

HIGH-YIELD PRINCIPLES IN

Microbiology

“Within one linear centimeter of your lower colon there lives and works more bacteria (about 100 billion) than all humans who have ever been born. Yet many people continue to assert that it is we who are in charge of the world.”

—Neil deGrasse Tyson

“What lies behind us and what lies ahead of us are tiny matters compared to what lies within us.”

—Henry S. Haskins

“Wise and humane management of the patient is the best safeguard against infection.”

—Florence Nightingale

“I sing and play the guitar, and I’m a walking, talking bacterial infection.”

—Kurt Cobain

Microbiology questions on the Step 1 exam often require two (or more) steps: Given a certain clinical presentation, you will first need to identify the most likely causative organism, and you will then need to provide an answer regarding some features of that organism or relevant antimicrobial agents. For example, a description of a child with fever and a petechial rash will be followed by a question that reads, “From what site does the responsible organism usually enter the blood?”

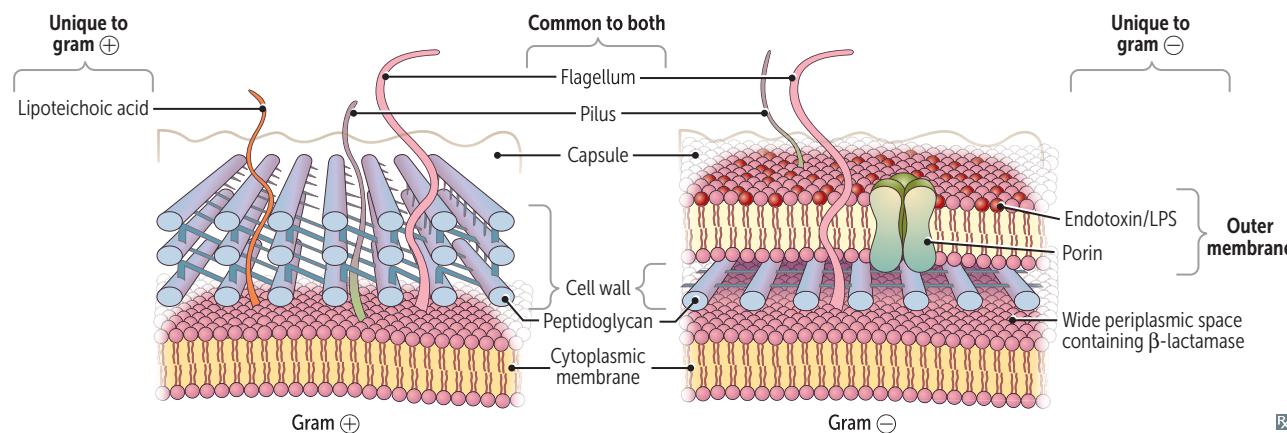
This section therefore presents organisms in two major ways: in individual microbial “profiles” and in the context of the systems they infect and the clinical presentations they produce. You should become familiar with both formats. When reviewing the systems approach, remind yourself of the features of each microbe by returning to the individual profiles. Also be sure to memorize the laboratory characteristics that allow you to identify microbes.

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► MICROBIOLOGY—BASIC BACTERIOLOGY

Bacterial structures

STRUCTURE	CHEMICAL COMPOSITION	FUNCTION
Appendages		
Flagellum	Proteins	Motility
Pilus/fimbria	Glycoprotein	Mediate adherence of bacteria to cell surface; sex pilus forms during conjugation
Specialized structures		
Spore	Keratinlike coat, dipicolinic acid, peptidoglycan, DNA	Survival: resist dehydration, heat, chemicals
Cell envelope		
Capsule	Discrete layer usually made of polysaccharides (and rarely proteins)	Protects against phagocytosis
Slime (S) layer	Loose network of polysaccharides	Mediates adherence to surfaces, plays a role in biofilm formation (eg, indwelling catheters)
Outer membrane	Outer leaflet: contains endotoxin (LPS/LOS) Embedded proteins: porins and other outer membrane proteins (OMPs) Inner leaflet: phospholipids	Gram \ominus only Endotoxin: lipid A induces TNF and IL-1; antigenic O polysaccharide component Most OMPs are antigenic Porins: transport across outer membrane
Periplasm	Space between cytoplasmic membrane and outer membrane in gram \ominus bacteria (peptidoglycan in middle)	Accumulates components exiting gram \ominus cells, including hydrolytic enzymes (eg, β -lactamases)
Cell wall	Peptidoglycan is a sugar backbone with peptide side chains cross-linked by transpeptidase	Netlike structure gives rigid support, protects against osmotic pressure damage
Cytoplasmic membrane	Phospholipid bilayer sac with embedded proteins (eg, penicillin-binding proteins [PBPs]) and other enzymes Lipoteichoic acids (gram positive) only extend from membrane to exterior	Site of oxidative and transport enzymes; PBPs involved in cell wall synthesis Lipoteichoic acids induce TNF- α and IL-1

Cell envelope

Stains**Gram stain**

First-line lab test in bacterial identification. Bacteria with thick peptidoglycan layer retain crystal violet dye (gram \oplus); bacteria with thin peptidoglycan layer turn red or pink (gram \ominus) with counterstain.

These bugs do not Gram stain well (**These Little Microbes May Unfortunately Lack Real Color But Are Everywhere**):

Treponema, Leptospira

Too thin to be visualized

Mycobacteria

Cell wall has high lipid content

Mycoplasma, Ureaplasma

No cell wall

Legionella, Rickettsia, Chlamydia, Bartonella, Anaplasma, Ehrlichia

Primarily intracellular; also, *Chlamydia* lack classic peptidoglycan because of \downarrow muramic acid

Giemsa stain

H pylori, Chlamydia, Borrelia, Rickettsia, Trypanosomes **A**, *Plasmodium*

Help! Certain Bugs Really Try my Patience

Periodic acid-Schiff stain

Stains glycogen, mucopolysaccharides; used to diagnose Whipple disease (*Tropheryma whipplei* **B**)

Ziehl-Neelsen stain (carbol fuchsin)

Acid-fast bacteria (eg, *Mycobacteria* **C**, *Nocardia*; stains mycolic acid in cell wall); protozoa (eg, *Cryptosporidium* oocysts)

Auramine-rhodamine stain is more often used for screening (inexpensive, more sensitive)

India ink stain

Cryptococcus neoformans **D**; mucicarmine can also be used to stain thick polysaccharide capsule red

Silver stain

Helicobacter pylori, Legionella, Bartonella henselae, and fungi (eg, *Coccidioides* **E**, *Pneumocystis jirovecii, Aspergillus fumigatus*)

HeLiCoPters Are silver

Fluorescent antibody stain

Used to identify many bacteria, viruses, *Pneumocystis jirovecii*, *Giardia*, and *Cryptosporidium*

Example is FTA-ABS for syphilis



Special culture requirements

BUG	MEDIA USED FOR ISOLATION	MEDIA CONTENTS/OTHER
<i>H influenzae</i>	Chocolate agar	Factors V (NAD^+) and X (hematin)
<i>N gonorrhoeae</i> , <i>N meningitidis</i>	Thayer-Martin agar	Selectively favors growth of <i>Neisseria</i> by inhibiting growth of gram \oplus organisms with vancomycin, gram \ominus organisms except <i>Neisseria</i> with trimethoprim and colistin, and fungi with nystatin Very typically cultures <i>Neisseria</i>
<i>B pertussis</i>	Bordet-Gengou agar (Bordet for <i>Bordetella</i>) Regan-Lowe medium	Potato extract Charcoal, blood, and antibiotic
<i>C diphtheriae</i>	Tellurite agar, Löffler medium	
<i>M tuberculosis</i>	Löwenstein-Jensen medium, Middlebrook medium, rapid automated broth cultures	
<i>M pneumoniae</i>	Eaton agar	Requires cholesterol
Lactose-fermenting enterics	MacConkey agar	Fermentation produces acid, causing colonies to turn pink
<i>E coli</i>	Eosin–methylene blue (EMB) agar	Colonies with green metallic sheen
<i>Brucella</i> , <i>Francisella</i> , <i>Legionella</i> , <i>Pasteurella</i>	Buffered charcoal yeast extract agar with cysteine and iron	The Ella siblings, Bruce , Francis , a legionnaire , and a pasteur (pastor), built the Sistine (cysteine) chapel out of charcoal and iron
Fungi	Sabouraud agar	“Sab’s a fun guy!”

Anaerobes

Examples include *Clostridoides*, *Clostridium*, *Bacteroides*, *Fusobacterium*, and *Actinomyces israelii*. They lack catalase and/or superoxide dismutase and are thus susceptible to oxidative damage. Generally foul smelling (short-chain fatty acids), are difficult to culture, and produce gas in tissue (CO_2 and H_2).

Anaerobes Can't Breathe Fresh Air.

Anaerobes are normal microbiota in GI tract, typically pathogenic elsewhere (eg, causes aspiration pneumonia). AminO₂glycosides are ineffective against anaerobes because these antibiotics require O₂ to enter into bacterial cell.

Facultative anaerobes

May use O₂ as a terminal electron acceptor to generate ATP, but can also use fermentation and other O₂-independent pathways.

Streptococci, staphylococci, and enteric gram ⊖ bacteria.

Intracellular bacteria**Obligate intracellular**

Rickettsia, *Chlamydia*, *Coxiella*

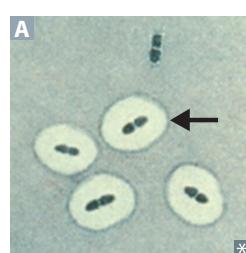
Rely on host ATP

Stay inside (cells) when it is Really Chilly and Cold

Facultative intracellular

Salmonella, *Neisseria*, *Brucella*, *Mycobacterium*, *Listeria*, *Francisella*, *Legionella*, *Yersinia pestis*

Some Nasty Bugs May Live FacultativeLY

Encapsulated bacteria

Examples are *Pseudomonas aeruginosa*, *Streptococcus pneumoniae* A, *Haemophilus influenzae* type b, *Neisseria meningitidis*, *Escherichia coli*, *Salmonella*, *Klebsiella pneumoniae*, and group B Strep. Their capsules serve as an antiphagocytic virulence factor.

Please SHiNE my SKiS.

Are opsonized, and then cleared by spleen.

Capsular polysaccharide +/- protein conjugate can serve as an antigen in vaccines. A polysaccharide antigen alone cannot be presented to T cells; immunogenicity can be enhanced by conjugating capsule antigens to a carrier protein.

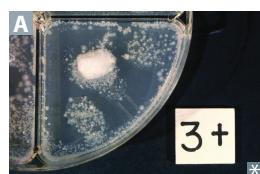
Asplenics (No Spleen Here) have ↓ opsonizing ability and thus ↑ risk for severe infections; need vaccines to protect against:

- *N meningitidis*
- *S pneumoniae*
- *H influenzae*

Urease-positive organisms

Proteus, *Cryptococcus*, *H pylori*, *Ureaplasma*, *Nocardia*, *Klebsiella*, *S epidermidis*, *S saprophyticus*. Urease hydrolyzes urea to release ammonia and $\text{CO}_2 \rightarrow \uparrow \text{pH}$. Predisposes to struvite (magnesium ammonium phosphate) stones, particularly *Proteus*.

Pee CHUNKSS.

Catalase-positive organisms

Catalase degrades H₂O₂ into H₂O and bubbles of O₂ **A** before it can be converted to microbicidal products by the enzyme myeloperoxidase. People with chronic granulomatous disease (NADPH oxidase deficiency) have recurrent infections with certain catalase \oplus organisms.

Catalase \oplus organisms include *Candida*, *Pseudomonas*, *Nocardia*, *Bordetella pertussis*, *Burkholderia cepacia*, *Helicobacter pylori*, *Aspergillus*, *Staphylococci*, *Serratia*, *Listeria*, *E. coli*. Catalase Positive: Notoriously **Big Bubbling HASSLE**.

Pigment-producing bacteria

<i>Actinomyces israelii</i> —yellow “sulfur” granules, which are composed of filaments of bacteria	Israel has yellow sand
<i>S. aureus</i> —golden yellow pigment	<i>Aureus</i> (Latin) = gold
<i>P. aeruginosa</i> —blue-green pigment (pyocyanin and pyoverdin)	<i>Aerugula</i> is green
<i>Serratia marcescens</i> —red pigment	Think red Sriracha hot sauce

In vivo biofilm-producing bacteria

<i>S. epidermidis</i>	Catheter and prosthetic device infections
Viridans streptococci (<i>S. mutans</i> , <i>S. sanguinis</i>)	Dental plaques, infective endocarditis
<i>P. aeruginosa</i>	Respiratory tree colonization in patients with cystic fibrosis, ventilator-associated pneumonia Contact lens–associated keratitis
Nontypeable (unencapsulated) <i>H. influenzae</i>	Otitis media

Spore-forming bacteria

Some gram + bacteria can form spores when nutrients are limited. Spores lack metabolic activity and are highly resistant to heat and chemicals. Core contains dipicolinic acid (responsible for heat resistance). Must autoclave to kill spores (as is done to surgical equipment) by steaming at 121°C for 15 minutes at a pressure of 15 psi. Hydrogen peroxide and iodine-based agents are also sporicidal.

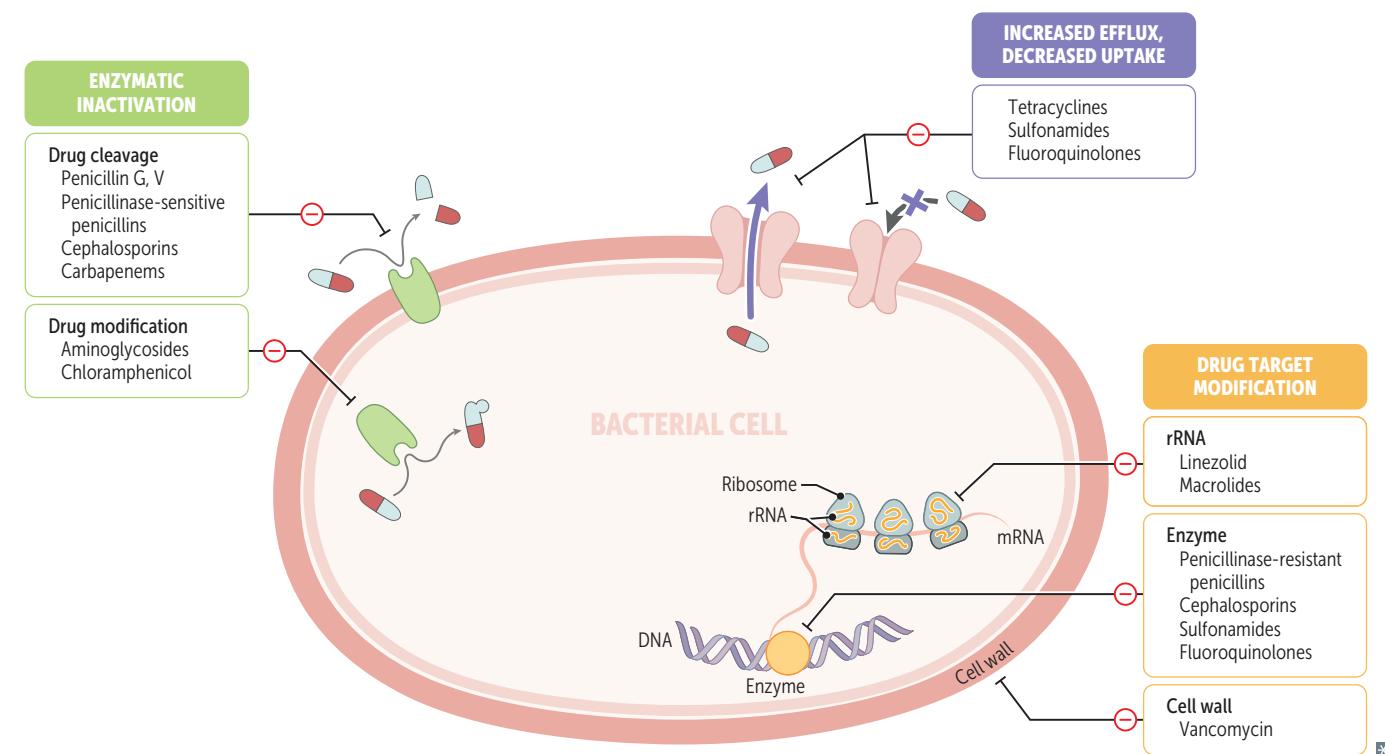
Examples: *B anthracis* (anthrax), *B cereus* (food poisoning), *Clostridium botulinum* (botulism), *Clostridioides difficile* (pseudomembranous colitis), *Clostridium perfringens* (gas gangrene), *Clostridium tetani* (tetanus).

Autoclave to kill **Bacillus** and **Clostridium** (ABC).

Bacterial virulence factors

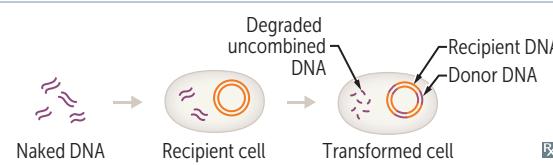
These promote evasion of host immune response.

Capsular polysaccharide	Highly charged, hydrophilic structure. Acts as barrier to phagocytosis and complement-mediated lysis. Major determinant of virulence.
Protein A	Binds Fc region of IgG. Prevents opsonization and phagocytosis. Expressed by <i>S aureus</i> .
IgA protease	Enzyme that cleaves IgA, allowing bacteria to adhere to and colonize mucous membranes. Secreted by <i>S pneumoniae</i> , <i>H influenzae</i> type b, and <i>Neisseria</i> (SHiN).
M protein	Helps prevent phagocytosis. Expressed by group A streptococci. Sequence homology with human cardiac myosin (molecular mimicry); possibly underlies the autoimmune response seen in acute rheumatic fever.

Antibiotic resistance mechanisms

Bacterial genetics**Transformation**

Horizontal gene transfer is the main mechanism for transfer of antibiotic resistance among bacteria.

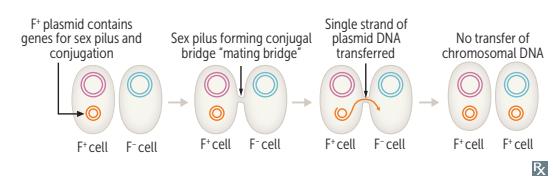


Competent bacteria can bind and import short pieces of environmental naked bacterial chromosomal DNA (from bacterial cell lysis). The transfer and expression of newly transferred genes is called transformation. A feature of many bacteria, especially *S. pneumoniae*, *H. influenzae* type b, and *Neisseria* (SHiN).

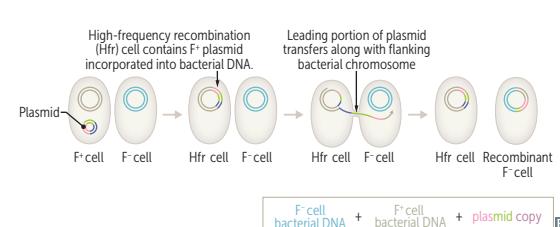
Adding deoxyribonuclease degrades naked DNA, preventing transformation.

Conjugation $F^+ \times F^-$

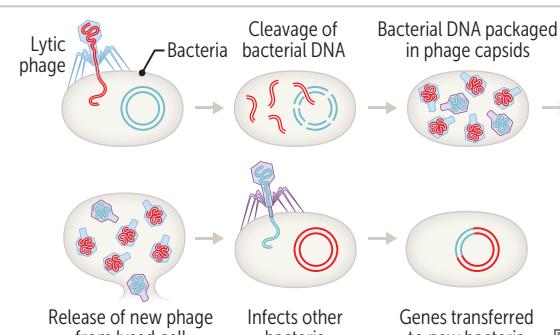
F^+ (fertility factor) plasmid contains genes required for sex pilus and conjugation. Bacteria without this plasmid are termed F^- . Sex pilus on F^+ bacterium contacts F^- bacterium. A single strand of plasmid DNA is transferred across the conjugal bridge ("mating bridge"). No transfer of chromosomal DNA.

 $Hfr \times F^-$

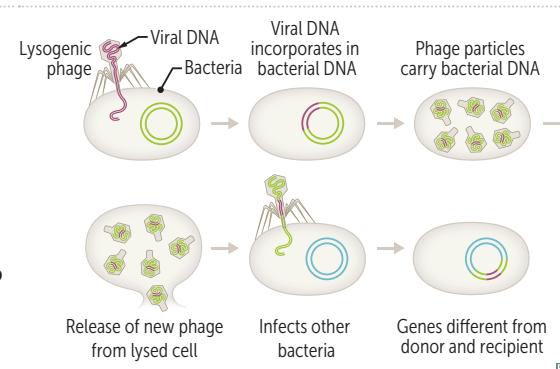
F^+ plasmid can become incorporated into bacterial chromosomal DNA, termed high-frequency recombination (Hfr) cell. Transfer of leading part of plasmid and a few flanking chromosomal genes. High-frequency recombination may integrate some of those bacterial genes. Recipient cell remains F^- but now may have new bacterial genes.

**Transduction****Generalized**

A "packaging" error. Lytic phage infects bacterium, leading to cleavage of bacterial DNA. Parts of bacterial chromosomal DNA may become packaged in phage capsid. Phage infects another bacterium, transferring these genes.

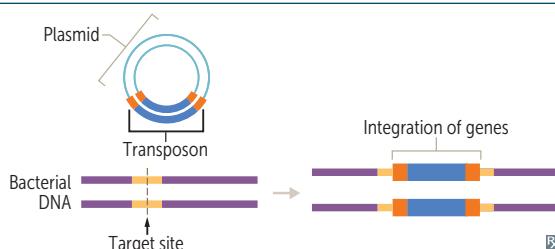
**Specialized**

An "excision" event. Lysogenic phage infects bacterium; viral DNA incorporates into bacterial chromosome. When phage DNA is excised, flanking bacterial genes may be excised with it. DNA is packaged into phage capsid and can infect another bacterium. Genes for the following 5 bacterial toxins are encoded in a lysogenic phage (**ABCD'S**): Group **A** strep erythrogenic toxin, **B**otulinum toxin, **C**holera toxin, **D**diphtheria toxin, **S**higa toxin.

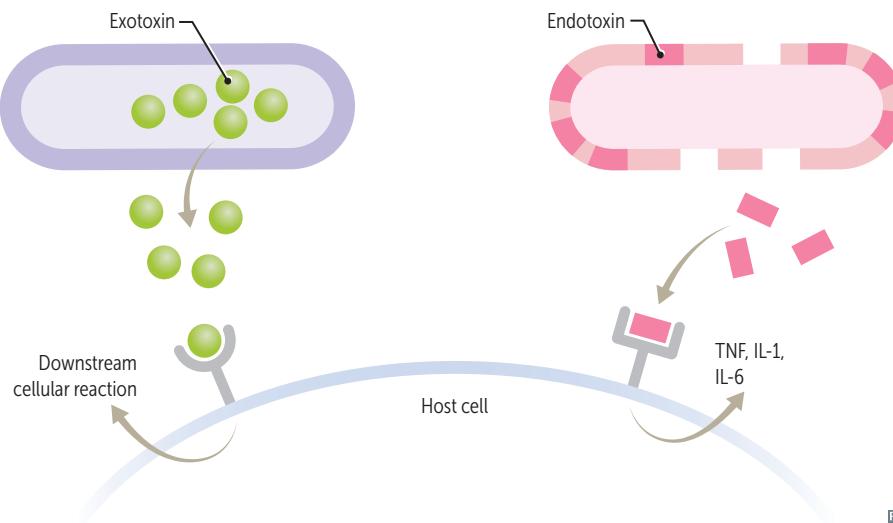


Bacterial genetics (continued)**Transposition**

A “jumping” process involving a transposon (specialized segment of DNA), which can copy and excise itself and then insert into the same DNA molecule or an unrelated DNA (eg, plasmid or chromosome). Critical in creating plasmids with multiple drug resistance and transfer across species lines (eg, Tn1546 with *vanA* from *Enterococcus* to *S aureus*).

**Main features of exotoxins and endotoxins**

	Exotoxins	Endotoxins
SOURCE	Certain species of gram \oplus and gram \ominus bacteria	Outer cell membrane of most gram \ominus bacteria
SECRETED FROM CELL	Yes	No
CHEMISTRY	Polypeptide	Lipid A component of LPS (structural part of bacteria; released when lysed)
LOCATION OF GENES	Plasmid or bacteriophage	Bacterial chromosome
TOXICITY	High (fatal dose on the order of 1 μg)	Low (fatal dose on the order of hundreds of micrograms)
CLINICAL EFFECTS	Various effects (see following pages)	Fever, shock (hypotension), DIC
MODE OF ACTION	Various modes (see following pages)	Induces TNF, IL-1, and IL-6
ANTIGENICITY	Induces high-titer antibodies called antitoxins	Poorly antigenic
VACCINES	Toxoids used as vaccines	No toxoids formed and no vaccine available
HEAT STABILITY	Destroyed rapidly at 60°C (except staphylococcal enterotoxin, <i>E coli</i> heat-stable toxin, and <i>B cereus</i> emetic toxin)	Stable at 100°C for 1 hr
TYPICAL DISEASES	Tetanus, botulism, diphtheria, cholera	Meningococcemia; sepsis by gram \ominus rods



Bacteria with exotoxins

BACTERIA	TOXIN	MECHANISM	MANIFESTATION
Inhibit protein synthesis			
<i>Corynebacterium diphtheriae</i>	Diphtheria toxin ^a	Inactivate elongation factor (EF-2) through ADP-ribosylation	Pharyngitis with pseudomembranes in throat and severe lymphadenopathy (bull neck), myocarditis
<i>Pseudomonas aeruginosa</i>	Exotoxin A ^a		Host cell death
<i>Shigella</i> spp	Shiga toxin ^a	Inactivate 60S ribosome by removing adenine from rRNA	Damages GI mucosa → dysentery
<i>Enterohemorrhagic E. coli</i>			Toxin-mediated injury and cytokine release → hemolytic-uremic syndrome (HUS; prototypically in EHEC serotype O157:H7) Unlike <i>Shigella</i> , EHEC does not invade host cells
Increase fluid secretion			
<i>Enterotoxigenic E. coli</i>	Heat-labile toxin (LT) ^a	Overactivates adenylate cyclase (\uparrow cAMP) → \uparrow Cl ⁻ secretion in gut and H ₂ O efflux	Watery diarrhea: “ labil e in the Air (Adenylate cyclase), stable on the Ground (Guanylate cyclase)”
	Heat-stable toxin (ST)	Overactivates guanylate cyclase (\uparrow cGMP) → \downarrow resorption of NaCl and H ₂ O in gut	Bacteria that \uparrow cAMP include <i>V cholerae</i> , <i>B anthracis</i> , <i>B pertussis</i> , <i>E. coli</i>
<i>Bacillus anthracis</i>	Anthrax toxin ^a	Mimics adenylate cyclase (\uparrow cAMP)	Likely responsible for characteristic edematous borders of black eschar in cutaneous anthrax
<i>Vibrio cholerae</i>	Cholera toxin ^a	Overactivates adenylate cyclase (\uparrow cAMP) by permanently activating G _s	Voluminous “rice-water” diarrhea
Inhibit phagocytic ability			
<i>Bordetella pertussis</i>	Pertussis toxin ^a	Activates adenylate cyclase (\uparrow cAMP) by inactivating inhibitory subunit (G _i)	Whooping cough —child coughs on expiration and “whoops” on inspiration; can cause “100-day cough” in adults; associated with posttussive emesis
Inhibit release of neurotransmitter			
<i>Clostridium tetani</i>	Tetanospasmin ^a	Both are proteases that cleave SNARE (soluble NSF attachment protein receptor), a set of proteins required for neurotransmitter release via vesicular fusion	Toxin prevents release of inhibitory (GABA and glycine) neurotransmitters from Renshaw cells in spinal cord → spastic paralysis, risus sardonicus, trismus (lockjaw), opisthotonus
<i>Clostridium botulinum</i>	Botulinum toxin ^a		Infant botulism—caused by ingestion of spores (eg, from soil, raw honey). Toxin produced in vivo Foodborne botulism—caused by ingestion of preformed toxin (eg, from canned foods)

^aAn AB toxin (also called two-component toxin [or three for anthrax]) with **B** enabling **Binding** and triggering uptake (endocytosis) of the **Active A** component. The A components are usually ADP ribosyltransferases; others have enzymatic activities as listed in chart.

Bacteria with exotoxins (continued)

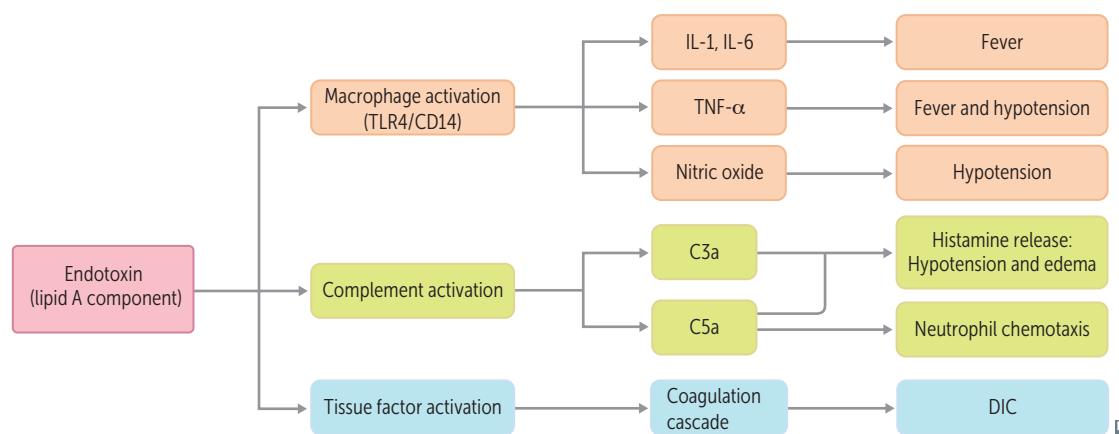
BACTERIA	TOXIN	MECHANISM	MANIFESTATION
Lyse cell membranes			
<i>Clostridium perfringens</i>	Alpha toxin	Phospholipase (lecithinase) that degrades tissue and cell membranes	Degradation of phospholipids → myonecrosis (“gas gangrene”) and hemolysis (“double zone” of hemolysis on blood agar)
<i>Streptococcus pyogenes</i>	Streptolysin O	Protein that degrades cell membrane	Lyses RBCs; contributes to β-hemolysis; host antibodies against toxin (ASO) used to diagnose rheumatic fever (do not confuse with immune complexes of poststreptococcal glomerulonephritis)
Superantigens causing shock			
<i>Staphylococcus aureus</i>	Toxic shock syndrome toxin (TSST-1)	Cross-links β region of TCR to MHC class II on APCs outside of the antigen binding site → overwhelming release of IL-1, IL-2, IFN-γ, and TNF-α → shock	Toxic shock syndrome: fever, rash, shock; other toxins cause scalded skin syndrome (exfoliative toxin) and food poisoning (heat-stable enterotoxin)
<i>Streptococcus pyogenes</i>	Erythrogenic exotoxin A		Toxic shock-like syndrome: fever, rash, shock; scarlet fever

Endotoxin

LPS found in outer membrane of gram \ominus bacteria (both cocci and rods). Composed of O-antigen + core polysaccharide + lipid A (the toxic component). *Neisseria* have lipooligosaccharide. Released upon cell lysis or by living cells by blebs detaching from outer surface membrane (vs exotoxin, which is actively secreted). Three main effects: macrophage activation (TLR4/CD14), complement activation, and tissue factor activation.

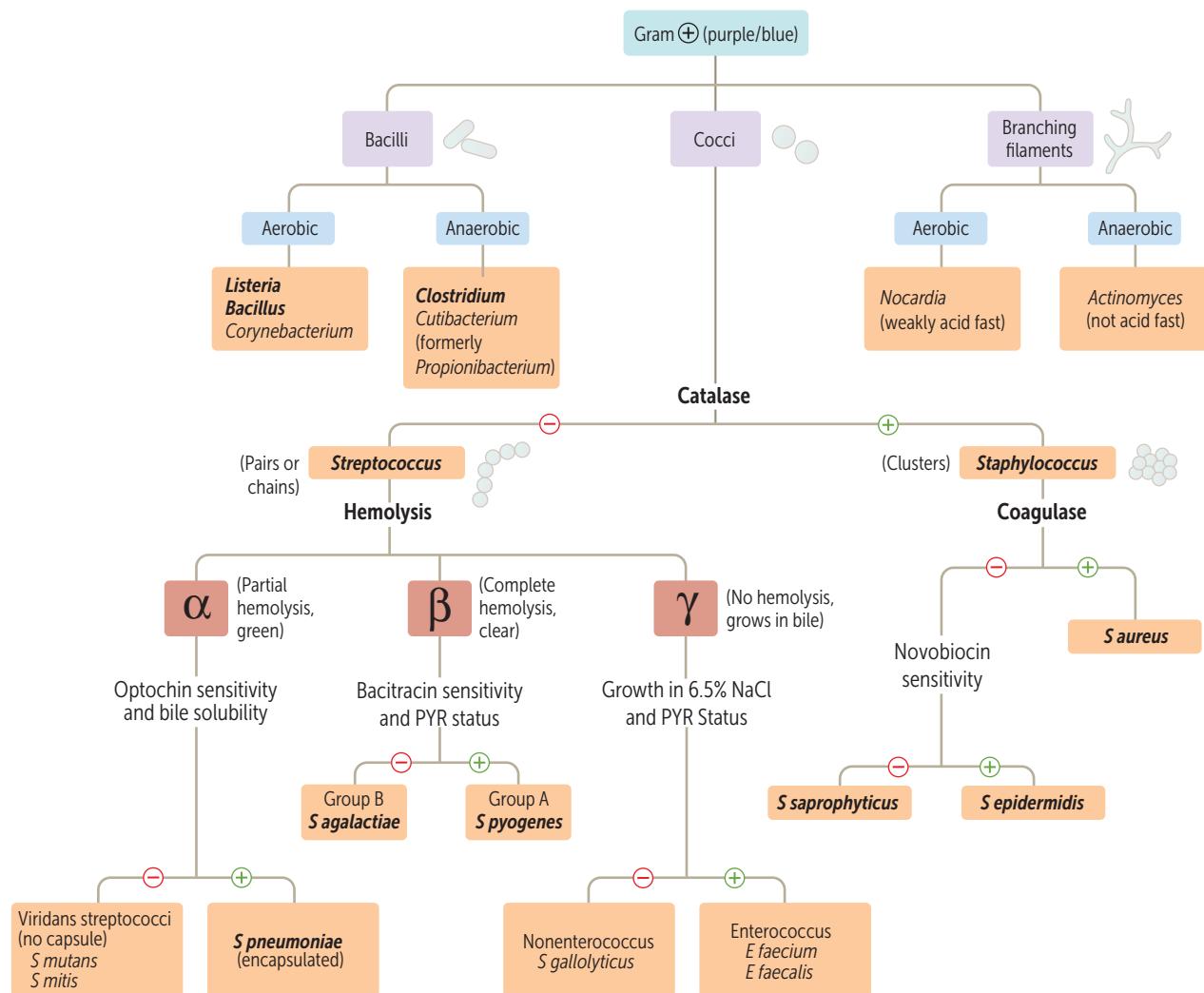
ENDOTOXINS:

Edema
Nitric oxide
DIC/**D**eath
Outer membrane
TNF- α
O-antigen + core polysaccharide + lipid A
eXtremely heat stable
IL-1 and **IL**-6
Neutrophil chemotaxis
Shock



► MICROBIOLOGY—CLINICAL BACTERIOLOGY

Gram-positive lab algorithm



Important **tests** are in bold. Important **pathogens** are in ***bold italics***.

Note: Enterococcus is either α - or γ -hemolytic.

PYR, Pyrrolidonyl aminopeptidase.

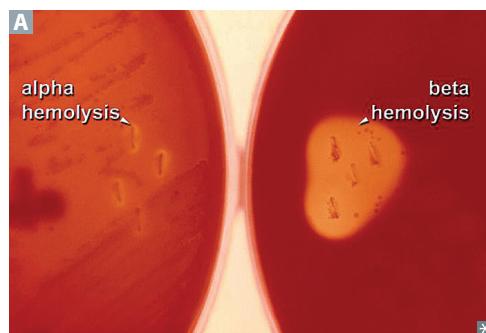
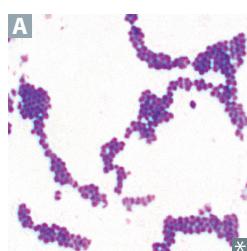


Hemolytic bacteria **α -hemolytic bacteria**

Partial oxidation of hemoglobin → greenish or brownish color without clearing around growth on blood agar **A**.
Include *Streptococcus pneumoniae* and viridans streptococci.

 β -hemolytic bacteria

Complete lysis of RBCs → pale/clear area surrounding colony on blood agar **A**.
Include *Staphylococcus aureus*, *Streptococcus pyogenes* (group A strep), *Streptococcus agalactiae* (group B strep), *Listeria monocytogenes*.

***Staphylococcus aureus***

Gram \oplus , β -hemolytic, catalase \oplus , coagulase \oplus cocci in clusters **A**. Protein A (virulence factor) binds Fc-IgG, inhibiting complement activation and phagocytosis. Commonly colonizes the skin, nares, ears, axilla, and groin.

Causes:

- Inflammatory disease—skin infections, organ abscesses, pneumonia (often after influenza virus infection), infective endocarditis, septic arthritis, and osteomyelitis.
- Toxin-mediated disease—toxic shock syndrome (TSST-1), scalded skin syndrome (exfoliative toxin), rapid-onset food poisoning (enterotoxins).

MRSA (methicillin-resistant *S aureus*)—important cause of serious healthcare-associated and community-acquired infections. Resistance due to altered penicillin-binding proteins (conferred by *mecA* gene). Some strains release Panton-Valentine leukocidin (PVL), which kills leukocytes and causes tissue necrosis.

TSST-1 is a superantigen that binds to MHC II and T-cell receptor, resulting in polyclonal T-cell activation and cytokine release.

Staphylococcal toxic shock syndrome (TSS)—fever, vomiting, diarrhea, rash, desquamation, shock, end-organ failure. TSS results in \uparrow AST, \uparrow ALT, \uparrow bilirubin. Associated with prolonged use of vaginal tampons or nasal packing.

Compare with *Streptococcus pyogenes* TSS (a toxic shock-like syndrome associated with painful skin infection).

S aureus food poisoning due to ingestion of preformed toxin → short incubation period (2–6 hr) followed by nonbloody diarrhea and emesis. Enterotoxin is heat stable → not destroyed by cooking.

S aureus makes coagulase and toxins. Forms fibrin clot around itself → abscess.

Staphylococcus epidermidis

Gram \oplus , catalase \oplus , coagulase \ominus , urease \oplus cocci in clusters. Novobiocin sensitive. Does not ferment mannitol (vs *S aureus*).

Normal microbiota of skin; contaminates blood cultures.

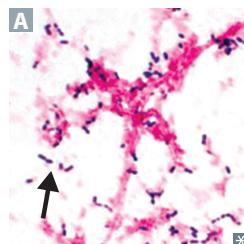
Infects prosthetic devices (eg, hip implant, heart valve) and IV catheters by producing adherent biofilms.

Staphylococcus saprophyticus

Gram \oplus , catalase \oplus , coagulase \ominus , urease \oplus cocci in clusters. Novobiocin resistant.

Normal microbiota of female genital tract and perineum.

Second most common cause of uncomplicated UTI in young females (most common is *E coli*).

Streptococcus pneumoniae

Gram \oplus , α -hemolytic, lancet-shaped diplococci **A**.

Encapsulated. IgA protease. Optochin sensitive and bile soluble.

Most commonly causes **MOPS**:

- **Meningitis**
- **Otitis media** (in children)
- **Pneumonia**
- **Sinusitis**

Pneumococcal pneumonia is associated with “rusty” sputum.

Patients with anatomic or functional hyposplenia or asplenia are predisposed to infection.

No virulence without capsule.

Pneumococcal vaccines are available in both conjugate (PCV13, PCV15, PCV20) and polysaccharide (PPSV23) formulations.

Viridans group streptococci

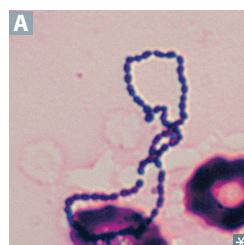
Gram \oplus , α -hemolytic cocci. Optochin resistant and bile insoluble. Normal microbiota of the oropharynx.

Streptococcus mutans and *S mitis* cause dental caries.

S sanguinis makes dextrans that bind to fibrin-platelet aggregates on damaged **heart** valves, causing infective endocarditis.

Viridans group strep live in the mouth, because they are not afraid **of-the-chin** (**op-to-chin** resistant).

Sanguinis = **blood**. Think, “there is lots of **blood** in the **heart**” (infective endocarditis).

Streptococcus pyogenes (group A streptococci)

Gram \oplus cocci in chains **A**. Group A strep cause:

- Pyogenic—pharyngitis, cellulitis, impetigo (“honey-crusted” lesions), erysipelas
- Toxigenic—scarlet fever, toxic shock-like syndrome, necrotizing fasciitis
- Immunologic—rheumatic fever, glomerulonephritis

Bacitracin sensitive, β -hemolytic, pyrrolidonyl arylamidase (PYR) \oplus . Hyaluronic acid capsule and M protein inhibit phagocytosis. Antibodies to M protein enhance host defenses. Structurally similar to host proteins (ie, myosin); can lead to autoimmunity (ie, carditis seen in acute rheumatic fever).

Diagnose strep pharyngitis via throat swab, which can be tested with an antigen detection assay (rapid, in-office results) or cultured on blood agar (results in 48 hours).

“Ph”ogenes **pharyngitis** can result in rheumatic “**p**hever” and glomerulone**ph**ritis.

Strains causing impetigo can induce glomerulonephritis.

Key virulence factors include DNase, erythrogenic exotoxin, streptokinase, streptolysin O. ASO titer or anti-DNase B antibodies indicate recent *S pyogenes* infection.

Scarlet fever—fine, blanching, generalized sandpaperlike rash sparing palms and soles, strawberry tongue, and circumoral pallor in the setting of group A streptococcal pharyngitis (erythrogenic toxin \oplus).

Streptococcus agalactiae (group B streptococci)

Gram \oplus cocci, bacitracin resistant, β -hemolytic, colonizes vagina; causes pneumonia, meningitis, and sepsis, mainly in **babies**. Polysaccharide capsule confers virulence. Produces CAMP factor, which enlarges the area of hemolysis formed by *S aureus*. (Note: CAMP stands for the authors of the test, not cyclic AMP.) Hippurate test \oplus . PYR \ominus . Screen pregnant patients at 35–37 weeks of gestation with rectal and vaginal swabs. Patients with \oplus culture receive intrapartum penicillin/ampicillin prophylaxis.

Streptococcus gallolyticus

Formerly *S bovis*. Gram \oplus cocci, colonizes the gut. Can cause bacteremia and infective endocarditis. Patients with *S gallolyticus* endocarditis have \uparrow incidence of colon cancer.

Bovis in the **blood** = **cancer** in the **colon**.

Enterococci

Gram \oplus cocci. Enterococci (*E faecalis* and *E faecium*) are normal colonic microbiota that are intrinsically resistant to penicillin G and cause UTI, biliary tract infections, and infective endocarditis (following GI/GU procedures). Catalase \ominus , PYR \oplus , typically nonhemolytic. VRE (vancomycin-resistant enterococci) are an important cause of healthcare-associated infection.

Enterococci are more resilient than streptococci, can grow in 6.5% NaCl and bile (lab test).

*Enter*o = intestine, *faecalis* = feces, *strepto* = twisted (chains), *coccus* = berry.

Bacillus anthracis

Gram \oplus , spore-forming rod that produces anthrax toxin, exotoxins consisting of protective antigen, lethal factor (inhibits MAP kinase \rightarrow macrophage apoptosis), and edema factor (acts as adenylyl cyclase \rightarrow \uparrow intracellular cAMP, upsetting homeostasis \rightarrow edema, necrosis). Has a polypeptide capsule (poly D-glutamate). Colonies show a halo of projections, sometimes called “medusa head” appearance.

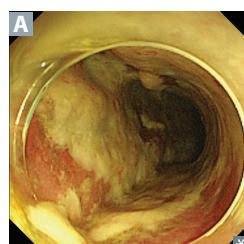
Cutaneous anthrax—painless papule surrounded by vesicles \rightarrow ulcer with black eschar **A** (painless, necrotic) \rightarrow uncommonly progresses to bacteremia and death.

Pulmonary anthrax—inhalation of spores, most commonly from contaminated animals or animal products, although also a potential bioweapon \rightarrow fulminant symptoms that rapidly progress to fever, pulmonary hemorrhage, mediastinitis (CXR may show widened mediastinum), and shock. Also called woolsorter’s disease. Prophylaxis with ciprofloxacin or doxycycline when exposed.

Both cutaneous and pulmonary anthrax may be complicated by hemorrhagic meningitis.

Bacillus cereus

Gram \oplus rod. Causes food poisoning. Spores survive cooking rice (reheated rice syndrome). Keeping rice warm results in germination of spores and enterotoxin formation. Emetic type causes nausea and vomiting within 1–5 hours. Caused by cereulide, a preformed toxin. Diarrheal type causes watery, nonbloody diarrhea and GI pain within 8–18 hours. Management: supportive care (antibiotics are ineffective against toxins).

Clostridioides difficile

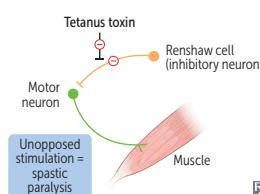
Produces toxins A and B, which damage enterocytes. Both toxins lead to watery diarrhea \rightarrow pseudomembranous colitis **A**. Often 2° to antibiotic use, especially clindamycin, ampicillin, cephalosporins, fluoroquinolones; associated with PPIs.
Fulminant infection: toxic megacolon, ileus, shock.

***Clostridium difficile* causes diarrhea.**

Diagnosed by PCR or antigen detection of one or both toxins in stool.
Treatment: oral vancomycin or fidaxomicin.
For recurrent cases, consider repeating prior regimen or fecal microbiota transplant.

Clostridia

Gram \oplus , spore-forming, obligate anaerobic rods. Tetanus toxin and botulinum toxin are proteases that cleave SNARE proteins involved in neurotransmission.

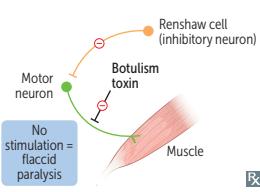
Clostridium tetani

Pathogen is noninvasive and remains localized to wound site. Produces tetanospasmin, an exotoxin causing tetanus. Tetanospasmin spreads by retrograde axonal transport to CNS and blocks release of GABA and glycine from Renshaw cells in spinal cord.

- Rx:** Causes **spastic** paralysis, trismus (lockjaw), risus sardonicus (raised eyebrows and open grin), opisthotonus (spasms of spinal extensors).

Tetanus is tetanic paralysis.

Prevent with tetanus vaccine. Treat with antitoxin \pm vaccine booster, antibiotics, diazepam (for muscle spasms), and wound debridement.

Clostridium botulinum

Produces a heat-labile toxin that damages SNARE proteins, thus preventing ACh release at the neuromuscular junction, causing botulism. In babies, ingestion of spores (eg, in honey) leads to disease (**floppy** baby syndrome). In adults, disease is caused by ingestion of preformed toxin (eg, in canned food).
Symptoms of botulism (the **5 D's**): **diplopia**, **dysarthria**, **dysphagia**, **dyspnea**, **descending flaccid** paralysis. Does not present with sensory deficits.

***Clostridium botulinum* is from bad bottles of food, juice, and honey.**

Treatment: human botulinum immunoglobulin. Local botulinum toxin A (Botox) injections used to treat focal dystonia, hyperhidrosis, muscle spasms, and cosmetic reduction of facial wrinkles.

Clostridium perfringens

Produces α -toxin (lecithinase, a phospholipase) that can cause myonecrosis (gas gangrene **A**; presents as soft tissue crepitus) and hemolysis. If heavily spore-contaminated food is cooked but left standing too long at $< 60^{\circ}\text{C}$, spore germinate \rightarrow vegetative bacteria ingested \rightarrow enterotoxin \rightarrow late-onset (10–12 hours) food poisoning symptoms, resolution in 24 hours.

***Clostridium perfringens* perforates a gangrenous leg.**

Spontaneous gas gangrene (via hematogenous seeding; associated with colonic malignancy) is most commonly caused by *Clostridium septicum*.

Corynebacterium diphtheriae

Gram \oplus rods occurring in angular arrangements; transmitted via respiratory droplets. Causes diphtheria via exotoxin encoded by β -prophage. Potent exotoxin inhibits protein synthesis via ADP-ribosylation of EF-2, leading to possible necrosis in pharynx, cardiac, and CNS tissue.

Symptoms include pseudomembranous pharyngitis (grayish-white membrane **A**) with lymphadenopathy ("bull's neck" appearance). Toxin dissemination may cause myocarditis, arrhythmias, neuropathies.

Lab diagnosis based on gram \oplus rods with metachromatic (blue and red) granules and \oplus Elek test for toxin.

Toxoid vaccine prevents diphtheria.

Coryne = club shaped (metachromatic granules on Löffler media).

Black colonies on cystine-tellurite agar.

ABCDEFG:

ADP-ribosylation

B-prophage

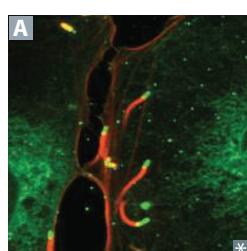
Corynebacterium

Ddiphtheriae

Elongation Factor 2

Granules

Treatment: diphtheria antitoxin +/- erythromycin or penicillin.

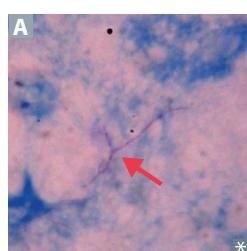
Listeria monocytogenes

Gram \oplus , facultative intracellular rod; acquired by ingestion of unpasteurized dairy products and cold deli meats, transplacental transmission, and by vaginal transmission during birth. Grows well at refrigeration temperatures ("cold enrichment").

Forms "rocket tails" (red in **A**) via actin polymerization that allow intracellular movement and cell-to-cell spread across cell membranes, thereby avoiding antibody. Listeriolysin generates pores in phagosomes, allowing its escape into cytoplasm. Characteristic tumbling motility in broth.

Can cause amnionitis, sepsis, and spontaneous abortion in pregnant patients; granulomatosis infantiseptica; meningitis in immunocompromised patients, neonates, and older adults; mild, self-limited gastroenteritis in healthy individuals.

Treatment: ampicillin.

Nocardia* vs *Actinomyces

Both are gram \oplus and form long, branching filaments resembling fungi.

Nocardia

Aerobe, catalase \oplus

Acid fast (weak) **A**

Found in soil

Causes pulmonary infections in immunocompromised (can mimic TB but with \ominus PPD); cutaneous infections after trauma in immunocompetent; can spread to CNS \rightarrow cerebral abscess

Treat with sulfonamides (TMP-SMX)

Treatment is a **SNAP**: Sulfonamides—*Nocardia*; *Actinomyces*—Penicillin

Actinomyces

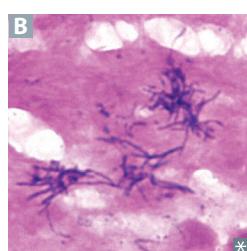
Anaerobe, catalase \ominus

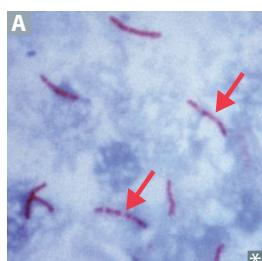
Not acid fast **B**

Normal oral, reproductive, and GI microbiota

Causes oral/facial abscesses that drain through sinus tracts; often associated with dental caries/extraction and other maxillofacial trauma; forms yellow "sulfur granules"; can also cause PID with IUDs

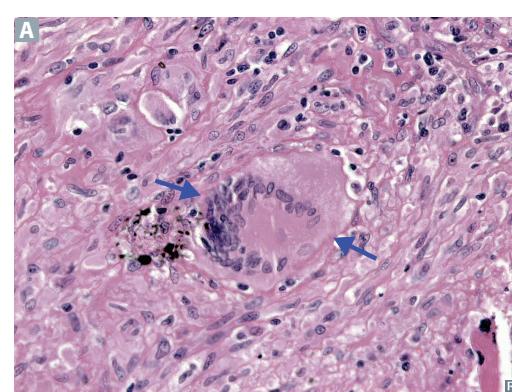
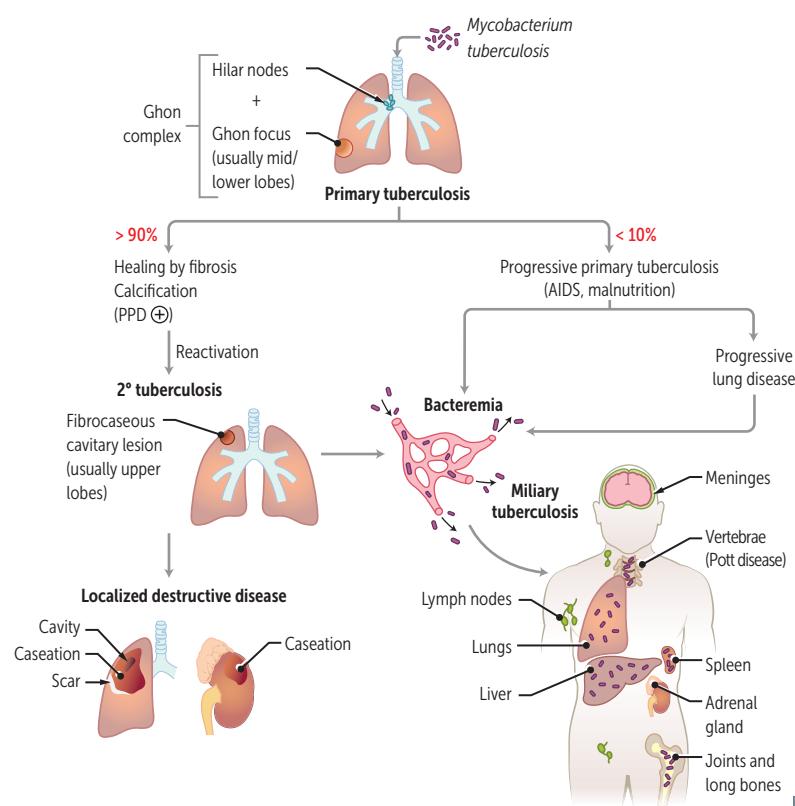
Treat with penicillin



Mycobacteria

Acid-fast rods (pink rods, arrows in A). Grows slowly in culture.
Mycobacterium tuberculosis (TB, often resistant to multiple drugs).
M avium-intracellulare (causes disseminated, non-TB disease in AIDS; often resistant to multiple drugs).
M scrofulaceum (cervical lymphadenitis in children).
M marinum (skin infection in aquarium handlers).

TB symptoms include fever, night sweats, weight loss, cough (nonproductive or productive), hemoptysis. Cord factor creates a “serpentine cord” appearance in virulent *M tuberculosis* strains; activates macrophages (promoting granuloma formation) and induces release of TNF- α . Sulfatides (surface glycolipids) inhibit phagolysosomal fusion.

Tuberculosis

Leprosy

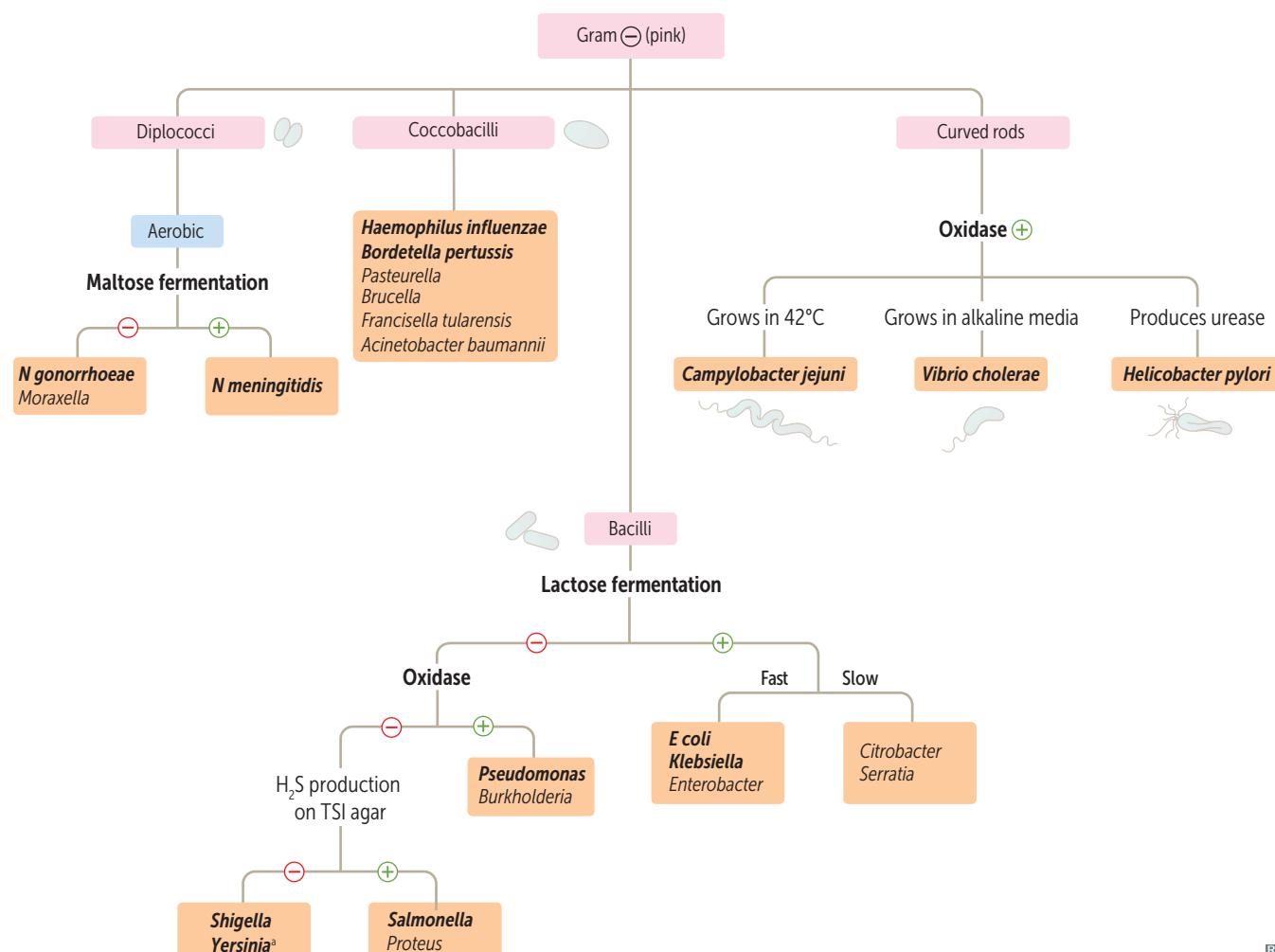
Also called Hansen disease. Caused by *Mycobacterium leprae*, an acid-fast bacillus that likes cool temperatures (infects skin and superficial nerves—"glove and stocking" loss of sensation) and cannot be grown in vitro. Diagnosed via skin biopsy or tissue PCR. Reservoir in United States: armadillos.

Leprosy has 2 forms (many cases fall temporarily between two extremes):

- **Lepromatous**—presents diffusely over the skin, with leonine (lionlike) facies **A**, and is communicable (high bacterial load); characterized by low cell-mediated immunity with a largely Th2 response. Lepromatous form can be lethal.
- **Tuberculoid**—limited to a few hypoesthetic, hairless skin plaques **B**; characterized by high cell-mediated immunity with a largely Th1 response and low bacterial load.

Treatment: **dapsone** and **rifampin** for tuberculoid form; **clofazimine** is added for lepromatous form.

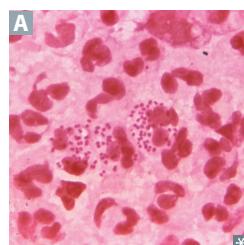
Daring rifles target cloaked leprechauns.

Gram-negative lab algorithm

Important tests are in **bold**. Important **pathogens** are in **bold italics**.

^aPleomorphic rod/coccobacillus



Neisseria

Gram \ominus diplococci. Metabolize glucose and produce IgA proteases. Contain lipooligosaccharides (LOS) with strong endotoxin activity.

N gonorrhoeae is often intracellular (within neutrophils) **A**.

Acid production: **meningococci**—maltose and glucose; **gonococci**—glucose.

Gonococci

No polysaccharide capsule

Meningococci

Polysaccharide capsule

No maltose acid detection

Maltose acid detection

No vaccine due to antigenic variation of pilus proteins

Vaccine (type B vaccine available for at-risk individuals)

Sexually or perinatally transmitted

Transmitted via respiratory and oral secretions.
More common among individuals in close quarters (eg, army barracks, college dorms)

Causes gonorrhea, septic arthritis, neonatal conjunctivitis (2–5 days after birth), pelvic inflammatory disease (PID), and Fitz-Hugh-Curtis syndrome

Causes meningococcemia with petechial hemorrhages and gangrene of toes **B**, meningitis, Waterhouse-Friderichsen syndrome (acute hemorrhagic adrenal insufficiency)

Diagnosed with NAAT

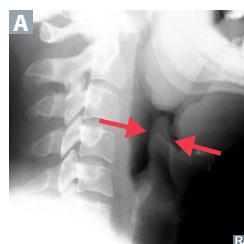
Diagnosed via culture-based tests or PCR

Condoms \downarrow sexual transmission, erythromycin eye ointment prevents neonatal blindness

Rifampin, ciprofloxacin, or ceftriaxone prophylaxis in close contacts

Treatment: single dose IM ceftriaxone; if chlamydial coinfection not excluded by molecular testing, add doxycycline

Treatment: ceftriaxone or penicillin G

Haemophilus influenzae

Small gram \ominus (coccobacillary) rod. Transmitted through respiratory droplets. Nontypeable (unencapsulated) strains are the most common cause of mucosal infections (otitis media, conjunctivitis, bronchitis) as well as invasive infections since the vaccine for capsular type b was introduced. Produces IgA protease.

Vaccine contains type b capsular polysaccharide (polyribosylribitol phosphate) conjugated to diphtheria toxoid or other protein. Given between 2 and 18 months of age.

Culture on chocolate agar, which contains factors V (NAD^+) and X (hematin) for growth; can also be grown with *S aureus*, which provides factor V via RBC hemolysis.

Does not cause the flu (influenza virus does).

Haemophilus causes epiglottitis (endoscopic appearance can be "cherry red" in children; "thumb sign" on lateral neck x-ray **A**), meningitis, otitis media, and pneumonia.

Treatment: amoxicillin +/- clavulanate for mucosal infections; ceftriaxone for meningitis; rifampin prophylaxis for close contacts.

***Burkholderia cepacia* complex**

Aerobic, catalase \oplus , gram \ominus rod. Causes pneumonia in patients with underlying lung disease, such as cystic fibrosis. Often multidrug resistant. Infection is a relative contraindication to undergoing lung transplant due to its association with poor outcomes.

Bordetella pertussis

Gram \ominus , aerobic coccobacillus. Virulence factors include pertussis toxin (disables G_i), adenylate cyclase toxin (\uparrow cAMP), and tracheal cytotoxin (destroys respiratory ciliated epithelium). Three clinical stages:

- Catarrhal—low-grade fevers, coryza.
- Paroxysmal—paroxysms of intense cough followed by inspiratory “whoop” (“whooping cough”), posttussive vomiting.
- Convalescent—gradual recovery of chronic cough.

Prevented by Tdap, DTaP vaccines (Tdap for preTeens and adulTs, DTaP for chilDren).

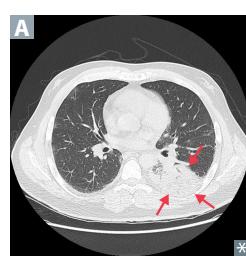
Produces lymphocytosis (unlike most acute bacterial infections).

Treatment: macrolides; if allergic use TMP-SMX.

Brucella

Gram \ominus , aerobic coccobacillus. Transmitted via ingestion of contaminated animal products (eg, unpasteurized milk). Survives in macrophages in the reticuloendothelial system. Can form non-caseating granulomas. Typically presents with undulant fever, night sweats, and arthralgia.

Treatment: doxycycline + rifampin or streptomycin.

Legionella pneumophila

Gram \ominus rod. Gram stains poorly—use silver stain. Grow on charcoal yeast extract medium with iron and cysteine. Detected by presence of antigen in urine. Labs may show hyponatremia and elevated transaminases.

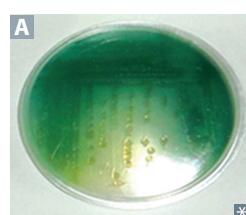
Aerosol transmission from environmental water source (eg, air conditioning systems, hot water tanks). Outbreaks associated with cruise ships, nursing homes. No person-to-person transmission.

Treatment: macrolide or quinolone.

Think of a French legionnaire (soldier) with his silver helmet, sitting around a campfire (charcoal) with his iron dagger—he is missing his sister (cysteine).

Legionnaires' disease—severe pneumonia (often unilateral and lobar A), fever, GI and CNS symptoms. Risk factors include older age, tobacco smoking, chronic lung disease.

Pontiac fever—mild flulike symptoms.

Pseudomonas aeruginosa

Aeruginosa—aerobic; motile, catalase \oplus , gram \ominus rod. Non-lactose fermenting. Oxidase \oplus .

Frequently found in water. Increased virulence in acidic environments. Has a grapelike odor.

PSEUDOMONAS is associated with:

Pneumonia, Sepsis, Ecthyma gangrenosum, UTIs, Diabetes, Osteomyelitis, Mucoid polysaccharide capsule, Otitis externa (swimmer's ear), Nosocomial (healthcare-associated) infections (eg, catheters, equipment), Addiction (injection drug use), Skin infections (eg, hot tub folliculitis, wound infection in burn victims).

Mucoid polysaccharide capsule may contribute to chronic pneumonia in patients with cystic fibrosis due to biofilm formation.

Produces **PEEP**: Phospholipase C (degrades cell membranes); Endotoxin (fever, shock); Exotoxin A (inactivates EF-2); green Pigment A.

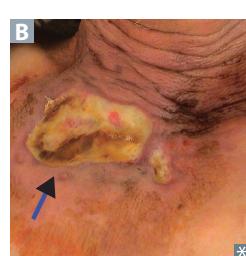
Corneal ulcers/keratitis in contact lens wearers/ minor eye trauma.

Ecthyma gangrenosum—rapidly progressive, necrotic cutaneous lesion B caused by *Pseudomonas* bacteremia. Typically seen in immunocompromised patients.

Treatments:

- Antipseudomonal penicillins in combination with β -lactamase inhibitor (eg, piperacillin-tazobactam)
- 3rd- and 4th-generation cephalosporins (eg, ceftazidime, cefepime)
- Monobactams
- Fluoroquinolones
- Carbapenems

Despite antipseudomonal activity, aminoglycoside monotherapy is avoided due to poor performance in acidic environments.



Salmonella vs Shigella Both *Salmonella* and *Shigella* are gram \ominus rods, non-lactose fermenters, oxidase \ominus , and can invade the GI tract via M cells of Peyer patches.

	<i>Salmonella typhi</i> (ty-Vi)	<i>Salmonella</i> spp. except <i>S typhi</i>	<i>Shigella</i>
RESERVOIRS	Humans only	Humans and animals	Humans only
SPREAD	Hematogenous spread	Hematogenous spread is rare	Cell to cell; no hematogenous spread
H ₂ S PRODUCTION	Yes	Yes	No
FLAGELLA	Yes (<i>salmon swim</i>)	Yes (<i>salmon swim</i>)	No
VIRULENCE FACTORS	Endotoxin; Vi capsule (pronounce “ty Vi ”)	Endotoxin	Endotoxin; Shiga toxin (enterotoxin)
INFECTIOUS DOSE (ID ₅₀)	High—large inoculum required; acid-labile (inactivated by gastric acids)	High	Low—very small inoculum required; acid stable (resistant to gastric acids)
EFFECT OF ANTIBIOTICS ON FECAL EXCRETION	Prolongs duration	Prolongs duration	Shortens duration (<i>shortens Shigella</i>)
IMMUNE RESPONSE	Primarily monocytes	PMNs in disseminated disease	Primarily PMN infiltration
GI MANIFESTATIONS	Constipation, followed by diarrhea	Diarrhea (possibly bloody)	Crampy abdominal pain → tenesmus, bloody mucoid stools (bacillary dysentery)
VACCINE	Oral vaccine contains live attenuated <i>S typhi</i> IM vaccine contains Vi capsular polysaccharide	No vaccine	No vaccine
UNIQUE PROPERTIES	Causes typhoid fever (salmon-colored truncal macular rash, abdominal pain, fever [pulse-temperature dissociation]; later GI ulceration and hemorrhage); treat with ceftriaxone or fluoroquinolone Carrier state with gallbladder colonization	Poultry, eggs, pets, and turtles are common sources Treatment is supportive; antibiotics are not indicated in immunocompetent individuals	4 F's: fingers, flies, food, feces In order of decreasing severity (less toxin produced): <i>S dysenteriae</i> , <i>S flexneri</i> , <i>S boydii</i> , <i>S sonnei</i> Invasion of M cells is key to pathogenicity; infectious dose is low

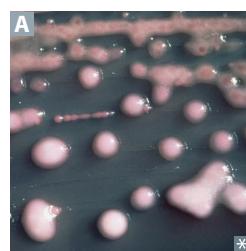
Yersinia enterocolitica Gram \ominus pleomorphic rod/coccobacillus with bipolar staining. Usually transmitted from pet feces (eg, cats, dogs), contaminated milk, or pork. Can cause acute bloody diarrhea, pseudoappendicitis (right lower abdominal pain due to mesenteric adenitis and/or terminal ileitis), reactive arthritis in adults.

Lactose-fermenting enteric bacteria Fermentation of lactose \rightarrow pink colonies on MacConkey agar. Examples include *Citrobacter*, *E. coli*, *Enterobacter*, *Klebsiella*, *Serratia*. **McCowkey CEEKS** milk. EMB agar—lactose fermenters grow as purple/black colonies. *E. coli* grows colonies with a green sheen.

Escherichia coli

Gram \ominus , indole \oplus rod. *E. coli* virulence factors: fimbriae (ie, P pili)—cystitis and pyelonephritis; K capsule—pneumonia, neonatal meningitis; LPS endotoxin—septic shock.

STRAIN	TOXIN AND MECHANISM	PRESENTATION
Enteroinvasive <i>E. coli</i>	Microbe invades intestinal mucosa and causes necrosis and inflammation.	EIEC is I nvasive; dysentery. Clinical manifestations similar to <i>Shigella</i> .
Enterotoxigenic <i>E. coli</i>	Produces heat-labile and heat-stable enterotoxins. No inflammation or invasion.	ETEC; T raveler's diarrhea (watery).
Enteropathogenic <i>E. coli</i>	No toxin produced. Adheres to apical surface, flattens villi, prevents absorption.	Diarrhea, usually in children (think EPEC and Pediatrics).
Enterohemorrhagic <i>E. coli</i>	O157:H7 is most common serotype in US. Often transmitted via undercooked meat, raw leafy vegetables. Shiga toxin causes hemolytic-uremic syndrome —triad of anemia, thrombocytopenia, and acute kidney injury due to microthrombi forming on damaged endothelium → mechanical hemolysis (with schistocytes on peripheral blood smear), platelet consumption → thrombocytopenia, and ↓ renal blood flow.	Dysentery (toxin alone causes necrosis and inflammation). Does not ferment sorbitol (vs other <i>E. coli</i>). EHEC associated with hemorrhage , hamburgers, hemolytic-uremic syndrome.

Klebsiella

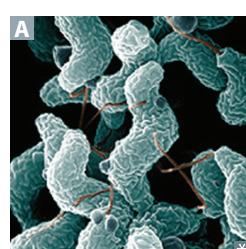
Gram \ominus rod; intestinal microbiota that causes lobar pneumonia; more common in patients with heavy alcohol use or with impaired host defenses. Very mucoid colonies **A** caused by abundant polysaccharide capsules. Dark red “currant jelly” sputum (blood/mucus).

Also cause of healthcare-associated UTIs.

Associated with evolution of multidrug resistance (MDR).

ABCDE's of Klebsiella:

- A**spiration pneumonia
- B**sscess in lungs and liver
- C**urrent jelly sputum
- D**iabetes mellitus
- E**tOH overuse

Campylobacter jejuni

Gram \ominus , comma or S shaped (with polar flagella) **A**, oxidase \oplus , grows at **42°C** (“**Campylobacter** likes the **hot campfire**”).

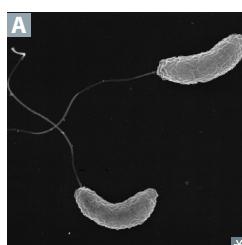
Major cause of bloody diarrhea, especially in children. Fecal-oral transmission through person-to-person contact or via ingestion of undercooked contaminated poultry or meat, unpasteurized milk. Contact with infected animals (dogs, cats, pigs) is also a risk factor.

Common antecedent to Guillain-Barré syndrome and reactive arthritis.

Proteus mirabilis

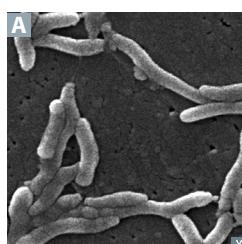
Gram \ominus , urease \oplus , facultative anaerobe, long flagellae with “swarming” motility.

Common cause of UTIs. Urease (virulence factor) hydrolyzes urea to carbon dioxide and ammonia → net increase in pH → promotes formation of struvite stones. Significant blockage of renal calyces results in branched stones called staghorn calculi.

Vibrio cholerae

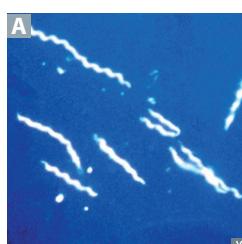
Gram \ominus , flagellated, comma shaped **A**, oxidase \oplus , grows in alkaline media. Endemic to developing countries. Produces profuse rice-water diarrhea via enterotoxin that permanently activates G_s, \uparrow cAMP. Sensitive to stomach acid (acid labile); requires large inoculum (high ID₅₀) unless host has \downarrow gastric acidity. Transmitted via ingestion of contaminated water or uncooked food (eg, raw shellfish). Treat promptly with oral rehydration solution.

Vibrio vulnificus—gram \ominus bacillus, usually found in marine environments. Causes severe wound infections or septicemia due to exposure to contaminated sea water. Presents as cellulitis that can progress to necrotizing fasciitis in high-risk patients, especially those with high serum iron (eg, cirrhosis, hemochromatosis). Serious wound infection requires surgical debridement.

Helicobacter pylori

Curved, flagellated (motile), gram \ominus rod **A** that is **triple** \oplus : catalase \oplus , oxidase \oplus , and urease \oplus (can use urea breath test or fecal antigen test for diagnosis). Urease produces ammonia, creating an alkaline environment, which helps *H pylori* survive in acidic mucosa. Colonizes mainly antrum of stomach; causes gastritis and peptic ulcers (especially duodenal). Risk factor for peptic ulcer disease, gastric adenocarcinoma, and MALT lymphoma.

Most common initial treatment is **triple** therapy: amoxicillin (metronidazole if penicillin allergy) + clarithromycin + proton pump inhibitor; **antibiotics cure Pylori**. Bismuth-based quadruple therapy if concerned about macrolide resistance.

Spirochetes

Spiral-shaped bacteria **A** with axial filaments. Includes *Leptospira*, *Treponema*, and *Borrelia*. Only *Borrelia* can be visualized using aniline dyes (Wright or Giemsa stain) in light microscopy due to size. *Treponema* is visualized by dark-field microscopy or direct fluorescent antibody (DFA) microscopy.

Little Twirling Bacteria.

Jarisch-Herxheimer reaction—flulike symptoms (fever, chills, headache, myalgia) after antibiotics are started due to host response to sudden release of bacterial antigens. Usually occurs during treatment of spirochetal infections.

Lyme disease

Caused by *Borrelia burgdorferi*, which is transmitted by the *Ixodes* deer tick **A** (also vector for *Anaplasma* spp. and protozoa *Babesia*). Natural reservoir is the mouse; deer are essential to tick life cycle but do not harbor *Borrelia*.

Common in northeastern United States. Stage 1—early localized: erythema migrans (typical “bulls-eye” configuration **B** is pathognomonic but not always present), flulike symptoms.

Stage 2—early disseminated: secondary lesions, carditis, AV block, facial nerve (Bell) palsy, migratory myalgias/transient arthritis.

Stage 3—late disseminated: encephalopathy, chronic arthritis, peripheral neuropathy.

A Key Lyme pie to the FACE:

Facial nerve palsy (typically bilateral)

Arthritis

Cardiac block

Erythema migrans

Treatment: doxycycline (1st line); amoxicillin (pregnant patients, children $<$ 8 years old); ceftriaxone if IV therapy required



Leptospira interrogans

Spirochete with hook-shaped ends found in water contaminated with animal urine.

Leptospirosis—flu-like symptoms, myalgias (classically of calves), jaundice, photophobia with conjunctival suffusion (erythema without exudate). Prevalent among surfers and in the tropics (eg, Hawaii).

Weil disease (icterohemorrhagic leptospirosis)—severe form with jaundice and azotemia from liver and kidney dysfunction, fever, hemorrhage, and anemia.

Syphilis

Caused by spirochete *Treponema pallidum*. Treatment: penicillin G.

Primary syphilis

Localized disease presenting with painless chancre. Use fluorescent or dark-field microscopy to visualize treponemes in fluid from chancre **A**. VDRL \oplus in $\sim 80\%$ of patients.

Secondary syphilis

Disseminated disease with constitutional symptoms, maculopapular rash **B** (including palms **C** and soles), condylomata lata **D** (smooth, painless, wartlike white lesions on genitals), lymphadenopathy, patchy hair loss; also confirmable with dark-field microscopy. Serologic testing: VDRL/RPR (nonspecific), confirm diagnosis with specific test (eg, FTA-ABS). Secondary syphilis = systemic. Latent syphilis (\oplus serology without symptoms) may follow.

Tertiary syphilis

Gummas **E** (chronic granulomas), aortitis (vasa vasorum destruction), neurosyphilis (tabes dorsalis, “general paresis”), Argyll Robertson pupil (constricts with accommodation but is not reactive to light).

Signs: broad-based ataxia, \oplus Romberg, Charcot joint, stroke without hypertension.

Congenital syphilis

Presents with facial abnormalities such as rhagades (linear scars at angle of mouth, black arrow in **F**), snuffles (nasal discharge, red arrow in **F**), saddle nose, notched (Hutchinson) teeth **G**, mulberry molars, and short maxilla; saber shins; CN VIII deafness.

To prevent, treat patient early in pregnancy, as placental transmission typically occurs after first trimester.

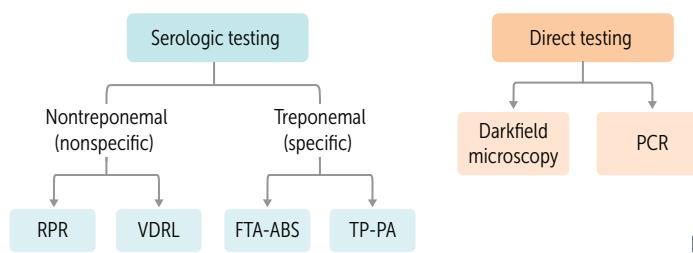


Diagnosing syphilis

VDRL and RPR detects nonspecific antibody that reacts with beef cardiolipin. Quantitative, inexpensive, and widely available test for syphilis (sensitive but not specific). Nontreponemal tests (VDRL, RPR) and direct testing revert to negative after treatment. Antibodies detected by treponemal tests (FTA-ABS, TP-PA) will remain positive.

False-Positive results on **VDRL** with:

- Pregnancy
- Viral infection (eg, EBV, hepatitis)
- Drugs (eg, chlorpromazine, procainamide)
- Rheumatic fever (rare)
- Lupus (anticardiolipin antibody) and Leprosy



Rx

Chlamydiae

Chlamydiae cannot make their own ATP. They are obligate intracellular organisms that cause mucosal infections. 2 forms:

- Elementary body (small, dense) is “enfectious” and enters cell via endocytosis; transforms into reticulate body.
- Reticulate body replicates in cell by fission; reorganizes into elementary bodies.

Chlamydia trachomatis causes neonatal and follicular adult conjunctivitis **A**, nongonococcal urethritis, PID, and reactive arthritis.

Chlamydophila pneumoniae and *Chlamydophila psittaci* cause atypical pneumonia; transmitted by aerosol.

Chlamydial cell wall lacks classic peptidoglycan (due to reduced muramic acid), rendering β-lactam antibiotics ineffective.

Chlamys = cloak (intracellular).

C psittaci—has an avian reservoir (parrots), causes atypical pneumonia.

Lab diagnosis: PCR, NAAT. Cytoplasmic inclusions (reticulate bodies) seen on Giemsa or fluorescent antibody-stained smear.

Treatment: doxycycline, azithromycin (for pregnant patients). Add ceftriaxone if concurrent gonorrhea testing is positive.

Chlamydia trachomatis* serotypes*Types A, B, and C**

Chronic infection, cause blindness due to follicular conjunctivitis in resource-limited areas.

ABC = Africa, Blindness, Chronic infection.

Types D–K

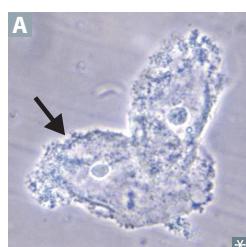
Urethritis/PID, ectopic pregnancy, neonatal pneumonia (staccato cough) with eosinophilia, neonatal conjunctivitis (1–2 weeks after birth).

D–K = everything else.

Neonatal disease can be acquired during vaginal birth if pregnant patient is infected.

Types L1, L2, and L3

Lymphogranuloma venereum—small, painless ulcers on genitals → swollen, painful inguinal lymph nodes that ulcerate (bubo). Treat with doxycycline.

Gardnerella vaginalis

A pleomorphic, gram-variable rod involved in bacterial vaginosis. Presents as a gray vaginal discharge with a fishy smell; nonpainful (vs vaginitis). Associated with sexual activity, but not sexually transmitted. Bacterial vaginosis is also characterized by overgrowth of certain anaerobic bacteria in vagina (due to ↓ lactobacilli). Clue cells (vaginal epithelial cells covered with *Gardnerella*) have stippled appearance along outer margin (arrow in A).

Amine whiff test—mixing discharge with 10% KOH enhances fishy odor.
Vaginal pH >4.5 during infection.
Treatment: metronidazole or clindamycin.

Zoonotic bacteria

SPECIES	DISEASE	TRANSMISSION AND SOURCE
<i>Anaplasma spp</i>	Anaplasmosis	<i>Ixodes</i> ticks (live on deer and mice)
<i>Bartonella spp</i>	Cat scratch disease, bacillary angiomatosis	Cat scratch
<i>Borrelia burgdorferi</i>	Lyme disease	<i>Ixodes</i> ticks (live on deer and mice)
<i>Borrelia recurrentis</i>	Relapsing fever	Louse (recurrent due to variable surface antigens)
<i>Brucella spp</i>	Brucellosis/undulant fever	Unpasteurized dairy; inhalation of or contact with infected animal tissue or fluids
<i>Campylobacter</i>	Bloody diarrhea	Feces from infected pets/animals; contaminated meats/foods/hands
<i>Chlamydophila psittaci</i>	Psittacosis	Parrots, other birds
<i>Coxiella burnetii</i>	Q fever	Aerosols of cattle/sheep amniotic fluid
<i>Ehrlichia chaffeensis</i>	Ehrlichiosis	<i>Amblyomma</i> (Lone Star tick)
<i>Francisella tularensis</i>	Tularemia	Ticks, rabbits, deer flies
<i>Leptospira spp</i>	Leptospirosis	Animal urine in water; recreational water use
<i>Mycobacterium leprae</i>	Leprosy	Humans with lepromatous leprosy; armadillo (rare)
<i>Pasteurella multocida</i>	Cellulitis, osteomyelitis	Animal bite, cats, dogs
<i>Rickettsia prowazekii</i>	Epidemic typhus	Human to human via human body louse
<i>Rickettsia rickettsii</i>	Rocky Mountain spotted fever	<i>Dermacentor</i> (dog tick)
<i>Rickettsia typhi</i>	Endemic typhus	Fleas
<i>Salmonella spp (except S typhi)</i>	Diarrhea (which may be bloody), vomiting, fever, abdominal cramps	Reptiles and poultry
<i>Yersinia pestis</i>	Plague	Fleas (rats and prairie dogs are reservoirs)

**Rickettsial diseases
and vector-borne
illnesses**

RASH COMMON

**Rocky Mountain
spotted fever**

Treatment: doxycycline.

Rickettsia rickettsii, vector is tick. Despite its name, disease occurs primarily in the South Atlantic states, especially North Carolina. Rash typically starts at wrists **A** and ankles and then spreads to trunk, palms, and soles.

Classic triad—headache, fever, rash (vasculitis). **Palms and soles** rash is seen in Coxsackievirus **A** infection (hand, foot, and mouth disease), Rocky Mountain spotted fever, and 2° Syphilis (you drive CARS using your palms and soles).

Typhus

Endemic (fleas)—*R typhi*. Epidemic (human body louse)—*R prowazekii*. Rash starts centrally and spreads out, sparing palms and soles.

Rickettsii on the wrists, typhus on the trunk.

RASH RARE

Ehrlichiosis

Ehrlichia, vector is tick. Monocytes with morulae **B** (mulberrylike inclusions) in cytoplasm.

MEGA:

Monocytes = Ehrlichiosis
Granulocytes = Anaplasmosis

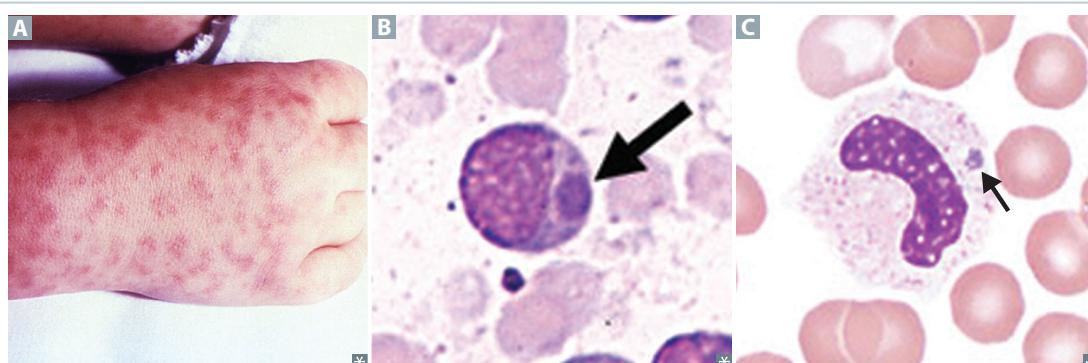
Anaplasmosis

Anaplasma, vector is tick. Granulocytes with morulae **C** in cytoplasm.

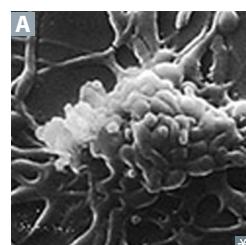
Q fever

Coxiella burnetii, no arthropod vector. Bacterium inhaled as aerosols from cattle/sheep amniotic fluid. Presents with headache, cough, flulike symptoms, pneumonia, possibly in combination with hepatitis. Common cause of culture ⊖ endocarditis.

Q fever is caused by a **Quite Complicated** bug because it has no rash or vector and its causative organism can survive outside in its endospore form. Not in the *Rickettsia* genus, but closely related.



**Mycoplasma
*pneumoniae***



Classic cause of atypical “walking pneumonia” (insidious onset, headache, nonproductive cough, patchy or diffuse interstitial infiltrate, macular rash).

Not seen on Gram stain. Pleiomorphic **A**.

Occurs frequently in those <30 years old; outbreaks in military recruits, prisons, colleges. Treatment: macrolides, doxycycline, or fluoroquinolone (penicillin ineffective since *Mycoplasma* has no cell wall).

Bacterial membrane contains sterols for stability. Grown on Eaton agar. CXR appears more severe than patient presentation. High titer of **cold** agglutinins (IgM), which can agglutinate RBCs. *Mycoplasma* gets **cold** without a **coat** (no cell wall).

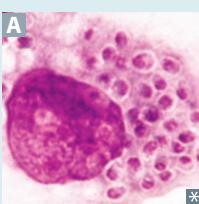
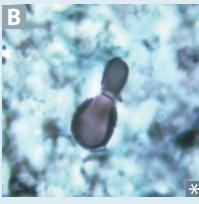
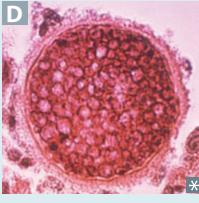
► MICROBIOLOGY—MYCOLOGY

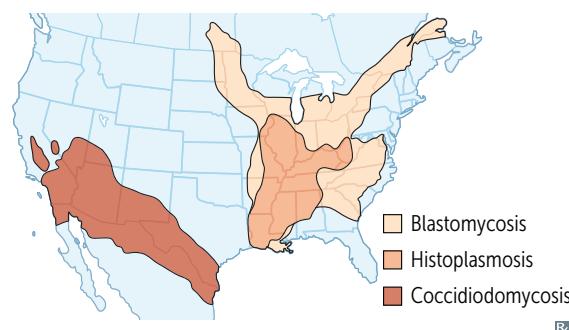
Systemic mycoses

All of the following can cause pneumonia and can disseminate.

All are caused by dimorphic fungi: **cold** (20°C) = **mold**; **heat** (37°C) = **yeast**. Only exception is *Coccidioides*, which is a spherule (not yeast) in tissue.

Systemic mycoses can form granulomas (like TB); cannot be transmitted person-to-person (unlike TB). Treatment: fluconazole or itraconazole for **local** infection; amphotericin B for **systemic** infection.

DISEASE	ENDEMIC LOCATION	PATHOLOGIC FEATURES	UNIQUE SIGNS/SYMPOMTS	NOTES
Histoplasmosis 	Mississippi and Ohio River Valleys	Macrophage filled with <i>Histoplasma</i> (smaller than RBC) A Tuberculate macroconidia on culture	Palatal/tongue ulcers, splenomegaly, pancytopenia, erythema nodosum	Histo hides (within macrophages) Associated with bird or bat droppings (eg, caves) Diagnosis via urine/serum antigen
Blastomycosis 	Eastern and Central US, Great Lakes	Broad -based budding of <i>Blastomyces</i> (same size as RBC) B	Inflammatory lung disease Disseminates to bone/skin (verrucous lesions C , may mimic SCC).	Blasto buds broadly 
Coccidioidomycosis 	Southwestern US, California	Spherule filled with endospores of <i>Coccidioides</i> (much larger than RBC) D	Disseminates to bone/skin Erythema nodosum (desert bumps) or multiforme Arthralgias (desert rheumatism) Can cause meningitis	Associated with dust exposure in endemic areas (eg, archeological excavations, earthquakes)
Paracoccidioidomycosis 	Latin America	Budding yeast of <i>Paracoccidioides</i> with “ captain’s wheel ” formation (much larger than RBC) E	Similar to blastomycosis, males > females	Paracoccidio parasails with the captain’s wheel all the way to Latin America



Opportunistic fungal infections***Candida albicans***

alba = white. Dimorphic; forms pseudohyphae and budding yeasts at 20°C **A**, germ tubes at 37°C **B**.

Systemic or superficial fungal infection. Causes oral **C** and esophageal thrush in immunocompromised (neonates, steroids, diabetes, AIDS), vulvovaginitis (diabetes, use of antibiotics), diaper rash, infective endocarditis (people who inject drugs), disseminated candidiasis (especially in neutropenic patients as host defense relies on phagocytes), chronic mucocutaneous candidiasis.

Treatment: oral fluconazole/topical azoles for vaginal; nystatin, azoles, or, rarely, echinocandins for oral; fluconazole, echinocandins, or amphotericin B for esophageal or systemic disease.

Aspergillus fumigatus

Acute angle (45°) **D** branching of septate hyphae.

Causes invasive aspergillosis in immunocompromised patients, especially those with neutrophil dysfunction (eg, chronic granulomatous disease) because *Aspergillus* is catalase \oplus .

Can cause aspergillomas **E** in pre-existing lung cavities, especially after TB infection.

Some species of *Aspergillus* produce aflatoxins (induce TP53 mutations leading to hepatocellular carcinoma).

Treatment: voriconazole or echinocandins (2nd-line).

Allergic bronchopulmonary aspergillosis (ABPA)—hypersensitivity response to *Aspergillus* growing in lung mucus. Associated with asthma and cystic fibrosis; may cause bronchiectasis and eosinophilia.

Cryptococcus neoformans

5–10 μm with narrow budding. Heavily encapsulated yeast. Not dimorphic. \oplus PAS staining.

Found in soil, pigeon droppings. Acquired through inhalation with hematogenous dissemination to meninges. Highlighted with India ink (clear halo **F**) and mucicarmine (red inner capsule **G**).

Latex agglutination test detects polysaccharide capsular antigen and is more sensitive and specific. Causes cryptococcosis, which can manifest with meningitis, pneumonia, and/or encephalitis (“soap bubble” lesions in brain), primarily in immunocompromised.

Treatment: amphotericin B + flucytosine followed by fluconazole for cryptococcal meningitis.

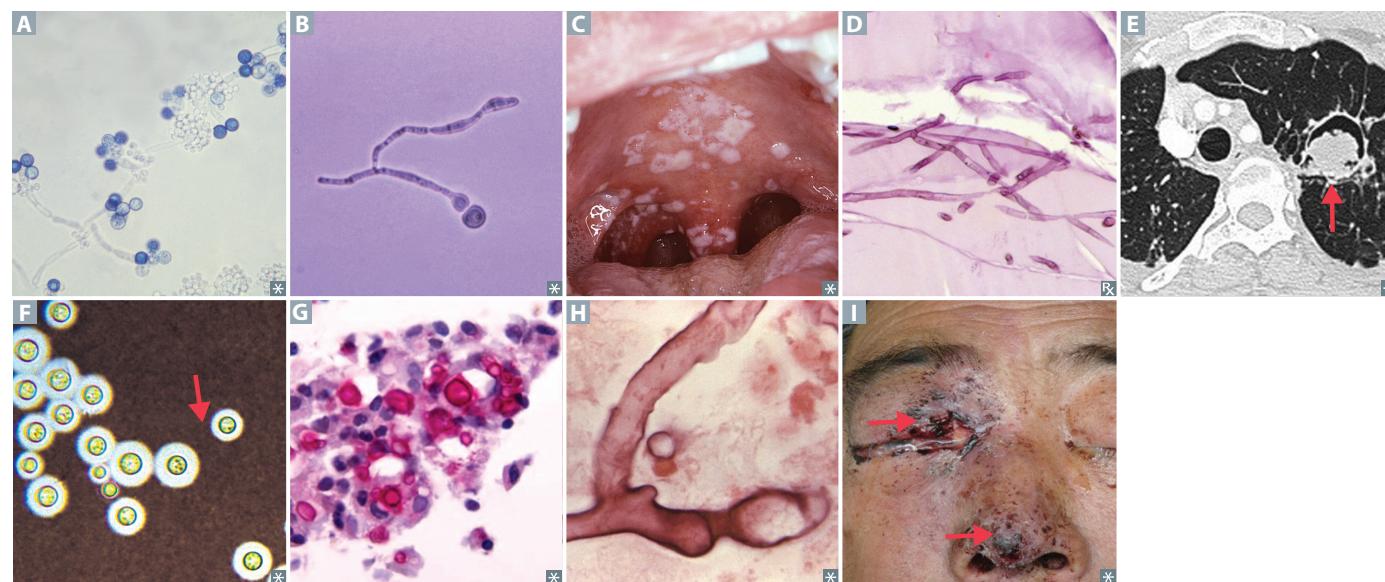
Mucor and Rhizopus spp

Irregular, broad, nonseptate hyphae branching at wide angles **H**.

Causes mucormycosis, mostly in patients with DKA and/or neutropenia (eg, leukemia). Inhalation of spores \rightarrow fungi proliferate in blood vessel walls, penetrate cribriform plate, and enter brain.

Rhinocerebral, frontal lobe abscess; cavernous sinus thrombosis. Headache, facial pain, black necrotic eschar on face **I**; may have cranial nerve involvement.

Treatment: surgical debridement, amphotericin B or isavuconazole.

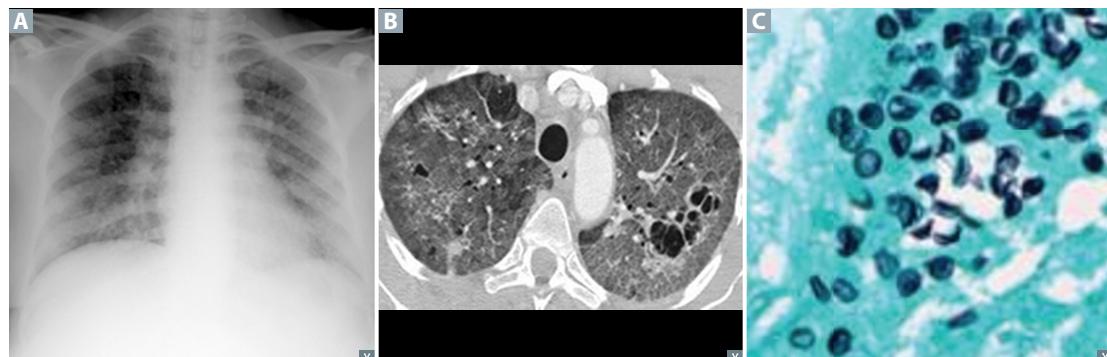


Pneumocystis jirovecii

Yeastlike fungus that causes *Pneumocystis* pneumonia (PCP), a diffuse interstitial pneumonia

A. Most infections are asymptomatic. Immunosuppression (eg, AIDS) predisposes to disease. Diffuse, bilateral ground-glass opacities on chest imaging, with pneumatoceles **B**. Diagnosed by bronchoalveolar lavage or lung biopsy. Disc-shaped yeast seen on methenamine silver stain of lung tissue **C** or with fluorescent antibody.

Treatment/prophylaxis: TMP-SMX, pentamidine, dapsone (prophylaxis as single agent, or treatment in combination with TMP), atovaquone. Start prophylaxis when CD4+ cell count drops to < 200 cells/mm³ in people living with HIV.

***Sporothrix schenckii***

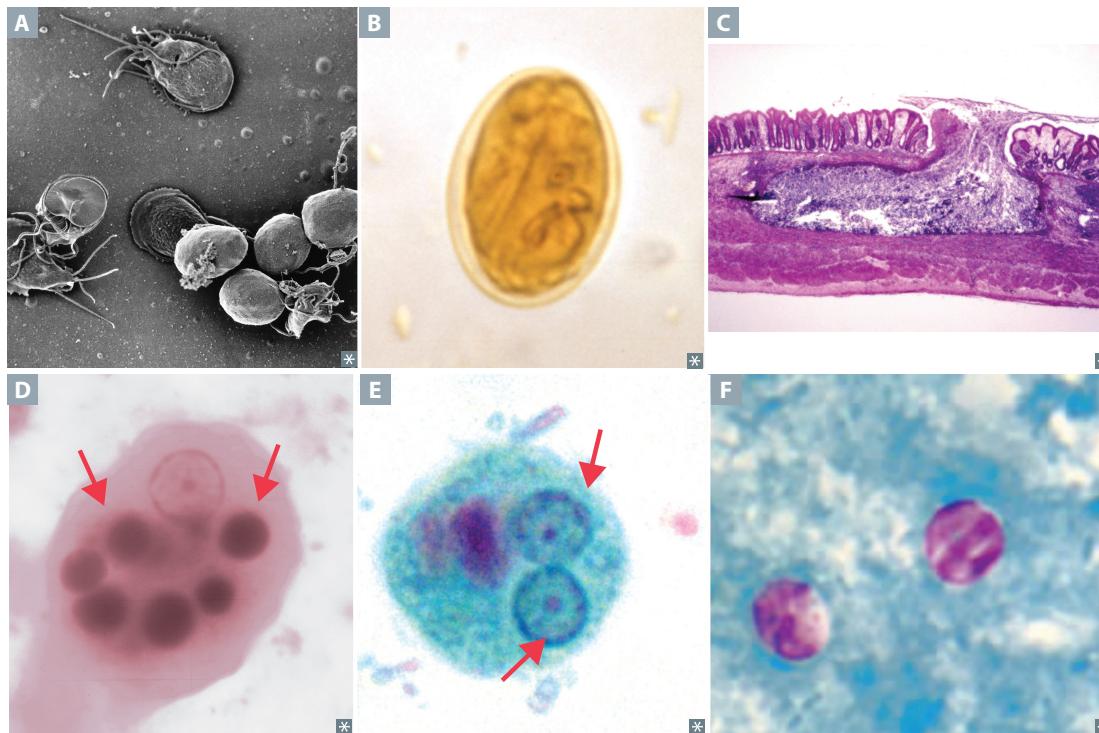
Causes sporotrichosis. Dimorphic fungus. Exists as a **cigar**-shaped yeast at 37 °C in the human body and as hyphae with spores in soil (conidia). Lives on vegetation. When spores are traumatically introduced into the skin, typically by a thorn ("**rose gardener's** disease"), causes local pustule or ulcer with nodules along draining lymphatics (ascending lymphangitis **A**). Disseminated disease possible in immunocompromised host.

Treatment: itraconazole or **potassium iodide** (only for cutaneous/lymphocutaneous). Think of a **rose gardener** who smokes a **cigar** and **pot**.

► MICROBIOLOGY—PARASITOLOGY

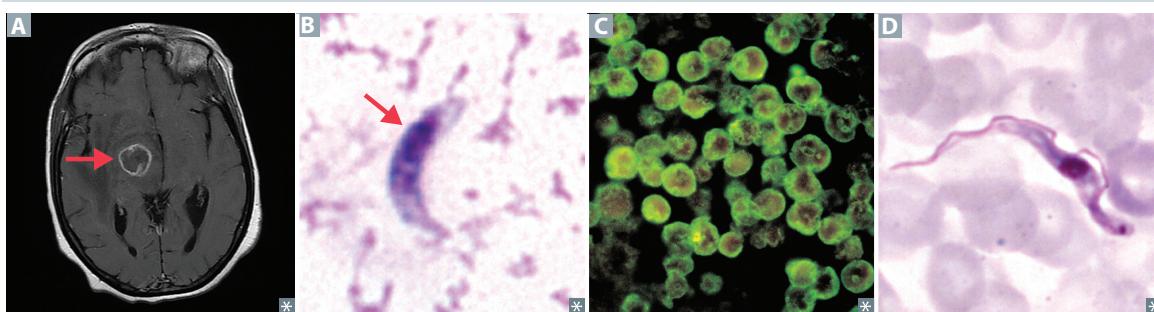
Protozoa—gastrointestinal infections

ORGANISM	DISEASE	TRANSMISSION	DIAGNOSIS	TREATMENT
<i>Giardia lamblia</i>	Giardiasis —bloating, flatulence, foul-smelling, nonbloody, fatty diarrhea (often seen in campers/hikers)—think fat-rich Ghirardelli chocolates for fatty stools of Giardia	Cysts in water	Multinucleated trophozoites A or cysts B in stool, antigen detection, PCR	Tinidazole, nitazoxanide, or metronidazole
<i>Entamoeba histolytica</i>	Amebiasis —bloody diarrhea (dysentery), liver abscess (“anchovy paste” exudate), RUQ pain; histology of colon biopsy shows flask-shaped ulcers C	Cysts in water	Serology, antigen testing, PCR, and/or trophozoites (with engulfed RBCs D in the cytoplasm) or cysts with up to 4 nuclei in stool E ; Entamoeba Eats Erythrocytes	Metronidazole; paromomycin for asymptomatic cyst passers
<i>Cryptosporidium</i>	Severe diarrhea in AIDS Mild disease (watery diarrhea) in immunocompetent hosts	Oocysts in water	Oocysts on acid-fast stain F , antigen detection, PCR	Prevention (eg, filtering); nitazoxanide (severe disease and/or immunocompromised)



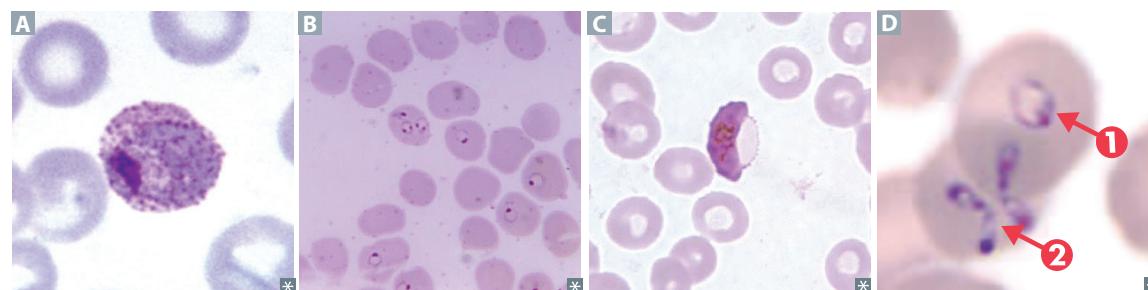
Protozoa—CNS infections

ORGANISM	DISEASE	TRANSMISSION	DIAGNOSIS	TREATMENT
<i>Toxoplasma gondii</i>	Immunocompetent: mononucleosis-like symptoms, ⊖ heterophile antibody test Reactivation in AIDS → brain abscesses usually seen as multiple ring-enhancing lesions on MRI A Congenital toxoplasmosis: classic triad of chorioretinitis, hydrocephalus, and intracranial calcifications	Cysts in meat (most common); oocysts in cat feces; crosses placenta (pregnant patients should avoid cats)	Serology, biopsy (tachyzoite) B ; PCR of amniotic fluid for possible intrauterine disease	Sulfadiazine + pyrimethamine Prophylaxis with TMP-SMX when CD4+ cell count < 100 cells/mm ³
<i>Naegleria fowleri</i>	Rapidly fatal meningoencephalitis	Swimming in warm freshwater; enters CNS through olfactory nerve via cribriform plate	Amoebas in CSF C	Amphotericin B has been effective for a few survivors
<i>Trypanosoma brucei</i>	African sleeping sickness — enlarged lymph nodes, recurring fever (due to antigenic variation), somnolence, coma	Tsetse fly, a painful bite	Trypomastigote in blood smear D	Suramin for blood- borne disease or melarsoprol for CNS penetration ("I sure am mellow when I'm sleeping ")



Protozoa—hematologic infections

ORGANISM	DISEASE	TRANSMISSION	DIAGNOSIS	TREATMENT
<i>Plasmodium</i>	Malaria—cyclic fevers, headache, anemia, splenomegaly; hypoglycemia in severe disease	<i>Anopheles</i> mosquito	Peripheral blood smear (also allows for identification of species)	If sensitive, chloroquine; if resistant, mefloquine, doxycycline or atovaquone/proguanil If life threatening, use intravenous quinine or artesunate (test for G6PD deficiency)
<i>P malariae</i>	72-hr fever cycle (quartan)		Trophozoite ring within RBC	
<i>P vivax/ovale</i>	48-hr fever cycle (tertian); dormant form (hypnozoite) in liver		Trophozoites and Schüffner stippling (small red granules) within RBC cytoplasm A	Add primaquine to target hypnozoites
<i>P falciparum</i>	Severe, irregular fever pattern; parasitized RBCs may occlude capillaries in brain (cerebral malaria), kidneys, lungs		Trophozoite ring (headphone shaped) within RBC B ; crescent-shaped gametocytes C	
<i>Babesia</i>	Babesiosis—fever and hemolytic anemia; predominantly in northeastern and north central United States; asplenia ↑ risk of severe disease due to inability to clear infected RBCs	<i>Ixodes</i> tick (also vector for <i>Borrelia burgdorferi</i> and <i>Anaplasma</i> spp)	Ring form D1 , “Maltese cross” D2 ; PCR	Atovaquone + azithromycin



Protozoa—others

ORGANISM	DISEASE	TRANSMISSION	DIAGNOSIS	TREATMENT
Visceral infections				
<i>Trypanosoma cruzi</i>	Chagas disease—dilated cardiomyopathy with apical atrophy, megacolon, megaesophagus; (<i>T. cruzi</i> causes big problems); predominantly in South America Unilateral periorbital swelling (Romaña sign) characteristic of acute stage	Triatomine insect (kissing bug) bites and defecates around the mouth or eyes → fecal transmission into bite site or mucosa	Trypomastigote in blood smear A	Benznidazole or nifurtimox
<i>Leishmania</i> spp	Visceral leishmaniasis (kala-azar)—spiking fevers, hepatosplenomegaly, pancytopenia Cutaneous leishmaniasis —skin ulcers B	Sandfly	Macrophages containing amastigotes C	Amphotericin B, sodium stibogluconate
Sexually transmitted infections				
<i>Trichomonas vaginalis</i>	Vaginitis —foul-smelling, greenish discharge; itching and burning; do not confuse with <i>Gardnerella vaginalis</i> , a gram-variable bacterium associated with bacterial vaginosis	Sexual (cannot exist outside human because it cannot form cysts)	Trophozoites (motile) D on wet mount; punctate cervical hemorrhages (“strawberry cervix”)	Metronidazole for patient and partner(s) (prophylaxis; check for STI)

**Nematode routes of infection**

Ingested—*Enterobius*, *Ascaris*, *Toxocara*, *Trichinella*, *Trichuris*
 Cutaneous—*Strongyloides*, *Ancylostoma*, *Necator*
 Bites—*Loa loa*, *Onchocerca volvulus*, *Wuchereria bancrofti*

You'll get sick if you **EATTT** these!

These get into your feet from the **SAND**

Lay **LOW** to avoid getting bitten

Nematodes (roundworms)

ORGANISM	DISEASE	TRANSMISSION	TREATMENT
Intestinal			
<i>Enterobius vermicularis</i> (pinworm)	Causes anal pruritus, worse at night (eggs A visualized via tape test). Most common in children aged 5–10.	Fecal-oral.	Bendazoles, pyrantel pamoate.
<i>Ascaris lumbricoides</i> (giant roundworm)	May cause obstruction at ileocecal valve, biliary obstruction, intestinal perforation, migrates from nose/mouth. Migration of larvae to alveoli → Löeffler syndrome (pulmonary eosinophilia).	Fecal-oral; knobby-coated, oval eggs seen in feces under microscope B .	Bendazoles.
<i>Strongyloides stercoralis</i> (threadworm)	GI (eg, duodenitis), pulmonary (eg, dry cough, hemoptysis), and cutaneous (eg, pruritus) symptoms. Hyperinfection syndrome can be caused by accelerated autoinfection in the immunocompromised.	Larvae in soil penetrate skin; rhabditiform larvae seen in feces under microscope.	Ivermectin or bendazoles.
<i>Ancylostoma spp.</i> , <i>Necator americanus</i> (hookworms)	Cause microcytic anemia by sucking blood from intestinal wall. Cutaneous larva migrans —pruritic, serpiginous rash C .	Larvae penetrate skin from walking barefoot on contaminated beach/soil.	Bendazoles or pyrantel pamoate.
<i>Trichinella spiralis</i>	Larvae enter bloodstream, encyst in striated muscle D → myositis. Trichinosis —fever, vomiting, nausea, periorbital edema, myalgia.	Undercooked meat (especially pork); fecal-oral (less likely).	Bendazoles.
<i>Trichuris trichiura</i> (whipworm)	Often asymptomatic; loose stools, anemia, rectal prolapse in children.	Fecal-oral.	Bendazoles.
Tissue			
<i>Toxocara canis</i>	Visceral larva migrans —migration into blood → inflammation of liver, eyes (visual impairment), CNS (seizures, coma), heart (myocarditis). Patients often asymptomatic.	Fecal-oral.	Bendazoles.
<i>Onchocerca volvulus</i>	Black skin nodules, river blindness (“ black sight”).	Female black fly.	Ivermectin (iver mectin for river blindness).
<i>Loa loa</i>	Swelling in skin, worm in conjunctiva.	Deer fly, horse fly, mango fly.	Diethylcarbamazine.
<i>Wuchereria bancrofti</i> , <i>Brugia malayi</i>	Lymphatic filariasis (elephantiasis) —worms invade lymph nodes → inflammation → lymphedema E ; symptom onset after 9 mo–1 yr.	Female mosquito.	Diethylcarbamazine.

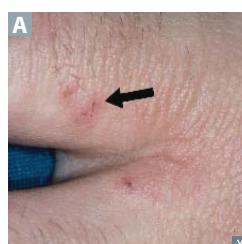


Cestodes (tapeworms)

ORGANISM	DISEASE	TRANSMISSION	TREATMENT
<i>Taenia solium</i> A	Intestinal tapeworm	Ingestion of larvae encysted in undercooked pork	Praziquantel
	Cysticercosis, neurocysticercosis (cystic CNS lesions, seizures) B	Ingestion of eggs in food contaminated with human feces	Praziquantel; albendazole for neurocysticercosis
<i>Diphyllobothrium latum</i>	Vitamin B₁₂ deficiency (“Diphyllo B₁₂ latum”; tapeworm competes for B₁₂ in intestine) → megaloblastic anemia	Ingestion of larvae in raw freshwater fish	Praziquantel, niclosamide
<i>Echinococcus granulosus</i> C	Hydatid cysts D (“eggshell calcification”) most commonly in liver E and lungs; cyst rupture can cause anaphylaxis	Ingestion of eggs in food contaminated with dog feces Sheep are an intermediate host	Albendazole; surgery for complicated cysts

**Trematodes (flukes)**

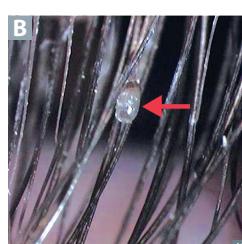
ORGANISM	DISEASE	TRANSMISSION	TREATMENT
<i>Schistosoma</i>	Liver and spleen enlargement (A shows <i>S. mansoni</i> egg with lateral spine), fibrosis, inflammation, portal hypertension; <i>S. mansoni</i> and <i>S. japonicum</i> can both also cause intestinal schistosomiasis, presenting with diarrhea, abdominal pain, iron deficiency anemia Chronic infection with <i>S. haematobium</i> (egg with terminal spine B) can lead to squamous cell carcinoma of the bladder (painless hematuria) and pulmonary hypertension	Snails are intermediate host; cercariae penetrate skin of humans in contact with contaminated fresh water (eg, swimming or bathing)	Praziquantel
<i>Clonorchis sinensis</i>	Biliary tract inflammation → pigmented gallstones Associated with cholangiocarcinoma	Undercooked fish	Praziquantel

Ectoparasites***Sarcoptes scabiei***

Mites burrow into stratum corneum and cause **scabies**—pruritus (worse at night) and serpiginous burrows (lines) often between fingers and toes **A**.

Common in children, crowded populations (jails, nursing homes); transmission through skin-to-skin contact (most common) or via fomites.

Treatment: permethrin cream, oral ivermectin, washing/drying all clothing/bedding, treat close contacts.

Pediculus humanus* and *Phthirus pubis

Blood-sucking lice that cause intense pruritus with associated excoriations, commonly on scalp and neck (head lice), waistband and axilla (body lice), or pubic and perianal regions (pubic lice).

Body lice can transmit *Rickettsia prowazekii* (epidemic typhus), *Borrelia recurrentis* (relapsing fever), *Bartonella quintana* (trench fever).

Treatment: pyrethroids, malathion, or ivermectin lotion, and nit **B** combing. Children with head lice can be treated at home without interrupting school attendance.

Cimex lectularius* and *Cimex hemipterus

Bed bugs. Blood-feeding insects that infest dwellings. Painless bites result in a range of skin reactions, typically pruritic, erythematous papules with central hemorrhagic punctum. A clustered or linear pattern of bites seen upon awakening is suggestive. Diagnosis is confirmed by direct identification of bed bugs in patient's dwelling.

Bed bugs can spread among rooms; cohabitants may exhibit similar symptoms. Infestations can also spread via travelers from infested hotels and the use of unwashed, used bedding.

Treatment: bites self resolve within 1 week. Eradication of the infestation is critical.

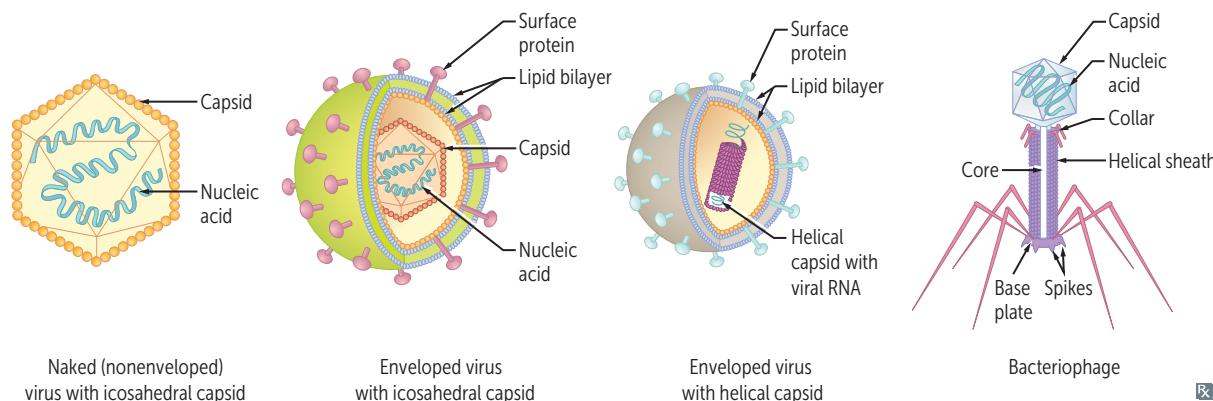
Parasite hints**ASSOCIATIONS**

- Biliary tract disease, cholangiocarcinoma
- Brain cysts, seizures
- Hematuria, squamous cell bladder cancer
- Liver (hydatid) cysts, exposure to infected dogs
- Iron deficiency anemia
- Myalgias, periorbital edema
- Nocturnal perianal pruritus
- Portal hypertension
- Vitamin B₁₂ deficiency

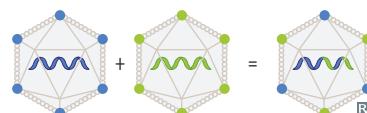
ORGANISM

- Clonorchis sinensis*
- Taenia solium* (neurocysticercosis)
- Schistosoma haematobium*
- Echinococcus granulosus*
- Ancylostoma*, *Necator*
- Trichinella spiralis*
- Enterobius*
- Schistosoma mansoni*, *Schistosoma japonicum*
- Diphyllobothrium latum*

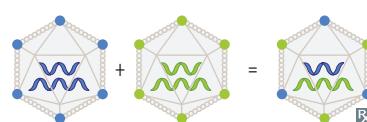
► MICROBIOLOGY—VIROLOGY

Viral structure—general features**Viral genetics****Recombination**

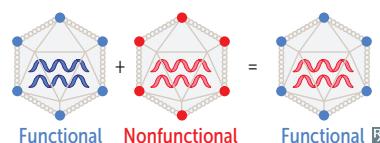
Exchange of genes between 2 chromosomes by crossing over within regions of significant base sequence homology.

**Reassortment**

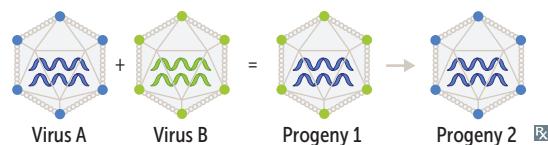
When viruses with segmented genomes (eg, influenza virus) exchange genetic material. For example, the 2009 novel H1N1 influenza A pandemic emerged via complex viral reassortment of genes from human, swine, and avian viruses. Has potential to cause antigenic shift. Reassortment of genome segments.

**Complementation**

When 1 of 2 viruses that infect the cell has a mutation that results in a nonfunctional protein, the nonmutated virus “complements” the mutated one by making a functional protein that serves both viruses. For example, hepatitis D virus requires the presence of replicating hepatitis B virus to supply HBsAg, the envelope protein for HDV.

**Phenotypic mixing**

Occurs with simultaneous infection of a cell with 2 viruses. For progeny 1, genome of virus A can be partially or completely coated (forming pseudovirion) with the surface proteins of virus B. Type B protein coat determines the tropism (infectivity) of the hybrid virus. Progeny from subsequent infection of a cell by progeny 1 will have a type A coat that is encoded by its type A genetic material.

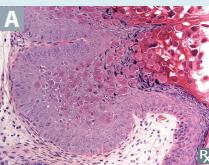


Viral genomes

Naked nucleic acids of most dsDNA viruses (except poxviruses and HBV) and \oplus strand ssRNA viruses are infectious. Naked nucleic acids of \ominus strand ssRNA and dsRNA viruses are not infectious because they lack the required polymerases to replicate. Virions of \ominus strand ssRNA viruses carry RNA-dependent RNA polymerases to transcribe \ominus strand to \oplus .

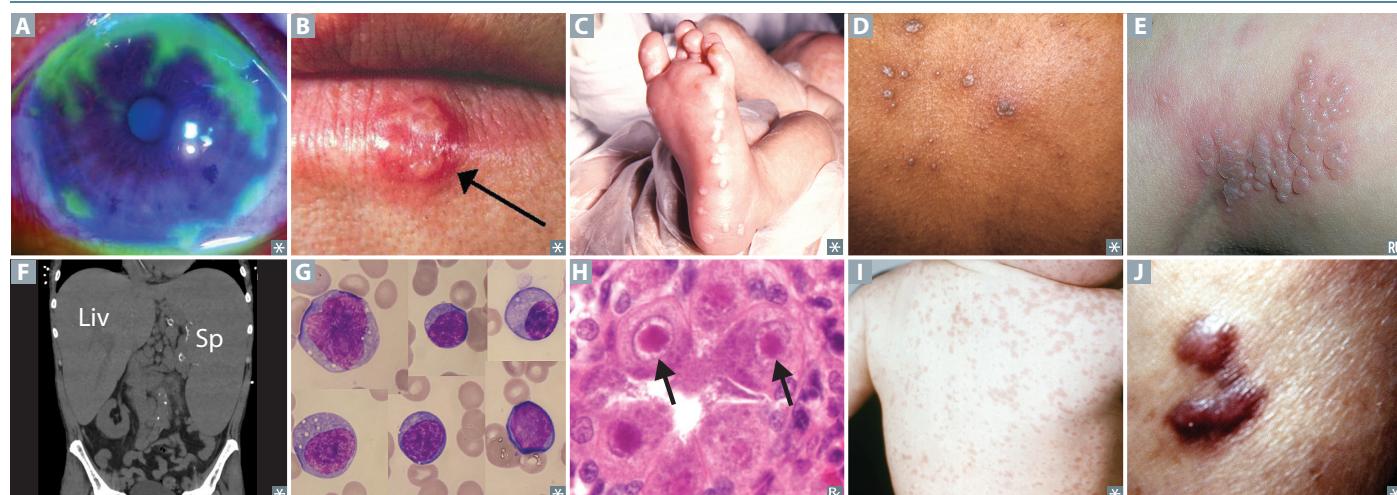
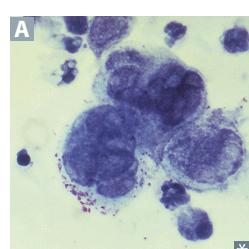
	CHARACTERISTICS	MNEMONIC
DNA viruses	All have dsDNA genomes (like our cells) except Parvoviridae (ssDNA). All are linear except papilloma-, polyoma-, and hepadnaviruses (circular).	Part of a virus
RNA viruses	All have ssRNA genomes except Reoviridae (dsRNA). \oplus stranded (\approx mRNA): retro- , toga- , flavi- , corona- , hepe- , calici- , and picornaviruses . \ominus stranded: arena- , bunya- , paramyxo- , orthomyxo- , filo- , and rhabdoviruses . Segmented: Bunya- , Orthomyxo- , Arena- , and Reoviruses .	Repeato-virus While at a retro toga party, I drank flavored Corona and ate hippie California pickles . Always bring polymerase or fail replication . BOAR
Viral envelopes	Generally, enveloped viruses acquire their envelopes from plasma membrane when they exit from cell. Exceptions include herpesviruses, which acquire envelopes from nuclear membrane.	Enveloped DNA viruses (herpesvirus , hepatnavirus , poxvirus) have helpful protection .

DNA viruses All are icosahedral and replicate in the nucleus (except poxvirus). “**Pox** is out of the **box** (nucleus).”

VIRAL FAMILY	ENVELOPE	DNA STRUCTURE	MEDICAL IMPORTANCE
Herpesviruses	Yes	DS and linear	See Herpesviruses entry
Poxvirus 	Yes	DS and linear (largest DNA virus)	Smallpox eradicated world wide by use of the live-attenuated vaccine Cowpox (“milkmaid blisters”) Molluscum contagiosum —flesh-colored papule with central umbilication; keratinocytes contain molluscum bodies A
Hepadnavirus	Yes	Partially DS and circular	HBV: <ul style="list-style-type: none">▪ Acute or chronic hepatitis▪ Not a retrovirus but has reverse transcriptase
Adenovirus 	No	DS and linear	Febrile pharyngitis B —sore throat Acute hemorrhagic cystitis Pneumonia Conjunctivitis—“pink eye” Gastroenteritis Myocarditis
Papillomavirus	No	DS and circular	HPV—warts, cancer (cervical, anal, penile, or oropharyngeal); serotypes 1, 2, 6, 11 associated with warts; serotypes 16, 18 associated with cancer
Polyomavirus	No	DS and circular	JC virus—progressive multifocal leukoencephalopathy (PML) in immunocompromised patients (eg, HIV) BK virus—transplant patients, commonly targets kidney JC : J unky C erebrum; BK : B ad K idney
Parvovirus	No	SS and linear (smallest DNA virus; <i>parvus</i> = small)	B19 virus—aplastic crises in sickle cell disease, “slapped cheek” rash in children (erythema infectiosum, or fifth disease); infects RBC precursors and endothelial cells → RBC destruction → hydrops fetalis and death in fetus, pure RBC aplasia and rheumatoid arthritis-like symptoms in adults

Herpesviruses Enveloped, DS, and linear viruses. Recent data suggest both HSV-1 and HSV-2 can affect both genital and extragenital areas.

VIRUS	ROUTE OF TRANSMISSION	CLINICAL SIGNIFICANCE	NOTES
Herpes simplex virus-1	Respiratory secretions, saliva	Gingivostomatitis, keratoconjunctivitis A , herpes labialis (cold sores) B , herpetic whitlow on finger, temporal lobe encephalitis, esophagitis, erythema multiforme. Responsible for a growing percentage of herpes genitalis.	Most commonly latent in trigeminal ganglia Most common cause of sporadic encephalitis, can present as altered mental status, seizures, and/or aphasia
Herpes simplex virus-2	Sexual contact, perinatal	Herpes genitalis, neonatal herpes C	Most commonly latent in sacral ganglia Viral meningitis more common with HSV-2 than with HSV-1
Varicella-zoster virus (HHV-3)	Respiratory secretions, contact with fluid from vesicles	Varicella-zoster (chickenpox D , shingles E), encephalitis, pneumonia Most common complication of shingles is post-herpetic neuralgia	Latent in dorsal root or trigeminal ganglia; CN V ₁ branch involvement can cause herpes zoster ophthalmicus
Epstein-Barr virus (HHV-4)	Respiratory secretions, saliva; also called “kissing disease,” (common in teens, young adults)	Mononucleosis —fever, hepatosplenomegaly F , pharyngitis, and lymphadenopathy (especially posterior cervical nodes); avoid contact sports until resolution due to risk of splenic rupture Associated with lymphomas (eg, endemic Burkitt lymphoma), nasopharyngeal carcinoma (especially Asian adults), lymphoproliferative disease in transplant patients	Infects B cells through CD21, “Must be 21 to drink Beer in a Barr ” Atypical lymphocytes on peripheral blood smear G —not infected B cells but reactive cytotoxic T cells ⊕ Monospot test—heterophile antibodies detected by agglutination of sheep or horse RBCs Use of amoxicillin (eg, for presumed strep pharyngitis) can cause maculopapular rash
Cytomegalovirus (HHV-5)	Congenital, transfusion, sexual contact, saliva, urine, transplant	Mononucleosis (⊖ Monospot) in immunocompetent patients; infection in immunocompromised, especially pneumonia in transplant patients; esophagitis; colitis; AIDS retinitis (“ sight omegalovirus”); hemorrhage, cotton-wool exudates, vision loss Congenital CMV	Infected cells have characteristic “owl eye” intranuclear inclusions H Latent in mononuclear cells
Human herpesviruses 6 and 7	Saliva	Roseola infantum (exanthem subitum): high fevers for several days that can cause seizures, followed by diffuse macular rash (starts on trunk then spreads to extremities) I ; usually seen in children < 2 years old	Roseola : fever first, Rosy (rash) later Self-limited illness HHV-7—less common cause of roseola
Human herpesvirus 8	Sexual contact	Kaposi sarcoma (neoplasm of endothelial cells). Seen in HIV/AIDS and transplant patients. Dark/violaceous plaques or nodules J representing vascular proliferations	Can also affect GI tract and lungs

Herpesviruses (continued)**HSV identification**

PCR of skin lesions is test of choice.

CSF PCR for herpes encephalitis.

Tzanck test (outdated)—a smear of an opened skin vesicle to detect multinucleated giant cells **A** commonly seen in HSV-1, HSV-2, and VZV infection.

Intranuclear eosinophilic Cowdry A inclusions also seen with HSV-1, HSV-2, VZV.

Receptors used by viruses

VIRUS	RECEPTOR(S)
CMV	Integrins (heparan sulfate)
EBV	CD21
HIV	CD4, CXCR4, CCR5
Parvovirus B19	P antigen on RBCs
Rabies	Nicotinic AChR
Rhinovirus	ICAM-1 (I CAMe to see the rhino)
SARS-CoV-2	ACE2

RNA viruses	All replicate in the cytoplasm (except retrovirus and influenza virus). “ Retro flu is outta cyt (sight).”		
VIRAL FAMILY	ENVELOPE	RNA STRUCTURE	MEDICAL IMPORTANCE
Reoviruses	No	DS linear Multisegmented	Rotavirus—important cause of diarrhea in young children; may be fatal.
Picornaviruses	No	SS \oplus linear	Poliovirus —polio-Salk/Sabin vaccines—IPV/OPV Echovirus —aseptic meningitis Rhinovirus —“common cold” Coxsackievirus —aseptic meningitis; herpangina (mouth blisters, fever); hand, foot, and mouth disease; myocarditis; pericarditis HAV —acute viral hepatitis
Hepeviruses	No	SS \oplus linear	HEV
Caliciviruses	No	SS \oplus linear	Norovirus—viral gastroenteritis
Flaviviruses	Yes	SS \oplus linear	HCV Yellow fever ^a Dengue ^a West Nile virus ^a —meningoencephalitis, acute asymmetric flaccid paralysis Zika virus ^a
Togaviruses	Yes	SS \oplus linear	Toga CREW —Chikungunya virus ^a (co-infection with dengue virus can occur), Rubella (formerly a togavirus), Eastern and Western equine encephalitis ^a
Matonavirus	Yes	SS \oplus linear	Rubella
Retroviruses	Yes	SS \oplus linear	Have reverse transcriptase HTLV—T-cell leukemia HIV—AIDS
Coronaviruses	Yes	SS \oplus linear	“Common cold,” SARS, COVID-19, MERS
Orthomyxoviruses	Yes	SS \ominus linear Multisegmented	Influenza virus
Paramyxoviruses	Yes	SS \ominus linear	PaRaMyxovirus: Parainfluenza—croup RSV—bronchiolitis in babies Measles, Mumps
Pneumoviruses	Yes	SS \ominus linear	RSV—bronchiolitis in babies
Rhabdoviruses	Yes	SS \ominus linear	Rabies
Filoviruses	Yes	SS \ominus linear	Ebola/Marburg virus disease—often fatal.
Arenaviruses	Yes	SS \oplus and \ominus circular Multisegmented	LCMV—lymphocytic choriomeningitis virus Lassa fever encephalitis—spread by rodents
Bunyaviruses	Yes	SS \ominus circular Multisegmented	California encephalitis ^a Sandfly/Rift Valley fevers ^a Crimean-Congo hemorrhagic fever ^a Hantavirus—hemorrhagic fever, pneumonia
Delta virus	Yes	SS \ominus circular	HDV is “Defective”; requires presence of HBV to replicate

SS, single-stranded; DS, double-stranded; \oplus , positive sense; \ominus , negative sense; ^a= arbovirus, arthropod borne (mosquitoes, ticks).

Picornavirus

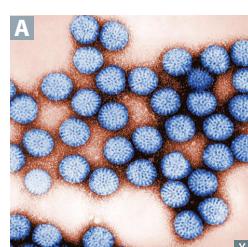
Includes Poliovirus, Echovirus, Rhinovirus, Coxsackievirus, and HAV. RNA is translated into 1 large polypeptide that is cleaved by virus-encoded proteases into functional viral proteins. Poliovirus, echovirus, and coxsackievirus are enteroviruses and can cause aseptic (viral) meningitis.

PicoRNAvirus = small RNA virus.
PERCH on a “peak” (pico).

Rhinovirus

A picornavirus. Nonenveloped RNA virus. Cause of common cold; > 100 serologic types. Acid labile—destroyed by stomach acid; therefore, does not infect the GI tract (unlike the other picornaviruses).

Rhino has a runny **nose**.

Rotavirus

Segmented dsRNA virus (a reovirus) **A**. Most important global cause of infantile gastroenteritis. Major cause of acute diarrhea in the United States during winter, especially in day care centers, kindergartens. Villous destruction with atrophy leads to ↓ absorption of Na^+ and loss of K^+ .

Rotavirus = right out the anus. CDC recommends routine vaccination of all infants except those with a history of intussusception (rare adverse effect of rotavirus vaccination) or SCID.

Influenza viruses

Orthomyxoviruses. Enveloped, \ominus ssRNA viruses with segmented genome. Contain hemagglutinin (binds sialic acid and promotes viral entry) and neuraminidase (promotes progeny virion release) antigens. Patients at risk for fatal bacterial superinfection, most commonly *S aureus*, *S pneumoniae*, and *H influenzae*. Treatment: supportive +/– neuraminidase inhibitor (eg, oseltamivir, zanamivir).

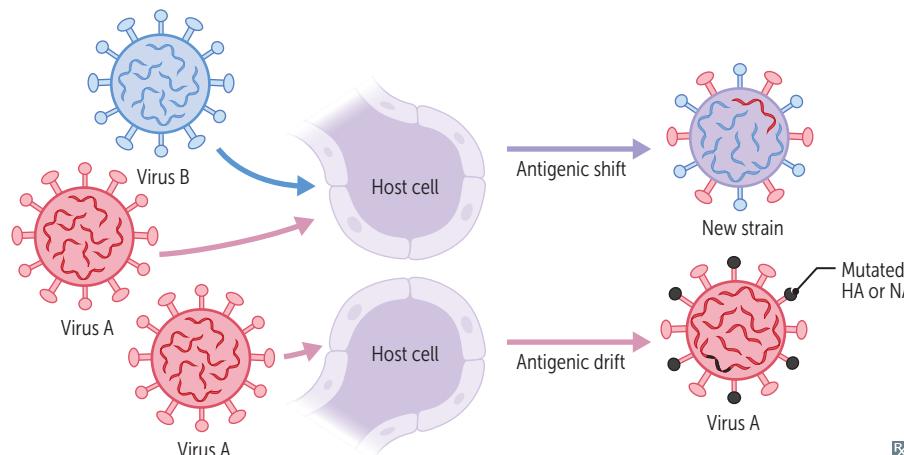
Hemagglutinin: lets the virus **in**
Neuraminidase: sends the virus **away**
 Reformulated vaccine (“the flu shot”) contains viral strains most likely to appear during the flu season, due to the virus’ rapid genetic change. Killed viral vaccine is most frequently used. Live attenuated vaccine contains temperature-sensitive mutant that replicates in the nose but not in the lung; administered intranasally. Sudden shift is more deadly than gradual drift.

Genetic/antigenic shift

Infection of 1 cell by 2 different segmented viruses (eg, swine influenza and human influenza viruses) → RNA segment reassortment → dramatically different virus (genetic shift) → major global outbreaks (pandemics).

Genetic/antigenic drift

Random mutation in hemagglutinin (HA) or neuraminidase (NA) genes → minor changes in HA or NA protein (drift) occur frequently → local seasonal outbreaks (epidemics).

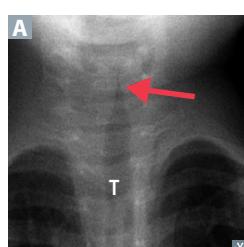
**Rubella virus**

A matonavirus. Causes rubella, formerly called German (3-day) measles. Fever, postauricular and other lymphadenopathy, arthralgias, and fine, maculopapular rash that starts on face and spreads centrifugally to involve trunk and extremities **A**.

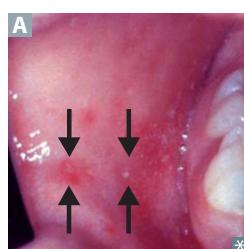
Causes mild disease in children but serious congenital disease (a TORCH infection). Congenital rubella findings include classic triad of sensorineural deafness, cataracts, and patent ductus arteriosus. “Blueberry muffin” appearance may be seen due to dermal extramedullary hematopoiesis.

Paramyxoviruses

Paramyxoviruses cause disease in children. They include those that cause parainfluenza (croup), mumps, measles, RSV, and human metapneumovirus. All subtypes can cause respiratory tract infection (bronchiolitis, pneumonia) in infants. All contain surface F (fusion) protein, which causes respiratory epithelial cells to fuse and form multinucleated cells. Palivizumab (monoclonal antibody against F protein) prevents pneumonia caused by RSV infection in premature infants. Palivizumab for paramyxovirus (RSV) prophylaxis in preemies.

Acute**laryngotracheobronchitis**

Also called croup. Caused by parainfluenza viruses. Virus membrane contains hemagglutinin (binds sialic acid and promotes viral entry) and neuraminidase (promotes progeny virion release) antigens. Results in a “seal-like” barking cough and inspiratory stridor. Narrowing of upper trachea and subglottis leads to characteristic steeple sign on x-ray **A**.

Measles (rubeola) virus

Usual presentation involves prodromal fever with cough, coryza, and conjunctivitis, then eventually Koplik spots (bright red spots with blue-white center on buccal mucosa **A**), followed 1–2 days later by a maculopapular rash that starts at the head/neck and spreads downward.

Lymphadenitis with Warthin-Finkeldey giant cells (fused lymphocytes) in a background of paracortical hyperplasia. Possible sequelae:

- Subacute sclerosing panencephalitis (SSPE): personality changes, dementia, autonomic dysfunction, death (occurs years later)
- Encephalitis (1:1000): symptoms appear within few days of rash
- Giant cell pneumonia (rare except in immunosuppressed)

4 C's of measles:

Cough

Coryza

Conjunctivitis

“C”oplik spots

Vitamin A supplementation can reduce morbidity and mortality from measles, particularly in malnourished children.

Pneumonia is the most common cause of measles-associated death in children.

Mumps virus

Uncommon due to effectiveness of MMR vaccine.

Symptoms: Parotitis **A**, Orchitis (inflammation of testes), aseptic Meningitis, and Pancreatitis. Can cause sterility (especially after puberty).

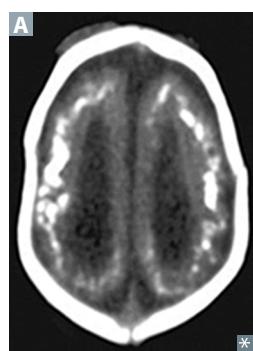
Mumps makes your parotid glands and testes as big as POM-Poms.

Arboviruses transmitted by *Aedes* mosquitoes

	Chikungunya virus	Dengue virus
VIRUS TYPE	Alphavirus/togaviridae.	Flavivirus.
SYMPTOMS	High fever, maculopapular rash, headache, lymphadenopathy, and inflammatory polyarthralgia. Arthralgias are more commonly reported (vs dengue); joint swelling is highly specific for Chikungunya. Thrombocytopenia, leukopenia, and hemorrhagic manifestations are less common.	Dengue fever: fever, rash, headache, myalgias, arthralgias, retro-orbital pain, neutropenia. Dengue hemorrhagic fever: dengue fever + bleeding and plasma leakage due to severe thrombocytopenia and RBC perturbations. Most common if infected with a different serotype after initial infection due to antibody-dependent enhancement of disease. May progress to dengue shock syndrome: plasma leakage → circulatory collapse.
DIAGNOSIS	RT-PCR, serology	
TREATMENT	Supportive. Steroids or disease-modifying antirheumatic drugs for chronic arthritis.	Supportive. Intravascular volume repletion or blood transfusion if severe shock.
PREVENTION	Minimize mosquito exposure. No vaccine currently available.	Live, recombinant vaccine available. Derived from the yellow fever virus backbone with insertion of genes for the envelope and pre-membrane proteins of dengue virus.

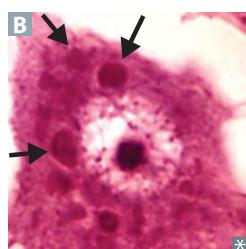
Yellow fever virus

A flavivirus (also an arbovirus) transmitted by *Aedes* mosquito bites. Virus has monkey or human reservoir. *Flavi* = yellow, jaundice. Symptoms: high fever, black vomitus, jaundice, hemorrhage, backache. May see Councilman bodies (eosinophilic apoptotic globules) on liver biopsy. Live, attenuated vaccine recommended for travelers to endemic countries.

Zika virus

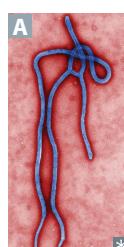
A flavivirus most commonly transmitted by *Aedes* mosquito bites. Causes conjunctivitis, low-grade pyrexia, and itchy rash in 20% of cases. Outbreaks more common in tropical and subtropical climates. May be complicated by Guillain-Barré syndrome. Supportive care, no definitive treatment. Diagnose with RT-PCR or serology. Sexual and vertical transmission occurs. In pregnancy, can lead to miscarriage or congenital Zika syndrome: brain imaging shows ventriculomegaly, subcortical calcifications **A**. Clinical features in the affected newborn include

- Microcephaly
- Ocular anomalies
- Motor abnormalities (spasticity, seizures)

Rabies virus

Bullet-shaped virus **A**. Negri bodies (cytoplasmic inclusions **B**) commonly found in Purkinje cells of cerebellum and in hippocampal neurons. Rabies has long incubation period (weeks to months) before symptom onset. Postexposure prophylaxis is wound cleaning plus immunization with killed vaccine and rabies immunoglobulin. Example of passive-active immunity. Travels to the CNS by migrating in a retrograde fashion (via dynein motors) up nerve axons after binding to ACh receptors. Progression of disease: fever, malaise → agitation, photophobia, hydrophobia, hypersalivation → paralysis, coma → death.

Infection more commonly from bat, raccoon, and skunk bites than from dog bites in the United States; aerosol transmission (eg, bat caves) also possible.

Ebola virus

A filovirus **A**. Following an incubation period of up to 21 days, presents with abrupt onset of fululike symptoms, diarrhea/vomiting, high fever, myalgia. Can progress to DIC, diffuse hemorrhage, shock. Diagnosed with RT-PCR within 48 hr of symptom onset. High mortality rate.

Transmission requires direct contact with bodily fluids, fomites (including dead bodies), infected bats or primates (apes/monkeys); high incidence of healthcare-associated infection.

Supportive care, no definitive treatment. Vaccination of contacts, strict isolation of infected individuals, and barrier practices for healthcare workers are key to preventing transmission.

Severe acute respiratory syndrome coronavirus 2

SARS-CoV-2 is a + ssRNA virus and the cause of the COVID-19 pandemic. Spread is via respiratory droplets, aerosols and fomites. Varying symptoms include: fever, myalgia, headache, nasal congestion, sneezing, cough, sore throat, nausea, diarrhea, anosmia, dysgeusia.

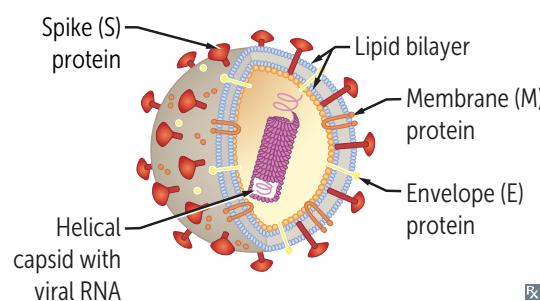
Severe cases may lead to complications like: pneumonia, hypercoagulability (DVT, PE, stroke), myocardial injury, neurologic sequelae, shock, organ failure, death.

Diagnosed by:

- NAAT (RT-PCR)
- Viral Antigen Test (RAT) → rapid, accessible, less sensitive than NAAT

Host cell entry occurs by attachment of viral spike protein to ACE2 receptor on cell membranes (highly expressed in the lungs, intestines, heart, and kidneys).

Vaccines: mRNA and viral vector vaccines induce immunity by presenting the spike protein to the immune system leading to anti-spike protein antibodies.



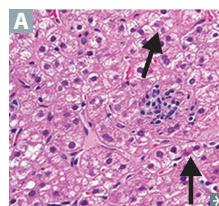
Hepatitis viruses

Signs and symptoms of all hepatitis viruses: episodes of fever, jaundice, ↑ ALT and AST. **N**Ak**E**d viruses (**HAV** and **HEV**) lack an envelope and are not destroyed by the gut: the **vowels** hit your **bowels**.

HBV DNA polymerase has DNA- and RNA-dependent activities. Upon entry into nucleus, the polymerase completes the partial dsDNA. Host RNA polymerase transcribes mRNA from viral DNA to make viral proteins. The DNA polymerase then reverse transcribes viral RNA to DNA, which is the genome of the progeny virus.

HCV lacks 3'-5' exonuclease activity → no proofreading ability → antigenic variation of HCV envelope proteins. Host antibody production lags behind production of new mutant strains of HCV.

Virus	HAV	HBV	HCV	HDV	HEV
FAMILY	RNA picornavirus	DNA hepadnavirus	RNA flavivirus	RNA deltavirus	RNA hepevirus
TRANSMISSION	Fecal-oral (shellfish, travelers, day care)	Parenteral (Blood), sexual (Bedroom), perinatal (Birthing)	Primarily blood (injection drug use, posttransfusion)	Parenteral, sexual, perinatal	Fecal-oral, especially waterborne
INCUBATION	Short (weeks)	Long (months)	Long	Superinfection (HDV after HBV) = short Coinfection (HDV with HBV) = long	Short
CLINICAL COURSE	Acute and self-limiting (adults), A symptomatic (children)	Initially like serum sickness (fever, arthralgias, rash); may progress to carcinoma	May progress to C irrhosis or C arcinoma	Similar to HBV	Fulminant hepatitis in E xpectant (pregnant) patients
PROGNOSIS	Good	Adults → mostly full resolution; neonates → worse prognosis	Majority develop stable, C hronic hepatitis C	Superinfection → worse prognosis	High mortality in pregnant patients
HCC RISK	No	Yes	Yes	Yes	No
LIVER BIOPSY	Hepatocyte swelling, monocyte infiltration, Councilman bodies A	Granular eosinophilic “ground glass” appearance due to accumulation of surface antigen within infected hepatocytes; cytotoxic T cells mediate damage	Lymphoid aggregates with focal areas of macrovesicular steatosis	Similar to HBV	Patchy necrosis
NOTES	Absent (no) carrier state	Carrier state common	Carrier state very common	Defective virus, D epends on HBV HBsAg coat for entry into hepatocytes	Enteric, E pидemic (eg, in parts of Asia, Africa, Middle East), no carrier state

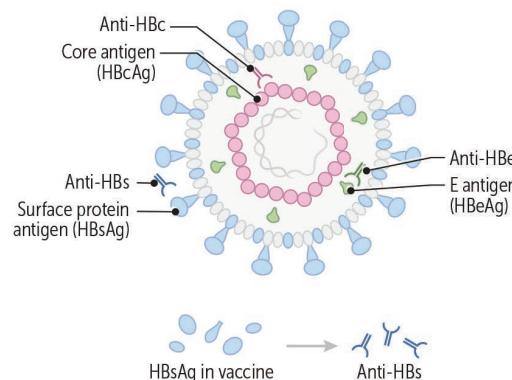
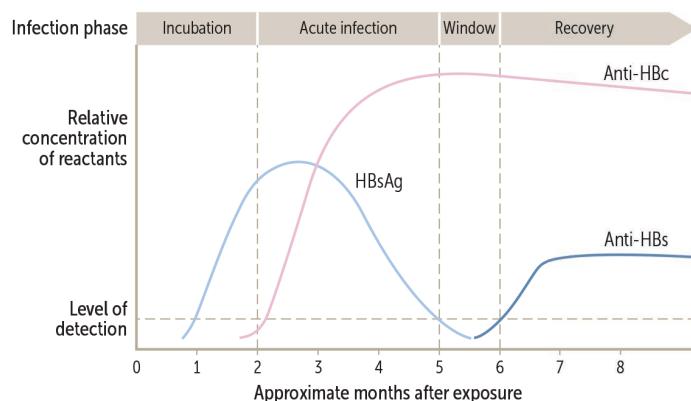


Extrahepatic manifestations of hepatitis B and C

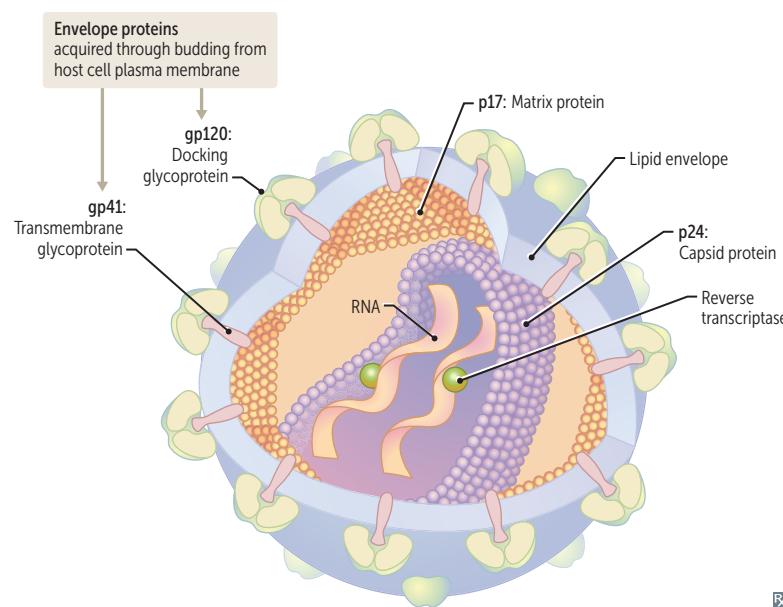
	Hepatitis B	Hepatitis C
HEMATOLOGIC	Aplastic anemia	Essential mixed cryoglobulinemia, ↑ risk B-cell NHL, ITP, autoimmune hemolytic anemia
RENAL	Membranous GN > membranoproliferative GN	Membranoproliferative GN > membranous GN
VASCULAR	Polyarteritis nodosa	Leukocytoclastic vasculitis
DERMATOLOGIC		Sporadic porphyria cutanea tarda, lichen planus
ENDOCRINE		↑ risk of diabetes mellitus, autoimmune hypothyroidism

Hepatitis serologic markers

Anti-HAV (IgM)	IgM antibody to HAV; best test to detect acute hepatitis A.
Anti-HAV (IgG)	IgG antibody indicates prior HAV infection and/or prior vaccination; protects against reinfection.
HBsAg	Antigen found on surface of HBV; indicates hepatitis B infection.
Anti-HBs	Antibody to HBsAg; indicates immunity to hepatitis B due to vaccination or recovery from infection.
HBcAg	Antigen associated with core of HBV.
Anti-HBc	Antibody to HBcAg; IgM = acute/recent infection; IgG = prior exposure or chronic infection. IgM anti-HBc may be the sole + marker of infection during window period.
HBeAg	Secreted by infected hepatocyte into circulation. Not part of mature HBV virion. Indicates active viral replication and therefore high transmissibility and poorer prognosis.
Anti-HBe	Antibody to HBeAg; indicates low transmissibility.



	HBsAg	Anti-HBs	Anti-HBc	HBeAg	Anti-HBe
Incubation	+				
Acute infection	+		+ (IgM)	+	
Window			+ (IgM)		+
Recovery		+	+ (IgM)		+
Chronic infection (high infectivity)	+		+ (IgG)	+	
Chronic infection (low infectivity)	+		+ (IgG)		+
Immunized		+			

HIV

Diploid genome (2 molecules of RNA).

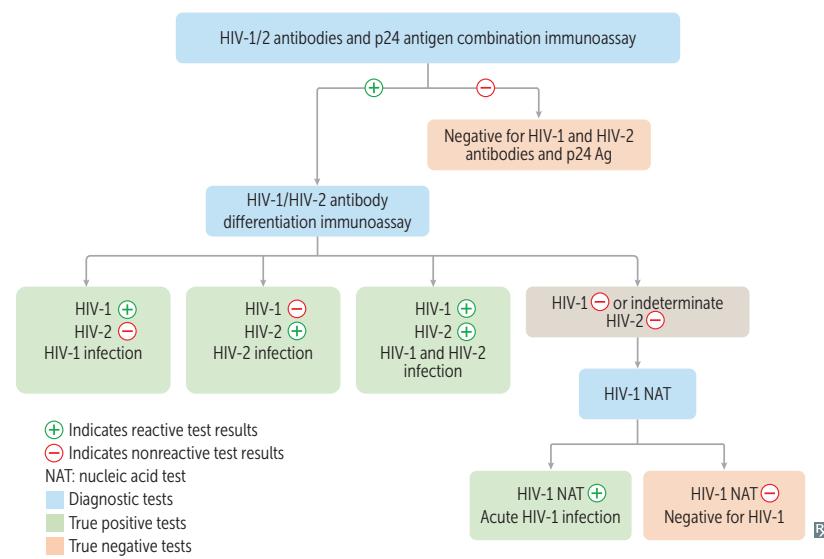
The 3 structural genes (protein coded for):

- **Env** (gp120 and gp41)—formed from cleavage of gp160 to form envelope glycoproteins.
 - gp120—attachment to host CD4+ T cell.
 - gp41 (forty-one)—fusion and entry.
- **gag** (p24 and p17)—capsid and matrix proteins, respectively.
- **pol**—Reverse transcriptase, Integrase, Protease; **RIP “Pol”** (Paul)

Reverse transcriptase synthesizes dsDNA from genomic RNA; dsDNA integrates into host genome.

Virus binds CD4 as well as a coreceptor, either CCR5 on macrophages (early infection) or CXCR4 on T cells (late infection).

Homozygous CCR5 mutation = immunity.
Heterozygous CCR5 mutation = slower course.

HIV diagnosis

HIV-1/2 Ag/Ab immunoassays detect viral p24 antigen capsid protein and IgG and/or IgM to HIV-1/2.

- Use for diagnosis. Very high sensitivity/specification, but may miss early HIV disease if tested within first 2 weeks of infection.
- A positive screening test is followed by a confirmatory HIV-1/2 differentiation immunoassay.

HIV RNA tests detect elevated HIV RNA and can be qualitative or quantitative.

- NAAT is qualitative, and is a sensitive method to detect HIV viremia in antibody-negative patients.
- Viral load tests (RT-PCR) are quantitative and determine amount of viral RNA in the plasma. Use to monitor response to treatment and transmissibility.

Western blot tests are no longer recommended by the CDC for confirmatory testing.

HIV-1/2 Ag/Ab testing is not recommended in babies with suspected HIV due to maternally transferred antibody. Use HIV viral load instead.

AIDS diagnosis: ≤ 200 CD4+ cells/mm³
(normal: 500–1500 cells/mm³) or HIV ⊕ with AIDS-defining condition (eg, *Pneumocystis pneumonia*).

Common diseases of HIV-positive adults ↓ CD4+ cell count → reactivation of past infections (eg, TB, HSV, shingles), dissemination of bacterial infections and fungal infections (eg, coccidioidomycosis), and non-Hodgkin lymphomas.

PATHOGEN	PRESENTATION	FINDINGS
CD4+ cell count < 500/mm³		
<i>Candida albicans</i>	Oral thrush	Scrapable white plaque, pseudohyphae on microscopy
EBV	Oral hairy leukoplakia	Unscrapable white plaque on lateral tongue
HHV-8	Kaposi sarcoma, localized cutaneous disease	Perivascular spindle cells invading and forming vascular tumors on histology
HPV	Squamous cell carcinoma at site(s) of sexual contact (most commonly anus, cervix, oropharynx)	
Mycobacterium tuberculosis	Increased risk of reactivation of latent TB infection	
CD4+ cell count < 200/mm³		
<i>Histoplasma capsulatum</i>	Fever, weight loss, fatigue, cough, dyspnea, nausea, vomiting, diarrhea	Oval yeast cells within macrophages
HIV	Dementia, HIV-associated nephropathy	Cerebral atrophy on neuroimaging
JC virus (reactivation)	Progressive multifocal leukoencephalopathy	Nonenhancing areas of demyelination on MRI
HHV-8	Kaposi sarcoma, disseminated disease (pulmonary, GI, lymphatic)	
<i>Pneumocystis jirovecii</i>	<i>Pneumocystis</i> pneumonia	“Ground-glass” opacities on chest imaging
CD4+ cell count < 100/mm³		
<i>Bartonella</i> spp	Bacillary angiomatosis	Multiple red to purple papules or nodules Biopsy with neutrophilic inflammation
<i>Candida albicans</i>	Esophagitis	White plaques on endoscopy; yeast and pseudohyphae on biopsy
CMV	Colitis, Retinitis, Esophagitis, Encephalitis, Pneumonitis (CREEP)	Linear ulcers on endoscopy, cotton-wool spots on fundoscopy Biopsy reveals cells with intranuclear (owl eye) inclusion bodies
<i>Cryptococcus neoformans</i>	Meningitis	Encapsulated yeast on India ink stain or capsular antigen +
<i>Cryptosporidium</i> spp	Chronic, watery diarrhea	Acid-fast oocysts in stool
EBV	B-cell lymphoma (eg, non-Hodgkin lymphoma, CNS lymphoma)	CNS lymphoma—ring enhancing, may be solitary (vs <i>Toxoplasma</i>)
Mycobacterium avium-intracellulare, Mycobacterium avium complex	Nonspecific systemic symptoms (fever, night sweats, weight loss, diarrhea) or superficial lymphadenitis	Most common if CD4+ cell count < 50/mm ³
Toxoplasma gondii	Brain abscesses	Multiple ring-enhancing lesions on MRI

Prions

Prion diseases are caused by the conversion of a normal (predominantly α -helical) protein termed prion protein (PrP^{C}) to a β -pleated form (PrP^{Sc}), which is transmissible via CNS-related tissue (iatrogenic CJD) or food contaminated by BSE-infected animal products (variant CJD). PrP^{Sc} resists protease degradation and facilitates the conversion of still more PrP^{C} to PrP^{Sc} . Resistant to standard sterilizing procedures, including standard autoclaving. Accumulation of PrP^{Sc} results in spongiform encephalopathy and dementia, ataxia, startle myoclonus, and death.

Creutzfeldt-Jakob disease—rapidly progressive dementia, typically sporadic (some familial forms).

Bovine spongiform encephalopathy—also called “mad cow disease.”

Kuru—acquired prion disease noted in tribal populations practicing human cannibalism.

► MICROBIOLOGY—SYSTEMS

Normal microbiota: dominant

Neonates delivered by C-section have microbiota enriched in skin commensals.

LOCATION	MICROORGANISM
Skin	<i>S epidermidis</i>
Nose	<i>S epidermidis</i> ; colonized by <i>S aureus</i>
Oropharynx	Viridans group streptococci
Dental plaque	<i>S mutans</i>
Colon	<i>B fragilis</i> > <i>E coli</i>
Vagina	<i>Lactobacillus</i> ; colonized by <i>E coli</i> and group B strep

Bugs causing food-borne illness

S aureus and *B cereus* food poisoning starts quickly and ends quickly (exotoxin-mediated).

MICROORGANISM	SOURCE OF INFECTION
<i>B cereus</i>	Reheated rice. “Food poisoning from reheated rice? Be serious!” (<i>B cereus</i>)
<i>C botulinum</i>	Improperly canned foods (toxins), raw honey (spores)
<i>C perfringens</i>	Reheated meat
<i>E coli</i> O157:H7	Undercooked meat
<i>L monocytogenes</i>	Deli meats, soft cheeses
<i>Salmonella</i>	Poultry, meat, and eggs
<i>S aureus</i>	Meats, mayonnaise, custard; preformed toxin
<i>V parahaemolyticus</i> and <i>V vulnificus</i> ^a	Raw/undercooked seafood

^a*V vulnificus* predominantly causes wound infections from contact with contaminated water or shellfish.

Bugs causing diarrhea**Bloody diarrhea**

<i>Campylobacter</i>	Comma- or S-shaped organisms; growth at 42°C
<i>E histolytica</i>	Protozoan; amebic dysentery; liver abscess
Enterohemorrhagic <i>E coli</i>	O157:H7; can cause HUS; makes Shiga toxin
Enteroinvasive <i>E coli</i>	Invades colonic mucosa
Salmonella (non-typhoidal)	Lactose \ominus ; flagellar motility; has animal reservoir, especially poultry and eggs
Shigella	Lactose \ominus ; very low ID ₅₀ ; produces Shiga toxin; human reservoir only; bacillary dysentery
Y enterocolitica	Day care outbreaks; pseudoappendicitis

Watery diarrhea

<i>C difficile</i>	Pseudomembranous colitis; associated with antibiotics and PPIs; occasionally bloody diarrhea
<i>C perfringens</i>	Also causes gas gangrene
Enterotoxigenic <i>E coli</i>	Travelers' diarrhea; produces heat-labile (LT) and heat-stable (ST) toxins
Protozoa	<i>Giardia, Cryptosporidium</i>
V cholerae	Comma-shaped organisms; rice-water diarrhea; often from infected seafood
Viruses	Norovirus (most common cause in developed countries), rotavirus (\downarrow incidence in developed countries due to vaccination), enteric adenovirus

Common causes of pneumonia

NEONATES (< 4 WK)	CHILDREN (4 WK–18 YR)	ADULTS (18–40 YR)	ADULTS (40–65 YR)	ADULTS (65 YR +)
Group B streptococci	Viruses (RSV)	<i>Mycoplasma</i>	<i>S pneumoniae</i>	<i>S pneumoniae</i>
<i>E coli</i>	<i>Mycoplasma</i>	<i>C pneumoniae</i>	<i>H influenzae</i>	Influenza virus
	<i>C trachomatis</i> (infants–3 yr)	<i>S pneumoniae</i>	Anaerobes	Anaerobes
	<i>C pneumoniae</i> (school-aged children)	Viruses (eg, influenza)	Viruses	<i>H influenzae</i>
	<i>S pneumoniae</i>		<i>Mycoplasma</i>	Gram \ominus rods
	Runts May Cough			
	Chunky Sputum			

Special groups

Alcohol overuse	<i>Klebsiella</i> , anaerobes usually due to aspiration (eg, <i>Peptostreptococcus, Fusobacterium, Prevotella, Bacteroides</i>)
Injection drug use	<i>S pneumoniae, S aureus</i>
Aspiration	Anaerobes
Atypical	<i>Mycoplasma, Chlamydophila, Legionella</i> , viruses (RSV, CMV, influenza, adenovirus)
Cystic fibrosis	<i>Pseudomonas, S aureus, S pneumoniae, Burkholderia cepacia</i>
Immunocompromised	<i>S aureus</i> , enteric gram \ominus rods, fungi, viruses, <i>P jirovecii</i> (with HIV)
Healthcare-associated	<i>S aureus, Pseudomonas</i> , other enteric gram \ominus rods
Postviral	<i>S pneumoniae, S aureus, H influenzae</i>
COPD	<i>S pneumoniae, H influenzae, M catarrhalis, Pseudomonas</i>

Common causes of meningitis

NEBORN (0–6 MO)	CHILDREN (6 MO–6 YR)	6–60 YR	60 YR +
Group B <i>Streptococcus</i>	<i>S pneumoniae</i>	<i>S pneumoniae</i>	<i>S pneumoniae</i>
<i>E coli</i>	<i>N meningitidis</i>	<i>N meningitidis</i>	<i>N meningitidis</i>
<i>Listeria</i>	<i>H influenzae</i> type b	Enteroviruses	<i>H influenzae</i> type b
	Group B <i>Streptococcus</i>	HSV	Group B <i>Streptococcus</i>
	Enteroviruses		<i>Listeria</i>

Give ceftriaxone and vancomycin empirically (add ampicillin if *Listeria* is suspected; add acyclovir if viral encephalitis is suspected).

Viral causes of meningitis: enteroviruses (especially coxsackievirus), HSV-2 (HSV-1 = encephalitis), HIV, West Nile virus (also causes encephalitis), VZV.

In HIV: *Cryptococcus* spp.

Note: Incidence of Group B streptococcal meningitis in neonates has ↓ greatly due to screening and antibiotic prophylaxis in pregnancy. Incidence of *H influenzae* meningitis has ↓ greatly due to conjugate *H influenzae* vaccinations. Today, cases are usually seen in unimmunized children.

Cerebrospinal fluid findings in meningitis

	OPENING PRESSURE	CELL TYPE	PROTEIN	GLUCOSE
Bacterial	↑	↑ PMNs	↑	↓
Fungal/TB	↑	↑ lymphocytes	↑	↓
Viral	Normal/↑	↑ lymphocytes	Normal/↑	Normal

Infections causing brain abscess

Most commonly viridans streptococci and *Staphylococcus aureus*. If dental infection or extraction precedes abscess, oral anaerobes commonly involved.

Multiple abscesses are usually from bacteremia; single lesions from contiguous sites: otitis media and mastoiditis → temporal lobe and cerebellum; sinusitis or dental infection → frontal lobe.

Toxoplasma reactivation in AIDS.

Osteomyelitis

RISK FACTOR	ASSOCIATED INFECTION
Assume if no other information is available	<i>S aureus</i> (most common overall)
Sexually active	<i>Neisseria gonorrhoeae</i> (rare), septic arthritis more common
Sickle cell disease	<i>Salmonella</i> , <i>S aureus</i>
Prosthetic joint replacement	<i>S aureus</i> , <i>S epidermidis</i>
Vertebral involvement	<i>S aureus</i> , <i>M tuberculosis</i> (Pott disease)
Cat and dog bites	<i>Pasteurella multocida</i>
Injection drug use	<i>S aureus</i> ; also <i>Pseudomonas</i> , <i>Candida</i>

Elevated ESR and CRP sensitive but not specific.

Radiographs are insensitive early but can be useful in chronic osteomyelitis (A, left). MRI is best for detecting acute infection and detailing anatomic involvement (A, right). Biopsy or aspiration with culture necessary to identify organism.

Red rashes of childhood

AGENT	ASSOCIATED SYNDROME/DISEASE	CLINICAL PRESENTATION
Coxsackievirus type A	Hand-foot-mouth disease	Oval-shaped vesicles on palms and soles A ; vesicles and ulcers in oral mucosa (herpangina)
Human herpesvirus 6	Roseola (exanthem subitum)	Asymptomatic rose-colored macules appear on body after several days of high fever; can present with febrile seizures; usually affects infants
Measles virus	Measles (rubeola)	Confluent rash beginning at head and moving down B ; preceded by cough, coryza, conjunctivitis, and blue-white (Koplik) spots on buccal mucosa
Parvovirus B19	Erythema infectiosum (fifth disease)	“Slapped cheek” rash on face C
Rubella virus	Rubella	Pink macules and papules begin at head and move down, remain discrete → fine desquamating truncal rash; postauricular lymphadenopathy
Streptococcus pyogenes	Scarlet fever	Sore throat, Circumoral pallor, group A strep, Rash (sandpaperlike D , from neck to trunk and extremities), Lymphadenopathy, Erythrogenic toxin, strawberry Tongue (SCARLET)
Varicella-zoster virus	Chickenpox	Vesicular rash begins on trunk E , spreads to face and extremities with lesions of different stages



Urinary tract infections

Cystitis presents with dysuria, frequency, urgency, suprapubic pain, and WBCs (but not WBC casts) in urine. Primarily caused by ascension of microbes from urethra to bladder. Ascension to kidney results in pyelonephritis, which presents with fever, chills, flank pain, costovertebral angle tenderness, hematuria, and WBC casts.

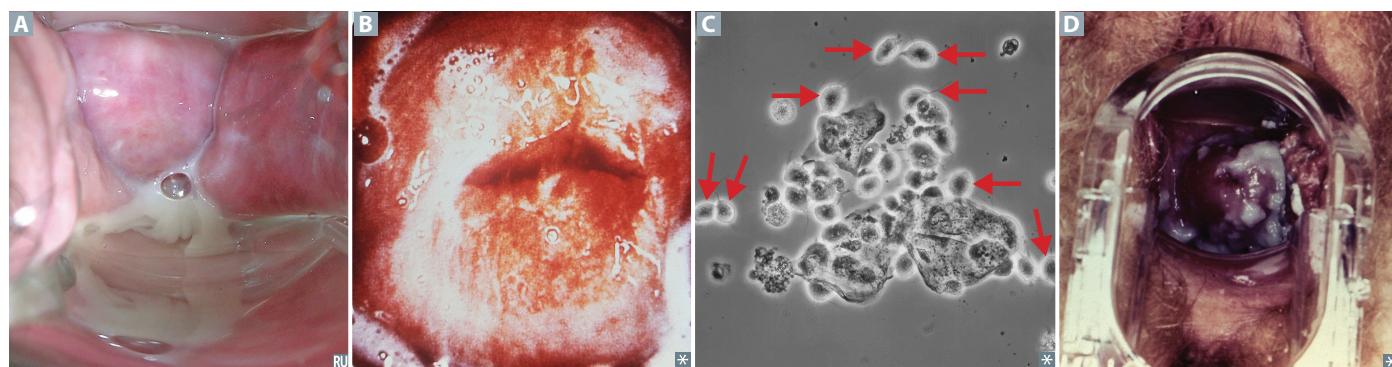
Ten times more common in females (shorter urethras colonized by fecal microbiota).

Risk factors: obstruction (eg, kidney stones, enlarged prostate), kidney surgery, catheterization, congenital GU malformation (eg, vesicoureteral reflux), diabetes, pregnancy.

SPECIES	FEATURES	COMMENTS
<i>Escherichia coli</i>	Leading cause of UTI. Colonies show strong pink lactose-fermentation on MacConkey agar.	Diagnostic markers: ⊕ Leukocyte esterase = evidence of WBC activity. ⊕ Nitrite test = reduction of urinary nitrates by gram ⊥ bacterial species (eg, <i>E coli</i>).
<i>Staphylococcus saprophyticus</i>	2nd leading cause of UTI, particularly in young, sexually active females.	
<i>Klebsiella pneumoniae</i>	3rd leading cause of UTI. Large mucoid capsule and viscous colonies.	
<i>Serratia marcescens</i>	Some strains produce a red pigment; often healthcare-associated and drug resistant.	
<i>Enterococcus</i>	Often healthcare-associated and drug resistant.	
<i>Proteus mirabilis</i>	Motility causes “swarming” on agar; associated with struvite stones. Produces urease.	
<i>Pseudomonas aeruginosa</i>	Blue-green pigment and fruity odor; usually healthcare-associated and drug resistant.	

Common vaginal infections

	Bacterial vaginosis	<i>Trichomonas vaginitis</i>	<i>Candida vulvovaginitis</i>
SIGNS AND SYMPTOMS	No inflammation Thin, white discharge A with fishy odor	Inflammation B (“strawberry cervix”) Frothy, yellow-green, foul-smelling discharge	Inflammation Thick, white, “cottage cheese” discharge D
LAB FINDINGS	Clue cells (bacteria-coated epithelial cells) pH > 4.5 ⊕ KOH whiff test	Motile pear-shaped trichomonads C pH > 4.5	Pseudohyphae pH normal (4.0–4.5)
TREATMENT	Metronidazole or clindamycin	Metronidazole Treat sexual partner(s)	Azoles



Sexually transmitted infections

DISEASE	CLINICAL FEATURES	PATHOGEN
AIDS	Opportunistic infections, Kaposi sarcoma, lymphoma	HIV
Chancroid	Painful genital ulcer(s) with exudate, inguinal adenopathy A	<i>Haemophilus ducreyi</i> (it's so painful, you “do cry”)
Chlamydia	Urethritis, cervicitis, epididymitis, conjunctivitis, reactive arthritis, PID	<i>Chlamydia trachomatis</i> (D–K)
Condylomata acuminata	Genital warts B , koilocytes	HPV-6 and -11
Herpes genitalis	Painful penile, vulvar, or cervical vesicles and ulcers C with bilateral tender inguinal lymphadenopathy; can cause systemic symptoms such as fever, headache, myalgia	HSV-2, less commonly HSV-1
Gonorrhea	Urethritis, cervicitis, PID, prostatitis, epididymitis, arthritis, creamy purulent discharge	<i>Neisseria gonorrhoeae</i>
Granuloma inguinale (Donovanosis)	Painless, beefy red ulcer that bleeds readily on contact D Uncommon in US	<i>Klebsiella (Calymmatobacterium) granulomatis</i> ; cytoplasmic Donovan bodies (bipolar staining) seen on microscopy
Hepatitis B	Jaundice	HBV
Lymphogranuloma venereum	Infection of lymphatics; painless genital ulcers, painful lymphadenopathy (ie, buboes E)	<i>C trachomatis</i> (L1–L3)
Primary syphilis	Painless chancre F , regional lymphadenopathy	<i>Treponema pallidum</i>
Secondary syphilis	Fever, diffuse lymphadenopathy, generalized rash, condylomata lata	
Tertiary syphilis	Gummas, tabes dorsalis, general paresis, aortitis, Argyll Robertson pupil	
Trichomoniasis	Vaginitis, strawberry cervix, motile in wet prep	<i>Trichomonas vaginalis</i>



TORCH infections

Microbes that may pass from mother to fetus. Transmission is transplacental in most cases, or via vaginal delivery (especially HSV-2). Nonspecific signs common to many **ToRCHHeS** infections include hepatosplenomegaly, jaundice, thrombocytopenia, and growth restriction.

Other important infectious agents include *Streptococcus agalactiae* (group B streptococci), *E. coli*, and *Listeria monocytogenes*—all causes of meningitis in neonates. Parvovirus B19 causes hydrops fetalis.

AGENT	MATERNAL ACQUISITION	MATERNAL MANIFESTATIONS	NEONATAL MANIFESTATIONS
<i>Toxoplasma gondii</i>	Cat feces or ingestion of undercooked meat	Usually asymptomatic; lymphadenopathy (rarely)	Classic triad: chorioretinitis, hydrocephalus, and intracranial calcifications, +/- “blueberry muffin” rash A
Rubella	Respiratory droplets	Rash, lymphadenopathy, polyarthritis, polyarthralgia	Classic triad: abnormalities of eye (cataracts B) and ear (deafness) and congenital heart disease (PDA); +/- “blueberry muffin” rash. I (eye) ♥ rubella earrings
Cytomegalovirus	Sexual contact, organ transplants	Usually asymptomatic; mononucleosis-like illness	Hearing loss, seizures, petechial rash, “blueberry muffin” rash, chorioretinitis, periventricular calcifications C CMV = Chorioretinitis, Microcephaly, periVentricular calcifications
HIV	Sexual contact, needlestick	Variable presentation depending on CD4+ cell count	Recurrent infections, chronic diarrhea
Herpes simplex virus-2	Skin or mucous membrane contact	Usually asymptomatic; herpetic (vesicular) lesions	Meningoencephalitis, herpetic (vesicular) lesions
Syphilis	Sexual contact	Chancres (1°) and disseminated rash (2°) are the two stages likely to result in fetal infection	Often results in stillbirth, hydrops fetalis; if child survives, presents with facial abnormalities (eg, notched teeth, saddle nose, rhinitis, short maxilla), saber shins, CN VIII deafness



Pelvic inflammatory disease



Ascending infection causing inflammation of the female gynecologic tract. PID may include salpingitis, endometritis, hydrosalpinx, and tubo-ovarian abscess.

Signs include cervical motion tenderness, adnexal tenderness, purulent cervical discharge **A**.

Top bugs—*Chlamydia trachomatis* (subacute, often undiagnosed), *Neisseria gonorrhoeae* (acute).

C trachomatis—most common bacterial STI in the United States.

Salpingitis is a risk factor for ectopic pregnancy, infertility, chronic pelvic pain, and adhesions. Can lead to perihepatitis (**Fitz-Hugh-Curtis syndrome**)—infection and inflammation of liver capsule and “violin string” adhesions of peritoneum to liver **B**.

Healthcare-associated infections

E coli (UTI) and *S aureus* (wound infection) are the two most common causes.

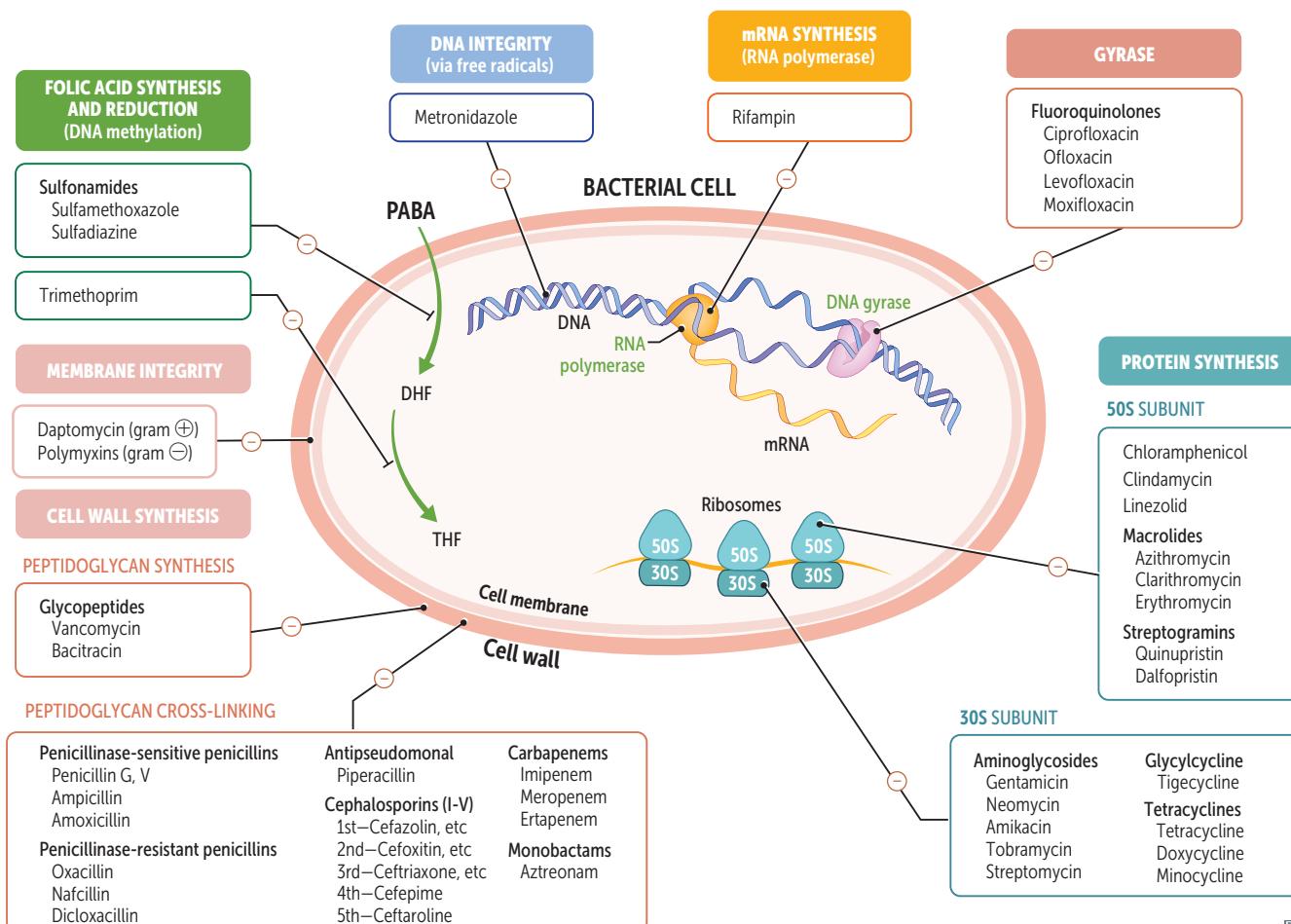
RISK FACTOR	PATHOGEN	UNIQUE SIGNS/SYMPOMTS
Antibiotic use, PPIs	<i>C difficile</i>	Watery diarrhea, leukocytosis
Aspiration (2° to altered mental status, old age)	Polymicrobial, gram ⊖ bacteria, often anaerobes	Right lower lobe infiltrate or right upper/middle lobe (patient recumbent); purulent malodorous sputum
Decubitus ulcers, surgical wounds, drains	<i>S aureus</i> (including MRSA), gram ⊖ anaerobes (<i>Bacteroides, Prevotella, Fusobacterium</i>)	Erythema, tenderness, induration, drainage from surgical wound sites
Intravascular catheters	<i>S aureus</i> (including MRSA), <i>S epidermidis</i> (long term)	Erythema, induration, tenderness, drainage from access sites
Mechanical ventilation, endotracheal intubation	Late onset: <i>P aeruginosa, Klebsiella, Acinetobacter, S aureus</i>	New infiltrate on CXR, ↑ sputum production; sweet odor (<i>Pseudomonas</i>)
Exposure to blood products, shared medical equipment, needlesticks	HBV, HCV	
Urinary catheterization	<i>Proteus</i> spp, <i>E coli, Klebsiella</i> (PECK)	Dysuria, leukocytosis, flank pain or costovertebral angle tenderness
Water aerosols	<i>Legionella</i>	Signs of pneumonia, GI symptoms (diarrhea, nausea, vomiting), neurologic abnormalities

Bugs affecting unvaccinated children

CLINICAL PRESENTATION	FINDINGS/LABS	PATHOGEN
Dermatologic		
Rash	Beginning at head and moving down with postauricular, posterior cervical, and suboccipital lymphadenopathy	Rubella virus
	Beginning at head and moving down; preceded by cough, coryza, conjunctivitis, and Koplik spots	Measles virus
Neurologic		
Meningitis	Microbe colonizes nasopharynx Can also lead to myalgia and paralysis	<i>H influenzae</i> type b Poliovirus
Tetanus	Muscle spasms and spastic paralysis (eg, lockjaw, opisthotonus)	<i>C tetani</i>
Respiratory		
Epiglottitis	Fever with dysphagia, drooling, inspiratory stridor, and difficulty breathing due to edema	<i>H influenzae</i> type b (also capable of causing epiglottitis in fully immunized children)
Pertussis	Low-grade fevers, coryza → whooping cough, posttussive vomiting → gradual recovery	<i>Bordetella pertussis</i>
Pharyngitis	Grayish pseudomembranes (may obstruct airways)	<i>Corynebacterium diphtheriae</i>

► MICROBIOLOGY—ANTIMICROBIALS

Antimicrobial therapy



Penicillin G, V

Penicillin G (IV and IM form), penicillin V (oral). Prototype β -lactam antibiotics.

MECHANISM	D-Ala-D-Ala structural analog. Bind penicillin-binding proteins (transpeptidases). Block transpeptidase cross-linking of peptidoglycan in cell wall. Activate autolytic enzymes.
CLINICAL USE	Mostly used for gram + organisms (<i>S pneumoniae</i> , <i>S pyogenes</i> , <i>Actinomyces</i>). Also used for gram - cocci (mainly <i>N meningitidis</i>) and spirochetes (mainly <i>T pallidum</i>). Bactericidal for gram + cocci, gram + rods, gram - cocci, and spirochetes. β -lactamase sensitive.
ADVERSE EFFECTS	Hypersensitivity reactions, direct Coombs + hemolytic anemia, drug-induced interstitial nephritis.
RESISTANCE	β -lactamase cleaves the β -lactam ring. Mutations in PBPs.

Penicillinase-sensitive penicillins Amoxicillin, ampicillin; aminopenicillins.

MECHANISM	Same as penicillin. Wider spectrum; penicillinase sensitive. Also combine with clavulanic acid to protect against destruction by β -lactamase.	Aminopenicillins are amped-up penicillin. Amoxicillin has greater oral bioavailability than ampicillin.
CLINICAL USE	Extended-spectrum penicillin— <i>H influenzae</i> , <i>H pylori</i> , <i>E coli</i> , Enterococci, <i>Listeria monocytogenes</i> , <i>Proteus mirabilis</i> , <i>Salmonella</i> , <i>Shigella</i> .	Coverage: ampicillin/amoxicillin HHELPSS kill enterococci.
ADVERSE EFFECTS	Hypersensitivity reactions, rash, pseudomembranous colitis.	
MECHANISM OF RESISTANCE	Penicillinase (a type of β -lactamase) cleaves β -lactam ring.	

Penicillinase-resistant penicillins Dicloxacillin, nafcillin, oxacillin.

MECHANISM	Same as penicillin. Narrow spectrum; penicillinase resistant because bulky R group blocks access of β -lactamase to β -lactam ring.	
CLINICAL USE	<i>S aureus</i> (except MRSA).	“Use naf (nafcillin) for staph .”
ADVERSE EFFECTS	Hypersensitivity reactions, interstitial nephritis.	
MECHANISM OF RESISTANCE	MRSA has altered penicillin-binding protein target site.	

Piperacillin Antipseudomonal penicillin.

MECHANISM	Same as penicillin. Extended spectrum. Penicillinase sensitive; use with β -lactamase inhibitors.
CLINICAL USE	<i>Pseudomonas</i> spp., gram \ominus rods, anaerobes.
ADVERSE EFFECTS	Hypersensitivity reactions.

Cephalosporins

MECHANISM	β -lactam drugs that inhibit cell wall synthesis but are less susceptible to penicillinases. Bactericidal.	Organisms typically not covered by 1st–4th generation cephalosporins are LAME : <i>Listeria</i> , Atypicals (<i>Chlamydia</i> , <i>Mycoplasma</i>), MRSA , and Enterococci .
CLINICAL USE	1st generation (cefazolin, cephalexin)—gram \oplus cocci, <i>Proteus mirabilis</i> , <i>E. coli</i> , <i>Klebsiella pneumoniae</i> . Cefazolin used prior to surgery to prevent <i>S. aureus</i> wound infections. 2nd generation (cefaclor, cefoxitin, cefuroxime, cefotetan)—gram \oplus cocci, <i>H. influenzae</i> , <i>Enterobacter aerogenes</i> , <i>Neisseria</i> spp., <i>Serratia marcescens</i> , <i>Proteus mirabilis</i> , <i>E. coli</i> , <i>Klebsiella pneumoniae</i> . 3rd generation (ceftriaxone, cefpodoxime, ceftazidime, cefixime)—serious gram \ominus infections resistant to other β -lactams. 4th generation (cefepime)—gram \ominus organisms, with \uparrow activity against <i>Pseudomonas</i> and gram \oplus organisms. 5th generation (ceftaroline)—broad gram \oplus and gram \ominus organism coverage; unlike 1st–4th generation cephalosporins, ceftaroline covers MRSA, and <i>Enterococcus faecalis</i> —does not cover <i>Pseudomonas</i> .	1st generation— \oplus PEcK . 2nd graders wear fake fox fur to tea parties. 2nd generation— \oplus HENS PEcK . Can cross blood-brain barrier. Ceftriaxone—meningitis, gonorrhea, disseminated Lyme disease. Ceftazidime for pseudomonaz.
ADVERSE EFFECTS	Hypersensitivity reactions, autoimmune hemolytic anemia, disulfiram-like reaction, vitamin K deficiency. Low rate of cross-reactivity even in penicillin-allergic patients. \uparrow nephrotoxicity of aminoglycosides.	
MECHANISM OF RESISTANCE	Inactivated by cephalosporinases (a type of β -lactamase). Structural change in penicillin-binding proteins (transpeptidases).	

 β -lactamase inhibitors

Include **Clavulanic acid**, **Avibactam**, **Sulbactam**, **Tazobactam**. Often added to penicillin antibiotics to protect the antibiotic from destruction by β -lactamase.

CAST (eg, amoxicillin-clavulanate, ceftazidime-avibactam, ampicillin-sulbactam, piperacillin-tazobactam).

Carbapenems

MECHANISM

Imipenem, meropenem, ertapenem.

Imipenem is a broad-spectrum, β -lactamase-resistant carbapenem. Binds penicillin-binding proteins → inhibition of cell wall synthesis → cell death. Always administered with cilastatin (inhibitor of renal dehydropeptidase I) to ↓ inactivation of drug in renal tubules.

With imipenem, “the kill is **lastin'** with **cilastatin**.”

Unlike other carbapenems, ertapenem is not active against *Pseudomonas*.

CLINICAL USE

Gram + cocci, gram - rods, and anaerobes. Wide spectrum and significant adverse effects limit use to life-threatening infections or after other drugs have failed. Meropenem has a ↓ risk of seizures and is stable to dehydropeptidase I.

ADVERSE EFFECTS

GI distress, rash, and CNS toxicity (seizures) at high plasma levels.

MECHANISM OF RESISTANCE

Inactivated by carbapenemases produced by, eg, *K pneumoniae*, *E coli*, *Klebsiella aerogenes*.

Aztreonam

MECHANISM

Less susceptible to β -lactamases. Prevents peptidoglycan cross-linking by binding to penicillin-binding protein 3. Synergistic with aminoglycosides. No cross-allergenicity with penicillins.

CLINICAL USE

Gram - rods only—no activity against gram + rods or anaerobes. For penicillin-allergic patients and those with renal insufficiency who cannot tolerate aminoglycosides.

ADVERSE EFFECTS

Usually nontoxic; occasional GI upset.

Vancomycin

MECHANISM

Inhibits cell wall peptidoglycan formation by binding D-Ala-D-Ala portion of cell wall precursors. Bactericidal against most bacteria (bacteriostatic against *C difficile*). Not susceptible to β -lactamases.

CLINICAL USE

Gram + bugs only—for serious, multidrug-resistant organisms, including MRSA, *S epidermidis*, sensitive *Enterococcus* species, and *C difficile* (oral route).

ADVERSE EFFECTS

Well tolerated in general but **not** trouble free: nephrotoxicity, ototoxicity, thrombophlebitis, diffuse flushing (**vancomycin infusion reaction A**—idiopathic reaction largely preventable by pretreatment with antihistamines and slower infusion rate), DRESS syndrome.



MECHANISM OF RESISTANCE

Occurs in bacteria (eg, *Enterococcus*) via amino acid modification of D-Ala-D-Ala to **D-Ala-D-Lac**. “If you **Lack** a **D-Ala** (dollar), you can’t ride the **van** (vancomycin).”

Protein synthesis inhibitors

Specifically target smaller bacterial ribosome (70S, made of 30S and 50S subunits), leaving human ribosome (80S) unaffected.

All are bacteriostatic, except aminoglycosides (bactericidal) and linezolid (variable).

30S inhibitors

Aminoglycosides
“Buy at 30, ccel (sell) at 50.”

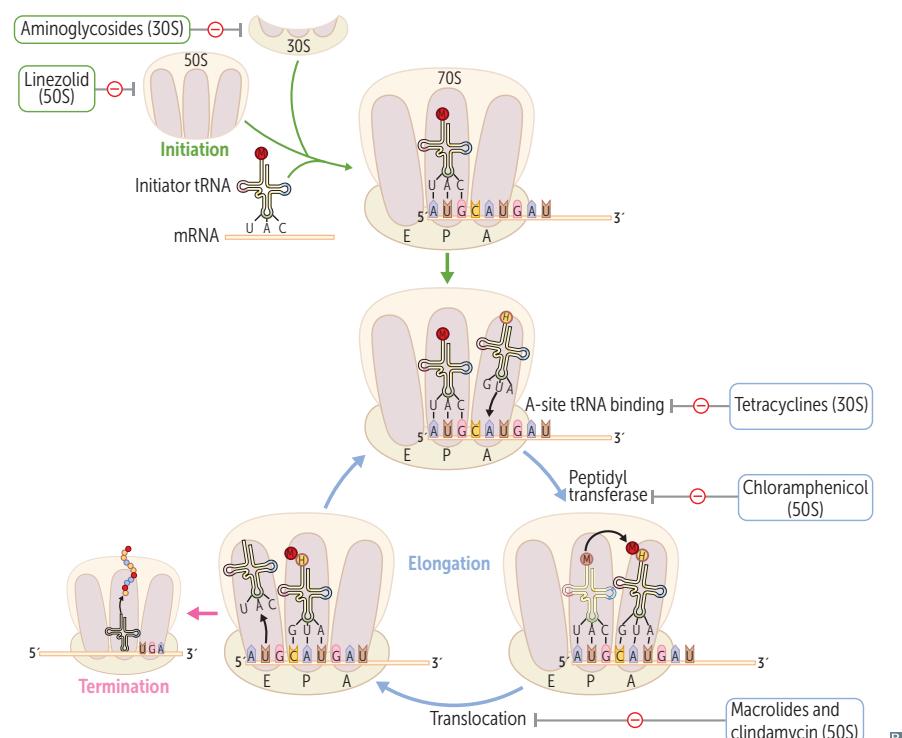
Tetracyclines

50S inhibitors

Chloramphenicol, Clindamycin

Erythromycin (macrolides)

Linezolid

**Aminoglycosides**

Gentamicin, Neomycin, Amikacin, Tobramycin, Streptomycin.
“Mean” (aminoglycoside) GNATS cannot kill anaerobes.

MECHANISM

Bactericidal; irreversible inhibition of initiation complex through binding of the 30S subunit. Can cause misreading of mRNA. Also block translocation. Require O₂ for uptake; therefore ineffective against anaerobes.

CLINICAL USE

Severe gram \ominus rod infections. Synergistic with β -lactam antibiotics.
Neomycin for bowel surgery.

ADVERSE EFFECTS

Nephrotoxicity, neuromuscular blockade (absolute contraindication with myasthenia gravis), ototoxicity (especially with loop diuretics), teratogenicity.

MECHANISM OF RESISTANCE

Bacterial transferase enzymes inactivate the drug by acetylation, phosphorylation, or adenylation.

Tetracyclines

Tetracycline, doxycycline, minocycline.

MECHANISM

Bacteriostatic; bind to 30S and prevent attachment of aminoacyl-tRNA. Limited CNS penetration.

Doxycycline is fecally eliminated and can be used in patients with renal failure. Do not take tetracyclines with milk (Ca^{2+}), antacids (eg, Ca^{2+} or Mg^{2+}), or iron-containing preparations because divalent cations inhibit drugs' absorption in the gut.

CLINICAL USE

Borrelia burgdorferi, *M pneumoniae*. Drugs' ability to accumulate intracellularly makes them very effective against *Rickettsia* and *Chlamydia*. Also used to treat acne. Doxycycline effective against community-acquired MRSA.

ADVERSE EFFECTS

GI distress, discoloration of teeth and inhibition of bone growth in children, photosensitivity.

“Teratocyclines” are teratogenic; generally avoided in pregnancy and in children (except doxycycline).

MECHANISM OF RESISTANCE

↓ uptake or ↑ efflux out of bacterial cells by plasmid-encoded transport pumps.

Tigecycline

MECHANISM

Tetracycline derivative. Binds to 30S, inhibiting protein synthesis. Generally bacteriostatic.

CLINICAL USE

Broad-spectrum anaerobic, gram ⊖, and gram ⊕ coverage. Multidrug-resistant organisms (eg, MRSA, VRE).

ADVERSE EFFECTS

Nausea, vomiting.

Chloramphenicol

MECHANISM

Blocks peptidyltransferase at 50S ribosomal subunit. Bacteriostatic.

CLINICAL USE

Meningitis (*Haemophilus influenzae*, *Neisseria meningitidis*, *Streptococcus pneumoniae*) and rickettsial diseases (eg, Rocky Mountain spotted fever [*Rickettsia rickettsii*]).

Limited use due to toxicity but often still used in developing countries because of low cost.

ADVERSE EFFECTS

Anemia (dose dependent), aplastic anemia (dose independent), gray baby syndrome (in premature infants because they lack liver UDP-glucuronosyltransferase).

MECHANISM OF RESISTANCE

Plasmid-encoded acetyltransferase inactivates the drug.

Clindamycin

MECHANISM

Blocks peptide transfer (translocation) at 50S ribosomal subunit. Bacteriostatic.

CLINICAL USE

Anaerobic infections (eg, *Bacteroides* spp., *C perfringens*) in aspiration pneumonia, lung abscesses, and oral infections. Also effective against invasive group A streptococcal infection.

Treats anaerobic infections above the diaphragm vs metronidazole (anaerobic infections below diaphragm).

ADVERSE EFFECTS

Pseudomembranous colitis (*C difficile* overgrowth), fever, diarrhea.

Linezolid

MECHANISM	Inhibits protein synthesis by binding to the 23S rRNA of the 50S ribosomal subunit and preventing formation of the initiation complex.
CLINICAL USE	Gram \oplus species including MRSA and VRE.
ADVERSE EFFECTS	Myelosuppression (especially thrombocytopenia), peripheral neuropathy, serotonin syndrome (due to partial MAO inhibition).
MECHANISM OF RESISTANCE	Point mutation of ribosomal RNA.

Macrolides

	Azithromycin, clarithromycin, erythromycin.
MECHANISM	Inhibit protein synthesis by blocking translocation (“macro slides ”); bind to the 50S ribosomal subunit. Bacteriostatic.
CLINICAL USE	Atypical pneumonias (<i>Mycoplasma</i> , <i>Chlamydia</i> , <i>Legionella</i>), STIs (<i>Chlamydia</i>), gram \oplus cocci (streptococcal infections in patients allergic to penicillin), and <i>B pertussis</i> .
ADVERSE EFFECTS	MACRO: Gastrointestinal Motility issues, Arrhythmia caused by prolonged QT interval, acute Cholestatic hepatitis , Rash , eOsinophilia . Increases serum concentration of theophylline, oral anticoagulants. Clarithromycin and erythromycin inhibit cytochrome P-450.
MECHANISM OF RESISTANCE	Methylation of 23S rRNA-binding site prevents binding of drug.

Polymyxins

	Colistin (polymyxin E), polymyxin B.
MECHANISM	Cation polypeptides that bind to phospholipids on cell membrane of gram \ominus bacteria. Disrupt cell membrane integrity → leakage of cellular components → cell death.
CLINICAL USE	Salvage therapy for multidrug-resistant gram \ominus bacteria (eg, <i>P aeruginosa</i> , <i>E coli</i> , <i>K pneumoniae</i>). Polymyxin B is a component of a triple antibiotic ointment used for superficial skin infections.
ADVERSE EFFECTS	Nephrotoxicity, neurotoxicity (eg, slurred speech, weakness, paresthesias), respiratory failure.

Sulfonamides

Sulfamethoxazole (SMX), sulfisoxazole, sulfadiazine.

MECHANISM

Inhibit dihydropteroate synthase, thus inhibiting folate synthesis. Bacteriostatic (bactericidal when combined with trimethoprim).

CLINICAL USE

Gram \oplus , gram \ominus , *Nocardia*. TMP-SMX for simple UTI.

ADVERSE EFFECTS

Stevens-Johnson syndrome, urticaria, liver damage, folate deficiency, optic neuritis, nephrotoxicity, agranulocytosis, hemolysis if G6PD deficient, kernicterus in infants.

MECHANISM OF RESISTANCE

Altered enzyme (bacterial dihydropteroate synthase), \downarrow uptake, or \uparrow PABA synthesis.

Dapsone**MECHANISM**

Similar to sulfonamides, but structurally distinct agent.

CLINICAL USE

Leprosy (lepromatous and tuberculoid), *Pneumocystis jirovecii* prophylaxis, or treatment when used in combination with TMP.

ADVERSE EFFECTS

Hemolysis if G6PD deficient, methemoglobinemia, agranulocytosis.

Trimethoprim**MECHANISM**

Inhibits bacterial dihydrofolate reductase. Bacteriostatic.

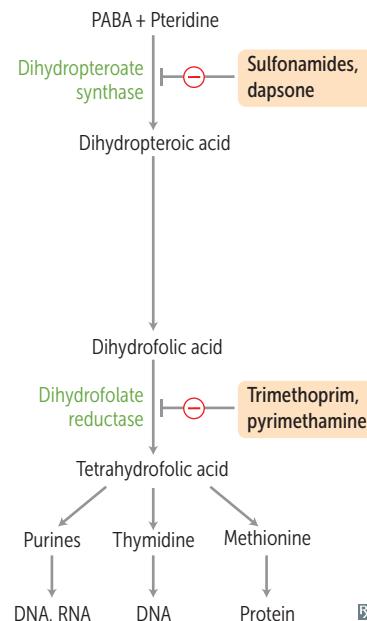
CLINICAL USE

Used in combination with sulfonamides (trimethoprim-sulfamethoxazole [TMP-SMX]), causing sequential block of folate synthesis. Combination used for UTIs, *Shigella*, *Salmonella*, *Pneumocystis jirovecii* pneumonia treatment and prophylaxis, toxoplasmosis prophylaxis.

ADVERSE EFFECTS

Hyperkalemia (at high doses; similar mechanism as potassium-sparing diuretics), megaloblastic anemia, leukopenia, granulocytopenia, which may be avoided with coadministration of leucovorin (folic acid).

TMP Treats Marrow Poorly.



Fluoroquinolones

MECHANISM	Ciprofloxacin, ofloxacin; respiratory fluoroquinolones: levofloxacin, moxifloxacin.
CLINICAL USE	Gram \ominus rods of urinary and GI tracts (including <i>Pseudomonas</i>), some gram \oplus organisms, otitis externa, community-acquired pneumonia.
ADVERSE EFFECTS	GI upset, superinfections, skin rashes, headache, dizziness. Less commonly, can cause leg cramps and myalgias. Contraindicated during pregnancy or breastfeeding and in children $<$ 18 years old due to possible damage to cartilage. Some may prolong QT interval.
MECHANISM OF RESISTANCE	Chromosome-encoded mutation in DNA gyrase, plasmid-mediated resistance, efflux pumps.

May cause tendonitis or tendon rupture in people $>$ 60 years old and in patients taking prednisone. Ciprofloxacin inhibits cytochrome P-450.
Fluoroquinolones hurt attachments to your **bones**.

Daptomycin

MECHANISM	Lipopeptide that disrupts cell membranes of gram \oplus cocci by creating transmembrane channels.
CLINICAL USE	<i>S aureus</i> skin infections (especially MRSA), bacteremia, infective endocarditis, VRE.
ADVERSE EFFECTS	Myopathy, rhabdomyolysis.

Not used for pneumonia (avidly binds to and is inactivated by surfactant). “Dapto-my-o-skin” is used for **skin** infections but can cause **myopathy**.

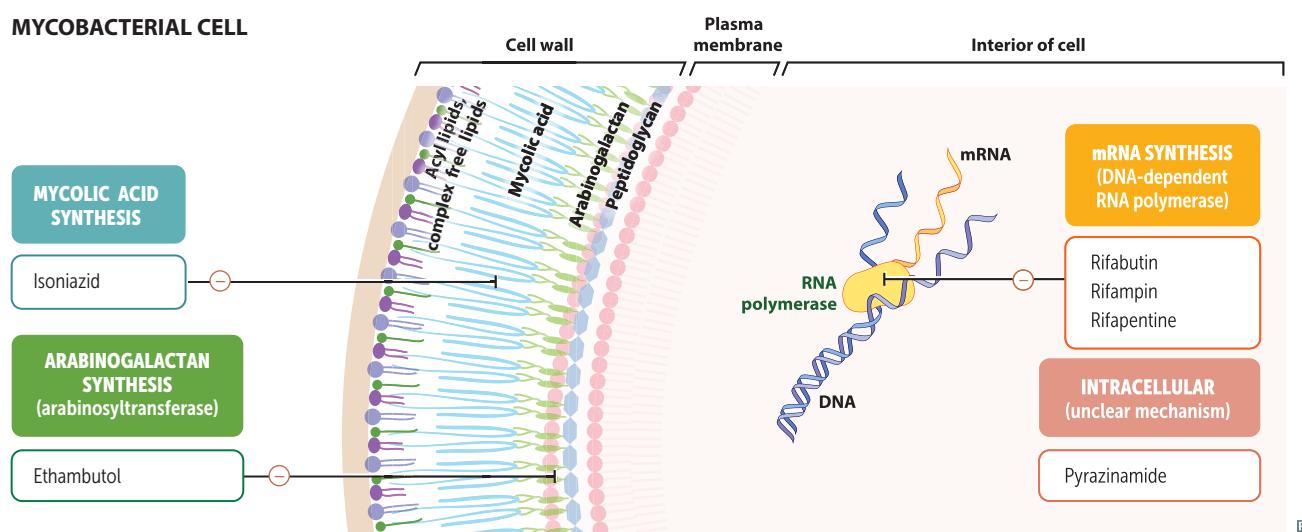
Metronidazole

MECHANISM	Forms toxic free radical metabolites in the bacterial cell that damage DNA. Bactericidal, antiprotozoal.
CLINICAL USE	Treats <i>Giardia</i> , <i>Entamoeba</i> , <i>Trichomonas</i> , <i>Gardnerella vaginalis</i> , Anaerobes (<i>Bacteroides</i> , <i>C difficile</i>). Can be used in place of amoxicillin in <i>H pylori</i> “triple therapy” in case of penicillin allergy.
ADVERSE EFFECTS	Disulfiram-like reaction (severe flushing, tachycardia, hypotension) with alcohol; headache, metallic taste.

GET GAP on the **Metro** with **metronidazole!**
Treats anaerobic infection **below** the diaphragm vs clindamycin (anaerobic infections **above** diaphragm).

Antituberculous drugs

DRUG	MECHANISM	ADVERSE EFFECTS	NOTES
Rifamycins Rifampin, rifabutin, rifapentine	Inhibit DNA-dependent RNA polymerase → ↓ mRNA synthesis Rifamycin resistance arises due to mutations in gene encoding RNA polymerase	Minor hepatotoxicity, drug interactions (CYP450 induction), red-orange discoloration of body fluids (nonhazardous adverse effect)	Rifabutin favored over rifampin in patients with HIV infection due to less CYP450 induction Monotherapy rapidly leads to resistance
Isoniazid	Inhibits mycolic acid synthesis → ↓ cell wall synthesis Bacterial catalase-peroxidase (encoded by <i>katG</i>) is needed to convert INH to active form INH resistance arises due to mutations in <i>katG</i>	Vitamin B ₆ deficiency (peripheral neuropathy, sideroblastic anemia), hepatotoxicity, drug interactions (CYP450 inhibition), drug-induced lupus INH overdose can lead to seizures (often refractory to benzodiazepines)	Administer with pyridoxine (vitamin B ₆) INH Injures Neurons and Hepatocytes (↑ risk of hepatotoxicity with ↑ age and alcohol overuse) Different INH half-lives in fast vs slow acetylators
Pyrazinamide	Mechanism uncertain	Hepatotoxicity, hyperuricemia	Works best at acidic pH (eg, in host phagolysosomes)
Ethambutol	Inhibits arabinosyltransferase → ↓ arabinogalactan synthesis → ↓ cell wall synthesis	Optic neuropathy (red-green color blindness or ↓ visual acuity, typically reversible)	Pronounce “ eyethambutol ”

MYCOBACTERIAL CELL

Antimycobacterial therapy

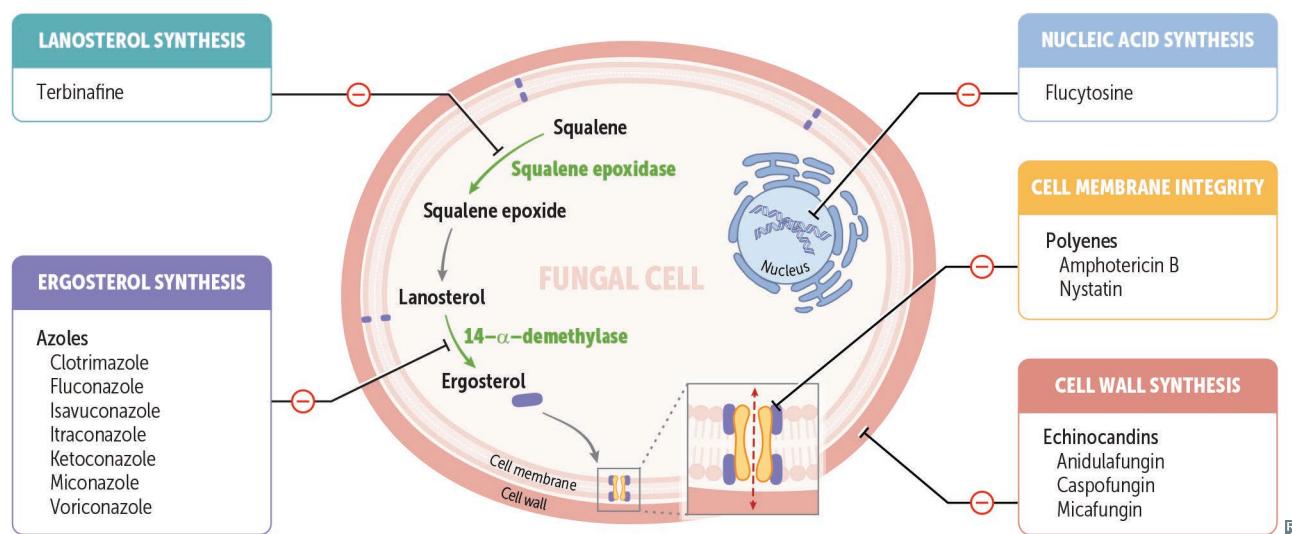
BACTERIUM	PROPHYLAXIS	TREATMENT
<i>M tuberculosis</i>	Rifamycin-based regimen for 3–4 months	Rifampin, Isoniazid, Pyrazinamide, Ethambutol (RIPE for treatment)
<i>M avium-intracellulare</i>	Azithromycin, rifabutin	Azithromycin or clarithromycin + ethambutol Can add rifabutin or ciprofloxacin
<i>M leprae</i>	N/A	Long-term treatment with dapsone and rifampin for tuberculoid form Add clofazimine for lepromatous form

Antimicrobial prophylaxis

CLINICAL SCENARIO	MEDICATION
Exposure to meningococcal infection	Ceftriaxone, ciprofloxacin, or rifampin
High risk for infective endocarditis and undergoing surgical or dental procedures	Amoxicillin
History of recurrent UTIs	TMP-SMX
Malaria prophylaxis for travelers	Atovaquone-proguanil, mefloquine, doxycycline, primaquine, or chloroquine (for areas with sensitive species)
Pregnant patients carrying group B strep	Intrapartum penicillin G or ampicillin
Prevention of gonococcal conjunctivitis in newborn	Erythromycin ointment on eyes
Prevention of postsurgical infection due to <i>S aureus</i>	Cefazolin; vancomycin if \oplus for MRSA
Prophylaxis of strep pharyngitis in child with prior rheumatic fever	Benzathine penicillin G or oral penicillin V

Prophylaxis in HIV infection/AIDS

CELL COUNT	PROPHYLAXIS	INFECTON
CD4+ < 200 cells/mm ³	TMP-SMX	<i>Pneumocystis</i> pneumonia
CD4+ < 100 cells/mm ³	TMP-SMX	<i>Pneumocystis</i> pneumonia and toxoplasmosis

Antifungal therapy**Amphotericin B**

MECHANISM	Binds ergosterol (unique to fungi); forms membrane pores that allow leakage of electrolytes.	Amphotericin “tears” holes in the fungal membrane by forming pores.
CLINICAL USE	Serious, systemic mycoses. <i>Cryptococcus</i> (amphotericin B +/- flucytosine for cryptococcal meningitis), <i>Blastomyces</i> , <i>Coccidioides</i> , <i>Histoplasma</i> , <i>Candida</i> , <i>Mucor</i> . Intrathecally for coccidioidal meningitis.	Supplement K ⁺ and Mg ²⁺ because of altered renal tubule permeability.
ADVERSE EFFECTS	Fever/chills (“shake and bake”), hypotension, nephrotoxicity, arrhythmias, anemia, IV phlebitis (“ amphotericible ”).	Hydration ↓ nephrotoxicity. Liposomal amphotericin ↓ toxicity.

Nystatin

MECHANISM	Same as amphotericin B. Topical use only as too toxic for systemic use.
CLINICAL USE	“Swish and swallow” for oral candidiasis (thrush); topical for diaper rash or vaginal candidiasis.

Flucytosine

MECHANISM	Inhibits DNA and RNA biosynthesis by conversion to 5-fluorouracil by cytosine deaminase.
CLINICAL USE	Systemic fungal infections (especially meningitis caused by <i>Cryptococcus</i>) in combination with amphotericin B.
ADVERSE EFFECTS	Myelosuppression.

Azoles

Clotrimazole, fluconazole, isavuconazole, itraconazole, ketoconazole, miconazole, voriconazole.

MECHANISM

Inhibit fungal sterol (ergosterol) synthesis by inhibiting the cytochrome P-450 enzyme that converts lanosterol to ergosterol.

CLINICAL USE

Local and less serious systemic mycoses. Fluconazole for chronic suppression of cryptococcal meningitis in people living with HIV and candidal infections of all types. Itraconazole may be used for *Blastomyces*, *Coccidioides*, *Histoplasma*, *Sporothrix schenckii*. Clotrimazole and miconazole for topical fungal infections. Voriconazole for *Aspergillus* and some *Candida*. Isavuconazole for serious *Aspergillus* and *Mucor* infections.

ADVERSE EFFECTS

Testosterone synthesis inhibition (gynecomastia, especially with ketoconazole), liver dysfunction (inhibits cytochrome P-450), QT interval prolongation.

Terbinafine**MECHANISM**

Inhibits the fungal enzyme squalene epoxidase.

CLINICAL USE

Dermatophytoses (especially onychomycosis—fungal infection of finger or toe nails).

ADVERSE EFFECTS

GI upset, headaches, hepatotoxicity, taste disturbance.

Echinocandins

Anidulafungin, caspofungin, micafungin.

MECHANISM

Inhibit cell wall synthesis by inhibiting synthesis of β -glucan.

CLINICAL USE

Invasive aspergillosis, *Candida*.

ADVERSE EFFECTS

GI upset, flushing (by histamine release).

Griseofulvin**MECHANISM**

Interferes with microtubule function; disrupts mitosis. Deposits in keratin-containing tissues (eg, nails).

CLINICAL USE

Oral treatment of superficial infections; inhibits growth of dermatophytes (tinea, ringworm).

ADVERSE EFFECTS

Teratogenic, carcinogenic, confusion, headaches, disulfiram-like reaction, ↑ cytochrome P-450 and warfarin metabolism.

Antiprotozoal therapy

Pyrimethamine-sulfadiazine (toxoplasmosis), suramin and melarsoprol (*Trypanosoma brucei*), nifurtimox (*T cruzi*), sodium stibogluconate (leishmaniasis).

Anti-mite/louse therapy

Permethrin, malathion (acetylcholinesterase inhibitor), topical or oral ivermectin. Used to treat scabies (*Sarcoptes scabiei*) and lice (*Pediculus* and *Pthirus*).

Chloroquine**MECHANISM**

Blocks detoxification of heme into hemozoin. Heme accumulates and is toxic to plasmodia.

CLINICAL USE

Treatment of plasmodial species other than *P falciparum* (due to drug resistance from membrane pump that ↓ intracellular concentration of drug).

ADVERSE EFFECTS

Retinopathy (dependent on cumulative dose); pruritus (especially in dark-skinned individuals).

Antihelminthic therapy

Pyrantel pamoate, ivermectin, mebendazole (treats “**bendy** worms” by disrupting microtubules and cellular motility), praziquantel ($\uparrow \text{Ca}^{2+}$ permeability, \uparrow vacuolization), diethylcarbamazine.

Oseltamivir, zanamivir

MECHANISM	Inhibit influenza neuraminidase $\rightarrow \downarrow$ release of progeny virus.
CLINICAL USE	Treatment and prevention of influenza A and B. Beginning therapy within 48 hours of symptom onset may shorten duration of illness.

Baloxavir

MECHANISM	Inhibits the “cap snatching” (transfer of the 5’ cap from cell mRNA onto viral mRNA) endonuclease activity of the influenza virus RNA polymerase $\rightarrow \downarrow$ viral replication.
CLINICAL USE	Treatment within 48 hours of symptom onset shortens duration of illness.

Remdesivir

MECHANISM	Prodrug of an ATP analog. The active metabolite inhibits viral RNA-dependent RNA polymerase and evades proofreading by viral exoribonuclease (ExoN) $\rightarrow \downarrow$ viral RNA production.
CLINICAL USE	Recently approved for treatment of COVID-19 requiring hospitalization.

Acyclovir, famciclovir, valacyclovir

MECHANISM	Guanosine analogs. Monophosphorylated by HSV/VZV thymidine kinase and not phosphorylated in uninfected cells \rightarrow few adverse effects. Triphosphate formed by cellular enzymes. Preferentially inhibit viral DNA polymerase by chain termination.
CLINICAL USE	No activity against CMV because CMV lacks the thymidine kinase necessary to activate guanosine analogs. Used for HSV-induced mucocutaneous and genital lesions as well as for encephalitis. Prophylaxis in patients who are immunocompromised. Also used as prophylaxis for immunocompetent patients with severe or recurrent infection. No effect on latent forms of HSV and VZV. Valacyclovir, a prodrug of acyclovir, has better oral bioavailability. For herpes zoster, use famciclovir.
ADVERSE EFFECTS	Obstructive crystalline nephropathy and acute kidney injury if not adequately hydrated.
MECHANISM OF RESISTANCE	Mutated viral thymidine kinase.

Ganciclovir

MECHANISM	Guanosine analog. 5'-monophosphate formed by a CMV viral kinase. Triphosphate formed by cellular kinases. Preferentially inhibits viral DNA polymerase.
CLINICAL USE	CMV, especially in patients who are immunocompromised. Valganciclovir, a prodrug of ganciclovir, has better oral bioavailability.
ADVERSE EFFECTS	Myelosuppression (leukopenia, neutropenia, thrombocytopenia), renal toxicity. More toxic to host enzymes than acyclovir.
MECHANISM OF RESISTANCE	Mutated viral kinase.

Foscarnet

MECHANISM	Viral DNA/RNA polymerase inhibitor and HIV reverse transcriptase inhibitor. Binds to pyrophosphate-binding site of enzyme. Does not require any kinase activation. Foscarnet = pyrofosphate analog.
CLINICAL USE	CMV retinitis in immunocompromised patients when ganciclovir fails; acyclovir-resistant HSV.
ADVERSE EFFECTS	Nephrotoxicity, multiple electrolyte abnormalities can lead to seizures.
MECHANISM OF RESISTANCE	Mutated DNA polymerase.

Cidofovir

MECHANISM	Preferentially inhibits viral DNA polymerase. Does not require phosphorylation by viral kinase.
CLINICAL USE	CMV retinitis in immunocompromised patients. Long half-life.
ADVERSE EFFECTS	Nephrotoxicity (coadminister cidofovir with probenecid and IV saline to ↓ toxicity).
MECHANISM OF RESISTANCE	Mutations in the viral DNA polymerase gene.

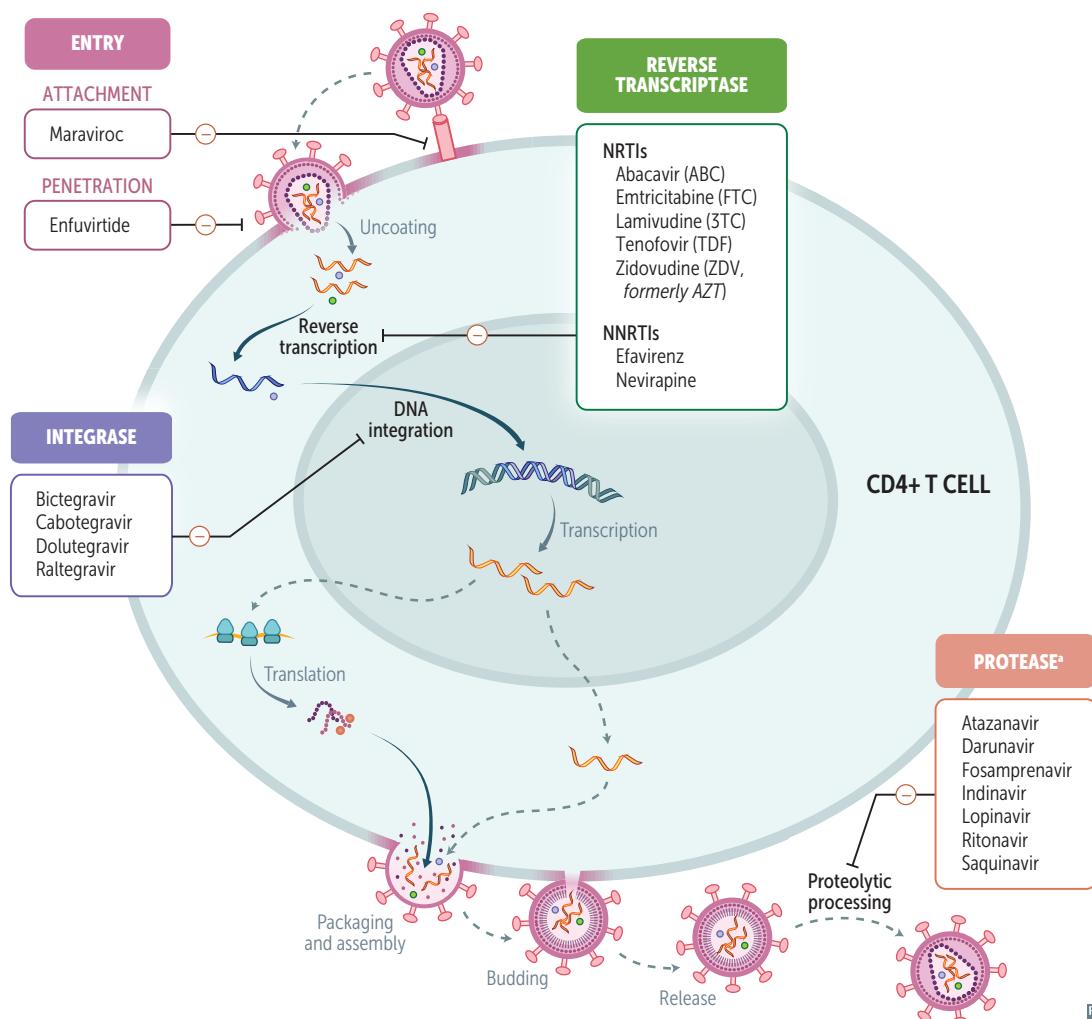
HIV therapy

Antiretroviral therapy (ART): often initiated at the time of HIV diagnosis. Strongest indication for use with patients presenting with AIDS-defining illness, low CD4+ cell counts (< 500 cells/mm³), or high viral load. Regimen consists of 3 drugs to prevent resistance: 2 NRTIs and preferably an integrase inhibitor. Most ARTs are active against both HIV-1 and HIV-2 (exceptions: NNRTIs and enfuvirtide not effective against HIV-2). Tenofovir + emtricitabine can be administered as pre-exposure prophylaxis.

DRUG	MECHANISM	ADVERSE EFFECTS
NRTIs		
Abacavir (ABC)	Competitively inhibit nucleotide binding to reverse transcriptase and terminate the DNA chain (lack a 3' OH group). Tenofovir is a nucleo Tide ; the others are nucleosides. All need to be phosphorylated to be active.	Myelosuppression (can be reversed with granulocyte colony-stimulating factor [G-CSF] and erythropoietin), nephrotoxicity.
Emtricitabine (FTC)		Abacavir contraindicated if patient has HLA-B*5701 mutation due to ↑ risk of hypersensitivity.
Lamivudine (3TC)		
Tenofovir (TDF)	ZDV can be used for general prophylaxis and during pregnancy to ↓ risk of fetal transmission.	
Zidovudine (ZDV, formerly AZT)	Have you dined (vudine) with my nuclear (nucleosides) family?	
NNRTIs		
Doravirine	Bind to reverse transcriptase at site different from NRTIs. Do not require phosphorylation to be active or compete with nucleotides.	Rash and hepatotoxicity are common to all NNRTIs. Vivid dreams and CNS symptoms are common with efavirenz.
Efavirenz		
Rilpivirine		
Integrase strand transfer inhibitors		
Bictegravir	Also called integrase inhibitors. Inhibit HIV genome integration into host cell chromosome by reversibly inhibiting HIV integrase.	↑ creatine kinase, weight gain.
Dolutegravir		

HIV therapy (continued)

DRUG	MECHANISM	ADVERSE EFFECTS
Protease inhibitors		
Atazanavir	Prevents maturation of new virions. Maturation depends on HIV-1 protease (<i>pol</i> gene), which cleaves the polypeptide products of HIV mRNA into their functional parts.	Hyperglycemia, GI intolerance (nausea, diarrhea).
Darunavir	All protease inhibitors require boosting with either ritonavir or cobicistat.	Rifampin (potent CYP/UGT inducer) ↓ protease inhibitor concentrations; use rifabutin instead.
Lopinavir		Ritonavir (cytochrome P-450 inhibitor) is only used as a boosting agent.
Ritonavir		
Entry inhibitors		
Enfuvirtide	Binds gp41, inhibiting viral entry. Enfuvirtide inhibits fusion .	Skin reaction at injection sites.
Maraviroc	Binds CCR-5 on surface of T cells/monocytes, inhibiting interaction with gp120. Maraviroc inhibits docking .	



^aAll protease inhibitors require boosting with either ritonavir (protease inhibitor only used as a boosting agent) or cobicistat (cytochrome P450 inhibitor).

Hepatitis C therapy

Chronic HCV infection treated with multidrug therapy that targets specific steps within HCV replication cycle (HCV-encoded nonstructural proteins). Examples of drugs are provided.

DRUG	MECHANISM	TOXICITY
NS5A inhibitors		
Elbasvir	Inhibits NS5A, a viral phosphoprotein that plays a key role in RNA replication	Headache, diarrhea
Ledipasvir		
Pibrentasvir	Exact mechanism unknown	
Velpatasvir		
NS5B inhibitors		
Sofosbuvir	Inhibits NS5B, an RNA-dependent RNA polymerase acting as a chain terminator Prevents viral RNA replication	Fatigue, headache
Glecaprevir	Inhibits NS3/4A, a viral protease, preventing viral replication	Headache, fatigue
Grazoprevir		
Alternative drugs		
Ribavirin	Inhibits synthesis of guanine nucleotides by competitively inhibiting IMP dehydrogenase	Hemolytic anemia, severe teratogen

Disinfection and sterilization

Goals include the reduction of pathogenic organism counts to safe levels (disinfection) and the inactivation of all microbes including spores (sterilization).

Autoclave^a	Pressurized steam at > 120°C. May not reliably inactivate prions.
Alcohols	Denature proteins and disrupt cell membranes.
Chlorhexidine	Disrupts cell membranes and coagulates intracellular components.
Chlorine^a	Oxidizes and denatures proteins.
Ethylene oxide^a	Alkylating agent.
Hydrogen peroxide^a	Free radical oxidation.
Iodine and iodophors	Halogenation of DNA, RNA, and proteins. May be sporicidal.
Quaternary amines	Impair permeability of cell membranes.

^aSporicidal.

Antimicrobials to avoid in pregnancy

ANTIMICROBIAL	ADVERSE EFFECTS
Sulfonamides	Kernicterus
Aminoglycosides	Ototoxicity
Fluoroquinolones	Cartilage damage
Clarithromycin	Embryotoxic
Tetracyclines	Discolored teeth, inhibition of bone growth
Ribavirin	Teratogenic
Griseofulvin	Teratogenic
Chloramphenicol	Gray baby syndrome

Safe children take really good care.

▶ NOTES

HIGH-YIELD PRINCIPLES IN

Pathology

“Digressions, objections, delight in mockery, carefree mistrust are signs of health; everything unconditional belongs in pathology.”

—Friedrich Nietzsche

“You cannot separate passion from pathology any more than you can separate a person’s spirit from his body.”

—Richard Selzer

“My business is not prognosis, but diagnosis. I am not engaged in therapeutics, but in pathology.”

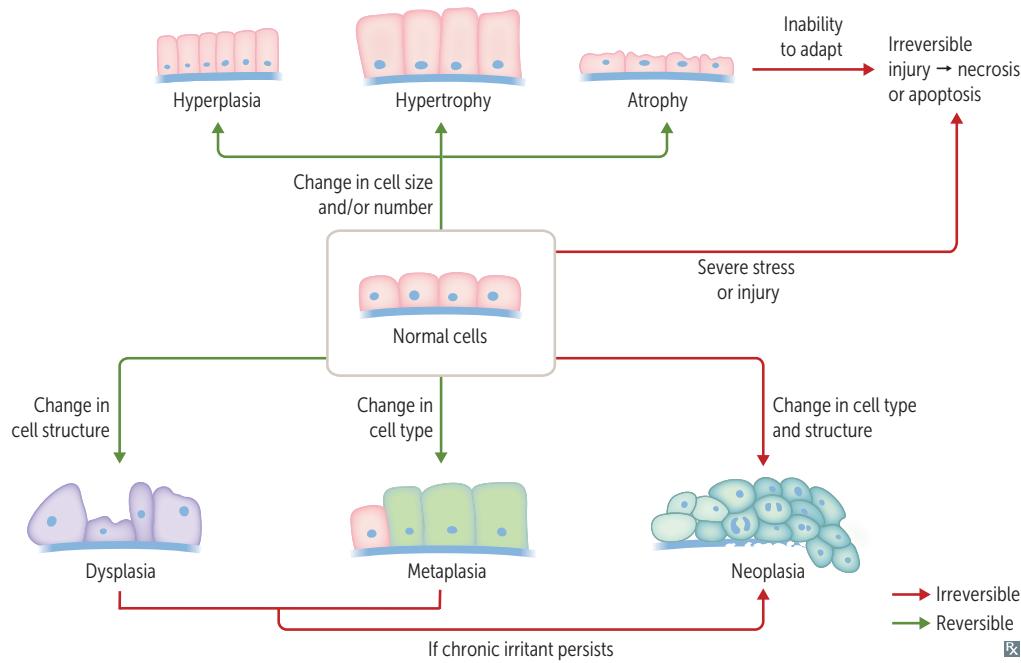
—H.L. Mencken

The fundamental principles of pathology are key to understanding diseases in all organ systems. Major topics such as inflammation and neoplasia appear frequently in questions across different organ systems, and such topics are definitely high yield. For example, the concepts of cell injury and inflammation are key to understanding the inflammatory response that follows myocardial infarction, a very common subject of board questions. Similarly, a familiarity with the early cellular changes that culminate in the development of neoplasias—for example, esophageal or colon cancer—is critical. Make sure you recognize the major tumor-associated genes and are comfortable with key cancer concepts such as tumor staging and metastasis. Finally, take some time to learn about the major systemic changes that come with aging, and how these physiologic alterations differ from disease states.

► Cellular Injury	202
► Inflammation	209
► Neoplasia	215
► Aging	225

▶ PATHOLOGY—CELLULAR INJURY

Cellular adaptations	Reversible changes that can be physiologic (eg, uterine enlargement during pregnancy) or pathologic (eg, myocardial hypertrophy 2° to systemic HTN). If stress is excessive or persistent, adaptations can progress to cell injury (eg, significant LV hypertrophy \rightarrow myocardial injury \rightarrow HF).
Hypertrophy	\uparrow structural proteins and organelles \rightarrow \uparrow in size of cells. Example: cardiac hypertrophy.
Hyperplasia	Controlled proliferation of stem cells and differentiated cells \rightarrow \uparrow in number of cells (eg, benign prostatic hyperplasia). Excessive stimulation \rightarrow pathologic hyperplasia (eg, endometrial hyperplasia), which may progress to dysplasia and cancer.
Atrophy	\downarrow in tissue mass due to \downarrow in size (\uparrow cytoskeleton degradation via ubiquitin-proteasome pathway and autophagy [programmed digestion of damaged/misfolded intracellular proteins]; \downarrow protein synthesis) and/or number of cells (apoptosis). Causes include disuse, denervation, loss of blood supply, loss of hormonal stimulation, poor nutrition.
Metaplasia	Reprogramming of stem cells \rightarrow replacement of one cell type by another that can adapt to a new stressor. Usually due to exposure to an irritant, such as gastric acid (\rightarrow esophageal epithelium replaced by intestinal epithelium, called Barrett esophagus) or tobacco smoke (\rightarrow respiratory ciliated columnar epithelium replaced by stratified squamous epithelium). May progress to dysplasia \rightarrow malignant transformation with persistent insult (eg, Barrett esophagus \rightarrow esophageal adenocarcinoma). Metaplasia of connective tissue can also occur (eg, myositis ossificans, the formation of bone within muscle after trauma).
Dysplasia	Disordered, precancerous epithelial cell growth; not considered a true adaptive response. Characterized by loss of uniformity of cell size and shape (pleomorphism); loss of tissue orientation; nuclear changes (eg, \uparrow nuclear:cytoplasmic ratio and clumped chromatin). Mild and moderate dysplasias (ie, do not involve entire thickness of epithelium) may regress with alleviation of inciting cause. Severe dysplasia often becomes irreversible and progresses to carcinoma in situ. Usually preceded by persistent metaplasia or pathologic hyperplasia.

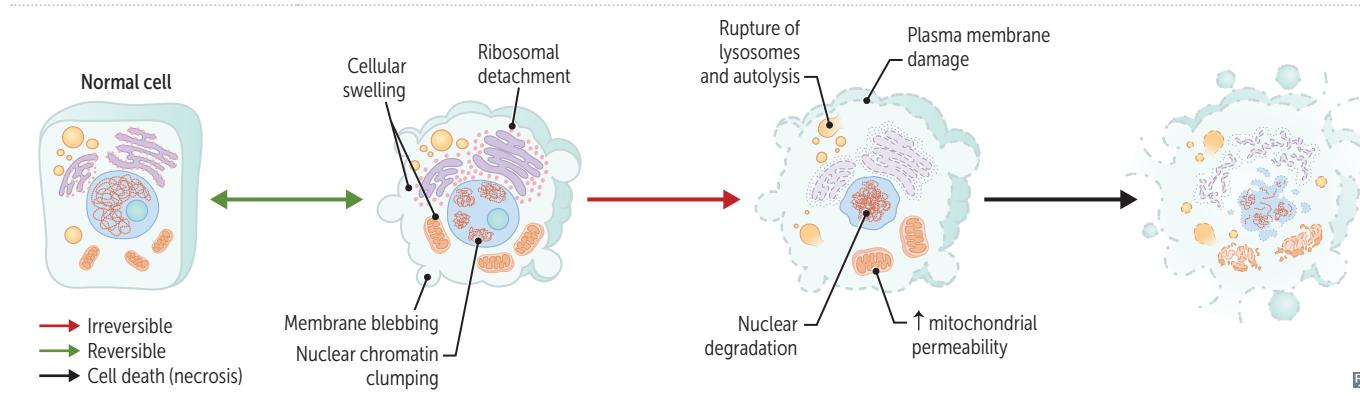


Cell injury**Reversible cell injury**

- ↓ ATP → ↓ activity of Ca^{2+} and Na^+/K^+ -ATPase pumps → cellular swelling (cytosol, mitochondria, endoplasmic reticulum/Golgi), which is the earliest morphologic manifestation
- Ribosomal/polysomal detachment → ↓ protein synthesis
- Plasma membrane changes (eg, blebbing)
- Nuclear changes (eg, chromatin clumping)
- Rapid loss of function (eg, myocardial cells are noncontractile after 1–2 minutes of ischemia)
- Myelin figures (aggregation of peroxidized lipids)

Irreversible cell injury

- Breakdown of plasma membrane → cytosolic enzymes (eg, troponin) leak outside of cell, influx of Ca^{2+} → activation of degradative enzymes
- Mitochondrial damage/dysfunction → loss of electron transport chain → ↓ ATP
- Rupture of lysosomes → autolysis
- Nuclear degradation: pyknosis (nuclear condensation) → karyorrhexis (nuclear fragmentation caused by endonuclease-mediated cleavage) → karyolysis (nuclear dissolution)
- Amorphous densities/inclusions in mitochondria



Apoptosis

ATP-dependent programmed cell death.

Intrinsic, extrinsic, and perforin/granzyme B pathways → activate caspases (cytosolic proteases)
→ cellular breakdown including cell shrinkage, chromatin condensation, membrane blebbing, and formation of apoptotic bodies, which are then phagocytosed.

Characterized by deeply eosinophilic cytoplasm and basophilic nucleus, pyknosis, and karyorrhexis. Cell membrane typically remains intact without significant inflammation (unlike necrosis). DNA laddering (fragments in multiples of 180 bp) is a sensitive indicator of apoptosis.

Intrinsic (mitochondrial) pathway

Involved in tissue remodeling in embryogenesis. Occurs when a regulating factor is withdrawn from a proliferating cell population (eg, ↓ IL-2 after a completed immunologic reaction → apoptosis of proliferating effector cells). Also occurs after exposure to injurious stimuli (eg, radiation, toxins, hypoxia).

Regulated by Bcl-2 family of proteins. **Bax** and **Bak** are proapoptotic (**Bad** for survival), while **Bcl-2** and **Bcl-xL** are antiapoptotic (**Be clever, live**).

BAX and **BAK** form pores in the mitochondrial membrane → release of cytochrome C from inner mitochondrial membrane into the cytoplasm → activation of caspases.

Bcl-2 keeps the mitochondrial membrane impermeable, thereby preventing cytochrome C release. **Bcl-2** overexpression (eg, follicular lymphoma t[14;18]) → ↓ caspase activation → tumorigenesis.

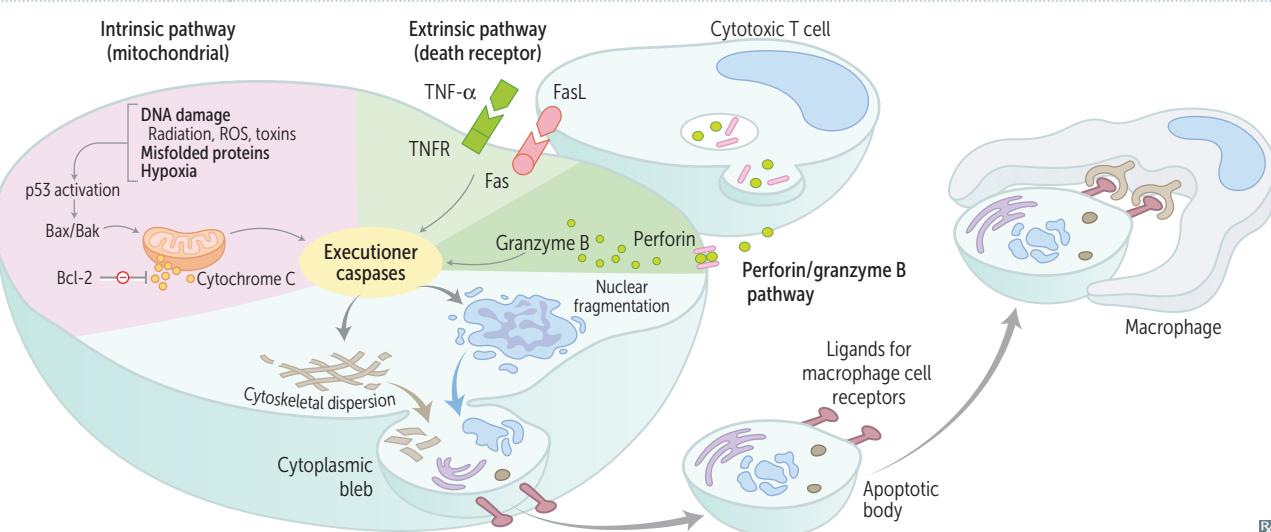
Extrinsic (death receptor) pathway

Ligand receptor interactions: FasL binding to Fas (CD95) or TNF- α binding to its receptor. Fas-FasL interaction is necessary in thymic medullary negative selection.

Autoimmune lymphoproliferative syndrome—caused by defective Fas-FasL interaction → failure of clonal deletion → ↑ numbers of self-reacting lymphocytes. Presents with lymphadenopathy, hepatosplenomegaly, autoimmune cytopenias.

Perforin/granzyme B pathway

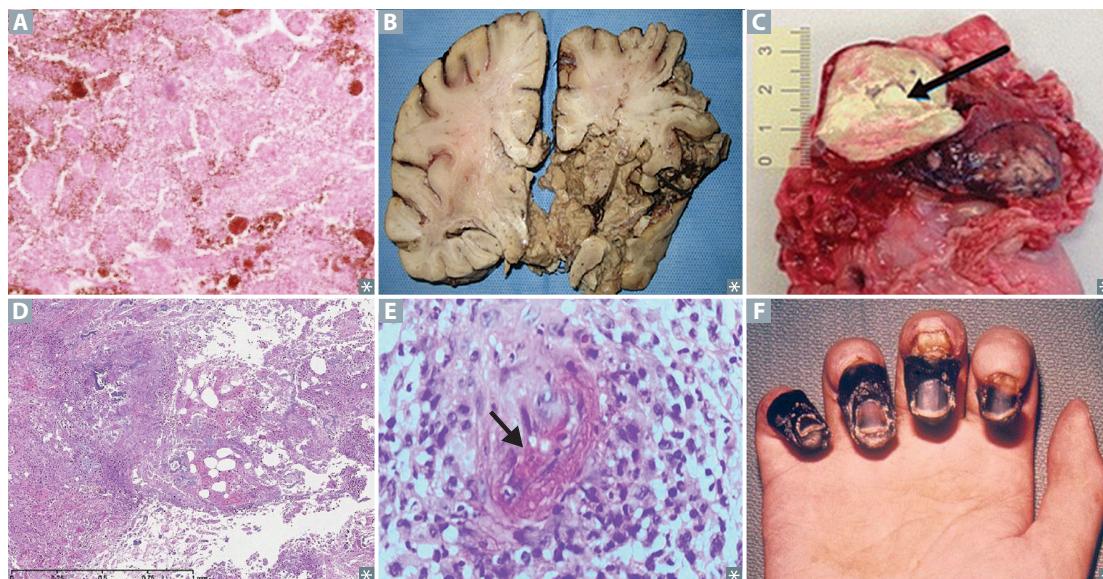
Release of granules containing perforin and granzyme B by immune cells (cytotoxic T-cell and natural killer cell) → perforin forms a pore for granzyme B to enter the target cell.

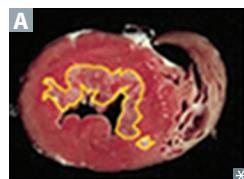


Necrosis

Exogenous injury → plasma membrane damage → intracellular components leak → cell undergoes enzymatic degradation and protein denaturation → local inflammatory reaction (unlike apoptosis).

TYPE	SEEN IN	DUE TO	HISTOLOGY
Coagulative	Ischemia/infarcts in most tissues (except brain)	Ischemia or infarction; injury denatures enzymes → proteolysis blocked	Preserved cellular architecture (cell outlines seen), but nuclei disappear; ↑ cytoplasmic binding of eosin stain (→ ↑ eosinophilia; red/pink color) A
Liquefactive	Bacterial abscesses, CNS infarcts	Neutrophils release lysosomal enzymes that digest the tissue	Early: cellular debris and macrophages Late: cystic spaces and cavitation (CNS) B Neutrophils and cell debris seen with bacterial infection
Caseous	TB, systemic fungi (eg, <i>Histoplasma capsulatum</i>), <i>Nocardia</i>	Macrophages wall off the infecting microorganism → granular debris	Fragmented cells and debris surrounded by lymphocytes and macrophages (granuloma) Cheeselike gross appearance C
Fat	Enzymatic: acute pancreatitis (saponification of peripancreatic fat) Nonenzymatic: traumatic (eg, injury to breast tissue)	Damaged pancreatic cells release lipase, which breaks down triglycerides; liberated fatty acids bind calcium → saponification (chalky-white appearance)	Outlines of dead fat cells without peripheral nuclei; saponification of fat (combined with Ca^{2+}) appears dark blue on H&E stain D
Fibrinoid	Immune vascular reactions (eg, polyarteritis nodosa) Nonimmune vascular reactions (eg, hypertensive emergency, preeclampsia)	Immune complex deposition (type III hypersensitivity reaction) and/or plasma protein (eg, fibrin) leakage from damaged vessel	Vessel walls contain eosinophilic layer of proteinaceous material E
Gangrenous	Distal extremity and GI tract, after chronic ischemia	Dry: ischemia F Wet: superinfection	Coagulative Liquefactive superimposed on coagulative



Ischemia

Inadequate blood supply to meet demand. Mechanisms include ↓ arterial perfusion (eg, atherosclerosis), ↓ venous drainage (eg, testicular torsion, Budd-Chiari syndrome), shock. Regions most vulnerable to hypoxia/ischemia and subsequent infarction:

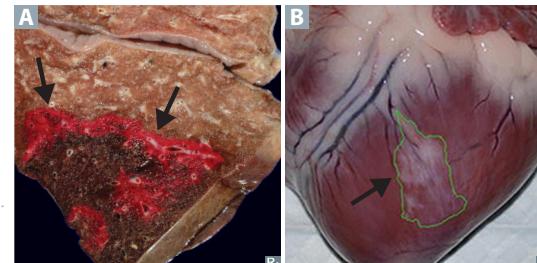
ORGAN	SUSCEPTIBLE REGION
Brain	ACA/MCA/PCA boundary areas ^{a,b}
Heart	Subendocardium of LV (yellow lines in A outline a subendocardial infarction)
Kidney	Straight segment of proximal tubule (medulla) Thick ascending limb (medulla)
Liver	Area around central vein (zone III)
Colon	Splenic flexure (Griffith point), ^a rectosigmoid junction (Sudeck point) ^a

^aWatershed areas (border zones) receive blood supply from most distal branches of 2 arteries with limited collateral vascularity. These areas are susceptible to ischemia from hypoperfusion.

^bNeurons most vulnerable to hypoxic-ischemic insults include Purkinje cells of the cerebellum and pyramidal cells of the hippocampus and neocortex (layers 3, 5, 6).

Types of infarcts**Red infarct**

Occurs in venous occlusion and tissues with multiple blood supplies (eg, liver, lung **A**, intestine, testes), and with reperfusion (eg, after angioplasty). Reperfusion injury is due to damage by free radicals.

**Pale infarct**

Occurs in solid organs with a single (end-arterial) blood supply (eg, heart **B**, kidney).

Free radical injury

Free radicals damage cells via membrane lipid peroxidation, protein modification, DNA breakage. Initiated via radiation exposure (eg, cancer therapy), metabolism of drugs (phase I), redox reactions, nitric oxide (eg, inflammation), transition metals (eg, iron, copper; form free radicals via Fenton reaction), WBC (eg, neutrophils, macrophages) oxidative burst.

Free radicals can be eliminated by scavenging enzymes (eg, catalase, superoxide dismutase, glutathione peroxidase), spontaneous decay, antioxidants (eg, vitamins A, C, E), and certain metal carrier proteins (eg, transferrin, ceruloplasmin).

Examples:

- Oxygen toxicity: retinopathy of prematurity (abnormal vascularization), bronchopulmonary dysplasia, reperfusion injury after thrombolytic therapy
- Drug/chemical toxicity: acetaminophen overdose (hepatotoxicity), carbon tetrachloride (converted by cytochrome P-450 into CCl_3 free radical → fatty liver [cell injury → ↓ apolipoprotein synthesis → fatty change], centrilobular necrosis)
- Metal storage diseases: hemochromatosis (iron) and Wilson disease (copper)

Ionizing radiation toxicity

Ionizing radiation causes DNA (eg, double strand breaks) and cellular damage both directly and indirectly through the production of free radicals. Complications usually arise when patient is exposed to significant doses (eg, radiotherapy, nuclear reactor accidents):

- Localized inflammation and fibrosis
- Neoplasia (eg, leukemia, thyroid cancer)

Acute radiation syndrome—develops after sudden whole-body exposure to high doses of ionizing radiation → nausea, vomiting, diarrhea, hair loss, erythema, cytopenias, headache, altered mental status.

Stem cells of rapidly regenerating tissues (eg, skin, bone marrow, GI tract, gonads) are the most susceptible to radiation injury.

Radiotherapy damages cancer cells more than healthy cells because cancer cells have dysfunctional DNA repair mechanisms in addition to high replicative rates.

Types of calcification

Calcium deposits appear deeply basophilic (arrow in A) on H&E stain.

Dystrophic calcification

In abnormal (diseased) tissues

Tends to be localized (eg, calcific aortic stenosis)

TB (lung and pericardium) and other granulomatous infections, liquefactive necrosis of chronic abscesses, fat necrosis, infarcts, thrombi, schistosomiasis, congenital CMV, toxoplasmosis, rubella, psammoma bodies, CREST syndrome, atherosclerotic plaques can become calcified

**Etiology**

2° to injury or necrosis

Metastatic calcification

In normal tissues

Widespread (ie, diffuse, metastatic)

Predominantly in interstitial tissues of kidney, lung, and gastric mucosa (these tissues lose acid quickly; ↑ pH favors Ca²⁺ deposition)

Nephrocalcinosis of collecting ducts may lead to nephrogenic diabetes insipidus and renal failure

2° to hyperphosphatemia (eg, chronic kidney disease) or hypercalcemia (eg, 1° hyperparathyroidism, sarcoidosis, hypervitaminosis D)

Psammoma bodies

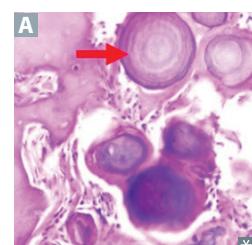
Concentrically laminated calcified spherules A.

PSOMMOMA Bodies.

Usually seen in certain types of tumors:

- Papillary carcinoma of thyroid gland and kidney
- Somatostatinoma
- Meningioma
- Mesothelioma
- Ovarian serous papillary cystadenocarcinoma
- Milk (prolactinoma)

Histology: Basophilic staining of Ca²⁺ deposits within tissue.

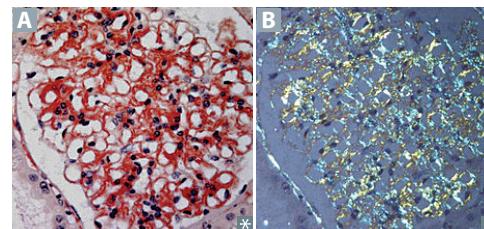


Amyloidosis

Extracellular deposition of protein in abnormal fibrillar form (β -pleated sheet configuration) → cell injury and apoptosis. Manifestations vary depending on involved organ and include:

- Renal—nephrotic syndrome.
- Cardiac—restrictive cardiomyopathy.
- GI—hepatosplenomegaly.
- Neurologic—peripheral neuropathy.
- Musculoskeletal—muscle enlargement (eg, macroglossia), carpal tunnel syndrome.
- Skin—waxy thickening, easy bruising.

Amyloid deposits are visualized by Congo red stain (red/orange on nonpolarized light **A**, apple-green birefringence on polarized light **B**), and H&E stain (amorphous pink).



COMMON TYPES	FIBRIL PROTEIN	NOTES
Systemic		
Primary amyloidosis	AL (from Ig Light chains)	Seen in plasma cell dyscrasias (eg, multiple myeloma)
Secondary amyloidosis	AA (serum Amyloid A)	Seen in chronic inflammatory conditions, (eg, rheumatoid arthritis, IBD, familial Mediterranean fever, protracted infection)
Transthyretin amyloidosis	Transthyretin	Sporadic (wild-type TTR)—slowly progressive, associated with aging; mainly affects the heart Hereditary (mutated TTR)—familial amyloid polyneuropathy and/or cardiomyopathy
Dialysis-related amyloidosis	β_2 -microglobulin	Seen in patients with ESRD on long-term dialysis
Localized		
Alzheimer disease	β -amyloid protein	Cleaved from amyloid precursor protein
Isolated atrial amyloidosis	ANP	Common, associated with aging; ↑ risk for atrial fibrillation
Type 2 diabetes mellitus	Islet amyloid polypeptide	Caused by deposition of amylin in pancreatic islets
Medullary thyroid cancer	Calcitonin	Secreted from tumor cells

► PATHOLOGY—INFLAMMATION

Inflammation

Response to eliminate initial cause of cell injury, to remove necrotic cells resulting from the original insult, and to initiate tissue repair. Divided into acute and chronic. The inflammatory response itself can be harmful to the host if the reaction is excessive (eg, septic shock), prolonged (eg, persistent infections such as TB), or inappropriate (eg, autoimmune diseases such as SLE).

SIGN	MECHANISM
Cardinal signs	
Rubor and calor	Redness and warmth. Vasodilation (relaxation of arteriolar smooth muscle) → ↑ blood flow. Mediated by histamine, prostaglandins, bradykinin, NO.
Tumor	Swelling. Endothelial contraction/disruption (eg, from tissue damage) → ↑ vascular permeability → leakage of protein-rich fluid from postcapillary venules into interstitial space (exudate) → ↑ interstitial oncotic pressure. Endothelial cell contraction is mediated by leukotrienes (C ₄ , D ₄ , E ₄), histamine, serotonin, bradykinin.
Dolor	Pain. Sensitization of sensory nerve endings. Mediated by bradykinin, PGE ₂ , histamine.
Functio laesa	Loss of function. Inflammation impairs function (eg, inability to make fist due to hand cellulitis).
Systemic manifestations (acute-phase reaction)	
Fever	Pyrogens (eg, LPS) induce macrophages to release IL-1 and TNF → ↑ COX activity in perivascular cells of anterior hypothalamus → ↑ PG E ₂ → ↑ temperature set point.
Leukocytosis	↑ WBC count; type of predominant cell depends on inciting agent or injury (eg, bacteria → ↑ neutrophils).
↑ plasma acute-phase reactants	Serum concentrations significantly change in response to acute and chronic inflammation. Produced by liver. Notably induced by IL-6.

Acute phase reactants

POSITIVE (UPREGULATED)

C-reactive protein	Opsonin; fixes complement and facilitates phagocytosis. Measured clinically as a nonspecific sign of ongoing inflammation.
Ferritin	Binds and sequesters iron to inhibit microbial iron scavenging.
Fibrinogen	Coagulation factor; promotes endothelial repair; correlates with ESR.
Haptoglobin	Binds extracellular hemoglobin, protects against oxidative stress.
Hepcidin	↓ iron absorption (by degrading ferroportin) and ↓ iron release (from macrophages) → anemia of chronic disease.
Procalcitonin	Increases in bacterial infections.
Serum amyloid A	Prolonged elevation can lead to secondary amyloidosis.

NEGATIVE (DOWNREGULATED)

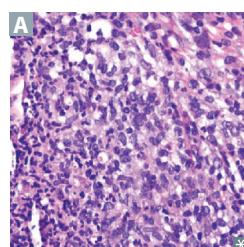
Albumin	Reduction conserves amino acids for positive reactants.
Transferrin	Internalized by macrophages to sequester iron.
Transthyretin	Also called prealbumin. Reduction conserves amino acids for positive reactants.

Erythrocyte sedimentation rate

RBCs normally remain separated via \ominus charges. Products of inflammation (eg, fibrinogen) coat RBCs \rightarrow $\downarrow \ominus$ charge \rightarrow \uparrow RBC aggregation. Denser RBC aggregates fall at a faster rate within a pipette tube \rightarrow \uparrow ESR. Often co-tested with CRP (more specific marker of inflammation).

\uparrow ESR	\downarrow ESR ^a
Most anemias	Sickle cell anemia (altered shape)
Infections	Polycythemia (\uparrow RBCs “dilute” aggregation factors)
Inflammation (eg, giant cell [temporal] arteritis, polymyalgia rheumatica)	HF
Cancer (eg, metastases, multiple myeloma)	Microcytosis
Renal disease (end-stage or nephrotic syndrome)	Hypofibrinogenemia
Pregnancy	

^aLower than expected.

Acute inflammation

Transient and early response to injury or infection. Characterized by neutrophils in tissue **A**, often with associated edema. Rapid onset (seconds to minutes) and short duration (minutes to days). Represents a reaction of the innate immune system (ie, less specific response than chronic inflammation).

STIMULI

Infections, trauma, necrosis, foreign bodies.

MEDIATORS

Toll-like receptors, arachidonic acid metabolites, neutrophils, eosinophils, antibodies (pre-existing), mast cells, basophils, complement, Hageman factor (factor XII).

Inflammasome—Cytoplasmic protein complex that recognizes products of dead cells, microbial products, and crystals (eg, uric acid crystals) \rightarrow activation of IL-1 and inflammatory response.

COMPONENTS

- Vascular: vasodilation (\rightarrow \uparrow blood flow and stasis) and \uparrow endothelial permeability (contraction of endothelial cells opens interendothelial junctions)
- Cellular: extravasation of leukocytes (mainly neutrophils) from postcapillary venules \rightarrow accumulation of leukocytes in focus of injury \rightarrow leukocyte activation

To bring cells and proteins to site of injury or infection.

OUTCOMES

- Resolution and healing (IL-10, TGF- β)
- Persistent acute inflammation (IL-8)
- Abscess (acute inflammation walled off by fibrosis)
- Chronic inflammation (antigen presentation by macrophages and other APCs \rightarrow activation of CD4+ Th cells)
- Scarring

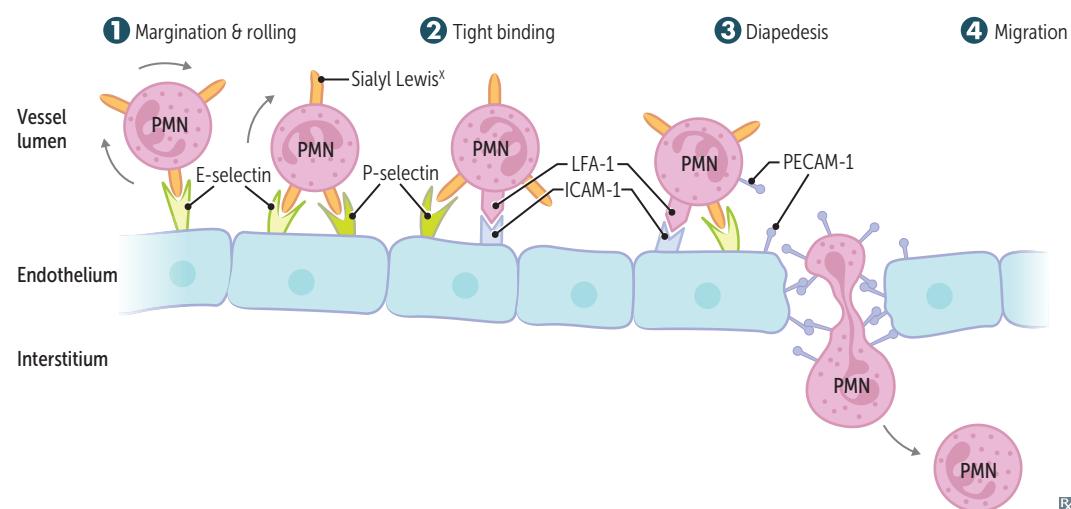
Leukocyte extravasation has 4 steps: margination and rolling, adhesion, transmigration, and migration (chemoattraction).

Macrophages predominate in the late stages of acute inflammation (peak 2–3 days after onset) and influence outcome by secreting cytokines.

Leukocyte extravasation

Extravasation predominantly occurs at postcapillary venules.

STEP	VASCULATURE/STROMA	LEUKOCYTE
① Margination and rolling— defective in leukocyte adhesion deficiency type 2 (\downarrow Sialyl Lewis ^X)	E-selectin (upregulated by TNF and IL-1) P-selectin (translocated to endothelial surface via exocytosis from Weibel-Palade bodies) GlyCAM-1, CD34	Sialyl Lewis ^X Sialyl Lewis ^X L-selectin
② Tight binding (adhesion)— defective in leukocyte adhesion deficiency type 1 (\downarrow CD18 integrin subunit)	ICAM-1 (CD54) VCAM-1 (CD106)	CD11/18 integrins (LFA-1, Mac-1) VLA-4 integrin
③ Diapedesis (transmigration)— WBC travels between endothelial cells and exits blood vessel	PECAM-1 (CD31)	PECAM-1 (CD31)
④ Migration—WBC travels through interstitium to site of injury or infection guided by chemotactic signals	Chemotactic factors: C5a, IL-8, LTB ₄ , 5-HETE, kallikrein, platelet-activating factor, N-formylmethionyl peptides	Various



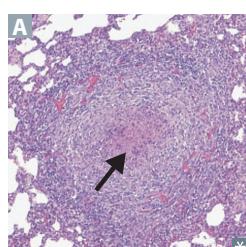
Chronic inflammation	Prolonged inflammation characterized by mononuclear infiltration (macrophages, lymphocytes, plasma cells), which leads to simultaneous tissue destruction and repair (including angiogenesis and fibrosis). May be preceded by acute inflammation.
STIMULI	Persistent infections (eg, TB, <i>T. pallidum</i> , certain fungi and viruses) → type IV hypersensitivity, autoimmune diseases, prolonged exposure to toxic agents (eg, silica) and foreign material.
MEDIATORS	Macrophages are the dominant cells. Interaction of macrophages and T cells → chronic inflammation. <ul style="list-style-type: none"> ▪ Th1 cells secrete IFN-γ → macrophage classical activation (proinflammatory) ▪ Th2 cells secrete IL-4 and IL-13 → macrophage alternative activation (repair and anti-inflammatory)
OUTCOMES	Scarring, amyloidosis, and neoplastic transformation (eg, chronic HCV infection → chronic inflammation → hepatocellular carcinoma; <i>Helicobacter pylori</i> infection → chronic gastritis → gastric adenocarcinoma).

Wound healing

TISSUE MEDIATORS	MEDIATOR	ROLE
FGF		Stimulates angiogenesis
TGF-β		Angiogenesis, fibrosis
VEGF		Stimulates angiogenesis
PDGF		Secreted by activated platelets and macrophages Induces vascular remodeling and smooth muscle cell migration Stimulates fibroblast growth for collagen synthesis
Metalloproteinases		Tissue remodeling
EGF		Stimulates cell growth via tyrosine kinases (eg, EGFR/ErbB1)
PHASE OF WOUND HEALING	EFFECTOR CELLS	CHARACTERISTICS
Inflammatory (up to 3 days after wound)	Platelets, neutrophils, macrophages	Clot formation, ↑ vessel permeability and neutrophil migration into tissue; macrophages clear debris 2 days later
Proliferative (day 3–weeks after wound)	Fibroblasts, myofibroblasts, endothelial cells, keratinocytes, macrophages	Deposition of granulation tissue and type III collagen, angiogenesis, epithelial cell proliferation, dissolution of clot, and wound contraction (mediated by myofibroblasts) Delayed second phase of wound healing in vitamin C and copper deficiency
Remodeling (1 week–6+ months after wound)	Fibroblasts	Type III collagen replaced by type I collagen, ↑ tensile strength of tissue Collagenases (require zinc to function) break down type III collagen Zinc deficiency → delayed wound healing

Granulomatous inflammation

A pattern of chronic inflammation. Can be induced by persistent T-cell response to certain infections (eg, TB), immune-mediated diseases, and foreign bodies. Granulomas “wall off” a resistant stimulus without completely eradicating or degrading it → persistent inflammation → fibrosis, organ damage.

HISTOLOGY

Focus of epithelioid cells (activated macrophages with abundant pink cytoplasm) surrounded by lymphocytes and multinucleated giant cells (formed by fusion of several activated macrophages).

Two types:

Caseating: associated with central necrosis **A**. Seen with infectious etiologies (eg, TB, fungal).
Noncaseating: no central necrosis. Seen with noninfectious etiologies (eg, sarcoidosis, Crohn disease).

MECHANISM

① APCs present antigens to CD4+ Th cells and secrete IL-12 → CD4+ Th cells differentiate into Th1 cells

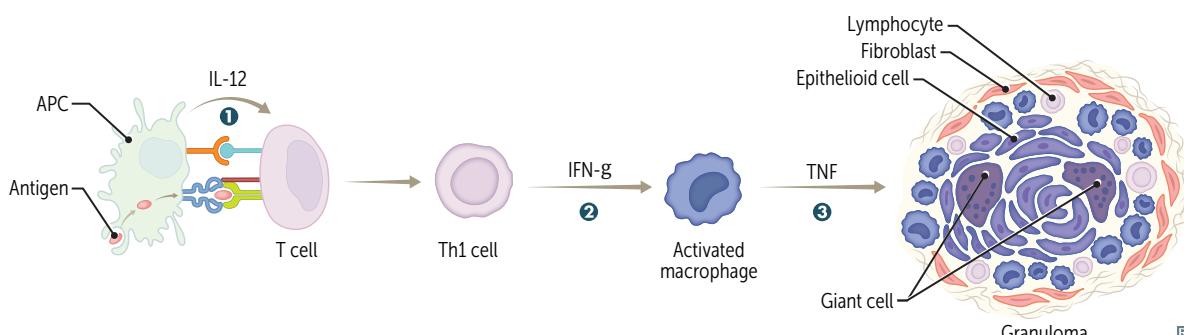
② Th1 secretes IFN- γ → macrophage activation

③ Macrophages ↑ cytokine secretion (eg, TNF) → formation of epithelioid macrophages and giant cells

Anti-TNF therapy can cause sequestering granulomas to break down → disseminated disease.

Always test for latent TB before starting anti-TNF therapy.

Associated with hypercalcemia due to ↑ 1 α -hydroxylase activity in activated macrophages, resulting in ↑ vitamin D activity.

**ETIOLOGIES****Infectious**

Bacterial: *Mycobacteria* (tuberculosis, leprosy), *Bartonella henselae* (cat scratch disease; stellate necrotizing granulomas), *Listeria monocytogenes* (granulomatosis infantiseptica), *Treponema pallidum* (3° syphilis)
Fungal: endemic mycoses (eg, histoplasmosis)
Parasitic: schistosomiasis
Catalase + organisms in chronic granulomatous disease

Noninfectious

Immune-mediated: sarcoidosis, Crohn disease, 1° biliary cholangitis, subacute (de Quervain/granulomatous) thyroiditis
Vasculitis: granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, giant cell (temporal) arteritis, Takayasu arteritis
Foreign bodies: berylliosis, talcosis, hypersensitivity pneumonitis

Scar formation

Occurs when repair cannot be accomplished by cell regeneration alone. Nonregenerated cells (2° to severe acute or chronic injury) are replaced by connective tissue. 70–80% of tensile strength regained at 3 months; little tensile strength regained thereafter. Excess TGF- β is associated with aberrant scarring, such as hypertrophic and keloid scars.

Hypertrophic scar A

COLLAGEN SYNTHESIS	↑ (type III collagen)
COLLAGEN ORGANIZATION	Parallel
EXTENT OF SCAR	Confined to borders of original wound
RECURRENCE	Infrequent
PREDISPOSITION	None

Keloid scar B

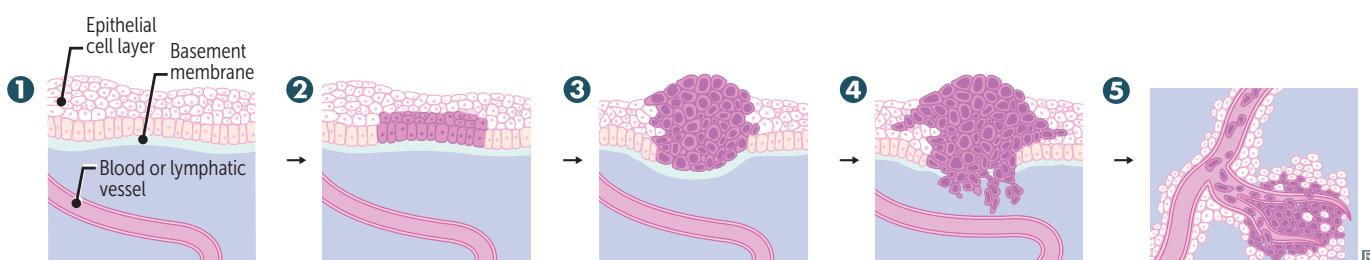
COLLAGEN SYNTHESIS	↑↑↑ (types I and III collagen)
COLLAGEN ORGANIZATION	Disorganized
EXTENT OF SCAR	Extends beyond borders of original wound with “clawlike” projections typically on earlobes, face, upper extremities
RECURRENCE	Frequent
PREDISPOSITION	↑ incidence in people with darker skin



▶ PATHOLOGY—NEOPLASIA

Neoplasia and neoplastic progression

Uncontrolled, often monoclonal proliferation of cells. Can be benign or malignant. Any neoplastic growth has two components: parenchyma (neoplastic cells) and supporting stroma (non-neoplastic; eg, blood vessels, connective tissue).

**Normal cells**

- ❶ Normal cells with basal → apical polarity. See cervical example, which shows normal cells and spectrum of dysplasia, as discussed below.

Dysplasia

- ❷ Loss of uniformity in cell size and shape (pleomorphism); loss of tissue orientation; nuclear changes (eg, ↑ nuclear:cytoplasmic ratio); often reversible.

Carcinoma in situ/ preinvasive

- ❸ Irreversible severe dysplasia that involves the entire thickness of epithelium but does not penetrate the intact basement membrane.

Invasive carcinoma

- ❹ Cells have invaded basement membrane using collagenases and hydrolases (metalloproteinases). Cell-cell contacts lost by inactivation of E-cadherin.

Metastasis

- ❺ Spread to distant organ(s) via lymphatics or blood.

Tumor nomenclature

Carcinoma implies epithelial origin, whereas **sarcoma** denotes mesenchymal origin. Both terms generally imply malignancy.

Benign tumors are usually well-differentiated and well-demarcated, with low mitotic activity, no metastases, and no necrosis.

Malignant tumors (cancers) may show poor differentiation, erratic growth, local invasion, metastasis, and ↓ apoptosis.

Terms for non-neoplastic malformations include hamartoma (disorganized overgrowth of tissues in their native location, eg, Peutz-Jeghers polyps) and choristoma (normal tissue in a foreign location, eg, gastric tissue located in distal ileum in Meckel diverticulum).

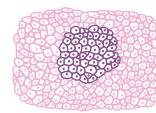
CELL TYPE	BENIGN	MALIGNANT
Epithelium	Adenoma, papilloma	Adenocarcinoma, papillary carcinoma
Mesenchyme		
Blood cells		Leukemia, lymphoma
Blood vessels	Hemangioma	Angiosarcoma
Smooth muscle	Leiomyoma	Leiomyosarcoma
Striated muscle	Rhabdomyoma	Rhabdomyosarcoma
Connective tissue	Fibroma	Fibrosarcoma
Bone	Osteoma	Osteosarcoma
Fat	Lipoma	Liposarcoma
Melanocyte	Nevus/mole	Melanoma

Tumor grade vs stage**Grade**

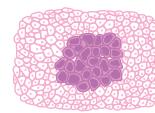
Degree of cell differentiation (tissue of origin resemblance) and mitotic activity on histology.

Ranges from low-grade (well differentiated) to high-grade (poorly differentiated or undifferentiated [anaplastic]).

Higher grade often correlates with higher aggressiveness.



Low grade



High grade

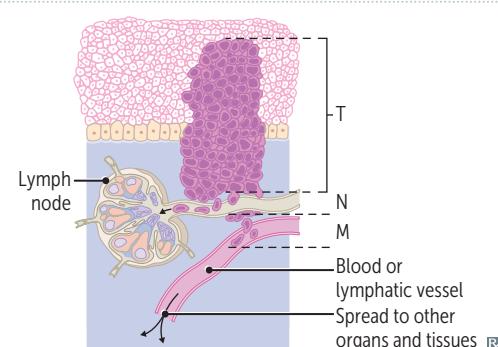
Stage

Degree of invasion and spread from initial site. Depth of invasion correlates to risk of metastasis. Based on clinical (c) or pathologic (p) findings.

TNM staging system (importance: M > N > T):

- Primary tumor size/invasion.
- Regional lymph node metastasis.
- Distant metastasis.

Stage generally has more prognostic value than grade (eg, a high-stage yet low-grade tumor is usually worse than a low-stage yet high-grade tumor). **Stage** (spread) determines **survival**.



Hallmarks of cancer Cancer is caused by (mostly acquired) DNA mutations that affect fundamental cellular processes (eg, growth, DNA repair, survival).

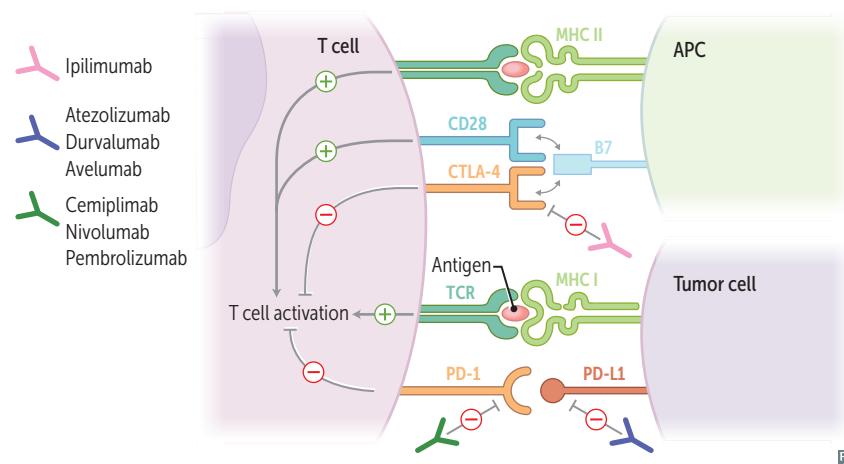
HALLMARK	MECHANISM
Growth signal self-sufficiency	Mutations in genes encoding: <ul style="list-style-type: none"> ▪ Proto-oncogenes → ↑ growth factors → autocrine loop (eg, ↑ PDGF in brain tumors) ▪ Growth factor receptors → constitutive signaling (eg, HER2 in breast cancer) ▪ Signaling molecules (eg, RAS) ▪ Transcription factors (eg, MYC) ▪ Cell cycle regulators (eg, cyclins, CDKs)
Anti-growth signal insensitivity	<ul style="list-style-type: none"> ▪ Mutations in tumor suppressor genes (eg, <i>Rb</i>) ▪ Loss of E-cadherin function → loss of contact inhibition (eg, <i>NF2</i> mutations)
Evasion of apoptosis	Mutations in genes that regulate apoptosis (eg, <i>TP53</i> , <i>BCL2</i> → follicular B cell lymphoma).
Limitless replicative potential	Reactivation of telomerase → maintenance and lengthening of telomeres → prevention of chromosome shortening and cell aging.
Sustained angiogenesis	↑ pro-angiogenic factors (eg, VEGF) or ↓ inhibitory factors. Factors may be produced by tumor or stromal cells. Vessels can sprout from existing capillaries (neoangiogenesis) or endothelial cells are recruited from bone marrow (vasculogenesis). Vessels may be leaky and/or dilated.
Warburg effect	Shift of glucose metabolism away from mitochondrial oxidative phosphorylation toward glycolysis, even in the presence of oxygen. Aerobic glycolysis provides rapidly dividing cancer cells with the carbon needed for synthesis of cellular structures, leading to ↑ lactic acid.
Immune evasion in cancer	Normally, immune cells can recognize and attack tumor cells. For successful tumorigenesis, tumor cells must evade the immune system. Multiple escape mechanisms exist: <ul style="list-style-type: none"> ▪ ↓ MHC class I expression by tumor cells → cytotoxic T cells are unable to recognize tumor cells. ▪ Tumor cells secrete immunosuppressive factors (eg, TGF-β) and recruit regulatory T cells to down regulate immune response. ▪ Tumor cells up regulate immune checkpoint molecules, which inhibit immune response.
Tissue invasion	Loss of E-cadherin function → loosening of intercellular junctions → metalloproteinases degrade basement membrane and ECM → cells attach to ECM proteins (eg, laminin, fibronectin) → cells migrate through degraded ECM (“locomotion”) → vascular dissemination.
Metastasis	Tumor cells or emboli spread via lymphatics or blood → adhesion to endothelium → extravasation and homing. Site of metastasis can be predicted by site of 1° tumor, as the target organ is often the first-encountered capillary bed. Some cancers show organ tropism (eg, lung cancers commonly metastasize to adrenals).

Immune checkpoint interactions

Signals that modulate T-cell activation and function → ↓ immune response against tumor cells.

Targeted by several cancer immunotherapies. Examples:

- Interaction between PD-1 (on T cells) and PD-L1/2 (on tumor cells or immune cells in tumor microenvironment) → T-cell dysfunction (exhaustion). Inhibited by antibodies against PD-1 (eg, cemiplimab, nivolumab, pembrolizumab) or PD-L1 (eg, atezolizumab, durvalumab, avelumab).
- CTLA-4 on T cells outcompetes CD28 for B7 on APCs → loss of T-cell costimulatory signal. Inhibited by antibodies against CTLA-4 (eg, ipilimumab).



Cancer epidemiology

Skin cancer (basal > squamous >> melanoma) is the most common cancer (not included below).

	MALES	FEMALES	CHILDREN (AGE 0–14)	NOTES
Cancer incidence	1. Prostate 2. Lung 3. Colon/rectum	1. Breast 2. Lung 3. Colon/rectum	1. Leukemia 2. CNS 3. Neuroblastoma	Lung cancer incidence has ↓ in males, but has not changed significantly in females.
Cancer mortality	1. Lung 2. Prostate 3. Colon/rectum	1. Lung 2. Breast 3. Colon/rectum	1. Leukemia 2. CNS 3. Neuroblastoma	Cancer is the 2nd leading cause of death in the United States (heart disease is 1st).

Common metastases

Most Carcinomas spread via Lymphatics; most Sarcomas spread Hematogenously (**CLaSH**). However, four carcinomas route hematogenously: follicular thyroid carcinoma, choriocarcinoma, renal cell carcinoma, and hepatocellular carcinoma. Metastasis to bone, liver, lung, and brain is more common than 1° malignancy in these organs. Metastases often appear as multiple lesions (vs 1° tumors which generally appear as solitary lesions).

SITE OF METASTASIS	1° TUMOR	NOTES
Bone	Prostate, breast >> lung > kidney, colon	Predilection for axial skeleton A Bone metastasis can be: <ul style="list-style-type: none"> ▪ Blastic (eg, prostate, small cell lung cancer) ▪ Mixed (eg, breast) ▪ Lytic (eg, kidney, colon, non-small cell lung cancer)
		
Liver	Colon > breast >> pancreas, lung, prostate	Scattered throughout liver parenchyma B
		
Lung	Colon, breast >> kidney, prostate	Typically involve both lungs
Brain	Lung > breast >> melanoma > colon, prostate	Usually seen at gray/white matter junction

Oncogenes

Gain of function mutation converts proto-oncogene (normal gene) to oncogene → ↑ cancer risk.
Requires damage to only **one** allele of a proto-oncogene.

GENE	GENE PRODUCT	ASSOCIATED NEOPLASM
ALK	Receptor tyrosine kinase	Lung adenocarcinoma
EGFR (ERBB1)	Receptor tyrosine kinase	Lung adenocarcinoma
HER2 (ERBB2)	Receptor tyrosine kinase	Breast and gastric carcinomas
RET	REceptor Tyrosine kinase	MEN2A and 2B, medullary and papillary thyroid carcinoma, pheochromocytoma
BCR-ABL	Non-receptor tyrosine kinase	CML, ALL
JAK2	Non-receptor tyrosine kinase	Myeloproliferative neoplasms
BRAF	Serine/threonine kinase	Melanoma, non-Hodgkin lymphoma, colorectal carcinoma, papillary thyroid carcinoma, hairy cell leukemia
c-KIT	CytoKine receptor (CD117)	Gastrointestinal stromal tumor (GIST), mastocytosis
MYCC (c-myc)	Transcription factor	Burkitt lymphoma
MYCN (N-myc)	Transcription factor	Neuroblastoma
KRAS	RAS GTPase	Pancreatic, colorectal, lung, endometrial cancers
BCL-2	Antiapoptotic molecule (inhibits apoptosis)	Follicular and diffuse large B-Cell Lymphomas

Tumor suppressor genes

Loss of function → ↑ cancer risk; both (**two**) alleles of a tumor suppressor gene must be lost for expression of disease (the Knudson 2-hit hypothesis).

GENE	GENE PRODUCT	ASSOCIATED CONDITION
APC	Negative regulator of β-catenin/WNT pathway	Colorectal cancer (associated with FAP)
BRCA1/BRCA2	BRCA1/BRCA2 proteins	BReast, ovarian, prostate, pancreatic Cancers
CDKN2A	p16, blocks G ₁ → S phase	Many cancers (eg, melanoma, lung, pancreatic)
DCC	DCC—Deleted in Colorectal Cancer	Colorectal cancer
SMAD4 (DPC4)	DPC—Deleted in Pancreatic Cancer	Pancreatic cancer, colorectal cancer
MEN1	MENin	Multiple Endocrine Neoplasia type 1
NF1	Neurofibromin (Ras GTPase activating protein)	NeuroFibromatosis type 1
NF2	Merlin (schwannomin) protein	NeuroFibromatosis type 2
PTEN	Negative regulator of PI3k/AKT pathway	Prostate, breast, and ENdometrial cancers
RB1	Inhibits E2F; blocks G ₁ → S phase	Retinoblastoma, osteosarcoma (Bone cancer)
TP53	p53, activates p21, blocks G ₁ → S phase	Most cancers, Li-Fraumeni (SBLA) syndrome (multiple malignancies at early age; Sarcoma, Breast/Brain, Lung/Leukemia, Adrenal gland)
TSC1	Hamartin protein	Tuberous sclerosis complex
TSC2	Tuberin (“2berin”)	Tuberous sclerosis complex
VHL	Inhibits hypoxia-inducible factor 1α	von Hippel-Lindau disease
WT1	Urogenital development transcription factor	Wilms Tumor (nephroblastoma)

Carcinogens

TOXIN	EXPOSURE	ORGAN	IMPACT
Aflatoxins (<i>Aspergillus</i>)	Stored grains and nuts	Liver	Hepatocellular carcinoma
Alkylating agents	Oncologic chemotherapy	Blood	Leukemia/lymphoma
Aromatic amines (eg, benzidine, 2-naphthylamine)	Textile industry (dyes), tobacco smoke (2-naphthylamine)	Bladder	Transitional cell carcinoma
Arsenic	Herbicides (vineyard workers), metal smelting, wood preservation	Liver Lung Skin	Hepatic angiosarcoma Lung cancer Squamous cell carcinoma
Asbestos	Old roofing material, shipyard workers	Lung	Bronchogenic carcinoma > mesothelioma
Tobacco smoke		Bladder Cervix Esophagus Kidney Larynx Lung Oropharynx Pancreas	Transitional cell carcinoma Squamous cell carcinoma Squamous cell carcinoma/ adenocarcinoma Renal cell carcinoma Squamous cell carcinoma Squamous cell and small cell carcinoma Squamous cell carcinoma Pancreatic adenocarcinoma
Ethanol		Esophagus Liver Breast	Squamous cell carcinoma Hepatocellular carcinoma Breast cancer
Ionizing radiation		Blood Thyroid	Leukemia Papillary thyroid carcinoma
Nickel, chromium, beryllium, silica	Occupational exposure	Lung	Lung cancer
Nitrosamines	Smoked foods	Stomach	Gastric cancer (intestinal type)
Radon	Byproduct of uranium decay, accumulates in basements	Lung	Lung cancer (2nd leading cause after tobacco smoke)
Vinyl chloride	Used to make PVC pipes	Liver	Hepatic angiosarcoma

Oncogenic microbes

MICROBE	ASSOCIATED CANCER
EBV	Burkitt lymphoma, Hodgkin lymphoma, nasopharyngeal carcinoma, 1° CNS lymphoma (in immunocompromised patients)
HBV, HCV	Hepatocellular carcinoma
HHV-8	Kaposi ("Kaposi's") sarcoma
HPV (usually types 16, 18)	Cervical and penile/anal carcinoma, head and neck cancer
<i>H pylori</i>	Gastric adenocarcinoma and MALT lymphoma
HTLV-1	Adult T-cell Leukemia/Lymphoma
Liver fluke (<i>Clonorchis sinensis</i>)	Cholangiocarcinoma
<i>Schistosoma haematobium</i>	Squamous cell bladder cancer

Serum tumor markers

Tumor markers should not be used as the 1° tool for cancer diagnosis or screening. They may be used to monitor tumor recurrence and response to therapy, but definitive diagnosis is made via biopsy. Some can be associated with non-neoplastic conditions.

MARKER	IMPORTANT ASSOCIATIONS	NOTES
Alkaline phosphatase	Metastases to bone or liver, Paget disease of bone, seminoma (PLAP).	Exclude hepatic origin by checking LFTs and GGT levels.
α-fetoprotein	Hepatocellular carcinoma, endodermal sinus (yolk sac) tumor, mixed germ cell tumor, ataxia-telangiectasia, neural tube defects.	Normally made by fetus. Transiently elevated in pregnancy. High levels associated with neural tube and abdominal wall defects, low levels associated with Down syndrome.
hCG	Hydatidiform moles and Choriocarcinomas (Gestational trophoblastic disease), testicular cancer, mixed germ cell tumor.	Produced by syncytiotrophoblasts of the placenta.
CA 15-3/CA 27-29	Breast cancer.	
CA 19-9	Pancreatic adenocarcinoma.	
CA 125	Epithelial ovarian cancer.	
Calcitonin	Medullary thyroid carcinoma (alone and in MEN2A, MEN2B).	Calcitonin.
CEA	Colorectal and pancreatic cancers. Minor associations: gastric, breast, and medullary thyroid carcinomas.	Carcinoembryonic Antigen. Very nonspecific.
Chromogranin	Neuroendocrine tumors.	
LDH	Testicular germ cell tumors, ovarian dysgerminoma, other cancers.	Can be used as an indicator of tumor burden.
Neuron-specific enolase	Neuroendocrine tumors (eg, small cell lung cancer, carcinoid tumor, neuroblastoma).	
PSA	Prostate cancer.	Prostate-Specific Antigen. Also elevated in BPH and prostatitis. Questionable risk/benefit for screening. Marker for recurrence after treatment.

Liquid biopsy

Noninvasive diagnostic test in body fluid (eg, blood, urine) using circulating tumor DNA (ctDNA), RNA (ctRNA), or circulating tumor cells (CTCs) for cancer profiling (eg, EGFR in lung cancer), treatment monitoring, and post-treatment surveillance (eg, colorectal cancer). Aids in early metastatic detection and personalized therapy.

Important immunohistochemical stains

Determine primary site of origin for metastatic tumors and characterize tumors that are difficult to classify. Can have prognostic and predictive value.

STAIN	TARGET	TUMORS IDENTIFIED
Chromogranin and synaptophysin	Neuroendocrine cells	Small cell carcinoma of the lung, carcinoid tumor, neuroblastoma
Cytokeratin	Epithelial cells	Epithelial tumors (eg, squamous cell carcinoma)
Desmin	Muscle	Muscle tumors (eg, rhabdomyosarcoma)
GFAP	NeuroGlia (eg, astrocytes, Schwann cells, oligodendrocytes)	Astrocytoma, Glioblastoma
Neurofilament	Neurons	Neuronal tumors (eg, neuroblastoma)
PSA	Prostatic epithelium	Prostate cancer
PECAM-1/CD-31	Endothelial cells	Vascular tumors (eg, angiosarcoma)
S-100	Neural crest cells	Melanoma, schwannoma, Langerhans cell histiocytosis
TRAP	Tartrate-resistant acid phosphatase	Hairy cell leukemia
Vimentin	Mesenchymal tissue (eg, fibroblasts, endothelial cells, macrophages)	Mesenchymal tumors (eg, sarcoma), but also many other tumors (eg, endometrial carcinoma, renal cell carcinoma, meningioma)

P-glycoprotein

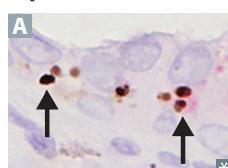
ATP-dependent efflux pump also called multidrug resistance protein 1 (MDR1). Expressed in some cancer cells to pump out toxins, including chemotherapeutic agents (one mechanism of ↓ responsiveness or resistance to chemotherapy over time).

Paraneoplastic syndromes

MANIFESTATION	DESCRIPTION/MECHANISM	MOST COMMONLY ASSOCIATED TUMOR(S)
Musculoskeletal and cutaneous		
Dermatomyositis	Progressive proximal muscle weakness, Gottron papules, heliotrope rash	Adenocarcinomas, especially ovarian
Acanthosis nigricans	Hyperpigmented velvety plaques in axilla and neck	Gastric adenocarcinoma and other visceral malignancies
Sign of Leser-Trélat	Sudden onset of multiple seborrheic keratoses	GI adenocarcinomas and other visceral malignancies
Hypertrophic osteoarthropathy	Abnormal proliferation of skin and bone at distal extremities → clubbing, arthralgia, joint effusions, periostosis of tubular bones	Adenocarcinoma of the lung
Endocrine		
Hypercalcemia	PTHrP ↑ 1,25-(OH) ₂ vitamin D ₃ (calcitriol)	SCa ²⁺ mous cell carcinomas of lung, head, and neck; renal, bladder, breast, and ovarian carcinomas Lymphoma
Cushing syndrome	↑ ACTH	Small cell lung cancer
Hyponatremia (SIADH)	↑ ADH	
Hematologic		
Polycythemia	↑ Erythropoietin Paraneoplastic rise to High hematocrit levels	Pheochromocytoma, renal cell carcinoma, HCC, hemangioblastoma, leiomyoma
Pure red cell aplasia	Anemia with low reticulocytes	
Good syndrome	Hypogammaglobulinemia	Thymoma
Trousseau syndrome	Migratory superficial thrombophlebitis	
Nonbacterial thrombotic endocarditis	Deposition of sterile platelet thrombi on heart valves	Adenocarcinomas, especially pancreatic
Neuromuscular		
Anti-NMDA receptor encephalitis	Psychiatric disturbance, memory deficits, seizures, dyskinesias, autonomic instability, language dysfunction	Ovarian teratoma
Opsoclonus-myoclonus ataxia syndrome	“Dancing eyes, dancing feet”	Neuroblastoma (children), small cell lung cancer (adults)
Paraneoplastic cerebellar degeneration	Antibodies against antigens in Purkinje cells	Small cell lung cancer (anti-Hu), gynecologic and breast cancers (anti-Yo), and Hodgkin lymphoma (anti-Tr)
Paraneoplastic encephalomyelitis	Antibodies against Hu antigens in neurons	
Lambert-Eaton myasthenic syndrome	Antibodies against presynaptic (P/Q-type) Ca ²⁺ channels at NMJ	Small cell lung cancer
Myasthenia gravis	Antibodies against postsynaptic ACh receptors at NMJ	Thymoma

► PATHOLOGY—AGING

Normal aging	Time-dependent progressive decline in organ function resulting in ↑ susceptibility to disease. Associated with genetic (eg, telomere shortening), epigenetic (eg, DNA methylation), and metabolic (eg, mitochondrial dysfunction) alterations.
Cardiovascular	↓ arterial compliance (↑ stiffness), ↑ aortic diameter, ↓ left ventricular cavity size and sigmoid-shaped interventricular septum (due to myocardial hypertrophy), ↑ left atrial cavity size, aortic and mitral valve calcification, ↓ maximum heart rate.
Gastrointestinal	↓ LES tone, ↓ gastric mucosal protection, ↓ colonic motility.
Hematopoietic	↓ bone marrow mass, ↑ bone marrow fat; less vigorous response to stressors (eg, blood loss).
Immune	Predominant effect on adaptive immunity: ↓ naïve B cells and T cells, preserved memory B cells and T cells. Immunosenescence impairs response to new antigens (eg, pathogens, vaccines).
Musculoskeletal	↓ skeletal muscle mass (sarcopenia), ↓ bone mass (osteopenia), joint cartilage thinning.
Nervous	↓ brain volume (neuronal loss), ↓ cerebral blood flow; function is preserved despite mild cognitive decline.
Special senses	Impaired accommodation (presbyopia), ↓ hearing (presbycusis), ↓ smell and taste.
Skin	Atrophy with flattening of dermal-epidermal junction; ↓ dermal collagen and ↓ elastin (wrinkles, senile purpura), ↓ sweat glands (heat stroke), ↓ sebaceous glands (xerosis cutis). <ul style="list-style-type: none"> ■ Intrinsic aging (chronological aging)—↓ biosynthetic capacity of dermal fibroblasts. ■ Extrinsic aging (photoaging)—degradation of dermal collagen and elastin from sun exposure (UVA); degradation products accumulate in dermis (solar elastosis).
Renal	↓ GFR (↓ nephrons), ↓ RBF, ↓ hormonal function. Voiding dysfunction (eg, urinary incontinence).
Reproductive	Males—testicular atrophy (↓ spermatogenesis), prostate enlargement, slower erection/ejaculation, longer refractory period. Less pronounced ↓ in libido as compared to females. Females—vulvovaginal atrophy; vaginal shortening, thinning, dryness, ↑ pH. Due to ↓ estrogen from exhaustion of ovarian follicles (menopause).
Respiratory	↑ lung compliance (↓ elastic recoil), ↓ chest wall compliance (↑ stiffness), ↓ respiratory muscle strength; ↓ FEV ₁ , ↓ FVC, ↑ RV (TLC is unchanged); ↑ A-a gradient, ↑ V/Q mismatch. Ventilatory response to hypoxia/hypercapnia is blunted. Less vigorous cough, slower mucociliary clearance.

Lipofuscin

A yellow-brown, “wear and tear” pigment **A** associated with normal aging.
Composed of polymers of lipids and phospholipids complexed with protein. May be derived through lipid peroxidation of polyunsaturated lipids of subcellular membranes.
Autopsy of older adult will reveal deposits in heart, colon, liver, kidney, eye, and other organs.

► NOTES