MEDICAL MICROBIOLOGY AND IMMUNOLOGY

SECOND EDITION

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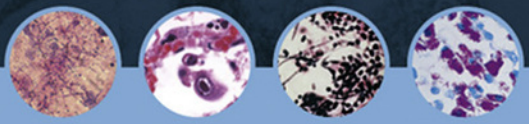

KEN S. ROSENTHAL

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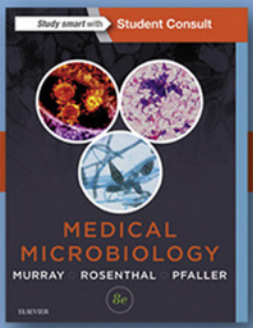

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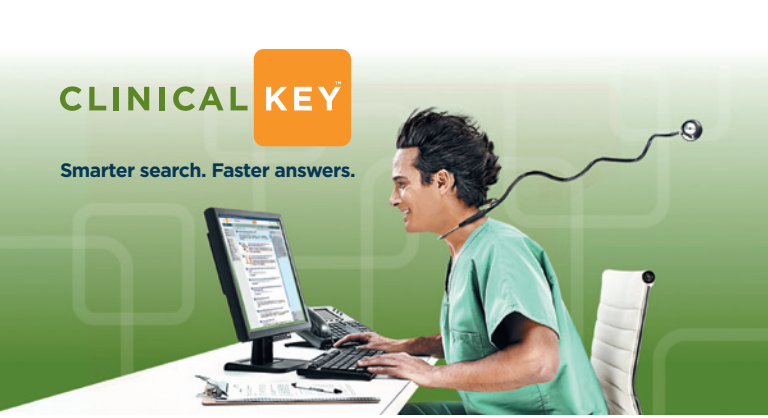

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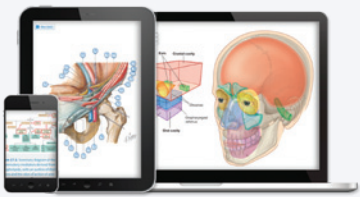

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Medical Microbiology and Immunology Flash Cards Second Edition

Ken S. Rosenthal, PhD

Professor of Biomedical Sciences and Director of Microbiology and Immunology

Roseman University of Health Sciences College of Medicine

Las Vegas, Nevada

Emeritus Professor

Northeast Ohio Medical University

Rootstown, Ohio

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1600 John F. Kennedy Blvd.
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FLASH CARDS, SECOND EDITION

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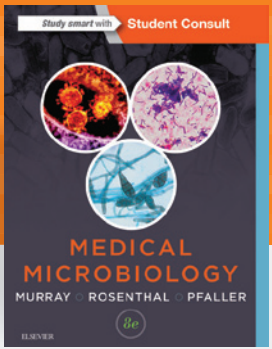

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	Gram Positive	Gram Negative
Bacillus		
Coccus		
Diplococcus		

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Tyson T. Schrickel, MD
Courtney Sherman, MD

Introduction

The ***Medical Microbiology and Immunology Flash Cards*** were developed by fourth-year medical students and their professor of medical microbiology and immunology to facilitate your review of microbiology and immunology and as a study aid for the course and USMLE Step 1 exam. They were also designed to be an excellent resource to help diagnose infectious diseases in your future patients.

Each card highlights the most important topics of microbiology, immunology, and infectious diseases in an easy-to-review manner with a single topic on each card. The different cards are formatted as **Microbe Cards**, **Concept Cards**, and **Disease Cards**.

- **Microbe Cards** provide pictures and data necessary to recognize, understand, diagnose, and treat each of the microbial infections. The most important bacteria, viruses, fungi, and parasites have their own cards, but they may share their cards with less-important microbes that are similar or in the same family.
- **Concept Cards** provide important concepts and details in easy-to-grasp charts, tables, and summaries and are grouped into cards for **Immunology**, **Antimicrobials**, **Basic Concepts**, and **Laboratory Identification**.
- **Disease Cards** provide lists, tables, and charts that group the relevant microbes with their diseases, the disease signs, and other facts to provide an infectious disease overview to the material.

Most cards have:

- **Full-color pictures** to trigger your memory and for fast identification
- **Essential Facts** to provide "need to know" characteristics of the microbe and likely topics for exam questions
- **Trigger Words** to provide the word associations that provide immediate association with the microbe on an exam or in the clinic

- **Case Studies** to provide familiarity with how the microbe will present in a patient or be presented in the case vignettes on the USMLE exam
- A **Study Break** to provide an interesting sidelight about the microbe to take your mind off the detail and give you something to tell friends to make you sound as intelligent as you are
- **Details** that are presented in outline format and include Structure, Lab ID, Virulence Factors, Diseases, Epidemiology, and Treatment
- **Quick ID** icons on bacteria cards to easily identify gram-positive and gram-negative bacilli, cocci, and diplococci

HINTS ON HOW TO USE THE CARDS

- Review the cards in order, regroup them by disease or other criteria, or shuffle them up.
- Use the front of the card to test yourself on the facts on the back of the card.
- Put the cards in the pocket of your lab coat and use them to learn more about your patients' diseases.
- Buy a pizza and play "Name That Disease." A player at the study session picks a card and says either: "Your patient presents with the following signs, now you must *name that disease!*"
- Use the DIVIRDEPT acronym to provide a logical clinical approach to your studies (see Card 1). For example, your patient has strep throat. How do you know that ? How did he or she get it? What causes the pathogenesis? What are the disease signs and consequences? What is the treatment?

Figure Credits

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PART A: IMMUNOLOGY

PART B: LABORATORY ID

1

DIVIRDEPT

Murray: *Medical Microbiology*, 8th Edition, Chapter 10

To study a microbe and its disease: **LEARN the DIVIRDEPT and CREATE A PATIENT (write your own case-based vignette):**

D: Disease characteristics at presentation and Differential Diagnosis
I: Identification methods that confirm diagnosis
V: Virulence mechanisms and pathophysiology
I: Innate, Immune, and Inflammation
- What is the protective antigen?
- What is the protective immune response?
- Does immunopathogenesis cause the disease?

R: Replication and structure (viruses); growth characteristics for other microbes
D: Other Disease characteristics
- Risk factors
- Time course
- Sequelae

E: Epidemiology
- Who: at-risk groups
- Where
- When: season of the year
- How: how is it spread
- Why: risk factors

P: Prevention
- Vaccine
- Quarantine
- Behavioral modification
- Education

T: Treatment

To determine the nature of the ailment: **INVITES + P:**

I: Infection
N: Neoplasm
V: Vascular and coronary
I: Inflammation and autoimmune
T: Toxin/drug complications
E: Endocrine (including paraneoplastic)
S: Structure (muscles, bone)
P: Neurologic and Psychiatric

DIVIRDEPT for Influenza

D: A 22-year old man has an acute onset of flu symptoms (fever, headache, chills, myalgia) with a sore throat and nonproductive cough.

I: Virus detection: reverse transcription–polymerase chain reaction (RT-PCR) genome assays; enzyme-linked immunosorbent assay (ELISA); hemagglutination, hemadsorption, and neutralization assay; serology: hemagglutination inhibition assays.

V: Rapid interferon alpha (IFNa) induction causes flu symptoms; hemagglutinin (HA) promotes viral binding to sialic acid; neuraminidase (NA) removes sialic acid from cell and mucus; virus replication kills ciliated epithelium; cell-mediated immunity causes inflammation.

I: **Innate:** Early: virus is excellent IFNa inducer, which can limit virus replication and activate natural killer (NK) cells, which act on virus-infected cells. **Immune:** Later: antibody to HA is protective. Cell-mediated immunity promotes clearance and inflammation.

R: Enveloped virus with eight single-stranded (–)RNA segments. Each segment encodes at least one protein. HA binds to sialic acid; virion enters by endocytosis, genome segments transcribed in nucleus (exception to rule), protein synthesis, replication in nucleus, assembly at plasma membrane and release.

D: Influenza, pneumonia, secondary bacterial pneumonia

E: Epidemics (genetic drift) and pandemics (genetic shift; A not B); influenza A (not B) is a zoonosis infecting birds, pigs, etc; aerosol spread to immune-naive children and others. Elderly may be immune due to earlier exposure; if not, then at highest risk for morbidity and mortality.

P: Annual inactivated or live attenuated vaccines containing three or four viruses.

T: NA inhibitors: oseltamivir and zanamivir for influenza A and B; M2 channel protein blockers: amantadine and rimantadine for only influenza A.

2

Immune Cell Characteristics

Murray: *Medical Microbiology*, 8th Edition, Chapter 10

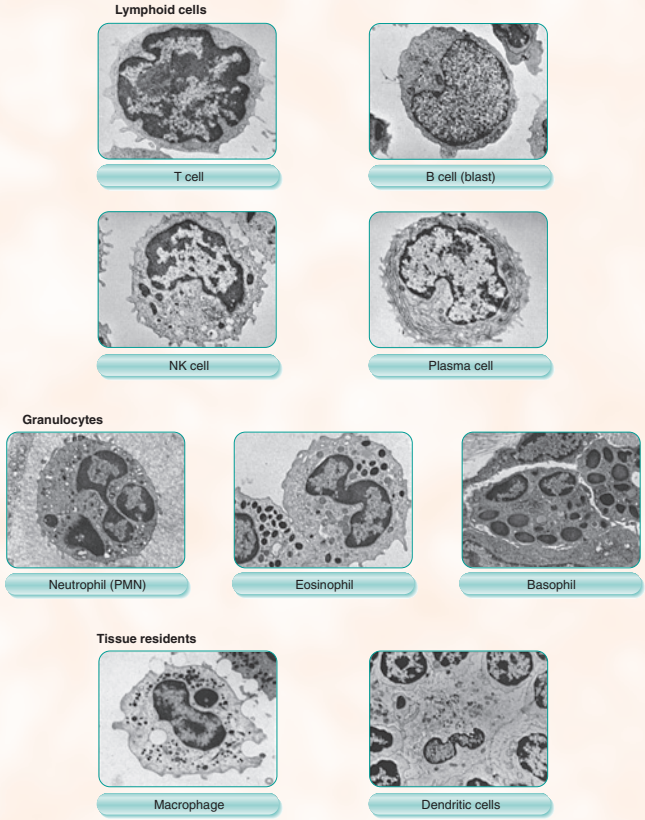

Figure 2-1: Morphology of primary cells involved in the immune response. (Pay attention to the nuclear size and shape.) NK, natural killer; PMN, polymorphonuclear neutrophil.

Immune Cell Characteristics

Table 2-1: Normal Blood Cell Counts

Cell Type	Mean Number per Microliter	Normal Range
White blood cells (leukocytes)	7400	4500-11,000
Neutrophils	4400	1800-7700
Eosinophils	200	0-450
Basophils	40	0-200
Lymphocytes	2500	1000-4800
Monocytes	300	0-800

Modified from Abbas AK, Lichtman AH, Pillai S, et al. *Cellular and molecular immunology,* ed 8, Philadelphia: Elsevier, 2015.

Table 2-2: Macrophages

M2	M1
Phagocyte	Phagocyte
APC	APC
Activated by IL-4 and other	Activated by interferon-gamma and TNF-α
Promote status quo and tissue repair, eliminate debris	Promote inflammation and fever
Promote tumor growth	Produce iNOS, ROS, enzymes
Angiogenesis	Produce TNF-α, IL-1, IL-6, IL-12, IL-23
Promote Th2 response	Promote Th17 and Th1 responses

APC, antigen-presenting cell; IL, interleukin; iNOS, inducible macrophage-type nitric oxide synthase; ROS, reactive oxygen species; Th, T-helper cell; TNF, tumor necrosis factor.

Table 2-3: Dendritic Cells (DCs): Octopus-like Cells With Tendrils

Myeloid DCs	Follicular DCs
Present to T cells	Present to B cells
Only cell that can initiate a new T-cell response	In B-cell areas of lymphoid tissues
Process proteins for presentation	Express sticky receptors to display antigen to B cells
MHC class I: CD8 T cells	Lack MHC class II
MHC class II: CD_4 T cells	

MHC, major histocompatibility complex.

3

T, B, and Other Cells

Murray: *Medical Microbiology,* 8th Edition, Chapter 9

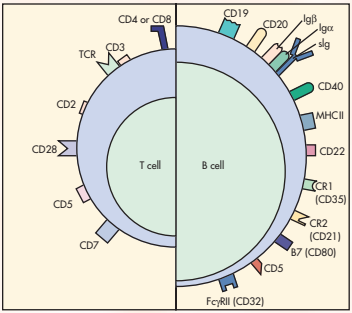

Figure 3-1: Surface markers of human B and T cells.

Table 3-1

Property	T Cell	B Cell
Origin	Bone marrow	Bone marrow
Maturation	Thymus	Bone marrow, fetal liver, Peyer patches
Functions	Helper: cytokine initiation and promotion of responses; cytokine promotion of macrophage and inflammation Cytotoxic: direct killing of cells	Antibody production Antigen presentation to T cells
Subsets	CD4 T cells: cytokines, helper T cells, killing through FasL CD8 T cells: cytokines; CTL killing through perforin and granzyme or FasL, suppressor cells NK T and γδ cells: innate-like responses T-regulatory cells	B cells: antibody production Plasma cells: antibody factories
Protective response	Resolution of intracellular bacteria and virus and fungal infections Antitumor responses Foreign tissue rejection	Antibacterial Limit spread of viruses: control viremia Opsonize microbes for phagocytosis
Antigen recognition	CD4 + TCR: MHC II presented antigenic peptide processed by exogenous route CD8 + TCR: MHC I presented antigenic peptide processed by endogenous route	Cell-surface immunoglobulin binds antigen to and activates B cells Produces antigen-specific antibody

CTL, cytotoxic T lymphocytes; DTH, delayed-type hypersensitivity; FasL, Fas ligand; MHC, major histocompatibility complex; NK, natural killer; TCR, T-cell receptor.

T, B, and Other Cells

Table 3-2

	Cell	Function
Surface immunoglobulin	B cell	B-cell receptor for antigen activation
α-β TCR	T-cell subset	Recognition of antigen
γ-δ TCR	T-cell subset	Recognition of antigen
Toll-like receptors (1-10)	Dendritic, macrophage, and other cells	Response to pathogen-associated molecules (eg, LPS)
CD2	T cells	Erythrocyte receptor (rosettes)
CD3	T cells	Subunit of TCR
CD4	T-cell subset	Coreceptor of TCR
CD8	T-cell subset	Coreceptor of TCR
CD11B	NK, myeloid cells	C3b receptor
CD14	Myeloid cells (dendritic cells, monocytes, macrophages)	LPS receptor
CD16	NK cell marker, also macrophage	Fc receptor for IgG
CD21	B cell	C3d receptor–B-cell activation, EBV receptor
CD25	T cell (activation marker); CD4-CD25 regulatory T cells	IL-2 receptor component
CD28	T cell	Binds to B7 molecules on APC to activate T cell (CD80, CD86 [B7])
CTLA-4	T cell	Binds to B7 molecules on APC to promote tolerance
CD40	B cell	Activates B cell
CD40L	T cell	Binds to CD40 to activate B cell
CD45RO	T cell, B cell	Marker for memory cell
CD56	NK	Adhesion molecule
CD80, CD86 (B7)	Antigen-presenting cell: B cell, dendritic cell, macrophage	Costimulator of T cells

APC, antigen presenting cell; CTLA, cytotoxic T-lymphocyte antigen; EBV, Epstein-Barr virus; IL, interleukin; LPS, lipopolysaccharide; NK, natural killer; TCR, T-cell receptor.

4 Antibody: Part One

Murray: *Medical Microbiology*, 8th Edition, Chapter 9

ESSENTIAL FACTS

- T-independent antigens are large repetitive structures: whole bacteria, flagellin, lipopolysaccharide (LPS); elicit immunoglobulin (Ig) M responses.
- T-dependent responses are proteins; elicit IgM and then T-cell help promotes IgG, IgE, IgA.
- An **epitope** is the smallest molecular structure recognized by antibodies or T cells.
  - Epitopes (haptens) may be too small to initiate the immune response.
- **Isotypes** are the same for all people.
- **Allotypes** are different for different people. (***Allo*** means different.)
- **Idiotypes** have different variable regions for different antigens. (There are lots of **idiots** in the world.)
- The **affinity** of an antibody for an epitope is the strength of the monovalent binding; **avidity** is for the entire multivalent molecule.
- The **anamnestic (secondary) response** is faster and stronger than the primary response.

IMMUNOGENETICS

- The variable region of immunoglobin is obtained from random recombination of the VDJ segments of the heavy chain gene and VJ-κ or VJ-λ genes of the light chain immunoglobulin genes.
- Class switching requires cytokines and interaction with T cells. Attachment of heavy chain genes to unchanged VDJ follows the order M and D, G (subtypes), E, A.
- Cytokine influence on class switching:
  - Th1: interferon γ to IgG
  - Th2: IL-4, IL-5 to IgG, IgE
  - IL-4, IL-5, TGF-β to IgA
- Somatic mutation and clonal selection occur during B-cell passage through germinal centers.

Antibody: Part One

- IgM and IgD are the only immunoglobulins that can be present on the same B cell.
- The same variable region can be present on IgM, IgD, IgG, IgE, or IgA.
- Somatic mutation occurs in the germinal center during growth of the B cell and causes changes in the variable region.
- Cell-surface immunoglobulins recognize the same epitope as the secreted antibody.
- Clonal expansion is caused by antigen binding to the best surface antibody that promotes that B cell's growth.

Table 4-1: Immunoglobulins

Ig	IgG	IgM	IgA	IgD	IgE
CD4 T-helper subclass association	TH1, TH2	T independent	TH2	—	TH2
Total Ig (%)	85	5–10	5–15	<1	<1
Molecular mass (kDa)	154	900	160 (+ dimer)	185	190
H-chain class	γ	μ	α	δ	E
Subclass	γ-1, γ-2, γ-3, γ-4	–	α-1, α-2	–	–
Serum half-life (days)	23	5	6	2–3	2–3
Principal site of action	Serum and tissue	Serum	Secretions	Receptor for B cells	Mast cells
Principal biologic effect	Resistance: opsonin, secondary response	Resistance: precipitin, primary response	Resistance: protection of mucous membranes	B-cell activation	Anaphylaxis
Complement fixation	+++	++++	+	–	–
Opsonin for macrophage, PMN	+				
Mucosal secretion	–	–	+	–	–
Crossing of placenta	+	–	–	–	–

PMN, Polymorphonuclear neutrophil (leukocyte); +/–, relative activity.

5

Antibody: Part Two

Murray: *Medical Microbiology*, 8th Edition, Chapter 9

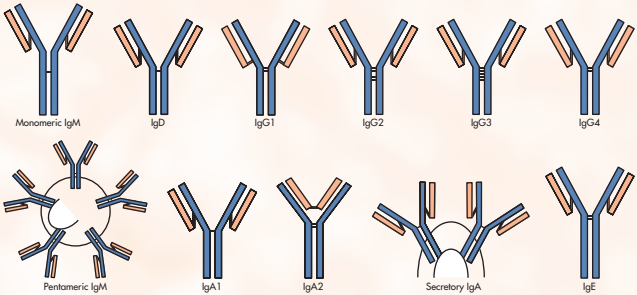

Figure 5-1: Comparative structure of the immunoglobulin (Ig) classes and subclasses in humans.

Antibody: Part Two

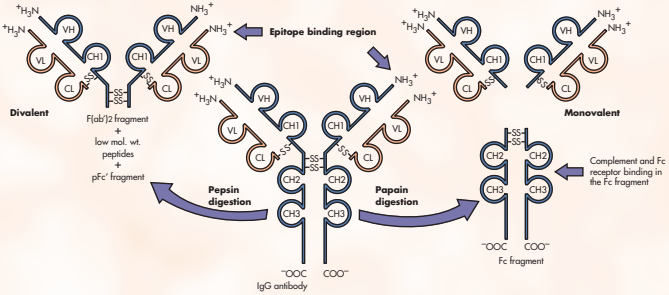

Figure 5-2: Proteolytic digestion of immunoglobulin G (IgG).

6

Complement Cascade

Murray: *Medical Microbiology*, 8th Edition, Chapter 7

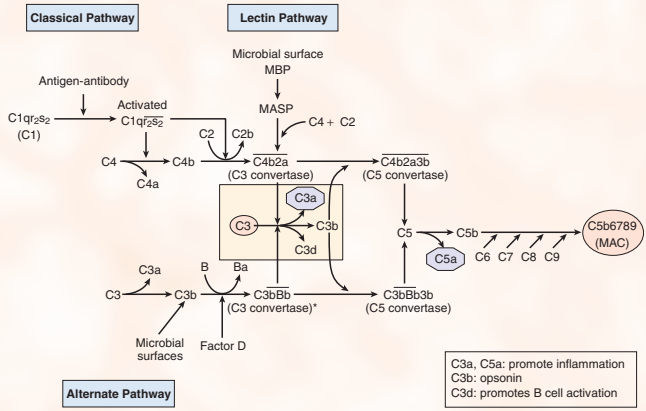

*Figure 6-1: The classical, lectin, and alternative complement pathways. *Stabilized by properdin.*

ESSENTIAL FACTS

- C3 is the key branch point of the complement cascade!
- Alternate pathway is activated by bacterial surfaces and components (eg, lipopolysaccharide).
- The classical pathway is activated by immune complexes.
- The mannose binding protein of the lectin pathway looks like C1q and binds to bacterial and fungal surface sugars instead of antibody.
- C3b and C4b are opsonins (bind to bacteria, etc, and promote uptake by phagocytes).
- C3a and C5a are chemotaxins and attract neutrophils and monocytes.
- C3a and C5a are anaphylatoxins and promote release of inflammatory mediators from mast cells and basophils.
- C3d promotes activation of B lymphocytes and shares its receptor on B cells with Epstein-Barr virus.

Complement Cascade

- C5b, C6, C7, C8, and C9 form the membrane attack complex.
- C1 inhibitor prevents inappropriate activation of the cascade.
- Decay-accelerating factor (DAF) blocks C3 and C5 convertases and factors H and I.
- Anaphylatoxin inhibitor blocks C3a and C5a.

Complement Deficiencies

- C1, C2, and C4 deficiency: immune complex diseases including glomerulonephritis, systemic lupus erythematosus, vasculitis, and susceptibility to pyogenic staphylococcal and streptococcal infections (related to deficiency in producing C3a and C5a to recruit neutrophils, and C3b to opsonize and clear immune complexes)
- C3, factor B, or factor D deficiency: disseminated pyogenic infections, vasculitis, and nephritis (related to deficiency in C3a, C5a, C3b, as described above)
- C5 through C9 deficiency: neisserial bacteria infections
- C1 inhibitor deficiency: hereditary angioedema
- DAF deficiency: complement-mediated, intravascular hemolysis; paroxysmal nocturnal hemoglobinuria

7

Cytokines

Murray: *Medical Microbiology,* 8th Edition, Chapter 7

Table 7-1: Innate Cytokine Responses

TNF-α	IL-1	IL-6	IL-23	IL-12
Acute phase	Acute phase	Acute phase	**Bridge to Th17 response**	**Bridge to Th1 response**
Diapedesis	Lymphocyte growth factor	Stimulates acute-phase protein synthesis		
Neutrophil activation		Production of neutrophils in bone marrow	Acts on memory T cells	Activates NK and T cells
Macrophage activation		Promotes B- and T-cell differentiation		
Promotes inflammation	Promotes inflammation	Il-6 and TGF-β promote Th17 response		
Fever	Fever			
Acute-phase protein synthesis in liver	Acute-phase protein synthesis in liver			
Cachexia				
High levels: septic shock, altered metabolism				

IL, interleukin; NK, natural killer; TGF, transforming growth factor; Th, T-helper cell.

Table 7-2: T Cell Cytokines and Their Functions

Cytokine	Th1	Th2	Th17	Treg	Function
GM-CSF	+++	+++	++		Growth factor
IL-3	++	++	++		Growth factor
IL-2	+++				Lymphocyte growth factor
TNF-β (LT)	+++				Inflammation
IFN-γ	+++				Macrophage activation, CD8 T cells, class switch IgG
IL-4		+++			Growth factor, class switch IgG, IgE, IgA
IL-5		+++			Class switch IgG, IgE, IgA
IL-10		+++		+++	Regulation of inflammation, B-cell growth factor
TGF-β				+++	Regulation of T-cell activation; tolerance With IL-1 and IL-6, promotes Th17 response

GM-CSF, granulocyte-macrophage colony-stimulating factor; Ig, immunoglobulin; IL, interleukin; Th, T-helper cell; Treg, regulatory T cell; TNF, tumor necrosis factor; TGF-β, transforming growth factor-β.

Cytokines

- Hematopoietic factors
  - IL-3, IL-5, IL-6, IL-7, IL-11, GM-CSF, G-CSF, M-CSF, Flt-3 ligand
- Lymphocyte growth
  - IL-2, IL-4, IL-7
- Promotes acute-phase responses
  - TNF-α, IL-1, IL-6
- Activates and reinforces local inflammatory responses
  - IL-12, IFN-γ, IL-23
- Suppresses/regulates responses
  - IL-10, TGF-β
- TGF-β suppresses both Th1 and Th2 responses
  - TGF-β is important for suppression of autoimmune responses
  - In immune-privileged sites (eg, the eye)
  - TGF-β plus IL-1 and IL-6 activate Th17 responses

8

Innate Immunity and Inflammation

Murray: *Medical Microbiology,* 8th Edition, Chapters 9 and 10

COMPONENTS OF INNATE IMMUNITY

Table 8-1

	Component	Function
BARRIERS	Skin	Prevent entry
	Acid and proteases in GI tract	Inactivate microbe
	Defensins and other peptides	Inactivate microbe
LOCAL CELLS	Langerhans cells	Produce cytokines, initiate immune response; antigen presentation
	Dendritic cells	Cytokine production, initiate immune response, and antigen presentation
	Macrophages	Cytokine production, phagocytosis, and killing microbe
	NK cells	Kill target cells, make interferon γ
CIRCULATING CELLS	Neutrophils	Phagocytosis and killing microbe
	Macrophages	See above
	NK cells	See above
	Immature dendritic cells	Cytokine production
PROTEINS	Complement	Microbe killing, chemotaxis, activation of inflammation
	C-reactive protein	Opsonization of microbes and activation of complement
	Mannose-binding protein	Opsonization of microbes and activation of complement
CYTOKINES	TNF-α, IL-1, IL-6	Acute phase responses, fever, etc
	Interferons α and β	Antiviral responses
	IL-12	Promote Th1 responses in T and NK cells

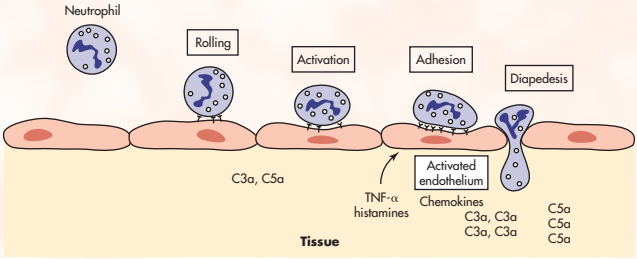

Figure 8-1: Neutrophil diapedesis in response to inflammatory signals.

Innate Immunity and Inflammation

ACUTE PHASE REACTANTS

α1-antitrypsin, α-glycoprotein, amyloid A and P, antithrombin, C-reactive protein, C1 esterase inhibitor, C3 complement, ceruloplasmin, fibrinogen, haptoglobin, lipopolysaccharide (LPS)-binding proteins, etc.

Antibacterial Activities in the Phagolysosome

- Oxygen dependent: macrophage and neutrophil
  - Hydrogen peroxide, superoxide, hydroxyl radicals, activated halides, nitrous oxide
- Oxygen independent: neutrophils
  - Acids, lysosome, lactoferrin, defensins, proteases

Type 1 Interferons α and β

- Produced by many cells, dendritic cells, and lymphocytes
- Produced in response to viral infection
- Double-stranded RNA is an excellent trigger for production.
- Interferon made in one infected cell binds to receptors on surrounding cells to activate the antiviral response.
- The antiviral response includes production of protein kinase R (PKR) and 2′5′A polymerase. These enzymes are inactive until the cell is infected and dsRNA (replicative intermediate for RNA virus) activates the enzymes, which result in *inhibition of protein synthesis.*
- No protein synthesis, no virus production
- Interferons also activate NK cells and other responses.

Innate Responses Are Activated by Toll-Like Receptors

- There are 10 Toll-like receptors (TLRs).
- TLRs recognize pathogen-associated molecular patterns (PAMPs).
- PAMPs include LPS, unmethylated GpC oligonucleotides, flagellin, and peptidoglycan.
- TLR activation will promote dendritic cell maturation and cytokine release and protective responses.

9 Immune Responses: Part One

Murray: *Medical Microbiology,* 8th Edition, Chapter 10

ESSENTIAL FACTS

Natural Killer (NK) Cells

- NK cells detect sick cells, including virus-infected cells.
- NK cells have an inhibitory receptor (KIR) that binds histocompatibility complex (MHC) molecules.
- NK cells have receptors for immunoglobulin and perform antibody-dependent cellular cytotoxicity (ADCC).
- NK cells can make interferon γ to support the initiation of a Th1 response.

Dendritic Cells (DCs)

- Myeloid DCs direct T cells, which tell other cells what to do with cell-cell interactions and cytokines.
- Follicular dendritic cells display but do not process antigen and activate B cells, not T cells.
- Immature DCs phagocytose antigen, and when activated by infection signals (through Toll-Like receptors), they make cytokines, mature to DCs, and move to the lymph node.
- DCs process and deliver antigen to the lymph node and present peptides on MHC II to CD4 and on MHC I to CD8 T cells.
- *Only myeloid DCs can initiate a primary antigen response in naive T cells.* Other antigen-presenting cells can reactivate mature and memory T cells.
- DCs make cytokines that promote the type of T-helper cell response.

Other Antigen-Presenting Cells

- B cells and macrophages

T Cells

- The T-cell receptor (TCR) has two different chains (α-β or γ-δ) that resemble immunoglobulin structure.
- The TCR gene matures by recombination of gene segments similar to the immunoglobulin gene without somatic mutation.

Immune Responses: Part One

- The TCR on CD4 T cells recognizes peptides presented by antigen-presenting cells.
- CD4 binds to MHC II on the antigen-presenting cell, and the TCR binds to MHC II and the peptide presented by MHC II.
- Antigen-presenting cells express MHC II molecules and include DCs, macrophages, and B cells.
- The TCR on CD8 T cells recognizes peptides presented by MHC I, which is on all nucleated cells.
- T cells require two signals to generate a response: antigen and sufficient B7 protein from antigen-presenting cell.
- TCR interaction with peptide without a second signal promotes apoptosis, a mechanism to eliminate reactions to self in the neonatal thymus.
- Activation of the T cell requires sufficient B7 protein on APC to fill CTLA4 (suppressive) and bind CD28 (activating) receptors on the T cell.

B Cells

- The germline immunoglobulin gene consists of many V, some D, and J gene segments that recombine to produce a single VDJ sequence per B cell, encoding the epitope binding sites. The intervening sequences are deleted.
- The VDJ unit is juxtaposed to the heavy chain genes.
- The heavy chain genes are in the same order as for expression: M, D, G, E, A: IgM, IgD, IgG, IgE, IgA.
- IgM and IgD are encoded by the same RNA, which is processed to give mRNAs for membrane and soluble IgM and membrane IgD.
- Switching to IgG or other immunoglobulin requires T cell help because it involves a major change in the cell: deletion of intervening DNA for the IgM and IgD heavy chain.

10

Immune Responses: Part Two

Murray: *Medical Microbiology,* 8th Edition, Chapter 10

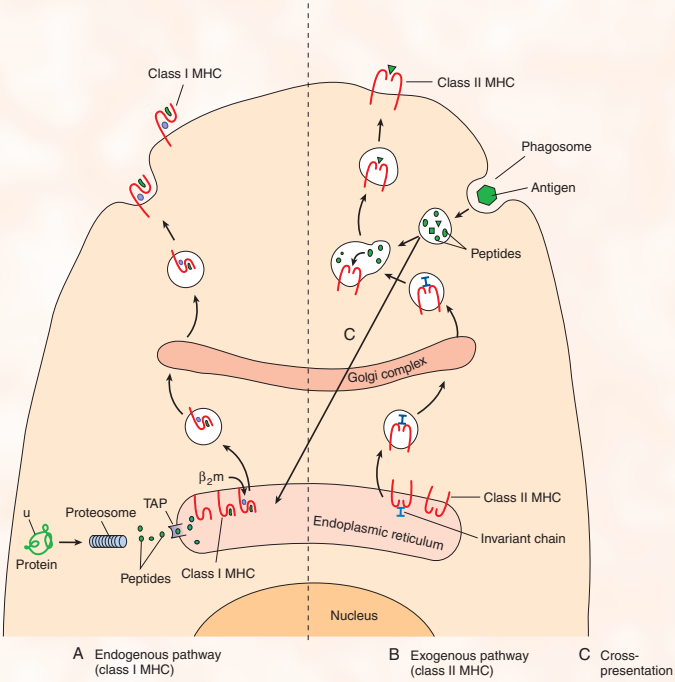

Figure 10-1: Endogenous antigen presentation by MHC I molecules is initiated with peptides produced by the proteasome, transported into the endoplasmic reticulum, and bound to the MHC I molecules that move to the cell membrane. For exogenous antigen presentation, MHC II molecules containing the invariant chain in their antigen-binding pocket acquire peptides produced by lysosomes. The peptides come from phagocytosed proteins, cells, virus, and so forth. Cross presentation takes exogenous antigen and presents it to CD8 T-cells on MHC I to allow presentation of peptides from viral, tumor, and apoptotic cell debris.

Immune Responses: Part Two

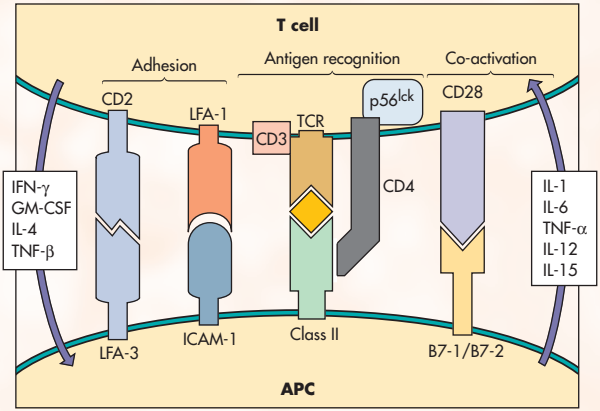

Figure 10-2: Interactions between antigen-presenting cells and CD4 T cells. B7-1 and B7-2 also bind to CTLA4 (suppressive); when it is saturated, they bind to CD28 (activating), ensuring proper activation of the T cell.

11

Th1 Versus Th2

Murray: *Medical Microbiology,* 8th Edition, Chapter 9

Cytokines Associated With Different Innate and Immune Responses

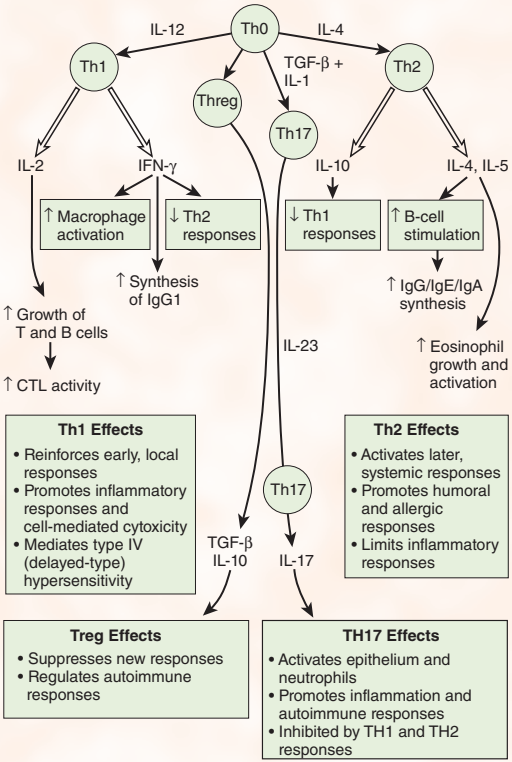

Figure 11-1: T-cell responses are determined by cytokines. Dendritic cells initiate and determine the type of CD4 T-cell responses by the cytokines they produce. Similarly, T cells tell other cells what to do with other cytokines. The response-defining cytokines are indicated. ↑, increase; ↓, decrease; CTL, cytotoxic T lymphocyte; IFN, interferon; Ig, immunoglobulin; IL, interleukin; TGF, transforming growth factor; Th, T-helper cell. (From Rosenthal KS, Tan M. Rapid reviews in microbiology and immunology, *ed 3. Philadelphia: Elsevier; 2010.)*

Th1 Versus Th2

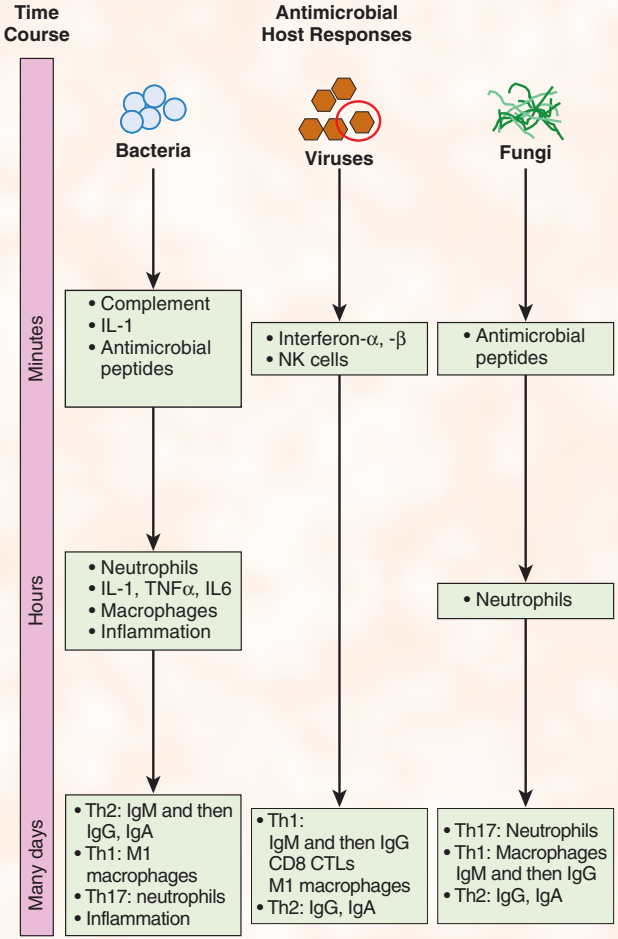

Figure 11-2

12

Hypersensitivity Reactions: Part One

Murray: *Medical Microbiology*, 8th Edition, Chapter 10

CASE STUDIES

Type I Hypersensitivity

Within minutes of being stung by a bee, a 13-year-old boy begins to show manifestations of shock.

Type II Hypersensitivity

An Rh-negative mother receives RhoGAM 48 hours before the birth of her second baby, whose father is Rh positive, to prevent complement lysis of the baby's red blood cells due to the presence of the mother's antibody to Rh factor.

Type III Hypersensitivity

A 9-year-old boy is stung by a wasp. The site swells, and redness appears after 6 hours and persists for 24 hours. (Antibody and insect proteins form immune complexes, which remain at the site and initiate a type III [Arthus-type] reaction 5 to 8 hours later.)

Type IV (Delayed-Type) Hypersensitivity (DTH)

Intradermal response to PPD tuberculin test within 3 days, poison ivy response, granuloma formation around mycobacterium.

ESSENTIAL FACTS

Type I = IgE-Mediated Responses

- Antibodies already present
- Antibodies bound to Fc receptor on mast cell and basophils
- Allergen-binding triggers initial response (vasoactive amines); later response: prostaglandins, leukotrienes, cytokines, etc
- Beneficial for eliminating parasitic worms from the gastrointestinal tract
- Common allergens: plant pollens, penicillin, foods (nuts, seafood, eggs, peas/beans, milk), mold spores, animal hair, insect venoms (bee, ant, wasp), dust mites

Hypersensitivity Reactions: Part One

Type II = Complement-Mediated Cytotoxicity
- Antibody to blood cells promotes killing
- Rh incompatibility, transfusion reactions
- Drug-induced hemolytic anemia (eg, penicillin reacts with cell surface and promotes attack)
- Goodpasture syndrome: Antibody to membrane protein promotes inflammation

Type III = Complement-Mediated, Soluble Antigen-Antibody Immune Complexes
- Antibodies already present
- Takes time for complement-mediated damage to build up
- Serum sickness (eg, multiple transfusions)
- Drug modification of proteins: penicillin, etc
- Immune complex diseases:
  - Chronic infections: hepatitis B virus, poststreptococcal glomerulonephritis
  - Autoimmune responses: systemic lupus erythematosus, rheumatoid arthritis
  - Drug modification of serum proteins: penicillin, sulfonamides

Type IV = CD_4 T-Cell Activation of Macrophages and Cytotoxic T Lymphocyes (Th_1 Response)
- Takes time for cellular infiltration and buildup of damage
- Essential for control of virus, intracellular bacteria
- Contact dermatitis: poison ivy, nickel metal
- Swelling and edema: PPD reaction
- Granuloma formation: tuberculosis

Penicillin Hypersensitivity
- Can be all four types

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Hypersensitivity Reactions: Part Two

Murray: *Medical Microbiology,* 8th Edition, Chapter 10

Importance of Specific Immune Components to Microbes

Table 13-1: Hypersensitivity Reactions

Onset Time	Key Features	Beneficial Effects	Pathologic Effects
TYPE I REACTION			
<30 min	IgE-dependent release of various mediators	Antiparasitic responses and toxin neutralization	Localized allergies (eg, **hay fever, asthma, food allergies**)
			Systemic anaphylaxis
TYPE II REACTION			
<8 h	Antibody- and complement-mediated cytotoxicity	Opsonization and direct lysis of extracellular bacteria and other susceptible microbes	Graft rejection (eg, **transfusion reactions, Rh disease**)
			Organ-specific tissue damage in some autoimmune diseases (eg, **Goodpasture syndrome**)
TYPE III REACTION			
<8 h	Deposition of soluble Ag-Ab complexes, which activate complement	Acute inflammatory reaction at site of extracellular microbes and their clearance	Arthus reaction (localized)
			Serum sickness and drug reactions (generalized)
			Systemic autoimmune diseases (eg, **SLE, multiple sclerosis**)
TYPE IV REACTION			
24–72 h (acute)	Delayed release of Th1 cytokines; activation of macrophages and CTLs	Protection against infection by fungi, intracellular bacteria, and viruses	Acute: contact dermatitis, **TB skin test**
>1 week (chronic)			Chronic: granuloma formation, **graft rejection**

Ab, antibody; Ag, antigen; CTL, cytotoxic T lymphocyte; RBCs, red blood cells; SLE, systemic lupus erythematosus; TB, tuberculosis.

Hypersensitivity Reactions: Part Two

Table 13-2: Clinical Manifestations of Delayed-Type (Type IV) Hypersensitivity Reactions

Type	Antigen	Clinical/Histologic Features
ACUTE REACTION (1–3 DAYS)		
Contact dermatitis	Epidermal (eg, poison ivy, chemicals, cosmetics)	Eczema with edema
Tuberculin reaction	Dermal (eg, PPD, other mycobacterial and fungal antigens)	Raised epidermis, many macrophages Local induration and swelling ± fever
CHRONIC (>1 WEEK)		
Graft rejection	Persistent exposure to alloantigens	T cells, fewer macrophages Thrombosis and necrosis of graft
Granuloma formation	Persistent exposure to infectious or noninfectious agents	T cells, many macrophages Skin induration Nodule composed of epithelioid cells, giant cells, and macrophages; fibrosis; ± necrosis

14

Immune Response to Infectious Agents

Murray: *Medical Microbiology,* 8th Edition, Chapter 10

Table 14-1: Importance of Host Responses

Effector	Extracellular Bacteria	Intracellular Bacteria	Viruses	Fungi	Parasites
Neutrophils	+++	–	+	++	
Macrophages	+++	++	++	++	++
Dendritic cells	++	++	++	++	++
NK cells	–	–	++	–	–
Complement	+++	+	+	+	+
Interferons α and β	–	–	+++	–	–
CD4 Th1 cells	+	++	++	++	++
CD8 CTLs	–	+	+++	–	–
Antibody	+++	+	+++	+	++ (IgE for worms)

CTL, cytotoxic T lymphocyte; NK, natural killer. –, not important; +, helpful; ++, important; +++, essential.

See Figure 11-2 for antimicrobial host responses.

Immune Response to Infectious Agents

Consequences of Immune Deficiencies

Table 14-2: Consequences of Immunodeficiencies

Immune Response	Consequences
C3	Severe bacterial infections
C1, C2, C3, C4	Pyogenic infections, immune complex diseases
Alternative pathway: C3, FB, FD	Disseminated pyogenic infections*
C5, C6, C7, C8, C9	Neisserial infections
IgA	Respiratory bacteria and viral infections
IgG2	Capsular bacteria
Immunoglobulin or B cells	Enteroviruses, bacteria, etc
CD4 T cells	Opportunistic diseases
Burn patients	*Pseudomonas, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pyogenes, Candida*
Asplenia	Encapsulated bacteria
Cystic fibrosis	Colonization by *S. aureus* and *Pseudomonas*
Chronic granulomatous disease (cannot make peroxides, hypochlorous acid, etc)	Most bacteria and fungi
Chediak-Higashi syndrome (cannot kill bacteria)	Recurrent bacterial infections

*Includes *Staphylococcus aureus, Streptococcus pyogenes,* and other bacteria.

15 Vaccines

Murray: *Medical Microbiology,* 8th Edition, Chapter 11

Vaccine ▼ Age ▶	Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months	19-23 months	2-3 years	4-6 years	12-26 years
Hepatitis B	HepB	HepB			HepB							
Rotavirus			Rota	Rota	Rota							
Diphtheria, tetanus, pertussis			DTaP	DTaP	DTaP		DTaP				DTaP	Tdap
Haemophilus influenzae type B			Hib	Hib	Hib	Hib						
Pneumococcal conjugate			PCV	PCV	PCV	PCV				PPV		
Inactivated poliovirus			IPV	IPV	IPV						IPV	
Influenza					Influenza (yearly)							
Measles, mumps, rubella						MMR					MMR	
Varicella						Varicella					Varicella	
Hepatitis A						HepA (2 doses)				HepA series		
Meningococcal							MCV4					
Human papillomavirus												HPV

Range of recommended ages Certain high-risk groups

Figure 15-1: Recommended immunization schedule from the Centers for Disease Control and Prevention.

ESSENTIAL FACTS

- **Passive immunization: immunoglobulin:** Rapid, temporary protection—like a drug treatment.
- **Live attenuated vaccine:** Induces innate cellular (Th1, Th2, Th17) and humoral responses; requires few booster shots; better memory response; may cause disease in immunocompromised people or may revert to virulent.
- **Inactivated (killed) vaccine:** Safe, requires large doses; requires boosters; primarily antibody response (Th2 type).
- The inactivated polio vaccine is recommended rather than the live vaccine because of safety.
- Influenza and other vaccines made in eggs are not appropriate for someone with egg allergies.
- The annual influenza vaccine is a mixture of hemagglutinin (HA) and neuraminidase (NA) from three or four different influenza A and B viruses predicted for the season.

Vaccines

Table 15-1: Bacterial Vaccines

Diphtheria	Toxoid DTaP or Tdap
Pertussis	Acellular (cellular fragments) in DTaP or Tdap
Tetanus	Toxoid in DTaP or Tdap
Haemophilus influenzae B (HiB)	Capsular polysaccharide conjugated to protein
Neisseria meningitidis A and C	Capsular polysaccharide or conjugated to protein
Streptococcus pneumoniae	Capsular polysaccharide (23 serotypes) Capsular polysaccharide protein conjugates (serotypes)
Vibrio cholerae	Killed cell
Salmonella typhi	Oral, live, or capsular polysaccharide
Mycobacterium tuberculosis	Live attenuated *M. bovis* (BCG) (*NOT IN UNITED STATES*)

Table 15-2: Viral Vaccines

Vaccine Type	Applications
LIVE ATTENUATED	Measles
	Mumps
	Rubella
	Varicella-zoster
	Polio (OPV; Sabin)
	Live attenuated influenza vaccine: mixture of influenza A and B strains predicted for the year
	Yellow fever
	Smallpox (Vaccinia virus)
	Rotavirus (live attenuated or virus for different species)
INACTIVATED	Polio (IPV, Salk)
	Rabies
	Influenza: mixture of influenza A and B strains predicted for the year
	Hepatitis A
	Japanese encephalitis virus
VIRUS-LIKE PARTICLE	Hepatitis B surface antigen
	Human papillomavirus

Table 15-3: Passive Immunization

Rabies: immediately after infection
Varicella-zoster (VZIG): for immunocompromised people; postexposure for pregnant women up to 20 weeks; newborns of mothers with active infection
Hepatitis A virus postexposure
Measles
Respiratory syncytial virus
Botulism **antitoxin**
Tetanus **antitoxin**

16

Molecular Biology Analysis

Murray: *Medical Microbiology,* 8th Edition, Chapter 43

ESSENTIAL FACTS

- Polymerase chain reaction (PCR) tests (for DNA viruses) and reverse transcriptase (RT)-PCR tests (for RNA viruses) are replacing isolation and immunologic tests for detection of viruses because these tests are rapid and very sensitive.
- RT-PCR, branched-chain DNA, and similar genomic assays quantitate virus load and can be used to follow the course of disease and efficacy of antiviral drug therapy (especially useful for HIV patients).
- In situ localization of human papillomavirus genomes is the histologic method of choice because the viral antigen is often not detectable.
- PCR of cerebrospinal fluid replaced brain biopsy for diagnosis of herpes simplex virus encephalitis.
- MALDI-TOP mass spectrometry identifies proteins and DNA sequences (obtained from PCR) to identify organism.

Molecular Biology Analysis

Table 16-1: Molecular Techniques

Technique	Purpose	Clinical Examples
RFLP	Comparison of DNA	Molecular epidemiology, HSV-1 strains
DNA electrophoresis	Comparison of DNA	Viral strain differences (up to 20,000 bases)
Pulsed-field gel electrophoresis	Comparison of DNA (large pieces of DNA)	Streptococcal strain comparisons
In situ hybridization	Detection and localization of DNA sequences in tissue	Detection of nonreplicating DNA virus (eg, cytomegalovirus, human papillomavirus)
Dot blot	Detection of DNA sequences in solution	Detection of viral DNA
Southern blot	Detection and characterization of DNA sequences by size	Identification of specific viral strains
Northern blot	Detection and characterization of RNA sequences by size	Identification of specific viral strains
PCR	Primer-directed amplification of very dilute DNA samples	Detection and identification of DNA viruses
RT-PCR	Primer-directed amplification of very dilute RNA samples	Detection and identification of RNA viruses
Branched-chain DNA	Specific amplification of very dilute DNA or RNA samples	Quantitation of DNA and RNA viruses
SDS-PAGE	Separation of proteins by molecular weight	Molecular epidemiology of HSV
MALDI-TOF mass spectrometry	Identification of DNA or protein sequences	Identification of bacteria, viruses, etc

HSV, Herpes simplex virus; MALDI-TOF, matrix-assisted laser desorption/ionization/time of flight; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; RT-PCR, reverse transcriptase polymerase chain reaction; SDS-PAGE, sodium dodecyl sulfate-polyacrylamide gel electrophoresis.

17

Serology: Part One

Murray: *Medical Microbiology*, 8th Edition, Chapter 54

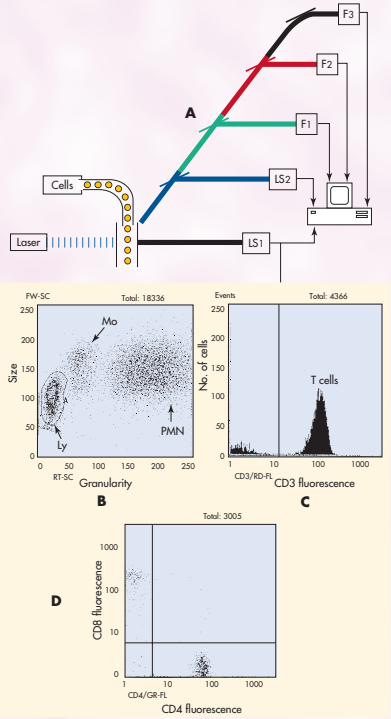

Figure 17-1: Flow cytometry data are used to analyze the numbers of specific cell populations in blood (eg, the CD4/CD8 ratio of an AIDS patient). Three different ways of presenting the data are shown. ***A,*** *Laser light is scattered by the cells and also excites fluorophores and is measured by detectors.* ***B,*** *Distinguishing cells by their physical properties: small-angle scatter indicates size, large-angle scatter indicates granularity. Circle around lymphocytes sets gates around the population for subsequent analysis.* ***C,*** *Histogram identifying the number of T cells by their expression of CD3.* ***D,*** *Comparison of CD4 and CD8 expression. Only the circled lymphocytes in* ***B*** *are analyzed ("gated") in* ***C****, and only the peak cells from* ***C*** *are analyzed in* ***D****. (Ly, lymphocyte; Mo, monocyte macrophage; PMN, polymorphonucleocytes; FW-SC, forward scatter; RT-SC, side or right angle scatter; RD-FL, red fluorescence; GR-FL, green fluorescence.)*

Serology: Part One

ESSENTIAL FACTS

- Serologic tests often give a positive or negative answer rather than a number; therefore the last dilution with positive values (titer) is reported as clinical data (eg, hemagglutination inhibition: dilution of antibody that blocks hemagglutination).
- A fourfold difference in titer is required for a significant difference between acute and convalescent sera.
- For enzyme-linked immunosorbent assay (ELISA) quantitation of antibody: antigen is adsorbed to a plastic surface, antibody binds, unbound is washed away, second antibody with enzyme attached is added, color-producing substrate is added, absorption is quantitated and compared to standards.
- For ELISA detection of antigen: antibody is adsorbed to a plastic surface to capture antigen for quantitation with a second enzyme-linked antibody.
- ELISA and radioimmunoassay (RIA) tests can give actual amounts of antigen (eg, p24 levels for HIV as an early indicator of infection) by comparison of results to a standard curve.
- ELISA tests can be set up to analyze antigen or antibody. The confirmation test for HIV analyzes antibody.

18

Serology: Part Two

Murray: *Medical Microbiology,* 8th Edition, Chapter 54

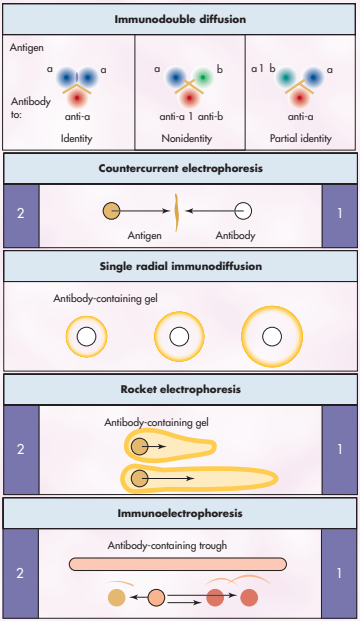

Figure 18-1: Ouchterlony double immunodiffusion is still used to distinguish Histoplasma *and* Blastomyces *antigen from serum or urine. Antigen is placed in the a or b wells, it diffuses in a circle in the agar, and meets the antibody diffusing out of the bottom well. At the equivalence point, the antibody-antigen complex is too big and precipitates. For identity, the same antigen is diffusing from both wells so that the concentration between the wells is twice the equivalence; therefore there is no precipitate. If they are different, then there are two different lines. If similar, then there is a combination of similar and different lines. Remember that a polyclonal antibody is used and many epitopes on the antigens are recognized.*

Serology: Part Two

Table 18-1: Selected Immunologic Techniques

Technique	Purpose	Clinical Examples
Ouchterlony double immunodiffusion*	Identify and compare antigen and antibody	Fungal antigen and antibody
Immunofluorescence*	Detection and localization of antigen	Viral antigen in biopsy (eg, rabies, herpes simplex virus)
Enzyme immunoassay	Same as immunofluorescence	Same as for immunofluorescence
Immunofluorescence flow cytometry	Population analysis of antigen-positive cells	Immunophenotyping
Enzyme-linked immunosorbent assay (ELISA)*	Quantitation of antigen or antibody	Viral antigen (rotavirus), viral antibody (anti-HIV)
Western blot*	Detection of antigen-specific antibody or antigen	Confirmation of anti-HIV seropositivity
Radioimmunoassay	Same as ELISA	Same as for ELISA
Complement fixation	Quantitate specific antibody titer	Fungal, viral antibody
Hemagglutination inhibition*	Antiviral antibody titer, serotype of virus strain	Seroconversion to current influenza strain, identification of influenza
Latex agglutination*	Quantitation and detection of antigen and antibody	Rheumatoid factor, fungal antigens, streptococcal antigens

HIV, Human immunodeficiency virus.
*The test can be set up for either antigen or antibody; it is important to know which is being measured.

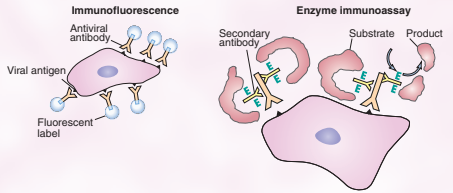

Figure 18-2: Immunofluorescence and enzyme immunoassay for detecting viral antigens localized to surface of infected cells.

19

Laboratory Diagnosis of Bacterial Diseases: Part One

Murray: *Medical Microbiology,* 8th Edition, Chapter 16

Table 19-1: Media for Isolating or Identifying Selected Bacteria

Medium	Bacteria	Comments and Examples
SELECTIVE/DIFFERENTIAL MEDIA		
Mannitol salt agar	*Staphylococcus aureus*	*S. aureus* grows on salted meats and makes toxin: diarrhea
MacConkey agar	Gram-negative enteric rods	Pink/purple colonies (lactose positive): *E. coli, Klebsiella* Colorless colonies (lactose negative): *Salmonella, Shigella, Proteus*
Eosin methylene blue (EMB) agar	Gram-negative enteric rods	Red-black colonies: *E. coli* Purple colonies: *Klebsiella* Colorless colonies: *Salmonella, Shigella*
Hektoen enteric (HE) agar	Gram-negative rods	Yellow-red colonies: *E. coli, Klebsiella* Green colonies: *Shigella* Green colonies, black center (hydrogen sulfide [H_2S]): *Salmonella*
SPECIAL MEDIA		
BCYE agar	*Legionella*	Cysteine and iron salts required
Chocolate agar	*Neisseria* and *Haemophilus* spp.	Medium supplies factors V (NAD) and X (hemin)
Lowenstein-Jensen agar	*Mycobacteria*	Slow growing; colorless or buff-colored colonies: *M. tuberculosis* and *M. leprae*
Tellurite agar	*Corynebacterium diphtheriae*	Gray to black colonies
Thayer-Martin medium	*Neisseria gonorrhoeae*	Selective chocolate agar medium

Laboratory Diagnosis of Bacterial Diseases: Part One

Table 19-2: Key Tests

Test	Bacteria
Catalase	Staphylococci (+), Strep (–)
Coagulase	*Staph aureus* (+), *Staph epidermidis* (–)
Hemolysis	*Streptococcus* (α, β, γ)
Oxidase	*Pseudomonas*, *Neisseria*, *Vibrio* (+)
Lactose fermentation (+)	*E. coli*, *Klebsiella*
Lactose fermentation (–)	*Salmonella, Shigella* (always significant) *Proteus, Pseudomonas*
Neisseria: sugar fermentation	**M**enin**G**itidis: **M**altose and **G**lucose **G**onorrhea: **G**lucose

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Laboratory Diagnosis of Bacterial Diseases: Part Two

Murray: *Medical Microbiology*, 8th Edition, Chapter 19

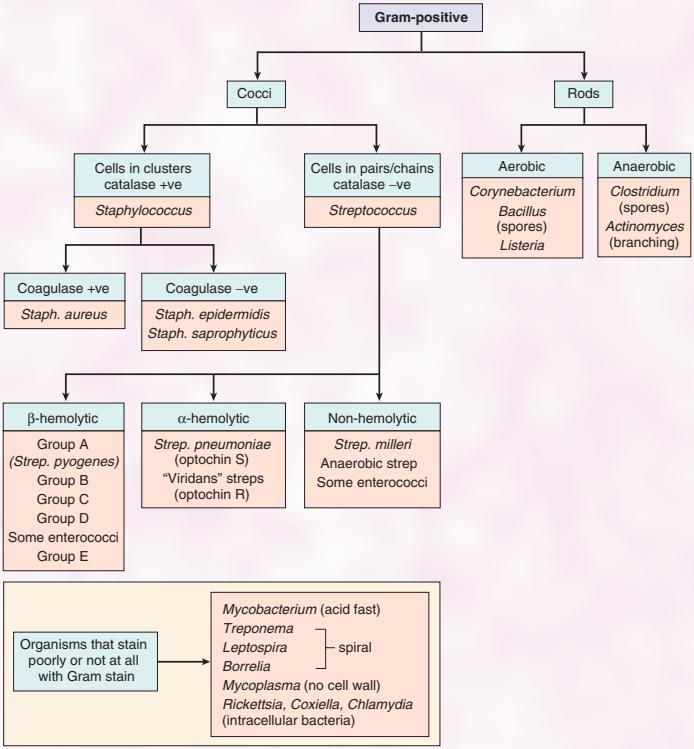

Figure 20-1: Identifying bacteria. The preliminary investigation of the bacteria of medical importance has traditionally been made on the basis of a few key characteristics. Further identification may then be made on the basis of biochemical and serologic tests. For gram-positive cocci, the branch points in the chart are defined by virulence properties.

Laboratory Diagnosis of Bacterial Diseases: Part Two

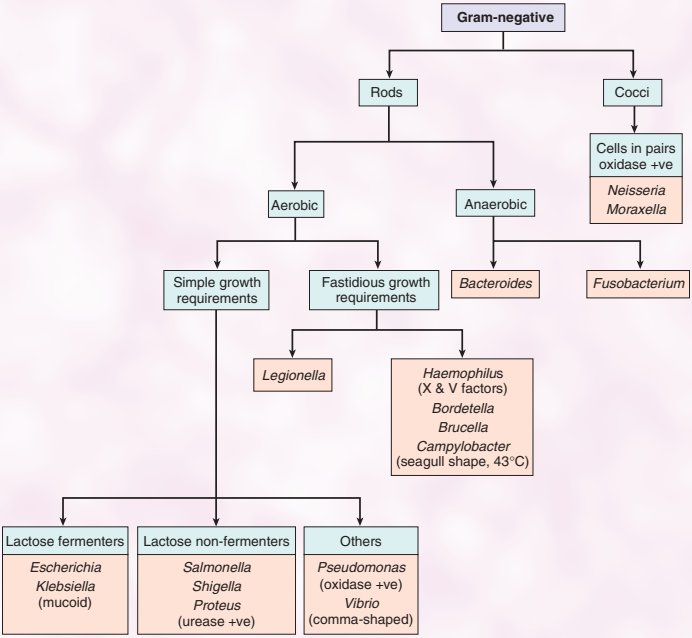

Figure 20-2: Flow chart for analysis of selected gram-negative bacteria.

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Laboratory Diagnosis of Viral Diseases

Murray: *Medical Microbiology*, 8th Edition, Chapter 39

Microscopic Examination of Clinical Specimens

1. Light microscopy: cytopathology (eg, vacuolization, necrosis, syncytia formation, inclusion bodies)
2. Electron microscopy: directly visualizes virions in cells and tissues (eg, rotavirus in stool)

Viral Isolation (growth in tissue culture)

1. Cytopathology
2. Confirmation by immunofluorescence
3. Confirmation by genomic assay (polymerase chain reaction [PCR], reverse transcriptase [RT]-PCR, etc)

Laboratory Assays for Detecting Viral Proteins

1. Hemagglutination (HA): HA on virions causes red blood cells (RBCs) to gel and remain suspended: influenza
2. Hemadsorption: RBCs stick to infected cells: influenza
3. Immunologic assays
   a. Immunofluorescence (IF)
      i. Direct: probe linked to antiviral antibody (Ab)
      ii. Indirect: probe linked to secondary Ab, which binds the primary antiviral Ab-Ag (antigen) complex
   b. Enzyme immunoassay (EIA): ELISA (enzyme-linked immunosorbent assay) and RIA (radioimmunoassay): quantitate free virions and viral proteins in a sample
   c. RIA

Viral Nucleic Acids

1. Southern blotting (DNA-DNA) and Northern blotting (DNA-RNA): detects electrophoretically separated genome sequences
2. In situ hybridization: detects viral DNA/RNA within infected cell
3. PCR: DNA viruses
4. RT-PCR: HIV, RNA viruses

Laboratory Diagnosis of Viral Diseases

Serology

1. Titer of antibody
   a. HA inhibition: specific antibody blocks HA (eg, influenza, parainfluenza, mumps)
   b. Tests for specific Ab: complement fixation, latex agglutination, ELISA, Western blot (HIV)
   c. Tests for defining serotype of virus: same assays as above
   d. Significance = fourfold increase in titer between acute and convalescent sera
2. Specific antigen expression defines disease course
   a. Epstein-Barr virus
   b. Hepatitis B virus

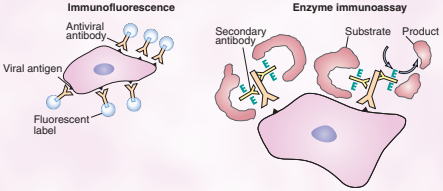

Figure 21-1: IF and EIA for detecting viral antigens localized to surface of infected cells.

Section II: Diseases

22

Normal Bacterial Flora

Murray: *Medical Microbiology,* 8th Edition, Chapters 19 and 31

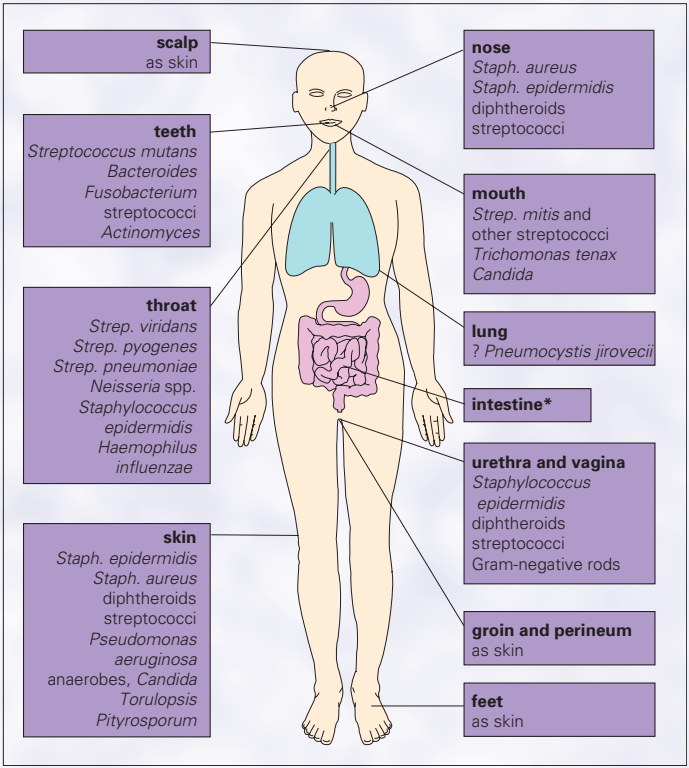

*Figure 22-1: Examples of organisms that occur as members of the normal flora and their location on the body. *See figure on reverse.*

Normal Bacterial Flora

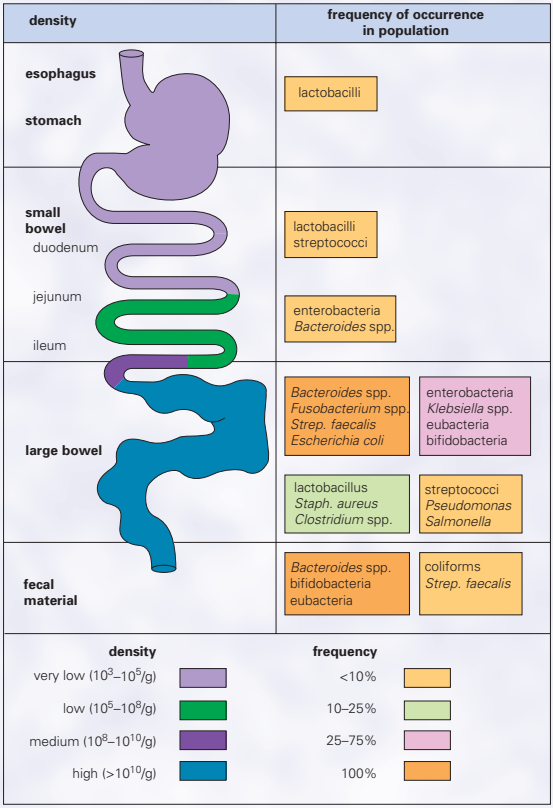

Figure 22-2: The longitudinal distribution, frequency of occurrence, and densities of the bacteria making up the normal flora of the human gastrointestinal tract.

23

Congenital and Perinatal Infections

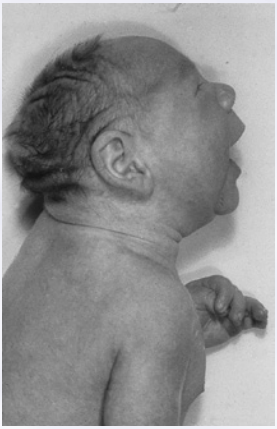

Figure 23-1: Infant with congenital cytomegalovirus; note microcephaly.

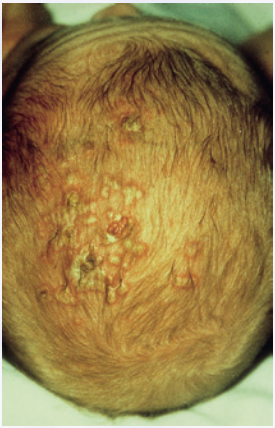

Figure 23-2: Herpes simplex virus vesicles around monitor implementation site.

Congenital and Perinatal Infections

Table 23-1: In Utero and Perinatal Infections

Microbe	Consequence
Cytomegalovirus	Most common congenital viral infection: microcephaly, retinitis, intracranial calcification, deafness, death
HSV	Sepsis-like signs, encephalitis, vesicles on skin—especially around a scalp monitor site
Varicella-zoster	Like HSV
Rubella	Microcephaly, deafness, cataracts
Parvovirus B19	Hydrops fetalis, fatal fetal anemia
Toxoplasma gondii	Encephalitis, microcephaly, intracranial calcifications, mental retardation, rash, blindness, etc
HBV	Persistent HBV infection/disease
HIV	Congenital infection: AIDS
Treponema pallidum (syphilis)	Multisystem syphilitic disease
Chlamydia trachomatis	Eye infections, pneumonia
Neisseria gonorrhoeae	Eye infections
Listeria monocytogenes	Congenital listeriosis: pneumonia, meningitis, sepsis
Group B β-hemolytic streptococci	Infections, sepsis, meningitis
Staphyloccocus aureus	Staphyloccocal scalded skin syndrome (toxin), sepsis, conjunctivitis, etc

AIDS, acquired immunodeficiency syndrome; HBV, hepatitis B virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus.

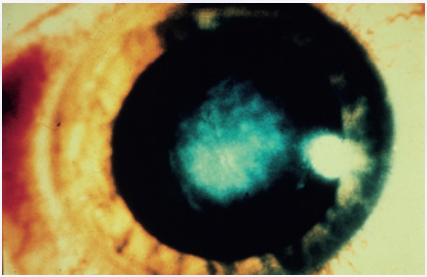

Figure 23-3: Cataract in an infant with congenital rubella.

TORCH Panel

The TORCH panel tests for the most troublesome neonatal infections: ***t***oxoplasmosis, ***o***ther infections, ***r***ubella, ***c***ytomegalovirus, and ***h***erpes simplex virus and ***h***uman immunodeficiency virus.

24 Diarrheal Diseases: Part One

Table 24-1: Major Infectious Agents of Diarrhea

Organism	Type of Diarrhea	Toxin Related	Notes/Key Words
BACTERIA			
Vibrio cholerae	Watery (NI)	Cholera toxin (↑ cAMP)	**Mucus flecks,** vomiting, dehydration
Bacillus cereus	Watery (NI)	Ingested enterotoxins	**Reheated rice** and beans
Campylobacter jejuni	Watery or bloody (I)	?	Raw meats and poultry, unpasteurized milk; fever
Clostridium difficile	Watery or bloody (I)	Toxin A (cholera-like), toxin B (cytotoxic)	**Antibiotic use;** pseudomembrane
Clostridium perfringens (type A)	Watery (NI)	Heat-labile enterotoxin (disrupts ion transport)	Leftover meat and poultry dishes
Escherichia coli (enterohemorrhagic)	Bloody (I-I)	Verotoxin (Shiga toxin)	**Uncooked hamburger;** hemorrhagic colitis, hemolytic uremic syndrome **(strain O157:H7)**
Escherichia coli (enterotoxic, enterotoxigenic)	Watery (NI)	Heat-labile enterotoxin (↑ cAMP); heat-stable enterotoxin (↑ cGMP)	**Traveler's diarrhea;** fever and vomiting sometimes
Salmonella spp.	Watery or bloody (I and I-I)	None	Poultry or eggs, contact with reptiles; **typhoid fever** (invasive *S. typhi*)
Shigella spp.	Watery, then bloody (I)	Shiga toxin inhibits protein synthesis	Mild disease (*S. sonnei*) common in daycare centers; severe invasive disease (*S. flexneri* and *S. dysenteriae*)
Staphylococcus aureus	Watery (NI)	Ingested enterotoxin	**Picnic foods** (cold cuts, potato salad), custards; rapid-onset nausea, vomiting
Vibrio parahaemolyticus	Watery (I and I-I)	None	**Shellfish**
Yersinia enterocolitica	Watery (I-I)	None	Cabbage, other raw vegetables

Continued

Diarrheal Diseases: Part One

Table 24-1: Major Infectious Agents of Diarrhea—cont'd

Organism	Type of Diarrhea	Toxin Related	Notes/Key Words
VIRUSES			
Norwalk virus	Watery (NI)	None	Often in **outbreaks** (schools, ships); nausea, vomiting, fever sometimes
Rotavirus	Watery (NI)	None	**Infants,** winter months; fever, vomiting, dehydration
Adenovirus	Watery (NI)	None	Infants
PROTOZOA			
Cryptosporidium spp.	Watery (NI)	None	Large fluid loss; most common in immunocompromised patients
Entamoeba histolytica	Bloody (I)	None	**Amebic dysentery;** lower abdominal pain, **mucus in stools**
Giardia lamblia	Watery (NI)	None	Contaminated stream water (campers, hikers); fatty, **foul-smelling stools**

cAMP, Cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; I, inflammatory; I-I, inflammatory, invasive; NI, noninflammatory.

25 Diarrheal Diseases: Part Two

Table 25-1: Infectious Causes of Diarrhea

	Onset	Source
FOOD POISONING (DUE TO PREFORMED TOXIN IN FOOD)		
Staphylococcus aureus	1–6 h	Cream, meat (even salted meat), poultry
Clostridium perfringens	8–20 h	Reheated meat
Clostridium botulinum	12–36 h	Canned food
Bacillus cereus	1–20 h	Reheated rice and meat dishes
INTESTINAL INFECTIONS		
Rotavirus	2–5 days	Fecal-oral
Norovirus	2–5 days	Fecal-oral
Salmonella	1–2 days	Eggs, poultry, contact with reptiles
Shigella	1–4 days	Fecal-oral
Campylobacter	1–4 days	Poultry, domestic animals
Vibrio cholerae	2 days	Fecal-oral, contaminated water
Escherichia coli	1–4 days	Traveler's diarrhea
Yersinia enterocolitica	Days to weeks	Pets (eg, dogs)
Giardia lamblia	1–2 weeks	Contaminated water
Entamoeba histolytica	Days to weeks	Contaminated food or water
Cryptosporidium	Days to weeks	Fecal-oral, opportunistic (eg, in AIDS)
Cystoisospora belli	3–14 days	Contaminated water, opportunistic

Diarrheal Diseases: Part Two

Logic to Diarrheas

- Blood, fecal leukocytes in stool = invasive/inflammatory disease: large intestine
- Fever = invasion (bacterial components such as endotoxin stimulate blood cell responses)
- Watery stool = toxin or virus induces an increase in electrolyte and water loss or inhibition of water uptake: small intestine
- Watery with fecal leukocytes: inflammatory diarrhea: large intestine
- ***P***ersistent diarrhea: think ***P***arasites

Time of Onset

- 1–6 hours: poisoned by preformed toxin: *Staphylococcus aureus, Bacillus cereus*
- 8–16 hours: toxin produced after infection: *Bacillus cereus, Clostridium perfringens*
- 24–48 hours: norovirus and rotavirus replication and cytopathology
- 48 hours: toxin produced after bacterial growth; enterotoxic/enterotoxigenic *Escherichia coli, Vibrio cholerae*
- >24 hours: adherence, growth, and invasion-induced diarrhea: enterohemorrhagic *Escherichia coli, Shigella, Salmonella, Campylobacter, Yersinia enterocolitica, Entamoeba histolytica, Giardia lamblia*

26 Food Poisoning and Watery Diarrhea

FOOD POISONING

Case Study

A woman attends her annual office picnic, which includes hot dogs, hamburgers, submarine sandwiches made with homemade salami and sausage, potato salad, and plenty of mayonnaise. Approximately 5 hours later she has watery diarrhea: ***Staphylococcus aureus* preformed enterotoxin.**

Causes

Vibrio parahaemolyticus* and *V. vulnificus

- Associated with seafood, especially shellfish
- Also, *V. vulnificus* infection of fisherman's hand (cut by a fin)

Bacillus cereus

- Reheated rice: can have either a long or short incubation
  - Long incubation period mimics *Clostridium perfringens*
  - Short incubation period mimics *Staphylococcus aureus*
  - Food poisoning from rice—"be serious" (*B. cereus*)

Clostridium perfringens

- Reheated meat dishes: *C. perfringens* likes to eat meat (can also cause gangrene)

Clostridium botulinum

- Improperly canned foods (bulging can from gas) OR honey ingestion in a baby ("floppy baby")

***Escherichia coli* O157:H7**

- In raw hamburger—bloody diarrhea; in a child can lead to hemolytic uremic syndrome—diarrhea and bloody urine

Salmonella

- Poultry, meat, and eggs (and reptile contact)

Food Poisoning and Watery Diarrhea

WATERY DIARRHEA

Case Studies

- A camper in the Colorado mountains drinks from the mountain stream. Days later he is overcome by watery diarrhea and foul-smelling stools. He notices abdominal pain that feels like it may be gas: *Giardia lamblia*
- Cruise ship and everyone has diarrhea: **Norwalk virus**
- Very dehydrated 2-year-old child with watery diarrhea, no fever, no blood: *rotavirus*
- Traveler returns from Mexico with diarrhea: *E. coli*
- Visitor to New Orleans has too many oysters: *V. cholerae* **or** *V. parahaemolyticus*

Causes

Bacteria

- *V. cholerae:* mucus flecks in stool (rice water), comma-shaped organism
- *V. parahaemolyticus:* shellfish
- **Enterotoxic/enterotoxigenic** *E. coli* (ETEC; traveler's diarrhea): *E. coli* with a *V. cholerae*–like toxin; enterohemorrhagic *E. coli* (EHEC): *E. coli* with a *Shigella* toxin
- *S. aureus* **enterotoxin**
- *B. cereus* **enterotoxin**

Viruses

- Rotavirus*:* the No. 1 cause of child diarrheal death
  - Outbreaks on the wards of children's hospitals
- Norwalk: outbreaks—the whole high school and cruise ship gets it

Protozoa

- *Cryptosporidium:* severe in AIDS, mild in competent host
- *Giardia lamblia:* cold-water streams contaminated with bear and other animal feces

27 Bloody Diarrhea and Parasite Diarrhea

BLOODY DIARRHEA

Case Studies

- A child presents to the emergency department with bloody diarrhea. The entire family ate the same dinner. Why did the child get sick? The mother breaded chicken just after cleaning the turtle's aquarium: ***Salmonella.***
- A child in daycare has very watery diarrhea with bloody mucus and polymorphonuclear cells in stool, with cramps and fever: ***Shigella.***
- A 40-year-old woman visited a rural village in India and soon after develops abdominal cramps, fever, and frequent watery diarrhea (more than 8 episodes per day) with blood and mucus for longer than 2 weeks: ***Entamoeba histolytica*** **(amebic dysentery).**

Causes

Salmonella

- Associated with reptiles, raw eggs, and undercooked chicken.
- ***Not normal flora.*** Do not forget that *Salmonella* is *motile* **(salmon swim upstream); lactose negative, H_2S positive.**

Shigella **(nasty)**

- Only 10 organisms are needed to cause disease.

Campylobacter jejuni

- USMLE is fond of the association with Guillain-Barré syndrome.
- Comma- or S-shaped; grows at 42°C.
- In poultry, raw meats, and unpasteurized milk products.

Enterohemorrhagic/enteroinvasive *Escherichia coli* (O157:H7)

- (Raw hamburger!); child with diarrhea then bloody urine = hemolytic uremic syndrome (HUS).

Yersinia enterocolitica

- **Not normal flora.** Do not confuse with the plague, which is *Yersinia pestis.*

Bloody Diarrhea and Parasite Diarrhea

PARASITE DIARRHEA

Entamoeba histolytica

- Amebiasis
- Bloody diarrhea that can lead to a liver abscess. USMLE likes the association of right upper quadrant pain with a liver abscess on computed tomography.
- Treat it by "running it over with the metro train" (metronidazole). (Metronidazole also treats *Clostridium difficile* and *Giardia lamblia*.)

Giardia lamblia

- Giardiasis: bloating, gas, foul-smelling stools
- Malabsorption: causing deficiency in fat-soluble vitamins A, D, E, K. Contaminated cold-water streams

Cryptosporidium

- Cysts in water supply: AIDS patients: severe diarrhea
- Competent hosts: mild diarrhea
- No known treatment
- ***Cystoisospora belli***
- Causes pain in the belly of AIDS patients
- Diarrhea
- Treatment: trimethoprim-sulfamethoxazole (TMP-SMX)

28

Encephalitis and Other CNS Diseases

Murray: *Medical Microbiology*, 8th Edition, Chapters 6 and 10

CASE STUDIES

- Patient has focal neurologic symptoms and seizures. MRI shows destruction of temporal lobe. Erythrocytes present in CSF and PCR are positive for viral DNA: **HSV encephalitis**
- A 70-year-old man from swampy area of New York develops fever, headache, muscle weakness, nausea, and vomiting and then progresses into a coma. MRI indicates no specific localization of lesions: **West Nile encephalitis**
- Immigrant boy from Indonesia develops fever, headache, and then vomits. He refuses to take pills and drink water because of pain on swallowing. Two days later he has a 41°C fever, is confused and delirious, becomes paralyzed, goes into coma, and dies. A brain biopsy during autopsy indicates Negri bodies. Father recalls son being bitten by a dog 6 months earlier: **rabies**
- A 65-year-old man has severe headaches, tremor in hand, and is forgetful and confused. His condition deteriorates, and he enters a coma with occasional clonic twitching. There are no gross abnormalities, no inflammation on autopsy, but intracellular vacuolation is seen throughout the cerebral cortex: **Creutzfeldt-Jakob disease**
- A 35-year-old British man undergoes a similar course of disease, but the time course is much quicker. **Creutzfeldt-Jakob variant disease**
- An AIDS patient who owns a cat develops seizures. A CT scan of the head shows a ring-enhancing lesion: **chronic toxoplasmosis**
- A baby is born with encephalitis, hydrocephalus, blindness, anemia, rash, jaundice, and pneumonia. The mother was infected with toxoplasmosis during the first trimester: **congenital toxoplasmosis**
- A man receiving immunosuppressive therapy begins to suffer from neurologic symptoms (memory loss, difficulty speaking and coordination, loss of some use of his arm): **JC virus = progressive multifocal leukoencephalopathy**

Encephalitis and Other CNS Diseases

Table 28-1

	Characteristics
VIRAL	
Herpes simplex virus	Frontal lobe; most common nonseasonal, always significant sequelae
Arboviruses: Flavi (Japanese, West Nile, St. Louis), Toga (equine encephalitis), Bunya (California encephalitis)	Seasonal, often resolves with minimal sequelae
Measles	
Mumps	
Rabies	Treatable by vaccination postinfection
HTLV-1 (retrovirus)	Tropical spastic paraparesis
SSPE (measles variant)	Slow virus disease
Prion: Creutzfeldt-Jacob disease, kuru, scrapie	Spongiform encephal**opathy** (***apathy*** for the immune response)
OTHER	
Toxoplasma	Rare complication
Cryptococcus	Meningoencephalitis
Plasmodium falciparum	Cerebral malaria
Treponema pallidum	Neurologic syphilis
Mycobacterium tuberculosis	Tuberculosis: chronic meningitis
Borrelia burgdorferi	Lyme disease
Various bacteria: *Streptococcus, Staphylococcus,* brain abscess, enterobacteria, etc	
Cysticercosis: *Taenia solium*	Pork tapeworm
Toxoplasmosis	Neonates, AIDS patients at high risk

AIDS, Acquired immunodeficiency syndrome; HTLV, human T-lymphotropic virus; SSPE, subacute sclerosing panencephalitis.

29 Meningitis

CASE STUDIES

- A young man was doing renovations in his apartment in New York City when he developed a headache and fever. One week later, his sister came to visit him and found him on his couch in a stupor. A spinal tap was performed in the emergency department, and multiple round organisms with a clear halo were visualized with an India ink preparation: ***Cryptococcus neoformans*** **meningitis**
- A 5-year-old child presents with sudden onset of fever, petechiae and purpura (black and blue marks) on the skin, malaise, and stiff neck. Cerebrospinal fluid (CSF) contains gram-negative diplococci: ***Neisseria meningitidis***
- A 9-year-old girl has a fever and skin rash and is suffering from nausea. She appears listless and has difficulty moving her head from side to side. CSF analysis shows normal glucose, no bacteria, and the presence of lymphocytes. Within 1 week the infant is fully recovered: **aseptic meningitis = coxsackievirus or echovirus**

ESSENTIAL FACTS

Treatment of bacterial meningitis and lysis of the bacteria release endotoxin and other pyrogenic substances, which may exacerbate the disease.

- Bacteria grow in the central nervous system (CNS) and ***increase protein***; they eat and ***decrease glucose***; neutrophils infiltrate and inflammation puts ***pressure*** on the system.
- Viruses sneak into the CNS and ***increase a little protein***; they do not eat, so ***glucose stays normal***; they might invite ***lymphocytes***.
- Fungi grow in the CNS and ***increase*** protein; they eat and may ***decrease glucose***; and they invite ***lymphocytes***.

Table 29-1: Analysis of Cerebrospinal Fluid in Meningitis

	Cerebrospinal Fluid Findings				
Probable Cause	**Pressure**	**Protein**	**Sugar**	**Lymphocytes**	**PMNs**
Bacterial	↑	↑	↓↓	N	↑
Viral	N	N	N	↑	N
Fungal/*Mycobacterium tuberculosis*	↑↑	↑	↓	↑	N

N, Normal values; PMNs, polymorphonuclear cells; ↑, increase; ↓, decrease.

Table 29-2: Microbial Causes of Meningitis

Cause	**Description**
BACTERIA	
Neisseria meningitidis	Capsule, endotoxin, petechiae, vaccines
Haemophilus influenzae	Capsule, endotoxin, vaccine for type B
Streptococcus pneumoniae	Capsule, vaccines
Listeria monocytogenes	
Mycobacterium tuberculosis	
NEONATAL BACTERIAL	
Group B streptococci	
Escherichia coli	
Listeria monocytogenes	
FUNGAL	
Cryptococcus neoformans	Capsule, India ink test
Coccidioides immitis	Desert regions of southwestern United States
VIRAL (ASEPTIC)	
HSV (especially HSV-2)	
Mumps	
Lymphocytic choriomeningitis virus	Spread in rodent urine and feces
Polio, coxsackieviruses, echoviruses, etc	
Arboviruses	Flulike prodrome may precede encephalitis

HSV, Herpes simplex virus.

Table 29-3: Most Common Causes by Age of Patient

Age	**Cause**
Neonates	Group B streptococci
	Escherichia coli
	Listeria
Children	*Haemophilus influenzae* B (vaccine preventable)
	Streptococcus pneumoniae
Adults	*Streptococcus pneumoniae*
	Neisseria meningitidis

30

Immune Deficiency Diseases: Inherited Disorders of Innate Response

Murray: *Medical Microbiology,* 8th Edition, Chapter 8

Table 30-1: Inherited Disorders of Innate Responses

Disease	Defect	Clinical Features
Chédiak-Higashi syndrome	Reduced ability of phagocytes to store materials in lysosomes and/or release their contents	Recurrent pyogenic infections (eg, *Staphylococcus* and *Streptococcus*)
Chronic granulomatous disease	Reduced production of H_2O_2 and superoxide anion due to lack of NADPH oxidase (especially in neutrophils)	Increased susceptibility to catalase-producing bacteria (eg, *Staphylococcus* spp.) and fungal infections
Job syndrome	Hyper-IgE, reduced Th17 but poorly controlled macrophage inflammation	Recurrent staphylococcal abscesses; eczema; bronchitis, candidiasis
Lazy-leukocyte syndrome	Severe impairment of neutrophil chemotaxis and migration	Recurrent low-grade infections
Leukocyte-adhesion deficiency	Defect in adhesion proteins reducing leukocyte migration into tissues and adherence to target cells	Recurrent bacterial and fungal infections; poor wound healing
Myeloperoxidase deficiency	Decreased production of HOCl and other reactive intermediates	Delayed killing of staphylococci and *Candida albicans*
Loss of spleen		Increased sensitivity to encapsulated bacteria
Pathogen pattern receptor deficiency	Decreased response to microbes	Increased risk to bacterial and fungal infections
COMPLEMENT DEFICIENCIES		
C1, C2, or C4		Lupus-like disease, immune complex disease
C3		Pyogenic (staphylococcal, streptococcal, etc) bacterial infections, severe
Factor D or properdin (factor P)		Pyogenic (staphylococcal, streptococcal, etc) bacterial infections, severe
C5, C6, C7, C8, or C9		Disseminated neisserial infections
C1 inhibitor		Hereditary angioedema
DAF deficiency		Complement-mediated intravascular hemolysis

DAF, Decay accelerating factor; DTH, delayed-type hypersensitivity; HOCl, hypochlorous acid; Ig, immunoglobulin; NADPH, reduced nicotinamide adenine dinucleotide phosphate.

31

Immune Deficiency Diseases: Primary Lymphocyte Immunodeficiencies

Murray: *Medical Microbiology,* 8th Edition, Chapter 8

Table 31-1: Primary Lymphocyte Immunodeficiencies

Disease	Immunologic Defects*	Other Features
B-CELL DEFICIENCIES (ANTIBODY)		
Bruton agammaglobulinemia	Defect in maturation of B cells: ↓ B-cell count; ↓ Ig of all isotypes	Recurrent pyogenic infections; small lymph nodes with poorly developed germinal centers; X-linked recessive
Common variable hypogammaglobulinemia	Defect in differentiation of B cells to plasma cells: ↓ Ig of all isotypes	Recurrent pyogenic infections; often associated with blood or autoimmune disorders
Selective IgA deficiency	Failure of B cells expressing membrane IgA to differentiate into plasma cells: ↓ IgA but normal levels of other isotypes	Recurrent respiratory and gastrointestinal infections; most common congenital B-cell defect
T-CELL DEFICIENCIES		
Chronic mucocutaneous candidiasis	Absence of T-cell response to *Candida* despite normal T-cell count and function	Recurrent candidal skin and mucous membrane infections; often associated with endocrine dysfunction
DiGeorge syndrome	Thymic aplasia due to defect in development of third and fourth brachial arches: ↓ T-cell count; ↓ or normal Ig levels	Recurrent viral, fungal, and protozoan infections; tetany resulting from hypocalcemia due to undeveloped parathyroid glands
Hyper-IgM syndrome (eg, CD40L deficiency)	Decreased B-cell activation and class switching due to T-cell defect: ↑ IgM; ↓ IgG and IgA	Poor response to T cell–dependent antigens; recurrent infections, especially *Pneumocystis jirovecii;* often associated with autoimmune blood disorders

Continued

Immune Deficiency Diseases: Primary Lymphocyte Immunodeficiencies

Table 31-1: Primary Lymphocyte Immunodeficiencies—cont'd

Disease	Immunologic Defects*	Other Features
COMBINED B- AND T-CELL DEFICIENCIES		
Ataxia-telangiectasia	↓ T-cell count and function; ↓ IgA, IgE, and IgG2	Cerebellar dysfunction (ataxia), dilation of small vessels (telangiectasia); recurrent bacterial infections of respiratory tract; autosomal recessive
Severe combined immunodeficiency (SCID)	Various defects that interrupt early lymphocyte development ↓ T- and B-cell counts; ↓ Ig of all isotypes	Recurrent infections of all types; short life span; may be X-linked (X-SCID) or autosomal recessive (eg, ADA deficiency)
Wiskott-Aldrich syndrome	Poor response to polysaccharide antigens and depressed T-cell function: ↓ IgM; ↑ IgA and IgE	Eczema, thrombocytopenia, and recurrent infections with encapsulated pyogenic bacteria; X-linked recessive

↓, Below normal; ↑, above normal.
*Immunoglobulin (Ig) arrows refer to serum antibody levels of indicated isotype.

32

Infections Associated With Defects in Immune Responses

Murray: *Medical Microbiology,* 8th Edition, Chapter 9

Table 32-1: Infections Associated With Defects in Immune Responses

Defect	Pathogen
Induction by physical means (eg, burns, trauma)	*Pseudomonas aeruginosa* *Staphylococcus aureus* *Staphylococcus epidermidis* *Streptococcus pyogenes* *Aspergillus* species *Candida* species
Granulocyte and monocyte defects in movement, phagocytosis, or killing or decreased number of cells (neutropenia)	*Staphylococcus aureus* *Streptococcus pyogenes* *Haemophilus influenzae* Gram-negative bacilli *Escherichia coli* *Klebsiella* species *Pseudomonas aeruginosa* *Nocardia* species *Aspergillus* species *Candida* species
Individual components of complement system	*Staphylococcus aureus* *Streptococcus pneumoniae* *Pseudomonas* species *Proteus* species *Neisseria* species
T cells	Herpes viruses: HSV, CMV, VZV, EBV, HHV6, HHV8 Enveloped viruses *Listeria monocytogenes* *Mycobacterium* species *Nocardia* species *Aspergillus* species *Candida* species *Cryptococcus neoformans* *Histoplasma capsulatum* *Pneumocystis jirovecii* *Strongyloides stercoralis*
B cells	Enteroviruses *Staphylococcus aureus* *Streptococcus* species *Haemophilus influenzae* *Neisseria meningitidis* *Escherichia coli* *Giardia lamblia* *Pneumocystis jiroveci*
Combined immunodeficiency	See pathogens listed for T cells and B cells

Infections Associated With Defects in Immune Responses

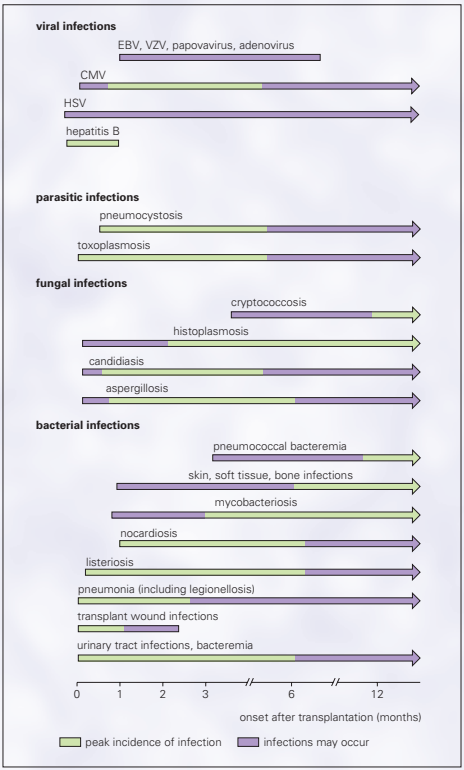

Figure 32-1: Timetable showing the time of onset and peak incidence of infections in patients after renal transplantation. The patient is at risk of some infections, particularly hepatitis B and wound infections, for a limited period only, immediately after transplantation. Other infections may develop after several weeks of immunosuppression, but the majority constitute a risk throughout the period of immunosuppression. Note that Pneumocystis jirovecii, *previously known as* Pneumocystis carinii *(pneumocystosis), is actually a fungus. CMV, Cytomegalovirus; EBV, Epstein-Barr virus; HSV, herpes simplex virus; VZV, varicella-zoster virus.*

33

Opportunistic Diseases in AIDS

Murray: *Medical Microbiology,* 8th Edition, Chapter 54

CASE STUDIES

- An AIDS patient fails to take his TMP-SMX medication regularly and gradually develops a fever, shortness of breath, and a nonproductive cough. A chest x-ray reveals a diffuse interstitial infiltrate, and bronchoalveolar lavage shows numerous cup-shaped organisms in a foamy alveolar exudate: ***Pneumocystis* pneumonia**
- An AIDS patient has retinitis and pneumonitis: **CMV**
- An AIDS patient has a thick, white coat on his tongue and gums that is painful: **thrush**, ***Candida albicans***
- An AIDS patient has chronic bronchitis, fever, night sweats, chills, and blood-tinged sputum, and x-ray indicates lung disease. The PPD test is weakly positive. Spread to other organs is indicated: ***Mycobacterium tuberculosis***
- A patient with AIDS presents with altered mentation after a neighbor complains of a strong odor of unclean cats in his apartment. A CT scan in the emergency room shows ring-enhanced lesions in the brain: ***Toxoplasma gondii***
- A patient with AIDS presents with fever, night sweats, weight loss, abdominal pain, fatigue, and diarrhea: **Disseminated *Mycobacterium avium-intracelllulare***

Opportunistic Diseases in AIDS

*Table 33-1: Indicator Diseases of AIDS**

Opportunistic infections	
Protozoal	Toxoplasmosis of the brain
	Cryptosporidiosis with diarrhea
	Cystoisosporiasis with diarrhea
Fungal	Candidiasis of the esophagus, trachea, and lungs
	Pneumocystis pneumonia
	Cryptococcosis (extrapulmonary)
	Histoplasmosis (disseminated)
	Coccidioidomycosis (disseminated)
Viral	Cytomegalovirus disease
	Herpes simplex virus infection (persistent or disseminated)
	Progressive multifocal leukoencephalopathy
	Hairy leukoplakia caused by EBV
Bacterial	*Mycobacterium avium-intracellulare* complex (disseminated)
	Any "atypical" mycobacterial disease
	Extrapulmonary tuberculosis
	Salmonella diarrhea and septicemia (recurrent)
	Pyogenic bacterial infections (multiple or recurrent)
Opportunistic neoplasias	Kaposi sarcoma
	EBV-associated lymphomas
	Primary lymphoma of the brain
	Other non-Hodgkin lymphomas
Other	HIV wasting syndrome
	HIV encephalopathy
	Lymphoid interstitial pneumonia

Modified from Belshe RB, editor: *Textbook of human virology*, ed 2, St. Louis, 1991, Mosby.
EBV, Epstein-Barr virus; HIV, human immunodeficiency virus.
*Manifestations of HIV infection–defining acquired immunodeficiency syndrome (AIDS) according to criteria of the Centers for Disease Control and Prevention.

34 Organ Systems

Table 34-1

Organ	Bacteria
HEART	
Endocarditis, subacute (slow onset)	*Viridans* streptococci* (especially associated with dental manipulation), group D streptococci (*S. bovis*),* *Enterococcus* species*
	HACEK organisms (*Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella*)
Acute (rapid onset)	*Staphylococcus aureus**
	Coagulase-negative staph (catheter)
IV drug abusers	*S. aureus**
	Group A streptococci
	Pseudomonas aeruginosa
	Enterococcus faecalis
Prosthetic valve	*Staphylococcus epidermidis**
	S. aureus
Myocarditis	Coxsackie B virus (B for body)
	Trypanosoma cruzi (Chagas disease)
	Trichinella spiralis
	Corynebacterium diphtheriae
Rheumatic fever	*Streptococcus pyogenes* sequelae
Myositis and myonecrosis	Coxsackie B virus (B for body)
	Dengue fever
	Anaerobic streptococci
	Clostridium perfringens (gangrene)
	T. cruzi (Chagas disease)
	Taenia solium
	T. spiralis
BONE	
Osteomyelitis	*S. aureus**
	Salmonella in sickle cell patients
Joint disease (septic infected)	*S. aureus**
	*Neisseria gonorrhoeae** (sexually active)
	Streptococcus species (<15 years)
	Streptococcus pneumoniae (<5 years)
	Gram-negative bacteria
STOMACH	
Ulcers	*Helicobacter pylori**: urease, motility, chronic infection
KIDNEY	
Pyelonephritis	*Escherichia coli*
	Staphylococcus saprophyticus
	Enterococcus
	Pseudomonas aeruginosa
LIVER	See hepatitis

*Most common cause.

Table 35-1: Comparative Features of Hepatitis Viruses

Feature	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E
Common name	"Infectious"	"Serum"	"Non-A, non-B posttransfusion"	"Delta agent"	"Enteric non-A, non-B"
Virus structure	Picornavirus; capsid, RNA	Hepadnavirus; envelope, DNA	Flavivirus; envelope, RNA	Viroid-like; envelope, circular RNA	Calici-like capsid, RNA
Transmission	Fecal-oral	Parenteral, sexual	Parenteral, sexual	Parenteral, sexual	Fecal-oral
Onset	Abrupt	Insidious	Insidious	Abrupt	Abrupt
Incubation period (days)	15–50	45–160	14–180	15–64	15–50
Severity	Mild	Occasionally severe	Usually subclinical; 80% chronicity	*Coinfection* with HBV occasionally severe; *superinfection* with HBV often severe	Normal patients, mild; pregnant women, severe
Mortality rate	<0.5%	1%–2%	~4%	High to very high	Normal patients, 1%–2%; pregnant women, 20%
Chronicity/ carrier state	No	Yes	Yes	Yes	No
Other disease associations	None	Primary hepatocellular carcinoma, cirrhosis	Primary hepatocellular carcinoma, cirrhosis	Cirrhosis, fulminant hepatitis	None
Laboratory diagnosis	Symptoms and anti-HAV IgM	Symptoms and serum levels of HBsAg, HBeAg, and anti-HBc IgM, PCR	Symptoms, anti-HCV ELISA, RT-PCR	Anti-HDV ELISA	—

ELISA, Enzyme-linked immunosorbent assay; HAV, hepatitis A virus; HBc, hepatitis B core [antigen]; HBeAg, hepatitis B early antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; IgM, immunoglobulin M; PCR, polymerase chain reaction.

Table 35-2: Other Causes of Liver Disease

Cause	Agent
DISEASE	
Hepatitis	Hepatitis A, B, C, D, E viruses
	Yellow fever virus
	Dengue and other hemorrhagic viruses
	Epstein-Barr virus
	Cytomegalovirus
Liver abscess	Mixed bacterial infection, including *Escherichia coli*
	Entamoeba histolytica
	Aspergillus (if patient is neutropenic)
PARASITES	
Animal liver flukes	*Schistosoma mansoni, Fasciola hepatica, Opisthorchis*
Protozoa	*Leishmania*
	Malaria
	Toxoplasma
Granulomas	Mycobacteria
	Syphilis

36 Muscle, Bone, and Joint

MUSCLE

Viruses

- Coxsackie B virus (B for body): myocarditis, pericarditis, pleurodynia (Bornholm disease)
- Dengue: breakbone fever

Bacteria

- Many

Parasites

- *Trypanosoma cruzi* (Chagas disease): acquired from reduviid bugs
- *Taenia solium* (pork tapeworm): acquired from poorly cooked pork
- *Trichinella spiralis:* acquired from poorly cooked pork or game (bear, boar, horse, etc)

BONE

- *Staphylococcus aureus:* most common cause of osteomyelitis; treat with nafcillin or clindamycin
- Streptococci (groups A and B): treat with penicillin
- *Pseudomonas aeruginosa* (puncture wounds, especially through sneakers): treat with cefepime, ceftazidime, or ciprofloxacin

JOINT

- *Haemophilus influenzae:* also common for children

Table 36-1: Arthralgia and Arthritis in Infectious Diseases

	Infectious Agent	Comments
Viral	Hepatitis B	Occurs in prodromal period; due to circulating immune complexes
	Rubella	Especially in young women, often follows live virus vaccine
	Mumps	Unusual, mostly in men
	Ross River and other togaviruses	Mosquito-transmitted infections in Australia (Ross River) and Africa
	Parvovirus	May follow adult infection
Reactive arthritis	*Campylobacter*, *Yersinia*, *Salmonella*, *Shigella*, *Chlamydia trachomatis* (Reiter syndrome*)	"Postinfectious" arthritis, HLA B27-associated, no bacterial invasion of joint, immune mediated
Septic arthritis	*Staphylococcus aureus*	Most common cause of suppurative arthritis
	Salmonella	Occurs in children
	Haemophilus influenzae	Occurs in children
	Neisseria gonorrhoeae	May affect multiple joints
	Mycobacterium tuberculosis	Often with bone lesions, especially weight-bearing joints and bones
	Borrelia burgdorferi	Arthritis a late feature of Lyme disease
	Streptococci, *Pseudomonas aeruginosa*	Uncommon
	Mycoplasma hominis	Bacteria can enter maternal blood during delivery and invade joints; uncommon
	Sporothrix schenckii	Fungal infection of joints

*Urethritis, arthritis, uveitis, mucocutaneous lesions; complicates 1%–2% of cases of chlamydial urethritis.

37 Ocular Infections

CASE STUDIES

- A 5-year-old child with sore throat and conjunctivitis: **adenovirus pharyngoconjunctivitis**
- A 45-year-old woman with dendritic scarring on cornea: **herpes simplex virus recurrent keratoconjunctivitis**
- Neonate does not receive eye treatments at birth and develops conjunctivitis: ***Chlamydia*** or **gonorrheal conjunctivitis**

Ocular Infections

Table 37-1

	Potential Causes
CONJUNCTIVITIS	Adenovirus (with pharyngitis?)
	HSV recurrent, leading to blindness
	Chlamydia trachomatis (serotypes D-K)
	Staphylococcus aureus
Neonate	*Chlamydia*
	Neisseria gonorrhoeae
KERATITIS	HSV—recurrent, leading to blindness
	Staphylococci
	Streptococci
	Enterobacteriaceae
	Pseudomonas aeruginosa
VIRAL RETINITIS	CMV (AIDS patients)
	HSV-1
	HSV-2 (neonates)
	Toxoplasma
ENDOPHTHALMITIS	*Candida, Aspergillus, Bacillus cereus,* etc

AIDS, Acquired immunodeficiency syndrome; CMV, cytomegalovirus; HSV, herpes simplex virus.

38 Respiratory Infections

CASE STUDIES

- A 70-year-old woman experiences rapid onset of fever with headache, myalgia (very sore muscles), sore throat, and nonproductive cough. The disease progresses to pneumonia with bacterial involvement. The woman's history shows no recent immunization with influenza vaccine: **influenza**
- A 2-year-old child coughs like a barking seal and has a sore throat, fever, and a hoarse voice. High-pitched noise on inhalation and difficulty breathing: **croup: parainfluenza virus**
- A 20-year-old woman has a nagging, nonproductive cough, low-grade fever, headache, and fatigue. She had pharyngitis before the cough began. Chest radiograph indicates bilateral diffuse interstitial pneumonia: ***Mycoplasma pneumonia*** (walking pneumonia)

Table 38-1: Pneumonias

Bacterial*	*Streptococcus pneumoniae*
	Chlamydophila pneumoniae
	Haemophilus influenzae
	Staphylococcus aureus
	Legionella
	Mycoplasma pneumoniae
	Mycobacterium tuberculosis
Adult viral	Influenza A and B (± bacterial pneumonia)
	Varicella-zoster
	Adenovirus
Child viral	Respiratory syncytial virus
	Parainfluenza
	Adenovirus
	Influenza A and B
	Varicella-zoster
Fungal (and other lung diseases)	Histoplasma
	Coccidioides immitis
	Aspergillus
	Cryptococcus

*Most common to least common.

Table 38-2: Upper Respiratory Infections

Common cold	Rhinovirus
	Coronavirus
	Coxsackievirus (and other enteroviruses)
	Parainfluenza
	Influenza
Croup	Parainfluenza
	Respiratory syncytial virus
	Influenza
Throat	*Streptococcus pyogenes*
	Common cold viruses
	Adenovirus
	Epstein-Barr virus
Epiglottitis	*Haemophilus influenzae* type B *(Streptococcus pneumoniae, Staphylococcus aureus)*
Earache: internal	*S. pneumoniae*
Internal	*H. influenzae* type B
Internal	*Moraxella catarrhalis*
External and internal	*S. aureus*
External	*Pseudomonas aeruginosa* (swimmer's ear)
Bronchitis	*Bordetella pertussis*
	M. catarrhalis
	Mycoplasma pneumoniae
	Chlamydophila pneumoniae
	Streptococcus pneumoniae
	H. influenzae
	Influenza
	Respiratory syncytial virus, *Rhinovirus*, parainfluenza, adenovirus, coronavirus

Table 38-3: Pneumonias in the Immunocompromised Host (AIDS)

Cytomegalovirus
Mycobacterium tuberculosis
Mycobacterium avium-intracellulare
Pneumocystis jirovecii
Fungal infections

39 Pneumonia

CASE STUDIES

- Typical pneumonia
  - Abrupt onset of high fever (>39°C), productive cough with blood-tinged sputum, chest pain
  - Chest radiograph: consolidated, whited-out infiltrate throughout lower lobe of lung
  - Elevated procalcitonin indicates bacterial infection
  - ***Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus***
- Atypical pneumonia
  - Slow onset of nonproductive cough, moderate fever (<39°C), headache, sore throat, gastrointestinal symptoms
  - Chest radiograph: patchy infiltrates
  - ***Chlamydia*, *Mycoplasma pneumoniae*, *Legionella*, *Klebsiella pneumoniae*, and fungi**

SPECIAL CASES

- Alcoholics: anaerobes
- Aspiration: anaerobes, *Klebsiella*
- Postviral: *Staphylococcus aureus*
- Neonate: group B streptococci, *Escherichia coli*
- Cystic fibrosis: *S. aureus* and *Pseudomonas aeruginosa* (colonization)

Pneumonia

Table 39-1: Pneumonia by Patient Age (Know the Top Agent in Each Category)

Youth (6 weeks–19 years)	RSV, parainfluenza, influenza viruses
	Mycoplasma
	Chlamydophila pneumoniae
	Streptococcus pneumoniae
Adults (20–60 years)	*Mycoplasma*
	C. pneumoniae
	S. pneumoniae
	Haemophilus influenzae
	Varicella-zoster virus (primary disease)
Older adults (>60 years)	*S. pneumoniae*
	RSV, parainfluenza, influenza viruses
	Anaerobes
	H. influenzae
	Gram-negative rods

RSV, Respiratory syncytial virus.

Table 39-2: Pneumonias

BACTERIAL PNEUMONIA	
Community acquired	*Streptococcus pneumoniae*
	Haemophilus influenzae
	Mycoplasma pneumoniae
	Chlamydophila pneumoniae
	Legionella
Nosocomial	*Staphylococcus*
	Gram-negative rods: *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa*
VIRAL PNEUMONIAS	Respiratory syncytial virus
	Parainfluenza
	Influenza
	Influenza + *S. aureus* superinfection
FUNGAL PNEUMONIAS	
Immunocompromised	*Pneumocystis* pneumonia
Immunocompetent and compromised	*Histoplasma capsulatum*
	Coccidioides immitis
	Blastomyces dermatitidis

40 Sexually Transmitted Diseases: Part One

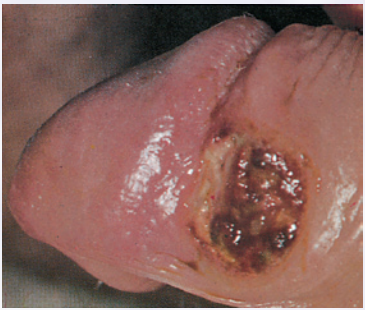

Figure 40-1: Chancre in primary syphilis.

CASE STUDIES

- An 18-year-old man presents with a painless sore on his penis. He states that he has had three sexual encounters in the past 2 weeks and wore protection only on one occasion. The VDRL test result was positive for a sexually transmitted disease: **syphilis** (primary with chancre). Treat with penicillin.
- A 26-year-old woman presents with pelvic pain. Also, she has been unsuccessful in her attempts to become pregnant. During physical examination there is marked cervical tenderness with a positive chandelier sign: **gonorrhea or chlamydia**, or both. Treat both with ceftriaxone + doxycycline.
- **A sexually active** woman in her mid-20s has ulcerative lesions on the vagina with pain, itching, dysuria, systemic symptoms, and a fever lasting 10 days. Pap smear shows **multinucleated giant cells and Cowdry type A inclusion bodies: vaginal herpes.**
- Koilocytic cells (enlarged nuclei and cytoplasmic vacuoles) seen in Pap smear: **cervical intraepithelial neoplasia** due to **human papilloma virus.**

Sexually Transmitted Diseases: Part One

- Nongonococcal urethritis with persistent watery discharge: **chlamydia.**
- A papule (ulcer) appears on the penis, then heals, but 2 weeks later the draining lymph nodes are very swollen (buboes): **lymphogranuloma venereum**, **chlamydia.**
- A sexually active woman has a slight watery discharge and vaginitis with itching and painful urination. A motile organism was observed by the hanging drop technique: ***Trichomonas vaginalis.***

ESSENTIAL FACTS

- STDs are insidious! STDs are shed before, or in the absence of, symptoms. All STDs have a long period of asymptomatic transmission.
- *Neisseria gonorrhoeae* and *Chlamydia trachomatis* are the most common cause of pelvic inflammatory disease (PID).
- *Neisseria gonorrhoeae* and *Chlamydia trachomatis* travel together and must both be treated to prevent PID.
- *Trichomonas vaginalis* and *C. albicans* cause vulvovaginitis, but *Candida albicans* is not an STD.

41 Sexually Transmitted Diseases: Part Two

Neisseria gonorrhoeae

- Diseases: urethritis, cervicitis, epididymitis, pelvic inflammatory disease (commonly a coinfection of *N. gonorrhoeae* and *Chlamydia trachomatis*, so must treat both), arthritis (one joint usually—USMLE favorite). Men: yellow discharge, Gram stain for determination of the disease. Women usually do not show symptoms until late in the course of the infection because of the large amount of normal flora in the female vagina.
- Culture on **Thayer-Martin or chocolate agar**

Chlamydia trachomatis

- **Types A, B, and C:** causes ***A***frican ***b***lindness and pregnancy ***c***aught in the oviduct (ectopic pregnancy)
- **Types D to K:** No. 1 sexually transmitted disease in the U.S.; neonatal conjunctivitis (reason for erythromycin eyedrops at birth and silver nitrate for gonorrhea)
- **Types L1, L2, and L3:** lymphogranuloma venereum: positive Frei test

Treponema pallidum (Syphilis) (USMLE Favorite)

- **Primary syphilis:** localized disease referring to the painless chancre in the genitals or penis
- **Secondary syphilis:** systemic disease: bumpy rash seen all over the body, including the palms and soles; gray, wartlike lesions (**condylomata lata**) on the genitals or anus (not to be confused with condylomata acuminata of human papilloma virus [HPV])
- **Tertiary syphilis:** gummas, aortitis (cystic medial necrosis of the aorta causing **a "tree bark" appearance** due to intimal wrinkling of the vessel), Argyl-Robinson pupil (later-stage development); tabes dorsalis (chews up the posterior columns of the spinal cord; slapping feet on walking); neurosyphilis
- **Congenital syphilis:** Hutchinson's triad (teeth, interstitial keratitis, cranial nerve VIII deafness), pointed teeth, mulberry molars, saber shins, saddle nose deformity

Sexually Transmitted Diseases: Part Two

Other

- *Haemophilus ducreyi:* painful chancroid
- HIV, herpes simplex virus, cytomegalovirus, hepatitis B, C, D
- HPV (condylomata acuminata; dysplasia; cervical cancer; Pap smears)
- *Trichomonas vaginalis* (protozoa, green, foul-smelling discharge: "*Infected sex from prostitute: Trick causes to moan*")
- *Gardnerella vaginalis* (green, fishy-smelling discharge. Clue cells seen in urine)

Table 41-1: Sexually Transmitted Diseases

Disease	Organisms	Clinical Features
AIDS	HIV	Opportunistic infections and neoplasms (Kaposi sarcoma, lymphoma)
Anogenital warts	HPV	Condylomata acuminata (types 6, 11); koilocytotic cells and possible progression to **squamous cell carcinoma** (types 16, 18, 31, 45)
Chancroid	*Haemophilus ducreyi*	**Painful** ulcers on external genitalia
Genital herpes	HSV type 2 (also HSV type 1)	**Painful** ulcerative lesions on genitalia; fever and swelling of regional lymph nodes
Granuloma inguinale	*Calymmatobacterium granulomatis*	Multiple ulcerating granulomatous lesions in inguinal region and genitalia; **Donovan bodies** (intracellular bacteria) seen in biopsy or smear
Hepatitis	Hepatitis virus (types B and C)	**Acute:** jaundice, rash, arthritis, nausea, right upper quadrant pain; **chronic:** cirrhosis, predisposition to primary hepatocellular carcinoma
Lymphogranuloma venereum	*C. trachomatis* (types L1-L3)	**Painless** genital lesions; draining lymph nodes; rectal strictures in women
Syphilis	*Treponema pallidum*	Hard, **painless** chancres on genitalia (1°) Gray, wartlike **painless** lesions (condylomata lata), fever, lymphadenopathy, skin rash (2°) Gummas, neurologic manifestations (tabes dorsalis, dementia), ascending aortic aneurysm (3°)
Trichomoniasis	*Trichomonas vaginalis*	Vulvovaginitis with frothy discharge; usually asymptomatic in men
Urethritis/ cervicitis	*Chlamydia trachomatis* (types D-K) and *Neisseria gonorrhoeae*	**Coinfection common** **Acute PID** associated with both diseases Conjunctivitis and Reiter syndrome (*Chlamydia*) Arthritis and pharyngitis (*Gonorrhea*)

AIDS, Acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; HPV, human papillomavirus; HSV, herpes simplex virus; PID, pelvic inflammatory disease.

42 Urinary Tract Infections

CASE STUDIES

- Woman with urinary tract infection (UTI): *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, or ***Staphylococcus saprophyticus***
- Patient presents with a fever and 1 week of frequency, dysuria, and a burning sensation on voiding. Physical examination reveals suprapubic pain and costovertebral angle tenderness: **pyelonephritis, probably *E. coli***

ESSENTIAL FACTS

- Most common: *E. coli!*
- Cystitis is associated with dysuria, frequency, urgency, and suprapubic pain.
  - Higher incidence in women.
  - No bacteremia
- Pyelonephritis is associated with flank pain, fever, chills, dysuria.
  - Bacteria travel retrograde from the urethra to the bladder to the kidneys.
  - Ten times more likely to occur in women than men because of their short urethra and the close proximity of the anus to the vagina.
  - May be accompanied by bacteremia.
- Urethritis is usually a sexually transmitted disease (STD).
  - *Neisseria gonorrhoeae* and *Chlamydia trachomatis* travel together and must be treated together to prevent pelvic inflammatory disease.
  - *Ureaplasma urealyticum*
  - *Trichomonas vaginalis*
  - Herpes simplex virus
- *Candida albicans* (vulvovaginitis) and *Staphylococus aureus* (toxic shock) cause urethritis but are not STDs.

Urinary Tract Infections

Escherichia coli
Most common cause of UTIs: 50% to 80% of cases. Gram negative. Has adhesin on fimbriae.

Staphylococcus saprophyticus
Common in sexually active young females: 10% to 30% of cases. Remember, novobiocin resistant.

Proteus mirabilis
Urease positive, swarming colonies on agar (motile). *"Proteus looked in the mirror and thought this is a good day to create a staghorn calculus, a struvite stone in the kidney."*

Klebsiella pneumoniae
Patients with a catheter; large mucoid capsules allow them to stick to the tubing.

Enterobacter cloacae
Capsule; immunocompromised, usually nosocomial, and often drug resistant

Pseudomonas aeruginosa
Gram negative, oxidase positive, smells like fruit on agar, and blue-green (pyocyanin pigment). Has adhesin on fimbriae. Drug resistant, cystic fibrosis lung colonization, hot tubs, infection of burn wounds.

Serratia marcescens
Nosocomial, drug resistant. USMLE likes the fact it can produce a red pigment on agar.

43 Skin Lesions and Rashes: Part One

CASE STUDIES

- A 4-year-old girl had a 3-day history of fever, rash on her hands and feet, vesicles and ulcers on the tongue and oral mucosa, irritability, and lack of appetite. On examination no other rashes are found: **hand-foot-mouth disease** = **Coxsackie A virus**
- A 10-year-old boy develops a high fever with **cough, coryza** (runny nose), and ***conjunctivitis (the 3 C's)*** and is sensitive to bright lights. After 48 hours, white vesicles are seen in his mouth, followed by a maculopapular rash beginning on the face and spreading over the trunk: **measles**
- A 6-year-old girl presents with a history of a **fever** and bright **red cheeks**, and then a macular **lacy rash** with a central clearing develops on her body. This rash fades and reoccurs and lasts 1 to 4 weeks: **erythema infectiosum (fifth disease) parvovirus B19**

Streptococcus pyogenes

- A 3-year-old child with pus-filled vesicles on her face, swollen lymph nodes: **pyoderma (impetigo)**
- A 65-year-old woman with red inflamed area on lower leg with bullae, swollen nodes: **erysipelas**
- Child with rash and strawberry tongue: **scarlet fever** (erythrogenic toxin)

Staphylococcus aureus

- Baby with blisterlike lesions over much of the body: **scalded skin syndrome**
- Large swollen area of redness on leg of diabetic patient: **carbuncle**
- Child with bullous lesions on face: **impetigo**

Skin Lesions and Rashes: Part One

Fungal Lesions

- A migrant farm worker presents with several large, warty nodules on his forearm. He states that he had cut himself while working in the fields and afterward, small, rough bumps had developed over the area. They slowly grew, coalescing into **cauliflower-like lesions: chromoblastomycosis**
- A woman presents with an itchy, flaky, erythematous rash with circular lesions and some central clearing on neck that expands in size. Rash started when she had to wear a turtleneck as part of her uniform. **Tinea capitis: scalp; tinea cruris: groin (jock itch); tinea pedis: athlete's foot; tinea unguium: nails**

Table 43-1

Presentation	Agent
Bullae	*Staphylococcus aureus*
	Streptococcus pyogenes
	Clostridium perfringens
Cellulitis	*S. pyogenes*
	S. aureus
	Anaerobes (*Bacteroides fragilis, Clostridium*, etc)
Folliculitis	*Pseudomonas aeruginosa* (whirlpool)
	S. aureus
Erysipelas	*S. pyogenes*
	S. aureus
Vesicles	Coxsackievirus A
	Herpes simplex virus
	Varicella-zoster virus
Petechiae/ecchymoses	*Neisseria*
	Coxsackievirus and echovirus
Maculopapular rash	Measles
	Rubella
	Human herpesvirus 6: exanthem subitum (roseola)
	Parvovirus B19: erythema infectiosum (fifth disease)

44 Skin Lesions and Rashes: Part Two

Table 44-1: Viral Skin Lesions

Viruses	Disease	Characteristics
Measles (paramyxovirus)	Measles (rubeola)	Maculopapular
Rubella (togavirus)	German measles	Maculopapular, macular
B19 (parvovirus)	Fifth disease (erythema infectiosum)	Postfever: slapped face, erythematous
HHV6	Roseola (exanthema subitum)	Postfever: macular/ maculopapular
HHV8	Kaposi sarcoma	Pigmented lesion
Herpes simplex virus	Herpes	Vesicles on skin or mucosal membrane
Varicella-zoster (herpes)	Chickenpox, shingles	Vesicular
Molluscum contagiosum (poxvirus)	Molluscum	Wartlike
Papillomaviruses	Warts	Warts
Animal pox viruses	Orf, etc	Vesicular lesion
Coxsackie A viruses	Hand-foot-and-mouth	Vesicular
Other enteroviruses	Boston exanthem	Petechiae, roseola-like
Colorado tick fever		Maculopapular

HHV, Human herpesvirus.

Table 44-2: Bacterial Skin Lesions

Bacteria	Disease	Characteristics
Streptococcus pyogenes	Scarlet fever	Erythematous (toxin)
	Erysipelas	Swollen erythematous areas
	Pyoderma	Abscesses
	Necrotizing fasciitis	Expanding areas of erythema, bullae, tissue destruction
Staphylococcus aureus	Staph scalded skin syndrome	Exfoliative (toxin)
	Furuncle (boil), carbuncle, impetigo	Redness, swelling, pustules, bullae
Propionibacterium	Acne	
Neisseria	Meningococcemia	Petechiae, ecchymoses (endotoxin)
Pseudomonas	Hot tub folliculitis	Folliculitis
Mycobacterium leprae	Leprosy	
Rickettsia rickettsii	Rocky Mountain spotted fever	Macular, papular rash (centripetal) spread from palms and soles to trunk
Rickettsia prowazekii	Epidemic typhus	In centrifugal spread, rash begins on trunk and spreads out; pink rash on extremities moves to stomach and buttocks
Borrelia burgdorferi	Lyme disease	Red ring of rash spreading from tick bite
Treponema pallidum	Syphilis	Maculopapular rash on hands and feet

Skin Lesions and Rashes: Part Two

Table 44-3: Fungal Skin Lesions

Fungi and Parasites	Disease	Characteristics
Microsporum	Tinea	Ringlike rash, scales
Trichophyton	Tinea	
Candida	Skin, nail, mucous membranes	Eczema, nodules (systemic)
Sporothrix schenckii	Sporotrichosis	Nodules/ulcers along lymphatics
Blastomyces dermatitidis	Blastomycosis	Papule, pustule, granuloma
Leishmania	Cutaneous leishmaniasis	Ulcers

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Zoonoses and Arthropod-Associated Diseases

Table 45-1: Arthropod-Associated Diseases

Disease	Etiologic Agent	Vector	Distribution*
BACTERIAL			
Lyme disease	*Borrelia burgdorferi*	Tick (*Ixodes*)	New England, West Coast
Epidemic relapsing fever	*Borrelia recurrentis*	Louse	Europe, N. Africa, India
Endemic relapsing fever	*Borrelia* spp.	Tick	N. and S. America, Africa, Asia
Tularemia	*Francisella tularensis*	Tick	Worldwide
Rocky Mountain spotted fever	*Rickettsia rickettsii*	Tick (*Dermacentor*)	Southeastern and south-central United States
Epidemic typhus	*Rickettsia prowazekii*	Louse	Worldwide
Murine typhus	*Rickettsia typhi*	Flea	Southeastern United States, near Gulf of Mexico
Plague	*Yersinia pestis*	Flea	Asia, Africa
PROTOZOAN			
Visceral leishmaniasis	*Leishmania donovani*	Sandfly (*Phlebotomus* spp.)	Tropical and subtropical areas
Malaria	*Plasmodium* spp.	Mosquito (*Anopheles*)	Worldwide
African sleeping sickness	*Trypanosoma brucei*	Tsetse fly	Africa
Chagas disease	*Trypanosoma cruzi*	Reduviid bug	Latin America
VIRAL			
Equine encephalitis (Eastern, Western, and Venezuelan)	Alphavirus (Togavirus)	Mosquito (different species)	N. and S. America
California encephalitis	Bunyavirus	Mosquito (*Culex*)	N. America
Yellow fever	Flavivirus	Mosquito (*Aedes*)	S. America, Africa
Dengue fever	Flavivirus	Mosquito (*Aedes*)	Tropics
St. Louis encephalitis	Flavivirus	Mosquito (*Culex*)	N. America
West Nile encephalitis	Flavivirus	Mosquito	Eastern United States, Africa, Asia
Colorado tick fever	Reovirus	Wood tick	N. America

*Outbreaks and spread of the vector may go beyond the indicated regions.

Zoonoses and Arthropod-Associated Diseases

Table 45-2: Animal-Associated Zoonotic Diseases

Bacteria	Disease	Animal
Bacillus anthracis	Anthrax	Sheep and goats
Yersinia pestis	Plague	Rats and fleas
Francisella tularensis	Tularemia	Rabbits, ticks, and flies
Pasteurella multocida	Pasteurella infection	Cat and dog bites and scratches
Bartonella henselae	Cat-scratch fever	Cat bite or scratch
Leptospira interrogans	Leptospirosis	Rats, dogs, and wild mammals
Brucella spp. *(B. abortus, B. melitensis, B. suis, B. canis)*	Brucellosis	Cows, goats, sheep, pigs, dogs
Coxiella burnetii	Q fever	Cows (tissue fluids, milk, placentas)
VIRUSES		
Lymphocytic choriomeningitis	Meningitis	Mouse, hamster
Lassa fever	Lassa hemorrhagic fever	African bush rat
Hantavirus	Hemorrhagic fevers	Mice and rats
Influenza A	Flu	Ducks and other fowl, pigs
PARASITES		
Trichinella spiralis	Trichinosis	Bears, seals, pigs, other animals
Taenia solium; T. saginata	Cysticercosis (tapeworms)	Pigs, cows
Diphyllobothrium latum	Fish tapeworm	Freshwater fish
Toxocara canis	Visceral larval migrans	Dogs
Paragonimus westermani	Oriental liver fluke	Freshwater crabs, crayfish, and mammals feeding on them

Section III: Bug Parade

PART A: BACTERIA

PART B: VIRUSES

PART C: FUNGI

PART D: PARASITES

46

Bacterial Cell Wall Structure: Gram Positive Versus Gram Negative: Part One

Murray: *Medical Microbiology*, 8th Edition, Chapter 2

Bacterial Plasma Membrane

- Contains energy production F1 adenosine triphosphatase (like mitochondria)
- Lacks steroids and sterols (except *Mycoplasma*, which steal sterols)

Peptidoglycan

- Has D and L amino acids
- Glycan chains cross-linked by peptide (AA) chains
- Basic building block: N-acetylglucosamine-N-acetylmuramic acid pentapeptide (NAG-NAM-AA_5)
- Mesh is crosslinked through peptide bond between third position (LYS or DAB or LYS-$[GLY]_5$) and D-alanine of the other chain

Gram-Positive Bacteria

- Thick peptidoglyan, teichoic and lipoteichoic acids
- Lipoteichoic acids trigger Toll-like receptors (TLR) but not as strongly as endotoxin

Gram-Negative Bacteria

- Thin peptidoglycan

Gram-Negative Outer Membrane

- Permeability barrier to large and hydrophobic molecules
- Porin channels allow some antibiotics to permeate
- **Only gram-negative bacteria have lipopolysaccharide (LPS)**
  - LPS is ENDOTOXIN
  - Endotoxin triggers TLR and activates innate and immune responses
  - LPS consists of lipid A, core, and O-antigen
  - Lipooligosaccharide (LOS) consists of lipid A and core (*Neisseria*)
- LPS is linked covalently and with divalent cations providing structure.

Bacterial Cell Wall Structure: Gram Positive Versus Gram Negative: Part One

Outside Structures (Some Gram-Positive or Gram-Negative Bacteria)

- Capsule/biofilm: polysaccharide (except for anthrax)
  - Virulence factor: antiphagocytic, poor antigen
- Pili (fimbriae)
  - Virulence factor: adhesion
  - Sex (gene transfer by conjugation)
- Secretory devices (type II, III, IV): virulence factors used to inject molecules
- Flagella: motility, antigens, TLR ligand
- Proteins: adhesion and other proteins

Table 46-1

Gram-Positive Bacteria P = PURPLE = POSITIVE	Gram-Negative Bacteria RED = NEGATIVE
Peptidoglycan: thick: traps precipitated Gram stain	Peptidoglycan: thin: does not trap stain!
Teichoic acid: affixed to peptidoglycan: antigenic, adherent to cells	One layer thick of glycan chains cross-linked by peptide
Lipoteichoic acid: teichoic acid with lipid tail; affixed to membrane; like teichoic acid	Periplasmic space: transport proteins and degradative proteins
Protein layer (?) (eg, M protein of streptococci)	Outer membrane: permeability barrier, structure, antigenicity
	Lipopolysaccharide = endotoxin
	Lipooligosaccharide for *Neisseria* = endotoxin
	Porins: channels for **small and hydrophilic** metabolites and some antibiotics

Mycobacteria

- Plasma membrane; peptidoglycan
- **Waxlike lipid coat:** essential structure, antiphagocytic, virulence factor!
- Mycolic acid and other lipids, polypeptides (eg, PPD)

Mycoplasma (no peptidoglycan!)

Chlamydia (elementary body, reticulate body)

Spore (see Card 51)

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Bacterial Cell Wall Structure: Gram Positive Versus Gram Negative: Part Two

Murray: *Medical Microbiology,* 8th Edition, Chapter 2

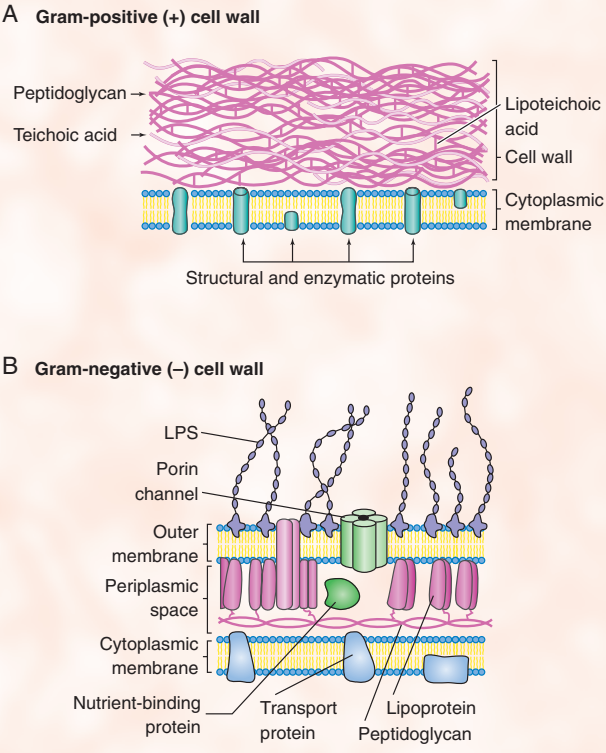

Figure 47-1: Structure of the cell wall of gram-positive and gram-negative bacteria. LPS, *Lipopolysaccharide.*

Bacterial Cell Wall Structure: Gram Positive Versus Gram Negative: Part Two

Table 47-1: Comparison of Gram-Positive and Gram-Negative Bacteria

Characteristic	Gram Positive	Gram Negative
STRUCTURAL		
Outer membrane	Absent	Present
Peptidoglycan layer	Thick	Thin
Lipopolysaccharide	Absent	Present
Teichoic acids	Many species	Absent
Capsule, pili, flagella	Some species	Some species
FUNCTIONAL		
Lysozyme	Very sensitive	Largely resistant
Antibiotic permeability	Very permeable to most	Impermeable to many
Sporulation	Some species	None
Exotoxin production	Some species	Some species

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Bacterial Cell Wall Structure: Peptidoglycan Synthesis

Murray: *Medical Microbiology*, 8th Edition, Chapter 12

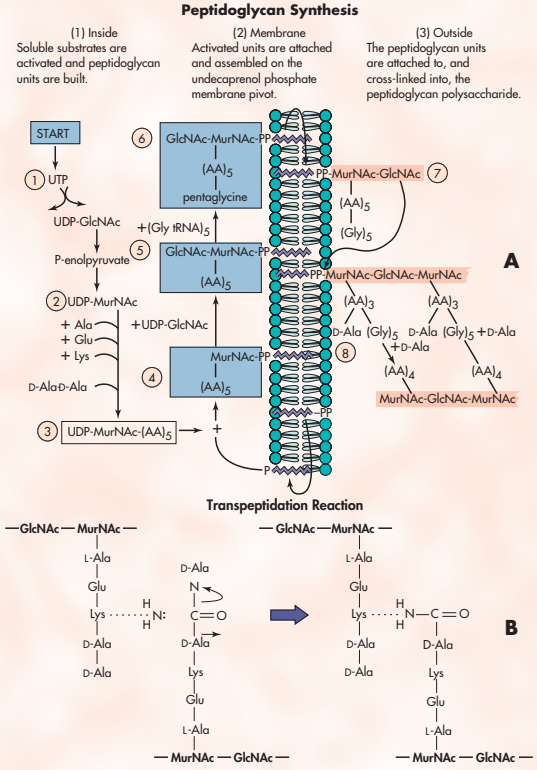

Figure 48-1: Peptidoglycan synthesis.

Bacterial Cell Wall Structure: Peptidoglycan Synthesis

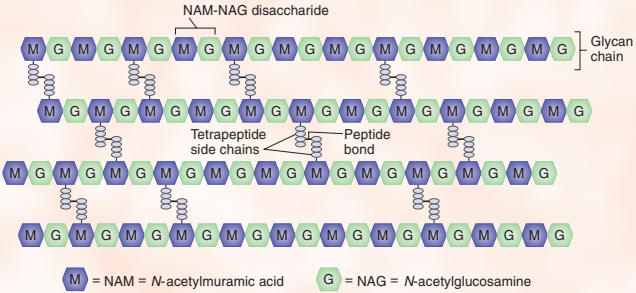

Figure 48-2: General structure of the peptidoglycan component of the cell wall. Glycan chains of alternating NAM and NAG residues are connected by peptide bonds between the side chains extending from NAM residues. Side chains commonly are tetrapeptides but are longer in some species. The thickness of the peptidoglycan layer increases as more chains are cross-linked.

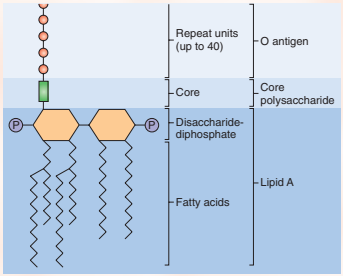

Figure 48-3: General structure of bacterial lipopolysaccharide (LPS). Lipid A and the core polysaccharide are present in all gram-negative bacteria, but some lack the O-antigen component. Covalent bonds and divalent cation bridges between phosphates of lipid A molecules link LPS into large aggregates, which help stabilize the outer membrane. Besides contributing to structural integrity of the outer membrane, lipid A mediates the endotoxin activity of LPS.

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Bacterial Classification

Murray: *Medical Microbiology,* 8th Edition, Chapter 12

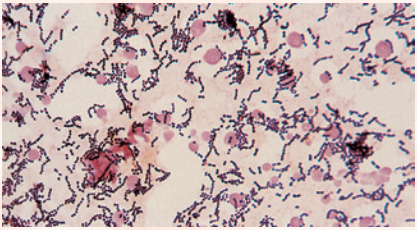

Figure 49-1: Gram-positive bacteria.

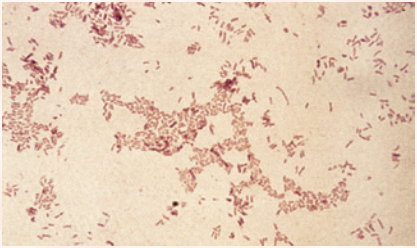

Figure 49-2: Gram-negative bacteria.

BASICS OF GRAM STAIN PROCEDURE

- Heat fix cells on slide
- Crystal violet
- Decolorize with acetone
- Counterstain with red safranin
- View

Bacterial Classification

INTERPRETATION

- Gram-positive bacteria retain the stain due to a thick peptidoglycan wall.
- **P = Purple = Positive!**
- Gram-negative bacteria have a thin peptidoglycan wall (one layer thick) and an outer membrane. The stain is washed away and replaced with a red counterstain.
- **Like with money, red means minus (ie, negative).**
- Old, starving and antibiotic-treated gram-positive bacteria will look negative.

BACTERIAL GROWTH AND METABOLISM

Nonselective Media

Hemolysis as an indicator on blood agar:

- Beta: clear zone around colony: *Streptococcus pyogenes*
- Alpha: greenish zone: *S. pneumoniae*
- Gamma: no hemolysis: *Enterococcus*

Selective and Indicator

- MacConkey's: selects for gram-negative enteric bacteria; indicates lactose fermenters by purple color of colony

Special Media

- Thayer-Martin: *Neisseria*
- Chocolate agar: *Neisseria, Haemophilus*
- Lowenstein-Jensen: *Mycobacterium*
- Egg yolk lecithin: *Clostridium difficile*
- Mannitol salt: *S. aureus*
- Buffered charcoal yeast extract (BCYE): *Legionella*

ESSENTIAL FACTS

- For enteric bacteria, oxidase-negative, lactose-negative bacteria are nasty: *Salmonella, Shigella* (also *Proteus*)
- *Pseudomonas* is oxidase-positive, lactose-negative bacterium and also is nasty.

50 Bacterial Genetics

Murray: *Medical Microbiology*, 8th Edition, Chapter 13

ESSENTIAL FACTS AND DEFINITIONS

- Many antibiotic resistance genes are encoded on plasmids or transposons and can be spread readily to different bacteria.
- Pathogenicity islands contain complete systems for pathogenesis (eg, *Salmonella* entry into cells is on large transposons).
- Conjugation goes from male bacteria (encodes the sex pilus) to the female.
- **Lysogenic** phages remain in cells until host gets sick; then they burst out by the **lytic** cycle.
- An operon contains the protein coding and control (promoter/repressor) genes (eg, *lac* operon).
- Cistron is the region of DNA that codes for a single protein.
- Promoter is the sequence recognized by the polymerase.
- Repressors bind to operators to prevent gene expression.
- Quorum sensing indicates sufficient bacteria to alter gene expression.

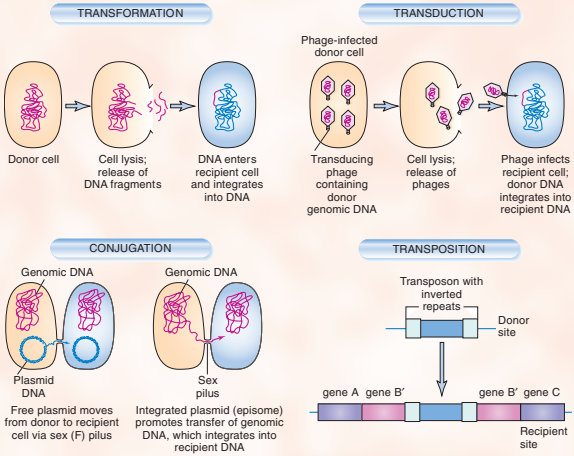

Figure 50-1: Bacterial gene-transfer mechanisms. Shading indicates recipient cell or DNA.

Bacterial Genetics

An allele is one version of a gene. Bacteria are haploid (one copy) and generally have one allele of their proteins. Human chromosomes are diploid and have two alleles of all but X chromosome genes (male).

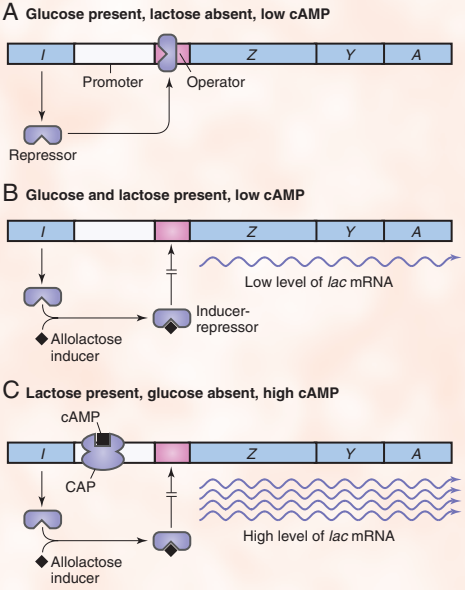

*Figure 50-2: Regulation of the lactose (*lac*) operon in* Escherichia coli. *The three structural genes in the* lac *operon (Z, Y, and A) encode enzymes that metabolize lactose. Transcription yields a single polycistronic mRNA, which is translated into the three proteins.* **A,** *Transcription is directly inhibited by binding of the* lac *repressor (encoded by the I gene) to the operator.* **B,** *In the presence of lactose the inducer allolactose forms. The molecule binds to the* lac *repressor forming a complex that cannot bind to the operator, thereby derepressing the operon.* **C,** *Transcription is stimulated by binding of the activator cyclic adenosine monophosphate (cAMP) to the catabolite activator protein (CAP). Thus the* lac *operon is fully "turned on" only when lactose is present and glucose is absent.*

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Bacterial Metabolism and Growth

Murray: *Medical Microbiology,* 8th Edition, Chapter 13

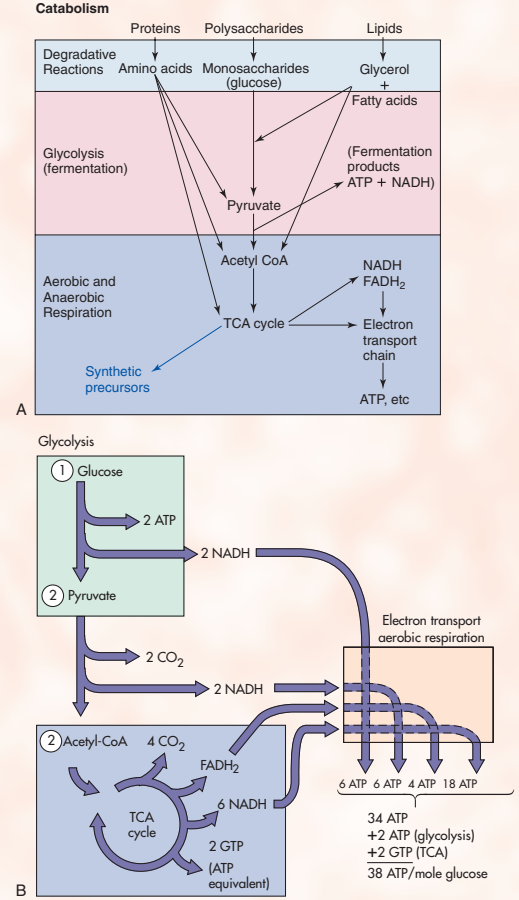

*Figure 51-1: Bacterial metabolism. **A**, Overview. **B**, Aerobic glucose metabolism.*

Bacterial Metabolism and Growth

SPORULATION

- Only **gram-positive** bacteria can sporulate.
- Spore is dehydrated, contains high concentrations of calcium and dipicolinic acid.
- The spore has a keratin-like outer protein coat.
- Germination of the spore requires disruption of the outer coat by heat, pH, and mechanical stress. Water and a triggering nutrient are required (eg, alanine) for reproduction.
- Initiation of germination weakens spore for inactivation.
- Two phases of autoclaving or twice the normal cycle are required to kill spores.

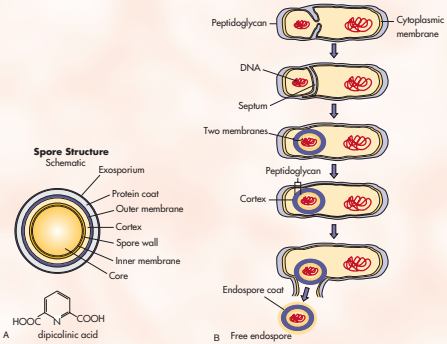

Figure 51-2: Sporulation.

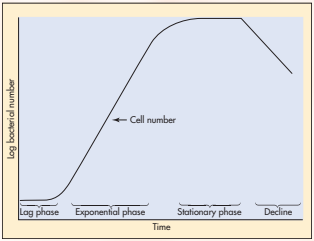

Figure 51-3: Bacterial growth phases starting with cells in stationary phase.

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Bacterial Pathogenesis

Murray: *Medical Microbiology*, 8th Edition, Chapter 14

Bacterial Virulence Mechanisms: "EAT RICE"

- Enzymes: degradative enzymes
- Adherence: pili, M protein, lipoteichoic acid, MSCRAMM (microbial surface components recognizing adhesive matrix molecules)
- Toxins: exo and endo
- Resistance to antibiotics
- Invasion of normally sterile body sites
- Circulation (septicemia/bacteremia): spread through host
- Evasion of immune responses: capsule, intracellular growth, catalase, evasion of lysosomal action

Adherence

- *Staphylococcus aureus:* Lipoteichoic acid
- Group A *Streptococcus:* Lipoteichoic acid and M protein
- *Escherichia coli:* Fimbriae (pili)
- *Neisseria gonorrhoeae:* Fimbriae

Invasion

- *Shigella, Salmonella,* enteroinvasive *E. coli* (EIEC)

Byproducts of Growth (Acid and Gas)

- *Clostridium perfringens:* gangrene

Induction of Inflammation and Immunopathology

- *Chlamydia:* lymphogranuloma venereum
- *Treponema pallidum:* syphilis
- *Borrelia burgdorferi:* Lyme disease
- *Streptococcus pyogenes:* rheumatic fever, poststreptococcal glomerulonephritis
- *Mycobacterium tuberculosis*: tuberculosis: granulomas

Evasion of Phagocytosis and Immune Clearance

- *Streptococcus pyogenes:* M protein
- *Legionella, M. tuberculosis, Chlamydia:* inhibition of phagolysosome fusion

Bacterial Pathogenesis

- *Salmonella, Mycobacterium:* resistance to lysosomal enzymes
- *S. pyogenes, C. perfringens:* kill phagocytic cells
- Intracellular growing bacteria
- Encapsulated bacteria

INTRACELLULAR GROWTH

Brucella
Francisella
Listeria
Neisseria
Salmonella
Chlamydia
Legionella
Mycobacterium
Rickettsia
Yersinia

Capsule

Neisseria meningitidis, Streptococcus pneumoniae, Haemophilus influenzae, etc

Antibiotic Resistance

Pseudomonas, Enterobacter, methicillin-resistant *Staphylococcus aureus* (MRSA), *Klebsiella, Acinetobacter,* etc

Toxins (See Toxin Card 53)

- Degradative enzymes
- Cytotoxic proteins
- A-B toxins

Superantigens

See Card 53.

Endotoxin

See Card 53.

53 Toxins: Part One

Murray: *Medical Microbiology,* 8th Edition, Chapter 14

Endotoxin

- Active component: lipid A
  - Lipopolysaccharide: all gram-negative bacteria
  - lipooligosaccharide: *Neisseria* (released from cell more readily and more active)
  - Action: activates macrophages, dendritic cells, and B cells through Toll-like receptor
  - Induction of endogenous pyogens: tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, prostaglandins (E2, etc): **fever**
  - Activates alternative complement cascade
- Consequences: symptoms of sepsis:
  - High fever
  - Hypotension
  - Shock
  - Hypotension
  - Vasodilation
  - Capillary leakage:
    - Petechiae and ecchymoses (especially with *Neisseria*)
    - Coagulation cascades: disseminated intravascular coagulation

Superantigens

- Active component: *Staphylococcus aureus* toxic shock syndrome toxin; streptococcal pyrogenic exotoxins
- Action: clamp T-cell receptor to MHC II on macrophage, B cell, or dendritic cell (antigen-presenting cell [APC])
- Activate T cell and APC to release ***too many*** cytokines: IL-1, IL-2, IL-6, TNF-α, TNF-β, interferon γ
- Kill T cells
- Cause shock, organ failure

Toxins: Part One

Degradative Enzymes (Examples)

- *Clostridium perfringens:* α toxin
- *S. aureus:* hemolysin, α toxin, leucocidin
- *Streptococcus pyogenes:* streptolysins O and S, erythrogenic toxin

Enterotoxins

- *S. aureus*
- *Escherichia coli*
- *Shigella*
- *Bacillus cereus*
- *Vibrio cholera*
- *Clostridium difficile*

Toxins: Part Two

Table 54-1: Properties of A-B Type Bacterial Toxins: The Action of the Toxin Defines the Disease

Toxin	Organism	Gene Location	Subunit Structure	Target Cell Receptor	Biologic Effects
Anthrax toxins	*Bacillus anthracis*	Plasmid	Three separate proteins (EF, LF, PA)	Unknown, probably glycoprotein	EF + PA: increase in target cell cAMP level, localized edema; LF + PA: death of target cells and experimental animals
Bordetella adenylate cyclase toxin	*Bordetella* species	Chromosomal	A-B	Unknown, probably glycolipid	Increase in target cell cAMP level, modified cell function or cell death
Botulinum toxin	*Clostridium botulinum*	Phage	A-B	Possibly ganglioside (GD_{1b})	Decrease in peripheral, presynaptic acetylcholine release, flaccid paralysis
Cholera toxin	*Vibrio cholerae*	Chromosomal	A-5B	Ganglioside (GM_1)	Activation of adenylate cyclase, increase in cAMP level, secretory diarrhea
Diphtheria toxin	*Corynebacterium diphtheriae*	Phage	A-B	Probably glycoprotein	Inhibition of protein synthesis, cell death
Heat-labile enterotoxins	*Escherichia coli*	Plasmid		Similar or identical to cholera toxin	

Continued

Table 54-1: Properties of A-B Type Bacterial Toxins: The Action of the Toxin Defines the Disease—cont'd

Toxin	Organism	Gene Location	Subunit Structure	Target Cell Receptor	Biologic Effects
Pertussis toxin	*Bordetella pertussis*	Chromosomal	A-5B	Unknown, probably glycoprotein	Block of signal transduction mediated by target G proteins
Pseudomonas exotoxin A	*Pseudomonas aeruginosa*	Chromosomal	A-B	Unknown, but different from diphtheria toxin	Similar or identical to diphtheria toxin
Shiga toxin	*Shigella dysenteriae*	Chromosomal	A-5B	Glycoprotein or glycolipid	Inhibition of protein synthesis, cell death
Shiga-like toxins	*Shigella* species, *E. coli*	Phage		Similar or identical to Shiga toxin	
Tetanus toxin	*Clostridium tetani*	Plasmid	A-B	Ganglioside (GT_1) and/or GD_{1b}	Decrease in neurotransmitter release from inhibitory neurons, spastic paralysis

Modified from Mandell G, Douglas G, Bennett J: *Principles and practice of infectious disease*, ed 3, New York, 1990, Churchill Livingstone.
cAMP, Cyclic adenosine monophosphate.

55

Antibacterial Agents: Part One

Murray: *Medical Microbiology,* 8th Edition, Chapter 17

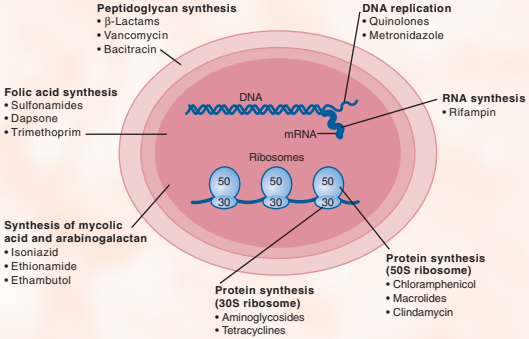

Figure 55-1: Primary cellular processes that are targets of antibiotic activity.

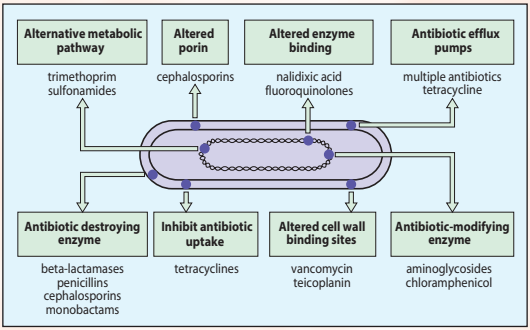

Figure 55-2: Mechanisms of antimicrobial resistance.

Antibacterial Agents: Part One

IMPORTANT TERMS

Bacteriostatic
Inhibits bacterial growth: reversibly inhibits a process (enzyme) or the enzyme can be replaced.

Bacteriocidal
Disrupts a membrane or inactivates the ribosome or DNA replicative machinery preventing replacement!

Minimum Inhibitory Concentration (MIC)
The concentration of antibacterial that stops growth of the bacteria (no growth in tube).

Minimum Bactericidal Concentration (MBC)
The concentration of antibacterial that kills bacteria (no growth upon plating).

Kirby-Bauer Test
Disk diffusion–based indicator of bacterial sensitivity or resistance based on antibiotic levels obtainable in blood. This test is not dependable for all tissues because drug distribution may differ for bone, brain, etc.

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Antibacterial Agents: Part Two

Murray: *Medical Microbiology,* 8th Edition, Chapter 17

Table 56-1: Properties of Common Antibiotics

Drug	Target Process or Structure	Resistance	Spectrum*
INHIBITORS OF PEPTIDOGLYCAN SYNTHESIS			
β-Lactams (penicillins, cephalosporins, carbapenems, monobactams)	Cross-linking of peptidoglycan	β-lactamase inactivation of drug Target-site mutation ↑ Target enzymes ↓ Permeability (gram negative)	Broad but varies with specific drug
Vancomycin	Elongation and cross-linking of peptidoglycan	↑ Target-site mutation ↓ Permeability (gram negative)	Gram-positive bacteria (staphylococci)
Bacitracin	Recycling of bactoprenol	Target-site mutation	Gram-positive bacteria
MEMBRANE DISRUPTERS			
Polymyxin/colistin	Outer membrane	—	Gram-negative bacteria
Daptomycin	Cytoplasmic membrane		*S. aureus*
INHIBITORS OF PROTEIN SYNTHESIS			
Aminoglycosides (streptomycin, gentamicin, kanamycin)	Assembly of subunits (bind 30S ribosomal subunit); misreading of mRNA	Enzymatic inactivation of drug Target-site mutation ↓ Drug uptake	Broad but varies with specific drug
Tetracycline (doxycycline)	Chain elongation (binds 30S subunit)	↓ Drug uptake ↑ Drug export	*Chlamydia, Rickettsia, Mycoplasma pneumoniae, Vibrio cholerae*, etc
Macrolides (erythromycin, azithromycin, clarithromycin)	Chain elongation (bind 50S subunit)	Target-site mutation	*Legionella, Mycoplasma, Chlamydia*
Clindamycin	Chain elongation (binds 50S subunit)	Target-site mutation	Anaerobic bacteria
Chloramphenicol	Chain elongation (binds 50S subunit)	Enzymatic inactivation of drug	—

Continued

Antibacterial Agents: Part Two

Table 56-1: Properties of Common Antibiotics—cont'd

Drug	Target Process or Structure	Resistance	Spectrum*
INHIBITORS OF NUCLEIC ACID SYNTHESIS			
Quinolones	Topoisomerase	Target-site mutation ↓ Permeability (gram negative)	Gram-negative and -positive bacteria (only 4th generation for anaerobes)
Rifampin	RNA polymerase	Target-site mutation	*Mycobacterium;* prophylaxis for *Haemophilus influenzae* and *Neisseria meningitidis*
Metronidazole	Disrupts DNA	Aerobic bacteria	Anaerobic bacteria; *Clostridium difficile*
ANTIMETABOLITES			
Sulfonamides† Dapsone Trimethoprim	Folic acid synthesis	Target-site mutation ↓ Need for folic acid	Gram-negative and -positive bacteria
Isoniazid Ethionamide	Mycolic acid synthesis	—	*Mycobacterium*
Ethambutol	Arabinogalactan synthesis	—	*Mycobacterium*

*Only a general guide to spectrum of these drugs.
†Sulfonamides are analogues of para-aminobenzoic acid, a substrate for dihydropteroate synthase. Dapsone also inhibits this enzyme. Trimethoprim inhibits dihydrofolate reductase, another enzyme in the pathway synthesizing folic acid.

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Bacillus anthracis and *B. cereus*: Part One

Murray: *Medical Microbiology,* 8th Edition, Chapter 20

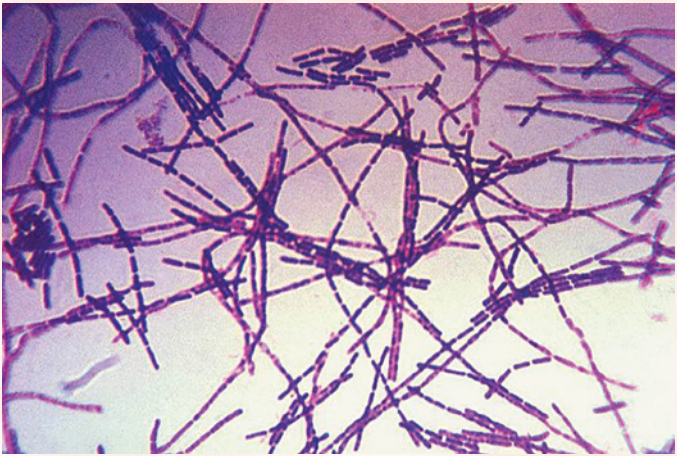

Figure 57-1: Gram stain of B. anthracis. *The blue/purple and boxcar shape are obvious.*

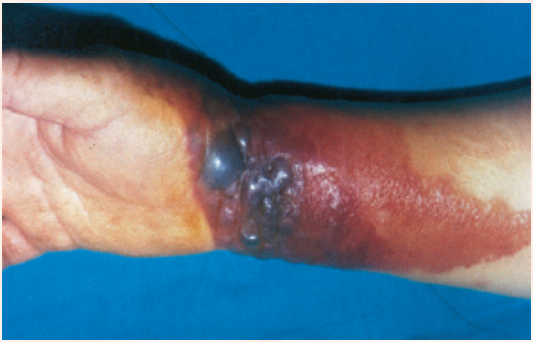

Figure 57-2: Anthrax on the forearm, as would be observed in a butcher, shepherd, or another at risk of infection.

Bacillus anthracis and *B. cereus*: Part One

CASE STUDIES

- Two days after shearing sheep, a shepherd notices a papule on his arm, which rapidly progresses to an ulcer and then a necrotic eschar. Lymphadenopathy and edema develop: **cutaneous anthrax**
- Three months after visiting a sheep farm, a man develops fever, cough, shortness of breath, headache, vomiting, chills, and chest pain. These progress to edema, swelling of mediastinal lymph nodes, shock, and death within 3 days: **inhalation anthrax**

TRIGGER WORDS

Sheep	Goat
Fur	Spore
Bioterror	Wool sorter's disease

ESSENTIAL FACTS

- Anthrax is usually associated with animal fur and is an occupational hazard for butchers, goatherds, shepherds, and sheepshearers.
- Virulence is plasmid encoded: enzymes for the **poly-D-glutamic acid capsule**
- Three plasmid encoded **exotoxins**: edema toxin-adenylate cyclase; lethal toxin-zinc metalloprotease; protective antigen

STUDY BREAK

Anthrax spores are extremely resistant to inactivation and may remain viable for millennia (eg, in Egyptian tombs). Anthrax spores have been developed as a prime bioterror agent and have been sent through the mail to terrorize legislators, reporters, and others.

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Bacillus anthracis and *B. cereus*: Part Two

Murray: *Medical Microbiology*, 8th Edition, Chapter 20

B. anthracis

STRUCTURE +

Gram-positive rod in long chains, spore-forming, polypeptide capsule

LAB ID

Growth characteristics and Gram stain

VIRULENCE FACTORS

Polypeptide capsule; toxins: edema, adenylate cyclase; lethal, zinc metalloprotease; protective antigen

DISEASES

Cutaneous anthrax
Inhalation anthrax (most deadly)

EPIDEMIOLOGY

Commonly found in fur of herbivores and in soil. Spores are viable for a long time and are difficult to inactivate.

PREVENTION

Vaccination of animals

TREATMENT

Ciprofloxacin or doxycycline and antitoxin

Bacillus anthracis and *B. cereus*: Part Two

B. cereus

TRIGGER WORDS

Rice
Preformed toxin
Heat-labile toxin—diarrhea
Toxigenic diarrhea
Heat-stable toxin—vomiting

STRUCTURE +

Gram-positive rod, sporulates

LAB ID

Isolation of organism from contaminated food

VIRULENCE FACTORS

Gastroenteritis
- Heat-stable entertoxin—emesis
- Heat-labile enterotoxin—diarrhea

Ocular: necrotic toxin, cereolysin, phospholipase C

DISEASES

Emetic form gastroenteritis: ingestion of heat-stable toxin from contaminated rice.
Like *Staphylococcus aureus* gastroenteritis, the incubation period is 1 to 6 hours. The individual is poisoned by preformed toxin.
Diarrheal form gastroenteritis: bacterial growth in gut produces toxin; sources are contaminated rice, meat, vegetables, and sauces.
Ocular infections after trauma

EPIDEMIOLOGY

Food-borne disease, rice and rice dishes

PREVENTION

Proper food storage

TREATMENT

Symptomatology

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Bordetella pertussis

Murray: *Medical Microbiology,* 8th Edition, Chapter 29

CASE STUDY

An unvaccinated child with cough who seems to be gasping for a breath and makes a whooping sound

TRIGGER WORDS

Bordet-Gengou agar
Vaccine
Whooping cough
DPT

ESSENTIAL FACTS

- Pertussis toxins inhibit macrophages and kill ciliated epithelium
- Incubation/catarrhal/paroxysmal/convalescent phases

STUDY BREAK

"Whooping" is a noise that comes from the voice box after a paroxysm, when the patient is suddenly able to breathe in again. Interestingly, only approximately 50% of those with whooping cough "whoop." In China, it is called the "100-day cough."

Bordetella pertussis

STRUCTURE –
Gram-negative coccobacillus

LAB ID
Bordet-Gengou agar

VIRULENCE FACTORS
Pertussis toxins, endotoxin, adhesins

DISEASES
Whooping cough

EPIDEMIOLOGY
Human host; vaccine preventable

PREVENTION
Acellular pertussis vaccine or whole inactivated cells given with diphtheria and tetanus toxoid vaccines

TREATMENT
Erythromycin and other macrolides

60

Campylobacter jejuni

Murray: *Medical Microbiology,* 8th Edition, Chapter 28

CASE STUDY

Diarrhea with more than 10 bloody bowel movements per day lasting for 1 week was attributed to undercooked chicken eaten during a camping trip.

TRIGGER WORDS

Bloody diarrhea
Undercooked poultry
Thin, curved, gram negative

ESSENTIAL FACTS

C. jejuni is the No. 1 cause of bloody diarrhea in the United States. Bloody diarrhea is caused by invasive disease.

C. jejuni

STRUCTURE –

Gram-negative, comma-shaped bacilli

LAB ID

Motile, oxidase positive

VIRULENCE FACTORS

S protein anticomplement (capsule-like) outer layer; adhesion; invasion; endotoxin

Campylobacter jejuni

DISEASES

Gastroenteritis (blood and pus in stool)

EPIDEMIOLOGY

Contaminated poultry or milk

PREVENTION

Proper cooking

TREATMENT

Rehydration, erythromycin or quinolones

C. fetus

DISEASES

Gastroenteritis progressing to septicemia and organs

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Chlamydia trachomatis and Related Bacteria

Murray: *Medical Microbiology,* 8th Edition, Chapter 35

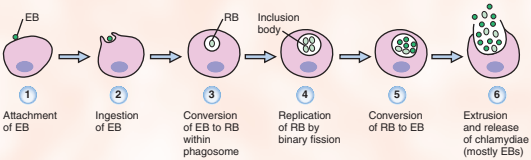

Figure 61-1: Growth cycle of Chlamydia trachomatis.

CASE STUDIES

- Man with nongonococcal urethritis, conjunctivitis, polyarthritis, mucocutaneous lesions: Reiter syndrome
- Previously promiscuous female tries to get pregnant and experiences an ectopic pregnancy
- A papule (ulcer) appears on the penis, then heals, but 2 weeks later the draining lymph nodes are very swollen (buboes): lymphogranuloma venereum (LGV)
- Conjunctivitis with in-turned eyelashes: trachoma
- Nongonococcal urethritis with persistent watery discharge
- 5-day-old child with swollen eyelids and profuse purulent discharge

TRIGGER WORDS

Sexually transmitted disease (STD)
Pelvic inflammatory disease (PID)
Trachoma
Intracellular inclusion bodies
Reticulate bodies (RBs)
Urinary tract infection (UTI)
Lymphogranuloma venereum (LGV)
Iodine stain
Elementary bodies (EBs)

ESSENTIAL FACTS

- EBs infect cells, which become RBs within phagolysosome, replicate, and acquire hard outer shell to become EBs. No cell wall.
- Leading cause of preventable blindness; common STD including nongonococcal urethritis, epididymitis, LGV, proctitis in homosexual men.

Chlamydia trachomatis and Related Bacteria

STUDY BREAK

Chlamydia was documented in ancient Egyptian times on papyruses. *Chlamydia* was first seen under a microscope in 1907.

STRUCTURE

Very small; lacks cell wall

LAB ID

Obligate intracellular, iodine stain

VIRULENCE FACTORS

The EB has a strong coat. The RB is the ***r***eplicative form.

DISEASES

Chlamydia trachomatis

LGV, Reiter syndrome, STD, conjunctivitis, ocular trachoma; coinfection often occurs with gonorrhea, but *Chlamydia* is not sensitive to β-lactam antibiotics.

Chlamydophila pneumoniae

Pharyngitis, bronchitis, pneumonia, sinusitis, Taiwan acute respiratory strain (TWAR)

Chlamydophila psittaci

Psittacosis (parrot) pneumonia is transmitted in bird excrement.

EPIDEMIOLOGY

Ubiquitous

TREATMENT

Doxycycline, azithromycin (no cell wall, no β-lactams)

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Clostridium perfringens and Other Clostridia: Part One

Murray: *Medical Microbiology,* 8th Edition, Chapter 30

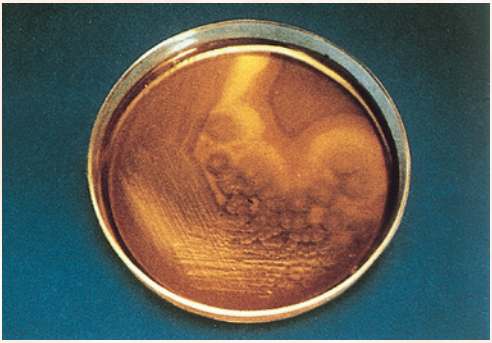

Figure 62-1: Double zone of hemolysis with C. perfringens *caused by complete hemolysis with θ toxin and partial hemolysis with the α toxin.*

CASE STUDIES

- A diabetic patient has poor blood circulation. One week after surgery on his leg, he develops intense pain around the site, followed by tissue destruction with subcutaneous gas. The leg was amputated to prevent further spread of infection: **gas gangrene**
- A hungry medical student eats a roast beef sandwich that has been sitting on the counter for a couple of days. After 16 hours, he has cramps and watery diarrhea but no fever, nausea, or vomiting. The diarrhea resolves after 24 hours: **clostridial food poisoning**

Clostridium perfringens and Other Clostridia: Part One

TRIGGER WORDS

C. perfringens

Box car shaped
Double zone of hemolysis
Lecithinase
Diarrhea
Toxins
Gas gangrene

C. botulinum

Botulism
Honey
Floppy baby
Food-borne
Spores

ESSENTIAL FACTS

C. perfringens

- Produces several tissue lytic toxins
- Grows in tissue that is poorly oxygenated, especially after *Staphylococcus aureus* has used up the oxygen
- Grows in meat (which is like tissue); ingestion leads to diarrhea

C. botulinum

- A-B toxin blocks release of acetylcholine to cause flaccid paralysis. Spores in raw honey cause infant botulism (floppy baby).

C. tetani

- Tetanospasmin: AB toxin blocks release of inhibitory neurotransmitters (eg, gamma-aminobutyric acid)—unregulated excitatory activity—tetanus
- Tetanolysin-hemolysin

STUDY BREAK

In World War I more soldiers died of tetanus than weapon injuries.

63

Clostridium perfringens and Other Clostridia: Part Two

Murray: *Medical Microbiology,* 8th Edition, Chapter 30

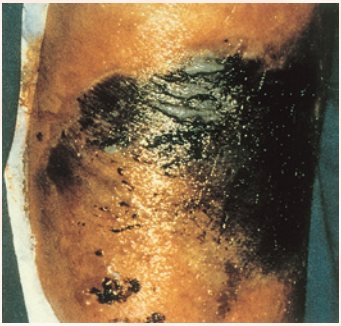

Figure 63-1: Cellulitis (gangrene).

STRUCTURE +

C. perfringens
Gram-positive rod, spore former

C. tetani
Tennis racquet (terminal spore)–shaped rods, anaerobe

LAB ID

Anaerobic, double zone of hemolysis, lecithinase detected on egg yolk agar

VIRULENCE FACTORS

Toxins

DISEASES

C. perfringens

- Food poisoning
- Gas gangrene: poor blood circulation puts individual at risk due to low oxygen tension in the tissues.

Clostridium perfringens and Other Clostridia: Part Two

C. botulinum
Botulism; flaccid paralysis

C. difficile
Antibiotic-associated (clindamycin/ampicillin) diarrhea, enterotoxin and cytotoxin, pseudomembranous colitis

C. tetani
Tetanus

EPIDEMIOLOGY

Present in soil, water, and intestines of animals and humans

PREVENTION

C. perfringens
None

C. tetani
Vaccine = toxoid in shot or booster

TREATMENT

C. perfringens
- Gangrene: surgical debridement plus high-dose penicillin or amputation
- Diarrhea: rehydration

C. difficile
Vancomycin metronidazole

C. botulinum* and *C. tetanus
Antitoxin sera

64

Corynebacterium diphtheriae, C. jeikeium, and *C. urealyticum*: Part One

Murray: *Medical Microbiology,* 8th Edition, Chapter 21

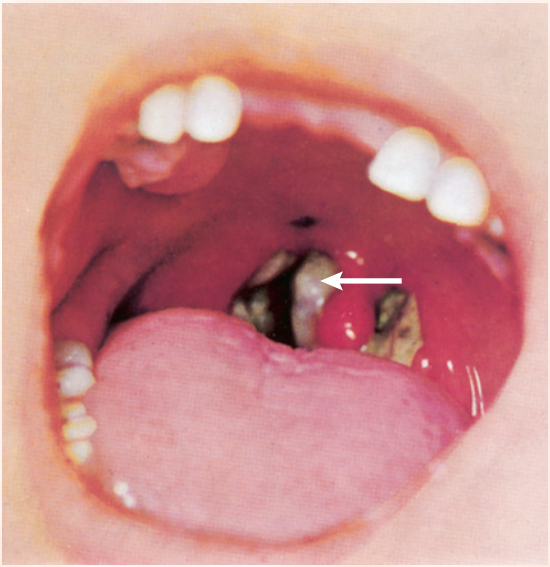

Figure 64-1: Pseudomembranes (arrow) *on tonsils.*

CASE STUDY

A 5-year-old suddenly complains of sore throat, malaise, and low-grade fever. Examination reveals a white, thick coating of the tonsils, uvula, and palate. Attempts to scrape the coating cause bleeding.

Corynebacterium diphtheriae, *C. jeikeium*, and *C. urealyticum*: Part One

TRIGGER WORDS

Pseudomembrane
Vaccine
A-B toxin
Schick test

ESSENTIAL FACTS

C. diphtheriae

- *C. diphtheriae* make an A-B toxin. The A subunit stops protein synthesis by catalyzing the inactivation of elongation factor 2.
- The vaccine is inactivated toxin (toxoid).
- The toxoid is used as the protein for the *Haemophilus influenzae* type B conjugate vaccine.
- Erythromycin

C. jeikeium

Antibiotic resistant, nosocomial, normal skin flora, catheter entry

STUDY BREAK

Diphtheria means "leathery skin" in Greek, which refers to the pseudomembrane.

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Corynebacterium diphtheriae, *C. jeikeium*, and *C. urealyticum*: Part Two

Murray: *Medical Microbiology*, 8th Edition, Chapter 21

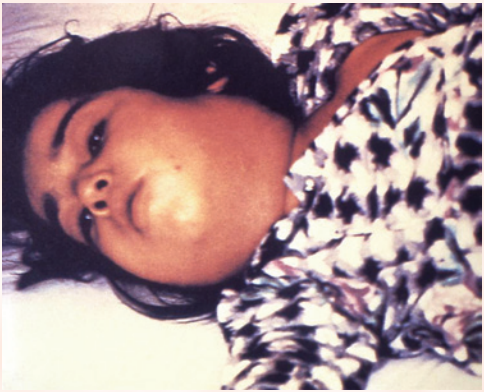

Figure 65-1: Bull neck swelling from enlarged lymph nodes.

STRUCTURE +

Gram-positive pleomorphic rod

LAB ID

- Growth on cysteine-tellurite agar, methylene blue staining
- Schick test for neutralizing antibodies

VIRULENCE FACTORS

A-B toxin catalyzes inactivation of elongation factor 2 and inactivation of protein synthesis.

Corynebacterium diphtheriae, *C. jeikeium*, and *C. urealyticum*: Part Two

DISEASES

C. diphtheriae
Diphtheria, cutaneous papule progressing to ulcer

C. jeikeium
Bacteremia, systemic infections

C. urealyticum
Urease, urinary tract infections, production of stones

EPIDEMIOLOGY

Asymptomatic normal flora. Unvaccinated people are at risk. Children and older adults are at risk.

PREVENTION

Inactivated toxin (toxoid), vaccine

TREATMENT

Passive immunity with antitoxin, penicillin, or erythromycin

66

Escherichia coli and Other Lactose-Positive, Gram-Negative Enteric Bacteria: Part One

Murray: *Medical Microbiology*, 8th Edition, Chapter 25

CASE STUDIES

- A month-old infant with high fever and rash will not eat, has a strange cry, is hard to arouse (lethargy), and has bulging fontanelles: **meningitis**
- Diarrheas
  - Watery diarrhea, cramps, nausea: enterotoxigenic *E. coli* **(ETEC)-like cholera**
  - Persistent infant diarrhea, possible blood and low-grade fever: **EAggEC** (enteroaggregative)
  - Fever, cramping, watery diarrhea, scant, bloody stools: **EIEC** (enteroinvasive)
  - Severe abdominal cramps, very bloody diarrhea, little or no fever: **EHEC** (enterohemorrhagic)
  - Child with EHEC + acute renal failure, thrombocytopenia, hemolytic anemia: hemolytic uremic syndrome: **(O157:H7)**
- Woman with bladder infection: **urinary tract infection (UTI)**

TRIGGER WORDS

Diarrhea	Neonatal meningitis	EHEC
Lactose positive	O157:H7	ETEC
UTI	EIEC	EAEC

ESSENTIAL FACTS

- Oxidase-negative, lactose-positive, gram-negative rod (purple colonies on MacConkey's plate)
- Most common cause of UTI in women
- Most commonly isolated gram-negative bacillus in bacteremia
- Type of diarrhea depends on plasmid-mediated virulence factors from other enteric bacteria

Escherichia coli and Other Lactose-Positive, Gram-Negative Enteric Bacteria: Part One

Table 66-1: Gastroenteritis Caused by E. coli

E. coli Strain	Site of Action	Clinical Features	Pathogenesis
Enterotoxigenic (ETEC)	Small intestine	Watery diarrhea, cramps, nausea, and low-grade fever in travelers and infants	Enterotoxins promote increased cAMP or cGMP, leading to fluid and electrolyte loss
Enteroaggregative (EAEC)	Small intestine	Persistent infant diarrhea, low-grade fever	Aggregative adherence to mucosa prevents fluid absorption
Enteropathogenic (EPEC)	Small intestine	Copious watery infant diarrhea with fever, nausea, vomiting, and nonbloody, mucus-filled stools	Adherence and destruction of epithelial cells
Enteroinvasive (EIEC)	Large intestine	Fever, cramping, watery diarrhea followed by development of dysentery with scant, bloody stools	Invasion and destruction of epithelial cells lining the colon
Enterohemorrhagic (EHEC)	Large intestine	Severe abdominal cramps, initial watery diarrhea followed by grossly bloody diarrhea, little or no fever (hemorrhagic colitis); hemolytic uremic syndrome associated with strain O157:H7	Cytotoxic verotoxin (shiga-like toxin) inhibits protein synthesis

cAMP, Cyclic adenosine monophosphate; *cGMP,* cyclic guanosine monophosphate.

STUDY BREAK

Traveler's diarrhea occurs when the local *E. coli* colonize the gut of their host. When commercial batches of hamburger are processed, ***E. coli*, including the O157:H7 strain**, may be mixed into the batch and remain viable and virulent unless cooked at high temperatures.

The *E. coli* bacterium propels itself with a "motor" that is only one-millionth of an inch in diameter, a thousand times smaller than the tiniest motors built to date by humans. The rotation of the bacterial motor comes from a current of protons. The efficiency of the motor approaches 100%.

67

Escherichia coli and Other Lactose-Positive, Gram-Negative Enteric Bacteria: Part Two

Murray: *Medical Microbiology*, 8th Edition, Chapter 25

E. coli

STRUCTURE –

Gram-negative bacilli

LAB ID

Oxidase negative, fast lactose fermenter (purple on MacConkey's agar)

VIRULENCE FACTORS

Endotoxin, heat labile (LT) and heat stable (ST), or *Shiga* enterotoxins, pili (adhesion)

DISEASES

Urinary tract infection (UTI), cystitis, pyelonephritis, sepsis, gastroenteritis, hemolytic uremic syndrome, thrombotic thrombocytopenic syndrome, neonatal pneumonia/sepsis/meningitis

EPIDEMIOLOGY

Ubiquitous

PREVENTION

Hygiene

TREATMENT

- UTI: trimethoprim-sulfamethoxazole
- Sepsis: cephalosporins
- Diarrhea: rehydration

Escherichia coli and Other Lactose-Positive, Gram-Negative Enteric Bacteria: Part Two

Klebsiella pneumoniae

CASE STUDY

A hospitalized alcoholic has aspiration pneumonia.

TRIGGER WORDS

Currant jelly (blood) sputum
Pneumonia
Capsule

VIRULENCE FACTORS

Thick capsule

DISEASES

Pneumonia in alcoholics and those with compromised pulmonary function; UTI; bacteremia

Serratia marcescens

DISEASES

Opportunistic infections

68

Filamentous Bacteria: *Actinomyces*

Murray: *Medical Microbiology,* 8th Edition, Chapter 31

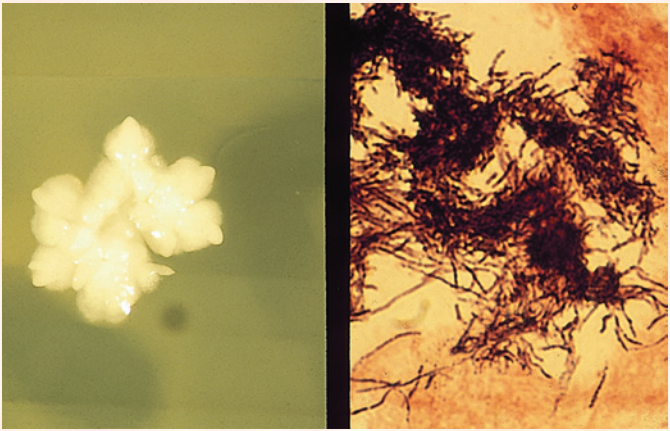

Figure 68-1: Actinomyces *colony (left) and gram-positive, filamentous bacteria (anaerobic) (right).*

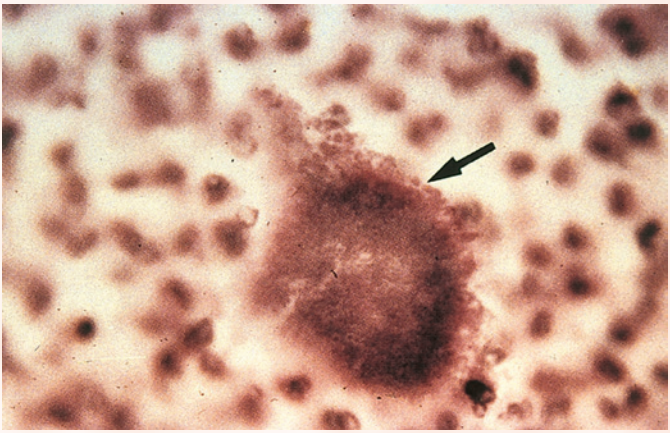

Figure 68-2: Sulfur granules.

Filamentous Bacteria: *Actinomyces*

CASE STUDY

A 35-year-old man with swollen skin on his jaw, fibrosis, and scarring with draining sinus tracts along the jaw and neck. A biopsy reveals a sulfur granule.

TRIGGER WORDS

Sulfur granules
Filamentous
Anaerobic

STRUCTURE

Filamentous, gram positive

LAB ID

Sulfur granule, anaerobic

VIRULENCE FACTORS

Access through trauma or surgery

DISEASES

Skin infections, abscesses with draining sinus tracts in cervicofacial region, mycetoma

EPIDEMIOLOGY

Normal flora gains entry on trauma

TREATMENT

Surgical debridement, long-term penicillin

69

Filamentous Bacteria: *Nocardia*

Murray: *Medical Microbiology,* 8th Edition, Chapter 22

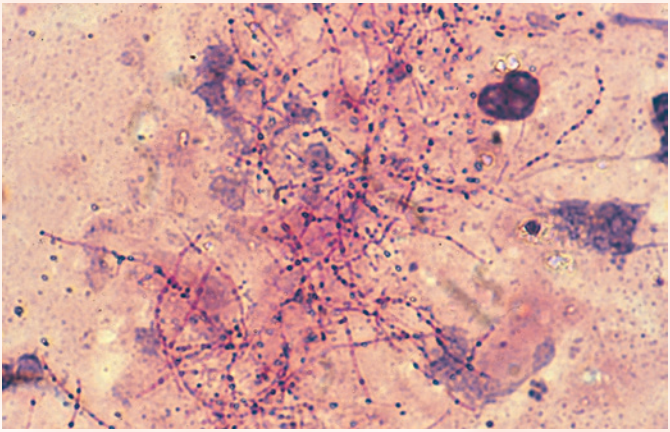

Figure 69-1: **Nocardia** *are strict aerobic, acid-fast, filamentous bacteria.*

Filamentous Bacteria: *Nocardia*

CASE STUDIES

- A 40-year-old Brazilian man has a painless swollen foot with nodules and multiple draining sinus tracts (mycetoma).
- A 45-year-old man with AIDS has pneumonia with cavitation. Disease spreads to the central nervous system (CNS) and subcutaneous tissues.

STRUCTURE

Filamentous

LAB ID

Filamentous, strict aerobe

VIRULENCE FACTORS

Opportunistic pathogen

DISEASES

Bronchopulmonary infections that can spread to cause cutaneous (mycetoma, cellulitis) or CNS (brain abscess) infections.

EPIDEMIOLOGY

Soil bacteria

TREATMENT

Surgical removal and antibiotic combinations, including sulfonamides

70

Francisella tularensis: Gram-Negative Intracellular

Murray: *Medical Microbiology*, 8th Edition, Chapter 29

CASE STUDY

A girl with a pet rabbit has several skin ulcers and painful, swollen, draining lymph nodes.

TRIGGER WORDS

Intracellular
Rabbit
Ulcer
Tularemia

ESSENTIAL FACTS

Control requires cell-mediated immunity because bacteria grow intracellularly. Only 10 organisms through wound or 50 by inhalation are required for infection. Considered a potential bioterror agent.

Francisella tularensis: Gram-Negative Intracellular

STRUCTURE

Very small gram-negative coccobacilli

LAB ID

Requires cysteine for growth (like *Legionella*)

VIRULENCE FACTORS

Capsule, intracellular growth, inhibition of phagolysosome fusion

DISEASES

Tularemia of different places depending on route of infection: ulceroglandular (skin from scratch or tick bite), oculoglandular, glandular, typhoidal-systemic, oropharyngeal, pneumonic

EPIDEMIOLOGY

Wild mammals, domestic animals (rabbits); hunters, pet owners, lab personnel at risk

PREVENTION

Protective clothing

TREATMENT

Doxycycline or ciprofloxacin

71

Brucella: Gram-Negative Intracellular

Murray: *Medical Microbiology*, 8th Edition, Chapter 29

CASE STUDY

A farmer who ate goat cheese made with unpasteurized milk has malaise, chills, sweats, and fever in waves.

TRIGGER WORDS

Undulant fever
Unpasteurized milk and cheese
Intracellular growth
Goats and sheep

ESSENTIAL FACTS

Pasteurization of milk and vaccination of animals has decreased occurrence of brucellosis.

Brucella: Gram-Negative Intracellular

STRUCTURE

Gram-negative coccobacillus

LAB ID

Cultured from blood, slow growth on blood agar, serology

VIRULENCE FACTORS

Intracellular growth, lipopolysaccharide

DISEASES

Undulant fever

EPIDEMIOLOGY

Transmitted in unpasteurized dairy products

PREVENTION

Pasteurization of dairy products

TREATMENT

Trimethoprim-sulfamethoxazole, doxycycline

72

Bacteroides fragilis and Other Gram-Negative Anaerobes

Murray: *Medical Microbiology,* 8th Edition, Chapter 31

CASE STUDIES

- Man with ruptured appendix. Foul-smelling pus yields mixed anaerobic infection, including *B. fragilis*
- Woman with pelvic inflammatory disease characterized by presence of abscesses.

TRIGGER WORDS

Foul smelling
Mixed infection
Abscess

ESSENTIAL FACTS

- Broad antibiotic resistance
- *Porphyromonas*, *Prevotella*, and *Fusobacterium* are similar to *B. fragilis*

STUDY BREAK

B. fragilis is present in normal intestinal flora, and its polysaccharide A is sufficient to initiate beneficial regulatory T-helper immune responses.

Bacteroides fragilis and Other Gram-Negative Anaerobes

STRUCTURE –

Anaerobic, gram-negative coccobacillus, pleomorphic

LAB ID

Foul smelling; resistant to kanamycin, vancomycin, and colistin; grows in bile

VIRULENCE FACTORS

Pili, capsule, cytolytic enzymes, endotoxin

DISEASES

Intraabdominal abscesses, pelvic infections, peritonitis, wound infection, bacteremia

EPIDEMIOLOGY

Ubiquitous

TREATMENT

Surgical removal, metronidazole

73

Haemophilus

Murray: *Medical Microbiology,* 8th Edition, Chapter 24

CASE STUDIES

Haemophilus influenzae
Three-year-old child with trouble breathing, sore throat, fever: **epiglottitis**

***H. influenzae* type B**
Cranky 3-year-old unvaccinated child with fever, severe headache, and stiff neck: **meningitis**

H. ducreyi
Sexually active man notices painful ulcer on penis and swollen inguinal node: **chancroid**

TRIGGER WORDS

X and V factors
Haemophilus influenza type B (Hib)
Capsule
Meningitis

ESSENTIAL FACTS

Capsule, normal flora. *Haemophilus* means "blood loving," and they require X factor (hematin) and V factor (nicotinamide adenine dinucleotide [NAD]). Grow on chocolate agar. Hib polysaccharide-protein conjugate vaccine at 2, 4, 6, and 15 months.

STUDY BREAK

Widespread use of the Hib vaccine has made *Haemophilus* meningitis and epiglottitis a rare disease, but epiglottitis in adults is increasing.

Haemophilus

STRUCTURE –
Gram-negative coccobacillus

LAB ID
Requires X and V factors, chocolate agar

VIRULENCE FACTORS
Polysaccharide capsule, endotoxin, adherence

DISEASES

H. influenzae
Meningitis, epiglottitis, pneumonia, otitis media

H. ducreyi
Gram-negative bacilli, pili, painful chancroid

Pasteurella multocida
Bite wound infections, especially from cats; chronic pulmonary disease. Treat with penicillin, fluoroquinolone, or tetracycline.

EPIDEMIOLOGY
Rare in children since vaccine

PREVENTION
Vaccine administered with DPT (Hib); conjugated to toxoid as carrier protein

TREATMENT
Broad-spectrum cephalosporins, azithromycin, fluoroquinolones

74

Helicobacter pylori

Murray: *Medical Microbiology*, 8th Edition, Chapter 28

CASE STUDY

A stressed-out 55-year-old woman notices blood in her stool and experiences intense stomach pain after eating. She is diagnosed with an ulcer. Urease breath test indicates presence of ***H. pylori.***

TRIGGER WORDS

Gastric or duodenal ulcer
Urease
Urease breath test

ESSENTIAL FACTS

- Bacterial urease production of ammonia neutralizes stomach acid, motile bacteria pass through mucus and adhere to epithelial cells. Cytotoxin, enzymes, and urease byproducts cause tissue damage. Inflammation causes ulcer.
- Detected by urease breath test
- Treated with triple-drug therapy

STUDY BREAK

- The association between *H. pylori* and ulcers was made by ingesting the bacteria on purpose.
- Most people are colonized with *H. pylori* by age 10.
- Broccoli contains a compound called *sulforaphane*, which researchers say is many times more potent than modern antibiotics when it comes to killing *H. pylori*.

Helicobacter pylori

STRUCTURE

Gram-negative bacilli

LAB ID

Motile, urease positive

VIRULENCE FACTORS

Multiple flagella, urease, adhesins, cytotoxin, immune escape mechanisms

DISEASES

Peptic ulcers

EPIDEMIOLOGY

Ubiquitous; fecal-oral transmission

PREVENTION

None

TREATMENT

Two-week triple therapy = amoxicillin, omeprazole, clarithromycin with bismuth or tetracycline, metronidazole, bismuth and omeprazole (proton pump inhibitor)

75

Legionella pneumophila

Murray: *Medical Microbiology,* 8th Edition, Chapter 29

CASE STUDY

A 60-year-old man with a 35-pack/year history of smoking is diagnosed with pneumonia.

TRIGGER WORDS

Air conditioning coolant
Shower
Other lukewarm water sources
Charcoal yeast agar (BCYE agar)
Silver stain

ESSENTIAL FACTS

- Atypical pneumonia
- Cysteine and iron required for growth
- Milder form of disease is called Pontiac fever

STUDY BREAK

Legionnaires' disease acquired its name in 1976 when an outbreak of pneumonia occurred among persons attending a convention of the American Legion in Philadelphia. The stigma caused an elegant hotel to fail. Later the bacterium causing the illness was named *Legionella*.

Legionella pneumophila

STRUCTURE –

Gram-negative coccobacillus

LAB ID

Aerobic, catalase positive, charcoal yeast agar plus cysteine and iron (BCYE)

VIRULENCE FACTORS

Capsule, growth in amoebas and macrophages

DISEASES

Legionnaires' disease

EPIDEMIOLOGY

Grows in lukewarm standing water sources and then becomes aerosolized.

PREVENTION

Proper chlorination of water sources

TREATMENT

Erythromycin, newer macrolides, fluoroquinolones

76

Listeria and *Erysipelothrix*: Part One

Murray: *Medical Microbiology,* 8th Edition, Chapter 21

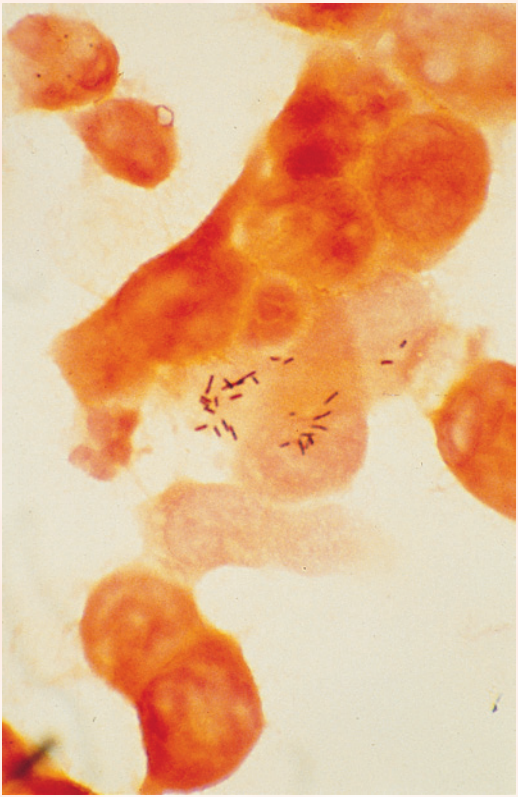

Figure 76-1: Intracellular and extracellular Listeria monocytogenes, *gram-positive bacilli.*

Listeria and *Erysipelothrix*: Part One

CASE STUDIES

- A neonate acquires *Listeria monocytogenes* transplacentally and presents with disseminated abscesses and granulomas in many organs. Treatment was not initiated quickly enough and the baby died: **early-onset *L. monocytogenes* disease**
- A 3-week-old baby has meningoencephalitis, fever, malaise (septicemia): **late-onset *L. monocytogenes* disease**
- A pregnant woman had chills and fever, then develops meningitis.

TRIGGER WORDS

Meningitis
Baby
Milk products
Undercooked meat
Intracellular growth
Cold enrichment
Motility

ESSENTIAL FACTS

- Produces exotoxin (listeriolysin O), phospholipases, and internalin proteins.
- Grows at refrigerator temperatures.
- As an intracellular bacteria, control of *Listeria* requires cell-mediated immunity.
- Pregnant women, neonates, cancer patients, and transplant recipients are at risk for serious outcomes.

STUDY BREAK

Listeria contamination of ice cream and other dairy products or meat can result in large recalls. In 1999, 30 million pounds of contaminated meat were discarded in one outbreak.

Listeria expressing fusion proteins of listerolysin and tumor proteins can be a vaccine that promotes CD8 T-cell responses.

77

Listeria and *Erysipelothrix*: Part Two

Murray: *Medical Microbiology*, 8th Edition, Chapter 21

Listeria

STRUCTURE +

Gram-positive rod

LAB ID

Selective medium and cold enrichment; motility and β-hemolysis; too few to be detectable in Gram stain of cerebrospinal fluid

VIRULENCE FACTORS

Exotoxin: listeriolysin O, phospholipases, and intracellular growth (internalin proteins)

DISEASES

- Neonates and babies: bacteremia, meningitis, meningoencephalitis
- Adults: flulike symptoms, bacteremia, meningitis

EPIDEMIOLOGY

Listeria is ubiquitous, but outbreaks are associated with contamination of food. The bacteria grow at refrigerator temperatures. Contamination can be on undercooked meats; milk, cheese, ice cream; raw vegetables (especially cabbage). Transplacental transmission is also possible.

PREVENTION

Cook food

TREATMENT

Ampicillin ± gentamicin

Listeria and *Erysipelothrix*: Part Two

Erysipelothrix

STRUCTURE +

Thin gram-positive rods

DISEASES

- Localized skin infections (erysipeloid), usually on hands at site of trauma
- Generalized cutaneous infection
- Septicemia with possible endocarditis

EPIDEMIOLOGY

Zoonotic; butchers, meat processors, and veterinarians are at risk.

TREATMENT

Penicillin

78

Mycoplasma and *Ureaplasma*

Murray: *Medical Microbiology,* 8th Edition, Chapter 33

CASE STUDY

A 20-year-old has a nagging, nonproductive cough, low-grade fever, headache, and fatigue. She had pharyngitis before the cough began. Chest radiograph indicates bilateral diffuse interstitial pneumonia.

TRIGGER WORDS

Walking pneumonia
No cell wall

ESSENTIAL FACTS

- *Mycoplasma* lack a cell wall and are therefore always resistant to β-lactam antibiotics.
- Outbreaks are common in military barracks.

STUDY BREAK

Atypical pneumonia is called walking pneumonia because in most cases the disease is not severe enough to confine the patient to bed or to warrant hospitalization.

Mycoplasma and *Ureaplasma*

STRUCTURE

No cell wall, smallest free-living bacteria; some *Mycoplasma* steal sterols

LAB ID

Positive cold agglutinin; slow growth, tiny colonies; fried-egg colony morphology except *M. pneumoniae*

VIRULENCE FACTORS

Adhesin binds to ciliated epithelium; bacteria promote inflammation and cytokine release.

DISEASES

M. pneumoniae
Walking pneumonia; may induce Stevens-Johnson syndrome

Ureaplasma urealyticum, M. hominis, M. genitalium
Nongonococcal urethritis

M. hominis
Pelvic inflammatory disease, pyelonephritis

EPIDEMIOLOGY

Ubiquitous, spread in nasal secretions

TREATMENT

Macrolides (erythromycin)

79

Neisseria meningitidis: Part One

Murray: *Medical Microbiology,* 8th Edition, Chapter 23

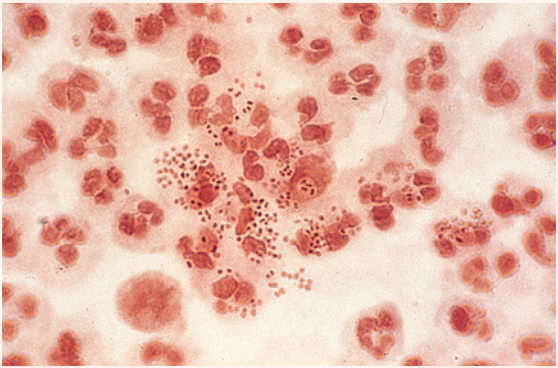

Figure 79-1: Gram-negative intracellular diplococci. **N. gonorrhoeae** *(pictured) looks the same as* **N. meningitidis.**

Neisseria meningitidis: Part One

CASE STUDY

- A 5-year-old child with sudden onset of fever, petechiae and purpura (black and blue marks) on the skin, malaise, and stiff neck. Cerebrospinal fluid (CSF) contains gram-negative diplococci.
- A 23-year old woman develops meningococcal septicemia. Disruption of blood vessels causes loss of circulation to extremities, and amputation is required.

TRIGGER WORDS

Gram-negative diplococci in CSF
Meningitis
Lipooligosaccharide (LOS)
Endotoxin
Septic shock
Petechiae
Purpura
Waterhouse-Friderichsen syndrome

ESSENTIAL FACTS

- Shedding of LOS, a potent endotoxin, causes petechiae, purpura, Waterhouse-Friderichsen syndrome, and septic shock.
- People with genetic deficiency in a C5-C9 component of complement are at high risk for disseminated *Neisseria* disease.

STUDY BREAK

Antibiotic treatment of *N. meningitidis* meningitis may exacerbate the disease because of release of outer membrane and cell wall components, which induce inflammation responses.

80

Neisseria meningitidis: Part Two

Murray: *Medical Microbiology,* 8th Edition, Chapter 23

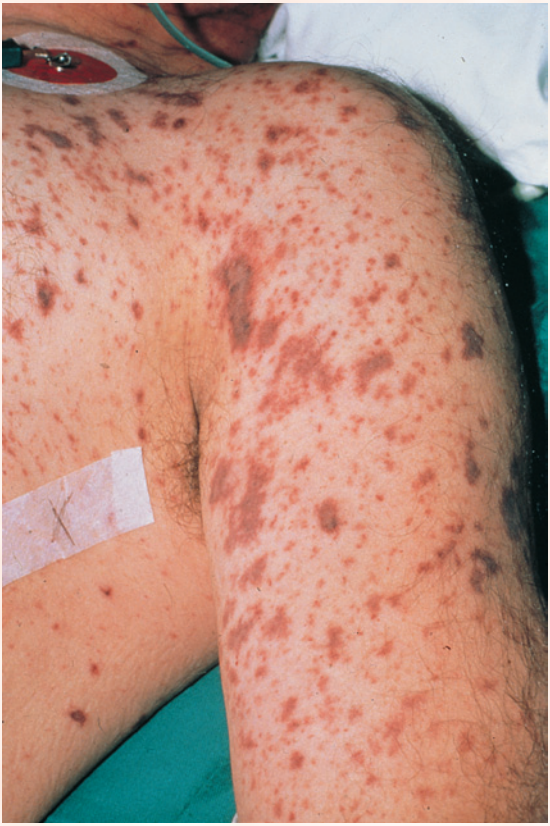

Figure 80-1: Petechiae characteristic of meningococcemia.

Neisseria meningitidis: Part Two

STRUCTURE

Gram-negative diplococci with capsule and lipooligosaccharide (LOS)

LAB ID

Gram stain of cerebrospinal fluid, growth on chocolate agar

VIRULENCE FACTORS

Capsule, LOS (endotoxin), pili

DISEASES

Meningococcemia, meningitis, Waterhouse-Friderichsen syndrome (including disseminated intravascular coagulation), disruption of blood vessels, loss of circulation to extremities, and septic shock

EPIDEMIOLOGY

Can be normal flora; transmitted by aerosols

PREVENTION

- Vaccination with polysaccharide or conjugate vaccine
- Contacts are treated with rifampin or fluoroquinolone (gets into mucosal colonization sites).

TREATMENT

Ceftriaxone

81

Neisseria gonorrhoeae: Part One

Murray: *Medical Microbiology,* 8th Edition, Chapter 23

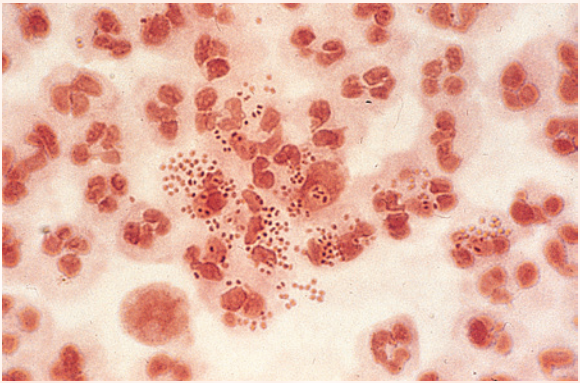

Figure 81-1: Note the intracellular gram-negative diplococci and polymorphonuclear cells.

Neisseria gonorrhoeae: Part One

CASE STUDIES

- A 22-year-old sexually active man with a green-yellow discharge from his urethra, difficulty and pain on urination. Discharge contains gram-negative diplococci: **local**
- Sexually active man with painful, inflamed joint. Aspirate contains gram-negative diplococci: **disseminated**
- Sexually active woman with fever, abdominal pain, cervical motion tenderness, and vaginal discharge: **pelvic inflammatory disease (PID)**
- Conjunctivitis in a newborn untreated with silver nitrate or erythromycin at birth
- A child with an immune defect in C5-C9 complement component has disseminated disease

TRIGGER WORDS

Gram-negative diplococci
Urethritis
Sexually transmitted disease
Thayer-Martin medium
Chocolate agar
Disseminated gonococcal infection

ESSENTIAL FACTS

- *N. gonorrhoeae* adheres with pili and then invades mucosal cells.
- Sugar fermentation test distinguishes *N. **g**onorrhoeae* (G for glucose) from *N. **m**ening**g**itidis* (M for maltose and G for glucose).
- The most common causes of PID are *N. gonorrhoeae* (acute, high fever) and *Chlamydia trachomatis* (subacute, often undiagnosed).

STUDY BREAK

Penicillin-resistant gonorrhea arose and spread to the United States during the Vietnam War, when sailors visited prostitutes who were taking low levels of penicillin. The low-level penicillin was sufficient to minimize symptoms but selected for resistance.

82

Neisseria gonorrhoeae: Part Two

Murray: *Medical Microbiology,* 8th Edition, Chapter 23

STRUCTURE

Gram-negative diplococci

LAB ID

Cell culture on chocolate or Thayer-Martin agar; fermentation tests (glucose); oxidase and catalase positive

VIRULENCE FACTORS

Pili, outer membrane invasion protein, immunoglobulin A protease, intracellular growth, shedding of lipooligosaccharide = endotoxin

DISEASES

Urethritis, PID, proctitis (homosexual males), pharyngitis, neonatal conjunctivitis, disseminated joint disease, arthritis

EPIDEMIOLOGY

Sexually transmitted disease

PREVENTION

Safe sex

TREATMENT

Ceftriaxone, azithromycin; treat for chlamydia also: azithromycin, tetracycline, doxycycline

83 *Mycobacterium leprae, M. avium* Complex, and *M. marinum*

Murray: *Medical Microbiology,* 8th Edition, Chapter 22

Figure 83-1: Lepromatous leprosy.

TRIGGER WORDS

Lepromatous leprosy
Tuberculoid leprosy
Cell-mediated immunity
Nerve damage

ESSENTIAL FACTS

M. leprae

- The less severe tuberculoid leprosy occurs if a Th1 immune response is activated (activation of macrophages and cell-mediated immunity).
- The more severe lepromatous leprosy occurs if a TH2 immune response is activated (promotes antibody production but antagonistic to Th1 responses).

M. avium Complex

- Pulmonary and disseminated disease in AIDS
- Treat with clarithromycin + ethambutol and rifabutin for long periods

M. marinum

- Seawater contamination of a cut in the skin causes a granuloma.

STUDY BREAK

The first animal model for leprosy was identified when a researcher noticed an unusual-looking armadillo on the road near the leprosy hospital.

Mycobacterium leprae, M. avium Complex, and *M. marinum*

STRUCTURE +

Gram-positive, acid-fast staining bacillus

LAB ID

Polymerase chain reaction, DNA probe, symptomatology

VIRULENCE FACTORS

Intracellular growth and neurotropism

DISEASES

Table 83-1 Leprosy

Property	Tuberculoid	Lepromatous
Skin appearance	Few plaques	Many nodules, papules, macules; tissue damage
Nerve involvement	Peripheral nerve damage	Peripheral nerve and sensory loss
Immune reactions	Delayed-type hypersensitivity (Th1)	No delayed-type hypersensitivity (Th2)
Skin lesions	Granulomatous with Langerhans cells and lymphocytes	Foamy macrophages
Acid-fast bacilli in lesion	Few or none	Many in skin, nerves, and organs

EPIDEMIOLOGY

Spread by contact and inhalation

PREVENTION

Special quarantine or disinfection procedures

TREATMENT

Dapsone and rifampin, plus clofazimine for lepromatous form

84

Mycobacterium tuberculosis: Part One

Murray: *Medical Microbiology,* 8th Edition, Chapter 22

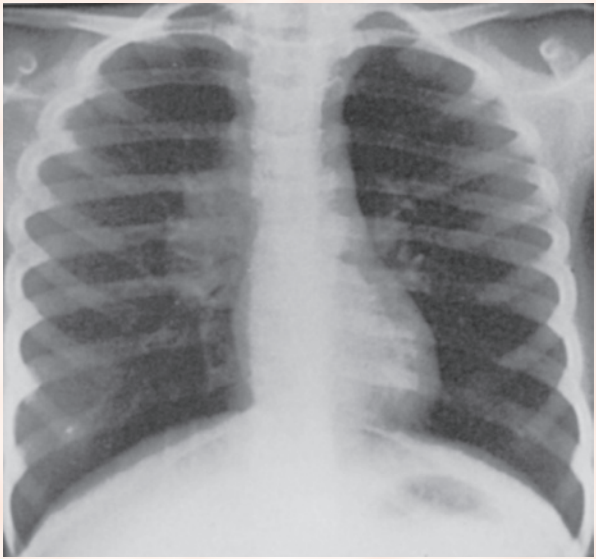

Figure 84-1: Tuberculosis.

Mycobacterium tuberculosis: Part One

CASE STUDY

A 67-year-old man is very tired and has no appetite, a dry persistent cough, fever, and chills and sweats. He lost 13 pounds in the last month without dieting. A chest radiograph shows bilateral upper lobe involvement, mediastinal and hilar lymphadenopathy. Sputum contained an acid-fast bacillus. Cultures on Lowenstein-Jensen medium were positive after 1 week in culture.

TRIGGER WORDS

Mantoux reaction
Purified protein derivative (PPD)
Acid fast
Granuloma
Caseation
Opportunistic disease
Ghon complexes
Isoniazid
Cell-mediated immunity (CMI)

ESSENTIAL FACTS

- *M. tuberculosis* has an outer layer consisting of mycosides (acid fastness), wax D (immunoadjuvant), cord factor (virulence), and antigenic proteins (DTH).
- CMI is essential for control of tuberculosis.
- Macrophages (controlled by CD4 T cells) wall off the tuberculosis (TB) bacteria in a tubercle (granuloma), which is the source of recurrence on immunosuppression.
- In the United States, spread of TB is controlled by screening with the PPD skin test for a DTH response instead of vaccination, as in Europe and other countries.
- Multiple-drug therapy is required to control TB.

STUDY BREAK

Robert Koch devised Koch's Postulates to prove that *M. tuberculosis* causes "consumption."

85

Mycobacterium tuberculosis: Part Two

Murray: *Medical Microbiology,* 8th Edition, Chapter 22

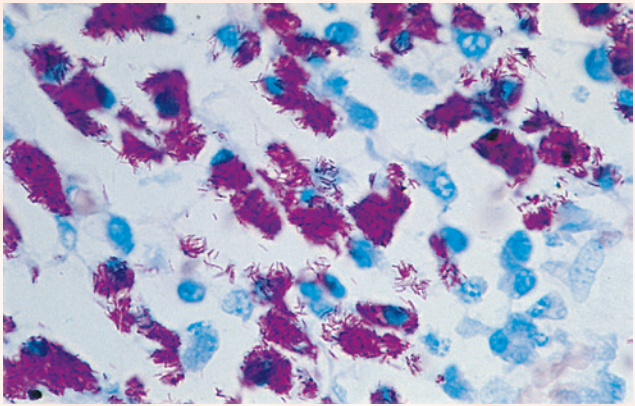

Figure 85-1: Acid-fast bacteria in tissue from patient with AIDS.

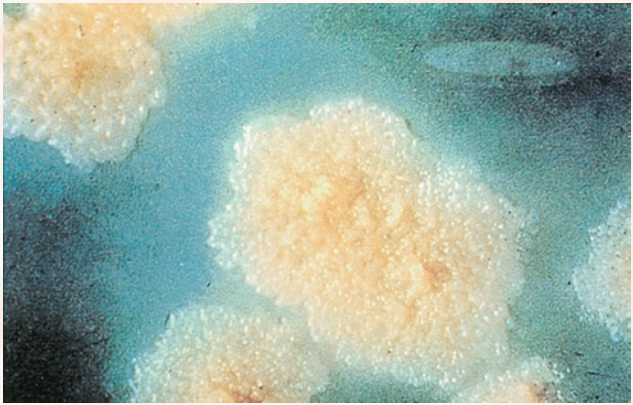

Figure 85-2: M. tuberculosis *grown on Lowenstein-Jensen agar.*

Mycobacterium tuberculosis: Part Two

STRUCTURE +

Acid-fast bacillus with external wax-mycolic acid layer outside thick peptidoglycan

LAB ID

Ziehl-Neelsen acid-fast stain, skin test (purified protein derivative [PPD]), interferon-γ release assay blood test (IGRA), polymerase chain reaction, culture on egg-based Lowenstein-Jensen medium

VIRULENCE FACTORS

Cord factor, waxy layered outer layers, intracellular growth in macrophages and other cells

DISEASES

Pulmonary tuberculosis (TB), secondary TB (in immunosuppressed people), miliary TB (systemic spread and tissue involvement)

EPIDEMIOLOGY

Ubiquitous. Immunosuppressed people are at highest risk.

PREVENTION

Bacille Calmette-Guérin (BCG) vaccine in Europe; screening (PPD) and lung radiograph and treatment in the United States

TREATMENT

Multidrug therapy: isoniazid, rifampin, and pyrazinamide. Also ethambutol and streptomycin. Multidrug-resistant strains exist.

86

Pseudomonas aeruginosa

Murray: *Medical Microbiology,* 8th Edition, Chapter 27

CASE STUDIES

- High school swim team member screams in pain when someone touches his ear: **external otitis** (swimmer's ear)
- Man notices red bumps all over legs and around nipples after spending too much time in a whirlpool: **folliculitis**
- Young white girl with cough and congestion diagnosed with cystic fibrosis
- Man with catheter has urinary tract infection (UTI)
- Burn patient with infected wounds

TRIGGER WORDS

Nosocomial infection
Opportunistic
Fruity smell
Cystic fibrosis
Antibiotic resistant
Burn patient

ESSENTIAL FACTS

- Antibiotic-resistant, toxin-producing, oxidase-positive/lactose-negative, gram-negative rod
- Opportunistic infection for the neutropenic, burn victims, and hospitalized patients
- Colonizes lung in cystic fibrosis patients

STUDY BREAK

Pseudomonas have coexisted with many antibiotic producers in the soil and have developed natural resistance. They are so hardy that they can survive in tincture of iodine and on a bar of soap. The first patented organism was a *Pseudomonas* that had a plasmid that encoded a metabolic pathway for degradation of oil.

Pseudomonas aeruginosa

STRUCTURE

Thin gram-negative bacilli

LAB ID

Blue-green pigment, nonlactose fermenter, oxidase positive, strict aerobe

VIRULENCE FACTORS

Capsule, endotoxin, exotoxin (targets ribosome), flagella, antibiotic resistance

DISEASES

P. aeruginosa

Pneumonia; external otitis (swimmer's ear); opportunistic disease, especially for burn patients; endocarditis; sepsis; UTI; nosocomial disease in burn and other hospitalized patients. Co-colonization of lungs with *Staphylococcus aureus* causes mucoid buildup for cystic fibrosis.

***Burkholderia cepacia* (Previously called *Pseudomonas*)**

- Respiratory infections, especially cystic fibrosis and patients with chronic granulomatous disease
- Also UTIs (especially catheterized patients), septicemia, opportunistic infections

EPIDEMIOLOGY

Ubiquitous, hard to disinfect and resistant to antibiotics, common hospital-acquired infection

TREATMENT

Combination therapy because highly resistant to antibiotics

87

Rickettsia and *Coxiella*

Murray: *Medical Microbiology*, 8th Edition, Chapter 34

CASE STUDY

A hunter in South Carolina was bitten by a tick and 7 days later had fever, chills, headache, and myalgia. Three days later, he had a petechial rash starting in the extremities and spreading to the trunk, including the palms and soles.

TRIGGER WORDS

Tick
Southeastern Atlantic and south central states
Obligate intracellular growth

ESSENTIAL FACTS

Appalachian Mountain area (not usually found in the Rocky Mountains despite the name)

Disease	Organism	Vector	Reservoir
Rocky Mountain spotted fever	*R. rickettsii*	Tick-borne 	Ticks, wild rodents
Ehrlichiosis	*E. chaffeensis* *E. phagocytophila* *E. ewingii*		Ticks
Rickettsialpox	*R. akari*	Mite-borne 	Mites, wild rodents
Scrub typhus	*O. tsutsugamushi*		Mites (chiggers), wild rodents
Epidemic typhus	*R. prowazekii*	Louse-borne 	Humans, squirrel fleas, flying squirrels
Trench fever	*R. quintana*†		Humans
Murine typhus	*R. typhi*	Flea-borne 	Wild rodents
Q fever	*C. burnetii*	None*	Cattle, sheep, goats, cats

* Tick vectors may be responsible for animal-to-animal transmission.
† *R. quintana* (*Bartonella quintana*) has been reclassified into the *Bartonella* genus.

Figure 87-1: Epidemiology of common* Rickettsia, Ehrlichia, Orientia, *and* Coxiella *infections.

Rickettsia and *Coxiella*

STRUCTURE

Small intracellular bacteria

LAB ID

Obligate intracellular, immunofluorescence

VIRULENCE FACTORS

Intracellular growth, replication in endothelial cells

DISEASES

Rickettsia rickettsii
Rocky Mountain spotted fever

Coxiella burnetii
Q fever, no positive Weil-Felix reaction, no rash, no insect vector

R. prowazekii
Epidemic typhus

R. typhi
Endemic typhus

EPIDEMIOLOGY

Spread by tick (wood tick)

PREVENTION

Avoid or prevent tick bites

TREATMENT

Tetracycline, doxycycline

STUDY BREAK

Rocky Mountain spotted fever is the most often reported tick-borne disease among Oklahoma residents every year.

88

Staphylococcus aureus, *S. epidermidis*, and *S. saprophyticus*: Part One

Murray: *Medical Microbiology*, 8th Edition, Chapter 18

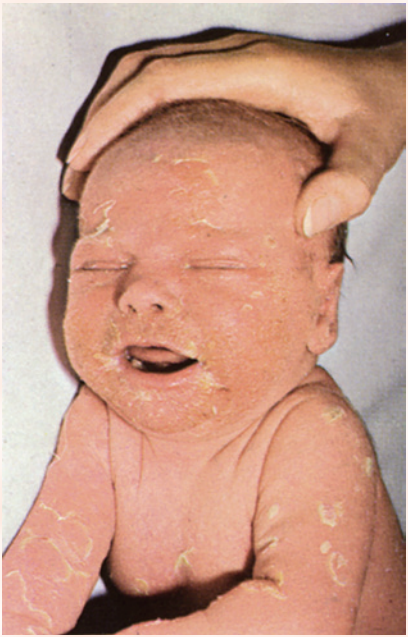

Figure 88-1: Staphylococcal scalded skin syndrome.

CASE STUDIES

- Individual with severe nausea, vomiting, and diarrhea within 4 hours of eating potato salad and ham: **preformed enterotoxin food poisoning**
- Young woman in shock with generalized flushing of the skin and mucous membranes. Exam shows tampon in vagina: **toxic shock syndrome toxin (TSST): superantigen**

Staphylococcus aureus, *S. epidermidis*, and *S. saprophyticus*: Part One

- Baby with blisterlike lesions over much of the body: **scalded skin syndrome**
- Large swollen area of redness on leg of diabetic patient: **carbuncle**
- Fever and swelling below knee for child after orthopedic surgery: **osteomyelitis**
- Child with bullous lesions on face: **impetigo**

TRIGGER WORDS

Grapelike clusters
Coagulase
Catalase
Toxins
Methicillin-resistant *S. aureus* (MRSA)

STUDY BREAK

S. aureus often spoils many picnics by colonizing mayonnaise-, egg-, or salted meat-containing foods.

"Staph" (Greek, *staphyle*) describes its grapelike clusters on Gram stain; "aureus" describes its gold-colored colonies on some media.

89

Staphylococcus aureus, *S. epidermidis*, and *S. saprophyticus*: Part Two

Murray: *Medical Microbiology*, 8th Edition, Chapter 18

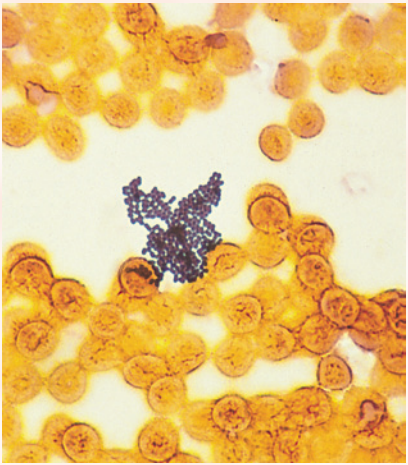

Figure 89-1: Gram stain: grapelike clusters.

STRUCTURE +

Gram-positive coccus

LAB ID

S. aureus

Catalase and coagulase positive, growth on mannitol salts

S. epidermidis

Catalase positive/coagulase negative

VIRULENCE FACTORS

Protein A, coagulase, teichoic acid adherence, β-lactamase, resistance to salt (growth on salted meats); toxins: enterotoxin, exfoliative toxin, toxic shock toxin (superantigen), leukocidin

Staphylococcus aureus, *S. epidermidis*, and *S. saprophyticus*: Part Two

DISEASES

S. aureus
Food poisoning, scalded skin syndrome, toxic shock syndrome, carbuncle, impetigo, endocarditis, osteomyelitis, pneumonia, wound infections

S. saprophyticus
Urinary tract infection

EPIDEMIOLOGY

S. aureus
Ubiquitous, normal flora

S. epidermidis
- Skin, normal flora
- Artificial heart valves, catheters, shunts, prosthetic joints

TREATMENT

S. aureus
β-Lactamase–resistant drugs: methicillin, nafcillin, oxacillin; methicillin-resistant: vancomycin, trimethoprim-sulfamethoxazole, daptomycin

S. epidermidis
Vancomycin treatment

90

Salmonella

Murray: *Medical Microbiology,* 8th Edition, Chapter 25

CASE STUDIES

- A bodybuilder drinks a power protein shake containing raw eggs. Six to 48 hours later he has nonbloody diarrhea with nausea, cramps, and vomiting lasting for 2 to 7 days: ***S. enteritidis***
- After 10 to 14 days, a cook who handled raw chicken and did not wash his hands suffers from fever, headache, myalgia, malaise, and anorexia: **typhoid fever *(S. typhi)***
- An AIDS patient has a gram-negative bacteremia. The isolate forms colorless colonies on MacConkey's agar.

TRIGGER WORDS

Dairy foods
Raw eggs and chicken
Nonbloody diarrhea
Motile
Nonlactose fermenter

ESSENTIAL FACTS

- Oxidase negative; lactose negative but produces hydrogen sulfide.
- During typhoid fever, *S. typhi* passes through M cells in the gut and establishes septicemia. *Salmonella* colonizing the gallbladder are the source of reinfection of the intestines and contagion.

STUDY BREAK

Salmonella has nothing to do with fish; it was named after US pathologist Daniel E. Salmon.

Typhoid Mary's real name was Mary Mallon, a "healthy carrier" of typhoid fever. Mallon is attributed with infecting 47 people with typhoid fever, three of whom died. Immunization for typhoid fever became available after 1911. Typhoid fever has a 10% fatality rate. Mallon was isolated on North Brother Island for 26 years to keep her from spreading the infection.

Salmonella

STRUCTURE

Gram-negative bacilli

LAB ID

Nonlactose fermenter, oxidase negative, motile; produces H_2S

VIRULENCE FACTORS

Multiple flagella; pathogenicity island encodes invasion mechanisms into cells; adhesion proteins on fimbriae for gut M proteins.

DISEASES

Enteric (typhoid) fever, gastroenteritis, bacteremia

EPIDEMIOLOGY

Fecal-oral spread; contaminated foods, especially poultry, eggs, dairy products; contact with birds and reptiles

PREVENTION

Vaccine, hygiene, proper food preparation

TREATMENT

Trimethoprim-sulfamethoxazole, fluoroquinolones, ceftriaxone

91

Shigella and *Proteus*

Murray: *Medical Microbiology,* 8th Edition, Chapter 25

CASE STUDY

A child in daycare has very watery diarrhea with bloody mucus and polymorphonuclear cells in stool, with cramps and fever: **shigellosis**

TRIGGER WORDS

Watery, bloody diarrhea
Gram-negative bacillus
Lactose negative
No hydrogen sulfide
Shiga toxin

ESSENTIAL FACTS

Shiga toxin, low inoculum, no animal reservoir

STUDY BREAK

Only 10 *Shigella* organisms, compared with 100,000 for *Salmonella*, can induce disease.

Shigella and *Proteus*

STRUCTURE –

Gram-negative bacilli

LAB ID

Nonlactose fermenter, oxidase negative, nonmotile, non-H_2S producing

VIRULENCE FACTORS

Shiga toxins (Stx-1, Stx-2), endotoxin, adherence and pathogenicity island encoded invasion proteins (type III secretion system)

DISEASES

Dysentery (invasive diarrhea)

EPIDEMIOLOGY

Prevalent in children in daycare centers, those in long-term care facilities, and their contacts; male homosexuals

PREVENTION

Hygiene

TREATMENT

Fluoroquinolone or trimethoprim-sulfamethoxazole, azithromycin

92

Streptococcus pneumoniae

Murray: *Medical Microbiology,* 8th Edition, Chapter 19

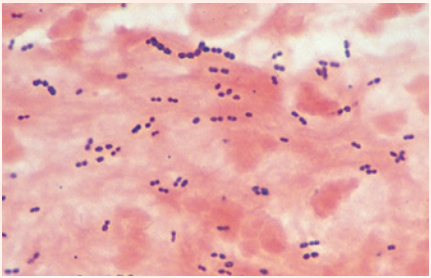

Figure 92-1: Gram stain of S. pneumoniae: *football-shaped gram-positive diploids.*

CASE STUDIES

- A 35-year-old man with abrupt onset of high fever, rigor, productive cough with blood in sputum, and chest pain around the middle lower lobes of lung: **pneumonia**
- His condition progresses with systemic symptoms (bacteremia) and then meningitis.
- A 2-year-old child with earache

TRIGGER WORDS

Gram-positive diploids
Capsule
P disk (optochin) sensitive
Polysaccharide and conjugate vaccines

ESSENTIAL FACTS

- Common cause of otitis media, meningitis, and community-acquired bacterial pneumonia (especially adults).
- The capsule prolongs the bacteria's presence in the blood and eventually reaches the meninges: meningitis.

Streptococcus pneumoniae

STRUCTURE

Gram-positive, football-shaped diplococcus

LAB ID

Alpha (greenish) hemolysis, P disk (optochin) sensitive

VIRULENCE FACTORS

Adhesins; enzymes: immunoglobulin A protease, pneumolysin; teichoic acid, peptidoglycan promotes inflammation through alternate C′ pathway and Toll-like receptors; capsule

DISEASES

Pneumonia, otitis media, bacteremia, meningitis

EPIDEMIOLOGY

Normal flora

PREVENTION

Anticapsular vaccine: 23 capsular polysaccharides or multiple (at least nine) polysaccharides conjugated to protein

TREATMENT

Penicillin, amoxicillin, fluoroquinolones, macrolides

STUDY BREAK

I once tried to pass off a Gram stain of *S. pneumoniae* (round cells in chains) as *S. pyogenes* (because it was a better Gram stain) to an audience of students and parents. An ER physician friend recognized the football-shaped diplococcus as *S. pneumoniae* but mentioned it to me in private rather than embarrass me.

93

Streptococcus pyogenes: Part One

Murray: *Medical Microbiology,* 8th Edition, Chapter 19

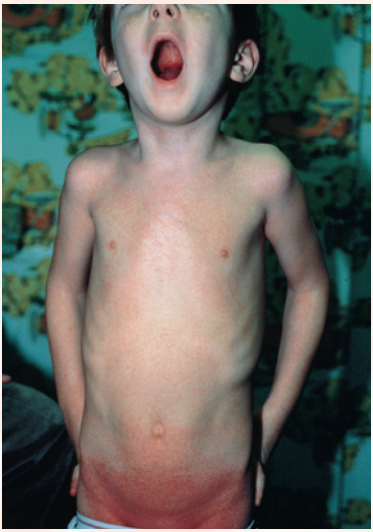

Figure 93-1: Scarlet fever.

CASE STUDIES

Suppurative Infections

- A 7-year-old child with a sore throat is tired and has a fever and headache. Bacterial cultures were sensitive to bacitracin (A disk). Treated with penicillin to prevent sequelae: **pharyngitis**
- A 3-year-old child with pus-filled vesicles on her face, swollen lymph nodes: **pyoderma** (impetigo)
- A 65-year-old woman with red, inflamed area on the lower leg with bullae, swollen nodes: **erysipelas**
- A 43-year-old emergency department technician with cellulitis around a cut on his arm, which progresses to bullae, extensive tissue destruction, gangrene, and then multiorgan failure: **necrotizing fasciitis**

Streptococcus pyogenes: Part One

Toxin-Mediated Diseases

- A child with rash and strawberry tongue: **scarlet fever**
- A cancer patient had a skin infection and then later had nonspecific systemic symptoms, including fever, chills, malaise, nausea, vomiting, and diarrhea. She progressed to shock and organ failure: **streptococcal toxic shock syndrome**

Autoimmune Sequelae

- Untreated child with *S. pyogenes* pharyngitis gets rheumatic fever characterized by inflammatory disease of the heart (endocarditis, pericarditis, myocarditis) and joint pain (arthritis). Acute-phase reactants are elevated. Disease signs include two major manifestations of Jones criteria.
- Alternative sequelae, glomerulonephritis

TRIGGER WORDS

β-Hemolysis
A disk (group A) bacitracin sensitivity
M protein
Streptolysins O and S
Gram-positive cocci in chains

ESSENTIAL FACTS

- Serotypic different M proteins can determine different diseases.
- Toxic shock syndrome is caused by a superantigen that binds MHC II to the T-cell receptor and nonspecifically activates a large amount of cytokine production, causing systemic symptoms.

STUDY BREAK

A father died, his daughter was very sick, and the ambulance driver and emergency department physician had sore throats; all were infected with the same flesh-eating (fasciitis) strain of *S. pyogenes*.

The A in the A disk stands for group A; the P in the P disk stands for *Pneumococcus*.

94

Streptococcus pyogenes: Part Two

Murray: *Medical Microbiology*, 8th Edition, Chapter 19

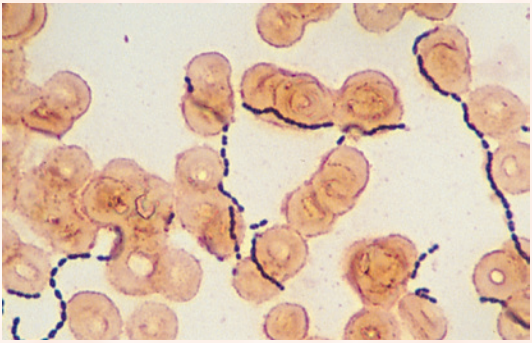

Figure 94-1: Gram stain of Streptococcus pyogenes.

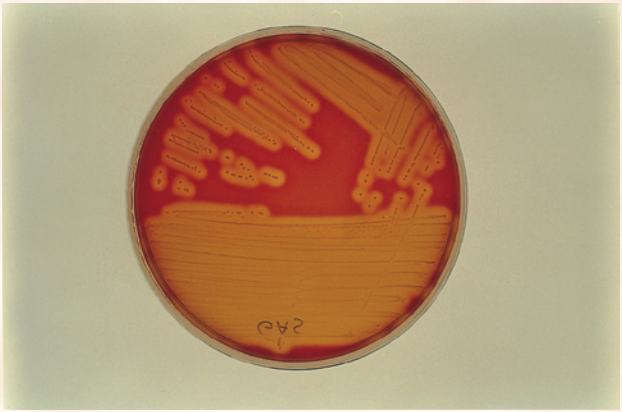

Figure 94-2: β-Hemolysis.

Streptococcus pyogenes: Part Two

STRUCTURE +

Gram-positive cocci singly or in long chains

LAB ID

Catalase negative; β-hemolytic; bacitracin sensitive (A disk), rapid strep antigen tests, ASO titer for rheumatic fever

VIRULENCE FACTORS

S. pyogenes has most of the potential virulence mechanisms, including adherence, toxins (including superantigens), manipulation of the immune response, capsule, and degradative enzymes.

- M protein: adhesion, antiphagocytic, degrades complement C3b
- Capsule
- Lipoteichoic acid binds to epithelial cells
- F protein: adheres to epithelial cells
- Streptolysins O and S: lyse leukocytes, platelets, and red blood cells
- Streptokinase: lyses blood clots, promotes spread
- Toxic shock toxin: superantigen

DISEASES

Pharyngitis, scarlet fever, skin and tissue disease (impetigo, erysipelas, cellulitis), necrotizing fasciitis, toxic shock syndrome; postinfection sequelae: rheumatic fever, acute glomerulonephritis

EPIDEMIOLOGY

Ubiquitous, fomites, direct contact

TREATMENT

Penicillin, cephalosporin, erythromycin

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Group B Streptococci, *Streptococcus viridans*, and *Enterococcus*

Murray: *Medical Microbiology*, 8th Edition, Chapter 19

Group B Streptococci and S. viridans

LAB ID

Usually β-hemolytic

VIRULENCE FACTORS

Causes disease in immune-deficient host

DISEASES

Group B Streptococci

- Neonatal group B streptococcal infection
  - **Early onset:** neonatal meningitis, pneumonia, and bacteremia (sepsis)
  - **Late onset:** (1 week to 3 months) bacteremia with meningitis
- Pregnant women: urinary tract infection (UTI), postpartum sepsis
- Diabetics and individuals with compromised immune responses: bacteremia, pneumonia, bone and joint infections, skin and soft tissue infections

S. viridans

Dental caries, subacute endocarditis, heart valve disease, intraabdominal infections

EPIDEMIOLOGY

Usually normal flora in upper respiratory, lower gastrointestinal (GI), and urinary tracts. Colonizes 60% of newborns.

PREVENTION

Vaccine, special quarantine or disinfection procedures

TREATMENT

Penicillin ± aminoglycoside

Group B Streptococci, *Streptococcus viridans*, and *Enterococcus*

Enterococcus *(previously Group D Strep)*

CASE STUDY

A man with an intravascular catheter develops bacteremia. The gram-positive cocci obtained from blood cultures were resistant to most antibiotics, including aminoglycosides, ampicillin, penicillin, and even vancomycin. The patient did not survive.

TRIGGER WORDS

Entero-feces-gut bug
Nosocomial
Antibiotic resistant

STRUCTURE +

Gram-positive cocci

LAB ID

Bile-esculin test, optochin resistant

VIRULENCE FACTORS

Antibiotic resistant

DISEASES

Bacteremia; UTI; nosocomial disease; endocarditis; intraabdominal abscess

EPIDEMIOLOGY

Normal flora in GI tract; common nosocomial infection, especially for those with catheters

TREATMENT

Aminoglycoside + ampicillin or vancomycin, but if resistant fluoroquinolones, linezolid, and other newer antibiotics

96

Treponema pallidum: Part One

Murray: *Medical Microbiology*, 8th Edition, Chapter 32

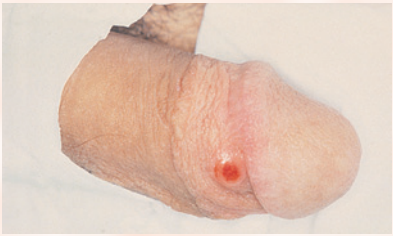

Figure 96-1: Primary: chancre.

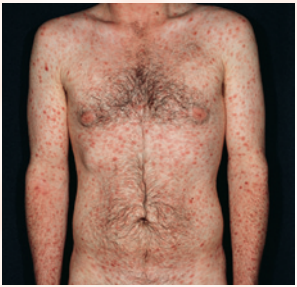

Figure 96-2: Secondary: disseminated rash.

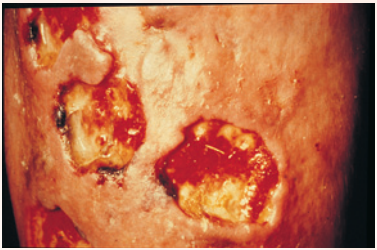

Figure 96-3: Tertiary: gumma.

Treponema pallidum: Part One

CASE STUDIES

- A sexually active man notices a painless ulcer (chancre) on his penis; a few weeks later he feels "lumps" in his inguinal area: **primary syphilis**
- The chancre resolves without treatment after 1 month, but after an additional month the man develops flulike symptoms, disseminated rash, and hepatitis: **secondary syphilis**
- The rash and symptoms resolve, but gummas form in the organs and skin and neurosyphilis occurs: **tertiary syphilis**

TRIGGER WORDS

Syphilis
Painless chancre
Gumma
VDRL test
FTA-ABS test
Spirochete
Unculturable
Sexually transmitted disease

ESSENTIAL FACTS

- *T. pallidum* is too anaerobic to be cultured.
- Each phase of disease appears to resolve but actually disseminates.
- Infection is detected by treponemal tests (FTA-ABS detection of antibodies in patient's blood) and nontreponemal tests (VDRL or RPR for antibody to cardiolipin in response to infection).

STUDY BREAK

Syphilis, the venereal disease that devastated the Western world until the advent of penicillin, was named for Syphilus, the shepherd hero from Greek mythology. Royalty of England and Europe were "rewarded" with syphilis for their infidelities, and some went mad with neurosyphilis.

97

Treponema pallidum: Part Two

Murray: *Medical Microbiology*, 8th Edition, Chapter 32

STRUCTURE

–

Spirochete, gram negative

LAB ID

- Anaerobe
- Treponemal tests (FTA-ABS) detect the antibody to the organism. Nontreponemal tests detect host reactions to the infection and may have false positives: VDRL or RPR for antibody to cardiolipin

VIRULENCE FACTORS

Hyaluronidase promotes invasion, adherence, and immunopathogenesis.

DISEASES

Syphilis

EPIDEMIOLOGY

Sexually transmitted disease

PREVENTION

Safe sex, monogamy

TREATMENT

Penicillin

98

Borrelia burgdorferi

Murray: *Medical Microbiology*, 8th Edition, Chapter 32

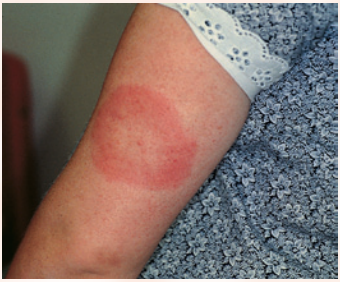

Figure 98-1: Borrelia burgdorferi: *Lyme disease.*

CASE STUDY

Woman notices a bull's eye–like lesion on her husband's back at the site of a tick bite after they got back from their camping trip in Connecticut.

TRIGGER WORDS

Erythema chronicum migrans
Deer tick
High grass

ESSENTIAL FACTS

Transmitted by deer tick

STUDY BREAK

Lyme disease was identified after a group of young children in Lyme, Connecticut, developed arthritis. Ticks should not be removed using petroleum jelly, lit cigarettes, or other home remedies; these methods may increase the chance of contracting a tick-borne disease.

Borrelia burgdorferi

STRUCTURE

–

Spirochete, gram negative

LAB ID

Motile, larger spirochetes visible under microscope

VIRULENCE FACTORS

Endotoxin, relapsing fever due to antigenic shift; Lyme disease due to induction of immunopathogenesis

DISEASES

- Lyme disease
- Relapsing fever: spread by ticks or lice
- High fever, chills, muscle aches, and headache result from bacteremia; symptoms go away and recur several times.

Table 98-1: Lyme Disease

Early Signs	Late Signs
Erythema migrans skin lesion >5 cm diameter around tick bite, *plus*: Flulike symptoms Swollen glands Musculoskeletal pain	Neurologic (meningitis, encephalitis); cardiac dysfunction; arthralgia and arthritis

EPIDEMIOLOGY

Ixodes ticks (deer ticks)

PREVENTION

Vaccine no longer produced; avoid and prevent tick bites

TREATMENT

- Lyme disease: doxycycline and amoxicillin (early) or ceftriaxone (late)
- Relapsing fever: tetracycline or erythromycin

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Vibrio cholerae: Part One

Murray: *Medical Microbiology,* 8th Edition, Chapter 26

CASE STUDY

Woman who vacationed in New Orleans ate at a seafood buffet with raw oysters. After 3 days she has severe watery diarrhea that is speckled with mucus.

TRIGGER WORDS

Comma (S) shaped
Rice water (mucus speckles) diarrhea
Shellfish
A-B toxin

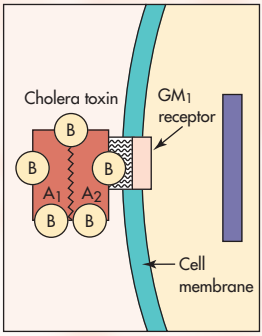
ESSENTIAL FACTS

Toxin B (binding) subunit binds to GM_1-ganglioside. A subunit enters and activates G proteins and adenyl cyclase; cyclic adenosine monophosphate promotes secretion of ions and water into intestinal lumen.

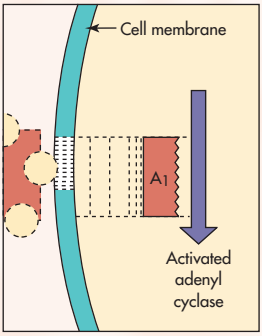
STUDY BREAK

Vibrio can still grow in salty water, even at 10°C. Shellfish are filter feeders and accumulate bacteria and viruses from their environment. Some say hot sauce kills the *Vibrio*, but this is unproven.

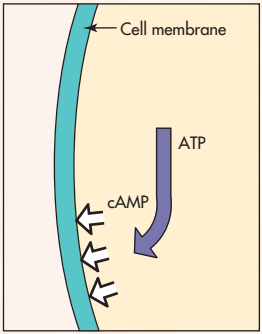
Vibrio cholerae: Part One



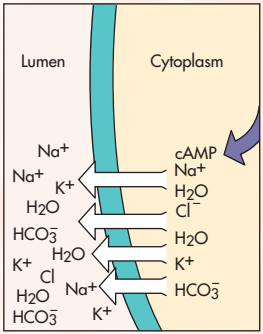
The complete toxin binding to the GM_1-ganglioside receptor on the cell membrane via the binding subunits (B).



The active portion (A_1) of the A subunit enters the cell and activates adenyl cyclase.



This activity results in accumulation of cyclic adenosine 3′, 5′–monophosphate (cAMP) along the cell membrane.



The cAMP causes the active secretion of sodium (Na^+), chloride (Cl^-), potassium (K^+), bicarbonate (HCO_3^-), and water (H_2O) out of the cell into the intestinal lumen.

Figure 99-1: Mechanism of action of cholera toxin.

100

Vibrio cholerae: Part Two

Murray: *Medical Microbiology*, 8th Edition, Chapter 26

STRUCTURE

–

Gram-negative, comma-shaped rod

LAB ID

Oxidase positive

VIRULENCE FACTORS

Cholera toxin (A-B type), single polar flagellum

DISEASES

Cholera, watery diarrhea

EPIDEMIOLOGY

- Contaminated water and shellfish; spread in contaminated food and water; increased prevalence during warm months
- Pandemics by O1 serotype (El Tor biotype)

PREVENTION

Improved hygiene

TREATMENT

Fluid and electrolytes; doxycycline; trimethoprim-sulfamethoxazole

Vibrio cholerae: Part Two

OTHER VIBRIOS

V. parahaemolyticus
Explosive, crampy diarrhea associated with shellfish

V. vulnificus
Contaminated seawater infections of wound progressing to vesicles, bullae, tissue necrosis, and septicemia with high mortality rate

101

Miscellaneous Gram-Negative Bacteria

Murray: *Medical Microbiology*, 8th Edition, Chapter 29

Bartonella henselae

- Cat-scratch fever: transmitted by cats. Regional adenopathy of draining lymph nodes
- Gram-negative bacillus
- Hard to grow
- Treat with erythromycin or tetracycline

Capnocytophaga

- Dog bites
- Filamentous gram-negative bacillus
- Sepsis in patients with splenectomy or hepatic dysfunction (cirrhosis)
- Treat with broad-spectrum cephalosporins, fluoroquinolones, etc

Calymmatobacterium

- Granuloma inguinale: granulomas of the genitalia and inguinal area
- Encapsulated appearance in tissue
- Cannot be grown in culture
- Donovan bodies in mononuclear phagocytes
- Treat with tetracycline, erythromycin, or trimethoprim-sulfamethoxazole (TMP-SMX)

Gardnerella vaginalis

- Genitourinary infections: bacterial vaginosis
- Gram variable
- Presence of clue cells (epithelial cells covered with bacteria in vaginal discharge): fishy smell after potassium hydroxide addition to vaginal discharge
- Sexually transmitted disease
- Treat with metronidazole, clindamycin

Miscellaneous Gram-Negative Bacteria

Moraxella catarrhalis
- Otitis media in children; sinusitis, bronchitis, bronchopneumonia in elderly
- Gram-negative, diplococci (looks like *Neisseria*)
- Produce β-lactamase
- Treat with cephalosporins, erythromycin (or other macrolides), tetracycline, TMP-SMX

Proteus
- Urinary tract infections, kidney stones
- Gram-negative bacillus, oxidase negative, nonlactose fermenter
- Motile, urease producer, pili (adherence)

Yersinia pestis
- Bubonic plague, pulmonary plague (buboes = swelling)
- Spread by flea bites, contact, inhalation
- Treat with streptomycin, tetracycline, chloramphenicol, TMP-SMX

Y. enterocolitica
- Enterocolitis, 1- to 10-day incubation period, watery diarrhea, fever, and abdominal pain
- Pseudoappendicitis!
- Invasive
- From contaminated food or water, from domesticated animals
- Grows at 4°C

Y. pseudotuberculosis
- Same as *Y. enterocolitica*, only worse!

102

HACEK Organisms: Subacute Endocarditis

Murray: *Medical Microbiology,* 8th Edition, Chapter 19

Subacute endocarditis bacteria if prior heart disease:

- Normal flora of oropharynx
- Small, gram-negative bacteria
- Anaerobes, hard to grow in culture

Haemophilus aphrophilus

- Normal flora of mouth

Actinobacillus actinomycetemcomitans

- Colonize mouth, cause periodontitis, endocarditis, bite wound infections
- Treat with ampicillin

Cardiobacterium hominis

- Normal flora of upper respiratory tract
- Endocarditis correlates with previous dental work
- Treat with penicillin or ampicillin

Eikenella corrodens

- Fastidious anaerobe, eats pits in agar, bleach-like odor
- In bite wounds and fistfight injuries
- Treat with penicillin, ampicillin, fluoroquinolones, but not usual antibiotics for bite wounds

Kingella kingae

- Septic arthritis in children
- Treat with β-lactams, tetracyclines, erythromycin, fluoroquinolones

103 Viral Classification: DNA and RNA

Murray: *Medical Microbiology,* 8th Edition, Chapter 36

Table 103-1: DNA Virus Families

Family	DNA Genome	Other Properties	Clinically Important Members
Parvoviridae	SS, linear	Nonenveloped; small Icosahedral capsid	B19 parvovirus
Papilloma, polyoma	DS, circular	Nonenveloped; small Icosahedral capsid	Human papilloma virus JC, BK polyomavirus
Adenoviridae	DS, linear	Nonenveloped; mid-size Icosadeltahedral capsid Encodes DNA polymerase	Adenovirus
Hepadnaviridae	DS, partially circular	Enveloped; small Replicates genome via RNA intermediate using viral reverse transcriptase	Hepatitis B virus
Herpesviridae	DS, linear	Enveloped; large Icosadeltahedral capsid Encodes DNA polymerase	Herpes simplex virus 1 (HSV-1) Herpes simplex virus 2 (HSV-2) Varicella-zoster virus (VZV) Cytomegalovirus (CMV) Human herpesvirus 6 (HHV-6) Epstein-Barr virus (EBV) Human herpesvirus 8 (HHV-8)
Poxviridae	DS, linear	Enveloped; largest virus (brick shaped) Produces mRNA and replicates genome in cytoplasm using viral enzymes	Molluscum contagiosum virus Vaccinia virus (used in vaccines) Variola (smallpox) virus (now eradicated) Animal pox viruses

DS, Double stranded; *SS,* single stranded.

Table 103-2: RNA Virus Families

Family	RNA Genome	Other Properties	Clinically Important Members
Arenaviridae	(–) SS, circular, segmented	Enveloped; mid-size Helical capsid Carries RDRP in virion	Lymphocytic choriomeningitis virus Lassa fever virus
Bunyaviridae	(–) SS, linear segmented	Enveloped; mid-size Helical capsid Carries RDRP in virion	California encephalitis virus Hantavirus
Caliciviridae	(+) SS, linear	Nonenveloped; small Icosahedral capsid Genome = mRNA	Norwalk virus

Continued

Viral Classification: DNA and RNA

Table 103-2: RNA Virus Families—cont'd

Family	RNA Genome	Other Properties	Clinically Important Members
Coronaviridae	(+) SS, linear	Enveloped; large Genome = mRNA	Coronaviruses SARS, MERS
Filoviridae	(–) SS, linear	Enveloped; mid-size Helical nucleocapsid Carries RDRP in virion	Ebola and Marburg viruses
Flaviviridae	(+) SS, linear	Enveloped; small Icosahedral capsid Genome = mRNA	Dengue virus Hepatitis C virus St. Louis encephalitis virus Yellow fever virus
Orthomyxoviridae	(–) SS, linear, segmented	Enveloped; large Helical nucleocapsid Carries RDRP in virion	Influenza viruses (types A, B, and C)
Paramyxoviridae	(–) SS, linear	Enveloped; large Helical nucleocapsid Carries RDRP in virion	Measles virus Mumps virus Parainfluenza virus Respiratory syncytial virus
Picornaviridae	(+) SS, linear	Nonenveloped; small Icosahedral capsid Genome = mRNA	Coxsackieviruses Echovirus Hepatitis A Poliovirus Rhinoviruses
Reoviridae	(+/–) DS, linear, segmented	Nonenveloped; mid-size Double capsid Carries RDRP in virion	Rotavirus
Retroviridae	(+) SS, linear (2 copies)	Enveloped; mid-size Helical capsid Reverse transcriptase in virion converts genome to cDNA	Human immunodeficiency virus (HIV) Human T-lymphotropic virus (HTLV)
Rhabdoviridae	(–) SS, linear	Enveloped; mid-size, bullet shaped Helical capsid Carries RDRP in virion	Rabies virus
Togaviridae	(+) SS, linear	Enveloped; small Icosahedral capsid Genome = mRNA	Rubella virus Eastern, Western, and Venezuelan equine encephalitis viruses

(+), Identical to mRNA sequence; (–), complementary to mRNA sequence; MERS, Middle East respiratory syndrome; SARS, severe acute respiratory syndrome; SS, single stranded; DS, double stranded; RDRP, RNA-dependent RNA polymerase.

104

Viral Structure and Classification: Part One

Murray: *Medical Microbiology,* 8th Edition, Chapter 36

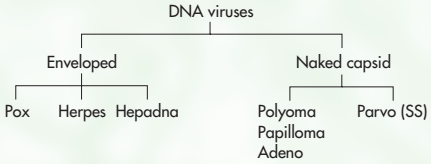


Figure 104-1: DNA viruses and their morphology.

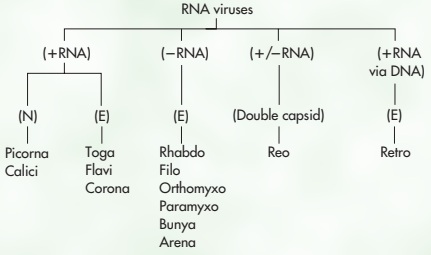


Figure 104-2: RNA viruses, their genome structure, and their morphology.

Table 104-1

DNA Viruses	RNA Viruses
DNA is permanent	RNA is short lived
Replicate in nucleus, except poxvirus	Replicate in cytoplasm, except retroviruses and orthomyxovirus
Genome is infectious (sufficient for replication)	Only (+)RNA virus genome is infectious
Use host RNA polymerase, except poxvirus	Must encode an RNA polymerase
Larger viruses encode DNA polymerase: adenovirus, herpesvirus, poxvirus	All (–)RNA viruses are enveloped and carry polymerase
Puny ***p***arvo-, ***p***olyoma- and ***p***apilloma viruses use cell's DNA polymerase	Segmented RNA viruses can change by reassortment of genome segments

Viral Structure and Classification: Part One

DNA Genome

- Parvovirus: single-stranded (linear) DNA: converted to double-stranded DNA for replication
- Polyomavirus: circular, double-stranded DNA
- Papillomavirus: double-stranded DNA
- Adenovirus: linear, double-stranded DNA with proteins attached to ends
- Herpesvirus: double-stranded DNA
- Poxvirus: linear with fused ends
- Hepadnavirus: incomplete circular, which encodes reverse transcriptase and replicates through RNA intermediate

RNA Genome

- Positive-sense (+)RNA: same sequence as mRNA
  - Translated into polyprotein
  - Replicative intermediate = (–)RNA
- Negative-sense (–)RNA: sequence complementary to mRNA (like photographic negative)
  - Cannot be translated
  - RNA polymerase is carried into cell with the nucleocapsid
  - Individual mRNA transcribed from genome
  - Full-length (+)RNA replicative intermediate transcribed from genome
- Double-stranded (+/–) segmented RNA: reoviruses
  - Double-stranded double capsid
  - Inner capsid shell contains RNA polymerase
  - Negative strand is used to transcribe individual (+)mRNAs
  - (+)mRNAs are enclosed in inner capsid and then used as templates for dsRNA
- Retroviruses: (+)RNA: two copies of genome, two tRNAs, carries reverse transcriptase
  - Generates circular complementary DNA copy (cDNA) on entry
  - Integrates into chromosome and is transcribed and replicated into RNA like a cellular gene

105

Viral Structure and Classification: Part Two

Murray: *Medical Microbiology,* 8th Edition, Chapter 36

KNOWING WHETHER A VIRUS IS NAKED CAPSID OR ENVELOPED ALLOWS PREDICTION OF MANY VIRAL PROPERTIES.

Table 105-1: Viral Structure: Naked Capsid

COMPONENT
Protein
PROPERTIES
Is environmentally stable to the following:
Temperature
Acid
Proteases
Detergents
Drying
Is released from cell by lysis
CONSEQUENCES
Can be spread easily (on fomites, from hand to hand, by dust, by small droplets)
Can dry out and retain infectivity
Can survive the adverse conditions of the gut
Can be resistant to detergents and poor sewage treatment
Antibody may be sufficient for immunoprotection

Table 105-2: Viral Structure: Envelope

COMPONENTS
Membrane
Lipids
Proteins
Glycoproteins
PROPERTIES
Is environmentally labile—is disrupted by the following:
Acid
Detergents
Drying
Heat
Modifies cell membrane during replication
Is released by budding and cell lysis
CONSEQUENCES
Must stay wet
Cannot survive the gastrointestinal tract
Spreads in large droplets, secretions, organ transplants, and blood transfusions
Does not need to kill the cell to spread
May need antibody and cell-mediated immune response for protection and control
Elicits hypersensitivity and inflammation to cause immunopathogenesis

Viral Structure and Classification: Part Two

Capsid Viruses

- Built from individual proteins-subunits-capsomeres-procapsid-capsid
- Cellular receptor binding in capsid valley: picornaviruses
- Binding to capsid fiber protein: adenoviruses, reoviruses

Enveloped Viruses

- Enveloped viruses acquire their envelope by budding from cellular membranes.
- Viruses that bud at the plasma membrane leave the cell without killing the cell.
- Viral glycoproteins are usually present at the cell membrane.
- Viral glycoproteins are viral attachment proteins (VAP).
- Neutralizing antibody is directed against the VAP.

Exceptions

Capsid viruses

- Rhinoviruses are sensitive to acid, unlike other picornaviruses.
- Hepatitis A virus (picorna) disease is nonlytic. Antibody blocks viremia but is controlled by cell-mediated immunity.

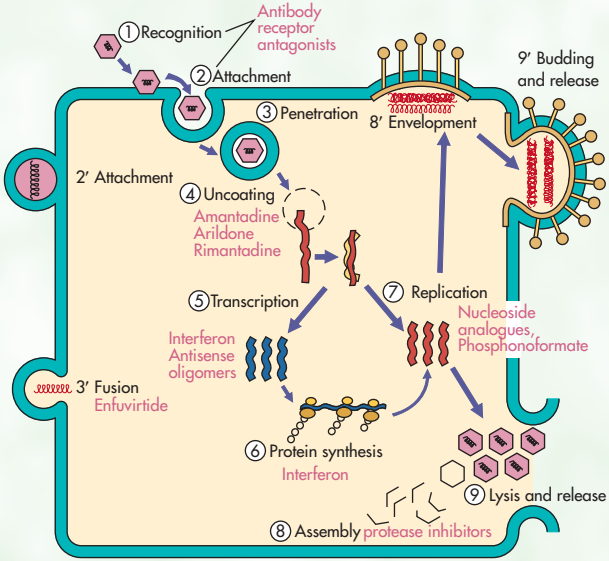
Enveloped viruses

- Hepatitis B and coronaviruses are somewhat resistant to acid and detergent and can pass through the gastrointestinal tract.
- Poxviruses assemble in the cytoplasm instead of budding from a membrane.

106

Viral Replication: Basic Steps

Murray: *Medical Microbiology,* 8th Edition, Chapter 36



Step Inhibited	Antiviral Drugs
1 Recognition 2 Attachment	Receptor antagonists, antiviral antibody
4 Uncoating	Amantadine, rimantadine
5 mRNA synthesis	Interferon, antisense oligomers
6 Protein synthesis	Interferon
7 Genome replication	Nucleos(t)ide analogues (eg, acyclovir, ganciclovir, AZT); non-nucleoside analogues (eg, phosphonoformate)
8 Assembly	Protease inhibitors (eg, saquinavir)

Figure 106-1: General scheme of virus replication and antiviral drugs.

Viral Replication: Basic Steps

Table 106-1: Basic Steps in Viral Replication

Step	Cellular Component	Viral Component
Recognition and attachment	Cellular receptor	Viral attachment protein: glycoprotein or capsid structure
Penetration	Receptor mediated endocytosis Fusion at cell surface Direct penetration of membrane	Viral glycoprotein or capsid protein
Uncoating	Release of genome from capsid	
mRNA synthesis	DNA viruses: cell polymerase, except poxvirus	RNA viruses: viral polymerase, except retrovirus
Early protein synthesis	Cellular ribosomes	Enzymes, polymerase, DNA binding proteins produced
Genome replication	Small DNA viruses: cellular DNA polymerase RNA viruses: viral pol	Large DNA viruses: viral pol
Late protein synthesis	Cellular ribosomes	Structural and other proteins produced: capsid and glycoproteins
Glycoprotein processing	ER, Golgi apparatus, etc	
Assembly		Protease, some viruses
Release		

ER, Endoplasmic reticulum.

107

Viral Replication: mRNA and Genome Replication

Murray: *Medical Microbiology,* 8th Edition, Chapter 36

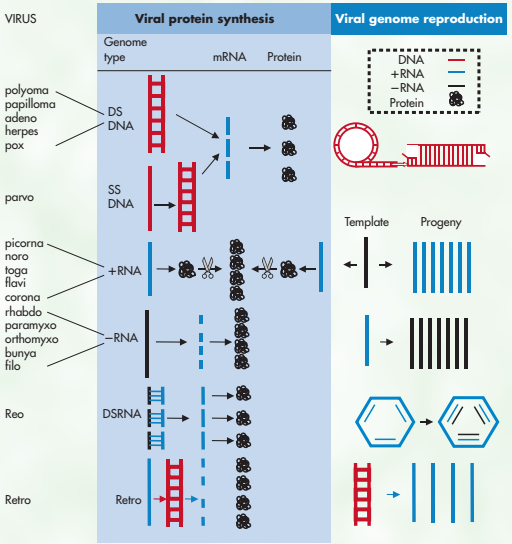


Figure 107-1: Viral macromolecular synthesis steps: The mechanisms of viral mRNA and protein synthesis and genome replication are determined by the structure of the genome. (1) Double-stranded DNA (DS DNA) uses host machinery in the nucleus (except poxviruses) to make mRNA, which is translated by host cell ribosomes into proteins. Replication of viral DNA occurs by semiconservative means, by rolling circle, linear, and in other ways. (2) Single-stranded DNA (SS DNA) is converted into DS DNA and replicates like DS DNA. (3) (+)RNA resembles an mRNA that binds to ribosomes to make a polyprotein that is cleaved into individual proteins. One of the viral proteins is an RNA polymerase that makes a (–)RNA template and then more (+)RNA genome progeny and mRNAs. (4) (–)RNA is transcribed into mRNAs, and a full-length (+)RNA template by an RNA polymerase is carried in the virion. The (+)RNA template is used to make (–)RNA genome progeny. (5) DS RNA acts like (–)RNA. The (–) strands are transcribed into mRNAs by an RNA polymerase in the capsid. (+)RNAs get encapsidated, and (–)RNAs are made in the capsid. (6) Retroviruses are (+)RNA that are converted to DNA (cDNA) by reverse transcriptase carried in the virion. cDNA integrates into the host chromosome, and the host makes mRNAs, proteins, and full-length RNA genome copies. (Note: When reviewing this figure, look at only one genome type at a time; cover the other genome types.)

Viral Replication: mRNA and Genome Replication

RNA Viruses

- (+) Stranded genome = mRNA: immediately translated into polyprotein; (–)RNA template is generated after polymerase is made.
- (–) Stranded genome: polymerase carried in virion makes individual mRNAs → translated into protein; full-length (+) RNA template needed for new genome production.
- (–) Stranded segmented genome (orthomyxovirus): like (–) stranded genome but mRNA and genome synthesized in nucleus.
- (+/–) Double-stranded RNA genome, double capsid virus (reoviruses): polymerase carried in virion transcribes segmented (–)RNA into individual mRNAs; (+)RNAs are sequestered into inner capsid and (+/–)RNA produced.
- Retroviruses ([+]RNA): reverse transcribed into cDNA, integrated into host DNA, transcribed and replicated by host.

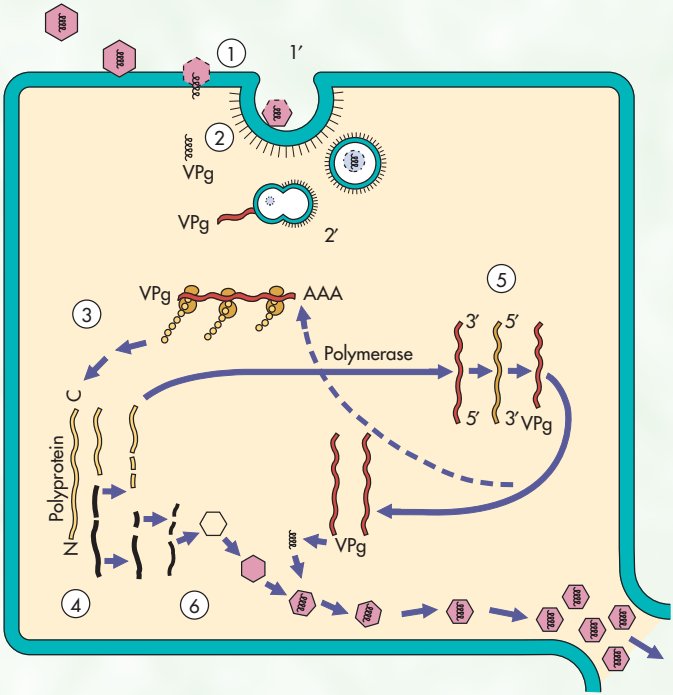
DNA Viruses

- Most DNA viruses: host transcribes DNA → mRNA, cellular or viral polymerase DNA → genome.
- Poxviruses: viral polymerase transcribes DNA → mRNA; viral polymerase replicates DNA → genome.
- Hepadnavirus: host polymerase generates RNA copy; viral reverse transcriptase generates viral DNA genome.

108

Examples for Viral Replication: Picornavirus and Rhabdovirus

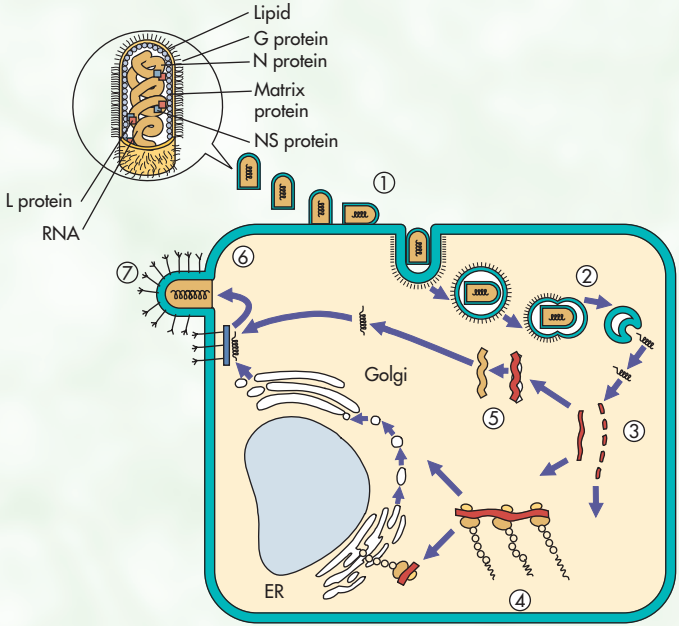
Murray: *Medical Microbiology,* 8th Edition, Chapter 36



PICORNAVIRUS—(+) RNA GENOME, NAKED CAPSID

Figure 108-1: Replication of picornaviruses: a simple (+)RNA virus. (1) Interaction of the picornaviruses with receptors on the cell surface defines the target cell and weakens the capsid. (2) The genome is injected through the virion and across the cell membrane. (2′) Capsids of some viruses disperse in the endosome and virions are released into the cytoplasm. (3) The genome is used as mRNA for protein synthesis. One large polyprotein is translated from the virion genome. (4) Then the polyprotein is proteolytically cleaved into individual proteins, including an RNA-dependent RNA polymerase. (5) The polymerase makes a (–) strand template from the genome and replicates the genome. A protein (VPg) is covalently attached to the 5′ end of the viral genome. (6) The structural proteins associate into the capsid structure, the genome is inserted, and the virions are released on cell lysis.

Examples for Viral Replication: Picornavirus and Rhabdovirus



RHABDOVIRUS—(–)RNA GENOME, ENVELOPED

Figure 108-2: Replication of the rhabdoviruses: a simple, enveloped (–)RNA virus. (1) Rhabdoviruses bind to the cell surface and are (2) endocytosed. The envelope fuses with the endosome vesicle membrane to deliver the nucleocapsid to the cytoplasm. The virion must carry a polymerase, which (3) produces five individual messenger RNAs (mRNAs) and a full-length (+) RNA template. (4) Proteins are translated from the mRNAs, including one glycoprotein (G), which is co-translationally glycosylated in the endoplasmic reticulum (ER), processed in the Golgi apparatus, and delivered to the cell membrane. (5) The genome is replicated from the (+)RNA template, and N, L, and NS proteins associate with the genome to form the nucleocapsid. (6) The matrix protein associates with the G protein–modified membrane, which is followed by assembly of the nucleocapsid. (7) The virus buds from the cell in a bullet-shaped virion.

109

Viral Pathogenesis

Murray: *Medical Microbiology,* 8th Edition, Chapter 37

Parameters Determining Which Disease

- Tissue expression of receptor: Epstein-Barr virus and B cells, human immunodeficiency virus (HIV) and CD4+ cells
- Tissue tropism of virus
- Route of entry: oral, respiratory routes, breaks in the skin, conjunctiva, genital tract, direct injection
- Site: local infection, spread by viremia or via neurons
- Tissue damage: virus action or immunopathology

Incubation Period

Short:

- Disease at site of infection: respiratory viruses; herpes simplex virus (HSV)

Medium:

- Lung-viremic spread-target tissue: measles, varicella zoster virus (VZV)

Long:

- Immune mediated: hepatitis
- Neuronal spread: rabies
- Defective virus: subacute sclerosing panencephalitis (measles variant)
- Cumulative: HIV, Creutzfeldt-Jacob disease

Types of Infection

- Cytolytic: virus kills cell
- Chronic: cell continues to make virus; no immune resolution
- Latent: virus remains dormant until reactivated
- Immortalizing: virus permanently promotes cell growth

Viral Pathogenesis

Evidence of Viral Pathogenesis

- Inclusion bodies
  - Negri bodies (cytoplasmic): rabies
  - Owl's eye nuclear bodies: cytomegalovirus, adenovirus
  - Cowdry type A nuclear bodies: HSV, VZV
  - Nuclear basophilic bodies: adenovirus
  - Acidophilic perinuclear bodies: reovirus
- Cytolysis: inhibition of cell function; disruption of cell structure
- Syncytia: HSV, VZV, HIV, measles, other paramyxoviruses

Immunopathogenesis

- Flulike symptoms: interferon-induced respiratory viruses and viremic viruses
- T-cell inflammation: enveloped viruses, hepatitis viruses
- Immune complex: hepatitis B virus (HBV)
- Hemorrhage: dengue, Ebola, Lassa fever viruses

Viral Escape From Immune Responses

- Cell-cell spread of virions: protects from antibody (HSV, VZV, retrovirus, paramyxovirus)
- Latency in certain cells (HSV, VZV, retrovirus)
- Antigenic shift in viral proteins (influenza A virus, HIV, hepatitis C virus)
- Lymphocyte destruction or injury (HIV killing of CD4 T cells)
- Inhibition of interferon antiviral activity (adenovirus, hepatitis B virus, HSV)
- Inactivation of complement (HSV)
- Viral antigen blocking immune response (HBsAg-HBV)
- Block of MHC I presentation of viral antigenic peptide (HSV, CMV)

110

Viruses and Human Cancer and Testable Topics

Murray: *Medical Microbiology*, 8th Edition, Chapter 38

Table 110-1

Virus	Cancer
EBV	African Burkitt lymphoma: children living in the malarial belt
	Nasopharyngeal carcinoma: common in China and Southeast Asia
	Hodgkin lymphoma: genome may be absent
	X-linked proliferative (Duncan) disease: defect in T-cell control of B-cell outgrowth
	Transplant-associated lymphoproliferative disease: immunosuppression allows EBV-induced B-cell outgrowth
HHV8	Kaposi sarcoma: viral-encoded cytokines promote cell growth: pathognomonic of AIDS
HPV (16, 18, etc)	Cervical carcinoma, laryngeal papilloma
HTLV-1	T-cell leukemia
HBV	Primary hepatocellular carcinoma
HCV	Primary hepatocellular carcinoma

AIDS, Acquired immunodeficiency syndrome; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HHV, human herpesvirus; HPV, human papillomavirus; HTLV, human T-lymphotropic virus.

Mechanisms of Viral Induction of Tumors

- DNA tumor viruses: do *not* replicate in infected tumor cells
  - Prevent activity of normal growth-suppressor proteins (eg, p53 and RB)
  - Act as mitogens to stimulate proliferation
  - Inhibit apoptosis
- RNA tumor viruses: replicate without killing cell
  - Fast-transforming viruses: encode proteins that function in cellular growth promoting pathways
  - Slow-transforming viruses: encode proteins or DNA sequences that promote expression of host growth-promoting genes

Viruses and Human Cancer and Testable Topics

Table 110-2: Testable Viral Properties

Properties	Virus
Replicates in nucleus	Most DNA viruses (not poxviruses) Orthomyxoviruses (influenza), retroviruses
Replicates in cytoplasm	Most RNA viruses Poxviruses
Encodes DNA polymerase	Adenovirus, herpesvirus, poxvirus
Encodes RNA polymerase	RNA viruses (except retroviruses) Poxviruses
Encodes and carries reverse transcriptase	Retroviruses, hepatitis B virus
Associated with human cancers	HTLV, EBV, HHV8, HPV, HBV, HCV
Makes a polyprotein	(+)RNA viruses: picorna-, corona-, calici-, toga-, and flaviviruses
Carries RNA-dependent RNA polymerase	(–)RNA viruses; dsRNA viruses:
Segmented genome: reassortment	Orthomyxoviruses (influenza), reoviruses, also retro-, arena-, and bunyaviruses, arenaviruses and bunyaviruses
Entry by fusion syncytia forming	HSV, VZV, retroviruses, paramyxoviruses

EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HHV, human herpesvirus; HPV, human papillomavirus; HSV, herpes simplex virus; HTLV, human T-cell lymphotropic virus 1; VZV, varicella zoster virus.

111

Antiviral Agents (Non-HIV)

Murray: *Medical Microbiology,* 8th Edition, Chapter 40

Table 111-1: Antiviral Drugs

Drug	Mechanism of Action	Approved Uses
NUCLEOSIDE ANALOGUES		
Acyclovir, penciclovir, valacyclovir, famciclovir	Inhibit viral DNA polymerase by causing premature chain termination; activated by viral thymidine kinase Protein kinase	HSV, VZV
Ganciclovir, valganciclovir	Inhibit viral DNA polymerase; activated by viruses	CMV
Cidofovir	Phosphorylated analogue does not need thymidine kinase	CMV
Iododeoxyuridine, trifluorothymidine	Incorporated into viral genome, leading to errors in replication and transcription	HSV
Ribavirin	Inhibits GTP-requiring enzymes and induces hypermutation of viral genome	RSV, hepatitis C virus
OTHER		
Amantadine, rimantadine	Inhibits uncoating of nucleocapsid by blocking H^+ channel formed by M2 protein and reducing fusion of viral envelope with endosome membrane	Influenza A virus
Oseltamivir (Tamiflu)	Neuraminidase inhibitor	Influenza A and B viruses
Phosphonoformate	Binds to viral DNA polymerase and inhibits its activity; requires no activation	CMV
Interferon α	Induces antiviral state in noninfected cells that interferes with synthesis of viral mRNAs and proteins, thereby limiting spread of infection; also stimulates host immune responses	Hepatitis B and C viruses, HPV

CMV, Cytomegalovirus; GTP, guanosine triphosphate; HPV, human papillomavirus; HSV, herpes simplex virus; RSV, respiratory syncytial virus; VZV, varicella-zoster virus.

Antiviral Agents (Non-HIV)

Mechanisms of Antiviral Resistance (Mutation in Target Protein)

- Mutation in viral thymidine kinase → resistance to acyclovir, penciclovir, and related nucleoside analogues that require activation by viral thymidine kinase to be effective
- Mutation in viral DNA polymerase → resistance to nucleoside or nonnucleoside inhibitors
- Mutation in reverse transcriptase → resistance to azidothymidine (AZT) and other anti-HIV nucleoside analogues
- Mutation in M2 channel protein and hemagglutinin → resistance to amantadine and rimantadine
- Mutation in neuraminidase: resistance to oseltamivir (Tamiflu)

112

Adenovirus: Part One

Family Adenoviridae

Murray: *Medical Microbiology,* 8th Edition, Chapter 42

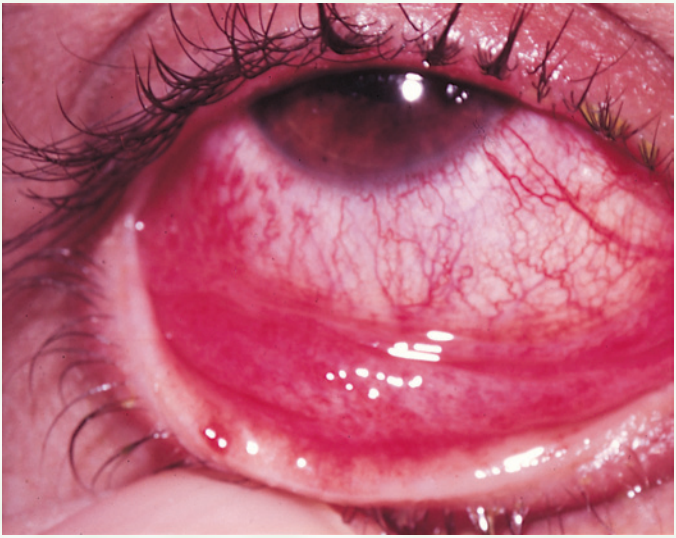


Figure 112-1: Conjunctivitis.

Adenovirus: Part One

Family Adenoviridae

CASE STUDIES

- A 4-year-old boy who returned from a camping trip 2 days ago complains of fever, cough, sore throat, and painful swallowing. A rapid Strep test is negative: **adenovirus pharyngitis**
- Viral diarrhea in an infant, other than rotavirus
- Several recruits at an army base complain of rapid onset of fever, cough, sore throat, runny nose

TRIGGER WORDS

Conjunctivitis, pharyngitis
Dense basophilic intranuclear inclusion bodies = diagnostic
Diarrhea in infant
Infectious genome
Icosadeltahedral capsid with fibers
Poorly chlorinated swimming pools

ESSENTIAL FACTS

- The naked capsid is resistant to detergents and acid and can be transmitted by the fecal-oral route.
- Adenovirus fibers determine the tissue tropism.
- Adenovirus encodes an oncogene that can immortalize hamster cells but not human cells.
- The most common adenoviruses are named with the lowest numbers.
- Attenuated strains are used as DNA vectors and for hybrid virus vaccines.

STUDY BREAK

Strains of adenovirus are responsible for more than 10% of childhood respiratory infections and are the second most important cause of primary gastroenteritis in infants. Modified adenoviruses are common vectors for gene replacement therapy and for vaccines.

113

Adenovirus: Part Two

Family Adenoviridae

Murray: *Medical Microbiology,* 8th Edition, Chapter 42

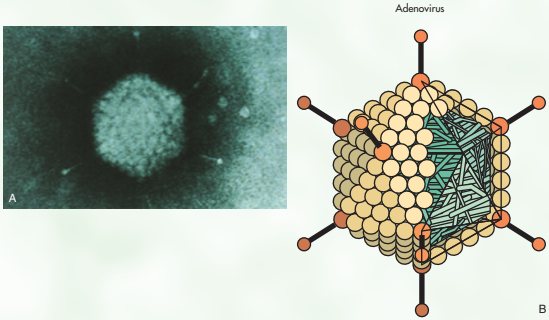


Figure 113-1: Adenovirus structure.

STRUCTURE

- Medium-sized naked icosadeltahedral capsid with fibers at vertices; linear dsDNA with end proteins

REPLICATION

- Fibers determine cell tropism.
- Virus encodes its own polymerase.
- E1a protein binds p53 and E1b protein binds p105RB (cellular growth suppressors) to promote cell growth.

LAB ID

- Dense basophilic intranuclear inclusion body within infected cells
- Polymerase chain reaction

VIRULENCE

- Lytic, latent (lymphoid, adenoid tissue), and transforming (hamster not human) infections

Adenovirus: Part Two

Family Adenoviridae

DISEASES

- **Acute febrile pharyngitis:** fever, sore throat, cough, coryza; common in young children (<3 years)
- **Acute respiratory disease (ARD):** rapid onset of fever, cough, sore throat, rhinorrhea, cervical adenitis; mostly in military recruits
- **Pharyngoconjunctival fever:** fever, sore throat, cough, coryza, conjunctivitis ("pink eye"); common in older children; outbreaks associated with poorly chlorinated swimming pools
- **Atypical pneumonia:** nonproductive cough, pulmonary infiltrates
- **Epidemic keratoconjunctivitis:** inflamed pebbled conjunctivitis and keratitis (adults); associated with irritation of the eye
- **Gastroenteritis:** diarrhea and vomiting in infants and children

EPIDEMIOLOGY

- Resistant to drying and detergents
- *Very contagious;* virions spread via aerosols, fecal-oral route, fomites, close contact, and inadequately chlorinated swimming pools

PREVENTION

- Live oral vaccine (types 4 and 7) for military recruits

TREATMENT

- Supportive care; cidofovir

114

Bunyaviruses and Arenaviruses: Part One

Murray: *Medical Microbiology,* 8th Edition, Chapter 53

CASE STUDY

A 23-year-old man suddenly has headache, nausea, vomiting, fever, and a stiff neck 2 days after a summer hike in the woods in Ohio. His cerebrospinal fluid had normal glucose but contained lymphocytes, not polymorphonuclear leukocytes. The lethargic patient was hospitalized but recovered with no sequelae after 5 days: **La Crosse encephalitis virus**

TRIGGER WORDS

Bunyaviruses

- California encephalitis viruses: *Culex* mosquito, arbovirus, woods, La Crosse virus, encephalitis, meningitis
- Hantaviruses: hemorrhagic, petechiae, ecchymosis, bleeding tissues, rodent feces and urine

Arenaviruses

- Lymphocytic choriomeningitis virus: rodents, flulike symptoms, slums, ribavirin
- Lassa fever: hemorrhagic, rodents, Africa

ESSENTIAL FACTS

- California encephalitis viruses are seasonal and usually do not cause permanent damage.
- Hantaviruses and arenaviruses are spread in rodent urine and feces.

STUDY BREAK

Many of the bunyaviruses have very unusual names based on where they were first discovered. The Sin Nombre hantavirus outbreak and many of the Lassa fever outbreaks in Africa result from overpopulation of rodents moving into human-inhabited areas.

Bunyaviruses and Arenaviruses: Part One

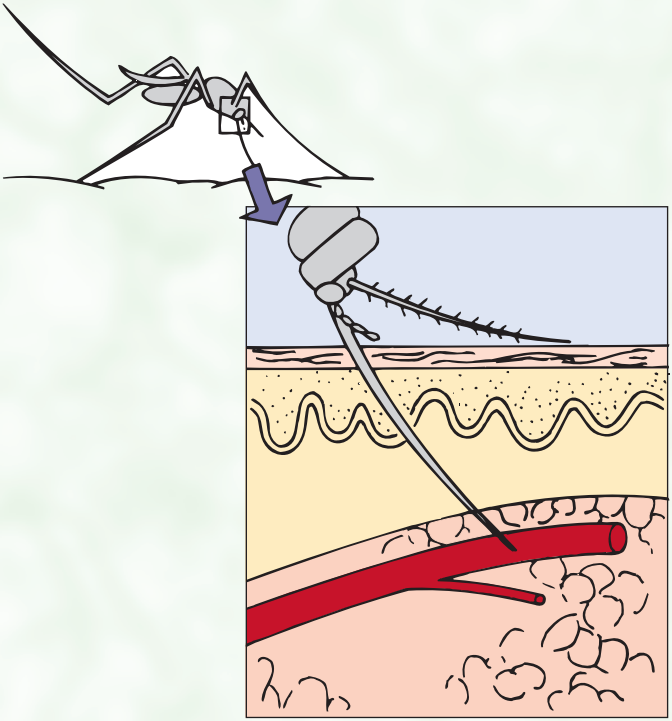


Figure 114-1: Mosquitoes transmit many bunyaviruses.

115

Bunyaviruses and Arenaviruses: Part Two

Murray: *Medical Microbiology*, 8th Edition, Chapter 53

Bunyaviruses

STRUCTURE

Enveloped, medium-sized segmented (–)RNA virus

LAB ID

Serology, reverse transcription polymerase chain reaction (RT-PCR)

DISEASES

Flulike symptoms, encephalitis, hemorrhagic fever

EPIDEMIOLOGY

- California encephalitis viruses: spread by arthropods (mosquitoes)
- Hantaviruses: spread in rodent urine and feces

PREVENTION

Limit exposure to vector

TREATMENT

Supportive

Bunyaviruses and Arenaviruses: Part Two

Arenaviruses

STRUCTURE

Enveloped, (–)RNA, two circular segments, contains captured ribosomes

LAB ID

RT-PCR, serology

DISEASES

Lassa fever; lymphocytic choriomeningitis

EPIDEMIOLOGY

Spread in rodent urine and feces

PREVENTION

Limit exposure to vector

TREATMENT

Ribavirin

116

Coronaviruses

Murray: *Medical Microbiology,* 8th Edition, Chapter 47

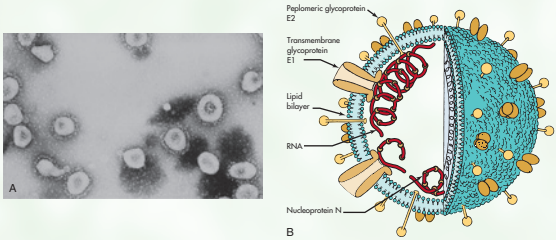


Figure 116-1

CASE STUDY

Adult with common cold

TRIGGER WORDS

Common cold
Severe acute respiratory syndrome (SARS)
Middle East respiratory syndrome (MERS)

ESSENTIAL FACTS

- **Coronaviruses cause 15% of common colds. SARS and MERS are caused by a coronavirus.**
- **Coronaviruses are the exception to the enveloped virus rule and are not inactivated on going through the gastrointestinal tract and can be transmitted by the fecal-oral route.**
- **Unlike other coronaviruses, lethal SARS and MERS can grow at 37°C in the lung.**

STUDY BREAK

The international SARS epidemic can be traced to one person staying in a popular Hong Kong hotel from where it was passed to travelers going to other places, including Toronto. Excellent epidemiology and disease control resulted in the control of the virus.

Coronaviruses

STRUCTURE

- Large, **enveloped** virus, (+)ssRNA genome. Glycoproteins form a halo around the envelope, which protects it from detergents and acid.
- Coronaviruses are relatively resistant to detergents and acids and pass through the gut.
- Replication: early genes are translated from genome [(+)RNA = mRNA], but several individual late mRNAs are transcribed from the (–)RNA template.
- Genome is infectious [(+)RNA = mRNA].

DISEASES

- **Common cold:** coronaviruses are responsible for approximately 15% of upper respiratory tract infections. The disease is similar to that caused by rhinoviruses.
- **SARS and MERS:** high fever (>38°C), chills, rigors, headache, dizziness, malaise, myalgia, cough or breathing difficulty. For SARS, a history of exposure to a person or place associated with SARS within the previous 10 days.

EPIDEMIOLOGY

Spread by respiratory droplets; MERS vector is camels

TREATMENT

Treat common cold symptoms; supportive care for SARS and MERS

MAJOR CAUSES OF THE COMMON COLD

Coronavirus, rhinovirus [picornavirus: (+)ssRNA], adenovirus (dsDNA virus), parainfluenza, influenza, respiratory syncytial virus

117

Herpes Simplex Virus: Part One

Family Herpesviridae

Murray: *Medical Microbiology,* 8th Edition, Chapter 55

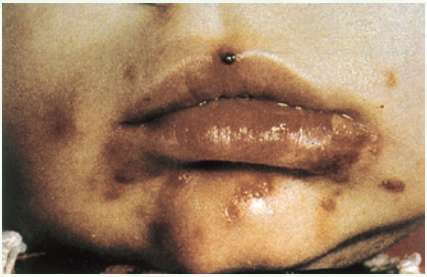


Figure 117-1: Primary HSV infection.

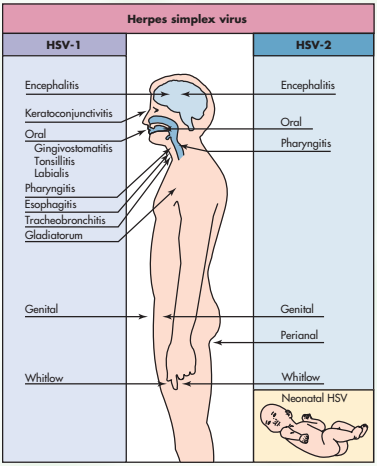


Figure 117-2: Disease syndromes of herpes simplex virus.

Herpes Simplex Virus: Part One

Family Herpesviridae

CASE STUDIES

- A 6-year-old girl with ulcerative rash and vesicles around and in the mouth. Tzanck smear shows multinucleated giant cells and Cowdry type A inclusion bodies: **oral herpes**
- Sexually active woman in mid-20s has ulcerative lesions on the vagina with pain, itching, dysuria, systemic symptoms, and a fever lasting 10 days. Pap smear shows multinucleated giant cells and Cowdry type A inclusion bodies: **vaginal herpes**
- Patient has focal neurologic symptoms and seizures. Magnetic resonance imaging shows destruction of temporal lobe. Erythrocytes are present in the cerebrospinal fluid, and polymerase chain reaction is positive for viral DNA: **encephalitis**
- Dendritic scar and clouding of cornea leading to blindness from recurrence of herpes simplex virus (HSV): **herpetic keratoconjunctivitis**
- Neonate appearing septic and not thriving, with blister on scalp at monitor site progressing to systemic and encephalitic disease: **neonatal HSV**
- Immunosuppressed person with oral and genital recurrence

TRIGGER WORDS

Enveloped, large DNA
Cowdry type A inclusion bodies
Neurotropic
Tzanck smear
Stress-induced recurrence
Syncytia
Multinucleated giant cells
Latent-recurrent

STUDY BREAK

HSV-1 used to be mostly above the waist and HSV-2 below the waist; methods of transmission have blurred the distinction. Everyone has a different stressor to cause recurrence; some may be embarrassing. Ask your friends about theirs.

Ninety percent of the population is infected with HSV-1 in childhood, and 30% of the population acquires HSV-2 through sexual transmission.

118

Herpes Simplex Virus: Part Two

Family Herpesviridae

Murray: *Medical Microbiology,* 8th Edition, Chapter 55

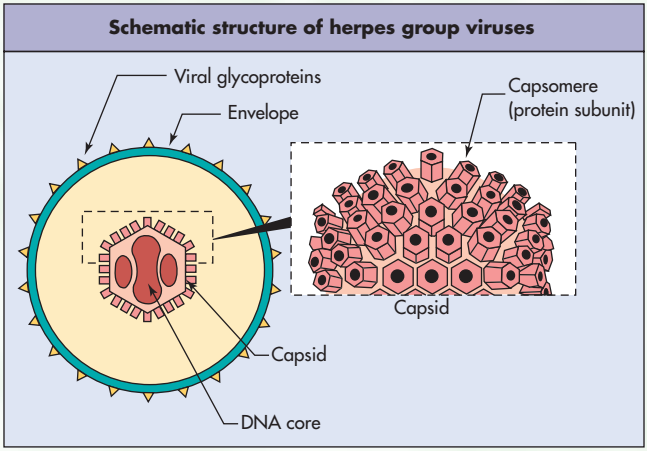


Figure 118-1: General structure of the herpesviruses.

STRUCTURE

Large, enveloped; linear dsDNA genome; icosadeltahedral nucleocapsid

REPLICATION

Binds to receptors on most cells; enters by fusion; three phases of mRNA/protein synthesis [(1) immediate-early = takeover; (2) early = enzymes including viral polymerase, which makes new genomes; (3) late = structural proteins]; assembly of capsid in nucleus; acquisition of envelope in cytoplasm; release by lysis or vesicular transport

Herpes Simplex Virus: Part Two

Family Herpesviridae

LAB ID

- Microscopic exam of cells in vesicle fluid or affected tissue (Tzanck and Pap smear) shows:
  - Rounded cells with extensive cell death
  - Syncytia (multinucleated giant cells)
  - Cowdry type A acidophilic nuclear inclusion bodies
- Tissue culture isolation and classic cytopathologic effect
- Polymerase chain reaction (PCR) or immunofluorescence confirmation
- Diagnosis of encephalitis: PCR to detect herpes simplex virus (HSV) genome in the cerebrospinal fluid

VIRULENCE FACTORS

Neurotropism: thymidine kinase; immune evasion genes; cell-cell transmission to escape antibody; latent recurrent disease latency in neurons with recurrence to the same dermatome

DISEASES

- Herpes labialis and gingivostomatosis: primary—vesicular lesion or asymptomatic; recurrent—milder
- Genital herpes
- Whitlow: fingers
- Encephalitis (not seasonal, like arboviral)
- Keratoconjunctivitis
- Meningitis
- Disseminated infection (compromised cell-mediated immunity and neonates)

EPIDEMIOLOGY

Direct contact with vesicle fluid (4 M's: ***m***ixing and ***m***atching of ***m***ucous ***m***embranes)

PREVENTION

Avoid contact

TREATMENT

Acyclovir, famciclovir, penciclovir, valacyclovir

119

Cytomegalovirus: Part One

Family Herpesviridae

Murray: *Medical Microbiology,* 8th Edition, Chapter 55

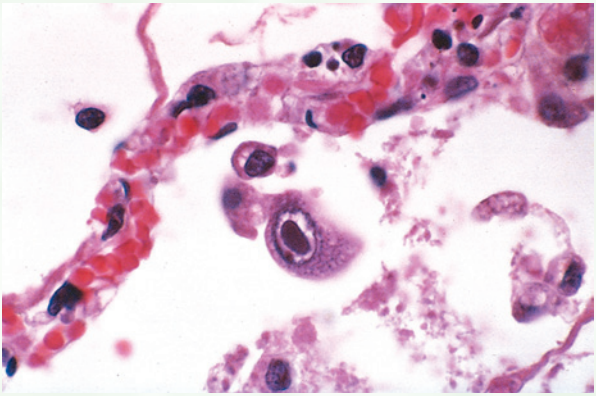


Figure 119-1: Owl's eye inclusion body.

Cytomegalovirus: Part One

Family Herpesviridae

CASE STUDIES

- A newborn exhibits microcephaly, intracerebral calcifications, hepatosplenomegaly, and a petechial rash. The mother had heterophile antibody–negative mononucleosis-like symptoms (**cytomegalovirus** [CMV] **mononucleosis**) during the third trimester of pregnancy: **congenital CMV infection**
- Patient with acquired immunodeficiency syndrome (AIDS) has retinitis

TRIGGER WORDS

Large owl's eye nuclear inclusion body
Swollen (megalo) cells
Opportunistic disease
Mononucleosis-like syndrome
Congenital CMV
Intracerebral calcifications
Microcephaly

ESSENTIAL FACTS

- Opportunistic disease; it rarely causes disease except in T cell–deficient patients (eg, AIDS).
- The most common infectious cause of congenital disease, especially serious if the mother was seronegative before infection.
- One of the six major congenitally acquired diseases (TORCH).
- Infection of epithelial cells and T cells causes it to be released into most secretions, blood, and semen.

STUDY BREAK

CMV is the perfect parasite. It infects and remains latent in a normal host but replicates and causes disease in an immunosuppressed host.

120

Cytomegalovirus: Part Two—HHV6

Family Herpesviridae

Murray: *Medical Microbiology*, 8th Edition, Chapter 55

Cytomegalovirus (CMV)

STRUCTURE

Large, enveloped, linear dsDNA genome with icosadeltahedral nucleocapsid

REPLICATION

Binds to receptors on most cells; enters by fusion; three phases of mRNA/protein synthesis [(1) immediate: early takeover; (2) early: viral polymerase makes new genomes; (3) late: structural proteins]; assembly of capsid in nucleus; acquisition of envelope in cytoplasm; release by lysis or cell-cell bridges.

LAB ID

- Congenital infection: anti-CMV antibody in cord blood suggests congenital transmission.
- Cytopathic changes in infected cells:
  - Large owl's eye nuclear inclusion body
  - Swollen (cyto*mega*lic) cells
- Virus isolation and cell culture in shell vial
- Immunofluorescence
- Polymerase chain reaction

DISEASES

- Asymptomatic infection in 80% of the worldwide population.
- Congenital infection: transmitted to fetus by placental route. Symptoms include hepatosplenomegaly, rash, chorioretinitis, deafness, microcephaly, and central nervous system calcifications.

Cytomegalovirus: Part Two—HHV6

Family Herpesviridae

- Infectious mononucleosis-like disease: older children and young adults (heterophile antibody negative).
- Opportunistic diseases in immunocompromised people (eg, acquired immunodeficiency syndrome): viremia, retinitis, colitis, pneumonitis, esophagitis; pneumonia in transplant recipients.

EPIDEMIOLOGY

Congenital: placental fetal transmission. Adults: spread via saliva, semen, blood, transfusion, or kidney transplantation.

PREVENTION

Only use seronegative donors for blood and kidney transplantation, especially in children.

TREATMENT

Ganciclovir, valganciclovir, foscarnet, cidofovir

Herpes Simplex Virus 6 (HSV-6)

CASE STUDY

Child with extremely **high fever** (103°F to 106°F) develops a maculopapular **rash**, due to an immune response, that appears on the trunk and then spreads to the other areas of the body, disappearing after 24 to 48 hours.

DISEASE

Roseola (exanthem subitum; sixth disease)

121

Epstein-Barr Virus (EBV): Part One

Family Herpesviridae

Murray: *Medical Microbiology,* 8th Edition, Chapter 43

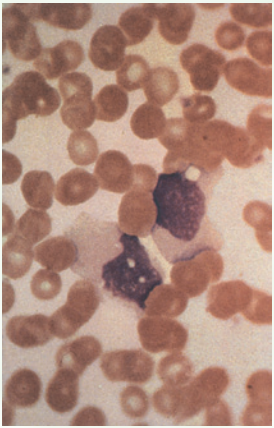


Figure 121-1: Atypical lymphocytes (Downey cell) in infectious mononucleosis.

CASE STUDIES

- A 21-year-old college student develops severe malaise, fatigue, fever, swollen glands, and pharyngitis. After treatment with ampicillin, a rash appears. Atypical lymphocytes are present in blood smear and heterophile antibody in serum: **heterophile antibody–positive infectious mononucleosis**
- A 45-year-old adult on immunosuppressive therapy has Hodgkin lymphoma. Lymphoma goes away with reduction of immunosuppressive therapy: **EBV-associated lymphoma**
- A 5-year-old child in New York has a relatively normal sore throat and fever: **EBV disease in a child**
- A 5-year-old child in the malarial belt of Africa has a poorly differentiated monoclonal B-cell lymphoma of the jaw: **EBV-associated African Burkitt lymphoma**
- An AIDS patient has white lesions coating tongue that are EBV antigen positive: **hairy oral leukoplakia**

Epstein-Barr Virus (EBV): Part One

Family Herpesviridae

TRIGGER WORDS

Fatigue
Pharyngitis
Heterophile antibody
Atypical lymphocytes
Rash
Monospot test
Ampicillin-induced rash

ESSENTIAL FACTS

- Epstein-**B(-cell)**arr virus.
- Targets and is the perfect parasite for the B cell.
- EBV disease in a child is mild but is **bolder** as we get **older**, causing mononucleosis.
- Mononucleosis is a war between lymphocytes, ***and T cells proliferate*** because of the constant contact with infected B cells.
- Can immortalize B cells, but the T cells increase during mononucleosis and are the atypical lymphocyte.
- Heterophile antibody recognizes Paul-Bunnell antigen on sheep, horse, and bovine erythrocytes but not guinea pig kidney cells.

STUDY BREAK

EBV is transmitted by sharing saliva. In young adults the common mode of transmission is by kissing ("kissing disease"). To prevent this disease, **you decide whether it is worth the risk.** (Keep in mind that the virus is ubiquitous.)

122

Epstein-Barr Virus (EBV): Part Two—HHV8

Family Herpesviridae

Murray: *Medical Microbiology,* 8th Edition, Chapter 43

STRUCTURE

Large, enveloped, linear, dsDNA in icosadeltahedral nucleocapsid

REPLICATION

- EBV binds to CD21 (C3d complement receptor) on B cells and some epithelial cells.
- Entry by fusion; three phases of mRNA/protein synthesis [(1) immediate: early takeover; enzymes including early viral polymerase, which makes new genomes; (3) late: structural proteins]; assembly of capsid in nucleus; acquisition of envelope in cytoplasm; release by lysis or vesicular transport.
- Latency occurs in memory B cells, replicates in activated B cells, stimulates growth of follicular B cells.

LAB ID

- Complete blood count: increased white blood cells with atypical lymphocytes (Downey cells)
- Monospot test or enzyme-lined immunosorbent assay: heterophile antibody detection (immunoglobulin M response to Paul-Bunnell antigen on horse red blood cells)
- Epstein-Barr nuclear antigen (EBNA): an early marker *inside* infected cells, but *antibodies to EBNA* are detected *after* resolution!
- Antibodies to early antigen (EA) and viral capsid antigen (VCA) but not EBNA = active infection
- Antibody to EBNA = resolution

VIRULENCE FACTORS

- Lymphotropic
- EBV replicates in active B cells and is latent in resting B cells.
- Nonproductive infection of B cells can induce their proliferation. Stimulation of B cells causes production of heterophile antibody. Immortalizing of B cells with malaria cofactor associated with Burkitt lymphoma.

Epstein-Barr Virus (EBV): Part Two—HHV8

Family Herpesviridae

- T cells control and resolve EBV infection and virus-induced cell proliferation.

DISEASES

- Infectious mononucleosis: fever, malaise, **fatigue**, chills, nausea, vomiting, **sore throat**, and enlarged lymph nodes and spleen. Rash may be present. Takes 2 to 4 weeks to resolve, but fatigue persists for several months.
- Burkitt lymphoma and nasopharyngeal carcinoma.
- Hairy oral leukoplakia (ie, raised, corrugated white lesion in mouth [tongue]), especially in people with acquired immunodeficiency syndrome (AIDS).
- B-cell lymphoma in AIDS and immunosuppressed patients.

EPIDEMIOLOGY

- Significant disease in adolescents and young adults; mild disease in children
- Transmission by **saliva** (child-to-child in daycare setting and by kissing in young adults)
- Asymptomatic shedding!

PREVENTION

Wash hands and avoid saliva sharing (eg, kissing, sharing toothbrush, water bottles)

TREATMENT

Symptomatic; massive spleen enlargement; patients should avoid contact sports to prevent splenic rupture.

Human Herpesvirus 8 (Kaposi Sarcoma Herpesvirus)

Lymphotropic: Kaposi sarcoma primarily affects patients with AIDS. Skin lesions are red to purple plaques or nodules and are found all over the body. In aggressive cases lymph nodes, lungs, and gastrointestinal tract may also be involved.

123

Varicella-Zoster Virus (VZV): Part One

Family Herpesviridae

Murray: *Medical Microbiology,* 8th Edition, Chapter 55

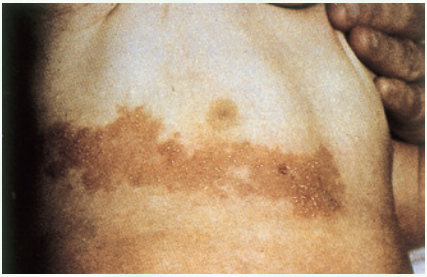


Figure 123-1: Zoster.

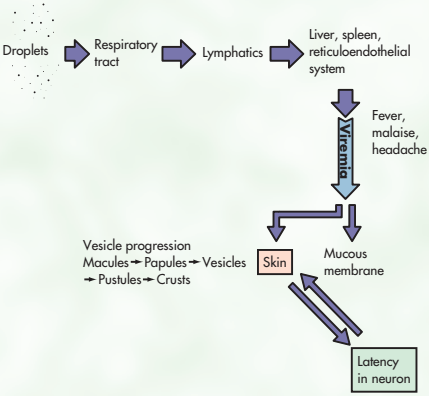


Figure 123-2: Course of VZV disease.

Varicella-Zoster Virus (VZV): Part One

Family Herpesviridae

CASE STUDIES

- A 5-year-old girl develops a fever and maculopapular rash on her abdomen 2 weeks after exposure on a school trip. Successive crops of lesions appear for 3 to 5 days, and the rash spreads peripherally: **varicella (chickenpox)**
- An adult complains of fever and malaise for 2 days and then develops painful vesicular lesions on the chest and back in a linear pattern along the ribs. The lesions do not cross the patient's midline. There are no other rashes. The patient has severe pain (postherpetic neuralgia) for a long time after the lesions resolve: **zoster (shingles)**

TRIGGER WORDS

Crops of vesicular lesions
All stages of lesions at once
Vesicles, latency
Multinucleated giant cells (syncytia) and Cowdry type A nuclear inclusion bodies
Neurotropic
Thymidine kinase
Shingles
Chickenpox

ESSENTIAL FACT

VZV is most similar to herpesvirus but is different.

STUDY BREAK

The term "chickenpox" is a variation of chick-pea pox, which describes the vesicular lesion. As Dr. Marty Myers says, imagine if we used the alternate name "garbanzo pox."

124

Varicella-Zoster Virus (VZV): Part Two

Family Herpesviridae

Murray: *Medical Microbiology*, 8th Edition, Chapter 55

STRUCTURE

Large, enveloped, linear dsDNA genome; icosadeltahedral nucleocapsid; detergent sensitive

LAB ID

- Clinical picture
- **Multinucleated giant cells** (syncytia) and **Cowdry type A nuclear inclusion bodies** are present in scrapings of vesicles; immunofluorescence, polymerase chain reaction, rarely cultured.

VIRULENCE FACTORS

Thymidine kinase facilitates growth in neurons; acquired from aerosols in lung and spreads by viremia; reactivation of latent VZV in neurons causes zoster.

DISEASES

Chickenpox

Ten to 14 days after exposure (maximum, 90 days), symptoms of fever, malaise, and headache appear, followed by a rash starting on the trunk and spreading peripherally. The lesions come in crops and progress from macule to papule to vesicle to pustule to crusts.

- Children: chickenpox, self-limiting; adults: pneumonia and rash, more severe; neonates and immunocompromised people: life threatening
- Different stages of the lesion can be seen at the same time (unlike poxvirus)
- Dewdrops on a rose petal: thin-walled vesicle on a maculopapular base is the hallmark of chickenpox

Varicella-Zoster Virus (VZV): Part Two

Family Herpesviridae

Shingles

Reactivation of latent virus often years after primary infection. Pain and tenderness followed by vesicles appearing in crops along the involved dermatome. Vesicles clear in 2 weeks, but adults can have postherpetic pain along the dermatome for a long duration.

EPIDEMIOLOGY

- Respiratory spread before the onset of symptoms
- Contact with lesions

PREVENTION

- Live attenuated varicella vaccine given after 1 year of age and for nonimmune adults
- Stronger vaccine for >60 years of age to prevent zoster
- VZV immune globulin (VZIg) for immunocompromised children who have been exposed

TREATMENT

- Antiviral drugs for shingles and immunocompromised people with chickenpox
- Nucleotide analogues: acyclovir, famciclovir, valacyclovir
  - Activated by thymidine kinase
  - Target DNA polymerase

Table 124-1: Comparison of Herpes Simplex Virus (HSV) and VZV

Properties	HSV	VZV
Dissemination	Contact	Aerosol and contact
Spread in the body	Local and enervating neuron	Lung, viremias, tissue, neurons
Neurotropic	+	+
Thymidine kinase	+	+
Antiviral drugs	+	+
Vaccine	NO	YES: live attenuated
Passive immunization	NO	YES: **VZIg**
Cell-mediated immune response	IMPORTANT	IMPORTANT
Antibody	NOT REQUIRED	IMPORTANT
Recurrence	Local, benign, stress induced	Dermatomal, painful, induced by loss of immunity

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Filoviridae: Ebola and Marburg Hemorrhagic Fever Viruses

Murray: *Medical Microbiology,* 8th Edition, Chapter 50

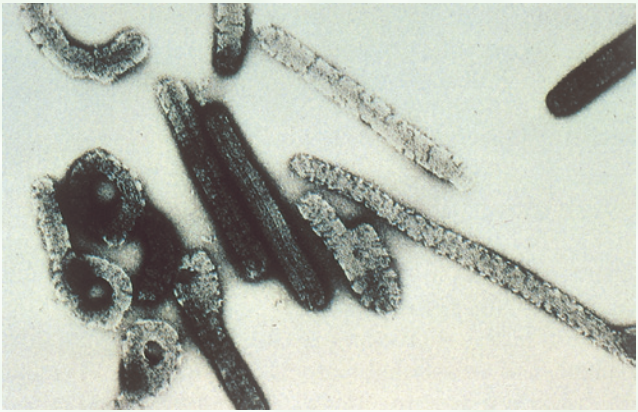

Figure 125-1: Electron micrograph of the Ebola virus.

Filoviridae: Ebola and Marburg Hemorrhagic Fever Viruses

CASE STUDY

A 33-year-old man initially presents to a clinic in Africa with flulike symptoms such as headache and myalgia. Within a few days he complains of nausea, vomiting blood (hematemesis), bloody diarrhea, fever of 40°C, and severe abdominal pain. The man dies the next day.

TRIGGER WORDS

African hemorrhagic fever
Quick fatal progression

ESSENTIAL FACTS

Ebola virus is so lethal that it often kills its population before it can spread to another site; this limits an outbreak.

STRUCTURE

Enveloped, linear (–)ssRNA genome; filament like

DISEASES

Hemorrhagic fever: extensive tissue necrosis; often fatal

EPIDEMIOLOGY

Monkeys to humans and also human-to-human through infected body fluids

PREVENTION

None: experimental vaccines available

TREATMENT

None

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Hepatitis A and E: Part One

Murray: *Medical Microbiology,* 8th Edition, Chapter 55

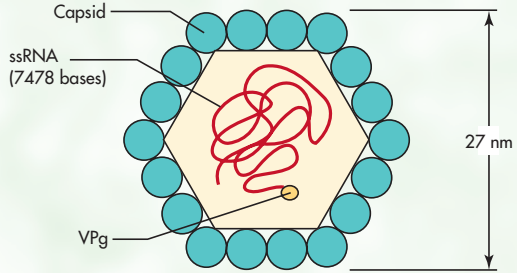

Figure 126-1: The picornavirus structure of hepatitis A virus. **VPg,** *Genome-linked protein.*

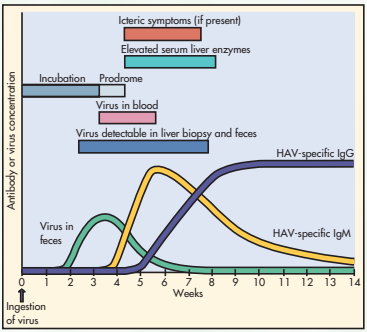

Figure 126-2: The course of hepatitis A virus (HAV) infection. **Ig,** *Immunoglobulin.*

Hepatitis A and E: Part One

CASE STUDIES

- A 36-year-old father of a 3-year-old child woke up with fever, fatigue, nausea, abdominal pain, and no appetite. Jaundice was noted 4 days later. Other adults from the child's daycare center had similar symptoms: **hepatitis A virus infection**
- A pregnant woman in Mexico has symptoms similar to those described above. The woman died: **hepatitis E virus infection**

TRIGGER WORDS

Fecal-oral spread
Daycare center
Shellfish
Acute, sudden-onset hepatitis
Foodborne

ESSENTIAL FACTS

- Hepatitis A is a picornavirus.
- Both hepatitis A and E are naked capsid viruses; hence fecal-oral spread.
- Hepatitis A is usually benign and self-limiting.
- Hepatitis E is lethal 20% of the time for pregnant women.

STUDY BREAK

The hepatitis A virus vaccine in the United States is an inactivated vaccine, but in China it is a live vaccine developed after an epidemic in Shanghai affected 300,000 people as a result of eating clams from a river contaminated with feces.

STRUCTURE

Hepatitis A (HAV) and E (HEV): small, naked icosahedral capsid, (+)ssRNA genome

LAB ID

- Immunoglobulin (Ig) M or IgG antibodies to HAV or HEV; polymerase chain reaction
- IgM = acute infection; IgG = past infection, lifelong immunity

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Hepatitis A and E: Part Two

Murray: *Medical Microbiology,* 8th Edition, Chapter 55

PATHOGENESIS

Following ingestion, virus replicates in the gastrointestinal tract, then viremia spreads it to the liver, where it replicates in the hepatocytes. Virions are released into the bile and shed into the stool 10 days before symptoms appear and for long after. Disease manifestations result from host immune responses.

DISEASES

Hepatitis A

Acute hepatitis with sudden onset, usually self-limiting, a benign infection. Acute disease occurs most often in school-aged children and young adults. Young children are usually asymptomatic (source of spread), with 1 in 100 children having complications.

Hepatitis E

Hepatitis E has a high mortality rate for pregnant women.

EPIDEMIOLOGY

- Fecal-oral spread
- Shellfish (filter feeders)
- Daycare centers
- Asymptomatic shedding

PREVENTION

- Chlorine treatment of water and sewage, good hygiene, avoid contaminated food and water (especially uncooked shellfish)
- Inactivated HAV vaccine

TREATMENT

HAV: passive immunization with immunoglobulin

Hepatitis A and E: Part Two

STUDY BREAK

Everything You Want to Know About Hepatitis (in the style of Dr. Seuss)

Hepatitis A, B, C
Hepatitis D, E, G
Liver is the target
But immune response hurts me
Liver suffers from A to G

Eat the virus, it won't stay
E and A go away
Poop, water, shellfish, dot dot A
That's the acute virus that goes away
Pregnant woman fears the E
It is deadly but not for me

B and C and also D
Blood, tissue, and semen can carry the three
B and C stays with me
PHC with C and B
For the baby, chronic B
HBsAg you will see

Anti-HBs no more sick
Vaccines do this, that's the trick

Treat the RT for the B
Immunize for A or B
Risky business A through G
Yellow eyes you will see

128

Hepatitis B: Part One

Hepadnaviruses

Murray: *Medical Microbiology,* 8th Edition, Chapter 55

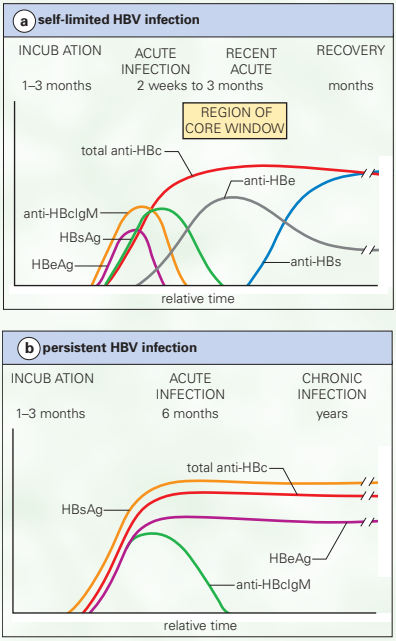

Figure 128-1: ***a,*** *Clinical and virologic course of acute hepatitis B, with recovery;* ***b,*** *clinical and virologic course for chronic hepatitis B.*

CASE STUDIES

- A 43-year-old man was tired, had poor appetite, then later had nausea, abdominal pain, fever, and chills. Still later, he developed jaundice, dark urine, and pale stools: **acute hepatitis B virus (HBV)**
- Child has slight abdominal pain, mild symptoms, and develops chronic HBV hepatitis

Hepatitis B: Part One

Hepadnaviruses

- An IV drug user has hepatitis B disease symptoms as described above but progresses to hepatic necrosis and death: coinfection with HBV and hepatitis D virus (HDV)

TRIGGER WORDS

Serum hepatitis
Chronic
Dane particle
Insidious onset
Hepatitis B surface antigen (HbsAg)

ESSENTIAL FACTS

- Hepatitis B disease is caused by immunopathogenesis.
- Resolution of HBV disease is due to immune response; therefore no pain, no cure (chronic infection).
- HBV is a very small DNA virus but replicates through an RNA intermediate.
- HBV encodes a reverse transcriptase and is susceptible to some of the anti-HIV drugs.
- Liver is a protein factory, and the virus uses it to make lots of HBsAg.
- Antibody to HbsAg cannot be detected until host stops making HbsAg (antibody-HbsAg complex cannot be assayed).

STUDY BREAK

The original HBV vaccine was prepared by purifying HbsAg from human blood. The current vaccine is the first human vaccine developed by genetic engineering and is made in yeast.

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Hepatitis B: Part Two

Hepadnaviruses

Murray: *Medical Microbiology,* 8th Edition, Chapter 55

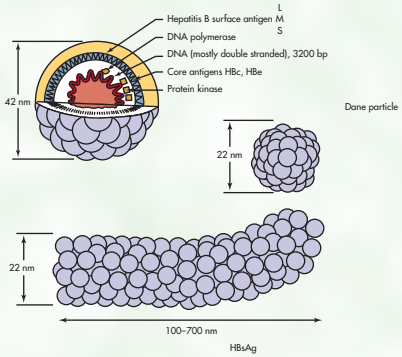

Figure 129-1: Hepatitis B virus (Dane particle) and HBsAg particles.

STRUCTURE

Small DNA, enveloped virus. Virion has incomplete circular double-stranded DNA.

REPLICATION

Host transcribes a longer than genome-length RNA, which is the template for DNA, reverse transcriptase makes DNA, RNA is degraded, genome is packaged into virion before completion of complementary strand. HBe and HBs are released from infected cell into blood.

LAB ID

- **Serology! See Table 129.1 and Fig. 129.1.**
- **HBV logic: If HBsAg, then hepatitis. If HBsAb and antiHBc, then cured. If only anti-HBsAg, then vaccinated. If HBe, then viremia.**

Hepatitis B: Part Two

Hepadnaviruses

Table 129-1: Interpretation of Serologic Markers of Hepatitis B Virus Infection

Serologic Reactivity	Disease State: Early (Presymptomatic)	Disease State: Early Acute	Disease State: Acute	Disease State: Chronic	Disease State: Late Acute	Healthy State: Resolved	Healthy State: Vaccinated
Anti-HBc	–	–	–*	+	+	+	–
Anti-HBe	–	–	–	–	+/–	+/–†	–
Anti-HBs	–	–	–	–	–	+	+
HBeAg	–	+	+	+	–	–	–
HBsAg	+	+	+	+	+	–	–
Infectious virus	+	+	+	+	+	–	–

HBc, Hepatitis B core; HBeAg, hepatitis B early antigen; HBsAg, hepatitis B surface antigen.
*Anti-HBc immunoglobulin M should be present.
†Anti-HBe may be negative after chronic disease.

PATHOGENESIS

Immunopathogenesis causes disease signs!

DISEASES

- Acute hepatitis B virus (HBV)
- Chronic HBV (risk factor for primary hepatocellular carcinoma)

EPIDEMIOLOGY

- Spread in blood, semen, vaginal secretions, mother's milk
- Asymptomatic shedding promotes dissemination

PREVENTION

- Blood supply screened for hepatitis B surface antigen (HBsAg) and anti-HBc
- Subunit vaccine with HBsAg

TREATMENT

- Hepatitis B immunoglobulin
- Antiviral drugs: reverse transcriptase inhibitor (eg, lamivudine); DNA polymerase inhibitors: adefovir dipivoxil, and famciclovir

130 Hepatitis C and D

Murray: *Medical Microbiology,* 8th Edition, Chapter 55

CASE STUDIES

- An IV drug user has hepatitis B disease symptoms but progresses to hepatitic necrosis and death: **coinfection with HBV and HDV**
- A seemingly healthy 45-year-old man has elevated liver enzymes and is positive for hepatitis C virus (HCV). Ten years later he requires a liver transplant due to cirrhosis: **HCV chronic-active disease**

TRIGGER WORDS

Non-A, non-B hepatitis
Chronic

ESSENTIAL FACTS

- Hepatitis C usually causes chronic infection.
- Hepatitis C is a flavivirus.
- Hepatitis D can only replicate in a cell that is also infected with hepatitis B virus (HBV).

Hepatitis C

STRUCTURE

Flavivirus: enveloped (+)RNA virus.

DISEASE

Usually causes chronic infection that can progress after 10 to 20 years to cirrhosis, liver failure, or hepatocellular carcinoma.

EPIDEMIOLOGY

Transmitted like HBV

Hepatitis C and D

PREVENTION

Blood supply is screened by enzyme-linked immunosorbent assay.

TREATMENT

- General antiviral action: Interferon alpha with ribavirin
- HCV-specific drugs: combination of protease (telaprevir, boceprevir, simeprevir), polymerase (sofosbuvir), or NS5A viral phosphoprotein (ledipasvir) inhibitors

Hepatitis D

REPLICATION

Requires HBV for replication

STRUCTURE

RNA in HBV envelope; very small, delta antigen

DISEASES

- Cirrhosis
- Fulminant hepatitis in HBV-infected individual
- Coinfection: longer incubation; superinfection (infection of HBV carrier): shorter incubation

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Human Immunodeficiency Virus: Part One

Family Retrovirus

Murray: *Medical Microbiology,* 8th Edition, Chapter 54

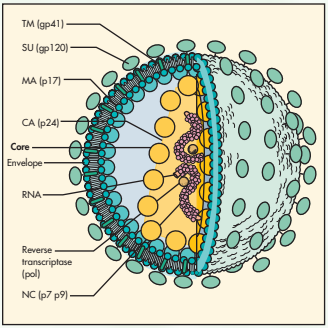

Figure 131-1: Cross-section of HIV.

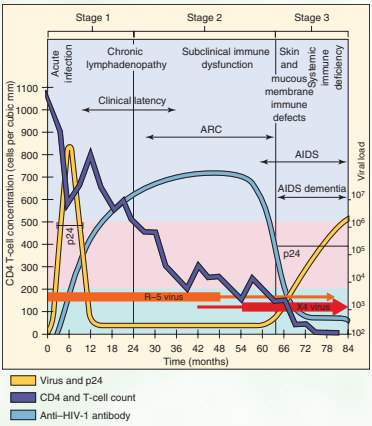

Figure 131-2: Clinical course of HIV infection. Note the serum virus concentration and CD4 count with regard to the course of disease.

Human Immunodeficiency Virus: Part One

Family Retrovirus

CASE STUDY

The patient had a thrush infection *(Candida albicans)* but has otherwise been healthy until recently. The patient presents with a chronic cough, and Gomori silver stain of a bronchoalveolar lavage shows *Pneumocystis jirovecii*. CD4 T-cell count is less than 200 per μL: **acquired immunodeficiency syndrome (AIDS) with *Pneumocystis* pneumonia (PCP).**

TRIGGER WORDS

AIDS
CD4
Chemokine receptor co-receptor
Opportunistic diseases: PCP, Kaposi sarcoma, *C. albicans* thrush, cytomegalovirus retinitis, and pneumonitis

ESSENTIAL FACTS

- HIV is a lentivirus, a subfamily of the Retrovirus family.
- HIV has a very high rate of mutation that alters the virus within an individual and facilitates development of antiviral drug resistance and antigenic change.
- The gp120 glycoprotein is the viral attachment protein, and antibodies to gp120 neutralize the virus.
- HIV infects cells bearing CD4 and a chemokine co-receptor later in the disease.
- Initial infection is macrophage and T-cell tropic (CCR5 co-receptor); later, mutation yields T-cell tropic virus (CXCR4 co-receptor).
- HIV replicates in activated CD4 T cells, and death of infected CD4 T cells results in immunodeficiency.

STUDY BREAK

With the success of highly active antiretrovirus therapy (HAART), AIDS has changed from a lethal to a chronic and manageable disease. However, the drugs are still expensive and have side effects. Like diabetes, it is not a disease one would choose to endure.

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Human Immunodeficiency Virus: Part Two

Family Retrovirus

Murray: *Medical Microbiology*, 8th Edition, Chapter 54

STRUCTURE

(+)ssRNA genome, enveloped. Virion contains two copies of (+) RNA genome (diploid), two tRNAs, reverse transcriptase, integrase, protease, and candy corn–shaped nucleocapsid.

- HIV genome = three basic retrovirus genes (*gag*, *pol*, and *env*) + *tat*, *rev*, *nef*, *vif*, *vpu*, *vpr*
- *gag* = nucleocapsid proteins
- *pol* = enzymes, reverse transcriptase, integrase, and protease
- *env* = envelope glycoproteins gp41 and gp120
  - gp120 = binding to CD4 and co-receptor (infectivity)
  - gp41 = fusion with the cell membrane

LAB ID

- **Enzyme-linked immunosorbent assay (ELISA):** screening test for *antibody* to HIV.
- **Western blot:** confirmatory test for *antibody* to HIV. Both ELISA and Western blot measure serum antibodies and cannot detect early infections prior to production of antibody.
- **Reverse transcription polymerase chain reaction (RT-PCR)/viral load tests:** used for screening to determine course of disease and follow drug therapy success.
- **p24** = nucleocapsid protein from gag = clinical monitor for viral load. Useful early in infection prior to antibody.
- CD4/CD8 T-cell ratio <1 is indicative of AIDS; Loss of both CD4 and CD8 indicates late-stage AIDS.

VIRULENCE FACTORS

- Virus targets cells that control the immune response: dendritic cells and macrophages initiate responses; CD4 T cells (T helper cells) control and develop immune responses causing deficiency.
- Macrophages are a good reservoir for viruses.
- HIV causes syncytia and passes directly from cell to cell to escape antibody.

Human Immunodeficiency Virus: Part Two

Family Retrovirus

DISEASES

AIDS. Lytic and latent infection in T cells. Persistent low-level productive infection in macrophages = reservoir and distribution for virus. CD4 levels <200 per μL. Onset of a classical opportunistic infection (Kaposi sarcoma, *Pneumocystis carinii* pneumonia) or >2 other opportunistic diseases are diagnostic.

EPIDEMIOLOGY

- Spread by blood, semen, and vaginal secretions. Also spread through intrauterine or perinatal transmission.
- Risk factors: sex with many partners; illegal IV drug use; medical personnel in contact with blood.

PREVENTION

Practice safe sex, avoid IV drug use, use clean needles, and avoid needle sticks (use universal precautions).

TREATMENT

- Antiretroviral therapy: RT inhibitors; protease inhibitors. Use of combinations: highly active antiretroviral therapy (HAART)
- Treatment and prophylaxis of opportunistic infections
- *P. jirovecii* pneumonia: trimethoprim-sulfamethoxazole

Table 132-1: Anti-HIV Target Steps

Step in Replication	Antiviral Drugs
Bind to CD4 and chemokine co-receptors (CXCR5 for T cells, CCR5 for macrophages)	Antibody, CCR5 antagonist
Entry by fusion	Fuzeon
Reverse transcription of genome into cDNA	Nucleoside analogues, etc
Genome integration into host chromosome	Raltegravir
RNA synthesized by host polymerase = mRNA and genome	
Protein synthesis	
Assembly at plasma membrane	
Release by budding through membrane	
Protease maturation of capsid within virion	Protease inhibitors

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Anti-HIV Agents

Murray: *Medical Microbiology,* 8th Edition, Chapter 40

Table 133-1: Selected Potential Antiviral Therapies for HIV Infection

Nucleoside analogue reverse transcriptase inhibitors: *prevent incorporation of viral genome into host DNA*
- Azidothymidine (AZT) (Zidovudine)
- Dideoxycytidine (ddC) (Zalcitabine)
- Dideoxyinosine (ddI) (Didanosine)
- d4T (Stavudine)
- 3TC (Lamivudine)
- ABC (Abacavir)
- FTC (Emtricitabine)

Non-nucleoside reverse transcriptase inhibitors: *prevent incorporation of viral genome into host DNA*
- Nevirapine (Viramune)
- Delavirdine (Rescriptor)
- Efavirenz (Sustiva)
- Rilpivirine (Edurant)

Protease inhibitors: *prevent cleavage of gag-pol protein, preventing complete virion formation and production of active reverse transcriptase(-navir)*
- Saquinavir (Invirase/Fortovase)
- Ritonavir (Norvir)
- Indinavir (Crixivan)
- Nelfinavir (Viracept)
- Amprenavir (Agenerase)
- Tipranavir (Aptivus)
- Darunavir (Prezista)

Highly active antiretroviral therapy (HAART) (combination): *harder to generate resistance mutations to multiple antiviral target sites*
- Efavirenz/tenofovir/emtricitabine (Atripla)
- Abacavir/zidovudine/lamivudine (Trizivir)
- Dolutegravir/abacavir/lamivudine (Triumeq)
- Emtricitabine/rilpivirine/tenofovir/disoproxil fumarate (Complera)
- Elvitegravir/cubicstat/tenofovir/emtricitabine (Stribild)

Integrase inhibitor: *prevent integration of cDNA into chromosome*
- Raltegravir

Binding and fusion inhibitors: *prevent entry into cell*
- Maraviroc: CCR5 inhibitor
- Enfuvirtide: fusion inhibitor

Anti-HIV Agents

TOXICITY

Reverse Transcriptase Inhibitors
Peripheral neuropathy, bone marrow suppression, rash (non-nucleosides), lactic acidosis (nucleosides), megaloblastic anemia (azidothymidine [AZT])

Protease Inhibitors
Hyperglycemia, gastrointestinal intolerance, lipid abnormalities, thrombocytopenia (indinavir)

CLINICAL USE

- Highly active antiretroviral therapy (HAART) usually involves combination therapy with both protease inhibitors and reverse transcriptase inhibitors. This therapy is begun when patients have low CD4 counts (<500 cells/μL) or a high viral load.
- During pregnancy, AZT is used to reduce the risk of fetal transmission of HIV.

RESISTANCE

- Mutation in reverse transcriptase
- Mutation in protease

134 Oncogenic Retroviruses: HTLV

Murray: *Medical Microbiology,* 8th Edition, Chapter 54

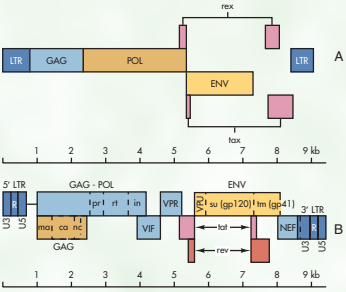

Figure 134-1: Comparison of HTLV and HIV genomes.

CASE STUDY

A 60-year-old Japanese man with skin lesions similar to Sézary syndrome. "Flower cells" (lobulated nuclei) are present in blood: **acute T-cell lymphocytic leukemia (ATLL).**

TRIGGER WORDS

Leukemia
CD4 T cell
Flower cell
Reverse transcriptase

ESSENTIAL FACTS

- Fast oncogenesis: encode viral oncogenes = analogues of cellular growth-stimulating proteins (eg, growth factor receptors, tyrosine kinases, guanosine triphosphate [GTP]-binding proteins, nuclear proteins)
- No human retroviruses encode oncogenes.
- Slow oncogenesis: indirect activation of growth by integration or transactivation of cellular genes (eg, human T-lymphotropic virus [HTLV-1])
- HTLV-1 is a slow oncogenic virus. It does **not** encode an oncogene.
- HTLV-1 induces cell growth by integration of its genome near growth-stimulating genes and then promotes their transcription.

Oncogenic Retroviruses: HTLV

- HTLV-1 turns on the interleukin (IL)-2 and IL-2 receptor genes to stimulate T-cell growth.

STUDY BREAK

Discovery of HTLV-1 occurred in the late 1970s, after Robert Gallo and colleagues figured out how to grow human T cells in cell culture.

STRUCTURE

Diploid (+)RNA genome in icosahedral capsid surrounded by envelope. Virion contains reverse transcriptase, integrase and protease, and two tRNAs.

REPLICATION

- Binds to CD4 (like HIV)
- Enters by fusion
- Reverse transcribes genome into cDNA
- Integrates genome into host chromosome
- RNA synthesized by host polymerase = mRNA and genome

VIRULENCE FACTORS

T-cell target; integration oncogenesis; stimulation of T-cell growth; long incubation period

DISEASES

- Adult T-cell leukemia/lymphoma
- HTLV-1–associated myelopathy: tropical spastic paraparesis (nononcogenic)

EPIDEMIOLOGY

- Transmitted and acquired like HIV! Also transmitted through breast milk.
- Endemic in areas of the Caribbean, southeastern United States, and Japan.

PREVENTION/TREATMENT

Screening of blood supply/treat symptoms

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Parainfluenza, Respiratory Syncytial Virus, and Metapneumovirus

Family Paramyxovirus

Murray: *Medical Microbiology,* 8th Edition, Chapter 48

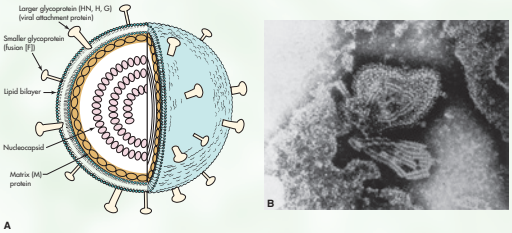

Figure 135-1

CASE STUDIES

- A 2-year-old child coughs like a barking seal, has a sore throat, fever, and a hoarse voice, with a high-pitched noise on inhalation and difficulty breathing: **croup (parainfluenza virus)**
- Infant with bronchiolitis has a low-grade fever, rapid heart rate, rapid breathing, and expiratory wheezing.

TRIGGER WORDS

Parainfluenza virus: croup, barking seal, respiratory stridor, pneumonia
Respiratory syncytial virus (RSV): infant, bronchiolitis

ESSENTIAL FACTS

- Paramyxoviruses are the most common cause of respiratory infection in children. All have one serotype *except* parainfluenza virus, which has four serotypes.
- Parainfluenza, RSV, and metapneumoviruses cause common colds and more serious outcomes.
- Virus is enveloped with fusion protein and can cause syncytia in cell culture.

Parainfluenza, Respiratory Syncytial Virus, and Metapneumovirus

Family Paramyxovirus

STRUCTURE

Enveloped; (–)ssRNA genome, large, glycoproteins mediate interaction and fusion with target cell

LAB ID

Syncytia can be seen in infected cells; enzyme-linked immunosorbent assay or reverse transcription polymerase chain reaction

DISEASES

Common cold, pneumonia, croup (parainfluenza), bronchiolitis (RSV)

EPIDEMIOLOGY

Respiratory, direct person-to-person, and fomites (inanimate objects) very contagious. Only infects humans. Contagious period begins before onset of symptoms = asymptomatic shedding. Infants and children at highest risk.

TREATMENT

For high-risk infants with RSV, aerosolized ribavirin, injected humanized anti-RSV monoclonal antibody (Synagis) or anti-RSV immune globulin (RespiGam).

STUDY BREAK

Metapneumovirus, which is related to RSV, is a common cause of respiratory infections but was not discovered until after 2000, when special tissue culture and genomic techniques were used. Parainfluenza, RSV, and metapneumovirus are common causes of the common cold.

136

Measles: Part One

Murray: *Medical Microbiology,* 8th Edition, Chapter 48

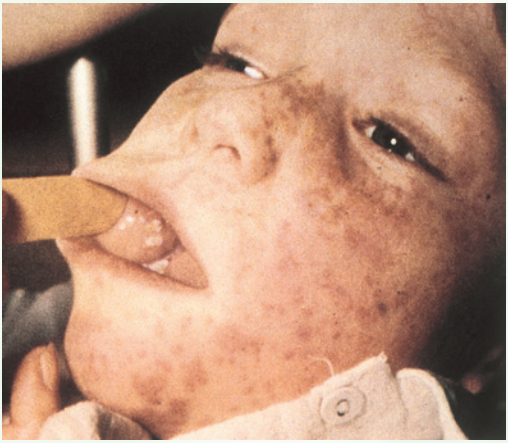

Figure 136-1: Child with measles: Note Koplik's spots, which usually precede but can be present with the rash.

CASE STUDY

A 10-year-old boy develops a high fever with **cough, coryza** (runny nose), and **conjunctivitis (the 3 C's)** and is sensitive to bright lights. After 48 hours, white vesicles are seen in his mouth, followed by a maculopapular rash beginning on the face and spreading over the trunk.

TRIGGER WORDS

Koplik's spots (blue-gray spots in mouth) = diagnostic
Prodrome: 3 C's + photophobia and high fever, then **rash**

Measles: Part One

ESSENTIAL FACTS

Measles (rubeola): Paramyxovirus family. **Complications:**

- **Secondary bacterial infections** such as pneumonia = 60% of deaths (includes the rare **giant cell pneumonia** in children without cell-mediated immunity)
- Lethal infection if undernourished, especially those deficient in vitamin A
- **Acute postinfectious encephalitis** = autoimmune demyelination
- **SSPE** (subacute sclerosing panencephalitis): Mutant defective virus causes lethal changes in personality, behavior, memory, myoclonic jerks, blindness, and spasticity. Onset occurs many months or years after measles. Very rare occurrence
- **German measles is rubella, a togavirus.**

STUDY BREAK

Measles remains a major killer in countries where vaccinations are not available. A killed vaccine actually made things worse because the immune response exacerbated the disease and caused *atypical measles*. Infants remain susceptible to serious measles disease because they cannot be immunized until after age 1 year.

137

Measles: Part Two

Murray: Medical Microbiology, 8th Edition, Chapter 48

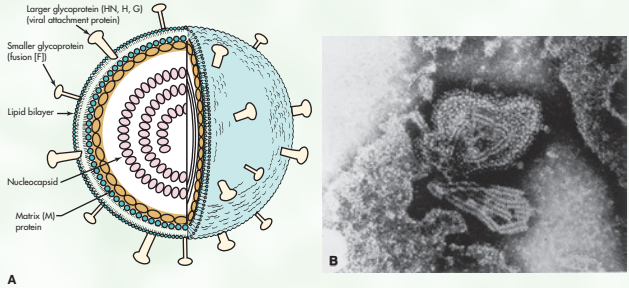

Figure 137-1: Measles virus. Note the glycoproteins in the envelope, the nucleocapsid that contains the polymerase, and the (–)RNA genome.

STRUCTURE

Like other paramyxoviruses. Enveloped; (–)ssRNA; large (only one serotype exists!); hemagglutinin (no neuraminidase) and fusion glycoproteins

REPLICATION

Virus enters **by fusion** and can make **syncytia.** Genome replication and mRNA production are like other (–)RNA viruses. Virus buds and is released from the plasma membrane.

LAB ID

Clinical diagnosis usually, but can see syncytia in infected cells; RT-PCR

COMPLICATIONS

Secondary bacterial infection, acute postinfectious encephalitis, subacute sclerosing panencephalitis

Measles: Part Two

EPIDEMIOLOGY

Respiratory spread; ***very contagious***

PREVENTION

MMR (measles, mumps, rubella) vaccine—live attenuated!

- Given after **12** months of age, booster at ~**12** years
- Cannot be given to immunodeficient persons or pregnant women

TREATMENT

Passive immunization with immunoglobulin G is given intravenously (IVIg) for unvaccinated and immunocompromised people after exposure.

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Mumps Paramyxovirus

Family Paramyxovirus

Murray: *Medical Microbiology,* 8th Edition, Chapter 48

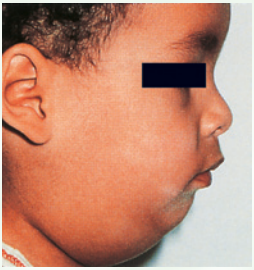

Figure 138-1: Parotitis in a child.

CASE STUDY

In late March a 10-year-old girl has a slight fever, headache, and loss of appetite for 24 hours. The next day her fever increases and her parotid glands have rapidly become swollen. Chewing causes pain.

TRIGGER WORDS

Parotitis: chipmunk cheeks
Orchitis (if bilateral, can lead to sterility, especially after puberty)
Pancreatitis and aseptic meningitis or encephalitis (5%)

ESSENTIAL FACTS

- Often asymptomatic or mild nonspecific symptoms
- Acute disease = fever, sudden onset of bilateral swelling of the parotid glands
- Orchitis and central nervous system involvement may follow after a few days (viremic spread).

Mumps Paramyxovirus

Family Paramyxovirus

STUDY BREAK

For the board exam, other than mumps, what genetic disease causes orchitis-like symptoms (and ears)? (fragile X syndrome)

STRUCTURE

Enveloped; (–)ssRNA; large (only one serotype!); hemagglutinin-neuraminidase and fusion glycoproteins

REPLICATION

Fusion entry and budding from plasma membrane for exit. Replication and transcription of genome as for other (–)RNA viruses.

LAB ID

- Syncytia in infected cells from saliva
- Can also do an enzyme-linked immunosorbent assay or reverse transcription polymerase chain reaction

DISEASES

Mumps: parotitis, orchitis, aseptic meningitis, encephalitis, deafness

EPIDEMIOLOGY

Respiratory, direct person-to-person, and fomites (inanimate objects): ***very contagious;*** only infects humans. Contagious period begins before onset of symptoms = asymptomatic shedding.

PREVENTION

MMR (measles, mumps, rubella) live vaccine given after 12 months of age.

139 Noroviruses and Other Caliciviridae

Murray: *Medical Microbiology,* 8th Edition, Chapter 47

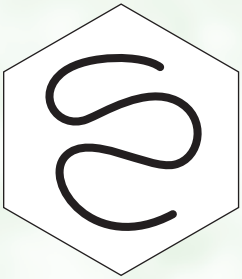

Figure 139-1

CASE STUDY

A 23-year-old woman complains of watery diarrhea five to seven times a day and nausea and vomiting three to four times a day for the past day and a half. Her father had a similar illness a few days ago and her mom has it now. The patient visited her parents over the weekend, and they shared a bathroom.

TRIGGER WORDS

Outbreaks of diarrheal disease
Nausea
Watery diarrhea and vomiting
Schools
Cruise ships

ESSENTIAL FACTS

- Most common cause of viral diarrhea in adults
- Noroviruses are like small versions of picornaviruses; similar properties but different diseases
- Norwalk virus is a norovirus in the Caliciviridae family.

Noroviruses and Other Caliciviridae

STUDY BREAK

This family of viruses gets its name from the Norwalk virus, discovered after an outbreak in Norwalk, Ohio. Most of us have had this disease, which includes diarrhea and vomiting at the same time.

STRUCTURE

Very small, linear (+)ssRNA; naked, icosahedral capsid

VIRULENCE

- Brush border function is compromised = diarrhea
- Delayed gastric emptying = vomiting

DISEASES

- Typical viral gastroenteritis (often older children and adults)
- Self-limited disease
- Noroviruses are the most common viral cause of diarrhea in adults, but rotaviruses are the most common viral cause of diarrhea in infants and young children.

EPIDEMIOLOGY

Spread via fecal-oral route through contaminated food, water, etc

PREVENTION

Wash your hands!

TREATMENT

Bismuth salicylate to reduce symptoms

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Orthomyxoviruses: Part One

Murray: *Medical Microbiology,* 8th Edition, Chapter 49

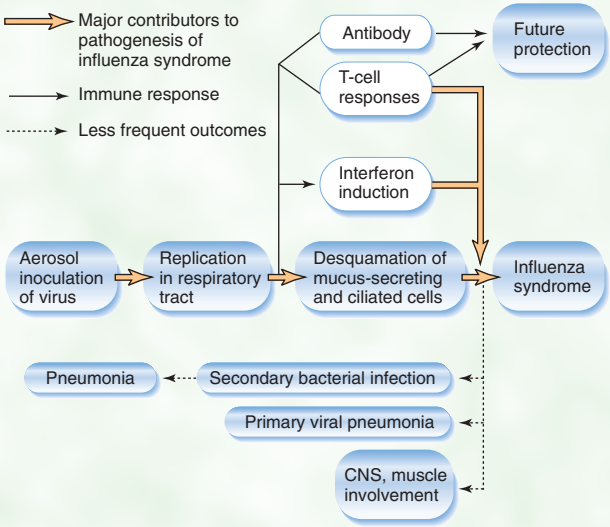

Figure 140-1: Pathogenesis of influenza.

CASE STUDY

A 70-year-old woman experiences rapid onset of fever with headache, myalgia (very sore muscles), sore throat, and nonproductive cough. The disease progresses to pneumonia with bacterial involvement. The woman's history shows no recent immunization with influenza vaccine.

Orthomyxoviruses: Part One

TRIGGER WORDS

Segmented genome = reassortment!
Hemagglutinin (HA) and neuraminidase (NA)
Antigenic drift (minor mutations) (outbreak/epidemic) versus shift (reassortment = pandemic)
Acute onset, fever, chills, and respiratory disease

ESSENTIAL FACTS

- Orthomyxoviruses = influenza viruses = types A and B, not C, cause disease.
- Patients are at high risk for secondary bacterial infections, especially pneumonia.
- Segmented genome allows mutation of a segment without inactivating the entire genome.
- Influenza A (not influenza B) is a zoonosis; reassortment of segments occurs on mixed infection of another animal (eg, pig infection with avian and pig and human viruses).
- Hemagglutination and hemadsorption indicate the presence of virus.
- Hemagglutination inhibition is a *serologic* assay to detect antibody!
- Aspirin + this virus (or varicella zoster [chickenpox]) in child = Reye syndrome = fatty liver change and acute encephalitis. High mortality rate. *Don't give your baby a baby aspirin.*

STUDY BREAK

The composition of the yearly flu vaccine represents a multimillion-dollar bet on which viruses will be present in the next year.

141

Orthomyxoviruses: Part Two

Murray: *Medical Microbiology,* 8th Edition, Chapter 49

STRUCTURE

- Enveloped; segmented (–)ssRNA genome; helical nucleocapsid; hemagglutinin (HA), neuraminidase (NA), M1, M2, polymerase, nonstructural protein (NS), nucleoprotein (NP) proteins
- Virus binds to sialic acid–containing proteins; enters in a coated vesicle and fuses when vesicle becomes acidified, M2 *(target for amantadine)* proton channel promotes uncoating of nucleocapsid; genome segments transcribed and replicated in nucleus *(exception to RNA virus rule)*; segments associate with proteins and the nucleocapsid associates with M1 proteins on HA and NA decorated plasma membrane, virus buds and is released.

LAB ID

Enzyme-linked immunosorbent assay: detect viral antigens in nasal secretions; reverse transcription polymerase chain reaction; hemagglutination

VIRULENCE FACTORS

Envelope glycoproteins (antigens):

- Hemagglutinin: viral attachment protein and also aggregates red blood cells
- NA: facilitates virion release from cell. Enzyme removes sialic acid from virion and host cells = minimizes clumping to allow release
- Virus infection kills ciliated epithelium.
- Cytokine production causes flu like symptoms.

DISEASES

- A and B cause influenza (fever, myalgia, nonproductive cough); pneumonia, secondary bacterial pneumonia
- C = common cold

Orthomyxoviruses: Part Two

EPIDEMIOLOGY

- Aerosol spread. Only flu A is a zoonosis (*A is for animals)*.
- **Antigenic drift** = minor changes due to mutation in the genes encoding HA or NA, which alters viral antigenicity (both A and B); promotes local outbreaks (epidemics).
- **Antigenic shift** in influenza A = major changes that result from reassortment of genome segments after coinfection with different strains of viruses (eg, human and swine [pig] or avian [duck]) to produce new hybrid viruses and promote pandemics.

PREVENTION

- Prophylactic use of drugs **listed below**
- Vaccines: Live cold-adapted influenza vaccine (ages 2-49), inactivated vaccines: HA and NA isolated from egg grown or tissue culture grown virus; recombinant HA

TREATMENT

- Antiviral drugs effective if given within 48 hours of infection. Amantadine and rimantadine (for A only) target M2 ion channel (block uncoating).
- Oseltamivir and zanamivir for A and B (neuraminidase inhibitors).
- Acetaminophen (not aspirin) can reduce symptoms.

142

Papillomaviruses and *Po*lyomaviruses (Formerly Pa*po*vaviridae): Part One

Murray: *Medical Microbiology,* 8th Edition, Chapter 41

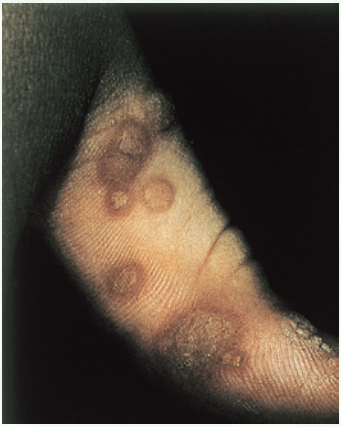

Figure 142-1: Common warts with thrombosed vessels (black dots).

CASE STUDIES

- Lesions on hands and feet with hyperplasia of prickle cells and hyperkeratosis seen microscopically: **skin warts**
- Growths on external genitalia and perianal regions: **anogenital warts**
- Child with tumor causing airway obstruction: **laryngeal papillomas**
- Koilocytic cells (enlarged nuclei and cytoplasmic vacuoles) seen in Pap smear: **cervical intraepithelial neoplasia (CIN)**
- A man receiving immunosuppressive therapy begins to suffer from neurologic symptoms (memory loss, difficulty speaking and coordination, loss of some use of his arm): **JC virus = progressive multifocal leukoencephalopathy (PML)**

Papillomaviruses and *Po*lyomaviruses (Formerly Pa*po*vaviridae): Part One

TRIGGER WORDS

- Papillomavirus: warts, koilocytes, CIN, cervical cancer, sexually transmitted disease
- Polyomaviruses: JC virus, demyelination, abnormal oligodendrocytes, opportunistic disease, PML; BK virus: kidney

ESSENTIAL FACTS

- Papillomaviruses and polyomaviruses must stimulate cell growth so that the cell's DNA polymerase will replicate the genome.
- Human papillomavirus (HPV) 16 and HPV-18 are present in most cervical carcinomas, but there are other high-risk HPV types.
- HPV evades immune control by making virus only in terminally differentiated skin and epithelial cells.
- PML in a patient with AIDS may resemble many other neurologic disorders.

STUDY BREAK

Papillomaviruses are tissue specific; for example, the common skin wart never occurs on mucous membranes.

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Papillomaviruses and *Po*lyomaviruses (Formerly Pa*po*vaviridae): Part Two

Murray: *Medical Microbiology*, 8th Edition, Chapter 41

STRUCTURE

Small, naked capsid; circular dsDNA

REPLICATION

Virus promotes cell growth and DNA production:

- Polyoma T antigen binds to and inactivates p53 and p105RB growth-suppressor proteins
- Human papillomavirus (HPV) E6 binds p53; E7 binds p105RB

Papillomaviruses

LAB ID

Virus cannot be isolated from tissue culture. Diagnosis is made by:

- Clinical picture
- Histology of lesion: **koilocytic cells** (enlarged nuclei and cytoplasmic vacuoles) seen in Pap smear = cervical intraepithelial neoplasia (CIN)
- **Polymerase chain reaction**

VIRULENCE FACTORS

Viral proteins E6 and E7 inactivate p53 and RB tumor suppressor proteins and promote hyperplasia of host cells.

DISEASES

- Skin warts (serotypes 1 and 4)
- Anogenital warts (6 and 11)
- Laryngeal papilloma (6 and 11)
- CIN (16, 18, 31, 33, 45, 52, and 58)

Papillomaviruses and *Po*lyomaviruses (Formerly Pa*po*vaviridae): Part Two

EPIDEMIOLOGY

Direct contact with skin warts, sexual contact, mother to infant, fomites

PREVENTION

Prevent contact. Vaccine—virus-like particle: divalent, tetravalent, and 9-valent vaccines.

TREATMENT

Nonsurgical removal, injection with interferon α, surgical removal

Polyomaviruses

DISEASES

BK virus and **JC virus** are usually asymptomatic.

- Primary site of infection = kidney (infection usually asymptomatic/latent)
- Reactivation: immunocompromised people and pregnancy
- **JC** = progressive multifocal leukoencephalopathy (think **C** for **C**ranial)
- Brain histology: abnormal oligodendrocytes near areas of demyelination
- B**K** = urinary tract infection (think **K** for **K**idney)

144

Parvovirus B19

Family Parvoviridae

Murray: *Medical Microbiology,* 8th Edition, Chapter 45

CASE STUDIES

- A 6-year-old girl has a history of a **fever** and bright **red cheeks**, followed by a macular lacy rash with a central clearing on her body. This rash fades and reoccurs and lasts 1 to 4 weeks: **erythema infectiosum** (fifth disease)
- Child with sickle cell anemia infected with parvovirus B19 undergoes aplastic crisis.
- Pregnant woman has an erythematous macropapular rash and then experiences arthralgia and arthritis. Woman has miscarriage due to **hydrops fetalis**.

TRIGGER WORDS

Slapped cheeks
Anemia
Lacy pattern rash
Hydrops fetalis

ESSENTIAL FACTS

- Parvovirus single-stranded DNA genome is converted to double strand for replication and transcription.
- Parvovirus B19 is targeted to erythroid precursor cells because they are rapidly growing and can make viral DNA. This reduces the levels of red blood cells causing aplastic crisis in people with chronic hemolytic anemia.

STUDY BREAK

Erythema infectiosum was named fifth disease because it was the fifth infectious pediatric rash to be described. The others are measles, smallpox, rubella, and chickenpox. (Sixth disease is exanthema subitum caused by human herpesvirus 6.)

Parvovirus B19

Family Parvoviridae

STRUCTURE

Very small, naked, icosahedral capsid; linear ssDNA virus

REPLICATION

Requires rapidly growing cells; hence erythroid precursor cells

VIRULENCE FACTORS

- After initial infection at site of entry (usually upper respiratory tract), there is viremic spread to rapidly dividing erythroid precursor cells in the bone marrow, where cytolytic replication and subsequent immune response cause manifestation of disease.
- Rash, arthralgia, and arthritis are caused by immune response to virus.

DISEASES

- Erythema infectiosum (fifth disease): common from ages 4 to 15 years. Biphasic: FIRST fever, flulike illness, and anemia (lytic infection); THEN erythematous rash of the cheeks ("slapped cheeks") and maculopapular rash with a central clearing on the body (lacy pattern rash). The rash can last up to 4 weeks.
- Aplastic crisis in sickle cell patients and those with chronic hemolytic anemia
- Polyarthritis in adults
- Fetal infection = stillbirth (hydrops fetalis)

EPIDEMIOLOGY

Erythema infectiosum: occurs mostly in children via respiratory spread

TREATMENT

Self-limiting illness; intravenous immunoglobulin used in aplastic crisis

145

Picornaviruses: Coxsackievirus (A and B) and Echovirus: Part One

Family Picornaviridae

Murray: *Medical Microbiology,* 8th Edition, Chapter 46

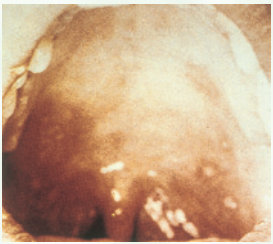

Figure 145-1: Coxsackie A virus disease: herpangina.

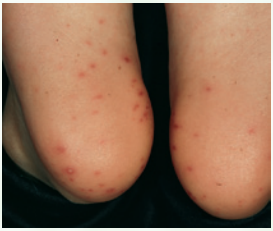

Figure 145-2: Hand-foot-mouth disease.

CASE STUDIES

- A 4-year-old girl had a 3-day history of fever, rash on her hands and feet, vesicles and ulcers on the tongue and oral mucosa, irritability, and lack of appetite. On examination no other rashes are found: **hand-foot-mouth disease = Coxsackie A**
- A 7-year-old boy develops a sudden fever, loss of appetite, sore throat, vomiting, and pain on swallowing. Exam shows vesiculopapular lesions on the tongue and roof of mouth: **herpangina = Coxsackie A**
- A young girl has swollen eyelids with redness, congestion, and pain in her eyes. Several other children from her nursery have these same symptoms: **acute hemorrhagic conjunctivitis = Coxsackie A**

Picornaviruses: Coxsackievirus (A and B) and Echovirus: Part One

Family Picornaviridae

- A 13-year-old boy suddenly develops a fever and severe paroxysmal chest pain, which lasts for 4 days. He also complains of headache, fatigue, and aching muscles: **epidemic pleurodynia = Coxsackie B**
- A 9-month-old girl has a fever and skin rash. She appears listless and has difficulty moving her head from side to side. Cerebrospinal fluid analysis shows normal glucose, no bacteria, and the presence of lymphocytes. Within 1 week, the infant is fully recovered: **aseptic meningitis = coxsackievirus or echovirus**

TRIGGER WORDS

Fecal-oral
Vesicular lesions
Coxsackie B for body

ESSENTIAL FACTS

- Picornaviridae = *Rhinovirus* (acid labile) and *Enterovirus* (acid stable): poliovirus, Coxsackie A, Coxsackie B, echovirus, hepatitis A virus
- Enteroviruses are the most common cause of nonbacterial meningitis in the United States.
- Enteroviruses rarely cause gastroenteritis.
- Coxsackie A virus diseases include vesicular rashes, central nervous system disease, and common cold.
- Coxsackie B virus diseases include muscle infections and neurologic diseases.
- Echoviruses cause neurologic disease, especially in infants.

STUDY BREAK

Coxsackieviruses are named after Coxsackie, NY.

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Picornaviruses: Coxsackievirus (A and B) and Echovirus: Part Two

Family Picornaviridae

Murray: *Medical Microbiology,* 8th Edition, Chapter 46

Figure 146-1

STRUCTURE

Small, naked icosahedral capsid, single-strand (+)RNA genome; acid and detergent stable; many serotypes

LAB ID

Clinical diagnosis, serology, reverse transcription polymerase chain reaction (RT-PCR) to detect virus in cerebrospinal fluid, blood, or clinical samples

VIRULENCE FACTORS

Can replicate in the gastrointestinal tract asymptomatically for long periods (remember: they are *entero*viruses) and are acid stable

Picornaviruses: Coxsackievirus (A and B) and Echovirus: Part Two

Family Picornaviridae

DISEASES

Coxsackie A and B and Echovirus

- Asymptomatic infection: virus isolated from stool
- Common cold
- Nonspecific febrile illness: fever, malaise, cough, and sore throat; lasts 4 to 6 days
- Aseptic meningitis with possible rash

Coxsackie A

- Herpangina: sudden onset of fever with vesicles and ulcers in the oropharynx; lasts 3 to 6 days
- Hand-foot-mouth disease: rash on hands and feet with vesicles in the mouth and mild fever

Coxsackie B (*B* for *B*ody)

- Pleurodynia: sudden sharp spasmodic chest pain associated with fever
- Myocarditis/pericarditis (mostly in neonates): chest pain, arrhythmias, cardiomyopathy, and heart failure

EPIDEMIOLOGY

Mostly fecal-oral route, but some also spread by aerosols

PREVENTION

Sanitation and hygiene

TREATMENT

Usually none required because self-limiting disease; supportive treatment for aseptic meningitis

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Poliovirus

Family Picornaviridae

Murray: *Medical Microbiology,* 8th Edition, Chapter 46

CASE STUDY

A child from Asia complains of a fever, abdominal pain, nausea, vomiting, and severe headache. He felt better after a few days but redeveloped a severe headache, neck stiffness, soreness of muscles, constipation, and muscle weakness: **poliomyelitis**

TRIGGER WORDS

Asymmetric flaccid paralysis
Major disease
Minor disease
Fecal-oral

ESSENTIAL FACTS

- Fecal-oral spread
- Four forms:
  1. Asymptomatic
  2. Mild illness: fever, nausea, vomiting, abdominal pain, and headache
  3. Nonparalytic: aseptic meningitis; symptoms of mild illness + neck stiffness and severe headaches
  4. Paralytic: can occur after a few days of mild illness; high fever, muscle stiffness, and pain = asymmetric flaccid paralysis due to destruction of lower motor neurons (LMNs)

STUDY BREAK

Outbreaks of paralytic poliomyelitis in the 1950s in the United States filled children's hospitals around the country; wards were set up in churches and schools, where people lay in iron lung machines that took the place of paralyzed diaphragms. The March of Dimes was created with President Roosevelt's help to spearhead the development of the poliovirus vaccine.

Poliovirus

Family Picornaviridae

STRUCTURE

Small, naked icosahedral capsid, ss(+)RNA genome; acid stable

LAB ID

Clinical picture, virus isolation from feces, serology, reverse transcription polymerase chain reaction to detect virus in cerebrospinal fluid and blood

VIRULENCE FACTORS

Virus multiplies in lymphoid tissue of pharynx and tonsils and mucosa of gastrointestinal tract. Virus spreads via blood and binds to muscle cells and neurons = paralysis

DISEASES

- Minor illnesses or abortive
- Nonparalytic (aseptic meningitis)
- Paralytic:
  - Flaccid paralysis due to large motor neuron destruction
  - Postpolio syndrome: degenerative neurologic disease decades after polio but not due to virus

EPIDEMIOLOGY

Virus excreted in feces; fecal-oral spread

PREVENTION

- Improve sanitation
- Vaccines (two types):
  1. Salk: killed virus given intramuscularly: recommended
  2. Sabin: live attenuated, oral: not recommended due to small potential for disease (genetic reversion)

TREATMENT

Supportive during active disease

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Rhinovirus

Family Picornaviridae

Murray: *Medical Microbiology,* 8th Edition, Chapter 46

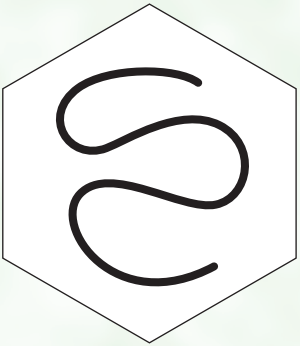

Figure 148-1

CASE STUDY

Several children from the same daycare present with **runny nose**, sneezing, watery eyes, headache, malaise, fever, and loss of appetite: common cold: ***Rhinovirus***

TRIGGER WORD

Runny nose

STUDY BREAK

Rhinovirus is one of the major causes of the common cold, along with enteroviruses, parainfluenza, respiratory syncytial virus, and coronavirus. Think ***rhino***ceros = nose and rhinorrhea.

STRUCTURE

Small, naked ss(+)RNA (>100 serotypes); acid labile, so *no* gastrointestinal transmission

Rhinovirus

Family Picornaviridae

VIRULENCE FACTORS

Multiplies in nasal and conjunctival mucosa and promotes release of inflammatory mediators. Cannot replicate at temperatures >33°C; therefore only upper respiratory infection (URI).

DISEASES

- URI
- Common cold
- Symptoms of **rhinorrhea**, sneezing, headache, sore throat, malaise, fever, chills
- Self-limiting illness because of immunoglobulin A and interferons produced by the host; peak symptoms at 3 to 4 days, but runny nose up to 7 to 10 days

EPIDEMIOLOGY

Spread by aerosols and fomites. Only 50% of those infected develop active illness. Asymptomatic people can spread Rhinovirus. High incidence in infants and children. ***Many serotypes.***

PREVENTION

Handwashing and respiratory precautions; no vaccine because of many serotypes

TREATMENT

Supportive

149

Poxviruses: Variola Virus (Smallpox), Animal Poxviruses, and Molluscum Contagiosum Virus: Part One

Family Poxviridae

Murray: *Medical Microbiology*, 8th Edition, Chapter 44

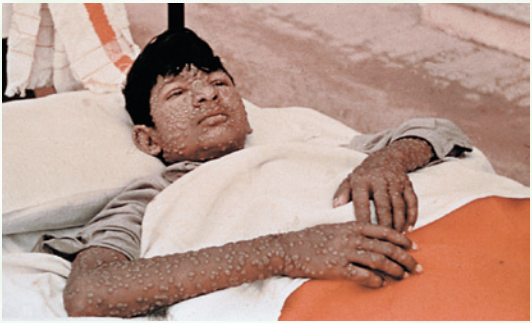

Figure 149-1: Child with smallpox. Note all lesions are in the same stage of development, unlike varicella-zoster virus.

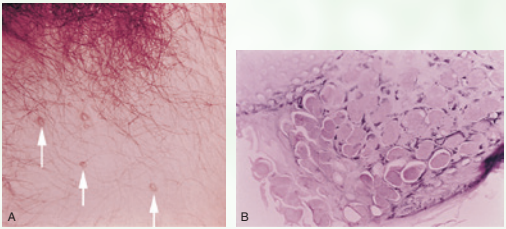

*Figure 149-2: Molluscum contagiosum. **A**, Note the cluster of wartlike lesions. **B**, Molluscum inclusion bodies in epithelial cells.*

Poxviruses: Variola Virus (Smallpox), Animal Poxviruses, and Molluscum Contagiosum Virus: Part One

Family Poxviridae

CASE STUDY

A 5-year-old child (or an HIV-positive patient) presents with a cluster of small, raised **skin-colored papules** on the chest for **3 months**. Each lesion has a central dimple but does *not* cause pain or itching. There is *no* redness: **molluscum contagiosum**

TRIGGER WORDS

Large, brick-shaped virus
Replicates in cytoplasm
Vesicular lesion
Zoonosis
Molluscum contagiosum: skin-colored papules with long duration
Smallpox: synchronized crop of vesicular lesions, vaccinia vaccine

ESSENTIAL FACTS

- Poxviruses are the largest and most complex viruses that infect humans.
- Poxviruses are the exception to most rules for DNA viruses; they replicate in the cytoplasm, encode both RNA polymerase and DNA polymerase, uncoatase, etc.
- Poxviruses share common antigens so that vaccinia can immunize against smallpox.

STUDY BREAK

Although natural smallpox was eradicated by an effective worldwide vaccine and quarantine program spearheaded by the World Health Organization, the former Soviet Union developed an enormous smallpox biologic warfare program. Smallpox remains a bioterror agent.

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Poxviruses: Variola Virus (Smallpox), Animal Poxviruses, and Molluscum Contagiosum Virus: Part Two

Family Poxviridae

Murray: *Medical Microbiology,* 8th Edition, Chapter 44

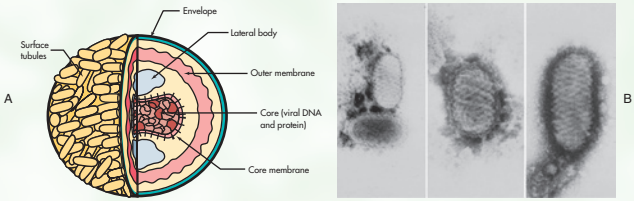

Figure 150-1: ***A,*** *Structure of the vaccina virus.* ***B,*** *Electron micrograph of orf virus.*

STRUCTURE

- Large, complex, brick-shaped virus with linear dsDNA; two-envelope structure
- Poxvirus carries its own RNA polymerase and DNA polymerase and is the only DNA virus that replicates in the cytoplasm.

LAB ID

Clinical presentation, polymerase chain reaction (PCR)

DISEASES

- **Smallpox:** vesiculopustular lesions starting on the face and extremities and spreading inward. After the lesions heal, they usually leave deep scars. Can lead to death.
- **Molluscum contagiosum:** small, skin-colored, centrally dimpled papular lesions on the trunk, genitals, and proximal extremities. Infection is benign and self-limiting. More common in patients with AIDS.
- **Animal pox viruses:** monkey pox—like mild smallpox; orf—large, localized, vesicular lesion

Poxviruses: Variola Virus (Smallpox), Animal Poxviruses, and Molluscum Contagiosum Virus: Part Two

Family Poxviridae

EPIDEMIOLOGY

- Variola: respiratory spread, contact, fomites; ***highly contagious***
- Animal poxviruses: contact
- Molluscum contagiosum: transmitted by close contact and fomites, not a zoonosis

PREVENTION

Smallpox eradication via vaccinia vaccine and quarantine

TREATMENT

Molluscum contagiosum: usually no treatment needed, but when extensive can be removed by scraping or with liquid nitrogen.

151

Prions

Murray: *Medical Microbiology,* 8th Edition, Chapter 56

CASE STUDY

A 65-year-old man had severe headaches, tremor of the hand, and was forgetful and confused. His condition deteriorated, and he entered a coma with occasional clonic twitching. There were no gross abnormalities, no inflammation on autopsy, but intracellular vacuolation was seen throughout the cerebral cortex.

TRIGGER WORDS

Spongiform encephalopathy
Variant CJD (vCJD)
Creutzfeldt-Jacob disease (CJD)
Beef

ESSENTIAL FACTS

- Spongiform encephalopathies are caused by a prion, a misfolded protein that recruits and refolds the normal version of the protein promoting aggregation.
- Buildup of the prion protein in the brain causes a spongelike vacuolar appearance.
- Prions are different forms of a protein that aggregate and do not elicit immune responses (encephalopathy).
- Prions are transmitted in food and through cuts in skin.
- Prion disease can be an infectious or a genetic disease.
- Other prion diseases include kuru, Gerstmann-Sträussler-Scheinker syndrome, and fatal familial insomnia.

STUDY BREAK

Scrapie is one of the first identified prion diseases. Kuru was discovered in the Fore tribe of New Guinea, who ate their relatives as part of the funeral. British cattle (mad cow disease) may have acquired prion disease when fed sheep protein meal and may have passed the disease to humans as a variant of CJD that affects younger people and progresses more rapidly than classical CJD.

Prions

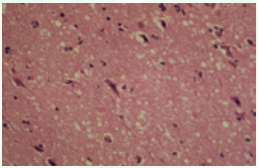

Figure 151-1: Spongiform encephalopathy in brain of a CJD patient.

STRUCTURE

Aggregated complex altered conformation of normal protein

LAB ID

Disease progression, protease resistance of prion protein

VIRULENCE FACTORS

- Host protein does not elicit immune response.
- Prion version of protein recruits normal version of protein by binding and changing their conformation.
- ***Very difficult to inactivate or disinfect.***

DISEASES

Infectious and genetic: CJD, kuru, Gerstmann-Sträussler-Scheinker disease, fatal familial insomnia

EPIDEMIOLOGY

Food and contact; incompletely sterilized surgical tools

PREVENTION

Carefully sterilize surgical tools.

TREATMENT

None

152

Rabies

Family Rhabdovirus

Murray: *Medical Microbiology,* 8th Edition, Chapter 50

CASE STUDY

Immigrant boy from Indonesia develops fever, headache, and vomits. He refuses to take pills and drink water due to pain on swallowing. Two days later he has a 41°C fever, is confused, delirious, becomes paralyzed, goes into coma, and dies. Autopsy indicates Negri bodies in a brain biopsy. Father recalls son being bitten on leg by a dog 6 months earlier.

TRIGGER WORDS

Dog bite
Aerosol
Coma
Negri bodies
Bats
Hydrophobia
Salivation

ESSENTIAL FACTS

- Rhabdoviruses have a characteristic bullet morphology (often shown as picture on exam questions).
- The closer the infection is to the brain, the faster the onset of disease (eg, transplant of cornea from rabies victim).
- Rabies is the only virus disease that can be treated by vaccination with a killed vaccine after infection because of the long incubation period.

STUDY BREAK

- Louis Pasteur's testing of his experimental vaccine on a human boy was ethical because rabies is ***always*** lethal if not treated.
- Vaccination of wild mammals (eg, skunks, raccoons) is done by dropping smelly baits containing a genetically engineered vaccinia virus that contains the G protein of rabies.

Rabies

Family Rhabdovirus

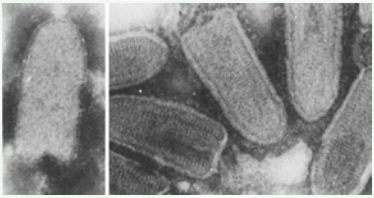

Figure 152-1: Rhabdoviridae seen by electron microscopy: rabies virus (left) *and vesicular stomatitis virus* (right).

STRUCTURE

- Bullet-shaped enveloped virus, (–)RNA genome
- Encodes only five proteins: G-glycoprotein, M-matrix, and nucleocapsid proteins (L-polymerase, nucleocapsid [N], and nonstructural [NS])

LAB ID

Negri bodies, immunofluorescence, reverse transcription polymerase chain reaction

DISEASES

Rabies

EPIDEMIOLOGY

Transmitted by mammal bite or aerosols from rabid bats (eg, people who go into bat caves)

PREVENTION

Vaccination of animals; vaccination of veterinarians and others at risk

TREATMENT

Wash bite site, instill and inject near site with human rabies immune globulin; vaccination with killed virus grown in human diploid cells

153

Rotavirus and Reoviridae

Murray: *Medical Microbiology,* 8th Edition, Chapter 51

Figure 153-1

CASE STUDY

A 1-year-old infant is hospitalized because of watery diarrhea, fever for 4 days, vomiting, and dehydration: **Rotavirus**

TRIGGER WORDS

Watery diarrhea in young child
Double capsid and double-stranded segmented RNA (remember: double-double)

ESSENTIAL FACTS

- No. 1 cause of infant death due to diarrhea
- Most important cause of infant gastroenteritis worldwide
- A major cause of acute diarrhea in the winter in the United States
- Most common cause of adult watery diarrhea is Norwalk virus, not Rotavirus

STUDY BREAK

The enzymes for capping mRNA were first discovered in the reovirus virion and then shown to be an important cellular function. Rotavirus NSP4 protein acts like a toxin to trigger watery diarrhea.

Rotavirus and Reoviridae

Rotavirus (Reovirus Family)

STRUCTURE

Naked **double** capsid, **double**-stranded RNA, segmented genome

LAB ID

Clinical symptoms, enzyme-linked immunosorbent assay for viral antigens or free virions in stool

DISEASES

Watery diarrhea. Most severe in infants (can be fatal due to dehydration), mild in children <2 years of age and adults. Self-limiting and complete recovery usually occurs. Secretory immunoglobulin A in intestines confers immunity.

EPIDEMIOLOGY

Fecal-oral route of spread, especially preschools and daycare centers

PREVENTION

Wash hands; reassortant and attenuated vaccines

TREATMENT

Fluid replacement, especially in infants

Colorado Tick Fever (Reovirus Family)

EPIDEMIOLOGY

Spread by wood ticks. Seen in western and northwestern United States (eg, Colorado) and Canada

DISEASE

Mild, self-limiting infection

154

Rubella

Family Togaviridae

Murray: *Medical Microbiology,* 8th Edition, Chapter 52

Figure 154-1

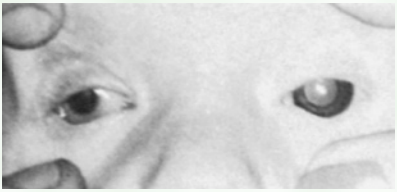

Figure 154-2: Cataracts in congenital rubella.

CASE STUDY

A child is born at 40 weeks' gestation to an apparently healthy mother. The child is born with cataracts, deafness, and is later determined to be mentally retarded: **congenital rubella**

TRIGGER WORDS

Rash	Vaccine	Congenital disease
Arthritis	Teratogen	Cataracts

ESSENTIAL FACTS

Rubella is the only relevant togavirus that is not an arbovirus.

STUDY BREAK

Because rubella infection is relatively benign, the primary purpose of the rubella vaccination program is to limit the spread of virus to seronegative mothers and hence protect the fetus from congenital disease.

Rubella

Family Togaviridae

STRUCTURE

Enveloped, linear single-strand (+)RNA genome, linear, icosahedral capsid

REPLICATION

Genome is an mRNA (early), but later in replication a smaller mRNA (late) is made from the (−)RNA template that encodes the structural proteins.

LAB ID

Serologic testing for anti-rubella immunoglobulin (Ig) M or fourfold increase in IgG antibodies (acute vs. convalescence). Commonly assayed by reverse transcription polymerase chain reaction (RT-PCR) in early pregnancy to determine the immune status of the mother.

DISEASES

German Measles or 3-Day Measles (Rubella)

- In children, disease is benign, consisting of **swollen glands and a pink maculopapular rash that lasts 3 days.** Rash starts on the face and spreads downward over the trunk and extremities.
- In **adults,** disease is more severe, with **arthralgia**, **arthritis,** and possible postinfectious (autoimmune) **encephalitis.**

Congenital Rubella

Transplacental infection of fetus until the twentieth week of gestation can lead to **cataracts**, **mental retardation**, **deafness**, **cardiac septal defects**, patent ductus arteriosus, and microcephaly. Maternal anti-rubella antibodies prevent viral spread to the placenta and fetus.

EPIDEMIOLOGY

Rubella transmission is by the **respiratory** route.

PREVENTION

Measles, mumps, rubella (MMR) live vaccine

TREATMENT

Symptomatic

155

Toga and Flavi Arboviruses: Part One

Murray: *Medical Microbiology*, 8th Edition, Chapter 52

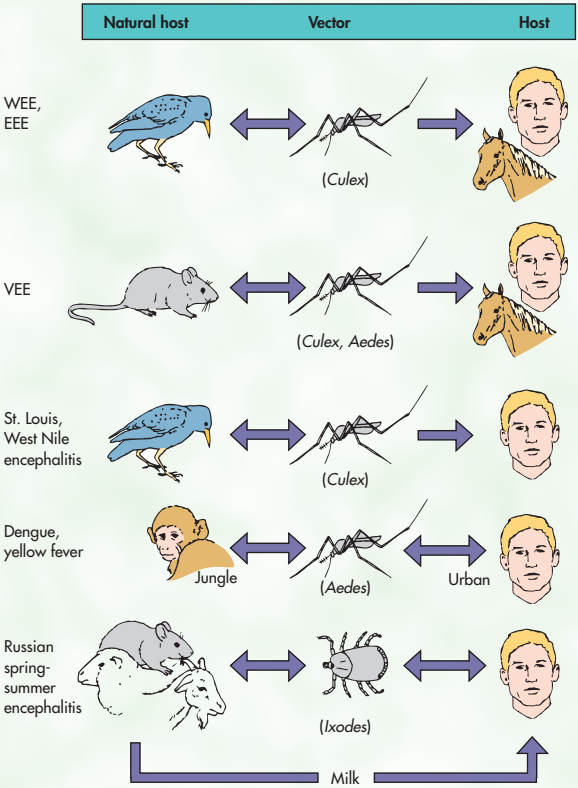

Figure 155-1: Patterns of alphavirus and flavivirus transmission. EEE, *Eastern equine encephalitis;* WEE, *western equine encephalitis.*

Toga and Flavi Arboviruses: Part One

CASE STUDIES

- A 70-year-old man from a swampy area of New York develops fever, headache, muscle weakness, nausea, and vomiting and then progresses into a coma. Magnetic resonance imaging indicates no specific localization of lesions: **West Nile encephalitis**
- A 42-year-old man presents with high fever, headache, vomiting, and backache after travel in Central America. Later he experiences bleeding gums, blood in urine, blood in vomit, petechiae, and jaundice: **yellow fever**
- Traveler to endemic region has high fever, headache, rash, and severe back and bone pain for 6 to 7 days: **dengue hemorrhagic fever (breakbone fever)**

TRIGGER WORDS

Arbovirus, encephalitis viruses: mosquito, seasonal encephalitis, swamp

Hemorrhagic viruses: blood everywhere, petechiae

ESSENTIAL FACTS

- **Most** togaviruses and flaviviruses can replicate in mosquitoes and humans.
- Most cases of West Nile and other encephalitis virus infections are asymptomatic, mild, or result in fever, headache, and body ache and nausea for ~4 days.
- Yellow fever and dengue fever viruses infect and damage and also induce immunopathogenesis toward endothelial cells lining blood vessels.

STUDY BREAK

When the blue jays and crows come back, the West Nile encephalitis virus outbreak is over.

156

Toga and Flavi Arboviruses: Part Two

Murray: *Medical Microbiology*, 8th Edition, Chapter 52

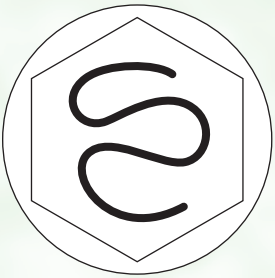

Figure 156-1: Togavirus and flavivirus: (+)RNA genome.

STRUCTURE

Enveloped; single-strand (+)RNA genome; linear; have icosahedral capsid

REPLICATION

- Togavirus: early proteins are translated from the genome and the late structural proteins are from a shorter mRNA produced from the (–)RNA template.
- Flavivirus: proteins translated from one polyprotein.

LAB ID

Serologic testing, reverse transcription polymerase chain reaction

DISEASES

Togaviruses

- Venezuelan equine (VEE), eastern equine (EEE), and western equine encephalitis (WEE) viruses, chikungunya virus
- Seasonal encephalitis: EEE, WEE, VEE, and West Nile encephalitis virus

Toga and Flavi Arboviruses: Part Two

Flaviviruses

- West Nile and St. Louis encephalitis viruses; dengue fever virus and yellow fever virus, Zika virus
- Dengue virus: Breakbone fever, dengue shock syndrome Second infection with a related strain causes a combination of immunopathology and viral pathology and a more serious outcome.

EPIDEMIOLOGY

Arboviruses (transmitted by mosquitoes). Natural host is birds; humans and horses are incidental hosts.

PREVENTION

Eliminate mosquitoes or their habitat; live yellow fever vaccine

TREATMENT

Treat symptoms

157

Fungi: Overview: Part One

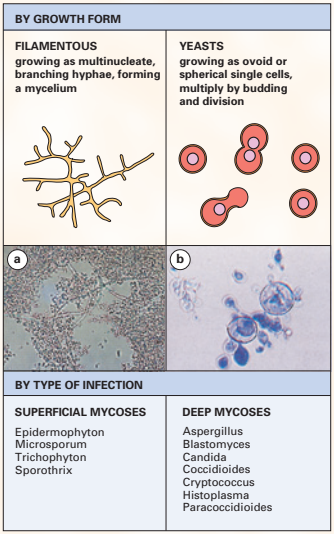

Figure 157-1: Two ways to classify fungi that cause disease: by growth form and by type of infection. **a**, *Hyphae in skin scraping from ringworm lesion. (Courtesy of DK Banerjee.)* **b**, *Spherical yeasts of Histoplasma. (Courtesy Y. Clayton and G. Midgley.)*

Fungi: Overview: Part One

Table 157-1: Important Fungal Diseases

Type	Anatomic Location	Representative Disease	Causative Organisms	Growth Form
Superficial	Hair shaft, dead layer of skin	Ptyriasis versicolor, tinea nigra, piedra	*Trichosporon* *Malassezia* *Exophiala*	Y/F
Cutaneous	Epidermis, hair, nails	Tinea (ringworm)	*Microsporum* *Trichophyton* *Epidermophyton*	F
Subcutaneous	Dermis, subcutis	Spirotrichosis	*Sporothrix*	Y*
		Mycetoma	Several genera	F
Systemic	Internal organs	Coccidioidomycosis	*Coccidioides*	‡
		Histoplasmosis	*Histoplasma*	Y
		Blastomycosis	*Blastomyces*	Y
		Paracoccidioidomycosis	*Paracoccidioides*	Y
Opportunistic	Internal organs	Cryptococcosis	*Cryptococcus*	Y
		Candidiasis	*Candida*	Y†
		Aspergillosis	*Aspergillus*	F*
		Pneumocystis pneumonia	*Pneumocystis*	NA

*Growth form in the body.
†Also forms pseudohyphae.
‡*Coccidioides* has an unusual growth form with yeastlike endospores within a spherule.
F, filamentous; NA, Y/F growth forms are not applicable; Y, yeast.

CLASSIFICATION

- Site and conditions of infection: superficial, cutaneous, subcutaneous, endemic, opportunistic
- Disease: eg, tinea, chromoblastomycosis, eumycotic mycetoma
- Diet: eg, dermatophytes; use keratinase to break down hair and nails
- Color: dematiaceous; melanin producing and brown
- Organism: *Histoplasma capsulatum*
- Morphology:
  - Molds
  - Yeasts
  - Dimorphic: molds at ambient (25°C) and yeast at body (37°C) temperatures

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Fungi: Overview: Part Two

FUNGAL MORPHOLOGY

Molds

- Hyphae: filamentous (hair-like structures)
  - Septate: defined cell walls
  - Aseptate: no cell walls dividing cells
  - Reproduce asexually at apical (tip) by cell division (mitosis) to elongate
  - Aerial hyphae (stick up into the air): produce conidia, or spores (conidiophore)
  - Vegetative hyphae: on the surface or invasive; feeding
- Spore (conidia) and spore holder (sporangium) and stalk (conidiophore) structures differ for different fungi

Yeasts

- Larger than bacteria, ovoid or spherical
- Reproduce by budding (blastoconidia) and fission

FUNGAL CELL WALL AND MEMBRANE STRUCTURE

Cell wall structure made up of glucans and mannans is different from bacteria cell walls.

- Resistant to KOH digestion
- Multilayered wall structure
- Most common cell wall polysaccharides:
  - Chitin
  - Mannans
  - Glucans *(Candida)*: synthesis inhibited by echinocandins
- Membrane uses **ergosterol** (not cholesterol) in membranes
  - Amphotericin and nystatin bind ergosterol to form a pore and disrupt membrane
  - Imidazoles and triazoles inhibit ergosterol synthesis

Fungi: Overview: Part Two

DISEASE MECHANISMS

- Invasion
  - Toxic byproducts
  - Degradation of tissue
  - Space filling
- Mycotoxicosis
- Immunopathology
  - Hypersensitivity (allergy and asthma)
  - Inflammation

IMMUNE RESPONSE

- Neutrophils and T cells are essential (especially Th17 and Th1)

LABORATORY IDENTIFICATION

- Isolation
  - Sabouraud dextrose agar (SDA or SAB agar),
  - Brain health infusion agar (BHI)
  - Blood agar
- KOH prep to dissolve tissue and show fungal structures
- Immune assays
- Genome assays

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Antifungal Agents

Murray: *Medical Microbiology,* 8th Edition, Chapter 61

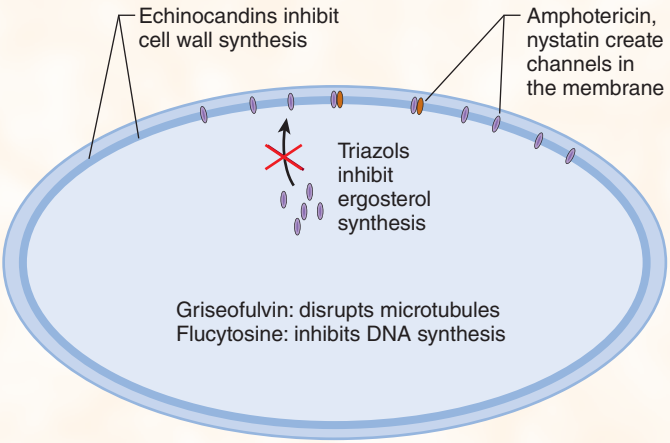

Figure 159-1: Ergosterol is the major antifungal target!

Table 159-1

Agent	Target	Mechanism
Polyenes (amphotericin B, nystatin)	Amphotericin: broad antifungal activity: invasive fungal infections: *Candida, Aspergillus, Cryptococcus,* etc Nystatin: dermatophytes, oral *Candida*	Membrane sterols (bind to ergosterol)
Azole derivatives (miconazole, ketoconazole, fluconazole, voriconazole, posaconazole, itraconazole)	Broad-spectrum antifungals: *Candida, Aspergillus, Cryptococcus,* dermatophytes, systemic mycoses (depending on specific drug)	Ergosterol biosynthesis
Nucleoside analogues (5-fluorocytosine)	Yeasts: *Cryptococcus, Candida, Chromomycosis*	DNA and RNA synthesis
Griseofulvin	Dermatophytes, tinea capitis	Inhibit microtubule function
Allylamines (naftifine, terbinafine)	Dermatophytes	Inhibit squalene epoxidase: ergosterol biosynthesis
Pentamidine	*Pneumocystis*	Inhibition of topoisomerase and DNA replication

Antifungal Agents

Table 159-2

Infection	Amphotericin	Triazoles*	Echinocandin†	Other
Ringworm				Topical: terbinafine, miconazole, ketoconazole, undecylenic acid, etc Oral: griseofulvin
Candida	++	++	++	
Aspergillus	++	++ (not fluconazole)	++	
Mucor		Posaconazole		
Fusarium		++ (not fluconazole)		
Cryptococcus neoformans	++	++		Flucytosine with amphotericin
Histoplasma capsulatum	++	++		
Blastomyces dermatitidis	++	++		
Coccidioides immitis	++	++		
Pneumocystis				Pentamidine, trimethoprim-sulfamethoxazole
Side effects	Fever, chills, nausea, vomiting, hypotension, hypoxemia, pain, renal failure	As a p450 inhibitor, drug-drug interactions can occur	Well tolerated	

*Include fluconazole, itraconazole, posaconazole, and voriconazole.
†Include caspofungin, micafungin, and anidulafungin.

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Aspergillus: Part One

Murray: *Medical Microbiology,* 8th Edition, Chapter 64

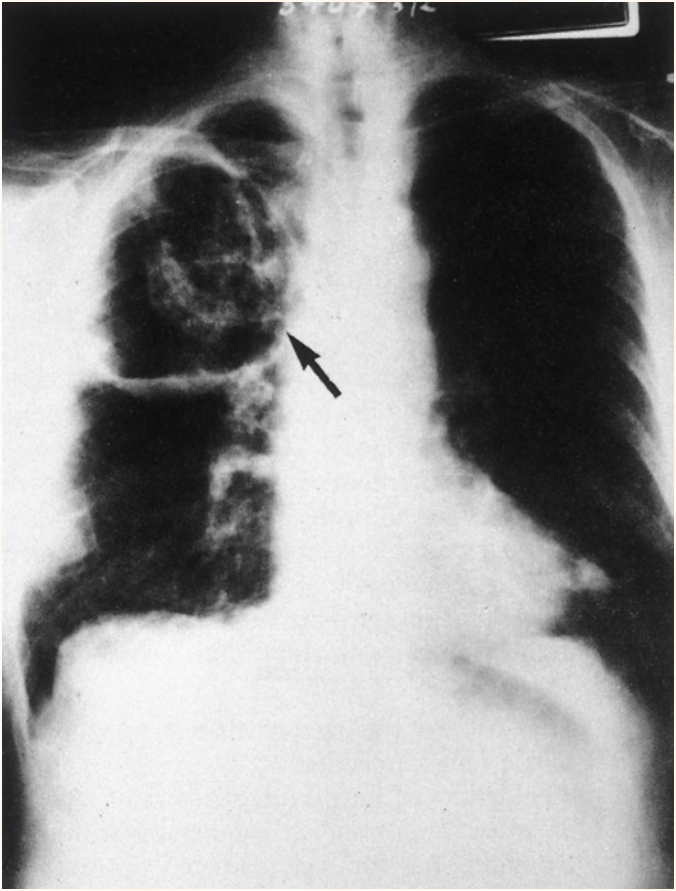

Figure 160-1: Aspergillus fumigatus *fungus ball on chest radiograph.*

Aspergillus: Part One

CASE STUDY

An elderly man presents with hemoptysis. He denied any fevers, night sweats, or past history of tuberculosis. He tells the physician that he had a past history of alcoholism and severe pneumonia. A chest radiograph shows a large cavitary lesion in the right upper lobe.

TRIGGER WORDS

"Fungus ball"
Septate, branching hyphae
Fruiting bodies
Hypersensitivity pneumonitis (allergic alveolitis)
Angioinvasive
Malt (grain) workers

ESSENTIAL FACTS

- Opportunistic mycoses for immunosuppressed people
- *Aspergillus fumigatus* is ubiquitous
- Transmitted by airborne spores
- Induces allergic reactions
- *Aspergillus flavus* can cause similar diseases

STUDY BREAK

Aflatoxin, a mycotoxin produced by *Aspergillus flavus*, is a potent hepatic carcinogen.

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Aspergillus: Part Two

Murray: *Medical Microbiology,* 8th Edition, Chapter 64

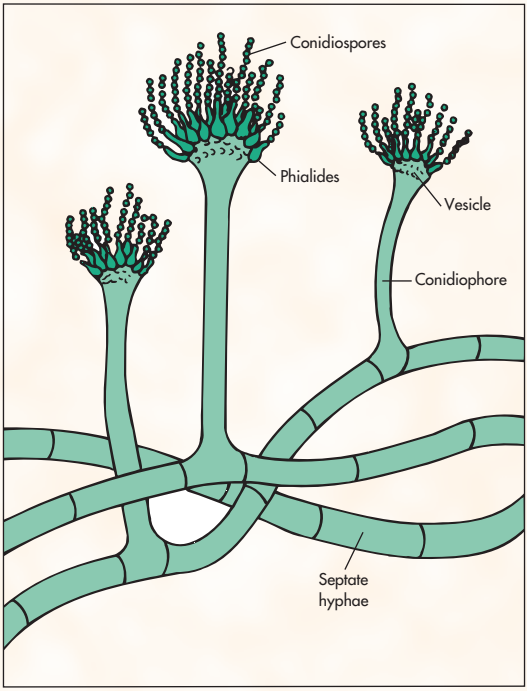

Figure 161-1: **Aspergillus** *fruiting bodies.*

Aspergillus: Part Two

STRUCTURE

Filamentous with branched, septate hyphae

LAB ID

Visualization of septate, branching hyphae in clinical specimens

VIRULENCE FACTORS

Tissue invasive; remains in mold form during infection

DISEASES

- Allergic aspergillosis: type I or type IV hypersensitivity; hypersensitivity pneumonitis; may lead to restrictive lung disease.
- Secondary colonization of cavitary lesions within the lungs previously caused by tuberculosis, abscesses, or malignancies leads to the formation of an aspergilloma, or "fungus ball," with few symptoms except hemoptysis.
- Systemic aspergillosis: fungus invades blood vessels and is usually rapidly fatal without aggressive treatment.

EPIDEMIOLOGY

Mold is ubiquitous.

PREVENTION

- Allergic aspergillosis: avoidance of exposure
- Systemic aspergillosis: treatment of immunosuppression

TREATMENT

- Aspergilloma (fungus ball): requires surgical excision.
- Allergic aspergillosis: treat as for hypersensitivity pneumonitis. Avoid exposure and corticosteroid treatment for acute attacks.
- Systemic aspergillosis: amphotericin B, itraconazole, voriconazole, caspofungin

162

Black and White Piedra

Murray: *Medical Microbiology,* 8th Edition, Chapter 62

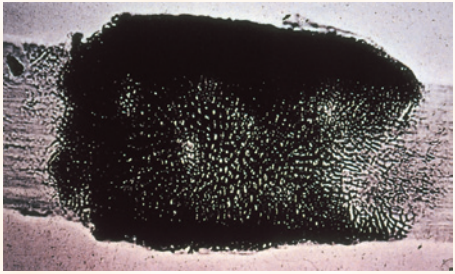

Figure 162-1: Microscopic view of black piedra showing the fungi spores within and along the hair shaft.

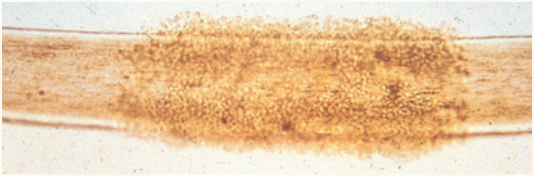

Figure 162-2: White piedra.

CASE STUDY

- A nurse found "nits" on a child. Physical exam shows tiny black nodules on the hair shaft. Microscopically, the nodules are packed with many small, round spores: **black piedra**
- A man presents with a greasy, white substance in his beard. Examination shows soft, pasty sleeves around the hair shafts: **white piedra**

TRIGGER WORDS

- **Black piedra:** Nodules along the hair shaft with ascospores
- **White piedra:** Sleeve or collar around the hair shaft; on mustache, beard, and scalp

Black and White Piedra

ESSENTIAL FACTS

Black Piedra

- *Piedraia hortae*; may be confused with the nits of pediculosis or abnormal hair growth.
- Affects everything above a shirt's collar, including mustache, beard, and scalp.

White Piedra

- *Trichosporon beigelii*
- May be confused with the nits of pediculosis

STRUCTURE

- Black piedra: nodules contain asci and ascospores of fungus.
- White piedra: collarette is composed of mycelia that rapidly fragment into arthroconidia.

LAB ID

Diagnosed easily by examining the nodules on affected hairs

DISEASES

Black or white piedra superficial fungal infections

EPIDEMIOLOGY

More common in lower socioeconomic classes

PREVENTION

Proper personal hygiene

TREATMENT

Cutting hair below the nodules removes the fungus.

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Blastomyces dermatitidis

Murray: *Medical Microbiology,* 8th Edition, Chapter 58

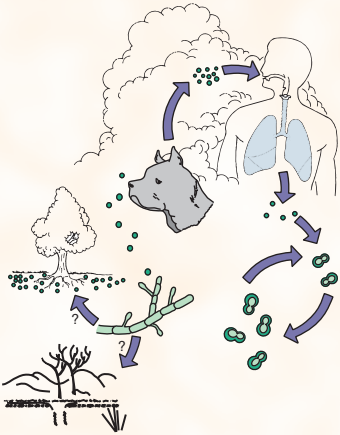

Figure 163-1: Natural history of the saprobic and parasitic cycle of Blastomyces dermatitidis.

CASE STUDY

- A tourist to Mississippi experiences fever, shortness of breath, and cough during his trip. He then develops skin nodules that begin to ulcerate. In the hospital, radiographs show lytic bone lesions, and he undergoes emergent treatment with amphotericin B.
- A month after hunting in Wisconsin, a 37-year-old Wisconsin man had flulike symptoms, bacterial-like pneumonia, and skin lesions on his face.

TRIGGER WORDS

Mississippi and Ohio River Valleys
Dimorphic fungus
Broad-based budding yeast
Granuloma

ESSENTIAL FACTS

- Systemic mycoses transmitted by inhalation of spores
- Endemic in midwestern United States
- Untreated blastomycosis rapidly fatal

Blastomyces dermatitidis

STUDY BREAK

For *Blastomyces*, think "BBB" for broad-based budding yeast.

STRUCTURE

Dimorphic fungi; tissue biopsies and lung abscesses show large broad-based budding yeast.

LAB ID

Biopsy analysis, immunologic identification of exoantigen (immunodiffusion; eg, Ouchterlony test), genome detection (polymerase chain reaction)

VIRULENCE FACTORS

Causes disease in healthy people; evades host defenses.

DISEASES

- Asymptomatic blastomycoses: most common.
- Symptomatic blastomycoses: mild pneumonia with cough, fever, and lung infiltrates on chest radiograph.
- Disseminated blastomycoses: fungi spreads hematogenously to the skin, bones, and prostate; causes granulomas that progress into suppurative ulcers and lytic bone and prostate lesions.

EPIDEMIOLOGY

Endemic to the midwestern United States, especially the Mississippi River Valley; symptomatic and disseminated infections occur in normal but especially immunocompromised patients.

PREVENTION

Treat underlying immunosuppression.

TREATMENT

All infections must be treated aggressively with itraconazole or amphotericin B because it can be rapidly fatal.

164

Candida albicans: Part One

Murray: *Medical Microbiology*, 8th Edition, Chapter 65

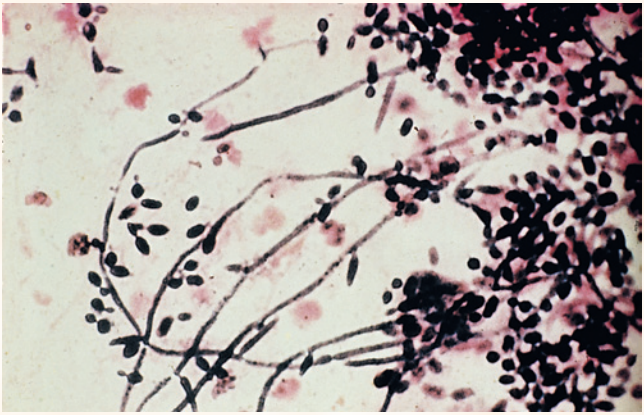

Figure 164-1: Gram stain of C. albicans.

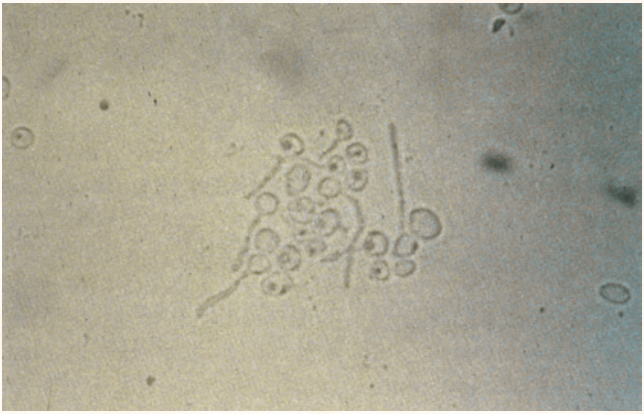

Figure 164-2: C. albicans *germ tubes after culture in serum.*

Candida albicans: Part One

CASE STUDIES

- During a 2-month well-baby exam, a physician notices several clumpy, white patches on the infant's buccal mucosa. The mother states that she had originally thought it was caused by formula residue but that she was unable to remove it. The baby also has some minor diaper rash that the mother is treating with baby powder.
- A patient with AIDS has a painful, thick, white coat on his tongue and gums: **thrush**

TRIGGER WORDS

White, curdlike, adhesive plaques on tongue and oral mucosa that bleed when removed for culture
"Cobblestones"
Endemic and opportunistic
Prolonged use of antibiotics
Immunocompromised: AIDS, diabetic people, transplant recipients, chemotherapy patients, babies
Vaginal yeast
Thrush

ESSENTIAL FACTS

- Normal flora in mucosal area (eg, mouth, vagina)
- *Candida albicans* is a common contaminant in urine, stool, and sputum cultures.
- Opportunistic mycoses cause cutaneous infections in the normal host and invasive, disseminating infections in immunocompromised people.
- Often affects the lungs, spleen, kidney, liver, heart, and brain.
- Other *Candida* species include *C. tropicalis*, *C. glabrata*, *C. pseudotropicalis*, *C. krusei*, and *C. parapsilosis*.

STUDY BREAK

There is an enormous over-the-counter market for treatment of vaginal yeast problems caused by *Candida*.

165

Candida albicans: Part Two

Murray: *Medical Microbiology,* 8th Edition, Chapter 65

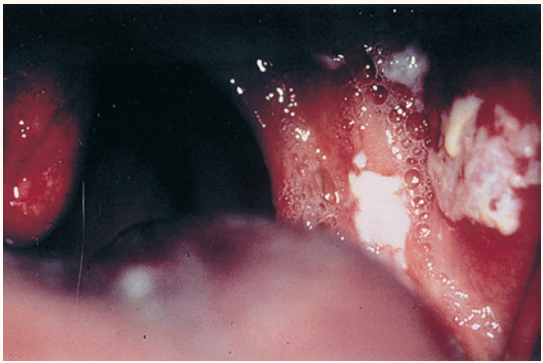

Figure 165-1: Thrush: C. albicans.

STRUCTURE

Pseudohyphae; budding yeasts

LAB ID

- Periodic acid–Schiff, calcofluor white, Gomori methenamine silver staining
- Identified and differentiated from other *Candida* fungi by ability to ferment and assimilate specific carbohydrates
- Germ tube test: hyphal growths

VIRULENCE FACTORS

Adhesins, secreted proteases and phospholipases, changes in antigen expression, colony morphology, and tissue affinities

Candida albicans: Part Two

DISEASES

- **Cutaneous candidiasis:** oral thrush; most common in diabetics, neonates, patients with AIDS and other forms of immunosuppression, patients on antibiotics or steroids
- **Vulvovaginitis:** increased frequency during pregnancy, menses, antibiotic use, and diabetes
- **Diaper rash:** erythematous, macerated skin beneath diaper and within skin folds
- **Chronic mucocutaneous candidiasis:** infections of skin, hair, nails, and oropharynx (esophagitis) seen in endocrine defects, such as hypoadrenalism, hypoparathyroidism, hypothyroidism, thymoma, and cell-mediated immune deficiency
- **Disseminated disease:** infection spreads through the blood, often affecting the lungs, spleen, kidney, liver, heart, and brain in immunocompromised patients; may cause endophthalmitis

EPIDEMIOLOGY

- Normal flora that causes disease in normal and special conditions
- Classic opportunistic disease for AIDS patients

PREVENTION

Limit duration of broad-spectrum antibiotic treatment; correction of underlying illnesses that increase susceptibility

TREATMENT

Varies according to disease:

- Oral thrush: swish and spit preparations of nystatin; imidazole lozenges, peroxide
- Vaginitis: imidazole vaginal suppositories
- Diaper rash: keep affected areas dry and clean; powders
- Chronic mucocutaneous: fluconazole and itraconazole topical creams may be used for skin infections
- Disseminated infections: amphotericin B alone or with 5-fluorocytosine; azoles and echinocandin

166

Chromoblastomycosis and Eumycotic Mycetomas: Part One

Murray: *Medical Microbiology*, 8th Edition, Chapter 63

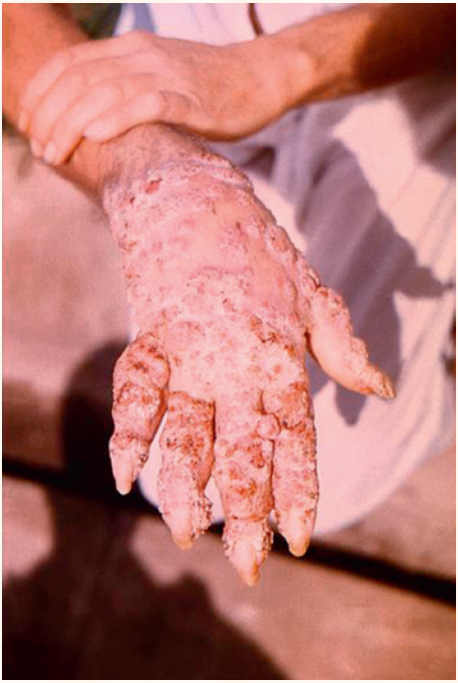

Figure 166-1: Clinical presentation of chromoblastomycosis.

Chromoblastomycosis and Eumycotic Mycetomas: Part One

CASE STUDIES

- A migrant farm worker presents with several large, warty nodules on his forearm. He cut himself while working in the fields and afterward small, rough bumps developed over the area. They grew slowly, coalescing into cauliflower-like lesions: **chromoblastomycosis**
- A homeless patient presents at a clinic with a swollen, painful foot. On physical exam the foot is deformed with many draining sinus tracts. Microscopic examination of the purulent fluid shows microcolonies, or small grains of fungal tissue: **eumycotic mycetoma**

TRIGGER WORDS

Chromoblastomycosis
Dematiaceous (brown or black, melanin-producing) fungus
Sclerotic bodies, outside growth type skin disease
Cauliflower-like, vegetative, verrucous (warty) nodules

Eumycotic Mycetoma
Dematiaceous fungus
Many draining sinus tracts
"Grains" of microcolonies in the exudates
Localized infection, deep layer of skin disease

ESSENTIAL FACTS

- Subcutaneous mycoses may be caused by several common soil fungi when inoculated into the tissue by a cut or puncture wound. Infection leads to the characteristic pseudoepitheliomatous hyperplasia.
- Bacterial infections by *Actinomyces*, *Nocardia*, *Streptomyces*, and *Actinomadura* infections mimic **eumycotic mycetoma**.

167

Chromoblastomycosis and Eumycotic Mycetomas: Part Two

Murray: *Medical Microbiology,* 8th Edition, Chapter 63

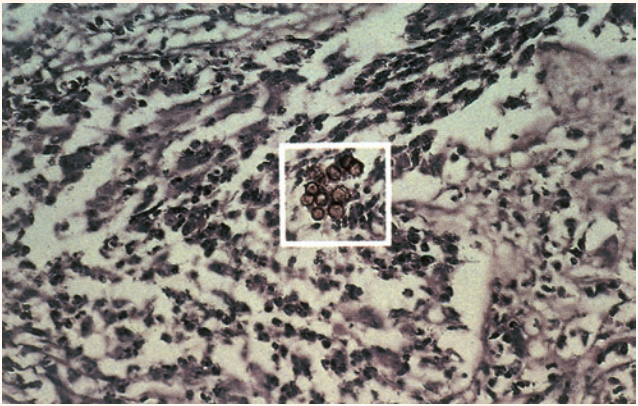

Figure 167-1: Chromoblastomycosis sclerotic Medlar bodies.

STRUCTURE

Varies according to etiologic agent

LAB ID

Characteristic pseudoepitheliomatous hyperplasia (cauliflower-like growths); copper-colored spherical cells in different stages of cell division appear in skin scrapings treated with KOH, known as *sclerotic bodies.*

VIRULENCE FACTORS

Low infective potential: contamination of a wound

DISEASES

Chromoblastomycosis

Chromoblastomycosis and Eumycotic Mycetomas: Part Two

EPIDEMIOLOGY

Uncommon in developed nations, although causative agents are found very commonly; usually affects patients with normal immunity.

PREVENTION

Wearing gloves and long sleeves while working

TREATMENT

Itraconazole, posaconazole; total excision of lesion or amputation may be necessary because antifungal drugs are generally ineffective.

168

Coccidioides immitis: Part One

Murray: *Medical Microbiology,* 8th Edition, Chapter 64

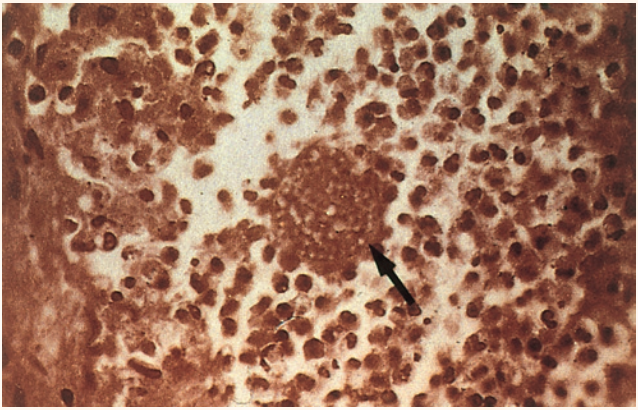

Figure 168-1: Multinucleate spherule of Coccidioides immitis.

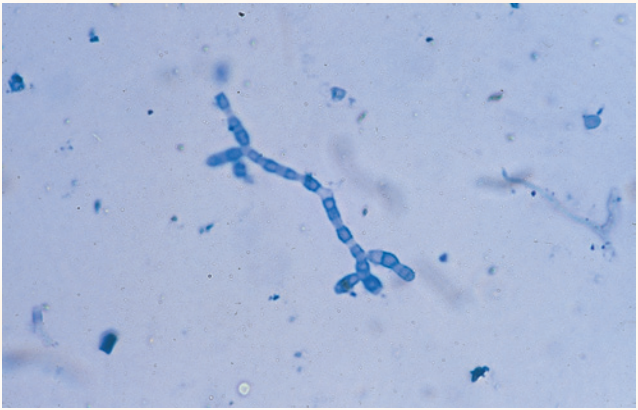

Figure 168-2: Hyphae and arthroconidia.

Coccidioides immitis: Part One

CASE STUDY

A woman traveled to Arizona for a business trip. During her stay, a dust storm hit the region. Afterward, she developed a fever, cough, and body aches. She also noticed small, erythematous nodules over her shins. She recovered from the illness with no treatment.

TRIGGER WORDS

San Joaquin River Valley
American deserts
Spherules
Skin test for antigen exposure

ESSENTIAL FACTS

C. immitis
Systemic mycoses transmitted by inhalation of arthroconidia; endemic in southwestern U.S. desert areas

Paracoccidioidomycosis *(Paracoccidioides brasiliensis)*
Central and South America (Brazil), dimorphic fungi, lung infection or disseminated disease

STUDY BREAK

The mycelia of *C. immitis* are so brittle that they are easily transmitted; *C. immitis* is a leading cause of laboratory-acquired infections.

169

Coccidioides immitis: Part Two

Murray: *Medical Microbiology,* 8th Edition, Chapter 64

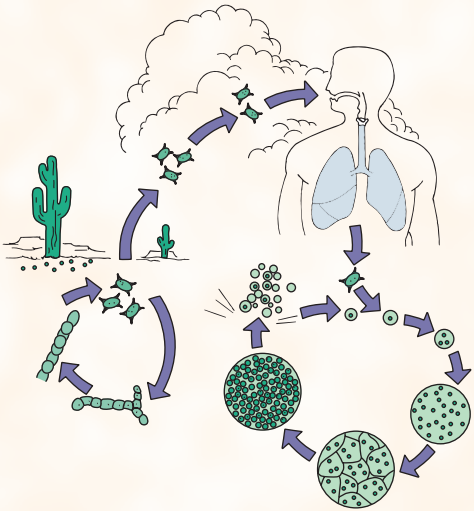

Figure 169-1: Natural history of the saprobic and parasitic cycle of C. immitis.

STRUCTURE

Dimorphic fungus; mycelia of *C. immitis* break to produce cylindrical arthroconidia; within the body, it grows as a multinucleate spherule (yeast-like).

LAB ID

- Skin test for fungal antigen that is analogous to the tuberculosis purified protein derivative test
- Identification of spore-containing spherules in tissues
- Nucleic acid detection, latex particle agglutinin antigen detection

Coccidioides immitis: Part Two

VIRULENCE FACTORS

Causes disease in healthy individuals; can evade host defenses

DISEASES

- Primary coccidioidomycosis (San Joaquin Valley fever); flu like illness with fever, cough, and joint pain; erythema nodosum and night sweats may also be present; disease is usually self-limiting; may disseminate to produce meningitis or skin infections or cause progressive pulmonary disease.
- Asymptomatic coccidioidomycosis is most common.

EPIDEMIOLOGY

Arid areas of the American continents; most prevalent in the San Joaquin Valley in California, Arizona, and Texas due to their semiarid climates; fungus spreads extensively during dust storms; disseminated disease occurs in immunocompromised people.

PREVENTION

Avoid exposure

TREATMENT

- Usually self-limited disease requiring no treatment
- Chronic or disseminated disease: amphotericin B, oral fluconazole, itraconazole, or other newer azole is required for months.

170

Cryptococcus neoformans: Part One

Murray: *Medical Microbiology,* 8th Edition, Chapter 65

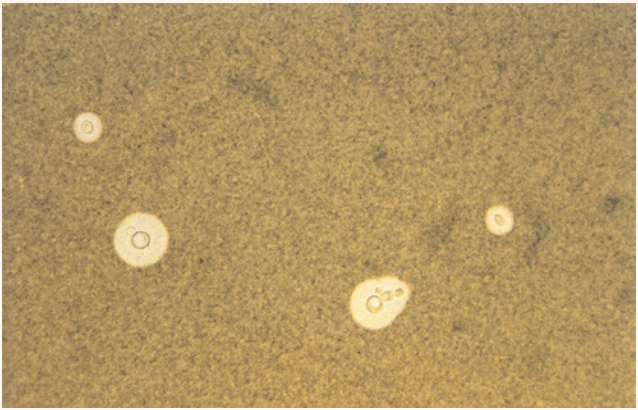

Figure 170-1: The clear capsule of C. neoformans *in cerebrospinal fluid is delineated by India ink.*

CASE STUDY

A young man was renovating an apartment in New York City in an area with significant pigeon droppings when he developed a headache and fever. One week later, his sister came to visit him and found him on his couch in a stupor. A spinal tap was performed in the emergency department, which revealed multiple round organisms with clear halos visualized with India ink: *C. neoformans* meningitis

TRIGGER WORDS

Pigeon and bird droppings (likes the amines)
Capsule
India ink preparations
Capsular antigens
Patients with AIDS, meningitis

Cryptococcus neoformans: Part One

ESSENTIAL FACTS

- Systemic mycosis is transmitted by inhalation and spreads into the central nervous system and to the skin and bones.
- A leading cause of fungal meningitis
- Capsule protects the fungus from phagocytosis and extends its time in the blood, allowing it to reach and remain in the meninges.
- Encapsulated organisms that cause meningitis (eg, *C. neoformans, S. pneumoniae, H. influenzae* B, *N. meningitidis*).

STUDY BREAK

- The ***crypt*** of *Cryptococcus* is the ***capsule*** that houses the ***round*** yeast (coccus).
- *C. neoformans* is a regular television star on medical dramas because the India ink test for organisms in cerebrospinal fluid from a meningitis patient is so diagnostic.

171

Cryptococcus neoformans: Part Two

Murray: *Medical Microbiology*, 8th Edition, Chapter 65

STRUCTURE

Monomorphic; encapsulated yeast

LAB ID

- Capsular antigen in blood
- India ink visualization of clear capsule around the organism in cerebrospinal fluid: rapid diagnosis but less sensitive
- Culture: definitive diagnosis

VIRULENCE FACTORS

Capsule prevents phagocytosis; predilection for the central nervous system (CNS); little or no inflammatory response in lungs or meninges

DISEASES

- Cryptococcal meningitis: headache, mental status changes, and fever of several weeks' duration; occurs by hematogenous spread of yeast from the lungs to the meninges
- Primary pulmonary cryptococcosis: usually asymptomatic; may develop a solitary nodule resembling a carcinoma
- Cutaneous and osseous infection: lytic and granulomatous lesions; may occur with or without CNS involvement

EPIDEMIOLOGY

Spread in pigeon droppings. Occurs throughout the world; symptomatic disease in normal people but immunocompromised people are highly susceptible.

Cryptococcus neoformans: Part Two

PREVENTION

Avoid exposure to bird droppings

TREATMENT

Amphotericin B with 5-fluorocytosine for meningitis; prolonged fluconazole or itraconazole administration for patients with AIDS

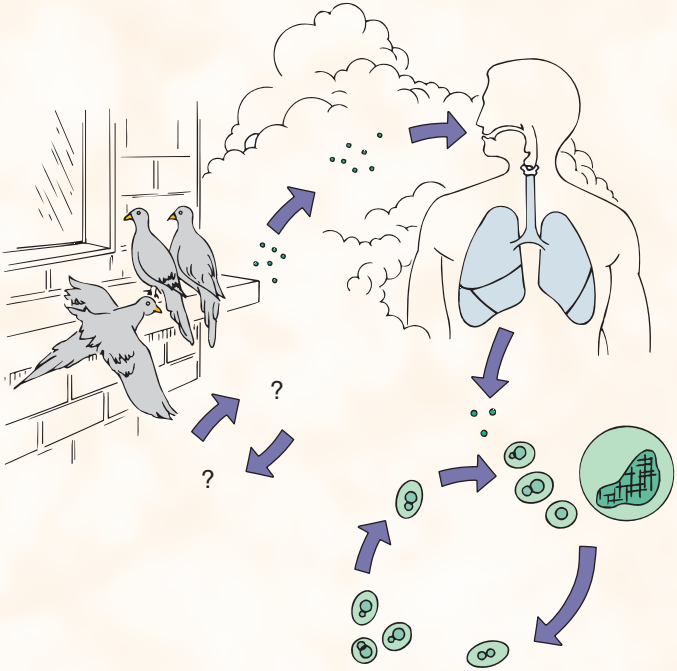

Figure 171-1: Natural history of the saprobic and parasitic cycle of C. neoformans.

172

Histoplasma capsulatum: Part One

Murray: *Medical Microbiology,* 8th Edition, Chapter 58

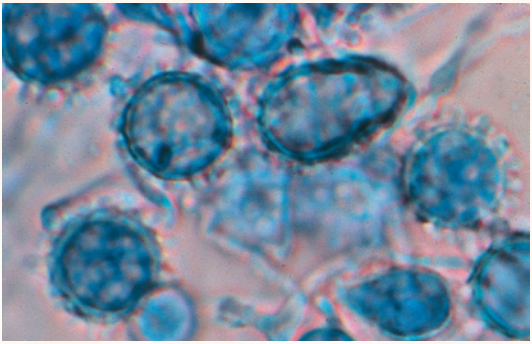

Figure 172-1: Tuberculate macroconidia and microconidia of H. capsulatum.

CASE STUDY

A Cincinnati native is being evaluated for lung cancer. Computed tomographic scans show numerous granulomatous masses in the lungs and spleen. A biopsy of a lesion reveals numerous yeasts within monocytes.

TRIGGER WORDS

Ohio and Mississippi River Valleys
Lung and spleen granulomas
Yeasts inside macrophages
Bird and bat droppings (likes the amines)
"Cincinnati spleen"

Histoplasma capsulatum: Part One

ESSENTIAL FACTS

Systemic mycoses: transmitted by inhalation of spores or hyphal elements, which are phagocytosed by alveolar macrophages. There may be a transient period of dissemination into the blood and spread to the spleen. Less than 1% become symptomatic and require therapy.

STUDY BREAK

Histoplasmosis is also known as "spelunker's disease" because it frequently infects cave explorers.

Symptoms of histoplasmosis may be confused with tuberculosis because both grow intracellularly in alveolar macrophages and cause granulomas.

173

Histoplasma capsulatum: Part Two

Murray: *Medical Microbiology*, 8th Edition, Chapter 58

STRUCTURE

Dimorphic; yeast form is found in mononuclear cells of the alveoli and bone marrow.

LAB ID

- Detection of exoantigen in serum or urine, rapid diagnosis
- Culture from the blood or sputum, requires 1 to 2 weeks
- Direct visualization of intracellular yeasts in infected tissue

VIRULENCE FACTORS

Replication within macrophages can allow spread to other tissues.

DISEASE

- Asymptomatic or mild flu like illness: occurs with normal exposure
- Acute pulmonary histoplasmosis occurs after prolonged, intense exposure
- Disseminated fever, weight loss, night sweats, splenomegaly: occurs with defects in cell-mediated immunity
- Chronic pulmonary histoplasmosis: similar to tuberculosis with a chronic granulomatous infection

EPIDEMIOLOGY

- Ohio and Mississippi River Valleys
- Places with large amounts of bat and bird excreta (caves, chicken coops, attics)
- Disseminated and chronic pulmonary histoplasmosis occurs in immunocompromised people

Histoplasma capsulatum: Part Two

PREVENTION

Reduce exposure to areas with bat and bird infestation

TREATMENT

No treatment for chronic case; amphotericin B for acute, symptomatic infection followed by itraconazole. Immunocompromised people may require lifelong itraconazole treatment.

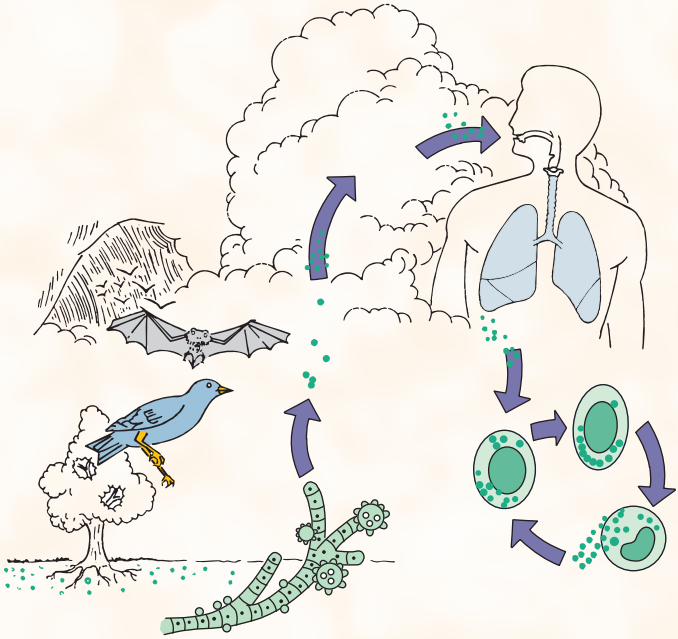

Figure 173-1: Natural history of the saprobic and parasitic cycles of H. capsulatum.

174

Pneumocystis jirovecii (P. carinii)

Murray: *Medical Microbiology,* 8th Edition, Chapter 65

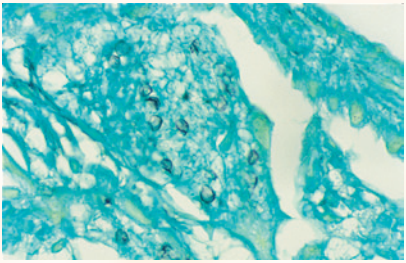

Figure 174-1: Gomori methenamine silver stain of lung biopsy. Note the rounded, cup-shaped organisms.

CASE STUDY

An AIDS patient fails to take his prescription for trimethoprim-sulfamethoxazole (TMP-SMX) regularly and gradually develops a fever, shortness of breath, and a nonproductive cough. A chest radiograph reveals a diffuse interstitial infiltrate, and bronchoalveolar lavage shows numerous cup-shaped organisms in a foamy alveolar exudate.

TRIGGER WORDS

Diffuse interstitial pneumonia
Gomori silver stain
AIDS patient/intravenous drug abuser
Fluffy, foamy alveolar exudate
Cup-shaped (flying saucer) organisms in lavage
Ground-glass appearance of lung on radiograph

ESSENTIAL FACTS

- Opportunistic mycoses is common in AIDS patients and severely immunocompromised people; transmitted by inhalation from environment.
- Lungs have a "cotton candy" or ground glass appearance due to the alveolar exudate; **diagnostic disease of AIDS.**

Pneumocystis jirovecii (P. carinii)

STRUCTURE

Cup-shaped or flying saucer–shaped fungi

LAB ID

Gomori silver stain of sputum, bronchoalveolar lavage, or a lung biopsy sample reveals the cup-shaped organisms.

VIRULENCE FACTORS

Attaches to pulmonary epithelial cells and forms a resistant cyst stage

DISEASES

Pneumocystosis: interstitial pneumonitis with plasma cell infiltrates. Radiographs show infiltrations spreading from hilar areas, giving lungs a cotton candy/ground-glass appearance.

EPIDEMIOLOGY

Common in AIDS patients and premature and malnourished children. Infections in normal hosts are completely asymptomatic.

PREVENTION

Prophylactic TMP-SMX given when CD4+ T-cell counts drop below 200 to 250 cells/mm^3.

TREATMENT

High-dose TMP-SMX or intravenous pentamidine

STUDY BREAK

P. jirovecci was initially called *P. carinii*, but it is now known that *P. carinii* infects only animals.

175

Pityriasis Versicolor: *Malassezia furfur*

Murray: *Medical Microbiology,* 8th Edition, Chapter 62

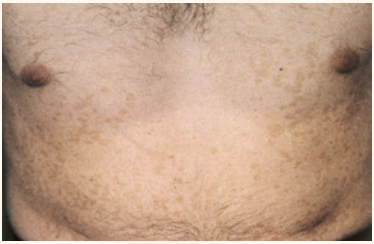

Figure 175-1: Clinical presentation of pityriasis versicolor.

CASE STUDY

A patient presents to his family physician with hypopigmented macules on his upper torso and arms. They do not itch, and he states that he first noticed the patches after he had been sunbathing during a recent vacation.

TRIGGER WORDS

Hypopigmented/hyperpigmented patches
"Spaghetti and meatballs" KOH preparation

ESSENTIAL FACTS

Superficial mycoses involving the outermost layers of the stratum corneum that result in cosmetic problems only. The causative organism is *Malassezia furfur.*

STUDY BREAK

Malassezia furfur is unusual in that it also often contaminates parenteral feeding preparations rich in lipids, producing a "furry" layer on the top of the solution.

Pityriasis Versicolor: *Malassezia furfur*

STRUCTURE

Hyphae with spherical yeast

LAB ID

Microscopic examinations of skin scrapings using KOH to dissolve nonfungal debris reveal hyphae (spaghetti) with spherical yeast (meatballs).

VIRULENCE FACTORS

Lipophilic nature allows it to thrive on oily patches of the skin. Because it only infects the stratum corneum, it usually does not evoke an immune response.

DISEASES

Pityriasis versicolor

EPIDEMIOLOGY

Most commonly infects the upper torso, arms, and abdomen (areas rich in sebaceous glands).

TREATMENT

Topical imidazoles; dandruff shampoo containing selenium sulfide

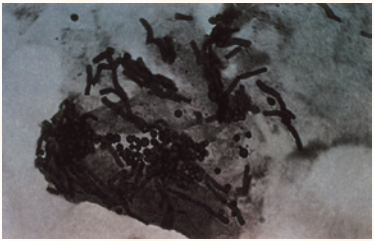

Figure 175-2: Pityriasis versicolor KOH preparation.

176

Rhizopus and *Mucor*

Murray: *Medical Microbiology,* 8th Edition, Chapter 65

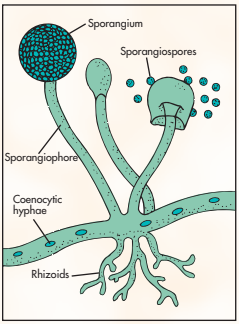

Figure 176-1: Asexual fruiting structure of Rhizopus *species.*

CASE STUDY

A patient with diabetic ketoacidosis develops a thick black discharge from her nostril. The infection spreads quickly into her brain, and she dies within hours.

TRIGGER WORDS

Acidotic diabetic
Paranasal sinus and ocular orbit involvement
Coenocytic (aseptate) hyphae
Black nasal discharge
Bread mold

ESSENTIAL FACTS

- Opportunistic mycoses: saprophytic fungi of many different ubiquitous species
- Transmitted by inhalation of airborne spores

STUDY BREAK

Rhizopus and *Mucor* also infect horses and are important veterinary pathogens. *Rhizopus nigricans* is the common bread mold.

Rhizopus and *Mucor*

STRUCTURE

Filamentous; coenocytic; broad, branching hyphae

LAB ID

Diagnosed by distinct morphology seen on biopsy

VIRULENCE FACTORS

Angio-invasiveness causes fungal emboli that obstruct blood vessels and cause ischemia and necrosis of the supplied tissues.

DISEASES

- Rhinocerebral zygomycosis: infection originates in paranasal sinuses and ocular orbit in acidotic or hyperglycemic diabetics and can rapidly spread to the palate and brain, leading to death. Patients have a black nasal discharge because of the ischemia and necrosis of the affected tissues.
- Pulmonary mucormycosis; gastrointestinal tract infections

EPIDEMIOLOGY

- Acidotic individuals (eg, diabetics)
- Pulmonary: neutropenic patients
- Gastrointestinal: malnourished children

PREVENTION

Treatment of hyperglycemia, acidosis, and immunosuppression

TREATMENT

Surgical debridement of necrotic tissue; amphotericin B, posaconazole

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Sporothrix schenckii

Murray: *Medical Microbiology,* 8th Edition, Chapter 63

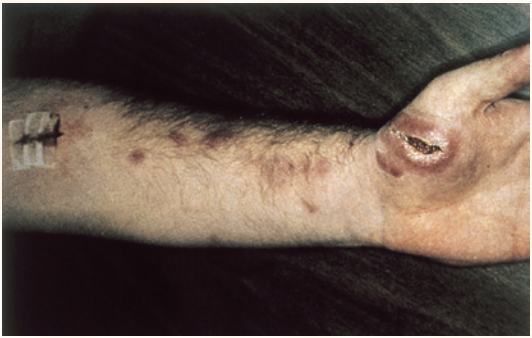

Figure 177-1: Clinical presentation of sporotrichosis.

CASE STUDY

A patient presents with a cutaneous ulcer and a series of nodules along his forearm. Several weeks earlier, he was punctured by a rose thorn while gardening. A painless bump developed at that site, which gradually enlarged and then ulcerated.

TRIGGER WORDS

Roses
Thorn prick
Splinter
Gardener

ESSENTIAL FACTS

Sporothrix schenckii are often present in soil or decaying vegetation and usually enter through cuts or puncture wounds from thorns, splinters, or sharp tools. The infection spreads along the lymphatic tracts that drain the site of inoculation.

Sporothrix schenckii

STUDY BREAK

Sporothrix schenckii can be remembered as one of the few occupational hazards of a rose gardener.

STRUCTURE

Dimorphic fungus: Culture at 37°C yields yeast; culture at 25°C yields branching hyphae.

LAB ID

Positively identified by culture: colonies become brown to black with age and produce a typical rosette pattern.

VIRULENCE FACTORS

Infects through wounds. The clinical manifestations are caused by the organism and the host's immune responses.

DISEASES

- Subcutaneous lymphangitic sporotrichosis: After inoculation (eg, by thorn), a painless nodule develops at the site of injury. It gradually enlarges and ulcerates as other nodules begin to appear along the lymphatic tracts.
- Pulmonary sporotrichosis, fixed cutaneous sporotrichosis, or mucocutaneous, extracutaneous, or disseminated disease may also occur.

EPIDEMIOLOGY

Gardeners and landscapers are at risk.

TREATMENT

- Subcutaneous lymphangitic: oral potassium iodide
- Extracutaneous: amphotericin B, itraconazole

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Tineas: *Microsporum*, *Trichophyton*, and *Epidermophyton*: Part One

Murray: *Medical Microbiology,* 8th Edition, Chapter 62

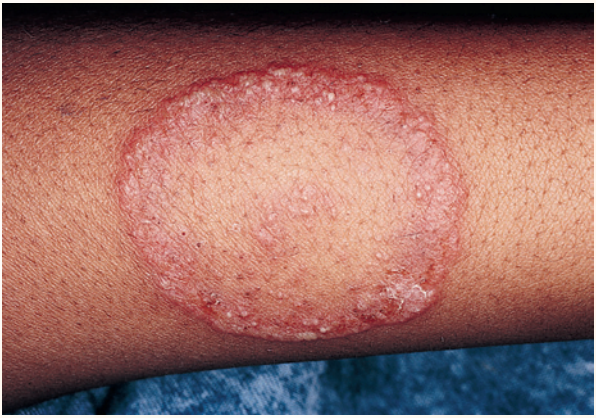

Figure 178-1: Tinea corporis.

CASE STUDY

A woman presents with a itchy, flaky, erythematous rash with circular lesions and some central clearing on the neck that expands in size. The rash started when she had to wear a turtleneck as part of her uniform.

TRIGGER WORDS

Keratin
Circular, scaling lesion with central clearing and hair loss
Discoloring
Crumbling nails
Azoles
Ringworm

Tineas: *Microsporum*, *Trichophyton*, and *Epidermophyton*: Part One

ESSENTIAL FACTS

- Dermatophytoses: *Microsporum*, *Trichophyton*, and *Epidermophyton*
- Cutaneous fungal infections of keratin-containing tissues: skin, hair, and nails
- Symptoms: itching, scaling, and redness of the affected skin
- **Tinea capitis:** scalp; **tinea cruris:** groin (jock itch); **tinea pedis:** athlete's foot; **tinea unguium:** nails

STUDY BREAK

Tinea pedis is a common infection in troops deployed to the Middle East because the fungi thrive in the warm, moist, dark environment of the troops' sweaty combat boots.

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Tineas: *Microsporum*, *Trichophyton*, and *Epidermophyton*: Part Two

Murray: *Medical Microbiology*, 8th Edition, Chapter 62

STRUCTURE

Branched hyphae

LAB ID

- Dissolve skin scrapings in KOH to reveal branched hyphae
- Use Wood's lamp (ultraviolet light of a specific wavelength) to examine hair and skin directly. Certain *Microsporum* species fluoresce bright green.

VIRULENCE FACTORS

Keratinase: causes scaling, hair loss, and brittle, flaky nails

DISEASES

Named according to the tissue or region that is affected:

- **Tinea corporis:** "ringworm"; infection of skin on the body that causes a round, red, bumpy, and scaly lesion that resembles a worm under the skin. The raised borders often expand with healing and clearing of the circle's center. May occur anywhere but prefers warm, moist areas.
- **Tinea cruris:** "jock itch"; itching and redness in patches on the groin and scrotum
- **Tinea pedis:** "athlete's foot"; cracking and peeling of the skin between the toes and on the soles
- **Tinea capitis:** "cradle cap"; scaly scalp lesions with loss of hair, which primarily occurs in children
- **Tinea unguium:** onychomycosis (yellow, thickened, crumbling nails)

Tineas: *Microsporum*, *Trichophyton*, and *Epidermophyton*: Part Two

EPIDEMIOLOGY

Close and crowded living conditions; depressed cell-mediated immunity

PREVENTION

Keep susceptible areas dry and clean.

TREATMENT

- Skin infections: topical imidazole or azoles; keep areas dry and exposed to air.
- **Tinea capitis**: griseofulvin; infection is cleared slowly because griseofulvin is incorporated into the newly synthesized keratin, inhibiting further infection as the old keratin is sloughed off.
- Ketoconazole and sulfur-containing shampoos
- **Tinea unguium**: azole antibiotics (topical or systemic); surgical or chemical removal of affected nail

180 Antiparasitic Agents

Murray: *Medical Microbiology,* 8th Edition, Chapter 72

Table 180-1

Life Cycle Stage	Drug	Mechanism
Schizont: prevents primary and *P. falciparum* and *P. malariae* infection	Quinoline drugs: chloroquine, mefloquine, halofantrine	Alters heme: prevents its metabolism
	Doxycycline	Disrupts mitochondria
	Artemisinin	Alters heme: prevents its metabolism
	Antifolates: TMP-SMX, pyrimethamine	Prevents folate metabolism
	Atovaquone-proguanil	Disrupts electron transport/ inhibits dihydrofolate reductase
Hepatic stage	Primaquine	Alters heme Prevents primary and late-onset illness Prevents all types of malaria

TMP-SMX, Trimethoprin-sulfamethoxazole.

Antimalarial Agents

- Drugs are active against specific stages of *Plasmodium* development.
  - *Plasmodium falciparum* and *P. malariae* treat blood phases of the plasmodia: chloroquine
  - *P. vivax* and *P. ovale* are hypnotized (hypnozoite) by the liver and need primaquine to treat blood and tissue phases.

Other Antiparasitic Agents

Table 180-2

Organism	Drug	Site of Attack
Plasmodium (malaria)	See front of card	See front of card
Plasmodium, Toxoplasma	Pyrimethamine, trimethoprim-sulfamethoxazole,	Folic acid pathway
	Doxycycline	Protein synthesis
Leishmania	Stibogluconate (antimonial compound)	Reduction of thiol groups
Ascaris, pinworm, hookworm	Pyrantel pamoate, piperazine	Neuromediators specific for parasites
Filaria, nematodes	Ivermectin	GABA-mediated mechanisms of parasite nervous system
Many nematodes, helminths, amebiasis, giardiasis, Ascaris	Benzimidazoles (mebendazole, albendazole)	Parasite-specific tubulin
Trypanosomes, *Leishmania*	Pentamidine	Topoisomerase II and DNA synthesis
Trypanosomes	Suramin	Enzyme inhibitor reduces ATP production
Trypanosomes (brain)	Melarsoprol	Enzyme inhibitor reduces ATP production
Amebiasis	Metronidazole	
Trematodes, cestodes and schistosomes	Praziquantel	Disrupts parasite surface to allow immune clearance

ATP, Adenosine triphosphate; GABA, γ-aminobutyric acid.

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Parasite Infections: Protozoa

Murray: *Medical Microbiology,* 8th Edition, Chapters 68 and 69

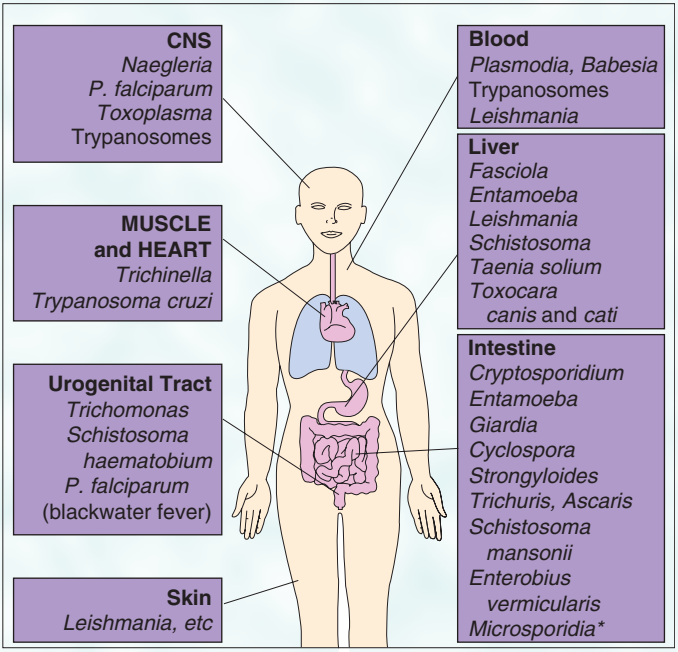


*Figure 181-1: The occurrence of protozoan parasites in the body. *Can also occur in other sites. CNS, Central nervous system.*

Parasite Infections: Protozoa

Table 181-1: Features of Medically Important Protozoa

Location	Species	Mode of Transmission	Disease
Intestinal tract	*Entamoeba histolytica*	Ingestion of cysts in food	Amebiasis
	Giardia lamblia		Giardiasis
	Cryptosporidium spp.		Cryptosporidiosis
	Cyclospora cayetanensis		Cyclosporiasis
	Microsporidia		Microsporidiosis
Urogenital tract	*Trichomonas vaginalis*	Sexual	Trichomoniasis
Blood and tissue	*Trypanosoma* spp.	Reduviid bug	Trypanosomiasis
	T. cruzi	Reduviid bug	Chagas disease
	T. gambiense	Tsetse fly	Sleeping sickness
	Leishmania spp., *L. donovani*	Sand fly	Visceral leishmaniasis (kala-azar)
	L. mexicana, L. tropica	Sand fly	Cutaneous leishmaniasis
	L. braziliensis	Sand fly	Mucocutaneous leishmaniasis
	Plasmodium spp. *P. vivax, P. ovale, P. malariae, P. falciparum*	*Anopheles* mosquito	Malaria
	Toxoplasma gondii	Ingestion of cysts in raw meat; contact with soil contaminated by cat feces	Toxoplasmosis
	Babesia spp.	Tick	Babesiosis

182

Protozoan Parasites: Diarrheas

Murray: *Medical Microbiology,* 8th Edition, Chapter 71

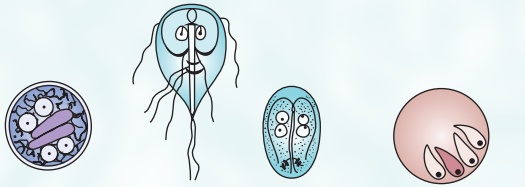


Figure 182-1: Protozoan enteric parasite.

CASE STUDIES

- After visiting a village in India, a 40-year-old woman developed abdominal cramps, fever, and frequent **watery diarrhea** (more than eight episodes per day) **with blood and mucus** for more than 2 weeks: ***Entamoeba histolytica* (amebic dysentery)**
- A 32-year-old person with **AIDS** develops watery, **nonbloody** diarrhea **without fever: cryptosporidiosis**
- Three weeks after returning from a **hiking trip in the Rocky Mountains**, a man developed a 10-day bout of abdominal cramping, severe flatus, and **foul-smelling** diarrhea with stools that float: **giardiasis (*Giardia lamblia*)**

TRIGGER WORDS

Giardia: old man looking over his shoulder (troph), contaminated creek water, foul-smelling diarrhea
Cryptosporidium: immune suppression, water supply
Entamoeba histolytica: amebic dysentery, liver abscess, multiple nuclei

ESSENTIAL FACTS

The cyst form of the protozoa is for transmission and the troph is for growth.

Protozoan Parasites: Diarrheas

STRUCTURE

Entamoeba histolytica: cysts (containing 1 to 4 nuclei) and trophs

Giardia lamblia: cyst with 4 nuclei and 4 parabasal bodies; recognizable flagellated trophs look like an old man looking over his shoulder

LAB ID

Cryptosporidium, Entamoeba histolytica: cysts in stool

Giardia lamblia: tests on successive days for cysts and trophs, immunologic tests for antigen

VIRULENCE FACTORS

Cryptosporidium, Entamoeba histolytica: invasive

Giardia lamblia: adherent and invasive

DISEASE

Entamoeba histolytica: amebic dysentery, liver abscess

Giardia lamblia: diarrhea

EPIDEMIOLOGY

Cryptosporidium: AIDS and immunosuppressed patients are at risk.
Entamoeba histolytica: fecal-oral spread, contaminated water supply
Giardia lamblia: animal urine, contaminated mountain creeks

PREVENTION

Cryptosporidium: Proper chlorination of water supply

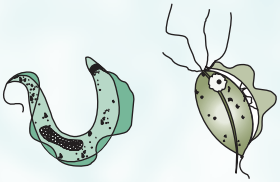
TREATMENT

Cryptosporidium: rehydration
Entamoeba histolytica, Giardia lamblia: metronidazole

183

Protozoan Parasites Found in Tissue: Part One

Murray: *Medical Microbiology,* 8th Edition, Chapter 71



Trypanosoma* and *Leishmania* spp.** ***Trichomonas vaginalis

Figure 183-1: Trypanosoma, Leishmania, *and* Trichomonas vaginalis.

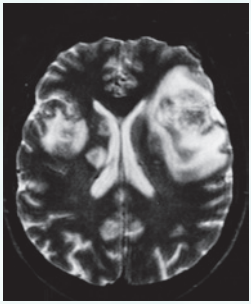


Figure 183-2: Magnetic resonance image of cerebral toxoplasmosis; note the abscesses.

CASE STUDIES

- A sexually active woman has a slight watery discharge, vaginitis with itching, and painful urination. A motile organism was observed by the hanging drop technique: ***Trichomonas vaginalis***
- A woman develops a mononucleosis-like fever, cervical lymphadenopathy, sore throat, muscle pain, and a rash. She has a cat: **toxoplasmosis**
- A patient with AIDS who owns a cat develops seizures. A computed tomographic scan of the head shows a ring-enhancing lesion: **chronic toxoplasmosis**
- A baby is born with encephalitis, hydrocephalus, blindness, anemia, rash, jaundice, and pneumonia. The mother was infected with toxoplasmosis during the first trimester of pregnancy: **congenital toxoplasmosis**
- A Latin American immigrant child develops fever, malaise, tachycardia. One eye has conjunctivitis and periorbital edema. Later, she experiences congestive heart failure: **Chagas disease** (South American trypanosomiasis)

Protozoan Parasites Found in Tissue: Part One

- A U.S. Marine returns from Iraq and has fever, chills, and sweats similar to malaria, diarrhea, and anemia. He becomes emaciated and develops pigmented granulomatous areas of the skin: **sand fly fever** (*Leishmania*)

TRIGGER WORDS

Trichomonas
Sexually transmitted disease
Hanging drop test for motility
Flagella

Toxoplasma
Cats
TORCH (***T****oxoplasma*, **o**ther, **r**ubella, **c**ytomegalovirus, **h**erpes)
Mononucleosis-like syndrome
Congenital infections

Leishmania
Sand flies
Blackening of skin
Trip to Asia or South America

Trypanosomes
Tsetse fly
Sleeping sickness
Trip to Asia or South America

STUDY BREAK

As with leprosy, an individual with a more active Th1 CD4 T-cell response is better protected against leishmania than a Th2-prone individual.

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Protozoan Parasites Found in Tissue: Part Two

Murray: *Medical Microbiology,* 8th Edition, Chapter 71

STRUCTURE

Trichomonas:
Flagellated troph

Toxoplasma:
Cyst and troph. Hundreds of organisms may be present in a cyst in the brain or other organ.

LAB ID

Trichomonas:
Hanging drop for motile trophs; DNA probes; immunofluorescence

Trypanosoma:
Trypanosomes in blood

Leishmania:
Giemsa-stained amastigotes in biopsy; polymerase chain reaction (PCR)

Toxoplasma:
Enzyme-linked immunosorbent assay for immunoglobulin M; presence of cysts or trophs in biopsy; PCR

LIFE CYCLE

Trichomonas:
Trophozoites as a sexually transmitted disease (STD)

Toxoplasma:
Ingested oocyst from cat feces or uncooked meat; development of tachyzoites and multiorganism cysts in tissue; transmission of sporozoites and bradyzoites

Trypanosoma:
Injection of trypomastigote in fly or reduviid bug saliva; replication in blood for transmission back to fly or bug

Leishmania:
Promastigotes in fly saliva become amastigotes and invade monocytes and macrophages, replicate in organs; amastigotes acquired by fly in blood meal

Protozoan Parasites Found in Tissue: Part Two

DISEASES

Trichomonas:
Urethritis, vaginitis

Toxoplasma:
Mononucleosis-like syndrome; brain and organ lesions in AIDS or other immunocompromised patients; congenital disease from infected mother: compromising brain, lung, heart, lymphoid organs, central nervous system (CNS), eyes

Trypanosoma:
South American Chagas disease: reduviid bug (fever; enlarged liver and spleen; orbital edema; Romana sign; megacolon, -esophagus, -cardia); African sleeping sickness: tsetse fly (fever, CNS involvement, blank look, lethargy)

Leishmania:
Kala-azar, leishmaniasis

EPIDEMIOLOGY

Trichomonas:
STD

Leishmania:
Asia, South America, transmitted by sand fly bite

Trypanosoma:
African sleeping sickness: Tsetse fly; Chagas disease: reduviid bug, South America

Toxoplasma:
In cat feces, TORCH

PREVENTION

Trichomonas: Safe sex

Toxoplasma: Pregnant women should avoid cat feces and raw meat.

TREATMENT

Trichomonas:
Metronidazole

Leishmania:
Stibogluconate

Trypanosoma:
Benzimidazole, nifurtimox

Toxoplasma:
Sulfonamides + pyrimethamine

185

Malarias: *Plasmodium* Species: Part One

Murray: *Medical Microbiology,* 8th Edition, Chapter 74

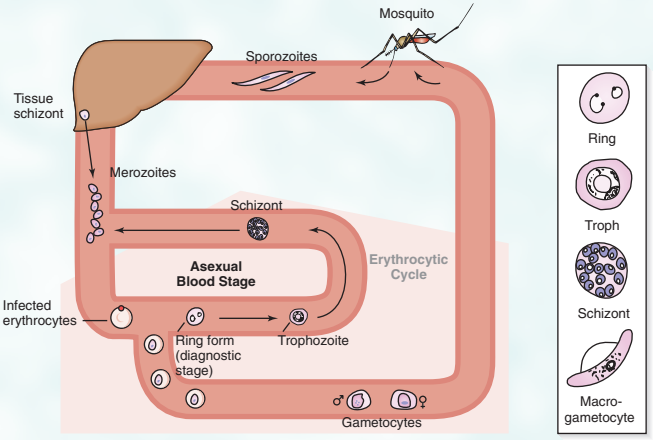

Figure 185-1: Life cycle of malaria.

Malarias: *Plasmodium* Species: Part One

CASE STUDY

A Marine returns from Africa feeling ill with flulike symptoms; 10 days later has bouts of fever, chills, and heavy sweating every other day. His urine is darker than usual and he has jaundice and splenomegaly: **malaria**

TRIGGER WORDS

Paroxysms of fever and chills
Ring form
Cyclic disease
Anopheles mosquito

ESSENTIAL FACTS

- **Fearsome:** *P. falciparum* infects all erythrocytes (worst outcome). Debris and sticky red blood cells clog capillaries.
- **Vivacious:** *P. vivax* infects only young erythrocytes. *P. vivax* can hide in the hepatocyte as a hypnozoite.
- **Mature:** *P. malariae* infects only old erythrocytes.

STUDY BREAK

- Malaria kills at least one child every 10 minutes.
- The intervals between paroxysms are related to the type of erythrocyte infected by the *Plasmodium* spp. and induced by the synchronous lysis of the infected erythrocytes and release of inducers of inflammation.
- Detection of the ring form in erythrocytes is diagnostic for malaria.

186

Malarias: *Plasmodium* Species: Part Two

Murray: *Medical Microbiology,* 8th Edition, Chapter 74

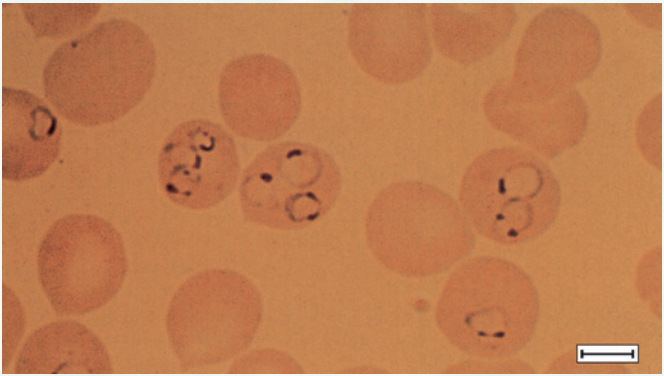

Figure 186-1: Ring forms in erythrocytes.

STRUCTURE

Ring forms in erythrocytes

LAB ID

Blood smear and detection of ring forms; rapid antigen detection test

LIFE CYCLE

Mosquito delivers sporozoites, merozoites develop in liver and infect erythrocytes, become trophozoites and then schizonts before lysing erythrocyte-releasing merozoites. Infected erythrocytes also develop gametocytes that infect mosquito during blood meal.

Malarias: *Plasmodium* Species: Part Two

DISEASES

- Malaria: initial flulike symptoms progressing to high fever, chills, sweating in 7 to 14 days. Brain, kidney, and liver damage may occur if untreated.
- *P. vivax* and *P. ovale* infect young erythrocytes—paroxysms at 48-hour intervals. Produce hypnozoites, which are latent in liver and can reactivate.
- *P. malariae* infects old erythrocytes; paroxysms at 72-hour intervals.
- *P. falciparum* infects all erythrocytes; paroxysms at 24 hours and then at 36 to 48 hours or continual symptoms; shortest prodrome period. Tertian malaria may include vomiting, nausea, and diarrhea. Plugging of capillaries may result in cerebral malaria, coma, and death. Possible kidney (blackwater fever) and liver damage.

EPIDEMIOLOGY

Mosquito habitat

PREVENTION

- Eliminate mosquito
- Chemoprophylaxis; mefloquine, chloroquine, doxycycline
- *P. vivax*: primaquine

TREATMENT

- Chloroquine, mefloquine
- Atovaquone-proguanil, artemisinin, doxycycline, mefloquine
- *P. vivax*: primaquine to treat the liver

187

Parasite Infections: Worms and Flukes

Murray: *Medical Microbiology,* 8th Edition, Chapters 68, 69, and 75–77

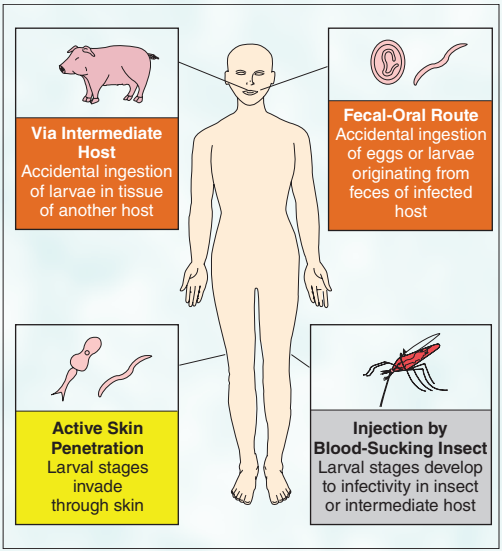

Figure 187-1: How helminth parasites enter the body. Test yourself by matching the appropriate parasite with each route.

Table 187-1: Worm and Fluke Infections

Species	Infectious Form	Transmission	Disease
NEMATODES			
Enterobius vermicularis (pinworm)	Egg	**Ingestion:** fecal-oral	Perianal itching
Ascaris lumbricoides (roundworm)	Egg	**Ingestion:** fecal-oral	GI tract,* migration to other tissues, pneumonitis
Toxocara spp.	Egg	**Ingestion:** fecal-oral	GI tract, migration to other tissues
Trichuris trichiura (whipworm)	Egg	**Ingestion:** fecal-oral	GI tract

Continued

Parasite Infections: Worms and Flukes

Table 187-1: Worm and Fluke Infections—cont'd

Species	Infectious Form	Transmission	Disease
Dracunculus medinensis	Larva	**Ingestion:** contaminated drinking water	Skin ulcers (spool up worm)
Necator americanus (hookworm)	Filariform larva	Contaminated soil, **direct skin penetration,** autoinfection	Microcytic anemia, pneumonitis, eosinophilia
Strongyloides stercoralis (threadworm)	Filariform larva	Contaminated soil, **direct skin penetration,** autoinfection	GI tract, dermatitis, pneumonitis, eosinophilia
Wuchereria bancrofti	Filariform larva	**Arthropod bite:** mosquito	Elephantiasis
Onchocerca volvulus	Filariform larva	**Arthropod bite:** blackflies	Blindness (worm in the eye)
Loa loa	Larva	**Arthropod bite:** mango fly	Tissue invasion, including eye
TREMATODES (FLUKES)			
Schistosoma mansonii	Cercaria	**Direct skin penetration:** maintained in snails	Liver, intestine, CNS, portal hypertension
Schistosoma haematobium	Cercaria	**Direct skin penetration:** maintained in snails	Blood vessels, bladder, bladder cancer
Schistosoma japonicum	Cercaria	**Direct skin penetration:** maintained in snails	Liver, intestine, CNS, portal hypertension
Opisthorchis (Clonorchis sinensis)	Metacercaria	**Ingestion:** freshwater fish	Liver disease, biliary tract
Paragonimus westermani	Metacercaria	**Ingestion:** freshwater fish	Lungs
CESTODES			
Taenia saginata	Encysted larva (cysticerci) in beef	**Ingestion:** meat	GI tract
Taenia solium	Egg, encysted larva (cysticerci) in pig	**Ingestion:** larva in pork, eggs in contaminated water	Cysticercosis: cysts and inflammation of brain, eyes, and muscle
Diphyllobothrium latum	Larva	**Ingestion:** fish	Vitamin B12 deficiency
Echinococcus multilocularis	Eggs passed by carnivores	**Ingestion:** eggs in meat	Hydatid cysts in liver, slow-growing tissue invasion

*GI tract disease could result in diarrhea, obstruction, perforation, and peritonitis.
CNS, Central nervous system; GI, gastrointestinal.

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Flukes and Flatworms: *Schistosoma* and *Taenia solium*

Murray: *Medical Microbiology,* 8th Edition, Chapters 68 and 76

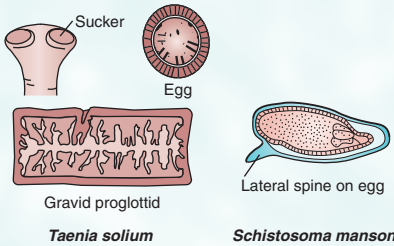

Figure 188-1

CASE STUDIES

Schistosoma

A Puerto Rican boy who normally plays in snail-containing streams has a cough (worms in lungs), abdominal pain, hepatosplenomegaly with ascitic fluid.

Taenia solium (Pork Tapeworm)

- A Mexican who had eaten undercooked pork has diarrhea, abdominal pain, and weight loss: **taeniasis**
- A patient has right-sided weakness and seizures. Computed tomography shows a cystic lesion in the brain: **cysticercosis**

TRIGGER WORDS

Snails
Penetration of skin
Fluke
S. mansoni (spine on egg)
Undercooked pork
Tapeworm
Cysticercosis
Taeniasis

ESSENTIAL FACTS

Schistosoma: The *Schistosoma* eggs grow in snails and hatch into larvae; the larvae are released into the water and then burrow through the skin of barefooted human waders.

Flukes and Flatworms: *Schistosoma* and *Taenia solium*

STRUCTURE

Schistosoma: eggs with characteristic spines
Taenia solium: spherical eggs with three pairs of hooklets

LAB ID

Schistosoma: eggs in stool or urine

LIFE CYCLE

Schistosoma: snails, motile cercaria larvae in water, skin penetration, male and female flukes in blood, release in feces and urine
Taenia solium:

- Egg → pig muscle → human ingestion; tapeworm in small intestine
- Cysticercosis: human-human (eg, autoinoculation) egg ingestion leads to invasion of intestine, circulation to tissues, cysticerci in muscle, brain, lungs, eyes, etc

DISEASES

Schistosoma: dermatitis. Diseases are due to immune responses to parasite. Migrating worms may cause cough, hepatitis, abdominal pain, or portal hypertension depending on migration of worms. Chronic disease.
Taenia solium: intestinal tape worm, cysticercosis

EPIDEMIOLOGY

Schistosoma snails are the intermediates.
Taenia solium: undercooked pork; fecal-oral human transmission

TREATMENT

Schistosoma: praziquantel
Taenia solium: albendazole and/or praziquantel with glucocorticosteroids

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Flukes and Flatworms: *Echinococcus granulosus* and *Diphyllobothrium latum*

Murray: *Medical Microbiology*, 8th Edition, Chapters 68 and 76

CASE STUDIES

***Echinococcus granulosus* (Dog Tapeworm)**
Kennel worker with right upper quadrant pain and bloody sputum. Computed tomography shows cystic lesions in liver and lungs: **hydatid cyst**

***Diphyllobothrium latum* (Fish Tapeworm)**
Person eats wild trout sushi and 2 weeks later develops abdominal cramping, nausea, vomiting, and vitamin B_{12} deficiency.

TRIGGER WORDS

Echinococcus granulosus
Dog
Hydatid cyst
Tapeworm

Diphyllobothrium latum
Raw fish
Tapeworm
Vitamin B_{12} deficiency

STUDY BREAK

The fish tapeworm is obtained from raw freshwater fish. There are no saltwater fish parasites that cause human disease.

STRUCTURE

D. latum: operculated egg
E. granulosus: spherical egg with thick striated shell

Flukes and Flatworms: *Echinococcus granulosus* and *Diphyllobothrium latum*

LIFE CYCLE

Diphyllobothrium latum
Coracidium → crustacean → fish → human, where scolex of tapeworm affixes to intestine → egg (1 month from infection to new eggs)

Echinococcus granulosus
Egg in dog feces ingested by human; hydatid cyst in liver, lungs

DISEASES

D. latum: abdominal cramping, nausea, vomiting, weight loss, vitamin B12 deficiency
E. granulosus: hydatid cyst in lungs, liver, bone, or brain

EPIDEMIOLOGY

D. latum: raw or undercooked freshwater fish
E. granulosus: dog feces

PREVENTION

E. granulosus: special quarantine or disinfection procedures

TREATMENT

D. latum: niclosamide, praziquantel, albendazole, paromomycin
E. granulosus: puncture, aspiration, injection, and reaspiration (PAIR); high-dose albendazole

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Worms: *Enterobius vermicularis* (Pinworm) and *Trichuris trichiura* (Whipworm)

Murray: *Medical Microbiology,* 8th Edition, Chapter 75

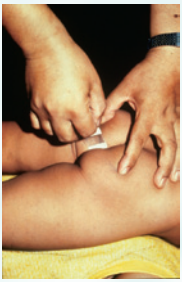

Figure 190-1: Tape test for pinworms.

Enterobius vermicularis (Pinworm)

CASE STUDY

A 3-year-old child has a rash with anal itching. The scotch tape test of the perianal region demonstrates eggs.

TRIGGER WORDS

Scotch tape test
Anal itching

ESSENTIAL FACT

The female pinworm comes out of the rectum to lay its eggs, which can be captured for viewing with the scotch tape test.

STRUCTURE

Small white worm

LAB ID

Scotch tape test for eggs

Worms: *Enterobius vermicularis* (Pinworm) and *Trichuris trichiura* (Whipworm)

LIFE CYCLE

Ingestion of eggs; larvae hatch in small intestine and move to large intestine, penetrate and develop in mucosa. Females lay eggs at night in perianal region.

DISEASES

Perianal itching, vaginal irritation

EPIDEMIOLOGY

Fecal-oral spread; self-reinfection

TREATMENT

Pyrantel pamoate or mebendazole

Trichuris trichiura (Whipworm)

STRUCTURE

Whip-like appearance with handle and lash

LAB ID

Bile-stained eggs with polar plugs

LIFE CYCLE

Ingestion of eggs; larvae form in small intestine, migrate to cecum, penetrate mucosa, and mature into adult worms.

DISEASES

Abdominal pain, bloody diarrhea, appendicitis due to the presence of worms

EPIDEMIOLOGY

Poor sanitation and use of human feces as fertilizer

TREATMENT

Mebendazole

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Worms: *Ascaris lumbricoides* (Roundworm) and *Trichinella spiralis*

Murray: *Medical Microbiology,* 8th Edition, Chapter 75

Ascaris lumbricoides (Roundworm)

CASE STUDY

An immigrant from Cambodia has severe cramping and admits to seeing a long, pearl-white worm in stool.

TRIGGER WORD

Pearl-white worm

STRUCTURE

Pink worms; thick-walled, knobby, coated, oval eggs

LAB ID

Eggs in stool

LIFE CYCLE

Ingestion of eggs; invasion, migration to lungs; larvae are coughed up to be swallowed and enter the gastrointestinal tract and small intestine to lay eggs.

DISEASES

Pneumonitis, liver damage, bowel obstruction (tangle of worms), peritonitis (worm perforation of bowel)

EPIDEMIOLOGY

Human-human fecal-oral transmission of eggs, use of human feces as fertilizer

TREATMENT

Mebendazole

Worms: *Ascaris lumbricoides* (Roundworm) and *Trichinella spiralis*

Trichinella spiralis

CASE STUDY

A hunter eats undercooked boar and bear (or pig) and has flulike syndrome progressing to persistent fever, gastrointestinal distress, muscle pain, eosinophilia, and splinter hemorrhages under his nails.

TRIGGER WORDS

Hunter
Pig
Eosinophilia
Meat
Splinter hemorrhages

STRUCTURE

Nematode worm

LAB ID

Encysted larvae in meat

LIFE CYCLE

Encysted larvae in animal (pig, bear, others) muscle, human ingestion. Larvae invade and enter bloodstream and establish infection in muscle.

DISEASES

Trichinosis (muscle pain, persistent fever, splinter hemorrhages under fingernails) progressing to myocarditis, encephalitis, and pneumonitis; death in 4 to 6 weeks.

EPIDEMIOLOGY

Undercooked wild meats; occurs in the United States

TREATMENT

Mebendazole

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Worms: *Necator americanus* (Hookworm) and *Strongyloides stercoralis* (Threadworm)

Murray: *Medical Microbiology,* 8th Edition, Chapter 75

Necator americanus (Hookworm)

TRIGGER WORDS

Hookworm
Pneumonitis
Anemia

STRUCTURE

Filariform larvae (infective form); rhabditiform larvae (noninfectious)

LIFE CYCLE

Penetration of skin by filariform larvae; larvae enter circulation, are carried to lungs, and coughed up and swallowed; develop to adulthood in small intestine

DISEASES

Pneumonitis, rash, gastrointestinal symptoms; anemia due to blood loss

EPIDEMIOLOGY

Direct contact with contaminated soil

TREATMENT

Mebendazole

Worms: *Necator americanus* (Hookworm) and *Strongyloides stercoralis* (Threadworm)

Strongyloides stercoralis (Threadworm)

TRIGGER WORDS

Threadworm
Pneumonitis
Dermatitis

STRUCTURE

Hookworm-like appearance

LAB ID

Larvae in stool

LIFE CYCLE

Rhabditiform larvae from soil penetrate skin, enter circulation, reach lung to be coughed up and swallowed; larvae are passed in stool or invade intestinal wall to reinfect host.

DISEASES

Pneumonitis, gastrointestinal problems; chronic disease

EPIDEMIOLOGY

Direct contact with contaminated soil

TREATMENT

Thiabendazole, mebendazole