host cell. (b) *Listeria* is able to use host cell components to cause infection. For example, phagocytosis allows it to enter host cells, and the host's cytoskeleton provides the materials to help the pathogen move to other cells. (credit a: modification of work by the Centers for Disease Control and Prevention; credit b: modification of work by Keith Ireton)

? Exercise 17.5.2.3

How does *Listeria* enter the nervous system?

Hansen's Disease (Leprosy)

Hansen's disease (also known as leprosy) is caused by a long, thin, filamentous rod-shaped bacterium *Mycobacterium leprae*, an obligate intracellular pathogen. *M. leprae* is classified as gram-positive bacteria, but it is best visualized microscopically with an acid-fast stain and is generally referred to as an acid-fast bacterium. Hansen's disease affects the PNS, leading to permanent damage and loss of appendages or other body parts.

Hansen's disease is communicable but not highly contagious; approximately 95% of the human population cannot be easily infected because they have a natural immunity to *M. leprae*. Person-to-person transmission occurs by inhalation into nasal mucosa or prolonged and repeated contact with infected skin. Armadillos, one of only five mammals susceptible to Hansen's disease, have also been implicated in transmission of some cases.[14]

In the human body, *M. leprae* grows best at the cooler temperatures found in peripheral tissues like the nose, toes, fingers, and ears. Some of the virulence factors that contribute to *M. leprae*'s pathogenicity are located on the capsule and cell wall of the bacterium. These virulence factors enable it to bind to and invade Schwann cells, resulting in progressive demyelination that gradually destroys neurons of the PNS. The loss of neuronal function leads to hypoesthesia (numbness) in infected lesions. *M. leprae* is readily phagocytized by macrophages but is able to survive within macrophages in part by neutralizing reactive oxygen species produced in the oxidative burst of the phagolysosome. Like *L. monocytogenes*, *M. leprae* also can move directly between macrophages to avoid clearance by immune factors.

The extent of the disease is related to the immune response of the patient. Initial symptoms may not appear for as long as 2 to 5 years after infection. These often begin with small, blanched, numb areas of the skin. In most individuals, these will resolve spontaneously, but some cases may progress to a more serious form of the disease. Tuberculoid (paucibacillary) Hansen's disease is marked by the presence of relatively few (three or less) flat, blanched skin lesions with small nodules at the edges and few bacteria present in the lesion. Although these lesions can persist for years or decades, the bacteria are held in check by an effective immune response including cell-mediated cytotoxicity. Individuals who are unable to contain the infection may later develop lepromatous (multibacillary) Hansen's disease. This is a progressive form of the disease characterized by nodules filled with acid-fast bacilli and macrophages. Impaired function of infected Schwann cells leads to peripheral nerve damage, resulting in sensory loss that leads to ulcers, deformities, and fractures. Damage to the ulnar nerve (in the wrist) by *M. leprae* is one of the most common causes of crippling of the hand. In some cases, chronic tissue damage can ultimately lead to loss of fingers or toes. When mucosal tissues are also involved, disfiguring lesions of the nose and face can also occur (Figure **17.5.2.7**).

Hansen's disease is diagnosed on the basis of clinical signs and symptoms of the disease, and confirmed by the presence of acid-fast bacilli on skin smears or in skin biopsy specimens (Figure **17.5.2.7**). *M. leprae* does not grow *in vitro* on any known laboratory media, but it can be identified by culturing *in vivo* in the footpads of laboratory mice or armadillos. Where needed, PCR and genotyping of *M. leprae* DNA in infected human tissue may be performed for diagnosis and epidemiology.

Hansen's disease responds well to treatment and, if diagnosed and treated early, does not cause disability. In the United States, most patients with Hansen's disease are treated in ambulatory care clinics in major cities by the National Hansen's Disease program, the only institution in the United States exclusively devoted to Hansen's disease. Since 1995, WHO has made multidrug therapy for Hansen's disease available free of charge to all patients worldwide. As a result, global prevalence of Hansen's disease has declined from about 5.2 million cases in 1985 to roughly 176,000 in 2014.[15] Multidrug therapy consists of dapsone and rifampicin for all patients and a third drug, clofazimin, for patients with multibacillary disease.

Currently, there is no universally accepted vaccine for Hansen's disease. India and Brazil use a tuberculosis vaccineagainst Hansen's disease because both diseases are caused by species of *Mycobacterium*. The effectiveness of this method is questionable, however, since it appears that the vaccine works in some populations but not in others.

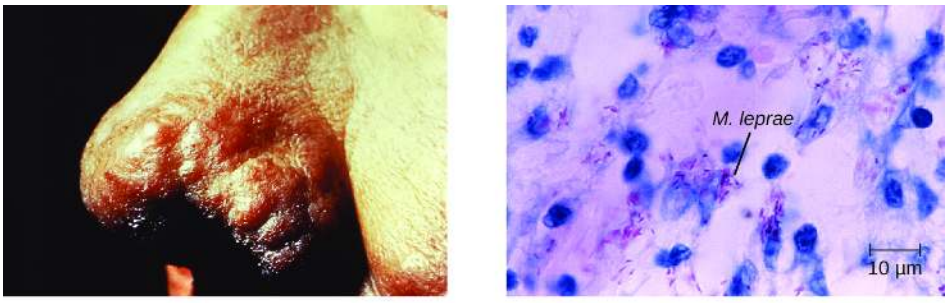


Figure **17.5.2.7**: (a) The nose of a patient with Hansen's disease. Note the lepromatous/multibacillary lesions around the nostril. (b) Hansen's disease is caused by *Mycobacterium leprae*, a gram-positive bacillus. (credit a, b: modifications of work by the Centers for Disease Control and Prevention)

Exercise 17.5.2.4

1. What prevents the progression from tuberculoid to lepromatus leprosy?
2. Why does Hansen's disease typically affect the nerves of the extremities?

Leper Colonies

Disfiguring, deadly diseases like leprosy have historically been stigmatized in many cultures. Before leprosy was understood, victims were often isolated in leper colonies, a practice mentioned frequently in ancient texts, including the Bible. But leper colonies are not just an artifact of the ancient world. In Hawaii, a leper colony established in the late nineteenth century persisted until the mid-twentieth century, its residents forced to live in deplorable conditions.[16] Although leprosy is a communicable disease, it is not considered contagious (easily communicable), and it certainly does not pose enough of a threat to justify the permanent isolation of its victims. Today, we reserve the practices of isolation and quarantine to patients with more dangerous diseases, such as Ebola or multiple-drug-resistant bacteria like *Mycobacterium tuberculosis* and *Staphylococcus aureus*. The ethical argument for this practice is that isolating infected patients is necessary to prevent the transmission and spread of highly contagious diseases—even when it goes against the wishes of the patient.

Of course, it is much easier to justify the practice of temporary, clinical quarantining than permanent social segregation, as occurred in leper colonies. In the 1980s, there were calls by some groups to establish camps for people infected with AIDS. Although this idea was never actually implemented, it begs the question—where do we draw the line? Are permanent isolation camps or colonies ever medically or socially justifiable? Suppose there were an outbreak of a fatal, contagious disease for which there is no treatment. Would it be justifiable to impose social isolation on those afflicted with the disease? How would we balance the rights of the infected with the risk they pose to others? To what extent should society expect individuals to put their own health at risk for the sake of treating others humanely?

Bacterial Infections of the Nervous System

Despite the formidable defenses protecting the nervous system, a number of bacterial pathogens are known to cause serious infections of the CNS or PNS. Unfortunately, these infections are often serious and life threatening. Figure **17.5.2.8** summarizes some important infections of the nervous system.

Bacterial Infections of the Nervous System					
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Antimicrobial Drugs**	**Vaccine**
Botulism	*Clostridium botulinum*	Blurred vision, drooping eyelids, difficulty swallowing and breathing, nausea, vomiting, often fatal	Ingestion of preformed toxin in food, ingestion of endospores in food by infants or immuno-compromised adults, bacterium introduced via wound or injection	Antitoxin; penicillin (for wound botulism)	None
Hansen's disease (leprosy)	*Mycobacterium leprae*	Hypopigmented skin, skin lesions, and nodules, loss of peripheral nerve function, loss of fingers, toes, and extremities	Inhalation, possible transmissible from armadillos to humans	Dapsone, rifampin, clofazimin	None
Haemophilus influenzae type b meningitis	*Haemophilus influenzae*	Nausea, vomiting, photophobia, stiff neck, confusion	Direct contact, inhalation of aerosols	Doxycycline, fluoroquinolones, second- and third-generation cephalosporins, and carbapenems	Hib vaccine
Listeriosis	*Listeria monocytogenes*	Initial flu-like symptoms, sepsis and potentially fatal meningitis in susceptible individu-als, miscarriage in pregnant women	Bacterium ingested with contaminated food or water	Ampicillin, gentamicin	None
Meningococcal meningitis	*Neisseria meningitidis*	Nausea, vomiting, photophobia, stiff neck, confusion; often fatal	Direct contact	Cephalosporins or penicillins	Meningococcal conjugate
Neonatal meningitis	*Streptococcus agalactiae*	Temperature instability, apnea, bradycardia, hypotension, feeding difficulty, irritability, limpness, seizures, bulging fontanel, stiff neck, opisthotonos, hemiparesis, often fatal	Direct contact in birth canal	Ampicillin plus gentamicin, cefotaxime, or both	None
Pneumococcal meningitis	*Streptococcus pneumoniae*	Nausea, vomiting, photophobia, stiff neck, confusion, often fatal	Direct contact, aerosols	Cephalosporins, penicillin	Pneumococcal vaccines
Tetanus	*Clostridium tetani*	Progressive spasmatic paralysis starting with the jaw, often fatal	Bacterium introduced in puncture wound	Penicillin, antitoxin	DTaP, Tdap

Figure **17.5.2.8**: Bacterial infections of the Nervous system.

Key Concepts and Summary

- **Bacterial meningitis** can be caused by several species of encapsulated bacteria, including *Haemophilus influenzae*, *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Streptococcus agalactiae* (group B streptococci). *H. influenzae* affects primarily young children and neonates, *N. meningitidis* is the only communicable pathogen and mostly affects children and young adults, *S. pneumoniae* affects mostly young children, and *S. agalactiae* affects newborns during or shortly after birth.
- Symptoms of bacterial meningitis include fever, neck stiffness, headache, confusion, convulsions, coma, and death.
- Diagnosis of bacterial meningitis is made through observations and culture of organisms in CSF. Bacterial meningitis is treated with antibiotics. *H. influenzae* and *N. meningitidis* have vaccines available.
- *Clostridium* species cause neurological diseases, including **botulism** and **tetanus**, by producing potent neurotoxins that interfere with neurotransmitter release. The PNS is typically affected. Treatment of *Clostridium* infection is effective only

through early diagnosis with administration of antibiotics to control the infection and antitoxins to neutralize the endotoxin before they enter cells.

- *Listeria monocytogenes* is a foodborne pathogen that can infect the CNS, causing meningitis. The infection can be spread through the placenta to a fetus. Diagnosis is through culture of blood or CSF. Treatment is with antibiotics and there is no vaccine.
- **Hansen's disease** (**leprosy**) is caused by the intracellular parasite *Mycobacterium leprae*. Infections cause demylenation of neurons, resulting in decreased sensation in peripheral appendages and body sites. Treatment is with multi-drug antibiotic therapy, and there is no universally recognized vaccine.

Footnotes

1. 1 Thigpen, Michael C., Cynthia G. Whitney, Nancy E. Messonnier, Elizabeth R. Zell, Ruth Lynfield, James L. Hadler, Lee H. Harrison et al., "Bacterial Meningitis in the United States, 1998–2007," *New England Journal of Medicine* 364, no. 21 (2011): 2016-25.
2. 2 Popovic, T., et al. World Health Organization, "Laboratory Manual for the Diagnosis of Meningitis Caused by *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenza*," 1999.
3. 3 US Centers for Disease Control and Prevention, "Meningococcal Disease," August 5, 2015. Accessed June 28, 2015. www.cdc.gov/meningococcal/sur...nce/index.html.
4. 4 US Centers for Disease Control and Prevention, "Recommended Immunization Schedule for Persons Aged 0 Through 18 Years, United States, 2016," February 1, 2016. Accessed on June 28, 2016. www.cdc.gov/vaccines/schedule...dolescent.html.
5. 5 National Meningitis Association, "Serogroup B Meningococcal Disease Outbreaks on U.S. College Campuses," 2016. Accessed June 28, 2016. http://www.nmaus.org/disease-prevent...ase/outbreaks/.
6. 6 United States Department of Health and Human Services, "Hib (Haemophilus Influenzae Type B)," Accessed June 28, 2016. http://www.vaccines.gov/diseases/hib/#.
7. 7 US Centers for Disease Control and Prevention, "Meningococcal Disease, Disease Trends," 2015. Accessed September 13, 2016. www.cdc.gov/meningococcal/sur...nce/index.html.
8. 8 Thigpen, Michael C., Cynthia G. Whitney, Nancy E. Messonnier, Elizabeth R. Zell, Ruth Lynfield, James L. Hadler, Lee H. Harrison et al., "Bacterial Meningitis in the United States, 1998–2007," *New England Journal of Medicine* 364, no. 21 (2011): 2016-25.
9. 9 Thigpen, Michael C., Cynthia G. Whitney, Nancy E. Messonnier, Elizabeth R. Zell, Ruth Lynfield, James L. Hadler, Lee H. Harrison et al., "Bacterial Meningitis in the United States, 1998–2007," *New England Journal of Medicine* 364, no. 21 (2011): 2016-25; Heath, Paul T., Gail Balfour, Abbie M. Weisner, Androulla Efstratiou, Theresa L. Lamagni, Helen Tighe, Liam AF O'Connell et al., "Group B Streptococcal Disease in UK and Irish Infants Younger than 90 Days," *The Lancet* 363, no. 9405 (2004): 292-4.
10. 10 UNFPA, UNICEF WHO, "Maternal and Neonatal Tetanus Elimination by 2005," 2000. www.unicef.org/immunization/f...tegy_paper.pdf.
11. 11 US Centers for Disease Control and Prevention, "Tetanus Vaccination," 2013. Accessed June 29, 2016. http://www.cdc.gov/tetanus/vaccination.html.
12. 12 Scallan, Elaine, Robert M. Hoekstra, Frederick J. Angulo, Robert V. Tauxe, Marc-Alain Widdowson, Sharon L. Roy, Jeffery L. Jones, and Patricia M. Griffin, "Foodborne Illness Acquired in the United States—Major Pathogens," *Emerging Infectious Diseases* 17, no. 1 (2011): 7-15.
13. 13 US Centers for Disease Control and Prevention, "*Listeria* Outbreaks," 2016. Accessed June 29, 2016. https://www.cdc.gov/listeria/outbreaks/index.html.
14. 14 Sharma, Rahul, Pushpendra Singh, W. J. Loughry, J. Mitchell Lockhart, W. Barry Inman, Malcolm S. Duthie, Maria T. Pena et al., "Zoonotic Leprosy in the Southeastern United States," *Emerging Infectious Diseases* 21, no. 12 (2015): 2127-34.
15. 15 World Health Organization, "Leprosy Fact Sheet," 2016. Accessed September 13, 2016. http://www.who.int/mediacentre/factsheets/fs101/en/.
16. 16 National Park Service, "A Brief History of Kalaupapa," Accessed February 2, 2016. www.nps.gov/kala/learn/histor...-kalaupapa.htm.

Contributor

- Nina Parker, (Shenandoah University), Mark Schneegurt (Wichita State University), Anh-Hue Thi Tu (Georgia Southwestern State University), Philip Lister (Central New Mexico Community College), and Brian M. Forster (Saint Joseph's University) with many contributing authors. Original content via Openstax (CC BY 4.0; Access for free at https://openstax.org/books/microbiology/pages/1-introduction)

This page titled 17.5.2: Bacterial Diseases of the Nervous System is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **26.2: Bacterial Diseases of the Nervous System** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

17.5.3: Acellular Pathogenic Diseases of the Nervous System

Learning Objectives

- Identify the most common acellular pathogens that can cause infections of the nervous system
- Compare the major characteristics of specific viral diseases affecting the nervous system

A number of different viruses and subviral particles can cause diseases that affect the nervous system. Viral diseases tend to be more common than bacterial infections of the nervous system today. Fortunately, viral infections are generally milder than their bacterial counterparts and often spontaneously resolve. Some of the more important acellular pathogens of the nervous system are described in this section.

Viral Meningitis

Although it is much more common than bacterial meningitis, viral meningitis is typically less severe. Many different viruses can lead to meningitis as a sequela of the primary infection, including those that cause herpes, influenza, measles, and mumps. Most cases of viral meningitis spontaneously resolve, but severe cases do occur.

Arboviral Encephalitis

Several types of insect-borne viruses can cause encephalitis. Collectively, these viruses are referred to as arboviruses (because they are arthropod-borne), and the diseases they cause are described as arboviral encephalitis. Most arboviruses are endemic to specific geographical regions. Arborviral encephalitis diseases found in the United States include eastern equine encephalitis (EEE), western equine encephalitis (WEE), St. Louis encephalitis, and West Nile encephalitis (WNE). Expansion of arboviruses beyond their endemic regions sometimes occurs, generally as a result of environmental changes that are favorable to the virus or its vector. Increased travel of infected humans, animals, or vectors has also allowed arboviruses to spread into new regions.

In most cases, arboviral infections are asymptomatic or lead to a mild disease. However, when symptoms do occur, they include high fever, chills, headaches, vomiting, diarrhea, and restlessness. In elderly patients, severe arboviral encephalitis can rapidly lead to convulsions, coma, and death.

Mosquitoes are the most common biological vectors for arboviruses, which tend to be enveloped ssRNA viruses. Thus, prevention of arboviral infections is best achieved by avoiding mosquitoes—using insect repellent, wearing long pants and sleeves, sleeping in well-screened rooms, using bed nets, etc.

Diagnosis of arboviral encephalitis is based on clinical symptoms and serologic testing of serum or CSF. There are no antiviral drugs to treat any of these arboviral diseases, so treatment consists of supportive care and management of symptoms.

Eastern equine encephalitis (EEE) is caused by eastern equine encephalitis virus (EEEV), which can cause severe disease in horses and humans. Birds are reservoirs for EEEV with accidental transmission to horses and humans by *Aedes*, *Coquillettidia*, and *Culex* species of mosquitoes. Neither horses nor humans serve as reservoirs. EEE is most common in US Gulf Coast and Atlantic states. EEE is one of the more severe mosquito-transmitted diseases in the United States, but fortunately, it is a very rare disease in the United States (Figure 17.5.3.1).[12]

Western equine encephalitis (WEE) is caused by western equine encephalitis virus (WEEV). WEEV is usually transmitted to horses and humans by the *Culex tarsalis* mosquitoes and, in the past decade, has caused very few cases of encephalitis in humans in the United States. In humans, WEE symptoms are less severe than EEE and include fever, chills, and vomiting, with a mortality rate of 3–4%. Like EEEV, birds are the natural reservoir for WEEV. Periodically, for indeterminate reasons, epidemics in human cases have occurred in North America in the past. The largest on record was in 1941, with more than 3400 cases.[3]

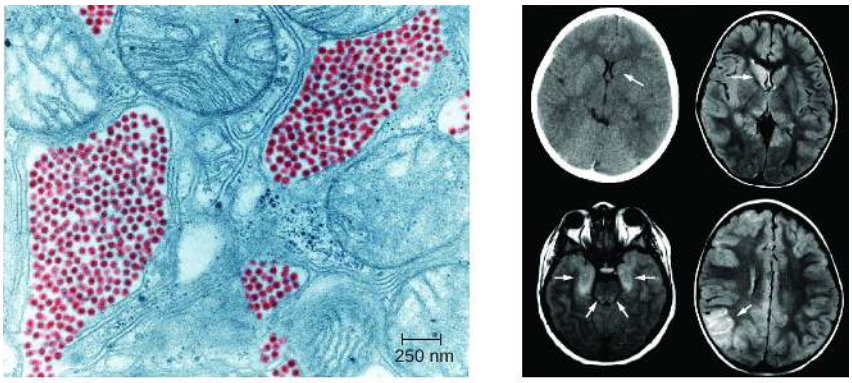


Figure 17.5.3.1: (a) A false color TEM of a mosquito salivary gland cell shows an infection of the eastern equine encephalitis virus (red). (b) CT (left) and MRI (right) scans of the brains of children with eastern equine encephalitis infections, showing abnormalities (arrows) resulting from the infection. (credit a, b: modifications of work by the Centers for Disease Control and Prevention)

St. Louis encephalitis (SLE), caused by St. Louis encephalitis virus (SLEV), is a rare form of encephalitis with symptoms occurring in fewer than 1% of infected patients. The natural reservoirs for SLEV are birds. SLEV is most often found in the Ohio-Mississippi River basin of the central United States and was named after a severe outbreak in Missouri in 1934. The worst outbreak of St. Louis encephalitis occurred in 1975, with over 2000 cases reported.[4]Humans become infected when bitten by *C. tarsalis*, *C. quinquefasciatus*, or *C. pipiens* mosquitoes carrying SLEV. Most patients are asymptomatic, but in a small number of individuals, symptoms range from mild flu-like syndromes to fatal encephalitis. The overall mortality rate for symptomatic patients is 5–15%.[5]

Japanese encephalitis, caused by Japanese encephalitis virus (JEV), is the leading cause of vaccine-preventable encephalitis in humans and is endemic to some of the most populous countries in the world, including China, India, Japan, and all of Southeast Asia. JEV is transmitted to humans by *Culex* mosquitoes, usually the species *C. tritaeniorhynchus*. The biological reservoirs for JEV include pigs and wading birds. Most patients with JEV infections are asymptomatic, with symptoms occurring in fewer than 1% of infected individuals. However, about 25% of those who do develop encephalitis die, and among those who recover, 30–50% have psychiatric, neurologic, or cognitive impairment.[6] Fortunately, there is an effective vaccine that can prevent infection with JEV. The CDC recommends this vaccine for travelers who expect to spend more than one month in endemic areas.

As the name suggests, West Nile virus (WNV) and its associated disease, West Nile encephalitis (WNE), did not originate in North America. Until 1999, it was endemic in the Middle East, Africa, and Asia; however, the first US cases were identified in New York in 1999, and by 2004, the virus had spread across the entire continental United States. Over 35,000 cases, including 1400 deaths, were confirmed in the five-year period between 1999 and 2004. WNV infection remains reportable to the CDC.

WNV is transmitted to humans by *Culex* mosquitoes from its natural reservoir, infected birds, with 70–80% of infected patients experiencing no symptoms. Most symptomatic cases involve only mild, flu-like symptoms, but fewer than 1% of infected people develop severe and sometimes fatal encephalitis or meningitis. The mortality rate in WNV patients who develop neurological disease is about 10%. More information about West Nile virus can be found in Modes of Disease Transmission.

Link to Learning

This interactive map identifies cases of several arboviral diseases in humans and reservoir species by state and year for the United States.

Exercise 17.5.3.1

1. Why is it unlikely that arboviral encephalitis viruses will be eradicated in the future?
2. Which is the most common form of viral encephalitis in the United States?

Clinical Focus: Part 2

Levofloxacin is a quinolone antibiotic that is often prescribed to treat bacterial infections of the respiratory tract, including pneumonia and bronchitis. But after taking the medication for a week, David returned to his physician sicker than before. He claimed that the antibiotic had no effect on his earlier symptoms. In addition, he now was experiencing headaches, a stiff neck, and difficulty focusing at work. He also showed the doctor a rash that had developed on his arms over the past week. His doctor, more concerned now, began to ask about David's activities over the past two weeks.

David explained that he had been recently working on a project to disassemble an old barn. His doctor collected sputum samples and scrapings from David's rash for cultures. A spinal tap was also performed to examine David's CSF. Microscopic examination of his CSF revealed encapsulated yeast cells. Based on this result, the doctor prescribed a new antimicrobial therapy using amphotericin B and flucytosine.

Exercise 17.5.3.2

1. Why was the original treatment ineffective?
2. Why is the presence of a capsule clinically important?

Zika Virus Infection

Zika virus infection is an emerging arboviral disease associated with human illness in Africa, Southeast Asia, and South and Central America; however, its range is expanding as a result of the widespread range of its mosquito vector. The first cases originating in the United States were reported in 2016.The Zika virus was initially described in 1947 from monkeys in the Zika Forest of Uganda through a network that monitored yellow fever. It was not considered a serious human pathogen until the first large-scale outbreaks occurred in Micronesia in 2007;[7] however, the virus has gained notoriety over the past decade, as it has emerged as a cause of symptoms similar to other arboviral infections that include fever, skin rashes, conjunctivitis, muscle and joint pain, malaise, and headache. Mosquitoes of the *Aedes* genus are the primary vectors, although the virus can also be transmitted sexually, from mother to baby during pregnancy, or through a blood transfusion.

Most Zika virus infections result in mild symptoms such as fever, a slight rash, or conjunctivitis. However, infections in pregnant women can adversely affect the developing fetus. Reports in 2015 indicate fetal infections can result in brain damage, including a serious birth defect called microcephaly, in which the infant is born with an abnormally small head (Figure 17.5.3.2).[8]

Diagnosis of Zika is primarily based on clinical symptoms. However, the FDA recently authorized the use of a Zika virus RNA assay, Trioplex RT-PCR, and Zika MAC-ELISA to test patient blood and urine to confirm Zika virus disease. There are currently no antiviral treatments or vaccines for Zika virus, and treatment is limited to supportive care.

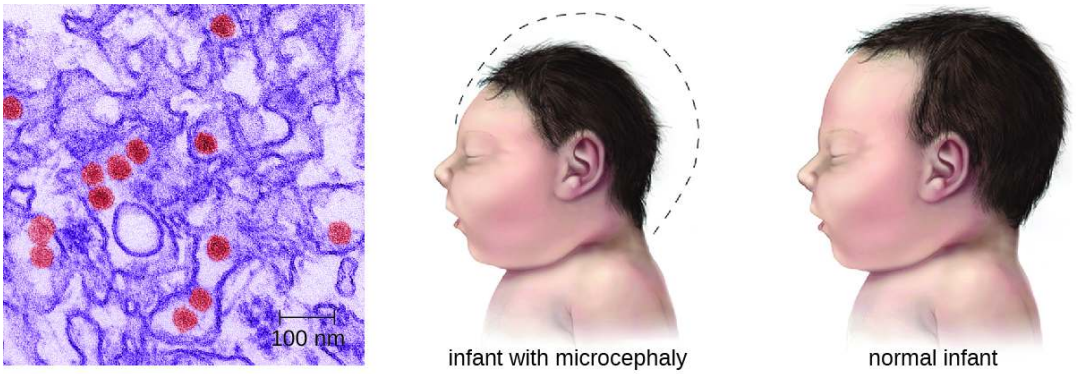


Figure 17.5.3.2: (a) This colorized electron micrograph shows Zika virus particles (red). (b) Women infected by the Zika virus during pregnancy may give birth to children with microcephaly, a deformity characterized by an abnormally small head and brain. (credit a, b: modifications of work by the Centers for Disease Control and Prevention)

? Exercise 17.5.3.3

1. What are the signs and symptoms of Zika virus infection in adults?
2. Why is Zika virus infection considered a serious public health threat?

Rabies

Rabies is a deadly zoonotic disease that has been known since antiquity. The disease is caused by rabies virus (RV), a member of the family Rhabdoviridae, and is primarily transmitted through the bite of an infected mammal. Rhabdoviridae are enveloped RNA viruses that have a distinctive bullet shape (Figure **17.5.3.3**); they were first studied by Louis Pasteur, who obtained rabies virus from rabid dogs and cultivated the virus in rabbits. He successfully prepared a rabies vaccine using dried nerve tissues from infected animals. This vaccine was used to first treat an infected human in 1885.

The most common reservoirs in the United States are wild animals such as raccoons (30.2% of all animal cases during 2014), bats (29.1%), skunks (26.3%), and foxes (4.1%); collectively, these animals were responsible for a total of 92.6% of animal rabies cases in the United States in 2014. The remaining 7.4% of cases that year were in domesticated animals such as dogs, cats, horses, mules, sheep, goats, and llamas.[9] While there are typically only one or two human cases per year in the United States, rabies still causes tens of thousands of human deaths per year worldwide, primarily in Asia and Africa.

The low incidence of rabies in the United States is primarily a result of the widespread vaccination of dogs and cats. An oral vaccine is also used to protect wild animals, such as raccoons and foxes, from infection. Oral vaccine programs tend to focus on geographic areas where rabies is endemic.[10] The oral vaccine is usually delivered in a package of bait that is dropped by airplane, although baiting in urban areas is done by hand to maximize safety.[11] Many countries require a quarantine or proof of rabies vaccination for domestic pets being brought into the country. These procedures are especially strict in island nations where rabies is not yet present, such as Australia.

The incubation period for rabies can be lengthy, ranging from several weeks or months to over a year. As the virus replicates, it moves from the site of the bite into motor and sensory axons of peripheral nerves and spreads from nerve to nerve using a process called retrograde transport, eventually making its way to the CNS through the spinal ganglia. Once rabies virus reaches the brain, the infection leads to encephalitis caused by the disruption of normal neurotransmitter function, resulting in the symptoms associated with rabies. The virions act in the synaptic spaces as competitors with a variety of neurotransmitters for acetylcholine, GABA, and glycine receptors. Thus, the action of rabies virus is neurotoxic rather than cytotoxic. After the rabies virus infects the brain, it can continue to spread through other neuronal pathways, traveling out of the CNS to tissues such as the salivary glands, where the virus can be released. As a result, as the disease progresses the virus can be found in many other tissues, including the salivary glands, taste buds, nasal cavity, and tears.

The early symptoms of rabies include discomfort at the site of the bite, fever, and headache. Once the virus reaches the brain and later symptoms appear, the disease is always fatal. Terminal rabies cases can end in one of two ways: either furious or paralytic rabies. Individuals with furious rabies become very agitated and hyperactive. Hydrophobia (a fear of water) is common in patients with furious rabies, which is caused by muscular spasms in the throat when swallowing or thinking about water. Excess salivation and a desire to bite can lead to foaming of the mouth. These behaviors serve to enhance the likelihood of viral transmission, although contact with infected secretions like saliva or tears alone is sufficient for infection. The disease culminates after just a few days with terror and confusion, followed by cardiovascular and respiratory arrest. In contrast, individuals with paralytic rabies generally follow a longer course of disease. The muscles at the site of infection become paralyzed. Over a period of time, the paralysis slowly spreads throughout the body. This paralytic form of disease culminates in coma and death.

Before present-day diagnostic methods were available, rabies diagnosis was made using a clinical case history and histopathological examination of biopsy or autopsy tissues, looking for the presence of Negri bodies. We now know these histologic changes *cannot* be used to confirm a rabies diagnosis. There are no tests that can detect rabies virus in humans at the time of the bite or shortly thereafter. Once the virus has begun to replicate (but before clinical symptoms occur), the virus can be detected using an immunofluorescence test on cutaneous nerves found at the base of hair follicles. Saliva can also be tested for viral genetic material by reverse transcription followed by polymerase chain reaction (RT-PCR). Even when these tests are performed, most suspected infections are treated as positive in the absence of contravening evidence. It is better that patients undergo unnecessary therapy because of a false-positiveresult, rather than die as the result of a false-negative result.

Human rabies infections are treated by immunization with multiple doses of an attenuated vaccine to develop active immunity in the patient (see the Clinical Focus feature in the chapter on Acellular Pathogens). Vaccination of an already-infected individual has the potential to work because of the slow progress of the disease, which allows time for the patient's immune system to develop antibodies against the virus. Patients may also be treated with human rabies immune globulin (antibodies to the rabies virus) to encourage passive immunity. These antibodies will neutralize any free viral particles. Although the rabies infection progresses slowly in peripheral tissues, patients are not normally able to mount a protective immune response on their own.



Figure 17.5.3.3: Virions of the rabies virus have a characteristic bullet-like shape. (credit: modification of work by the Centers for Disease Control and Prevention)

? Exercise 17.5.3.4

1. How does the bite from an infected animal transmit rabies?
2. What is the goal of wildlife vaccination programs for rabies?
3. How is rabies treated in a human?

Poliomyelitis

Poliomyelitis (polio), caused by poliovirus, is a primarily intestinal disease that, in a small percentage of cases, proceeds to the nervous system, causing paralysis and, potentially, death. Poliovirus is highly contagious, with transmission occurring by the fecal-oral route or by aerosol or droplet transmission. Approximately 72% of all poliovirus infections are asymptomatic; another 25% result only in mild intestinal disease, producing nausea, fever, and headache.[12] However, even in the absence of symptoms, patients infected with the virus can shed it in feces and oral secretions, potentially transmitting the virus to others. In about one case in every 200, the poliovirus affects cells in the CNS.[13]

After it enters through the mouth, initial replication of poliovirus occurs at the site of implantation in the pharynx and gastrointestinal tract. As the infection progresses, poliovirus is usually present in the throat and in the stool before the onset of symptoms. One week after the onset of symptoms, there is less poliovirus in the throat, but for several weeks, poliovirus continues to be excreted in the stool. Poliovirus invades local lymphoid tissue, enters the bloodstream, and then may infect cells of the CNS. Replication of poliovirus in motor neurons of the anterior horn cells in the spinal cord, brain stem, or motor cortex results in cell destruction and leads to flaccid paralysis. In severe cases, this can involve the respiratory system, leading to death. Patients with impaired respiratory function are treated using positive-pressure ventilation systems. In the past, patients were sometimes confined to Emerson respirators, also known as iron lungs (Figure 17.5.3.4).

Direct detection of the poliovirus from the throat or feces can be achieved using reverse transcriptase PCR (RT-PCR) or genomic sequencing to identify the genotype of the poliovirus infecting the patient. Serological tests can be used to determine whether the patient has been previously vaccinated. There are no therapeutic measures for polio; treatment is limited to various supportive measures. These include pain relievers, rest, heat therapy to ease muscle spasms, physical therapy and corrective braces if necessary to help with walking, and mechanical ventilation to assist with breathing if necessary.



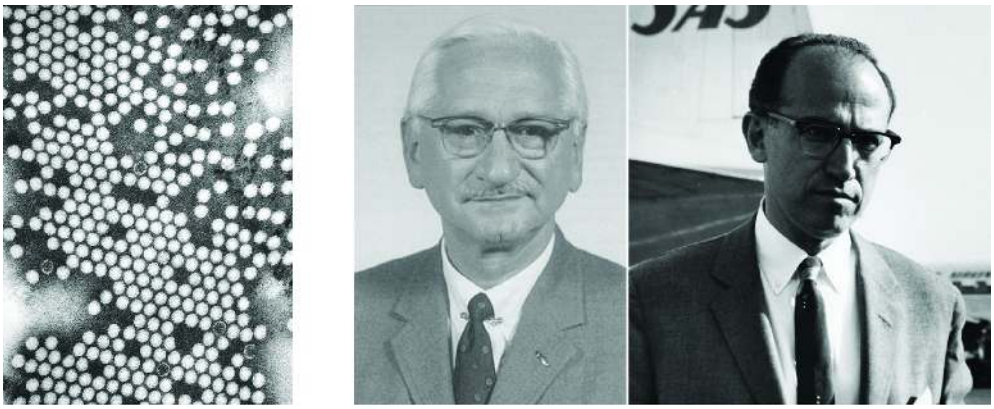
(a) (b)

Figure 17.5.3.4: (a) An Emerson respiratory (or iron lung) that was used to help some polio victims to breathe. (b) Polio can also result in impaired motor function. (credit b: modification of work by the Centers for Disease Control and Prevention)

Two different vaccines were introduced in the 1950s that have led to the dramatic decrease in polio worldwide (Figure 17.5.3.5). The Salk vaccine is an inactivated polio virus that was first introduced in 1955. This vaccine is delivered by intramuscular injection. The Sabin vaccine is an oral polio vaccine that contains an attenuated virus; it was licensed for use in 1962. There are three serotypes of poliovirus that cause disease in humans; both the Salk and the Sabin vaccines are effective against all three.

Attenuated viruses from the Sabin vaccine are shed in the feces of immunized individuals and thus have the potential to infect nonimmunized individuals. By the late 1990s, the few polio cases originating in the United States could be traced back to the Sabin vaccine. In these cases, mutations of the attenuated virus following vaccination likely allowed the microbe to revert to a virulent form. For this reason, the United States switched exclusively to the Salk vaccine in 2000. Because the Salk vaccine contains an inactivated virus, there is no risk of transmission to others (see Vaccines). Currently four doses of the vaccine are recommended for children: at 2, 4, and 6–18 months of age, and at 4–6 years of age.

In 1988, WHO launched the Global Polio Eradication Initiative with the goal of eradicating polio worldwide through immunization. That goal is now close to being realized. Polio is now endemic in only a few countries, including Afghanistan, Pakistan, and Nigeria, where vaccination efforts have been disrupted by military conflict or political instability.



(a) (b)

Figure 17.5.3.5: (a) Polio is caused by the poliovirus. (b) Two American virologists developed the first polio vaccines: Albert Sabin (left) and Jonas Salk (right). (credit a: modification of work by the Centers for Disease Control and Prevention)

The Terror of Polio

In the years after World War II, the United States and the Soviet Union entered a period known as the Cold War. Although there was no armed conflict, the two super powers were diplomatically and economically isolated from each other, as represented by the so-called Iron Curtain between the Soviet Union and the rest of the world. After 1950, migration or travel outside of the

Soviet Union was exceedingly difficult, and it was equally difficult for foreigners to enter the Soviet Union. The United States also placed strict limits on Soviets entering the country. During the Eisenhower administration, only 20 graduate students from the Soviet Union were allowed to come to study in the United States per year.

Yet even the Iron Curtain was no match for polio. The Salk vaccine became widely available in the West in 1955, and by the time the Sabin vaccine was ready for clinical trials, most of the susceptible population in the United States and Canada had already been vaccinated against polio. Sabin needed to look elsewhere for study participants. At the height of the Cold War, Mikhail Chumakov was allowed to come to the United States to study Sabin's work. Likewise, Sabin, an American microbiologist, was allowed to travel to the Soviet Union to begin clinical trials. Chumakov organized Soviet-based production and managed the experimental trials to test the new vaccine in the Soviet Union. By 1959, over ten million Soviet children had been safely treated with Sabin's vaccine.

As a result of a global vaccination campaign with the Sabin vaccine, the overall incidence of polio has dropped dramatically. Today, polio has been nearly eliminated around the world and is only rarely seen in the United States. Perhaps one day soon, polio will become the third microbial disease to be eradicated from the general population [small pox and rinderpest (the cause of cattle plague) being the first two].

Exercise 17.5.3.5

1. How is poliovirus transmitted?
2. Compare the pros and cons of each of the two polio vaccines.

Transmissible Spongiform Encephalopathies

Acellular infectious agents called prions are responsible for a group of related diseases known as transmissible spongiform encephalopathies (TSEs) that occurs in humans and other animals (see Viroids, Virusoids, and Prions). All TSEs are degenerative, fatal neurological diseases that occur when brain tissue becomes infected by prions. These diseases have a slow onset; symptoms may not become apparent until after an incubation period of years and perhaps decades, but death usually occurs within months to a few years after the first symptoms appear.

TSEs in animals include scrapie, a disease in sheep that has been known since the 1700s, and chronic wasting disease, a disease of deer and elk in the United States and Canada. Mad cow disease is seen in cattle and can be transmitted to humans through the consumption of infected nerve tissues. Human prion diseases include Creutzfeldt-Jakob disease and kuru, a rare disease endemic to Papua New Guinea.

Prions are infectious proteinaceous particles that are not viruses and do not contain nucleic acid. They are typically transmitted by exposure to and ingestion of infected nervous system tissues, tissue transplants, blood transfusions, or contaminated fomites. Prion proteins are normally found in a healthy brain tissue in a form called PrP^{C}. However, if this protein is misfolded into a denatured form (PrP^{Sc}), it can cause disease. Although the exact function of PrP^{C} is not currently understood, the protein folds into mostly alpha helices and binds copper. The rogue protein, on the other hand, folds predominantly into beta-pleated sheets and is resistant to proteolysis. In addition, PrP^{Sc} can induce PrP^{C} to become misfolded and produce more rogue protein (Figure **17.5.3.6**).

As PrP^{Sc} accumulates, it aggregates and forms fibrils within nerve cells. These protein complexes ultimately cause the cells to die. As a consequence, brain tissues of infected individuals form masses of neurofibrillary tangles and amyloid plaques that give the brain a spongy appearance, which is why these diseases are called spongiform encephalopathy (Figure 6.4.3). Damage to brain tissue results in a variety of neurological symptoms. Most commonly, affected individuals suffer from memory loss, personality changes, blurred vision, uncoordinated movements, and insomnia. These symptoms gradually worsen over time and culminate in coma and death.

The gold standard for diagnosing TSE is the histological examination of brain biopsies for the presence of characteristic amyloid plaques, vacuoles, and prion proteins. Great care must be taken by clinicians when handling suspected prion-infected materials to avoid becoming infected themselves. Other tissue assays search for the presence of the 14-3-3 protein, a marker for prion diseases like Creutzfeldt-Jakob disease. New assays, like RT-QuIC (real-time quaking-induced conversion), offer new hope to effectively detect the abnormal prion proteins in tissues earlier in the course of infection. Prion diseases cannot be cured. However, some

medications may help slow their progress. Medical support is focused on keeping patients as comfortable as possible despite progressive and debilitating symptoms.

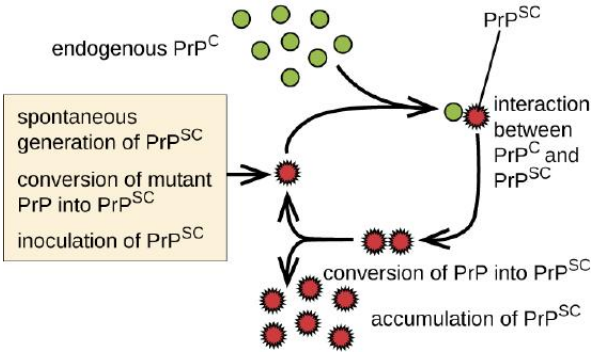


Figure **17.5.3.6**: The replicative cycle of misfolded prion proteins.

Link to Learning

Because prion-contaminated materials are potential sources of infection for clinical scientists and physicians, both the World Health Organization and CDC provide information to inform, educate and minimize the risk of infections due to prions.

Exercise 17.5.3.6

1. Do prions reproduce in the conventional sense?
2. What is the connection between prions and the removal of animal byproducts from the food of farm animals?

Acellular Infections of the Nervous System

Serious consequences are the common thread among these neurological diseases. Several cause debilitating paralysis, and some, such as Creutzfeldt-Jakob disease and rabies, are always or nearly always fatal. Since few drugs are available to combat these infections, vector control and vaccination are critical for prevention and containment. Figure **17.5.3.7** summarizes some important viral and prion infections of the nervous system.

Acellular Infections of the Nervous System						
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Diagnostic Tests**	**Antimicrobial Drugs**	**Vaccine**
Arboviral encephalitis (eastern equine, western equine, St. Louis, West Nile, Japanese)	EEEV, WEEV, SLEV, WNV, JEV	In mild cases, fever, chills, headaches, and restlessness; in serious cases, encephalitis leading to convulsions, coma, and death	From bird reservoirs to humans (and horses) by mosquito vectors of various species	Serologic testing of serum or CSF	None	Human vaccine available for JEV only; no vaccines available for other arboviruses
Creutzfeldt-Jacob Disease and other TSEs	Prions	Memory loss, confusion, blurred vision, uncoordi-nated movement, insomnia, coma, death	Exposure to infected nerve tissue via consumption or transplant, inherited	Tissue biopsy	None	None
Poliomyelitis	Poliovirus	Asymptomatic or mild nausea, fever, headache in most cases; in neurological infections, flaccid paralysis and potentially fatal respiratory paralysis	Fecal-oral route or contact with droplets or aerosols	Culture of poliovirus, PCR	None	Attenuated vaccine (Sabin), killed vaccine (Salk)
Rabies	Rabies virus (RV)	Fever, headaches, hyperactivity, hydrophobia, excessive salivation, terrors, confusion, spreading paralysis, coma, always fatal if not promptly treated	From bite of infected mammal	Viral antigen in tissue, antibodies to virus	Attenuated vaccine, rabies immunoglobulin	Attenuated vaccine
Viral meningitis	HSV-1, HSV-2, varicella zoster virus, mumps virus, influenza virus, measles virus	Nausea, vomiting, photophobia, stiff neck, confusion, symptoms generally resolve within 7–10 days	Sequela of primary viral infection	Testing of oral, fecal, blood, or CSF samples	Varies depending on cause	Varies depending on cause
Zika virus infection	Zika virus	Fever, rash, conjunctivitis; in pregnant women, can cause fetal brain damage and microcephaly	Between humans by *Aedes* spp. mosquito vectors, also may be transmitted sexually or via blood transfusion	Zika virus RNA assay, Trioplex RT-PCR, Zika MAC-ELISA test	None	None

Figure **17.5.3.7**: Acellular infections of the Nervous system.

Key Concepts and Summary

- **Viral meningitis** is more common and generally less severe than bacterial menigitis. It can result from secondary sequelae of many viruses or be caused by infections of arboviruses.
- Various types of **arboviral encephalitis** are concentrated in particular geographic locations throughout the world. These mosquito-borne viral infections of the nervous system are typically mild, but they can be life-threatening in some cases.
- **Zika virus** is an emerging arboviral infection with generally mild symptoms in most individuals, but infections of pregnant women can cause the birth defect microcephaly.
- **Polio** is typically a mild intestinal infection but can be damaging or fatal if it progresses to a neurological disease.

- **Rabies** is nearly always fatal when untreated and remains a significant problem worldwide.
- **Transmissible spongiform encephalopathies** such as **Creutzfeldt-Jakob disease** and **kuru** are caused by prions. These diseases are untreatable and ultimately fatal. Similar prion diseases are found in animals.

Footnotes

1. 1 US Centers for Disease Control and Prevention, “Eastern Equine Encephalitis Virus Disease Cases and Deaths Reported to CDC by Year and Clinical Presentation, 2004–2013,” 2014. www.cdc.gov/EasternEquineEnce..._2004-2013.pdf.
2. 2 US Centers for Disease Control and Prevention, “Eastern Equine Encephalitis, Symptoms & Treatment, 2016,” Accessed June 29, 2016. https://www.cdc.gov/easternequineenc.../symptoms.html.
3. 3 US Centers for Disease Control and Prevention, “Western Equine Encephalitis—United States and Canada, 1987,” *Morbidity and Mortality Weekly Report* 36, no. 39 (1987): 655.
4. 4 US Centers for Disease Control and Prevention, “Saint Louis encephalitis, Epidemiology & Geographic Distribution,” Accessed June 30, 2016. http://www.cdc.gov/sle/technical/epi.html.
5. 5 US Centers for Disease Control and Prevention, “Saint Louis encephalitis, Symptoms and Treatment,” Accessed June 30, 2016. http://www.cdc.gov/sle/technical/symptoms.html.
6. 6 US Centers for Disease Control and Prevention, “Japanese Encephalitis, Symptoms and Treatment,” Accessed June 30, 2016. www.cdc.gov/japaneseencephali...oms/index.html.
7. 7 Sikka, Veronica, Vijay Kumar Chattu, Raaj K. Popli, Sagar C. Galwankar, Dhanashree Kelkar, Stanley G. Sawicki, Stanislaw P. Stawicki, and Thomas J. Papadimos, “The Emergence of Zika Virus as a Global Health Security Threat: A Review and a Consensus Statement of the INDUSEM Joint Working Group (JWG),” *Journal of Global Infectious Diseases* 8, no. 1 (2016): 3.
8. 8 Mlakar, Jernej, Misa Korva, Nataša Tul, Mara Popović, Mateja Poljšak-Prijatelj, Jerica Mraz, Marko Kolenc et al., “Zika Virus Associated with Microcephaly,” *New England Journal of Medicine* 374, no. 10 (2016): 951-8.
9. 9 US Centers for Disease Control and Prevention, “Rabies, Wild Animals,” 2016. Accessed September 13, 2016. www.cdc.gov/rabies/location/u...d_animals.html.
10. 10 Slate, Dennis, Charles E. Rupprecht, Jane A. Rooney, Dennis Donovan, Donald H. Lein, and Richard B. Chipman, “Status of Oral Rabies Vaccination in Wild Carnivores in the United States,” *Virus Research* 111, no. 1 (2005): 68-76.
11. 11 Finnegan, Christopher J., Sharon M. Brookes, Nicholas Johnson, Jemma Smith, Karen L. Mansfield, Victoria L. Keene, Lorraine M. McElhinney, and Anthony R. Fooks, “Rabies in North America and Europe,” *Journal of the Royal Society of Medicine* 95, no. 1 (2002): 9-13. www.ncbi.nlm.nih.gov/pmc/articles/PMC1279140/.
12. 12 US Centers for Disease Control and Prevention, “Global Health – Polio,” 2014. Accessed June 30, 2016. http://www.cdc.gov/polio/about/index.htm.
13. 13 US Centers for Disease Control and Prevention, “Global Health – Polio,” 2014. Accessed June 30, 2016. http://www.cdc.gov/polio/about/index.htm.

This page titled 17.5.3: Acellular Pathogenic Diseases of the Nervous System is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **26.3: Acellular Pathogenic Diseases of the Nervous System** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

17.5.4: Neuromycoses and Parasitic Diseases of the Nervous System

Learning Objectives

- Identify the most common fungi that can cause infections of the nervous system
- Compare the major characteristics of specific fungal diseases affecting the nervous system

Fungal infections of the nervous system, called neuromycoses, are rare in healthy individuals. However, neuromycoses can be devastating in immunocompromised or elderly patients. Several eukaryotic parasites are also capable of infecting the nervous system of human hosts. Although relatively uncommon, these infections can also be life-threatening in immunocompromised individuals. In this section, we will first discuss neuromycoses, followed by parasitic infections of the nervous system.

Cryptococcocal Meningitis

Cryptococcus neoformans is a fungal pathogen that can cause meningitis. This yeast is commonly found in soils and is particularly associated with pigeon droppings. It has a thick capsule that serves as an important virulence factor, inhibiting clearance by phagocytosis. Most *C. neoformans* cases result in subclinical respiratory infections that, in healthy individuals, generally resolve spontaneously with no long-term consequences (see Respiratory Mycoses). In immunocompromised patients or those with other underlying illnesses, the infection can progress to cause meningitisand granuloma formation in brain tissues. *Cryptococcus* antigens can also serve to inhibit cell-mediated immunity and delayed-type hypersensitivity.

Cryptococcus can be easily cultured in the laboratory and identified based on its extensive capsule (Figure **17.5.4.1**). *C. neoformans* is frequently cultured from urine samples of patients with disseminated infections.

Prolonged treatment with antifungal drugs is required to treat cryptococcal infections. Combined therapy is required with amphotericin B plus flucytosine for at least 10 weeks. Many antifungal drugs have difficulty crossing the blood-brain barrier and have strong side effects that necessitate low doses; these factors contribute to the lengthy time of treatment. Patients with AIDS are particularly susceptible to *Cryptococcus* infections because of their compromised immune state. AIDS patients with cryptococcosis can also be treated with antifungal drugs, but they often have relapses; lifelong doses of fluconazole may be necessary to prevent reinfection.

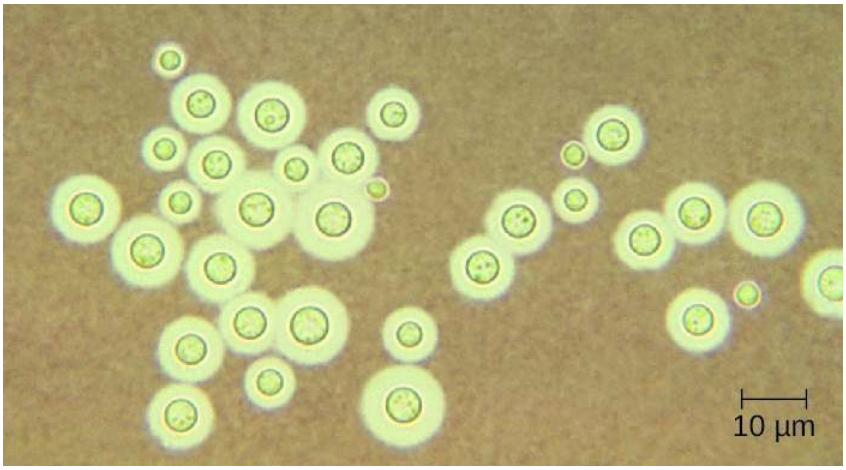


Figure **17.5.4.1**: An India ink-negative stain of *C. neoformans* showing the thick capsules around the spherical yeast cells. (credit: modification of work by Centers for Disease Control and Prevention)

Exercise 17.5.4.1

1. Why are neuromycoses infections rare in the general population?
2. How is a cryptococcal infection acquired?

Neuromycoses

Neuromycoses typically occur only in immunocompromised individuals and usually only invade the nervous system after first infecting a different body system. As such, many diseases that sometimes affect the nervous system have already been discussed in previous chapters. Figure **17.5.4.2** presents some of the most common fungal infections associated with neurological disease. This table includes only the neurological aspects associated with these diseases; it does not include characteristics associated with other body systems.

Neuromycoses					
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Diagnostic Tests**	**Antimicrobial Drugs**
Aspergillosis	*Aspergillus fumigatus*	Meningitis, brain abscesses	Dissemination from respiratory infection	CSF, routine culture	Amphotericin B, voriconazole
Candidiasis	*Candida albicans*	Meningitis	Oropharynx or urogenital	CSF, routine culture	Amphotericin B, flucytosine
Coccidioido-mycosis (Valley fever)	*Coccidioides immitis*	Meningitis (in about 1% of infections)	Dissemination from respiratory infection	CSF, routine culture	Amphotericin B, azoles
Cryptococcosis	*Cryptococcus neoformans*	Meningitis, granuloma formation in brain	Inhalation	Negative stain of CSF, routine culture	Amphotericin B, flucytosine
Histoplasmosis	*Histoplasma capsulatum*	Meningitis, granulomas in the brain	Dissemination from respiratory infection	CSF, routine culture	Amphotericin B, itraconazole
Mucormycosis	*Rhizopus arrhizus*	Brain abscess	Nasopharynx	CSF, routine culture	Amphotericin B, azoles

Figure **17.5.4.2**: Neuromycoses.

Clinical Focus: Resolution

David's new prescription for two antifungal drugs, amphotericin B and flucytosine, proved effective, and his condition began to improve. Culture results from David's sputum, skin, and CSF samples confirmed a fungal infection. All were positive for *C. neoformans*. Serological tests of his tissues were also positive for the *C. neoformans* capsular polysaccharide antigen.

Since *C. neoformans* is known to occur in bird droppings, it is likely that David had been exposed to the fungus while working on the barn. Despite this exposure, David's doctor explained to him that immunocompetent people rarely contract cryptococcal meningitis and that his immune system had likely been compromised by the anti-inflammatory medication he was taking to treat his Crohn's disease. However, to rule out other possible causes of immunodeficiency, David's doctor recommended that he be tested for HIV.

After David tested negative for HIV, his doctor took him off the corticosteroid he was using to manage his Crohn's disease, replacing it with a different class of drug. After several weeks of antifungal treatments, David managed a full recovery.

Amoebic Meningitis

Primary amoebic meningoencephalitis (PAM) is caused by *Naegleria fowleri*. This amoeboflagellate is commonly found free-living in soils and water. It can exist in one of three forms—the infective amoebic trophozoite form, a motile flagellate form, and a resting cyst form. PAM is a rare disease that has been associated with young and otherwise healthy individuals. Individuals are typically infected by the amoeba while swimming in warm bodies of freshwater such as rivers, lakes, and hot springs. The pathogenic trophozoite infects the brain by initially entering through nasal passages to the sinuses; it then moves down olfactory nerve fibers to penetrate the submucosal nervous plexus, invades the cribriform plate, and reaches the subarachnoid space. The subarachnoid space is highly vascularized and is a route of dissemination of trophozoites to other areas of the CNS, including the brain (Figure **17.5.4.3**). Inflammation and destruction of gray matter leads to severe headaches and fever. Within days, confusion and convulsions

occur and quickly progress to seizures, coma, and death. The progression can be very rapid, and the disease is often not diagnosed until autopsy.

N. fowleri infections can be confirmed by direct observation of CSF; the amoebae can often be seen moving while viewing a fresh CSF wet mount through a microscope. Flagellated forms can occasionally also be found in CSF. The amoebae can be stained with several stains for identification, including Giemsa-Wright or a modified trichrome stain. Detection of antigens with indirect immunofluorescence, or genetic analysis with PCR, can be used to confirm an initial diagnosis. *N. fowleri* infections are nearly always fatal; only 3 of 138 patients with PAM in the United States have survived.[1] A new experimental drug called miltefosine shows some promise for treating these infections. This drug is a phosphotidylcholine derivative that is thought to inhibit membrane function in *N. fowleri*, triggering apoptosis and disturbance of lipid-dependent cell signaling pathways.[2] When administered early in infection and coupled with therapeutic hypothermia (lowering the body's core temperature to reduce the cerebral edema associated with infection), this drug has been successfully used to treat primary amoebic encephalitis.

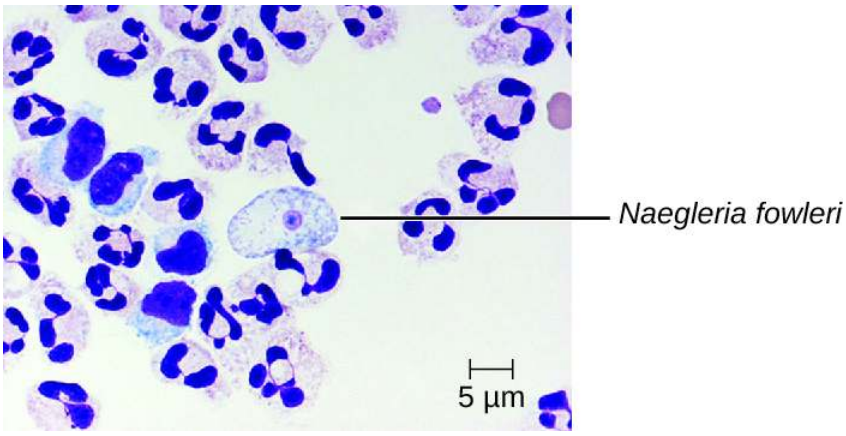
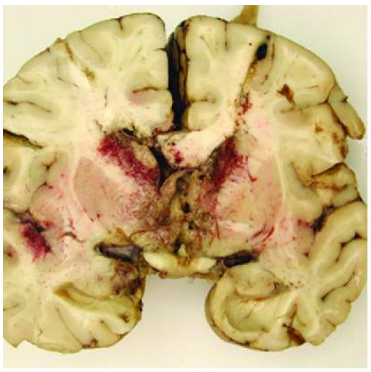


Figure **17.5.4.3**: Free-living amoeba in human brain tissue from a patient suffering from PAM. (credit: modification of work by the Centers for Disease Control and Prevention)

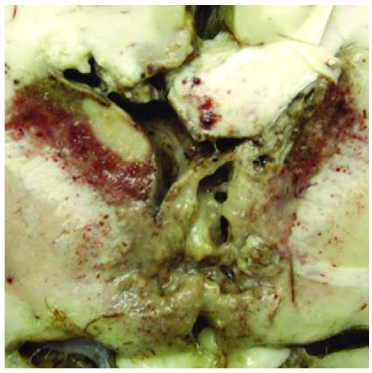
Granulomatous Amoebic Encephalitis

Acanthamoeba and *Balamuthia* species are free-living amoebae found in many bodies of fresh water. Human infections by these amoebae are rare. However, they can cause amoebic keratitis in contact lens wearers (see Protozoan and Helminthic Infections of the Eyes), disseminated infections in immunocompromised patients, and granulomatous amoebic encephalitis (GAE) in severe cases. Compared to PAM, GAE tend to be subacute infections. The microbe is thought to enter through either the nasal sinuses or breaks in the skin. It is disseminated hematogenously and can invade the CNS. There, the infections lead to inflammation, formation of lesions, and development of typical neurological symptoms of encephalitis (Figure **17.5.4.4**). GAE is nearly always fatal.

GAE is often not diagnosed until late in the infection. Lesions caused by the infection can be detected using CT or MRI. The live amoebae can be directly detected in CSF or tissue biopsies. Serological tests are available but generally are not necessary to make a correct diagnosis, since the presence of the organism in CSF is definitive. Some antifungal drugs, like fluconazole, have been used to treat acanthamoebal infections. In addition, a combination of miltefosine and voriconazole (an inhibitor of ergosterol biosynthesis) has recently been used to successfully treat GAE. Even with treatment, however, the mortality rate for patients with these infections is high.



(a)



(b)

Figure **17.5.4.4**: (a) Brain tissue from a patient who died of granulomatous amebic encephalitis (GAE) caused by *Balamuthia mandrillaris*. (b) A close-up of the necrosis in the center of the brain section. (credit a, b: modifications of work by the Centers for Disease Control and Prevention)

? Exercise 17.5.4.2

How is granulomatous amoebic encephalitis diagnosed?

Human African Trypanosomiasis

Human African trypanosomiasis (also known as African sleeping sickness) is a serious disease endemic to two distinct regions in sub-Saharan Africa. It is caused by the insect-borne hemoflagellate *Trypanosoma brucei*. The subspecies *Trypanosoma brucei rhodesiense* causes East African trypanosomiasis (EAT), and another subspecies, *Trypanosoma brucei gambiense* causes West African trypanosomiasis (WAT). A few hundred cases of EAT are currently reported each year.[3] WAT is more commonly reported and tends to be a more chronic disease. Around 7000 to 10,000 new cases of WAT are identified each year.[4]

T. brucei is primarily transmitted to humans by the bite of the tsetse fly (*Glossina* spp.). Soon after the bite of a tsetse fly, a chancre forms at the site of infection. The flagellates then spread, moving into the circulatory system (Figure **17.5.4.5**). These systemic infections result in an undulating fever, during which symptoms persist for two or three days with remissions of about a week between bouts. As the disease enters its final phase, the pathogens move from the lymphatics into the CNS. Neurological symptoms include daytime sleepiness, insomnia, and mental deterioration. In EAT, the disease runs its course over a span of weeks to months. In contrast, WAT often occurs over a span of months to years.

Although a strong immune response is mounted against the trypanosome, it is not sufficient to eliminate the pathogen. Through antigenic variation, *Trypanosoma* can change their surface proteins into over 100 serological types. This variation leads to the undulating form of the initial disease. The initial septicemia caused by the infection leads to high fevers. As the immune system responds to the infection, the number of organisms decrease, and the clinical symptoms abate. However, a subpopulation of the pathogen then alters its surface coat antigens by antigenic variation and evades the immune response. These flagellates rapidly proliferate and cause another bout of disease. If untreated, these infections are usually fatal.

Clinical symptoms can be used to recognize the early signs of African trypanosomiasis. These include the formation of a chancre at the site of infection and Winterbottom's sign. Winterbottom's sign refers to the enlargement of lymph nodes on the back of the neck —often indicative of cerebral infections. *Trypanosoma* can be directly observed in stained samples including blood, lymph, CSF, and skin biopsies of chancres from patients. Antibodies against the parasite are found in most patients with acute or chronic disease. Serologic testing is generally not used for diagnosis, however, since the microscopic detection of the parasite is sufficient. Early diagnosis is important for treatment. Before the nervous system is involved, drugs like pentamidine (an inhibitor of nuclear metabolism) and suramin (mechanism unclear) can be used. These drugs have fewer side effects than the drugs needed to treat the second stage of the disease. Once the sleeping sickness phase has begun, harsher drugs including melarsoprol (an arsenic derivative) and eflornithine can be effective. Following successful treatment, patients still need to have follow-up examinations of their CSF for two years to detect possible relapses of the disease. The most effective means of preventing these diseases is to control the insect vector populations.

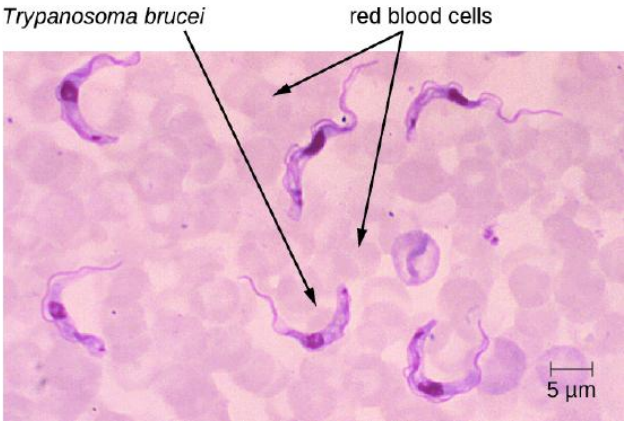


Figure 17.5.4.5: Trypanosoma brucei, the causative agent of African sleeping sickness, in a human blood smear. (credit: modification of work by the Centers for Disease Control and Prevention)

? Exercise 17.5.4.3

1. What is the symptom of a systemic *Trypanosoma* infection?
2. What are the symptoms of a neurological *Trypanosoma* infection?
3. Why are trypanosome infections so difficult to eradicate?

Neurotoxoplasmosis

Toxoplasma gondii is an ubiquitous intracellular parasite that can cause neonatal infections. Cats are the definitive host, and humans can become infected after eating infected meat or, more commonly, by ingesting oocysts shed in the feces of cats (see Parasitic Infections of the Circulatory and Lymphatic Systems). *T. gondii* enters the circulatory system by passing between the endothelial cells of blood vessels.[5] Most cases of toxoplasmosis are asymptomatic. However, in immunocompromised patients, neurotoxoplasmosis caused by *T. gondii* infections are one of the most common causes of brain abscesses.[6] The organism is able to cross the blood-brain barrier by infecting the endothelial cells of capillaries in the brain. The parasite reproduces within these cells, a step that appears to be necessary for entry to the brain, and then causes the endothelial cell to lyse, releasing the progeny into brain tissues. This mechanism is quite different than the method it uses to enter the bloodstream in the first place.[7]

The brain lesions associated with neurotoxoplasmosis can be detected radiographically using MRI or CAT scans (Figure 17.5.4.6). Diagnosis can be confirmed by direct observation of the organism in CSF. RT-PCR assays can also be used to detect *T. gondii* through genetic markers.

Treatment of neurotoxoplasmosis caused by *T. gondii* infections requires six weeks of multi-drug therapy with pyrimethamine, sulfadiazine, and folinic acid. Long-term maintenance doses are often required to prevent recurrence.

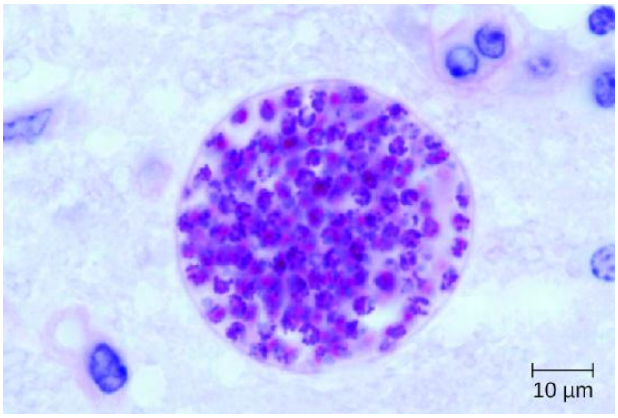


Figure 17.5.4.6: This *Toxoplasma gondii* cyst, observed in mouse brain tissue, contains thousands of inactive parasites. (credit: modification of work by USDA)

Exercise 17.5.4.4

1. Under what conditions is *Toxoplasma* infection serious?
2. How does *Toxoplasma* circumvent the blood-brain barrier?

Neurocysticercosis

Cysticercosis is a parasitic infection caused by the larval form of the pork tapeworm, *Taenia solium*. When the larvae invade the brain and spinal cord, the condition is referred to as neurocysticercosis. This condition affects millions of people worldwide and is the leading cause of adult onset epilepsy in the developing world.[8]

The life cycle of *T. solium* is discussed in Helminthic Infections of the Gastrointestinal Tract. Following ingestion, the eggs hatch in the intestine to form larvae called cysticerci. Adult tapeworms form in the small intestine and produce eggs that are shed in the feces. These eggs can infect other individuals through fecal contamination of food or other surfaces. Eggs can also hatch within the intestine of the original patient and lead to an ongoing autoinfection. The cystercerci, can migrate to the blood and invade many tissues in the body, including the CNS.

Neurocysticercosis is usually diagnosed through noninvasive techniques. Epidemiological information can be used as an initial screen; cysticercosis is endemic in Central and South America, Africa, and Asia. Radiological imaging (MRI and CT scans) is the primary method used to diagnose neurocysticercosis; imaging can be used to detect the one- to two-centimeter cysts that form around the parasites (Figure **17.5.4.7**). Elevated levels of eosinophils in the blood can also indicate a parasitic infection. EIA and ELISA are also used to detect antigens associated with the pathogen.

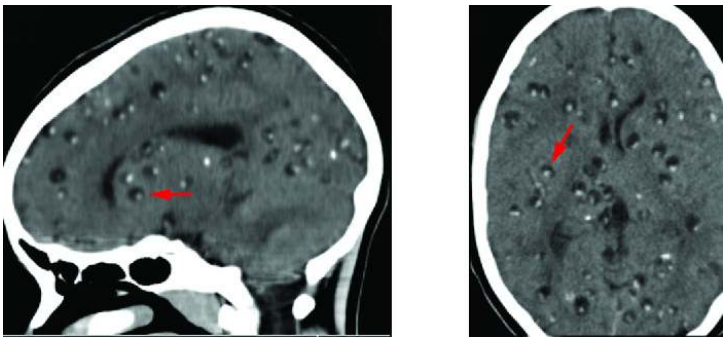


Figure **17.5.4.7**: Brain CT scans of sagittal (left) and axial (right) sections of a brain with neurocysticercosis. Numerous cysts are visible in both images, as indicated by the arrows. (credit: modification of work by Segamwenge IL, Kioko NP)

The treatment for neurocysticercosis depends on the location, number, size, and stage of cysticerci present. Antihelminthic chemotherapy includes albendazole and praziquantel. Because these drugs kill viable cysts, they may acutely increase symptoms by provoking an inflammatory response caused by the release of *Taenia* cysticerci antigens, as the cysts are destroyed by the drugs. To alleviate this response, corticosteroids that cross the blood-brain barrier(e.g., dexamethasone) can be used to mitigate these effects. Surgical intervention may be required to remove intraventricular cysts.

Parasitic Diseases of the Nervous System

Parasites that successfully invade the nervous system can cause a wide range of neurological signs and symptoms. Often, they inflict lesions that can be visualized through radiologic imaging. A number of these infections are fatal, but some can be treated (with varying levels of success) by antimicrobial drugs (Figure **17.5.4.8**).

Parasitic Diseases of the Nervous System					
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Diagnostic Tests**	**Antimicrobial Drugs**
Granulomatous amoebic encephalitis (GAE)	*Acantham-oeba* spp., *Balamuthia mandrillaris*	Inflammation, lesions in CNS, almost always fatal	Freshwater ameobae invade CNS via breaks in skin or sinuses	CT scan, MRI, CSF	Fluconazole, miltefosine, voriconazole
Human African trypanosomiasis	*Trypanosoma brucei gambiense, T. brucei rhodesiense*	Chancre, Winterbottom's sign, undulating fever, lethargy, insomnia, usually fatal if untreated	Protozoan transmitted via bite of tsetse fly	Blood smear	Pentamidine and suramine (initial phase); melarsoprol and eflornithine (final phase)
Neurocysticer-cosis	*Taenia solium*	Brain cysts, epilepsy	Ingestion of tapeworm eggs in fecally contaminated food or surfaces	CT scan, MRI	Albendazole, praziquantel, dexamethasone
Neurotoxoplas-mosis	*Toxoplasma gondii*	Brain abscesses, chronic encephalitis	Protozoan transmitted via contact with oocytes in cat feces	CT scan, MRI, CSF	Pyrimethamine, sulfadiazine, folinic acid
Primary amoebic meningoencepha-litis (PAM)	*Naegleria fowleri*	Headache, seizures, coma, almost always fatal	Freshwater ameobae invade brain via nasal passages	CSF, IFA, PCR	Miltefosine (experimental)

Figure **17.5.4.8**: Parasitic diseases of the Nervous system.

? Exercise 17.5.4.5

1. What neurological condition is associated with neurocysticercosis?
2. How is neurocysticercosis diagnosed?

Key Concepts and Summary

- **Neuromycoses** are uncommon in immunocompetent people, but immunocompromised individuals with fungal infections have high mortality rates. Treatment of neuromycoses require prolonged therapy with antifungal drugs at low doses to avoid side effects and overcome the effect of the blood-brain barrier.
- Some protist infections of the nervous systems are fatal if not treated, including **primary amoebic meningitis**, **granulomatous amoebic encephalitis**, **human African trypanosomiasis**, and **neurotoxoplasmosis**.
- The various forms of ameobic encephalitis caused by the different amoebic infections are typically fatal even with treatment, but they are rare.
- **African trypanosomiasis** is a serious but treatable disease endemic to two distinct regions in sub-Saharan Africa caused by the insect-borne hemoflagellate *Trypanosoma brucei*.
- **Neurocysticercosis** is treated using antihelminthic drugs or surgery to remove the large cysts from the CNS.

Footnotes

1. 1 US Centers for Disease Control and Prevention, "*Naegleria fowleri*—Primary Amoebic Meningoencephalitis (PAM)—Amebic Encephalitis," 2016. Accessed June 30, 2016. http://www.cdc.gov/parasites/naegleria/treatment.html.
2. 2 Dorlo, Thomas PC, Manica Balasegaram, Jos H. Beijnen, and Peter J. de Vries, "Miltefosine: A Review of Its Pharmacology and Therapeutic Efficacy in the Treatment of Leishmaniasis," *Journal of Antimicrobial Chemotherapy* 67, no. 11 (2012): 2576-97.
3. 3 US Centers for Disease Control and Prevention, "Parasites – African Trypanosomiasis (also known as Sleeping Sickness), East African Trypanosomiasis FAQs," 2012. Accessed June 30, 2016. www.cdc.gov/parasites/sleepin...faqs-east.html.

4. 4 US Centers for Disease Control and Prevention, “Parasites – African Trypanosomiasis (also known as Sleeping Sickness), Epidemiology & Risk Factors,” 2012. Accessed June 30, 2016. www.cdc.gov/parasites/sleepin...kness/epi.html.
5. 5 Carruthers, Vern B., and Yasuhiro Suzuki, “Effects of *Toxoplasma gondii* Infection on the Brain,” *Schizophrenia Bulletin* 33, no. 3 (2007): 745-51.
6. 6 Uppal, Gulshan, “CNS Toxoplasmosis in HIV,” 2015. Accessed June 30, 2016. emedicine.medscape.com/articl...98-overview#a3.
7. 7 Konradt, Christoph, Norikiyo Ueno, David A. Christian, Jonathan H. Delong, Gretchen Harms Pritchard, Jasmin Herz, David J. Bzik et al., “Endothelial Cells Are a Replicative Niche for Entry of *Toxoplasma gondii* to the Central Nervous System,” *Nature Microbiology* 1 (2016): 16001.
8. 8 DeGiorgio, Christopher M., Marco T. Medina, Reyna Durón, Chi Zee, and Susan Pietsch Escueta, “Neurocysticercosis,” *Epilepsy Currents* 4, no. 3 (2004): 107-11.

This page titled 17.5.4: Neuromycoses and Parasitic Diseases of the Nervous System is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **26.4: Neuromycoses and Parasitic Diseases of the Nervous System** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

17.5.E: Nervous System Infections (Exercises)

26.1: Anatomy of the Nervous System

The human nervous system can be divided into two interacting subsystems: the peripheral nervous system (PNS) and the central nervous system (CNS). The CNS consists of the brain and spinal cord. The peripheral nervous system is an extensive network of nerves connecting the CNS to the muscles and sensory structures.

Multiple Choice

What is the outermost membrane surrounding the brain called?

A. pia mater
B. arachnoid mater
C. dura mater
D. alma mater

Answer

C

What term refers to an inflammation of brain tissues?

A. encephalitis
B. meningitis
C. sinusitis
D. meningoencephalitis

Answer

A

Nerve cells form long projections called _____.

A. soma
B. axons
C. dendrites
D. synapses

Answer

B

Chemicals called _____ are stored in neurons and released when the cell is stimulated by a signal.

A. toxins
B. cytokines
C. chemokines
D. neurotransmitters

Answer

D

The central nervous system is made up of

A. sensory organs and muscles.
B. the brain and muscles.
C. the sensory organs and spinal cord.
D. the brain and spinal column.

Answer

D

Matching

Match each strategy for microbial invasion of the CNS with its description.

___intercellular entry	A. pathogen gains entry by infecting peripheral white blood cells
___transcellular entry	B. pathogen bypasses the blood-brain barrier by travel along the olfactory or trigeminal cranial nerves
___leukocyte-facilitated entry	C. pathogen passes through the cells of the blood-brain barrier
___nonhematogenous entry	D. pathogen passes between the cells of the blood-brain barrier

Answer

D, C, A, B

Fill in the Blank

The cell body of a neuron is called the _____.

Answer

soma

A signal is transmitted down the _____ of a nerve cell.

Answer

axon

The _____ is filled with cerebrospinal fluid.

Answer

subarachnoid space

The _____ _____ prevents access of microbes in the blood from gaining access to the central nervous system.

Answer

blood-brain barrier

The _____ are a set of membranes that cover and protect the brain.

Answer

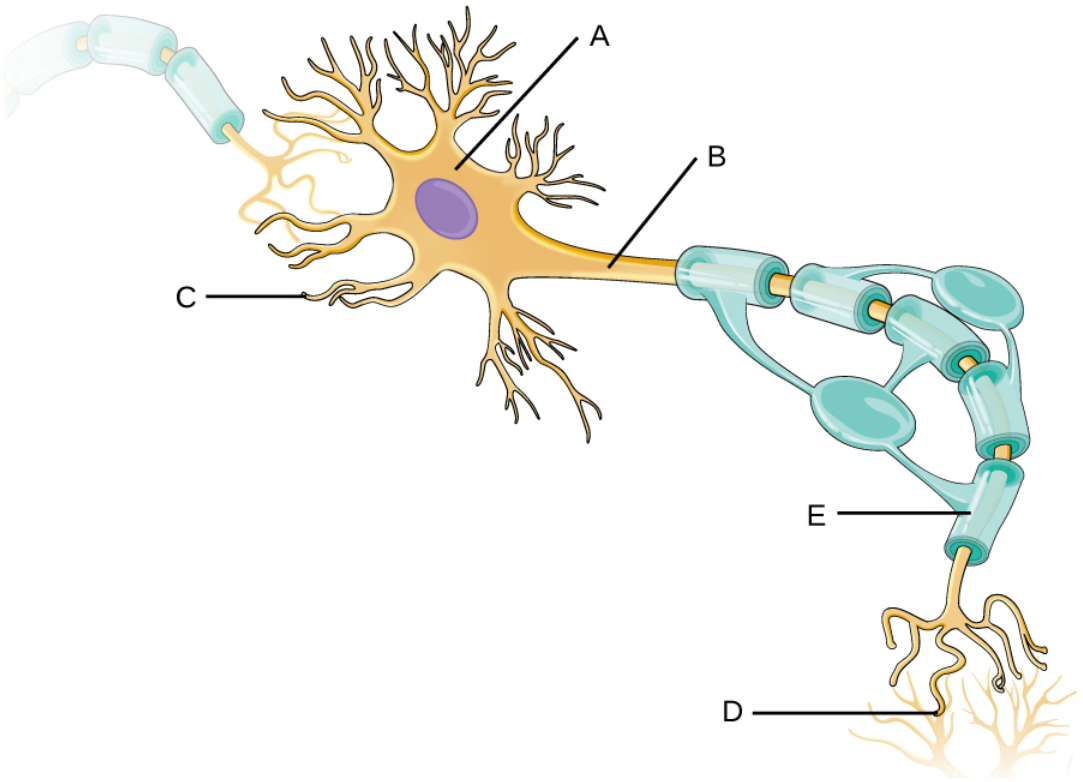
meninges

Short Answer

Briefly describe the defenses of the brain against trauma and infection.

Describe how the blood-brain barrier is formed.

Identify the type of cell shown, as well as the following structures: axon, dendrite, myelin sheath, soma, and synapse.



Critical Thinking

What important function does the blood-brain barrier serve? How might this barrier be problematic at times?

26.2: Bacterial Diseases of the Nervous System

Bacterial infections that affect the nervous system are serious and can be life-threatening. Fortunately, there are only a few bacterial species commonly associated with neurological infections.

Multiple Choice

Which of the following organisms causes epidemic meningitis cases at college campuses?

A. *Haemophilus influenzae* type b
B. *Neisseria meningitidis*
C. *Streptococcus pneumoniae*
D. *Listeria monocytogenes*

Answer

B

Which of the following is the most common cause of neonatal meningitis?

A. *Haemophilus influenzae b*
B. *Streptococcus agalactiae*
C. *Neisseria meningitidis*
D. *Streptococcus pneumoniae*

Answer

B

What sign/symptom would NOT be associated with infant botulism?

A. difficulty suckling
B. limp body
C. stiff neck
D. weak cry

Answer

C

Which of the following can NOT be prevented with a vaccine?

A. tetanus
B. pneumococcal meningitis
C. meningococcal meningitis
D. listeriosis

Answer

D

How is leprosy primarily transmitted from person to person?

A. contaminated toilet seats
B. shaking hands
C. blowing nose
D. sexual intercourse

Answer

C

Fill in the Blank

The form of meningitis that can cause epidemics is caused by the pathogen _____.

Answer

Neisseria meningitidis

The symptoms of tetanus are caused by the neurotoxin _____.

Answer

tetanospasmin

_____ is another name for leprosy.

Answer

Hansen's disease

Botulism prevents the release of the neurotransmitter _____.

Answer

acetylcholine

_____ is a neurological disease that can be prevented with the DTaP vaccine.

Answer

Tetanus

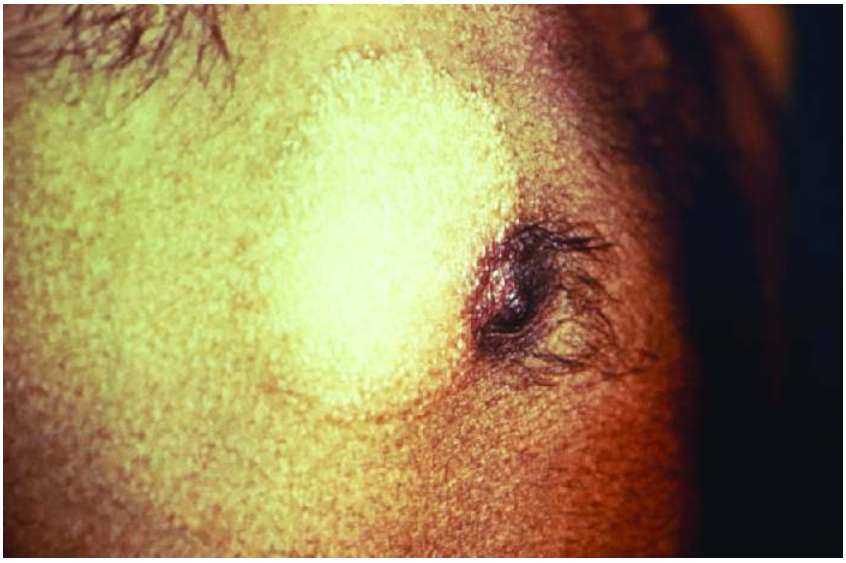
Tetanus patients exhibit _____ when muscle spasms causes them to arch their backs.

Answer

opisthotonos

Short Answer

A physician suspects the lesion and pustule pictured here are indicative of tuberculoid leprosy. If the diagnosis is correct, what microorganism would be found in a skin biopsy?



(credit: Centers for Disease Control and Prevention)

Critical Thinking

Explain how tetanospasmin functions to cause disease.

The most common causes of bacterial meningitis can be the result of infection by three very different bacteria. Which bacteria are they and how are these microbes similar to each other?

Explain how infant botulism is different than foodborne botulism.

26.3: Acellular Pathogenic Diseases of the Nervous System

A number of different viruses and subviral particles can cause diseases that affect the nervous system. Viral diseases tend to be more common than bacterial infections of the nervous system today. Fortunately, viral infections are generally milder than their bacterial counterparts and often spontaneously resolve. Some of the more important acellular pathogens of the nervous system are described in this section.

Multiple Choice

Which of these diseases can be prevented with a vaccine for humans?

A. eastern equine encephalitis
B. western equine encephalitis
C. West Nile encephalitis
D. Japanese encephalitis

Answer

D

Which of these diseases does NOT require the introduction of foreign nucleic acid?

A. kuru
B. polio
C. rabies
D. St. Louis encephalitis

Answer

A

Which of these is true of the Sabin but NOT the Salk polio vaccine?

A. requires four injections
B. currently administered in the United States
C. mimics the normal route of infection
D. is an inactivated vaccine

Answer

C

Which of the following animals is NOT a typical reservoir for the spread of rabies?

A. dog
B. bat
C. skunk
D. chicken

Answer

D

Fill in the Blank

The rogue form of the prion protein is called _____.

Answer

PrP^{Sc}

_____ are the most common reservoir for the rabies virus worldwide.

Answer

Dogs

_____ was the scientist who developed the inactivated polio vaccine.

Answer

Jonas Salk

_____ is a prion disease of deer and elk.

Answer

Chronic wasting disease

The rogue form of prion protein exists primarily in the _____ conformation.

Answer

beta sheet

Short Answer

Explain how a person could contract variant Creutzfeldt-Jakob disease by consuming products from a cow with bovine spongiform encephalopathy (mad cow disease).

Critical Thinking

If the Sabin vaccine is being used to eliminate polio worldwide, explain why a country with a near zero infection rate would opt to use the Salk vaccine but not the Sabin vaccine?

26.4: Neuromycoses and Parasitic Diseases of the Nervous System

Fungal infections of the nervous system, called neuromycoses, are rare in healthy individuals. However, neuromycoses can be devastating in immunocompromised or elderly patients. Several eukaryotic parasites are also capable of infecting the nervous system of human hosts. Although relatively uncommon, these infections can also be life-threatening in immunocompromised individuals. In this section, we first discuss neuromycoses, followed by parasitic infections of the nervous system.

Multiple Choice

Which of these diseases results in meningitis caused by an encapsulated yeast?

A. cryptococcosis
B. histoplasmosis
C. candidiasis
D. coccidiomycosis

Answer

A

What kind of stain is most commonly used to visualize the capsule of cryptococcus?

A. Gram stain
B. simple stain
C. negative stain
D. fluorescent stain

Answer

C

Which of the following is the causative agent of East African trypanosomiasis?

A. *Trypanosoma cruzi*
B. *Trypanosoma vivax*
C. *Trypanosoma brucei rhodanese*
D. *Trypanosoma brucei gambiense*

Answer

C

Which of the following is the causative agent of primary amoebic meningoencephalitis?

A. *Naegleria fowleri*
B. *Entameba histolyticum*
C. *Amoeba proteus*
D. *Acanthamoeba polyphaga*

Answer

A

What is the biological vector for African sleeping sickness?

A. mosquito
B. tsetse fly
C. deer tick
D. sand fly

Answer

B

How do humans usually contract neurocysticercosis?

A. the bite of an infected arthropod
B. exposure to contaminated cat feces
C. swimming in contaminated water
D. ingestion of undercooked pork

Answer

D

Which of these is the most important cause of adult onset epilepsy?

A. neurocysticercosis
B. neurotoxoplasmosis
C. primary amoebic meningoencephalitis
D. African trypanosomiasis

Answer

A

Fill in the Blank

The _____ is the main virulence factor of *Cryptococcus neoformans*.

Answer

capsule

The drug of choice for fungal infections of the nervous system is _____.

Answer

Amphotericin B

The larval forms of a tapeworm are known as _____.

Answer

cysticerci

_____ sign appears as swollen lymph nodes at the back of the neck in early African trypanosomiasis.

Answer

Winterbottom’s

_____ African trypanosomiasis causes a chronic form of sleeping sickness.

Answer

West

The definitive host for *Toxoplasma gondii* is _____.

Answer

cats

Trypanosomes can evade the immune response through _____ variation.

Answer

antigenic

Short Answer

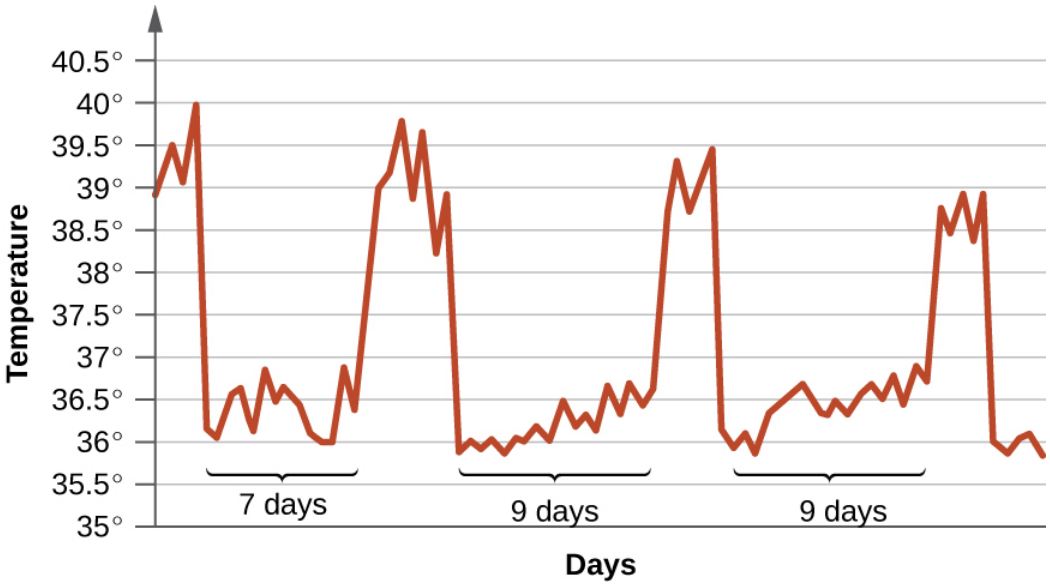
Why do nervous system infections by fungi require such long treatment times?

Briefly describe how humans are infected by *Naegleria fowleri*.

Briefly describe how humans can develop neurocysticercosis.

Critical Thinking

The graph shown tracks the body temperature of a patient infected with *Trypanosoma brucei*. How would you describe this pattern, and why does it occur?



(credit: modification of work by Wellcome Images)

Fungal meningoencephalitis is often the ultimate cause of death for AIDS patients. What factors make these infections more problematic than those of bacterial origin?

Compare East African trypanosomiasis with West African trypanosomiasis.

This page titled 17.5.E: Nervous System Infections (Exercises) is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **26.E: Nervous System Infections (Exercises)** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

17.6: Fungal Diseases of the Respiratory System

This page titled 17.6: Fungal Diseases of the Respiratory System is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.5: Fungal Diseases of the Respiratory System** is licensed CC BY-SA 4.0.

17.6.1: Histoplasmosis

Learning Objectives

- Describe the traits associated with and mode of transmission for Histoplasma capsulatum

Histoplasmosis (also known as “Cave disease,” “Darling’s disease,” “Ohio valley disease,” “Reticuloendotheliosis,” “Spelunker’s Lung,” and “Caver’s disease”) is a disease caused by the fungus Histoplasma capsulatum. Symptoms of this infection vary greatly, but the disease primarily affects the lungs. Other organs are occasionally affected; this is called disseminated histoplasmosis and can be fatal if left untreated. Histoplasmosis is common among AIDS patients due to their suppressed immune system.

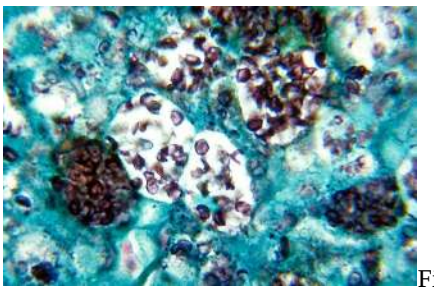


Figure: **Histoplasmosis**: This is a Methenamine silver strain of Histoplasma capsulatum that shows histopathologic changes in the histoplasmosis.

If symptoms of histoplasmosis infection occur, they will start within 3 to 17 days after exposure, with the average being 12 to 14 days. Most affected individuals have clinically silent manifestations and show no apparent ill effects. The acute phase of histoplasmosis is characterized by non-specific respiratory symptoms, often cough or flu-like. Chest X-ray findings are normal in 40 to 70% of cases. Chronic histoplasmosis cases can resemble tuberculosis, and disseminated histoplasmosis affects multiple organ systems and is fatal unless treated.



Figure: **Acute pulmonary histoplasmosis**: This is a chest X-ray of a patient with acute pulmonary histoplasmosis.

Histoplasmosis may be divided into the following types: primary pulmonary histoplasmosis, progressive disseminated histoplasmosis, primary cutaneous histoplasmosis, and African histoplasmosis.

Histoplasma capsulatum is found throughout the world. It is endemic in certain areas of the United States, particularly in states bordering the Ohio River valley and the lower Mississippi River. It is also common in caves in southern and East Africa. Positive histoplasmin skin tests occur in as many as 90% of the people living in areas where Histoplasma capsulatum is common, such as the eastern and central United States.

Histoplasma capsulatum grows in soil and material contaminated with bird or bat droppings (guano). The fungus has been found in poultry house litter, caves, areas harboring bats, and in bird roosts (particularly those of starlings). The fungus is thermally dimorphic: in the environment it grows as a brownish mycelium, and at body temperature (37 °C in humans) it morphs into a yeast.

The inoculum is represented principally by microconidia that, once inhaled into the alveolar spaces, germinate and then transform into budding yeast cells. Histoplasmosis is not contagious, but is contracted by inhalation of the spores from disturbed soil or guano.

Histoplasmosis can be diagnosed by samples containing the fungusken from sputum, blood, or infected organs. It can also be diagnosed by detection of antigens in blood or urine samples by ELISA or PCR. It can also be diagnosed by a test for antibodies against Histoplasma in the blood. Histoplasma skin tests indicate whether a person has been exposed, but do not indicate whether they have the disease. Formal histoplasmosis diagnoses are often confirmed only by culturing the fungus directly. Cutaneous manifestations of disseminated disease are diverse and often present as a nondescript rash with systemic complaints. Diagnosis is best established by urine antigen testing. Blood cultures may take up to 6 weeks for diagnostic growth to occur and serum antigen testing often comes back with a false negative before 4 weeks of disseminated infection.

It is not practical to test or decontaminate most sites that may be contaminated with Histoplasma capsulatum, so precautions to reduce a person's risk of exposure are important. Precautions common to all geographical locations would be to avoid accumulations of bird or bat droppings.

Antifungal medications are used to treat severe cases of acute histoplasmosis and all cases of chronic and disseminated disease. Typical treatment of severe disease first involves treatment with amphotericin B, followed by oral itraconazole. Treatment with itraconazole will need to continue for at least a year in severe cases.

In many milder cases, oral itraconazole or ketoconazole is sufficient. Asymptomatic disease is typically not treated. Past infection results in partial protection against ill effects if reinfected.

Key Points

- Histoplasmosis is s a disease caused by the fungus Histoplasma capsulatum, which is usually found in soil, and often associated with decaying bat guano or bird droppings.
- Cases of histoplasmosis have declined acutely since the Industrial Revolution as quality of life improved dramatically and humans were no longer living in their own squalor.
- Symptoms of this infection vary greatly, but the disease affects primarily the lungs. Occasionally, other organs are affected, and it can be fatal if left untreated.

Key Terms

- **Histoplasmosis**: Histoplasmosis is a disease caused by the fungus Histoplasma capsulatum. Symptoms of this infection vary greatly, but the disease primarily affects the lungs. Other organs are occassionally affected; this is called disseminated histoplasmosis and can be fatal if left untreated.
- **fungus**: Any member of the kingdom Fungi; a eukaryotic organism typically having chitin cell walls but no chlorophyll or plastids. Fungi may be unicellular or multicellular.

This page titled 17.6.1: Histoplasmosis is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.5A: Histoplasmosis** is licensed CC BY-SA 4.0.

17.6.2: Coccidiomycosis

Learning Objectives

- Describe the mode of transmission, symptoms and diagnostic test associated with Coccidioidomycosis immitis

Coccidioidomycosis (commonly known as “Valley fever”, as well as “California fever”, “Desert rheumatism”, and “San Joaquin Valley fever”) is a fungal disease caused by *Coccidioides immitis* or *C. posadasii*. It is endemic in certain parts of Arizona, California, Nevada, New Mexico, Texas, Utah and northwestern Mexico.



Figure: **Coccidioidomycosis**: Histopathological changes in a case of coccidioidomycosis of the lung showing a large fibrocaseous nodule.

C. immitis resides in the soil in certain parts of the southwestern United States, northern Mexico, and parts of Central and South America. It is dormant during long dry spells, then develops as a mold with long filaments that break off into airborne spores when the rains come. The spores, known as arthroconidia, are swept into the air by disruption of the soil, such as occurs during construction, farming, or an earthquake.

Infection is caused by inhalation of the particles. The disease is not transmitted from person to person. The infection ordinarily resolves leaving the patient with a specific immunity to re-infection. *C. immitis* is a dimorphic saprophytic organism that grows as a mycelium in the soil and produces a spherule form in the host organism.

The disease is usually mild, with flu-like symptoms and rashes. The Mayo Clinic estimates that half the population in some affected areas have suffered from the disease. On occasion, those particularly susceptible may develop a serious or even fatal illness. Serious complications include severe pneumonia, lung nodules, and disseminated disease, where the fungus spreads throughout the body. The disseminated form of Valley Fever can devastate the body, causing skin ulcers, abscesses, bone lesions, severe joint pain, heart inflammation, urinary tract problems, meningitis, and often death. In order of decreasing risk, people of Filipino, African, Native American, Hispanic, and Asian descent are susceptible to the disseminated form of the disease. Men and pregnant women, and people with weakened immune systems (such as from AIDS), are more susceptible than non-pregnant women.

It has been known to infect humans, cattle, deer, dogs, elk, fish, mules, livestock, apes, kangaroos, wallabies, tigers, bears, badgers, otters and marine mammals.

Symptomatic infection (40% of cases) usually presents as an influenza-like illness with fever, cough, headaches, rash, and myalgia (muscle pain). Some patients fail to recover and develop chronic pulmonary infection or widespread disseminated infection (affecting meninges, soft tissues, joints, and bone). Severe pulmonary disease may develop in HIV-infected persons.

An additional risk is that health care providers who are unfamiliar with it or are unaware that the patient has been exposed to it may misdiagnose it as cancer and subject the patient to unnecessary surgery.

Coccidioidomycosis may be divided into the following types: Primary pulmonary coccidioidomycosis; Disseminated coccidioidomycosis; and Primary cutaneous coccidioidomycosis.

The fungal infection can be demonstrated by microscopic detection of diagnostic cells in body fluids, exudates, sputum and biopsy-tissue. With specific nucleotide primers, *C.immitis* DNA can be amplified by PCR. It can also be detected in cultures by morphological identification, or by using molecular probes that hybridize with *C.immitis* RNA. An indirect demonstration of fungal infection can be achieved also by serologic analysis detecting fungal antigen or host antibody produced against the fungus.

There are no published prospective studies that examine optimal antifungal therapy for coccidioidomycosis. Mild cases often do not require treatment. Oral Fluconazole and intravenous Amphotericin B are used in progressive or disseminated disease, or in which patients are immunocompromised. Alternatively, itraconazole or ketoconazole may be used. Posaconazole and voriconazole have also been used. There is currently no practical preventative measures available for people who live or travel through Valley Fever endemic areas. It is recommended to avoid airborne dust or dirt, though this is not a guaranteed manner of prevention. People in certain occupations may be advised to wear face masks.

Key Points

- C. immitis resides in the soil in certain parts of the southwestern United States, northern Mexico, and parts of Central and South America.
- Infection is caused by inhalation of the particles.
- The disease is usually mild, with flu-like symptoms and rashes.

Key Terms

- **Coccidioidomycosis**: Coccidioidomycosis is a fungal disease caused by Coccidioides immitis or C. posadasii. It is endemic in certain parts of Arizona, California, Nevada, New Mexico, Texas, Utah and northwestern Mexico.
- **fungal**: Of or pertaining to a fungus or fungi
- **inhalation**: The substance (medicament) which is inhaled.

This page titled 17.6.2: Coccidiomycosis is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.5B: Coccidiomycosis** is licensed CC BY-SA 4.0.

17.6.3: Pneumocystis Pneumonia

Learning Objectives

- Review the symptoms associated with pneumocystis pneumonia and the methods of diagnosis

Pneumocystis pneumonia (PCP) or pneumocystosis is a form of pneumonia, caused by the yeast-like fungus (which had previously been erroneously classified as a protozoan) Pneumocystis jirovecii. This pathogen is specific to humans; it has not been shown to infect other animals. Other species of Pneumocystis that parasitize other animals have not been shown to infect humans.

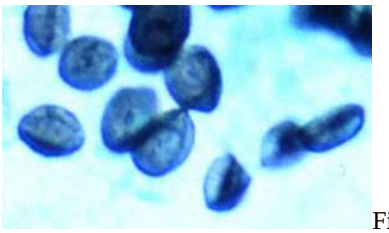


Figure: **Pneumocystis jirovecii pneumonia**: Pneumocystis jirovecii cysts from bronchoalveolar lavage, stained with Toluidin blue O stain

Pneumocystis is commonly found in the lungs of healthy people, but being a source of opportunistic infection, it can cause a lung infection in people with a weak immune system. Pneumocystis pneumonia is especially seen in people with cancer, HIV/AIDS and the use of medications that affect the immune system.

Nomenclature of Pneumocystis Pneumonia

The older name Pneumocystis carinii (which now only applies to the Pneumocystis species that is found in rats), is still in common usage. As a result, Pneumocystis pneumonia (PCP) is also known as Pneumocystis jiroveci[i] pneumonia and (incorrectly) as Pneumocystis carinii pneumonia.

Regarding nomenclature, when the name of Pneumocystis pneumonia changed from P. carinii pneumonia to P. jirovecii pneumonia, it was at first felt that it could no longer be referred to as “PCP”. However, because the term PCP was already in common usage, it was rationalized that the term PCP could continue to be used, as it stood for PneumoCystis (jirovecii) Pneumonia.

Symptoms of Pneumocystis Pneumonia

Symptoms of PCP include fever, non-productive cough (because sputum is too viscous to become productive), shortness of breath (especially on exertion), weight loss, and night sweats. There is usually not a large amount of sputum with PCP unless the patient has an additional bacterial infection. The fungus can invade other visceral organs (such as the liver, spleen, and kidney), but only in a minority of cases.

Pneumothorax is a well-known complication of PCP. An acute history of chest pain with breathlessness and diminished breath sounds is typical of pneumothorax.

The risk of pneumonia due to Pneumocystis jirovecii increases when CD4 positive cell levels are less than 200 cells/µl. In these immunosuppressed individuals the manifestations of the infection are highly variable. The disease attacks the interstitial, fibrous tissue of the lungs, with marked thickening of the alveolar septa and alveoli, leading to significant hypoxia which can be fatal if not treated aggressively. In this situation LDH levels increase and gas exchange is compromised. Oxygen is less able to diffuse into the blood, leading to hypoxia. Hypoxia, along with high arterial carbon dioxide (CO_2) levels, stimulates hyper-ventilatory effort, thereby causing dyspnea (breathlessness).

Diagnosis and Treatment of Pneumocystis Pneumonia

The diagnosis can be confirmed by the characteristic appearance of the chest x-ray, which shows widespread pulmonary infiltrates, and an arterial oxygen level (PaO2) that is strikingly lower than would be expected from symptoms. Gallium 67 scans are also use in the diagnosis. They are abnormal in approximately 90% of cases and are often positive before the chest x-ray becomes abnormal. The diagnosis can be definitively confirmed by histological identification of the causative organism in sputum or bronchio-alveolar

lavage (lung rinse). Staining with toluidine blue, silver stain, periodic-acid schiff stain, or an immunofluorescence assay will show the characteristic cysts. The cysts resemble crushed ping-pong balls and are present in aggregates of 2 to 8 (and not to be confused with Histoplasma or Cryptococcus, which typically do not form aggregates of spores or cells). A lung biopsy would show thickened alveolar septa with fluffy eosinophilic exudate in the alveoli. Both the thickened septa and the fluffy exudate contribute to dysfunctional diffusion capacity which is characteristic of this pneumonia.

Pneumocystis infection can also be diagnosed by immunofluorescent or histochemical staining of the specimen, and more recently by molecular analysis of polymerase chain reaction products comparing DNA samples. Notably, simple molecular detection of Pneumocystis jirovecii in lung fluids does not mean that a person has Pneumocystis pneumonia or infection by HIV. The fungus appears to be present in healthy individuals in the general population.

Antipneumocystic medication is used with concomitant steroids in order to avoid inflammation, which causes an exacerbation of symptoms about four days after treatment begins if steroids are not used. By far the most commonly used medication is trimethoprim-sulfamethoxazole, but some patients are unable to tolerate this treatment due to allergies. Other medications that are used, alone or in combination, include pentamidine, trimetrexate, dapsone, atovaquone, primaquine, pafuramidine maleate (under investigation), and clindamycin. Treatment is usually for a period of about 21 days. However, pneumocystis pneumonia can be prevented by the drug TMP-SMX.

Pentamidine is less often used as its major limitation is the high frequency of side effects. These include acute pancreatitis, renal failure, hepatotoxicity, leukopenia, rash, fever, and hypoglycemia.

Key Points

- Pneumocystis jirovecii is a pathogen that is specific to humans.
- Pneumocystis is commonly found in the lungs of healthy people, but, being a source of opportunistic infection, it can cause a lung infection in people with a weak immune system.
- Symptoms of PCP include fever, non-productive cough, shortness of breath, weight loss, and night sweats.

Key Terms

- **Pneumocystis pneumonia**: Pneumocystis pneumonia (PCP) or pneumocystosis is a form of pneumonia, caused by the yeast-like fungus Pneumocystis jirovecii. This pathogen is specific to humans; it has not been shown to infect other animals.
- **Opportunistic**: An opportunistic infection is an infection caused by pathogens, particularly opportunistic pathogens—those that take advantage of certain situations—such as bacterial, viral, fungal or protozoan infections that usually do not cause disease in a healthy host, one with a healthy immune system. A compromised immune system, however, presents an “opportunity” for the pathogen to infect.
- **Symptoms**: A symptom is a departure from normal function or feeling which is noticed by a patient, indicating the presence of disease or abnormality. A symptom is subjective, observed by the patient, and cannot be measured directly.

This page titled 17.6.3: Pneumocystis Pneumonia is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.5C: Pneumocystis Pneumonia** is licensed CC BY-SA 4.0.

17.6.4: Blastomycosis

Learning Objectives

- Describe the causes and symptoms of blastomycosis

Blastomycosis (also known as “North American blastomycosis,” “Blastomycetic dermatitis,” and “Gilchrist’s disease”) is a fungal infection caused by the organism Blastomyces dermatitidis. Endemic to portions of North America, blastomycosis causes clinical symptoms similar to histoplasmosis.

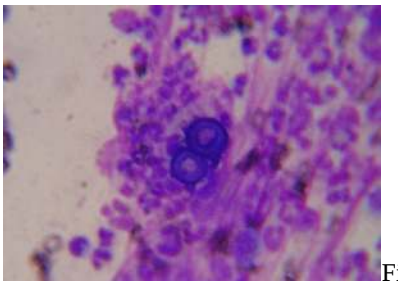


Figure: **Blastomycosis**: Blastomyces dermatitidis, the causative agent of blastomycosis.

Symptoms

Blastomycosis can present in one of the following ways:

- A flu-like illness with fever, chills, myalgia, headache, and a nonproductive cough which resolves within days
- An acute illness resembling bacterial pneumonia, with symptoms of high fever, chills, a productive cough, and pleuritic chest pain
- A chronic illness that mimics tuberculosis or lung cancer, with symptoms of low-grade fever, a productive cough, night sweats, and weight loss
- A fast, progressive, and severe disease that manifests as ARDS, with fever, shortness of breath, tachypnea, hypoxemia, and diffuse pulmonary infiltrates
- Skin lesions, usually asymptomatic, that appear as ulcerated lesions with small pustules at the margins
- Bone lytic lesions that can cause bone or joint pain.
- Prostatitis may be asymptomatic or may cause pain on urinating. Laryngeal involvement causes hoarseness.

Infection occurs by inhalation of the fungus from its natural soil habitat. Once inhaled in the lungs, Blastomycosis multiply and may disseminate through the blood and lymphatics to other organs, including the skin, bone, genitourinary tract, and brain. The incubation period is 30 to 100 days, although infection can be asymptomatic.

Diagnosis

Once suspected, the diagnosis of blastomycosis can usually be confirmed by demonstration of the characteristic, broad-based budding organisms in sputum or tissues by KOH prep, cytology, or histology. Tissue biopsy of skin or other organs may be required in order to diagnose extra-pulmonary disease. Blastomycosis is histologically associated with granulomatous nodules. Commercially available urine antigen testing appears to be quite sensitive in suggesting the diagnosis in cases where the organism is not readily detected. While culture of the organism remains the definitive diagnostic standard, its slow growing nature can lead to delays in treatment of up to several weeks.

Treatment

Itraconazole given orally is the treatment of choice for most forms of the disease. Ketoconazole may also be used. Cure rates are high, and the treatment over a period of months is usually well tolerated. Amphotericin B is considerably more toxic, and is usually reserved for immunocompromised patients who are critically ill and those with central nervous system disease. Fluconazole has also been tested on patients in Canada.

Key Points

- Infection occurs by inhalation of the fungus from its natural soil habitat.
- Once suspected, the diagnosis of blastomycosis can usually be confirmed by demonstration of the characteristic, broad-based budding organisms in sputum or tissues by KOH prep, cytology, or histology.
- Once inhaled in the lungs, Blastomycosis multiply and may disseminate through the blood and lymphatics to other organs, including the skin, bone, genitourinary tract, and brain.

Key Terms

- **fungal**: Of or pertaining to a fungus or fungi
- **Blastomycosis**: Blastomycosis is a fungal infection caused by the organism Blastomyces dermatitidis. Endemic to portions of North America, blastomycosis causes clinical symptoms similar to histoplasmosis.
- **inhalation**: The substance (medicament) which is inhaled.

This page titled 17.6.4: Blastomycosis is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.5D: Blastomycosis** is licensed CC BY-SA 4.0.

17.6.5: Other Fungi Involved in Respiratory Disease

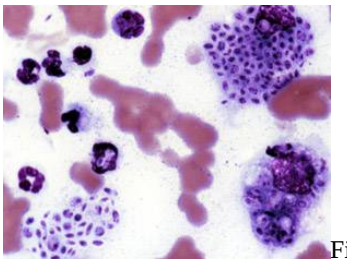
Learning Objectives

- Compare and contrast the various forms of sporotrichosis: cutaneous/skin, pulmonary and disseminated sporotrichosis

Sporotrichosis (also known as “Rose gardener’s disease”) is caused by the infection of the fungus *Sporothrix schenckii* . This fungal disease usually affects the skin, although other rare forms can affect the lungs, joints, bones, and even the brain. Because roses can spread the disease, it is one of a few diseases referred to as rose-thorn or rose-gardeners’ disease.

Because S. schenckii is naturally found in soil, hay, sphagnum moss, and plants, it usually affects farmers, gardeners, and agricultural workers. It enters through small cuts and abrasions in the skin to cause the infection. In cases of sporotrichosis affecting the lungs, the fungal spores enter through the respiratory pathways. Sporotrichosis can also be acquired from handling cats with the disease; it is an occupational hazard for veterinarians.

Sporotrichosis progresses slowly – the first symptoms may appear from one to 12 weeks (average three weeks) after the initial exposure to the fungus. Serious complications can also develop in patients who have a compromised immune system.

 Figure: **Sporotrichosis**: Cytologic preparation from a case of feline sporotrichosis; phagocytic cells show numerous variably-shaped yeast forms within.

Forms and symptoms of sporotrichosis include: cutaneous or skin sporotrichosis; pulmonary sporotrichosis; and disseminated sporotrichosis.

Cutaneous or skin sporotrichosis: This is the most common form of the disease. Symptoms include nodular lesions or bumps in the skin at the point of entry and also along lymph nodes and vessels. The lesion starts off small and painless, and ranges in color from pink to purple. Left untreated, the lesion becomes larger and looks similar to a boil. More lesions will appear, until a chronic ulcer develops. Usually, cutaneous sporotrichosis lesions occur in the finger, hand, and arm.

Pulmonary sporotrichosis: This rare form of the disease occurs when S. schenckii spores are inhaled. Symptoms include productive coughing, nodules and cavitations of the lungs, fibrosis, and swollen hilar lymph nodes. Patients with this form of sporotrichosis are susceptible to developing tuberculosis and pneumonia.

Disseminated sporotrichosis: this occurs when the infection spreads from the primary site to secondary sites in the body and develops into a rare and critical form. The infection can spread to joints and bones (called osteoarticular sporotrichosis) as well as the central nervous system and the brain (called sporotrichosis meningitis). The symptoms include weight loss, anorexia, and the appearance of bony lesions.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: ***CC BY-SA: Attribution-ShareAlike***

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- Histoplasmosis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Histoplasmosis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- fungus. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/fungus**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Boundless. **Provided by**: Boundless Learning. **Located at**: **www.boundless.com//microbiolo...histoplasmosis**. **License**: ***CC BY-SA: Attribution-ShareAlike***

- Chest%20X-ray%20acute%20pulmonary%20histoplasmosis%20PHIL%203954. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ch..._PHIL_3954.jpg**. **License**: ***Public Domain: No Known Copyright***
- Histoplasmosis%20capsulatum. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Hi...capsulatum.jpg**. **License**: ***Public Domain: No Known Copyright***
- Coccidioidomycosis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Coccidioidomycosis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- inhalation. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/inhalation**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- fungal. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/fungal**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Boundless. **Provided by**: Boundless Learning. **Located at**: **www.boundless.com//microbiolo...idioidomycosis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Chest%20X-ray%20acute%20pulmonary%20histoplasmosis%20PHIL%203954. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ch..._PHIL_3954.jpg**. **License**: ***Public Domain: No Known Copyright***
- Histoplasmosis%20capsulatum. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Hi...capsulatum.jpg**. **License**: ***Public Domain: No Known Copyright***
- Coccidioidomycosis 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Co...mycosis_01.jpg**. **License**: ***Public Domain: No Known Copyright***
- Pneumocystis pneumonia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Pneumocystis_pneumonia**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Boundless. **Provided by**: Boundless Learning. **Located at**: **www.boundless.com//microbiolo...ition/symptoms**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Boundless. **Provided by**: Boundless Learning. **Located at**: **www.boundless.com//microbiolo...stis-pneumonia**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Opportunistic. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/Opportunistic**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Chest%20X-ray%20acute%20pulmonary%20histoplasmosis%20PHIL%203954. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ch..._PHIL_3954.jpg**. **License**: ***Public Domain: No Known Copyright***
- Histoplasmosis%20capsulatum. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Hi...capsulatum.jpg**. **License**: ***Public Domain: No Known Copyright***
- Coccidioidomycosis 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Co...mycosis_01.jpg**. **License**: ***Public Domain: No Known Copyright***
- Pneumocystis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Pneumocystis.jpg**. **License**: ***Public Domain: No Known Copyright***
- Blastomycosis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Blastomycosis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- fungal. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/fungal**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Boundless. **Provided by**: Boundless Learning. **Located at**: **www.boundless.com//microbiolo.../blastomycosis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- inhalation. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/inhalation**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Chest%20X-ray%20acute%20pulmonary%20histoplasmosis%20PHIL%203954. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Chest_X-ray_acute_pulmonary_histoplasmosis_PHIL_3954.jpg**. **License**: ***Public Domain: No Known Copyright***
- Histoplasmosis%20capsulatum. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Histoplasmosis_capsulatum.jpg**. **License**: ***Public Domain: No Known Copyright***
- Coccidioidomycosis 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Co...mycosis_01.jpg**. **License**: ***Public Domain: No Known Copyright***
- Pneumocystis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Pneumocystis.jpg**. **License**: ***Public Domain: No Known Copyright***

- Blastomycosis cropped. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Bl...is_cropped.JPG**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Sporotrichosis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Sporotrichosis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- fungus. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/fungus**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Sporotrichosis. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/Sporotrichosis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Chest%20X-ray%20acute%20pulmonary%20histoplasmosis%20PHIL%203954. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Chest_X-ray_acute_pulmonary_histoplasmosis_PHIL_3954.jpg**. **License**: ***Public Domain: No Known Copyright***
- Histoplasmosis%20capsulatum. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Histoplasmosis_capsulatum.jpg**. **License**: ***Public Domain: No Known Copyright***
- Coccidioidomycosis 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Co...mycosis_01.jpg**. **License**: ***Public Domain: No Known Copyright***
- Pneumocystis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Pneumocystis.jpg**. **License**: ***Public Domain: No Known Copyright***
- Blastomycosis cropped. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Bl...is_cropped.JPG**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Feline sporotrichosis 4. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Fe...richosis_4.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***

Key Points

- In cases of sporotrichosis affecting the lungs, the fungal spores enter through the respiratory pathways.
- Sporotrichosis progresses slowly – the first symptoms may appear from one to 12 weeks (average three weeks) after the initial exposure to the fungus.
- Forms and symptoms of sporotrichosis include: cutaneous or skin sporotrichosis; pulmonary sporotrichosis; and disseminated sporotrichosis.

Key Terms

- **fungus**: Any member of the kingdom Fungi; a eukaryotic organism typically having chitin cell walls but no chlorophyll or plastids. Fungi may be unicellular or multicellular.
- **Sporotrichosis**: A disease caused by the infection of the fungus Sporothrix schenckii, usually affecting the skin, although other rare forms can affect the lungs, joints, bones, and even the brain. Because roses can spread the disease, it is often referred to as rose-thorn or rose-gardeners' disease.

This page titled 17.6.5: Other Fungi Involved in Respiratory Disease is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.5E: Other Fungi Involved in Respiratory Disease** is licensed CC BY-SA 4.0.

17.7: Fungal and Protozoan Diseases of the Digestive System

This page titled 17.7: Fungal and Protozoan Diseases of the Digestive System is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.10: Fungal and Protozoan Diseases of the Digestive System** is licensed CC BY-SA 4.0.

17.7.1: Ergot Poisoning

Learning Objectives

- List the causes and effects of ergot poisoning

Ergot poisoning is a type of illness associated with the ingestion of alkaloids produced by the fungi *Claviceps purpurea (C. purpurea)*. *Claviceps purpurea* is a fungus classified under the fungi genus *Claviceps*. This specific type of fungus is found on rye, and also on crops like wheat and barley. In addition, *Claviceps purpurea* can effect plants and crops that are typically considered forage plants. Thus, this type of fungus can also result in diseases within livestock.

The life cycle of *C. purpurea* begins when an ergot kernel, called a sclerotium, infects the host. The fungi continues to undergo proliferation and destroys the plant ovary. The first stage of ergot infection is a white soft tissue, called Sphacelia segetum, that drops out of the host. The white soft tissue contains asexual spores which infect additional host plants. This tissue, present within the host, is then converted into a hard Sclerotium clavus within the husk. At this specific stage, the alkaloids and lipids accumulate.


Figure: **Example of Ergot on Wheat**: This image shows ergot on a wheat spike.

The alkaloids, responsible for the ergot poisoning, are naturally occurring compounds that are mainly comprised of basic nitrogen atoms. Alkaloids are produced within various organisms as a secondary metabolite. Secondary metabolites are most commonly produced in plants as a defense system. The alkaloids produced by fungi are often toxic. Specifically, the alkaloid produced by *Claviceps purpurea* is ergoline based.

In cases of ergot poisoning (also known as ergotoxicosis or traditionally, Saint Anthony's Fire) alkaloids accumulate in the system due to the consumption of contaminated grain products. The symptoms which present in individuals with ergot poisoning can be classified as convulsive symptoms and gangrenous symptoms. The convulsive symptoms include seizures and effects on the central nervous system that range from hallucinations to psychotic episodes. The gangrenous symptoms are a result of vasoconstriction induced by the alkaloids. Peripheral systems, such as fingers and toes, are typically affected. More recently, ergot poisoning has been associated with an increased intake of ergot-based drugs. These drugs include those that promote vasoconstriction for treating migraines and Parkinson's disease.

Key Points

- Ergot fungi typically infect rye, wheat and forage plants.
- Ingestion of the alkaloid toxins produced by the fungi can result in ergot poisoning in humans and foraging animals.
- Ergot poisoning can have either convulsive central nervous system effects or gangrenous symptoms caused by vasoconstriction effects.

Key Terms

- **alkaloids**: A class of organic heterocyclic bases.
- **gangrenous**: To be afflicted with gangrene.

This page titled 17.7.1: Ergot Poisoning is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.10A: Ergot Poisoning** is licensed CC BY-SA 4.0.

17.7.2: Aflatoxin Poisoning

Learning Objectives

- Summarize the causes and effects of alfatoxin poisoning

Aflatoxins are categorized as mycotoxins that are typically produced by species of *Aspergillus*. Aflatoxins, although only synthesized by a few *Aspergillus* species, are considered to be one of the most important mycotoxins identified to date. Both *Aspergillus flavus* and *Aspergillus parasiticus* are well known for their production of aflatoxins. Aflatoxins are most commonly transmitted to humans through the diet. Aflatoxins grow on whole grains and contaminate food supplies during processing, storage, or transport when there are favorable conditions for mold growth, specifically for the *Aspergillus* species.


Figure: **Aspergillus flavus**: A species of Aspergillus that causes aflatoxin poisoning.

Aflatoxin poisoning, or aflatoxicosis, occurs when there is ingestion of aflatoxin contaminated foods. Upon ingestion or exposure to aflatoxin, it is common to see injury to the liver. Aflatoxicosis is a primarily hepatic disease, as the liver is the target organ for this toxin in mammals. Although the liver demonstrates the ability to metabolize the ingested aflatoxins, the intermediate formed is a reactive epoxide or a less harmful hydroxylated form referred to as M1. There have been various studies stating that metabolic activation of aflatoxins is required for the aflatoxin to exert its carcinogenic effects. These metabolites are harmful to the liver and have been implicated in liver cancer development. The aflatoxins produced by these *Aspergillus* species have been show to produce adducts (altered forms of DNA). These adducts are now used as a diagnostic factor to test for aflatoxin exposure by testing blood and urine.

Aflatoxin poisoning or aflatoxicosis is rarely diagnosed in developed countries but continues to be an issue in underdeveloped countries. In developed countries, commercial crops are screened for the presence of aflatoxins. However, in underdeveloped or developing countries, screening methods are lacking, or are in the process of being introduced. Interestingly, a rise in homegrown food has been correlated with a slight increase in aflatoxin exposure via diet.

Aflatoxin poisoning can be diagnosed as either acute or chronic. In cases of acute aflatoxicosis, an individual has been exposed to moderate to high levels of aflatoxins. Acute aflatoxicosis is characterized by symptoms such as hemorrhaging; acute liver damage and issues with digestion; and absorption and metabolism of nutrients. In cases of chronic aflatoxicosis, an individual has been exposed to low to moderate levels of aflatoxins. Chronic aflatoxicosis is characterized by symptoms such as dysfunctional food conversion and slow growth rates.

Key Points

- Aspergillus flavus and Aspergillus parasiticus are two commonly known species of Aspergillus that can aflatoxin poisoning.
- Aflatoxin poisoning can result in either acute aflatoxicosis, which is a result of moderate to high level ingestion; or chronic aflatoxicosis, which results from ingestion of low to moderate levels of aflatoxins.
- Aspergillus species which cause aflatoxin poisoning are often found in crops in underdeveloped countries, due to lack of detection techniques and inadequate harvesting and storage.

Key Terms

- **mycotoxins**: a substance produced by a mold or fungus.

This page titled 17.7.2: Aflatoxin Poisoning is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.10B: Aflatoxin Poisoning** is licensed CC BY-SA 4.0.

17.7.3: Giardiasis

Learning Objectives

- Summarize the life cycle and route of transmission for Giardia lamblia

Giardiasis is a protozoan disease caused by *Giardia lamblia*. Giardiasis, referred to as beaver fever, is a common cause of gastroenteritis worldwide. The protozoa, *Giardia lamblia*, also referred to as *Giardia intestinalis* or *Giardia duodenalis*, infects humans via the fecal-oral route and is also suspected to be zoonotic. The organism is commonly found in soil, food, or water that has been contaminated with fecal matter from infected humans or animals. Beavers typically spread the parasite in their fecal matter in rivers and streams hence, giardiasis is commonly referred to as beaver fever. Individuals susceptible to infection by *Giardia lamblia* are those who come in frequent contact with individuals already infected. Travelers that spend time in wilderness area are at an increased risk due to ingestion of contaminated food or water sources and a lack of medical care or supplies.

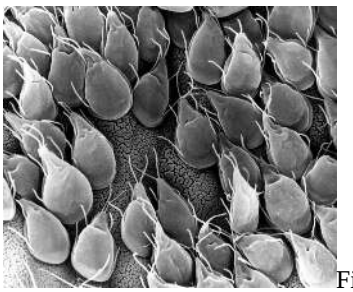


Figure: **Giardia infecting a small intestine**: A scanning electron micrograph of the surface of the small intestine of a gerbil infested with Giardia sp. protozoal, present in the trophozoite stage.

The life cycle, structure, and organization of *Giardia lamblia* promotes its survival for long periods of time outside the body. The organism itself is protected by an outer shell that provides protection against numerous harsh environments. In addition, the shell provides protection against disinfectants including chlorine. The cysts and trophozoites, found in the fecal matter, are extremely resistant to harsh environments. It is the cysts that are ingested and passed from exposure to contaminated food, water, or by the fecal-oral route. Once in the host, the trophozoites multiply via binary fission. They can either remain free within the lumen or attach to the mucosa by a sucking disk. Once the parasites move towards the colon, the encystation phase occurs and the cysts are infectious when passed in the stool.

Giardiasis is characterized as a disease of the gastrointestinal system. The symptoms include from fever, diarrhea, hematuria, stomach cramping, vomiting, flatulence, and loose stool. The symptoms are typically present one to two weeks post infection and can disappear and reappear cyclically. The pathogenecity of *Giardia lamblia* is characterized by its ability to coat the inside of the intestinal wall and inhibit nutrient absorption. The ability of the protozoan to block nutrient absorption can result in vitamin B12 deficiency. Additionally, a development of lactose intolerance is often associated with giardiasis infection.

Key Points

- Giardia lamblia is transmitted by exposure or ingestion of fecal contaminated sources such as soil, food, and water.
- Giardiasis is a common worldwide cause of gastroenteritis.
- The structure and life cycle of Giardia lamblia allow for survival in harsh environments and resistance against numerous types of disinfectants.

Key Terms

- **giardiasis**: an infectious diarrheal disease caused by the Giardia lamblia parasite
- **zoonotic**: of or relating to zoonosis, the transmission of an infectious disease between species.
- **hematuria**: The presence of blood in the urine.

This page titled 17.7.3: Giardiasis is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.10C: Giardiasis** is licensed CC BY-SA 4.0.

17.7.4: Cryptosporidiosis

Learning Objectives

- Outline the life cycle of Cryptosporidium

Cryptosporidiosis is a type of parasitic disease caused by the parasite *Cryptosporidium*. Cryptosporidiosis is typically spread through the fecal-oral route and can be spread through contaminated water as well. Cryptosporiodiosis is one of most common waterborne diseases identified worldwide. The transmission of *Cryptosporidium* is based on successful ingestion of oocysts which are able to implant and infect the epithelial tissue of the intestine, hence, the gastrointestinal symptoms associated with cryptosporidiosis.

Cryptosporidium is classified as a protozoan within the Phylum Apicomplexa. Other pathogens classified in this phylum include the malaria parasite and the parasite that causes toxoplasmosis. The life cycle of *Cryptosporidium* allows for growth in a single host. The spore phase of the life cycle, also referred to as the oocyst stage, is the stage that allows survival of the pathogen in numerous harsh environments. The oocyst allows for survival against harsh chemicals including harsh disinfectants such as chlorine. The life cycle is characterized by the presence of both an asexual and sexual stage. The oocysts, once ingested, excyst within the small intestine and release sporozoites which attach to the microvilli. The sporozoites then develop into trophozoites and undergo asexual reproduction via schizogony. The trophozoites then develop into Type 1 and Type 2 merozoites which can either cause auto infection (Type 1) or undergo releasal and attach the epithelial cells (Type 2). Once released and attached, they will either develop in macrogamonts or microgamonts which correlate with male and female forms. Sexual reproduction occurs than zyogotes are developed. The zygote further develops into the oocyst which can either reinfect the host by rupturing and releasing sporozoites or be excreted into the environment.

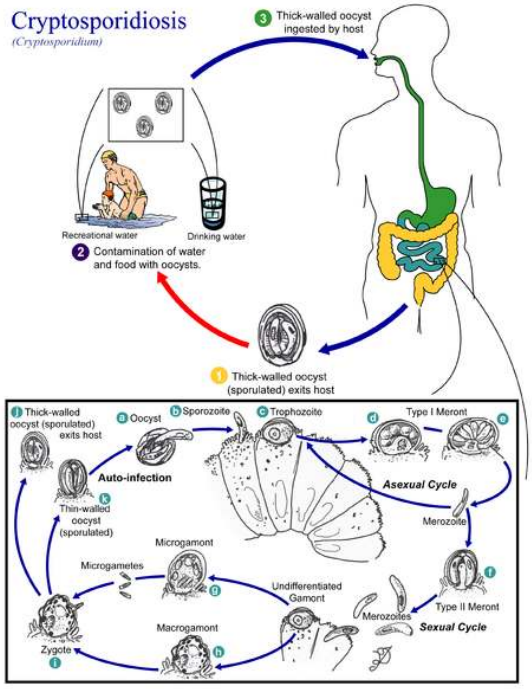


Figure: **Life cycle of Cryptosporidium**: An overview of the life cycle of Cryptosporidium.

The major symptom associated with individuals infected with *Cryptosporidium* is diarrhea. However, cryptosporidiosis is prevalent in immunocompromised individuals, such as those infected with the HIV virus. The symptoms of cryptosporidiosis in these cases are much more severe and can be fatal. The oocysts can initiate infections by attaching to the brush border of the small intestine and attacking the epithelial cells. Additional symptoms associated with cryptosporidiosis include abdominal cramping, malnutrition, weight loss, and nausea.

Key Points

- Cryptosporidium is commonly transmitted through food and water that has been contaminated with the feces of an infected individual.
- Cryptosporidium is commonly found in immunocompromised individuals that exhibit symptoms associated with this disease such as acute or persistent diarrhea.
- The life cycle of Cryptosporidium involves both asexual and sexual reproduction.

Key Terms

- **excyst**: The break down of a cyst wall.
- **schizogony**: A form of asexual reproduction in protozoans characterized by multiple divisions.

This page titled 17.7.4: Cryptosporidiosis is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.10D: Cryptosporidiosis** is licensed CC BY-SA 4.0.

17.7.5: Cyclospora Diarrheal Infection

Learning Objectives

- Outline the life cycle of Cyclospora cayetanensis

Cyclospora diarrheal infection, commonly referred to as travelers diarrhea or cyclosporiasis, is caused by a specific species of *Cyclospora*. The protozoan that are categorized as cyclospora are defined by the spherical shape of the sporocysts. Specifically, *Cyclospora cayetanensis* is the species associated with the disease in both humans and primates. Cyclospora can be transmitted by consuming contaminated food or water. In 2012, cyclospora caused about 500 infections in 2012 in the US from a salad mix imported from Mexico and used in restaurants in Texas and Arkansas.

Life Cycle of Cyclospora

The life cycle of Cyclospora begins when the host is exposed and ingests the pathogen either in its oocyst or spore form. The oocyst is comprised of sporocytes which contain sporozoites. Upon release of the sporozoites, the epithelial cells of the intestine are penetrated. Within the intestinal cells, the sporozoites undergo multiple fission and develop into meronts which contain merozoites. The merozoites then undergo division and produce micro- and macro-gametes representing male and female gametes, respectively.

These gametes then reproduce and result in the formation of oocysts. It is the oocysts which pass through the intestinal tract and are released into the feces. The oocysts demonstrate the ability to undergo sporulation in a crop and water host as well beginning with the oocyst stage. It is during the oocyst stage that cyclospora exhibit a high resistance to disinfectants.

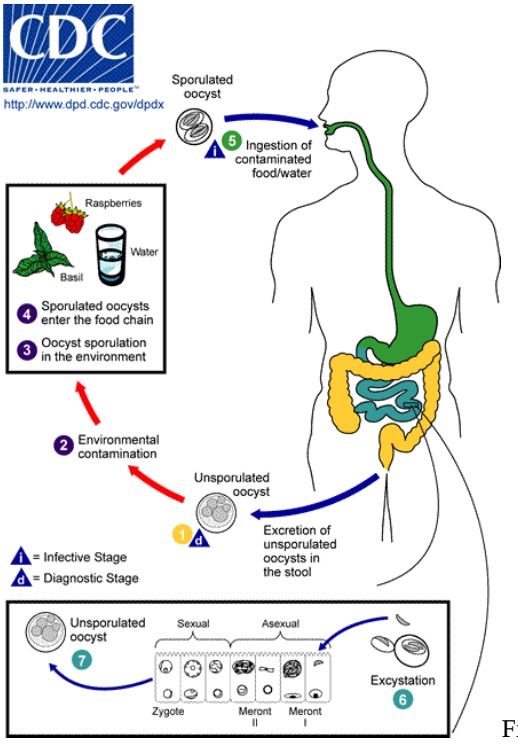


Figure: **Life cycle of cyclospora**: Cyclosporiasis (Cyclospora cayetanesis) When freshly passed in stools, the oocyst is not infective (1) (thus, direct fecal-oral transmission cannot occur; this differentiates Cyclospora from another important coccidian parasite, Cryptosporidium). In the environment (2), sporulation occurs after days or weeks at temperatures between 22°C to 32°C, resulting in division of the sporont into two sporocysts, each containing two elongate sporozoites (3). Fresh produce and water can serve as vehicles for transmission (4) and the sporulated oocysts are ingested (in contaminated food or water) (5). The oocysts excyst in the gastrointestinal tract, freeing the sporozoites which invade the epithelial cells of the small intestine (6). Inside the cells they undergo asexual multiplication and sexual development to mature into oocysts, which will be shed in stools (7). The potential mechanisms of contamination of food and water are still under investigation.

Symptoms of Cyclospora

The symptoms associated with this disease are categorized as gastroenteritis based issues. The symptoms range from watery, loose stool, weight loss, cramping, fatigue, vomiting, fever and nausea. The symptoms can be extremely severe if presented in an immunocompromised patient, such as a patient living with AIDS. The transmission of cyclospora to humans most often occurs by ingesting contaminated foods. In regions of the world where there is lack of health regulations, the chances of cyclospora exposure is increased. Often times, the contaminants include fresh fruits and vegetables which have been exposed to contaminated soil. Individuals exposed to these pathogens in these of regions are at high risk for developing cyclosporiasis, hence, the origin of the commonly known name, traveler's diarrhea.

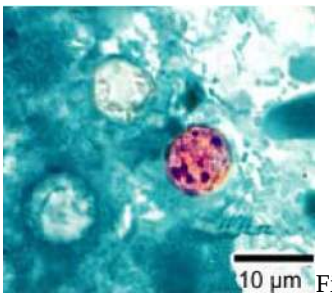


Figure: **Cyclospora cayetanensis oocysts**: A photomicrograph of oocysts from Cyclospora cayetanensis derived from a fresh stool sample.

Key Points

- The life cycle of Cyclospora begins as the host ingests the oocyst form.
- Cyclospora is transmitted through fecal matter and is commonly found on contaminated fruits and vegetables in countries or areas with a lack of stringent health regulations.
- Cyclospora causes gastroenteritis with symptoms ranging from diarrhea to loss of appetite, weight loss, cramping, nausea and fatigue.

Key Terms

- **meronts**: After infecting a host cell, a trophozoite increases in size and during this process, the organism is referred to as a meront.
- **sporocysts**: a cysts that develops from a sporoblasts and results in the production of sporozoites.

This page titled 17.7.5: Cyclospora Diarrheal Infection is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.10E: Cyclospora Diarrheal Infection** is licensed CC BY-SA 4.0.

17.7.6: Amoebic Dysentery (Amoebiasis)

Learning Objectives

- Outline the life cycle of Entamoeba histolytica

Amoebic dysentery, also referred to as amoebiasis, is caused by the ameoba *Entamoeba histolytica.* Dysentery is characterized as an inflammatory disorder of the intestine that results in severe diarrhea containing both mucus and blood in the feces, often accompanied with fever and abdominal pain.

The route of transmission for ameobic dysentery is the fecal-oral route. Transmission and infection occur upon exposure or ingestion of contaminated food and water. The infective cysts are passed via infected stool. The ameoba also demonstrates the ability to spread as free amoebae or trophozoites, meaning the cysts are not absolutely necessary; however, these states do not survive long outside of the host.

Ameobic dysentery is seen in both developing and industrialized countries, although it is most common in tropical areas. Ameobic cysts are often found in areas of the world where the use of human feces for fertilizer is common, often referred to as 'night soil'. Upon ingestion of contaminated foods or water, the cysts will move into the intestinal area. These cysts are protected from stomach acids and are able to evade destruction. Once in the intestine, the cyst breaks open and releases the amoebas which then burrow into and damage the intestinal walls.

The amoebae or trophozoites are able to divide via binary fission and and produce cysts. If they are passed in the feces as is, instead of developing into cysts, their survival rate decreases as they are unable to survive in harsh environments. Interestingly, individuals can be asymptomatic if infected with trophozoites and can function as carriers by passing cysts in their stool.

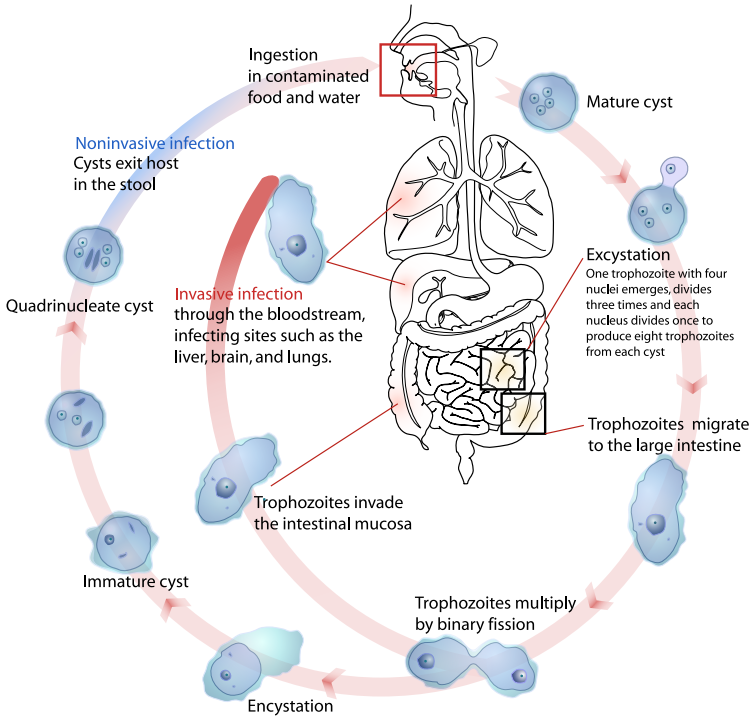


Figure: **Life Cycle of Entamoeba histolytica**: An overview of the life cycle of E. histolytica, the source of amoebic dysentery.

Symptoms of individuals infected with *Entamoeba histolytica* include ulcers, abdominal cramps, diarrhea, bloody stools, liquid stools, fever and vomiting.

Key Points

- Amoebiasis is transmitted via food or water contaminated with fecal matter from an infected individual.

- The pathogen, Entamoeba histolytica, is mainly found in tropical areas and is protected from degradation and destruction by its protective shell, formed during its cyst stage.
- The cyst stage is typically passed in the feces and then ingested to cause infection.
- The amoebas are able to burrow into the walls of the intestines, causing damage.

Key Terms

- **trophozoites**: A protozoan in the feeding stage of its life cycle.

This page titled 17.7.6: Amoebic Dysentery (Amoebiasis) is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.10F: Amoebic Dysentery (Amoebiasis)** is licensed CC BY-SA 4.0.

17.7.7: Legionellosis

Learning Objectives

- Discuss the mode of infection for the bacteria Legionella

Legionellosis, commonly referred to as Legionnaire's disease, is caused by the pathogenic, gram-negative bacteria *Legionella*. It is characterized by flu- and pneumonia -like symptoms, including fevers and chills. In advanced stages of the disease, there are gastrointestinal and nervous system issues which result in diarrhea and nausea.

Legionella are a type of bacterium that reside within amoebae in the natural environment. The specific species most associated with legionellosis is *Legionella pneumophilia*, an aquatic organism. Legionella transmission occurs via aerosols and infection occurs when upon inhalation of the bacteria. After being inhaled, the bacteria infect the *macrophages* of the alveolar and exploit the host machinery to create an environment that promotes bacterial replication. However, the bacteria are not spread from one person to another. In the 1970s, the CDC investigated a large outbreak of legionellosis at Baptist Hospital that was spread through its air conditioner.



Figure: **Legionella pneumophila**: A microscopic image of Legionella pneumophila, the cause of Legionellosis.

Individuals infected with legionellosis have similar symptoms as those diagnosed with pneumonia. Symptoms include high fevers, chills, cough, muscle aches and headaches. For a diagnosis of legionellosis, x-rays and diagnostic tests are used to identify the bacteria. Individuals particularly at risk are older individuals, those immunocompromised or with chronic lung disease.

Legionellosis can take on two distinct forms commonly referred to as legion fever or pontiac fever. Legion fever resembles acute influenza and is the more severe form of the disease, characterized by high fever and pneumonia. Pontiac fever is a milder version and results in mild respiratory illness without the development of pneumonia.

Common sources of Legionella include swimming pools, cooling towers, hot-water systems such as spas, fountains, freshwater ponds and creeks. As seen, the major source for Legionella bacteria is infected water. The bacteria can become suspended in water droplets which are then inhaled into the lungs.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: *CC BY-SA: Attribution-ShareAlike*

Key Points

- Legionella pneumophila is an aquatic organism that is transmitted via aerosols.
- Legionellosis is caused by exposure to contaminated water sources including water towers, spas, fountains, swimming pools and cooling towers.
- Legionellosis-infected individuals have pneumonia -like symptoms with moderate to high fever ranges, chills and a dry cough.

Key Terms

- **macrophages**: A type of white blood cell that targets foreign material, including bacteria and viruses.
- **Legionnaire's disease**: The more severe form of legionellosis which produces high fever and pneumonia.

This page titled 17.7.7: Legionellosis is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.10G: Legionellosis** is licensed CC BY-SA 4.0.

17.8: Helminthic Diseases of the Digestive System

This page titled 17.8: Helminthic Diseases of the Digestive System is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.12: Helminthic Diseases of the Digestive System** is licensed CC BY-SA 4.0.

17.8.1: Tapeworms

Learning Objectives

- Compare and contrast the routes of transmission for various tapeworms and describe their life cycles

Tapeworms are characterized as adult parasitic flatworms that target and infect the digestive tract. Typically, transmission occurs by ingestion of a live tapeworm larva which is found in undercooked or contaminated food. Once inside the digestive tract, the larvae can then grow and develop into a large tapeworm. There are various types of tapeworms identified to date that are capable of infecting humans. A few common tapeworms include the pork tapeworm (*Taenia solium*), the beef tapeworm (*Taenia saginata*), and the fish tapeworm (*Diphyllobothrium spp*.).

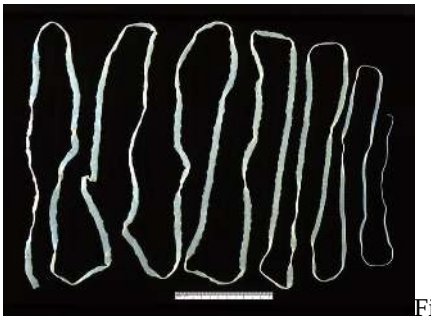
Taenia solium

Taenia solium, the pork tapeworm, infects both pigs and humans. Humans are typically infected by ingesting infected pork. *Taenia solium* will target the intestinal area in humans. Using the four suckers and two rows of hooks present on its scolex, it lodges itself against the intestinal wall. Once anchored, the tapeworm continues to grow in the intestine and will pass its eggs through the feces. When *Taenia solium* is in its larval stage, it is referred to as a cysticercus and can cause cysticercosis. Cysticercosis occurs when the cysticerci reach the central nervous system and cause neurological issues.


Figure: ***Scolex of the Taenia solium****: An image of the scolex of the Taenia solium.*

Taenia saginata

Taenia saginata, the beef tapeworm, is capable of infecting both cattle and humans. Infection by *Taenia saginata* is referred to as taeniasis in humans and occurs by ingestion of contaminated meat that has been improperly handled. Taeniasis is caused by the ability of the tapeworm to lodge itself in the small intestine of the human and release fertilized eggs through the feces. The eggs can then infect cattle upon ingestion. Upon infection of the cattle, the fertilized eggs will develop into zygotes which will exit the digestive tract and enter into the circulatory system. The larval stages will then form cysts, referred to as Cysticercus bovis, within the muscular system of the cattle. Therefore, if humans ingest under prepared meat with cysts, the cysts will break open into the digestive system and develop into an adult tapeworm in the human host.


Figure: ***Tapeworm****: An adult Taenia saginata.*

Diphyllobothrium spp.

Diphyllobothrium spp, the fish tapeworm, encompasses various species that can infect humans upon ingestion of under cooked or raw fish. For example, these tapeworms include those found on broad fish and salmon. Interestingly, only a few species of these tapeworms are found to infect humans on a frequent basis. The tapeworms found in fish exhibit the ability to also infect canines, felines, bears, and mussels.

The life cycle for fish tapeworms includes movement through numerous hosts. The mammal host is considered the definitive host as this is the site of worm reproduction. The immature eggs are passed through the feces of the mammal host and then infect a freshwater host. This freshwater host is considered to be the intermediate host. The intermediate host is then ingested by a second intermediate host which includes the fish. The larvae, which developed in the first intermediate host, then migrate out into the flesh of the fish (the second intermediate host). The larvae develop into a more mature form and constitute the infective stage for the definitive host. It is important to note that many second intermediate hosts are ingested by larger predator species that are utilized as a food source for humans. Therefore, it is not necessary for humans to directly eat the second intermediate host in order to be infected.

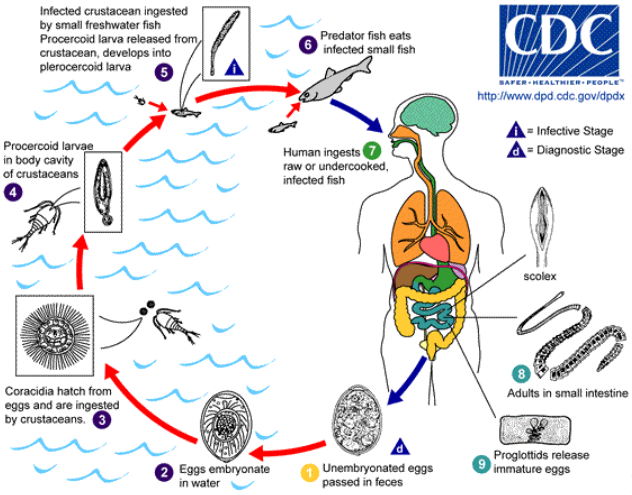


Figure: ***Diphylloborthrium latum life cycle****: Overview of the life cycle of Diphylloborthrium latum. Note the various hosts which are necessary for successful transmission.*

Key Points

- There are numerous types of tapeworms capable of infecting humans including beef, pork, and fish tapeworms.
- Taenia solium, the pork tapeworm, are passed via infected feces to the pig host but requires ingestion of under cooked pork by a human to ensure transmission.
- Taenia saginata, the beef tapeworm, are passed to humans by ingesting under cooked or raw beef that has been infected with the cyst stage in the life cycle.
- Diphyllobothrium spp, the fish tapeworm, requires multiple hosts to successfully infect a human host.

Key Terms

- **scolex**: The “head” of the tapeworm that contains suckers and rows of hooks by which it attaches itself to the host.

This page titled 17.8.1: Tapeworms is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.12A: Tapeworms** is licensed CC BY-SA 4.0.

17.8.2: Hydatid Disease

Learning Objectives

- Outline the life cycle of Echinococcus granulosus

Hydatid disease, commonly referred to as echinococcosis, is a result of infection by the tapeworm included in the *Echinococcus spp*. *Echinococcus multilocularis* results in alveolar echinococcosis and *Echinococcus vogeli* can cause polycystic echinococcosis. In individuals that develop alveolar echinococcosis, which is extremely rare, cysts develop and grow within the alveolar, liver, lungs, and brain. In the cases of alveolar echinococcosis, the parasite responsible, *Echinococcus multilocularis*, is associated with dogs, cats, wolves and most commonly, foxes, serving as the definitive hosts. The intermediate hosts include small rodents. In individuals that develop polycystic echinococcosis, there is the development of slow growing cysts within the body that exhibit the capability to infiltrate surrounding areas. Cysts are typically found in the liver and in the thorax or abdominal cavity. The parasite responsible for polycystic echinococcosis, *Echinococcus vogeli*, uses dogs or bush dogs as a definitive host and rodents as an intermediate hosts.

Echinococcus granulosus is a tapeworm found in dogs, who function as the definitive host, as well as sheep, cattle, goats, and pigs who serve as intermediate hosts. *Echinococcus granulosus* are capable of infecting humans, resulting in hydatid disease, and cause slowly enlarging cysts that develop in vital organs such as the liver or lungs, also referred to as cystic echinococcosis. However, the growth of these cysts are slow and may go unnoticed for a significant duration of time. This form of echinococcosis is more prevalent and commonly found in humans. The adult *Echinococcus granulosus* targets the small bowel of the definitive hosts and release eggs through the feces. After ingestion by the intermediate hosts, the eggs will hatch and penetrate the intestinal wall. The exiting of the intestinal wall results in circulation of oncospheres that will target various organs, including the liver and lungs. The oncospheres undergo further growth and form cysts. The definitive host will then become infected upon ingestion of the cyst-containing organs of the infected intermediate host. It is within the definitive host that the cyst will develop into the adult stage and the cycle continues and repeats.

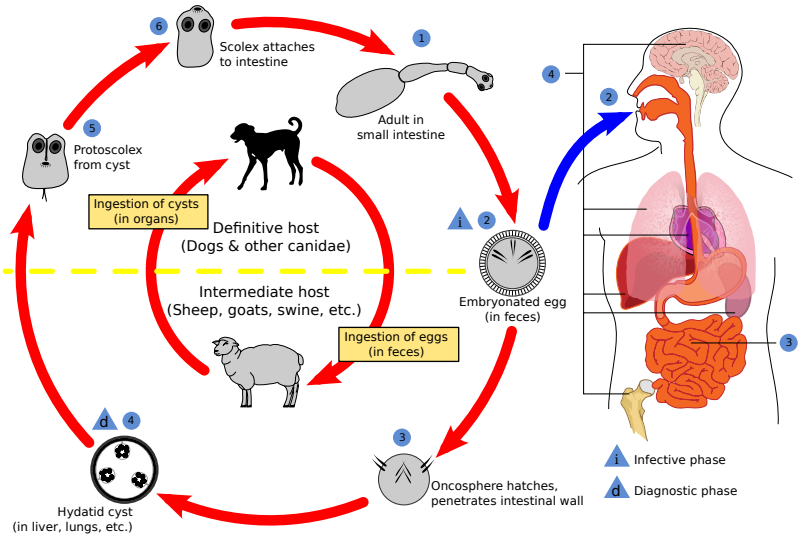


Figure: ***Overview of the Echinococcus life cycle****: A general overview of the various hosts and steps involved in the life cycle of Echinococcus species.*

Hydatid disease is characterized by the growth of these cysts into the adult stage for the tapeworm. Individuals infected with Echinococcus species that develop hydatid disease may not develop symptoms for many years after infection. However, if symptoms develop, it may present in the form of pain or discomfort due to the growing cysts in the upper abdominal regions. Additionally, rupture of fluid within the cysts can result in various medical issues including allergic reactions or death.

Key Points

- *Echinococcus granulosus* causes hydatid disease, or cystic echinococcus and causes slowly enlarging cysts to develop in vital organs.
- *Echinococcus multilocularis* results in alveolar echinococcosis and *Echinococcus vogeli* can cause polycystic echinococcosis.
- Individuals infected with *Echinococcus* species who develop hydatid disease may not develop symptoms for many years after infection.

Key Terms

- **echinococcosis**: a parasitic disease of both animals and humans, also known as hydatid disease.

This page titled 17.8.2: Hydatid Disease is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.12B: Hydatid Disease** is licensed CC BY-SA 4.0.

17.8.3: Nematodes

Learning Objectives

- Compare and contrast mechanisms of infection for the parasitic nematodes: *Ascaris lumbricoides* and *Enterobius*

Nematodes, or roundworms, are the most diverse phylum of pseudocoelomates and one of the most diverse animal phyla. Nematodes are characterized by the presence of a tubular digestive system with openings at both ends. They can be found in various ecosystems ranging from the polar regions to the tropics, fresh to marine water and various terrestrial environments ranging from mountains, deserts and oceanic floors. Nematodes are also capable of exhibiting parasitic behavior that contribute to digestive system diseases. Analysis of parasitic nematodes reveals the presence of specific body structures which promote parasitic behaviors such as ridges, rings or bristles that allow for attachment. Parasitic nematodes that commonly infect humans include ascarids (*Ascaris*), pinworms (*Enterobius*), whipworms (*Trichuris trichiura*), filarias and hookworms. The following is a brief overview of two of these types of roundworms, including *Ascaris* and *Enterobious*.

Ascariasis

Ascariasis is a disease that is caused by the parasitic roundworm *Ascaris lumbricoides*. Ascariasis is commonly found in tropical and sub-tropical regions and is transmitted by ingesting food contaminated with *Ascaris* eggs that are typically present in the feces of an infected individual. Upon ingestion of *Ascaris* eggs, the larvae continue development and hatch within the intestine of the host. The larvae burrow through the intestinal wall and begin circulation in the system and migrate to the lungs. Once they have migrated to the lungs, the larvae break into the alveoli and continue to move through the trachea and esophagus where they are eventually coughed up and swallowed. For a second time, the larvae enter into the intestine and mature into adult worms. Individuals affected with ascariasis can be asymptomatic or suffer from visceral damage due to the travel of the larvae through the body. The presence of the worms within the intestine may also result in malabsorption or intestinal blockage.

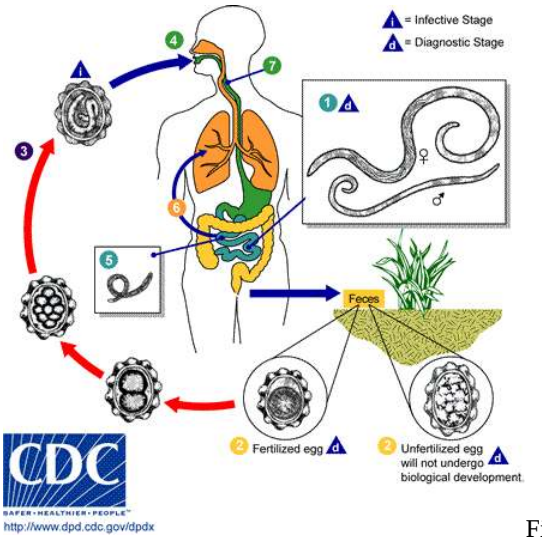


Figure: **Ascariasis Life Cycle**: An overview and summary of the life cycle leading to Ascariasis.

Enterobius

Enterobius, referred to as pinworm, is a type of parasitic nematode that is commonly found in the intestine of children. This infection is often called enterobiasis. The entire life cycle of the pinworm occurs within the human gastrointestinal tract. The life cycle begins with ingestion or insertion of eggs in the anus that have been transmitted via human-to-human contact. The life cycle of the *Enterobious* ends with eggs laid in the anus and transfered to surfaces that come in contact with this region, such as fingernails, hands, night-clothing and bed linens. Infection by pinworm is more prevalent in children due to their behaviors. Upon infection with eggs, they travel to the small intestine and hatch. The pinworm larvae will then migrate towards the colon and undergo molting which allows for further development. After two molt cycles, the larvae have developed into adults. The pinworms

exhibit the ability to mate in the small intestine. Shortly after mating, the male worms die and are passed out via the feces. However, the female pinworms will attach to the mucus and wait for the egg-laying process to begin. The egg-laying process begins with the migration of the females towards the rectum. The eggs, which are covered with a sticky covering, are then released and deposited on the outside or near the anus. The cycle begins again once eggs are ingested and infect an additional host.

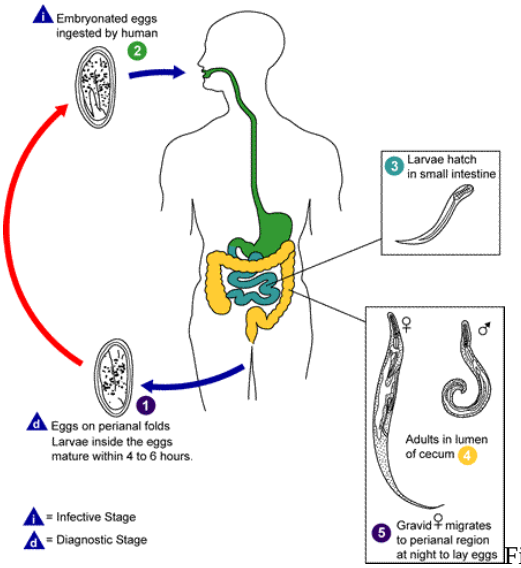


Figure: ***Overview of the pinworm life cycle****: Overview of the pinworm life cycle, specifically Enterobius vermicularis.*

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: ***CC BY-SA: Attribution-ShareAlike***

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- Helminths, Soil-Transmitted. **Provided by**: Centers for Disease Control and Prevention. **Located at**: **wwwnc.cdc.gov/travel/yellowbo...intestinal.htm**. **License**: ***Public Domain: No Known Copyright***
- Tapeworm infection. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Tapeworm_infection**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Taenia saginata. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Taenia_saginata**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Taenia solium. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Taenia_solium**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Fish tapeworm. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Fish_tapeworm**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Parasitic worm. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Parasitic_worm**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Parasites: About Parasites. **Provided by**: Centers for Disease Control and Prevention. **Located at**: **http://www.cdc.gov/parasites/about.html**. **License**: ***Public Domain: No Known Copyright***
- Taenia saginata. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Taenia_saginata**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- scolex. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/scolex**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Taenia solium scolex. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ta...ium_scolex.JPG**. **License**: ***Public Domain: No Known Copyright***
- D latum LifeCycle. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:D_..._LifeCycle.gif**. **License**: ***Public Domain: No Known Copyright***

- Taenia saginata adult 5260 lores. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...5260_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- Echinococcosis. **Provided by**: Centers for Disease Control and Prevention. **Located at**: **wwwnc.cdc.gov/travel/yellowbo...nococcosis.htm**. **License**: ***Public Domain: No Known Copyright***
- Parasites - Echinococcosis: Biology. **Provided by**: Centers for Disease Control and Prevention. **Located at**: **http://www.cdc.gov/parasites/echinoc...s/biology.html**. **License**: ***Public Domain: No Known Copyright***
- Parasites - Echinococcosis. **Provided by**: Centers for Disease Control and Prevention. **Located at**: **http://www.cdc.gov/parasites/echinococcosis/**. **License**: ***Public Domain: No Known Copyright***
- Parasites - Echinococcosis: Cystic Echinococcosis (CE) FAQs. **Provided by**: Centers for Disease Control and Prevention. **Located at**: **http://www.cdc.gov/parasites/echinoc...o/ce-faqs.html**. **License**: ***Public Domain: No Known Copyright***
- Echinococcosis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Echinoc...Echinococcosis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Echinococcosis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Echinococcosis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Alveolar echinococcosis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Alveolar_echinococcosis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Echinococcosis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Echinococcosis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Echinococcosis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Echinoc...Echinococcosis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- echinococcosis. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/echinococcosis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Taenia solium scolex. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Ta...ium_scolex.JPG**. **License**: ***Public Domain: No Known Copyright***
- D latum LifeCycle. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:D_..._LifeCycle.gif**. **License**: ***Public Domain: No Known Copyright***
- Taenia saginata adult 5260 lores. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...5260_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- File:CDC Echinococcus Life Cycle.svg - Wikipedia, the free encyclopedia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/w/index.php?...cle.svg&page=1**. **License**: ***Public Domain: No Known Copyright***
- **Provided by**: U.S. Food and Drug Administration. **Located at**: **www.fda.gov/food/foodsafety/f.../ucm070800.htm**. **License**: ***Public Domain: No Known Copyright***
- Pinworms. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Pinworms**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- **Provided by**: United States Department of Agriculture. **Located at**: **soils.usda.gov/sqi/concepts/s...nematodes.html**. **License**: ***Public Domain: No Known Copyright***
- Ascarids. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Ascarids**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Helminthic therapy. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Helminthic_therapy**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Nematode. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Nematode**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- nematode. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/nematode**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- visceral. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/visceral**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Taenia solium scolex. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Taenia_solium_scolex.JPG**. **License**: ***Public Domain: No Known Copyright***
- D latum LifeCycle. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:D_latum_LifeCycle.gif**. **License**: ***Public Domain: No Known Copyright***

- Taenia saginata adult 5260 lores. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Taenia_saginata_adult_5260_lores.jpg**. **License**: ***Public Domain: No Known Copyright***
- File:CDC Echinococcus Life Cycle.svg - Wikipedia, the free encyclopedia. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/w/index.php?title=File:CDC_Echinococcus_Life_Cycle.svg&page=1**. **License**: ***Public Domain: No Known Copyright***
- Enterobius vermicularis LifeCycle. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:En..._LifeCycle.gif**. **License**: ***Public Domain: No Known Copyright***
- Ascariasis LifeCycle - CDC Division of Parasitic Diseases. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:As...c_Diseases.gif**. **License**: ***Public Domain: No Known Copyright***

Key Points

- Parasitic nematodes often contain specific body structures which promote parasitic behaviors such as ridges, rings or bristles that allow for attachment.
- Two major types of roundworms that commonly infect humans include Ascaris and Enterobious.
- Ascariasis is a disease that is caused by the parasitic roundworm Ascaris lumbricoides and is transmitted by ingesting food contaminated with Ascaris eggs.
- Enterobius, referred to as pinworm, causes enterobiasis and is commonly found in the intestine of children. The entire life cycle of the pinworm occurs within the human gastrointestinal tract.

Key Terms

- **visceral**: of or relating to the viscera – the internal organs of the body
- **nematode**: A small invertebrate animal of the phylum Nematoda.

This page titled 17.8.3: Nematodes is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.12C: Nematodes** is licensed CC BY-SA 4.0.

17.9: Fungal and Protozoan Diseases of the Reproductive System

This page titled 17.9: Fungal and Protozoan Diseases of the Reproductive System is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.17: Fungal and Protozoan Diseases of the Reproductive System** is licensed CC BY-SA 4.0.

17.9.1: Vulvovaginal Candidiasis

Learning Objectives

- Analyze the symptoms and factors involved in vulvovaginal candidiasis

Candidal vulvovaginitis or vaginal thrush is an infection of the vagina's mucous membranes by Candida albicans. Up to 75% of women will have this infection at some point in their lives, and approximately 5% will have recurring episodes. It is the second most common cause of vaginal inflammation after bacterial vaginosis.


Figure: **Candida albicans**: Tramsmission photomicrograph showing a number of Candida albicans chlamydospores.

It is most commonly caused by a type of fungus known as Candida albicans. The Candida species of fungus is found naturally in the vagina, and is usually harmless. However, if the conditions in the vagina change, Candida albicans can cause the symptoms of thrush. Symptoms of thrush can also be caused by Candida glabrata, Candida krusei, Candida parapsilosis, and Candida tropicalis. Non-albican Candida are commonly found in complicated cases of vaginal thrush such that first line treatment is ineffective. These cases are more likely in immunocompromised patients.

It is not known exactly how changes in the vagina trigger thrush, but it may be due to a hormone (chemical) imbalance. In most cases, the cause of the hormonal changes is unknown. Some possible risk factors have been identified, such as taking antibiotics.

The symptoms of vaginal thrush include vulval itching, vulval soreness and irritation, pain or discomfort during sexual intercourse (superficial dyspareunia), pain or discomfort during urination (dysuria) and vaginal discharge, which is usually odorless. The discharge can be thin and watery, or thick and white, like cottage cheese.

In addition to the above symptoms of thrush, vulvovaginal inflammation can also be present. The signs of vulvovaginal inflammation include erythema (redness) of the vagina and vulva, vagina fissuring (cracked skin), oedema (swelling from a build-up of fluid), also in severe cases, satellite lesions (sores in the surrounding area). This is rare, but may indicate the presence of another fungal condition, or the herpes simplex virus (the virus that causes genital herpes).

While vulvovaginal candidiasis is caused by a the yeast Candida there are many predisposing factors:

- Infection occurs in about 30% of women who are taking a course of oral antibiotics. The evidence of the effect of oral contraceptives is controversial.
- In pregnancy, changes in the levels of female sex hormones, such as estrogen, make a woman more likely to develop a yeast infection. During pregnancy, the Candida fungus is more prevalent (common), and recurrent infection is also more likely.
- Frequency of sexual intercourse appears to be related to the frequency of infections, however infections often occur without sex. Tight-fitting clothing, such as tights and thong underwear, do not appear to increase the risk. Neither do personal hygiene methods.
- Those with poorly controlled diabetes have increased rates of infection while those with well-controlled diabetes do not.
- The risk of developing thrush is also increased in a immunodeficiency, for example, by an immunosuppressive condition, such as HIV or AIDS, or receiving chemotherapy. This is because in these circumstances the body's immune system, which usually fights off infection, is unable to effectively control the spread of the Candida fungus.

Key Points

- Up to 75% of women will have this infection at some point in their lives, and approximately 5% will have recurring episodes. It is the second most common cause of vaginal inflammation after bacterial vaginosis.

- The Candida species of fungus is found naturally in the vagina, and is usually harmless.
- It is not known exactly how changes in the vagina trigger thrush, but it may be due to a hormone (chemical) imbalance. In most cases, the cause of the hormonal changes is unknown. Some possible risk factors have been identified, such as taking antibiotics.

Key Terms

- **Candida albicans**: a diploid asexual fungus (a form of yeast). An overgrowth results in candidiasis in immunocompromised patients.
- **vulvovaginal candidiasis**: candidal vulvovaginitis or vaginal thrush is an infection of the vagina's mucous membranes by Candida albicans.

This page titled 17.9.1: Vulvovaginal Candidiasis is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.17A: Vulvovaginal Candidiasis** is licensed CC BY-SA 4.0.

17.9.2: Trichomoniasis

Learning Objectives

- Outline the causes and symptoms associated with trichomoniasis

Trichomoniasis, sometimes referred to as “trich”, is a common cause of vaginitis. It is a sexually transmitted disease, and is caused by the single-celled protozoan parasite Trichomonas vaginalis producing mechanical stress on host cells and then ingesting cell fragments after cell deat. Trichomoniasis is primarily an infection of the urogenital tract; the most common site of infection is the urethra and the vagina in women. Typically, only women experience symptoms associated with Trichomonas infection.

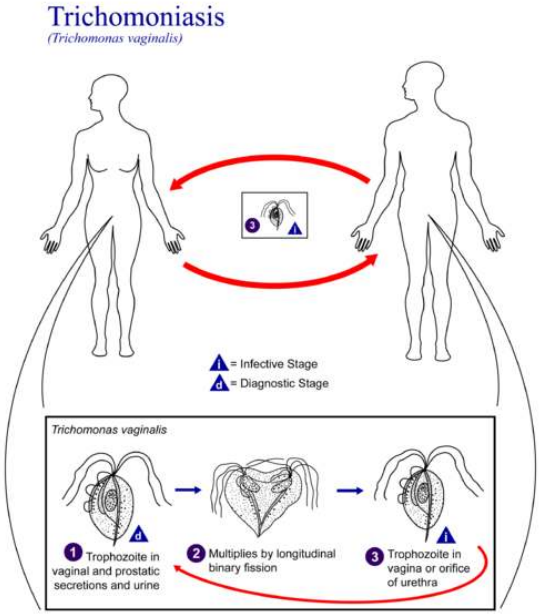


Figure: **Trichomoniasis vaginalis**: Trichomoniasis is primarily an infection of the urogenital tract; the most common site of infection is the urethra and the vagina in women.

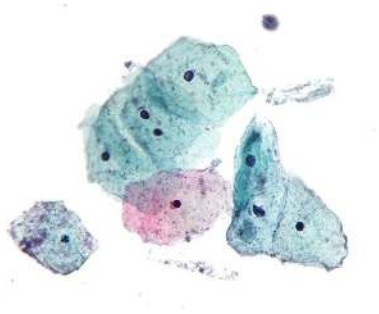


Figure: **Micrograph showing Trichomoniasis**: Micrograph showing a positive result for trichomoniasis. A trichomonas organism is seen on the top-right of the image.

Symptoms include inflammation of the cervix (cervicitis), urethra (urethritis), and vagina (vaginitis) which produces an itching or burning sensation. Discomfort may increase during intercourse and urination. There may also be a yellow-green, itchy, frothy, foul-smelling (“fishy” smell) vaginal discharge. In rare cases, lower abdominal pain can occur. Symptoms usually appear in women within 5 to 28 days of exposure. In many cases, men may hold the parasite for some years without any signs (dormant). Some sexual health specialists have stated that the condition can probably be carried in the vagina for years, despite standard tests being negative. While symptoms are most common in women, some men may temporarily exhibit symptoms such as an irritation inside the penis, mild discharge or slight burning after urination or ejaculation. Trichomoniasis is diagnosed by visually observing the trichomonads via a microscope. In women, the examiner collects the specimen during a pelvic examination by inserting a speculum

into the vagina and then using a cotton-tipped applicator to collect the sample. The sample is then placed onto a microscopic slide and sent to a laboratory to be analyzed.

Key Points

- Trichomoniasis is a sexually transmitted disease, and is caused by the single-celled protozoan parasite Trichomonas vaginalis producing mechanical stress on host cells and then ingesting cell fragments after cell death.
- Symptoms usually appear in women within 5 to 28 days of exposure. In many cases, men may hold the parasite for some years without any signs (dormant).
- Trichomoniasis is diagnosed by visually observing the trichomonads via a microscope.

Key Terms

- **trichomoniasis**: A common sexually transmitted disease caused by the parasite Trichomonas vaginalis and infecting the urinary tract or vagina.
- **vaginitis**: Inflammation of the vagina.
- **trichomonads**: flagellate protozoa of the genus Trichomonas.

This page titled 17.9.2: Trichomoniasis is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.17B: Trichomoniasis** is licensed CC BY-SA 4.0.

17.9.3: The TORCH Panel of Tests

Learning Objectives

- Summarize the importance of a TORCH panel of tests

TORCH complex is a medical acronym for a set of perinatal infections (which are infections passed from a pregnant woman to her fetus). TORCH infections can lead to severe fetal anomalies or even fetal loss. They are a group of viral, bacterial, and protozoan infections that gain access to the fetal bloodstream through the placenta via the chorionic villi. Haematogenous transmission may occur at any time during gestation or occasionally at the time of delivery via maternal-to-fetal transfusion. The TORCH panel is used to screen for certain infectious diseases that can cause birth defects in a baby if the mother contracts them during the pregnancy. The TORCH panel of tests acronym spells out as follows:

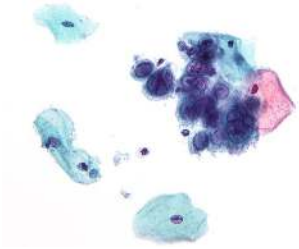


Figure: **Herpes Simplex Virus**: Micrograph of a pap test showing changes (upper-right of image) associated with Herpes Simplex Virus, a TORCH infection.

- T – Toxoplasmosis / Toxoplasma gondii
- O – Other infections
- R – Rubella
- C – Cytomegalovirus
- H – Herpes simplex virus

The “other infections” included under the letter O include Coxsackievirus, Syphilis, Varicella-Zoster Virus, HIV, and Parvovirus B19. Hepatitis B is also sometimes included among “other infections,” but Hepatitis B is a large virus and does not cross the placenta, hence it cannot infect the fetus unless there have been breaks in the maternal-fetal barrier, such as can occur due to bleeding during childbirth or during amniocentesis.

TORCH infections cause a syndrome characterized by microcephaly, sensorineural deafness, chorioretinitis, hepatosplenomegaly, and thrombocytopenia. Symptoms of a TORCH infection may include fever and difficultly feeding. The newborn is often small for their gestational age. A petechial rash on the skin may be present, with small reddish or purplish spots due to bleeding from capillaries under the skin. An enlarged liver and spleen (hepatosplenomegaly) is common, as is jaundice. However, jaundice is less common in Hepatitis B because a newborn’s immune system is not developed well enough to mount a response against liver cells, as would normally be the cause of jaundice in an older child or adult. Hearing impairment, eye problems, mental retardation, autism, and death can be caused by TORCH infections. The TORCH panel is valuable for checking for infections because the mother often has a mild infection with few or no symptoms. It is also possible for genetic conditions (such as Aicardi-Goutieres syndrome) to present in a similar manner.

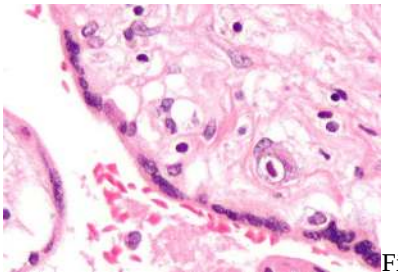


Figure: **Cytomegalovirus infection**: Hematoxylin and Eosin stain showing cytomegalovirus (CMV) infection of the placenta (CMV placentitis), a TORCH infection. The characteristic large nucleus of a CMV infected cell is seen off-center at the bottom-right of the image.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: *CC BY-SA: Attribution-ShareAlike*

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- Vulvovaginal candidiasis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Vulvovaginal_candidiasis**. **License**: *CC BY-SA: Attribution-ShareAlike*
- vulvovaginal candidiasis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/vulvovaginal%20candidiasis**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Candida albicans. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/Candida_albicans**. **License**: *CC BY-SA: Attribution-ShareAlike*
- tramsmission photomicrograph depicted a number of Candida albicans chlamydospores | Flickr - Photo Sharing!. **Provided by**: Flickr. **Located at**: **http://www.flickr.com/photos/36128932@N03/3382099313/**. **License**: *CC BY: Attribution*
- Trichomoniasis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Trichomoniasis**. **License**: *CC BY-SA: Attribution-ShareAlike*
- vaginitis. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/vaginitis**. **License**: *CC BY-SA: Attribution-ShareAlike*
- trichomonads. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/trichomonads**. **License**: *CC BY-SA: Attribution-ShareAlike*
- trichomoniasis. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/trichomoniasis**. **License**: *CC BY-SA: Attribution-ShareAlike*
- tramsmission photomicrograph depicted a number of Candida albicans chlamydospores | Flickr - Photo Sharing!. **Provided by**: Flickr. **Located at**: **http://www.flickr.com/photos/36128932@N03/3382099313/**. **License**: *CC BY: Attribution*
- Trichomoniasis 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Trichomoniasis_01.png**. **License**: ***Public Domain: No Known Copyright***
- Trichomonas pap test. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Trichomonas_pap_test.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Torch panel. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Torch_panel**. **License**: *CC BY-SA: Attribution-ShareAlike*
- haematogenous. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/haematogenous**. **License**: *CC BY-SA: Attribution-ShareAlike*
- petechial. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/petechial**. **License**: *CC BY-SA: Attribution-ShareAlike*
- TORCH complex. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/TORCH%20complex**. **License**: *CC BY-SA: Attribution-ShareAlike*
- tramsmission photomicrograph depicted a number of Candida albicans chlamydospores | Flickr - Photo Sharing!. **Provided by**: Flickr. **Located at**: **http://www.flickr.com/photos/36128932@N03/3382099313/**. **License**: *CC BY: Attribution*
- Trichomoniasis 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Trichomoniasis_01.png**. **License**: *Public Domain: No Known Copyright*
- Trichomonas pap test. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Trichomonas_pap_test.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Herpes simplex virus pap test. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Herpes_simplex_virus_pap_test.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- CMV placentitis1 mini. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:CMV_placentitis1_mini.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*

Key Points

- The TORCH complex acronym spells out: T – Toxoplasmosis / Toxoplasma gondii; O – Other infections; R – Rubella; C – Cytomegalovirus; H – Herpes simplex virus.

- TORCH infections cause a syndrome characterized by microcephaly, sensorineural deafness, chorioretinitis, hepatosplenomegaly, and thrombocytopenia.
- Symptoms of a TORCH infection may include fever and difficulty feeding, with the newborn often small for their gestational age.

Key Terms

- **haematogenous**: Spread by blood.
- **petechial**: Characterised by, pertaining to, or resembling petechiae (small, nonraised haemorrhages on the skin).
- **TORCH complex**: TORCH complex is a medical acronym for a set of perinatal infections (which are infections that are passed from a pregnant woman to her fetus).

This page titled 17.9.3: The TORCH Panel of Tests is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.17C: The TORCH Panel of Tests** is licensed CC BY-SA 4.0.

17.10: Fungal Skin and Nail Diseases

Learning Objectives

- Describe how fungal skin and nail diseases arise, their characteristic symptoms and the treatment options available

A cutaneous condition is any medical condition that affects the integumentary system — the organ system that comprises the entire surface of the body and includes skin, hair, nails, and related muscle and glands. Conditions of the human integumentary system constitute a broad spectrum of diseases, also known as dermatoses, as well as many nonpathologic states (like, in certain circumstances, melanonychia and racquet nails). Common fungal skin and nail diseases include athlete's foot, jock itch, and ringworm.

Athlete's foot (also known as ringworm of the foot and tinea pedis;) is an infection of the skin that is caused by a fungi in the genus Trichophyton. While it is typically transmitted in moist communal areas where people walk barefoot, the disease requires a warm moist environment, such as the inside of a shoe, in order to incubate. Athlete's foot causes scaling, flaking, and itching of the affected skin. Blisters and cracked skin may also occur, leading to exposed raw tissue, pain, swelling, and inflammation. Secondary bacterial infection can accompany the fungal infection, sometimes requiring a course of oral antibiotics. Athlete's foot can usually be diagnosed by visual inspection of the skin, but where the diagnosis is in doubt direct microscopy of a potassium hydroxide preparation (known as a KOH test) may help rule out other possible causes, such as eczema or psoriasis. Without medication athlete's foot resolves in 30–40% of cases and topical antifungal medication consistently produce much higher percentages of a cure. Conventional treatment typically involves daily or twice daily application of a topical medication in conjunction with hygiene measures outlined in the above section on prevention. Keeping feet dry and practicing good hygiene is crucial to preventing reinfection. Severe or prolonged fungal skin infections may require treatment with oral antifungal medication.



Figure: **Athlete's Foot**. A severe case of athlete's foot.

Tinea cruris, also known as crotch itch, crotch rot, Dhobie itch, eczema marginatum, gym itch, jock itch, jock rot, and ringworm of the groin is a dermatophyte fungal infection of the groin region in any sex, though more often seen in males. As the common name for this condition implies, it causes itching or a burning sensation in the groin area, thigh skin folds, or anus. It may involve the inner thighs and genital areas, as well as extending back to the perineum and perianal areas. Affected areas may appear red, tan, or brown, with flaking, rippling, peeling, or cracking skin. Opportunistic infections (infections that are caused by a diminished immune system) are frequent. Fungus from other parts of the body (commonly tinea pedis or 'athlete's foot') can contribute to this itch. A warm, damp environment allowing the fungus to cultivate greatly contributes; especially with tight, sweaty, or rubbing clothing such as a jockstrap. Medical professionals suggest keeping the groin area clean and dry by drying off thoroughly after bathing and putting on dry clothing right away after swimming or perspiring. Other recommendations to prevent this infection are: not sharing clothing or towels with others, showering immediately after athletic activities, wearing loose cotton underwear, avoiding tight-fitting clothes, and using antifungal powders. Tinea cruris is best treated with topical antifungal medications of the allylamine or azole type.

Dermatophytosis or ringworm is a clinical condition caused by fungal infection of the skin in humans, pets such as cats, and domesticated animals such as sheep and cattle. The term "ringworm" is a misnomer, since the condition is caused by fungi of several different species and not by parasitic worms. The fungi that cause parasitic infection (dermatophytes) feed on keratin, the material found in the outer layer of skin, hair, and nails. These fungi thrive on skin that is warm and moist, but may also survive directly on the outsides of hair shafts or in their interiors. In pets, the fungus responsible for the disease survives in skin and on the

outer surface of hairs. Advice often given to prevent this infection includes: avoiding sharing clothing, sports equipment, towels, or sheets and washing clothes in hot water with fungicidal soap after suspected exposure to ringworm. After being exposed to places where the potential of being infected is high, one should wash with an antibacterial and anti-fungal soap or one that contains tea tree oil, which contains terpinen-4-ol. Antifungal treatments include topical agents such as miconazole, terbinafine, clotrimazole, ketoconazole, or tolnaftate applied twice daily until symptoms resolve — usually within one or two weeks

Key Points

- Athlete's foot (also known as ringworm of the foot and tinea pedis) is an infection of the skin that causes scaling, flaking, and itching of affected areas and is caused by a fungi in the genus Trichophyton.
- Tinea cruris, also known as jock itch, is a dermatophyte fungal infection of the groin region in any sex, though more often seen in males.
- Dermatophytosis or ringworm is a clinical condition caused by fungal infection of the skin in humans, pets such as cats, and domesticated animals such as sheep and cattle.

Key Terms

- **jock itch**: a fungal infection, tinea cruris, of the groin region, due to the fungus Trichophyton rubrum and others.
- **ringworm**: a contagious fungal affliction of the skin, characterized by ring-shaped discoloured patches, covered by vesicles or scales.
- **athlete's foot**: a fungal infection of the skin of the foot, usually between the toes, caused by the pathogen fungi. Scientific name: tinea pedis.

This page titled 17.10: Fungal Skin and Nail Diseases is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.18E: Fungal Skin and Nail Diseases** is licensed CC BY-SA 4.0.

17.11: Parasitic Skin Diseases

Learning Objectives

- Describe how the parasitic skin infections creeping eruption, lice and scabies arise and the treatment options available

A cutaneous condition is any medical condition that affects the integumentary system — the organ system that comprises the entire surface of the body and includes skin, hair, nails, and related muscle and glands. The major function of this system is as a barrier against the external environment. Conditions of the human integumentary system constitute a broad spectrum of diseases, also known as dermatoses, as well as many nonpathologic states (like, in certain circumstances, melanonychia and racquet nails). Common parasitic skin diseases include creeping eruption, lice, and scabies.

Cutaneous larva migrans (abbreviated CLM) is a skin disease in humans caused by the larvae of various nematode parasites of the hookworm family (Ancylostomatidae). The most common species that cayse this disease in the Americas is Ancylostoma braziliense. Colloquially called creeping eruption due to the way it looks, the disease is also somewhat ambiguously known as “ground itch” or (in some parts of the southern U.S.) “sandworms,” as the larvae like to live in sandy soil. Another vernacular name is plumber’s itch. The medical term CLM literally means “wandering larvae in the skin. ” These parasites are found in dog and cat feces and although they are able to infect the deeper tissues of these animals (through to the lungs and then the intestinal tract), in humans they are only able to penetrate the outer layers of the skin and thus create the typical wormlike burrows visible underneath the skin . The parasites apparently lack the collagenase enzymes required to penetrate through the basement membrane deeper into the skin. The infection causes a red, intense itching eruption. The itching can become very painful and if scratched may allow a secondary bacterial infection to develop but it will stop after the parasites are dead. Systemic (oral) agents to treat this infection include albendazole (trade name Albenza) and ivermectin (trade name Stromectol).


Figure: **Larva Migrans Cutanea**. Typical “creeping eruption” associated with cutaneous larva migrans.

Louse (plural: lice) is the common name for members of over 3,000 species of wingless insects of the order Phthiraptera, three of which are classified as human disease agents. They are obligate ectoparasites of every avian and mammalian order except for monotremes (the platypus and echidnas), bats, whales, dolphins, porpoises, and pangolins. Most lice are scavengers, feeding on skin and other debris found on the host’s body, but some species feed on sebaceous secretions and blood. Most are found only on specific types of animals, and, in some cases, only to a particular part of the body. Some animals are known to host up to 15 different species, although one to three is typical for mammals, and two to six for birds. For example, in humans, different species of louse inhabit the scalp and pubic hair. Lice generally cannot survive for long if removed from their host. Humans host three different kinds of lice: head lice, body lice, and pubic lice. Lice infestations can be controlled with lice combs and medicated shampoos or washes.

Scabies (from Latin: scabere, “to scratch”), known colloquially as the seven-year itch, is a contagious skin infection that occurs among humans and other animals. The disease may be transmitted from objects, but is most often transmitted by direct skin-to-skin contact, with a higher risk with prolonged contact. Initial infections require four to six weeks to become symptomatic. Reinfection, however, may manifest symptoms within as little as 24 hours. Because the symptoms are allergic, their delay in onset is often mirrored by a significant delay in relief after the parasites have been eradicated. The characteristic symptoms of a scabies infection include intense itching and superficial burrows . The burrow tracks are often linear, to the point that a neat “line” of four or more

closely placed and equally developed mosquito-like “bites” is almost diagnostic of the disease. Scabies may be diagnosed clinically in geographical areas where it is common when diffuse itching presents along with either lesions in two typical spots or there is itchiness of another household member. The classical sign of scabies is the burrows made by the mites within the skin. To detect the burrow, the suspected area is rubbed with ink from a fountain pen or a topical tetracycline solution, which glows under a special light. A number of medications are effective in treating scabies with permethrin being the most effective treatment. However, treatment must often involve the entire household or community to prevent re-infection. Options to improve itchiness include antihistamines.


Figure: **Acarodermatitis**. Scabies of the foot.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Structures of the Skin. **Provided by**: Boundless Learning. **Located at**: **http://%20**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- skin. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Skin**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- stratum germinativum. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/stratum%20germinativum**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Epidermis (skin). **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Epidermis_(skin)**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- keratinocyte. **Located at**: **en.Wikipedia.org/wiki/keratinocyte**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Integumentary system. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Integumentary_system**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Human Physiology/Integumentary System. **Provided by**: Wikibooks. **Located at**: **en.wikibooks.org/wiki/Human_P..._System%23Skin**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Merkel cells. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Merkel%20cells**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- human skin. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Human_skin**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Vitamin D. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Vitamin...on_in_the_skin**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- skin flora. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Skin_flora**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- mutualistic. **Provided by**: Wikipedia. **Located at**: **en.wiktionary.org/wiki/mutualistic**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- commensal. **Provided by**: Wikipedia. **Located at**: **en.wiktionary.org/wiki/commensal**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Staphylococcus epidermidis 01. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Staphylococcus_epidermidis_01.png**. **License**: ***Public Domain: No Known Copyright***
- skin infection. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Skin_infection**. **License**: ***CC BY-SA: Attribution-ShareAlike***

- cellulitis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Cellulitis**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Erysipelas. **Located at**: **en.Wikipedia.org/wiki/Erysipelas**. **License**: *CC BY-SA: Attribution-ShareAlike*
- impetigo. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Impetigo**. **License**: *CC BY-SA: Attribution-ShareAlike*
- cellulitis. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/cellulitis**. **License**: *CC BY-SA: Attribution-ShareAlike*
- erysipelas. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/erysipelas**. **License**: *CC BY-SA: Attribution-ShareAlike*
- impetigo. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/impetigo**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Cellulitis3. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Cellulitis3.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- facial erysipelas. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Fa...erysipelas.jpg**. **License**: ***Public Domain: No Known Copyright***
- Impetigo2011. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Impetigo2011.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- wart. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Wart**. **License**: *CC BY-SA: Attribution-ShareAlike*
- cold sore. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/cold_sore**. **License**: *CC BY-SA: Attribution-ShareAlike*
- skin disease. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Skin_disease**. **License**: *CC BY-SA: Attribution-ShareAlike*
- wart. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/wart**. **License**: *CC BY-SA: Attribution-ShareAlike*
- shingles. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/shingles**. **License**: *CC BY-SA: Attribution-ShareAlike*
- herpes simplex. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Herpes_simplex**. **License**: *CC BY-SA: Attribution-ShareAlike*
- zoster. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/zoster**. **License**: *CC BY-SA: Attribution-ShareAlike*
- herpes zoster neck. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Herpes_zoster_neck.png**. **License**: *CC BY-SA: Attribution-ShareAlike*
- dornwarzen. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Dornwarzen.jpg**. **License**: ***Public Domain: No Known Copyright***
- herpes. **Provided by**: Wikimedia. **Located at**: **upload.wikimedia.org/Wikipedia/commons/d/da/Herpes(PHIL_1573_lores).jpg**. **License**: ***Public Domain: No Known Copyright***
- jock itch. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Jock_itch**. **License**: *CC BY-SA: Attribution-ShareAlike*
- athlete's foot. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Athlete's_foot**. **License**: *CC BY-SA: Attribution-ShareAlike*
- ringworm. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Ringworm**. **License**: *CC BY-SA: Attribution-ShareAlike*
- ringworm. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/ringworm**. **License**: *CC BY-SA: Attribution-ShareAlike*
- jock itch. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/jock_itch**. **License**: *CC BY-SA: Attribution-ShareAlike*
- athlete's foot. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/athlete's_foot**. **License**: *CC BY-SA: Attribution-ShareAlike*
- feet fungus. **Provided by**: Wikimedia. **Located at**: **upload.wikimedia.org/wikipedi...FeetFungal.JPG**. **License**: *CC BY-SA: Attribution-ShareAlike*
- scabies. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Scabies**. **License**: *CC BY-SA: Attribution-ShareAlike*

- cutaneous larva migrans. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/cutaneo...arva%20migrans**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- lice. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Lice**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- scabies. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/scabies**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- creeping eruption. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Creeping_eruption**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- louse. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/louse**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- larva mirgrans cutanea. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:La...ns_Cutanea.jpg**. **License**: ***Public Domain: No Known Copyright***
- scabies. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Scabies**. **License**: *Other*. **License Terms**: GNU: http://www.gnu.org/copyleft/fdl.html
- Curation and Revision. **Provided by**: Boundless.com. **License**: ***CC BY-SA: Attribution-ShareAlike***

Key Points

- Cutaneous larva migrans is a skin disease in humans caused by the larvae of various nematode parasites of the hookworm family (Ancylostomatidae) and characterized by a red, intense itching eruption.
- Humans host three different kinds of lice (head lice, body lice, and pubic lice). Lice infestations can be controlled with lice combs and medicated shampoos or washes.
- Scabies, known colloquially as the seven-year itch, is a contagious skin infection that occurs among humans and other animals.

Key Terms

- **scabies**: an infestation of parasitic mites, Sarcoptes scabiei, causing intense itching caused by the mites burrowing into the skin of humans and other animals. It is easily transmissible from human to human; secondary skin infection may occur.
- **cutaneous larva migrans**: a skin disease in humans, caused by the larvae of various nematode parasites of the hookworm family (Ancylostomatidae).
- **louse**: a small parasitic wingless insect of the order Phthiraptera.

This page titled 17.11: Parasitic Skin Diseases is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.18F: Parasitic Skin Diseases** is licensed CC BY-SA 4.0.

17.12: Other Infectious Eye Diseases

Fungi and viruses such as herpes simplex can cause eye infections.

LEARNING OBJECTIVES

Summarize the various types of herpes simplex keratitis: dendritic ulcer (epithelial keratitis) and disciform keratitis (stromal keratitis)

KEY TAKEAWAYS

Key Points

- Improper hygiene is a major cause of fungal contamination of contact lenses.
- Herpetic simplex keratitis is a form of keratitis caused by recurrent herpes simplex virus in cornea.
- Primary infection most commonly manifests as blepharoconjunctivitis i.e. infection of lids and conjunctiva that heals without scarring.

Key Terms

- **ulcer**: An open sore of the skin, eyes, or mucous membrane, often caused by an initial abrasion and generally maintained by an inflammation and/or an infection.
- **keratitis**: Inflammation of the cornea.
- **conjunctivitis**: An inflammation of the conjunctiva often due to infection.

Microbial corneal infection is the most serious and “most common vision threatening” complication of wearing contact lenses, which is believed to be strongly associated with contact lens cases. Such infections “are being increasingly recognized as an important cause of morbidity and blindness” and “may even be life-threatening. ” While the cornea is believed to be the most common site for fungal eye infections, other parts of the eye such as the orbit, sclera, and eyelids may also be involved.

Fungal Infections of the Eye

Factors that contribute to fungal contamination of contact lenses include, but not limited to, hygiene negligence such as: improper sterilization and disinfection of contact lenses, use of contaminated lenses, contaminated contact lens case, contaminated contact lens solution, wearing of contact lenses during eye infections and introduction of micro-organisms from the environment.

Diagnosis is determined”by recognition of typical clinical features and through direct microscopic detection of fungi in scrapes, biopsy specimens, and other samples. “Ultimately, cultures that are made from the samples isolated from patients is what “confirms diagnosis. ” Other tests that may also be used if needed include “histopathological, immunohistochemical, or DNA -based tests. Pathogenesis of the fungal contaminants includes a wide range of factors such as invasiveness, toxigenicity, and host factors. Once diagnosis is accessed, specific anti-fungal therapy can be administered. One of the most popular and common treatments used”for life-threatening and severe ophthalmic mycoses is amphotericin B which is a specific anti-fungal drug. For the treatment for filamentous fungal keratitis, “topical natamycin is usually the first choice. For the treatment of yeast keratitis, topical amphotericin B is usually the first choice. Current advances in further treatments include evaluations of triazoles such as itraconazole and fluconazole” as therapeutic options in ophthalmic mycoses.

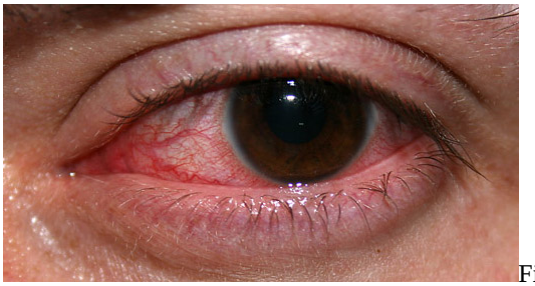


Figure: **Keratitis**: An eye with non-ulcerative sterile keratitis.

Viral Infections of the Eye

Herpes Simplex Virus

Herpetic simplex keratitis is a form of keratitis caused by recurrent herpes simplex virus in cornea. Herpes simplex virus (HSV) infection is very common in humans. HSV is a double-stranded DNA virus that has icosahedral capsid. HSV-1 infections are found more commonly in the oral area and HSV-2 in the genital area. Primary infection most commonly manifests as blepharoconjunctivitis i.e. infection of lids and conjunctiva that heals without scarring. Lid vesicles and conjunctivitis are seen in primary infection. Corneal involvement is rarely seen in primary infection. Recurrent herpes of the eye in turn is caused by reactivation of the virus in a latently infected sensory ganglion, transport of the virus down the nerve axon to sensory nerve endings, and subsequent infection of ocular surface. The following classification of herpes simplex keratitis is important for understanding this disease:



Figure: **Herpes simplex blepharitis**: Primary eye infection with herpes simplex virus most commonly manifests as blepharoconjunctivitis i.e. infection of lids and conjunctiva that heals without scarring. Lid vesicles and conjunctivitis are seen in primary infection.

Dendritic Ulcer (Epithelial Keratitis)

This classic herpetic lesion consists of a linear branching corneal ulcer (dendritic ulcer). During eye exam the defect is examined after staining with fluorescein dye. The underlying corneal has minimal inflammation. Patients with epithelial keratitis complain of foreign-body sensation, light sensitivity, redness, and blurred vision. Focal or diffuse reduction in corneal sensation develops following recurrent epithelial keratitis. In immune deficient patients or with the use of corticosteroids the ulcer may become large and in these cases it is called geographic ulcer.

Disciform Keratitis (Stromal Kieratitis)

Stromal keratitis manifests as a disc-shaped area of corneal edema. Longstanding corneal edema leads to permanent scarring. It is the major cause of decreased vision associated with HSV. Localized endotheliis (localized inflammation of corneal endothelial layer) is the cause of disciform keratitis.

Diagnostic testing is seldom needed because of its classic clinical features and is not useful in stromal keratitis as there is usually no live virus. Laboratory tests are indicated in complicated cases when the clinical diagnosis is uncertain and in all cases of suspected neonatal herpes infection. Corneal smears or impression cytology specimens can be analyzed by culture, antigen detection, or fluorescent antibody testing. Demonstration of HSV is possible with viral culture. Serologic tests in turn may show a rising antibody titer during primary infection but are of no diagnostic assistance during recurrent episodes.

Treatment of herpes of the eye is different based on its presentation. Epithelial keratitis is caused by live virus. Stromal disease is an immune response. Metaherpetic ulcer results from inability of the corneal epithelium to heal. Epithelial keratitis is treated with topical antivirals, which are very effective with low incidence of resistance. Acyclovir ophthalmic ointment and Trifluridine eye drops have similar effectiveness but are more effective than Idoxuridine and Vidarabine eye drops. Topical antiviral medications are not absorbed by the cornea through an intact epithelium, but orally administered acyclovir penetrates an intact cornea and anterior chamber.

Cytomegalovirus Retinitis

Cytomegalovirus retinitis, also known as CMV retinitis, is an inflammation of the retina of the eye that can lead to blindness. Caused by human cytomegalovirus, it occurs predominantly in people whose immune system has been compromised.

Parasitic Infections of the Eye

Acanthamoeba

Acanthamoeba is a microscopic, free-living ameba (single-celled living organism) commonly found in the environment that can cause rare, but severe, eye illness. Acanthamoeba causes three main types of illness involving the eye (Acanthamoeba keratitis), the brain and spinal cord (Granulomatous Encephalitis), and infections that can spread throughout the entire body (disseminated infection).

Toxoplasma gondii

A single-celled parasite called Toxoplasma gondii causes a disease known as toxoplasmosis. While the parasite is found throughout the world, more than 60 million people in the United States may be infected with the Toxoplasma parasite. Of those who are infected, very few have symptoms because a healthy person's immune system usually keeps the parasite from causing illness.

Signs and symptoms of ocular toxoplasmosis can include reduced vision, blurred vision, pain (often with bright light), redness of the eye, and sometimes tearing. Ophthalmologists sometimes prescribe medicine to treat active disease. Whether or not medication is recommended depends on the size of the eye lesion, the location, and the characteristics of the lesion (acute active, versus chronic not progressing). An ophthalmologist will provide the best care for ocular toxoplasmosis.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: ***CC BY-SA: Attribution-ShareAlike***

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- OpenStax College, Biology. October 17, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44761/latest...ol11448/latest. **License**: ***CC BY: Attribution***
- Ophthalmology/Anatomy of the Eye. **Provided by**: Wikibooks. **Located at**: http://en.wikibooks.org/wiki/Ophthal...omy_of_the_Eye. **License**: ***CC BY-SA: Attribution-ShareAlike***
- rod. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/rod. **License**: ***CC BY-SA: Attribution-ShareAlike***
- cone. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/cone. **License**: ***CC BY-SA: Attribution-ShareAlike***
- retina. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/retina. **License**: ***CC BY-SA: Attribution-ShareAlike***
- OpenStax College, Vision. October 17, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44761/latest...e_36_05_02.png. **License**: ***CC BY: Attribution***
- OpenStax College, Vision. October 17, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44761/latest...e_36_05_03.jpg. **License**: ***CC BY: Attribution***
- Human microbiome. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Human_m...unctival_flora. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Human flora. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Human_flora. **License**: ***CC BY-SA: Attribution-ShareAlike***
- List of human flora. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/List_of...an_flora%23Eye. **License**: ***CC BY-SA: Attribution-ShareAlike***
- lysozyme. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/lysozyme. **License**: ***CC BY-SA: Attribution-ShareAlike***
- lachrymal gland. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/lachrymal%20gland. **License**: ***CC BY-SA: Attribution-ShareAlike***
- conjunctiva. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/conjunctiva. **License**: ***CC BY-SA: Attribution-ShareAlike***

- OpenStax College, Vision. October 17, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44761/latest...e_36_05_02.png. **License**: *CC BY: Attribution*
- OpenStax College, Vision. October 17, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44761/latest...e_36_05_03.jpg. **License**: *CC BY: Attribution*
- Tear system. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:Te...tem.svg%23file. **License**: *CC BY-SA: Attribution-ShareAlike*
- Conjunctivitis. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Conjunctivitis. **License**: *CC BY-SA: Attribution-ShareAlike*
- Chlamydial infection. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Chlamyd...%23Eye_disease. **License**: *CC BY-SA: Attribution-ShareAlike*
- Keratitis. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Keratitis. **License**: *CC BY-SA: Attribution-ShareAlike*
- keratitis. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/keratitis. **License**: *CC BY-SA: Attribution-ShareAlike*
- conjunctivitis. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/conjunctivitis. **License**: *CC BY-SA: Attribution-ShareAlike*
- OpenStax College, Vision. October 17, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44761/latest...e_36_05_02.png. **License**: *CC BY: Attribution*
- OpenStax College, Vision. October 17, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44761/latest...e_36_05_03.jpg. **License**: *CC BY: Attribution*
- Tear system. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:Te...tem.svg%23file. **License**: *CC BY-SA: Attribution-ShareAlike*
- Clare-314. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:Clare-314.jpg. **License**: *CC BY-SA: Attribution-ShareAlike*
- Conjunctivitis. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Conjunctivitis. **License**: *CC BY: Attribution*
- Fungal contamination of contact lenses. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Fungal_...contact_lenses. **License**: *CC BY-SA: Attribution-ShareAlike*
- Ocular herpes. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Ocular_herpes. **License**: *CC BY-SA: Attribution-ShareAlike*
- ulcer. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/ulcer. **License**: *CC BY-SA: Attribution-ShareAlike*
- keratitis. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/keratitis. **License**: *CC BY-SA: Attribution-ShareAlike*
- conjunctivitis. **Provided by**: Wiktionary. **Located at**: en.wiktionary.org/wiki/conjunctivitis. **License**: *CC BY-SA: Attribution-ShareAlike*
- Cytomegalovirus retinitis. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Cytomegalovirus_retinitis. **License**: *CC BY-SA: Attribution-ShareAlike*
- Toxoplasmosis. **Provided by**: Centers for Disease Control and Prevention. **Located at**: http://www.cdc.gov/parasites/toxoplasmosis/gen_info/faqs.html. **License**: ***Public Domain: No Known Copyright***
- Acanthamoeba Infection FAQs. **Provided by**: Centers for Disease Control and Prevention. **Located at**: http://www.cdc.gov/parasites/acanthamoeba/gen_info/acanthamoeba.html. **License**: ***Public Domain: No Known Copyright***
- OpenStax College, Vision. October 17, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44761/latest...e_36_05_02.png. **License**: *CC BY: Attribution*
- OpenStax College, Vision. October 17, 2013. **Provided by**: OpenStax CNX. **Located at**: http://cnx.org/content/m44761/latest...e_36_05_03.jpg. **License**: *CC BY: Attribution*
- Tear system. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:Te...tem.svg%23file. **License**: *CC BY-SA: Attribution-ShareAlike*
- Clare-314. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/File:Clare-314.jpg. **License**: *CC BY-SA: Attribution-ShareAlike*
- Conjunctivitis. **Provided by**: Wikipedia. **Located at**: en.Wikipedia.org/wiki/Conjunctivitis. **License**: *CC BY: Attribution*

- Clare-314. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Clare-314.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Herpes%25252520simplex%25252520blepharitis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:He...lepharitis.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***

This page titled 17.12: Other Infectious Eye Diseases is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.19D: Other Infectious Eye Diseases** is licensed CC BY-SA 4.0.

17.13: Fungal, Protozoan, Prion, and Other Diseases of the Nervous System

This page titled 17.13: Fungal, Protozoan, Prion, and Other Diseases of the Nervous System is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **15.22: Fungal, Protozoan, Prion, and Other Diseases of the Nervous System** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

17.13.1: Cryptococcosis

Learning Objectives

- Recognize the causes and symptoms associated with cryptococcosis

Cryptococcosis, or cryptococcal disease, is a potentially fatal fungal disease. It is caused by one of two species: Cryptococcus neoformans and Cryptococcus gattii. These were all previously thought to be subspecies of C. neoformans, but have now been identified as distinct species. Cryptococcosis is believed to be acquired by inhalation of the infectious propagule from the environment. Although the exact nature of the infectious propagule is unknown, the leading hypothesis is the basidiospore created through sexual or asexual reproduction.

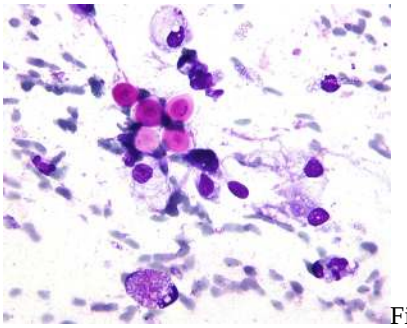


Figure: **Cryptococcus**: A micrograph of cryptococcus (purple), the fungus that can cause cryptococcosis.

Causes

Cryptococcal meningitis (infection of the meninges, the tissue covering the brain) is believed to result from dissemination of the fungus from either an observed or unappreciated pulmonary infection. Often there is also silent dissemination throughout the brain when meningitis is present. Cryptococcus gattii causes infections in immunocompetent people (those having a functioning immune system), but C. neoformans v. grubii, and v. neoformans usually only cause clinically evident infections in persons who have some form of defect in their immune systems (immunocompromised persons). People who have defects in their cell-mediated immunity; for example, people with AIDS; are especially susceptible to disseminated cryptococcosis. Cryptococcosis is often fatal, even if treated. The ten-week survival averages near 70% with optimal therapy.

Although the most common presentation of cryptococcosis is of C. neoformans infection in an immunocompromised person (such as persons living with AIDS), the C. gattii is being increasingly recognised as a pathogen in presumptively immunocompetent hosts, especially in Canada and Australia. This may be due to rare exposure and high pathogenicity, or to unrecognised isolated defects in immunity, specific for this organism.

Cryptococcosis is a defining opportunistic infection for AIDS. Other conditions which pose an increased risk include certain lymphomas (e.g. Hodgkin's lymphoma), sarcoidosis, liver cirrhosis, and patients on long-term corticosteroid therapy. Distribution is worldwide in soil. The prevalence of cryptococcosis has been increasing over the past 20 years for many reasons, including the increase in incidence of AIDS and the expanded use of immunosuppressive drugs.

Treatment

Treatment options in non-AIDS patients who have reduced immune-system function is not well studied. Intravenous Amphotericin B combined with oral flucytosine may be effective. Every attempt should be made to reduce the amount of immunosuppressive medication until the infection is resolved. Persons living with AIDS often have a greater chance of disease and higher mortality (30-70% at ten-weeks), but recommended therapy is with antifungal agents such as Amphotericin B and flucytosine.

Cryptococcosis in Animals

Cryptococcosis is also seen in cats and occasionally dogs. It is the most common deep fungal disease in cats, usually leading to chronic infection of the nose and sinuses, and skin ulcers. Cats may develop a bump over the bridge of the nose from local tissue

inflammation. It can be associated with feline leukemia virus infection in cats. Cryptococcosis is most common in dogs and cats, but cattle, sheep, goats, horses, wild animals and birds can also be infected. Soil, fowl manure, and pigeon droppings are among the sources of infection.

Key Points

- Cryptococcal meningitis is caused when the disease-causing fungus gets in the membranes around the brain.
- Cryptococcosis is an opportunistic infection, it often affects people who are immune -compromised, such as people who have AIDS.
- As people who get cryptoccosis often have other health problems, even treatment with anti- fungal agents may not cure the infection.
- Cryptococcosis can infect animals such as cats; it is not solely a human pathogen.

Key Terms

- **meninges**: The three membranes that envelop the brain and spinal cord.
- **propagule**: A reproductive particle released by an organism that may germinate into another.

This page titled 17.13.1: Cryptococcosis is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.22A: Cryptococcosis** is licensed CC BY-SA 4.0.

17.13.2: African Trypanosomiasis

Learning Objectives

- Outline the life cycle of Trypanosoma brucei and its route of transmission that causes African trypanosomiasis

Human African trypanosomiasis, sleeping sickness, African lethargy, or Congo trypanosomiasis is a parasitic disease of people and animals, caused by protozoa of the species Trypanosoma brucei and transmitted by the tsetse fly. The disease is endemic in some regions of sub-Saharan Africa, covering areas in about 37 countries containing more than 60 million people. An estimated 50-70 thousand people are currently infected, the number having declined somewhat in recent years. The number of reported cases was below ten thousand in 2009, the first time in 50 years. Many cases are believed to go unreported. About 48 thousand people died of it in 2008. Four major epidemics have occurred in recent history: one from 1896-1906, primarily in Uganda and the Congo Basin, two epidemics in 1920 and 1970 in several African countries, and a recent 2008 epidemic in Uganda.

Transmission

The tsetse fly (genus Glossina) is a large, brown, biting fly that serves as both a host and vector for the trypanosome parasites. While taking blood from a mammalian host, an infected tsetse fly injects metacyclic trypomastigotes into skin tissue. From the bite, parasites first enter the lymphatic system and then pass into the bloodstream. Inside the mammalian host, they transform into bloodstream trypomastigotes, and are carried to other sites throughout the body, reach other body fluids (e.g., lymph, spinal fluid), and continue to replicate by binary fission. The entire life cycle of African trypanosomes is represented by extracellular stages. A tsetse fly becomes infected with bloodstream trypomastigotes when taking a blood meal on an infected mammalian host. In the fly's midgut, the parasites transform into procyclic trypomastigotes, multiply by binary fission, leave the midgut, and transform into epimastigotes. The epimastigotes reach the fly's salivary glands and continue multiplication by binary fission.The entire life cycle of the fly takes about three weeks.

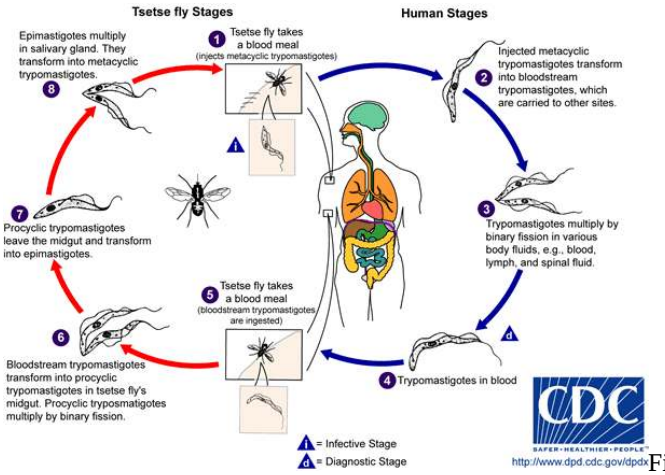


Figure: **Life Cycle of the Trypanosoma brucei parasite**: Here is an outline of the life cycle of the protozoa Trypanosoma brucei, the parasite responsible for African trypanosomiasis (sleeping sickness).

In addition to the bite of the tsetse fly, the disease can be transmitted by, mother-to-child infection; the trypanosome can sometimes cross the placenta and infect the fetus. Transmission can also occur in laboratories by accidental infections; for example, through the handling of blood of an infected person and organ transplantation, though this is uncommon. Blood transfusions and possibly sexual contact, are two other causes.

Symptoms

African trypanosomiasis symptoms occur in two stages. The first stage, known as the haemolymphatic phase, is characterized by fever, headaches, joint pains, and itching. Invasion of the circulatory and lymphatic systems by the parasites is associated with severe swelling of lymph nodes, often to tremendous sizes. If left untreated, the disease overcomes the host's defenses and can cause more extensive damage, broadening symptoms to include anemia, endocrine, cardiac, and kidney dysfunctions. The second

phase, the neurological phase, begins when the parasite invades the central nervous system by passing through the blood–brain barrier. The term “sleeping sickness” comes from the symptoms of the neurological phase. The symptoms include confusion, reduced coordination, and disruption of the sleep cycle, with bouts of fatigue punctuated with manic periods, leading to daytime slumber and night-time insomnia. Without treatment, the disease is invariably fatal, with progressive mental deterioration leading to coma and death. Damage caused in the neurological phase is irreversible.

Key Points

- The disease is caused by protozoa of the species Trypanosoma brucei, which in a mammalian blood system become a trypomastigote and travels throughout the host mammalian and infects spinal fluid and lymph nodes.
- The protozoa Trypanosoma brucei infects the tsetse fly when it feeds on the blood of an infected mammal. Once infected a tsetse fly can transmit the disease to other mammals.
- Initially, sleeping sickness has many symptoms of other viral infections, but if left untreated it will affect the nervous system, causing lethargy.

Key Terms

- **trypomastigote**: A stage in unicellular life-cycle, typically trypanosomes, where the flagellum is posterior of the nucleus, and connected to the cell body by a long undulating membrane.
- **epimastigotes**: A stage in unicellular life-cycle, typically trypanosomes, where the flagellum is anterior of the nucleus, and attached the cell body by a short membrane.

This page titled 17.13.2: African Trypanosomiasis is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.22B: African Trypanosomiasis** is licensed CC BY-SA 4.0.

17.13.3: Amoebic Meningoencephalitis

Learning Objectives

- Summarize the route of transmission and effects of infection by Naegleria fowleri

Primary amoebic meningoencephalitis (PAM, or PAME) is a disease of the central nervous system caused by infection from *Naegleria fowleri*.

Naegleria fowleri is commonly referred to as an amoeba but is actually a unicellular parasitic protist that is ubiquitous in soils and warm, stagnant bodies of freshwater, especially during the summer months. Patients typically have a history of exposure to a natural body of water.

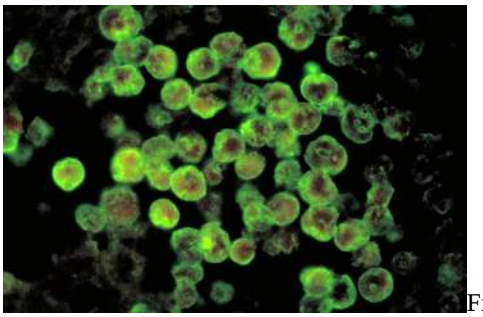


Figure: **Naegleria fowleri**: Antibody detection (green) of Naegleria fowleri, the organism responsible for Primary amoebic meningoencephalitis (PAM).

The organism specifically prefers temperatures above 32 °C, as might be found in a tropical climate or in water heated by geothermal activity. The organism is extremely sensitive to chlorine (<0.5 ppm). Exposure to the organism is extremely common due to its wide distribution in nature.

However, thus far the only route for Naegleria fowleri to enter the central nervous system is via deep insufflation of infected water as it attaches itself to the olfactory nerve, which is exposed only at the extreme vertical terminus of the paranasal sinuses.

When this occurs, it then migrates through the cribiform plate and into the olfactory bulbs of the forebrain, where it multiplies itself greatly by feeding on nerve tissue. During this stage, occurring approximately 3–7 days post-infection, the typical symptoms are parosmia, rapidly progressing to anosmia (with resultant ageusia) as the nerve cells of the olfactory bulbs are consumed and replaced with necrotic lesions.

After the organisms have multiplied and largely consumed the olfactory bulbs, the infection rapidly spreads through the mitral cell axons to the rest of the cerebrum, resulting in onset of frank encephalitic symptoms, including cephalgia (headache), nausea, and rigidity of the neck muscles, progressing to vomiting, delirium, seizures, and eventually irreversible coma. Death usually occurs within 14 days of exposure as a result of respiratory failure when the infection spreads to the brain stem, destroying the autonomic nerve cells of the medulla oblongata.

The disease is both exceptionally rare and highly lethal: there have been fewer than 200 confirmed cases in recorded medical history as of 2004, and 300 cases as of 2008, with an in-hospital case fatality rate of ~97% (3% patient survival rate). Its high mortality rate is largely blamed on the unusually non-suggestive symptomology in its early stages, compounded by the necessity of microbial culture of the cerebrospinal fluid to effect a positive diagnosis. The parasite also demonstrates a particularly rapid late-stage propagation through the nerves of the olfactory system to many parts of the brain simultaneously (including the vulnerable medulla).

Michael Beach, a recreational waterborne-illness specialist for the Centers for Disease Control and Prevention, stated in remarks to the Associated Press that the wearing of nose-clips to prevent nasal uptake of contaminated water would be an effective protection against contracting PAM, noting that, “You’d have to have water going way up in your nose to begin with”.

PAM can be effectively treated with antimicrobiotics, if the patient is treated early enough.

Key Points

- Amoebic meningoencephalitis is not actually caused by an ameoba but rather Naegleria fowleri a protist found in warm fresh water.
- Once Naegleria fowleri enters deep into the nasal passage, digesting through the olfactory bulbs it then migrates into the forebrain, where the protists eat neuronal tissue in the brain, leading to death within 14 days from initial exposure.
- The disease is largely asymptomatic until its final stages; often by the time it is diagnosed, it is too late to treat, causing a very high mortality rate.
- Antimicrobial drugs can combat Naegleria fowleri infection if it is treated soon enough. Avoiding the infection by wearing nose plugs when swimming in warm water is a good preventative measure.

Key Terms

- **anosmia**: Inability to smell; to perceive odors.
- **protist**: Any of the eukaryotic unicellular organisms including protozoans, slime molds and some algae; historically grouped into the kingdom Protoctista.
- **parosmia**: A distorted sense of smell, often resulting in phantom, non-existent, and mostly unpleasant, smells.
- **ageusia**: Partial or complete loss of the sense of taste.

This page titled 17.13.3: Amoebic Meningoencephalitis is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.22C: Amoebic Meningoencephalitis** is licensed CC BY-SA 4.0.

17.13.4: Bovine Spongiform Encephalopathy

Learning Objectives

- Recognize the route of transmission and causes of bovine spongiform encephalopathy (BSE)

Bovine spongiform encephalopathy (BSE), commonly known as mad cow disease, is a fatal neurodegenerative disease in cattle that causes a spongy degeneration in the brain and spinal cord. BSE has a long incubation period, about 30 months to eight years, usually affecting adult cattle at a peak age of four to five years, all breeds being equally susceptible.

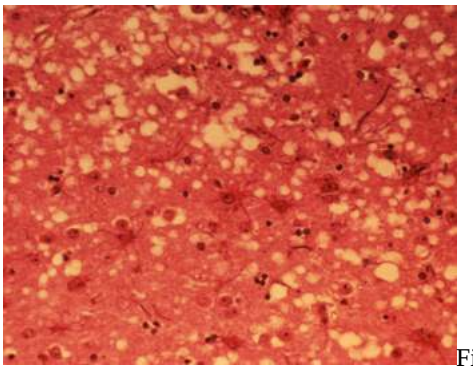


Figure: **Bovine spongiform encephalopathy (BSE)**: A cow suffering from BSE. The disease has progressed so far the animal cannot stand.

In the United Kingdom, the country worst affected, more than 180,000 cattle have been infected and 4.4 million slaughtered during the eradication program. The disease may be most easily transmitted to human beings by eating food contaminated with the brain, spinal cord or digestive tract of infected carcasses. However, it should also be noted that the infectious agent, although most highly concentrated in nervous tissue, can be found in virtually all tissues throughout the body, including blood. In humans, it is known as new variant Creutzfeldt–Jakob disease (vCJD or nvCJD), and by October 2009, had killed 166 people in the United Kingdom and 44 elsewhere. Between 460,000 and 482,000 BSE-infected animals had entered the human food chain before controls on high-risk offal were introduced in 1989.

The infectious agent in BSE is believed to be a specific type of misfolded protein called a prion. Prions will not disappear even if the beef containing them is cooked. Prion proteins carry the disease between individuals and cause deterioration of the brain.

BSE is a type of transmissible spongiform encephalopathy (TSE). TSEs can arise in animals that carry an allele which causes previously normal protein molecules to contort by themselves from an alpha helix arrangement to a beta sheet, which is the disease-causing shape for the particular protein. Transmission can occur when healthy animals come in contact with tainted tissues from others with the disease. In the brain, these proteins cause native cellular prion protein to deform into the infectious state, which then goes on to deform further prion protein in an exponential cascade. This results in protein aggregates, which then form dense plaque fibers, leading to the microscopic appearance of “holes” in the brain, degeneration of physical and mental abilities, and ultimately death.

 Figure: **BSE infected brain tissue**: This micrograph of brain tissue reveals the cytoarchitectural histopathologic changes found in bovine spongiform encephalopathy. The presence of vacuoles, i.e. microscopic "holes" in the gray matter, gives the brain of BSE-affected cows a sponge-like appearance when tissue sections are examined in the lab.

Different hypotheses exist for the origin of prion proteins in cattle. Two leading hypotheses suggest it may have jumped species from the disease scrapie in sheep, or that it evolved from a spontaneous form of "mad cow disease" that has been seen occasionally in cattle for many centuries. In the fifth century BC, Hippocrates described a similar illness in cattle and sheep, which he believed also occurred in man. Publius Flavius Vegetius Renatus recorded cases of a disease with similar characteristics in the fourth and fifth centuries. Recent research suggests mad cow disease is caused by a genetic mutation within a gene called the prion protein gene. The research shows, for the first time, that a 10-year-old cow from Alabama with an atypical form of bovine spongiform encephalopathy had the same type of prion protein gene mutation as found in human patients with the genetic form of Creutzfeldt–Jakob disease, also called genetic CJD, for short. Besides having a genetic origin, other human forms of prion diseases can be sporadic, as in sporadic CJD, as well as foodborne. They are contracted when people eat products contaminated with mad cow disease. This form of Creutzfeldt-Jakob disease is called variant CJD.

Key Points

- BSE is probably caused by a misfolded protein known as a prion; a prion can cause other correctly folded proteins to misfold thus propagating the disease.
- Cooking of prions does not destroy them.
- Evidence exists that when the prions in cows that cause BSE are consumed by humans this causes prion transmission to humans and the neurodegenerative Creutzfeldt-Jakob disease.

Key Terms

- **prion**: A self-propagating misfolded conformer of a protein that is responsible for a number of diseases that affect the brain and other neural tissue.
- **beta sheet**: A secondary structure in proteins consisting of multiple strands connected laterally.
- **alpha helix**: A secondary structure found in many proteins, where the amino acids are arranged in a coil, or helix, with almost no free space on the inside and all side chains being pointed towards the outside.

This page titled 17.13.4: Bovine Spongiform Encephalopathy is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.22D: Bovine Spongiform Encephalopathy** is licensed CC BY-SA 4.0.

17.13.5: Variant Creutzfeldt-Jakob Disease

Learning Objectives

- Generalize the role of prions in Creutsfeldt-Jakob disease

Creutzfeldt–Jakob disease, or CJD, is a degenerative neurological disorder (brain disease) that is incurable and invariably fatal. CJD is occasionally called a human form of mad cow disease (bovine spongiform encephalopathy or BSE), even though classic CJD is not related to BSE. However, given that BSE is believed to be the cause of variant Creutzfeldt–Jakob disease (vCJD) in humans, the two are often confused. In CJD, the brain tissue develops holes and takes on a sponge-like texture. This is due to a type of infectious protein called a prion. Prions are misfolded proteins which replicate by converting their properly folded counterparts.

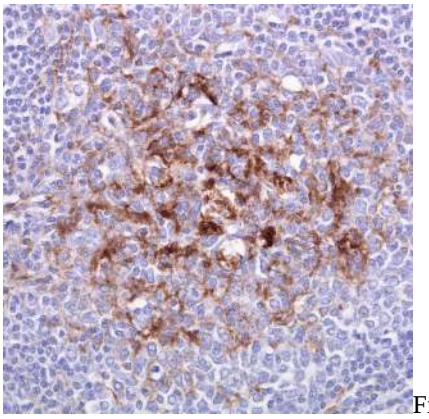


Figure: **A tonsil biopsy**: The brown staining is for the prion protein responsible for variant Creutzfeldt–Jakob disease prion.

Transmissible spongiform encephalopathy diseases are caused by prions. Thus, the diseases are sometimes called prion diseases. Other prion diseases include Gerstmann–Sträussler–Scheinker syndrome (GSS), fatal familial insomnia (FFI) and Kuru in humans; as well as bovine spongiform encephalopathy (BSE, commonly known as mad cow disease) in cattle, chronic wasting disease (CWD) in elk and deer, and Scrapie in sheep. Alpers' syndrome in infants is also thought to be a transmissible spongiform encephalopathy caused by a prion.

The prion that is believed to cause Creutzfeldt–Jakob exhibits at least two stable conformations. One, the native state, is water-soluble and present in healthy cells. As of 2007, its biological function is presumably in transmembrane transport or signaling. The other conformational state is relatively water-insoluble and readily forms protein aggregates. People can also acquire CJD genetically through a mutation of the gene that codes for the prion protein (PRNP). This occurs in only 5–10% of all CJD cases.

The CJD prion is dangerous because it promotes refolding of native proteins into the diseased state. The number of misfolded protein molecules will increase exponentially and the process leads to a large quantity of insoluble protein in affected cells. This mass of misfolded proteins disrupts cell function and causes cell death. Mutations in the gene for the prion protein can cause a misfolding of the dominantly alpha helical regions into beta pleated sheets. This change in conformation disables the ability of the protein to undergo digestion. Once the prion is transmitted, the defective proteins invade the brain and are produced in a self-sustaining feedback loop.

Key Points

- Bovine spongiform encephalopathy (BSE) is believed to be the cause of variant Creutzfeldt–Jakob (vCJD); BSE is a prion disease that affects cattle. In both humans and cattle the disease causes large holes in the brain.
- The prion the misfoled protein that causes vCJD has two conformations: one is the native form and is water soluble; the other is the disease form, which is water insoluble.
- The misfolded prion proteins can cause other normally folded pre-prion proteins to become prions, which disrupts the native proteins disrupting function leading to cell death.
- There is no known treatment for vCJD, except avoiding BSE contaminated meat.

Key Terms

- **Creutzfeldt–Jakob disease**: a rare, progressive, currently fatal disease of the nervous system, characterized by dementia and loss of muscle control; a prion disease, apparently transmissible from animals to humans by eating infected tissue, as well as from tissue interchanges among humans
- **prion**: A self-propagating misfolded conformer of a protein that is responsible for a number of diseases that affect the brain and other neural tissue.
- **transmembrane**: traversing a cellular membrane

This page titled 17.13.5: Variant Creutzfeldt-Jakob Disease is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.22E: Variant Creutzfeldt-Jakob Disease** is licensed CC BY-SA 4.0.

17.13.6: Chronic Fatigue Syndrome

Learning Objectives

- Recognize the major symptoms associated with chronic fatigue syndrome

Chronic fatigue syndrome (CFS) is the most common name used to designate a significantly debilitating medical disorder or group of disorders. Generally defined by persistent fatigue accompanied by other specific symptoms for a minimum of six months in adults (and 3 months in children/adolescents), not due to ongoing exertion, not substantially relieved by rest, and not caused by other medical conditions. The disorder may also be referred to as myalgic encephalomyelitis (ME), post-viral fatigue syndrome (PVFS), chronic fatigue immune dysfunction syndrome (CFIDS), or several other terms.



Figure: **Chronic fatigue syndrome**: Sufferers of chronic fatigue syndrome experience tiredness and unrefreshing sleep.

Biological, genetic, infectious and psychological mechanisms have been proposed for the development and persistence of symptoms but the etiology of CFS is not understood and may have multiple causes. There is no diagnostic laboratory test or biomarker for CFS. Symptoms of CFS include post-exertional malaise; unrefreshing sleep; widespread muscle and joint pain; sore throat; headaches of a type not previously experienced; cognitive difficulties; chronic, often severe, mental and physical exhaustion; and other characteristic symptoms in a previously healthy and active person. Persons with CFS may report additional symptoms such as muscle weakness, increased sensitivity to light, sounds and smells, orthostatic intolerance, digestive disturbances, depression, and cardiac and respiratory problems. It is unclear if these symptoms represent co-morbid conditions or are produced by an underlying etiology of CFS. CFS symptoms vary from person to person in number, type, and severity.

The majority of CFS cases start suddenly, usually accompanied by a “flu-like illness” while a significant proportion of cases begin within several months of severe adverse stress. An Australian prospective study found that after infection by viral and non-viral pathogens, a sub-set of individuals met the criteria for CFS, with the researchers concluding that “post-infective fatigue syndrome is a valid illness model for investigating one pathophysiological pathway to CFS”. However, accurate prevalence and exact roles of infection and stress in the development of CFS are currently unknown.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: ***CC BY-SA: Attribution-ShareAlike***

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- Cryptococcosis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Cryptococcosis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Cryptococcosis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Cryptococcosis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Cryptococcosis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Cryptococcosis**. **License**: ***CC BY-SA: Attribution-ShareAlike***

- propagule. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/propagule**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- meninges. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/meninges**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Cryptococcus. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...yptococcus.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- African trypanosomiasis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/African_trypanosomiasis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- epimastigote. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/epimastigote%23English**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- African trypanosomiasis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/African_trypanosomiasis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- African trypanosomiasis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/African_trypanosomiasis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- epimastigotes. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/epimastigotes**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- trypomastigote. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/trypomastigote**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Cryptococcus. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...yptococcus.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- AfrTryp LifeCycle. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi..._LifeCycle.gif**. **License**: ***Public Domain: No Known Copyright***
- Amoebic meningoencephalitis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Amoebic...goencephalitis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Amoebic meningoencephalitis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Amoebic...goencephalitis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Amoebic meningoencephalitis. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Amoebic...goencephalitis**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- parosmia. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/parosmia**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- anosmia. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/anosmia**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- protist. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/protist**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- ageusia. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/ageusia**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Cryptococcus. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...yptococcus.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- AfrTryp LifeCycle. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi..._LifeCycle.gif**. **License**: ***Public Domain: No Known Copyright***
- Mu00e9ningo-encu00e9phalite amibienne primitive. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi..._primitive.JPG**. **License**: ***Public Domain: No Known Copyright***
- Bovine spongiform encephalopathy. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Bovine_...encephalopathy**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Aphis.usda.gov BSE 5. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi....gov_BSE_5.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Bovine spongiform encephalopathy. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Bovine_spongiform_encephalopathy**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- prion. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/prion**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- alpha helix. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/alpha_helix**. **License**: ***CC BY-SA: Attribution-ShareAlike***

- beta sheet. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/beta_sheet**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Cryptococcus. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...yptococcus.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- AfrTryp LifeCycle. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi..._LifeCycle.gif**. **License**: ***Public Domain: No Known Copyright***
- Mu00e9ningo-encu00e9phalite amibienne primitive. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi..._primitive.JPG**. **License**: ***Public Domain: No Known Copyright***
- Aphis.usda.gov BSE 5. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi....gov_BSE_5.jpg**. **License**: ***Public Domain: No Known Copyright***
- Aphis.usda.gov BSE 3. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi....gov_BSE_3.jpg**. **License**: ***Public Domain: No Known Copyright***
- Variant Creutzfeldt-Jakob disease. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Variant...-Jakob_disease**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Variant Creutzfeldt-Jakob disease. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Variant...-Jakob_disease**. **License**: *CC BY-SA: Attribution-ShareAlike*
- prion. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/prion**. **License**: *CC BY-SA: Attribution-ShareAlike*
- transmembrane. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/transmembrane**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Creutzfeldt. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Creutzf...?Jakob+disease**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Cryptococcus. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...yptococcus.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- AfrTryp LifeCycle. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi..._LifeCycle.gif**. **License**: ***Public Domain: No Known Copyright***
- Mu00e9ningo-encu00e9phalite amibienne primitive. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi..._primitive.JPG**. **License**: ***Public Domain: No Known Copyright***
- Aphis.usda.gov BSE 5. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Aphis.usda.gov_BSE_5.jpg**. **License**: ***Public Domain: No Known Copyright***
- Aphis.usda.gov BSE 3. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi....gov_BSE_3.jpg**. **License**: ***Public Domain: No Known Copyright***
- VCJD Tonsil. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/Fi...CJD_Tonsil.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Chronic fatigue syndrome. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Chronic_fatigue_syndrome.JPG**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Chronic fatigue syndrome. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Chronic_fatigue_syndrome**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Chronic fatigue syndrome. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Chronic_fatigue_syndrome**. **License**: *CC BY-SA: Attribution-ShareAlike*
- encephalomyelitis. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/encephalomyelitis**. **License**: *CC BY-SA: Attribution-ShareAlike*
- morbid. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/morbid**. **License**: *CC BY-SA: Attribution-ShareAlike*
- orthostatic. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/orthostatic**. **License**: *CC BY-SA: Attribution-ShareAlike*
- prevalence. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/prevalence**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Cryptococcus. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Cryptococcus.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- AfrTryp LifeCycle. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:AfrTryp_LifeCycle.gif**. **License**: *Public Domain: No Known Copyright*

- Mu00e9ningo-encu00e9phalite amibienne primitive. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:M%C3%A9ningo-enc%C3%A9phalite_amibienne_primitive.JPG**. **License**: ***Public Domain: No Known Copyright***
- Aphis.usda.gov BSE 5. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Aphis.usda.gov_BSE_5.jpg**. **License**: ***Public Domain: No Known Copyright***
- Aphis.usda.gov BSE 3. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Aphis.usda.gov_BSE_3.jpg**. **License**: ***Public Domain: No Known Copyright***
- VCJD Tonsil. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:VCJD_Tonsil.jpg**. **License**: ***CC BY-SA: Attribution-ShareAlike***
- Chronic fatigue syndrome. **Provided by**: Wikimedia. **Located at**: **commons.wikimedia.org/wiki/File:Chronic_fatigue_syndrome.JPG**. **License**: ***CC BY-SA: Attribution-ShareAlike***

Key Points

- CFS is typified by extreme fatigue even in the absence of any type of exertion, and can affect people of all ages.
- There can be many non-fatigue symptoms associated with CFS, with many people exhibiting several different symptoms.
- While no direct association has been shown between a given virus and CFS, the onset of CFS is often preceded with viral infection type symptoms.

Key Terms

- **orthostatic**: Of, or relating to upright posture.
- **morbid**: Of, or relating to disease.
- **prevalence**: the total number of cases of a disease in the given statistical population at a given time, divided by the number of individuals in the population
- **encephalomyelitis**: Inflammation of the brain and spinal cord.

This page titled 17.13.6: Chronic Fatigue Syndrome is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **15.22F: Chronic Fatigue Syndrome** is licensed CC BY-SA 4.0.

18: Immunization

This page titled 18: Immunization is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Boundless.

- **12.1: Immunization** by Boundless is licensed CC BY-SA 4.0. Original source: https://courses.lumenlearning.com/boundless-microbiology/.

18.1: Passive Immunization

Learning Objectives

- Describe how artificial and natural passive immunity function to provide antibody protection against microorganisms

There are two types of passive immunity: artificial and natural. Artificial passive immunity is achieved by infusion of serum or plasma containing high concentrations of antibody. This form of passive immunity provides immediate antibody protection against microorganisms such as hepatitis A by administering preformed antibodies. These antibodies have been produced by another person or animal that has been actively immunized, but the ultimate recipient has not produced them. The recipient will only temporarily benefit from passive immunity for as long as the antibodies persist in their circulation.This type of immunity is short acting, and is typically seen in cases where a patient needs immediate protection from a foreign body and cannot form antibodies quickly enough independently.

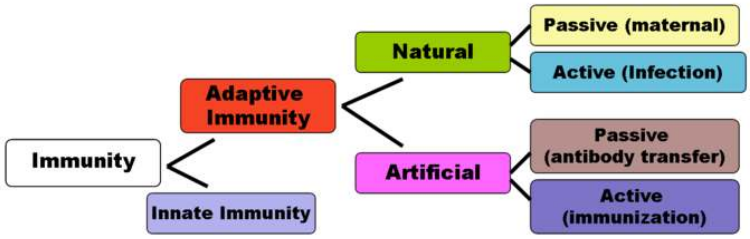


Figure: ***Immunity****: Natural immunity occurs through contact with a disease causing agent, when the contact was not deliberate, where as artificial immunity develops only through deliberate actions of exposure. Both natural and artificial immunity can be further subdivided, depending on the amount of time the protection lasts. Passive immunity is short lived, and usually lasts only a few months, whereas protection via active immunity lasts much longer, and is sometimes life-long.*

Passive immunity can also be acquired naturally by the fetus due to the transfer of antibodies by the maternal circulation in utero through the placenta around the third month of gestation. Immunity in newborn babies is only temporary and starts to decrease after the first few weeks, or months. Breast milk also contains antibodies, which means that babies who are breastfed have passive immunity for longer periods of time. The thick, yellowish milk (colostrum) that is produced during the first few days after birth is particularly rich in antibodies. For the newborn to have lasting protection, active immunity must be received. The first immunisation, given when a baby is two months old, includes whooping cough and Hib (haemophilus influenza type b) because immunity to these diseases decreases the fastest. Passive immunity to measles, mumps and rubella (MMR) usually lasts for about a year, which is why the MMR is given just after the baby's first birthday.

Key Points

- Passive immunization provides humoral immunity.
- Artificial passive immunization is the injection of preformed antibody solution when a patient is incapable of producing antibodies fast enough to combat a disease.
- Natural passive immunization is the transfer of antibodies through the placenta of a pregnant woman to the fetus. Immunity lasts for a couple of months after the baby is born, after which active immunization is required.

Key Terms

- **in utero**: Occurring or residing within the uterus or womb; unborn.

This page titled 18.1: Passive Immunization is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **12.1A: Passive Immunization** is licensed CC BY-SA 4.0.

18.2: Vaccination

Learning Objectives

- Describe how active immunity to diseases can be acquired by natural exposure or by vaccination

Active immunity to diseases can be acquired by natural exposure (in response to actually contracting an infectious disease) or it may be acquired intentionally, via the administration of an antigen, commonly known as vaccination.


Figure: **Vaccination:**: a child receiving an oral polio vaccine.

Vaccination has proven to be an effective way to stimulate the human body's natural ability to produce antibodies, without contracting the disease and suffering any of its effects. This is also known as 'acquired' resistance.

The various antigenic materials used in these vaccinations (or immunization) may be of animal or plant origin. Some vaccinations are composed of live suspensions of weak or attenuated cells or viruses, deadened cells or viruses, or extracted bacterial products such as the *toxoids* used to immunize against diphtheria and tetanus.

Vaccinations are developed to stimulate the body's production of antibodies without the manifestation of clinical signs and symptoms of the disease in *immunocompetent* hosts. Moreover, active immunization should cause permanent antigenic memory or lifelong immunity.

Vaccinations are usually given at specific ages and dates according to the recommended schedule provided by The Center for Disease Control. Sometimes booster vaccinations are needed to provide additional *immunity* in certain individuals and in certain cases.

Once your immune system has been trained to resist a disease, you are said to be immune to it. Before vaccines were developed, the only way to acquire immunity to a disease was to actually get it and, with luck, survive it. Even today, the risk of contracting some of these infectious diseases, like measles and chicken pox, can have devastating, long-term complications, like blindness.

Despite some of the various controversies surrounding vaccines over the years, the tiny proportion of risk is far outweighed by the numerous benefits. Certain infectious diseases, such as Smallpox, have been completely eradicated. Global mass vaccination drives have met with enormous success in reducing the incidence of many diseases.

Another consideration is that the newer vaccination programs also protect older age groups. By these vaccinated children not contracting these diseases, their parents, grandparents, friends and relatives (not vaccinated against these diseases themselves) will also be protected.

Key Points

- Immunization is the administration of antigenic solution, usually orally or via injection, to protect against infectious bacterial and viral diseases.

- Vaccinations are usually given at specific ages and dates as per the recommended schedule provided by The Center for Disease Control.
- Vaccines stimulate the body to produce antibodies without manifesting clinical signs and symptoms of the disease in immunocompetent hosts.

Key Terms

- **toxoids**: bacterial toxins whose toxicity has been inactivated or suppressed.
- **immunity**: the state of being insusceptible to a specific thing.
- **immunocompetent**: Having a functioning immune system.

This page titled 18.2: Vaccination is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **12.1B: Vaccination** is licensed CC BY-SA 4.0.

18.3: Types of Vaccines

Not all vaccines are the same. The way in which the body responds to a vaccine depends on the type of vaccine being administered. It is important for health professionals to understand the type of vaccines being administered and how it induces an immune response. This section includes descriptions of different types of vaccines.

Live-attenuated Vaccines

Live-attenuated vaccines induce an immune response that **mimics a natural infection** which often creates an effective and longer-lasting immunity. Live-attenuated vaccines use a weakened form of the infectious agent (virus or bacteria) to produce an immune response without causing illness. In general, clients who receive these vaccines can have lifetime protection after one or two doses.

Before administering live-attenuated vaccines, health professionals need to consider the following:

1. Clients with immunocompromising diseases or conditions.
2. Clients who take immunosuppressant agents.
3. Clients for whom immunity is uncertain.
4. Clients who are or may be pregnant.

Individuals with immune deficiency, such as those on **immunosuppressant agents** or with underlying conditions such as uncontrolled HIV, have a weakened immune system and can get very sick with live-attenuated vaccines. In general, people who are undergoing chemotherapy, who are severely immunocompromised, or who have an uncertain immune status should not receive live vaccines because of the risk of disease caused by vaccine strains. Health professionals should consult **the most responsible provider** before vaccination. Health professionals should refer to the Vaccination of Specific Population of the Canada Immunization Guide for specific information.

Screening Questions for Immunizing with Live Vaccines

1. Does the vaccine recipient have any immunocompromising conditions, or have they taken any medications in the past three months that cause immunosuppression, including **corticosteroids**?

2. If giving a live vaccine to young child (note: live vaccines are not given to infants (<12 months of age), consider:

- Is there a known or suspected family history of congenital immunodeficiency disorder, HIV infection, or a history of failure to thrive AND recurrent serious infections?

3. Has the vaccine recipient received any other live vaccines in the past four weeks?

4. Has the vaccine recipient received any transfusions of blood or blood products in the last year?

Inactivated/Killed Vaccines

Inactivated vaccines, sometimes referred to as killed vaccines, are composed of either whole or partial **pathogens that are not alive** and therefore **cannot replicate**. Pathogens become inactivated through exposure to heat, chemicals, and other purification processes. These types of vaccines prevent diseases caused by bacteria and viruses.

In this case, inactivated/killed vaccines refer to whole pathogen vaccines. Inactivated vaccines use the killed version of the pathogen and its **antigens** to induce an immune response. Typically, these vaccines provide immune protection that is not as effective as live-attenuated vaccines and often **require multiple doses over time** in order to sustain immunity as the **antibody titers** diminish. Generally, the first dose of an inactivated vaccine serves to prime the immune system, while protective immunity (antibody) is provided after the second or third dose. Inactivated vaccines are safer for use in immunocompromised individuals since the vaccine contains inactivated or killed pathogens.

Toxoid (inactivated toxin) Vaccines

Toxoid vaccines are used to prevent diseases caused by bacteria. The vaccine uses a toxin (rendered harmless) made by the pathogen that causes the disease. As a result, the body produces an **immune response targeted to the toxin** rather than the

pathogen itself. It is important to note that toxins are typically responsible for symptoms of a disease, such that exposure to the toxin can elicit immunity.

Toxoid vaccines are safe because they **cannot cause the disease**. Toxoid vaccines typically require **booster** vaccinations to sustain immunity.

Subunit Vaccines: Recombinant, Polysaccharide and Conjugate Vaccines

Subunit vaccines use a **piece of the pathogen**, such as its protein, sugar, or **capsid,** to provoke an immune response. These vaccines elicit a strong and targeted response to a part of the pathogen and are typically suitable for anyone, including immunocompromised individuals. For sustained immunity, clients typically need multiple doses of vaccine.

While recombinant, polysaccharide, and conjugate are all forms of subunit inactivated vaccines, each target a particular molecular structure. Polysaccharide vaccines consist of long-chained sugar molecules attached to the surface of bacteria such as pneumococcus and meningococcus. Recombinant vaccines are genetically engineered vaccines, whereby pathogenic agents have been cloned, expressed, and purified into a vaccine.

There are several different types of vaccines available, each with a different set of properties and uses. Scientific advances and new technology will continue to change and improve the vaccine landscape. **Table 1.1.** offers examples of some of the vaccines associated with the various vaccine types.

Table 1.1: Vaccine Types

Vaccine type	**Vaccines**
Live-attenuated	Measles, mumps, rubella (combined vaccine) Varicella (chickenpox), Zoster (shingles) Influenza (nasal spray) Oral Polio Vaccine (OPV) Rotavirus Yellow fever
Inactivated/Killed	Polio (IPV) Hepatitis A Rabies
Toxoid (inactivated toxin)	Diphtheria Tetanus
Subunit/Conjugate	Hepatitis B Influenza (injection) *Haemophilus influenza* type b (Hib) Human papillomavirus (HPV) Pertussis Pneumococcal Meningococcal Zoster (shingles)

Points of Consideration

The body produces a greater immune response the more **analogous** the vaccine is to the original disease-causing pathogen. Live-attenuated vaccines more closely resemble their pathogen, making ongoing vaccinations less likely to achieve sustained immunity. Most live-attenuated vaccines in Canada are viral; however, there are two bacterial attenuated vaccines (typhoid and tuberculosis) that are available under special circumstances.

An interactive or media element has been excluded from this version of the text. You can view it online here:
https://ecampusontario.pressbooks.pub/immunizations/?p=34

Attribution Statement

Content in this section was adapted, with editorial changes, from Page 8: Canadian Immunization Guide: Part 1 – Key Immunization Information by the Government of Canada and is reproduced under non-commercial conditions.

Content in **Table 1.1** was adapted, with editorial changes, from https://www.vaccines.gov, which is in the public domain.

This page titled 18.3: Types of Vaccines is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

18.4: Development of New Vaccines

Learning Objectives

- Describe how new vaccines are being developed to help eradicate several infectious global diseases

National Immunization Programs

The implementation of large-scale, comprehensive national immunization programs, and the considerable successes that were achieved in the eradication of smallpox and the reduction of polio, measles, pertussis, tetanus, and meningitis, were among the most notable achievements of the 20th century. Even in the poorest countries, immunizations have been able to achieve significant progress in disease control. There is good reason to expect that these advances will be sustained and will progress even further in the 21stcentury.

Vaccines for Infectious Diseases



Figure: **Human papillomavirus vaccine**: Gardasil is a human papillomavirus vaccine on the market and it protects against HPV-16 and HPV-18 which cause 70% of cervical cancers, 80% of anal cancers, 60% of vaginal cancers, and 40% of vulvar cancers.

A number of new vaccines with major potential for controlling infectious diseases have just been licensed or are at advanced stages of development. Among the illnesses targeted are rotavirus diarrhea, pneumococcal disease, and cervical cancer (as caused by human papillomavirus), which together kill more than a million people each year, most of them in developing countries.

In addition to these efforts against global diseases, progress is being made on a vaccine for the regional menace posed by meningococcal meningitis serogroup A, which causes frequent epidemics and high death rates and disability in African countries south of the Sahara. Continuing intensive efforts are under way to develop effective vaccines for AIDS, malaria, tuberculosis, dengue, leishmaniasis, and enteric diseases, among others and to adapt new technologies to improve formulation and delivery. The World Health Organization (WHO) facilitates the development of vaccines against infectious diseases of major public health importance, helps improve existing immunization technologies, and ensures that these advances are made available to the people who need them the most.

Key Points

- The World Health Organization (WHO) oversees the development and distribution of vaccines for underdeveloped countries.
- Vaccines for rotavirus diarrhea, pneumococcal disease, and meningococcal infections have been licensed and are approved for development.
- Vaccines for cancer treatment are gaining traction and are based on training the body to recognize cancer cells as foreign.

Key Terms

- **vaccine**: a substance given to stimulate the body’s production of antibodies and provide immunity against a disease, prepared from the agent that causes the disease, or a synthetic substitute.
- **immunization**: the process by which an individual is exposed to a material that is designed to prime his or her immune system against that material.

This page titled 18.4: Development of New Vaccines is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **12.1C: Development of New Vaccines** is licensed CC BY-SA 4.0.

18.5: Vaccine Safety

Learning Objectives

- Describe the possible side effects of vaccine administration

Vaccines are biological products with biological effects. Vaccines are made with a variety of ingredients including antigens, stabilizers, adjuvants, and preservatives; they may also contain residual by-products from the production process. These might be the cause of allergic reactions and side effects.

Vaccines carry risks, ranging from rashes or tenderness at the site of injection to fever-associated seizures called febrile convulsions and dangerous infections in those with compromised immune systems. Technological advances have made modern vaccines purer and safer than their historical counterparts. Most developed countries have switched to the inactivated polio vaccine and stopped using whole-cell pertussis (whooping cough) vaccines, which are made from killed bacteria and cause relatively high rates of arm swelling, febrile convulsions and periods of limpness or unresponsiveness.

Researchers have long known that some individuals are more susceptible to vaccine risks than others. Immunocompromised individuals have generally been discouraged from receiving live-virus vaccines. Some speculate that children with metabolic disorders might be prone to vaccine side effects. Safer vaccines and manufacturing processes are also in the works. New influenza vaccine doses are produced in cell culture, rather than the industry-standard chicken eggs. This process will improve reliability and reduce allergic reactions to egg proteins. Researchers are also developing replacements for vaccines that can be risky for vulnerable groups. These include current smallpox vaccines that cannot safely be given to immunocompromised people; the tuberculosis vaccine, which is not recommended for HIV-positive infants; and the yellow-fever vaccine, which puts elderly people at particular risk of a yellow-fever-like illness. Researchers are quick to emphasize that the benefits of vaccines still greatly outweigh the risks.

 Figure: **Preparation of Measles Vaccine**: Workers preparing measles vaccine in chicken eggs.

LICENSES AND ATTRIBUTIONS

CC LICENSED CONTENT, SHARED PREVIOUSLY

- Curation and Revision. **Provided by**: Boundless.com. **License**: *CC BY-SA: Attribution-ShareAlike*

CC LICENSED CONTENT, SPECIFIC ATTRIBUTION

- Passive immunity. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Passive_immunity**. **License**: *CC BY-SA: Attribution-ShareAlike*
- in utero. **Provided by**: Wiktionary. **Located at**: http://en.wiktionary.org/wiki/in_utero. **License**: *CC BY-SA: Attribution-ShareAlike*
- Immunity. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Immunity.png**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Vacination. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Vacination**. **License**: *CC BY-SA: Attribution-ShareAlike*
- toxoids. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/toxoids**. **License**: *CC BY-SA: Attribution-ShareAlike*

- immunity. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/immunity**. **License**: *CC BY-SA: Attribution-ShareAlike*
- immunocompetent. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/immunocompetent**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Immunity. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Immunity.png**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Vaccination-polio-india. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Vaccination-polio-india.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- World Health Organization. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/World_Health_Organization**. **License**: *CC BY-SA: Attribution-ShareAlike*
- immunization. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/immunization**. **License**: *CC BY-SA: Attribution-ShareAlike*
- vaccine. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/vaccine**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Immunity. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Immunity.png**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Vaccination-polio-india. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Vaccination-polio-india.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Gardasil vaccine and box new. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Gardasil_vaccine_and_box_new.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Vaccine. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Vaccine**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Subunit vaccine. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/Subunit...ine%23Vaccines**. **License**: *CC BY-SA: Attribution-ShareAlike*
- limpness. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/limpness**. **License**: *CC BY-SA: Attribution-ShareAlike*
- convulsion. **Provided by**: Wiktionary. **Located at**: **en.wiktionary.org/wiki/convulsion**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Immunity. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Immunity.png**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Vaccination-polio-india. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Vaccination-polio-india.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Gardasil vaccine and box new. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Gardasil_vaccine_and_box_new.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*
- Preparation of measles vaccines. **Provided by**: Wikipedia. **Located at**: **en.Wikipedia.org/wiki/File:Preparation_of_measles_vaccines.jpg**. **License**: *CC BY-SA: Attribution-ShareAlike*

Key Points

- Vaccines can cause side effects in immunocompromised people, and allergic reactions due to the ingredients used to make them stable.
- Side effects from vaccines are rare and most reported ailments after vaccination have not been proven to be caused by vaccination (e.g. autism, asthma).
- Researchers continue to ameliorate vaccines composition making them safer and effective.

Key Terms

- **convulsion**: An intense, paroxysmal, involuntary muscular contraction.
- **subunit vaccine**: a vaccine that presents an antigen to the immune system without introducing viral particles, whole or otherwise
- **limpness**: Property of being limp.

This page titled 18.5: Vaccine Safety is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) .

- **12.1D: Vaccine Safety** is licensed CC BY-SA 4.0.

CHAPTER OVERVIEW

19: Vaccine Safety

Learning Objectives

By the end of this chapter, you will be able to:

- Define vaccine safety.
- Describe key regulatory bodies and stakeholders involved in vaccine safety in Canada.
- Explain the components of pre-license and post-license evaluation.
- Analyze reportable adverse events following immunization (AEFI).

19.1: Non-Severe Events
19.2: Anaphylaxis
19.3: Vaccine Facts
19.4: Self Assessment
19.5: Vaccine Safety
19.6: Evaluation of Vaccines Pre-License
19.7: Canada Vigilance Program
19.8: Reflective Questions
19.9: Key Takeaways
19.10: References

This page titled 19: Vaccine Safety is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

19.1: Non-Severe Events

It is always important to assess the client after administering a vaccine. Health professionals need to recognize the **difference between severe events** such as anaphylaxis (see next section) and **non-severe events** that may occur immediately after vaccine administration. **Table 4.4** outlines some symptoms that may seem severe and mimic the signs of anaphylaxis but do not pose a life-threatening risk.

Table 4.4: Non-Severe Events

Non-Severe Event	Description	Management
Fainting	• A client who faints suddenly becomes pale, diaphoretic (sweaty), nauseous, and may collapse or experience brief loss of consciousness. • Fainting may occur before or after an injection. Fainting is sometimes accompanied by a brief clonic seizure activity (i.e., rhythmic jerking of the limbs).	PREVENT: If you observe early signs of fainting, encourage the client to sit on the floor or lay down to avoid injury from fall in the event of loss of consciousness. RECOGNIZE: Recovery of consciousness usually occurs within a minute or two, but the person may remain pale, diaphoretic, and mildly hypotensive for several minutes. RESPOND: Put the client in the recumbent position. Assess the client for injury. REASSURE: Reassure client and family.
Anxiety	A client experiencing anxiety may appear fearful, pale, and diaphoretic (sweaty). They may also indicate feeling light-headed, dizzy, and numb or tingly in the face and/or extremities. The client may hyperventilate.	PREVENT: If you observe early signs of anxiety, offer the client reassurance and let them know you will not leave them alone. RECOGNIZE: Symptoms of acute anxiety are stressful for the client but will pass. RESPOND: Demonstrate calm breathing (**diaphragmatic breathing**) for the client and encourage them to do the same. It will help the client slow down their breath.
Breath-holding	Young children may hold their breath when they are upset and crying hard. The child may appear suddenly silent but visibly agitated. Facial flushing and perioral cyanosis deepen as breath-holding continues.	PREVENT: Use comfort and evidence-informed measures to prevent pain from injection. RECOGNIZE: Some spells end with resumption of crying, but others end with a brief period of unconsciousness during which breathing resumes. RESPOND: Encourage parent/caregiver to distract the child if possible. Never scold a child for breath-holding.

Points of Consideration

Health professionals are encouraged to be proactive and report adverse events when they are uncertain whether the event is caused by the vaccine. Expected and mild events that do not require reporting include: fever without any other symptoms, injection site reaction that lasts less than four days, vasovagal syncope (fainting) without injury, or events that are clearly related to other causes.

This page titled 19.1: Non-Severe Events is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

19.2: Anaphylaxis

Anaphylaxis is a potentially **life-threatening allergic reaction** resulting from exposure to an allergen. Although anaphylaxis is extremely rare (one per one million doses administered), health professionals who administer vaccines need to **know the signs and symptoms** of anaphylaxis and how to **administer appropriate interventions without delay**.

Signs and symptoms of anaphylaxis (see **Table 4.5**) typically develop within minutes of exposure to an allergen. In fact, most instances of anaphylaxis occur within the first 30 minutes of exposure to an allergen, although some reactions may develop later. Clinical signs involve at least two body systems to classify the reaction as anaphylaxis. It is important for providers to recognize that symptoms of anaphylaxis vary, but the treatment is the same. Severe anaphylaxis includes obstructive swelling of the upper airway with bronchospasms and hypotension. A sudden drop in blood pressure can cause shock and loss of consciousness. If a client loses consciousness it is rarely the only manifestation of anaphylaxis and is typically a late event.

Table 4.5: Anaphylaxis Signs and Symptoms

Body System	**Likelihood system is part of anaphylactic response**	**Signs and Symptoms**
Skin/Mucosa	80-90%	• Itchy, urticaria (hive) rash. • Progressive, painless swelling (angioedema) around the face and mouth, which may be preceded by itchiness, tearing, nasal congestion, or facial flushing.
Respiratory	70%	Sneezing, coughing, wheezing, labored breathing, and upper airway swelling (indicated by hoarseness and/or difficulty swallowing) possibly causing airway obstruction.
Gastrointestinal	45%	Crampy abdominal pain, nausea, and vomiting.
Cardiovascular	Up to 45%	Chest pain, palpitations, tachycardia, sudden reduction in blood pressure, or symptoms of end-organ dysfunction (e.g. hypotonia and incontinence). In infants symptoms may also include fussiness, irritability, drowsiness, or lethargy.
Central Nervous System	Up to 15%	Uneasiness, altered mental status, dizziness, or confusion.

Points of Consideration

During the consent phase, all clients should be screened for contraindications, including a previous history of anaphylaxis to any vaccine. Screening for contraindications is of utmost importance. All clients should be reminded to stay for at least 15 minutes after vaccination to monitor for side effects.

Responding to Anaphylaxis

Health professionals should review their institutional policies for medical directives in the management of anaphylaxis and know where to access an anaphylaxis management kit. Epinephrine is the treatment of choice for anaphylaxis. **Prompt administration of epinephrine is the priority** and should not be delayed because failure to administer epinephrine promptly could result in serious anaphylaxis. The risk of administering epinephrine inappropriately is less severe than anaphylaxis. If uncertain, err on the side of treatment; there are no contraindications to the use of epinephrine. If time is lost early in the treatment of an acute anaphylactic episode, subsequent management can become more difficult.

Some basic procedures for responding to anaphylaxis are outlined in **Table 4.6**.

Table 4.6: Procedure for Responding to Anaphylaxis

Assess	Assess for airway, breathing and circulation (ABCs), level of consciousness (LOC)/mental status, and approximate body weight. *Respond to ABC and LOC as per the program specific policies and procedures outlined by your institution.
Call for Assistance	Depending on your institutional policies, calling for assistance may require you to call 9-1-1, use the emergency call bell, or call for a colleague. Be prepared and know what you should do in an emergency.
Position	If the client is in respiratory distress, place them in the recumbent position or a position of comfort. If the client is vomiting or unconscious place them on their side. If the client is pregnant place them in a semi-recumbent position on their left side with legs elevated.
Intervention	Refer to your institutional policies for protocols on the management of anaphylaxis. Know who is responsible for injecting epinephrine intramuscularly. Refer to guidelines and site protocol. Record time and dose. Monitor for repeat dose. A general guide is: **Inject epinephrine intramuscularly in the mid-anterolateral aspect of the thigh:** 0.01 mg/kg body weight of 1:1000 (1 mg/mL) solution ○ ADOLESCENT or ADULT: maximum – 0.5 mg ○ CHILD: maximum – 0.3 mg
Monitoring	If applicable, notify the client's next of kin. Monitor and record vital signs every five minutes and reassess frequently. Ensure client remains in recumbent position until transfer. Sudden death can occur quickly if the client sits, stands, or is placed in an upright position suddenly after giving epinephrine. Therefore, it is important for the client to be placed in the recumbent position with their lower extremities elevated and monitored closely after epinephrine is given.

This section was remixed with editorial and content changes from the Canadian Immunization Guide by the Government of Canada and is reproduced under non-commercial conditions.

This page titled 19.2: Anaphylaxis is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

19.3: Vaccine Facts

It is important for health professionals to equip themselves with the correct information about vaccines and vaccine safety. **Table 4.7** provides quick facts for health professionals to promote evidence-informed discussions about vaccine safety.

Table 4.7: Quick Facts for Vaccine Safety

Quick Fact	Description
Vaccines are the most effective way to protect against vaccine-preventable diseases.	• Vaccines protect individuals and communities, especially people who are unable to receive vaccines due to medical conditions or age. • Vaccines are a cost-effective strategy.
Vaccines train the immune system to defend rapidly against vaccine-preventable diseases.	• Children are naturally exposed to many antigens; vaccines do not significantly add to their daily exposure. • Vaccines help the body develop defenses against serious diseases.
Vaccines are safe.	• Vaccines have been extensively tested in Canada. • Health Canada supervises all aspects of vaccine production by manufacturers to ensure safety, efficacy, and quality. • Vaccines are rigorously monitored after being authorized for marketing. • Every batch of vaccine is tested for safety and quality. • Canada has a comprehensive vaccine safety monitoring system to alert public health to trends in reporting adverse events following immunization. • Ongoing quality and safety monitoring occurs after vaccines have been administered.
The risks of vaccine-preventable diseases are many times greater than the risk of serious adverse reaction following immunization.	• Serious adverse events are rare and are outweighed by the risk of the diseases and their complications. • Effective treatments for many vaccine- preventable diseases such as polio do not exist. • Most adverse events are minor and resolve quickly (e.g. injection site reaction). • Vaccine recipients are observed for 15 minutes to watch for signs and symptoms of adverse reactions.
Vaccines are not linked to chronic conditions like autism, multiple sclerosis, asthma, or sudden infant death syndrome.	• There is no evidence that any vaccines cause chronic illnesses. This has been tested in large population studies and continues to be studied.
Multiple injections are an effective way of ensuring up to date immunization.	• Evidence has shown that multiple injections at one visit cause less pain, discomfort, and disruption than waiting several days between vaccines. • Generally, infants have similar immune responses whether vaccines are given at the same time or different visits.
Vaccine-preventable diseases can occur at any time.	• Even if a disease is uncommon in Canada, it can be imported from other countries to Canada by travellers. For example, outbreaks of measles in Canada continue to occur from importation of measles cases abroad.
Unvaccinated people have a much greater chance of getting a vaccine-preventable disease.	• It may not be possible to avoid exposure to a vaccine-preventable disease. For example, an unvaccinated person can get measles by breathing the air in a room that was occupied hours before by a measles-infected person.
Vaccine-preventable diseases re-appear quickly if immunization	• There is potential for re-emergence of vaccine-preventable

coverage drops.	diseases when vaccine coverage rates are low.
Vaccines may contain additional substances to ensure effectiveness and safety. These substances are safe.	• The main ingredients of vaccines are killed or weakened viruses or bacteria or their parts. Parts are called antigens and they train the immune system to recognize and prevent disease. • Additional substances may be required in the vaccine to ensure effectiveness and safety. • Very small amounts of preservatives, such as phenol, 2-phenoxyethanol, or thimerosal, may be added to a vaccine to prevent the growth of other disease-causing microbes in the vaccine when it is used.

Attribution Statement

This section was adapted with editorial changes, retrieved from Page 5: Canadian Immunization Guide: Part 1 – Key Immunization Information by the Government of Canada and is reproduced under non-commercial conditions.

This page titled 19.3: Vaccine Facts is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

19.4: Self Assessment

An interactive or media element has been excluded from this version of the text. You can view it online here:
https://ecampusontario.pressbooks.pub/immunizations/?p=138

This page titled 19.4: Self Assessment is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

19.5: Vaccine Safety

Canada has one of the best vaccine safety programs in the world. There is a strong system in place to monitor the safety of vaccines. **Every batch of vaccine is tested** according to strict guidelines for safety and quality before it is used. After vaccines are given, **severe or unusual reactions are monitored** by public health agencies at the local, provincial, and national level.

Health professionals play an important role in the implementation and evaluation of vaccines throughout the **vaccine life cycle**. When health professionals are knowledgeable about the rigour of vaccine testing both pre and post-licensure, it positions them to have informed conversations with clients and respond to concerns related to vaccine safety. Before any vaccine is approved for use in Canada, it must meet numerous requirements including in-depth scientific reviews on **efficacy**, stability, **teratogenicity**, toxicity, and safety. After vaccines have been licensed for use, rigorous evaluation continues to ensure ongoing safety. Post-marketing surveillance of **adverse events following immunization** add to the continuous safety checks following vaccine licensure.

An interactive or media element has been excluded from this version of the text. You can view it online here:
https://ecampusontario.pressbooks.pub/immunizations/?p=140

This page titled 19.5: Vaccine Safety is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

19.6: Evaluation of Vaccines Pre-License

Before Health Canada issues a notice of compliance (NOC) (commonly known as a “license”) the vaccine must meet a number of sequential tests. During clinical trial phases, the number of subjects participating in the vaccine study increases incrementally, making the population being studied more heterogenous as the phases advance. Regulatory oversight occurs at each stage to ensure safety and identify possible risk. A condensed version of the various stages of pre-license approval are described in **Table 4.1**. The vaccine is considered for licensing (also referred to as “authorized for marketing”) once it has a proven positive **benefit-to-risk profile**.

Table 4.1: Pre-License Evaluation Stages

Life Cycle Phase	Regulatory Requirements	Description
Pre-clinical testing	**Food and Drugs Act and Regulations**, **Good Laboratory Practice (GLP)**	Provides information on efficacy and safety in laboratory and animal testing.
Clinical trials	Food and Drugs Act and Regulations, **Good Clinical Practice (GCP)**	Provides safety and efficacy data on humans in different phases of trial. • Phase I (10-99 subjects): very common adverse reactions (occurring in 10% or more of doses). • Phase II (100-1,000 subjects): common adverse reactions (occurring in 1% to less than 10% of doses). • Phase III (1,000-30,000 subjects): uncommon (occurring in 0.1% to less than 1% of subjects) and some rare (occurring in 0.01% to less than 0.1% of subjects) adverse reactions.
Validation of manufacturing process and control	Food and Drugs Act and Regulations, including **Good Manufacturing Practice (GMP)** as well as World Health Organization, International Conference on Harmonization, and other international quality guidelines	Assesses quality of vaccine production process. Applies to all steps in the manufacturing process from seed lot production to delivery as well as quality control tests. Documentation on production process, quality control, and facilities must be submitted to the regulator for review prior to approval.
On-site evaluation of the manufacturing process	Food and Drugs Act and Regulations, including Good Manufacturing Practice (GMP) as well as with World Health Organization, International Conference on	Monitors and ensures quality of vaccine production. Health Canada product specialists are sent to the manufacturing site to assess the manufacturing process.

	Harmonization, and other international quality guidelines	
Consistency testing	Food and Drugs Act and Regulations, including Good Manufacturing Practice (GMP)	Ensures quality of vaccine. Samples from at least three consecutive lots are tested in Health Canada laboratories to ensure that the product is manufactured consistently.
Establishing licensing	Food and Drugs Act and Regulations, including Good Manufacturing Practice (GMP)	Ensures that the facilities in which the product (the active pharmaceutical ingredient) is manufactured are appropriate to the specifications that apply to that product.

An interactive or media element has been excluded from this version of the text. You can view it online here:
https://ecampusontario.pressbooks.pub/immunizations/?p=142

Attribution Statement

Content in Table 4.1 was adapted, with editorial changes, from Page 2 of the Canada Immunization Guide: Part 2 – Vaccine Safety by the Government of Canada and is reproduced under non-commercial conditions.

This page titled 19.6: Evaluation of Vaccines Pre-License is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

19.7: Canada Vigilance Program

Under the Food and Drugs Act (1985) and Regulations, pharmaceutical companies are **legally required to report serious adverse reactions** related to a vaccine. The Canada Vigilance Program offers oversight after vaccines have been licensed, with systemic safeguards to ensure that vaccines have continued monitoring. The program includes safety reports, surveillance systems, risk management plans, and product risk/benefit assessments.

Safety Reports

According to the Food and Drugs Act (1985), pharmaceutical companies are required to prepare an **annual report** that comprehensively analyzes all adverse drug reactions occurring anywhere in the world. Drug companies are also responsible for notifying Health Canada if they become aware of any significant issues that could affect the benefit-risk profile.

Canadian Adverse Events Following Immunization Surveillance System (CAEFISS)

All health professionals must **report adverse events** following immunization (AEFI) to local authorities, who report to provincial authorities, who in turn report to federal authorities. CAEFISS is responsible for using this information for ongoing safety monitoring and AEFI investigations in Canada. An AEFI may or may not have a causal relationship to the use of the vaccine.

Evaluation of Vaccines Post-License

The safety profile of a vaccine is heavily scrutinized before licensure. Rigorous monitoring and evaluation **continues once the vaccine is available** to the general population to identify potential rare side effects and frequency of adverse events following immunization. This period is often referred to as the **post-marketing period** because the vaccine continues to be monitored after it is licensed. **Table 4.2** outlines the various stages of post-license evaluations.

Table 4.2: Post-License Evaluation Stages

Life Cycle Phase	Regulatory Requirements	Description
Lot release program	Food and Drugs Act and Regulations	Ensures that each marketed lot of vaccine does not differ from vaccine lots shown to be safe and effective in clinical trials.
Establishment inspections	Food and Drugs Act and Regulations, including GMP	Ensures that the facilities in which the product (the active pharmaceutical ingredient) is manufactured are appropriate to the specifications that apply to that product. Generally, inspections occur every two to three years; however, inspections can be more or less frequent depending on the activity and product.
Post-marketing studies	Not required by regulation, but suggested by Health Canada. Researchers may conduct large studies to test causal relationship between a vaccine and adverse events.	Phase IV (≥ 100 thousand subjects). Expand data on vaccine safety profile in target population to identify rare adverse events not detected during pre-marketing phase. Assess safety profile in special populations not studied as part of pre-authorization trials (e.g., immunocompromised, diabetics, etc.). Study possible interactions with other vaccines.
Adverse Events Following Immunization (AEFI) surveillance systems	Food and Drugs Act and Regulations by market authorization holders. CAEFISS activities are undertaken voluntarily, although some jurisdictions require AEFI reporting as part of public health legislation.	Detect new vaccine safety signals which could be: • increased severity or frequency of previously known adverse reactions. • unexpected adverse reactions. Conduct special investigations to determine root cause of **vaccine safety signals**.
Studies designed to test hypotheses related to vaccine adverse event association	May be requested by regulators in response to new safety signals.	Test hypothesis that a vaccine can cause an AEFI, including very rare events.

AEFIs should be reported:

- When the event has a temporal association with a vaccine. A causal relationship does not need to be proven before reporting.
- When the event is serious or unexpected (e.g., life threatening or results in death, requires hospitalization or prolongation of an existing hospitalization, results in residual disability, or causes congenital malformation).
- If there is any doubt as to whether or not an event should be reported, health professionals should always choose to report the event.

Table 4.3 is an example of a protocol for reporting adverse events. Each province and territory has their own reporting system outlining local and provincial/territorial activities. It is important that health professionals know what and how to report in their jurisdiction. The Public Health Agency of Canada has a national reporting form that is available. Completed forms are sent to the local public health unit. All reports are eventually reported up to CAEFISS at a national level.

Table 4.3: Adverse Event Type Requiring Reporting

Adverse Event Type	**TEMPORAL CRITERIA** for Non-live vaccines	**TEMPORAL CRITERIA** for Live vaccines
Injection Site Reactions		
Pain, redness, or swelling lasting 4 days or more OR extending beyond the nearest joint	0 to 48 hours	0 to 48 hours
Infected abscess	0 to 7 days	0 to 7 days
Sterile abscess	0 to 7 days	0 to 7 days
Nodule	0 to 7 days	0 to 7 days
Cellulitis	0 to 7 days	0 to 7 days
Systemic Reactions		
Rash	0 to 7 days	5 to 42 days
Adenopathy/lymphadenopathy	0 to 7 days	5 to 42 days

Severe vomiting/diarrhea	0 to 72 hours	0 to 42 days
Parotitis	N/A	5 to 30 days
Hypotonic-hyporesponsive episode (HHE); under 2 years of age only	0 to 48 hours	0 to 48 hours
Persistent crying/screaming; under 2 years of age only	0 to 72 hours	0 to 72 hours
Allergic reactions		
Event managed as anaphylaxis (i.e., epinephrine administered)	0 to 24 hours	0 to 24 hours
Oculorespiratory Syndrome (ORS)	0 to 24 hours	0 to 24 hours
Allergic skin reaction (e.g., hives)	0 to 48 hours	0 to 48 hours
Neurologic events		
Convulsions/seizure	0 to 72 hours	5 to 42 days
Encephalopathy/encephalitis	0 to 15 days	5 to 42 days

Meningitis	0 to 15 days	5 to 42 days
Anaesthesia/paraesthesia	0 to 15 days	0 to 42 days
Paralysis	0 to 15 days	5 to 42 days
Myelitis/acute disseminated encephalomyelitis	0 to 15 days	5 to 42 days
Guillian Barré Syndrome (GBS)	1 to 8 weeks	1 to 8 weeks
Bell's palsy	0 to 3 months	0 to 3 months
Other events of interest		
Arthritis/arthralgia	0 to 15 days	1 to 3 weeks
Intussusception	N/A	0 to 42 days
Thrombocytopenia	0 to 30 days	0 to 30 days
Syncope (fainting) with injury	0 to 30 minutes	0 to 30 minutes
Other severe/unusual events	Reportable regardless of timeline	Reportable regardless of timeline

As a health professional, it is important to monitor adverse events and follow the steps below:

Step 1

- Advise clients to contact you or your team if they experience an adverse event after vaccination.

Step 2

- Complete either the local form or the Public Health Agency of Canada form for reporting an AEFI. A user guide is available.
- Submit the completed form to the local public health unit or consult them if you have any questions.

An interactive or media element has been excluded from this version of the text. You can view it online here:
https://ecampusontario.pressbooks.pub/immunizations/?p=144

Attribution Statement

Table 4.3 was adapted with editorial changes from "Adverse Event Following Immunization Reporting for Health Care Providers in Ontario" by Public Health Ontario. Contact the copyright holder for appropriate permission.

This page titled 19.7: Canada Vigilance Program is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

19.8: Reflective Questions

1. Why are vaccines safe?
2. Who should avoid vaccines?
3. What do health professionals need to know about vaccine safety?
4. How can health professionals best communicate information about vaccine safety to clients?

This page titled 19.8: Reflective Questions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

19.9: Key Takeaways

The key takeaways of this chapter are:

- Vaccine safety is a highly regulated, scrutinous process in Canada.
- Vaccines undergo various stages of research before receiving license issuance by Health Canada.
- Vaccine evaluation is ongoing, even after licensure. Post-marketing surveillance is important to ensure vaccines continue to be safe and to detect rare or serious adverse events.
- Health professionals are required by law to report adverse events following immunization.
- Adverse events following immunization should be reported when the event is serious or unexpected, and there is no other clear cause for the event. A causal relationship is not required to report the adverse event.

This page titled 19.9: Key Takeaways is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

19.10: References

Government of Canada. (2016). Page 2: Canadian Immunization Guide: Part 2 – Vaccine Safety. Retrieved from: https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-2-vaccine-safety/page-2-vaccine-safety.html

Government of Canada. (2016). Page 4: Canadian Immunization Guide: Part 2 – Vaccine Safety. Retrieved from: https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-2-vaccine-safety/page-4-early-vaccine-reactions-including-anaphylaxis.html

Government of Canada. (2016). Page 5: Canadian Immunization Guide: Part 1 – Key Immunization Information. Retrieved from: https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-1-key-immunization-information/page-5-communicating-effectively-immunization.html

Public Health Ontario. (n.d.). Adverse Event Following Immunization Reporting: For Health Care Providers in Ontario. Retrieved from: https://www.publichealthontario.ca/-/media/documents/aefi-reporting-overview.pdf?la=en

This page titled 19.10: References is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

CHAPTER OVERVIEW

20: Human Health and Disease

20.1: Human Health and Disease
20.2: The Gut Microbiome
20.3: The Oral Microbiome
20.4: The Skin Microbiome
20.5: The Respiratory Microbiome
20.6: The Vaginal Microbiome
20.7: Mental Health and Multi-Microbiome Interactions

This page titled 20: Human Health and Disease is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

This page titled 20: Human Health and Disease is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Dylan Parks via source content that was edited to the style and standards of the LibreTexts platform.

20.1: Human Health and Disease

Human Health and Disease

The human microbiome plays a vital role in maintaining homeostasis of various organ systems and protecting against infectious agents. It can be subcategorized into local or regional microbiomes throughout the body, such as the gut, oral, skin, lung, and vaginal microbiomes. These manicured microecosystems are highly organized and complex, with each person having their own distinct makeup and distribution of various microorganisms. Though, individual microbiomes are unique, there is still capacity to understand key role players in the community and their potential for adaptation to improve human health in general.

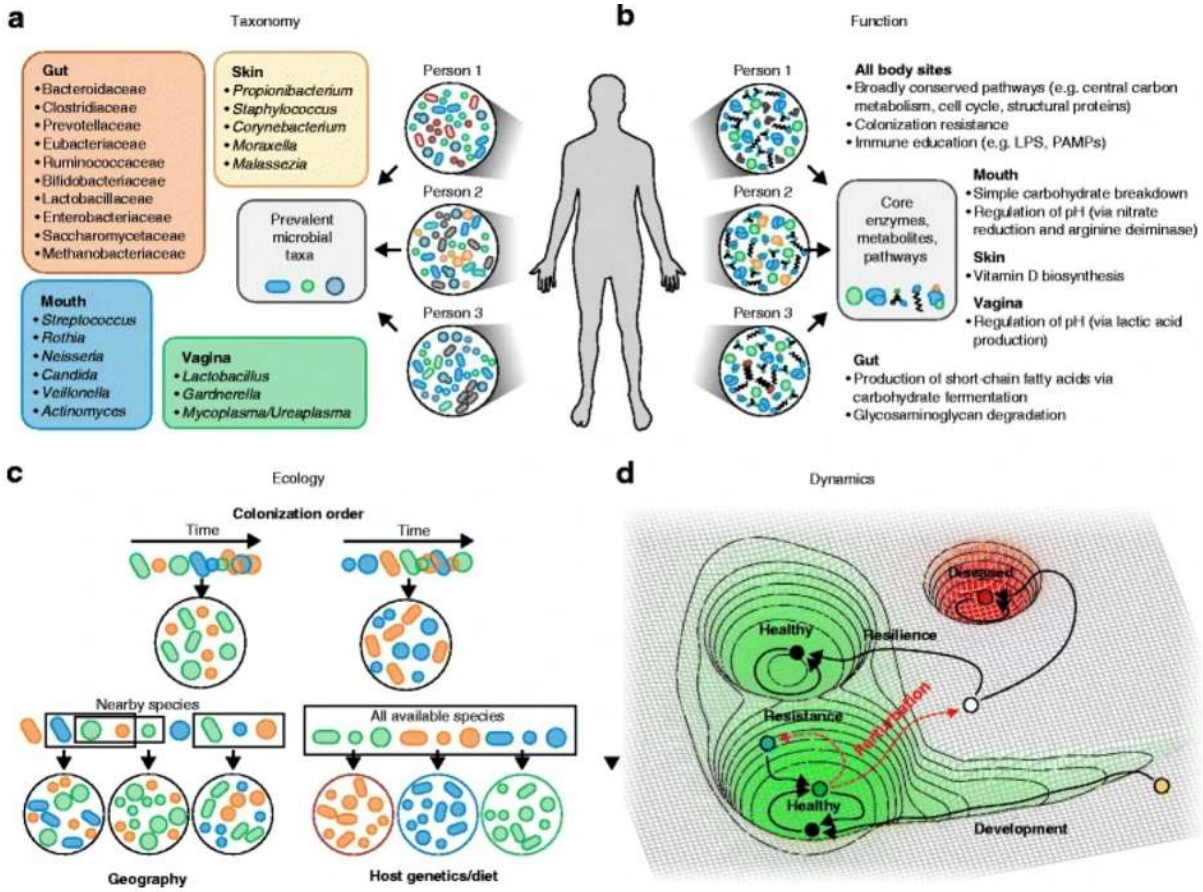


Figure 1.

Possible definitions of a healthy microbiome: composition, function, dynamics, and ecology. a Early definitions of a "healthy" microbiome generally focused on sets of taxa that might be expected to be found prevalently in healthy people. While purely taxonomic cores of any type have remained elusive, even in relatively narrowly defined populations, each body-site habitat possesses strong phylogenetic enrichments. Typical genera (or families in the gut) in healthy populations at different sites are shown here. **b** Metagenomic measurements have allowed the functional potential of the microbiome at different sites to be assessed. These studies have yielded more consistently shared functional cores of body-wide and niche-specific pathways that are maintained in health. LPS lipopolysaccharide, PAMP pathogen-associated molecular pattern. **c** Ecological assembly patterns provide another possible definition of a healthy microbiome, because each host may draw from a "typical" meta-population of potential microbes through a mix of partially stochastic processes. These processes may include the order in which microbes colonize their respective human habitat (affected by geography and early exposures, for example), the prolonged availability of each microbe in the host's local environment, and host selection. **d** The healthy microbiome can also be characterized in terms of its dynamics, depicted here in a simplified model as a conceptual energy landscape. The infant microbiome (yellow point) starts out in an unstable state and gradually descends towards one of potentially several healthy adult attractor states. Perturbations (dashed red arrows) can either be resisted (green point) or can move the microbiome out of the healthy state, after which a resilient microbiome will return to a healthy state (not necessarily the original healthy state) or fall into an unhealthy state (red). (Lloyd-Price et al., 2016).

Disruption, or dysbiosis, of the microbiome can cause serious diseases and allow for opportunistic infections to occur. This disturbance can be caused by a variety of factors including changes in diet, exercise, geographical location, age, habits, as well as medical intervention like antimicrobial chemotherapy. This change in microbial composition subsequently leads to the development and exacerbation of a number of diseases impacting essentially every aspect of human physiology including the digestive, respiratory, integumentary, central nervous, and reproductive systems. Alternatively, dysbiosis may be the result of a particular disease, and in other cases disease-dysbiosis may be bidirectional (Silverman et al., 2019). The human microbiome can be influenced by many of the above mentioned factors, but also others like life partners, pet ownership, and occupation, which do not necessarily correlate with or contribute to dysbiosis (Kiecolt-Glaser et al., 2019, Kates et al., 2020).

A major driving feature of many of these elements is the host's genetics, which can also directly impact their microbiome (Tabrett and Horton, 2020). Part of the gut microbiome and even individual types of bacteria have been shown to be heritable (Kurilshikov et al., 2017), and it is likely that other areas of the human microbiome, like the skin microbiome, could be passed from parent to offspring as well (Si et al., 2015). The host genotype is intimately linked to its microbiome and has been shown to affect dysbiosis-induced diseases such as inflammatory bowel disease and atopic dermatitis (Knights et al., 2013, Dabrowska and Witkiewicz, 2016, Woo and Sibley, 2020). Host genetics and their microbiome can even indirectly affect one's susceptibility to other diseases. For example, the attractiveness of mosquitos to particular individuals is an heritable trait which is influenced by the many factors, including the skin microbiome; therefore altering the potential of contracting a mosquito-borne pathogen, such as a *Plasmodium* parasite which causes malaria (Martinez et al., 2020). It seems there is a combination between environmental factors, host genetics, behavior, and others that continually build and adapt the human microbiome, however, is worthy to note that the former may play a larger role in shaping particular microbiomes, such as the gut microbiome (Rothschild et al., 2018).



Media Attributions

- Figure 1 – Possible definitions of a healthy microbiome: composition, function, dynamics, and ecology by Lloyd-Price et al., 2016 adapted by Dylan Parks. Licensed under Creative Commons Attribution 4.0 International License http://creativecommons.org/licenses/by/4.0/
- Video 1 – You have the microbiome you deserve by Research Square. Licensed under Creative Commons: By Attribution 3.0 License https://creativecommons.org/licenses/by/3.0/

References

1. Dąbrowska, K., & Witkiewicz, W. (2016). Correlations of Host Genetics and Gut Microbiome Composition. *Frontiers in Microbiology*, *7*, 1357. https://www.frontiersin.org/article/10.3389/fmicb.2016.01357
2. Kates, A. E., Jarrett, O., Skarlupka, J. H., Sethi, A., Duster, M., Watson, L., Suen, G., Poulsen, K., & Safdar, N. (2020). Household Pet Ownership and the Microbial Diversity of the Human Gut Microbiota. *Frontiers in Cellular and Infection Microbiology*, *10*, 73. https://www.frontiersin.org/article/10.3389/fcimb.2020.00073
3. Kiecolt-Glaser, J. K., Wilson, S. J., & Madison, A. (2019). Marriage and Gut (Microbiome) Feelings: Tracing Novel Dyadic Pathways to Accelerated Aging. *Psychosomatic Medicine*, *81*(8), 704–710. https://doi.org/10.1097/PSY.0000000000000647

4. Knights, D., Lassen, K. G., & Xavier, R. J. (2013). Advances in inflammatory bowel disease pathogenesis: linking host genetics and the microbiome. *Gut*, *62*(10), 1505. https://doi.org/10.1136/gutjnl-2012-303954
5. Kurilshikov, A., Wijmenga, C., Fu, J., & Zhernakova, A. (2017). Host Genetics and Gut Microbiome: Challenges and Perspectives. *Trends in Immunology*, *38*(9), 633–647. https://doi.org/https://doi.org/10.1016/j.it.2017.06.003
6. Martinez J., Showering, A., Oke, C., Jones, R. T., & Logan, J. G. (2020) Differential attraction in mosquito–human interactions and implications for disease control. *Phil. Trans. R. Soc. B. Biol. Sci*, *376(1818)*, 20190811. https://doi.org/10.1098/rstb.2019.0811
7. Rothschild, D., Weissbrod, O., Barkan, E., Kurilshikov, A., Korem, T., Zeevi, D., Costea, P. I., Godneva, A., Kalka, I. N., Bar, N., Shilo, S., Lador, D., Vila, A. V., Zmora, N., Pevsner-Fischer, M., Israeli, D., Kosower, N., Malka, G., Wolf, B. C., … Segal, E. (2018). Environment dominates over host genetics in shaping human gut microbiota. *Nature*, *555*(7695), 210–215. https://doi.org/10.1038/nature25973
8. Si, J., Lee, S., Park, J. M., Sung, J., & Ko, G. (2015). Genetic associations and shared environmental effects on the skin microbiome of Korean twins. *BMC Genomics*, *16*(1), 992. https://doi.org/10.1186/s12864-015-2131-y
9. Silverman, G. J., Azzouz, D. F., & Alekseyenko, A. v. (2019). Systemic Lupus Erythematosus and dysbiosis in the microbiome: cause or effect or both? *Current Opinion in Immunology*, *61*, 80–85. https://doi.org/10.1016/j.coi.2019.08.007
10. Tabrett, A., & Horton, M. W. (2020). The influence of host genetics on the microbiome. *F1000Research*, *9*, F1000 Faculty Rev-84. https://doi.org/10.12688/f1000research.20835.1
11. Woo, T. E., & Sibley, C. D. (2020). The emerging utility of the cutaneous microbiome in the treatment of acne and atopic dermatitis. *Journal of the American Academy of Dermatology*, *82*(1), 222–228. https://doi.org/10.1016/j.jaad.2019.08.078

This page titled 20.1: Human Health and Disease is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Dylan Parks via source content that was edited to the style and standards of the LibreTexts platform.

- **3.1: Human Health and Disease** by Dylan Parks is licensed CC BY 4.0. Original source: https://uta.pressbooks.pub/microbiomeshealthandtheenvironment.

20.2: The Gut Microbiome

The Gut Microbiome

The microbiome associated with the human gastrointestinal tract, termed the gut microbiome, may arguably be the most important component of the collective human microbiome. It has been shown to affect numerous other regions of the body and serves a role in many types of diseases throughout it. This is because many of the microbial products are absorbed in the alimentary canal and distributed throughout the body via the cardiovascular system.

Sample procurement to characterize the gut microbiome usually comes in the form of fecal matter, which readily available and less invasive. However, there are novel attempts to characterize gut microbiome constituents by sampling the mucosal-luminal interface (Yan et al., 2020). DNA and other features of interest can then be extracted from the microbes to provide information regarding gut microbiome composition and function.

Composition

The gut microbiome is quite versatile and its composition can vary widely among individuals with different ethnicities, across geographic locations, and with age (Yatsunenko et al., 2012, Gaulke and Sharpton, 2018). The host's genetics do play a role in the composition of the gut microbiome, as certain members are heritable, while other's abundances are the causal result of congenital diseases (Xu et al., 2020). Though diet, which is closely related to the aforementioned variables, may be the single strongest influencing factor when it comes to structuring this digestive community and alterations are reflected in both short-term and long-term dietary interventions (David et al., 2014, Xu and Knight, 2015). Indeed, the type of diet, such as a high-fat diet, will have a direct impact on the gut microbiome. More specifically, the unique macromolecules within the gut can modify microbial abundance and predicted functions. For example, a certain oil in the diet could result in higher microbial richness, however, this diversity may not alone be a predictor of better health outcomes (Abulizi et al., 2019). Dietary vitamin content and even receptors required for processing them are in part modulated by the microbiome. For example, vitamin D deficiency and downregulation of its affiliated receptor is associated with pathogenesis of various diseases and their restoration promotes healthy host-microbe homeostasis (Jin et al., 2015). It is also interesting to note that diet usually changes throughout the year as certain food items become available or absent depending on the season. An increased gut prevalence of Bacteroidetes, which can digest complex plant carbohydrates, could be explained by a diet consisting heavily of produce during a harvest season (Davenport et al., 2014). The composition and diversity of the gut microbiome can even be linked to personality traits. Those individuals with larger social networks have a more diverse gut microbiome, and those affected by stress and anxiety show an altered composition with reduced diversity (Johnson, 2020). The connection between the gut microbiome and mental states and behaviors will be discussed more in the section "Mental Health".

Video Quiz

Dysbiosis and Disease

The gastrointestinal mucosal immune system modulates and responds to the gut microbiome, where the resident members aid in its development and transient pathogens cause dysfunction, leading to various diseases (Shi et al., 2017). Inflammatory diseases such as systemic lupus erythematosus, rheumatoid arthritis, IBD, and ankylosing spondylitis are implicated in the impaired interaction between the intestinal microbiota and mucosal immune system (Arbuckle et al., 2003, Mikuls et al., 2012, Costello et al., 2015). Microbial dysbiosis within these cases are marked by changes in composition and diversity of specific groups of organisms (Shi et al., 2017). So, the gut microbiome can not only serve as an indicator for such diseases, but may also eventually become a target for treatment, with maintaining proper homeostasis a major goal.

Gut microbiome dysbiosis, whether it causes a particular disease or manifests as a result of it, is quickly becoming the focus of many gastrointestinal illnesses. Specific members of the gut microbiome (e.g. bacteriome, mycobiome, virome) can even vary and be affected differently depending on the disease and its severity. For example, while much of the focus is usually on bacteria in the gut, it is important to not discount the contributions of other microorganisms like bacteriophages and fungi. The gut phageome can vary in diversity, complexion, and in so has been shown to contribute to diseases like IBD, malnutrition, and AIDS (Norman et al., 2015, Reyes et al., 2015, Monaco et al., 2016, Shkoporov and Hill, 2019). Similarly, the gut mycobiome has shown to have roles in IBD, colorectal cancer, and even neurological diseases (Forbes et al., 2019, Gu et al., 2019, Qin et al., 2021). Though, it is likely

the complex interactions between all members of the gut microbiome with the host undoubtedly play a role in various degrees for the progression of gastrointestinal and other diseases.

Those with Inflammatory Bowel Disease (IBD) experience substantial fluctuations in the gut microbiome, which is implicated due to signs and symptoms of the disease state, diet, as well as increased medication during flare ups (Walters et al., 2014, Halfvarson et al., 2017). IBD is a blanket term for two disorders, ulcerative colitis and Crohn's disease, which are characterized by chronic inflammation of the gastrointestinal tract and commonly results in frequent diarrhea, abdominal pain, bloody stool, weight loss, and fatigue. It is likely that the gut microbiome plays both a role in the development of these conditions and is affected by the induced changes. The gut virome component responds to disease-induced environmental change of IBD patients by shifting from virulent to temperate bacteriophage core, which subsequently affects the bacteriome and dysbiosis condition (Clooney et al., 2019). A familial study of patients with Crohn's disease showed an increase in the number of pathogenic bacteria, and a decrease in beneficial bacteria. In particular, three potentially pathogenic biofilm-forming species from both the bacteriome (*Serratia marcescens* and *Escherichia coli*) and mycobiome (*Candida tropicalis*) interact with each other and impact the host immune system by increasing levels of proinflammatory cytokines and mucolytic enzymes which cause oxidative and tissue damage (Hoarau et al., 2016).



Diabetes mellitus is another disease in which its progression is partially in response to gut microbiome dysbiosis. While there are other factors that play into diabetes such as culture, genetics, age, lifestyle, etc., this can be interlinked with an individual's microbiome. Studies over both type 1 and type 2 diabetes have shown that a change in the gastrointestinal microbial ecology is associated with diabetic subjects as compared with their healthy counterparts (Giongo et al., 2010, Larsen et al., 2010, Musso et al., 2011, Sohail et al., 2017). Type 1 diabetes stems from destruction of pancreatic beta cells, which results in decreased insulin production and elevated blood glucose levels. The gut microbiome may contribute to the disease by dysbiosis-associated immune regulation causing destruction of the beta cells and/or gut leakiness, endotoxemia, and chronic low-grade inflammation associated with certain enteric microbes (Cani et al., 2007, Lee et al., 2011, McDermott and Huffnagle, 2014, Sohail et al., 2017). Type 2 diabetes is characterized by the body's improper regulation and secretion of insulin and is associated by hyperglycemia. Physiological changes in the GI tract could be induced by dysbiosis in the gut microbiome leading to gut permeability and insulin resistance (Everard and Cani, 2013). In general, the gut microbiota composition is less in terms of diversity and richness for those with type 2 diabetes, though an increase in abundance of certain groups like *Bifidobacterium* could improve conditions associated with pathogenesis (Cani et al., 2007, Sohail et al., 2017). It seems that an alteration of the microbial gut profile has considerable effects on host metabolism, gastrointestinal physiology, gut fermentation capabilities, and immunity which can have many other downstream implications (Boulange et al., 2016).

Obesity is commonly associated with type 2 diabetes as well as other comorbidities that are linked to gut microbiome dysbiosis. As mentioned earlier, diet strongly affects the composition and function of the gut microbial community and subsequently impacts the host's metabolic capabilities. In fact, a high-fat/calorie or improper diet that results in dysbiosis is evident earlier than the signs of the host's metabolic abnormalities, and so gut microbiome dysbiosis may be the principle ingredient responsible for the progression of obesity and type 2 diabetes (Nagpal et al., 2018). A high-sugar diet seems to promote an abundance of *Mollicutes*, a class within Firmicutes, which in turn suppresses Bacteroidetes (Turnbaugh et al., 2008), and this higher ratio of Firmicutes/Bacteroidetes has been proposed as a biomarker and hallmark indicator for obesity (de Bandt et al., 2011, Zou et al., 2020). However, it is important

to consider other factors such as physical activity and medication that could cause a variation in diversity of the gut microbiome, as this ratio does not always definitively denote obesity (Magne et al., 2020). Though, there are similarities between many of the microbiome-linked contributing factors of pathogenesis progression for diet-induced diseases. For example, a high-fat diet induces increased gut permeability that allows exogenously produced bacterial compounds (e.g. lipopolysaccharides) to diffuse through the intestinal barrier, which then can interact with immune cells and lead to inflammation (Cani et al., 2007, Nagpal and Yadav, 2017). However, diet isn't the sole factor that can promote gut leakiness, and it seems that obesity in general causes an altered gastrointestinal state (Nagpal et al., 2018).



Chemotherapeutic Intervention and C. diff

Medication and antimicrobial drugs can also have drastic effects on the gut microbiome that invoke risk of secondary infections, allergies, and other diseases like obesity (Becattini et al., 2016). Though many of these prescribed treatments are necessary to combat infectious diseases, the aftermath may have more serious consequences. Not only does antimicrobial therapy disrupt the resident microbiome, but misuse, suboptimal dosing, and patient noncompliance can create conditions conducive to fostering antimicrobial resistance through selective pressure.

Clostridioides difficile (commonly called C. diff) infections are directly associated with antibiotic-induced dysbiosis in the gastrointestinal tract. *C. difficile* is part of the normal microbiota, however, as an opportunistic pathogen it can invade or colonize empty niches brought about by dysbiosis and cause potentially fatal episodes of pseudomembranous colitis, which is associated with abdominal cramping, pain, sepsis, and bouts of diarrhea (Kho and Lal, 2018). Infection and transmission of this organism has been well known for its prevalence in hospital settings, primarily affecting the elderly and immunocompromised, however, community-associated infections have recently increased in what was once considered low-risk populations (Rouphael et al., 2008, Baker et al., 2010, Hensgens et al., 2012, Benson et al., 2015, Johanesen et al., 2015). It is also alarming that this organism has resistance mechanisms to many commonly prescribed antimicrobials, including β-lactams, aminoglycosides, lincomycin, tetracyclines, and erythromycin (George et al., 1978), and more recently 'hypervirulent' strains have developed resistance to fluoroquinolones (He et al., 2013, Johanesen et al., 2015). *C. difficile* infections have an enrichment of fungi that associate with the bacteriome and perhaps antifungal therapy could help improve treatment success if administered in conjunction with specific antibacterial drugs (Stewart et al., 2019). Though, theseinfections can have lingering impacts on the gut microbiome, as further antimicrobial therapy that is usually required can perpetuate the situation. The inflammation as a result of the disease induces the production of antimicrobial peptides by epithelial cells and neutrophils which inhibit the growth of the natural resident commensal microbes (Leber et al., 2015).

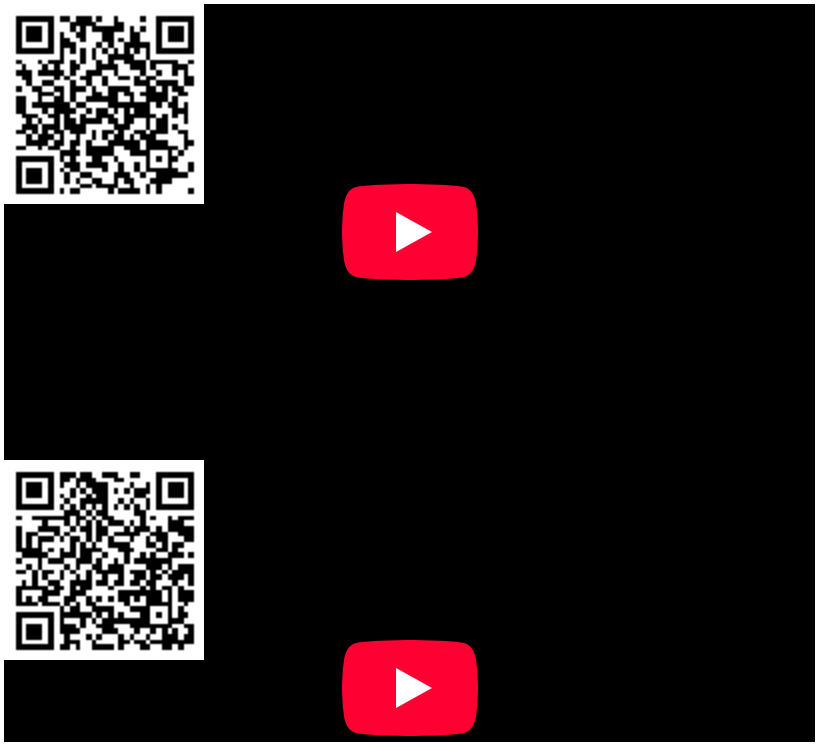
While many events of gut dysbiosis are directly linked to the chemotherapeutic effects on microbes since they are prescribed to target microbes responsible for the infection, some medications which are meant to address other diseases, like antidepressants for mental health, have undesired effects on the microbiome (Maier and Typas, 2017). In the cases of multi-drug combinations (e.g. non-steroidal anti-inflammatory drugs (NSAIDs), antidepressants, laxatives, proton-pump inhibitors (PPIs), etc.), it is not the number of drugs that affect gut microbiome diversity, but rather the types of drugs (Rogers and Aronoff, 2016). Though these scenarios become complicated as it is difficult to ascertain whether the alterations observed on the microbiome are from the drug's mechanism of action, a downstream side effect, or originate from the condition that is being treated, and it is likely a complex

combination of all factors for each disease and medication (Rogers and Aronoff, 2016, Maier and Typas, 2017, Jackson et al., 2018).

Fecal Microbiota Transplant

Although pharmaceutical drugs are of dire importance to treat various diseases, whether they are infectious in nature or not, other avenues must be pursued for those that may benefit from restoration of the gut microbiome. Probiotics and fecal microbiota transplant (FMT) can serve as viable options for the prevention and treatment of gut microbiome dysbiosis. Probiotics are considered foodstuffs with microorganisms, usually bacteria (many being lactic acid bacteria) and yeast, and their byproducts that have a beneficial effect on human health when introduced into the body. Many probiotics are commercially available to consumers in the forms of products like yogurt, kefir, buttermilk, sauerkraut, pickles, premade vitamin supplements and many others (more information about probiotics and fermented foods can be found in the section "Food and Fermentation: Your Microbiome is What you Eat"). Specifically, probiotics can be used for the treatment and prevention of many of the aforementioned gut microbiome dysbiosis-associated diseases, especially those induced by antibiotics (Kim et al., 2019). The beneficial microbes outcompete pathogens for resources or prevent them from establishing a niche in which to grow (Ouwehand et al., 1999).

In more extreme cases of gut microbiome dysfunction and disease, like those from *C. difficile* infection (CDI) in which antibiotics are ineffective and can potentially exacerbate the problem, other measures must be taken. Fecal microbiota transplant therapy takes a stool sample containing the gut microbiome from a healthy donor and relocates it into the infected patient's colon. The introduced microbiota then helps move the gut microbiome towards homeostasis by restoring the structure of beneficial microbes and metabolites (Fujimoto et al., 2021). This procedure is usually reserved for those patients with recurrent CDI and has shown to be highly successful and is considered safer and more effective than prolonged antibiotic usage (Mattila et al., 2012, Cammarota et al., 2015), though is also being investigated for first-line treatment of CDI (Camacho-Ortiz et al., 2017). FMT has gained traction for its success and is being further considered as a therapeutic option in other treatment protocols, such as those for cancer patients undergoing cancer immunotherapy to help improve response or manage toxicity (McQuade et al., 2020), and individuals undergoing allogenic hematopoietic stem cell transplant for hematological disorders that experience graft-versus-host disease complications from it (Zhang et al., 2021). However, precautions must be taken for FMT, as the donor's sample could potentially harbor other pathogenic microbes, like multi-drug resistant *Escherichia coli*, that can result in pathogenesis, further complications, and even death for the recipient (DeFilipp et al., 2019, Martinez-Gili et al., 2020). More comprehensive research and FMT trials must be performed in order to optimize this procedure to better match donors with recipients and to further understand the exact mechanisms of microbiome rehabilitation.



Conclusion

Gut microbiome intervent[redacted]ike IBD, diabetes, obesity, colorectal cancer, etc., and offers a viable alternative to many traditional pharmaceutical interventions. Though, the gut microbiome is plastic and continually changes with its host's environment and lifestyle, so stabilization is constant work. Additionally, creating an ideal 'cocktail' of microbes that will maintain homeostasis when implemented can be challenge. While there are general members of the gut microbiome that exist at a constant level and show some correlation to normal health, there may not be a true 'standard' gut microbiome due to the vast differences between people across the world. So, this type of therapy may require a more unique and individualized approach that depends on the disease and characteristics of both the host and their microbiome.

Check Your Understanding

- What factors influence the composition of the gut microbiome?
- How is gut microbiome dysbiosis brought about?
- What diseases are associated with gut microbiome dysbiosis? Are features of pathogenesis always a cause or effect of these events? Explain.
- Explain the treatment options that are available for gut microbiome dysbiosis.

Media Attributions

- Video 1 – Gut microbiome and individual genetics by Latest Thinking. Licensed under Creative Commons: By Attribution 3.0 License https://creativecommons.org/licenses/by/3.0/
- Video 2 – Diet and gut microbiome interactions in irritable bowel syndrome by Research Square. Licensed under Creative Commons: By Attribution 3.0 License https://creativecommons.org/licenses/by/3.0/
- Video 3 – Microbiome and Obesity – Martin Blaser by National Human Genome Research Institute. Licensed under Creative Commons: By Attribution 3.0 License https://creativecommons.org/licenses/by/3.0/
- Video 4 – Gut microbiome composition after multi-donor fecal microbiota transplantation for obesity by Research Square. Licensed under Creative Commons: By Attribution 3.0 License https://creativecommons.org/licenses/by/3.0/
- Video 5 – Rob Knight: Fecal Transplants? The Disgusting is Par for the Course by World Economic Forum. Licensed under Creative Commons: By Attribution 3.0 License https://creativecommons.org/licenses/by/3.0/

References

1. Abulizi, N., Quin, C., Brown, K., Chan, Y. K., Gill, S. K., & Gibson, D. L. (2019). Gut Mucosal Proteins and Bacteriome Are Shaped by the Saturation Index of Dietary Lipids. *Nutrients*, *11*(2). https://doi.org/10.3390/nu11020418
2. Arbuckle, M. R., McClain, M. T., Rubertone, M. v, Scofield, R. H., Dennis, G. J., James, J. A., & Harley, J. B. (2003). Development of Autoantibodies before the Clinical Onset of Systemic Lupus Erythematosus. *New England Journal of Medicine*, *349*(16), 1526–1533. https://doi.org/10.1056/NEJMoa021933
3. Baker, S. S., Faden, H., Sayej, W., Patel, R., & Baker, R. D. (2010). Increasing Incidence of Community-Associated Atypical Clostridium difficile Disease in Children. *Clinical Pediatrics*, *49*(7), 644–647. https://doi.org/10.1177/0009922809360927
4. Becattini, S., Taur, Y., & Pamer, E. G. (2016). Antibiotic-Induced Changes in the Intestinal Microbiota and Disease. *Trends in Molecular Medicine*, *22*(6), 458–478. https://doi.org/10.1016/j.molmed.2016.04.003
5. Benson L, Song X, Campos J, Singh N. Changing epidemiology of Clostridium difficile-associated disease in children. Infect Control Hosp Epidemiol. 2007 Nov;28(11):1233-5. doi: 10.1086/520732. Epub 2007 Aug 27. PMID: 17926272.
6. Boulangé, C. L., Neves, A. L., Chilloux, J., Nicholson, J. K., & Dumas, M.-E. (2016). Impact of the gut microbiota on inflammation, obesity, and metabolic disease. *Genome Medicine*, *8*(1), 42. https://doi.org/10.1186/s13073-016-0303-2
7. Camacho-Ortiz, A., Gutiérrez-Delgado, E. M., Garcia-Mazcorro, J. F., Mendoza-Olazarán, S., Martínez-Meléndez, A., Palau-Davila, L., Baines, S. D., Maldonado-Garza, H., & Garza-González, E. (2017). Randomized clinical trial to evaluate the effect of fecal microbiota transplant for initial Clostridium difficile infection in intestinal microbiome. *PLOS ONE*, *12*(12), e0189768-. https://doi.org/10.1371/journal.pone.0189768

8. Cammarota, G., Masucci, L., Ianiro, G., Bibbò, S., Dinoi, G., Costamagna, G., Sanguinetti, M., & Gasbarrini, A. (2015). Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent Clostridium difficile infection. *Alimentary Pharmacology & Therapeutics*, *41*(9), 835–843. https://doi.org/10.1111/apt.13144
9. Cani, P. D., Amar, J., Iglesias, M. A., Poggi, M., Knauf, C., Bastelica, D., Neyrinck, A. M., Fava, F., Tuohy, K. M., Chabo, C., Waget, A., Delmée, E., Cousin, B., Sulpice, T., Chamontin, B., Ferrières, J., Tanti, J.-F., Gibson, G. R., Casteilla, L., … Burcelin, R. (2007). Metabolic Endotoxemia Initiates Obesity and Insulin Resistance. *Diabetes*, *56*(7), 1761. https://doi.org/10.2337/db06-1491
10. Clooney, A. G., Sutton, T. D. S., Shkoporov, A. N., Holohan, R. K., Daly, K. M., O'Regan, O., Ryan, F. J., Draper, L. A., Plevy, S. E., Ross, R. P., & Hill, C. (2019). Whole-Virome Analysis Sheds Light on Viral Dark Matter in Inflammatory Bowel Disease. *Cell Host & Microbe*, *26*(6), 764-778.e5. https://doi.org/10.1016/j.chom.2019.10.009
11. Costello, M.-E., Ciccia, F., Willner, D., Warrington, N., Robinson, P. C., Gardiner, B., Marshall, M., Kenna, T. J., Triolo, G., & Brown, M. A. (2015). Brief Report: Intestinal Dysbiosis in Ankylosing Spondylitis. *Arthritis & Rheumatology*, *67*(3), 686–691. https://doi.org/https://doi.org/10.1002/art.38967
12. Davenport, E. R., Mizrahi-Man, O., Michelini, K., Barreiro, L. B., Ober, C., & Gilad, Y. (2014). Seasonal Variation in Human Gut Microbiome Composition. *PLOS ONE*, *9*(3), e90731-. https://doi.org/10.1371/journal.pone.0090731
13. David, L. A., Maurice, C. F., Carmody, R. N., Gootenberg, D. B., Button, J. E., Wolfe, B. E., Ling, A. v, Devlin, A. S., Varma, Y., Fischbach, M. A., Biddinger, S. B., Dutton, R. J., & Turnbaugh, P. J. (2014). Diet rapidly and reproducibly alters the human gut microbiome. *Nature*, *505*(7484), 559–563. https://doi.org/10.1038/nature12820
14. de Bandt, J.-P., Waligora-Dupriet, A.-J., & Butel, M.-J. (2011). Intestinal microbiota in inflammation and insulin resistance: relevance to humans. *Current Opinion in Clinical Nutrition & Metabolic Care*, *14*(4). https://journals.lww.com/co-clinicalnutrition/Fulltext/2011/07000/Intestinal_microbiota_in_inflammation_and_insulin.5.aspx
15. DeFilipp, Z., Bloom, P. P., Torres Soto, M., Mansour, M. K., Sater, M. R. A., Huntley, M. H., Turbett, S., Chung, R. T., Chen, Y.-B., & Hohmann, E. L. (2019). Drug-Resistant E. coli Bacteremia Transmitted by Fecal Microbiota Transplant. *New England Journal of Medicine*, *381*(21), 2043–2050. https://doi.org/10.1056/NEJMoa1910437
16. Everard, A., & Cani, P. D. (2013). Diabetes, obesity and gut microbiota. *Best Practice & Research Clinical Gastroenterology*, *27*(1), 73–83. https://doi.org/10.1016/j.bpg.2013.03.007
17. Forbes, J. D., Bernstein, C. N., Tremlett, H., van Domselaar, G., & Knox, N. C. (2019). A Fungal World: Could the Gut Mycobiome Be Involved in Neurological Disease? *Frontiers in Microbiology*, *9*, 3249. https://www.frontiersin.org/article/10.3389/fmicb.2018.03249
18. Fujimoto, K., Kimura, Y., Allegretti, J. R., Yamamoto, M., Zhang, Y., Katayama, K., Tremmel, G., Kawaguchi, Y., Shimohigoshi, M., Hayashi, T., Uematsu, M., Yamaguchi, K., Furukawa, Y., Akiyama, Y., Yamaguchi, R., Crowe, S. E., Ernst, P. B., Miyano, S., Kiyono, H., … Uematsu, S. (2021). Functional Restoration of Bacteriomes and Viromes by Fecal Microbiota Transplantation. *Gastroenterology*, *160*(6), 2089-2102.e12. https://doi.org/10.1053/j.gastro.2021.02.013
19. Gaulke, C. A., & Sharpton, T. J. (2018). The influence of ethnicity and geography on human gut microbiome composition. *Nature Medicine*, *24*(10), 1495–1496. https://doi.org/10.1038/s41591-018-0210-8
20. George, R. H., Symonds, J. M., Dimock, F., Brown, J. D., Arabi, Y., Shinagawa, N., Keighley, M. R., Alexander-Williams, J., & Burdon, D. W. (1978). Identification of Clostridium difficile as a cause of pseudomembranous colitis. *British Medical Journal*, *1*(6114), 695. https://doi.org/10.1136/bmj.1.6114.695
21. Giongo, A., Gano, K. A., Crabb, D. B., Mukherjee, N., Novelo, L. L., Casella, G., Drew, J. C., Ilonen, J., Knip, M., Hyöty, H., Veijola, R., Simell, T., Simell, O., Neu, J., Wasserfall, C. H., Schatz, D., Atkinson, M. A., & Triplett, E. W. (2011). Toward defining the autoimmune microbiome for type 1 diabetes. *The ISME Journal*, *5*(1), 82–91. https://doi.org/10.1038/ismej.2010.92
22. Gu, Y., Zhou, G., Qin, X., Huang, S., Wang, B., & Cao, H. (2019). The Potential Role of Gut Mycobiome in Irritable Bowel Syndrome. *Frontiers in Microbiology*, *10*, 1894. https://www.frontiersin.org/article/10.3389/fmicb.2019.01894
23. Halfvarson, J., Brislawn, C. J., Lamendella, R., Vázquez-Baeza, Y., Walters, W. A., Bramer, L. M., D'Amato, M., Bonfiglio, F., McDonald, D., Gonzalez, A., McClure, E. E., Dunklebarger, M. F., Knight, R., & Jansson, J. K. (2017). Dynamics of the human gut microbiome in inflammatory bowel disease. *Nature Microbiology*, *2*(5), 17004. https://doi.org/10.1038/nmicrobiol.2017.4
24. He, M., Miyajima, F., Roberts, P., Ellison, L., Pickard, D. J., Martin, M. J., Connor, T. R., Harris, S. R., Fairley, D., Bamford, K. B., D'Arc, S., Brazier, J., Brown, D., Coia, J. E., Douce, G., Gerding, D., Kim, H. J., Koh, T. H., Kato, H., … Lawley, T. D.

(2013). Emergence and global spread of epidemic healthcare-associated Clostridium difficile. *Nature Genetics*, *45*(1), 109–113. https://doi.org/10.1038/ng.2478

25. Hensgens, M. P. M., Keessen, E. C., Squire, M. M., Riley, T. v, Koene, M. G. J., de Boer, E., Lipman, L. J. A., & Kuijper, E. J. (2012). Clostridium difficile infection in the community: a zoonotic disease? *Clinical Microbiology and Infection*, *18*(7), 635–645. https://doi.org/10.1111/j.1469-0691.2012.03853.x
26. Hoarau, G., Mukherjee, P. K., Gower-Rousseau, C., Hager, C., Chandra, J., Retuerto, M. A., Neut, C., Vermeire, S., Clemente, J., Colombel, J. F., Fujioka, H., Poulain, D., Sendid, B., Ghannoum, M. A., & A, B. R. (2021). Bacteriome and Mycobiome Interactions Underscore Microbial Dysbiosis in Familial Crohn's Disease. *MBio*, *7*(5), e01250-16. https://doi.org/10.1128/mBio.01250-16
27. Jackson, M. A., Verdi, S., Maxan, M.-E., Shin, C. M., Zierer, J., Bowyer, R. C. E., Martin, T., Williams, F. M. K., Menni, C., Bell, J. T., Spector, T. D., & Steves, C. J. (2018). Gut microbiota associations with common diseases and prescription medications in a population-based cohort. *Nature Communications*, *9*(1), 2655. https://doi.org/10.1038/s41467-018-05184-7
28. Jin, D., Wu, S., Zhang, Y., Lu, R., Xia, Y., Dong, H., & Sun, J. (2015). Lack of Vitamin D Receptor Causes Dysbiosis and Changes the Functions of the Murine Intestinal Microbiome. *Clinical Therapeutics*, *37*(5), 996-1009.e7. https://doi.org/10.1016/j.clinthera.2015.04.004
29. Johanesen, P. A., Mackin, K. E., Hutton, M. L., Awad, M. M., Larcombe, S., Amy, J. M., & Lyras, D. (2015). Disruption of the Gut Microbiome: Clostridium difficile Infection and the Threat of Antibiotic Resistance. *Genes*, *6*(4), 1347–1360. https://doi.org/10.3390/genes6041347
30. Johnson, K. V.-A. (2020). Gut microbiome composition and diversity are related to human personality traits. *Human Microbiome Journal*, *15*, 100069. https://doi.org/10.1016/j.humic.2019.100069
31. Kho, Z. Y., & Lal, S. K. (2018). The Human Gut Microbiome – A Potential Controller of Wellness and Disease. *Frontiers in Microbiology*, *9*, 1835. https://www.frontiersin.org/article/10.3389/fmicb.2018.01835
32. Kim, S. K., Guevarra, R. B., Kim, Y. T., Kwon, J., Kim, H., Cho, J. H., Kim, H. B., & Lee, J. H. (2019). Role of Probiotics in Human Gut Microbiome-Associated Diseases. *Journal of Microbiology and Biotechnology*, *29*(9), 1335–1340. https://doi.org/10.4014/jmb.1906.06064
33. Larsen, N., Vogensen, F. K., van den Berg, F. W. J., Nielsen, D. S., Andreasen, A. S., Pedersen, B. K., Al-Soud, W. A., Sørensen, S. J., Hansen, L. H., & Jakobsen, M. (2010). Gut Microbiota in Human Adults with Type 2 Diabetes Differs from Non-Diabetic Adults. *PLOS ONE*, *5*(2), e9085-. https://doi.org/10.1371/journal.pone.0009085
34. Leber, A., Viladomiu, M., Hontecillas, R., Abedi, V., Philipson, C., Hoops, S., Howard, B., & Bassaganya-Riera, J. (2015). Systems Modeling of Interactions between Mucosal Immunity and the Gut Microbiome during Clostridium difficile Infection. *PLOS ONE*, *10*(7), e0134849-. https://doi.org/10.1371/journal.pone.0134849
35. Lee, Y. K., Menezes, J. S., Umesaki, Y., & Mazmanian, S. K. (2011). Proinflammatory T-cell responses to gut microbiota promote experimental autoimmune encephalomyelitis. *Proceedings of the National Academy of Sciences*, *108*(Supplement 1), 4615. https://doi.org/10.1073/pnas.1000082107
36. Magne, F., Gotteland, M., Gauthier, L., Zazueta, A., Pesoa, S., Navarrete, P., & Balamurugan, R. (2020). The Firmicutes/Bacteroidetes Ratio: A Relevant Marker of Gut Dysbiosis in Obese Patients? *Nutrients*, *12*(5). https://doi.org/10.3390/nu12051474
37. Martinez-Gili, L., McDonald, J. a K., Liu, Z., Kao, D., Allegretti, J. R., Monaghan, T. M., Barker, G. F., Miguéns Blanco, J., Williams, H. R. T., Holmes, E., Thursz, M. R., Marchesi, J. R., & Mullish, B. H. (2020). Understanding the mechanisms of efficacy of fecal microbiota transplant in treating recurrent Clostridioides difficile infection and beyond: the contribution of gut microbial-derived metabolites. *Gut Microbes*, *12*(1), 1810531. https://doi.org/10.1080/19490976.2020.1810531
38. Mattila, E., Uusitalo–Seppälä, R., Wuorela, M., Lehtola, L., Nurmi, H., Ristikankare, M., Moilanen, V., Salminen, K., Seppälä, M., Mattila, P. S., Anttila, V., & Arkkila, P. (2012). Fecal Transplantation, Through Colonoscopy, Is Effective Therapy for Recurrent Clostridium difficile Infection. *Gastroenterology*, *142*(3), 490–496. https://doi.org/https://doi.org/10.1053/j.gastro.2011.11.037
39. McDermott, A. J., & Huffnagle, G. B. (2014). The microbiome and regulation of mucosal immunity. *Immunology*, *142*(1), 24–31. https://doi.org/https://doi.org/10.1111/imm.12231
40. McQuade, J. L., Ologun, G. O., Arora, R., & Wargo, J. A. (2020). Gut Microbiome Modulation Via Fecal Microbiota Transplant to Augment Immunotherapy in Patients with Melanoma or Other Cancers. *Current Oncology Reports*, *22*(7), 74. https://doi.org/10.1007/s11912-020-00913-y

41. Mikuls, T. R., Thiele, G. M., Deane, K. D., Payne, J. B., O'Dell, J. R., Yu, F., Sayles, H., Weisman, M. H., Gregersen, P. K., Buckner, J. H., Keating, R. M., Derber, L. A., Robinson, W. H., Holers, V. M., & Norris, J. M. (2012). Porphyromonas gingivalis and disease-related autoantibodies in individuals at increased risk of rheumatoid arthritis. *Arthritis & Rheumatism*, *64*(11), 3522–3530. https://doi.org/https://doi.org/10.1002/art.34595
42. Monaco, C. L., Gootenberg, D. B., Zhao, G., Handley, S. A., Ghebremichael, M. S., Lim, E. S., Lankowski, A., Baldridge, M. T., Wilen, C. B., Flagg, M., Norman, J. M., Keller, B. C., Luévano, J. M., Wang, D., Boum, Y., Martin, J. N., Hunt, P. W., Bangsberg, D. R., Siedner, M. J., … Virgin, H. W. (2016). Altered Virome and Bacterial Microbiome in Human Immunodeficiency Virus-Associated Acquired Immunodeficiency Syndrome. *Cell Host & Microbe*, *19*(3), 311–322. https://doi.org/https://doi.org/10.1016/j.chom.2016.02.011
43. Musso, G., Gambino, R., & Cassader, M. (2011). Interactions Between Gut Microbiota and Host Metabolism Predisposing to Obesity and Diabetes. *Annual Review of Medicine*, *62*(1), 361–380. https://doi.org/10.1146/annurev-med-012510-175505
44. Nagpal, R., & Yadav, H. (2017). Bacterial Translocation from the Gut to the Distant Organs: An Overview. *Annals of Nutrition and Metabolism*, *71(suppl 1)*(Suppl. 1), 11–16. https://doi.org/10.1159/000479918
45. Nagpal, R., Newman, T. M., Wang, S., Jain, S., Lovato, J. F., & Yadav, H. (2018). Obesity-Linked Gut Microbiome Dysbiosis Associated with Derangements in Gut Permeability and Intestinal Cellular Homeostasis Independent of Diet. *Journal of Diabetes Research*, *2018*, 3462092. https://doi.org/10.1155/2018/3462092
46. Norman, J. M., Handley, S. A., Baldridge, M. T., Droit, L., Liu, C. Y., Keller, B. C., Kambal, A., Monaco, C. L., Zhao, G., Fleshner, P., Stappenbeck, T. S., McGovern, D. P. B., Keshavarzian, A., Mutlu, E. A., Sauk, J., Gevers, D., Xavier, R. J., Wang, D., Parkes, M., & Virgin, H. W. (2015). Disease-Specific Alterations in the Enteric Virome in Inflammatory Bowel Disease. *Cell*, *160*(3), 447–460. https://doi.org/https://doi.org/10.1016/j.cell.2015.01.002
47. Ouwehand, A. C., Kirjavainen, P. v, Grönlund, M.-M., Isolauri, E., & Salminen, S. J. (1999). Adhesion of probiotic micro-organisms to intestinal mucus. *International Dairy Journal*, *9*(9), 623–630. https://doi.org/10.1016/S0958-6946(99)00132-6
48. Qin, X., Gu, Y., Liu, T., Wang, C., Zhong, W., Wang, B., & Cao, H. (2021). Gut mycobiome: A promising target for colorectal cancer. *Biochimica et Biophysica Acta (BBA) – Reviews on Cancer*, *1875*(1), 188489. https://doi.org/10.1016/j.bbcan.2020.188489
49. Reyes, A., Blanton, L. v, Cao, S., Zhao, G., Manary, M., Trehan, I., Smith, M. I., Wang, D., Virgin, H. W., Rohwer, F., & Gordon, J. I. (2015). Gut DNA viromes of Malawian twins discordant for severe acute malnutrition. *Proceedings of the National Academy of Sciences*, *112*(38), 11941. https://doi.org/10.1073/pnas.1514285112
50. Rogers, M. A. M., & Aronoff, D. M. (2016). The influence of non-steroidal anti-inflammatory drugs on the gut microbiome. *Clinical Microbiology and Infection*, *22*(2), 178.e1-178.e9. https://doi.org/10.1016/j.cmi.2015.10.003
51. Rouphael, N. G., O'Donnell, J. A., Bhatnagar, J., Lewis, F., Polgreen, P. M., Beekmann, S., Guarner, J., Killgore, G. E., Coffman, B., Campbell, J., Zaki, S. R., & McDonald, L. C. (2008). Clostridium difficile–associated diarrhea: an emerging threat to pregnant women. *American Journal of Obstetrics and Gynecology*, *198*(6), 635.e1-635.e6. https://doi.org/10.1016/j.ajog.2008.01.062
52. Shi, N., Li, N., Duan, X., & Niu, H. (2017). Interaction between the gut microbiome and mucosal immune system. *Military Medical Research*, *4*(1), 14. https://doi.org/10.1186/s40779-017-0122-9
53. Shkoporov, A. N., & Hill, C. (2019). Bacteriophages of the Human Gut: The "Known Unknown" of the Microbiome. *Cell Host & Microbe*, *25*(2), 195–209. https://doi.org/10.1016/j.chom.2019.01.017
54. Sohail, M. U., Althani, A., Anwar, H., Rizzi, R., & Marei, H. E. (2017). Role of the Gastrointestinal Tract Microbiome in the Pathophysiology of Diabetes Mellitus. *Journal of Diabetes Research*, *2017*, 9631435. https://doi.org/10.1155/2017/9631435
55. Stewart, D. B., Wright, J., Maria, F., McLimans, C. J., Vasily, T., Isabella, A., Owen, B., Hoi-Tong, W., Jeff, B., Rebecca, D., Regina, L., & Rosa, K.-B. (2021). Integrated Meta-omics Reveals a Fungus-Associated Bacteriome and Distinct Functional Pathways in Clostridioides difficile Infection. *MSphere*, *4*(4), e00454-19. https://doi.org/10.1128/mSphere.00454-19
56. Turnbaugh, P. J., Bäckhed, F., Fulton, L., & Gordon, J. I. (2008). Diet-Induced Obesity Is Linked to Marked but Reversible Alterations in the Mouse Distal Gut Microbiome. *Cell Host & Microbe*, *3*(4), 213–223. https://doi.org/10.1016/j.chom.2008.02.015
57. Xu, F., Fu, Y., Sun, T., Jiang, Z., Miao, Z., Shuai, M., Gou, W., Ling, C., Yang, J., Wang, J., Chen, Y., & Zheng, J.-S. (2020). The interplay between host genetics and the gut microbiome reveals common and distinct microbiome features for complex human diseases. *Microbiome*, *8*(1), 145. https://doi.org/10.1186/s40168-020-00923-9

58. Xu, Z., & Knight, R. (2015). Dietary effects on human gut microbiome diversity. *British Journal of Nutrition*, *113*(S1), S1–S5. https://doi.org/DOI: 10.1017/S0007114514004127
59. Yan, A., Butcher, J., Mack, D., & Stintzi, A. (2020). Virome Sequencing of the Human Intestinal Mucosal–Luminal Interface. *Frontiers in Cellular and Infection Microbiology*, *10*, 593. https://www.frontiersin.org/article/10.3389/fcimb.2020.582187
60. Yatsunenko, T., Rey, F. E., Manary, M. J., Trehan, I., Dominguez-Bello, M. G., Contreras, M., Magris, M., Hidalgo, G., Baldassano, R. N., Anokhin, A. P., Heath, A. C., Warner, B., Reeder, J., Kuczynski, J., Caporaso, J. G., Lozupone, C. A., Lauber, C., Clemente, J. C., Knights, D., … Gordon, J. I. (2012). Human gut microbiome viewed across age and geography. *Nature*, *486*(7402), 222–227. https://doi.org/10.1038/nature11053
61. Zhang, F., Zuo, T., Yeoh, Y. K., Cheng, F. W. T., Liu, Q., Tang, W., Cheung, K. C. Y., Yang, K., Cheung, C. P., Mo, C. C., Hui, M., Chan, F. K. L., Li, C.-K., Chan, P. K. S., & Ng, S. C. (2021). Longitudinal dynamics of gut bacteriome, mycobiome and virome after fecal microbiota transplantation in graft-versus-host disease. *Nature Communications*, *12*(1), 65. https://doi.org/10.1038/s41467-020-20240-x
62. Zou, Y., Ju, X., Chen, W., Yuan, J., Wang, Z., Aluko, R. E., & He, R. (2020). Rice bran attenuated obesity via alleviating dyslipidemia, browning of white adipocytes and modulating gut microbiota in high-fat diet-induced obese mice. *Food & Function*, *11*(3), 2406–2417. https://doi.org/10.1039/C9FO01524H

This page titled 20.2: The Gut Microbiome is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Dylan Parks via source content that was edited to the style and standards of the LibreTexts platform.

- **3.2: The Gut Microbiome** by Dylan Parks is licensed CC BY 4.0. Original source: https://uta.pressbooks.pub/microbiomeshealthandtheenvironment.

20.3: The Oral Microbiome

The Oral Microbiome

The oral microbiome as with other site-specific microbiomes on and inside the human body is very distinct for each individual and its makeup and function is reflective of a variety of factors. Even within the context of the oral cavity, there are several unique niches with their own microbial ecosystem, including saliva, tongue, teeth, gingiva, throat, tonsils, and others. Each of these habitats exhibit diverse and complex interactions between bacteria, archaea, fungi, viruses, and protozoa, where dysfunction can lead to a number diseases, both rare and common (Wade, 2013, Sampaio-Maia et al., 2016).

Factors Affecting Composition

The composition of the oral microbiome and its respective niches is inherently dependent on host genetics, but other factors and habits such diet and smoking have a substantial effect on diversity. Members of the oral cavity demonstrate more heritability than the gut microbiome, and higher abundances of certain heritable organisms, such as *Prevotella pallens*, are associated with a lack of dental caries, while on the other hand, *Streptococcus mutans* and *Lactobacillus* species are linked to cavities (Davenport, 2017, Xiao et al., 2018). Detection of the specific groups of microbes has traditionally been difficult since many are fastidious and cannot be cultivated. So other techniques like metagenomics, metatranscriptomics, and proteomics have been implemented to better characterize the microorganisms present and their respective roles (Parahitiyawa et al., 2010, Grassl et al., 2016). These studies have found that the oral microbiota is quite different even between healthy individuals, and so it may be the microbial functionality that is more important in the progression of various diseases, such as the role of biofilm formation, plaque buildup, and sugar metabolism in the development of dental caries (Segata et al., 2012, Takahashi et al., 2010, Duran-Pinedo and Frias-Lopez, 2015, Sato et al., 2015, Davenport, 2017).

Dysbiosis and Disease

The oral cavity is such a dynamic location that constantly experiences a variety of different foods, drinks, oral hygiene products, and other environmental stimuli with each composed of a multitude of macromolecules, compounds, and potentially other microorganisms, and so it makes sense that its microbiome often fluctuates in diversity (Parahitiyawa et al., 2010). Though there are differences in composition between individuals, specific sites, and over periods of time, species such as *Streptococcus mitis* and *Granulicatella adiacens* are conserved and generally present throughout the oral microbiome, while the presence of other specific microbes are associated with a particular disease (Aas et al., 2005). However, diseases like Periodontitis, which is the chronic inflammation of the gums and tooth supporting structures and one of the most common oral diseases, has many organisms associated with the condition, so discerning which ones are primarily responsible is a complex task. There are a variety of viruses that cause oral-related conditions, such as the Human papilloma virus (HPV) which is known for causing lesions and warts in the mouth, as well as head and neck squamous cell carcinoma (Kumaraswamy and Vidhya, 2011). An increase of the protozoa *Entamoeba gingivalis* and *Trichomonas tenax* are observed in patients with gingival disease, but are not the causative agents, rather just taking advantage of the increased food sources (bacteria and food debris) from poor hygiene (Wantland et al., 1958). There is also a variety of fungi present in the oral cavity with *Candida* species being the most common, and many of the members in the oral mycobiome are responsible for chronic diseases, however correlation isn't exactly clear (Ghannoum et al., 2010). Archaea, primarily methanogens, are also present in the oral microbiome, and while there aren't technically any known pathogens in this domain, there is an increase in abundance observed in patients with periodontitis (Lepp et al., 2004, Mattarazo et al., 2011, Wade, 2013, Willis and Gabaldon, 2020).

Generally, the oral microbiome is linked with aspects oral health and has primary implications in dental and periodontal diseases, however it can contribute to vitality and diseases in other parts of the body such as cardiovascular disease, stroke, Alzheimer's disease, cystic fibrosis, rheumatoid arthritis, diabetes, pneumonia, and preterm birth (Seymour et al., 2007, Duran-Pinedo and Frias-Lopez, 2015, Kori et al., 2020, Willis and Gabaldon, 2020). Additionally, the oral microbiome is implicated in various forms of cancer including esophageal, pancreatic, gastric, liver, colorectal, and oral (Willis and Gabaldon, 2020, Bakhti et al., 2021, Mohammed et al., 2021). In many of these types of cancers the Gram-negative anaerobe, *Fusobacterium nucleatum*, is a primary culprit as it can promote cancer by activation of cell proliferation, promotion of cellular invasion, induction of chronic inflammation and immune evasion (Al-hebshi et al., 2017, McIlvanna et al., 2021). Another contributing factor to cancer development is the use of tobacco products which cause oral microbiome dysbiosis (Al-habshi et al., 2017, Gopinath et al., 2021,

Sajid et al., 2021). As with other microbiomes, deviation from the normal composition can result in altered function and progression of disease.

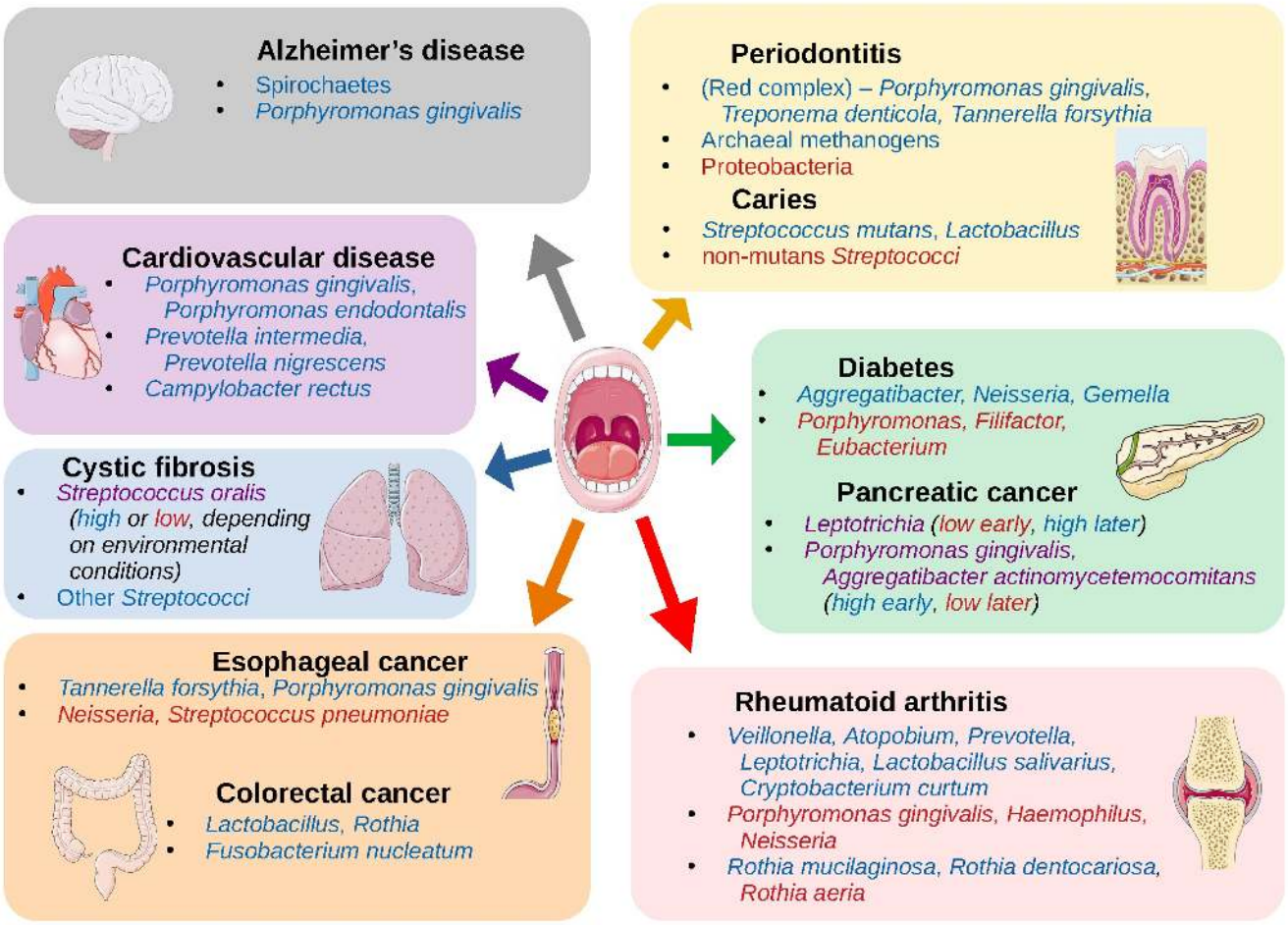


Figure 1. Oral and systemic diseases associated with the oral microbiome. A representation of the associations found between diseases with increases or decreases of the abundances of organisms in the oral cavity. Organisms listed in blue have been shown to be increased in abundance in the oral cavity in individuals presenting with the noted disease, and organisms listed in red have been shown to be decreased. Those in purple may be either increased or decreased depending on the conditions or progression of the disease. (Willis and Gabaldon, 2020).

Disease	Associated Organisms	Inhibited Organisms
Periodontitis	Phyla: Spirochaetes, Synergistetes and Bacteroidetes Classes: Clostridia, Negativicutes and Erysipelotrichia Genera: *Prevotella, Fusobacterium* Species: *Porphyromonas gingivalis, Treponema denticola, Tannerella forsythia, Filifactor alocis, Parvimonas micra, Aggregatibacter actinomycetemcomitans* Archaea: *Methanobrevibacter oralis, Methanobacterium curvum/congolense*, and *Methanosarcina mazeii*	Phyla: Proteobacteria Classes: Bacilli Genera: *Streptococcus, Actinomyces, Granulicatella*
Dental caries	Genera: *Neisseria, Selenomonas, Propionibacterium* Species: *Streptococcus mutans, Lactobacillus* spp. Fungi: *Candida albicans*	Species: non-mutans *Streptococci, Corynebacterium matruchotii, Capnocytophaga gingivalis, Eubacterium IR009, Campylobacter rectus, Lachnospiraceae sp. C1*
Oral cancer	Species: *Capnocytophaga gingivalis, Prevotella melaninogenica* and *Streptococcus mitis, Peptostreptococcus stomatis*, Streptococcus salivarius*, Streptococcus gordonii*, Gemella haemolysans*, Gemella morbillorum*, Johnsonella ignava* and Streptococcus parasanguinis I**	Species: *Granulicatella adiacens**
Esophageal cancer	Species: *Tannerella forsythia, Porphyromonas gingivalis*	Genera: *Neisseria* Species: *Streptococcus pneumoniae*

Figure 2. Examples of metagenomic studies of associations between the oral microbiome and oral diseases. The first column indicates a disease, the second indicates organisms that have been found at higher abundances in individuals presenting with the disease, and the third indicates organisms at lower abundances. (*) indicates taxa associated with oral cancer from a study in which samples were from tumor and non-tumor sites in the same patients and disease treatment is not specified. References: Matarazzo et al., 2011, Lepp et al., 2004, Vartoukian et al, 2009, Griffen et al., 2012, Costalonga and Herzberg, 2014, Liu et al., 2012, Jorth et al., 2014, Haubek, 2010, Koo and Bowen, 2014, Gross et al., 2010, Wang and Ganly, 2014, Pushalkar et al., 2012, Mager et al., 2005, Peters et al., 2017, Willis and Gabaldon, 2020.

Saliva

Saliva is an important component in maintaining homeostasis in the oral cavity, as it lubricates food, initiates the digestive process, and defends against bacteria. Disruption in secretion can lead to changes in the oral microbiome which promotes progression of oral and other diseases (Grassl et al., 2016). Since saliva contacts virtually all surfaces within the oral cavity it is involved with all other duties of the mouth, and adaptive and innate immune defense mechanisms can be considered the most important in terms of microbiological clinical relevance. The protein and gycoprotein content regulates the oral microbiome by promoting the colonization of commensal microbiota while helping eliminate pathogenic microbes (Cross and Ruhl, 2018). These macromolecules aid in bacterial adhesion and biofilm formation so that they aren't dislodged by salivary flow and other oral physiological processes (Mandel, 1987). The establishment of beneficial microbes prevents pathogenic bacteria from gaining a foothold, and the agglutinins found in saliva aid in removal through binding and then swallowing (Scannapieco, 1994). The co-evolution of the microbiota and humans has cultivated the development of specific bacterial adhesins for colonization of the preferred microorganisms, thus establishing a mutualism, though pathogenic microbes are quick to adapt to changing binding motifs (Springer and Gagneux, 2013, Cross and Ruhl, 2018).

Saliva can harbor numerous microbes, with one milliliter containing approximately one hundred million microbial cells (Marsh et al., 2015) and over 600 different species (Dewhirst et al., 2020, Willis and Gabaldon, 2020). In one study, the prominent genera found across various types of saliva samples (i.e. spit, drool, and oral rinse) from healthy individuals were *Streptococcus* (17.5%), *Prevotella* (15.5%), *Veillonella* (15.3%), *Neisseria* (12.7%) and *Haemophilus* (10%) (Lim et al., 2017). Though it can be difficult to differentiate a core salivary microbiota from other specific oral niches since it coats the oral cavity.

For those suffering from various diseases, the relative abundance of certain microorganisms and general composition of the oral microbiota is altered as compared to healthy controls. For example, patients suffering from chronic obstructive pulmonary disease

(COPD) and periodontitis have varying abundances of *Veillonella*, *Rothia*, *Actinomyces*, and *Fusobacterium* in saliva samples (Lin et al., 2020). Periodontitis and COPD are comorbid diseases that are commonly associated with other conditions like rheumatoid arthritis, diabetes mellitus, and cardiovascular diseases (Scher et al., 2014, Wang et al., 2014, Chrysanthakopoulos and Chrysanthakopoulos, 2014, Lin et al., 2020). Dysfunction of bacterial ecology in saliva is exacerbated by COPD and periodontitis, and so restoration of the salivary microbiota may treat or reduce the severity of these diseases and their comorbidities (Jeffcoat et al., 2014, Zhou et al., 2014, Lin et al., 2020).

Alterations of the salivary microbiome are also associated with certain human viral infections like the herpes virus, influenza, and SARS-CoV (Blostein et al., 2021, Miller et al., 2021). Saliva generally is beneficial to oral health, though changes in it's makeup could be detrimental and further aggravate disease. For instance, the saliva microbiota and their byproducts could be responsible for increased susceptibility of infection of gum tissues with herpes simplex virus 1, especially in individuals with periodontitis lesions (Zuo et al., 2019). Eukaryotic viruses can also directly interact with oral bacteria and affect disease severity, as is the case with streptococci and influenza which results in an increased viral load (Kamio et al., 2015). Similarly, among patients with COVID-19 there are differences in the salivary bacterial community based on SARS-CoV-2 viral load, though the exact dynamics and repercussions of the interaction isn't yet well understood. It is possible that COVID-19-induced inflammation could directly impact the oral microbiome and contribute to other diseases connected with dysbiosis (Miller et al., 2021).

Dysbiosis of the fungal component in the salivary microbiome also contributes to overall oral microbial community changes and detrimental effects to the human host. The mycobiome is an important constituent of the oral microbiome though its member's abundance is much less than that of the bacteriome. There are two main genera in the salivary mycobiome: *Candida* and *Malassezia*, where the former is associated with dental plaque bacteria, carbohydrate-rich microbial communities, and acidic pH conditions which contribute to dental caries (Hong et al., 2020). Other interactions between the mycobiome and bacteriome in saliva has been observed in the chronic inflammatory disease oral lichen planus (OLP). OLP causes swelling, discoloration, and open sores of the mucosal membranes in the oral cavity, primarily affecting the buccal region (cheek), but the lips, gingiva, and tongue may also be affected. Similar to plaque buildup and cavity formation, this disease is characterized by an increased abundance of genera *Candida*, but also *Aspergillus*, as well as a decrease in biodiversity (Li et al., 2019).

While diversity and abundance of specific groups within the salivary microbiome are associated with various diseases, it is important to consider other factors like diet, lifestyle habits, and genetics that can influence the progression of any particular disease.

Teeth, Plaque, and Cavities

Plaque formation occurs when a multispecies biofilm builds layers on the surface of teeth over time. This structure not only contains a variety of microbes, some of which are pathogenic, but proteins, carbohydrates, minerals, antimicrobial peptides and other compounds that dictate its structure and activity (Amerongen and Veerman, 2002, Flemmig and Beikler, 2011, Zarco et al., 2011). For normal healthy individuals, plaque biofilms are important in maintaining oral homeostasis and good tooth conditions as they can trap pathogens or prevent them from thriving due to competitive inhibition. However, regular detachment of these biofilms through oral hygiene and salivary flow are necessary to prevent pathogen establishment and their escape from immune responses and antimicrobial therapy (Avila et al., 2009, Filoche et al., 2009, Van Essche et al., 2010, Flemmig and Beikler, 2011, Zarco et al., 2011).

The persistence of oral biofilms contributes directly to cavity formation as carbohydrate-fermenting microbes within produce acidic byproducts which lower oral pH and damage tooth enamel (Selwitz et al., 2007, Ling et al., 2010). Cavities form once the surface layers of the tooth wear away and lesions form in the dentin, resulting in oral pain, tooth decay and loss (Selwitz et al., 2007, Zarco et al., 2011). Dental caries are the most prevalent disease for children worldwide, and dental care is the most common unmet need among children in the United States (Loesche and Grenier, 1976, Acs et al., 1999, Low et al., 1999, Peterson et al., 2013).

The fastidious nature of several members of plaque polymicrobial communities have made it traditionally difficult to characterize an exact consortium responsible for dental caries, however, recent studies using NGS technologies have detailed a few signature genera. *Streptococcus mutans* and *Lactobacilli* spp. are the primary culprits, but other genera such as *Fusobacterium*, *Bifidobacterium*, and *Actinomyces* are found in high abundance in people with cavities (Munson et al., 2004, Chhour et al., 2005, Corby et al., 2005, Peterson et al., 2013). The fungal yeast, *Candida albicans*, is also found regularly in children with severe early childhood caries (S-ECC) (Xiao et al., 2018). Interestingly, other members of *Streptococcus* including *S. parasanguinis*, *S. mitis*, *S.*

oralis, and *S. sanguinis* are associated with individuals exhibiting good dental health (Corby et al., 2005, Peterson et al., 2013). Overall, during the progression of caries there is a reduction in species diversity in these communities (Peterson et al., 2013).

Gingivae and Periodontitis

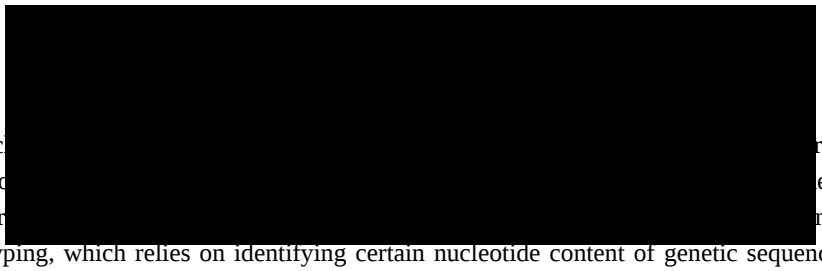
Aside from dental caries, periodontitis, a.k.a. 'gum disease', is the other most common oral disease in humans, and it also results from alterations in oral microbial ecology. This inflammatory condition affects the supporting structures surrounding the teeth where the microbial communities that inhabit the subgingival area serve to trigger its onset (Hajishengallis and Lamont, 2012, Hong et al., 2015). Though progression of the disease comes in episodes, the continual breakdown of periodontium tissue (gingiva, periodontal ligament, cementum, and alveolar bone) leads to alveolar bone breakdown, formation of pocket lesions, and tooth loss (Listgarten, 1986). This condition is very difficult treat as specific antibiotics must be administered, though they are often unsuccessful as pathogens can hide in plaque, develop resistance, and quickly recolonize through reserves in the mucous membranes of the oral cavity. Once pockets form in the periodontium, periodontitis becomes irreversible, as the tissues are unable to reattach to the bone and the pathogens within cannot be completely eradicated or removed (Pihlstrom et al., 2005, Horz and Conrads, 2007, Van Essche et al., 2011, Zarco et al., 2011).

Culture-based studies have shown that periodontitis is associated with varying levels of abundance of three bacterial species: *Porphyromonas gingivalis*, *Tannerella forsythia* and *Treponema denticola*, which are collective referred to as the 'red complex' (Socransky et al., 1998, Rocas et al., 2001, Socransky and Hafajee, 2005, Teles et al., 2010). More recent genetic analysis has revealed other bacteria associated with the disease, including those from the classes Clostridia, Negativicutes, and Erysipelotrichia; the genera *Synergistes*, *Prevotella*, and *Fusobacterium*; and the species *Filifactor alocis* (Vartoukian et al, 2009, Griffen et al., 2012, Costalonga and Herzberg, 2014, Willis and Gabaldon, 2020). Some methanogenic archaeal species have even been implicated in the disease, and perhaps serve a metabolic role as a 'hydrogen sink' for secondary fermenters (Lepp et al., 2004, Matarazzo et al., 2011). Viruses, both eukaryotic and bacteriophages, are also thought to play a part in the etiology of periodontitis. While bacteriophages manage biofilm formation through bacterial predation, the role of eukaryotic viruses found in the oral cavity such as those in the Herpesvirus family, is more enigmatic (Martinez et al., 2021). The protist *Trichomonas tenax* is frequently found in patients with severe periodontitis, though it is not known if its presence is a cause or a result of the disease (Benabdelkader et al., 2019. It is generally thought that this condition arises from events of dysbiosis causing an increase in community diversity and richness which then alters antagonistic/synergistic relationships, metabolic functions, and the oral environment (Kolenbrander et al., 2006, Shi et al., 2015, Ng et al., 2021). Those bacteria that may be absent or inhibited during dysbiosis conditions, and are associated with good periodontal health include those from the phylum Proteobacteria and the Firmicutes, class Bacilli, and the genera *Streptococcus*, *Actinomyces*, and *Granulicatella* (Griffen et al., 2012, Liu et al., 2012, Willis and Gabaldon, 2020).

Periodontitis resulting from oral microbiome dysbiosis has been linked to other diseases like chronic kidney disease, as well as several types of cancers including oral, esophageal, gastric, lung, pancreatic, prostate, hematologic, and breast (Fitzpatrick and Katz, 2010, Ioanndiou and Swede, 2011, Michaud et al., 2017). These associations stemming from the oral cavity could be due to dysbiosis-induced microbiome changes and recruitment of disease causing pathogens, production of harmful microbial-derived byproducts, and/or modulation of the immune system causing an increase in proinflammatory cytokines (Abnet et al., 2005, Kurkivuori et al., 2007, Chalabi et al., 2008, Meurman, 2010, Willis and Gabaldon, 2020). In reality, there are likely a multitude of factors and interactions between microbial communities and the host that lead to the progression of these diseases, however, it is still important to determine certain organismal signatures or functions that could indicate a condition and perhaps aid in diagnosis or treatment.



Tongue



The tongue is another nic ral centerpiece that comes into contact with the rest c e serves as an ideal model to analyze changing micr ng a novel computational method known as oligotyping, which relies on identifying certain nucleotide content of genetic sequences, a better resolution of microbial taxonomic distribution can be achieved (Eren et al., 2014, Welch et al., 2014, Wilbert et al., 2020). As expected, the tongue experiences large fluctuations in relative abundance across taxa, but this isn't completely explained by obvious human behavior such as oral hygiene and food/liquid intake. The complex microbial organization that is observed is likely a combination of many factors, like other microbiomes, such as host immunity, physiology influenced by circadian rhythm, epithelial cell renewal, other microbial (e.g. bacteriophage) interactions, as well as certain host behaviors and lifestyles (Welch et al., 2014, Wilbert et al., 2020).

The changing microbiome of the tongue can also be linked to various diseases and conditions in both the oral cavity and throughout the rest of the body. Viewing the tongue for diagnosis isn't a novel approach either, as traditional Chinese medical practices have viewed tongue phenotypes to discern various illnesses for thousands of years, and currently physical aspects of the tongue are being connected with its microbiome composition to better diagnosis certain diseases like oral, liver, gastric, colorectal, and pancreatic head cancers (Jiang et al., 2012, Han et al., 2014, Mukherjee et al., 2017, Cui et al., 2019 Lu et al., 2019, Mohammed et al., 2021). It is also interesting that members of the tongue microbiome can help regulate blood pressure and cardiovascular health through metabolism of dietary nitrate, and oral hygiene (e.g. tongue cleaning) can help promote the growth of these beneficial organisms (Tribble et al., 2019). While good habits like proper oral hygiene can cultivate a healthy oral microbiome and improve overall health, bad habits like smoking negatively affect microbial communities which contributes to various diseases. For example, metagenomic analysis investigating bacterial species and their gene content showed significant differences of certain species, strains, and metabolic pathways within the tongue microbiome between smokers and never smokers (Sato et al., 2020). This further demonstrates the usefulness of tongue microbiome analysis as a reliable technique to explore and diagnosis certain diseases and conditions.

Conclusion

Though not as well characterized as the gut microbiome, the oral microbiome has a significant impact on human health. Within the oral cavity, specific niche microbiomes of saliva, teeth, gums, and tongue are each compositionally unique and implicated in various conditions and diseases. Moreover still, other oral niches like the buccal mucosa, palate, pharynx, and tonsils not detailed here are distinctive and have certain associated diseases initiated with respective microbiome dysbiosis (Gao et al., 2014, Fukui et al., 2018, van der Meulen et al., 2018). Areas within the oral microbiome may eventually become routine sites for medical observation since samples are easily acquired, especially saliva, and microbial analysis can serve as a fast and reliable option for diagnosis and potential treatment of oral disorders as well as other diseases.

As the oral cavity is the initial point of contact and entrance for foreign microbial loads into the body, oral disease and its associated microbial ecology appear to serve as a conduit for a multitude of other diseases. In a sense the oral microbiome can be considered a precursor to the gut and lung microbiomes, as microbes are undoubtedly mixed with food, drink, and air before being swallowed or inhaled and taken further into the respective system. It is therefore important to understand and better characterize the oral microbiome so that medical diagnosis and intervention can be improved. However, with vast differences in microbial community diversity and composition between humans across the word, this will be quite the challenge to determine normalized healthy consortia respective to people of various geographic regions, ages, lifestlyes, etc.

Hotspot Quiz

Check Your Understanding

- What aspects of the oral microbiome allow for the formation of unique niches?
- How does dysbiosis within the oral microbiome contribute to certain diseases? (What aspects of changes in microbial community diversity and richness could cause oral and other diseases?)

- Why may saliva sampling be considered a viable option for diagnosis of oral and other diseases?
- How do oral biofilms contribute to cavity formation and tooth decay?
- Why are microbial infections associated with periodontitis hard to treat?
- How do certain lifestyles influence various niches of the oral microbiome and lead to disease?

Media Attributions

- Video 1 – GM2: Periodontal Microbiome – Murray Brilliant by National Human Genome Research Institute. Licensed under Creative Commons: By Attribution 3.0 License https://creativecommons.org/licenses/by/3.0/
- Figure 1 – Oral and systemic diseases associated with the oral microbiome by Willis and Gabaldon, 2020, caption adapted by Dylan Parks. Licensed under Creative Commons: By Attribution 4.0 License http://creativecommons.org/licenses/by/4.0/
- Images of body sites and organs in Figure 1 by Servier Medical Art. Licensed under Creative Commons: By Attribution 3.0 License https://creativecommons.org/licenses/by/3.0/
- Figure 2 – Examples of metagenomic studies of associations between the oral microbiome and oral diseases by Willis and Gabaldon, 2020, caption adapted by Dylan Parks. Licensed under Creative Commons: By Attribution 4.0 License http://creativecommons.org/licenses/by/4.0/

References

1. Aas, J. A., Paster, B. J., Stokes, L. N., Ingar, O., & Dewhirst, F. E. (2005). Defining the Normal Bacterial Flora of the Oral Cavity. *Journal of Clinical Microbiology*, *43*(11), 5721–5732. https://doi.org/10.1128/JCM.43.11.5721-5732.2005
2. Abnet, C. C., Qiao, Y.-L., Dawsey, S. M., Dong, Z.-W., Taylor, P. R., & Mark, S. D. (2005). Tooth loss is associated with increased risk of total death and death from upper gastrointestinal cancer, heart disease, and stroke in a Chinese population-based cohort. *International Journal of Epidemiology*, *34*(2), 467–474. https://doi.org/10.1093/ije/dyh375
3. Acs, G., Shulman, R., Ng, M. W., & Chussid, S. (1999). The effect of dental rehabilitation on the body weight of children with early childhood caries. *Pediatric dentistry*, *21*(2), 109–113.
4. Al-hebshi, N. N., Alharbi, F. A., Mahri, M., & Chen, T. (2017). Differences in the Bacteriome of Smokeless Tobacco Products with Different Oral Carcinogenicity: Compositional and Predicted Functional Analysis. *Genes, 8(4), 106.* https://doi.org/10.3390/genes8040106
5. Al-hebshi, N. N., Nasher, A. T., Maryoud, M. Y., Homeida, H. E., Chen, T., Idris, A. M., & Johnson, N. W. (2017). Inflammatory bacteriome featuring Fusobacterium nucleatum and Pseudomonas aeruginosa identified in association with oral squamous cell carcinoma. *Scientific Reports*, *7*(1), 1834. https://doi.org/10.1038/s41598-017-02079-3
6. Amerongen, A. V. N., & Veerman, E. C. I. (2002). Saliva – the defender of the oral cavity. *Oral Diseases*, *8*(1), 12–22. https://doi.org/10.1034/j.1601-0825.2002.1o816.x
7. Avila, M., Ojcius, D. M., & Yilmaz, Ö. (2009). The Oral Microbiota: Living with a Permanent Guest. *DNA and Cell Biology*, *28*(8), 405–411. https://doi.org/10.1089/dna.2009.0874
8. Bakhti, S. Z., & Latifi-Navid, S. (2021). Oral microbiota and Helicobacter pylori in gastric carcinogenesis: what do we know and where next? *BMC Microbiology*, *21*(1), 71. https://doi.org/10.1186/s12866-021-02130-4
9. Benabdelkader, S., Andreani, J., Gillet, A., Terrer, E., Pignoly, M., Chaudet, H., Aboudharam, G., & la Scola, B. (2019). Specific clones of Trichomonas tenax are associated with periodontitis. *PLOS ONE*, *14*(3), e0213338-. https://doi.org/10.1371/journal.pone.0213338
10. Blostein, F., Foote, S., Salzman, E., McNeil, D. W., Marazita, M. L., Martin, E. T., & Foxman, B. (2021). Associations Between Salivary Bacteriome Diversity and Salivary Human Herpesvirus Detection in Early Childhood: A Prospective Cohort Study. *Journal of the Pediatric Infectious Diseases Society*, *10*(8), 856–863. https://doi.org/10.1093/jpids/piab044
11. Chalabi, M., Moghim, S., Mogharehabed, A., Najafi, F., & Rezaie, F. (2008). EBV and CMV in chronic periodontitis: a prevalence study. *Archives of Virology*, *153*(10), 1917. https://doi.org/10.1007/s00705-008-0186-7
12. Chhour, K. L., Nadkarni, M. A., Byun, R., Martin, F. E., Jacques, N. A., & Hunter, N. (2005). Molecular Analysis of Microbial Diversity in Advanced Caries. *Journal of Clinical Microbiology*, *43*(2), 843–849. https://doi.org/10.1128/JCM.43.2.843-849.2005
13. Chrysanthakopoulos, N. A., & Chrysanthakopoulos, P. A. (2016). Association between indices of clinically-defined periodontitis and self-reported history of systemic medical conditions. *Journal of Investigative and Clinical Dentistry*, *7*(1), 27–

36. https://doi.org/10.1111/jicd.12119
14. Corby, P. M., Lyons-Weiler, J., Bretz, W. A., Hart, T. C., Aas, J. A., Boumenna, T., Goss, J., Corby, A. L., Junior, H. M., Weyant, R. J., & Paster, B. J. (2005). Microbial Risk Indicators of Early Childhood Caries. *Journal of Clinical Microbiology*, *43*(11), 5753–5759. https://doi.org/10.1128/JCM.43.11.5753-5759.2005
15. Costalonga, M., & Herzberg, M. C. (2014). The oral microbiome and the immunobiology of periodontal disease and caries. *Immunology Letters*, *162*(2, Part A), 22–38. https://doi.org/10.1016/j.imlet.2014.08.017
16. Cross, B. W., & Ruhl, S. (2018). Glycan recognition at the saliva – oral microbiome interface. *Cellular Immunology*, *333*, 19–33. https://doi.org/10.1016/j.cellimm.2018.08.008
17. Cui, J., Cui, H., Yang, M., Du, S., Li, J., Li, Y., Liu, L., Zhang, X., & Li, S. (2019). Tongue coating microbiome as a potential biomarker for gastritis including precancerous cascade. *Protein & Cell*, *10*(7), 496–509. https://doi.org/10.1007/s13238-018-0596-6
18. Davenport, E. R. (2017). Tooth Be Told, Genetics Influences Oral Microbiome. *Cell Host & Microbe*, *22*(3), 251–253. https://doi.org/https://doi.org/10.1...om.2017.08.018
19. Dewhirst, F. E., Tuste, C., Jacques, Paster, B. J., Tanner, A. C. R., Wen-Han, Y., Abirami, L., & Wade, W. G. (2010). The Human Oral Microbiome. *Journal of Bacteriology*, *192*(19), 5002–5017. https://doi.org/10.1128/JB.00542-10
20. Duran-Pinedo, A. E., & Frias-Lopez, J. (2015). Beyond microbial community composition: functional activities of the oral microbiome in health and disease. *Microbes and Infection*, *17*(7), 505–516. https://doi.org/10.1016/j.micinf.2015.03.014
21. Eren, A. M., Borisy, G. G., Huse, S. M., & Mark Welch, J. L. (2014). Oligotyping analysis of the human oral microbiome. *Proceedings of the National Academy of Sciences*, *111*(28), E2875. https://doi.org/10.1073/pnas.1409644111
22. Filoche, S., Wong, L., & Sissons, C. H. (2009). Oral Biofilms: Emerging Concepts in Microbial Ecology. *Journal of Dental Research*, *89*(1), 8–18. https://doi.org/10.1177/0022034509351812
23. Fitzpatrick, S. G., & Katz, J. (2010). The association between periodontal disease and cancer: A review of the literature. *Journal of Dentistry*, *38*(2), 83–95. https://doi.org/10.1016/j.jdent.2009.10.007
24. Flemmig, T. F., & Beikler, T. (2011). Control of oral biofilms. *Periodontology 2000*, *55*(1), 9–15. https://doi.org/10.1111/j.1600-0757.2010.00383.x
25. Fukui, Y., Aoki, K., Ishii, Y., & Tateda, K. (2018). The palatine tonsil bacteriome, but not the mycobiome, is altered in HIV infection. *BMC Microbiology*, *18*(1), 127. https://doi.org/10.1186/s12866-018-1274-9
26. Gao, Z., Kang, Y., Yu, J., & Ren, L. (2014). Human Pharyngeal Microbiome May Play A Protective Role in Respiratory Tract Infections. *Genomics, Proteomics & Bioinformatics*, *12*(3), 144–150. https://doi.org/10.1016/j.gpb.2014.06.001
27. Ghannoum, M. A., Jurevic, R. J., Mukherjee, P. K., Cui, F., Sikaroodi, M., Naqvi, A., & Gillevet, P. M. (2010). Characterization of the Oral Fungal Microbiome (Mycobiome) in Healthy Individuals. *PLOS Pathogens*, *6*(1), e1000713-. https://doi.org/10.1371/journal.ppat.1000713
28. Gopinath, D., Wie, C. C., Banerjee, M., Thangavelu, L., Kumar R, P., Nallaswamy, D., Botelho, M. G., & Johnson, N. W. (2021). Compositional profile of mucosal bacteriome of smokers and smokeless tobacco users. *Clinical Oral Investigations*. https://doi.org/10.1007/s00784-021-04137-7
29. Grassl, N., Kulak, N. A., Pichler, G., Geyer, P. E., Jung, J., Schubert, S., Sinitcyn, P., Cox, J., & Mann, M. (2016). Ultra-deep and quantitative saliva proteome reveals dynamics of the oral microbiome. *Genome Medicine*, *8*(1), 44. https://doi.org/10.1186/s13073-016-0293-0
30. Griffen, A. L., Beall, C. J., Campbell, J. H., Firestone, N. D., Kumar, P. S., Yang, Z. K., Podar, M., & Leys, E. J. (2012). Distinct and complex bacterial profiles in human periodontitis and health revealed by 16S pyrosequencing. *The ISME Journal*, *6*(6), 1176–1185. https://doi.org/10.1038/ismej.2011.191
31. Gross, E. L., Leys, E. J., Gasparovich, E. R., Firestone, N. D., Swartzbaum, J. A., Janies, D. A., Asnani, K., & Griffen, A. L. (2010). Bacterial 16S Sequence Analysis of Severe Caries in Young Permanent Teeth. *Journal of Clinical Microbiology*, *48*(11), 4121–4128. https://doi.org/10.1128/JCM.01232-10
32. Hajishengallis, G., & Lamont, R. J. (2012). Beyond the red complex and into more complexity: the polymicrobial synergy and dysbiosis (PSD) model of periodontal disease etiology. *Molecular Oral Microbiology*, *27*(6), 409–419. https://doi.org/10.1111/j.2041-1014.2012.00663.x
33. Han, S., Chen, Y., Hu, J., & Ji, Z. (2014). Tongue images and tongue coating microbiome in patients with colorectal cancer. *Microbial Pathogenesis*, *77*, 1–6. https://doi.org/10.1016/j.micpath.2014.10.003

34. Haubek, D. (2010). The highly leukotoxic JP2 clone of Aggregatibacter actinomycetemcomitans: Evolutionary aspects, epidemiology and etiological role in aggressive periodontitis. APMIS, 118.
35. Hong, B. Y., Hoare, A., Cardenas, A., Dupuy, A. K., Choquette, L., Salner, A. L., Schauer, P. K., Hegde, U., Peterson, D. E., Dongari-Bagtzoglou, A., Strausbaugh, L. D., & Diaz, P. I. (2020). The Salivary Mycobiome Contains 2 Ecologically Distinct Mycotypes. *Journal of Dental Research*, *99*(6), 730–738. https://doi.org/10.1177/0022034520915879
36. Horz, H.-P., & Conrads, G. (2007). Diagnosis and anti-infective therapy of periodontitis. *Expert Review of Anti-Infective Therapy*, *5*(4), 703–715. https://doi.org/10.1586/14787210.5.4.703
37. Ioannidou, E., & Swede, H. (2011). Disparities in Periodontitis Prevalence among Chronic Kidney Disease Patients. *Journal of Dental Research*, *90*(6), 730–734. https://doi.org/10.1177/0022034511402209
38. Jeffcoat, M. K., Jeffcoat, R. L., Gladowski, P. A., Bramson, J. B., & Blum, J. J. (2014). Impact of Periodontal Therapy on General Health: Evidence from Insurance Data for Five Systemic Conditions. *American Journal of Preventive Medicine*, *47*(2), 166–174. https://doi.org/10.1016/j.amepre.2014.04.001
39. Jiang, B., Liang, X., Chen, Y., Ma, T., Liu, L., Li, J., Jiang, R., Chen, T., Zhang, X., & Li, S. (2012). Integrating next-generation sequencing and traditional tongue diagnosis to determine tongue coating microbiome. *Scientific Reports*, *2*(1), 936. https://doi.org/10.1038/srep00936
40. Jorth, P., Turner, K. H., Gumus, P., Nizam, N., Buduneli, N., & Whitely, M. (2014). Metatranscriptomics of the Human Oral Microbiome during Health and Disease. *MBio*, *5*(2), e01012-14. https://doi.org/10.1128/mBio.01012-14
41. Kamio, N., Imai, K., Shimizu, K., Cueno, M. E., Tamura, M., Saito, Y., & Ochiai, K. (2015). Neuraminidase-producing oral mitis group streptococci potentially contribute to influenza viral infection and reduction in antiviral efficacy of zanamivir. *Cellular and Molecular Life Sciences*, *72*(2), 357–366. https://doi.org/10.1007/s00018-014-1669-1
42. Kolenbrander, P. E., Palmer, R. J., Jr, Rickard, A. H., Jakubovics, N. S., Chalmers, N. I., & Diaz, P. I. (2006). Bacterial interactions and successions during plaque development. *Periodontology 2000*, *42*, 47–79. https://doi.org/10.1111/j.1600-0757.2006.00187.x
43. Koo, H., & Bowen, W. H. (2014). Candida albicans and Streptococcus mutans: a potential synergistic alliance to cause virulent tooth decay in children. *Future Microbiology*, *9*(12), 1295–1297. https://doi.org/10.2217/fmb.14.92
44. Kori, J. A., Saleem, F., Ullah, S., & Azim, M. K. (2020). Characterization of Oral bacteriome dysbiosis in type 2 diabetic patients. *MedRxiv*, 2020.04.09.20052613. https://doi.org/10.1101/2020.04.09.20052613
45. Kumaraswamy, K. L., & Vidya, M. (2011). Human papilloma virus and oral infections: An update. *Journal of Cancer Research and Therapeutics*, 7(2), 120-127. https://doi.org/10.4103/0973-1482.82915
46. Kurkivuori, J., Salaspuro, V., Kaihovaara, P., Kari, K., Rautemaa, R., Grönroos, L., Meurman, J. H., & Salaspuro, M. (2007). Acetaldehyde production from ethanol by oral streptococci. *Oral Oncology*, *43*(2), 181–186. https://doi.org/10.1016/j.oraloncology.2006.02.005
47. Lepp, P. W., Brinig, M. M., Ouverney, C. C., Palm, K., Armitage, G. C., & Relman, D. A. (2004). Methanogenic *Archaea* and human periodontal disease. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(16), 6176. https://doi.org/10.1073/pnas.0308766101
48. Li, Y., Wang, K., Zhang, B., Tu, Q., Yao, Y., Cui, B., Ren, B., He, J., Shen, X., van Nostrand, J. D., Zhou, J., Shi, W., Xiao, L., Lu, C., & Zhou, X. (2019). Salivary mycobiome dysbiosis and its potential impact on bacteriome shifts and host immunity in oral lichen planus. *International Journal of Oral Science*, *11*(2), 13. https://doi.org/10.1038/s41368-019-0045-2
49. Lim, Y., Totsika, M., Morrison, M., & Punyadeera, C. (2017). The saliva microbiome profiles are minimally affected by collection method or DNA extraction protocols. *Scientific Reports*, *7*(1), 8523. https://doi.org/10.1038/s41598-017-07885-3
50. Lin, M., Li, X., Wang, J., Cheng, C., Zhang, T., Han, X., Song, Y., Wang, Z., & Wang, S. (2020). Saliva Microbiome Changes in Patients With Periodontitis With and Without Chronic Obstructive Pulmonary Disease. *Frontiers in Cellular and Infection Microbiology*, *10*, 124. https://www.frontiersin.org/article/10.3389/fcimb.2020.00124
51. Ling, Z., Kong, J., Jia, P., Wei, C., Wang, Y., Pan, Z., Huang, W., Li, L., Chen, H., & Xiang, C. (2010). Analysis of Oral Microbiota in Children with Dental Caries by PCR-DGGE and Barcoded Pyrosequencing. *Microbial Ecology*, *60*(3), 677–690. https://doi.org/10.1007/s00248-010-9712-8
52. Listgarten, M. A. (1986). Pathogenesis of periodontitis. *Journal of Clinical Periodontology*, *13*(5), 418–425. https://doi.org/10.1111/j.1600-051X.1986.tb01485.x
53. Liu, B., Faller, L. L., Klitgord, N., Mazumdar, V., Ghodsi, M., Sommer, D. D., Gibbons, T. R., Treangen, T. J., Chang, Y.-C., Li, S., Stine, O. C., Hasturk, H., Kasif, S., Segrè, D., Pop, M., & Amar, S. (2012). Deep Sequencing of the Oral Microbiome

Reveals Signatures of Periodontal Disease. *PLOS ONE*, *7*(6), e37919-. https://doi.org/10.1371/journal.pone.0037919
54. Loesche, W. J., & Grenier, E. (1976). Detection of Streptococcus mutans in plaque samples by the direct fluorescent antibody test. *Journal of dental research*, *55*, A87–A93. https://doi.org/10.1177/00220345760550012701l
55. Low, W., Tan, S., & Schwartz, S. (1999). The effect of severe caries on the quality of life in young children. *Pediatric Dentistry*, *21*(6), 325–326. http://europepmc.org/abstract/MED/10509332
56. Lu, H., Ren, Z., Li, A., Li, J., Xu, S., Zhang, H., Jiang, J., Yang, J., Luo, Q., Zhou, K., Zheng, S., & Li, L. (2019). Tongue coating microbiome data distinguish patients with pancreatic head cancer from healthy controls. *Journal of Oral Microbiology*, *11*(1), 1563409. https://doi.org/10.1080/20002297.2018.1563409
57. Mager, D. L., Haffajee, A. D., Devlin, P. M., Norris, C. M., Posner, M. R., & Goodson, J. M. (2005). The salivary microbiota as a diagnostic indicator of oral cancer: A descriptive, non-randomized study of cancer-free and oral squamous cell carcinoma subjects. *Journal of Translational Medicine*, *3*(1), 27. https://doi.org/10.1186/1479-5876-3-27
58. Mandel, I. D. (1987). The Functions of Saliva. *Journal of Dental Research*, *66*(1_suppl), 623–627. https://doi.org/10.1177/00220345870660S103
59. Marsh, P. D., Do, T., Beighton, D., & Devine, D. A. (2016). Influence of saliva on the oral microbiota. *Periodontology 2000*, *70*(1), 80–92. https://doi.org/10.1111/prd.12098
60. Martínez, A., Kuraji, R., & Kapila, Y. L. (2021). The human oral virome: Shedding light on the dark matter. *Periodontology 2000*, *87*(1), 282–298. https://doi.org/10.1111/prd.12396
61. Matarazzo, F., Ribeiro, A. C., Feres, M., Faveri, M., & Mayer, M. P. A. (2011). Diversity and quantitative analysis of Archaea in aggressive periodontitis and periodontally healthy subjects. *Journal of Clinical Periodontology*, *38*(7), 621–627. https://doi.org/10.1111/j.1600-051X.2011.01734.x
62. McIlvanna, E., Linden, G. J., Craig, S. G., Lundy, F. T., & James, J. A. (2021). Fusobacterium nucleatum and oral cancer: a critical review. *BMC Cancer*, *21*(1), 1212. https://doi.org/10.1186/s12885-021-08903-4
63. Michaud, D. S., Fu, Z., Shi, J., & Chung, M. (2017). Periodontal Disease, Tooth Loss, and Cancer Risk. *Epidemiologic Reviews*, *39*(1), 49–58. https://doi.org/10.1093/epirev/mxx006
64. Miller E. H., Annavajhala, M. K., Chong, A. M., Park, H., Nobel, Y. R., Soroush, A., Blackett, J. W., Krigel, A., Phipps, M. M., Freedberg, D. E., Zucker, J., Sano, E. D., Uhlemann, E. C., & Abrams, J. A.(2021). Oral Microbiome Alterations and SARS-CoV-2 Saliva Viral Load in Patients with COVID-19. *Microbiology Spectrum*, *9*(2), e00055-21. https://doi.org/10.1128/Spectrum.00055-21
65. Mohammed, M. M. A., al Kawas, S., & Al-Qadhi, G. (2021). Tongue-coating microbiome as a cancer predictor: A scoping review. *Archives of Oral Biology*, *132*, 105271. https://doi.org/10.1016/j.archoralbio.2021.105271
66. Mukherjee, P. K., Wang, H., Retuerto, M., Zhang, H., Burkey, B., Ghannoum, M. A., & Eng, C. (2017). Bacteriome and mycobiome associations in oral tongue cancer. *Oncotarget*, *8*(57), 97273–97289. https://doi.org/10.18632/oncotarget.21921
67. Munson, M. A., Banerjee, A., Watson, T. F., & Wade, W. G. (2004). Molecular Analysis of the Microflora Associated with Dental Caries. *Journal of Clinical Microbiology*, *42*(7), 3023–3029. https://doi.org/10.1128/JCM.42.7.3023-3029.2004
68. Ng, E., Tay, J. R. H., Balan, P., Ong, M. M. A., Bostanci, N., Belibasakis, G. N., & Seneviratne, C. J. (2021). Metagenomic sequencing provides new insights into the subgingival bacteriome and aetiopathology of periodontitis. *Journal of Periodontal Research*, *56*(2), 205–218. https://doi.org/10.1111/jre.12811
69. Parahitiyawa, N. B., Scully, C., Leung, W. K., Yam, W. C., Jin, L. J., & Samaranayake, L. P. (2010). Exploring the oral bacterial flora: current status and future directions. *Oral Diseases*, *16*(2), 136–145. https://doi.org/10.1111/j.1601-0825.2009.01607.x
70. Peters, B. A., Wu, J., Pei, Z., Yang, L., Purdue, M. P., Freedman, N. D., Jacobs, E. J., Gapstur, S. M., Hayes, R. B., & Ahn, J. (2017). Oral Microbiome Composition Reflects Prospective Risk for Esophageal Cancers. *Cancer Research*, *77*(23), 6777. https://doi.org/10.1158/0008-5472.CAN-17-1296
71. Peterson, S. N., Snesrud, E., Liu, J., Ong, A. C., Kilian, M., Schork, N. J., & Bretz, W. (2013). The Dental Plaque Microbiome in Health and Disease. *PLOS ONE*, *8*(3), e58487-. https://doi.org/10.1371/journal.pone.0058487
72. Pihlstrom, B. L., Michalowicz, B. S., & Johnson, N. W. (2005). Periodontal diseases. *The Lancet*, *366*(9499), 1809–1820. https://doi.org/10.1016/S0140-6736(05)67728-8
73. Pushalkar, S., Ji, X., Li, Y., Estilo, C., Yegnanarayana, R., Singh, B., Li, X., & Saxena, D. (2012). Comparison of oral microbiota in tumor and non-tumor tissues of patients with oral squamous cell carcinoma. *BMC Microbiology*, *12*(1), 144. https://doi.org/10.1186/1471-2180-12-144

74. Rôças, I. N., Siqueira, J. F., Jr, Santos, K. R., & Coelho, A. M. (2001). “Red complex” (Bacteroides forsythus, Porphyromonas gingivalis, and Treponema denticola) in endodontic infections: a molecular approach. *Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics*, *91*(4), 468–471. https://doi.org/10.1067/moe.2001.114379
75. Sajid, M., Srivastava, S., Joshi, L., & Bharadwaj, M. (2021). Impact of smokeless tobacco-associated bacteriome in oral carcinogenesis. *Anaerobe*, *70*, 102400. https://doi.org/10.1016/j.anaerobe.2021.102400
76. Sampaio-Maia, B., Caldas, I. M., Pereira, M. L., Pérez-Mongiovi, D., & Araujo, R. (2016). Chapter Four – The Oral Microbiome in Health and Its Implication in Oral and Systemic Diseases. In S. Sariaslani & G. Michael Gadd (Eds.), *Advances in Applied Microbiology* (Vol. 97, pp. 171–210). Academic Press. https://doi.org/10.1016/bs.aambs.2016.08.002
77. Sato, N., Kakuta, M., Hasegawa, T., Yamaguchi, R., Uchino, E., Kobayashi, W., Sawada, K., Tamura, Y., Tokuda, I., Murashita, K., Nakaji, S., Imoto, S., Yanagita, M., & Okuno, Y. (2020). Metagenomic analysis of bacterial species in tongue microbiome of current and never smokers. *Npj Biofilms and Microbiomes*, *6*(1), 11. https://doi.org/10.1038/s41522-020-0121-6
78. Sato, Y., Yamagishi, J., Yamashita, R., Shinozaki, N., Ye, B., Yamada, T., Yamamoto, M., Nagasaki, M., & Tsuboi, A. (2015). Inter-Individual Differences in the Oral Bacteriome Are Greater than Intra-Day Fluctuations in Individuals. *PLOS ONE*, *10*(6), e0131607-. https://doi.org/10.1371/journal.pone.0131607
79. Scannapieco, F. A. (1994). Saliva-Bacterium Interactions in Oral Microbial Ecology. *Critical Reviews in Oral Biology & Medicine*, *5*(3), 203–248. https://doi.org/10.1177/10454411940050030201
80. Scher, J. U., Bretz, W. A., & Abramson, S. B. (2014). Periodontal disease and subgingival microbiota as contributors for rheumatoid arthritis pathogenesis: modifiable risk factors? *Current Opinion in Rheumatology*, *26*(4), 424–429. https://doi.org/10.1097/BOR.0000000000000076
81. Segata, N., Haake, S. K., Mannon, P., Lemon, K. P., Waldron, L., Gevers, D., Huttenhower, C., & Izard, J. (2012). Composition of the adult digestive tract bacterial microbiome based on seven mouth surfaces, tonsils, throat and stool samples. *Genome Biology*, *13*(6), R42. https://doi.org/10.1186/gb-2012-13-6-r42
82. Selwitz, R. H., Ismail, A. I., & Pitts, N. B. (2007). Dental caries. *The Lancet*, *369*(9555), 51–59. https://doi.org/10.1016/S0140-6736(07)60031-2
83. Seymour, G. J., Ford, P. J., Cullinan, M. P., Leishman, S., & Yamazaki, K. (2007). Relationship between periodontal infections and systemic disease. *Clinical Microbiology and Infection*, *13*(s4), 3–10. https://doi.org/10.1111/j.1469-0691.2007.01798.x
84. Shi, B., Chang, M., Martin, J., Mitreva, M., Lux, R., Klokkevold, P., Sodergren, E., Weinstock, G. M., Haake, S. K., & Li, H. (2021). Dynamic Changes in the Subgingival Microbiome and Their Potential for Diagnosis and Prognosis of Periodontitis. *MBio*, *6*(1), e01926-14. https://doi.org/10.1128/mBio.01926-14
85. Socransky, S. S., & Haffajee, A. D. (2005). Periodontal microbial ecology. *Periodontology 2000*, *38*(1), 135–187. https://doi.org/10.1111/j.1600-0757.2005.00107.x
86. Socransky, S. S., Haffajee, A. D., Cugini, M. A., Smith, C., & Kent Jr., R. L. (1998). Microbial complexes in subgingival plaque. *Journal of Clinical Periodontology*, *25*(2), 134–144. https://doi.org/10.1111/j.1600-051X.1998.tb02419.x
87. Springer, S. A., & Gagneux, P. (2013). Glycan Evolution in Response to Collaboration, Conflict, and Constraint *. *Journal of Biological Chemistry*, *288*(10), 6904–6911. https://doi.org/10.1074/jbc.R112.424523
88. Takahashi, N., Washio, J., & Mayanagi, G. (2010). Metabolomics of Supragingival Plaque and Oral Bacteria. *Journal of Dental Research*, *89*(12), 1383–1388. https://doi.org/10.1177/0022034510377792
89. Teles, R. P., Gursky, L. C., Faveri, M., Rosa, E. A., Teles, F. R. F., Feres, M., Socransky, S. S., & Haffajee, A. D. (2010). Relationships between subgingival microbiota and GCF biomarkers in generalized aggressive periodontitis. *Journal of Clinical Periodontology*, *37*(4), 313–323. https://doi.org/10.1111/j.1600-051X.2010.01534.x
90. Tribble, G. D., Angelov, N., Weltman, R., Wang, B.-Y., Eswaran, S. v, Gay, I. C., Parthasarathy, K., Dao, D.-H. v, Richardson, K. N., Ismail, N. M., Sharina, I. G., Hyde, E. R., Ajami, N. J., Petrosino, J. F., & Bryan, N. S. (2019). Frequency of Tongue Cleaning Impacts the Human Tongue Microbiome Composition and Enterosalivary Circulation of Nitrate. *Frontiers in Cellular and Infection Microbiology*, *9*, 39. https://www.frontiersin.org/article/10.3389/fcimb.2019.00039
91. van der Meulen, T. A., Harmsen, H. J. M., Bootsma, H., Liefers, S. C., Vich Vila, A., Zhernakova, A., Fu, J., Wijmenga, C., Spijkervet, F. K. L., Kroese, F. G. M., & Vissink, A. (2018). Dysbiosis of the buccal mucosa microbiome in primary Sjögren’s syndrome patients. *Rheumatology*, *57*(12), 2225–2234. https://doi.org/10.1093/rheumatology/key215
92. Van Essche, M., Quirynen, M., Sliepen, I., Loozen, G., Boon, N., van Eldere, J., & Teughels, W. (2011). Killing of anaerobic pathogens by predatory bacteria. *Molecular Oral Microbiology*, *26*(1), 52–61. https://doi.org/10.1111/j.2041-1014.2010.00595.x

93. Vartoukian, S. R., Palmer, R. M., & Wade, W. G. (2009). Diversity and Morphology of Members of the Phylum “Synergistetes” in Periodontal Health and Disease. *Applied and Environmental Microbiology*, *75*(11), 3777–3786. https://doi.org/10.1128/AEM.02763-08
94. Wade, W. G. (2013). The oral microbiome in health and disease. *Pharmacological Research*, *69*(1), 137–143. https://doi.org/10.1016/j.phrs.2012.11.006
95. Wang, L., Ganly, I. (2014). The oral microbiome and oral cancer. *Clinics in Laboratory Medicine*, 34, 711–719. https://doi.org/10.1016/j.cll.2014.08.004
96. Wang, T.-F., Jen, I.-A., Chou, C., & Lei, Y.-P. (2014). Effects of periodontal therapy on metabolic control in patients with type 2 diabetes mellitus and periodontal disease: a meta-analysis. *Medicine*, *93*(28), e292–e292. https://doi.org/10.1097/MD.0000000000000292
97. Wantland, W. W., Wantland, E. M., Remo, J. W., & Winquist, D. L. (1958). Studies on Human Mouth Protozoa. *Journal of Dental Research*, *37*(5), 949–950. https://doi.org/10.1177/00220345580370052601
98. Welch, J. L., Utter, D. R., Rossetti, B. J., Mark Welch, D. B., Eren, A. M., & Borisy, G. G. (2014). Dynamics of tongue microbial communities with single-nucleotide resolution using oligotyping. *Frontiers in Microbiology*, *5*, 568. https://www.frontiersin.org/article/10.3389/fmicb.2014.00568
99. Wilbert, S. A., Mark Welch, J. L., & Borisy, G. G. (2020). Spatial Ecology of the Human Tongue Dorsum Microbiome. *Cell Reports*, *30*(12), 4003-4015.e3. https://doi.org/10.1016/j.celrep.2020.02.097
100. Willis, J. R., & Gabaldón, T. (2020). The Human Oral Microbiome in Health and Disease: From Sequences to Ecosystems. *Microorganisms*, *8*(2). https://doi.org/10.3390/microorganisms8020308
101. Xiao, J., Grier, A., Faustoferri, R. C., Alzoubi, S., Gill, A. L., Feng, C., Liu, Y., Quivey, R. G., Kopycka-Kedzierawski, D. T., Koo, H., & Gill, S. R. (2018). Association between Oral Candida and Bacteriome in Children with Severe ECC. *Journal of Dental Research*, *97*(13), 1468–1476. https://doi.org/10.1177/0022034518790941
102. Zarco, M. F., Vess, T. J., & Ginsburg, G. S. (2012). The oral microbiome in health and disease and the potential impact on personalized dental medicine. *Oral Diseases*, *18*(2), 109–120. https://doi.org/10.1111/j.1601-0825.2011.01851.x
103. Zhou, X., Han, J., Liu, Z., Song, Y., Wang, Z., & Sun, Z. (2014). Effects of periodontal treatment on lung function and exacerbation frequency in patients with chronic obstructive pulmonary disease and chronic periodontitis: A 2-year pilot randomized controlled trial. *Journal of Clinical Periodontology*, *41*(6), 564–572. https://doi.org/https://doi.org/10.1111/jcpe.12247
104. Zuo, Y., Whitbeck, J. C., Haila, G. J., Hakim, A. A., Rothlauf, P. W., Eisenberg, R. J., Cohen, G. H., & Krummenacher, C. (2019). Saliva enhances infection of gingival fibroblasts by herpes simplex virus 1. *PLOS ONE*, *14*(10), e0223299-. https://doi.org/10.1371/journal.pone.0223299

This page titled 20.3: The Oral Microbiome is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Dylan Parks via source content that was edited to the style and standards of the LibreTexts platform.

- **3.3: The Oral Microbiome** by Dylan Parks is licensed CC BY 4.0. Original source: https://uta.pressbooks.pub/microbiomeshealthandtheenvironment.

20.4: The Skin Microbiome

The Skin Microbiome

The microorganisms that inhabit the largest human organ are important in a variety of ways in regard to host health. The skin microbiome defends against pathogens, educates the immune system, helps wound healing, and moderates progression of diseases, and in return receives nutrients and real estate for colonization, creating a symbiotic establishment (Byrd et al., 2018). As the primary external interface to the environment, the skin serves as the initial physical barrier against invasion of potential pathogens. The territory of the skin itself is harsh for most microbes; its cool, acidic, dry, and considered nutrient poor, and so only those organisms that have adapted to these conditions can successfully colonize it. A majority of these microbes rely on obtaining nutrients from sweat, sebum, and dead skin cells by using proteases and lipases to break apart various compounds to liberate usable resources (Byrd et al., 2018). Though, there are adverse conditions and a general lack of food for microbes on the skin, there is still quite a diverse community which is unique to certain individuals and body locations.

Better characterization of the skin microbiome and its site-specific diversity can allow for greater understanding of skin diseases such as atopic dermatitis, acne, rosacea, and psoriasis that are associated with dysbiosis (Grice and Segre, 2011). The role of resident and transient microorganisms are important in the onset and progression of these types of diseases, and their study may help in diagnosis and treatment protocols.



Composition and Stability

Within a single square centimeter on the skin there can be up to one billion microorganisms, and this mixed community of bacteria, viruses, protozoa, fungi, and mites can be both good and bad for host health (Grice and Segre, 2011, Weyrich et al., 2015). Overall, there are four main bacterial phyla that constitute the human skin microbiome: Actinobacteria, Firmicutes, Proteobacteria, and Bacteroidetes (in descending order of abundance) (Grice et al., 2009). Microbial composition primarily depends on the specific location of skin site, and particularly whether it is dry, moist, or sebaceous (i.e. oily). Moist areas like the bend of the elbow or the feet harbor bacteria like *Staphylococcus* or *Corynebacterium* species and tend to have higher species diversity, while sebaceous locations promote the growth of *Propionibacterium* species and are lower in diversity (Grice et al., 2009, Oh et al., 2016, Byrd et al., 2018).

The composition of fungi on the skin also depends on location and physiological properties. Fungal members of the skin microbiome primarily consist of species from the genus *Malassezia*, with some from *Penicillium* and *Aspergillus*, and less of a few other genera. Specifically, the community of fungi on the feet have a high amount of diversity and it tends to change more over time as compared with other locations on the body. This may be due to environmental exposure, sock and shoe usage, or the fact that specific sites like plantar heels, toe webs and toenails are commonly infected by fungal pathogens, which can be difficult to treat. (Findley et al., 2013).

Small arthropods less than half a millimeter also colonize the skin and makeup part of the microbiota. Two species of mites from the genus *Demodex* utilize lipids produced in the sebaceous regions of the skin; the larger species *D. folliculorum* tends to cluster around hair follicles while the smaller *D. brevis* situated near the eyelid rim is more antisocial (Schommer and Gallo, 2013). These

lipid-eating mites normally have a symbiotic relationship with humans, however, they could potentially serve as mechanical vectors for transport of pathogenic bacteria, and their population buildup and/or associated events of dysbiosis could promote inflammatory reactions (Lacey et al., 2009, Lacey et al., 2011).

Eukaryotic viruses on the skin are primarily transient, exhibit lower site-specific affinity, and the most different from person to person. This is likely due to the fact that they are obligate intracellular pathogens with special constraints. Also, maybe as expected, various bacteriophage abundance in certain sites is dependent on the corresponding bacterial genera (Oh et al., 2016).

Microbial communities on the skin remain stable despite the constantly changing external environment that humans bring about. Over both short- and long-term time intervals, sebaceous sites are the most stable, and moist areas like the feet are the least stable. Interestingly, dry sites with high environmental contact and disruption, like the palms of hands, exhibit community stability over time (Oh et al., 2016). Though, variability and stability may be dependent on individual host habits and lifestyles. At an early age, however, there are drastic changes in the skin microbiome until it becomes established. At birth, the baby transitions from an essentially sterile environment in the womb, to open air and constant microbial exposure where initial colonization of the skin begins. The method of delivery also affects initial community composition on the skin. When a baby is born conventionally through the vaginal canal, the members of the skin microbiome reflect the vaginal microbiome, and if born via cesarean section, the infant's skin community more closely resembles that of the mother's skin (Dominguez-Bello et al., 2010). In the initial few months, the skin community predominately consists of *Streptococci* and *Staphylococci* bacteria, but as aging ensues the abundance of these genera decrease and diversity and numbers of others begins to increase and level out (Capone et al., 2011). This has long-term effects on health, as the evolution of an infant's skin microbiome helps to regulate and mature both the skin and immune system.

Hot Spot Quiz

Immune System Interaction

Exposure to potentially pathogenic microorganisms at a young age can help educate the immune system. Immediately after childbirth, initial skin colonization by microorganisms is allowed without the classical inflammatory response, though shortly after this period, these microbes promote the development of distinct components of the immune system for future pathogen encounters (PrabhuDas et al., 2011, Naik et al., 2012, Naik et al., 2015, Belkaid and Harrison, 2017). This has been observed in infant's skin microbiome and an early colonization of *Staphylococcus aureus* being associated with a lower risk of developing atopic dermatitis, as the immune system is prepared for this organism that can exacerbate and perpetuate the disease (Kennedy et al., 2017, Blicharz et al., 2019). *S. aureus* can further modulate the immune system through toxin production and colonization, which initiates leukocyte responses and stimulates the adaptive and innate immune systems (Niebuhr, et al., 2011, Nakamura et al., 2013, Nakatsuji et al., 2016). Skin colonization of *Staphylococcus epidermidis* elicits similar immune responses, and a pre-association with this microbe could help defend against certain fungal and parasitic skin infections (Naik et al., 2012, Naik et al., 2015). Further investigation of microbe and immune system interactions will help uncover exact molecular functions and relationships, which could have future implications in therapy and treatment of skin diseases (Byrd et al., 2018).

Pathogens, Dysbiosis, and Skin Diseases

The skin microbiome also contributes to human health and combating infectious diseases in a preventative measure. In addition to educating the immune system, the commensal microorganisms that call the epidermis home help to prevent pathogen invasion by physically taking up niches and secreting certain antimicrobial compounds. For example, *S. epidermidis*, which is a part of the normal microbial flora of the skin, produces antimicrobial peptides and proteases that selectively targets and inhibits growth of pathogens such as *S. aureus* (Cogen et al., 2010, Iwase et al., 2010, Schommer and Gallo, 2013).

Though many commensal microorganisms on the skin can help to prevent pathogen colonization, these microbes themselves may be opportunistic pathogens and can cause an infection when certain conditions arise. For example, *S. epidermidis* is a common cause of infections when transmitted from the skin into the body, usually through a medical procedure like catheterization (Otto, 2012). Staphylococci are known for their ability to form biofilms on medical devices, which make them more difficult to treat (Otto, 2009). The fungi, *Candida albicans*, is another normal skin resident that can cause opportunistic infections. It is though that disruption of the normal skin flora, such as antibiotic therapy, could induce virulence factor production by the yeast, resulting in penetration of epidermal tissue and a subsequent case of candidiasis (Kuhbacher et al., 2017). Other skin diseases associated with dysbiosis, or various skin pathogens, include atopic dermatitis, acne, rosacea, psoriasis, and chronic wound healing.

Atopic dermatitis (AD), the most common form of eczema, is a chronic inflammatory condition of the skin that is caused by a mutation in several genes, including the fillagrin gene responsible for encoding a protein that helps maintain epidermal health (Bierber, 2008). AD is characterized by itchy, dry rashes that become vulnerable to infection when the skin barrier is breached by constant scratching, and occurs more frequently in areas with low microbial diversity, such as the inside of the elbow or back of the knee (Weyrich et al., 2015). *S. aureus* colonization is directly related to disease severity of AD, as it produces virulence factors that disrupt the integrity of the skin barrier. There is also an increase in abundance of *S. epidermidis*, and *Clostridium* and *Serratia* species, and this increase of select species suggests that a lower amount of microbial diversity plays a role in the progression of AD (Kong et al., 2012, Oh et al., 2013, Williams and Gallo, 2015). Selectively targeting pathogens such as *S. aureus* for treatment of AD proves to be difficult as the normal microbiota also suffers resulting in dysbiosis.



Psoriasis is similar to AD in that the disease results in inflamed, scaly skin plaques that are itchy and painful. This condition is also associated with altered microbial diversity, and there is an association with the development of psoriasis and oral streptococcal infections, though the connection is not exactly known (Norlind, 1955, Owen et al., 2000). Within psoriatic lesions, there is an increase Proteobacteria and Firmicutes, a decrease in Actinobacteria, and specifically a decrease within the genera *Propionibacterium* (Gao et al., 2008, Fahlen et al., 2012, Statnikov et al., 2013). Though there is a decrease in general of microbial diversity in psoriatic lesions, there hasn't been any specific microbial causative agent identified for the disease.

Rosacea is a common chronic dermatosis which primarily manifests as persisting erythema (redness), telangiectasia (dilated or broken blood vessels), bulging, swelling, and/or raised patches in superficial facial skin (Picardo and Ottaviani, 2014). Like other cutaneous diseases, development of rosacea is linked with skin microbiome composition, and how those communities influence skin immune responses. In particular, an increase in *Demodex* mite abundance and density is observed in those with rosacea. They potentially contribute to the disease state through immune system activation, damaging epithelial tissue, and/or the exposure of antigenic proteins of bacteria released from their digestive tract (Forton and Seys, 1993, Georgala et al., 2001, Lacey et al., 2007, Koller et al., 2011, Casas et al., 2012, Forton, 2012,). The induced reactions from microbiome shifts, genetics, and environmental factors then likely invoke other inflammatory triggers, which includes overgrowth of certain bacteria like *S. epidermidis* (Schommer and Gallo, 2013).

Acne (acne vulgaris) is a skin condition that results from hair follicles and sebaceous glands that are clogged with oil, bacteria, and dead skin cells, which creates whiteheads and blackheads. *Propionibacterium acnes* is a primary etiological agent in acne; it's secretion of lipases, proteases, and hyaluronidases damage skin pores and induce inflammatory responses (McKelvey et al., 2012). Although this species of microbe is part of the normal skin microbiota, there are differences in certain strains of *P. acnes* that may explain differential virulence. Some disease-associated strains also have genes for antibiotic resistance, making treatment options other than chemotherapy a necessity (Fitz-Gibbon et al., 2013). Other commensal microorganisms, like *S. epidermidis*, could interact with *P. acnes* and be implicated in acne formation also, further demonstrating that residents can become pathogenic when opportunistic conditions arise (Bek-Thomsen et al., 2008, Weyrich et al., 2015, Dreno et al., 2017).

Chronic skin wounds (duration longer than three months) and their capacity to heal are also affected by the skin microbiome, especially in those individuals who are elderly, obese, immunocompromised, or diabetic (Weyrich et al., 2015, Byrd et al., 2018). Though the lesions or ulcers may not be initially caused by a microorganism, their presence, infection, and polymicrobial biofilm

formation can be deleterious to the healing process and cause further complications (McKelvey et al., 2012, Wolcott et al., 2013). Analysis of skin wound microbiomes have shown a compilation of a diverse array of genera, but that microbial diversity is lower as compared with healthy skin (Gardiner et al., 2017, Kalan et al., 2019). Perhaps a higher microbial diversity allows for easier elimination of potential pathogens from the wound and promotes faster healing. An increase in facultative anaerobes, specifically the genus *Enterobacter*, are significant indicators in the persistence of chronic wounds and their lack of healing, possibly due to their versatile metabolism (Verbanic et al., 2020). Antibiotic therapy is an option to eliminate certain bacterial pathogens for chronic wounds, however, the resulting changes in the microbiome and addressing fungal and viral constituents may necessitate multiple different treatment approaches (Price et al., 2009). Further studies are needed in order to see whether individual therapy and targeted therapeutic intervention would promote faster healing in cases with chronic wounds (Kong, 2011, Weyrich et al., 2015, Verbanic et al., 2020).

It is likely that changes in microbial community composition and the elicited immune response work in combination with host genetics and other environmental factors to cause various cutaneous disorders (Weyrich et al., 2015). This makes treatment of these complex conditions difficult, and targeting a few potential pathogens is rarely successful, especially if it is not known whether their presence is a cause or effect. So, future therapeutic efforts may focus on a similar approach to treating gut dysbiosis with FMT, and as so, use healthy skin microbiota transplants to repair and stabilize the skin microbiome for patients inflicted with skin diseases (Williams and Gallo, 2015).

Conclusion

The skin microbiome is incredibly complex, resilient, and has a strong influence on health and disease. Characterization and defining a normal skin microbiome could help in future diagnosis and treatment of disease, although factors like differences in host genetics, lifestyles, and particular skin locations must be accounted for. As research and medical technologies advance, it may be possible to utilize these microbial neighbors on the skin in efforts to promote better overall health.



Check Your Understanding

- What features of human skin affect the composition and stability of its microbiome?
- How is the skin microbiome influenced in early life, and what implications does this have in human health?
- What diseases are associated with dysbiosis of the skin microbiome? How do these come about and what particular microorganisms are associated with each?
- How do certain members of the skin microbiome impede the healing process of chronic wounds?

Media Attributions:

- Video 1 – A mixed community of skin microbiome representatives influences cutaneous processes by Research Square. Licensed under Creative Commons: By Attribution 3.0 License https://creativecommons.org/licenses/by/3.0/
- Video 2 – Eczema, Immunity, and the Skin Microbiome – Heidi Hong by National Human Genome Research Institute. Licensed under Creative Commons: By Attribution 3.0 License https://creativecommons.org/licenses/by/3.0/

- Video 3 – Expansion of known skin microbes could aid skin health research by Research Square. Licensed under Creative Commons: By Attribution 3.0 License https://creativecommons.org/licenses/by/3.0/
- Hot Spot Quiz Image – Skin Microbiome by Jane Ades, NHGRI under Public Domain

References

1. Bek-Thomsen, M., Lomholt, H. B., & Kilian, M. (2008). Acne is Not Associated with Yet-Uncultured Bacteria. *Journal of Clinical Microbiology*, *46*(10), 3355–3360. https://doi.org/10.1128/JCM.00799-08
2. Belkaid, Y., & Harrison, O. J. (2017). Homeostatic Immunity and the Microbiota. *Immunity*, *46*(4), 562–576. https://doi.org/10.1016/j.immuni.2017.04.008
3. Bierber, T. (2008). Mechanisms of disease: atopic dermatitis. *N Engl J Med*, *358*, 358-1483.
4. Blicharz, L., Rudnicka, L., & Samochocki, Z. (2019). Staphylococcus aureus: an underestimated factor in the pathogenesis of atopic dermatitis? *Postepy Dermatologii i Alergologii*, *36*(1), 11–17. https://doi.org/10.5114/ada.2019.82821
5. Byrd, A. L., Belkaid, Y., & Segre, J. A. (2018). The human skin microbiome. *Nature Reviews Microbiology*, *16*(3), 143–155. https://doi.org/10.1038/nrmicro.2017.157
6. Capone, K. A., Dowd, S. E., Stamatas, G. N., & Nikolovski, J. (2011). Diversity of the Human Skin Microbiome Early in Life. *Journal of Investigative Dermatology*, *131*(10), 2026–2032. https://doi.org/10.1038/jid.2011.168
7. Casas, C., Paul, C., Lahfa, M., Livideanu, B., Lejeune, O., Alvarez-Georges, S., Saint-Martory, C., Degouy, A., Mengeaud, V., Ginisty, H., Durbise, E., Schmitt, A. M., & Redoulès, D. (2012). Quantification of Demodex folliculorum by PCR in rosacea and its relationship to skin innate immune activation. *Experimental Dermatology*, *21*(12), 906–910. https://doi.org/10.1111/exd.12030
8. Cogen, A. L., Yamasaki, K., Sanchez, K. M., Dorschner, R. A., Lai, Y., MacLeod, D. T., Torpey, J. W., Otto, M., Nizet, V., Kim, J. E., & Gallo, R. L. (2010). Selective Antimicrobial Action Is Provided by Phenol-Soluble Modulins Derived from Staphylococcus epidermidis, a Normal Resident of the Skin. *Journal of Investigative Dermatology*, *130*(1), 192–200. https://doi.org/10.1038/jid.2009.243
9. Dominguez-Bello, M. G., Costello, E. K., Contreras, M., Magris, M., Hidalgo, G., Fierer, N., & Knight, R. (2010). Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proceedings of the National Academy of Sciences*, *107*(26), 11971. https://doi.org/10.1073/pnas.1002601107
10. Dreno, B., Martin, R., Moyal, D., Henley, J. B., Khammari, A., & Seité, S. (2017). Skin microbiome and acne vulgaris: Staphylococcus, a new actor in acne. *Experimental Dermatology*, *26*(9), 798–803. https://doi.org/10.1111/exd.13296
11. Fahlén, A., Engstrand, L., Baker, B. S., Powles, A., & Fry, L. (2012). Comparison of bacterial microbiota in skin biopsies from normal and psoriatic skin. *Archives of Dermatological Research*, *304*(1), 15–22. https://doi.org/10.1007/s00403-011-1189-x
12. Findley, K., & Grice, E. A. (2014). The Skin Microbiome: A Focus on Pathogens and Their Association with Skin Disease. *PLOS Pathogens*, *10*(11), e1004436-. https://doi.org/10.1371/journal.ppat.1004436
13. Findley, K., Oh, J., Yang, J., Conlan, S., Deming, C., Meyer, J. A., Schoenfeld, D., Nomicos, E., Park, M., Becker, J., Benjamin, B., Blakesley, R., Bouffard, G., Brooks, S., Coleman, H., Dekhtyar, M., Gregory, M., Guan, X., Gupta, J., … Program, N. I. H. I. S. C. C. S. (2013). Topographic diversity of fungal and bacterial communities in human skin. *Nature*, *498*(7454), 367–370. https://doi.org/10.1038/nature12171
14. Fitz-Gibbon, S., Tomida, S., Chiu, B.-H., Nguyen, L., Du, C., Liu, M., Elashoff, D., Erfe, M. C., Loncaric, A., Kim, J., Modlin, R. L., Miller, J. F., Sodergren, E., Craft, N., Weinstock, G. M., & Li, H. (2013). Propionibacterium acnes Strain Populations in the Human Skin Microbiome Associated with Acne. *Journal of Investigative Dermatology*, *133*(9), 2152–2160. https://doi.org/10.1038/jid.2013.21
15. Forton, F. M. N. (2012). Papulopustular rosacea, skin immunity and Demodex: pityriasis folliculorum as a missing link. *Journal of the European Academy of Dermatology and Venereology*, *26*(1), 19–28. https://doi.org/10.1111/j.1468-3083.2011.04310.x
16. Forton, F., & Seys, B. (1993). Density of Demodex folliculorum in rosacea: a case-control study using standardized skin-surface biopsy. *British Journal of Dermatology*, *128*(6), 650–659. https://doi.org/10.1111/j.1365-2133.1993.tb00261.x
17. Gao, Z., Tseng, C., Strober, B. E., Pei, Z., & Blaser, M. J. (2008). Substantial Alterations of the Cutaneous Bacterial Biota in Psoriatic Lesions. *PLOS ONE*, *3*(7), e2719-. https://doi.org/10.1371/journal.pone.0002719
18. Gardiner M, Vicaretti M, Sparks J, Bansal S, Bush S, Liu M, Darling A, Harry E, Burke CM. (2017). A longitudinal study of the diabetic skin and wound microbiome. *PeerJ* 5:e3543 https://doi.org/10.7717/peerj.3543

19. Georgala, S., Katoulis, A. C., Kylafis, G. D., Koumantaki-Mathioudaki, E., Georgala, C., & Aroni, K. (2001). Increased density of Demodex folliculorum and evidence of delayed hypersensitivity reaction in subjects with papulopustular rosacea. *Journal of the European Academy of Dermatology and Venereology*, *15*(5), 441–444. https://doi.org/10.1046/j.1468-3083.2001.00331.x
20. Grice, E. A., & Segre, J. A. (2011). The skin microbiome. *Nature Reviews Microbiology*, *9*(4), 244–253. https://doi.org/10.1038/nrmicro2537
21. Grice, E. A., Kong, H. H., Conlan, S., Deming, C. B., Davis, J., Young, A. C., Nisc Comparative Sequencing Program, Bouffard, G. G., Blakesley, R. W., Muray, P. R., Green, E. D., Turner, M. L., & Segre, J. A. (2009). Topographical and Temporal Diversity of the Human Skin Microbiome. *Science*, *324*(5931), 1190–1192. https://doi.org/10.1126/science.1171700
22. Iwase, T., Uehara, Y., Shinji, H., Tajima, A., Seo, H., Takada, K., Agata, T., & Mizunoe, Y. (2010). Staphylococcus epidermidis Esp inhibits Staphylococcus aureus biofilm formation and nasal colonization. *Nature*, *465*(7296), 346–349. https://doi.org/10.1038/nature09074
23. Kalan, L. R., Meisel, J. S., Loesche, M. A., Horwinski, J., Soaita, I., Chen, X., Uberoi, A., Gardner, S. E., & Grice, E. A. (2019). Strain- and Species-Level Variation in the Microbiome of Diabetic Wounds Is Associated with Clinical Outcomes and Therapeutic Efficacy. *Cell Host & Microbe*, *25*(5), 641-655.e5. https://doi.org/10.1016/j.chom.2019.03.006
24. Kennedy, E. A., Connolly, J., Hourihane, J. O., Fallon, P. G., McLean, W. H. I., Murray, D., Jo, J.-H., Segre, J. A., Kong, H. H., & Irvine, A. D. (2017). Skin microbiome before development of atopic dermatitis: Early colonization with commensal staphylococci at 2 months is associated with a lower risk of atopic dermatitis at 1 year. *Journal of Allergy and Clinical Immunology*, *139*(1), 166–172. https://doi.org/10.1016/j.jaci.2016.07.029
25. Koller, B., Müller-Wiefel, A. S., Rupec, R., Korting, H. C., & Ruzicka, T. (2011). Chitin Modulates Innate Immune Responses of Keratinocytes. *PLOS ONE*, *6*(2), e16594-. https://doi.org/10.1371/journal.pone.0016594
26. Kong, H. H. (2011). Skin microbiome: genomics-based insights into the diversity and role of skin microbes. *Trends in Molecular Medicine*, *17*(6), 320–328. https://doi.org/10.1016/j.molmed.2011.01.013
27. Kong, H. H., Oh, J., Deming, C., Conlan, S., Grice, E. A., Beatson, M. A., Nomicos, E., Polley, E. C., Komarow, H. D., Program, N. C. S., Murray, P. R., Turner, M. L., & Segre, J. A. (2012). Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. *Genome Research*, *22*(5), 850–859. http://genome.cshlp.org/content/22/5/850.abstract
28. Kuhbacher, A., Burger-Kentischer, A., & Rupp, S. (2017). Interaction of *Candida* species with the skin. *Microorganisms*. *5(2)*, 32. https://doi.org/10.3390/microorganisms5020032
29. Lacey, N., Delaney, S., Kavanagh, K., & Powell, F. C. (2007). Mite-related bacterial antigens stimulate inflammatory cells in rosacea. *British Journal of Dermatology*, *157*(3), 474–481. https://doi.org/10.1111/j.1365-2133.2007.08028.x
30. Lacey, N., Kavanagh, K., & Tseng, S. C. G. (2009). Under the lash: Demodex mites in human diseases. *The Biochemist*, *31*(4), 20–24. https://doi.org/10.1042/BIO03104020
31. Lacey, N., Ní Raghallaigh, S., & Powell, F. C. (2011). Demodex mites – commensals, parasites or mutualistic organisms? *Dermatology*, *222*(2), 128-30. doi:http://dx.doi.org/10.1159/000323009
32. McKelvey, K., Xue, M., Whitmont, K., Shen, K., Cooper, A., & Jackson, C. (2012). Potential anti-inflammatory treatments for chronic wounds. *Wound Practice & Research: Journal of the Australian Wound Management Association*, *20*(2), 86–89. https://search.informit.org/doi/10.3316/informit.656354654775105
33. Naik, S., Bouladoux, N., Linehan, J. L., Han, S.-J., Harrison, O. J., Wilhelm, C., Conlan, S., Himmelfarb, S., Byrd, A. L., Deming, C., Quinones, M., Brenchley, J. M., Kong, H. H., Tussiwand, R., Murphy, K. M., Merad, M., Segre, J. A., & Belkaid, Y. (2015). Commensal–dendritic-cell interaction specifies a unique protective skin immune signature. *Nature*, *520*(7545), 104–108. https://doi.org/10.1038/nature14052
34. Naik, S., Bouladoux, N., Wilhelm, C., Molloy, M. J., Salcedo, R., Kastenmuller, W., Deming, C., Quinones, M., Koo, L., Conlan, S., Spencer, S., Hall, J. A., Dzutsev, A., Kong, H., Campbell, D. J., Trinchieri, G., Segre, J. A., & Belkaid, Y. (2012). Compartmentalized control of skin immunity by resident commensals. *Science (New York, N.Y.)*, *337*(6098), 1115–1119. https://doi.org/10.1126/science.1225152
35. Nakamura, Y., Oscherwitz, J., Cease, K. B., Chan, S. M., Muñoz-Planillo, R., Hasegawa, M., Villaruz, A. E., Cheung, G. Y. C., McGavin, M. J., Travers, J. B., Otto, M., Inohara, N., & Núñez, G. (2013). Staphylococcus δ-toxin induces allergic skin disease by activating mast cells. *Nature*, *503*(7476), 397–401. https://doi.org/10.1038/nature12655
36. Nakatsuji, T., Chen, T. H., Two, A. M., Chun, K. A., Narala, S., Geha, R. S., Hata, T. R., & Gallo, R. L. (2016). Staphylococcus aureus Exploits Epidermal Barrier Defects in Atopic Dermatitis to Trigger Cytokine Expression. *Journal of Investigative*

Dermatology, *136*(11), 2192–2200. https://doi.org/10.1016/j.jid.2016.05.127
37. Niebuhr, M., Gathmann, M., Scharonow, H., Mamerow, D., Mommert, S., Balaji, H., & Werfel, T. (2011). Staphylococcal Alpha-Toxin Is a Strong Inducer of Interleukin-17 in Humans. *Infection and Immunity*, *79*(4), 1615–1622. https://doi.org/10.1128/IAI.00958-10
38. Norlind, R. (1955). Significance of infections in origin of psoriasis. *Acta Rheumatol Scand*, *1*, 135-44.
39. Oh, J., Byrd, A. L., Park, M., Kong, H. H., & Segre, J. A. (2016). Temporal Stability of the Human Skin Microbiome. *Cell*, *165*(4), 854–866. https://doi.org/10.1016/j.cell.2016.04.008
40. Oh, J., Freeman, A. F., Program, N. C. S., Park, M., Sokolic, R., Candotti, F., Holland, S. M., Segre, J. A., & Kong, H. H. (2013). The altered landscape of the human skin microbiome in patients with primary immunodeficiencies. *Genome Research*, *23*(12), 2103–2114. http://genome.cshlp.org/content/23/12/2103.abstract
41. Otto, M. (2009). Staphylococcus epidermidis — the “accidental” pathogen. *Nature Reviews Microbiology*, *7*(8), 555–567. https://doi.org/10.1038/nrmicro2182
42. Otto, M. (2012). Molecular basis of Staphylococcus epidermidis infections. *Seminars in Immunopathology*, *34*(2), 201–214. https://doi.org/10.1007/s00281-011-0296-2
43. Owen, C. M., Chalmers, R., O’Sullivan, T., & Griffiths, C. E.M. (2000) Antistreptococcal interventions for guttate and chronic plaque psoriasis. *Cochrane Database of Systematic Reviews*, 2. Art. No.: CD001976. DOI: 10.1002/14651858.CD001976.
44. PrabhuDas, M., Adkins, B., Gans, H., King, C., Levy, O., Ramilo, O., & Siegrist, C.-A. (2011). Challenges in infant immunity: implications for responses to infection and vaccines. *Nature Immunology*, *12*(3), 189–194. https://doi.org/10.1038/ni0311-189
45. Price, L. B., Liu, C. M., Melendez, J. H., Frankel, Y. M., Engelthaler, D., Aziz, M., Bowers, J., Rattray, R., Ravel, J., Kingsley, C., Keim, P. S., Lazarus, G. S., & Zenilman, J. M. (2009). Community Analysis of Chronic Wound Bacteria Using 16S rRNA Gene-Based Pyrosequencing: Impact of Diabetes and Antibiotics on Chronic Wound Microbiota. *PLOS ONE*, *4*(7), e6462-. https://doi.org/10.1371/journal.pone.0006462
46. Schommer, N. N., & Gallo, R. L. (2013). Structure and function of the human skin microbiome. *Trends in Microbiology*, *21*(12), 660–668. https://doi.org/10.1016/j.tim.2013.10.001
47. Statnikov, A., Alekseyenko, A. v, Li, Z., Henaff, M., Perez-Perez, G. I., Blaser, M. J., & Aliferis, C. F. (2013). Microbiomic Signatures of Psoriasis: Feasibility and Methodology Comparison. *Scientific Reports*, *3*(1), 2620. https://doi.org/10.1038/srep02620
48. Verbanic, S., Shen, Y., Lee, J., Deacon, J. M., & Chen, I. A. (2020). Microbial predictors of healing and short-term effect of debridement on the microbiome of chronic wounds. *Npj Biofilms and Microbiomes*, *6*(1), 21. https://doi.org/10.1038/s41522-020-0130-5
49. Weyrich, L. S., Dixit, S., Farrer, A. G., Cooper, A. J., & Cooper, A. J. (2015). The skin microbiome: Associations between altered microbial communities and disease. *Australasian Journal of Dermatology*, *56*(4), 268–274. https://doi.org/10.1111/ajd.12253
50. Williams, M. R., & Gallo, R. L. (2015). The Role of the Skin Microbiome in Atopic Dermatitis. *Current Allergy and Asthma Reports*, *15*(11), 65. https://doi.org/10.1007/s11882-015-0567-4
51. Wolcott, R., Costerton, J. W., Raoult, D., & Cutler, S. J. (2013). The polymicrobial nature of biofilm infection. *Clinical Microbiology and Infection*, *19*(2), 107–112. https://doi.org/10.1111/j.1469-0691.2012.04001.x

---

This page titled 20.4: The Skin Microbiome is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Dylan Parks via source content that was edited to the style and standards of the LibreTexts platform.

- **3.4: The Skin Microbiome** by Dylan Parks is licensed CC BY 4.0. Original source: https://uta.pressbooks.pub/microbiomeshealthandtheenvironment.

20.5: The Respiratory Microbiome

The Respiratory Microbiome

The respiratory microbiome (specifically the lower portions) was once thought to be nonexistent, as many considered healthy lungs to be a sterile environment. Like other microbiomes though, the upper and lower respiratory system are environments rich with bacteria, fungi, archaea, and viruses, and because of the novelty of study many of the members in these groups have not been identified. However, it is known that many of such organisms are not only responsible for or exacerbate a number of pulmonary diseases, but that the respiratory microbiome can help to mitigate infection and influence treatment of certain illnesses (Unger and Bogaert, 2017, Watson et al., 2019).

The human respiratory system begins with the upper respiratory system; starting with the nose and nostrils, then proceeds to the nasal cavity, pharynx, and larynx. The lower respiratory system then starts with the trachea, moves to the bronchi and bronchioles, and ends with the lungs. Each of these structures and areas have their own microbial niche which serve various roles in maintaining health, but also have the potential to be compromised. The respiratory system is similar to the oral and digestive system, in that they interact intimately with external stimuli and bring in foreign matter and microbes during regular biological processes, like inhalation. These systems also have overlapping parts (e.g. oral cavity and pharynx), where their respective microbiomes serve similar roles such as resistance to disruptive environmental factors and host defense (Dickson et al., 2014, Zaura et al., 2014, Hakansson et al., 2018). The mucosal surfaces of the respiratory tract also have a natural healthy biofilm where the resident microbiota reside to maintain homeostatic functions, however, as an extension of dysbiosis, these biofilms can become altered and obtain pathogenic microbes which contribute to respiratory diseases (Hamilos, 2019).

Composition

Immediately after birth the respiratory microbiome becomes colonized, though the collection of microbes found here during infancy is not much different than other locations in the body, and generally reflect the mode of delivery (Dominguez-Bello et al., 2010). The respiratory microbiome, as well as others, become differentiated over time when the different species of microbes adapt and outcompete each other based on their niche, host genetics, and environmental factors (Bosch et al., 2016). Colonization additionally depends on microbial immigration, microbial elimination, and relative reproduction rates of its members (Figure 1) (Dickson and Huffnagle, 2015). With age, the respiratory microbiome of each particular individual reflects the aforementioned factors as well as other lifestyle habits, and so they can be vastly different between people. Although these respiratory microbiomes are unique, a core set of microbes can be defined, with most of them being aerobic or facultatively anaerobic (Stearns et al., 2015, Hakansson et al., 2018).

Microbial composition also depends on the specific structure or niche within the respiratory system. The nasal microbiome largely consists of *Staphylococci*, *Corynebacteria*, and *Streptococci*, which is most likely due to its similarity and proximity to the skin (Mika et al., 2015, Shilts et al., 2016). Communities within the paranasal sinuses are highly diverse and include lactic-acid producing bacteria such as *Lactobacilli*, *Enterococcus*, and *Pediococcus*, and once in the nasopharynx the collection of microbes becomes more complex and favors oxygen-utilizing groups (Abreu et al., 2012, Biesbroek et. al, 2014, Teo et al., 2015). In the lower respiratory system, the microbiome resembles a bit of a mix from both the nasal and oral cavities, with a majority of bacteria from the genera *Streptococcus*, *Fusobacteria*, *Pseudomonas*, *Veillonella*, and *Prevotella* (Cui et al., 2014, Beck et al., 2015, Dickson and Huffnagle, 2015, Hakansson et al., 2018).

While much focus of the respiratory microbiome has been on bacteria (like many other microbiomes), study of the mycobiome and virome components have revealed their importance in pulmonary health and disease. Fungal spores are commonly inhaled, especially in high numbers during peak seasons, and depending on the particular organism and host immune health, they can cause infection and respiratory complications (Pashley et al., 2012, Denning et al., 2014, Nguyen et al., 2015). For healthy people, the respiratory mycobiome is predominated by environmental fungi including *Aspergillus*, *Cladosporium*, and *Penicillium* species (Charlson et al., 2012, van Woerden et al., 2012, Underhill and Iliev, 2014). However, members from these genera and other more well-known fungal pathogens, like *Candida albicans*, can be implicated in respiratory illnesses due to microbial community changes (Nguyen et al., 2015). The respiratory virome can also modulate various pulmonary diseases through respective bacterial interactions and host immune response. For bacteriophage composition, there are observed differences between healthy individuals and patients suffering from diseases associated with respective bacterial infections (Wilner et al., 2009). There is a diverse range of

eukaryotic viruses that make up the normal human and respiratory virome, with the majority consisting of adenoviruses, herpesviruses and human papillomaviruses (HPVs), though these may only be transient and quickly cleared by the immune system or via the mucociliary escalator (Wilner et al., 2009, Popgeorgiev et al., 2013). More research needs to be conducted over the normal respiratory virome to determine its functionality and importance, though usually more focus is catered to those viruses directly involved in pathogenesis and dysbiosis.

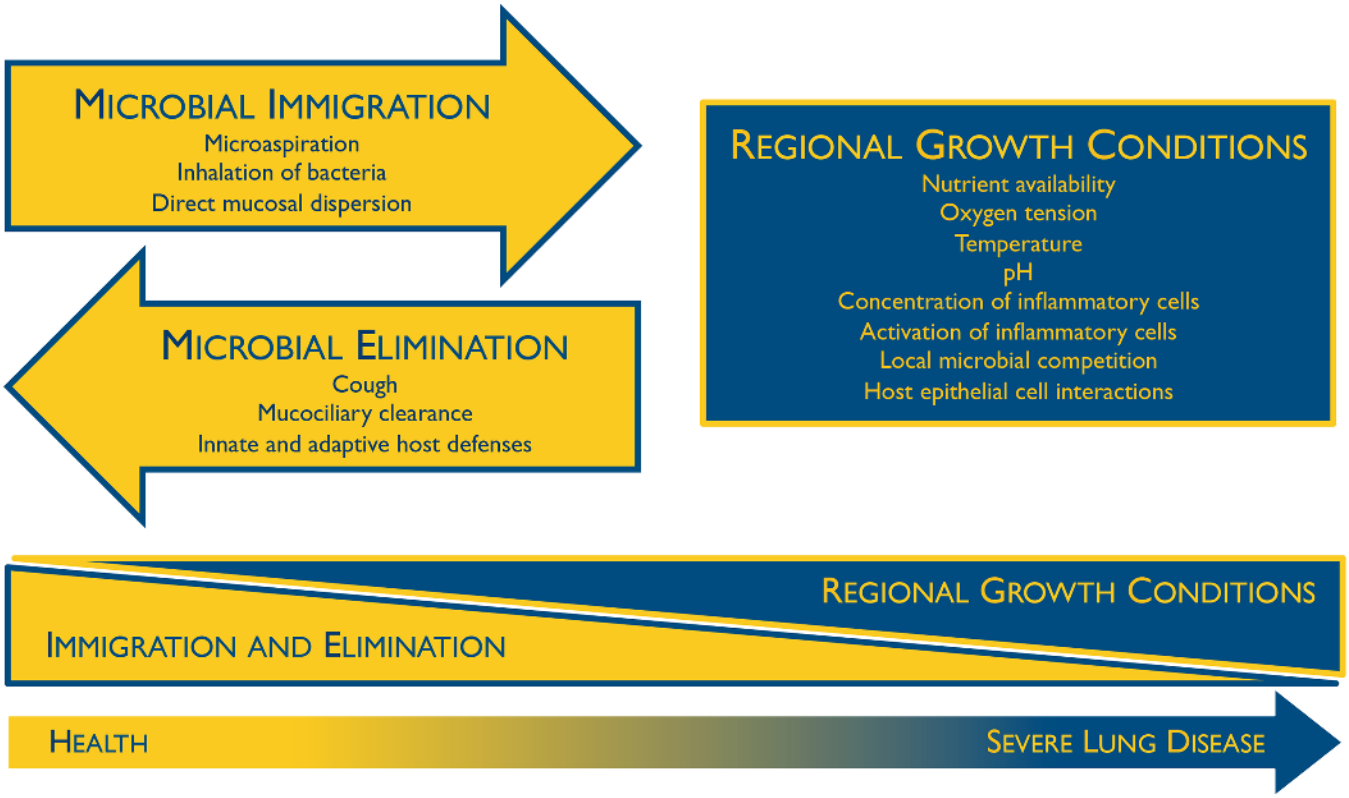


Figure 1. Ecological determinants of the respiratory microbiome. The constitution of the respiratory microbiome is determined by three factors: microbial immigration, microbial elimination, and the relative reproduction rates of its members. In health, community membership is primarily determined by immigration and elimination; in advanced lung disease, membership is primarily determined by regional growth conditions. Adapted from Dickson et al., 2014.

Dysbiosis and Disease

The normal matrix of organisms in the respiratory system maintain homeostasis through their complex interactive network with each other and their host. Pathogens like *Streptococcus pneumoniae* and *Haemophilus influenzae* are actually part of the resident respiratory microbiome and interact with commensal microbes, however, they can incite infection when they are not kept in check due to community perturbation (de Steenhuijsen et al., 2015). During events of dysbiosis, pathogens and opportunistic pathogens can contribute to and exacerbate several respiratory diseases including asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, pneumonia, otitis media, and other acute infections like influenza.

Asthma is a chronic lung disease that usually develops at an early age, and its complex etiology makes it difficult to treat. People with asthma experience inflammation and tightening of their airways and a production of extra mucus impairs breathing, talking, and being active. The prevalence of asthma has increased in recent decades, and a decrease in microbe exposure during youth could be partially responsible (Ober and Yao, 2011, Prescott, 2013). Proper development of the immune system is reliant on contact with microbes, and those individuals who are regularly subjected to a diverse variety of microorganisms at an early age have a reduced risk of developing asthma (Ownby et al., 2002, Fujimura et al., 2010, Fall et al., 2015). Aside from grooming the immune system, the intake of microbes influences the composition of the mucosal microbiota that lines the air passageways, which could directly affect asthma development (Durack et al., 2016). Indeed epidemiologic studies have shown that the disruption of the microbiome, such as in the case of antibiotic use during childhood, create a predisposition for this allergic disease (Khalkhali et al., 2014). Specifically, the increased presence of genus *Haemophilus* and other *Proteobacteria*, as well as the fungus *Aspergillus fumigatus* in

the respiratory system are signature of asthma patients (Hilty et al., 2010, Teo et al., 2015, Urb et al., 2015). These pathogens would normally be cleared by the immune system or stifled by the resident microbiota, however, early childhood dysbiosis resulting in hampered immune functions and/or a discontent microbial consortium in the respiratory system contribute to the development of this condition.

Chronic obstructive pulmonary disease (COPD) is another chronic inflammatory lung disease that causes obstructed airflow to the lungs and is exacerbated by microbial dysbiosis. Emphysema, a condition where the alveoli are damaged due to cigarette smoke and other irritants, and chronic bronchitis, a condition characterized by inflammation of the lining of the airways, are the most common contributors to COPD. An alteration of the lower respiratory microbiome causing reduced diversity or the presence of specific organisms can further aggravate COPD causing a worsening of symptoms (Huang et al., 2014). Viral infections, like those caused by the rhinovirus, are commonly detected (in about half the patients) during COPD exacerbations (Seemungal et al., 2001, Rohde et al., 2003, Mallia et al., 2011). Also during these bouts, there is an increase in pathogens from the bacterial genera *Haemophilus*, *Pseudomonas*, and *Moraxella* and a general shift towards the phylum Proteobacteria in the respiratory microbiome (Huang et al., 2014, Millares et al., 2014). Additionally, patients with COPD exhibit a decline or absence of certain normal lung organisms that could contribute to mucosal homeostasis and prevention of pathogen overgrowth, such as Firmicutes *(Streptococcus spp*.), as well as Bacteroidetes (*Prevotella spp.*) (Fukata and Arditi, 2014, Sze et al., 2015, Hakansson et al., 2018). These compositional changes are at least partially brought about by current COPD treatments like steroid and antibiotic usage, and so future therapy may need to take the respiratory microbiome into further consideration for various approaches (Wang et al., 2016).

Cystic fibrosis (CF) is a genetic disease that causes normal cellular secretion of mucus, sweat, and digestive juices to become thicker and viscous. In the respiratory system, the buildup of sticky mucus can clog airways, impair lung function, and make breathing difficult. Bacterial pathogens, like *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Haemophilus parainfluenzae*, tend to grow in the sputum and can cause infections which worsening CF conditions (Keogh and Stanojevic, 2018). Their biofilm-forming capabilities also contribute to the excess mucus production, further causing complications as infectious agents can be resilient and persistent (Høiby et al, 2010, Orazi and O'Toole, 2017). While changes in the microbiome are not typically responsible for exacerbations of CF, antibiotic administration is the primary treatment option to eliminate these pathogens residing in the mucus, however, prolonged use can result in decreased microbiome diversity and dysbiosis in the respiratory system as well as other areas (Zhao et al., 2012, Carmody et al., 2013 Price et al., 2013, Dickson et al., 2014).

Pneumonia is a microbial infection of the lungs that can cause the alveoli to fill with pus or other liquids, and severe cases can be life-threatening, especially to children, the elderly, and those who are immunocompromised (Wardlaw et al., 2006, Chalmers et al., 2011, Valley et al., 2015). The intensity of the infection is directly correlated with the microbial load and diversity, so etiologic determination is important for proper treatment, as the onset of pneumonia can have bacterial, fungal, or viral origins (Dickson et al., 2014, Iwai et al., 2014). Viral pneumonia is commonly caused by influenza or rhinovirus, however, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has now also become a major cause post 2019 (Jain et al., 2015, Zhou et al., 2020, Pettigrew et al., 2021). Respiratory viral infections are the most common cause acute respiratory illnesses, and often times, these viral infections then lead to secondary bacterial infections, like pneumonia, due to host immune reactions and induced dysbiosis in the respiratory tract and gastrointestinal system (Hanada et al., 2018). *Streptococcus pneumoniae* is the most common culprit for bacterial pneumonia, and while it regularly resides in the upper respiratory tract, under dysbiotic conditions this organism can proliferate and spread to the lower respiratory tract and cause illness (File, 2003, de Steenhuijsen Piters et al., 2014). In patients with pneumonia, there is a decrease in many Gram-negative anaerobic bacteria that are apart of the resident microbiota, some of which are associated with a reduced risk of hospital-acquired pneumonia and clearance of *S. pneumoniae* (Bousbia et al., 2012, de Steenhuijsen Piters et al., 2014, Krone et al., 2014). Although, changes in the respiratory microbiome are more apparent in bacterial pneumonia rather than viral, it is not known whether this alteration in microbial consortia is a cause or effect of the disease, though it is likely conditional of both circumstances (Ramos-Sevillano et al., 2019, Pettigrew et al., 2021).



Conclusion



The respiratory microbior veral pulmonary illnesses. While much of its charact portant for management of respiratory diseases (Nguyen et al., 2016). As antibiotic resistance continues to surge, novel approaches are necessary to mitigate not only respiratory illnesses, but to maintain general health. And similarly to other microbiome-related treatments, like fecal microbiota transplant for the gut, eventually oral or aerosol administered microbiota may be implemented to treat pulmonary conditions (Huang and Boushey, 2015). Continual research detailing both core and individual respiratory microbiomes will push the advancement of these 'futuristic' medical motions.

Drag and Drop Quiz

Drag each contributing factor of the respiratory microbiome composition into the appropriate category.

Check your Understanding

- How is the colonization of the respiratory microbiome influenced, and what factors affect its composition over time?
- What factors of the respiratory microbiome affect the development of asthma?
- Which microorganisms are implicated in COPD and periods of exacerbation? How does dysbiosis contribute to this chronic condition?
- Why do you think a greater change is observed in the respiratory microbiota in patients with bacterial pneumonia versus viral?

Media Attributions

- Figure 1 – Ecological Determinants of the Respiratory Microbiome by Dickson and Huffnagle, 2015. Licensed under Creative Commons: Attribution 4.0 International (CC BY 4.0) License https://creativecommons.org/licenses/by/4.0/
- Video 1 – The Lung Microbiome: Challenging Old Paradigms about Microbes by National Human Genome Research Institute. Licensed under Creative Commons: By Attribution 3.0 License https://creativecommons.org/licenses/by/3.0/

References

1. Abreu, N. A., Nagalingam, N. A., Song, Y., Roediger, F. C., Pletcher, S. D., Goldberg, A. N., & Lynch, S. V. (2012). Sinus Microbiome Diversity Depletion and Corynebacterium tuberculostearicum Enrichment Mediates Rhinosinusitis. *Science Translational Medicine*, *4*(151), 151ra124-151ra124. https://doi.org/10.1126/scitranslmed.3003783
2. Beck, J. M., Schloss, P. D., Venkataraman, A., Twigg, H., Jablonski, K. A., Bushman, F. D., Campbell, T. B., Charlson, E. S., Collman, R. G., Crothers, K., Curtis, J. L., Drews, K. L., Flores, S. C., Fontenot, A. P., Foulkes, M. A., Frank, I., Ghedin, E., Huang, L., Lynch, S. v, … Young, V. B. (2015). Multicenter Comparison of Lung and Oral Microbiomes of HIV-infected and HIV-uninfected Individuals. *American Journal of Respiratory and Critical Care Medicine*, *192*(11), 1335–1344. https://doi.org/10.1164/rccm.201501-0128OC
3. Biesbroek, G., Tsivtsivadze, E., Sanders, E. A. M., Montijn, R., Veenhoven, R. H., Keijser, B. J. F., & Bogaert, D. (2014). Early Respiratory Microbiota Composition Determines Bacterial Succession Patterns and Respiratory Health in Children. *American Journal of Respiratory and Critical Care Medicine*, *190*(11), 1283–1292. https://doi.org/10.1164/rccm.201407-1240OC
4. Bosch, A. A. T. M., Levin, E., van Houten, M. A., Hasrat, R., Kalkman, G., Biesbroek, G., de Steenhuijsen Piters, W. A. A., de Groot, P.-K. C. M., Pernet, P., Keijser, B. J. F., Sanders, E. A. M., & Bogaert, D. (2016). Development of Upper Respiratory Tract Microbiota in Infancy is Affected by Mode of Delivery. *EBioMedicine*, *9*, 336–345. https://doi.org/10.1016/j.ebiom.2016.05.031
5. Bousbia, S., Papazian, L., Saux, P., Forel, J. M., Auffray, J.-P., Martin, C., Raoult, D., & la Scola, B. (2012). Repertoire of Intensive Care Unit Pneumonia Microbiota. *PLOS ONE*, *7*(2), e32486-. https://doi.org/10.1371/journal.pone.0032486
6. Carmody, L. A., Zhao, J., Schloss, P. D., Petrosino, J. F., Murray, S., Young, V. B., Li, J. Z., & LiPuma, J. J. (2013). Changes in Cystic Fibrosis Airway Microbiota at Pulmonary Exacerbation. *Annals of the American Thoracic Society*, *10*(3), 179–187. https://doi.org/10.1513/AnnalsATS.201211-107OC

7. Chalmers, J. D., Taylor, J. K., Mandal, P., Choudhury, G., Singanayagam, A., Akram, A. R., & Hill, A. T. (2011). Validation of the Infectious Diseases Society of America/American Thoratic Society Minor Criteria for Intensive Care Unit Admission in Community-Acquired Pneumonia Patients Without Major Criteria or Contraindications to Intensive Care Unit Care. *Clinical Infectious Diseases*, *53*(6), 503–511. https://doi.org/10.1093/cid/cir463
8. Charlson, E. S., Diamond, J. M., Bittinger, K., Fitzgerald, A. S., Yadav, A., Haas, A. R., Bushman, F. D., & Collman, R. G. (2012). Lung-enriched Organisms and Aberrant Bacterial and Fungal Respiratory Microbiota after Lung Transplant. *American Journal of Respiratory and Critical Care Medicine*, *186*(6), 536–545. https://doi.org/10.1164/rccm.201204-0693OC
9. Cui, L., Morris, A., Huang, L., Beck, J. M., Twigg, H. L., von Mutius, E., & Ghedin, E. (2014). The Microbiome and the Lung. *Annals of the American Thoracic Society*, *11*(Supplement 4), S227–S232. https://doi.org/10.1513/AnnalsATS.201402-052PL
10. de Steenhuijsen Piters, W. A. A., Huijskens, E. G. W., Wyllie, A. L., Biesbroek, G., van den Bergh, M. R., Veenhoven, R. H., Wang, X., Trzciński, K., Bonten, M. J., Rossen, J. W. A., Sanders, E. A. M., & Bogaert, D. (2016). Dysbiosis of upper respiratory tract microbiota in elderly pneumonia patients. *The ISME Journal*, *10*(1), 97–108. https://doi.org/10.1038/ismej.2015.99
11. Denning, D. W., Pashley, C., Hartl, D., Wardlaw, A., Godet, C., del Giacco, S., Delhaes, L., & Sergejeva, S. (2014). Fungal allergy in asthma–state of the art and research needs. *Clinical and Translational Allergy*, *4*(1), 14. https://doi.org/10.1186/2045-7022-4-14
12. Dickson, R. P., & Huffnagle, G. B. (2015). The Lung Microbiome: New Principles for Respiratory Bacteriology in Health and Disease. *PLOS Pathogens*, *11*(7), e1004923-. https://doi.org/10.1371/journal.ppat.1004923
13. Dickson, R. P., Martinez, F. J., & Huffnagle, G. B. (2014). The role of the microbiome in exacerbations of chronic lung diseases. *The Lancet*, *384*(9944), 691–702. https://doi.org/10.1016/S0140-6736(14)61136-3
14. Dominguez-Bello, M. G., Costello, E. K., Contreras, M., Magris, M., Hidalgo, G., Fierer, N., & Knight, R. (2010). Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proceedings of the National Academy of Sciences*, *107*(26), 11971. https://doi.org/10.1073/pnas.1002601107
15. Durack, J., Boushey, H. A., & Lynch, S. v. (2016). Airway Microbiota and the Implications of Dysbiosis in Asthma. *Current Allergy and Asthma Reports*, *16*(8), 52. https://doi.org/10.1007/s11882-016-0631-8
16. Fall, T., Lundholm, C., Örtqvist, A. K., Fall, K., Fang, F., Hedhammar, Å., Kämpe, O., Ingelsson, E., & Almqvist, C. (2015). Early Exposure to Dogs and Farm Animals and the Risk of Childhood Asthma. *JAMA Pediatrics*, *169*(11), e153219–e153219. https://doi.org/10.1001/jamapediatrics.2015.3219
17. File, T. M. (2003). Community-acquired pneumonia. *The Lancet*, *362*(9400), 1991–2001. https://doi.org/10.1016/S0140-6736(03)15021-0
18. Fujimura, K. E., Johnson, C. C., Ownby, D. R., Cox, M. J., Brodie, E. L., Havstad, S. L., Zoratti, E. M., Woodcroft, K. J., Bobbitt, K. R., Wegienka, G., Boushey, H. A., & Lynch, S. v. (2010). Man's best friend? The effect of pet ownership on house dust microbial communities. *The Journal of Allergy and Clinical Immunology*, *126*(2), 410-412.e4123. https://doi.org/10.1016/j.jaci.2010.05.042
19. Fukata, M., & Arditi, M. (2013). The role of pattern recognition receptors in intestinal inflammation. *Mucosal Immunology*, *6*(3), 451–463. https://doi.org/10.1038/mi.2013.13
20. Hakansson, A. P., Orihuela, C. J., & Bogaert, D. (2018). Bacterial-Host Interactions: Physiology and Pathophysiology of Respiratory Infection. *Physiological Reviews*, *98*(2), 781–811. https://doi.org/10.1152/physrev.00040.2016
21. Hamilos, D. L. (2019). Biofilm Formations in Pediatric Respiratory Tract Infection. *Current Infectious Disease Reports*, *21*(2), 6. https://doi.org/10.1007/s11908-019-0658-9
22. Hanada, S., Pirzadeh, M., Carver, K. Y., & Deng, J. C. (2018). Respiratory Viral Infection-Induced Microbiome Alterations and Secondary Bacterial Pneumonia. *Frontiers in Immunology*, *9*, 2640. https://www.frontiersin.org/article/10.3389/fimmu.2018.02640
23. Hilty, M., Burke, C., Pedro, H., Cardenas, P., Bush, A., Bossley, C., Davies, J., Ervine, A., Poulter, L., Pachter, L., Moffatt, M. F., & Cookson, W. O. C. (2010). Disordered Microbial Communities in Asthmatic Airways. *PLOS ONE*, *5*(1), e8578-. https://doi.org/10.1371/journal.pone.0008578
24. Høiby, N., Ciofu, O., & Bjarnsholt, T. (2010). Pseudomonas aeruginosa biofilms in cystic fibrosis. *Future Microbiology*, *5*(11), 1663–1674. https://doi.org/10.2217/fmb.10.125
25. Huang, Y. J., & Boushey, H. A. (2015). The microbiome in asthma. *Journal of Allergy and Clinical Immunology*, *135*(1), 25–30. https://doi.org/10.1016/j.jaci.2014.11.011

26. Huang, Y. J., Sethi, S., Murphy, T., Nariya, S., Boushey, H. A., & Lynch, S. V. (2014). Airway microbiome dynamics in exacerbations of chronic obstructive pulmonary disease. *Journal of clinical microbiology*, *52*(8), 2813–2823. https://doi.org/10.1128/JCM.00035-14
27. Iwai, S., Huang, D., Fong, S., Jarlsberg, L. G., Worodria, W., Yoo, S., Cattamanchi, A., Davis, J. L., Kaswabuli, S., Segal, M., Huang, L., & Lynch, S. v. (2014). The Lung Microbiome of Ugandan HIV-Infected Pneumonia Patients Is Compositionally and Functionally Distinct from That of San Franciscan Patients. *PLOS ONE*, *9*(4), e95726-. https://doi.org/10.1371/journal.pone.0095726
28. Jain, S., Self, W. H., Wunderink, R. G., Fakhran, S., Balk, R., Bramley, A. M., Reed, C., Grijalva, C. G., Anderson, E. J., Courtney, D. M., Chappell, J. D., Qi, C., Hart, E. M., Carroll, F., Trabue, C., Donnelly, H. K., Williams, D. J., Zhu, Y., Arnold, S. R., … Finelli, L. (2015). Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults. *New England Journal of Medicine*, *373*(5), 415–427. https://doi.org/10.1056/NEJMoa1500245
29. Keogh, R. H., & Stanojevic, S. (2018). A guide to interpreting estimated median age of survival in cystic fibrosis patient registry reports. *Journal of Cystic Fibrosis*, *17*(2), 213–217. https://doi.org/10.1016/j.jcf.2017.11.014
30. Khalkhali, H. R., Oshnouei, S., Salarilak, S., Rahimi Rad, M., Karamyar, M., & Khashabi, J. (2014). Effects of antibiotic consumption on children 2-8 years of age developing asthma. *Epidemiology and Health*, *36*, e2014006–e2014006. https://doi.org/10.4178/epih/e2014006
31. Krone, C. L., Biesbroek, G., Trzciński, K., Sanders, E. A. M., & Bogaert, D. (2014). Respiratory microbiota dynamics following Streptococcus pneumoniae acquisition in young and elderly mice. *Infection and Immunity*, *82*(4), 1725–1731. https://doi.org/10.1128/iai.01290-13
32. Mallia, P., Message, S. D., Gielen, V., Contoli, M., Gray, K., Kebadze, T., Aniscenko, J., Laza-Stanca, V., Edwards, M. R., Slater, L., Papi, A., Stanciu, L. A., Kon, O. M., Johnson, M., & Johnston, S. L. (2011). Experimental Rhinovirus Infection as a Human Model of Chronic Obstructive Pulmonary Disease Exacerbation. *American Journal of Respiratory and Critical Care Medicine*, *183*(6), 734–742. https://doi.org/10.1164/rccm.201006-0833OC
33. Mika, M., Mack, I., Korten, I., Qi, W., Aebi, S., Frey, U., Latzin, P., & Hilty, M. (2015). Dynamics of the nasal microbiota in infancy: A prospective cohort study. *Journal of Allergy and Clinical Immunology*, *135*(4), 905-912.e11. https://doi.org/10.1016/j.jaci.2014.12.1909
34. Millares, L., Ferrari, R., Gallego, M., Garcia-Nuñez, M., Pérez-Brocal, V., Espasa, M., Pomares, X., Monton, C., Moya, A., & Monsó, E. (2014). Bronchial microbiome of severe COPD patients colonised by Pseudomonas aeruginosa. *European Journal of Clinical Microbiology & Infectious Diseases*, *33*(7), 1101–1111. https://doi.org/10.1007/s10096-013-2044-0
35. Nguyen, L. D. N., Deschaght, P., Merlin, S., Loywick, A., Audebert, C., van Daele, S., Viscogliosi, E., Vaneechoutte, M., & Delhaes, L. (2016). Effects of Propidium Monoazide (PMA) Treatment on Mycobiome and Bacteriome Analysis of Cystic Fibrosis Airways during Exacerbation. *PLOS ONE*, *11*(12), e0168860-. https://doi.org/10.1371/journal.pone.0168860
36. Nguyen, L. D. N., Viscogliosi, E., & Delhaes, L. (2015). The lung mycobiome: an emerging field of the human respiratory microbiome. *Frontiers in Microbiology*, *6*, 89. https://www.frontiersin.org/article/10.3389/fmicb.2015.00089
37. Ober, C., & Yao, T.-C. (2011). The genetics of asthma and allergic disease: a 21st century perspective. *Immunological Reviews*, *242*(1), 10–30. https://doi.org/10.1111/j.1600-065X.2011.01029.x
38. Orazi, G., & O'Toole, G. A. (2021). Pseudomonas aeruginosa Alters Staphylococcus aureus Sensitivity to Vancomycin in a Biofilm Model of Cystic Fibrosis Infection. *MBio*, *8*(4), e00873-17. https://doi.org/10.1128/mBio.00873-17
39. Ownby, D. R., Johnson, C. C., & Peterson, E. L. (2002). Exposure to Dogs and Cats in the First Year of Life and Risk of Allergic Sensitization at 6 to 7 Years of Age. *JAMA*, *288*(8), 963–972. https://doi.org/10.1001/jama.288.8.963
40. Pashley, C. H., Fairs, A., Free, R. C., & Wardlaw, A. J. (2012). DNA analysis of outdoor air reveals a high degree of fungal diversity, temporal variability, and genera not seen by spore morphology. *Fungal Biology*, *116*(2), 214–224. https://doi.org/10.1016/j.funbio.2011.11.004
41. Pettigrew, M. M., Tanner, W., & Harris, A. D. (2021). The Lung Microbiome and Pneumonia. *The Journal of Infectious Diseases*, *223*(Supplement_3), S241–S245. https://doi.org/10.1093/infdis/jiaa702
42. Popgeorgiev, N., Temmam, S., Raoult, D., & Desnues, C. (2013). Describing the Silent Human Virome with an Emphasis on Giant Viruses. *Intervirology*, *56*(6), 395–412. https://doi.org/10.1159/000354561
43. Prescott, S. L. (2013). Early-life environmental determinants of allergic diseases and the wider pandemic of inflammatory noncommunicable diseases. *Journal of Allergy and Clinical Immunology*, *131*(1), 23–30. https://doi.org/https://doi.org/10.1016/j.jaci.2012.11.019

44. Price, K. E., Hampton, T. H., Gifford, A. H., Dolben, E. L., Hogan, D. A., Morrison, H. G., Sogin, M. L., & O'Toole, G. A. (2013). Unique microbial communities persist in individual cystic fibrosis patients throughout a clinical exacerbation. *Microbiome*, *1*(1), 27. https://doi.org/10.1186/2049-2618-1-27
45. Ramos-Sevillano, E., Wade, W. G., Mann, A., Gilbert, A., Lambkin-Williams, R., Killingley, B., Nguyen-Van-Tam, J. S., & Tang, C. M. (2019). The Effect of Influenza Virus on the Human Oropharyngeal Microbiome. *Clinical Infectious Diseases*, *68*(12), 1993–2002. https://doi.org/10.1093/cid/ciy821
46. Rohde, G., Wiethege, A., Borg, I., Kauth, M., Bauer, T. T., Gillissen, A., Bufe, A., & Schultze-Werninghaus, G. (2003). Respiratory viruses in exacerbations of chronic obstructive pulmonary disease requiring hospitalisation: a case-control study. *Thorax*, *58*(1), 37. https://doi.org/10.1136/thorax.58.1.37
47. SEEMUNGAL, T., HARPER-OWEN, R., BHOWMIK, A., MORIC, I., SANDERSON, G., MESSAGE, S., MacCALLUM, P., MEADE, T. W., JEFFRIES, D. J., JOHNSTON, S. L., & WEDZICHA, J. A. (2001). Respiratory Viruses, Symptoms, and Inflammatory Markers in Acute Exacerbations and Stable Chronic Obstructive Pulmonary Disease. *American Journal of Respiratory and Critical Care Medicine*, *164*(9), 1618–1623. https://doi.org/10.1164/ajrccm.164.9.2105011
48. Shilts, M. H., Rosas-Salazar, C., Tovchigrechko, A., Larkin, E. K., Torralba, M., Akopov, A., Halpin, R., Peebles, R. S., Moore, M. L., Anderson, L. J., Nelson, K. E., Hartert, T. v, & Das, S. R. (2016). Minimally Invasive Sampling Method Identifies Differences in Taxonomic Richness of Nasal Microbiomes in Young Infants Associated with Mode of Delivery. *Microbial Ecology*, *71*(1), 233–242. https://doi.org/10.1007/s00248-015-0663-y
49. Stearns, J. C., Davidson, C. J., McKeon, S., Whelan, F. J., Fontes, M. E., Schryvers, A. B., Bowdish, D. M. E., Kellner, J. D., & Surette, M. G. (2015). Culture and molecular-based profiles show shifts in bacterial communities of the upper respiratory tract that occur with age. *The ISME Journal*, *9*(5), 1246–1259. https://doi.org/10.1038/ismej.2014.250
50. Sze, M. A., Dimitriu, P. A., Suzuki, M., McDonough, J. E., Campbell, J. D., Brothers, J. F., Erb-Downward, J. R., Huffnagle, G. B., Hayashi, S., Elliott, W. M., Cooper, J., Sin, D. D., Lenburg, M. E., Spira, A., Mohn, W. W., & Hogg, J. C. (2015). Host Response to the Lung Microbiome in Chronic Obstructive Pulmonary Disease. *American Journal of Respiratory and Critical Care Medicine*, *192*(4), 438–445. https://doi.org/10.1164/rccm.201502-0223OC
51. Teo, S. M., Mok, D., Pham, K., Kusel, M., Serralha, M., Troy, N., Holt, B. J., Hales, B. J., Walker, M. L., Hollams, E., Bochkov, Y. A., Grindle, K., Johnston, S. L., Gern, J. E., Sly, P. D., Holt, P. G., Holt, K. E., & Inouye, M. (2015). The Infant Nasopharyngeal Microbiome Impacts Severity of Lower Respiratory Infection and Risk of Asthma Development. *Cell Host & Microbe*, *17*(5), 704–715. https://doi.org/https://doi.org/10.1016/j.chom.2015.03.008
52. Teo, S. M., Mok, D., Pham, K., Kusel, M., Serralha, M., Troy, N., Holt, B. J., Hales, B. J., Walker, M. L., Hollams, E., Bochkov, Y. A., Grindle, K., Johnston, S. L., Gern, J. E., Sly, P. D., Holt, P. G., Holt, K. E., & Inouye, M. (2015). The Infant Nasopharyngeal Microbiome Impacts Severity of Lower Respiratory Infection and Risk of Asthma Development. *Cell Host & Microbe*, *17*(5), 704–715. https://doi.org/10.1016/j.chom.2015.03.008
53. Underhill, D. M., & Iliev, I. D. (2014). The mycobiota: interactions between commensal fungi and the host immune system. *Nature Reviews Immunology*, *14*(6), 405–416. https://doi.org/10.1038/nri3684
54. Unger, S. A., & Bogaert, D. (2017). The respiratory microbiome and respiratory infections. *Journal of Infection*, *74*, S84–S88. https://doi.org/10.1016/S0163-4453(17)30196-2
55. Urb, M., Snarr, B. D., Wojewodka, G., Lehoux, M., Lee, M. J., Ralph, B., Divangahi, M., King, I. L., McGovern, T. K., Martin, J. G., Fraser, R., Radzioch, D., & Sheppard, D. C. (2015). Evolution of the Immune Response to Chronic Airway Colonization with Aspergillus fumigatus Hyphae. *Infection and immunity*, *83*(9), 3590–3600. https://doi.org/10.1128/IAI.00359-15
56. Valley, T. S., Sjoding, M. W., Ryan, A. M., Iwashyna, T. J., & Cooke, C. R. (2015). Association of Intensive Care Unit Admission With Mortality Among Older Patients With Pneumonia. *JAMA*, *314*(12), 1272–1279. https://doi.org/10.1001/jama.2015.11068
57. van Woerden, H. C., Gregory, C., Brown, R., Marchesi, J. R., Hoogendoorn, B., & Matthews, I. P. (2013). Differences in fungi present in induced sputum samples from asthma patients and non-atopic controls: a community based case control study. *BMC Infectious Diseases*, *13*(1), 69. https://doi.org/10.1186/1471-2334-13-69
58. Wang, Z., Bafadhel, M., Haldar, K., Spivak, A., Mayhew, D., Miller, B. E., Tal-Singer, R., Johnston, S. L., Ramsheh, M. Y., Barer, M. R., Brightling, C. E., & Brown, J. R. (2016). Lung microbiome dynamics in COPD exacerbations. *European Respiratory Journal*, *47*(4), 1082. https://doi.org/10.1183/13993003.01406-2015
59. Wardlaw, T., Salama, P., Johansson, E. W., & Mason, E. (2006). Pneumonia: the leading killer of children. *The Lancet*, *368*(9541), 1048–1050. https://doi.org/10.1016/S0140-6736(06)69334-3

60. Watson, R. L., de Koff, E. M., & Bogaert, D. (2019). Characterising the respiratory microbiome. *European Respiratory Journal*, *53*(2), 1801711. https://doi.org/10.1183/13993003.01711-2018
61. Willner, D., Furlan, M., Haynes, M., Schmieder, R., Angly, F. E., Silva, J., Tammadoni, S., Nosrat, B., Conrad, D., & Rohwer, F. (2009). Metagenomic Analysis of Respiratory Tract DNA Viral Communities in Cystic Fibrosis and Non-Cystic Fibrosis Individuals. *PLOS ONE*, *4*(10), e7370-. https://doi.org/10.1371/journal.pone.0007370
62. Zaura, E., Nicu, E. A., Krom, B. P., & Keijser, B. J. F. (2014). Acquiring and maintaining a normal oral microbiome: current perspective. *Frontiers in Cellular and Infection Microbiology*, *4*, 85. https://www.frontiersin.org/article/10.3389/fcimb.2014.00085
63. Zhao, J., Schloss, P. D., Kalikin, L. M., Carmody, L. A., Foster, B. K., Petrosino, J. F., Cavalcoli, J. D., VanDevanter, D. R., Murray, S., Li, J. Z., Young, V. B., & LiPuma, J. J. (2012). Decade-long bacterial community dynamics in cystic fibrosis airways. *Proceedings of the National Academy of Sciences*, *109*(15), 5809. https://doi.org/10.1073/pnas.1120577109
64. Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., Xiang, J., Wang, Y., Song, B., Gu, X., Guan, L., Wei, Y., Li, H., Wu, X., Xu, J., Tu, S., Zhang, Y., Chen, H., & Cao, B. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet*, *395*(10229), 1054–1062. https://doi.org/10.1016/S0140-6736(20)30566-3

This page titled 20.5: The Respiratory Microbiome is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Dylan Parks via source content that was edited to the style and standards of the LibreTexts platform.

- **3.5: The Respiratory Microbiome** by Dylan Parks is licensed CC BY 4.0. Original source: https://uta.pressbooks.pub/microbiomeshealthandtheenvironment.

20.6: The Vaginal Microbiome

The Vaginal Microbiome

The vaginal microbiome is a reproductive organ-specific niche that harbors a unique collection of microorganisms that are important in a variety of aspects to human health. This microbial community has significance in maintaining vaginal homeostasis, protecting against urogenital infections, host immunity, and reproductive capacities. In recent years, next generation sequencing (NGS) techniques have been employed to classify the vaginal microbiome into community state types (CSTs), or vaginotypes, based upon composition, which can enhance epidemiological studies to make better associations between the microbiome and host-vaginal health (France et al., 2020, Mancabelli et al., 2021).

Composition and Role

The vaginal microbiome is composed of over 200 different bacterial species, though it is primarily dominated by members from *Lactobacillus* genus (Ma et al., 2012, Auriemma et al., 2021). The *Lactobacilli* protect the vagina from potential pathogen invasion through their fermentation of vaginal epithelial cell-produced glycogen into lactic acid, which lowers vaginal pH, as well as their production of various antimicrobial compounds, and resource/space competitive inhibition (Boskey et al., 2001, Amabebe and Anumba, 2018, Chee et al., 2020, Jang et al., 2019). Though, the bacteriome is usually the emphasized feature of the vaginal microbiome, it also harbors protists, fungi, archaea and viruses, with each occupying their own niche in the normal healthy network (Belay et al., 1990, Bradford and Ravel, 2017, Happel et al., 2020, Chacra and Fenollar, 2021). The composition isn't always fixed however, as factors like the menstrual cycle, hormone fluctuation, sexual partners, hygiene, genetics, age, the environment, drug use, and other aspects of lifestyle can affect the microbial makeup (Aagaard et al., 2012, Fettweis et al., 2014, Hyman et al., 2014, Zapata and Quagliarello, 2015, Martin and Marrazzo, 2016, Diop et al., 2019, Chacra and Fenollar, 2021).

As mentioned earlier, using 16S rRNA sequencing, the vaginal microbiome has been categorized into CSTs and allowed for deeper analysis, where comparisons of the consortia within these classifications can be used to make associations with host and vaginal health. There are 5 main CSTs each predominated by a particular species of *Lactobacilli*, except for group IV, which has been further dissected into additional subgroups: CST I—*L. crispatus* dominated, CST II—*L. gasseri* dominated, CST III—*L. iners* dominated, and CST V—*L. jensenii* dominated (Ravel et al., 2011, France et al., 2020, Chacra and Fenollar, 2021, Mancabelli et al., 2021). CST IV is not dominated by any particular species, and contains a mixture of both strict and facultative anaerobes including *Gardnerella*, *Atopobium*, *Lactobacillus*, *Bifidobacterium*, etc., where certain controversial subgroups (e.g. CST IV-A, CST IV-B, CST IV-C, CST IV-D, CST IV-G, etc.) have various combinations depending on the study (Gajer et al., 2012, Albert et al., 2015, France et al., 2020, Mancabelli et al., 2021). Each of the five groups has correlations with vaginal pH, microbial colonization and biodiversity, as well as host characteristics such as pregnancy, ethnicity, and age, though it is not always absolute (France et al., 2020, Mancabelli et al., 2021). With reproducible organization of the vaginal microbiome, connections can be made with medical conditions, which could benefit treatment and diagnosis of vaginal diseases and associated affairs.



As with other microbiomes associated with the human body, disturbance of the resident vaginal microbiome can result in complications of health. Many diseases of the urogenital tract such as bacterial vaginosis (BV), urinary tract infections (UTIs), yeast infections, and several sexually transmitted infections (STIs) are caused by pathogenic microbes associated with dysbiosis (Taha et al., 1998, Donders et al., 2000, Wiesenfeld et al., 2003; Lai et al., 2009, De Seta et al., 2019, Mancabelli et al., 2021). Normally, the local flora maintains homeostasis, however, changes in composition provide opportunistic pathogens a window to proliferate and invade.

Bacterial vaginosis, associated with CST IV, stems from a perturbance of the vaginal flora, specifically a decrease in *Lactobacilli* and an increase in other microbes like *Gardnerlla vaginalis*, *Atopboium vaginae*, *Ureaplasma urealyticum*, and others that are only usually found in low numbers (Gajer et al., 2012, Margolis and Fredricks, 2015, Onderdonk et al., 2016, Zozaya et al., 2016). This condition can be asymptomatic in up to half the women with BV, and in the others can be diagnosed by observed changes in vaginal discharge or by the Nugent scoring system which utilizes a Gram stain (Figure 1) (Nugent et al., 1991, Amsel et al., 1983, Schwebke, 2000). While not exactly considered a sexually transmitted disease, bacterial vaginosis is commonly associated with certain sexual practices, though other factors such as hygiene, nutrition, intrauterine devices, hormonal changes, and certain comorbidities can contribute to susceptibility (Avonts et al, 1990, Calzolari et al., 2000, Neggers et al., 2007, Verstraelen et al., 2010, Zabor et al, 2010, Margolis and Fredricks, 2015). Women with this disease also have a higher risk to contract sexually transmitted infections, and it can be linked to reproductive complications and poor infant health (Wiesenfeld et al., 2003, Prince et al., 2015, Chacra and Fenollar, 2021). Typically, antibiotics targeting anaerobic bacteria are administered to treat BV, however recurrence is common, likely due to the antimicrobial-resistant nature of biofilms formed by the pathogens and/or regular exposure to external reservoirs (Swidinski et al., 2008, Oduyebo et al., 2009, Marrazzo et al., 2012, Bradshaw and Sobel, 2016). Probiotics, specifically containing *L. crispatus*, may be the better option, and vaginal microbiota transplantation from a healthy donors is a promising treatment course of action (Hemmerling et al., 2010, Ma et al., 2019).

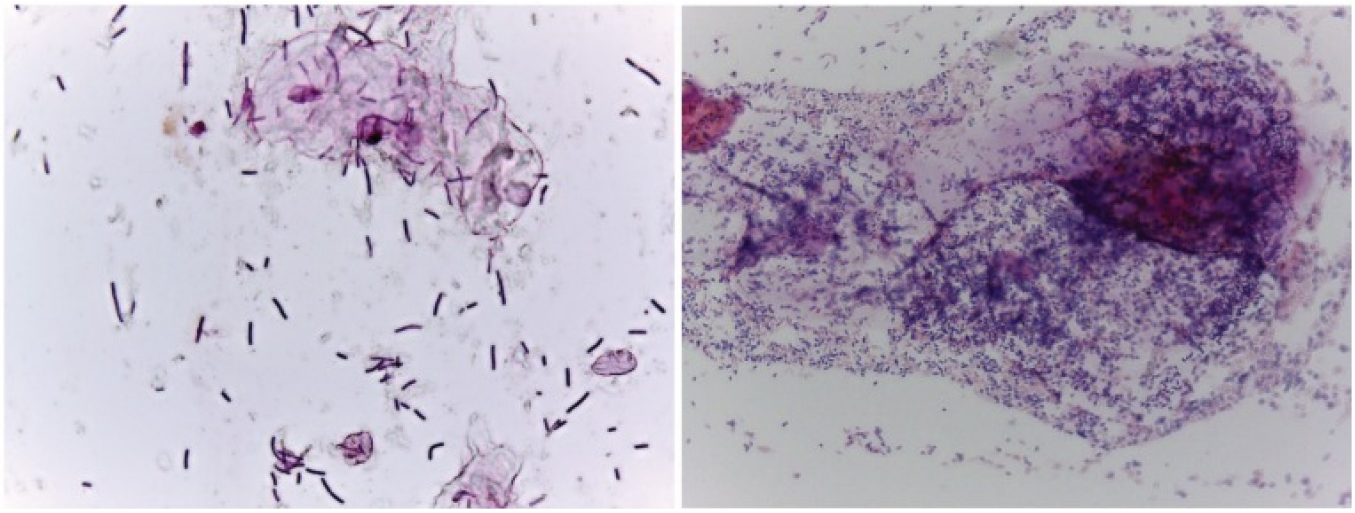


Figure 1. Examples of Gram-stained slides from women with (right, Nugent score = 9) and without (left, Nugent score = 1) BV. In women with a lactobacilli-dominated microbiome (left), long purple rods are the main morphotype. In contrast, women with BV tend to have a lot more bacteria overall, with a significant fraction that do not stain as Gram-positive (i.e. pink). Morphotypes in BV tend not to be long Gram-positive rods. Although not part of the Nugent scoring system, women with BV tend to have large conglomerations of bacteria associated with epithelial cells as seen in the upper right quadrant (Lewis and Gilbert, 2020).

Urinary tract infections are a common problem, especially for females, which are disproportionately affected. This infection is most likely to occur in the urethra or bladder (though in severe cases the kidneys can be affected), which causes pain in the pelvic area and during urination, the frequent urge to urinate, and the presence of blood in urine (Lee and Neild, 2007, Sheerin, 2011, Hooton, 2012). The vaginal microbiome, or more specifically some normal residents, like *Escherichia coli*, can move to the urogenital tract and cause issues resulting in a UTI, which often occurs via sexual activity (Nicolle et al., 1982, Foxman, 2014, Stapleton, 2016,

Lewis and Gilbert, 2020). Other fastidious microorganisms, like those abundant in women experiencing BV, contribute to a higher risk of contracting an infection in the urinary tract as compared with those not suffering from dysbiosis in the vagina (Hillebrand et al., 2002, Sumati and Saritha, 2009). In these cases, the vaginal opening may harbor potential uropathogens (Figure 2) and transient exposure to the urinary tract could prompt colonization or other reactions (e.g. immunomodulation) that results in a UTI (Lewis and Gilbert, 2020). Antibiotics are traditionally used to treat UTIs, however probiotics and estrogen administration could help to restore the *Lactobacillus* colonization and protect against complicated and recurrent infections (Raz and Stamm, 1993, Eriksen, 1999, Prais et al., 2003, Stapleton et al., 2011, Tan and Chlebicki, 2016, Lewis and Gilbert, 2020).

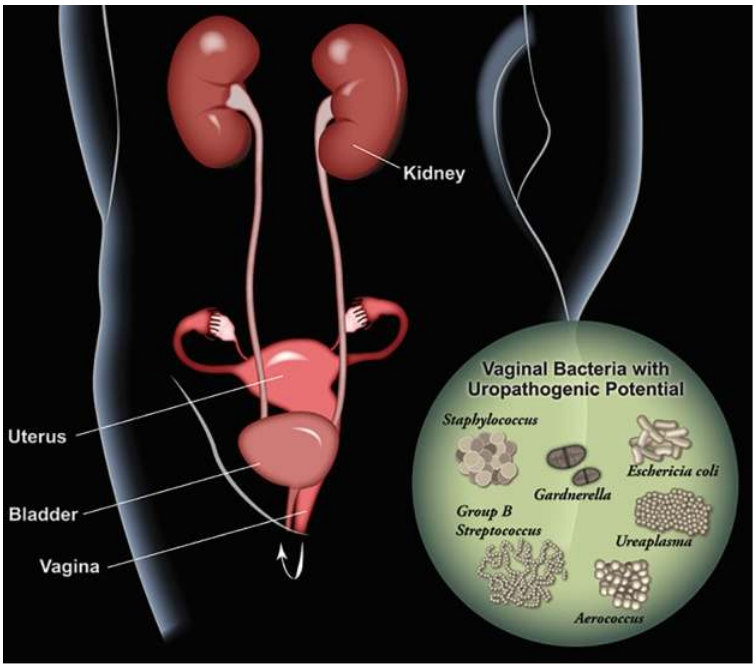


Figure 2. Schematic illustrating vaginal bacteria with potential to impact the urinary tract. The vagina can serve as a reservoir for several bacterial species known to be causes of UTI (E. coli, GBS, Staphylococcus) as well as underappreciated potential uropathogens (G. vaginalis, Aerococcs Ureaplasma) that can cause UTI and have been associated with urological conditions such as urgency incontinence and “sterile” pyuria (Lewis and Gilbert, 2020).

Yeast infection of the vaginal region caused by *Candida* species, also known as vulvovaginal candidiasis (VVC), is a common condition with severe symptoms and a high recurrence rate (Oerlemans et al., 2020). Those affected experience vaginal itchiness or soreness, dyspareunia (painful intercourse), abnormal vaginal discharge, redness, swelling, and thinning of the vaginal wall (Chew and Than, 2016, Oerlemans et al., 2020). While it is the second-most common infection of the vagina behind BV, this disease primarily affects premenopausal women with a low vaginal pH value under 4.5 (Kim and Park, 2017, Gupta et al., 2019). The exact cause of VVC isn’t exactly clear, though it is thought it can come as a result of microbiome dysbiosis induced by prolonged antibiotic usage, which allows various *Candida* species to overgrow and establish an infection (Goldacre et al., 1979, Mitchell, 2004, Peters et al., 2014, van de Wijgert and Verwijs, 2020). Traditionally, antifungal medication has been used to treat VVC, however administration of probiotic vaginal microbes may be more prudent as their mechanisms of pathogen colonization and biofilm formation inhibition are more effective to prevent disease recurrence (Petrova et al., 2016, Tachedjian et al., 2017, Allonsius et al., 2019, Oerlemans et al., 2020, van de Wijgert and Verwijs, 2020).

Individuals with vaginal microbiome dysbiosis characterized by a decrease in abundance of *Lactobacilli* species (i.e. BV) are at a higher risk of contracting sexually transmitted infections, such as those caused by *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, *Chlamydia trachomatis*, and *Mycoplasma genitalium* (Martin et al., 1999, Cherpes et al., 2003, Peipert et al., 2008, Brotman et al., 2010, Molenaar et al., 2018, De Seta et al., 2022). Infections caused by these organisms usually result in symptoms similar to other genital infections such as vaginal itching, pain, unusual discharge, rash, etc. which like other conditions (e.g. vaginitis), result in decreased epithelial integrity and can exacerbate pathogen invasion (Miller and Shattock, 2003, Greenbaum et al., 2019). In those individuals with BV and non-inflamed tissue, the increased risk for STIs could be due to the negative effects dysbiosis-related bacteria have on the innate immune system (Murphy and Mitchell, 2016, Liebenberg et al., 2017). Similarly, contraction of

sexually transmitted viral infections like human immunodeficiency virus (HIV), herpesviruses, and human papillomavirus (HPV) are frequently associated with vaginal dysbiosis, immunomodulation, and disruption of the epithelial barrier (Sewankambo et al., 1997, Borgdorff et al., 2016, Siqueira et al., 2019, Torcia, 2019, De Seta et al., 2022). While there is correlation between vaginal dysbiosis and STIs, the protective mechanisms of the resident vaginal microbiota are unknown and still need to be uncovered (De Seta et al., 2022).



Reproduction, Pregnancy, and Infant health

The vaginal microbiome has further implications in host immunity, fertility, pregnancy, spontaneous preterm birth, and infant health (Anahtar et al., 2015, Fettweis et al., 2019, Gupta et al., 2020, Xu et al., 2020). Indeed, there are a multitude of factors that affect reproduction like age, genetics, hormone levels, fallopian tube blockage, menstrual cycle, and vaginal pH, however only recently has the vaginal microbiome been studied for its association with various fertility factors (Xu et al., 2020, Fan et al., 2022).

Changes in the resident vaginal flora and infections by certain pathogens can cause complications for reproductive health and pregnancy. For example, infection by Group B *Streptococcus* (GBS) has been associated with a decline in ovarian function, pregnancy loss, preterm delivery, and is the leading cause of bacteremia and meningitis in newborns (Zaleznik et al., 2000, Phares et al., 2008, Kolter and Henneke, 2017, Tazi et al., 2019, Xu et al., 2020). The vaginal microbiome of pregnant women is less rich and diverse than non-pregnant individuals, likely caused by changes in sex hormone levels (Farage et al., 2010, Aagaard et al., 2012). These alterations can cause shifts in the vaginal microbiome that could then result in infection and a risk of preterm or spontaneous labor (Wylie et al., 2018, Fettweis et al., 2019, Feehily et al., 2020, Gupta et al., 2020).

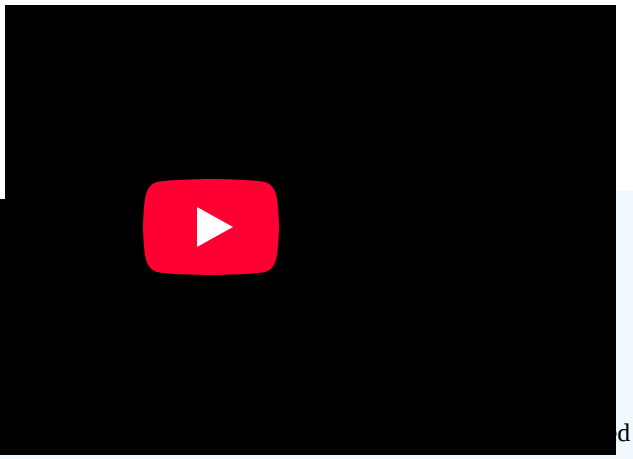
Infants become introduced to the microbial world via their mother, and predominately right after birth where vaginal versus cesarean delivery has a great impact on composition (Chu et al., 2017). However, exposure may happen earlier *in utero*, as this environment may not be as sterile as once thought as some studies have shown the presence of microbes in the placenta and amniotic fluid (Aagaard et al., 2014, Collado et al., 2016, Kolter and Henneke, 2017). The establishment of a newborn's microbiome has profound effects on the development of immunity and metabolism as well as the onset of diseases like atopic dermatitis and obesity in later life (Rautava et al., 2012, Collado et al., 2016, Ta et al., 2020).

Conclusion

The vaginal microbiome is a complex community which affects many facets of human health and disease including urogenital, reproductive, immune, and infant. Characterization of the vaginal flora has allowed categorization into community state types which can help to predict and diagnose disease states. Within so, these dynamic changes that occur under various conditions produce a unique fingerprint for the vaginal microbiome which can be analyzed and potentially treated in a specific manner (Ceccarani et al., 2019, Lagenaur et al., 2020, Abou Chacra and Fenollar, 2021). While antibiotic administration has its benefits, novel approaches using targeted application of probiotic microbiomes (e.g. a gel containing specific *Lactobacilli* species) could help in treating diseases associated with vaginal dysbiosis by restoring those disrupted communities, as well as alleviating certain negative consequences of chemotherapy (Pino et al., 2019, Lagenaur et al., 2020 Oerlemans et al., 2020). More in-depth and continued research of the vaginal microbiome is necessary to illuminate the interactions and connections of it members to human health.

Drag and Drop Quiz

Drag the species of bacteri



Check your Understanding

- Explain vaginal mic
- Which CST is associ
- How does BV contri
- How does the vagina
- Where does a newbo
- What alternatives to d diseases?

Media Attributions

- Video 1 – VALENCIA: A nearest centroid classification for vaginal microbial communities by Research Square. Licensed under Creative Commons: By Attribution 3.0 License https://creativecommons.org/licenses/by/3.0/
- Figure 1 – Examples of Gram-stained slides from women with (right, Nugent score = 9) and without (left, Nugent score = 1) BV by Lewis and Gilbert, 2020. Licensed under Creative Commons Attribution 4.0 License https://creativecommons.org/licenses/by/4.0/
- Figure 2 – Schematic illustrating vaginal bacteria with potential to impact the urinary tract by Lewis and Gilbert, 2020. Licensed under Creative Commons Attribution 4.0 License https://creativecommons.org/licenses/by/4.0/
- Video 2 – Beyond bacterial vaginosis: vaginal lactobacilli and HIV risk by Research Square. Licensed under Creative Commons: By Attribution 3.0 License https://creativecommons.org/licenses/by/3.0/
- Video 3 – A temporal model of cervicovaginal microbiota identifies targets to promote reproductive health by Research Square. Licensed under Creative Commons: By Attribution 3.0 License https://creativecommons.org/licenses/by/3.0/

References

1. Aagaard, K., Ma, J., Antony, K. M., Ganu, R., Petrosino, J., & Versalovic, J. (2014). The Placenta Harbors a Unique Microbiome. *Science Translational Medicine*, *6*(237), 237ra65-237ra65. https://doi.org/10.1126/scitranslmed.3008599
2. Aagaard, K., Riehle, K., Ma, J., Segata, N., Mistretta, T.-A., Coarfa, C., Raza, S., Rosenbaum, S., van den Veyver, I., Milosavljevic, A., Gevers, D., Huttenhower, C., Petrosino, J., & Versalovic, J. (2012). A Metagenomic Approach to Characterization of the Vaginal Microbiome Signature in Pregnancy. *PLOS ONE*, *7*(6), e36466-. https://doi.org/10.1371/journal.pone.0036466
3. Abou Chacra, L., & Fenollar, F. (2021). Exploring the global vaginal microbiome and its impact on human health. *Microbial Pathogenesis*, *160*, 105172. https://doi.org/10.1016/j.micpath.2021.105172
4. Albert, A. Y. K., Chaban, B., Wagner, E. C., Schellenberg, J. J., Links, M. G., van Schalkwyk, J., Reid, G., Hemmingsen, S. M., Hill, J. E., Money, D., & Group, V. R. (2015). A Study of the Vaginal Microbiome in Healthy Canadian Women Utilizing cpn60-Based Molecular Profiling Reveals Distinct Gardnerella Subgroup Community State Types. *PLOS ONE*, *10*(8), e0135620-. https://doi.org/10.1371/journal.pone.0135620
5. Allonsius, C. N., Vandenheuvel, D., Oerlemans, E. F. M., Petrova, M. I., Donders, G. G. G., Cos, P., Delputte, P., & Lebeer, S. (2019). Inhibition of Candida albicans morphogenesis by chitinase from Lactobacillus rhamnosus GG. *Scientific Reports*, *9*(1), 2900. https://doi.org/10.1038/s41598-019-39625-0
6. Amabebe, E., & Anumba, D. O. C. (2018). The Vaginal Microenvironment: The Physiologic Role of Lactobacilli. *Frontiers in Medicine*, *5*, 181. https://doi.org/10.3389/fmed.2018.00181
7. Amsel, R., Totten, P. A., Spiegel, C. A., Chen, K. C. S., Eschenbach, D., & Holmes, K. K. (1983). Nonspecific vaginitis: Diagnostic criteria and microbial and epidemiologic associations. *The American Journal of Medicine*, *74*(1), 14–22. https://doi.org/10.1016/0002-9343(83)91112-9
8. Anahtar, M. N., Byrne, E. H., Doherty, K. E., Bowman, B. A., Yamamoto, H. S., Soumillon, M., Padavattan, N., Ismail, N., Moodley, A., Sabatini, M. E., Ghebremichael, M. S., Nusbaum, C., Huttenhower, C., Virgin, H. W., Ndung'u, T., Dong, K. L.,

Walker, B. D., Fichorova, R. N., & Kwon, D. S. (2015). Cervicovaginal Bacteria Are a Major Modulator of Host Inflammatory Responses in the Female Genital Tract. *Immunity*, *42*(5), 965–976. https://doi.org/10.1016/j.immuni.2015.04.019

9. Auriemma, R. S., Scairati, R., del Vecchio, G., Liccardi, A., Verde, N., Pirchio, R., Pivonello, R., Ercolini, D., & Colao, A. (2021). The Vaginal Microbiome: A Long Urogenital Colonization Throughout Woman Life. *Frontiers in Cellular and Infection Microbiology*, *11*, 613. https://www.frontiersin.org/article/10.3389/fcimb.2021.686167
10. AVONTS, D., SERCU, M., HEYERICK, P., VANDERMEEREN, I., MEHEUS, A., & PIOT, P. (1990). Incidence of Uncomplicated Genital Infections in Women Using Oral Contraception or an Intrauterine Device: A Prospective Study. *Sexually Transmitted Diseases*, *17*(1), 23–29. http://www.jstor.org/stable/44971143
11. Belay, N., Mukhopadhyay, B., E, C. de M., Galask, R., & Daniels, L. (1990). Methanogenic bacteria in human vaginal samples. *Journal of Clinical Microbiology*, *28*(7), 1666–1668. https://doi.org/10.1128/jcm.28.7.1666-1668.1990
12. Boskey, E. R., Cone, R. A., Whaley, K. J., & Moench, T. R. (2001). Origins of vaginal acidity: high d/l lactate ratio is consistent with bacteria being the primary source. *Human Reproduction*, *16*(9), 1809–1813. https://doi.org/10.1093/humrep/16.9.1809
13. Bradford, L. L., & Ravel, J. (2017). The vaginal mycobiome: A contemporary perspective on fungi in women's health and diseases. *Virulence*, *8*(3), 342–351. https://doi.org/10.1080/21505594.2016.1237332
14. Bradshaw, C. S., & Sobel, J. D. (2016). Current Treatment of Bacterial Vaginosis—Limitations and Need for Innovation. *The Journal of Infectious Diseases*, *214*(suppl_1), S14–S20. https://doi.org/10.1093/infdis/jiw159
15. Brotman, R. M., Klebanoff, M. A., Nansel, T. R., Yu, K. F., Andrews, W. W., Zhang, J., & Schwebke, J. R. (2010). Bacterial vaginosis assessed by gram stain and diminished colonization resistance to incident gonococcal, chlamydial, and trichomonal genital infection. *The Journal of infectious diseases*, *202*(12), 1907–1915. https://doi.org/10.1086/657320
16. Calzolari, E., Masciangelo, R., Milite, V., & Verteramo, R. (2000). Bacterial vaginosis and contraceptive methods. *International Journal of Gynecology & Obstetrics*, *70*(3), 341–346. https://doi.org/https://doi.org/10.1016/S0020-7292(00)00217-4
17. Ceccarani, C., Foschi, C., Parolin, C., D'Antuono, A., Gaspari, V., Consolandi, C., Laghi, L., Camboni, T., Vitali, B., Severgnini, M., & Marangoni, A. (2019). Diversity of vaginal microbiome and metabolome during genital infections. *Scientific Reports*, *9*(1), 14095. https://doi.org/10.1038/s41598-019-50410-x
18. Chee, W. J. Y., Chew, S. Y., & Than, L. T. L. (2020). Vaginal microbiota and the potential of Lactobacillus derivatives in maintaining vaginal health. *Microbial Cell Factories*, *19*(1), 203. https://doi.org/10.1186/s12934-020-01464-4
19. Cherpes, T. L., Meyn, L. A., Krohn, M. A., Lurie, J. G., & Hillier, S. L. (2003). Association between acquisition of herpes simplex virus type 2 in women and bacterial vaginosis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, *37*(3), 319–325. https://doi.org/10.1086/375819
20. Chew, S. Y., & Than, L. T. L. (2016). Vulvovaginal candidosis: contemporary challenges and the future of prophylactic and therapeutic approaches. *Mycoses*, *59*(5), 262–273. https://doi.org/https://doi.org/10.1111/myc.12455
21. Chu, D. M., Ma, J., Prince, A. L., Antony, K. M., Seferovic, M. D., & Aagaard, K. M. (2017). Maturation of the infant microbiome community structure and function across multiple body sites and in relation to mode of delivery. *Nature Medicine*, *23*(3), 314–326. https://doi.org/10.1038/nm.4272
22. Collado, M. C., Rautava, S., Aakko, J., Isolauri, E., & Salminen, S. (2016). Human gut colonisation may be initiated in utero by distinct microbial communities in the placenta and amniotic fluid. *Scientific Reports*, *6*(1), 23129. https://doi.org/10.1038/srep23129
23. de Seta, F., Campisciano, G., Zanotta, N., Ricci, G., & Comar, M. (2019). The Vaginal Community State Types Microbiome-Immune Network as Key Factor for Bacterial Vaginosis and Aerobic Vaginitis. *Frontiers in Microbiology*, *10*, 2451. https://www.frontiersin.org/article/10.3389/fmicb.2019.02451
24. de Seta, F., Lonnee-Hoffmann, R., Campisciano, G., Comar, M., Verstraelen, H., Vieira-Baptista, P., Ventolini, G., & Lev-Sagie, A. (2022). The Vaginal Microbiome: III. The Vaginal Microbiome in Various Urogenital Disorders. *Journal of Lower Genital Tract Disease*, *26*(1). https://journals.lww.com/jlgtd/Fulltext/2022/01000/The_Vaginal_Microbiome__III__The_Vaginal.17.aspx
25. Diop, K., Dufour, J.-C., Levasseur, A., & Fenollar, F. (2019). Exhaustive repertoire of human vaginal microbiota. *Human Microbiome Journal*, *11*, 100051. https://doi.org/10.1016/j.humic.2018.11.002
26. Donders, G. G. G., Bosmans, E., Dekeersmaecker, A., Vereecken, A., van Bulck, B., & Spitz, B. (2000). Pathogenesis of abnormal vaginal bacterial flora. *American Journal of Obstetrics and Gynecology*, *182*(4), 872–878. https://doi.org/10.1016/S0002-9378(00)70338-3

27. Eriksen B. (1999). A randomized, open, parallel-group study on the preventive effect of an estradiol-releasing vaginal ring (Estring) on recurrent urinary tract infections in postmenopausal women. *American journal of obstetrics and gynecology*, *180*(5), 1072–1079. https://doi.org/10.1016/s0002-9378(99)70597-1
28. Fan, W., Kan, H., Liu, H. Y., Wang, T. L., He, Y. N., Zhang, M., Li, Y. X., Li, Y. J., Meng, W., Li, Q., Hu, A. Q., & Zheng, Y. J. (2022). Association between Human Genetic Variants and the Vaginal Bacteriome of Pregnant Women. *MSystems*, *6*(4), e00158-21. https://doi.org/10.1128/mSystems.00158-21
29. Farage, M. A., Miller, K. W., & Sobel, J. D. (2010). Dynamics of the Vaginal Ecosystem—Hormonal Influences. *Infectious Diseases: Research and Treatment*, *3*, IDRT.S3903. https://doi.org/10.4137/IDRT.S3903
30. Feehily, C., Crosby, D., Walsh, C. J., Lawton, E. M., Higgins, S., McAuliffe, F. M., & Cotter, P. D. (2020). Shotgun sequencing of the vaginal microbiome reveals both a species and functional potential signature of preterm birth. *Npj Biofilms and Microbiomes*, *6*(1), 50. https://doi.org/10.1038/s41522-020-00162-8
31. Fettweis, J. M., Brooks, J. P., Serrano, M. G., Sheth, N. U., Girerd, P. H., Edwards, D. J., Strauss, J. F., Consortium, T. V. M., Jefferson, K. K., & Buck, G. A. (2014). Differences in vaginal microbiome in African American women versus women of European ancestry. *Microbiology (Reading, England)*, *160*(Pt 10), 2272–2282. https://doi.org/10.1099/mic.0.081034-0
32. Fettweis, J. M., Serrano, M. G., Brooks, J. P., Edwards, D. J., Girerd, P. H., Parikh, H. I., Huang, B., Arodz, T. J., Edupuganti, L., Glascock, A. L., Xu, J., Jimenez, N. R., Vivadelli, S. C., Fong, S. S., Sheth, N. U., Jean, S., Lee, V., Bokhari, Y. A., Lara, A. M., … Buck, G. A. (2019). The vaginal microbiome and preterm birth. *Nature Medicine*, *25*(6), 1012–1021. https://doi.org/10.1038/s41591-019-0450-2
33. Foxman B. (2014). Urinary tract infection syndromes: occurrence, recurrence, bacteriology, risk factors, and disease burden. *Infectious disease clinics of North America*, *28*(1), 1–13. https://doi.org/10.1016/j.idc.2013.09.003
34. France, M. T., Ma, B., Gajer, P., Brown, S., Humphrys, M. S., Holm, J. B., Waetjen, L. E., Brotman, R. M., & Ravel, J. (2020). VALENCIA: a nearest centroid classification method for vaginal microbial communities based on composition. *Microbiome*, *8*(1), 166. https://doi.org/10.1186/s40168-020-00934-6
35. Gajer, P., Brotman, R. M., Bai, G., Sakamoto, J., Schütte, U. M., Zhong, X., Koenig, S. S., Fu, L., Ma, Z. S., Zhou, X., Abdo, Z., Forney, L. J., & Ravel, J. (2012). Temporal dynamics of the human vaginal microbiota. *Science translational medicine*, *4*(132), 132ra52. https://doi.org/10.1126/scitranslmed.3003605
36. Goldacre, M. J., Watt, B., Loudon, N., Milne, L. J., Loudon, J. D., & Vessey, M. P. (1979). Vaginal microbial flora in normal young women. *British Medical Journal*, *1*(6176), 1450. https://doi.org/10.1136/bmj.1.6176.1450
37. Greenbaum, S., Greenbaum, G., Moran-Gilad, J., & Weintraub, A. Y. (2019). Ecological dynamics of the vaginal microbiome in relation to health and disease. *American Journal of Obstetrics and Gynecology*, *220*(4), 324–335. https://doi.org/https://doi.org/10.1016/j.ajog.2018.11.1089
38. Gupta, P., Singh, M. P., & Goyal, K. (2020). Diversity of Vaginal Microbiome in Pregnancy: Deciphering the Obscurity. *Frontiers in Public Health*, *8*, 326. https://www.frontiersin.org/article/10.3389/fpubh.2020.00326
39. Gupta, S., Kakkar, V., & Bhushan, I. (2019). Crosstalk between Vaginal Microbiome and Female Health: A review. *Microbial Pathogenesis*, *136*, 103696. https://doi.org/10.1016/j.micpath.2019.103696
40. Happel, A. U., Varsani, A., Balle, C., Passmore, J. A., & Jaspan, H. (2020). The Vaginal Virome-Balancing Female Genital Tract Bacteriome, Mucosal Immunity, and Sexual and Reproductive Health Outcomes?. *Viruses*, *12*(8), 832. https://doi.org/10.3390/v12080832
41. Hemmerling, A., Harrison, W., Schroeder, A., Park, J., Korn, A., Shiboski, S., Foster-Rosales, A., & Cohen, C. R. (2010). Phase 2a Study Assessing Colonization Efficiency, Safety, and Acceptability of Lactobacillus crispatus CTV-05 in Women With Bacterial Vaginosis. *Sexually Transmitted Diseases*, *37*(12). https://journals.lww.com/stdjournal/Fulltext/2010/12000/Phase_2a_Study_Assessing_Colonization_Efficiency,.3.aspx
42. Hillebrand, L., Harmanli, O. H., Whiteman, V., & Khandelwal, M. (2002). Urinary tract infections in pregnant women with bacterial vaginosis. *American journal of obstetrics and gynecology*, *186*(5), 916–917. https://doi.org/10.1067/mob.2002.123987
43. Hooton, T. M. (2012). Uncomplicated Urinary Tract Infection. *New England Journal of Medicine*, *366*(11), 1028–1037. https://doi.org/10.1056/NEJMcp1104429
44. Hyman, R. W., Fukushima, M., Jiang, H., Fung, E., Rand, L., Johnson, B., Vo, K. C., Caughey, A. B., Hilton, J. F., Davis, R. W., & Giudice, L. C. (2014). Diversity of the Vaginal Microbiome Correlates With Preterm Birth. *Reproductive Sciences*, *21*(1), 32–40. https://doi.org/10.1177/1933719113488838

45. Jang, S. J., Lee, K., Kwon, B., You, H. J., & Ko, G. (2019). Vaginal lactobacilli inhibit growth and hyphae formation of Candida albicans. *Scientific Reports*, *9*(1), 8121. https://doi.org/10.1038/s41598-019-44579-4
46. Kim, J.-M., & Park, Y. J. (2017). Probiotics in the Prevention and Treatment of Postmenopausal Vaginal Infections: Review Article. *Jmm*, *23*(3), 139–145. https://doi.org/10.6118/jmm.2017.23.3.139
47. Kolter, J., & Henneke, P. (2017). Codevelopment of Microbiota and Innate Immunity and the Risk for Group B Streptococcal Disease. *Frontiers in Immunology*, *8*, 1497. https://www.frontiersin.org/article/10.3389/fimmu.2017.01497
48. Lagenaur, L. A., Hemmerling, A., Chiu, C., Miller, S., Lee, P. P., Cohen, C. R., & Parks, T. P. (2021). Connecting the Dots: Translating the Vaginal Microbiome Into a Drug. *The Journal of Infectious Diseases*, *223*(Supplement_3), S296–S306. https://doi.org/10.1093/infdis/jiaa676
49. Lai, S. K., Hida, K., Shukair, S., Wang, Y. Y., Figueiredo, A., Cone, R., Hope, T. J., & Hanes, J. (2009). Human immunodeficiency virus type 1 is trapped by acidic but not by neutralized human cervicovaginal mucus. *Journal of virology*, *83*(21), 11196–11200. https://doi.org/10.1128/JVI.01899-08
50. Lee, J. B. L., & Neild, G. H. (2007). Urinary tract infection. *Medicine*, *35*(8), 423–428. https://doi.org/10.1016/j.mpmed.2007.05.009
51. Lewis, A. L., & Gilbert, N. M. (2020). Roles of the vagina and the vaginal microbiota in urinary tract infection: evidence from clinical correlations and experimental models. *GMS Infectious Diseases*, *8*, Doc02–Doc02. https://doi.org/10.3205/id000046
52. Liebenberg, L. J. P., Masson, L., Arnold, K. B., Mckinnon, L. R., Werner, L., Proctor, E., Archary, D., Mansoor, L. E., Lauffenburger, D. A., Abdool Karim, Q., Abdool Karim, S. S., & Passmore, J.-A. S. (2017). Genital-Systemic Chemokine Gradients and the Risk of HIV Acquisition in Women. *Journal of Acquired Immune Deficiency Syndromes (1999)*, *74*(3), 318–325. https://doi.org/10.1097/QAI.0000000000001218
53. Ma, B., Forney, L. J., & Ravel, J. (2012). Vaginal Microbiome: Rethinking Health and Disease. *Annual Review of Microbiology*, *66*(1), 371–389. https://doi.org/10.1146/annurev-micro-092611-150157
54. Mancabelli, L., Tarracchini, C., Milani, C., Lugli, G. A., Fontana, F., Turroni, F., van Sinderen, D., & Ventura, M. (2021). Vaginotypes of the human vaginal microbiome. *Environmental Microbiology*, *23*(3), 1780–1792. https://doi.org/https://doi.org/10.1111/1462-2920.15441
55. Margolis, E., & Fredricks, D. N. (2015). Chapter 83 – Bacterial Vaginosis-Associated Bacteria. In Y.-W. Tang, M. Sussman, D. Liu, I. Poxton, & J. Schwartzman (Eds.), *Molecular Medical Microbiology (Second Edition)* (pp. 1487–1496). Academic Press. https://doi.org/10.1016/B978-0-12-397169-2.00083-4
56. Marrazzo, J. M., Fiedler, T. L., Srinivasan, S., Thomas, K. K., Liu, C., Ko, D., Xie, H., Saracino, M., & Fredricks, D. N. (2012). Extravaginal Reservoirs of Vaginal Bacteria as Risk Factors for Incident Bacterial Vaginosis. *The Journal of Infectious Diseases*, *205*(10), 1580–1588. https://doi.org/10.1093/infdis/jis242
57. Martin, D. H., & Marrazzo, J. M. (2016). The Vaginal Microbiome: Current Understanding and Future Directions. *The Journal of Infectious Diseases*, *214*(suppl_1), S36–S41. https://doi.org/10.1093/infdis/jiw184
58. Martin, H. L., Richardson, B. A., Nyange, P. M., Lavreys, L., Hillier, S. L., Chohan, B., Mandaliya, K., Ndinya-Achola, J. O., Bwayo, J., & Kreiss, J. (1999). Vaginal lactobacilli, microbial flora, and risk of human immunodeficiency virus type 1 and sexually transmitted disease acquisition. *The Journal of infectious diseases*, *180*(6), 1863–1868. https://doi.org/10.1086/315127
59. Miller, C. J., & Shattock, R. J. (2003). Target cells in vaginal HIV transmission. *Microbes and Infection*, *5*(1), 59–67. https://doi.org/10.1016/S1286-4579(02)00056-4
60. Mitchell, H. (2004). Vaginal discharge—causes, diagnosis, and treatment. *BMJ*, *328*(7451), 1306. https://doi.org/10.1136/bmj.328.7451.1306
61. Molenaar, M. C., Singer, M., & Ouburg, S. (2018). The two-sided role of the vaginal microbiome in Chlamydia trachomatis and Mycoplasma genitalium pathogenesis. *Journal of reproductive immunology*, *130*, 11–17. https://doi.org/10.1016/j.jri.2018.08.006
62. Murphy, K., & Mitchell, C. M. (2016). The Interplay of Host Immunity, Environment and the Risk of Bacterial Vaginosis and Associated Reproductive Health Outcomes. *The Journal of Infectious Diseases*, *214*(suppl_1), S29–S35. https://doi.org/10.1093/infdis/jiw140
63. Neggers, Y. H., Nansel, T. R., Andrews, W. W., Schwebke, J. R., Yu, K., Goldenberg, R. L., & Klebanoff, M. A. (2007). Dietary Intake of Selected Nutrients Affects Bacterial Vaginosis in Women. *The Journal of Nutrition*, *137*(9), 2128–2133. https://doi.org/10.1093/jn/137.9.2128

64. Nicolle, L. E., Harding, G. K., Preiksaitis, J., & Ronald, A. R. (1982). The association of urinary tract infection with sexual intercourse. *The Journal of infectious diseases*, *146*(5), 579–583. https://doi.org/10.1093/infdis/146.5.579
65. Nugent, R. P., Krohn, M. A., & Hillier, S. L. (1991). Reliability of diagnosing bacterial vaginosis is improved by a standardized method of gram stain interpretation. *Journal of Clinical Microbiology*, *29*(2), 297–301. https://doi.org/10.1128/jcm.29.2.297-301.1991
66. Oduyebo, O. O., Anorlu, R. I., & Ogunsola, F. T. (2009). The effects of antimicrobial therapy on bacterial vaginosis in non-pregnant women. *The Cochrane database of systematic reviews*, (3), CD006055. https://doi.org/10.1002/14651858.CD006055.pub2
67. Oerlemans, E. F. M., Bellen, G., Claes, I., Henkens, T., Allonsius, C. N., Wittouck, S., van den Broek, M. F. L., Wuyts, S., Kiekens, F., Donders, G. G. G., & Lebeer, S. (2020). Impact of a lactobacilli-containing gel on vulvovaginal candidosis and the vaginal microbiome. *Scientific Reports*, *10*(1), 7976. https://doi.org/10.1038/s41598-020-64705-x
68. Onderdonk, A. B., Delaney, M. L., & Fichorova, R. N. (2016). The Human Microbiome during Bacterial Vaginosis. *Clinical Microbiology Reviews*, *29*(2), 223–238. https://doi.org/10.1128/CMR.00075-15
69. Peipert, J. F., Lapane, K. L., Allsworth, J. E., Redding, C. A., Blume, J. D., & Stein, M. D. (2008). Bacterial vaginosis, race, and sexually transmitted infections: does race modify the association?. *Sexually transmitted diseases*, *35*(4), 363–367. https://doi.org/10.1097/OLQ.0b013e31815e4179
70. Peters, B. M., Yano, J., Noverr, M. C., & Fidel Jr, P. L. (2014). Candida Vaginitis: When Opportunism Knocks, the Host Responds. *PLOS Pathogens*, *10*(4), e1003965-. https://doi.org/10.1371/journal.ppat.1003965
71. Petrova, M. I., Imholz, N. C. E., Verhoeven, T. L. A., Balzarini, J., van Damme, E. J. M., Schols, D., Vanderleyden, J., & Lebeer, S. (2016). Lectin-Like Molecules of Lactobacillus rhamnosus GG Inhibit Pathogenic Escherichia coli and Salmonella Biofilm Formation. *PLOS ONE*, *11*(8), e0161337-. https://doi.org/10.1371/journal.pone.0161337
72. Phares, C. R., Lynfield, R., Farley, M. M., Mohle-Boetani, J., Harrison, L. H., Petit, S., Craig, A. S., Schaffner, W., Zansky, S. M., Gershman, K., Stefonek, K. R., Albanese, B. A., Zell, E. R., Schuchat, A., & Schrag, S. J. (2008). Epidemiology of Invasive Group B Streptococcal Disease in the United States, 1999-2005. *JAMA*, *299*(17), 2056–2065. https://doi.org/10.1001/jama.299.17.2056
73. Pino, A., Bartolo, E., Caggia, C., Cianci, A., & Randazzo, C. L. (2019). Detection of vaginal lactobacilli as probiotic candidates. *Scientific Reports*, *9*(1), 3355. https://doi.org/10.1038/s41598-019-40304-3
74. Prais, D., Straussberg, R., Avitzur, Y., Nussinovitch, M., Harel, L., & Amir, J. (2003). Bacterial susceptibility to oral antibiotics in community acquired urinary tract infection. *Archives of Disease in Childhood*, *88*(3), 215. https://doi.org/10.1136/adc.88.3.215
75. Prince, A. L., Chu, D. M., Seferovic, M. D., Antony, K. M., Ma, J., & Aagaard, K. M. (2015). The Perinatal Microbiome and Pregnancy: Moving Beyond the Vaginal Microbiome. *Cold Spring Harbor Perspectives in Medicine*, *5*(6). https://doi.org/10.1101/cshperspect.a023051
76. Quin, C., Vollman, D. M., Ghosh, S., Haskey, N., Estaki, M., Pither, J., Barnett, J. A., Jay, M. N., Birnie, B. W., & Gibson, D. L. (2020). Fish oil supplementation reduces maternal defensive inflammation and predicts a gut bacteriome with reduced immune priming capacity in infants. *The ISME Journal*, *14*(8), 2090–2104. https://doi.org/10.1038/s41396-020-0672-9
77. Rautava, S., Luoto, R., Salminen, S., & Isolauri, E. (2012). Microbial contact during pregnancy, intestinal colonization and human disease. *Nature Reviews Gastroenterology & Hepatology*, *9*(10), 565–576. https://doi.org/10.1038/nrgastro.2012.144
78. Ravel, J., Gajer, P., Abdo, Z., Schneider, G. M., Koenig, S. S. K., McCulle, S. L., Karlebach, S., Gorle, R., Russell, J., Tacket, C. O., Brotman, R. M., Davis, C. C., Ault, K., Peralta, L., & Forney, L. J. (2011). Vaginal microbiome of reproductive-age women. *Proceedings of the National Academy of Sciences*, *108*(Supplement 1), 4680. https://doi.org/10.1073/pnas.1002611107
79. Raz, R., & Stamm, W. E. (1993). A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. *The New England journal of medicine*, *329*(11), 753–756. https://doi.org/10.1056/NEJM199309093291102
80. Schwebke, J. R. (2000). Asymptomatic bacterial vaginosis: Response to therapy. *American Journal of Obstetrics and Gynecology*, *183*(6), 1434–1439. https://doi.org/https://doi.org/10.1067/mob.2000.107735
81. Sewankambo, N., Gray, R. H., Wawer, M. J., Paxton, L., McNaim, D., Wabwire-Mangen, F., Serwadda, D., Li, C., Kiwanuka, N., Hillier, S. L., Rabe, L., Gaydos, C. A., Quinn, T. C., & Konde-Lule, J. (1997). HIV-1 infection associated with abnormal vaginal flora morphology and bacterial vaginosis. *Lancet (London, England)*, *350*(9077), 546–550. https://doi.org/10.1016/s0140-6736(97)01063-5
82. Sheerin, N. S. (2011). Urinary tract infection. *Medicine*, *39*(7), 384–389. https://doi.org/10.1016/j.mpmed.2011.04.003

83. Siqueira, J. D., Curty, G., Xutao, D., Hofer, C. B., Machado, E. S., Seuánez, H. N., Soares, M. A., Delwart, & E., Soares, E. A. (2019). Composite Analysis of the Virome and Bacteriome of HIV/HPV Co-Infected Women Reveals Proxies for Immunodeficiency. *Viruses*, 11(5):422. https://doi.org/10.3390/v11050422
84. Stapleton A. E. (2016). The Vaginal Microbiota and Urinary Tract Infection. *Microbiology spectrum*, *4*(6), 10.1128/microbiolspec.UTI-0025-2016. https://doi.org/10.1128/microbiolspec.UTI-0025-2016
85. Stapleton, A. E., Au-Yeung, M., Hooton, T. M., Fredricks, D. N., Roberts, P. L., Czaja, C. A., Yarova-Yarovaya, Y., Fiedler, T., Cox, M., & Stamm, W. E. (2011). Randomized, placebo-controlled phase 2 trial of a Lactobacillus crispatus probiotic given intravaginally for prevention of recurrent urinary tract infection. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, *52*(10), 1212–1217. https://doi.org/10.1093/cid/cir183
86. Sumati, A. H., & Saritha, N. K. (2009). Association of urinary tract infection in women with bacterial vaginosis. *Journal of global infectious diseases*, *1*(2), 151–152. https://doi.org/10.4103/0974-777X.56254
87. Swidsinski, A., Mendling, W., Loening-Baucke, V., Swidsinski, S., Dörffel, Y., Scholze, J., Lochs, H., & Verstraelen, H. (2008). An adherent Gardnerella vaginalis biofilm persists on the vaginal epithelium after standard therapy with oral metronidazole. *American Journal of Obstetrics and Gynecology*, *198*(1), 97.e1-97.e6. https://doi.org/10.1016/j.ajog.2007.06.039
88. Ta, L. D. H., Chan, J. C. Y., Yap, G. C., Purbojati, R. W., Drautz-Moses, D. I., Koh, Y. M., Tay, C. J. X., Huang, C.-H., Kioh, D. Y. Q., Woon, J. Y., Tham, E. H., Loo, E. X. L., Shek, L. P. C., Karnani, N., Goh, A., van Bever, H. P. S., Teoh, O. H., Chan, Y. H., Lay, C., … Lee, B. W. (2020). A compromised developmental trajectory of the infant gut microbiome and metabolome in atopic eczema. *Gut Microbes*, *12*(1), 1801964. https://doi.org/10.1080/19490976.2020.1801964
89. Tachedjian, G., Aldunate, M., Bradshaw, C. S., & Cone, R. A. (2017). The role of lactic acid production by probiotic Lactobacillus species in vaginal health. *Research in Microbiology*, *168*(9), 782–792. https://doi.org/10.1016/j.resmic.2017.04.001
90. Taha, T. E., Hoover, D. R., Dallabetta, G. A., Kumwenda, N. I., Mtimavalye, L. A. R., Yang, L.-P., Liomba, G. N., Broadhead, R. L., Chiphangwi, J. D., & Miotti, P. G. (1998). Bacterial vaginosis and disturbances of vaginal flora: association with increased acquisition of HIV. *AIDS*, *12*(13). https://journals.lww.com/aidsonline/...aginal.19.aspx
91. Tan, C. W., & Chlebicki, M. P. (2016). Urinary tract infections in adults. *Singapore Medical Journal*, *57*(9), 485–490. https://doi.org/10.11622/smedj.2016153
92. Tazi, A., Plainvert, C., Anselem, O., Ballon, M., Marcou, V., Seco, A., el Alaoui, F., Joubrel, C., el Helali, N., Falloukh, E., Frigo, A., Raymond, J., Trieu-Cuot, P., Branger, C., le Monnier, A., Azria, E., Ancel, P.-Y., Jarreau, P. H., Mandelbrot, L., … Poyart, C. (2019). Risk Factors for Infant Colonization by Hypervirulent CC17 Group B Streptococcus: Toward the Understanding of Late-onset Disease. *Clinical Infectious Diseases*, *69*(10), 1740–1748. https://doi.org/10.1093/cid/ciz033
93. Torcia, M. G. (2019). Interplay among Vaginal Microbiome, Immune Response and Sexually Transmitted Viral Infections. *International Journal of Molecular Sciences*, 20(2):266. https://doi.org/10.3390/ijms20020266
94. van de Wijgert, J., & Verwijs, M. C. (2020). Lactobacilli-containing vaginal probiotics to cure or prevent bacterial or fungal vaginal dysbiosis: a systematic review and recommendations for future trial designs. *BJOG: An International Journal of Obstetrics & Gynaecology*, *127*(2), 287–299. https://doi.org/10.1111/1471-0528.15870
95. Verstraelen, H., Verhelst, R., Vaneechoutte, M., & Temmerman, M. (2010). The epidemiology of bacterial vaginosis in relation to sexual behaviour. *BMC Infectious Diseases*, *10*(1), 81. https://doi.org/10.1186/1471-2334-10-81
96. Wiesenfeld, H. C., Hillier, S. L., Krohn, M. A., Landers, D. v, & Sweet, R. L. (2003). Bacterial Vaginosis Is a Strong Predictor of Neisseria gonorrhoeae and Chlamydia trachomatis Infection. *Clinical Infectious Diseases*, *36*(5), 663–668. https://doi.org/10.1086/367658
97. Wylie, K. M., Wylie, T. N., Cahill, A. G., Macones, G. A., Tuuli, M. G., & Stout, M. J. (2018). The vaginal eukaryotic DNA virome and preterm birth. *American Journal of Obstetrics and Gynecology*, *219*(2), 189.e1-189.e12. https://doi.org/10.1016/j.ajog.2018.04.048
98. Xu, J., Bian, G., Zheng, M., Lu, G., Chan, W.-Y., Li, W., Yang, K., Chen, Z.-J., & Du, Y. (2020). Fertility factors affect the vaginal microbiome in women of reproductive age. *American Journal of Reproductive Immunology*, *83*(4), e13220. https://doi.org/10.1111/aji.13220
99. Zabor, E. C., Klebanoff, M., Yu, K., Zhang, J., Nansel, T., Andrews, W., Schwebke, J., & Jeffcoat, M. (2010). Association between periodontal disease, bacterial vaginosis, and sexual risk behaviours. *Journal of Clinical Periodontology*, *37*(10), 888–893. https://doi.org/10.1111/j.1600-051X.2010.01593.x

100. Zaleznik, D. F., Rench, M. A., Hillier, S., Krohn, M. A., Platt, R., Lee, M.-L. T., Flores, A. E., Ferrieri, P., & Baker, C. J. (2000). Invasive Disease Due to Group B Streptococcus in Pregnant Women and Neonates from Diverse Population Groups. *Clinical Infectious Diseases*, *30*(2), 276–281. https://doi.org/10.1086/313665
101. Zapata, H. J., & Quagliarello, V. J. (2015). The Microbiota and Microbiome in Aging: Potential Implications in Health and Age-Related Diseases. *Journal of the American Geriatrics Society*, *63*(4), 776–781. https://doi.org/10.1111/jgs.13310
102. Zozaya, M., Ferris, M. J., Siren, J. D., Lillis, R., Myers, L., Nsuami, M. J., Eren, A. M., Brown, J., Taylor, C. M., & Martin, D. H. (2016). Bacterial communities in penile skin, male urethra, and vaginas of heterosexual couples with and without bacterial vaginosis. *Microbiome*, *4*(1), 16. https://doi.org/10.1186/s40168-016-0161-6

This page titled 20.6: The Vaginal Microbiome is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Dylan Parks via source content that was edited to the style and standards of the LibreTexts platform.

- **3.6: The Vaginal Microbiome** by Dylan Parks is licensed CC BY 4.0. Original source: https://uta.pressbooks.pub/microbiomeshealthandtheenvironment.

20.7: Mental Health and Multi-Microbiome Interactions

Mental Health and Multi-Microbiome Interactions

It may seem obvious that localized microbiomes are responsible for diseases related to their respective areas (e.g., IBD and the gut microbiome or AD and the skin microbiome), however, it is a fascinating phenomenon that various microbiomes can affect each other and influence health in different parts of the body. Even more captivating is the link between certain microbiomes and mental health conditions presuming the brain is devoid of microbes.

These links between microbiomes are referred to as axes, and initial connections began with the most well-studied microbiome, the gut. Since many gut-derived microbial-produced molecules and compounds are spread through the bloodstream, associations with various organs are formed, such as the gut-brain axis, gut-skin axis, gut-lung axis, or a combination of multiple; gut-brain-skin axis. There are likely overlapping connections between all microbial components that form the human holobiome, thus teasing apart the exact members and their functions is a dutiful task.

Gut Interaction with Other Microbiomes

As mentioned earlier, the dissemination of molecules and compounds from the gut to the rest of the body creates an interconnected highway affecting most, if not all, parts of the body. Certainly, juxtaposed regions such as the oral cavity and the proximal portions of the GI tract have a relationship between their microbiomes, which it termed the gut-oral axis (GOA). These linked microbiomes have been shown to have immunomodulatory roles in the development of rheumatoid arthritis (RA) and osteoarthritis (OA) under dysbiosis, where the abundance of oral *Porphyromonas gingivalis* and intestinal *Prevotella copri* could be responsible (Drago et al., 2019, du Teil Espina et al., 2019). It has also been proposed that dysbiosis of the gut-oral microbiome axis is implicated in cirrhosis of the liver through pathogen invasion, resultant systemic inflammation, and impaired immunity and liver function (Acharya et al., 2017). Even gastrointestinal conditions like IBD and cancer of the colon, liver, and pancreas are linked with both the gut and oral microbiome dysbiosis, further demonstrating this strong interorgan connection to human health (Park et al., 2021).

The gut and the skin microbiomes are also linked via the gut-skin axis (GSA), and as the primary interface to the environment, they have major roles in physiological health (Figure 1). Dysbiosis of the gut-skin microbiome axis has influence on both GI and cutaneous disorders such as IBD, celiac disease, atopic dermatitis, psoriasis, acne, and other dermatologic issues, where each of these diseases can be associated with the ‘partner disease’ (i.e. a disease in one system linked to a disease in another system) (O’Neill et al., 2016, Salem et al., 2018, De Pessemier et al., 2021). Though crosstalk is bidirectional, more research seems to have focused on skin disorders and homeostasis as a result of gut microbiome health, where diet, immunomodulation, intestinal permeability, and metabolite secretion are major contributing factors (De Pessemier et al., 2021). However, there is evidence that *Mallassezia restricta*, a fungal member of the skin microbiota, is associated with Crohn’s disease and can exacerbate colitis (Limon et al., 2019, Sinha et al., 2021).

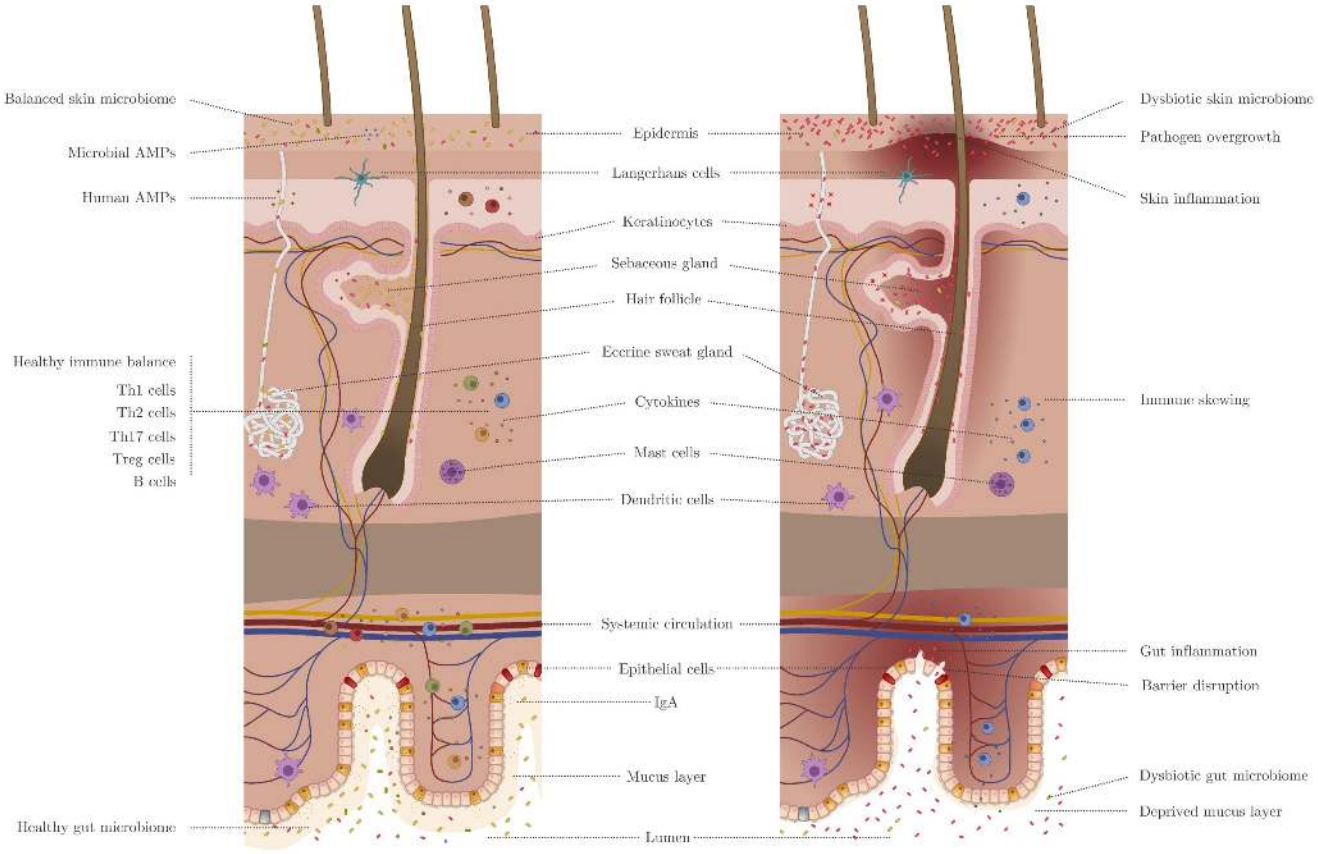


Figure 1. Inflammatory and microbial influences between the gut and skin for a healthy state (left) and a dysbiotic state (right): The intestinal and epidermal barriers are connected through the systemic circulation (blood and lymph) and are visualized here together in a simplistic manner. The dysbiotic state is characterized by an impaired gut barrier (imbalance in gut microbiome, reduced mucus layer, reduced IgA secretion, barrier disruption, intestinal permeation into the bloodstream, and gut inflammation) and an impaired skin barrier (imbalance in skin microbiome, reduced human and microbial antimicrobial peptides (AMP) production, skin rashes/thickening/lesions, and skin inflammation). Gut and skin dysbiosis are connected through an immune imbalance (Th2 skewing in this example), whereas crosstalk can be bidirectional (De Pessemier et al., 2021).

The gut-lung axis (GLA) has roles in the regulation of immunity and the development of various respiratory diseases. (Frati et al., 2019). The respiratory system and GI tract are connected by the mesenteric lymphatic system, where intact or fragmented microbes and their metabolites enter systemic circulation after passing through the intestinal barrier and can migrate to the pulmonary system to modulate immune responses (Enaud et al., 2020). The pathophysiology of diseases such as atopy and asthma are complicated and can be contributed to a variety of factors, however, there is evidence that dysbiosis of the gut microbiome contributes to the development of asthma, particularly in youths who exhibit a decrease in *Lachnospira* and increase in *Clostridium* spp. (Penders et al., 2007, Watson et al.,2019). Gut dysbiosis is also involved in chronic obstructive pulmonary disease (COPD) exacerbation, where fiber deficiency in an individual's diet can contribute to chronic inflammation. Metabolism of fiber by gut microbes produces anti-inflammatory short-chain fatty acids (SCFAs), which could reduce inflammation both systemically and in the lungs, and so targeted dietary intervention for these patients may be a viable treatment addition for COPD and other respiratory diseases associated with inflammation like COVID-19 (Li et al., 2018, Vaughan et al., 2019, Allali et al., 2021). Moreover, SCFAs also have an important role in the defense against secondary infections in those afflicted by viral respiratory infections, further demonstrating the importance of gut microbiome health in connection with the GLA (Sensio et al., 2020).

Like other axes, immunomodulation by the gut microbiome also has influence on the gut-vagina axis (GVA), though it is less extensively studied. One promising avenue of treating vaginal diseases, specifically cervical cancer associated with human papilloma virus (HPV), is the use of mucosal lactic-acid bacteria (LAB)-based vaccines to modulate the gut microbiome. The approach could work as a prophylactic or for direct therapy, and be more easily administered via an oral route instead of parenteral (Taghinezhad-S, et al., 2021). Endometriosis and infertility are also disorders associated with sex hormone levels and

inflammation, which once again are influenced by the gut microbiome composition and state. Specifically, there are some members in the gut who can affect the levels of circulating estrogen through metabolic processes and an altered state could lead to increased risk or symptom severity of these disorders (Salliss et al., 2022). Other female reproductive-associated diseases such as polycystic ovarian syndrome (PCOS), also associated with gut dysbiosis, could be ameliorated by diet modification and restoration of gut homeostasis. Here, the use of flaxseed oil could increase diminished levels of SCFAs observed in those with PCOS and protect against inflammation characteristic of the disease (Wang et al., 2020).

The maternal microbiome, including gut, vagina, and breast milk, can greatly influence the colonization and health of the infant after birth, but also affect the fetus prior to delivery. Fetal immune development is most likely influenced in the womb from translocation of maternal gut microbes and/or their metabolites across the placental barrier or ingestion of amniotic fluids (Walker et al., 2017, Nyangahu and Jaspan, 2019). Post-reproduction, the infant gut microbiome is continually developed through initial diet, and more specifically vertical transmission of the contents in the mother's breast milk which includes its own unique microbiome (Ojo-Okunola et al., 2018, Ojo-Okunola et al., 2019, Quin et al., 2020). The human milk microbiome promotes infant gut colonization of probiotic strains which have roles in programming the immune and metabolic systems, as well as anti-infective, anti-allergic, and anti-tumor properties (Heikkila and Saris, 2003, Olivares et al., 2006, Lara-Villoslada et al., 2007, Civardi et al., 2015, Hassan et al., 2015, Walker and Iyengar, 2015, Boix-Amoros et al., 2016, Ojo-Okunola et al., 2018).



Mental Health Axes

The thought of microorganisms controlling aspects of cognitive function in their host, especially humans, is fascinating to say the least. While connections between other microbiomes, organ systems, and diseases may be less surprising, the microbial link to psychiatric, neurodevelopmental, age-related, and neurodegenerative disorders is very much intriguing. The human microbiome can communicate with the brain in a variety of ways; through the immune system, metabolism, endocrine system, circulatory system, and the nervous system, where microbes, their induced immune response, and their metabolites such as short-chain fatty acids, branched chain amino acids, and peptidoglycans are involved (Figure 2) (Liang et al., 2018, Cryan et al., 2019, Olsen and Hicks, 2019, Hadian et al., 2020, Bear et al., 2021). Several local microbiomes each contribute affects to the mental state, and whether it is gut-, skin-, oral-, lung-, etc. derived can dictate roles in various disorders. This is not just a one-way street though, as microbes around the body can alter mental states but also be affected by governance of the brain in a bi-directional manner (Ma et al., 2019).

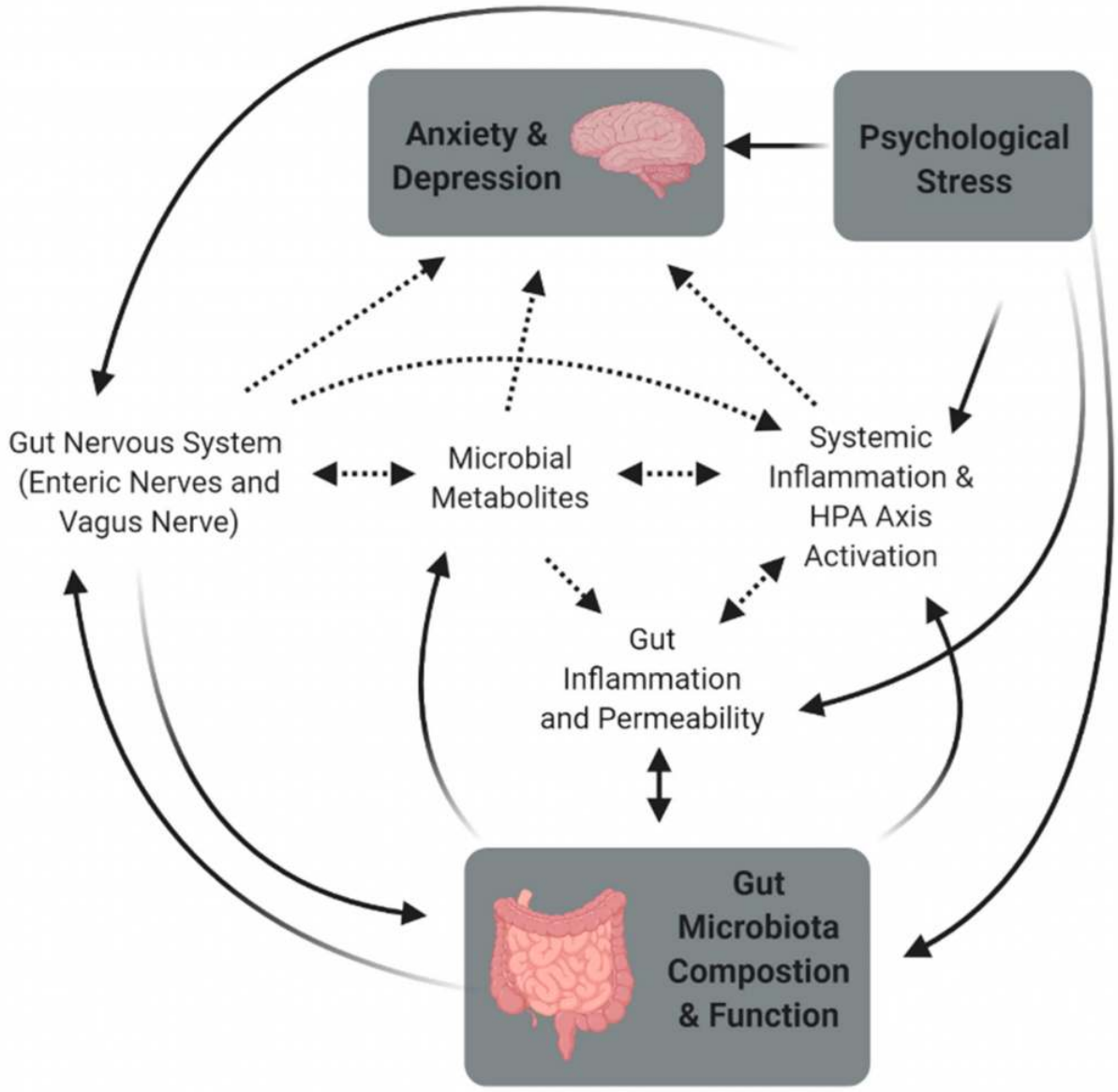


Figure 2.
The proposed mechanisms of the microbiome-gut-brain axis (MGBA) are complex and intertwined. Emerging research shows that psychological stress interacts not only directly with the brain and mood, but also with many of the MGBA mechanisms thought to contribute to changes in mood with alteration of the gut microbiota. Solid lines indicate strong evidence of an effect, and dotted lines show proposed mechanisms with limited but emerging evidence. Abbreviations: HPA; Hypothalamic-Pituitary-Adrenal (Bear et al., 2021).

Gut-Brain

Similar to other types of microbiome and organ interactions, the gut's role in mental health is central and most well studied, which makes sense as it is the largest repository of microorganisms associated with the human body. The gut-brain axis (GBA; and gut plus essentially every other microbiome and brain axis, e.g., gut-skin-brain) is implicated in a number of cognitive functions and disorders including autism, anxiety, depression, stress, pain sensitivity, learning capacities, memory loss, moods and emotions, behavior (dietary, social, and reproductive), schizophrenia, Parkinson's disease, and Alzheimer's disease (Desbonnet et al., 2013, Stumpf et al., 2013, Dash et al., 2015, Gareau, 2016, Luczynski et al., 2016, Hoban et al., 2017, Liang et al., 2018, Manderino et al., 2017, Nishida and Ochman, 2017, Vuong et al., 2017, Cowan et al., 2018, Cryan et al., 2019, Bear et al., 2021, Narengaowa et al., 2021). The gut microbiome actually develops in sync with the brain and psychology, and disturbances during different stages of growth can result in the onset of different diseases (Figure 3) (Borre et al., 2014, Gur et al., 2015, Sampson and Mazmanian, 2015,

Dinan and Cryan, 2016, Luczynski et al., 2016, Sharon et al., 2016, Kundu et al., 2017, Vuong et al., 2017, Carlson et al., 2018, Liang et al., 2018).

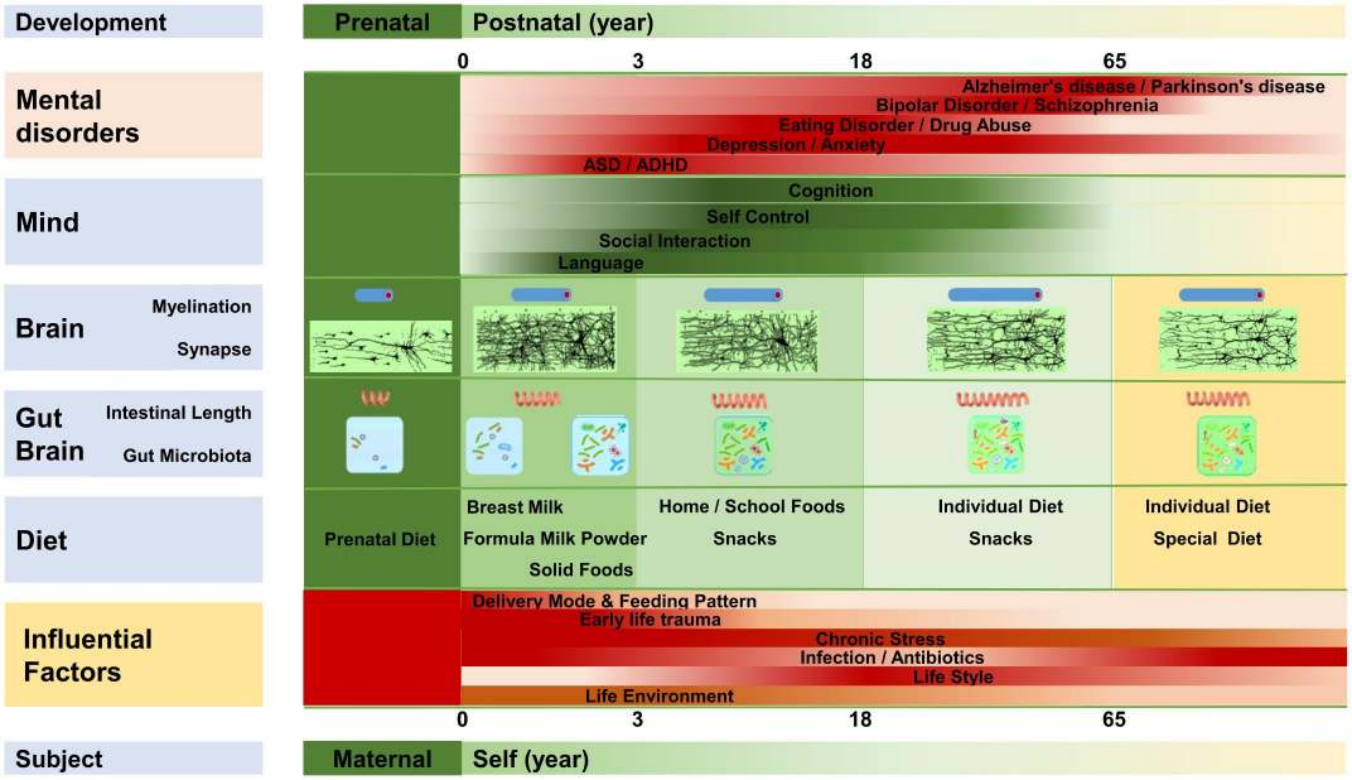


Figure 3. The gut-brain, brain, and mentality develop almost synchronously throughout the lifespan. The gut-brain, brain, and mentality undergo similar developmental patterns; all three are susceptible to several factors that influence the gut microbiota. Myelination, intestinal length, and the gut microbiota develop almost synchronously. Diet plays an important role in the maturation of the gut-brain and brain, and mentality is regulated by the development of the brain and gut-brain. Microbiota disruption at different stages is likely to increase the incidence of different mental disorders (Liang et al., 2018).

Early perturbation of the gut microbiome during the post-natal period, and even within the womb, can especially increase susceptibility to developing mental disorders since these are critical stages for development of the gut-brain axis and mind (Borre et al., 2014, Gur et al., 2015, Diaz Heijtz, 2016, Mika et al., 2016, Slykerman et al., 2016, O'Mahony et al., 2017, Liang et al., 2018). Even up through senescence, an abnormal gut microbiota is linked with several mental disorders, though the good news is that they can be remedied or improved by returning the gut to a homeostatic state. As the prevalence of mental disorders and neurological diseases have been steadily increasing, healing mental health by exploring and implementing options such as fecal microbiota transplant, diet intervention, probiotics, prebiotics, and psychobiotics are a must (Cryan and Dinan, 2012, Dinan et al., 2013, Liang et al., 2015, Pirbaglou et al., 2016, He et al., 2017, Kang et al., 2017, Mika et al., 2017, Bruce-Keller et al., 2018, Liang et al., 2018, Yang et al., 2018, Kesika et al., 2021, Margolis et al., 2021).

There are several ideas as to why there has been an increase in mental and neurological disorders in relation to the human microbiome. The "Gut Microbiota" hypothesis suggests this escalation is a direct result from gut microbiome dysbiosis due to factors of modern society such as diet, antibiotics, and stress (Liang et al., 2018b). The "Old Friends" hypothesis proposes that the co-evolution of early humanity with its microbiota in a less civilized and more natural ecosystem promoted the development of a stronger immune system, but now changes in lifestyle and environment leads to weaker immunity and subsequent disorders (Strachan, 1989, Rook and Lowry, 2008, Kramer et al., 2013, Rook, 2013). Lastly, the "Leaky Gut" theory implies that damage to the mucosal barrier of the gut increases intestinal permeability, which allows biomolecules and microorganisms to gain access various parts of the body that they normally couldn't, and thereafter cause disease (Leclercq et al., 2012, Smythies and Smythies, 2014, Kelly et al., 2015, Potgieter et al., 2015, Slyepchenko et al., 2017, Liang et al., 2018). All of theses propositions are clear in their indication that the gut microbiome and its part in immune development has a definite role in the functioning of the mind, though the exact extent and mechanisms remain to be discovered.

The majority of human mi some degree, though there are some questions as to w

The oral microbiome can act, or via the circulatory system where blood can t circumventricular organs (Figure 4) (Olsen and Si s to the bloodstream can commonly occur during d activity and inflammation (Olsen, 2008). These oral Alzheimer's disease (AD), dementia, Down's syndro oral dysbiosis) (Ilievski et al., 2018, Olsen and Hicks, 2019, Maitre et al., 2020). Oral dysbiosis can also promote the development of ASD by affecting the metabolome and thus can create a troublesome positive feedback loop (Mussap et al., 2016, Wang et al., 2016).

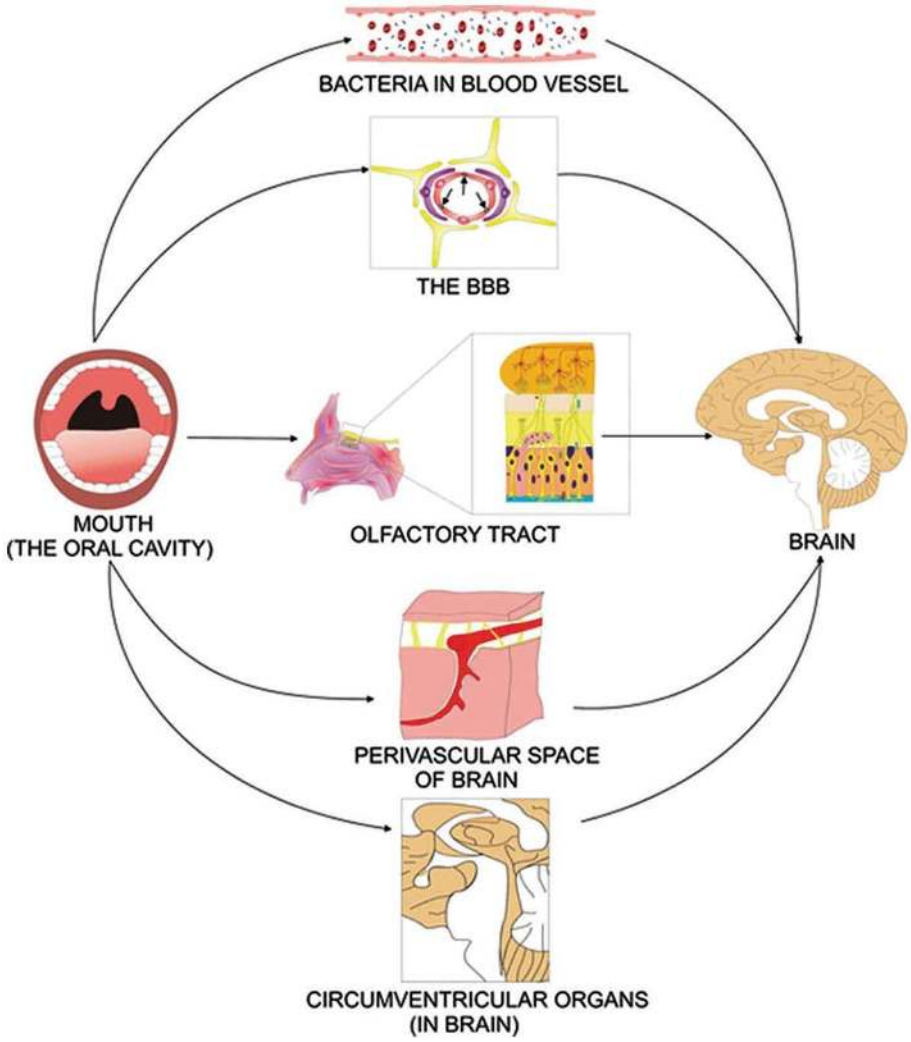


Figure 4. Direct and indirect mechanisms of infecting the brain. In the direct mechanism, the oral cavity infects the olfactory tract, and the olfactory nerve transfer the bacteria to the brain. In other mechanisms, bacteria inside the mouth infect the blood and find their way via blood, blood–brain barrier (BBB), perivascular spaces and circumventricular organs to the brain (Olsen and Hicks, 2019).

Concerning the skin-brain axis, dysbiosis of the skin microbiome and chronic wounds can elicit systemic effects and induce neural responses that eventually affect the central nervous system (Figure 5) (Hadian et al., 2020). Chronic wounds exhibit persistent inflammation and can have various etiologies including diabetic foot ulcers (DFU), venous ulcers, arterial ulcers, pressure ulcers,

surgical wounds, and other traumatic wounds (Green et al., 2014, Renner and Erfurt-Berge, 2017, Bui et al., 2018, Pedras et al., 2018, Hadian et al., 2020). In these cases, a compromised skin barrier can allow pathogens and their derivatives to enter the bloodstream, and if the skin is in a dysbiotic state, then abundant pathogens such as *Staphylococcus aureus* and *Pseudomonas aeruginosa* can amplify this effect by inducing epithelial permeability (Roy et al., 2014, Basler et al., 2017). These microbes, metabolites, pro-inflammatory mediators, and other constituents circulate within the blood, potentially induce permeability in the blood-brain barrier (BBB), and eventually reach the brain to cause disorders such as wound-associated depression, anxiety, and other cognitive disorders (Wang et al., 2011, Zhang et al., 2015, Hadian et al., 2020). The skin-brain axis acts in a bi-direction manner too, with studies showing connections between certain mental disorders like post-traumatic stress disorder, and skin diseases associated with dysbiosis like psoriasis, chronic urticaria (hives), and atopic dermatitis (Gupta et al., 2017, Beri, 2018).

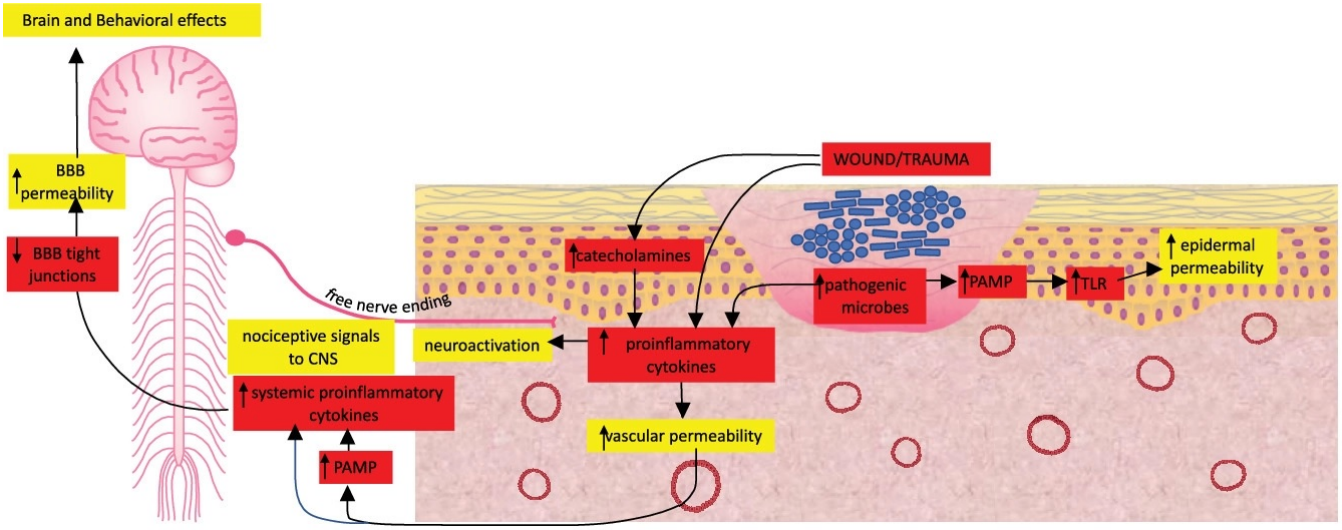


Figure 5. The chronic wound with its microbiota induces localized inflammatory alterations that can result in systemic effects by increasing both epidermal and vascular permeability and activating neurons to generate nocioceptive signals—all ultimately culminating in central nervous system effects. Red: Proposed mediators. Yellow: Proposed downstream events. BBB: blood brain barrier, CNS: central nervous system, PAMP: pathogen associated molecular pattern, TLR: toll like receptor (Hadian et al., 2020).

The lung-brain axis connects pulmonary microbes to neurodegenerative disorders and behavior characteristics, and though not much research has focused on this specific link, there are indications that air pollution can be a trigger. Pollutants in the air come from a variety of sources including engine emissions, coal combustion, biomass burning, and secondary photochemical products, such as ground level ozone (O_3) (Mumaw et al., 2016). These compounds can be a source of chronic neuroinflammation and persistently affect microglial cells in the central nervous system, which in turn can increase risk of diseases such as Alzheimer's disease, Parkinson's disease, and autism, as well as elicit a decline in cognitive function in the elderly (Power et al., 2011, Wellenius et al., 2012, Roberts et al., 2013, Volk et al., 2013, Heneka et al., 2014, Jung et al., 2015, Kirrane et al., 2015, Mumaw et al., 2016). It is likely that air pollution also negatively affects the lung microbiome, and dysbiosis could further aggravate immune responses and cognitive disruption (Mousavi et al., 2021, Whiteside et al., 2021).

Is there a brain microbiome?

That is, are there resident microbes residing with a living brain? With many neurodegenerative and neuropsychiatric diseases lacking a clear etiology, determining any and all potential associations could help in therapeutic efforts (Link, 2021). The healthy brain is an assumedly sterile environment, though the same was once thought about other organs like the lungs. Interestingly, one study found evidence for the existence of viable bacteria in the human brain. Here, researchers were interested to see whether microbial invasion accompanied damaged brains observed in HIV/AIDS. After sequencing total RNA from cerebral white matter, they found bacteria and phage sequences in both experimental and control brain samples, which was further validated by 16S rRNA gene target amplification and *in situ* staining (Branton et al., 2013, Link, 2021).

If there were resident microbes in the brain, they would certainly be at much lower abundances as compared with other regions such as the gut or the oral cavity. Though there has been much interest in characterizing the presence of pathogens in unhealthy brains for disorders like Alzheimer's disease, which is an arduous feat in itself, finding residents in a healthy state could prove even

more difficult (Zhan et al., 2016, Alonzo et al., 2018, Dominy et al., 2019, Link, 2021). That is, identification approaches could easily miss novel or fastidious microorganisms, and contamination is hard to avoid. Furthermore, a wide-range of controlled and unbiased studies are necessary to catalogue a possible brain microbiome, however, completing this task in humans brings about ethical implications and sampling limitations (Link, 2021). It is fascinating to consider the prospect of symbiotic brain microorganisms, and how they could influence our health or who we are.

Conclusion

Mental faculties contribute greatly to human health, and therefore characterizing the involvement of the human microbiome is of substantial importance. Many of these select microbiomes overlap, and the disorders associated with each are likely entangled in a complex array. Brain functions are extremely complex as is, and piecing together the microbial puzzle within their reach further complicates matters. However, there is great optimism in considering the human microbiome as a source or target for advanced therapy to resolve mental disorders and other diseases, which could drastically change the way we think about medicine.

Discussion Concept Mapping

With a partner or as a class, connect two or more microbiomes using a concept map. Explain how and/or why the various microbiomes are linked (e.g., disease cause vs. effect, direct vs. indirect, pathways, consortia translocation, factors affecting composition, etc.).

Check your Understanding

- In what ways does the gut microbiome connect with other microbiomes and regions of the body? How does it influence the development of diseases in these areas?
- How could early use of antibiotics influence the development of asthma in children?
- How could gut microbiome metabolites (SCFAs) contribute to healthy human states?
- In what ways does the human microbiome communicate with the brain?
- What options are available to treat mental disorders through the gut microbiome?
- Why have mental illnesses been increasing in prevalence and how could the gut microbiome be involved?
- How are microbiomes, other than the gut, implicated in mental health?
- What role does skin microbiome dysbiosis and chronic wounds have in the development of cognitive disorders?

Media Attributions

- Figure 1 – Inflammatory and microbial influences between the gut and skin for a healthy state by De Pessemier et al., 2021. Licensed under the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).
- Video 1 – Remodeling of the maternal gut microbiome during pregnancy is shaped by parity by Research Square. Licensed under Creative Commons: By Attribution 3.0 License https://creativecommons.org/licenses/by/3.0/
- Figure 2 – Gut-brain interactions with mental health by Bear et al., 2021. Licensed under the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).
- Figure 3 – Development of the gut-brain over time by Liang et al., 2018. Licensed under the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).
- Video 2 – Functional GI Disorders: The role of the gut-brain interaction, microbiome and nutrition by UMMCVideos. Licensed under Creative Commons Attribution license (reuse allowed).
- Figure 4 – Direct and indirect mechanisms of infecting the brain by Olsen and Hicks, 2019 licensed under under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0

This page titled 20.7: Mental Health and Multi-Microbiome Interactions is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Dylan Parks via source content that was edited to the style and standards of the LibreTexts platform.

- **3.7: Mental Health and Multi-Microbiome Interactions** by Dylan Parks is licensed CC BY 4.0. Original source: https://uta.pressbooks.pub/microbiomeshealthandtheenvironment.

21: Cancer Immunobiology and Immunotherapy

Learning Objectives

- Explain how the adaptive specific immune response responds to tumors
- Discuss the risks and benefits of tumor vaccines

Cancer involves a loss of the ability of cells to control their cell cycle, the stages each eukaryotic cell goes through as it grows and then divides. When this control is lost, the affected cells rapidly divide and often lose the ability to differentiate into the cell type appropriate for their location in the body. In addition, they lose contact inhibition and can start to grow on top of each other. This can result in formation of a tumor. It is important to make a distinction here: The term “cancer” is used to describe the diseases resulting from loss of cell-cycle regulation and subsequent cell proliferation. But the term “tumor” is more general. A “tumor” is an abnormal mass of cells, and a tumor can be benign (not cancerous) or malignant (cancerous).

Traditional cancer treatment uses radiation and/or chemotherapy to destroy cancer cells; however, these treatments can have unwanted side effects because they harm normal cells as well as cancer cells. Newer, promising therapies attempt to enlist the patient’s immune system to target cancer cells specifically. It is known that the immune system can recognize and destroy cancerous cells, and some researchers and immunologists also believe, based on the results of their experiments, that many cancers are eliminated by the body’s own defenses before they can become a health problem. This idea is not universally accepted by researchers, however, and needs further investigation for verification.

Cell-Mediated Response to Tumors

Cell-mediated immune responses can be directed against cancer cells, many of which do not have the normal complement of self-proteins, making them a target for elimination. Abnormal cancer cells may also present tumor antigens. These tumor antigens are not a part of the screening process used to eliminate lymphocytes during development; thus, even though they are self-antigens, they can stimulate and drive adaptive immune responses against abnormal cells.

Presentation of tumor antigens can stimulate naïve helper T cells to become activated by cytokines such as IL-12 and differentiate into T_H1 cells. T_H1 cells release cytokines that can activate natural killer (NK) cells and enhance the killing of activated cytotoxic T cells. Both NK cells and cytotoxic T cells can recognize and target cancer cells, and induce apoptosis through the action of perforins and granzymes. In addition, activated cytotoxic T cells can bind to cell-surface proteins on abnormal cells and induce apoptosis by a second killing mechanism called the CD95 (Fas) cytotoxic pathway.

Despite these mechanisms for removing cancerous cells from the body, cancer remains a common cause of death. Unfortunately, malignant tumors tend to actively suppress the immune response in various ways. In some cancers, the immune cells themselves are cancerous. In leukemia, lymphocytes that would normally facilitate the immune response become abnormal. In other cancers, the cancerous cells can become resistant to induction of apoptosis. This may occur through the expression of membrane proteins that shut off cytotoxic T cells or that induce regulatory T cells that can shut down immune responses.

The mechanisms by which cancer cells alter immune responses are still not yet fully understood, and this is a very active area of research. As scientists’ understanding of adaptive immunity improves, cancer therapies that harness the body’s immune defenses may someday be more successful in treating and eliminating cancer.

Exercise 21.1

1. How do cancer cells suppress the immune system?
2. Describe how the immune system recognizes and destroys cancer cells.

Cancer Vaccines

There are two types of cancer vaccines: preventive and therapeutic. Preventive vaccines are used to prevent cancer from occurring, whereas therapeutic vaccines are used to treat patients with cancer. Most preventive cancer vaccines target viral infections that are known to lead to cancer. These include vaccines against human papillomavirus (HPV)and hepatitis B, which help prevent cervical and liver cancer, respectively.

Most therapeutic cancer vaccines are in the experimental stage. They exploit tumor-specific antigens to stimulate the immune system to selectively attack cancer cells. Specifically, they aim to enhance T_H1 function and interaction with cytotoxic T cells, which, in turn, results in more effective attack on abnormal tumor cells. In some cases, researchers have used genetic engineering to develop antitumor vaccines in an approach similar to that used for DNA vaccines (see Micro Connections: DNA vaccines). The vaccine contains a recombinant plasmid with genes for tumor antigens; theoretically, the tumor gene would not induce new cancer because it is not functional, but it could trick the immune system into targeting the tumor gene product as a foreign invader.

The first FDA-approved therapeutic cancer vaccine was sipuleucel-T (Provenge), approved in 2010 to treat certain cases of prostate cancer.[1] This unconventional vaccine is custom designed using the patient's own cells. APCs are removed from the patient and cultured with a tumor-specific molecule; the cells are then returned to the patient. This approach appears to enhance the patient's immune response against the cancer cells. Another therapeutic cancer vaccine (talimogene laherparepvec, also called T-VEC or Imlygic) was approved by the FDA in 2015 for treatment of melanoma, a form of skin cancer. This vaccine contains a virus that is injected into tumors, where it infects and lyses the tumor cells. The virus also induces a response in lesions or tumors besides those into which the vaccine is injected, indicating that it is stimulating a more general (as opposed to local) antitumor immune response in the patient.

? Exercise 21.2

1. Explain the difference between preventative and therapeutic cancer vaccines.
2. Describe at least two different approaches to developing therapeutic anti-cancer vaccines.

Using Viruses to Cure Cancer

Viruses typically destroy the cells they infect—a fact responsible for any number of human diseases. But the cell-killing powers of viruses may yet prove to be the cure for some types of cancer, which is generally treated by attempting to rid the body of cancerous cells. Several clinical trials are studying the effects of viruses targeted at cancer cells. Reolysin, a drug currently in testing phases, uses reoviruses (respiratory enteric orphan viruses) that can infect and kill cells that have an activated Ras-signaling pathway, a common mutation in cancerous cells. Viruses such as rubeola (the measles virus) can also be genetically engineered to aggressively attack tumor cells. These modified viruses not only bind more specifically to receptors overexpressed on cancer cells, they also carry genes driven by promoters that are only turned on within cancer cells. Herpesvirus and others have also been modified in this way.

Key Concepts and Summary

- Cancer results from a loss of control of the cell cycle, resulting in uncontrolled cell proliferation and a loss of the ability to differentiate.
- Adaptive and innate immune responses are engaged by **tumor** antigens, self-molecules only found on abnormal cells. These adaptive responses stimulate helper T cells to activate cytotoxic T cells and NK cells of innate immunity that will seek and destroy cancer cells.
- New anticancer therapies are in development that will exploit natural adaptive immunity anticancer responses. These include external stimulation of cytotoxic T cells and therapeutic vaccines that assist or enhance the immune response.

Footnotes

1. 1 National Institutes of Health, National Cancer Institute. "Cancer Vaccines." www.cancer.gov/about-cancer/c...-fact-sheet#q8. Accessed on May 20, 2016.

This page titled 21: Cancer Immunobiology and Immunotherapy is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **19.5: Cancer Immunobiology and Immunotherapy** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

CHAPTER OVERVIEW

22: Skin and Eye Infections

The human body is covered in skin, and like most coverings, skin is designed to protect what is underneath. One of its primary purposes is to prevent microbes in the surrounding environment from invading underlying tissues and organs. But in spite of its role as a protective covering, skin is not itself immune from infection. Certain pathogens and toxins can cause severe infections or reactions when they come in contact with the skin. Other pathogens are opportunistic, breaching the skin's natural defenses through cuts, wounds, or a disruption of normal microbiota resulting in an infection in the surrounding skin and tissue. Still other pathogens enter the body via different routes—through the respiratory or digestive systems, for example—but cause reactions that manifest as skin rashes or lesions.

Nearly all humans experience skin infections to some degree. Many of these conditions are, as the name suggests, "skin deep," with symptoms that are local and non-life-threatening. At some point, almost everyone must endure conditions like acne, athlete's foot, and minor infections of cuts and abrasions, all of which result from infections of the skin. But not all skin infections are quite so innocuous. Some can become invasive, leading to systemic infection or spreading over large areas of skin, potentially becoming life-threatening.



Figure **22.1**: The skin is an important barrier to pathogens, but it can also develop infections. These raised lesions (left) are typical of folliculitis, a condition that results from the inflammation of hair follicles. Acne lesions (right) also result from inflammation of hair follicles. In this case, the inflammation results when hair follicles become clogged with complex lipids, fatty acids, and dead skin cells, producing a favorable environment for bacteria.

22.1: Anatomy and Normal Microbiota of the Skin and Eyes

22.2: Bacterial Infections of the Skin and Eyes

22.3: Viral Infections of the Skin and Eyes

22.4: Mycoses of the Skin and Eyes

22.5: Protozoan and Helminthic Infections of the Eyes

This page titled 22: Skin and Eye Infections is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

22.1: Anatomy and Normal Microbiota of the Skin and Eyes

Learning Objectives

- Describe the major anatomical features of the skin and eyes
- Compare and contrast the microbiomes of various body sites, such as the hands, back, feet, and eyes
- Explain how microorganisms overcome defenses of skin and eyes in order to cause infection
- Describe general signs and symptoms of disease associated with infections of the skin and eyes

Clinical Focus: Part 1

Sam, a college freshman with a bad habit of oversleeping, nicked himself shaving in a rush to get to class on time. At the time, he didn't think twice about it. But two days later, he noticed the cut was surrounded by a reddish area of skin that was warm to the touch. When the wound started oozing pus, he decided he had better stop by the university's clinic. The doctor took a sample from the lesion and then cleaned the area.

Exercise 22.1.1

What type of microbe could be responsible for Sam's infection?

Human skin is an important part of the innate immune system. In addition to serving a wide range of other functions, the skin serves as an important barrier to microbial invasion. Not only is it a physical barrier to penetration of deeper tissues by potential pathogens, but it also provides an inhospitable environment for the growth of many pathogens. In this section, we will provide a brief overview of the anatomy and normal microbiota of the skin and eyes, along with general symptoms associated with skin and eye infections.

Layers of the Skin

Human skin is made up of several layers and sublayers. The two main layers are the epidermis and the dermis. These layers cover a third layer of tissue called the hypodermis, which consists of fibrous and adipose connective tissue (Figure **22.1.1**).

The epidermis is the outermost layer of the skin, and it is relatively thin. The exterior surface of the epidermis, called the stratum corneum, primarily consists of dead skin cells. This layer of dead cells limits direct contact between the outside world and live cells. The stratum corneum is rich in keratin, a tough, fibrous protein that is also found in hair and nails. Keratin helps make the outer surface of the skin relatively tough and waterproof. It also helps to keep the surface of the skin dry, which reduces microbial growth. However, some microbes are still able to live on the surface of the skin, and some of these can be shed with dead skin cells in the process of desquamation, which is the shedding and peeling of skin that occurs as a normal process but that may be accelerated when infection is present.

Beneath the epidermis lies a thicker skin layer called the dermis. The dermis contains connective tissue and embedded structures such as blood vessels, nerves, and muscles. Structures called hair follicles (from which hair grows) are located within the dermis, even though much of their structure consists of epidermal tissue. The dermis also contains the two major types of glands found in human skin: sweat glands (tubular glands that produce sweat) and sebaceous glands (which are associated with hair follicles and produce sebum, a lipid-rich substance containing proteins and minerals).

Perspiration (sweat) provides some moisture to the epidermis, which can increase the potential for microbial growth. For this reason, more microbes are found on the regions of the skin that produce the most sweat, such as the skin of the underarms and groin. However, in addition to water, sweat also contains substances that inhibit microbial growth, such as salts, lysozyme, and antimicrobial peptides. Sebum also serves to protect the skin and reduce water loss. Although some of the lipids and fatty acids in sebum inhibit microbial growth, sebum contains compounds that provide nutrition for certain microbes.

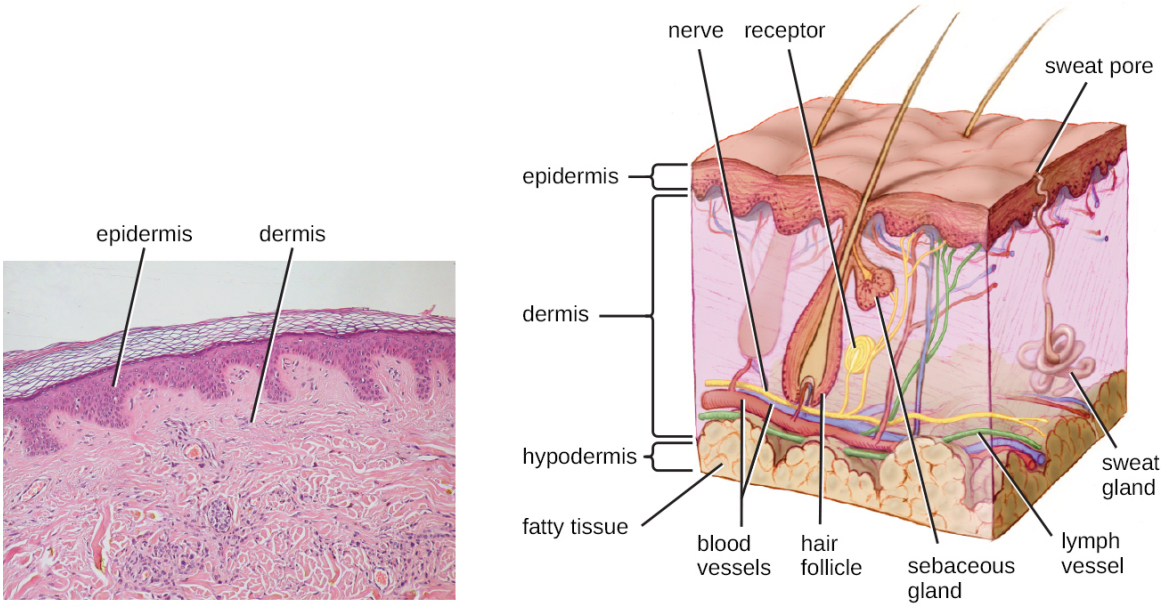


Figure **22.1.1**: (a) A micrograph of a section through human skin shows the epidermis and dermis. (b) The major layers of human skin are the epidermis, dermis, and hypodermis. (credit b: modification of work by National Cancer Institute)

? Exercise 22.1.2

How does desquamation help with preventing infections?

Normal Microbiota of the Skin

The skin is home to a wide variety of normal microbiota, consisting of commensal organisms that derive nutrition from skin cells and secretions such as sweat and sebum. The normal microbiota of skin tends to inhibit transient-microbe colonization by producing antimicrobial substances and outcompeting other microbes that land on the surface of the skin. This helps to protect the skin from pathogenic infection.

The skin's properties differ from one region of the body to another, as does the composition of the skin's microbiota. The availability of nutrients and moisture partly dictates which microorganisms will thrive in a particular region of the skin. Relatively moist skin, such as that of the nares (nostrils) and underarms, has a much different microbiota than the dryer skin on the arms, legs, hands, and top of the feet. Some areas of the skin have higher densities of sebaceous glands. These sebum-rich areas, which include the back, the folds at the side of the nose, and the back of the neck, harbor distinct microbial communities that are less diverse than those found on other parts of the body.

Different types of bacteria dominate the dry, moist, and sebum-rich regions of the skin. The most abundant microbes typically found in the dry and sebaceous regions are Betaproteobacteria and Propionibacteria, respectively. In the moist regions, *Corynebacterium* and *Staphylococcus* are most commonly found (Figure **22.1.2**). Viruses and fungi are also found on the skin, with *Malassezia* being the most common type of fungus found as part of the normal microbiota. The role and populations of viruses in the microbiota, known as viromes, are still not well understood, and there are limitations to the techniques used to identify them. However, Circoviridae, Papillomaviridae, and Polyomaviridaeappear to be the most common residents in the healthy skin virome.[123]

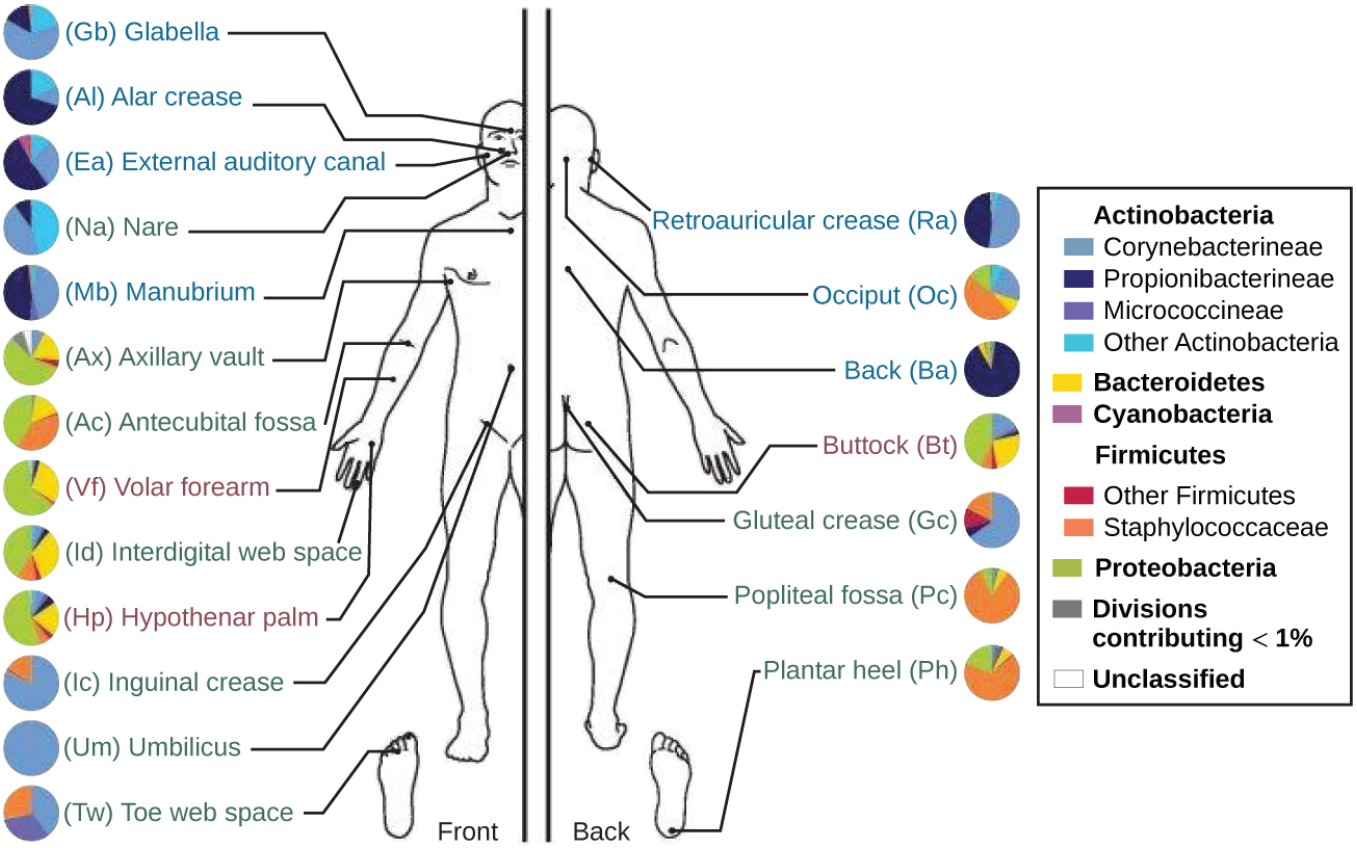


Figure **22.1.2**: The normal microbiota varies on different regions of the skin, especially in dry versus moist areas. The figure shows the major organisms commonly found in different locations of a healthy individual's skin and external mucosa. Note that there is significant variation among individuals. (credit: modification of work by National Human Genome Research Institute)

? Exercise 22.1.3

What are the four most common bacteria that are part of the normal skin microbiota?

Infections of the Skin

While the microbiota of the skin can play a protective role, it can also cause harm in certain cases. Often, an opportunistic pathogen residing in the skin microbiota of one individual may be transmitted to another individual more susceptible to an infection. For example, methicillin-resistant *Staphylococcus aureus* (MRSA) can often take up residence in the nares of health care workers and hospital patients; though harmless on intact, healthy skin, MRSA can cause infections if introduced into other parts of the body, as might occur during surgery or via a post-surgical incision or wound. This is one reason why clean surgical sites are so important.

Injury or damage to the skin can allow microbes to enter deeper tissues, where nutrients are more abundant and the environment is more conducive to bacterial growth. Wound infections are common after a puncture or laceration that damages the physical barrier of the skin. Microbes may infect structures in the dermis, such as hair follicles and glands, causing a localized infection, or they may reach the bloodstream, which can lead to a systemic infection.

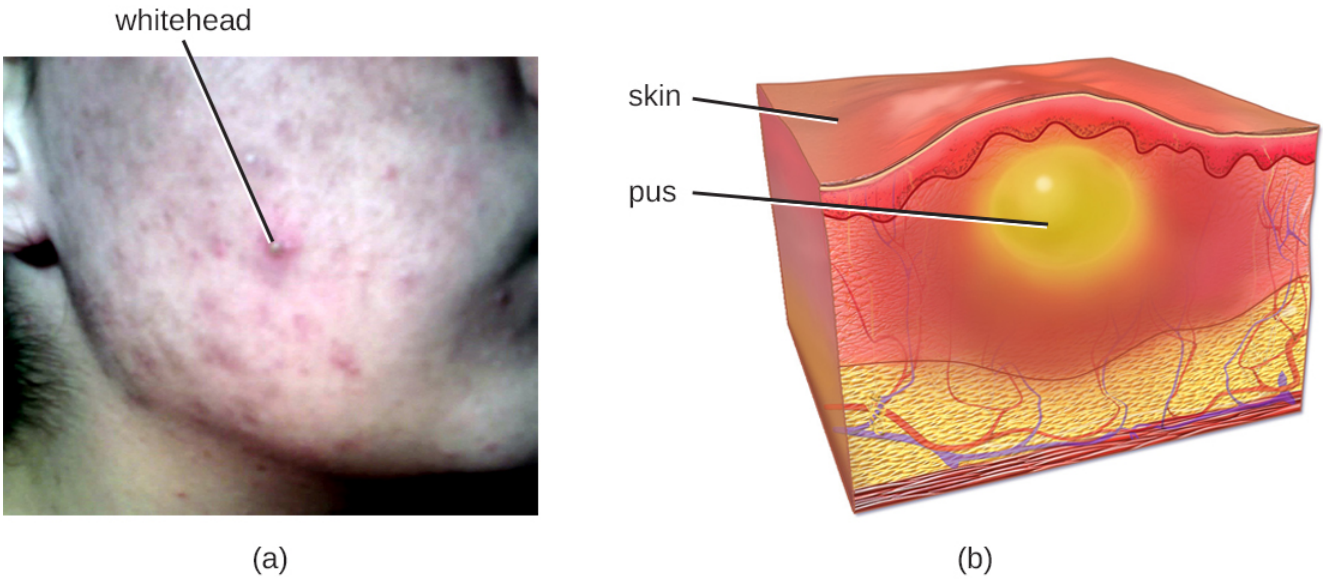


Figure **22.1.3**: (a) Acne is a bacterial infection of the skin that manifests as a rash of inflamed hair follicles (folliculitis). The large whitehead near the center of the cheek is an infected hair follicle that has become purulent (or suppurative), leading to the formation of a furuncle. (b) An abscess is a pus-filled lesion. (credit b: modification of work by Bruce Blaus)

In some cases, infectious microbes can cause a variety of rashes or lesions that differ in their physical characteristics. These rashes can be the result of inflammation reactions or direct responses to toxins produced by the microbes. Table **22.1.1** lists some of the medical terminology used to describe skin lesions and rashes based on their characteristics; Figure **22.1.3** and Figure **22.1.4** illustrate some of the various types of skin lesions. It is important to note that many different diseases can lead to skin conditions of very similar appearance; thus the terms used in the table are generally not exclusive to a particular type of infection or disease.

Table **22.1.1**: Some Medical Terms Associated with Skin Lesions and Rashes

Term	Definition
abscess	localized collection of pus
bulla (pl., bullae)	fluid-filled blister no more than 5 mm in diameter
carbuncle	deep, pus-filled abscess generally formed from multiple furuncles
crust	dried fluids from a lesion on the surface of the skin
cyst	encapsulated sac filled with fluid, semi-solid matter, or gas, typically located just below the upper layers of skin
folliculitis	a localized rash due to inflammation of hair follicles
furuncle (boil)	pus-filled abscess due to infection of a hair follicle
macules	smooth spots of discoloration on the skin
papules	small raised bumps on the skin
pseudocyst	lesion that resembles a cyst but with a less defined boundary
purulent	pus-producing; suppurative
pustules	fluid- or pus-filled bumps on the skin
pyoderma	any suppurative (pus-producing) infection of the skin
suppurative	producing pus; purulent
ulcer	break in the skin; open sore
vesicle	small, fluid-filled lesion
wheal	swollen, inflamed skin that itches or burns, such as from an insect bite

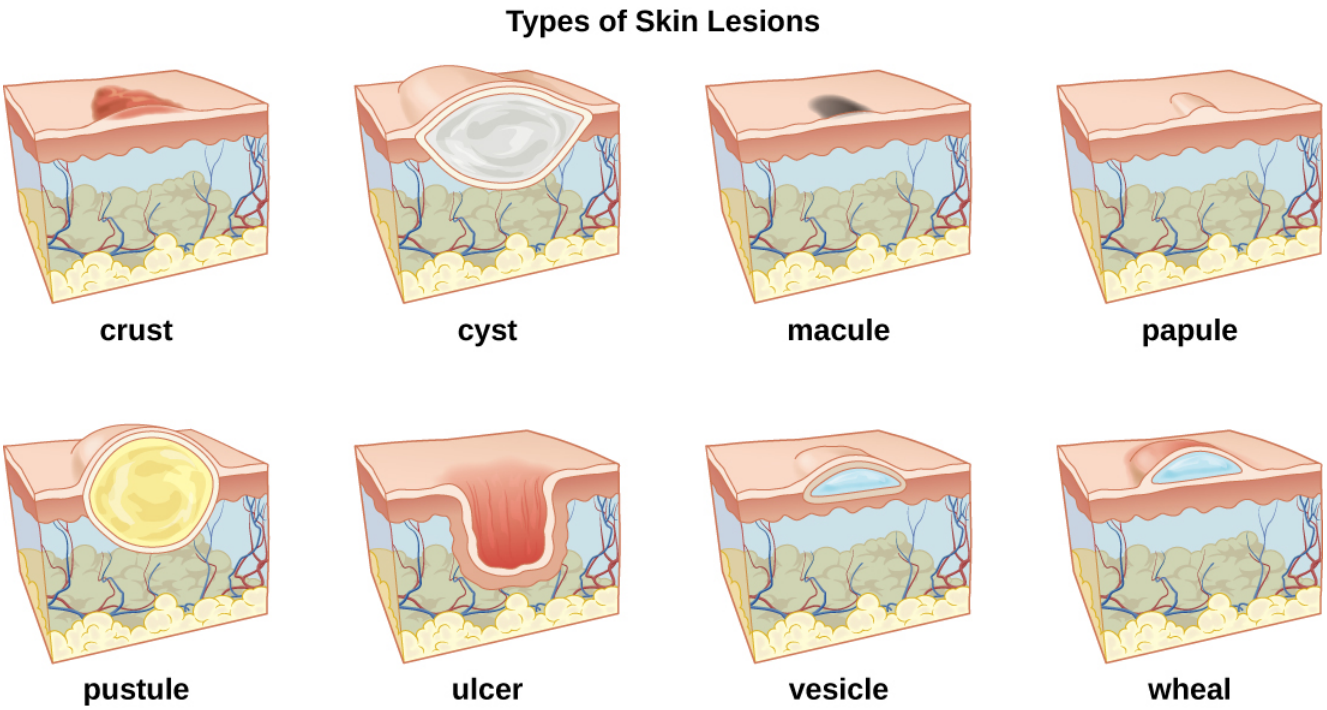


Figure 22.1.4: Numerous causes can lead to skin lesions of various types, some of which are very similar in appearance. (credit:

modification of work by Bruce Blaus)

? Exercise 22.1.4

How can asymptomatic health care workers transmit bacteria such as MRSA to patients?

Anatomy and Microbiota of the Eye

Although the eye and skin have distinct anatomy, they are both in direct contact with the external environment. An important component of the eye is the nasolacrimal drainage system, which serves as a conduit for the fluid of the eye, called tears. Tears flow from the external eye to the nasal cavity by the lacrimal apparatus, which is composed of the structures involved in tear production (Figure 22.1.5). The lacrimal gland, above the eye, secretes tears to keep the eye moist. There are two small openings, one on the inside edge of the upper eyelid and one on the inside edge of the lower eyelid, near the nose. Each of these openings is called a lacrimal punctum. Together, these lacrimal puncta collect tears from the eye that are then conveyed through lacrimal ducts to a reservoir for tears called the lacrimal sac, also known as the dacrocyst or tear sac.

From the sac, tear fluid flows via a nasolacrimal duct to the inner nose. Each nasolacrimal duct is located underneath the skin and passes through the bones of the face into the nose. Chemicals in tears, such as defensins, lactoferrin, and lysozyme, help to prevent colonization by pathogens. In addition, mucins facilitate removal of microbes from the surface of the eye.

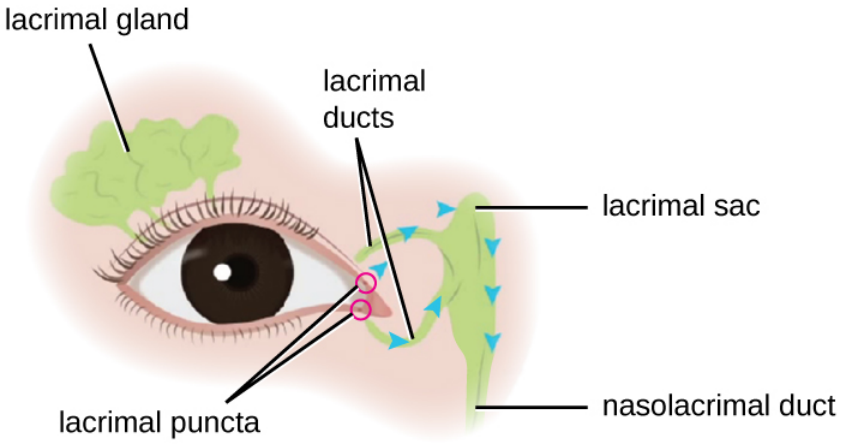


Figure 22.1.5: The lacrimal apparatus includes the structures of the eye associated with tear production and drainage. (credit: modification of work by "Evidence Based Medical Educator Inc."/YouTube)

The surfaces of the eyeball and inner eyelid are mucous membranes called conjunctiva. The normal conjunctival microbiota has not been well characterized, but does exist. One small study (part of the Ocular Microbiome project) found twelve genera that were consistently present in the conjunctiva.[4] These microbes are thought to help defend the membranes against pathogens. However, it is still unclear which microbes may be transient and which may form a stable microbiota.[5]

Use of contact lenses can cause changes in the normal microbiota of the conjunctiva by introducing another surface into the natural anatomy of the eye. Research is currently underway to better understand how contact lenses may impact the normal microbiota and contribute to eye disease.

The watery material inside of the eyeball is called the vitreous humor. Unlike the conjunctiva, it is protected from contact with the environment and is almost always sterile, with no normal microbiota (Figure 22.1.6).

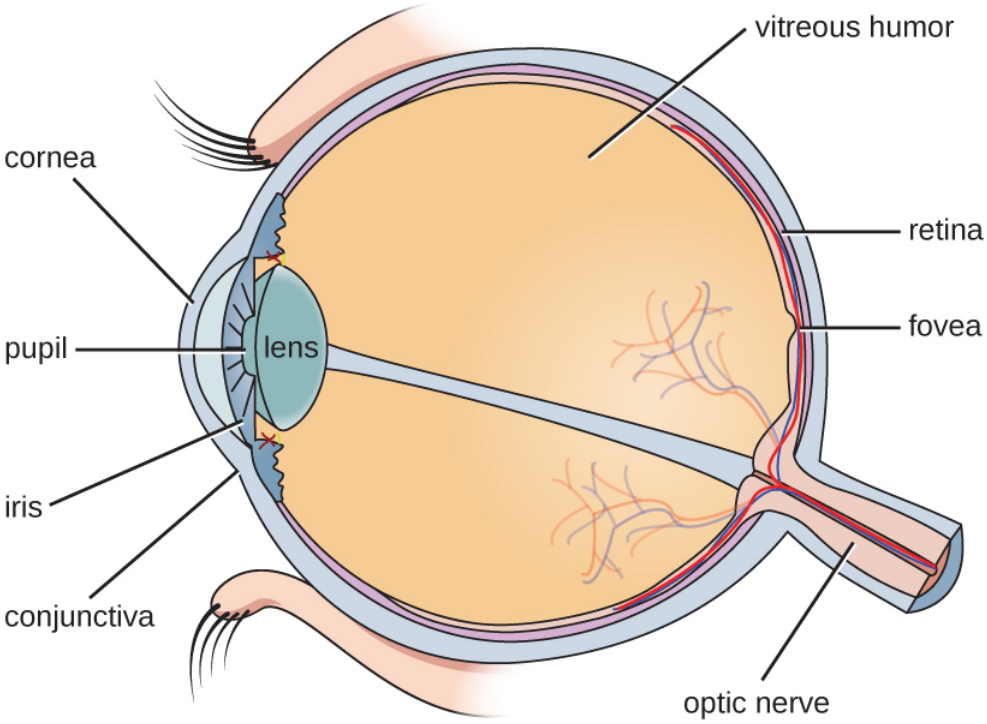


Figure 22.1.6: Some microbes live on the conjunctiva of the human eye, but the vitreous humor is sterile.

Infections of the Eye

The conjunctiva is a frequent site of infection of the eye; like other mucous membranes, it is also a common portal of entry for pathogens. Inflammation of the conjunctiva is called conjunctivitis, although it is commonly known as pinkeyebecause of the pink appearance in the eye. Infections of deeper structures, beneath the cornea, are less common (Figure 22.1.7). Conjunctivitis occurs in multiple forms. It may be acute or chronic. Acute purulent conjunctivitis is associated with pus formation, while acute hemorrhagic conjunctivitis is associated with bleeding in the conjunctiva. The term blepharitis refers to an inflammation of the eyelids, while keratitis refers to an inflammation of the cornea (Figure 22.1.7); keratoconjunctivitis is an inflammation of both the cornea and the conjunctiva, and dacryocystitis is an inflammation of the lacrimal sac that can often occur when a nasolacrimal duct is blocked.



(a) (b) (c)

Figure 22.1.7: (a) Conjunctivitis is inflammation of the conjunctiva. (b) Blepharitis is inflammation of the eyelids. (c) Keratitis is inflammation of the cornea. (credit a: modification of work by Lopez-Prats MJ, Sanz Marco E, Hidalgo-Mora JJ, Garcia-Delpech S, Diaz-Llopis M; credit b, c: modification of work by Centers for Disease Control and Prevention)

Infections leading to conjunctivitis, blepharitis, keratoconjunctivitis, or dacryocystitis may be caused by bacteria or viruses, but allergens, pollutants, or chemicals can also irritate the eye and cause inflammation of various structures. Viral infection is a more likely cause of conjunctivitis in cases with symptoms such as fever and watery discharge that occurs with upper respiratory infection and itchy eyes. Table 22.1.2 summarizes some common forms of conjunctivitis and blepharitis.

Table 22.1.2: Types of Conjunctivities and Blepharitis

Condition	Description	Causative Agent(s)
Acute purulent conjunctivitis	Conjunctivitis with purulent discharge	Bacterial (*Haemophilus*, *Staphylococcus*)
Acute hemorrhagic conjunctivitis	Involves subconjunctival hemorrhages	Viral (Picornaviradae)
Acute ulcerative blepharitis	Infection involving eyelids; pustules and ulcers may develop	Bacterial (*Staphylococcal*) or viral (herpes simplex, varicella-zoster, etc.)
Follicular conjunctivitis	Inflammation of the conjunctiva with nodules (dome-shaped structures that are red at the base and pale on top)	Viral (adenovirus and others); environmental irritants
Dacryocystitis	Inflammation of the lacrimal sac often associated with a plugged nasolacrimal duct	Bacterial (*Haemophilus*, *Staphylococcus*, *Streptococcus*)
Keratitis	Inflammation of cornea	Bacterial, viral, or protozoal; environmental irritants
Keratoconjunctivitis	Inflammation of cornea and conjunctiva	Bacterial, viral (adenoviruses), or other causes (including dryness of the eye)
Nonulcerative blepharitis	Inflammation, irritation, redness of the eyelids without ulceration	Environmental irritants; allergens
Papillary conjunctivitis	Inflammation of the conjunctiva; nodules and papillae with red tops develop	Environmental irritants; allergens

? Exercise 22.1.5

How does the lacrimal apparatus help to prevent eye infections?

Key Concepts and Summary

- Human skin consists of two main layers, the **epidermis** and **dermis**, which are situated on top of the **hypodermis**, a layer of connective tissue.
- The skin is an effective physical barrier against microbial invasion.
- The skin's relatively dry environment and normal microbiota discourage colonization by transient microbes.
- The skin's normal microbiota varies from one region of the body to another.
- The **conjunctiva** of the eye is a frequent site for microbial infection, but deeper eye infections are less common; multiple types of conjunctivitis exist.

Footnotes

1. 1 Belkaid, Y., and J.A. Segre. "Dialogue Between Skin Microbiota and Immunity," *Science* 346 (2014) 6212:954–959.
2. 2 Foulongne, Vincent, et al. "Human Skin Microbiota: High Diversity of DNA Viruses Identified on the Human Skin by High Throughput Sequencing." *PLoS ONE* (2012) 7(6): e38499. doi: 10.1371/journal.pone.0038499.
3. 3 Robinson, C.M., and J.K. Pfeiffer. "Viruses and the Microbiota." *Annual Review of Virology* (2014) 1:55–59. doi: 10.1146/annurev-virology-031413-085550.
4. 4 Abelson, M.B., Lane, K., and Slocum, C.. "The Secrets of Ocular Microbiomes." *Review of Ophthalmology* June 8, 2015. www.reviewofophthalmology.com...isease/c/55178. Accessed Sept 14, 2016.
5. 5 Shaikh-Lesko, R. "Visualizing the Ocular Microbiome." *The Scientist* May 12, 2014. http://www.the-scientist.com/?articl...lar-Microbiome. Accessed Sept 14, 2016.

This page titled 22.1: Anatomy and Normal Microbiota of the Skin and Eyes is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style

and standards of the LibreTexts platform.

- **21.1: Anatomy and Normal Microbiota of the Skin and Eyes** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

22.2: Bacterial Infections of the Skin and Eyes

Learning Objectives

- Identify the most common bacterial pathogens that cause infections of the skin and eyes
- Compare the major characteristics of specific bacterial diseases affecting the skin and eyes

Despite the skin's protective functions, infections are common. Gram-positive *Staphylococcus* spp. and *Streptococcus* spp. are responsible for many of the most common skin infections. However, many skin conditions are not strictly associated with a single pathogen. Opportunistic pathogens of many types may infect skin wounds, and individual cases with identical symptoms may result from different pathogens or combinations of pathogens.

In this section, we will examine some of the most important bacterial infections of the skin and eyes and discuss how biofilms can contribute to and exacerbate such infections. Key features of bacterial skin and eye infections are also summarized in the Disease Profile boxes throughout this section.

Staphylococcal Infections of the Skin

Staphylococcus species are commonly found on the skin, with *S. epidermidis* and *S. hominis* being prevalent in the normal microbiota. *S. aureus* is also commonly found in the nasal passages and on healthy skin, but pathogenic strains are often the cause of a broad range of infections of the skin and other body systems.

S. aureus is quite contagious. It is spread easily through skin-to-skin contact, and because many people are chronic nasal carriers (asymptomatic individuals who carry *S. aureus* in their nares), the bacteria can easily be transferred from the nose to the hands and then to fomites or other individuals. Because it is so contagious, *S. aureus* is prevalent in most community settings. This prevalence is particularly problematic in hospitals, where antibiotic-resistant strains of the bacteria may be present, and where immunocompromised patients may be more susceptible to infection. Resistant strains include methicillin-resistant *S. aureus* (MRSA), which can be acquired through health-care settings (hospital-acquired MRSA, or HA-MRSA) or in the community (community-acquired MRSA, or CA-MRSA). Hospital patients often arrive at health-care facilities already colonized with antibiotic-resistant strains of *S. aureus* that can be transferred to health-care providers and other patients. Some hospitals have attempted to detect these individuals in order to institute prophylactic measures, but they have had mixed success (see Eye on Ethics: Screening Patients for MRSA).

When a staphylococcal infection develops, choice of medication is important. As discussed above, many staphylococci (such as MRSA) are resistant to some or many antibiotics. Thus, antibiotic sensitivity is measured to identify the most suitable antibiotic. However, even before receiving the results of sensitivity analysis, suspected *S. aureus* infections are often initially treated with drugs known to be effective against MRSA, such as trimethoprim-sulfamethoxazole(TMP/SMZ), clindamycin, a tetracycline (doxycycline or minocycline), or linezolid.

The pathogenicity of staphylococcal infections is often enhanced by characteristic chemicals secreted by some strains. Staphylococcal virulence factors include hemolysins called staphylolysins, which are cytotoxic for many types of cells, including skin cells and white blood cells. Virulent strains of *S. aureus* are also coagulase-positive, meaning they produce coagulase, a plasma-clotting protein that is involved in abscess formation. They may also produce leukocidins, which kill white blood cells and can contribute to the production of pus and Protein A, which inhibits phagocytosis by binding to the constant region of antibodies. Some virulent strains of *S. aureus* also produce other toxins, such as toxic shock syndrome toxin-1 (see Virulence Factors of Bacterial and Viral Pathogens).

To confirm the causative agent of a suspected staphylococcal skin infection, samples from the wound are cultured. Under the microscope, gram-positive *Staphylococcus* species have cellular arrangements that form grapelike clusters; when grown on blood agar, colonies have a unique pigmentation ranging from opaque white to cream. A catalase testis used to distinguish *Staphylococcus* from *Streptococcus*, which is also a genus of gram-positive cocci and a common cause of skin infections. *Staphylococcus* species are catalase-positive while *Streptococcus* species are catalase-negative.

Other tests are performed on samples from the wound in order to distinguish coagulase-positive species of *Staphylococcus* (CoPS) such as *S. aureus* from common coagulase-negative species (CoNS) such as *S. epidermidis*. Although CoNS are less likely than CoPS to cause human disease, they can cause infections when they enter the body, as can sometimes occur via catheters, indwelling medical devices, and wounds. Passive agglutination testing can be used to distinguish CoPS from CoNS. If the sample is coagulase-positive, the sample is generally presumed to contain *S. aureus*. Additional genetic testing would be necessary to identify the particular strain of *S. aureus*.

Another way to distinguish CoPS from CoNS is by culturing the sample on mannitol salt agar (MSA). *Staphylococcus* species readily grow on this medium because they are tolerant of the high concentration of sodium chloride (7.5% NaCl). However, CoPS such as *S. aureus* ferment mannitol (which will be evident on a MSA plate), whereas CoNS such as *S. epidermidis* do not ferment mannitol but can be distinguished by the fermentation of other sugars such as lactose, malonate, and raffinose (Figure **22.2.1**).

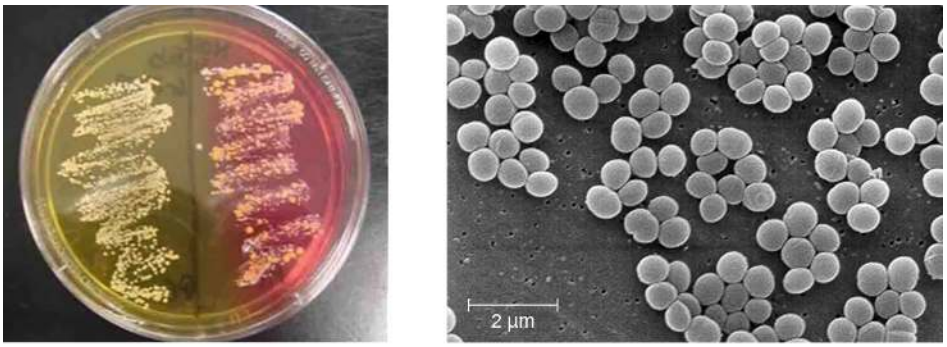


Figure **22.2.1**: (a) A mannitol salt agar plate is used to distinguish different species of staphylococci. In this plate, *S. aureus* is on the left and *S. epidermidis* is in the right. Because *S. aureus* is capable of fermenting mannitol, it produces acids that cause the color to change to yellow. (b) This scanning electron micrograph shows the characteristic grapelike clusters of *S. aureus*. (credit a: modification of work by "ScienceProfOnline"/YouTube; credit b: modification of work by Centers for Disease Control and Prevention)

Screening Patients for MRSA

According to the CDC, 86% of invasive MRSA infections are associated in some way with healthcare, as opposed to being community-acquired. In hospitals and clinics, asymptomatic patients who harbor MRSA may spread the bacteria to individuals who are more susceptible to serious illness.

In an attempt to control the spread of MRSA, hospitals have tried screening patients for MRSA. If patients test positive following a nasal swab test, they can undergo decolonization using chlorhexidine washes or intranasal mupirocin. Some studies have reported substantial reductions in MRSA disease following implementation of these protocols, while others have not. This is partly because there is no standard protocol for these procedures. Several different MRSA identification tests may be used, some involving slower culturing techniques and others rapid testing. Other factors, such as the effectiveness of general hand-washing protocols, may also play a role in helping to prevent MRSA transmission. There are still other questions that need to be addressed: How frequently should patients be screened? Which individuals should be tested? From where on the body should samples be collected? Will increased resistance develop from the decolonization procedures?

Even if identification and decolonization procedures are perfected, ethical questions will remain. Should patients have the right to decline testing? Should a patient who tests positive for MRSA have the right to decline the decolonization procedure, and if so, should hospitals have the right to refuse treatment to the patient? How do we balance the individual's right to receive care with the rights of other patients who could be exposed to disease as a result?

Superficial Staphylococcal Infections

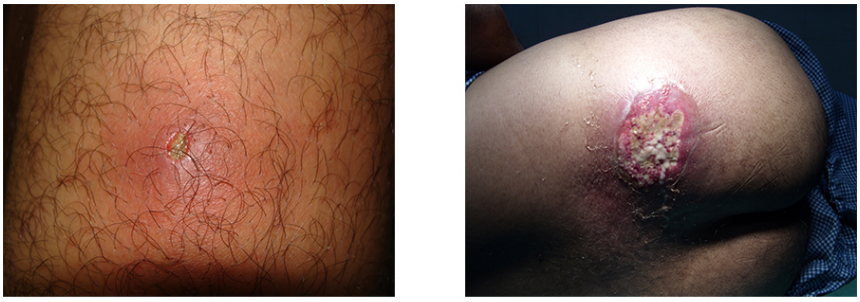
S. aureus is often associated with pyoderma, skin infections that are purulent. Pus formation occurs because many strains of *S. aureus* produce leukocidins, which kill white blood cells. These purulent skin infections may initially manifest as folliculitis, but can lead to furuncles or deeper abscesses called carbuncles.

Folliculitis generally presents as bumps and pimples that may be itchy, red, and/or pus-filled. In some cases, folliculitis is self-limiting, but if it continues for more than a few days, worsens, or returns repeatedly, it may require medical treatment. Sweat, skin injuries, ingrown hairs, tight clothing, irritation from shaving, and skin conditions can all contribute to folliculitis. Avoidance of tight clothing and skin irritation can help to prevent infection, but topical antibiotics (and sometimes other treatments) may also help. Folliculitis can be identified by skin inspection; treatment is generally started without first culturing and identifying the causative agent.

In contrast, furuncles (boils) are deeper infections (Figure **22.2.2**). They are most common in those individuals (especially young adults and teenagers) who play contact sports, share athletic equipment, have poor nutrition, live in close quarters, or have weakened immune systems. Good hygiene and skin care can often help to prevent furuncles from becoming more infective, and they generally resolve on their own. However, if furuncles spread, increase in number or size, or lead to systemic symptoms such as fever and chills, then medical care is needed. They may sometimes need to be drained (at which time the pathogens can be cultured) and treated with antibiotics.

When multiple boils develop into a deeper lesion, it is called a carbuncle (Figure **22.2.2**). Because carbuncles are deeper, they are more commonly associated with systemic symptoms and a general feeling of illness. Larger, recurrent, or worsening carbuncles require medical treatment, as do those associated with signs of illness such as fever. Carbuncles generally need to be drained and treated with antibiotics. While carbuncles are relatively easy to identify visually, culturing and laboratory analysis of the wound may be recommended for some infections because antibiotic resistance is relatively common.

Proper hygiene is important to prevent these types of skin infections or to prevent the progression of existing infections.



(a) (b)

Figure **22.2.2**: Furuncles (boils) and carbuncles are infections of the skin often caused by *Staphylococcus* bacteria. (a) A furuncle contains pus and exhibits swelling. (b) A carbuncle is a pus-filled lesion that is typically deeper than the furuncle. It often forms from multiple furuncles. (credit a: modification of work by “Mahdouch”/Wikimedia Commons; credit b: modification of work by “Drvgaikwad”/Wikimedia Commons)

Staphylococcal scalded skin syndrome (SSSS) is another superficial infection caused by *S. aureus* that is most commonly seen in young children, especially infants. Bacterial exotoxins first produce erythema (redness of the skin) and then severe peeling of the skin, as might occur after scalding (Figure **22.2.3**). SSSS is diagnosed by examining characteristics of the skin (which may rub off easily), using blood tests to check for elevated white blood cell counts, culturing, and other methods. Intravenous antibiotics and fluid therapy are used as treatment.



Figure **22.2.3**: A newborn with staphylococcal scalded skin syndrome (SSSS), which results in large regions of peeling, dead skin. (credit: modification of work by D Jeyakumari, R Gopal, M Eswaran, and C MaheshKumar)

Impetigo

The skin infection impetigo causes the formation of vesicles, pustules, and possibly bullae, often around the nose and mouth. Bullae are large, fluid-filled blisters that measure at least 5 mm in diameter. Impetigo can be diagnosed as either nonbullous or bullous. In nonbullous impetigo, vesicles and pustules rupture and become encrusted sores. Typically the crust is yellowish, often with exudate draining from the base of the lesion. In bullous impetigo, the bullae fill and rupture, resulting in larger, draining, encrusted lesions (Figure **22.2.4**).

Especially common in children, impetigo is particularly concerning because it is highly contagious. Impetigo can be caused by *S. aureus* alone, by *Streptococcus pyogenes* alone, or by coinfection of *S. aureus* and *S. pyogenes*. Impetigo is often diagnosed through observation of its characteristic appearance, although culture and susceptibility testing may also be used.

Topical or oral antibiotic treatment is typically effective in treating most cases of impetigo. However, cases caused by *S. pyogenes* can lead to serious sequelae (pathological conditions resulting from infection, disease, injury, therapy, or other trauma) such as acute glomerulonephritis (AGN), which is severe inflammation in the kidneys.



Figure **22.2.4**: Impetigo is characterized by vesicles, pustules, or bullae that rupture, producing encrusted sores. (credit: modification of work by FDA)

Nosocomial *S. epidermidis* Infections

Though not as virulent as *S. aureus*, the staphylococcus *S. epidermidis* can cause serious opportunistic infections. Such infections usually occur only in hospital settings. *S. epidermidis* is usually a harmless resident of the normal skin microbiota. However, health-care workers can inadvertently transfer *S. epidermidis* to medical devices that are inserted into the body, such as catheters, prostheses, and indwelling medical devices. Once it has bypassed the skin barrier, *S. epidermidis* can cause infections inside the body that can be difficult to treat. Like *S. aureus*, *S. epidermidis* is resistant to many antibiotics, and localized infections can become systemic if not treated quickly. To reduce the risk of nosocomial (hospital-acquired) *S. epidermidis*, health-care workers must follow strict procedures for handling and sterilizing medical devices before and during surgical procedures.

? Exercise 22.2.1

Why are *Staphylococcus aureus* infections often purulent?

Streptococcal Infections of the Skin

Streptococcus are gram-positive cocci with a microscopic morphology that resembles chains of bacteria. Colonies are typically small (1–2 mm in diameter), translucent, entire edge, with a slightly raised elevation that can be either nonhemolytic, alpha-hemolytic, or beta-hemolytic when grown on blood agar (Figure **22.2.5**). Additionally, they are facultative anaerobes that are catalase-negative.

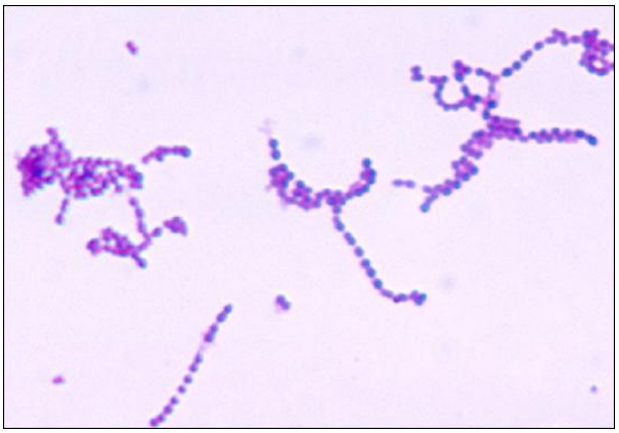


Figure **22.2.5**: Streptococcus pyogenes forms chains of cocci. (credit: modification of work by Centers for Disease Control and Prevention)

The genus *Streptococcus* includes important pathogens that are categorized in serological Lancefield groups based on the distinguishing characteristics of their surface carbohydrates. The most clinically important streptococcal species in humans is *S. pyogenes*, also known as group A streptococcus (GAS). *S. pyogenes* produces a variety of extracellular enzymes, including streptolysins O and S, hyaluronidase, and streptokinase. These enzymes can aid in transmission and contribute to the inflammatory response.[1] *S. pyogenes* also produces a capsule and M protein, a streptococcal cell wall protein. These virulence factors help the bacteria to avoid phagocytosis while provoking a substantial immune response that contributes to symptoms associated with streptococcal infections.

S. pyogenes causes a wide variety of diseases not only in the skin, but in other organ systems as well. Examples of diseases elsewhere in the body include pharyngitis and scarlet fever, which will be covered in later chapters.

Cellulitis, Erysipelas, and Erythema Nosodum

Common streptococcal conditions of the skin include cellulitis, erysipelas, and erythema nodosum. An infection that develops in the dermis or hypodermis can cause cellulitis, which presents as a reddened area of the skin that is warm to the touch and painful. The causative agent is often *S. pyogenes*, which may breach the epidermis through a cut or abrasion, although cellulitis may also be caused by staphylococci. *S. pyogenes* can also cause erysipelas, a condition that presents as a large, intensely inflamed patch of skin involving the dermis (often on the legs or face). These infections can be suppurative, which results in a bullous form of erysipelas. Streptococcal and other pathogens may also cause a condition called erythema nodosum, characterized by inflammation in the subcutaneous fat cells of the hypodermis. It sometimes results from a streptococcal infection, though other pathogens can also cause the condition. It is not suppurative, but leads to red nodules on the skin, most frequently on the shins (Figure **22.2.6**).

In general, streptococcal infections are best treated through identification of the specific pathogen followed by treatment based upon that particular pathogen's susceptibility to different antibiotics. Many immunological tests, including agglutination reactions and ELISAs, can be used to detect streptococci. Penicillin is commonly prescribed for treatment of cellulitis and erysipelas because resistance is not widespread in streptococci at this time. In most patients, erythema nodosum is self-limiting and is not treated with antimicrobial drugs. Recommended treatments may include nonsteroidal anti-inflammatory drugs (NSAIDs), cool wet compresses, elevation, and bed rest.



(a) (b) (c)

Figure **22.2.6**: S. pyogenes can cause a variety of skin conditions once it breaches the skin barrier through a cut or wound. (a) Cellulitis presents as a

painful, red rash. (b) Erysipelas presents as a raised rash, usually with clear borders. (c) Erythema nodosum is characterized by red lumps or nodules, typically on the lower legs. (credit a: modification of work by "Bassukas ID, Gaitanis G, Zioga A, Boboyianni C, Stergiopoulou C; credit b: modification of work by Centers for Disease Control and Prevention; credit c: modification of work by Dean C, Crow WT)

Necrotizing Fasciitis

Streptococcal infections that start in the skin can sometimes spread elsewhere, resulting in a rare but potentially life-threatening condition called necrotizing fasciitis, sometimes referred to as flesh-eating bacterial syndrome. *S. pyogenes* is one of several species that can cause this rare but potentially-fatal condition; others include *Klebsiella*, *Clostridium*, *Escherichia coli*, *S. aureus*, and *Aeromonas hydrophila*.

Necrotizing fasciitis occurs when the fascia, a thin layer of connective tissue between the skin and muscle, becomes infected. Severe invasive necrotizing fasciitis due to *Streptococcus pyogenes* occurs when virulence factors that are responsible for adhesion and invasion overcome host defenses. *S. pyogenes* invasins allow bacterial cells to adhere to tissues and establish infection. Bacterial proteases unique to *S. pyogenes* aggressively infiltrate and destroy host tissues, inactivate complement, and prevent neutrophil migration to the site of infection. The infection and resulting tissue death can spread very rapidly, as large areas of skin become detached and die. Treatment generally requires debridement (surgical removal of dead or infected tissue) or amputation of infected limbs to stop the spread of the infection; surgical treatment is supplemented with intravenous antibiotics and other therapies (Figure **22.2.7**).

Necrotizing fasciitis does not always originate from a skin infection; in some cases there is no known portal of entry. Some studies have suggested that experiencing a blunt force trauma can increase the risk of developing streptococcal necrotizing fasciitis.[2]



(a) (b)

Figure **22.2.7**: (a) The left leg of this patient shows the clinical features of necrotizing fasciitis. (b) The same patient's leg is surgically debrided to remove the infection. (credit a, b: modification of work by Piotr Smuszkiewicz, Iwona Trojanowska, and Hanna Tomczak)

? Exercise 22.2.2

How do staphylococcal infections differ in general presentation from streptococcal infections?

Clinical Focus: Part 2

Observing that Sam's wound is purulent, the doctor tells him that he probably has a bacterial infection. She takes a sample from the lesion to send for laboratory analysis, but because it is Friday, she does not expect to receive the results until the following Monday. In the meantime, she prescribes an over-the-counter topical antibiotic ointment. She tells Sam to keep the wound clean and apply a new bandage with the ointment at least twice per day.

Exercise 22.2.3

1. How would the lab technician determine if the infection is staphylococcal or streptococcal? Suggest several specific methods.
2. What tests might the lab perform to determine the best course of antibiotic treatment?

Pseudomonas Infections of the Skin

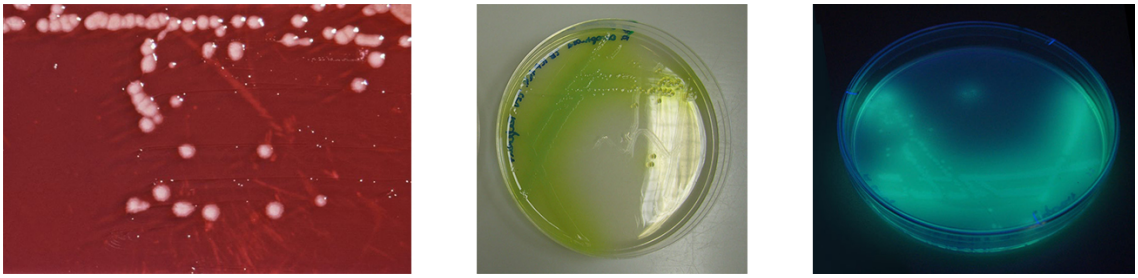
Another important skin pathogen is *Pseudomonas aeruginosa*, a gram-negative, oxidase-positive, aerobic bacillus that is commonly found in water and soil as well as on human skin. *P. aeruginosa* is a common cause of opportunistic infections of wounds and burns. It can also cause hot tub rash, a condition characterized by folliculitis that frequently afflicts users of pools and hot tubs (recall the Clinical Focus case in Microbial Biochemistry). *P. aeruginosa* is also the cause of otitis externa (swimmer's ear), an infection of the ear canal that causes itching, redness, and discomfort, and can progress to fever, pain, and swelling (Figure 22.2.8).



(a) (b)

Figure 22.2.8: (a) Hot tub folliculitis presents as an itchy red rash. It is typically caused by *P. aeruginosa*, a bacterium that thrives in wet, warm environments such as hot tubs. (b) Otitis externa (swimmer's ear) may also be caused by *P. aeruginosa* or other bacteria commonly found in water. Inflammation of the outer ear and ear canal can lead to painful swelling. (credit b: modification of work by Klaus D. Peter)

Wounds infected with *P. aeruginosa* have a distinctive odor resembling grape soda or fresh corn tortillas. This odor is caused by the 2-aminoacetophenone that is used by *P. aeruginosa* in quorum sensing and contributes to its pathogenicity. Wounds infected with certain strains of *P. aeruginosa* also produce a blue-green pus due to the pigments pyocyanin and pyoverdin, which also contribute to its virulence. Pyocyanin and pyoverdin are siderophores that help *P. aeruginosa* survive in low-iron environments by enhancing iron uptake. *P. aeruginosa* also produces several other virulence factors, including phospholipase C (a hemolysin capable of breaking down red blood cells), exoenzyme S(involved in adherence to epithelial cells), and exotoxin A (capable of causing tissue necrosis). Other virulence factors include a slime that allows the bacterium to avoid being phagocytized, fimbriae for adherence, and proteases that cause tissue damage. *P. aeruginosa* can be detected through the use of cetrimide agar, which is selective for *Pseudomonas* species (Figure 22.2.9).



(a) (b) (c)

Figure 22.2.9: (a) These *P. aeruginosa* colonies are growing on xylose lysine sodium deoxycholate (XLD) agar. (b) *Pseudomonas* spp. can produce a variety of blue-green pigments. (c) *Pseudomonas* spp. may produce fluorescein, which fluoresces green under ultraviolet light under the right conditions. (credit a: modification of work by Centers for Disease Control and Prevention)

Pseudomonas spp. tend to be resistant to most antibiotics. They often produce β-lactamases, may have mutations affecting porins (small cell wall channels) that affect antibiotic uptake, and may pump some antibiotics out of the cell, contributing to this resistance. Polymyxin B and gentamicin are effective, as are some fluoroquinolones. Otitis externa is typically treated with ear drops containing acetic acid, antibacterials, and/or steroids to reduce inflammation; ear drops may also include antifungals because

fungi can sometimes cause or contribute to otitis externa. Wound infections caused by *Pseudomonas* spp. may be treated with topical antibiofilm agents that disrupt the formation of biofilms.

? Exercise 22.2.4

Name at least two types of skin infections commonly caused by *Pseudomonas* spp.

Acne

One of the most ubiquitous skin conditions is acne. Acne afflicts nearly 80% of teenagers and young adults, but it can be found in individuals of all ages. Higher incidence among adolescents is due to hormonal changes that can result in overproduction of sebum.

Acne occurs when hair follicles become clogged by shed skin cells and sebum, causing non-inflammatory lesions called comedones. Comedones (singular "comedo") can take the form of whitehead and blackhead pimples. Whiteheads are covered by skin, whereas blackhead pimples are not; the black color occurs when lipids in the clogged follicle become exposed to the air and oxidize (Figure 22.2.10).

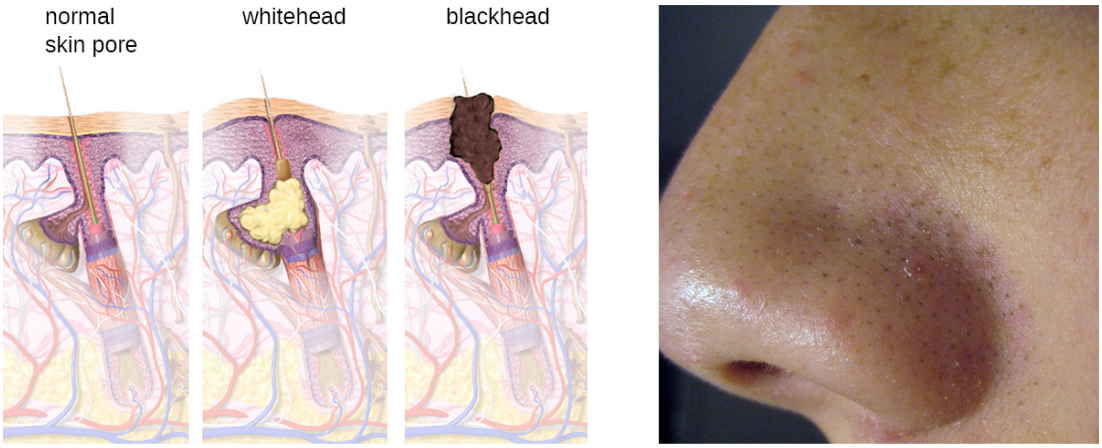


Figure 22.2.10: (a) Acne is characterized by whitehead and blackhead comedones that result from clogged hair follicles. (b) Blackheads, visible as black spots on the skin, have a dark appearance due to the oxidation of lipids in sebum via exposure to the air. (credit a: modification of work by Bruce Blaus)

Often comedones lead to infection by *Propionibacterium acnes*, a gram-positive, non-spore-forming, aerotolerant anaerobic bacillus found on skin that consumes components of sebum. *P. acnes* secretes enzymes that damage the hair follicle, causing inflammatory lesions that may include papules, pustules, nodules, or pseudocysts, depending on their size and severity.

Treatment of acne depends on the severity of the case. There are multiple ways to grade acne severity, but three levels are usually considered based on the number of comedones, the number of inflammatory lesions, and the types of lesions. Mild acne is treated with topical agents that may include salicylic acid (which helps to remove old skin cells) or retinoids (which have multiple mechanisms, including the reduction of inflammation). Moderate acne may be treated with antibiotics (erythromycin, clindamycin), acne creams (e.g., benzoyl peroxide), and hormones. Severe acne may require treatment using strong medications such as isotretinoin (a retinoid that reduces oil buildup, among other effects, but that also has serious side effects such as photosensitivity). Other treatments, such as phototherapy and laser therapy to kill bacteria and possibly reduce oil production, are also sometimes used.

? Exercise 22.2.5

What is the role of *Propionibacterium acnes* in causing acne?

Clinical Focus: Resolution

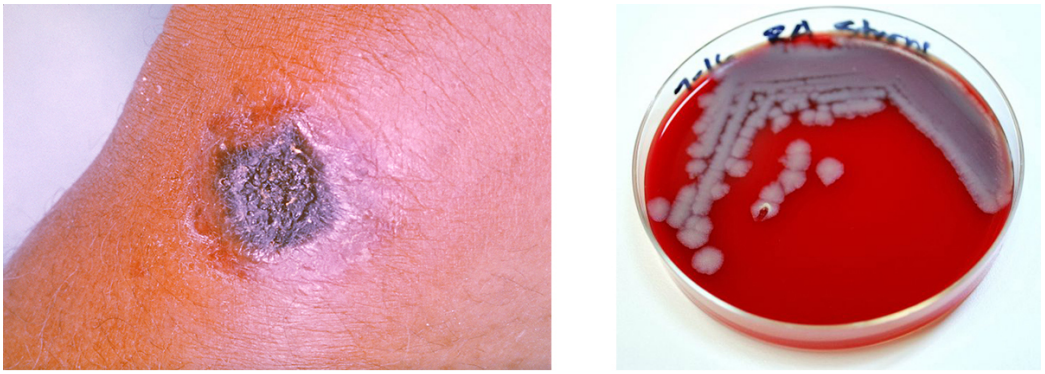
Sam uses the topical antibiotic over the weekend to treat his wound, but he does not see any improvement. On Monday, the doctor calls to inform him that the results from his laboratory tests are in. The tests show evidence of both *Staphylococcus* and *Streptococcus* in his wound. The bacterial species were confirmed using several tests. A passive agglutination test confirmed the presence of *S. aureus*. In this type of test, latex beads with antibodies cause agglutination when *S. aureus* is present. *Streptococcus pyogenes* was confirmed in the wound based on bacitracin (0.04 units) susceptibility as well as latex agglutination tests specific for *S. pyogenes*.

Because many strains of *S. aureus* are resistant to antibiotics, the doctor had also requested an antimicrobial susceptibility test (AST) at the same time the specimen was submitted for identification. The results of the AST indicated no drug resistance for the *Streptococcus* spp.; the *Staphylococcus* spp. showed resistance to several common antibiotics, but were susceptible to cefoxitin and oxacillin. Once Sam began to use these new antibiotics, the infection resolved within a week and the lesion healed.

Anthrax

The zoonotic disease anthrax is caused by *Bacillus anthracis*, a gram-positive, endospore-forming, facultative anaerobe. Anthrax mainly affects animals such as sheep, goats, cattle, and deer, but can be found in humans as well. Sometimes called wool sorter's disease, it is often transmitted to humans through contact with infected animals or animal products, such as wool or hides. However, exposure to *B. anthracis* can occur by other means, as the endospores are widespread in soils and can survive for long periods of time, sometimes for hundreds of years.

The vast majority of anthrax cases (95–99%) occur when anthrax endospores enter the body through abrasions of the skin.[3] This form of the disease is called cutaneous anthrax. It is characterized by the formation of a nodule on the skin; the cells within the nodule die, forming a black eschar, a mass of dead skin tissue (Figure **22.2.11**). The localized infection can eventually lead to bacteremia and septicemia. If untreated, cutaneous anthrax can cause death in 20% of patients.[4] Once in the skin tissues, *B. anthracis* endospores germinate and produce a capsule, which prevents the bacteria from being phagocytized, and two binary exotoxins that cause edema and tissue damage. The first of the two exotoxins consists of a combination of protective antigen (PA) and an enzymatic lethal factor (LF), forming lethal toxin (LeTX). The second consists of protective antigen (PA) and an edema factor (EF), forming edema toxin (EdTX).



(a) (b)

Figure **22.2.11**: (a) Cutaneous anthrax is an infection of the skin by *B. anthracis*, which produces tissue-damaging exotoxins. Dead tissues accumulating in this nodule have produced a small black eschar. (b) Colonies of *B. anthracis* grown on sheep's blood agar. (credit a, b: modification of work by Centers for Disease Control and Prevention)

Less commonly, anthrax infections can be initiated through other portals of entry such as the digestive tract (gastrointestinal anthrax) or respiratory tract (pulmonary anthrax or inhalation anthrax). Typically, cases of noncutaneous anthrax are more difficult to treat than the cutaneous form. The mortality rate for gastrointestinal anthrax can be up to 40%, even with treatment. Inhalation anthrax, which occurs when anthrax spores are inhaled, initially causes influenza-like symptoms, but mortality rates are approximately 45% in treated individuals and 85% in those not treated. A relatively new form of the disease, injection anthrax, has been reported in Europe in intravenous drug users; it occurs when drugs are contaminated with *B. anthracis*. Patients with injection

anthrax show signs and symptoms of severe soft tissue infection that differ clinically from cutaneous anthrax. This often delays diagnosis and treatment, and leads to a high mortality rate.[5]

B. anthracis colonies on blood agar have a rough texture and serrated edges that eventually form an undulating band (Figure **22.2.11**). Broad spectrum antibiotics such as penicillin, erythromycin, and tetracycline are often effective treatments.

Unfortunately, *B. anthracis* has been used as a biological weapon and remains on the United Nations' list of potential agents of bioterrorism.[6] Over a period of several months in 2001, a number of letters were mailed to members of the news media and the United States Congress. As a result, 11 individuals developed cutaneous anthrax and another 11 developed inhalation anthrax. Those infected included recipients of the letters, postal workers, and two other individuals. Five of those infected with pulmonary anthrax died. The anthrax spores had been carefully prepared to aerosolize, showing that the perpetrator had a high level of expertise in microbiology.[7]

A vaccine is available to protect individuals from anthrax. However, unlike most routine vaccines, the current anthrax vaccine is unique in both its formulation and the protocols dictating who receives it.[8] The vaccine is administered through five intramuscular injections over a period of 18 months, followed by annual boosters. The US Food and Drug Administration (FDA) has only approved administration of the vaccine prior to exposure for at-risk adults, such as individuals who work with anthrax in a laboratory, some individuals who handle animals or animal products (e.g., some veterinarians), and some members of the United States military. The vaccine protects against cutaneous and inhalation anthrax using cell-free filtrates of microaerophilic cultures of an avirulent, nonencapsulated strain of *B. anthracis*.[9] The FDA has not approved the vaccine for routine use *after* exposure to anthrax, but if there were ever an anthrax emergency in the United States, patients could be given anthrax vaccine after exposure to help prevent disease.

? Exercise 22.2.6

What is the characteristic feature of a cutaneous anthrax infection?

Bacterial Infections of the Skin

Bacterial infections of the skin can cause a wide range of symptoms and syndromes, ranging from the superficial and relatively harmless to the severe and even fatal. Most bacterial skin infections can be diagnosed by culturing the bacteria and treated with antibiotics. Antimicrobial susceptibility testing is also often necessary because many strains of bacteria have developed antibiotic resistance. Figure **22.2.12** summarizes the characteristics of some common bacterial skin infections.

Bacterial Infections of the Skin				
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Antimicrobial Drugs**
Acne	*Propionibacterium acnes*	Comedones (whiteheads, blackheads); papules, pustules, nodules, or pseudocysts	Not transmissible; clogged pores become infected by normal skin microbiota (*P. acnes*)	Erythromycin, clindamycin
Anthrax (cutaneous)	*Bacillus anthracis*	Eschar at site of infection; may lead to septicemia and can be fatal	Entry of *B. anthracis* endospores through cut or abrasion	Penicillin, erythromycin, or tetracycline
Cellulitis	*Streptococcus pyogenes*	Localized inflammation of dermis and hypodermis; skin red, warm, and painful to the touch	Entry of *S. pyogenes* through cut or abrasion	Oral or intravenous antibiotics (e.g., penicillin)
Erysipelas	*S. pyogenes*	Inflamed, swollen patch of skin, often on face; may be suppurative	Entry of *S. pyogenes* through cut or abrasion	Oral or intravenous antibiotics (e.g., penicillin)
Erythema nodosum	*S. pyogenes*	Small red nodules, often on shins	Associated with other streptococcal infection	None or anti-inflammatory drugs for severe cases
Impetigo	*Staphylococcus aureus, S. pyogenes*	Vesicles, pustules, and sometimes bullae around nose and mouth	Highly contagious, especially via contact	Topical or oral antibiotics
Necrotizing fasciitis	*S. pyogenes, Klebsiella, Clostridium,* others	Infection of fascia and rapidly spreading tissue death; can lead to septic shock and death	Entry of bacteria through cut or abrasion	Intravenous broad-spectrum antibiotics
Otitis externa	*Pseudomonas aeruginosa*	Itching, redness, discomfort of ear canal, progressing to fever, pain, swelling	*P. aeruginosa* enters ear canal via pool or other water	Acidic ear drops with antibiotics, antifungals, steroids
Staphylococcal scalded skin syndrome (SSSS)	*S. aureus*	Erythema and severe peeling of skin	Infection of skin and mucous membranes, especially in children	Intravenous antibiotics, fluid therapy
Wound infections	*P. aeruginosa,* others	Formation of biofilm in or on wound	Exposure of wound to microbes in environment; poor wound hygiene	Polymyxin B, gentamicin, fluoroquinolones, topical anti-biofilm agents

Figure **22.2.12**: Bacterial infections of the skin

Bacterial Conjunctivitis

Like the skin, the surface of the eye comes in contact with the outside world and is somewhat prone to infection by bacteria in the environment. Bacterial conjunctivitis (pinkeye) is a condition characterized by inflammation of the conjunctiva, often accompanied by a discharge of sticky fluid (described as acute purulent conjunctivitis) (Figure **22.2.13**). Conjunctivitis can affect one eye or both, and it usually does not affect vision permanently. Bacterial conjunctivitis is most commonly caused by *Haemophilus influenzae*, but can also be caused by other species such as *Moraxella catarrhalis*, *S. pneumoniae*, and *S. aureus*. The causative agent may be identified using bacterial cultures, Gram stain, and diagnostic biochemical, antigenic, or nucleic acid profile tests of the isolated pathogen. Bacterial conjunctivitis is very contagious, being transmitted via secretions from infected individuals, but it is also self-limiting. Bacterial conjunctivitis usually resolves in a few days, but topical antibiotics are sometimes prescribed. Because this condition is so contagious, medical attention is recommended whenever it is suspected. Individuals who use contact lenses should discontinue their use when conjunctivitis is suspected. Certain symptoms, such as blurred vision, eye pain, and light sensitivity, can be associated with serious conditions and require medical attention.

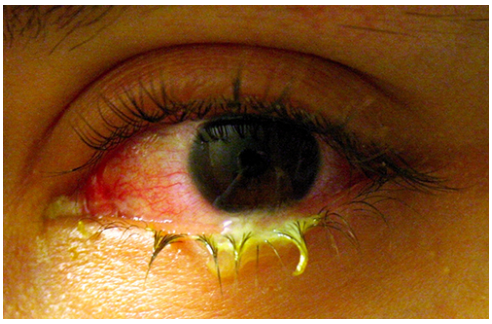


Figure **22.2.13**: Acute, purulent, bacterial conjunctivitis causes swelling and redness in the conjunctiva, the membrane lining the whites of the eyes and the inner eyelids. It is often accompanied by a yellow, green, or white discharge, which can dry and become encrusted on the eyelashes. (credit: "Tanalai"/Wikimedia Commons)

Neonatal Conjunctivitis

Newborns whose mothers have certain sexually transmitted infections are at risk of contracting ophthalmia neonatorum or inclusion conjunctivitis, which are two forms of neonatal conjunctivitis contracted through exposure to pathogens during passage through the birth canal. Gonococcal ophthalmia neonatorum is caused by *Neisseria gonorrhoeae*, the bacterium that causes the STD gonorrhea (Figure **22.2.14**). Inclusion (chlamydial) conjunctivitis is caused by *Chlamydia trachomatis*, the anaerobic, obligate, intracellular parasite that causes the STD chlamydia.

To prevent gonoccocal ophthalmia neonatorum, silver nitrate ointments were once routinely applied to all infants' eyes shortly after birth; however, it is now more common to apply antibacterial creams or drops, such as erythromycin. Most hospitals are required by law to provide this preventative treatment to all infants, because conjunctivitis caused by *N. gonorrhoeae*, *C. trachomatis*, or other bacteria acquired during a vaginal delivery can have serious complications. If untreated, the infection can spread to the cornea, resulting in ulceration or perforation that can cause vision loss or even permanent blindness. As such, neonatal conjunctivitis is treated aggressively with oral or intravenous antibiotics to stop the spread of the infection. Causative agents of inclusion conjunctivitis may be identified using bacterial cultures, Gram stain, and diagnostic biochemical, antigenic, or nucleic acid profile tests.

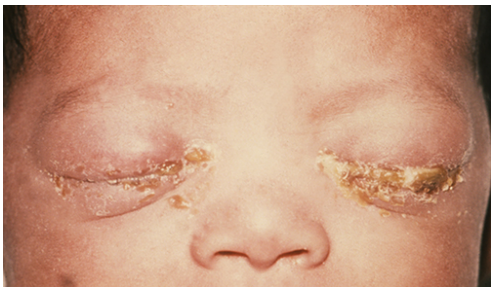


Figure **22.2.14**: A newborn suffering from gonoccocal opthalmia neonatorum. Left untreated, purulent discharge can scar the cornea, causing loss of vision or permanent blindness. (credit: Centers for Disease Control and Prevention)

? Exercise 22.2.7

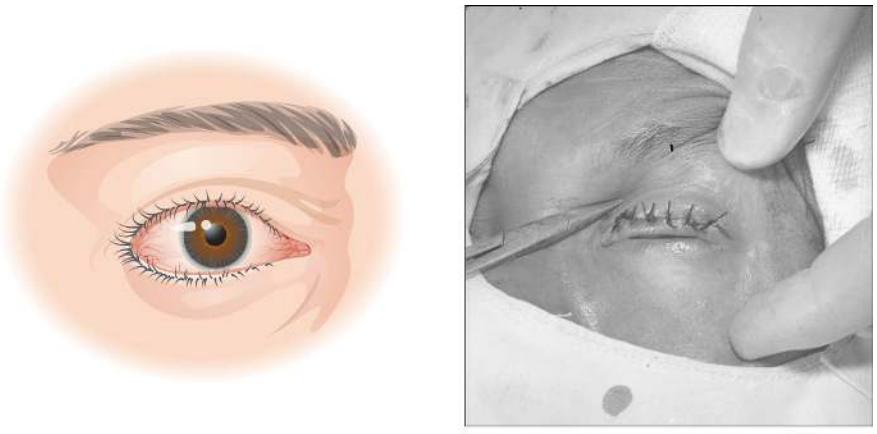
Compare and contrast bacterial conjunctivitis with neonatal conjunctivitis.

Trachoma

Trachoma, or granular conjunctivitis, is a common cause of preventable blindness that is rare in the United States but widespread in developing countries, especially in Africa and Asia. The condition is caused by the same species that causes neonatal inclusion conjunctivitis in infants, *Chlamydia trachomatis*. *C. trachomatis* can be transmitted easily through fomites such as contaminated towels, bed linens, and clothing and also by direct contact with infected individuals. *C. trachomatis* can also be spread by flies that transfer infected mucous containing *C. trachomatis* from one human to another.

Infection by *C. trachomatis* causes chronic conjunctivitis, which leads to the formation of necrotic follicles and scarring in the upper eyelid. The scars turn the eyelashes inward (a condition known as trichiasis) and mechanical abrasion of the cornea leads to

blindness (Figure 22.2.15). Antibiotics such as azithromycin are effective in treating trachoma, and outcomes are good when the disease is treated promptly. In areas where this disease is common, large public health efforts are focused on reducing transmission by teaching people how to avoid the risks of the infection.



(a) (b)

Figure 22.2.15: (a) If trachoma is not treated early with antibiotics, scarring on the eyelid can lead to trichiasis, a condition in which the eyelashes turn inward. (b) Trichiasis leads to blindness if not corrected by surgery, as shown here. (credit b: modification of work by Otis Historical Archives National Museum of Health & Medicine)

? Exercise 22.2.8

Why is trachoma rare in the United States?

SAFE Eradication of Trachoma

Though uncommon in the United States and other developed nations, trachoma is the leading cause of preventable blindness worldwide, with more than 4 million people at immediate risk of blindness from trichiasis. The vast majority of those affected by trachoma live in Africa and the Middle East in isolated rural or desert communities with limited access to clean water and sanitation. These conditions provide an environment conducive to the growth and spread of *Chlamydia trachomatis*, the bacterium that causes trachoma, via wastewater and eye-seeking flies.

In response to this crisis, recent years have seen major public health efforts aimed at treating and preventing trachoma. The Alliance for Global Elimination of Trachoma by 2020 (GET 2020), coordinated by the World Health Organization (WHO), promotes an initiative dubbed “SAFE,” which stands for “Surgery, Antibiotics, Facial cleanliness, and Environmental improvement.” The Carter Center, a charitable, nongovernment organization led by former US President Jimmy Carter, has partnered with the WHO to promote the SAFE initiative in six of the most critically impacted nations in Africa. Through its Trachoma Control Program, the Carter Center trains and equips local surgeons to correct trichiasis and distributes antibiotics to treat trachoma. The program also promotes better personal hygiene through health education and improves sanitation by funding the construction of household latrines. This reduces the prevalence of open sewage, which provides breeding grounds for the flies that spread trachoma.

Bacterial Keratitis

Keratitis can have many causes, but bacterial keratitis is most frequently caused by *Staphylococcus epidermidis*and/or *Pseudomonas aeruginosa*. Contact lens users are particularly at risk for such an infection because *S. epidermidis* and *P. aeruginosa* both adhere well to the surface of the lenses. Risk of infection can be greatly reduced by proper care of contact lenses and avoiding wearing lenses overnight. Because the infection can quickly lead to blindness, prompt and aggressive treatment with antibiotics is important. The causative agent may be identified using bacterial cultures, Gram stain, and diagnostic biochemical, antigenic, or nucleic acid profile tests of the isolated pathogen.

? Exercise 22.2.9

Why are contact lens wearers at greater risk for developing keratitis?

Biofilms and Infections of the Skin and Eyes

When treating bacterial infections of the skin and eyes, it is important to consider that few such infections can be attributed to a single pathogen. While biofilms may develop in other parts of the body, they are especially relevant to skin infections (such as those caused by *S. aureus* or *P. aeruginosa*) because of their prevalence in chronic skin wounds. Biofilms develop when bacteria (and sometimes fungi) attach to a surface and produce extracellular polymeric substances (EPS) in which cells of multiple organisms may be embedded. When a biofilm develops on a wound, it may interfere with the natural healing process as well as diagnosis and treatment.

Because biofilms vary in composition and are difficult to replicate in the lab, they are still not thoroughly understood. The extracellular matrix of a biofilm consists of polymers such as polysaccharides, extracellular DNA, proteins, and lipids, but the exact makeup varies. The organisms living within the extracellular matrix may include familiar pathogens as well as other bacteria that do not grow well in cultures (such as numerous obligate anaerobes). This presents challenges when culturing samples from infections that involve a biofilm. Because only some species grow *in vitro*, the culture may contain only a subset of the bacterial species involved in the infection.

Biofilms confer many advantages to the resident bacteria. For example, biofilms can facilitate attachment to surfaces on or in the host organism (such as wounds), inhibit phagocytosis, prevent the invasion of neutrophils, and sequester host antibodies. Additionally, biofilms can provide a level of antibiotic resistance not found in the isolated cells and colonies that are typical of laboratory cultures. The extracellular matrix provides a physical barrier to antibiotics, shielding the target cells from exposure. Moreover, cells within a biofilm may differentiate to create subpopulations of dormant cells called persister cells. Nutrient limitations deep within a biofilm add another level of resistance, as stress responses can slow metabolism and increase drug resistance.

Bacterial Infections of the Eyes

A number of bacteria are able to cause infection when introduced to the mucosa of the eye. In general, bacterial eye infections can lead to inflammation, irritation, and discharge, but they vary in severity. Some are typically short-lived, and others can become chronic and lead to permanent eye damage. Prevention requires limiting exposure to contagious pathogens. When infections do occur, prompt treatment with antibiotics can often limit or prevent permanent damage. Figure **22.2.16** summarizes the characteristics of some common bacterial infections of the eyes.

Bacterial Infections of the Eyes				
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Antimicrobial Drugs**
Acute bacterial conjunctivitis	*Haemophilus influenzae*	Inflammation of conjunctiva with purulent discharge	Exposure to secretions from infected individuals	Broad-spectrum topical antibiotics
Bacterial keratitis	*Staphylococcus epidermidis, Pseudomonas aeruginosa*	Redness and irritation of eye, blurred vision, sensitivity to light; progressive corneal scarring, which can lead to blindness	Exposure to pathogens on contaminated contact lenses	Antibiotic eye drops (e.g., with fluoroquinolones)
Neonatal conjunctivitis	*Chlamydia trachomatis, Neisseria gonorrhoeae*	Inflammation of conjunctiva, purulent discharge, scarring and perforation of cornea; may lead to blindness	Neonate exposed to pathogens in birth canal of mother with chlamydia or gonorrhea	Erythromycin
Trachoma (granular conjunctivitis)	*C. trachomatis*	Chronic conjunctivitis, trichiasis, scarring, blindness	Contact with infected individuals or contaminated fomites; transmission by eye-seeking flies	Azithromycin

Figure **22.2.16**: Bacterial infections of the eyes

Key Concepts and Summary

- *Staphylococcus* and *Streptococcus* cause many different types of skin infections, many of which occur when bacteria breach the skin barrier through a cut or wound.
- *S. aureus* are frequently associated with purulent skin infections that manifest as **folliculitis**, **furuncles**, or **carbuncles**. *S. aureus* is also a leading cause of staphylococcal scalded skin syndrome (SSSS).
- *S. aureus* is generally drug resistant and current MRSA strains are resistant to a wide range of antibiotics.
- Community-acquired and hospital-acquired staphyloccocal infections are an ongoing problem because many people are asymptomatic carriers.
- **Group A streptococci (GAS)**, *S. pyogenes*, is often responsible for cases of **cellulitis**, **erysipelas**, and **erythema nosodum**. GAS are also one of many possible causes of **necrotizing fasciitis**.
- *P. aeruginosa* is often responsible for infections of the skin and eyes, including wound and burn infections, **hot tub rash**, **otitis externa**, and bacterial **keratitis**.
- **Acne** is a common skin condition that can become more inflammatory when *Propionibacterium acnes* infects hair follicles and pores clogged with dead skin cells and sebum.
- Cutaneous **anthrax** occurs when *Bacillus anthracis* breaches the skin barrier. The infection results in a localized black **eschar** on skin. Anthrax can be fatal if *B. anthracis* spreads to the bloodstream.
- Common bacterial **conjunctivitis** is often caused by *Haemophilus influenzae* and usually resolves on its own in a few days. More serious forms of conjunctivitis include gonococcal **ophthalmia neonatorum**, **inclusion conjunctivitis** (chlamydial), and **trachoma**, all of which can lead to blindness if untreated.
- **Keratitis** is frequently caused by *Staphylococcus epidermidis* and/or *Pseudomonas aeruginosa*, especially among contact lens users, and can lead to blindness.
- Biofilms complicate the treatment of wound and eye infections because pathogens living in biofilms can be difficult to treat and eliminate.

Footnotes

1. 1 Starr, C.R. and Engelberg N.C. “Role of Hyaluronidase in Subcutaneous Spread and Growth of Group A Streptococcus.” *Infection and Immunity* 2006(7:1): 40–48. doi: 10.1128/IAI.74.1.40-48.2006.
2. 2 Nuwayhid, Z.B., Aronoff, D.M., and Mulla, Z.D.. “Blunt Trauma as a Risk Factor for Group A Streptococcal Necrotizing Fasciitis.” *Annals of Epidemiology* (2007) 17:878–881.

3. 3 Shadomy, S.V., Traxler, R.M., and Marston, C.K. “Infectious Diseases Related to Travel: Anthrax” 2015. Centers for Disease Control and Prevention. wwwnc.cdc.gov/travel/yellowbo...travel/anthrax. Accessed Sept 14, 2016.
4. 4 US FDA. “Anthrax.” 2015. www.fda.gov/BiologicsBloodVac.../ucm061751.htm. Accessed Sept 14, 2016.
5. 5 Berger, T., Kassirer, M., and Aran, A.A.. “Injectional Anthrax—New Presentation of an Old Disease.” *Euro Surveillance* 19 (2014) 32. http://www.ncbi.nlm.nih.gov/pubmed/25139073. Accessed Sept 14, 2016.
6. 6 United Nations Office at Geneva. “What Are Biological and Toxin Weapons?” http://www.unog.ch/80256EE600585943/...2571860035A6DB?. Accessed Sept 14, 2016.
7. 7 Federal Bureau of Investigation. “Famous Cases and Criminals: Amerithrax or Anthrax Investigation.” www.fbi.gov/history/famous-c...-investigation. Accessed Sept 14, 2016.
8. 8 Centers for Disease Control and Prevention. “Anthrax: Medical Care: Prevention: Antibiotics.” www.cdc.gov/anthrax/medical-c...revention.html. Accessed Sept 14, 2016.
9. 9 Emergent Biosolutions. AVA (BioThrax) vaccine package insert (Draft). Nov 2015. www.fda.gov/downloads/biologi...ductsblas/ucm0

This page titled 22.2: Bacterial Infections of the Skin and Eyes is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **21.2: Bacterial Infections of the Skin and Eyes** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

22.3: Viral Infections of the Skin and Eyes

Learning Objectives

- Identify the most common viruses associated with infections of the skin and eyes
- Compare the major characteristics of specific viral diseases affecting the skin and eyes

Until recently, it was thought that the normal microbiota of the body consisted primarily of bacteria and some fungi. However, in addition to bacteria, the skin is colonized by viruses, and recent studies suggest that Papillomaviridae, Polyomaviridae and Circoviridae also contribute to the normal skin microbiota. However, some viruses associated with skin are pathogenic, and these viruses can cause diseases with a wide variety of presentations.

Numerous types of viral infections cause rashes or lesions on the skin; however, in many cases these skin conditions result from infections that originate in other body systems. In this chapter, we will limit the discussion to viral skin infections that use the skin as a portal of entry. Later chapters will discuss viral infections such as chickenpox, measles, and rubella—diseases that cause skin rashes but invade the body through portals of entry other than the skin.

Papillomas

Papillomas (warts) are the expression of common skin infections by human papillomavirus (HPV) and are transmitted by direct contact. There are many types of HPV, and they lead to a variety of different presentations, such as common warts, plantar warts, flat warts, and filiform warts. HPV can also cause sexually-transmitted genital warts, which will be discussed in Urogenital System Infections. Vaccination is available for some strains of HPV.

Common warts tend to develop on fingers, the backs of hands, and around nails in areas with broken skin. In contrast, plantar warts (also called foot warts) develop on the sole of the foot and can grow inwards, causing pain and pressure during walking. Flat warts can develop anywhere on the body, are often numerous, and are relatively smooth and small compared with other wart types. Filiform warts are long, threadlike warts that grow quickly.

In some cases, the immune system may be strong enough to prevent warts from forming or to eradicate established warts. However, treatment of established warts is typically required. There are many available treatments for warts, and their effectiveness varies. Common warts can be frozen off with liquid nitrogen. Topical applications of salicylic acidmay also be effective. Other options are electrosurgery (burning), curettage (cutting), excision, painting with cantharidin (which causes the wart to die so it can more easily be removed), laser treatments, treatment with bleomycin, chemical peels, and immunotherapy (Figure 22.3.1).



(a) (b)

Figure 22.3.1: Warts can vary in shape and in location. (a) Multiple plantar warts have grown on this toe. (b) A filiform wart has grown on this eyelid.

Oral Herpes

Another common skin virus is herpes simplex virus (HSV). HSV has historically been divided into two types, HSV-1 and HSV-2. HSV-1 is typically transmitted by direct oral contact between individuals, and is usually associated with oral herpes. HSV-2 is

usually transmitted sexually and is typically associated with genital herpes. However, both HSV-1 and HSV-2 are capable of infecting any mucous membrane, and the incidence of genital HSV-1 and oral HSV-2 infections has been increasing in recent years. In this chapter, we will limit our discussion to infections caused by HSV-1; HSV-2 and genital herpes will be discussed in Urogenital System Infections.

Infection by HSV-1 commonly manifests as cold sores or fever blisters, usually on or around the lips (Figure **22.3.2**). HSV-1 is highly contagious, with some studies suggesting that up to 65% of the US population is infected; however, many infected individuals are asymptomatic.[1] Moreover, the virus can be latent for long periods, residing in the trigeminal nerve ganglia between recurring bouts of symptoms. Recurrence can be triggered by stress or environmental conditions (systemic or affecting the skin). When lesions are present, they may blister, break open, and crust. The virus can be spread through direct contact, even when a patient is asymptomatic.

While the lips, mouth, and face are the most common sites for HSV-1 infections, lesions can spread to other areas of the body. Wrestlers and other athletes involved in contact sports may develop lesions on the neck, shoulders, and trunk. This condition is often called herpes gladiatorum. Herpes lesions that develop on the fingers are often called herpetic whitlow.

HSV-1 infections are commonly diagnosed from their appearance, although laboratory testing can confirm the diagnosis. There is no cure, but antiviral medications such as acyclovir, penciclovir, famciclovir, and valacyclovir are used to reduce symptoms and risk of transmission. Topical medications, such as creams with *n*-docosanol and penciclovir, can also be used to reduce symptoms such as itching, burning, and tingling.

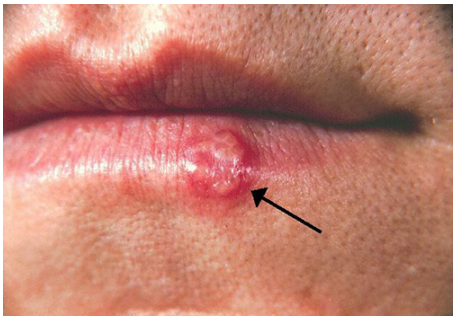


Figure **22.3.2**: This cold sore was caused by HSV-1. (credit: Centers for Disease Control and Prevention)

? Exercise 22.3.1

What are the most common sites for the appearance of herpetic lesions?

Roseola and Fifth Disease

The viral diseases roseola and fifth disease are somewhat similar in terms of their presentation, but they are caused by different viruses. Roseola, sometimes called roseola infantum or exanthem subitum (“sudden rash”), is a mild viral infection usually caused by human herpesvirus-6 (HHV-6) and occasionally by HHV-7. It is spread via direct contact with the saliva or respiratory secretions of an infected individual, often through droplet aerosols. Roseola is very common in children, with symptoms including a runny nose, a sore throat, and a cough, along with (or followed by) a high fever (39.4 ºC). About three to five days after the fever subsides, a rash may begin to appear on the chest and abdomen. The rash, which does not cause discomfort, initially forms characteristic macules that are flat or papules that are firm and slightly raised; some macules or papules may be surrounded by a white ring. The rash may eventually spread to the neck and arms, and sometimes continues to spread to the face and legs. The diagnosis is generally made based upon observation of the symptoms. However, it is possible to perform serological tests to confirm the diagnosis. While treatment may be recommended to control the fever, the disease usually resolves without treatment within a week after the fever develops. For individuals at particular risk, such as those who are immunocompromised, the antiviral medication ganciclovir may be used.

Fifth disease (also known as erythema infectiosum) is another common, highly contagious illness that causes a distinct rash that is critical to diagnosis. Fifth disease is caused by parvovirus B19, and is transmitted by contact with respiratory secretions from an infected individual. Infection is more common in children than adults. While approximately 20% of individuals will be

asymptomatic during infection,[2] others will exhibit cold-like symptoms (headache, fever, and upset stomach) during the early stages when the illness is most infectious. Several days later, a distinct red facial rash appears, often called “slapped cheek” rash (Figure **22.3.3**). Within a few days, a second rash may appear on the arms, legs, chest, back, or buttocks. The rash may come and go for several weeks, but usually disappears within seven to twenty-one days, gradually becoming lacy in appearance as it recedes.

In children, the disease usually resolves on its own without medical treatment beyond symptom relief as needed. Adults may experience different and possibly more serious symptoms. Many adults with fifth disease do not develop any rash, but may experience joint pain and swelling that lasts several weeks or months. Immunocompromised individuals can develop severe anemia and may need blood transfusions or immune globulin injections. While the rash is the most important component of diagnosis (especially in children), the symptoms of fifth disease are not always consistent. Serological testing can be conducted for confirmation.



(a)



(b)

Figure **22.3.3**: (a) Roseola, a mild viral infection common in young children, generally begins with symptoms similar to a cold, followed by a pink, patchy rash that starts on the trunk and spreads outward. (b) Fifth disease exhibits similar symptoms in children, except for the distinctive “slapped cheek” rash that originates on the face.

? Exercise 22.3.2

Identify at least one similarity and one difference between roseola and fifth disease.

Viral Conjunctivitis

Like bacterial conjunctivitis viral infections of the eye can cause inflammation of the conjunctiva and discharge from the eye. However, viral conjunctivitis tends to produce a discharge that is more watery than the thick discharge associated with bacterial conjunctivitis. The infection is contagious and can easily spread from one eye to the other or to other individuals through contact with eye discharge.

Viral conjunctivitis is commonly associated with colds caused by adenoviruses; however, other viruses can also cause conjunctivitis. If the causative agent is uncertain, eye discharge can be tested to aid in diagnosis. Antibiotic treatment of viral conjunctivitis is ineffective, and symptoms usually resolve without treatment within a week or two.

Herpes Keratitis

Herpes infections caused by HSV-1 can sometimes spread to the eye from other areas of the body, which may result in keratoconjunctivitis. This condition, generally called herpes keratitis or herpetic keratitis, affects the conjunctiva and cornea, causing irritation, excess tears, and sensitivity to light. Deep lesions in the cornea may eventually form, leading to blindness. Because keratitis can have numerous causes, laboratory testing is necessary to confirm the diagnosis when HSV-1 is suspected; once confirmed, antiviral medications may be prescribed.

Viral Infections of the Skin and Eyes

A number of viruses can cause infections via direct contact with skin and eyes, causing signs and symptoms ranging from rashes and lesions to warts and conjunctivitis. All of these viral diseases are contagious, and while some are more common in children (fifth disease and roseola), others are prevalent in people of all ages (oral herpes, viral conjunctivitis, papillomas). In general, the best means of prevention is avoiding contact with infected individuals. Treatment may require antiviral medications; however, several of these conditions are mild and typically resolve without treatment. Figure **22.3.4** summarizes the characteristics of some common viral infections of the skin and eyes.

Viral Infections of the Skin and Eyes

Disease	Pathogen	Signs and Symptoms	Transmission	Antimicrobial Drugs
Fifth disease	Parvovirus B19	May have initial cold-like symptoms; “slapped cheek” rash	Highly contagious via respiratory secretions of infected individuals	None
Herpes keratitis	Herpes simplex virus 1 (HSV-1)	Inflammation of conjunctiva and cornea; irritation, excess tears, sensitivity to light; lesions in cornea leading to blindness	Direct eye contact with discharge from herpes lesions elsewhere in the body or from another infected individual	Acyclovir, ganciclovir, famiclovir, valacyclovir
Oral herpes	Herpes simplex virus 1 (HSV-1)	May cause initial systemic symptoms; cold sores	Highly contagious via direct contact with infected individuals	Acyclovir, penciclovir, famiclovir, valacyclovir
Papillomas	Human papillomavirus (HPV)	Common warts, plantar warts, flat warts, filiform warts, and others	Contact with infected individuals	Topical salicylic acid, cantharidin
Roseola (roseola infantum, exanthem subitum)	Human herpesvirus 6 (HHV-6), human herpesvirus 7 (HHV-7)	Initial cold-like symptoms with high fever, followed by a macular or papular rash three to five days later	Spread by viral and respiratory secretions of infected individuals	Typically none; ganciclovir for immunocompromised patients
Viral conjunctivitis	Adenoviruses and others	Inflammation of the conjunctiva; watery, nonpurulent discharge	Associated with common cold; contagious via contact with eye discharge	None

Figure **22.3.4**: Viral infections of the skin and eyes

Key Concepts and Summary

- **Papillomas** (warts) are caused by human papillomaviruses.
- **Herpes simplex virus** (especially HSV-1) mainly causes **oral herpes**, but lesions can appear on other areas of the skin and mucous membranes.
- **Roseola** and **fifth disease** are common viral illnesses that cause skin rashes; roseola is caused by HHV-6 and HHV-7 while fifth disease is caused by parvovirus 19.
- **Viral conjunctivitis** is often caused by adenoviruses and may be associated with the common cold. **Herpes keratitis** is caused by herpesviruses that spread to the eye.

Footnotes

1. 1 Wald, A., and Corey, L. “Persistence in the Population: Epidemiology, Transmission.” In: A. Arvin, G. Campadelli-Fiume, E. Mocarski et al. *Human Herpesviruses: Biology, Therapy, and Immunoprophylaxis*. Cambridge: Cambridge University Press, 2007. www.ncbi.nlm.nih.gov/books/NBK47447/. Accessed Sept 14, 2016.

2. 2 Centers for Disease Control and Prevention. “Fifth Disease.” http://www.cdc.gov/parvovirusb19/fifth-disease.html. Accessed Sept 14, 2016.

This page titled 22.3: Viral Infections of the Skin and Eyes is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **21.3: Viral Infections of the Skin and Eyes** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

22.4: Mycoses of the Skin and Eyes

Learning Objectives

- Identify the most common fungal pathogens associated with cutaneous and subcutaneous mycoses
- Compare the major characteristics of specific fungal diseases affecting the skin

Many fungal infections of the skin involve fungi that are found in the normal skin microbiota. Some of these fungi can cause infection when they gain entry through a wound; others mainly cause opportunistic infections in immunocompromised patients. Other fungal pathogens primarily cause infection in unusually moist environments that promote fungal growth; for example, sweaty shoes, communal showers, and locker rooms provide excellent breeding grounds that promote the growth and transmission of fungal pathogens.

Fungal infections, also called mycoses, can be divided into classes based on their invasiveness. Mycoses that cause superficial infections of the epidermis, hair, and nails, are called cutaneous mycoses. Mycoses that penetrate the epidermis and the dermis to infect deeper tissues are called subcutaneous mycoses. Mycoses that spread throughout the body are called systemic mycoses.

Tineas

A group of cutaneous mycoses called tineas are caused by dermatophytes, fungal molds that require keratin, a protein found in skin, hair, and nails, for growth. There are three genera of dermatophytes, all of which can cause cutaneous mycoses: *Trichophyton*, *Epidermophyton*, and *Microsporum*. Tineas on most areas of the body are generally called ringworm, but tineas in specific locations may have distinctive names and symptoms (see Table **22.4.1** and Figure **22.4.1**). Keep in mind that these names—even though they are Latinized—refer to locations on the body, not causative organisms. Tineas can be caused by different dermatophytes in most areas of the body.

Table **22.4.1**: Tineas and locations

Some Common Tineas and Location on the Body	
Tinea corporis (ringworm)	Body
Tinea capitis (ringworm)	Scalp
Tinea pedis (athlete's foot)	Feet
Tinea barbae (barber's itch)	Beard
Tinea cruris (jock itch)	Groin
Tinea unguium (onychomycosis)	Toenails, fingernails



(a) (b) (c)

Figure **22.4.1**: Tineas are superficial cutaneous mycoses and are common. (a) Tinea barbae (barber's itch) occurs on the lower face. (b) Tinea pedis (athlete's foot) occurs on the feet, causing itching, burning, and dry, cracked skin between the toes. (c) A close-up view of tinea corporis (ringworm) caused by *Trichophyton mentagrophytes*. (credit a, c: modification of work by Centers for Disease Control and Prevention; credit b: modification of work by Al Hasan M, Fitzgerald SM, Saoudian M, Krishnaswamy G)

Dermatophytes are commonly found in the environment and in soils and are frequently transferred to the skin via contact with other humans and animals. Fungal spores can also spread on hair. Many dermatophytes grow well in moist, dark environments. For example, tinea pedis (athlete's foot) commonly spreads in public showers, and the causative fungi grow well in the dark, moist confines of sweaty shoes and socks. Likewise, tinea cruris (jock itch) often spreads in communal living environments and thrives in warm, moist undergarments.

Tineas on the body (tinea corporis) often produce lesions that grow radially and heal towards the center. This causes the formation of a red ring, leading to the misleading name of ringworm recall the Clinical Focus case in The Eukaryotes of Microbiology.

Several approaches may be used to diagnose tineas. A Wood's lamp (also called a black lamp) with a wavelength of 365 nm is often used. When directed on a tinea, the ultraviolet light emitted from the Wood's lamp causes the fungal elements (spores and hyphae) to fluoresce. Direct microscopic evaluation of specimens from skin scrapings, hair, or nails can also be used to detect fungi. Generally, these specimens are prepared in a wet mount using a potassium hydroxide solution (10%–20% aqueous KOH), which dissolves the keratin in hair, nails, and skin cells to allow for visualization of the hyphae and fungal spores. The specimens may be grown on Sabouraud dextrose CC (chloramphenicol/cyclohexamide), a selective agar that supports dermatophyte growth while inhibiting the growth of bacteria and saprophytic fungi (Figure **22.4.2**). Macroscopic colony morphology is often used to initially identify the genus of the dermatophyte; identification can be further confirmed by visualizing the microscopic morphology using either a slide culture or a sticky tape prep stained with lactophenol cotton blue.

Various antifungal treatments can be effective against tineas. Allylamine ointments that include terbinafine are commonly used; miconazole and clotrimazole are also available for topical treatment, and griseofulvin is used orally.

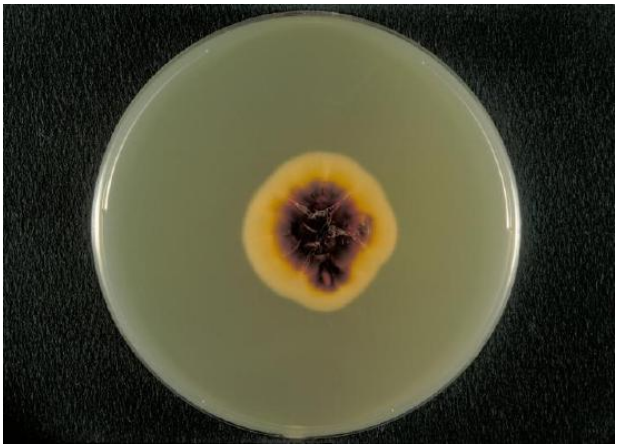


Figure **22.4.2**: To diagnose tineas, the dermatophytes may be grown on a Sabouraud dextrose CC agar plate. This culture contains a strain of *Trichophyton rubrum*, one of the most common causes of tineas on various parts of the body. (credit: Centers for Disease Control and Prevention)

? Exercise 22.4.1

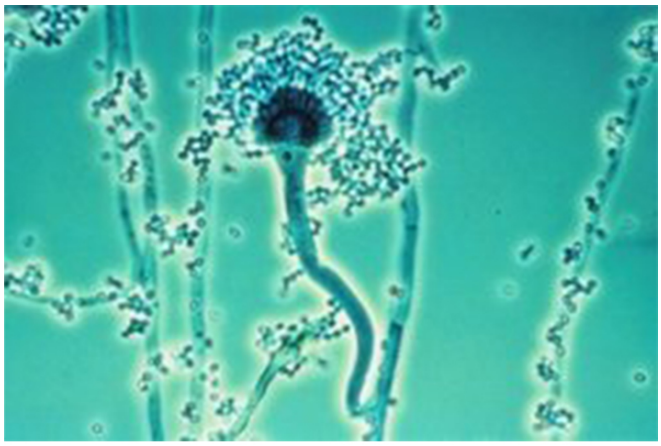
Why are tineas, caused by fungal molds, often called ringworm?

Cutaneous Aspergillosis

Another cause of cutaneous mycoses is *Aspergillus*, a genus consisting of molds of many different species, some of which cause a condition called aspergillosis. Primary cutaneous aspergillosis, in which the infection begins in the skin, is rare but does occur. More common is secondary cutaneous aspergillosis, in which the infection begins in the respiratory system and disseminates systemically. Both primary and secondary cutaneous aspergillosis result in distinctive eschars that form at the site or sites of infection (Figure **22.4.3**). Pulmonary aspergillosis will be discussed more thoroughly in Respiratory Mycoses).



(a)



(b)

Figure 22.4.3: (a) Eschar on a patient with secondary cutaneous aspergillosis. (b) Micrograph showing a conidiophore of *Aspergillus*. (credit a: modification of work by Santiago M, Martinez JH, Palermo C, Figueroa C, Torres O, Trinidad R, Gonzalez E, Miranda Mde L, Garcia M, Villamarzo G; credit b: modification of work by U.S. Department of Health and Human Services)

Primary cutaneous aspergillosis usually occurs at the site of an injury and is most often caused by *Aspergillus fumigatus* or *Aspergillus flavus*. It is usually reported in patients who have had an injury while working in an agricultural or outdoor environment. However, opportunistic infections can also occur in health-care settings, often at the site of intravenous catheters, venipuncture wounds, or in association with burns, surgical wounds, or occlusive dressing. After candidiasis, aspergillosis is the second most common hospital-acquired fungal infection and often occurs in immunocompromised patients, who are more vulnerable to opportunistic infections.

Cutaneous aspergillosis is diagnosed using patient history, culturing, histopathology using a skin biopsy. Treatment involves the use of antifungal medications such as voriconazole (preferred for invasive aspergillosis), itraconazole, and amphotericin B if itraconazole is not effective. For immunosuppressed individuals or burn patients, medication may be used and surgical or immunotherapy treatments may be needed.

? Exercise 22.4.2

Identify the sources of infection for primary and secondary cutaneous aspergillosis.

Candidiasis of the Skin and Nails

Candida albicans and other yeasts in the genus *Candida* can cause skin infections referred to as cutaneous candidiasis. *Candida* spp. are sometimes responsible for intertrigo, a general term for a rash that occurs in a skin fold, or other localized rashes on the skin. *Candida* can also infect the nails, causing them to become yellow and harden (Figure 22.4.4).



(a)



(b)



(c)

Figure 22.4.4: (a) This red, itchy rash is the result of cutaneous candidiasis, an opportunistic infection of the skin caused by the yeast *Candida albicans*. (b) Fungal infections of the nail (tinea unguium) can be caused by dermatophytes or *Candida* spp. The nail becomes yellow, brittle, and prone to breaking. This condition is relatively common among adults. (c) *C. albicans* growing on Sabouraud

dextrose agar. (credit a: modification of work by U.S. Department of Veterans Affairs; credit c: modification of work by Centers for Disease Control and Prevention)

Candidiasis of the skin and nails is diagnosed through clinical observation and through culture, Gram stain, and KOH wet mounts. Susceptibility testing for anti-fungal agents can also be done. Cutaneous candidiasis can be treated with topical or systemic azole antifungal medications. Because candidiasis can become invasive, patients suffering from HIV/AIDS, cancer, or other conditions that compromise the immune system may benefit from preventive treatment. Azoles, such as clotrimazole, econazole, fluconazole, ketoconazole, and miconazole; nystatin; terbinafine; and naftifine may be used for treatment. Long-term treatment with medications such as itraconazole or ketoconazole may be used for chronic infections. Repeat infections often occur, but this risk can be reduced by carefully following treatment recommendations, avoiding excessive moisture, maintaining good health, practicing good hygiene, and having appropriate clothing (including footwear).

Candida also causes infections in other parts of the body besides the skin. These include vaginal yeast infections (see Fungal Infections of the Reproductive System) and oral thrush (see Microbial Diseases of the Mouth and Oral Cavity).

? Exercise 22.4.3

What are the signs and symptoms of candidiasis of the skin and nails?

Sporotrichosis

Whereas cutaneous mycoses are superficial, subcutaneous mycoses can spread from the skin to deeper tissues. In temperate regions, the most common subcutaneous mycosis is a condition called sporotrichosis, caused by the fungus *Sporothrix schenkii* and commonly known as rose gardener's disease or rose thorn disease (recall Case in Point: Every Rose Has Its Thorn). Sporotrichosis is often contracted after working with soil, plants, or timber, as the fungus can gain entry through a small wound such as a thorn-prick or splinter. Sporotrichosis can generally be avoided by wearing gloves and protective clothing while gardening and promptly cleaning and disinfecting any wounds sustained during outdoor activities.

Sporothrix infections initially present as small ulcers in the skin, but the fungus can spread to the lymphatic system and sometimes beyond. When the infection spreads, nodules appear, become necrotic, and may ulcerate. As more lymph nodes become affected, abscesses and ulceration may develop over a larger area (often on one arm or hand). In severe cases, the infection may spread more widely throughout the body, although this is relatively uncommon.

Sporothrix infection can be diagnosed based upon histologic examination of the affected tissue. Its macroscopic morphology can be observed by culturing the mold on potato dextrose agar, and its microscopic morphology can be observed by staining a slide culture with lactophenol cotton blue. Treatment with itraconazole is generally recommended.

? Exercise 22.4.4

Describe the progression of a *Sporothrix schenkii* infection.

Mycoses of the Skin

Cutaneous mycoses are typically opportunistic, only able to cause infection when the skin barrier is breached through a wound. Tineas are the exception, as the dermatophytes responsible for tineas are able to grow on skin, hair, and nails, especially in moist conditions. Most mycoses of the skin can be avoided through good hygiene and proper wound care. Treatment requires antifungal medications. Figure 22.4.5 summarizes the characteristics of some common fungal infections of the skin.

Mycoses of the Skin				
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Antimicrobial Drugs**
Aspergillosis (cutaneous)	*Aspergillus fumigatus, Aspergillus flavus*	Distinctive eschars at site(s) of infection	Entry via wound (primary cutaneous aspergillosis) or via the respiratory system (secondary cutaneous aspergillosis); commonly a hospital-acquired infection	Itraconazole, voriconazole, amphotericin B
Candidiasis (cutaneous)	*Candida albicans*	Intertrigo, localized rash, yellowing of nails	Overgrowth of normal skin microbiota, especially in moist, dark areas	Azoles
Sporotrichosis (rose gardener's disease)	*Sporothrix schenkii*	Subcutaneous ulcers and abscesses; may spread to a large area, e.g., hand or arm	Entry via thorn prick or other wound	Itraconazole
Tineas	*Trichophyton* spp., *Epidermophyton* spp., *Microsporum* spp.	Itchy, ring-like lesions (ringworm) at sites of infection	Contact with dermatophytic fungi, especially in warm, moist environments conducive to fungal growth	Terbinafine, miconazole, clotrimazole, griseofulvin

Figure **22.4.5**: Mycoses of the skin

Key Concepts and Summary

- Mycoses can be cutaneous, subcutaneous, or systemic.
- Common cutaneous mycoses include tineas caused by dermatophytes of the genera Trichophyton, Epidermophyton, and Microsporum. Tinea corporis is called ringworm. Tineas on other parts of the body have names associated with the affected body part.
- Aspergillosis is a fungal disease caused by molds of the genus Aspergillus. Primary cutaneous aspergillosis enters through a break in the skin, such as the site of an injury or a surgical wound; it is a common hospital-acquired infection. In secondary cutaneous aspergillosis, the fungus enters via the respiratory system and disseminates systemically, manifesting in lesions on the skin.
- The most common subcutaneous mycosis is sporotrichosis (rose gardener's disease), caused by Sporothrix schenkii.
- Yeasts of the genus Candida can cause opportunistic infections of the skin called candidiasis, producing intertrigo, localized rashes, or yellowing of the nails.

This page titled 22.4: Mycoses of the Skin and Eyes is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **21.4: Mycoses of the Skin and Eyes** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

22.5: Protozoan and Helminthic Infections of the Eyes

Learning Objectives

- Identify two parasites that commonly cause infections of the skin and eyes
- Identify the major characteristics of specific parasitic diseases affecting the skin and eyes

Many parasitic protozoans and helminths use the skin or eyes as a portal of entry. Some may physically burrow into the skin or the mucosa of the eye; others breach the skin barrier by means of an insect bite. Still others take advantage of a wound to bypass the skin barrier and enter the body, much like other opportunistic pathogens. Although many parasites enter the body through the skin, in this chapter we will limit our discussion to those for which the skin or eyes are the primary site of infection. Parasites that enter through the skin but travel to a different site of infection will be covered in other chapters. In addition, we will limit our discussion to microscopic parasitic infections of the skin and eyes. Macroscopic parasites such as lice, scabies, mites, and ticks are beyond the scope of this text.

Acanthamoeba Infections

Acanthamoeba is a genus of free-living protozoan amoebae that are common in soils and unchlorinated bodies of fresh water. (This is one reason why some swimming pools are treated with chlorine.) The genus contains a few parasitic species, some of which can cause infections of the eyes, skin, and nervous system. Such infections can sometimes travel and affect other body systems. Skin infections may manifest as abscesses, ulcers, and nodules. When acanthamoebae infect the eye, causing inflammation of the cornea, the condition is called *Acanthamoeba* keratitis. Figure **22.5.1** illustrates the *Acanthamoeba* life cycle and various modes of infection.

While *Acanthamoeba* keratitis is initially mild, it can lead to severe corneal damage, vision impairment, or even blindness if left untreated. Similar to eye infections involving *P. aeruginosa*, *Acanthamoeba* poses a much greater risk to wearers of contact lenses because the amoeba can thrive in the space between contact lenses and the cornea. Prevention through proper contact lens care is important. Lenses should always be properly disinfected prior to use, and should never be worn while swimming or using a hot tub.

Acanthamoeba can also enter the body through other pathways, including skin wounds and the respiratory tract. It usually does not cause disease except in immunocompromised individuals; however, in rare cases, the infection can spread to the nervous system, resulting in a usually fatal condition called granulomatous amoebic encephalitis (GAE) (see Fungal and Parasitic Diseases of the Nervous System). Disseminated infections, lesions, and *Acanthamoeba* keratitis can be diagnosed by observing symptoms and examining patient samples under the microscope to view the parasite. Skin biopsies may be used.

Acanthamoeba keratitis is difficult to treat, and prompt treatment is necessary to prevent the condition from progressing. The condition generally requires three to four weeks of intensive treatment to resolve. Common treatments include topical antiseptics (e.g., polyhexamethylene biguanide, chlorhexidine, or both), sometimes with painkillers or corticosteroids (although the latter are controversial because they suppress the immune system, which can worsen the infection). Azoles are sometimes prescribed as well. Advanced cases of keratitis may require a corneal transplant to prevent blindness.

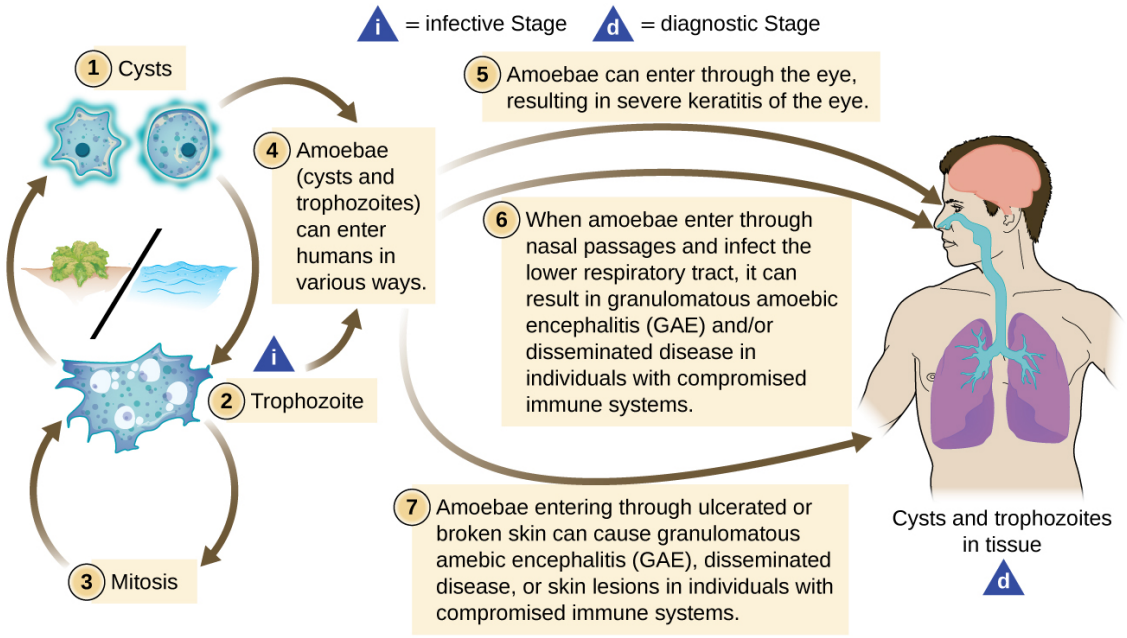


Figure 22.5.1: Acanthamoeba spp. are waterborne parasites very common in unchlorinated aqueous environments. As shown in this life cycle, *Acanthamoeba* cysts and trophozoites are both capable of entering the body through various routes, causing infections of the eye, skin, and central nervous system. (credit: modification of work by Centers for Disease Control and Prevention)



Acanthamoeba cyst (a) *Acanthamoeba* trophozoite (b) (c)

Figure 22.5.2: (a) An *Acanthamoeba* cyst. (b) An *Acanthamoeba* trophozoite (c) The eye of a patient with *Acanthamoeba* keratitis. The fluorescent color, which is due to sodium fluorescein application, highlights significant damage to the cornea and vascularization of the surrounding conjunctiva. (credit a: modification of work by Centers for Disease Control and Prevention; credit b, c: modification of work by Jacob Lorenzo-Morales, Naveed A Kahn and Julia Walochnik)

? Exercise 22.5.1

How are *Acanthamoeba* infections acquired?

Loiasis

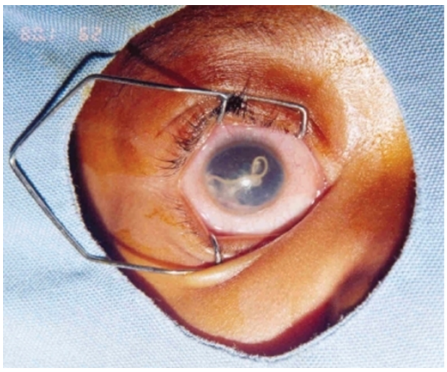
The helminth *Loa loa*, also known as the African eye worm, is a nematode that can cause loiasis, a disease endemic to West and Central Africa (Figure 22.5.3). The disease does not occur outside that region except when carried by travelers. There is evidence that individual genetic differences affect susceptibility to developing loiasis after infection by the *Loa loa* worm. Even in areas in which *Loa loa* worms are common, the disease is generally found in less than 30% of the population.[1] It has been suggested that travelers who spend time in the region may be somewhat more susceptible to developing symptoms than the native population, and the presentation of infection may differ.[2]

The parasite is spread by deerflies (genus *Chrysops*), which can ingest the larvae from an infected human via a blood meal (Figure 22.5.3). When the deerfly bites other humans, it deposits the larvae into their bloodstreams. After about five months in the human

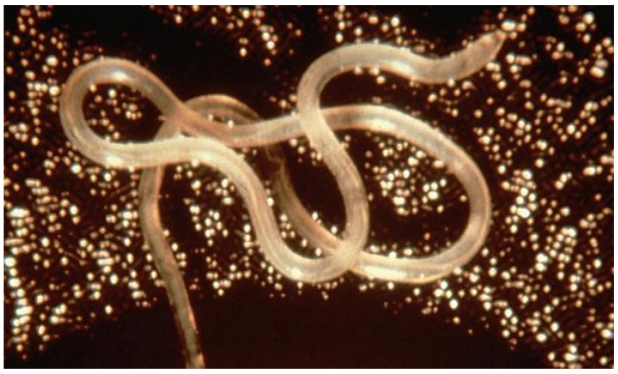
body, some larvae develop into adult worms, which can grow to several centimeters in length and live for years in the subcutaneous tissue of the host.

The name “eye worm” alludes to the visible migration of worms across the conjunctiva of the eye. Adult worms live in the subcutaneous tissues and can travel at about 1 cm per hour. They can often be observed when migrating through the eye, and sometimes under the skin; in fact, this is generally how the disease is diagnosed. It is also possible to test for antibodies, but the presence of antibodies does not necessarily indicate a current infection; it only means that the individual was exposed at some time. Some patients are asymptomatic, but in others the migrating worms can cause fever and areas of allergic inflammation known as Calabar swellings. Worms migrating through the conjunctiva can cause temporary eye pain and itching, but generally there is no lasting damage to the eye. Some patients experience a range of other symptoms, such as widespread itching, hives, and joint and muscle pain.

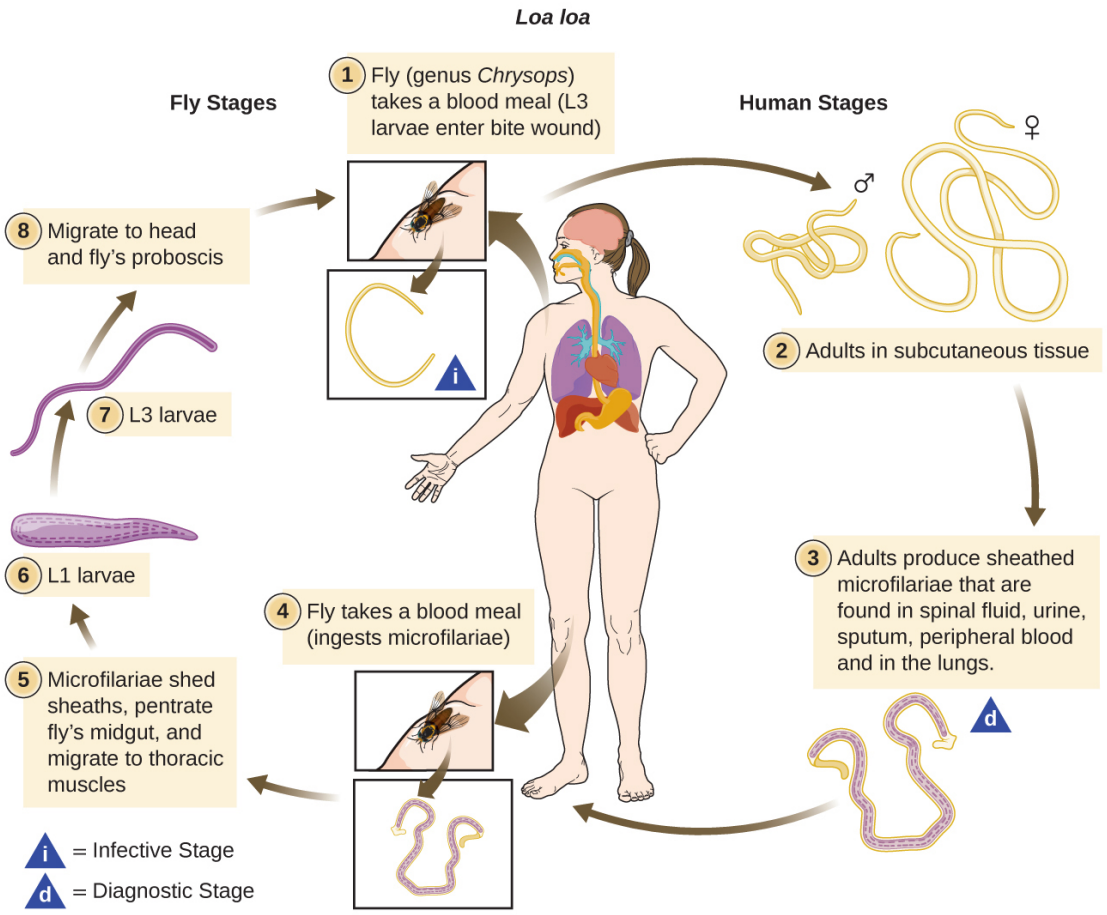
Worms can be surgically removed from the eye or the skin, but this treatment only relieves discomfort; it does not cure the infection, which involves many worms. The preferred treatment is diethylcarbamazine, but this medication produces severe side effects in some individuals, such as brain inflammation and possible death in patients with heavy infections. Albendazole is also sometimes used if diethylcarbamazine is not appropriate or not successful. If left untreated for many years, loiasis can damage the kidneys, heart, and lungs, though these symptoms are rare.



(a)



(b)



(c)

Figure **22.5.3**: This *Loa loa* worm, measuring about 55 mm long, was extracted from the conjunctiva of a patient with loiasis. The *Loa loa* has a complex life cycle. Biting deerflies native to the rain forests of Central and West Africa transmit the larvae between humans. (credit a: modification of work by Eballe AO, Epée E, Koki G, Owono D, Mvogo CE, Bella AL; credit b: modification of work by NIAID; credit c: modification of work by Centers for Disease Control and Prevention)

? Exercise 22.5.2

Describe the most common way to diagnose loiasis.

Link to Learning

See a video of a live *Loa loa* microfilaria under the microscope.

Parasitic Skin and Eye Infections

The protozoan *Acanthamoeba* and the helminth *Loa loa* are two parasites capable of causing infections of the skin and eyes. Figure 22.5.4 summarizes the characteristics of some common fungal infections of the skin.

Parasitic Skin and Eye Infections				
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Antimicrobial Drugs**
Acanthamoeba keratitis	*Acanthamoeba*	Inflammation and damage to cornea; vision impairment or blindness	Exposure to pathogens in contaminated water or on contact lenses	Polyhexamethylene biguanide, chlorhexidine, azoles
Loiasis	*Loa loa*	Recurring fever and localized Calabar swelling, itching, and skin or eye pain during subcutaneous migration of worms	Larvae transmitted between humans by deerfly vector	Diethylcarbamazine, albendazole

Figure 22.5.4: Parasitic skin and eye infections

Key Concepts and Summary

The protozoan *Acanthamoeba* and the helminth *Loa loa* are two parasites that can breach the skin barrier, causing infections of the skin and eyes. ***Acanthamoeba* keratitis** is a parasitic infection of the eye that often results from improper disinfection of contact lenses or swimming while wearing contact lenses. **Loiasis**, or eye worm, is a disease endemic to Africa that is caused by parasitic worms that infect the subcutaneous tissue of the skin and eyes. It is transmitted by deerfly vectors.

Footnotes

1. 1 Garcia, A.. et al. “Genetic Epidemiology of Host Predisposition Microfilaraemia in Human Loiasis.” *Tropical Medicine and International Health* 4 (1999) 8:565–74. http://www.ncbi.nlm.nih.gov/pubmed/10499080. Accessed Sept 14, 2016.
2. 2 Spinello, A., et al. “Imported *Loa loa* Filariasis: Three Cases and a Review of Cases Reported in Non-Endemic Countries in the Past 25 Years.” *International Journal of Infectious Disease* 16 (2012) 9: e649–e662. DOI: http://dx.doi.org/10.1016/j.ijid.2012.05.1023.

This page titled 22.5: Protozoan and Helminthic Infections of the Eyes is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by Renee J. LeClair (Virginia Tech Libraries' Open Education Initiative) via source content that was edited to the style and standards of the LibreTexts platform.

- **21.5: Protozoan and Helminthic Infections of the Eyes** by OpenStax is licensed CC BY 4.0. Original source: https://openstax.org/details/books/microbiology.

Index

A

Acanthamoeba
22.5: Protozoan and Helminthic Infections of the Eyes

Acanthamoeba keratitis
22.5: Protozoan and Helminthic Infections of the Eyes

acne
22.2: Bacterial Infections of the Skin and Eyes

Active Naturally Acquired Immunity
10.4.3A: Naturally Acquired Immunity

acute glomerulonephritis
17.1.2: Bacterial Infections of the Respiratory Tract

acute otitis media
17.1.2: Bacterial Infections of the Respiratory Tract

acute rheumatic fever
17.1.2: Bacterial Infections of the Respiratory Tract

adaptive immune response
10.3.3A: Major Histocompatibility Complex (MHC) Molecules
10.3.5: An Overview of the Steps Involved in Adaptive Immune Responses

adaptive immunity
11.1: Architecture of the Immune System

ADCC
11.1: Architecture of the Immune System

Addison disease
14.2: Autoimmune Disorders

Adenoviruses
15.10.8: Double-Stranded DNA Viruses-Adenoviruses

affinity
13.1: Practical Applications of Monoclonal and Polyclonal Antibodies

African trypanosomiasis
17.5.4: Neuromycoses and Parasitic Diseases of the Nervous System

Agammaglobulinemias
14.8: Primary Immunodeficiency

agar
16.4: Algae

agglutination
10.4.2G: Agglutination of Microorganisms
11.1: Architecture of the Immune System
13.3: Agglutination Assays

AIDS
17.4.3: Viral Infections of the Circulatory and Lymphatic Systems

algae
16.4: Algae

algal blooms
16.4: Algae

Allergen
12: Hypersensitivities

allergy
12: Hypersensitivities

alveoli
17.1.1: Anatomy and Normal Microbiota of the Respiratory Tract

Amoebiasis
17.3.5: Protozoan Infections of the Gastrointestinal Tract

AMPs
7.2: Chemical Defenses

Anamnestic Response
10.4.1F: Anamnestic (Memory) Response
10.5.1: Cell-Mediated Immunity - An Overview

anaphylaxis
12: Hypersensitivities

anaplasmosis
17.4.2: Bacterial Infections of the Circulatory and Lymphatic Systems

anergy
11.3: T Lymphocytes

Animal Viral Infections
15.10.10: Treatment of Animal Viral Infections

anthrax
22.2: Bacterial Infections of the Skin and Eyes

antibodies
10.4.1: Antibodies (Immunoglobulins)
11.1: Architecture of the Immune System

antibody
10.4.1B: Antibody Structure

Antibody Diversity
10.4.1D: Generation of Antibody Diversity

antibody isotypes
10.4.1B: Antibody Structure

anticancer therapies
21: Cancer Immunobiology and Immunotherapy

antigenic drift
17.1.3: Viral Infections of the Respiratory Tract

antigenic shift
17.1.3: Viral Infections of the Respiratory Tract

antigens
11.1: Architecture of the Immune System

Antimicrobial peptides
7.2: Chemical Defenses

antinuclear antibodies
13.5: Fluorescent Auto-Antibody Techniques

antiretroviral therapy
17.4.3: Viral Infections of the Circulatory and Lymphatic Systems

apoptosis
10.5.3: Activating Macrophages and NK Cells

arachnoid mater
17.5.1: Anatomy of the Nervous System

arboviral encephalitis
17.5.3: Acellular Pathogenic Diseases of the Nervous System

arboviruses
17.5.3: Acellular Pathogenic Diseases of the Nervous System

archaea
1.1: Classification - The Three Domain System

Ascariasis
17.3.6: Helminthic Infections of the Gastrointestinal Tract

Ascaris lumbricoides
17.8.3: Nematodes

Ascomycota
16.3: Fungi

Aspergillosis
17.1.4: Respiratory Mycoses
22.4: Mycoses of the Skin and Eyes

attachment
15.2: The Viral Life Cycle

autoimmune diseases
14.2: Autoimmune Disorders

B

B cells
11.4: B Lymphocytes and Antibodies

B lymphocytes
11.4: B Lymphocytes and Antibodies

Babesiosis
17.4.4: Parasitic Infections of the Circulatory and Lymphatic Systems

bacillus
1.2: Sizes, Shapes, and Arrangements of Bacteria

bacitracin
1.7: Ways in which Chemical Control Agents Affect Bacteria

bacteria
1.1: Classification - The Three Domain System

bacterial adherence
10.4.2F: Preventing Bacterial Adherence

Bacterial Chromosome
1.5B: The Bacterial Chromosome and Nucleoid

bacterial meningitis
17.5.2: Bacterial Diseases of the Nervous System

bacterial pneumonia
17.1.2: Bacterial Infections of the Respiratory Tract

bacterial vaginosis
17.2.3: Bacterial Infections of the Reproductive System

bacteriophage
15.6F: Virulent Bacteriophages and T4

Bacteriophages
15.3: Isolation, Culture, and Identification of Viruses

Basidiomycota
16.3: Fungi

basophils
7.3: Cellular Defenses

biofilms
1.4A: Glycocalyx (Capsules) and Biofilms

biosynthesis
15.2: The Viral Life Cycle

Blastomycosis
17.1.4: Respiratory Mycoses

botulism
6.8D: Botulism
17.5.2: Bacterial Diseases of the Nervous System

bovine spongiform encephalopathy
17.13.4: Bovine Spongiform Encephalopathy

bradykinin
7.2: Chemical Defenses

bronchi
17.1.1: Anatomy and Normal Microbiota of the Respiratory Tract

bronchioles
17.1.1: Anatomy and Normal Microbiota of the Respiratory Tract

bronchitis
17.1.1: Anatomy and Normal Microbiota of the Respiratory Tract

brucellosis
17.4.2: Bacterial Infections of the Circulatory and Lymphatic Systems

bubonic plague
17.4.2: Bacterial Infections of the Circulatory and Lymphatic Systems

C

cancer
21: Cancer Immunobiology and Immunotherapy
candidiasis
17.2.5: Fungal Infections of the Reproductive System
22.4: Mycoses of the Skin and Eyes
capsid
15.1: Viruses
carboxysomes
1.5F: Inclusion Bodies and Organelles Used for Photosynthesis
carbuncles
22.2: Bacterial Infections of the Skin and Eyes
carrageenan
16.4: Algae
caspases
10.5.2: Activating Antigen-Specific Cytotoxic T-Lymphocytes
CD8
10.5.2: Activating Antigen-Specific Cytotoxic T-Lymphocytes
celiac disease
14.2: Autoimmune Disorders
cellular immunity
11.1: Architecture of the Immune System
cellulitis
22.2: Bacterial Infections of the Skin and Eyes
central nervous system
17.5.1: Anatomy of the Nervous System
central tolerance
11.3: T Lymphocytes
cervical cancer
17.2.4: Viral Infections of the Reproductive System
cervix
17.2.1: Anatomy and Normal Microbiota of the Urogenital Tract
Cestodes
17.3.6: Helminthic Infections of the Gastrointestinal Tract
Chagas Disease
17.4.4: Parasitic Infections of the Circulatory and Lymphatic Systems
Chancroid
17.2.3: Bacterial Infections of the Reproductive System
chemical mediators
7.2: Chemical Defenses
chickenpox
17.1.3: Viral Infections of the Respiratory Tract
chikungunya fever
17.4.3: Viral Infections of the Circulatory and Lymphatic Systems
chlamydia
17.2.3: Bacterial Infections of the Reproductive System
chlamydial
22.2: Bacterial Infections of the Skin and Eyes
Chlamydial pneumonia
17.1.2: Bacterial Infections of the Respiratory Tract
cholera
17.3.3: Bacterial Infections of the Gastrointestinal Tract
cilia
16.1: Unicellular Eukaryotic Microorganisms
circulatory system
17.4.1: Anatomy of the Circulatory and Lymphatic Systems
class switching.
11.4: B Lymphocytes and Antibodies
clonal expansion
10.4.1E: Clonal Selection and Clonal Expansion
clonal selection
10.4.1E: Clonal Selection and Clonal Expansion
10.5.1: Cell-Mediated Immunity - An Overview
Coccidioidomycosis
17.1.4: Respiratory Mycoses
coccobacillus
1.2: Sizes, Shapes, and Arrangements of Bacteria
coccus
1.2: Sizes, Shapes, and Arrangements of Bacteria
colitis
17.3.1: Anatomy and Normal Microbiota of the Digestive System
combinatorial diversity
10.5.1: Cell-Mediated Immunity - An Overview
common cold
17.1.3: Viral Infections of the Respiratory Tract
complement activatio
11.1: Architecture of the Immune System
complement proteins
7.2: Chemical Defenses
complement system
7.2: Chemical Defenses
8.5: The Complement System
complex
15.1: Viruses
conjunctiva
22.1: Anatomy and Normal Microbiota of the Skin and Eyes
conjunctivitis
22.2: Bacterial Infections of the Skin and Eyes
contractile vacuoles
16.1: Unicellular Eukaryotic Microorganisms
Conventional Immunodeficiencies
14.8: Primary Immunodeficiency
Coombs' test
13.3: Agglutination Assays
coronaviruses
17.1.3: Viral Infections of the Respiratory Tract
CRISPR
1.5C: Plasmids and Transposons
Cryptococcosis
17.1.4: Respiratory Mycoses
cryptosporidiosis
17.7.4: Cryptosporidiosis
culture
4.1: Culture Media
cutaneous
22.4: Mycoses of the Skin and Eyes
cyanophycin granules
1.5F: Inclusion Bodies and Organelles Used for Photosynthesis
Cyclosporiasis
17.3.5: Protozoan Infections of the Gastrointestinal Tract
cystitis
6.4B: Cystitis
17.2.2: Bacterial Infections of the Urinary System
cytokine storm
11.3: T Lymphocytes
cytokines
7.2: Chemical Defenses
9.11C: Cytokines Important in Innate Immunity
10.5.3: Activating Macrophages and NK Cells
10.5.4: Stimulating Cells to Secrete Cytokines
cytomegalovirus
17.4.3: Viral Infections of the Circulatory and Lymphatic Systems
cytopathic effects
15.3: Isolation, Culture, and Identification of Viruses
cytoplasm
1.5A: Cytoplasm
cytotoxic T cells
11.3: T Lymphocytes

D

dendritic cells
7.3: Cellular Defenses
dengue fever
17.4.3: Viral Infections of the Circulatory and Lymphatic Systems
dental caries
17.3.2: Microbial Diseases of the Mouth and Oral Cavity
dermatophytes
22.4: Mycoses of the Skin and Eyes
dermis
22.1: Anatomy and Normal Microbiota of the Skin and Eyes
diapedesis
9.11G: Inflammation
Differential media
4.3: Selective and Differential Media
Diphtheria
17.1.2: Bacterial Infections of the Respiratory Tract
diplococcus
1.2: Sizes, Shapes, and Arrangements of Bacteria
Direct ELISA
13.4: Enzyme Immunoassays (EIA) and Enzyme-Linked Immunosorbent Assays (ELISA)
direct hemagglutination assay
13.3: Agglutination Assays
Direct immunofluorescence
13.5: Fluorescent Auto-Antibody Techniques
dura mater
17.5.1: Anatomy of the Nervous System
dysentery
17.3.1: Anatomy and Normal Microbiota of the Digestive System

E

Ebola
17.4.3: Viral Infections of the Circulatory and Lymphatic Systems
Ebola virus
17.4.3: Viral Infections of the Circulatory and Lymphatic Systems

echinococcosis
17.8.2: Hydatid Disease
Ehrlichiosis
17.4.2: Bacterial Infections of the Circulatory and Lymphatic Systems
encephalitis
17.5.1: Anatomy of the Nervous System
endocarditis
17.4.1: Anatomy of the Circulatory and Lymphatic Systems
17.4.2: Bacterial Infections of the Circulatory and Lymphatic Systems
Endogenous antigens
10.5.2: Activating Antigen-Specific Cytotoxic T-Lymphocytes
endospores
1.5E: Endospores
endothelia
7.1: Physical Defenses
endotoxin
2.3A: Toxins
Enhanced Attachment (Phagocytosis)
10.4.2A: Opsonization
enteritis
17.3.1: Anatomy and Normal Microbiota of the Digestive System
Enterobactin
2.3E: Siderophores
Enterobius
17.8.3: Nematodes
Enzyme immunoassays
13.4: Enzyme Immunoassays (EIA) and Enzyme-Linked Immunosorbent Assays (ELISA)
eosinophils
7.3: Cellular Defenses
epidemic typhus
17.4.2: Bacterial Infections of the Circulatory and Lymphatic Systems
epidermis
22.1: Anatomy and Normal Microbiota of the Skin and Eyes
epididymis
17.2.1: Anatomy and Normal Microbiota of the Urogenital Tract
Epigenome
1.5B: The Bacterial Chromosome and Nucleoid
epiglottis
17.1.1: Anatomy and Normal Microbiota of the Respiratory Tract
epitopes
11.1: Architecture of the Immune System
ergosterols
16.3: Fungi
erysipelas
22.2: Bacterial Infections of the Skin and Eyes
erythema nosodum
22.2: Bacterial Infections of the Skin and Eyes
erythrocytes
7.3: Cellular Defenses
eschar
22.2: Bacterial Infections of the Skin and Eyes
Eukarya
1.1: Classification - The Three Domain System
exotoxin
2.3A: Toxins
10.4.2D: Neutralization of Exotoxins
Extravasation
7.4: Pathogen Recognition and Phagocytosis

F

FAB
10.4.1B: Antibody Structure
Fallopian tubes
17.2.1: Anatomy and Normal Microbiota of the Urogenital Tract
FasL/Fas interactions
10.5.2: Activating Antigen-Specific Cytotoxic T-Lymphocytes
Ferrichrome
2.3E: Siderophores
Fever
9.11I: Fever
fifth disease
22.3: Viral Infections of the Skin and Eyes
fimbriae
1.4C: Fimbriae and Pili
flocculants
13.2: Detecting Antigen-Antibody Complexes in vitro
Flow cytometry
13.5: Fluorescent Auto-Antibody Techniques
flu
15.9.3: Replicative Cycle of Influenza A
17.1.3: Viral Infections of the Respiratory Tract
flukes
16.2: Parasitic Helminths
folliculitis
22.2: Bacterial Infections of the Skin and Eyes
foodborne illness
17.3.1: Anatomy and Normal Microbiota of the Digestive System
foodborne pathogen
17.5.2: Bacterial Diseases of the Nervous System
formed elements
7.3: Cellular Defenses
fungi
16.3: Fungi
furuncles
22.2: Bacterial Infections of the Skin and Eyes

G

gas gangrene
17.4.2: Bacterial Infections of the Circulatory and Lymphatic Systems
gas vesicles
1.5F: Inclusion Bodies and Organelles Used for Photosynthesis
gastritis
17.3.1: Anatomy and Normal Microbiota of the Digestive System
gastroenteritis
17.3.1: Anatomy and Normal Microbiota of the Digestive System
17.3.4: Viral Infections of the Gastrointestinal Tract
gastrointestinal tract
17.3.4: Viral Infections of the Gastrointestinal Tract
gene translocation
10.5.1: Cell-Mediated Immunity - An Overview
generalized
15.2: The Viral Life Cycle
genital herpes
17.2.4: Viral Infections of the Reproductive System
genital warts
17.2.4: Viral Infections of the Reproductive System
Ghon complexes
17.1.2: Bacterial Infections of the Respiratory Tract
Giardiasis
17.3.5: Protozoan Infections of the Gastrointestinal Tract
17.7.3: Giardiasis
gingivitis
17.3.2: Microbial Diseases of the Mouth and Oral Cavity
gingivostomatitis
17.3.2: Microbial Diseases of the Mouth and Oral Cavity
glial cells
17.5.1: Anatomy of the Nervous System
Glycocalyx
1.4A: Glycocalyx (Capsules) and Biofilms
glycogen granules
1.5F: Inclusion Bodies and Organelles Used for Photosynthesis
glycopeptides
1.7: Ways in which Chemical Control Agents Affect Bacteria
gonorrhea
17.2.3: Bacterial Infections of the Reproductive System
granulocytes
7.3: Cellular Defenses
granulomatous amoebic encephalitis
17.5.4: Neuromycoses and Parasitic Diseases of the Nervous System
granzymes
11.3: T Lymphocytes
Graves disease
14.2: Autoimmune Disorders
Group A streptococci
22.2: Bacterial Infections of the Skin and Eyes

H

haematogenous
17.9.3: The TORCH Panel of Tests
Haemophilus ducreyi
2.1B: Opportunistic Microorganisms
Hansen’s disease
17.5.2: Bacterial Diseases of the Nervous System
Hashimoto thyroiditis
14.2: Autoimmune Disorders
helical
15.1: Viruses
Helicobacter pylori
3.4: Helicobacter pylori
Helminth parasites
16.2: Parasitic Helminths
22.5: Protozoan and Helminthic Infections of the Eyes
Helminthic worms
16.2: Parasitic Helminths
17.3.6: Helminthic Infections of the Gastrointestinal Tract
Helminths
17.3.6: Helminthic Infections of the Gastrointestinal Tract

helper T cells
11.3: T Lymphocytes
hemagglutination
13.3: Agglutination Assays
hematopoiesis
7.3: Cellular Defenses
hemolytic disease of the newborn
12: Hypersensitivities
hemolytic transfusion reaction
12: Hypersensitivities
Hepadnavirus
15.10.9: Retroviruses and Hepadnavirus
hepatitis
17.3.1: Anatomy and Normal Microbiota of the Digestive System
herpes
22.3: Viral Infections of the Skin and Eyes
Herpes keratitis
22.3: Viral Infections of the Skin and Eyes
Herpes simplex virus
22.3: Viral Infections of the Skin and Eyes
Herpesviruses
15.10.3: Double-Stranded DNA Viruses - Herpesviruses
Herpetic Gingivostomatitis
17.3.2: Microbial Diseases of the Mouth and Oral Cavity
histamine
7.2: Chemical Defenses
histoplasmosis
17.1.4: Respiratory Mycoses
HIV Attachment
15.8B: HIV Attachment and Host Cell Entry
Horizontal Gene Transfer
1.1: Classification - The Three Domain System
host ranges
15.1: Viruses
hot tub rash
22.2: Bacterial Infections of the Skin and Eyes
human African trypanosomiasis
17.5.4: Neuromycoses and Parasitic Diseases of the Nervous System
human immunodeficiency virus
17.4.3: Viral Infections of the Circulatory and Lymphatic Systems
Human papillomaviruses
17.2.4: Viral Infections of the Reproductive System
humoral immunity
10.4: Humoral Immunity
11.1: Architecture of the Immune System
hybridomas
13.1: Practical Applications of Monoclonal and Polyclonal Antibodies
Hydatid Disease
17.8.2: Hydatid Disease
hypersensitivities
10.2: Hypersensitivities
12: Hypersensitivities
hypodermis
22.1: Anatomy and Normal Microbiota of the Skin and Eyes
Hypogammaglobulinemias
14.8: Primary Immunodeficiency

I

IgA
11.1: Architecture of the Immune System
IgD
11.1: Architecture of the Immune System
IgE
11.1: Architecture of the Immune System
IgG
10.4.2D: Neutralization of Exotoxins
11.1: Architecture of the Immune System
IgM
11.1: Architecture of the Immune System
immune complexes
12: Hypersensitivities
immunocytochemistry
13.4: Enzyme Immunoassays (EIA) and Enzyme-Linked Immunosorbent Assays (ELISA)
immunodeficiency
2.1B: Opportunistic Microorganisms
10.1: Immunodeficiency
15.10.6: Immunodeficiency
immunoelectrophoresis
13.2: Detecting Antigen-Antibody Complexes in vitro
Immunofiltration and immunochromatographic assays
13.4: Enzyme Immunoassays (EIA) and Enzyme-Linked Immunosorbent Assays (ELISA)
Immunofluorescence
13.5: Fluorescent Auto-Antibody Techniques
immunogens
11.1: Architecture of the Immune System
immunoglobulins
10.4.1: Antibodies (Immunoglobulins)
11.1: Architecture of the Immune System
immunohistochemistry
13.4: Enzyme Immunoassays (EIA) and Enzyme-Linked Immunosorbent Assays (ELISA)
Immunostaining
13.4: Enzyme Immunoassays (EIA) and Enzyme-Linked Immunosorbent Assays (ELISA)
Inclusion Bodies
1.5F: Inclusion Bodies and Organelles Used for Photosynthesis
inclusion conjunctivitis
22.2: Bacterial Infections of the Skin and Eyes
indirect agglutination assays
13.3: Agglutination Assays
Indirect ELISA
13.4: Enzyme Immunoassays (EIA) and Enzyme-Linked Immunosorbent Assays (ELISA)
Indirect immunofluorescence
13.5: Fluorescent Auto-Antibody Techniques
Infections of the GI Tract
17.3.3: Bacterial Infections of the Gastrointestinal Tract
17.3.4: Viral Infections of the Gastrointestinal Tract
17.3.5: Protozoan Infections of the Gastrointestinal Tract
inflammation
9.11G: Inflammation
inflammatory response
10.4.2I: Promoting an Inflammatory Response
influenza
17.1.3: Viral Infections of the Respiratory Tract
Influenza A
15.9.3: Replicative Cycle of Influenza A
intertrigo
22.4: Mycoses of the Skin and Eyes
intracellular pathogens
2.4A: Intracellular Pathogens
Isoniazid
1.3C: The Acid-Fast Cell Wall

J

junctional diversity
10.5.1: Cell-Mediated Immunity - An Overview

K

keratitis
22.2: Bacterial Infections of the Skin and Eyes
kidneys
17.2.1: Anatomy and Normal Microbiota of the Urogenital Tract
kuru
17.5.3: Acellular Pathogenic Diseases of the Nervous System

L

larynx
17.1.1: Anatomy and Normal Microbiota of the Respiratory Tract
last universal common ancestor
1.1: Classification - The Three Domain System
latency
15.2: The Viral Life Cycle
lateral flow tests
13.4: Enzyme Immunoassays (EIA) and Enzyme-Linked Immunosorbent Assays (ELISA)
lconjunctiva
22.1: Anatomy and Normal Microbiota of the Skin and Eyes
Legionnaires disease
17.1.2: Bacterial Infections of the Respiratory Tract
Leishmaniasis
17.4.4: Parasitic Infections of the Circulatory and Lymphatic Systems
leprosy
6.8E: Leprosy
17.5.2: Bacterial Diseases of the Nervous System
Leptospirosis
6.4D: Leptospirosis
17.2.2: Bacterial Infections of the Urinary System
leukocytes
7.3: Cellular Defenses
lichens
16.5: Lichens
Listeria monocytogenes
17.5.2: Bacterial Diseases of the Nervous System
Loiasis
22.5: Protozoan and Helminthic Infections of the Eyes
long attachment pili
1.4C: Fimbriae and Pili
Luria Broth
4.2: Complex and Synthetic Media
Lyme disease
4.5: Special Culture Techniques
17.4.2: Bacterial Infections of the Circulatory and Lymphatic Systems

lymph nodes
10.3.4: The Lymphoid System
lymphadenitis
17.4.1: Anatomy of the Circulatory and Lymphatic Systems
lymphangitis
17.4.1: Anatomy of the Circulatory and Lymphatic Systems
lymphatic system
17.4.1: Anatomy of the Circulatory and Lymphatic Systems
Lymphoid System
10.3.4: The Lymphoid System
lysogenic cycle
15.2: The Viral Life Cycle
Lysogeny
2.3D: Plasmids and Lysogeny
lysogeny broth
4.1: Culture Media
lytic
15.2: The Viral Life Cycle
lytic cycle
15.2: The Viral Life Cycle

M

MAC
7.2: Chemical Defenses
macrophages
7.3: Cellular Defenses
10.5.3: Activating Macrophages and NK Cells
magnetosomes
1.5F: Inclusion Bodies and Organelles Used for Photosynthesis
major histocompatibility class (MHC) I/II molecule
9.5: Natural Killer Cells
Major histocompatibility complex
10.3.3A: Major Histocompatibility Complex (MHC) Molecules
11.2: Antigens, Antigen Presenting Cells, and Major Histocompatibility Complexes
malaria
17.4.4: Parasitic Infections of the Circulatory and Lymphatic Systems
Mast cells
7.3: Cellular Defenses
maturation
15.2: The Viral Life Cycle
measles
17.1.3: Viral Infections of the Respiratory Tract
membrane attack complex
7.2: Chemical Defenses
10.4.2B: Cytolysis by the Membrane Attack Complex (MAC)
memory
11.1: Architecture of the Immune System
Memory B cells
11.4: B Lymphocytes and Antibodies
memory T cell subtypes
11.3: T Lymphocytes
meninges
17.5.1: Anatomy of the Nervous System
meningitis
6.8C: Meningitis
17.5.1: Anatomy of the Nervous System
MERS
17.1.3: Viral Infections of the Respiratory Tract
Metagenomics
15.17B: Viral Roles in Ecosystems
MHC
11.2: Antigens, Antigen Presenting Cells, and Major Histocompatibility Complexes
MHC I
11.2: Antigens, Antigen Presenting Cells, and Major Histocompatibility Complexes
MHC II
11.2: Antigens, Antigen Presenting Cells, and Major Histocompatibility Complexes
Microsporidia
16.3: Fungi
microtiter plates
13.3: Agglutination Assays
monoclonal antibodies
13.1: Practical Applications of Monoclonal and Polyclonal Antibodies
monocytes
7.3: Cellular Defenses
Mucormycosis
17.1.4: Respiratory Mycoses
mucus
7.1: Physical Defenses
multiple sclerosis
14.2: Autoimmune Disorders
mumps
17.3.2: Microbial Diseases of the Mouth and Oral Cavity
murine typhus
17.4.2: Bacterial Infections of the Circulatory and Lymphatic Systems
myasthenia gravis
14.2: Autoimmune Disorders
Mycobacterium tuberculosis
1.3C: The Acid-Fast Cell Wall
mycolic acids
1.3C: The Acid-Fast Cell Wall
Mycoplasma pneumonia
17.1.2: Bacterial Infections of the Respiratory Tract
mycoses
17.1.4: Respiratory Mycoses
22.4: Mycoses of the Skin and Eyes

N

nasal cavity
17.1.1: Anatomy and Normal Microbiota of the Respiratory Tract
Natural killer
7.3: Cellular Defenses
Natural Killer Cells
10.4.2C: Antibody-dependent Cellular Cytotoxicity (ADCC) by Natural Killer Cells
necrotizing fasciitis
22.2: Bacterial Infections of the Skin and Eyes
Neisseria gonorrhoeae
1.4C: Fimbriae and Pili
Nematodes
16.2: Parasitic Helminths
17.3.6: Helminthic Infections of the Gastrointestinal Tract
17.8.3: Nematodes
Neonatal herpes
17.2.4: Viral Infections of the Reproductive System
Neurocysticercosis
17.5.4: Neuromycoses and Parasitic Diseases of the Nervous System
Neuromycoses
17.5.4: Neuromycoses and Parasitic Diseases of the Nervous System
neurons
17.5.1: Anatomy of the Nervous System
neurotoxoplasmosis
17.5.4: Neuromycoses and Parasitic Diseases of the Nervous System
neutralization
11.1: Architecture of the Immune System
Neutralization assays
13.3: Agglutination Assays
neutrophils
7.3: Cellular Defenses
NK
7.3: Cellular Defenses
NK cells
9.5: Natural Killer Cells
10.3.3G: Natural Killer Cells (NK Cells)
10.5.3: Activating Macrophages and NK Cells
Nongonococcal urethritis
17.2.2: Bacterial Infections of the Urinary System
Nonspecific innate immunity
7.1: Physical Defenses
Noroviruses
17.3.4: Viral Infections of the Gastrointestinal Tract
nucleoid
1.5B: The Bacterial Chromosome and Nucleoid
Nutritional Immunity
9.11H: Nutritional Immunity

O

ophthalmia neonatorum
22.2: Bacterial Infections of the Skin and Eyes
opportunistic diseases
2.1B: Opportunistic Microorganisms
opsonization
1.4C: Fimbriae and Pili
7.2: Chemical Defenses
10.4.2A: Opsonization
11.1: Architecture of the Immune System
oral herpes
22.3: Viral Infections of the Skin and Eyes
oral thrush
17.3.2: Microbial Diseases of the Mouth and Oral Cavity
origin of replication
1.5B: The Bacterial Chromosome and Nucleoid
Osmotic Lysis
1.7: Ways in which Chemical Control Agents Affect Bacteria
osteomyelitis
17.4.2: Bacterial Infections of the Circulatory and Lymphatic Systems
otitis
17.1.1: Anatomy and Normal Microbiota of the Respiratory Tract
otitis externa
22.2: Bacterial Infections of the Skin and Eyes
otitis media
17.1.2: Bacterial Infections of the Respiratory Tract
otitis media with effusion
17.1.2: Bacterial Infections of the Respiratory Tract

Ouchterlony assay
13.2: Detecting Antigen-Antibody Complexes in vitro

P

pamps
7.4: Pathogen Recognition and Phagocytosis
Papillomas
22.3: Viral Infections of the Skin and Eyes
parasites
16.2: Parasitic Helminths
Parasitic Skin Diseases
6.6F: Parasitic Skin Diseases
17.11: Parasitic Skin Diseases
parasitism
16.5: Lichens
Passive Immunization
18.1: Passive Immunization
Passive Naturally Acquired Immunity
10.4.3A: Naturally Acquired Immunity
pattern recognition receptors
7.4: Pathogen Recognition and Phagocytosis
pellicles
16.1: Unicellular Eukaryotic Microorganisms
penetration
15.2: The Viral Life Cycle
penicillins
1.7: Ways in which Chemical Control Agents Affect Bacteria
peptic ulcers
17.3.3: Bacterial Infections of the Gastrointestinal Tract
peptidoglycan
1.3: The Peptidoglycan Cell Wall
1.7: Ways in which Chemical Control Agents Affect Bacteria
perforin
11.3: T Lymphocytes
Perforins
10.5.3: Activating Macrophages and NK Cells
Periodontal disease
17.3.1: Anatomy and Normal Microbiota of the Digestive System
17.3.2: Microbial Diseases of the Mouth and Oral Cavity
periodontitis
17.3.2: Microbial Diseases of the Mouth and Oral Cavity
peripheral nervous system
17.5.1: Anatomy of the Nervous System
peripheral tolerance
11.3: T Lymphocytes
periplasm
1.3C: The Acid-Fast Cell Wall
peristalsis
7.1: Physical Defenses
Pertussis
17.1.2: Bacterial Infections of the Respiratory Tract
phagocytes
7.4: Pathogen Recognition and Phagocytosis
phagocytosis
7.4: Pathogen Recognition and Phagocytosis
9.11E: Phagocytosis
phagolysosome
7.4: Pathogen Recognition and Phagocytosis
pharyngitis
17.1.1: Anatomy and Normal Microbiota of the Respiratory Tract
pharynx
17.1.1: Anatomy and Normal Microbiota of the Respiratory Tract
phosphatidyinositol mannosides
1.3C: The Acid-Fast Cell Wall
Photosynthesic Organelles
1.5F: Inclusion Bodies and Organelles Used for Photosynthesis
phylogenetic tree
1.1: Classification - The Three Domain System
phylogeny
1.1: Classification - The Three Domain System
physical barriers
7.1: Physical Defenses
pia mater
17.5.1: Anatomy of the Nervous System
pili
1.4C: Fimbriae and Pili
pilin
1.4C: Fimbriae and Pili
pilus
2.2B: Pili and Pilus Assembly
Pinworms
17.3.6: Helminthic Infections of the Gastrointestinal Tract
17.8.3: Nematodes
plantibodies
13.1: Practical Applications of Monoclonal and Polyclonal Antibodies
plaques
15.3: Isolation, Culture, and Identification of Viruses
plasma
7.2: Chemical Defenses
plasma cells
11.4: B Lymphocytes and Antibodies
plasmids
1.5C: Plasmids and Transposons
2.3D: Plasmids and Lysogeny
platelets
7.3: Cellular Defenses
PMNs
7.3: Cellular Defenses
Pneumocystis pneumonia
17.1.4: Respiratory Mycoses
Polio
17.5.3: Acellular Pathogenic Diseases of the Nervous System
polyclonal antibody
13.1: Practical Applications of Monoclonal and Polyclonal Antibodies
Polyclonal antisera
13.1: Practical Applications of Monoclonal and Polyclonal Antibodies
polyhedral
15.1: Viruses
polyhydroxybutyrate granules
1.5F: Inclusion Bodies and Organelles Used for Photosynthesis
polyphyletic
16.1: Unicellular Eukaryotic Microorganisms
Pox Viruses
15.10.7: Double-Stranded DNA Viruses - Pox Viruses
precipitin
13.2: Detecting Antigen-Antibody Complexes in vitro
precipitin ring test
13.2: Detecting Antigen-Antibody Complexes in vitro
primary amoebic meningitis
17.5.4: Neuromycoses and Parasitic Diseases of the Nervous System
Primary Immunodeficiency
14.8: Primary Immunodeficiency
primary response
11.1: Architecture of the Immune System
prion
2.4A: Intracellular Pathogens
15.16C: Prions
prions
15.4: Viroids, Virusoids, and Prions
15.16C: Prions
17.5.3: Acellular Pathogenic Diseases of the Nervous System
prostaglandins
7.2: Chemical Defenses
prostate
17.2.1: Anatomy and Normal Microbiota of the Urogenital Tract
proteasome
10.5.2: Activating Antigen-Specific Cytotoxic T-Lymphocytes
proteinaceous
15.4: Viroids, Virusoids, and Prions
Protists
16.1: Unicellular Eukaryotic Microorganisms
PRRs
7.4: Pathogen Recognition and Phagocytosis
pseudomembrane
17.1.2: Bacterial Infections of the Respiratory Tract
pseudopodia
16.1: Unicellular Eukaryotic Microorganisms
psoriasis
14.2: Autoimmune Disorders
puerperal fever
17.4.2: Bacterial Infections of the Circulatory and Lymphatic Systems
Pyelonephritis
17.2.2: Bacterial Infections of the Urinary System

Q

Q fever
17.1.2: Bacterial Infections of the Respiratory Tract

R

Rabies
17.5.3: Acellular Pathogenic Diseases of the Nervous System
radial immunodiffusion
13.2: Detecting Antigen-Antibody Complexes in vitro
regulatory T cells
11.3: T Lymphocytes
relapsing fever
17.4.2: Bacterial Infections of the Circulatory and Lymphatic Systems
release
15.2: The Viral Life Cycle

respiratory syncytial virus
17.1.3: Viral Infections of the Respiratory Tract
Retroviral RNA Genome
15.8C: Retroviral RNA Genome
Retroviruses
15.8A: Double-Stranded RNA Viruses - Retroviruses
15.10.9: Retroviruses and Hepadnavirus
rheumatic fever
17.4.2: Bacterial Infections of the Circulatory and Lymphatic Systems
rheumatoid arthritis
14.2: Autoimmune Disorders
rhinitis
17.1.1: Anatomy and Normal Microbiota of the Respiratory Tract
ribosomes
1.5D: Ribosomes
ringworm
22.4: Mycoses of the Skin and Eyes
Rocky Mountain spotted fever
17.4.2: Bacterial Infections of the Circulatory and Lymphatic Systems
rod
1.2: Sizes, Shapes, and Arrangements of Bacteria
Roseola
22.3: Viral Infections of the Skin and Eyes
Rotaviruses
17.3.4: Viral Infections of the Gastrointestinal Tract
roundworms
16.2: Parasitic Helminths
17.8.3: Nematodes
rubella
17.1.3: Viral Infections of the Respiratory Tract

S

salmonellosis
17.3.3: Bacterial Infections of the Gastrointestinal Tract
sarcina
1.2: Sizes, Shapes, and Arrangements of Bacteria
SARS
17.1.3: Viral Infections of the Respiratory Tract
scabies
6.6F: Parasitic Skin Diseases
17.11: Parasitic Skin Diseases
scarlet fever
1.1: Scarlet Fever
17.1.2: Bacterial Infections of the Respiratory Tract
Schistosomiasis
17.4.4: Parasitic Infections of the Circulatory and Lymphatic Systems
Secondary Immunodeficiency
14.10: Secondary Immunodeficiency
secondary response
11.1: Architecture of the Immune System
Selective Media
4.3: Selective and Differential Media
sepsis
17.4.1: Anatomy of the Circulatory and Lymphatic Systems
17.4.2: Bacterial Infections of the Circulatory and Lymphatic Systems
seroconversion
13.3: Agglutination Assays
serovars
13.3: Agglutination Assays
sex pili
1.4C: Fimbriae and Pili
Shigellosis
17.3.3: Bacterial Infections of the Gastrointestinal Tract
shingles
17.1.3: Viral Infections of the Respiratory Tract
short attachment pili
1.4C: Fimbriae and Pili
siderophores.
2.3E: Siderophores
sinusitis
17.1.1: Anatomy and Normal Microbiota of the Respiratory Tract
SIRS
17.4.1: Anatomy of the Circulatory and Lymphatic Systems
soft chancres
17.2.3: Bacterial Infections of the Reproductive System
specialized transduction
15.2: The Viral Life Cycle
specificity
11.1: Architecture of the Immune System
13.1: Practical Applications of Monoclonal and Polyclonal Antibodies
spiral
1.2: Sizes, Shapes, and Arrangements of Bacteria
spirillum
1.2: Sizes, Shapes, and Arrangements of Bacteria
spirochete
1.2: Sizes, Shapes, and Arrangements of Bacteria
sporotrichosis
22.4: Mycoses of the Skin and Eyes
Staphylococcal Food Poisoning
17.3.3: Bacterial Infections of the Gastrointestinal Tract
staphylococcus
1.2: Sizes, Shapes, and Arrangements of Bacteria
strep throat
17.1.2: Bacterial Infections of the Respiratory Tract
streptobacillus
1.2: Sizes, Shapes, and Arrangements of Bacteria
streptococcus
1.2: Sizes, Shapes, and Arrangements of Bacteria
Streptococcus pneumoniae
3.8: Streptococcus pneumoniae
Streptococcus pyogenes
3.9: Streptococcus pyogenes
Strongyloidiasis
17.3.6: Helminthic Infections of the Gastrointestinal Tract
subcutaneous
22.4: Mycoses of the Skin and Eyes
Superantigens
11.3: T Lymphocytes
14.3: Superantigens
Svedberg unit
1.5D: Ribosomes
syphilis
6.5F: Syphilis
17.2.3: Bacterial Infections of the Reproductive System
systemic
22.4: Mycoses of the Skin and Eyes
systemic lupus erythematosus
14.2: Autoimmune Disorders

T

T. vaginalis
17.2.6: Protozoan Infections of the Reproductive System
tapeworms
16.2: Parasitic Helminths
17.8.1: Tapeworms
17.8.2: Hydatid Disease
tcr
11.3: T Lymphocytes
tetanus
3.1: Clostridium tetani
17.5.2: Bacterial Diseases of the Nervous System
tetrad
1.2: Sizes, Shapes, and Arrangements of Bacteria
Th1 cells
10.5.3: Activating Macrophages and NK Cells
11.3: T Lymphocytes
th17 cells
11.3: T Lymphocytes
Th2 cells
11.3: T Lymphocytes
The Three Domain System
1.1: Classification - The Three Domain System
thrombocytes
7.3: Cellular Defenses
Thrush
17.3.2: Microbial Diseases of the Mouth and Oral Cavity
Thymic selection
11.3: T Lymphocytes
Tinea corporis
22.4: Mycoses of the Skin and Eyes
tineas
22.4: Mycoses of the Skin and Eyes
tooth decay
17.3.1: Anatomy and Normal Microbiota of the Digestive System
topoisomerases
1.5B: The Bacterial Chromosome and Nucleoid
TORCH infections
17.9.3: The TORCH Panel of Tests
toxic shock syndrome
17.4.2: Bacterial Infections of the Circulatory and Lymphatic Systems
Toxoplasmosis
17.4.4: Parasitic Infections of the Circulatory and Lymphatic Systems
trachea
17.1.1: Anatomy and Normal Microbiota of the Respiratory Tract
trachoma
22.2: Bacterial Infections of the Skin and Eyes
transendothelial migration
7.4: Pathogen Recognition and Phagocytosis
transmissible spongiform encephalopathies
15.4: Viroids, Virusoids, and Prions
17.5.3: Acellular Pathogenic Diseases of the Nervous System
transposons
1.5C: Plasmids and Transposons
15.8A: Double-Stranded RNA Viruses - Retroviruses

trematodes
17.3.6: Helminthic Infections of the Gastrointestinal Tract
trench fever
17.4.2: Bacterial Infections of the Circulatory and Lymphatic Systems
trichomoniasis
17.2.6: Protozoan Infections of the Reproductive System
Trichuriasis
17.3.6: Helminthic Infections of the Gastrointestinal Tract
tubercles
17.1.2: Bacterial Infections of the Respiratory Tract
tuberculosis
17.1.2: Bacterial Infections of the Respiratory Tract
Tularemia
17.4.2: Bacterial Infections of the Circulatory and Lymphatic Systems
tumor
21: Cancer Immunobiology and Immunotherapy
tumor antigens
21: Cancer Immunobiology and Immunotherapy
type I diabetes mellitus
14.2: Autoimmune Disorders
type I hypersensitivity
12: Hypersensitivities
Type II hypersensitivities
12: Hypersensitivities
Type III hypersensitivities
12: Hypersensitivities
Type IV hypersensitivities
12: Hypersensitivities
Typhoid fever
6.3D: Typhoid Fever
17.3.3: Bacterial Infections of the Gastrointestinal Tract

U

ulcers
17.3.1: Anatomy and Normal Microbiota of the Digestive System
uncoating
15.2: The Viral Life Cycle
ureters
17.2.1: Anatomy and Normal Microbiota of the Urogenital Tract
urethra
17.2.1: Anatomy and Normal Microbiota of the Urogenital Tract
urinary bladder
17.2.1: Anatomy and Normal Microbiota of the Urogenital Tract
urinary system
17.2.1: Anatomy and Normal Microbiota of the Urogenital Tract

V

vaccination
18.2: Vaccination
vagina
17.2.1: Anatomy and Normal Microbiota of the Urogenital Tract
vaginal candidiasis
17.2.5: Fungal Infections of the Reproductive System
vibrio
1.2: Sizes, Shapes, and Arrangements of Bacteria
Viral conjunctivitis
22.3: Viral Infections of the Skin and Eyes
Viral cultivation
15.3: Isolation, Culture, and Identification of Viruses
Viral Exit
15.7D: Viral Exit
Viral filtrate
15.3: Isolation, Culture, and Identification of Viruses
viral genome
15.12.3: Viral Genomes
viral meningitis
17.5.3: Acellular Pathogenic Diseases of the Nervous System
Viral Pathogens
15.17A: Emergence of Viral Pathogens
Virions
15.1: Viruses
viroid
15.16B: Viroids
viroids
15.4: Viroids, Virusoids, and Prions
viruses
15.1: Viruses
virusoids
15.4: Viroids, Virusoids, and Prions
15.16B: Viroids
vulva
17.2.1: Anatomy and Normal Microbiota of the Urogenital Tract

W

western blot assays
13.2: Detecting Antigen-Antibody Complexes in vitro
Woese
1.1: Classification - The Three Domain System

Y

yellow fever
4.5: Special Culture Techniques
17.4.3: Viral Infections of the Circulatory and Lymphatic Systems
Yersiniabactin
2.3E: Siderophores

Z

Zika (Virus)
17.5.3: Acellular Pathogenic Diseases of the Nervous System
Zika virus
17.5.3: Acellular Pathogenic Diseases of the Nervous System
Zygomycota
16.3: Fungi

Glossary

Sample Word 1 | Sample Definition 1

Detailed Licensing

Overview

Title: Block V Preparation Materials

Webpages: 440

Applicable Restrictions: Noncommercial

All licenses found:

- CC BY-NC-SA 4.0: 99.8% (439 pages)
- Undeclared: 0.2% (1 page)

By Page

- Block V Preparation Materials - *CC BY-NC-SA 4.0*
  - Front Matter - *CC BY-NC-SA 4.0*
    - TitlePage - *CC BY-NC-SA 4.0*
    - InfoPage - *CC BY-NC-SA 4.0*
    - Table of Contents - *Undeclared*
    - Licensing - *CC BY-NC-SA 4.0*
  - 1: Basic Microbiology and Infection Control - *CC BY-NC-SA 4.0*
    - 1.1: Classification - The Three Domain System - *CC BY-NC-SA 4.0*
    - 1.2: Sizes, Shapes, and Arrangements of Bacteria - *CC BY-NC-SA 4.0*
    - 1.3: The Peptidoglycan Cell Wall - *CC BY-NC-SA 4.0*
      - 1.3.1: Damage of the Cell Wall - *CC BY-NC-SA 4.0*
      - 1.3A: The Gram-Positive Cell Wall - *CC BY-NC-SA 4.0*
      - 1.3B: The Gram-Negative Cell Wall - *CC BY-NC-SA 4.0*
      - 1.3C: The Acid-Fast Cell Wall - *CC BY-NC-SA 4.0*
    - 1.4: Structures Outside the Cell Wall - *CC BY-NC-SA 4.0*
      - 1.4A: Glycocalyx (Capsules) and Biofilms - *CC BY-NC-SA 4.0*
      - 1.4B: Flagella - *CC BY-NC-SA 4.0*
      - 1.4C: Fimbriae and Pili - *CC BY-NC-SA 4.0*
    - 1.5: Cellular Components within the Cytoplasm - *CC BY-NC-SA 4.0*
      - 1.5A: Cytoplasm - *CC BY-NC-SA 4.0*
      - 1.5B: The Bacterial Chromosome and Nucleoid - *CC BY-NC-SA 4.0*
      - 1.5C: Plasmids and Transposons - *CC BY-NC-SA 4.0*
      - 1.5D: Ribosomes - *CC BY-NC-SA 4.0*
      - 1.5E: Endospores - *CC BY-NC-SA 4.0*
      - 1.5F: Inclusion Bodies and Organelles Used for Photosynthesis - *CC BY-NC-SA 4.0*
    - 1.6: An Overview to Control of Microorganisms - *CC BY-NC-SA 4.0*
    - 1.7: Ways in which Chemical Control Agents Affect Bacteria - *CC BY-NC-SA 4.0*
    - 1.8: Ways in which Bacteria May Resist Chemical Control Agents - *CC BY-NC-SA 4.0*
  - 2: Pathogenicity - *CC BY-NC-SA 4.0*
    - 2.1: Overview of Microbe-Host Interactions - *CC BY-NC-SA 4.0*
      - 2.1A: Normal Microbiota and Host Relationships - *CC BY-NC-SA 4.0*
      - 2.1B: Opportunistic Microorganisms - *CC BY-NC-SA 4.0*
      - 2.1C: Cooperation Among Microorganisms - *CC BY-NC-SA 4.0*
    - 2.2: Penetrating Host Defenses - *CC BY-NC-SA 4.0*
      - 2.2A: Penetrating Host Defenses - *CC BY-NC-SA 4.0*
      - 2.2B: Pili and Pilus Assembly - *CC BY-NC-SA 4.0*
      - 2.2C: Biofilms and Infections - *CC BY-NC-SA 4.0*
    - 2.3: Damaging Host Cells - *CC BY-NC-SA 4.0*
      - 2.3A: Toxins - *CC BY-NC-SA 4.0*
      - 2.3B: Direct Damage - *CC BY-NC-SA 4.0*
      - 2.3C: Type III and Type IV Secretion - *CC BY-NC-SA 4.0*
      - 2.3D: Plasmids and Lysogeny - *CC BY-NC-SA 4.0*
      - 2.3E: Siderophores - *CC BY-NC-SA 4.0*
    - 2.4: Surviving Within the Host and Exiting the Host - *CC BY-NC-SA 4.0*
      - 2.4A: Intracellular Pathogens - *CC BY-NC-SA 4.0*
      - 2.4B: Extracellular Immune Avoidance - *CC BY-NC-SA 4.0*

- 2.4C: Regulating Virulence - *CC BY-NC-SA 4.0*
- 2.4D: Portals of Exit - *CC BY-NC-SA 4.0*
- 2.5: Pathogenicity and Other Microbes - *CC BY-NC-SA 4.0*
  - 2.5A: Fungi - *CC BY-NC-SA 4.0*
  - 2.5B: Protozoa - *CC BY-NC-SA 4.0*
  - 2.5C: Helminths - *CC BY-NC-SA 4.0*
  - 2.5D: Algae - *CC BY-NC-SA 4.0*

3: Bacteria - *CC BY-NC-SA 4.0*
- 3.1: Clostridium tetani - *CC BY-NC-SA 4.0*
- 3.2: Escherichia coli - *CC BY-NC-SA 4.0*
- 3.3: Haemophilus influenzae - *CC BY-NC-SA 4.0*
- 3.4: Helicobacter pylori - *CC BY-NC-SA 4.0*
- 3.5: Neisseria gonorrhoeae - *CC BY-NC-SA 4.0*
- 3.6: Neisseria meningitidis - *CC BY-NC-SA 4.0*
- 3.7: Staphylococcus aureus - *CC BY-NC-SA 4.0*
- 3.8: Streptococcus pneumoniae - *CC BY-NC-SA 4.0*
- 3.9: Streptococcus pyogenes - *CC BY-NC-SA 4.0*
- 3.10: Vibrio cholerae - *CC BY-NC-SA 4.0*

4: Culturing Bacteria - *CC BY-NC-SA 4.0*
- 4.1: Culture Media - *CC BY-NC-SA 4.0*
- 4.2: Complex and Synthetic Media - *CC BY-NC-SA 4.0*
- 4.3: Selective and Differential Media - *CC BY-NC-SA 4.0*
- 4.4: Aseptic Technique, Dilution, Streaking, and Spread Plates - *CC BY-NC-SA 4.0*
- 4.5: Special Culture Techniques - *CC BY-NC-SA 4.0*

5: Entry into the Host - *CC BY-NC-SA 4.0*
- 5.1: Portals of Microbe Entry - *CC BY-NC-SA 4.0*
- 5.2: Colonization and Growth - *CC BY-NC-SA 4.0*
- 5.3: Pathogenicity Islands and Virulence Factors - *CC BY-NC-SA 4.0*
- 5.4: Adherence - *CC BY-NC-SA 4.0*
- 5.5: Host Risk Factors - *CC BY-NC-SA 4.0*
- 5.6: Innate Resistance - *CC BY-NC-SA 4.0*

6: Bacterial Infections - *CC BY-NC-SA 4.0*
- 6.1: Bacterial Diseases of the Respiratory System - *CC BY-NC-SA 4.0*
  - 6.1A: Pharyngitis - *CC BY-NC-SA 4.0*
    - 1.1: Scarlet Fever - *CC BY-NC-SA 4.0*
  - 6.1C: Diphtheria - *CC BY-NC-SA 4.0*
  - 6.1D: Otitis Media - *CC BY-NC-SA 4.0*
  - 6.1E: Whooping Cough - *CC BY-NC-SA 4.0*
  - 6.1F: Tuberculosis - *CC BY-NC-SA 4.0*
  - 6.1G: Bacterial Pneumonias - *CC BY-NC-SA 4.0*
- 6.2: Bacterial Diseases of the Mouth - *CC BY-NC-SA 4.0*
  - 6.2A: Tooth and Gum Infections - *CC BY-NC-SA 4.0*
  - 6.2B: Dental Caries - *CC BY-NC-SA 4.0*
  - 6.2C: Periodontal Disease - *CC BY-NC-SA 4.0*
- 6.3: Bacterial Diseases of the Digestive System - *CC BY-NC-SA 4.0*
  - 6.3A: Bacterial Gastroenteritis - *CC BY-NC-SA 4.0*
  - 6.3B: Staphylococcal Food Poisoning - *CC BY-NC-SA 4.0*
  - 6.3C: Salmonellosis - *CC BY-NC-SA 4.0*
  - 6.3D: Typhoid Fever - *CC BY-NC-SA 4.0*
  - 6.3E: Cholera - *CC BY-NC-SA 4.0*
  - 6.3F: Noncholera Vibrios - *CC BY-NC-SA 4.0*
  - 6.3G: Pathogenic Escherichia coli - *CC BY-NC-SA 4.0*
  - 6.3H: Campylobacter - *CC BY-NC-SA 4.0*
  - 6.3I: Peptic Ulcer Disease - *CC BY-NC-SA 4.0*
  - 6.3J: Listeriosis - *CC BY-NC-SA 4.0*
- 6.4: Bacterial Diseases of the Urinary System - *CC BY-NC-SA 4.0*
  - 6.4A: Urinary Tract Infection (UTI) - *CC BY-NC-SA 4.0*
  - 6.4B: Cystitis - *CC BY-NC-SA 4.0*
  - 6.4C: Pyelonephritis - *CC BY-NC-SA 4.0*
  - 6.4D: Leptospirosis - *CC BY-NC-SA 4.0*
- 6.5: Bacterial Diseases of the Reproductive System - *CC BY-NC-SA 4.0*
  - 6.5A: Prostatitis - *CC BY-NC-SA 4.0*
  - 6.5B: Prostatitis - *CC BY-NC-SA 4.0*
  - 6.5C: Gonorrhea - *CC BY-NC-SA 4.0*
  - 6.5D: Nongonococcal Urethritis (NGU) - *CC BY-NC-SA 4.0*
  - 6.5E: Pelvic Inflammatory Disease (PID) - *CC BY-NC-SA 4.0*
  - 6.5F: Syphilis - *CC BY-NC-SA 4.0*
  - 6.5G: Genital Ulcer Diseases - *CC BY-NC-SA 4.0*
  - 6.5H: Lymphogranuloma Venereum - *CC BY-NC-SA 4.0*
  - 6.5I: Group B Streptococcus Colonization - *CC BY-NC-SA 4.0*
  - 6.5J: Chancroid (Soft Chancre) - *CC BY-NC-SA 4.0*
  - 6.5K: Bacterial Vaginosis - *CC BY-NC-SA 4.0*
  - 6.5L: Chlamydia - *CC BY-NC-SA 4.0*
- 6.6: Microbial Diseases of the Skin - *CC BY-NC-SA 4.0*

- 6.6A: Structure of the Skin- Epidermis - *CC BY-NC-SA 4.0*
- 6.6B: Microbiota of the Skin - *CC BY-NC-SA 4.0*
- 6.6C: Bacterial Skin Diseases - *CC BY-NC-SA 4.0*
- 6.6D: Viral Skin Diseases - *CC BY-NC-SA 4.0*
- 6.6E: Fungal Skin and Nail Diseases - *CC BY-NC-SA 4.0*
- 6.6F: Parasitic Skin Diseases - *CC BY-NC-SA 4.0*

- 6.7: Microbial Diseases of the Eye - *CC BY-NC-SA 4.0*
  - 6.7A: Anatomy of the Eye - *CC BY-NC-SA 4.0*
  - 6.7B: Normal Eye Microbiota - *CC BY-NC-SA 4.0*
  - 6.7C: Bacterial Eye Diseases - *CC BY-NC-SA 4.0*
  - 6.7D: Other Infectious Eye Diseases - *CC BY-NC-SA 4.0*
- 6.8: Microbial Diseases of the Nervous System - *CC BY-NC-SA 4.0*
  - 6.8A: Functions of the Nervous System - *CC BY-NC-SA 4.0*
  - 6.8B: Subdivisions of the Nervous System - *CC BY-NC-SA 4.0*
  - 6.8C: Meningitis - *CC BY-NC-SA 4.0*
  - 6.8D: Botulism - *CC BY-NC-SA 4.0*
  - 6.8E: Leprosy - *CC BY-NC-SA 4.0*
  - 6.8F: Tetanus - *CC BY-NC-SA 4.0*
  - 6.8G: Paralysis-Causing Bacterial Neurotoxins - *CC BY-NC-SA 4.0*

- 7: Innate Nonspecific Host Defenses - *CC BY-NC-SA 4.0*
  - 7.1: Physical Defenses - *CC BY-NC-SA 4.0*
  - 7.2: Chemical Defenses - *CC BY-NC-SA 4.0*
  - 7.3: Cellular Defenses - *CC BY-NC-SA 4.0*
  - 7.4: Pathogen Recognition and Phagocytosis - *CC BY-NC-SA 4.0*
- 8: Basic Immunology Review - *CC BY-NC-SA 4.0*
  - 8.1: Overview of the Immune System - *CC BY-NC-SA 4.0*
  - 8.2: Anatomical Barriers to Infection, Mechanical Removal of Microbes, and Bacterial Antagonism by Normal Body Microbiota - *CC BY-NC-SA 4.0*
  - 8.3: Cells and Organs of the Immune System - *CC BY-NC-SA 4.0*
  - 8.4: Antimicrobial Enzymes and Antimicrobial Peptides - *CC BY-NC-SA 4.0*
  - 8.5: The Complement System - *CC BY-NC-SA 4.0*
- 9: Innate Immunity - *CC BY-NC-SA 4.0*
  - 9.1: Overview of Immunity - *CC BY-NC-SA 4.0*
  - 9.2: The Innate Immune Response - *CC BY-NC-SA 4.0*
  - 9.3: The Innate Immune System- An Overview - *CC BY-NC-SA 4.0*
  - 9.4: Overview of Human-Microbial Reactions - *CC BY-NC-SA 4.0*
  - 9.5: Natural Killer Cells - *CC BY-NC-SA 4.0*
  - 9.6: Physical and Chemical Barriers - *CC BY-NC-SA 4.0*
  - 9.7: The Complement System - *CC BY-NC-SA 4.0*
  - 9.8: Pathogen Recognition - *CC BY-NC-SA 4.0*
  - 9.9: Defense Cells in the Blood- The Leukocytes - *CC BY-NC-SA 4.0*
  - 9.10: Defense Cells in the Tissue - Dendritic Cells, Macrophages, and Mast Cells - *CC BY-NC-SA 4.0*
  - 9.11: Early Induced Innate Immunity - *CC BY-NC-SA 4.0*
    - 9.11A: Pathogen-Associated Molecular Patterns (PAMPs) and Danger-Associated Molecular Patterns (DAMPs) - *CC BY-NC-SA 4.0*
    - 9.11B: Pattern-Recognition Receptors (PRRs) - *CC BY-NC-SA 4.0*
    - 9.11C: Cytokines Important in Innate Immunity - *CC BY-NC-SA 4.0*
    - 9.11D: Harmful Effects Associated with Abnormal Pattern-Recognition Receptor Responses, Variations in Innate Immune Signaling Pathways, and/or Levels of Cytokine Production - *CC BY-NC-SA 4.0*
    - 9.11E: Phagocytosis - *CC BY-NC-SA 4.0*
    - 9.11F: Natural Killer Cells (NK Cells) and Invariant Natural Killer T-Lymphocytes (iNKT Cells) - *CC BY-NC-SA 4.0*
    - 9.11G: Inflammation - *CC BY-NC-SA 4.0*
    - 9.11H: Nutritional Immunity - *CC BY-NC-SA 4.0*
    - 9.11I: Fever - *CC BY-NC-SA 4.0*
    - 9.11J: The Acute Phase Response - *CC BY-NC-SA 4.0*
    - 9.11K: Intraepithelial T-lymphocytes and B-1 cells - *CC BY-NC-SA 4.0*
- 10: Adaptive Immunity - *CC BY-NC-SA 4.0*
  - 10.1: Immunodeficiency - *CC BY-NC-SA 4.0*
    - 10.1.E: Immunodeficiency (Exercises) - *CC BY-NC-SA 4.0*
  - 10.2: Hypersensitivities - *CC BY-NC-SA 4.0*
    - 10.2.E: Hypersensitivities (Exercises) - *CC BY-NC-SA 4.0*
  - 10.3: Introduction to Adaptive Immunity - *CC BY-NC-SA 4.0*

- 10.3.1: An Overview of Innate and Adaptive Immunity - *CC BY-NC-SA 4.0*
- 10.3.2: Antigens and Epitopes - *CC BY-NC-SA 4.0*
- 10.3.3: Major Cells and Key Cell Surface Molecules Involved in Adaptive Immune Responses - *CC BY-NC-SA 4.0*
  - 10.3.3A: Major Histocompatibility Complex (MHC) Molecules - *CC BY-NC-SA 4.0*
  - 10.3.3B: Antigen-Presenting Cells (APCs) - *CC BY-NC-SA 4.0*
  - 10.3.3C: T4-Lymphocytes (T4-Cells) - *CC BY-NC-SA 4.0*
  - 10.3.3D: T8-Lymphocytes (T8-Cells) - *CC BY-NC-SA 4.0*
  - 10.3.3E: Invarient Natural Killer T-Lymphocytes (iNKT Cells) - *CC BY-NC-SA 4.0*
  - 10.3.3F: B-Lymphocytes (B-Cells) - *CC BY-NC-SA 4.0*
  - 10.3.3G: Natural Killer Cells (NK Cells) - *CC BY-NC-SA 4.0*
- 10.3.4: The Lymphoid System - *CC BY-NC-SA 4.0*
- 10.3.5: An Overview of the Steps Involved in Adaptive Immune Responses - *CC BY-NC-SA 4.0*
- 10.3.E: Introduction to Adaptive Immunity (Exercises) - *CC BY-NC-SA 4.0*

- 10.4: Humoral Immunity - *CC BY-NC-SA 4.0*
  - 10.4.1: Antibodies (Immunoglobulins) - *CC BY-NC-SA 4.0*
    - 10.4.1B: Antibody Structure - *CC BY-NC-SA 4.0*
    - 10.4.1C: The 5 Classes (Isotypes) of Human Antibodies - *CC BY-NC-SA 4.0*
    - 10.4.1D: Generation of Antibody Diversity - *CC BY-NC-SA 4.0*
    - 10.4.1E: Clonal Selection and Clonal Expansion - *CC BY-NC-SA 4.0*
    - 10.4.1F: Anamnestic (Memory) Response - *CC BY-NC-SA 4.0*
  - 10.4.2: Ways That Antibodies Help to Defend the Body - *CC BY-NC-SA 4.0*
    - 10.4.2A: Opsonization - *CC BY-NC-SA 4.0*
    - 10.4.2B: Cytolysis by the Membrane Attack Complex (MAC) - *CC BY-NC-SA 4.0*
    - 10.4.2C: Antibody-dependent Cellular Cytotoxicity (ADCC) by Natural Killer Cells - *CC BY-NC-SA 4.0*
    - 10.4.2D: Neutralization of Exotoxins - *CC BY-NC-SA 4.0*
    - 10.4.2E: Neutralization of Viruses - *CC BY-NC-SA 4.0*
    - 10.4.2F: Preventing Bacterial Adherence - *CC BY-NC-SA 4.0*
    - 10.4.2G: Agglutination of Microorganisms - *CC BY-NC-SA 4.0*
    - 10.4.2H: Immobilization of Bacteria and Protozoans - *CC BY-NC-SA 4.0*
    - 10.4.2I: Promoting an Inflammatory Response - *CC BY-NC-SA 4.0*
  - 10.4.3: Naturally and Artificially Acquired Active and Passive Immunity - *CC BY-NC-SA 4.0*
    - 10.4.3A: Naturally Acquired Immunity - *CC BY-NC-SA 4.0*
    - 10.4.3B: Artificially Acquired Immunity - *CC BY-NC-SA 4.0*
  - 10.4.E: Humoral Immunity (Exercises) - *CC BY-NC-SA 4.0*
- 10.5: Cell-Mediated Immunity - *CC BY-NC-SA 4.0*
  - 10.5.1: Cell-Mediated Immunity - An Overview - *CC BY-NC-SA 4.0*
  - 10.5.2: Activating Antigen-Specific Cytotoxic T-Lymphocytes - *CC BY-NC-SA 4.0*
  - 10.5.3: Activating Macrophages and NK Cells - *CC BY-NC-SA 4.0*
  - 10.5.4: Stimulating Cells to Secrete Cytokines - *CC BY-NC-SA 4.0*
  - 10.5.E: Cell-Mediated Immunity (Exercises) - *CC BY-NC-SA 4.0*

- 11: Specific Adaptive Host Defenses - *CC BY-NC-SA 4.0*
  - 11.1: Architecture of the Immune System - *CC BY-NC-SA 4.0*
  - 11.2: Antigens, Antigen Presenting Cells, and Major Histocompatibility Complexes - *CC BY-NC-SA 4.0*
  - 11.3: T Lymphocytes - *CC BY-NC-SA 4.0*
  - 11.4: B Lymphocytes and Antibodies - *CC BY-NC-SA 4.0*
- 12: Hypersensitivities - *CC BY-NC-SA 4.0*
  - 12.1: Type I (Anaphylactic) Reactions - *CC BY-NC-SA 4.0*
  - 12.2: Diagnosis and Treatment of Allergy - *CC BY-NC-SA 4.0*
  - 12.3: Type II (Cytotoxic) Reactions - *CC BY-NC-SA 4.0*
  - 12.4: Type III (Immune Complex) Reactions - *CC BY-NC-SA 4.0*
  - 12.5: Type IV (Delayed Cell-Mediated) Reactions - *CC BY-NC-SA 4.0*

- 12.6: Immunity Disorders- Hypersensitivity - *CC BY-NC-SA 4.0*

- 13: Laboratory Analysis of the Immune Response - *CC BY-NC-SA 4.0*
  - 13.1: Practical Applications of Monoclonal and Polyclonal Antibodies - *CC BY-NC-SA 4.0*
  - 13.2: Detecting Antigen-Antibody Complexes in vitro - *CC BY-NC-SA 4.0*
  - 13.3: Agglutination Assays - *CC BY-NC-SA 4.0*
  - 13.4: Enzyme Immunoassays (EIA) and Enzyme-Linked Immunosorbent Assays (ELISA) - *CC BY-NC-SA 4.0*
  - 13.5: Fluorescent Auto-Antibody Techniques - *CC BY-NC-SA 4.0*
  - 13.E: Laboratory Analysis of the Immune Response (Exercises) - *CC BY-NC-SA 4.0*
- 14: Immunodeficiencies - *CC BY-NC-SA 4.0*
  - 14.1: Immunity Disorders- Autoimmune Diseases - *CC BY-NC-SA 4.0*
    - 14.1A: Immunodeficiency - *CC BY-NC-SA 4.0*
  - 14.2: Autoimmune Disorders - *CC BY-NC-SA 4.0*
  - 14.3: Superantigens - *CC BY-NC-SA 4.0*
  - 14.4: Immunity Disorders- Immunodeficiencies - *CC BY-NC-SA 4.0*
  - 14.5: Cell-Mediated Autoimmune Reactions - *CC BY-NC-SA 4.0*
  - 14.6: Immune Complex Autoimmune Reactions - *CC BY-NC-SA 4.0*
  - 14.7: Cytotoxic Autoimmune Reactions - *CC BY-NC-SA 4.0*
  - 14.8: Primary Immunodeficiency - *CC BY-NC-SA 4.0*
  - 14.9: Primary Immunodeficiency Diseases - *CC BY-NC-SA 4.0*
  - 14.10: Secondary Immunodeficiency - *CC BY-NC-SA 4.0*
  - 14.11: Secondary Immunodeficiency Diseases - *CC BY-NC-SA 4.0*
  - 14.12: Immunotherapy for Cancer - *CC BY-NC-SA 4.0*
  - 14.13: The Roles of Genetics and Gender in Autoimmune Disease - *CC BY-NC-SA 4.0*
- 15: Acellular Pathogens - *CC BY-NC-SA 4.0*
  - 15.1: Viruses - *CC BY-NC-SA 4.0*
  - 15.2: The Viral Life Cycle - *CC BY-NC-SA 4.0*
  - 15.3: Isolation, Culture, and Identification of Viruses - *CC BY-NC-SA 4.0*
  - 15.4: Viroids, Virusoids, and Prions - *CC BY-NC-SA 4.0*
  - 15.5: Viral Replication - *CC BY-NC-SA 4.0*
    - 15.5A: General Features of Virus Replication - *CC BY-NC-SA 4.0*
    - 15.5B: Steps of Virus Infections - *CC BY-NC-SA 4.0*
    - 15.5C: Tissue Tropism in Animal Viruses - *CC BY-NC-SA 4.0*
    - 15.5D: Animal Viruses - *CC BY-NC-SA 4.0*
    - 15.5E: Plant Virus Life Cycles - *CC BY-NC-SA 4.0*
  - 15.6: Viral Diversity - *CC BY-NC-SA 4.0*
    - 15.6A: Overview of Bacterial Viruses - *CC BY-NC-SA 4.0*
    - 15.6B: RNA Bacteriophages - *CC BY-NC-SA 4.0*
    - 15.6C: Single-Stranded DNA Bacteriophages - *CC BY-NC-SA 4.0*
    - 15.6D: Double-Stranded DNA Bacteriophages - *CC BY-NC-SA 4.0*
    - 15.6E: Mu- A Double-Stranded Transposable DNA Bacteriophage - *CC BY-NC-SA 4.0*
    - 15.6F: Virulent Bacteriophages and T4 - *CC BY-NC-SA 4.0*
    - 15.6G: Temperate Bacteriophages - Lambda and P1 - *CC BY-NC-SA 4.0*
    - 15.6H: Viruses of Archaea - *CC BY-NC-SA 4.0*
  - 15.7: Positive-Strand RNA Viruses in Animals - *CC BY-NC-SA 4.0*
    - 15.7A: Positive-Strand RNA Viruses of Animals - *CC BY-NC-SA 4.0*
    - 15.7B: Virus Attachment and Genome Entry - *CC BY-NC-SA 4.0*
    - 15.7C: Viral Replication and Gene Expression - *CC BY-NC-SA 4.0*
    - 15.7D: Viral Exit - *CC BY-NC-SA 4.0*
  - 15.8: Retroviruses- Double-Stranded RNA Viruses - *CC BY-NC-SA 4.0*
    - 15.8A: Double-Stranded RNA Viruses - Retroviruses - *CC BY-NC-SA 4.0*
    - 15.8B: HIV Attachment and Host Cell Entry - *CC BY-NC-SA 4.0*
    - 15.8C: Retroviral RNA Genome - *CC BY-NC-SA 4.0*
    - 15.8D: Replicative Cycle of HIV - *CC BY-NC-SA 4.0*
  - 15.9: Negative-Strand RNA Viruses in Animals - *CC BY-NC-SA 4.0*
    - 15.9.1: Negative-Strand RNA Viruses of Animals - *CC BY-NC-SA 4.0*

- 15.9.2: Attachment and Entry to the Host Cell - *CC BY-NC-SA 4.0*
- 15.9.3: Replicative Cycle of Influenza A - *CC BY-NC-SA 4.0*

- 15.10: DNA Viruses in Eukaryotes - *CC BY-NC-SA 4.0*
  - 15.10.1: Plant DNA Viruses - *CC BY-NC-SA 4.0*
  - 15.10.2: Replication of Double-Stranded DNA Viruses of Animals - *CC BY-NC-SA 4.0*
  - 15.10.3: Double-Stranded DNA Viruses - Herpesviruses - *CC BY-NC-SA 4.0*
  - 15.10.4: Attachment and Entry of Herpes Simplex - *CC BY-NC-SA 4.0*
  - 15.10.5: Replication of Herpes Simplex Virus - *CC BY-NC-SA 4.0*
  - 15.10.6: Immunodeficiency - *CC BY-NC-SA 4.0*
  - 15.10.7: Double-Stranded DNA Viruses - Pox Viruses - *CC BY-NC-SA 4.0*
  - 15.10.8: Double-Stranded DNA Viruses- Adenoviruses - *CC BY-NC-SA 4.0*
  - 15.10.9: Retroviruses and Hepadnavirus - *CC BY-NC-SA 4.0*
  - 15.10.10: Treatment of Animal Viral Infections - *CC BY-NC-SA 4.0*
- 15.11: Viruses and Cancer - *CC BY-NC-SA 4.0*
  - 15.11.1: Cancer Viruses - *CC BY-NC-SA 4.0*
  - 15.11.2: DNA Oncogenic Viruses - *CC BY-NC-SA 4.0*
  - 15.11.3: RNA Oncogenic Viruses - *CC BY-NC-SA 4.0*
- 15.12: Overview of Viruses - *CC BY-NC-SA 4.0*
  - 15.12.1: Discovery and Detection of Viruses - *CC BY-NC-SA 4.0*
  - 15.12.2: Nature of the Virion - *CC BY-NC-SA 4.0*
  - 15.12.3: Viral Genomes - *CC BY-NC-SA 4.0*
  - 15.12.4: Host Range - *CC BY-NC-SA 4.0*
  - 15.12.5: Viral Size - *CC BY-NC-SA 4.0*
- 15.13: Structure of Viruses - *CC BY-NC-SA 4.0*
  - 15.13A: Viral Morphology - *CC BY-NC-SA 4.0*
  - 15.13B: General Morphology - *CC BY-NC-SA 4.0*
  - 15.13C: Complex and Asymmetrical Virus Particles - *CC BY-NC-SA 4.0*
- 15.14: Classifying Viruses - *CC BY-NC-SA 4.0*
  - 15.14.1: The International Committee on Taxonomy of Viruses - *CC BY-NC-SA 4.0*
  - 15.14.2: The Baltimore Virus Classification - *CC BY-NC-SA 4.0*
  - 15.14.3: Evolution of Viruses - *CC BY-NC-SA 4.0*
  - 15.14.4: Medical Importance of Viruses - *CC BY-NC-SA 4.0*
- 15.15: Culturing Viruses - *CC BY-NC-SA 4.0*
  - 15.15A: Batch Culture of Bacteriophages - *CC BY-NC-SA 4.0*
  - 15.15B: Tissue Culture of Animal Viruses - *CC BY-NC-SA 4.0*
  - 15.15C: Inoculation of Live Animals - *CC BY-NC-SA 4.0*
  - 15.15D: Viral Identification - *CC BY-NC-SA 4.0*
- 15.16: Subviral Entities - *CC BY-NC-SA 4.0*
  - 15.16A: Defective Viruses - *CC BY-NC-SA 4.0*
  - 15.16B: Viroids - *CC BY-NC-SA 4.0*
  - 15.16C: Prions - *CC BY-NC-SA 4.0*
- 15.17: Viral Ecology - *CC BY-NC-SA 4.0*
  - 15.17A: Emergence of Viral Pathogens - *CC BY-NC-SA 4.0*
  - 15.17B: Viral Roles in Ecosystems - *CC BY-NC-SA 4.0*

- 16: The Eukaryotes of Microbiology - *CC BY-NC-SA 4.0*
  - 16.1: Unicellular Eukaryotic Microorganisms - *CC BY-NC-SA 4.0*
  - 16.2: Parasitic Helminths - *CC BY-NC-SA 4.0*
  - 16.3: Fungi - *CC BY-NC-SA 4.0*
  - 16.4: Algae - *CC BY-NC-SA 4.0*
  - 16.5: Lichens - *CC BY-NC-SA 4.0*
  - 16.E: The Eukaryotes of Microbiology (Exercises) - *CC BY-NC-SA 4.0*
- 17: Systemic Infections - *CC BY-NC-SA 4.0*
  - 17.1: Respiratory System Infections - *CC BY-NC-SA 4.0*
    - 17.1.1: Anatomy and Normal Microbiota of the Respiratory Tract - *CC BY-NC-SA 4.0*
    - 17.1.2: Bacterial Infections of the Respiratory Tract - *CC BY-NC-SA 4.0*
    - 17.1.3: Viral Infections of the Respiratory Tract - *CC BY-NC-SA 4.0*
    - 17.1.4: Respiratory Mycoses - *CC BY-NC-SA 4.0*
    - 17.1.E: Respiratory System Infections (Exercises) - *CC BY-NC-SA 4.0*
  - 17.2: Urogenital System Infections - *CC BY-NC-SA 4.0*
    - 17.2.1: Anatomy and Normal Microbiota of the Urogenital Tract - *CC BY-NC-SA 4.0*
    - 17.2.2: Bacterial Infections of the Urinary System - *CC BY-NC-SA 4.0*
    - 17.2.3: Bacterial Infections of the Reproductive System - *CC BY-NC-SA 4.0*

- 17.2.4: Viral Infections of the Reproductive System - *CC BY-NC-SA 4.0*
- 17.2.5: Fungal Infections of the Reproductive System - *CC BY-NC-SA 4.0*
- 17.2.6: Protozoan Infections of the Reproductive System - *CC BY-NC-SA 4.0*
- 17.2.E: Urogenital System Infections (Exercises) - *CC BY-NC-SA 4.0*

- 17.3: Digestive System Infections - *CC BY-NC-SA 4.0*
  - 17.3.1: Anatomy and Normal Microbiota of the Digestive System - *CC BY-NC-SA 4.0*
  - 17.3.2: Microbial Diseases of the Mouth and Oral Cavity - *CC BY-NC-SA 4.0*
  - 17.3.3: Bacterial Infections of the Gastrointestinal Tract - *CC BY-NC-SA 4.0*
  - 17.3.4: Viral Infections of the Gastrointestinal Tract - *CC BY-NC-SA 4.0*
  - 17.3.5: Protozoan Infections of the Gastrointestinal Tract - *CC BY-NC-SA 4.0*
  - 17.3.6: Helminthic Infections of the Gastrointestinal Tract - *CC BY-NC-SA 4.0*
  - 17.3.E: Digestive System Infections (Exercises) - *CC BY-NC-SA 4.0*
- 17.4: Circulatory and Lymphatic System Infections - *CC BY-NC-SA 4.0*
  - 17.4.1: Anatomy of the Circulatory and Lymphatic Systems - *CC BY-NC-SA 4.0*
  - 17.4.2: Bacterial Infections of the Circulatory and Lymphatic Systems - *CC BY-NC-SA 4.0*
  - 17.4.3: Viral Infections of the Circulatory and Lymphatic Systems - *CC BY-NC-SA 4.0*
  - 17.4.4: Parasitic Infections of the Circulatory and Lymphatic Systems - *CC BY-NC-SA 4.0*
  - 17.4.E: Circulatory and Lymphatic System Infections (Exercises) - *CC BY-NC-SA 4.0*
- 17.5: Nervous System Infections - *CC BY-NC-SA 4.0*
  - 17.5.1: Anatomy of the Nervous System - *CC BY-NC-SA 4.0*
  - 17.5.2: Bacterial Diseases of the Nervous System - *CC BY-NC-SA 4.0*
  - 17.5.3: Acellular Pathogenic Diseases of the Nervous System - *CC BY-NC-SA 4.0*
  - 17.5.4: Neuromycoses and Parasitic Diseases of the Nervous System - *CC BY-NC-SA 4.0*
  - 17.5.E: Nervous System Infections (Exercises) - *CC BY-NC-SA 4.0*
- 17.6: Fungal Diseases of the Respiratory System - *CC BY-NC-SA 4.0*
  - 17.6.1: Histoplasmosis - *CC BY-NC-SA 4.0*
  - 17.6.2: Coccidiomycosis - *CC BY-NC-SA 4.0*
  - 17.6.3: Pneumocystis Pneumonia - *CC BY-NC-SA 4.0*
  - 17.6.4: Blastomycosis - *CC BY-NC-SA 4.0*
  - 17.6.5: Other Fungi Involved in Respiratory Disease - *CC BY-NC-SA 4.0*
- 17.7: Fungal and Protozoan Diseases of the Digestive System - *CC BY-NC-SA 4.0*
  - 17.7.1: Ergot Poisoning - *CC BY-NC-SA 4.0*
  - 17.7.2: Aflatoxin Poisoning - *CC BY-NC-SA 4.0*
  - 17.7.3: Giardiasis - *CC BY-NC-SA 4.0*
  - 17.7.4: Cryptosporidiosis - *CC BY-NC-SA 4.0*
  - 17.7.5: Cyclospora Diarrheal Infection - *CC BY-NC-SA 4.0*
  - 17.7.6: Amoebic Dysentery (Amoebiasis) - *CC BY-NC-SA 4.0*
  - 17.7.7: Legionellosis - *CC BY-NC-SA 4.0*
- 17.8: Helminthic Diseases of the Digestive System - *CC BY-NC-SA 4.0*
  - 17.8.1: Tapeworms - *CC BY-NC-SA 4.0*
  - 17.8.2: Hydatid Disease - *CC BY-NC-SA 4.0*
  - 17.8.3: Nematodes - *CC BY-NC-SA 4.0*
- 17.9: Fungal and Protozoan Diseases of the Reproductive System - *CC BY-NC-SA 4.0*
  - 17.9.1: Vulvovaginal Candidiasis - *CC BY-NC-SA 4.0*
  - 17.9.2: Trichomoniasis - *CC BY-NC-SA 4.0*
  - 17.9.3: The TORCH Panel of Tests - *CC BY-NC-SA 4.0*
- 17.10: Fungal Skin and Nail Diseases - *CC BY-NC-SA 4.0*
- 17.11: Parasitic Skin Diseases - *CC BY-NC-SA 4.0*
- 17.12: Other Infectious Eye Diseases - *CC BY-NC-SA 4.0*
- 17.13: Fungal, Protozoan, Prion, and Other Diseases of the Nervous System - *CC BY-NC-SA 4.0*
  - 17.13.1: Cryptococcosis - *CC BY-NC-SA 4.0*
  - 17.13.2: African Trypanosomiasis - *CC BY-NC-SA 4.0*
  - 17.13.3: Amoebic Meningoencephalitis - *CC BY-NC-SA 4.0*
  - 17.13.4: Bovine Spongiform Encephalopathy - *CC BY-NC-SA 4.0*
  - 17.13.5: Variant Creutzfeldt-Jakob Disease - *CC BY-NC-SA 4.0*
  - 17.13.6: Chronic Fatigue Syndrome - *CC BY-NC-SA 4.0*

- 18: Immunization - *CC BY-NC-SA 4.0*
  - 18.1: Passive Immunization - *CC BY-NC-SA 4.0*
  - 18.2: Vaccination - *CC BY-NC-SA 4.0*
  - 18.3: Types of Vaccines - *CC BY-NC-SA 4.0*
  - 18.4: Development of New Vaccines - *CC BY-NC-SA 4.0*
  - 18.5: Vaccine Safety - *CC BY-NC-SA 4.0*
- 19: Vaccine Safety - *CC BY-NC-SA 4.0*
  - 19.1: Non-Severe Events - *CC BY-NC-SA 4.0*
  - 19.2: Anaphylaxis - *CC BY-NC-SA 4.0*
  - 19.3: Vaccine Facts - *CC BY-NC-SA 4.0*
  - 19.4: Self Assessment - *CC BY-NC-SA 4.0*
  - 19.5: Vaccine Safety - *CC BY-NC-SA 4.0*
  - 19.6: Evaluation of Vaccines Pre-License - *CC BY-NC-SA 4.0*
  - 19.7: Canada Vigilance Program - *CC BY-NC-SA 4.0*
  - 19.8: Reflective Questions - *CC BY-NC-SA 4.0*
  - 19.9: Key Takeaways - *CC BY-NC-SA 4.0*
  - 19.10: References - *CC BY-NC-SA 4.0*
- 20: Human Health and Disease - *CC BY-NC-SA 4.0*
  - 20.1: Human Health and Disease - *CC BY-NC-SA 4.0*
  - 20.2: The Gut Microbiome - *CC BY-NC-SA 4.0*
  - 20.3: The Oral Microbiome - *CC BY-NC-SA 4.0*
  - 20.4: The Skin Microbiome - *CC BY-NC-SA 4.0*
  - 20.5: The Respiratory Microbiome - *CC BY-NC-SA 4.0*
  - 20.6: The Vaginal Microbiome - *CC BY-NC-SA 4.0*
  - 20.7: Mental Health and Multi-Microbiome Interactions - *CC BY-NC-SA 4.0*
- 21: Cancer Immunobiology and Immunotherapy - *CC BY-NC-SA 4.0*
- 22: Skin and Eye Infections - *CC BY-NC-SA 4.0*
  - 22.1: Anatomy and Normal Microbiota of the Skin and Eyes - *CC BY-NC-SA 4.0*
  - 22.2: Bacterial Infections of the Skin and Eyes - *CC BY-NC-SA 4.0*
  - 22.3: Viral Infections of the Skin and Eyes - *CC BY-NC-SA 4.0*
  - 22.4: Mycoses of the Skin and Eyes - *CC BY-NC-SA 4.0*
  - 22.5: Protozoan and Helminthic Infections of the Eyes - *CC BY-NC-SA 4.0*
- Back Matter - *CC BY-NC-SA 4.0*
  - Index - *CC BY-NC-SA 4.0*
  - Glossary - *CC BY-NC-SA 4.0*
  - Detailed Licensing - *CC BY-NC-SA 4.0*
  - Detailed Licensing - *CC BY-NC-SA 4.0*

Detailed Licensing

Overview

Title: Block V Preparation Materials

Webpages: 440

Applicable Restrictions: Noncommercial

All licenses found:

- CC BY-NC-SA 4.0: 99.8% (439 pages)
- Undeclared: 0.2% (1 page)

By Page

- Block V Preparation Materials - *CC BY-NC-SA 4.0*
  - Front Matter - *CC BY-NC-SA 4.0*
    - TitlePage - *CC BY-NC-SA 4.0*
    - InfoPage - *CC BY-NC-SA 4.0*
    - Table of Contents - *Undeclared*
    - Licensing - *CC BY-NC-SA 4.0*
  - 1: Basic Microbiology and Infection Control - *CC BY-NC-SA 4.0*
    - 1.1: Classification - The Three Domain System - *CC BY-NC-SA 4.0*
    - 1.2: Sizes, Shapes, and Arrangements of Bacteria - *CC BY-NC-SA 4.0*
    - 1.3: The Peptidoglycan Cell Wall - *CC BY-NC-SA 4.0*
      - 1.3.1: Damage of the Cell Wall - *CC BY-NC-SA 4.0*
      - 1.3A: The Gram-Positive Cell Wall - *CC BY-NC-SA 4.0*
      - 1.3B: The Gram-Negative Cell Wall - *CC BY-NC-SA 4.0*
      - 1.3C: The Acid-Fast Cell Wall - *CC BY-NC-SA 4.0*
    - 1.4: Structures Outside the Cell Wall - *CC BY-NC-SA 4.0*
      - 1.4A: Glycocalyx (Capsules) and Biofilms - *CC BY-NC-SA 4.0*
      - 1.4B: Flagella - *CC BY-NC-SA 4.0*
      - 1.4C: Fimbriae and Pili - *CC BY-NC-SA 4.0*
    - 1.5: Cellular Components within the Cytoplasm - *CC BY-NC-SA 4.0*
      - 1.5A: Cytoplasm - *CC BY-NC-SA 4.0*
      - 1.5B: The Bacterial Chromosome and Nucleoid - *CC BY-NC-SA 4.0*
      - 1.5C: Plasmids and Transposons - *CC BY-NC-SA 4.0*
      - 1.5D: Ribosomes - *CC BY-NC-SA 4.0*
      - 1.5E: Endospores - *CC BY-NC-SA 4.0*
      - 1.5F: Inclusion Bodies and Organelles Used for Photosynthesis - *CC BY-NC-SA 4.0*
    - 1.6: An Overview to Control of Microorganisms - *CC BY-NC-SA 4.0*
    - 1.7: Ways in which Chemical Control Agents Affect Bacteria - *CC BY-NC-SA 4.0*
    - 1.8: Ways in which Bacteria May Resist Chemical Control Agents - *CC BY-NC-SA 4.0*
  - 2: Pathogenicity - *CC BY-NC-SA 4.0*
    - 2.1: Overview of Microbe-Host Interactions - *CC BY-NC-SA 4.0*
      - 2.1A: Normal Microbiota and Host Relationships - *CC BY-NC-SA 4.0*
      - 2.1B: Opportunistic Microorganisms - *CC BY-NC-SA 4.0*
      - 2.1C: Cooperation Among Microorganisms - *CC BY-NC-SA 4.0*
    - 2.2: Penetrating Host Defenses - *CC BY-NC-SA 4.0*
      - 2.2A: Penetrating Host Defenses - *CC BY-NC-SA 4.0*
      - 2.2B: Pili and Pilus Assembly - *CC BY-NC-SA 4.0*
      - 2.2C: Biofilms and Infections - *CC BY-NC-SA 4.0*
    - 2.3: Damaging Host Cells - *CC BY-NC-SA 4.0*
      - 2.3A: Toxins - *CC BY-NC-SA 4.0*
      - 2.3B: Direct Damage - *CC BY-NC-SA 4.0*
      - 2.3C: Type III and Type IV Secretion - *CC BY-NC-SA 4.0*
      - 2.3D: Plasmids and Lysogeny - *CC BY-NC-SA 4.0*
      - 2.3E: Siderophores - *CC BY-NC-SA 4.0*
    - 2.4: Surviving Within the Host and Exiting the Host - *CC BY-NC-SA 4.0*
      - 2.4A: Intracellular Pathogens - *CC BY-NC-SA 4.0*
      - 2.4B: Extracellular Immune Avoidance - *CC BY-NC-SA 4.0*

- 2.4C: Regulating Virulence - *CC BY-NC-SA 4.0*
- 2.4D: Portals of Exit - *CC BY-NC-SA 4.0*
- 2.5: Pathogenicity and Other Microbes - *CC BY-NC-SA 4.0*
  - 2.5A: Fungi - *CC BY-NC-SA 4.0*
  - 2.5B: Protozoa - *CC BY-NC-SA 4.0*
  - 2.5C: Helminths - *CC BY-NC-SA 4.0*
  - 2.5D: Algae - *CC BY-NC-SA 4.0*

3: Bacteria - *CC BY-NC-SA 4.0*
- 3.1: Clostridium tetani - *CC BY-NC-SA 4.0*
- 3.2: Escherichia coli - *CC BY-NC-SA 4.0*
- 3.3: Haemophilus influenzae - *CC BY-NC-SA 4.0*
- 3.4: Helicobacter pylori - *CC BY-NC-SA 4.0*
- 3.5: Neisseria gonorrhoeae - *CC BY-NC-SA 4.0*
- 3.6: Neisseria meningitidis - *CC BY-NC-SA 4.0*
- 3.7: Staphylococcus aureus - *CC BY-NC-SA 4.0*
- 3.8: Streptococcus pneumoniae - *CC BY-NC-SA 4.0*
- 3.9: Streptococcus pyogenes - *CC BY-NC-SA 4.0*
- 3.10: Vibrio cholerae - *CC BY-NC-SA 4.0*

4: Culturing Bacteria - *CC BY-NC-SA 4.0*
- 4.1: Culture Media - *CC BY-NC-SA 4.0*
- 4.2: Complex and Synthetic Media - *CC BY-NC-SA 4.0*
- 4.3: Selective and Differential Media - *CC BY-NC-SA 4.0*
- 4.4: Aseptic Technique, Dilution, Streaking, and Spread Plates - *CC BY-NC-SA 4.0*
- 4.5: Special Culture Techniques - *CC BY-NC-SA 4.0*

5: Entry into the Host - *CC BY-NC-SA 4.0*
- 5.1: Portals of Microbe Entry - *CC BY-NC-SA 4.0*
- 5.2: Colonization and Growth - *CC BY-NC-SA 4.0*
- 5.3: Pathogenicity Islands and Virulence Factors - *CC BY-NC-SA 4.0*
- 5.4: Adherence - *CC BY-NC-SA 4.0*
- 5.5: Host Risk Factors - *CC BY-NC-SA 4.0*
- 5.6: Innate Resistance - *CC BY-NC-SA 4.0*

6: Bacterial Infections - *CC BY-NC-SA 4.0*
- 6.1: Bacterial Diseases of the Respiratory System - *CC BY-NC-SA 4.0*
  - 6.1A: Pharyngitis - *CC BY-NC-SA 4.0*
    - 1.1: Scarlet Fever - *CC BY-NC-SA 4.0*
  - 6.1C: Diphtheria - *CC BY-NC-SA 4.0*
  - 6.1D: Otitis Media - *CC BY-NC-SA 4.0*
  - 6.1E: Whooping Cough - *CC BY-NC-SA 4.0*
  - 6.1F: Tuberculosis - *CC BY-NC-SA 4.0*
  - 6.1G: Bacterial Pneumonias - *CC BY-NC-SA 4.0*
- 6.2: Bacterial Diseases of the Mouth - *CC BY-NC-SA 4.0*
  - 6.2A: Tooth and Gum Infections - *CC BY-NC-SA 4.0*
  - 6.2B: Dental Caries - *CC BY-NC-SA 4.0*
  - 6.2C: Periodontal Disease - *CC BY-NC-SA 4.0*
- 6.3: Bacterial Diseases of the Digestive System - *CC BY-NC-SA 4.0*
  - 6.3A: Bacterial Gastroenteritis - *CC BY-NC-SA 4.0*
  - 6.3B: Staphylococcal Food Poisoning - *CC BY-NC-SA 4.0*
  - 6.3C: Salmonellosis - *CC BY-NC-SA 4.0*
  - 6.3D: Typhoid Fever - *CC BY-NC-SA 4.0*
  - 6.3E: Cholera - *CC BY-NC-SA 4.0*
  - 6.3F: Noncholera Vibrios - *CC BY-NC-SA 4.0*
  - 6.3G: Pathogenic Escherichia coli - *CC BY-NC-SA 4.0*
  - 6.3H: Campylobacter - *CC BY-NC-SA 4.0*
  - 6.3I: Peptic Ulcer Disease - *CC BY-NC-SA 4.0*
  - 6.3J: Listeriosis - *CC BY-NC-SA 4.0*
- 6.4: Bacterial Diseases of the Urinary System - *CC BY-NC-SA 4.0*
  - 6.4A: Urinary Tract Infection (UTI) - *CC BY-NC-SA 4.0*
  - 6.4B: Cystitis - *CC BY-NC-SA 4.0*
  - 6.4C: Pyelonephritis - *CC BY-NC-SA 4.0*
  - 6.4D: Leptospirosis - *CC BY-NC-SA 4.0*
- 6.5: Bacterial Diseases of the Reproductive System - *CC BY-NC-SA 4.0*
  - 6.5A: Prostatitis - *CC BY-NC-SA 4.0*
  - 6.5B: Prostatitis - *CC BY-NC-SA 4.0*
  - 6.5C: Gonorrhea - *CC BY-NC-SA 4.0*
  - 6.5D: Nongonococcal Urethritis (NGU) - *CC BY-NC-SA 4.0*
  - 6.5E: Pelvic Inflammatory Disease (PID) - *CC BY-NC-SA 4.0*
  - 6.5F: Syphilis - *CC BY-NC-SA 4.0*
  - 6.5G: Genital Ulcer Diseases - *CC BY-NC-SA 4.0*
  - 6.5H: Lymphogranuloma Venereum - *CC BY-NC-SA 4.0*
  - 6.5I: Group B Streptococcus Colonization - *CC BY-NC-SA 4.0*
  - 6.5J: Chancroid (Soft Chancre) - *CC BY-NC-SA 4.0*
  - 6.5K: Bacterial Vaginosis - *CC BY-NC-SA 4.0*
  - 6.5L: Chlamydia - *CC BY-NC-SA 4.0*
- 6.6: Microbial Diseases of the Skin - *CC BY-NC-SA 4.0*

- 6.6A: Structure of the Skin- Epidermis - *CC BY-NC-SA 4.0*
- 6.6B: Microbiota of the Skin - *CC BY-NC-SA 4.0*
- 6.6C: Bacterial Skin Diseases - *CC BY-NC-SA 4.0*
- 6.6D: Viral Skin Diseases - *CC BY-NC-SA 4.0*
- 6.6E: Fungal Skin and Nail Diseases - *CC BY-NC-SA 4.0*
- 6.6F: Parasitic Skin Diseases - *CC BY-NC-SA 4.0*

- 6.7: Microbial Diseases of the Eye - *CC BY-NC-SA 4.0*
  - 6.7A: Anatomy of the Eye - *CC BY-NC-SA 4.0*
  - 6.7B: Normal Eye Microbiota - *CC BY-NC-SA 4.0*
  - 6.7C: Bacterial Eye Diseases - *CC BY-NC-SA 4.0*
  - 6.7D: Other Infectious Eye Diseases - *CC BY-NC-SA 4.0*
- 6.8: Microbial Diseases of the Nervous System - *CC BY-NC-SA 4.0*
  - 6.8A: Functions of the Nervous System - *CC BY-NC-SA 4.0*
  - 6.8B: Subdivisions of the Nervous System - *CC BY-NC-SA 4.0*
  - 6.8C: Meningitis - *CC BY-NC-SA 4.0*
  - 6.8D: Botulism - *CC BY-NC-SA 4.0*
  - 6.8E: Leprosy - *CC BY-NC-SA 4.0*
  - 6.8F: Tetanus - *CC BY-NC-SA 4.0*
  - 6.8G: Paralysis-Causing Bacterial Neurotoxins - *CC BY-NC-SA 4.0*

- 7: Innate Nonspecific Host Defenses - *CC BY-NC-SA 4.0*
  - 7.1: Physical Defenses - *CC BY-NC-SA 4.0*
  - 7.2: Chemical Defenses - *CC BY-NC-SA 4.0*
  - 7.3: Cellular Defenses - *CC BY-NC-SA 4.0*
  - 7.4: Pathogen Recognition and Phagocytosis - *CC BY-NC-SA 4.0*
- 8: Basic Immunology Review - *CC BY-NC-SA 4.0*
  - 8.1: Overview of the Immune System - *CC BY-NC-SA 4.0*
  - 8.2: Anatomical Barriers to Infection, Mechanical Removal of Microbes, and Bacterial Antagonism by Normal Body Microbiota - *CC BY-NC-SA 4.0*
  - 8.3: Cells and Organs of the Immune System - *CC BY-NC-SA 4.0*
  - 8.4: Antimicrobial Enzymes and Antimicrobial Peptides - *CC BY-NC-SA 4.0*
  - 8.5: The Complement System - *CC BY-NC-SA 4.0*
- 9: Innate Immunity - *CC BY-NC-SA 4.0*
  - 9.1: Overview of Immunity - *CC BY-NC-SA 4.0*
  - 9.2: The Innate Immune Response - *CC BY-NC-SA 4.0*
  - 9.3: The Innate Immune System- An Overview - *CC BY-NC-SA 4.0*
  - 9.4: Overview of Human-Microbial Reactions - *CC BY-NC-SA 4.0*
  - 9.5: Natural Killer Cells - *CC BY-NC-SA 4.0*
  - 9.6: Physical and Chemical Barriers - *CC BY-NC-SA 4.0*
  - 9.7: The Complement System - *CC BY-NC-SA 4.0*
  - 9.8: Pathogen Recognition - *CC BY-NC-SA 4.0*
  - 9.9: Defense Cells in the Blood- The Leukocytes - *CC BY-NC-SA 4.0*
  - 9.10: Defense Cells in the Tissue - Dendritic Cells, Macrophages, and Mast Cells - *CC BY-NC-SA 4.0*
  - 9.11: Early Induced Innate Immunity - *CC BY-NC-SA 4.0*
    - 9.11A: Pathogen-Associated Molecular Patterns (PAMPs) and Danger-Associated Molecular Patterns (DAMPs) - *CC BY-NC-SA 4.0*
    - 9.11B: Pattern-Recognition Receptors (PRRs) - *CC BY-NC-SA 4.0*
    - 9.11C: Cytokines Important in Innate Immunity - *CC BY-NC-SA 4.0*
    - 9.11D: Harmful Effects Associated with Abnormal Pattern-Recognition Receptor Responses, Variations in Innate Immune Signaling Pathways, and/or Levels of Cytokine Production - *CC BY-NC-SA 4.0*
    - 9.11E: Phagocytosis - *CC BY-NC-SA 4.0*
    - 9.11F: Natural Killer Cells (NK Cells) and Invariant Natural Killer T-Lymphocytes (iNKT Cells) - *CC BY-NC-SA 4.0*
    - 9.11G: Inflammation - *CC BY-NC-SA 4.0*
    - 9.11H: Nutritional Immunity - *CC BY-NC-SA 4.0*
    - 9.11I: Fever - *CC BY-NC-SA 4.0*
    - 9.11J: The Acute Phase Response - *CC BY-NC-SA 4.0*
    - 9.11K: Intraepithelial T-lymphocytes and B-1 cells - *CC BY-NC-SA 4.0*
- 10: Adaptive Immunity - *CC BY-NC-SA 4.0*
  - 10.1: Immunodeficiency - *CC BY-NC-SA 4.0*
    - 10.1.E: Immunodeficiency (Exercises) - *CC BY-NC-SA 4.0*
  - 10.2: Hypersensitivities - *CC BY-NC-SA 4.0*
    - 10.2.E: Hypersensitivities (Exercises) - *CC BY-NC-SA 4.0*
  - 10.3: Introduction to Adaptive Immunity - *CC BY-NC-SA 4.0*

- 10.3.1: An Overview of Innate and Adaptive Immunity - *CC BY-NC-SA 4.0*
- 10.3.2: Antigens and Epitopes - *CC BY-NC-SA 4.0*
- 10.3.3: Major Cells and Key Cell Surface Molecules Involved in Adaptive Immune Responses - *CC BY-NC-SA 4.0*
  - 10.3.3A: Major Histocompatibility Complex (MHC) Molecules - *CC BY-NC-SA 4.0*
  - 10.3.3B: Antigen-Presenting Cells (APCs) - *CC BY-NC-SA 4.0*
  - 10.3.3C: T4-Lymphocytes (T4-Cells) - *CC BY-NC-SA 4.0*
  - 10.3.3D: T8-Lymphocytes (T8-Cells) - *CC BY-NC-SA 4.0*
  - 10.3.3E: Invarient Natural Killer T-Lymphocytes (iNKT Cells) - *CC BY-NC-SA 4.0*
  - 10.3.3F: B-Lymphocytes (B-Cells) - *CC BY-NC-SA 4.0*
  - 10.3.3G: Natural Killer Cells (NK Cells) - *CC BY-NC-SA 4.0*
- 10.3.4: The Lymphoid System - *CC BY-NC-SA 4.0*
- 10.3.5: An Overview of the Steps Involved in Adaptive Immune Responses - *CC BY-NC-SA 4.0*
- 10.3.E: Introduction to Adaptive Immunity (Exercises) - *CC BY-NC-SA 4.0*

- 10.4: Humoral Immunity - *CC BY-NC-SA 4.0*
  - 10.4.1: Antibodies (Immunoglobulins) - *CC BY-NC-SA 4.0*
    - 10.4.1B: Antibody Structure - *CC BY-NC-SA 4.0*
    - 10.4.1C: The 5 Classes (Isotypes) of Human Antibodies - *CC BY-NC-SA 4.0*
    - 10.4.1D: Generation of Antibody Diversity - *CC BY-NC-SA 4.0*
    - 10.4.1E: Clonal Selection and Clonal Expansion - *CC BY-NC-SA 4.0*
    - 10.4.1F: Anamnestic (Memory) Response - *CC BY-NC-SA 4.0*
  - 10.4.2: Ways That Antibodies Help to Defend the Body - *CC BY-NC-SA 4.0*
    - 10.4.2A: Opsonization - *CC BY-NC-SA 4.0*
    - 10.4.2B: Cytolysis by the Membrane Attack Complex (MAC) - *CC BY-NC-SA 4.0*
    - 10.4.2C: Antibody-dependent Cellular Cytotoxicity (ADCC) by Natural Killer Cells - *CC BY-NC-SA 4.0*
    - 10.4.2D: Neutralization of Exotoxins - *CC BY-NC-SA 4.0*
    - 10.4.2E: Neutralization of Viruses - *CC BY-NC-SA 4.0*
    - 10.4.2F: Preventing Bacterial Adherence - *CC BY-NC-SA 4.0*
    - 10.4.2G: Agglutination of Microorganisms - *CC BY-NC-SA 4.0*
    - 10.4.2H: Immobilization of Bacteria and Protozoans - *CC BY-NC-SA 4.0*
    - 10.4.2I: Promoting an Inflammatory Response - *CC BY-NC-SA 4.0*
  - 10.4.3: Naturally and Artificially Acquired Active and Passive Immunity - *CC BY-NC-SA 4.0*
    - 10.4.3A: Naturally Acquired Immunity - *CC BY-NC-SA 4.0*
    - 10.4.3B: Artificially Acquired Immunity - *CC BY-NC-SA 4.0*
  - 10.4.E: Humoral Immunity (Exercises) - *CC BY-NC-SA 4.0*
- 10.5: Cell-Mediated Immunity - *CC BY-NC-SA 4.0*
  - 10.5.1: Cell-Mediated Immunity - An Overview - *CC BY-NC-SA 4.0*
  - 10.5.2: Activating Antigen-Specific Cytotoxic T-Lymphocytes - *CC BY-NC-SA 4.0*
  - 10.5.3: Activating Macrophages and NK Cells - *CC BY-NC-SA 4.0*
  - 10.5.4: Stimulating Cells to Secrete Cytokines - *CC BY-NC-SA 4.0*
  - 10.5.E: Cell-Mediated Immunity (Exercises) - *CC BY-NC-SA 4.0*

- 11: Specific Adaptive Host Defenses - *CC BY-NC-SA 4.0*
  - 11.1: Architecture of the Immune System - *CC BY-NC-SA 4.0*
  - 11.2: Antigens, Antigen Presenting Cells, and Major Histocompatibility Complexes - *CC BY-NC-SA 4.0*
  - 11.3: T Lymphocytes - *CC BY-NC-SA 4.0*
  - 11.4: B Lymphocytes and Antibodies - *CC BY-NC-SA 4.0*

- 12: Hypersensitivities - *CC BY-NC-SA 4.0*
  - 12.1: Type I (Anaphylactic) Reactions - *CC BY-NC-SA 4.0*
  - 12.2: Diagnosis and Treatment of Allergy - *CC BY-NC-SA 4.0*
  - 12.3: Type II (Cytotoxic) Reactions - *CC BY-NC-SA 4.0*
  - 12.4: Type III (Immune Complex) Reactions - *CC BY-NC-SA 4.0*
  - 12.5: Type IV (Delayed Cell-Mediated) Reactions - *CC BY-NC-SA 4.0*

- 12.6: Immunity Disorders- Hypersensitivity - *CC BY-NC-SA 4.0*

- 13: Laboratory Analysis of the Immune Response - *CC BY-NC-SA 4.0*
  - 13.1: Practical Applications of Monoclonal and Polyclonal Antibodies - *CC BY-NC-SA 4.0*
  - 13.2: Detecting Antigen-Antibody Complexes in vitro - *CC BY-NC-SA 4.0*
  - 13.3: Agglutination Assays - *CC BY-NC-SA 4.0*
  - 13.4: Enzyme Immunoassays (EIA) and Enzyme-Linked Immunosorbent Assays (ELISA) - *CC BY-NC-SA 4.0*
  - 13.5: Fluorescent Auto-Antibody Techniques - *CC BY-NC-SA 4.0*
  - 13.E: Laboratory Analysis of the Immune Response (Exercises) - *CC BY-NC-SA 4.0*
- 14: Immunodeficiencies - *CC BY-NC-SA 4.0*
  - 14.1: Immunity Disorders- Autoimmune Diseases - *CC BY-NC-SA 4.0*
    - 14.1A: Immunodeficiency - *CC BY-NC-SA 4.0*
  - 14.2: Autoimmune Disorders - *CC BY-NC-SA 4.0*
  - 14.3: Superantigens - *CC BY-NC-SA 4.0*
  - 14.4: Immunity Disorders- Immunodeficiencies - *CC BY-NC-SA 4.0*
  - 14.5: Cell-Mediated Autoimmune Reactions - *CC BY-NC-SA 4.0*
  - 14.6: Immune Complex Autoimmune Reactions - *CC BY-NC-SA 4.0*
  - 14.7: Cytotoxic Autoimmune Reactions - *CC BY-NC-SA 4.0*
  - 14.8: Primary Immunodeficiency - *CC BY-NC-SA 4.0*
  - 14.9: Primary Immunodeficiency Diseases - *CC BY-NC-SA 4.0*
  - 14.10: Secondary Immunodeficiency - *CC BY-NC-SA 4.0*
  - 14.11: Secondary Immunodeficiency Diseases - *CC BY-NC-SA 4.0*
  - 14.12: Immunotherapy for Cancer - *CC BY-NC-SA 4.0*
  - 14.13: The Roles of Genetics and Gender in Autoimmune Disease - *CC BY-NC-SA 4.0*
- 15: Acellular Pathogens - *CC BY-NC-SA 4.0*
  - 15.1: Viruses - *CC BY-NC-SA 4.0*
  - 15.2: The Viral Life Cycle - *CC BY-NC-SA 4.0*
  - 15.3: Isolation, Culture, and Identification of Viruses - *CC BY-NC-SA 4.0*
  - 15.4: Viroids, Virusoids, and Prions - *CC BY-NC-SA 4.0*
  - 15.5: Viral Replication - *CC BY-NC-SA 4.0*
    - 15.5A: General Features of Virus Replication - *CC BY-NC-SA 4.0*
    - 15.5B: Steps of Virus Infections - *CC BY-NC-SA 4.0*
    - 15.5C: Tissue Tropism in Animal Viruses - *CC BY-NC-SA 4.0*
    - 15.5D: Animal Viruses - *CC BY-NC-SA 4.0*
    - 15.5E: Plant Virus Life Cycles - *CC BY-NC-SA 4.0*
  - 15.6: Viral Diversity - *CC BY-NC-SA 4.0*
    - 15.6A: Overview of Bacterial Viruses - *CC BY-NC-SA 4.0*
    - 15.6B: RNA Bacteriophages - *CC BY-NC-SA 4.0*
    - 15.6C: Single-Stranded DNA Bacteriophages - *CC BY-NC-SA 4.0*
    - 15.6D: Double-Stranded DNA Bacteriophages - *CC BY-NC-SA 4.0*
    - 15.6E: Mu- A Double-Stranded Transposable DNA Bacteriophage - *CC BY-NC-SA 4.0*
    - 15.6F: Virulent Bacteriophages and T4 - *CC BY-NC-SA 4.0*
    - 15.6G: Temperate Bacteriophages - Lambda and P1 - *CC BY-NC-SA 4.0*
    - 15.6H: Viruses of Archaea - *CC BY-NC-SA 4.0*
  - 15.7: Positive-Strand RNA Viruses in Animals - *CC BY-NC-SA 4.0*
    - 15.7A: Positive-Strand RNA Viruses of Animals - *CC BY-NC-SA 4.0*
    - 15.7B: Virus Attachment and Genome Entry - *CC BY-NC-SA 4.0*
    - 15.7C: Viral Replication and Gene Expression - *CC BY-NC-SA 4.0*
    - 15.7D: Viral Exit - *CC BY-NC-SA 4.0*
  - 15.8: Retroviruses- Double-Stranded RNA Viruses - *CC BY-NC-SA 4.0*
    - 15.8A: Double-Stranded RNA Viruses - Retroviruses - *CC BY-NC-SA 4.0*
    - 15.8B: HIV Attachment and Host Cell Entry - *CC BY-NC-SA 4.0*
    - 15.8C: Retroviral RNA Genome - *CC BY-NC-SA 4.0*
    - 15.8D: Replicative Cycle of HIV - *CC BY-NC-SA 4.0*
  - 15.9: Negative-Strand RNA Viruses in Animals - *CC BY-NC-SA 4.0*
    - 15.9.1: Negative-Strand RNA Viruses of Animals - *CC BY-NC-SA 4.0*

- 15.9.2: Attachment and Entry to the Host Cell - *CC BY-NC-SA 4.0*
- 15.9.3: Replicative Cycle of Influenza A - *CC BY-NC-SA 4.0*

- 15.10: DNA Viruses in Eukaryotes - *CC BY-NC-SA 4.0*
  - 15.10.1: Plant DNA Viruses - *CC BY-NC-SA 4.0*
  - 15.10.2: Replication of Double-Stranded DNA Viruses of Animals - *CC BY-NC-SA 4.0*
  - 15.10.3: Double-Stranded DNA Viruses - Herpesviruses - *CC BY-NC-SA 4.0*
  - 15.10.4: Attachment and Entry of Herpes Simplex - *CC BY-NC-SA 4.0*
  - 15.10.5: Replication of Herpes Simplex Virus - *CC BY-NC-SA 4.0*
  - 15.10.6: Immunodeficiency - *CC BY-NC-SA 4.0*
  - 15.10.7: Double-Stranded DNA Viruses - Pox Viruses - *CC BY-NC-SA 4.0*
  - 15.10.8: Double-Stranded DNA Viruses- Adenoviruses - *CC BY-NC-SA 4.0*
  - 15.10.9: Retroviruses and Hepadnavirus - *CC BY-NC-SA 4.0*
  - 15.10.10: Treatment of Animal Viral Infections - *CC BY-NC-SA 4.0*
- 15.11: Viruses and Cancer - *CC BY-NC-SA 4.0*
  - 15.11.1: Cancer Viruses - *CC BY-NC-SA 4.0*
  - 15.11.2: DNA Oncogenic Viruses - *CC BY-NC-SA 4.0*
  - 15.11.3: RNA Oncogenic Viruses - *CC BY-NC-SA 4.0*
- 15.12: Overview of Viruses - *CC BY-NC-SA 4.0*
  - 15.12.1: Discovery and Detection of Viruses - *CC BY-NC-SA 4.0*
  - 15.12.2: Nature of the Virion - *CC BY-NC-SA 4.0*
  - 15.12.3: Viral Genomes - *CC BY-NC-SA 4.0*
  - 15.12.4: Host Range - *CC BY-NC-SA 4.0*
  - 15.12.5: Viral Size - *CC BY-NC-SA 4.0*
- 15.13: Structure of Viruses - *CC BY-NC-SA 4.0*
  - 15.13A: Viral Morphology - *CC BY-NC-SA 4.0*
  - 15.13B: General Morphology - *CC BY-NC-SA 4.0*
  - 15.13C: Complex and Asymmetrical Virus Particles - *CC BY-NC-SA 4.0*
- 15.14: Classifying Viruses - *CC BY-NC-SA 4.0*
  - 15.14.1: The International Committee on Taxonomy of Viruses - *CC BY-NC-SA 4.0*
  - 15.14.2: The Baltimore Virus Classification - *CC BY-NC-SA 4.0*
  - 15.14.3: Evolution of Viruses - *CC BY-NC-SA 4.0*
  - 15.14.4: Medical Importance of Viruses - *CC BY-NC-SA 4.0*
- 15.15: Culturing Viruses - *CC BY-NC-SA 4.0*
  - 15.15A: Batch Culture of Bacteriophages - *CC BY-NC-SA 4.0*
  - 15.15B: Tissue Culture of Animal Viruses - *CC BY-NC-SA 4.0*
  - 15.15C: Inoculation of Live Animals - *CC BY-NC-SA 4.0*
  - 15.15D: Viral Identification - *CC BY-NC-SA 4.0*
- 15.16: Subviral Entities - *CC BY-NC-SA 4.0*
  - 15.16A: Defective Viruses - *CC BY-NC-SA 4.0*
  - 15.16B: Viroids - *CC BY-NC-SA 4.0*
  - 15.16C: Prions - *CC BY-NC-SA 4.0*
- 15.17: Viral Ecology - *CC BY-NC-SA 4.0*
  - 15.17A: Emergence of Viral Pathogens - *CC BY-NC-SA 4.0*
  - 15.17B: Viral Roles in Ecosystems - *CC BY-NC-SA 4.0*

- 16: The Eukaryotes of Microbiology - *CC BY-NC-SA 4.0*
  - 16.1: Unicellular Eukaryotic Microorganisms - *CC BY-NC-SA 4.0*
  - 16.2: Parasitic Helminths - *CC BY-NC-SA 4.0*
  - 16.3: Fungi - *CC BY-NC-SA 4.0*
  - 16.4: Algae - *CC BY-NC-SA 4.0*
  - 16.5: Lichens - *CC BY-NC-SA 4.0*
  - 16.E: The Eukaryotes of Microbiology (Exercises) - *CC BY-NC-SA 4.0*
- 17: Systemic Infections - *CC BY-NC-SA 4.0*
  - 17.1: Respiratory System Infections - *CC BY-NC-SA 4.0*
    - 17.1.1: Anatomy and Normal Microbiota of the Respiratory Tract - *CC BY-NC-SA 4.0*
    - 17.1.2: Bacterial Infections of the Respiratory Tract - *CC BY-NC-SA 4.0*
    - 17.1.3: Viral Infections of the Respiratory Tract - *CC BY-NC-SA 4.0*
    - 17.1.4: Respiratory Mycoses - *CC BY-NC-SA 4.0*
    - 17.1.E: Respiratory System Infections (Exercises) - *CC BY-NC-SA 4.0*
  - 17.2: Urogenital System Infections - *CC BY-NC-SA 4.0*
    - 17.2.1: Anatomy and Normal Microbiota of the Urogenital Tract - *CC BY-NC-SA 4.0*
    - 17.2.2: Bacterial Infections of the Urinary System - *CC BY-NC-SA 4.0*
    - 17.2.3: Bacterial Infections of the Reproductive System - *CC BY-NC-SA 4.0*

- 17.2.4: Viral Infections of the Reproductive System - *CC BY-NC-SA 4.0*
- 17.2.5: Fungal Infections of the Reproductive System - *CC BY-NC-SA 4.0*
- 17.2.6: Protozoan Infections of the Reproductive System - *CC BY-NC-SA 4.0*
- 17.2.E: Urogenital System Infections (Exercises) - *CC BY-NC-SA 4.0*

- 17.3: Digestive System Infections - *CC BY-NC-SA 4.0*
  - 17.3.1: Anatomy and Normal Microbiota of the Digestive System - *CC BY-NC-SA 4.0*
  - 17.3.2: Microbial Diseases of the Mouth and Oral Cavity - *CC BY-NC-SA 4.0*
  - 17.3.3: Bacterial Infections of the Gastrointestinal Tract - *CC BY-NC-SA 4.0*
  - 17.3.4: Viral Infections of the Gastrointestinal Tract - *CC BY-NC-SA 4.0*
  - 17.3.5: Protozoan Infections of the Gastrointestinal Tract - *CC BY-NC-SA 4.0*
  - 17.3.6: Helminthic Infections of the Gastrointestinal Tract - *CC BY-NC-SA 4.0*
  - 17.3.E: Digestive System Infections (Exercises) - *CC BY-NC-SA 4.0*
- 17.4: Circulatory and Lymphatic System Infections - *CC BY-NC-SA 4.0*
  - 17.4.1: Anatomy of the Circulatory and Lymphatic Systems - *CC BY-NC-SA 4.0*
  - 17.4.2: Bacterial Infections of the Circulatory and Lymphatic Systems - *CC BY-NC-SA 4.0*
  - 17.4.3: Viral Infections of the Circulatory and Lymphatic Systems - *CC BY-NC-SA 4.0*
  - 17.4.4: Parasitic Infections of the Circulatory and Lymphatic Systems - *CC BY-NC-SA 4.0*
  - 17.4.E: Circulatory and Lymphatic System Infections (Exercises) - *CC BY-NC-SA 4.0*
- 17.5: Nervous System Infections - *CC BY-NC-SA 4.0*
  - 17.5.1: Anatomy of the Nervous System - *CC BY-NC-SA 4.0*
  - 17.5.2: Bacterial Diseases of the Nervous System - *CC BY-NC-SA 4.0*
  - 17.5.3: Acellular Pathogenic Diseases of the Nervous System - *CC BY-NC-SA 4.0*
  - 17.5.4: Neuromycoses and Parasitic Diseases of the Nervous System - *CC BY-NC-SA 4.0*
  - 17.5.E: Nervous System Infections (Exercises) - *CC BY-NC-SA 4.0*
- 17.6: Fungal Diseases of the Respiratory System - *CC BY-NC-SA 4.0*
  - 17.6.1: Histoplasmosis - *CC BY-NC-SA 4.0*
  - 17.6.2: Coccidiomycosis - *CC BY-NC-SA 4.0*
  - 17.6.3: Pneumocystis Pneumonia - *CC BY-NC-SA 4.0*
  - 17.6.4: Blastomycosis - *CC BY-NC-SA 4.0*
  - 17.6.5: Other Fungi Involved in Respiratory Disease - *CC BY-NC-SA 4.0*
- 17.7: Fungal and Protozoan Diseases of the Digestive System - *CC BY-NC-SA 4.0*
  - 17.7.1: Ergot Poisoning - *CC BY-NC-SA 4.0*
  - 17.7.2: Aflatoxin Poisoning - *CC BY-NC-SA 4.0*
  - 17.7.3: Giardiasis - *CC BY-NC-SA 4.0*
  - 17.7.4: Cryptosporidiosis - *CC BY-NC-SA 4.0*
  - 17.7.5: Cyclospora Diarrheal Infection - *CC BY-NC-SA 4.0*
  - 17.7.6: Amoebic Dysentery (Amoebiasis) - *CC BY-NC-SA 4.0*
  - 17.7.7: Legionellosis - *CC BY-NC-SA 4.0*
- 17.8: Helminthic Diseases of the Digestive System - *CC BY-NC-SA 4.0*
  - 17.8.1: Tapeworms - *CC BY-NC-SA 4.0*
  - 17.8.2: Hydatid Disease - *CC BY-NC-SA 4.0*
  - 17.8.3: Nematodes - *CC BY-NC-SA 4.0*
- 17.9: Fungal and Protozoan Diseases of the Reproductive System - *CC BY-NC-SA 4.0*
  - 17.9.1: Vulvovaginal Candidiasis - *CC BY-NC-SA 4.0*
  - 17.9.2: Trichomoniasis - *CC BY-NC-SA 4.0*
  - 17.9.3: The TORCH Panel of Tests - *CC BY-NC-SA 4.0*
- 17.10: Fungal Skin and Nail Diseases - *CC BY-NC-SA 4.0*
- 17.11: Parasitic Skin Diseases - *CC BY-NC-SA 4.0*
- 17.12: Other Infectious Eye Diseases - *CC BY-NC-SA 4.0*
- 17.13: Fungal, Protozoan, Prion, and Other Diseases of the Nervous System - *CC BY-NC-SA 4.0*
  - 17.13.1: Cryptococcosis - *CC BY-NC-SA 4.0*
  - 17.13.2: African Trypanosomiasis - *CC BY-NC-SA 4.0*
  - 17.13.3: Amoebic Meningoencephalitis - *CC BY-NC-SA 4.0*
  - 17.13.4: Bovine Spongiform Encephalopathy - *CC BY-NC-SA 4.0*
  - 17.13.5: Variant Creutzfeldt-Jakob Disease - *CC BY-NC-SA 4.0*
  - 17.13.6: Chronic Fatigue Syndrome - *CC BY-NC-SA 4.0*

- 18: Immunization - *CC BY-NC-SA 4.0*
  - 18.1: Passive Immunization - *CC BY-NC-SA 4.0*
  - 18.2: Vaccination - *CC BY-NC-SA 4.0*
  - 18.3: Types of Vaccines - *CC BY-NC-SA 4.0*
  - 18.4: Development of New Vaccines - *CC BY-NC-SA 4.0*
  - 18.5: Vaccine Safety - *CC BY-NC-SA 4.0*
- 19: Vaccine Safety - *CC BY-NC-SA 4.0*
  - 19.1: Non-Severe Events - *CC BY-NC-SA 4.0*
  - 19.2: Anaphylaxis - *CC BY-NC-SA 4.0*
  - 19.3: Vaccine Facts - *CC BY-NC-SA 4.0*
  - 19.4: Self Assessment - *CC BY-NC-SA 4.0*
  - 19.5: Vaccine Safety - *CC BY-NC-SA 4.0*
  - 19.6: Evaluation of Vaccines Pre-License - *CC BY-NC-SA 4.0*
  - 19.7: Canada Vigilance Program - *CC BY-NC-SA 4.0*
  - 19.8: Reflective Questions - *CC BY-NC-SA 4.0*
  - 19.9: Key Takeaways - *CC BY-NC-SA 4.0*
  - 19.10: References - *CC BY-NC-SA 4.0*
- 20: Human Health and Disease - *CC BY-NC-SA 4.0*
  - 20.1: Human Health and Disease - *CC BY-NC-SA 4.0*
  - 20.2: The Gut Microbiome - *CC BY-NC-SA 4.0*
  - 20.3: The Oral Microbiome - *CC BY-NC-SA 4.0*
  - 20.4: The Skin Microbiome - *CC BY-NC-SA 4.0*
  - 20.5: The Respiratory Microbiome - *CC BY-NC-SA 4.0*
  - 20.6: The Vaginal Microbiome - *CC BY-NC-SA 4.0*
  - 20.7: Mental Health and Multi-Microbiome Interactions - *CC BY-NC-SA 4.0*
- 21: Cancer Immunobiology and Immunotherapy - *CC BY-NC-SA 4.0*
- 22: Skin and Eye Infections - *CC BY-NC-SA 4.0*
  - 22.1: Anatomy and Normal Microbiota of the Skin and Eyes - *CC BY-NC-SA 4.0*
  - 22.2: Bacterial Infections of the Skin and Eyes - *CC BY-NC-SA 4.0*
  - 22.3: Viral Infections of the Skin and Eyes - *CC BY-NC-SA 4.0*
  - 22.4: Mycoses of the Skin and Eyes - *CC BY-NC-SA 4.0*
  - 22.5: Protozoan and Helminthic Infections of the Eyes - *CC BY-NC-SA 4.0*
- Back Matter - *CC BY-NC-SA 4.0*
  - Index - *CC BY-NC-SA 4.0*
  - Glossary - *CC BY-NC-SA 4.0*
  - Detailed Licensing - *CC BY-NC-SA 4.0*
  - Detailed Licensing - *CC BY-NC-SA 4.0*