Bacteria

Jason Ryan, MD, MPH

Types of Organisms

Prokaryotes

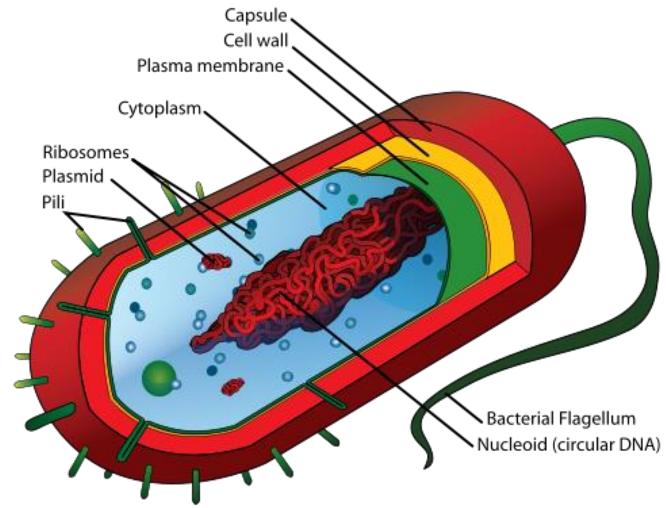
- Very old form of life
- No membrane-bound organelles
- No nucleus
- Nuclear material free inside cell
- Bacteria are prokaryotes

Eukaryotes

- More modern form of life
- Membrane-bound organelles
- Nucleus
- Plant and animal cells
- Protozoa
- Fungi

Bacteria

- Single cell organisms
- Cell wall is key component
- Protects organism
  - General support
  - Osmotic pressure
- Target for immune system
- Target for antibiotics
- Differentiates bacteria



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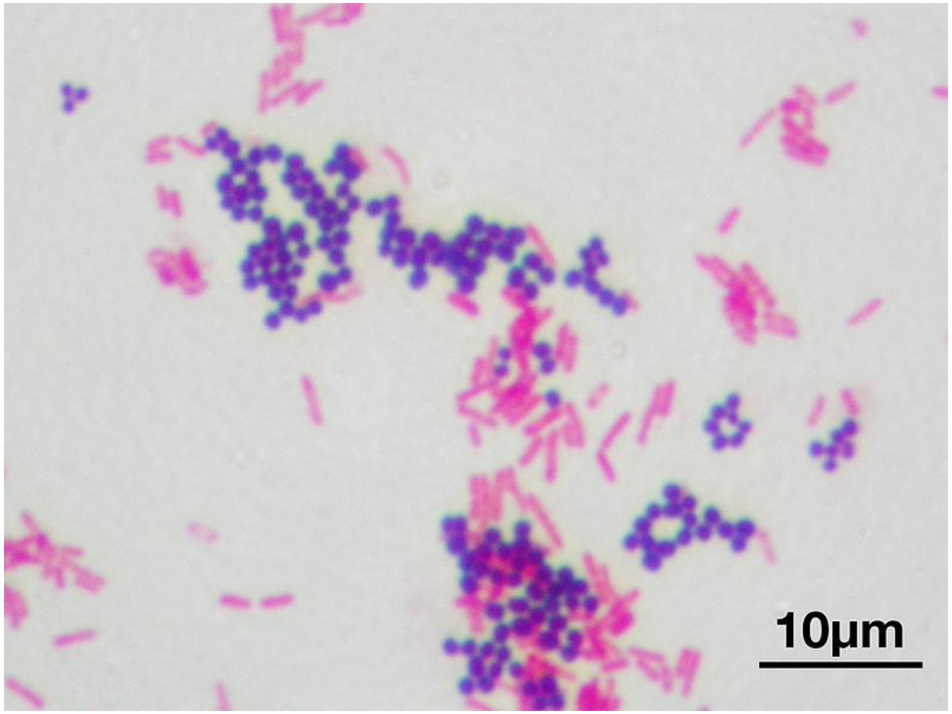
Gram Stain

- Different for gram (+) and gram (-) bacteria



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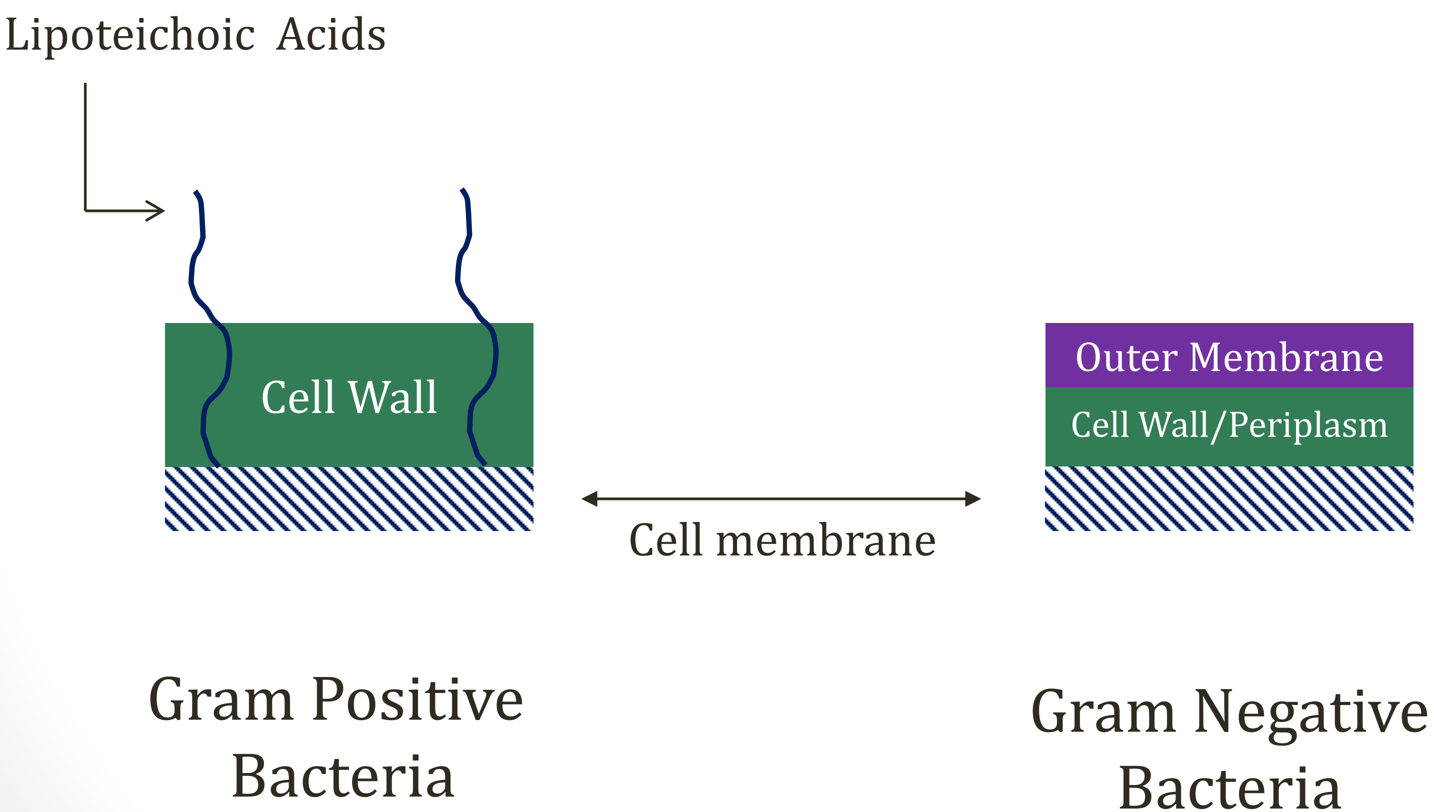
Cell Walls



Lipoteichoic Acids
Cell Wall
Outer Membrane
Cell Wall/Periplasm
Cell membrane
Gram Positive Bacteria
Gram Negative Bacteria

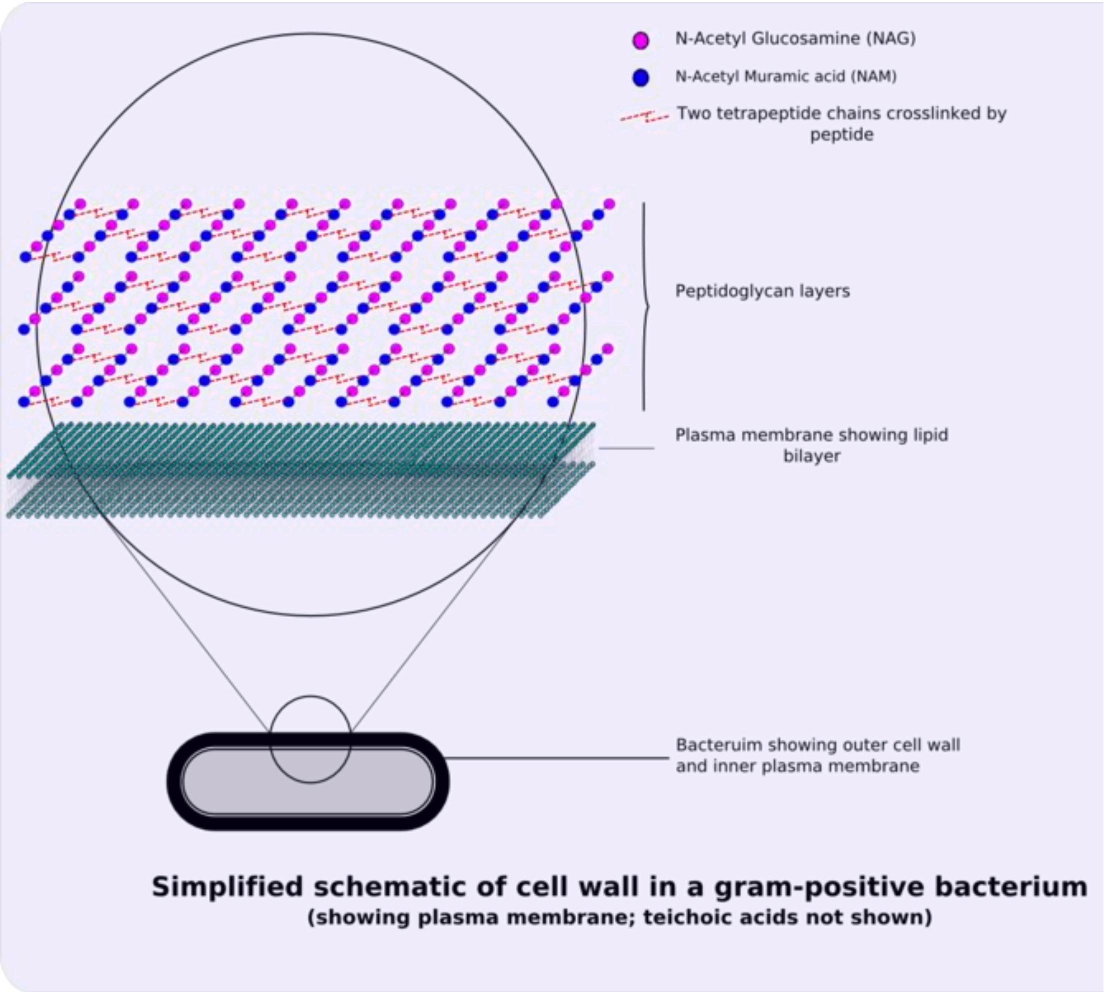
Peptidoglycan

- Major structural component of bacterial cell walls
- Polymer sheets of sugars and peptides
- Sheets cross-linked to other sheets

Peptidoglycan

- Sugars:
  - *N*-acetylglucosamine (NAG)
  - *N*-acetylmuramic acid (NAM)
- Peptides:
  - Attached to NAM
  - Three to five amino acids
- Sugar/peptide backbone makes chains
- Chains cross-linked by peptide cross-bridges
- Site of action some antibiotics
  - Penicillin, cephalosporins

Peptidoglycan



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Peptidoglycan

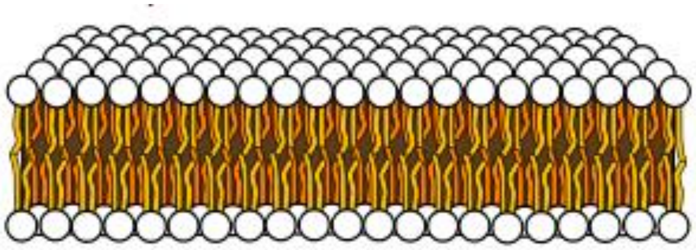
- Gram positive bacteria
  - Up to 40 sheets
  - 50% or more of cell wall
- Gram negative bacteria
  - Very few sheets
  - 5-10% cell wall
- Thick layer in gram (+) bugs retains the gram stain
  - Makes them purple

Unique Cell Walls

- Mycoplasma
  - No cell wall
  - Does not gram stain
  - Cell membrane has sterols for extra stability
- Mycobacteria
  - Cell wall has mycolic acid
  - Does not gram stain well
  - Special stains used (Ziehl-Neelsen)
- Chlamydia
  - Lacks muramic acid

Cell Membrane

- Present in gram (+) and gram (-) bacteria
- Phospholipid bilayer
- Electron transport and oxidative phosphorylation
- Enzymes and carrier molecules



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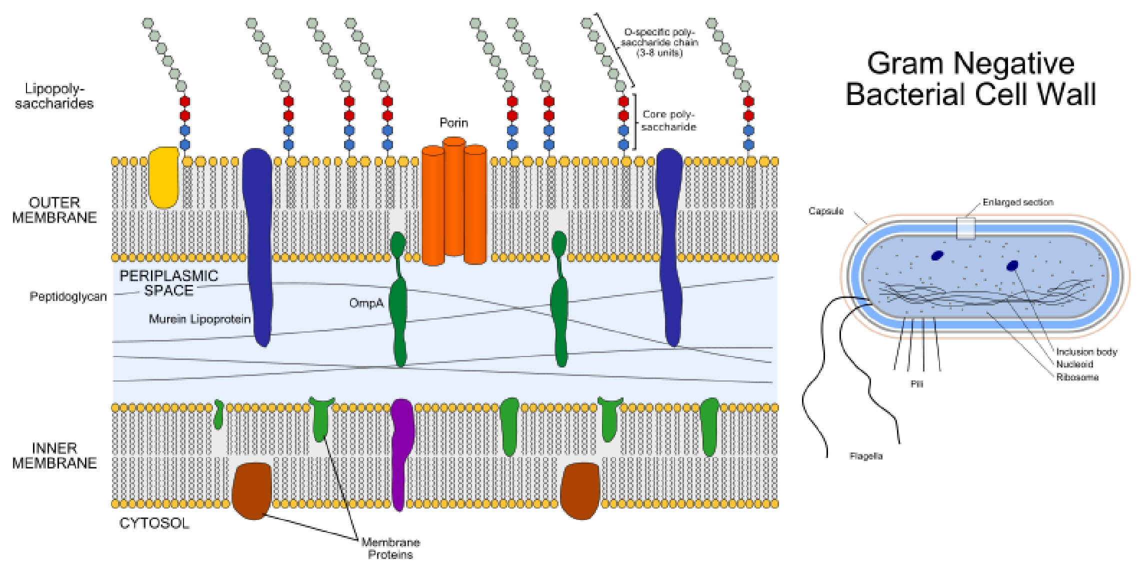
Gram Positive Bacteria

- Unique feature: lipoteichoic acid (LTA)
- Major surface antigen for immune reaction
- In animal studies, LTA has induced:
  - Arthritis
  - Uveitis
  - Meningeal inflammation
  - Cascades resulting in septic shock and multi-organ failure
- Induces cytokine release
- Binds antibodies → activates complement cascade

Gram Negative Bacteria

- Unique feature #1: Periplasm
  - Space between cell membrane and outer membrane
  - Contains many enzymes
  - B-lactamase → inactivates antibiotics



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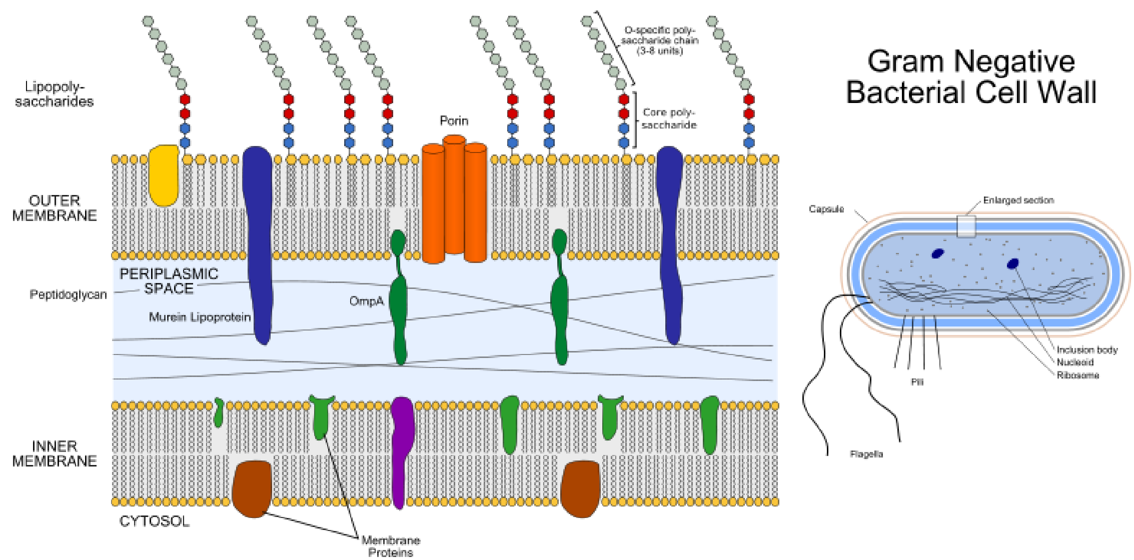
Gram Negative Bacteria

- Unique feature #2: Outer Membrane
- Contains outer layer of lipopolysaccharide (LPS)
- Major immune trigger for gram (-) bacteria



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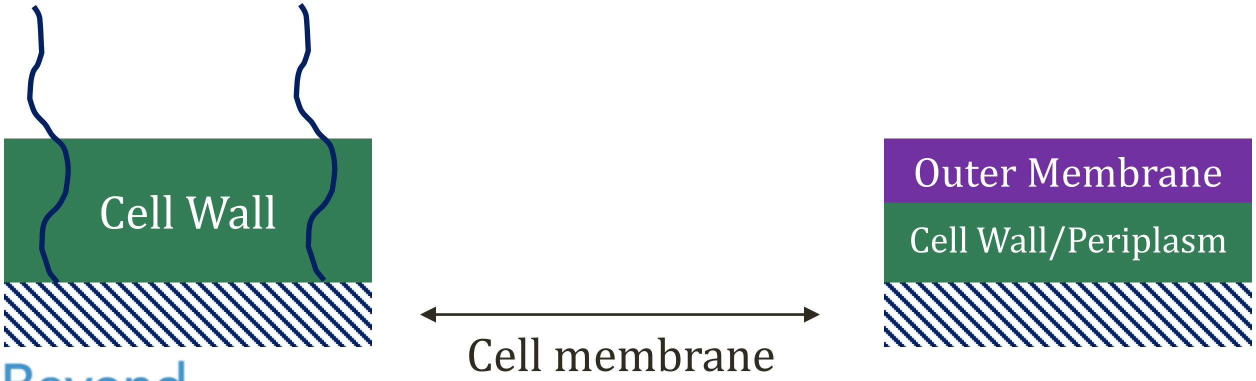
Lipopolysaccharide

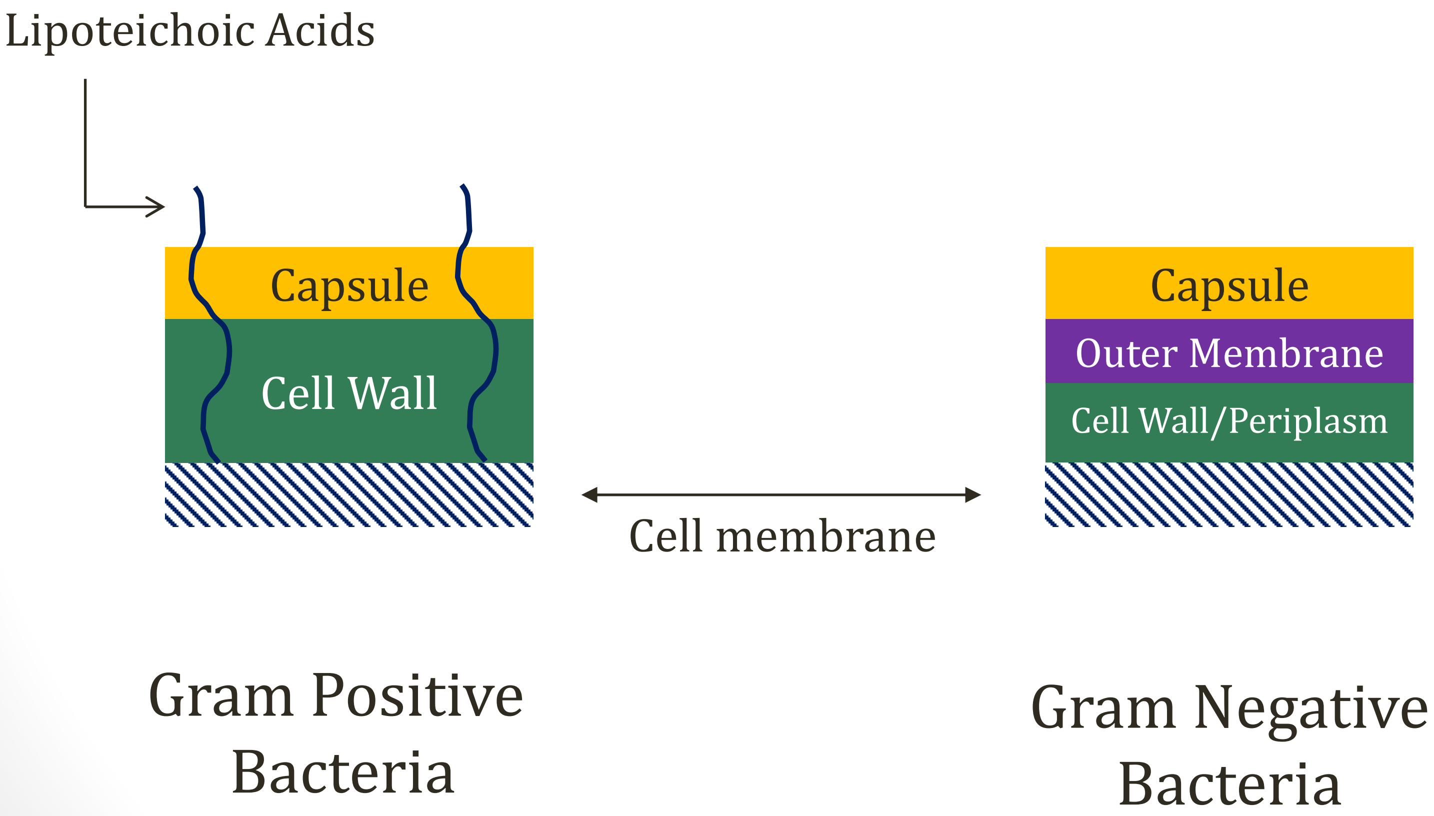
- Components:
  - Polysaccharide
  - Lipid A
  - O antigen
- Lipid A
  - Highly toxic
  - Triggers cytokine release
- O antigen
  - Target for antibodies

Key Point

- Different major surface antigens trigger the immune system in gram (+) and gram (-) bacteria
- Gram positive bacteria
  - Cell wall and membrane
  - Lipoteichoic acid (LTA)
- Gram negative bacteria
  - Outer membrane
  - Lipopolysaccharide (LPS)



Capsules



Lipoteichoic Acids
Capsule
Cell Wall
Capsule
Outer Membrane
Cell Wall/Periplasm
Cell membrane
Gram Positive Bacteria
Gram Negative Bacteria

Capsules

- Sticky, gelatinous layer
- Secreted by bacteria
- Helps attach to host cells
- Protects against phagocytosis
- Mostly water with some polysaccharide
    - Special exception: Bacillus anthracis (anthrax)
    - Capsule is protein (d-glutamate)
    - Major virulence factor
    - Allows unimpeded growth

Quellung Reaction

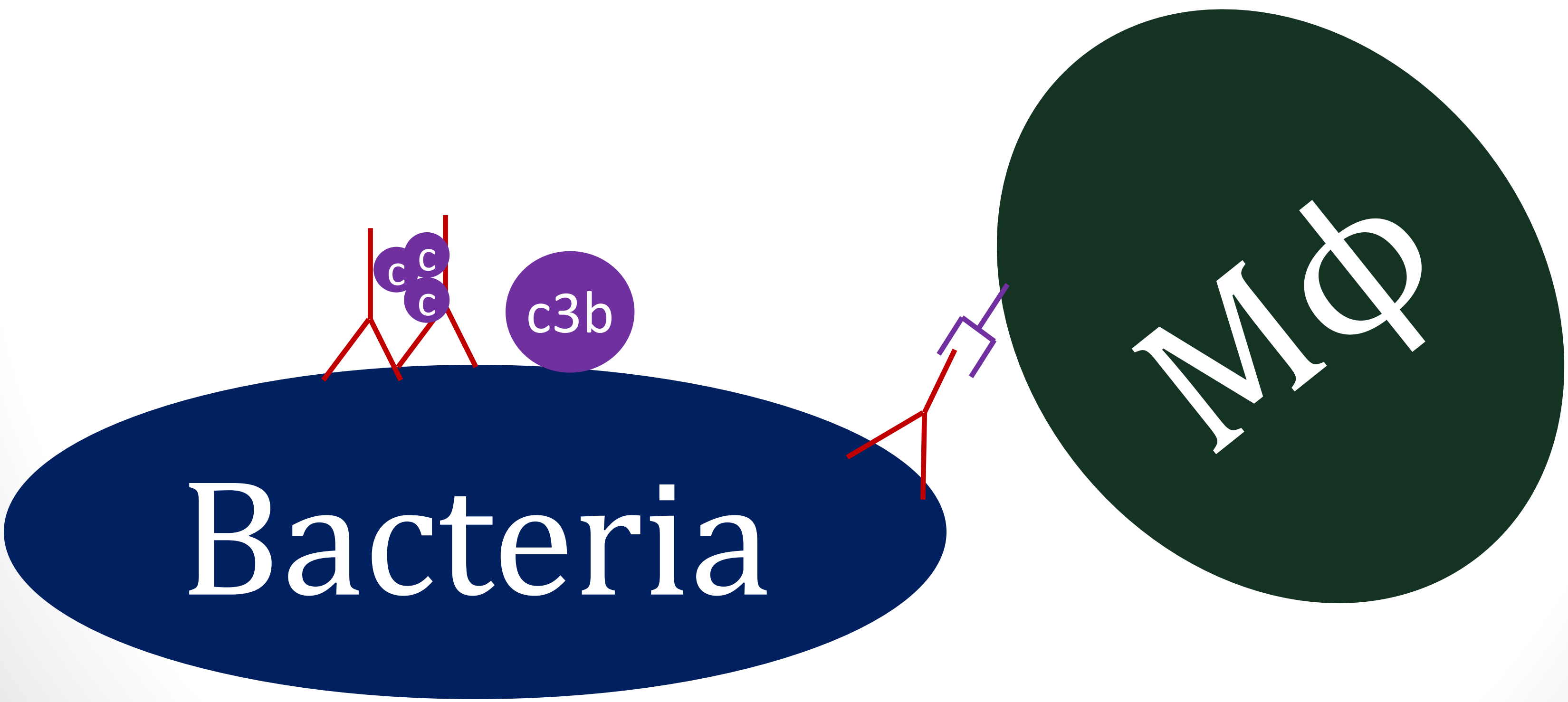
- Largely historical
- Used to detect strep pneumonia
- Rabbit antiserum added to bacterial slide
- Capsule swells when visualized under microscope
- Positive Quellung in encapsulated bugs
  - Strep pneumonia
  - H. influenza
  - N. meningitidis
  - E. Coli
  - Salmonella
  - Klebsiella
  - Group B strep (agalactiae)

Capsules and Immunology

- B-cells secrete capsular antibodies (IgG)
  - Antibodies bind capsule
- Phagocytosis consume bacteria
  - Via Fc receptors
- Antibodies bind complement
  - Formation of MAC → cell death
  - Formation C3b → opsonin

Capsules and Immunology

- Loss of antibodies/B-cells or complement
- Recurrent encapsulated bacterial infections



Capsules and Immunology

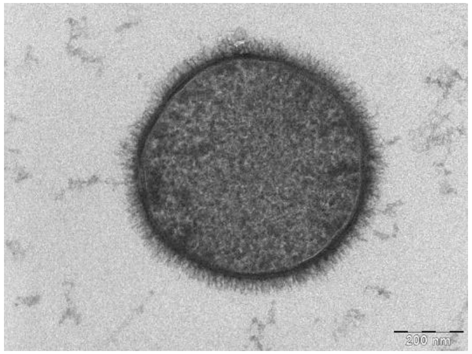
- Asplenia
  - Risk of sepsis from encapsulated bacteria
  - Loss of splenic phagocytes

Capsular Vaccines

- Capsular polysaccharides are basis for many vaccines
- Polysaccharides in capsule often weakly immunogenic
- "Conjugated" to an immune stimulator protein
  - diphtheria toxoid, tetanus toxoid, meningococcal outer membrane protein, mutant diphtheria protein
- Many conjugated vaccines for encapsulated bacteria
  - Neisseria meningitides
  - Streptococcus pneumonia
  - Haemophilus influenzae type b

Glycocalyx

- "Sugar coat" made of polysaccharides
- Similar to capsule
- Bacteria with distinct, firmly attached gelatinous layer have a capsule
- Bacteria with irregular, slimy fuzz layer have a glycocalyx
- Used to adhere to surfaces (i.e. catheters)
- S. epidermidis : biofilms



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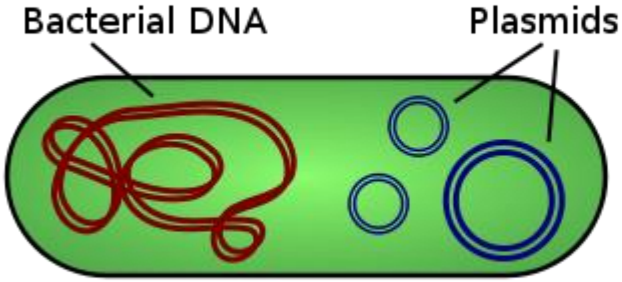
Pili and Fimbria

- Structurally similar to flagella
- Made of proteins
- Appendage or arm of bacteria
- Allows adherence to surfaces (ordinary pili)
- Attaches to another bacteria for conjugation (sex pili)
- Key bacteria:
  - E. Coli (UTIs/Pyelonephritis)
  - Neisseria Gonorrhea (antigenic variation)

Plasmids

- Small DNA molecule within a cell
- Physically separated from chromosomal DNA
- Can replicate independently
- Can contain genes for antibiotic resistance, toxins
- Can be transferred one bacteria to another



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Flagellum

- Long, protein arms
- Used for motility

Ribosomes

- Site of protein synthesis in bacteria
- Two subunits: 50S and 30S
  - S=sedimentation coefficient or Svedberg unit
- Different from ribosomes in eukaryotic cells
  - Allows selective toxicity of antibiotics
- Site of action of antibiotics
  - Tetracyclines: Bind to 30S subunit
  - Aminoglycosides: Interferes with 30S protein synthesis

Spores

- Some bacteria can enter a dormant state called a spore
  - "Spore forming bacteria"
- Can survive long period of starvation
- Resistant to dehydration, heat, chemicals
- No metabolic activity

Spores Components

- Coat:
  - Outermost layer
  - "Keratin-like" protein
  - Impermeable to many chemicals, antibacterial agents
- Cortex/Core Wall
  - Innermost layer
  - Peptidoglycans
- Dipicolinic acid
  - Large amounts inside spore
  - May help with heat resistance

Spore Forming Bacteria

- Bacillus anthracis
- Bacillus cereus
- Clostridium perfringens
- Clostridium tetani
- Clostridium Botulinum

Shapes and Stains

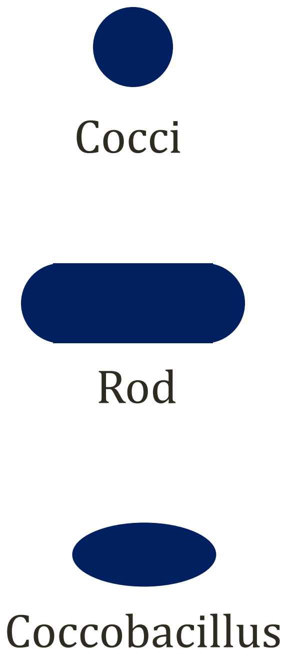
Jason Ryan, MD, MPH

Identification of Bacteria

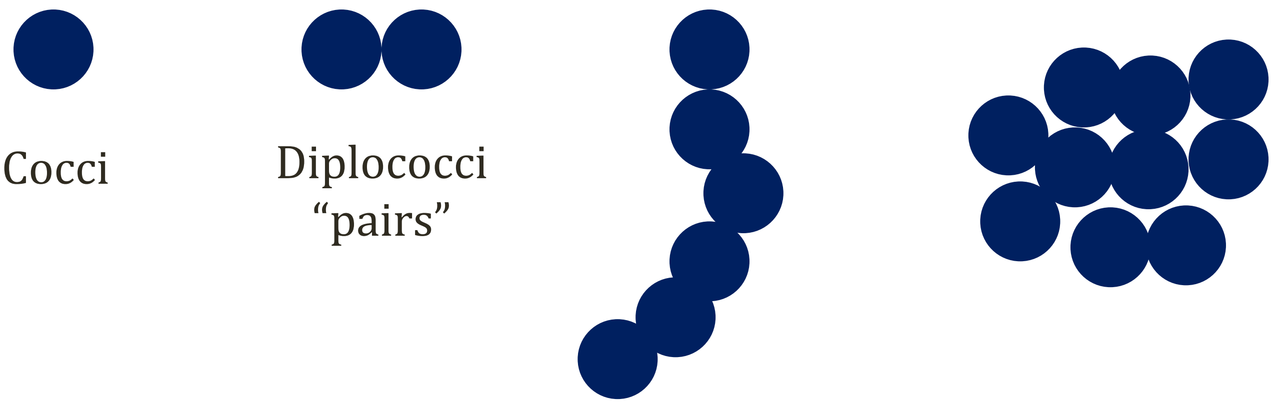
- Shape
- Color after staining
- Special tests

Bacterial Shapes

- Coccus (sphere)
- Rod (bacilli)
- Coccobacillus
- Other



Cocci



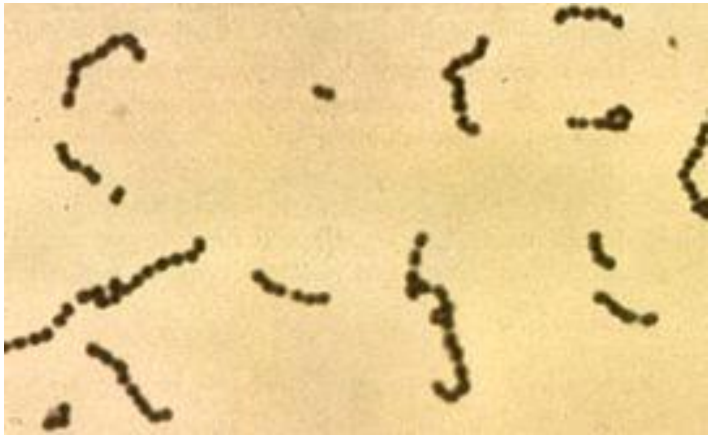
Cocci

Diplococci
"pairs"

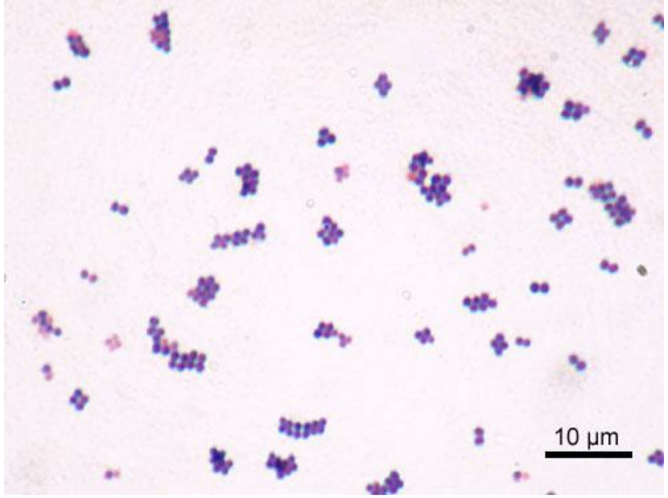
Streptococci
"Chains"

Staphylococci
"Bunches"
"Clusters"

Cocci



Streptococci
"Chains"



Staphylococci
"Bunches"
"Clusters"

Image courtesy GrahamColm/Wikipedia

Image courtesy Y Tambe/Wikipedia

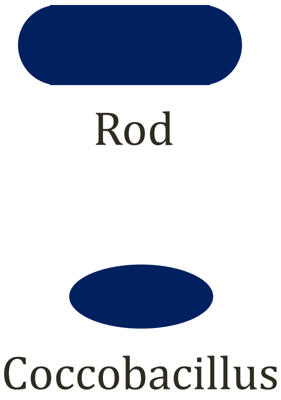
Cocci

- Most cocci are gram positive
  - Streptococcus
  - Staphylococcus
- Very few gram negative bugs are cocci
  - Neisseria (meningitidis/gonorrhea)
  - Moraxella catarrhalis

Rods

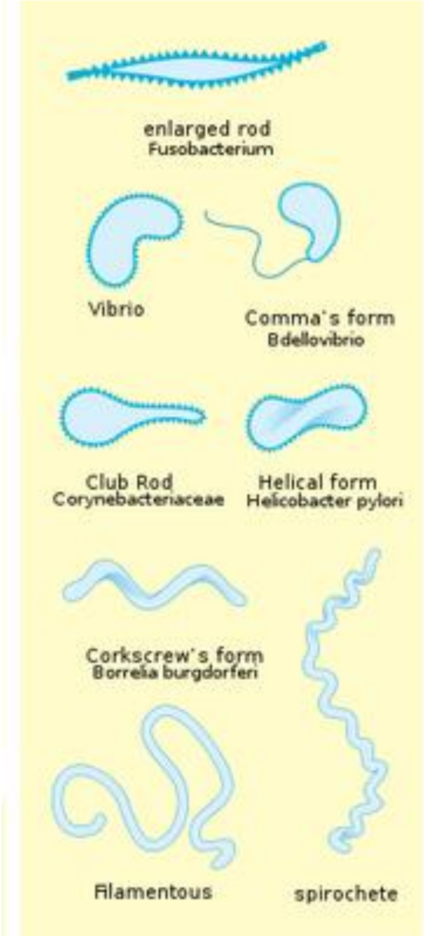
Bacilli

- Most rods (and coccobacillus) are gram negative
- Few gram positive rods
  - Corynebacterium (diphtheria)
  - Clostridium
  - Listeria
  - Bacillus (anthrax, cereus)



Other Shapes

- Branching/Filamentous
  - Resemble fungi
  - Actinomyces
  - Nocardia
- Spirochetes
  - Treponema (syphilis)
  - Borrelia (Lyme disease)
  - Leptospira (leptospirosis)
- Vibrio
  - Vibrio cholerae



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Pleomorphic Bacteria

- Take on many shapes
- Rickettsia
- Chlamydia

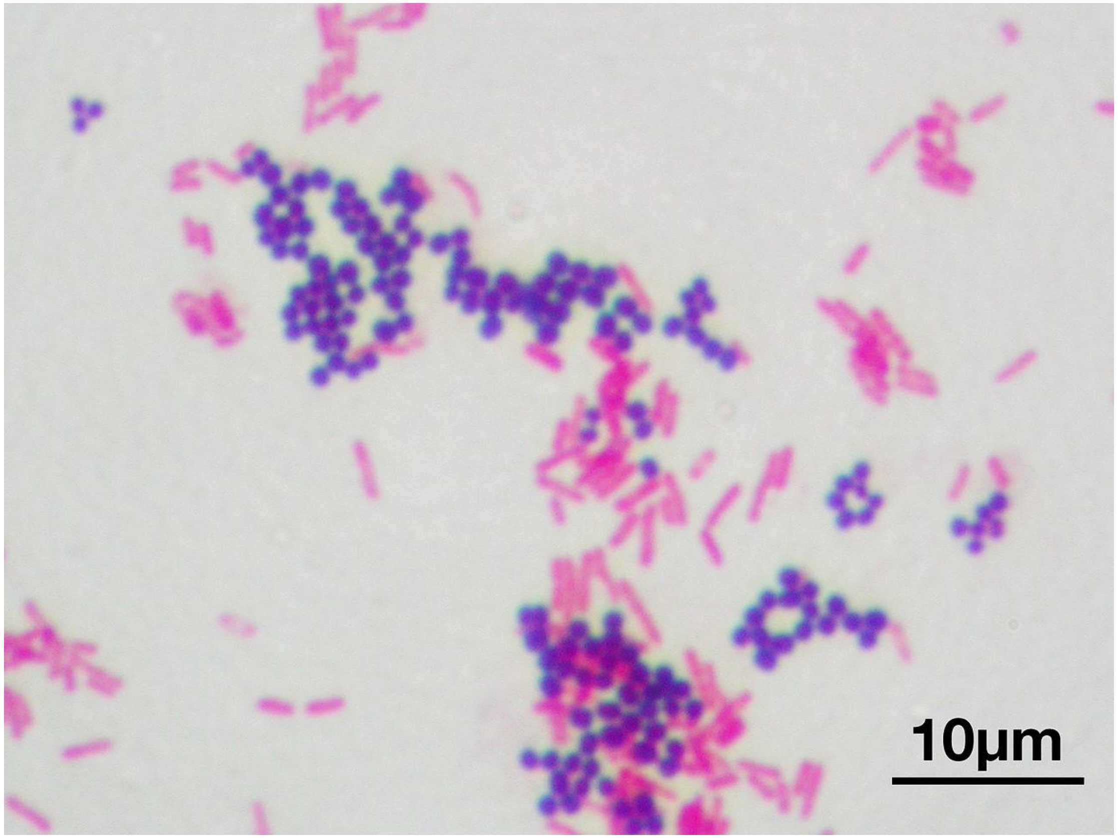
Common Bacterial Stains

- Gram Stain
- Giemsa
- Ziehl-Neelsen
- Silver
- India Ink – Cryptococcus (fungi)

Simple Stains

- Methylene blue, safranin, and crystal violet
- Add to fixed preparation of bacteria
- Wash away
- Stain remains behind to show bacteria
- Used to see number bacteria, shapes

Gram Stain



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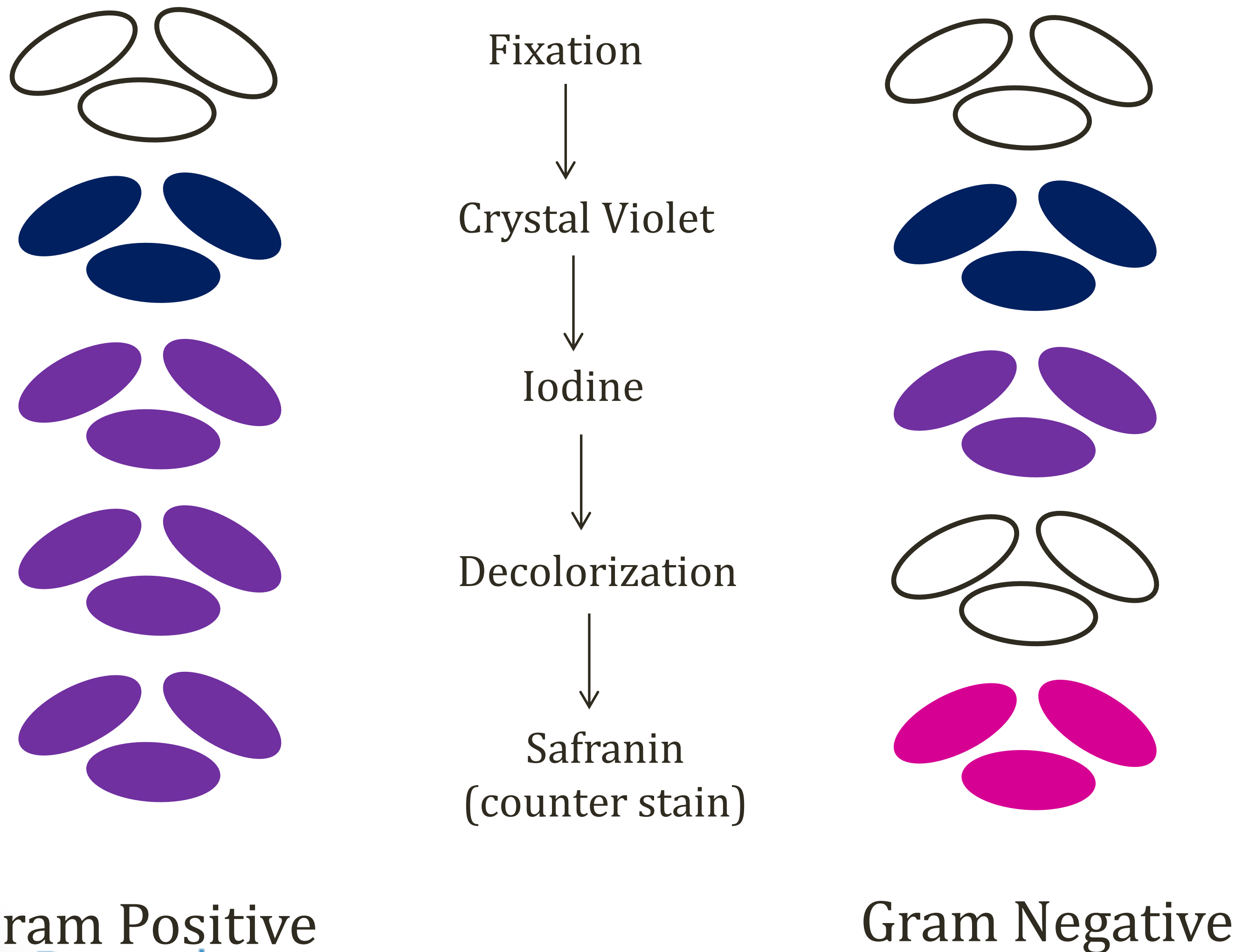
Gram Stain



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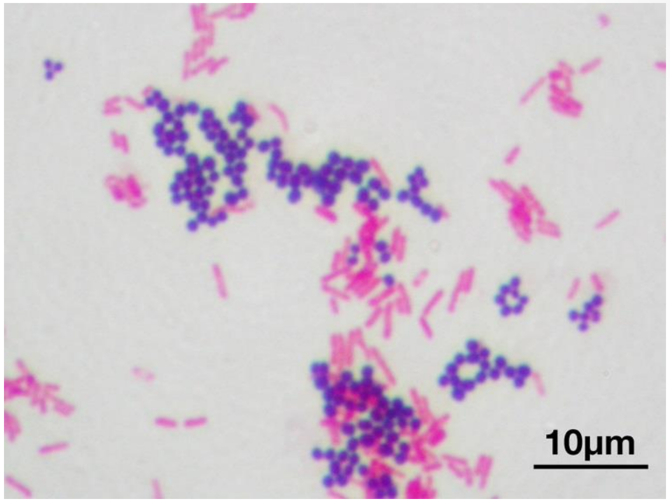
Gram Stain



- Purple = Gram Positive
  - Retain crystal violet in cell walls
- Red = Gram Negative
  - Do not retain crystal violet in cell walls
  - Take up Safranin counter stain
- Thick cell wall of peptidoglycan in gram positive bacteria makes them purple

Image courtesy of Y tambe /Wikipedia

Gram Stain Limitations

- Some bugs do not gram stain well
- Treponema (syphilis)
  - Too thin to see
- Mycobacteria (tuberculosis)
  - Mycolic acids in cell wall
- Mycoplasma
  - No cell wall
- Intracellular bacteria
  - Rickettsia (obligate intracellular)
  - Chlamydia (obligate intracellular; no muramic acid cell wall)
  - Legionella (mostly intracellular)

Giemsa Stain

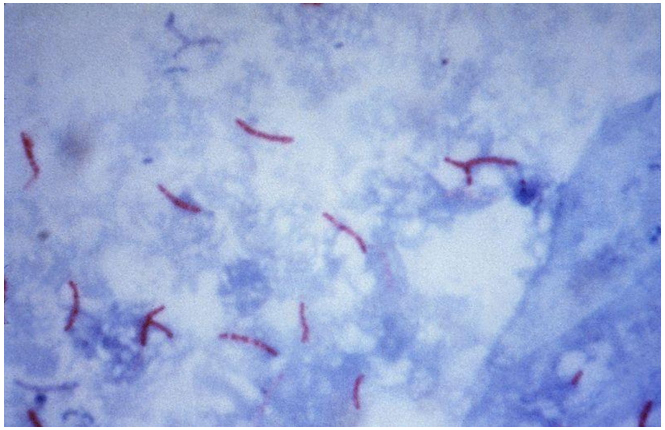
- Mixture of methylene blue, eosin, and Azure B
- Discoverer: Gustav Giemsa (1867–1948)
  - Looking for method to easily visualize plasmodium (malaria)
- Enters cells and stains nucleic acids
  - Used for blood smears, marrow

Giemsa Stain

- Protozoa
  - Plasmodium
  - Trypanosomes
- Intracellular bugs
  - Chlamydia
  - Rickettsia
  - Borrelia (sometimes intracellular)

Ziehl-Neelsen

- The “acid fast” stain
- Contains carbolfuchsin
- Used to detect mycobacterium (especially TB)
- Also used for Nocardia
- Acid fast bugs resists decolorization with acid solvents



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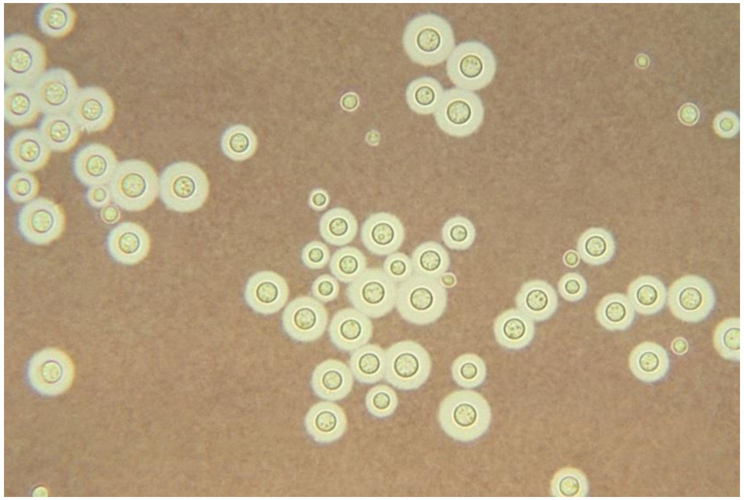
Silver Stain

- Special stain for 3 organisms
- Pneumocystis pneumonia (HIV/AIDS)
  - Fungal infection
  - Diffuse interstitial pneumonia
- Legionella
  - Pneumonia
  - Contaminates water (outbreaks in nursing homes)
- H. Pylori
  - Gastric ulcers

India Ink

- Negative stain
- Background stained, not bug
- Unstained organisms stand out in contrast
- Primarily used for cryptococcus neoformans
  - Large polysaccharide capsule creates “halos”



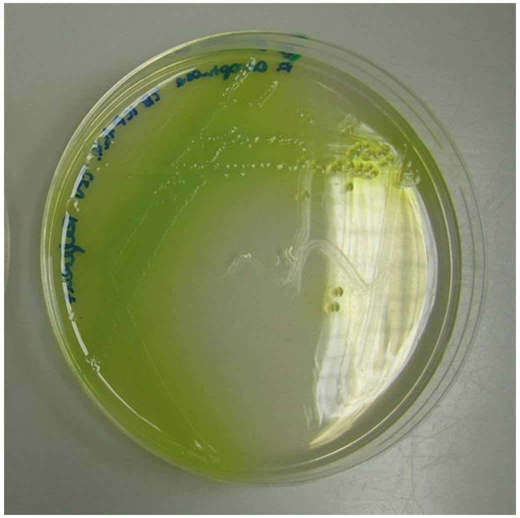
India Ink stain shows yeast with “halos”

Image courtesy of Crisco 1492

Pigments

- Some bacteria produce special colors
- Staph Aureus
  - Golden, yellow color
- Pseudomonas aeruginosa
  - Blue-green pigment (pyocyanin)
- Serratia
  - Red pigment
- Actinomyces
  - Filamentous bacteria that "cements" together
  - Colonies have yellow-orange appearance
  - Known as "**sulfur granules**"

Pseudomonas (blue-green)



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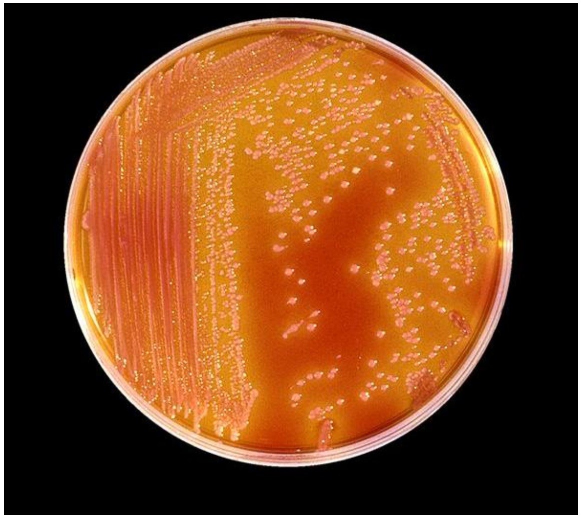
Serratia (red)



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Staph Aureus (gold-yellow)

Matthias M./Wikipedia

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Bacterial Culture

Jason Ryan, MD, MPH

Growth Plate

- Agar in Petri dish
  - Semi-solid substance from seaweed
  - Bacteria usually don't consume/decompose
- Nutrients added to support growth
  - Sugar
  - Water
  - Salts
  - Amino acids
- Many, many commercially available

Image courtesy Wikipedia/Public Domain

Culture Media

- Non-selective
  - General purpose
  - Grows many bugs
  - Example: Nutrient agar
  - Also, blood agar: most commonly used non-selective media
- Selective
  - Contains toxic substances
  - Only certain bugs will grow
  - Thayer-Martin Media grows only Neisseria

Culture Media

- Enriched
  - Special nutrients added so many bugs will grow
  - Blood agar
  - Chocolate agar
- Differential
  - Different bugs grow with different patterns
  - Blood agar: alpha, beta hemolysis

Culture Media

- Blood agar
  - Enriched (blood)
  - Differential (hemolytic patterns)
- Eosin Methylene Blue
  - Selective (only gram negatives)
  - Differential (lactose fermenters)

Fastidious Bacteria

- Fastidious = attentive to detail
- Fastidious organisms require special nutrients
- May not grow on standard media
- Some examples:
  - H. Influenza
  - Legionella

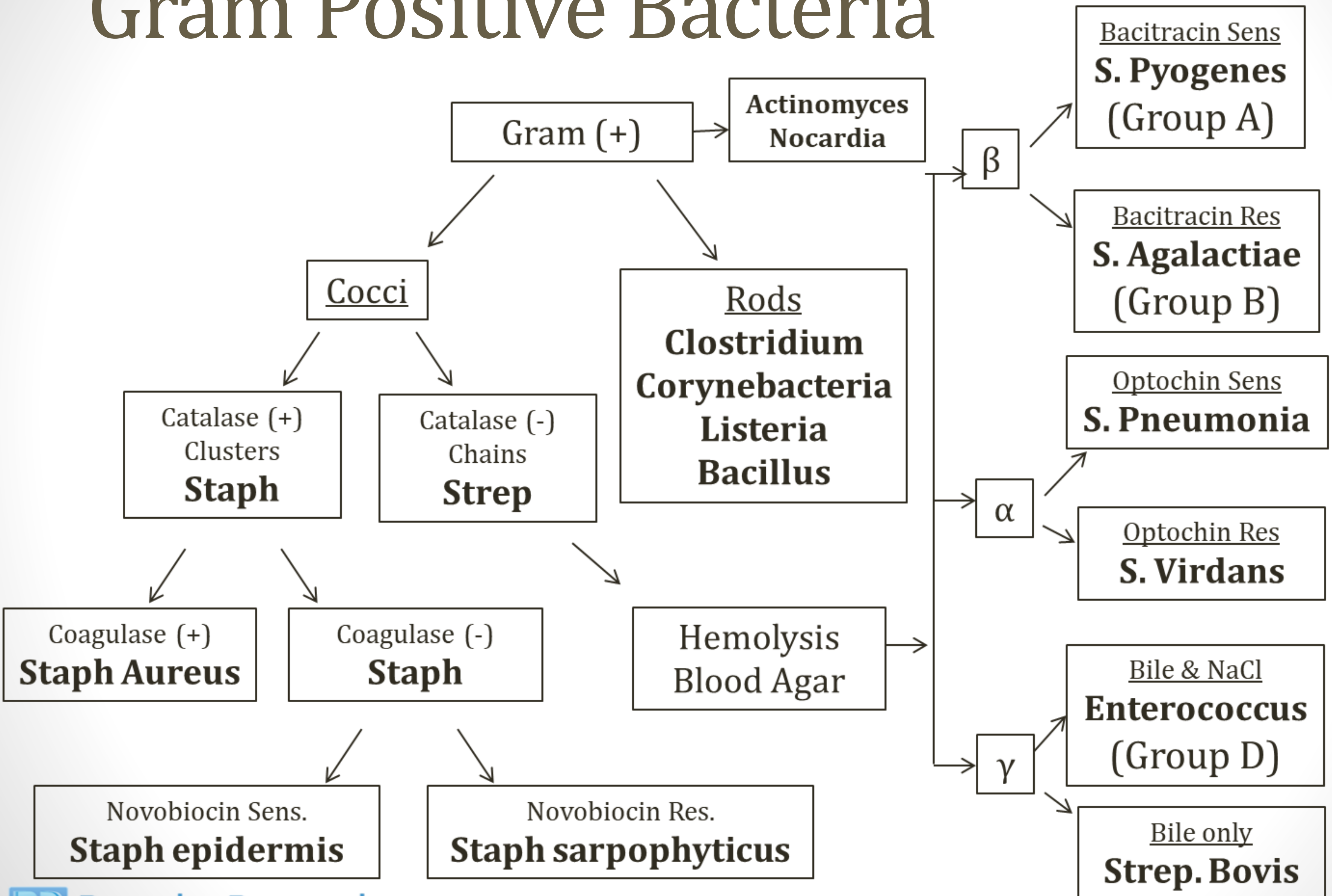
Blood Agar

- Contain mammalian blood – usually 5% sheep blood
- Non-selective
- Enriched (blood)
- Differential by hemolysis pattern

<u>Hemolysis Patterns</u>
Beta = lysis
Alpha = partial
Gamma = no lysis

Image courtesy Y tambe/Wikipedia

Gram Positive Bacteria



Blood Agar

- Commonly used to differentiate species of streptococcus
  - Alpha
  - Beta
  - Gamma
- Special feature of pseudomonas:
  - Beta-hemolytic
  - Greenish-metallic appearing colonies
  - Production of the pigments pyoverdin and pyocyanin
- Staph Aureus
  - Beta hemolytic

Chocolate Agar

- Variant of blood agar
- Contains red blood cells that are lysed (heating)
- Contains NAD (factor V) and hemin (factor X)
  - NAD from inside RBCs
  - Media heated such that they are not destroyed
- H. Influenzae will grow
- Classic scenario:
  - Bacteria won't grow on blood agar unless S. Aureus present

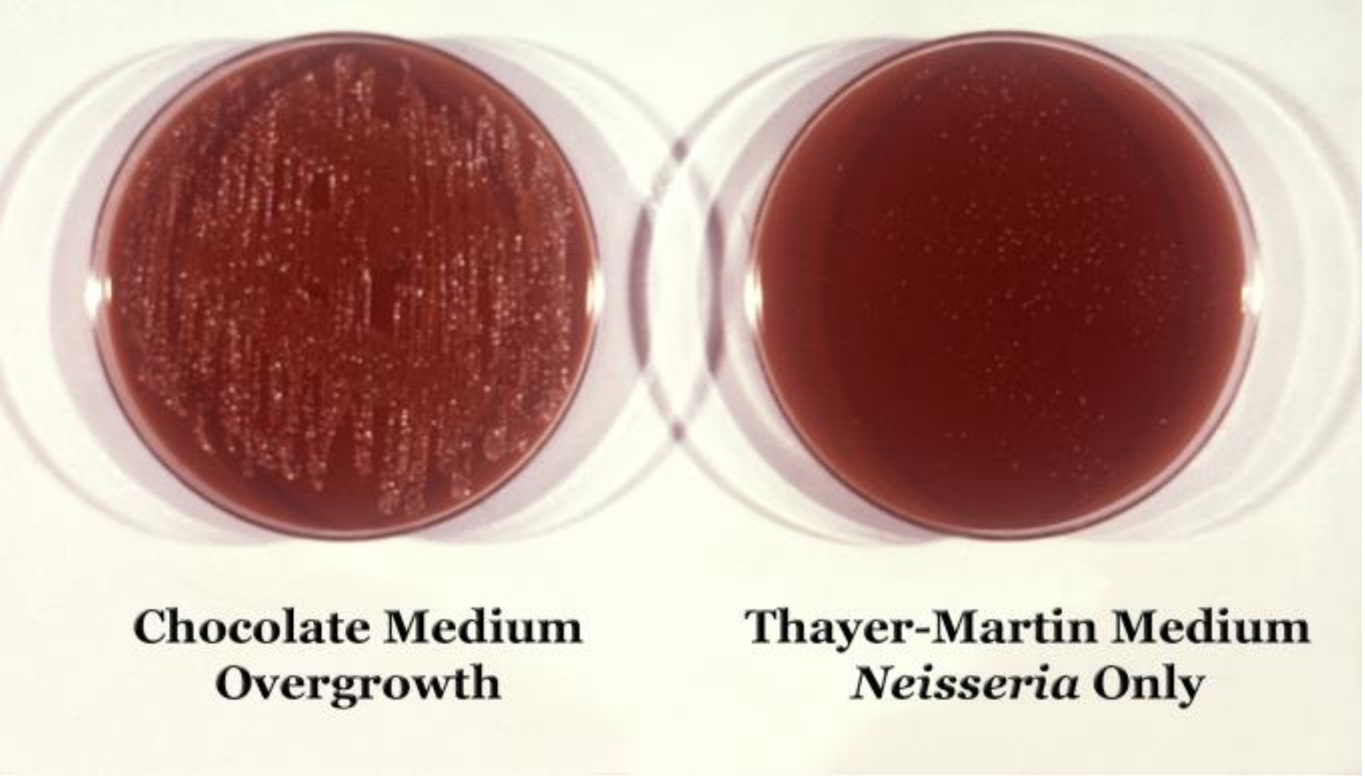
Thayer-Martin Media

VPN/VCN

- Enriched, selective media for Neisseria
- Neisseria often from sites with lots of other flora
  - Throat, genitalia
  - Need very selective media
- Supplemented chocolate agar
- Vancomycin: Kills most Gram-positive organisms
- Colistin (polymyxin): Kills most Gram-negatives
  - Except Neisseria
- Nystatin: Kills most fungi

Thayer-Martin Media

VPN/VCN



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Bordet-Gengou Agar

Potato Agar

- Classic special media for Bordetella pertussis
  - Whooping cough
  - Extremely rare due to vaccination
- Prepared from potatoes → high in starch
  - Favorable to pertussis bacteria

Loeffler's Media/Tellurite Plate

- Loffler's Media
  - Selective media for Corynebacterium diphtheriae
- Tellurite Media (Cysteine-Tellurite Agar)
  - Differential media for C. diphtheria
  - C. diphtheria reduces potassium tellurite to tellurium
  - Produces gray-black colored colonies

Lowenstein-Jensen Agar

- Special media for Mycobacterium tuberculosis
- Eggs, flour, glycerol, salt
- M. tuberculosis is SLOW growing
- Several weeks for visible colonies to appear
- M. tuberculosis: Ziehl-Neelsen stain

Eaton's Agar

- Culture of mycoplasma pneumonia
- Bacteria has no cell wall
- Poorly visualized with gram stain
- Eaton medium specialized for m. pneumonia growth
  - Require cholesterol to grow
- Takes days to weeks to grow
- Culture rarely used in modern era
- Diagnosis via:
  - Serology (antibody testing)
  - PCR (bacterial DNA)
  - Cold agglutinins (IM antibodies)
- Usually treated empirically

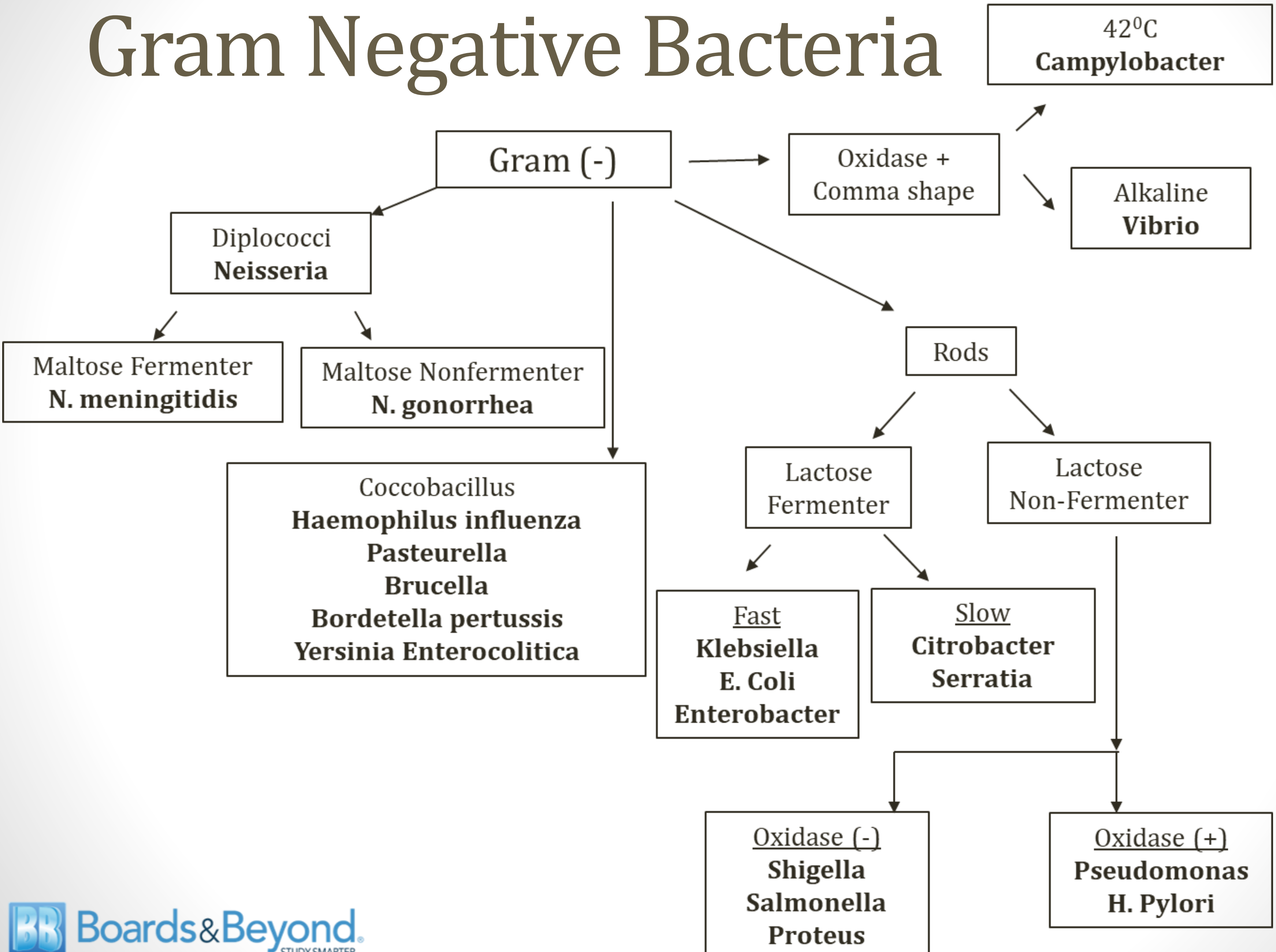
MacConkey's Agar

- Selective media for gram (-) bacteria
- Contains bile salts as inhibitors of growth
- Inhibit Gram (+) bacteria
- Also differential for lactose fermenters
  - Lactose fermentation produces acid → turns agar pink
  - Non-lactose fermenters are colorless

MacConkey's Agar

Image courtesy Wikipedia/Public Domain

Gram Negative Bacteria



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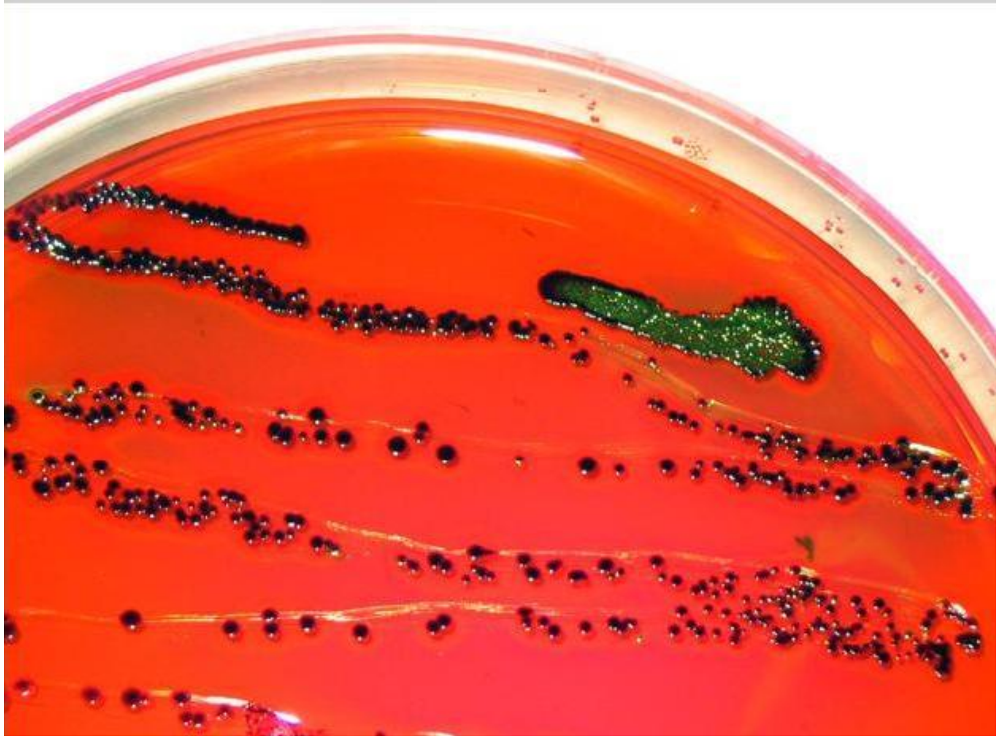
Eosin-Methylene Blue Agar

EMB

- Similar in function to MacConkey's Agar
- Eosin Y and methylene blue as inhibitors
- Inhibit Gram (+) bacteria
- Also differential for lactose fermenters
  - Lactose fermenters (Escherichia coli) appear as colonies with green metallic sheen or blue–black to brown color
  - Bacteria that do not ferment lactose appear as colorless or transparent colonies

Eosin-Methylene Blue Agar

EMB



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Sorbitol MacConkey Agar

- Detection of E. Coli O157:H7 strains (Shiga-like toxin)
- O157:H7 cannot ferment sorbitol (other E. Coli can)
- O157:H7 grows as colorless colonies on this medium
- Other E. Coli produce pink colonies

Buffered Charcoal Yeast Extract

BCYE

- Contains dyes that give Legionella distinct color
- Antibiotics added: inhibits growth of competing bugs
- Very important to culture this bacteria
  - Can contaminate water supplies
  - Cause outbreaks
- Urinary antigen test also available
  - Only useful "type 1 infection"
  - Negative test is not 100%

Sabouraud's Agar

- Selective media for fungi
- Developed by a French dermatologist
  - Growth of fungi in skin, hair, or nails (dermatophyte)
- Acid or antibiotics inhibit bacterial growth

Special Growth Requirements

Jason Ryan, MD, MPH

Bacterial Growth Environments

- Obligate anaerobes
- Obligate aerobes
- Facultative anaerobes
- Intracellular bacteria

Energy Production

- Respiration
  - Electron transport chain
  - Makes ATP
  - Requires oxygen
- Fermentation
  - Sugars → acids
  - Makes ATP (less)
  - Does not use oxygen

Superoxide Dismutase & Catalase

- Enzymes of aerobic organisms
- Superoxide radical (O_2^-) produced by bacterial metabolism
- Superoxide dismutase
  - Catalyzes superoxide (O_2^-) radical to O_2 or hydrogen peroxide
- Catalase
  - Converts hydrogen peroxide (H_2O_2) to oxygen and water
- Need these enzymes to survive in oxygen environments

Obligate Aerobes

- Use O_2 system to generate ATP
- Oxygen is final electron acceptor during respiration
- Can generate lots of energy (more than anaerobes)
- Contain superoxide dismutase
- Key bacteria:
  - Pseudomonas aeruginosa
  - Mycobacterium tuberculosis
  - Nocardia (opportunistic infections)

Obligate Anaerobes

- Lack catalase or superoxide dismutase
- Common among normal flora of gut and mouth
  - 99% fecal flora
  - 100x more anaerobes than aerobes in mouth
- Don't cause communicable diseases
- Often live near mucosal surfaces
- Disease when surfaces breakdown
- Often present in abscesses
- Aminoglycosides ineffective (require O_2)

Obligate Anaerobes

- Uses fermentation (no O_2)
- Byproducts are often gases like CO_2 and H_2
- Also produce short chain fatty acids
  - Acetic acid, isobutyric acid, many others
- Results in "foul smell"

Obligate Anaerobes

- Actinomyces (gums; dental abscesses)
- Bacteroides (abdominal abscesses)
- Clostridium (botulinum; perfringens; tetani)

Key Anaerobic Infections

- Abdominal abscesses/perforations
  - Contain many gram (-) flora of GI tract
  - Also contain Bacteroides fragilis (anaerobe)
  - B. fragilis resistant to many antibiotics
  - Treatment: Metronidazole + gram (-) agent
- Aspiration pneumonia
  - Mouth anaerobes enter lungs
  - Peptostreptococcus, Fusobacterium, Prevotella
  - Treatment: Clindamycin

Facultative Anaerobes

- Can live without oxygen but use it if available
- Perform respiration and fermentation
- Pasteur effect: Oxygen inhibits fermentation
- Many common bacteria fall in this category
  - Staph
  - Strep
  - E. Coli

Aerotolerant Anaerobes

- Similar to facultative anaerobes
- Always use fermentation even in presence of oxygen
- Rare
- Few examples relevant to clinical disease

Obligate Intracellular Bacteria

- Cannot synthesize their own ATP (chlamydia)
- Or depend on host for ATP (rickettsia)
- Will not gram stain well (inside other cells)
- Difficult to grown (need cell culture)
- Rickettsia
  - Rocky Mountain spotted fever
  - Diagnosed clinically or with serology (antibody tests)
- Chlamydia
  - Diagnosis: Nucleic Acid Amplification Testing (DNA testing)

Facultative Intracellular Bacteria

- Mycobacterium (macrophages)
- Legionella (macrophages)
- Salmonella (intestinal cells)
- Neisseria (urethral epithelial cells)
- Listeria (monocytes, macrophages)
- Brucella (macrophages and neutrophils)
- Francisella (macrophages)
- Yersinia pestis (macrophages)

Virulence

Jason Ryan, MD, MPH

Virulence Factors

- Bacterial features that allow evasion of host defenses
- Key examples to know:
  - Protein A
  - IgA protease
  - M protein

Protein A

- Key virulence factor of Staph Aureus
- Part of peptidoglycan cell wall
- Inhibits phagocytosis
- Binds Fc portion of IgG antibodies
- Prevents opsonization and phagocytosis by macrophages
- Prevents complement activation

IgA Protease

- Enzymes that cleave IgA
- IgA key for mucosal immunity
- Protease allows colonization of mucosal surfaces
- S. pneumonia
- H. influenza
- Neisseria (gonorrhoeae and meningitidis)

M Protein

- Surface molecule of group A strep (pyogenes)
  - Strep throat, rheumatic fever
- M protein prevents phagocytosis
  - Binds factor H
  - Breaks down C3-convertase, prevent opsonization by C3b

M Protein

- Shares properties with myosin
  - May be the basis of rheumatic heart disease
- Post-strep complications
  - Rheumatic heart disease
  - Glomerulonephritis
  - Different M protein subtypes associated each complication

Bacterial Toxins

- Endotoxin
  - Only in gram (-) bacteria
  - Component of outer cell membrane
  - Lipopolysaccharide (LPS)
- Exotoxin
  - Proteins synthesized by some bacteria

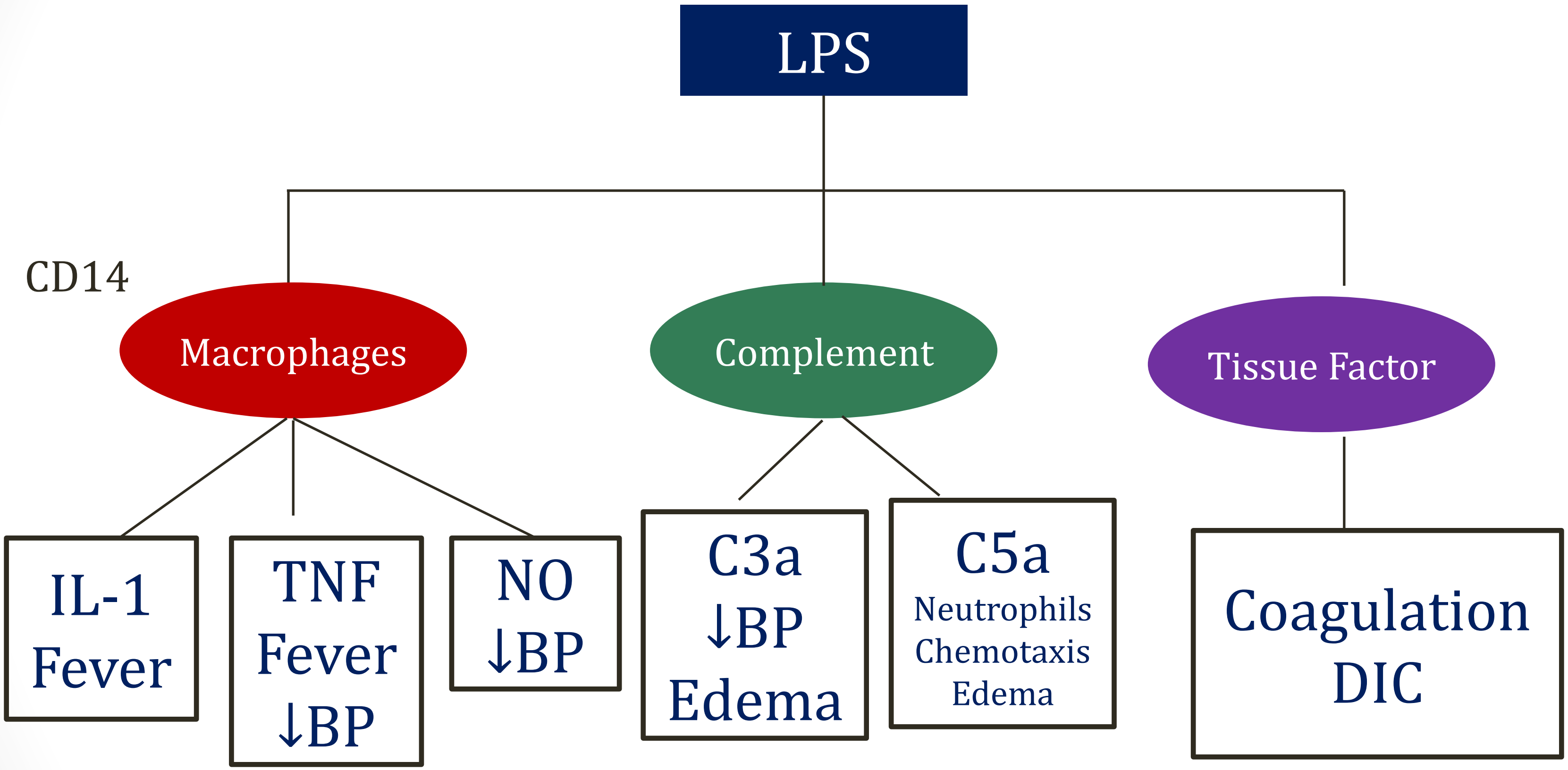
Endotoxin

- Component of gram (-) bacterial cell wall
- Released when bacteria die (not secreted)
- Lipopolysaccharide complex (LPS)
- Many different variants
- All have lipid A core
  - Responsible for most of the toxicity
- O antigen
  - Terminal end sugars that vary among bacterial strains
  - Do not cause disease by themselves

Endotoxin

- Can cause fever, shock
- Triggers TNF and IL-1 release
  - Key immune components of sepsis and septic shock
- Generates weak antibody response
  - Can't vaccinate against endotoxin
- Heat stable (tolerates high temps)

Endotoxin


LPS
CD14
Macrophages
Complement
Tissue Factor
IL-1
Fever
TNF
Fever
↓BP
NO
↓BP
C3a
↓BP
Edema
C5a
Neutrophils
Chemotaxis
Edema
Coagulation
DIC

Lipooligosaccharide

LOS

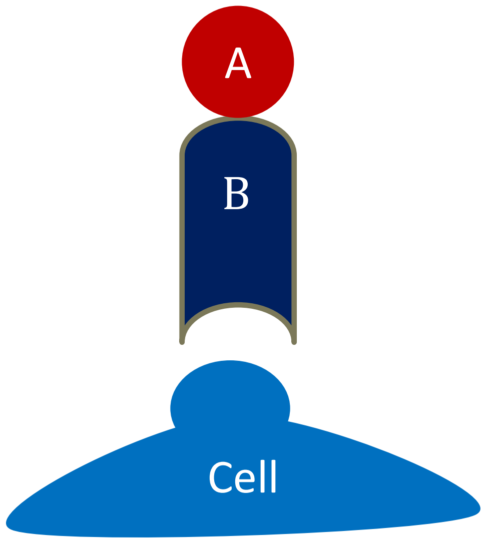
- Endotoxin
- Similar to LPS with some structural differences
- Lacks O-antigen
- Found on non-enteric gram negatives
- Neisseria meningitidis is most important example

Endotoxin

- Classic examples of endotoxin reactions
  - Meningococcemia
  - Gram (-) sepsis

Exotoxins

- Proteins secreted by bacteria → disease symptoms
- Classic structure: two component "A-B" polypeptide
- A component is toxic (A for active)
- B component binds to cell surfaces (B for binding)
- Various mechanisms of entry after B binding



Exotoxins

- Many known exotoxins with various toxic effects
- General categories:
  - Inhibit protein synthesis
  - Increase fluid secretion
  - Inhibit phagocytosis
  - Inhibit neurotransmitter release
  - Lyse cell membranes
  - Superantigens

Toxin Mechanisms

Protein Synthesis Inhibitors

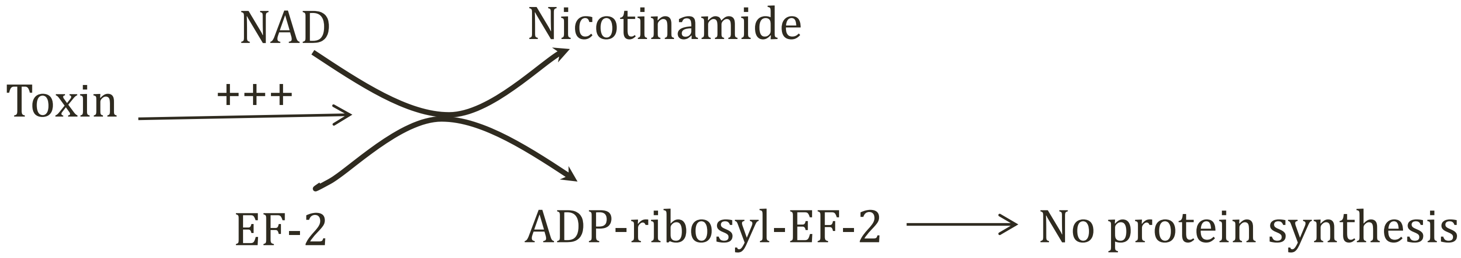
- Corynebacterium diphtheria
- Pseudomonas aeruginosa
- Shigella
- Enterohemorrhagic E. Coli (EHEC)

ADP Ribosylation

- Two toxins work by adding ADP-Ribose to proteins
  - Diphtheria toxin
  - Exotoxin A (pseudomonas aeruginosa)
- Addition of ADP-Ribose makes protein dysfunctional

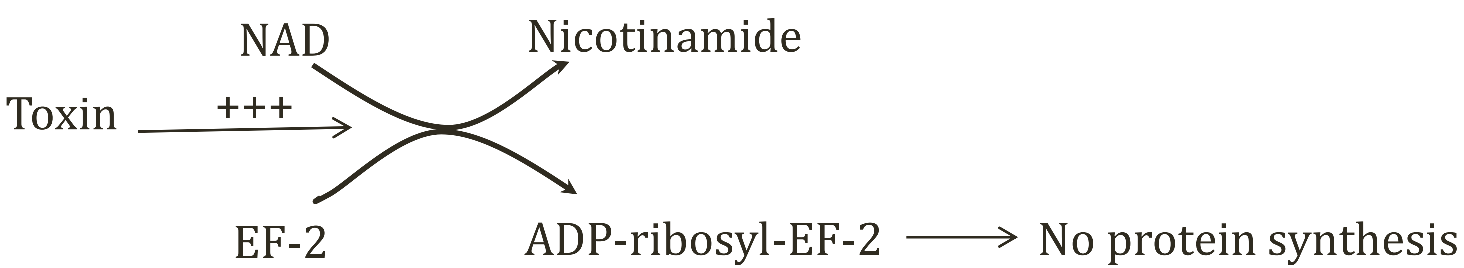
Corynebacterium Diphtheria

- Sore throat with membrane, swollen nodes
- Largely eradicated by vaccination
  - Diphtheria–pertussis–tetanus (DPT) vaccine
- Diphtheria toxin: Inactivates elongation factor (EF-2)
- EF-2 necessary for protein synthesis
- Lethal toxin



Pseudomonas aeruginosa

- Causes many types of infection
  - Skin, sepsis, pneumonia
- Secretes exotoxin A
- Same mechanism as diphtheria toxin



Shigella

- Causes infectious diarrhea
- Secretes shiga toxin
- Binds to 60S ribosome in cells
- Removes a specific adenine residue from rRNA in the 60S ribosomal subunit
- Halts protein synthesis
- Special note:
  - Invasion of GI mucosal cells is main cause of disease
  - Non-toxigenic strains cause significant disease

Enterohemorrhagic E. Coli (EHEC)

- Some E. Coli strains produce “shiga-like” toxin
- Same mechanism as shiga toxin
- Typically causes bloody diarrhea
- Classic serotype is E. coli O157:H7
- Do not invade host cells
  - Attach to intestinal epithelial cells
  - Disease from secretion of proteins into host cells
  - Toxin

Shiga Toxin

- Also stimulates cytokine release
- When reaches systemic circulation, can lead to hemolytic uremic syndrome

Key Points

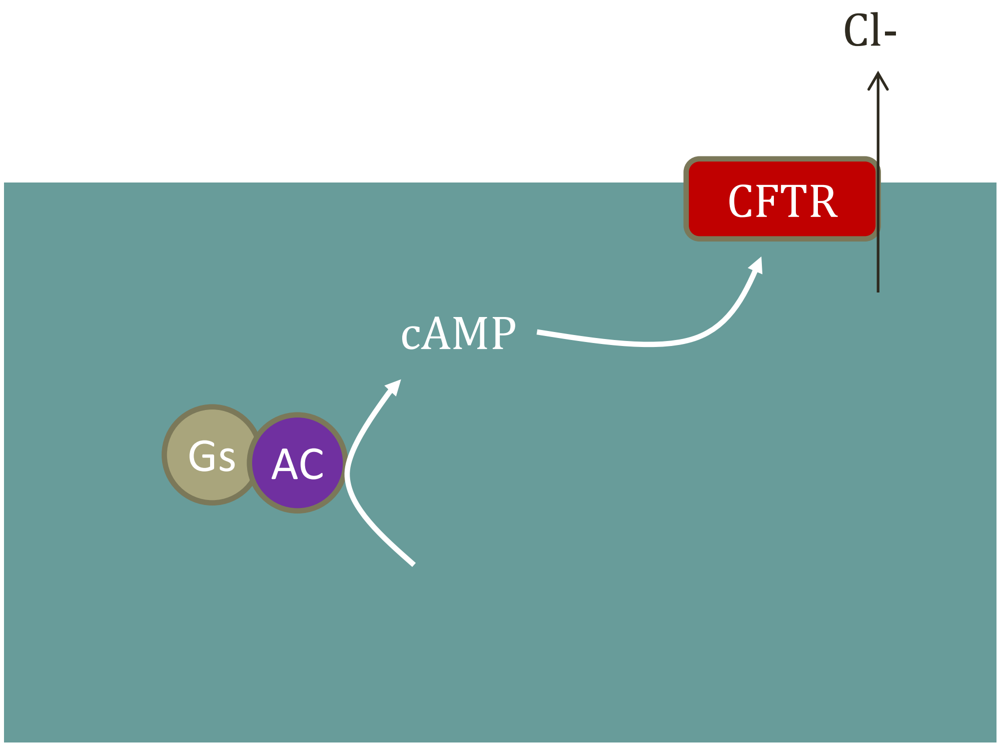
- Shigella and EHEC produce shiga toxins
- Both cause bloody diarrhea
- Shigella
  - Disease from bacterial invasion of mucosa
  - Toxin less important in disease than invasion
- EHEC
  - Do not invade cells
  - Disease from toxin (inflammation)
  - Hemolytic uremic syndrome

Toxin Mechanisms

Increase Fluid Secretion

- Enterotoxigenic E. Coli (ETEC)
- Bacillus anthracis
- Vibrio cholera

Fluid Secretion in GI Tract



Key Points:
#1: Amount of Cl- secreted ≈ amount of water in GI tract
#2: To increase Cl- secretion, active Gs or AC

Enterotoxigenic E. Coli
(ETEC)

- Two toxins differentiated by heat stability
  - Heat labile toxin (LT)
  - Heat stable toxin (ST)

E. Coli Heat Labile Toxin

- Activates adenylate cyclase (↑cAMP)
- Increases water in gut → diarrhea

E. Coli Heat Stable Toxin

- Activates guanylate cyclase
- Increases cGMP
- Stimulation of chloride secretion
- Inhibition of sodium chloride absorption
- More water in gut → diarrhea

Bacillus Anthracis

- Anthrax makes three proteins: protective antigen (PA), lethal factor (LF), and edema factor (EF)
- Alone they cause no known physiological effects
- In pairs they produce toxicity
- Edema toxin = PA + EF
- Mimics adenylate cyclase
- Multiple sites of disease
  - Skin (most common)
  - Lungs (inhalation → necrotizing pneumonia)
  - GI (ulcers)
- Skin and GI lesions often have edematous borders
  - May be caused by edema factor

Vibrio Cholera

- Cholera toxin
- Permanently activates Gs → ↑cAMP
- Voluminous "rice-water" diarrhea
- Common in areas with lack of clean water
- Death: profound dehydration, electrolyte losses, shock
- Aggressive volume repletion is mainstay of treatment

Toxin Mechanisms

Inhibitors of Phagocytosis

- Bordetella pertussis (whooping cough)
- Pertussis toxin
- Shown to inhibit G_i proteins
- Allows over-activation of adenylate cyclase
- ↑cAMP levels in cells in neutrophils
- Result: impaired recruitment of neutrophils

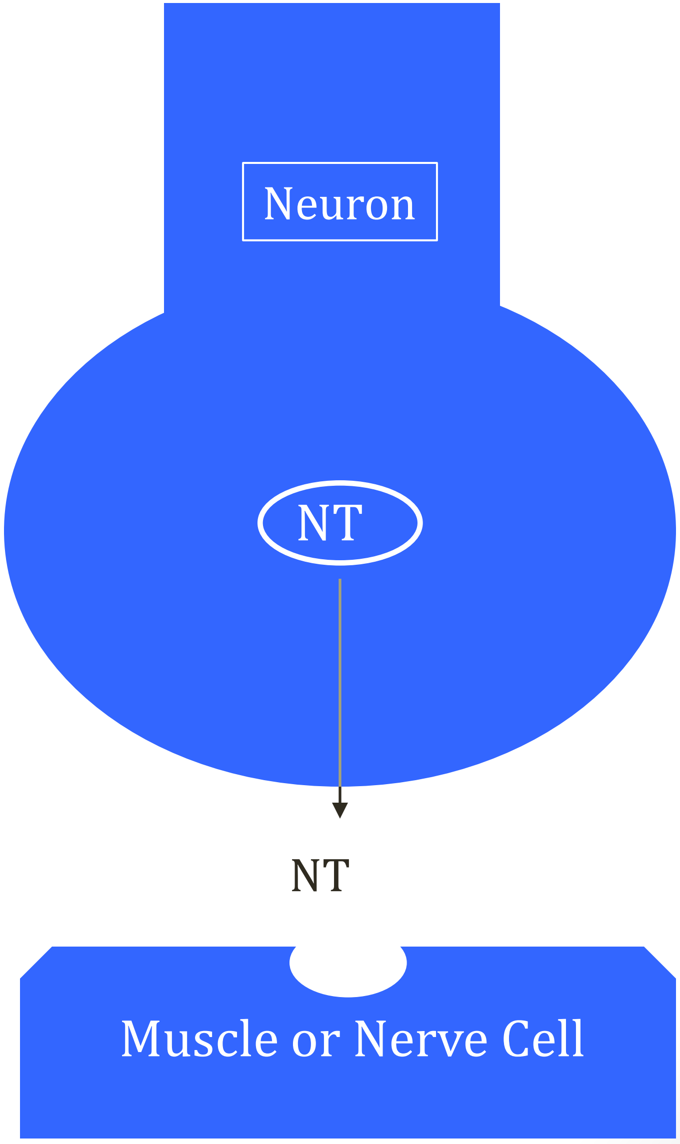
Toxin Mechanisms

Neurotoxins

- Clostridium tetani
- Clostridium botulinum
- Both work by disruption of SNARE proteins

SNARE Proteins

SNARE proteins present in vesicles
Allow vesicles to "dock" and unload NT



Neurotoxins

- Clostridium tetani
  - Tetanospasmin
  - Works in spinal cord (Renshaw cells)
  - Inhibits inhibitory neurons (GABA and glycine)
  - Result: Muscles always on (rigid)
- Clostridium botulinum
  - Botulinum toxin
  - Works at neuromuscular junctions
  - Prevents Ach release (no muscle contraction)
  - Result: Muscles floppy (flaccid paralysis)

Toxin Mechanisms

Lysis of Cell Membranes

- Clostridium perfringens
- Strep pyogenes

Clostridium perfringens

Gas gangrene

- Alpha toxin
- Phospholipase C enzyme
- Degrades phosphatidylcholine and sphingomyelin
- Muscle breakdown (myonecrosis)
- Causes a decline in muscle blood flow
- Forms occlusive plugs: platelets, leukocytes, fibrin
- Result: Low O_2 environment favorable to bacteria

Strep Pyogenes

Strep Throat/Rheumatic Fever /Glomerulonephritis

- Streptolysin O
- "Cytolysin" (lysis cells)
- Responsible for beta hemolysis (also streptolysin S)
- Anti-streptolysin O (ASO) antibodies
  - Elevated following strep infection
  - Can be useful in suspected rheumatic heart disease or post-strep glomerulonephritis

Toxoid Vaccines

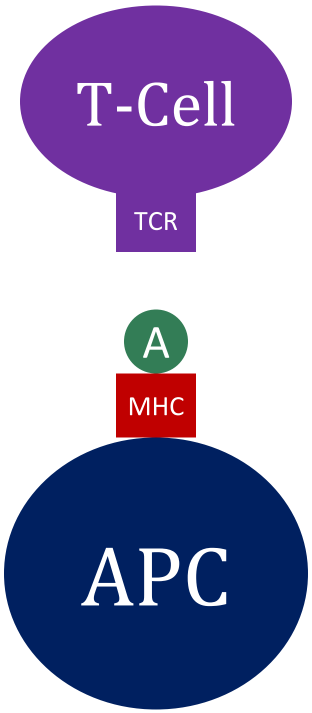
- Toxoid = inactivated bacterial toxin
- Used for vaccination
- Used to prevent diphtheria and tetanus
- Part of DTaP combined immunization
  - Diphtheria
  - Tetanus
  - “Acellular” Pertussis (inactive toxin plus bacterial elements)

Exotoxin Genetics

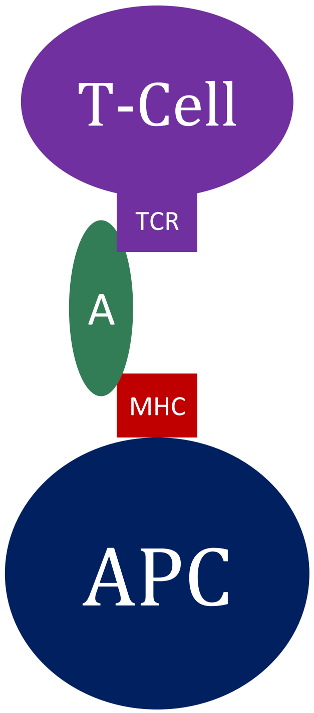
- Many exotoxin genes not part of chromosome
- Plasmid-encoded
  - E. coli heat-labile toxin
- Bacteriophage-encoded
  - Corynebacterium diphtheriae
  - Strep pyogenes erythrogenic
  - E. Coli shiga-like toxin
  - Botulinum toxin
  - Cholera toxin

Superantigens

- Activate a MASSIVE number of T-cells



Normal Antigen



Super Antigen

Superantigens

- Typical antigen response: <1% T-cells
- Superantigen: 2-20% T-cells
- HUGE release of cytokines (IFN-γ and IL-2)
- Massive vasodilation and shock

Superantigens

- Staph aureus
  - Toxic shock syndrome toxin (TSST-1)
- Strep pyogenes (group A strep)
  - Pyrogenic exotoxin A or C
- Both can cause toxic shock syndrome
  - More common with staph
  - Strep TSS often associated with necrotizing fasciitis

Toxic Shock Syndrome

- Fever, shock (hypotension), red rash
- Diffuse, red erythroderma (resembles sunburn)
- After weeks: desquamation of palms/soles
- Diarrhea is common
- Multi-organ system failure often results
- Classic scenarios (staph + packing):
  - Women using tampons
  - Surgical wound with packing

Growth and Genetics

Jason Ryan, MD, MPH

Boards&Beyond
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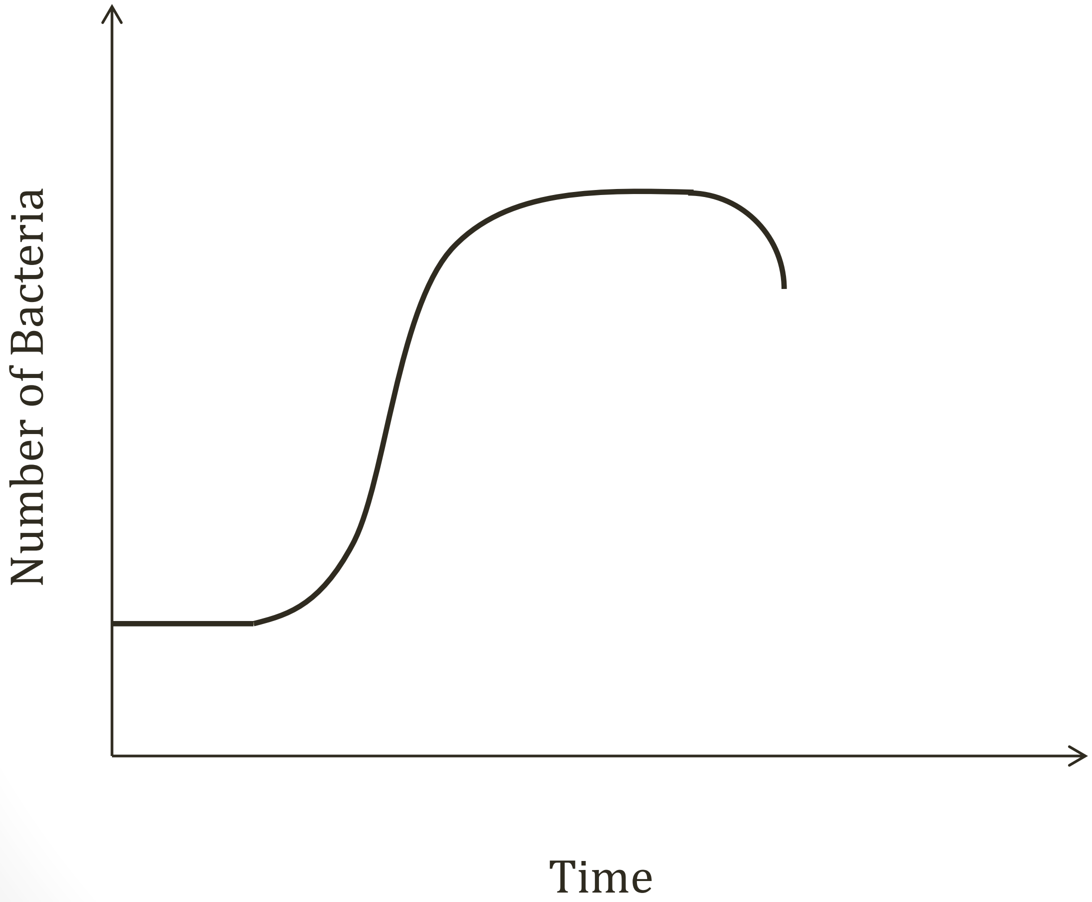
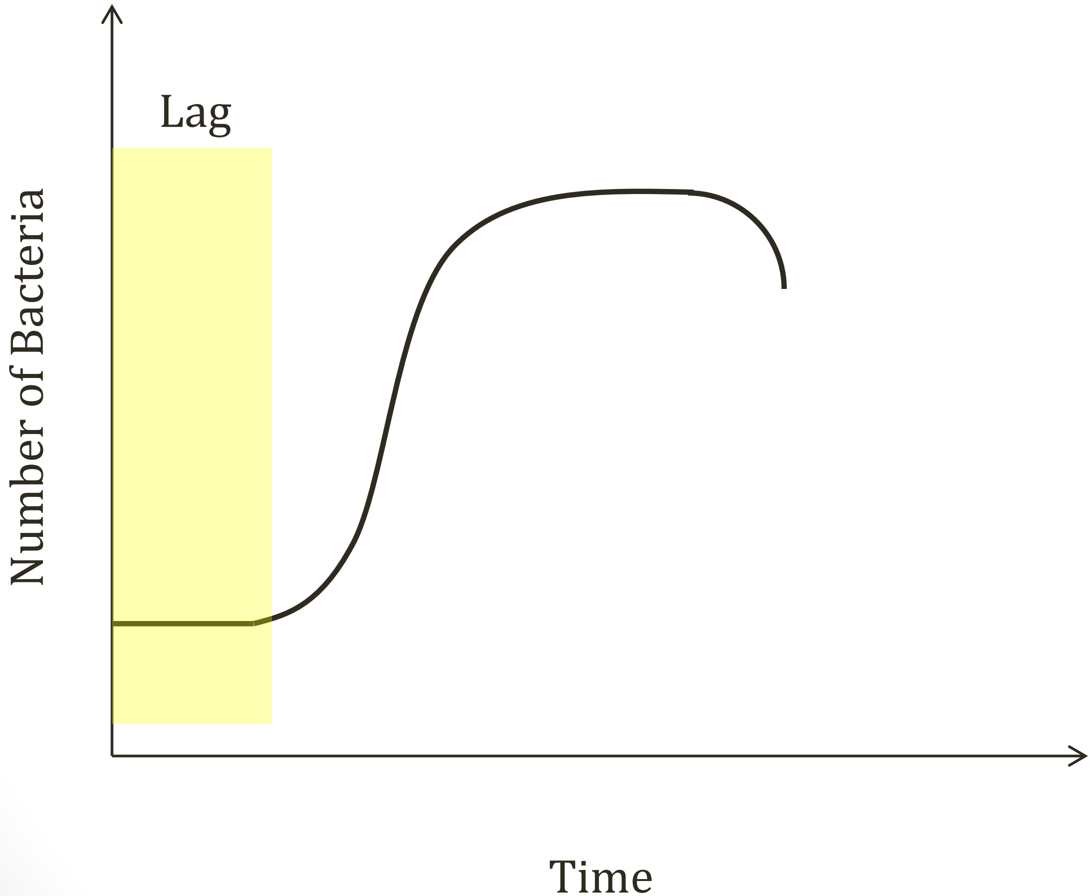
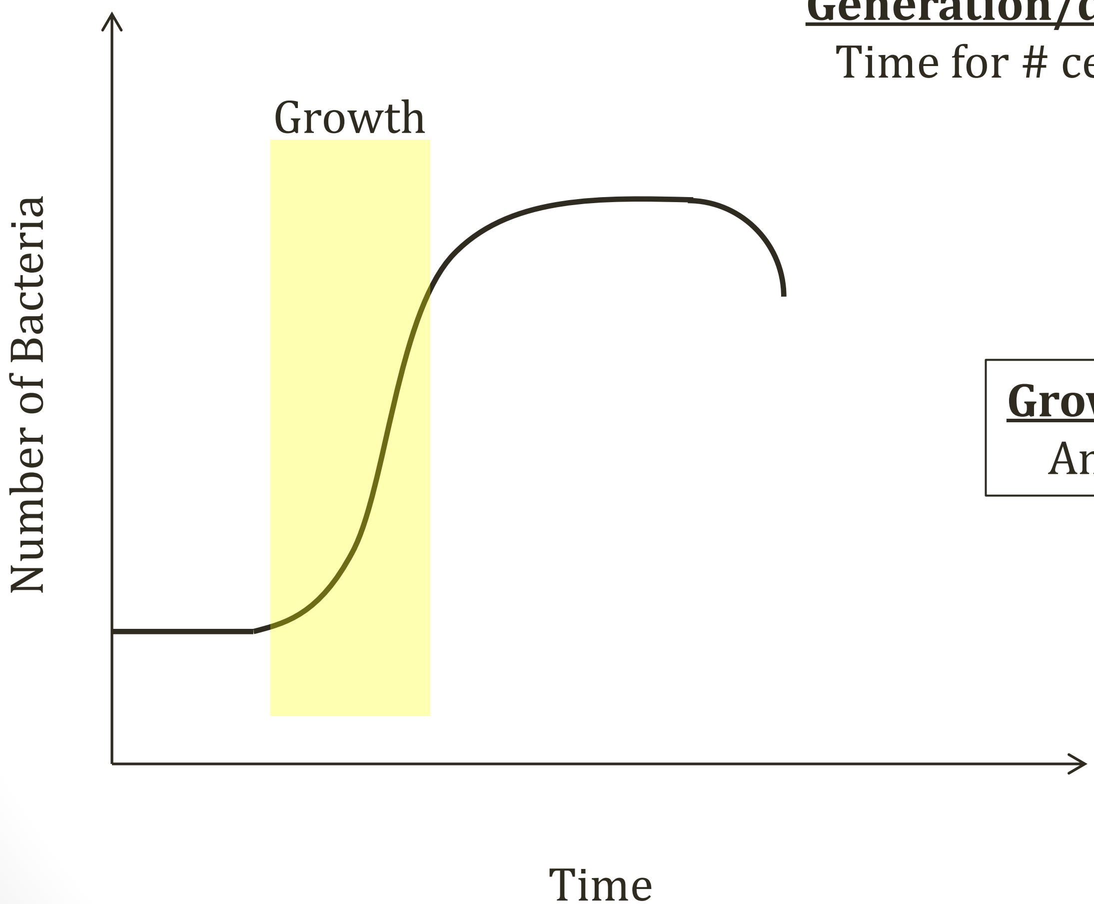
Bacterial Growth Curve



Bacterial Growth Curve



Bacterial Growth Curve



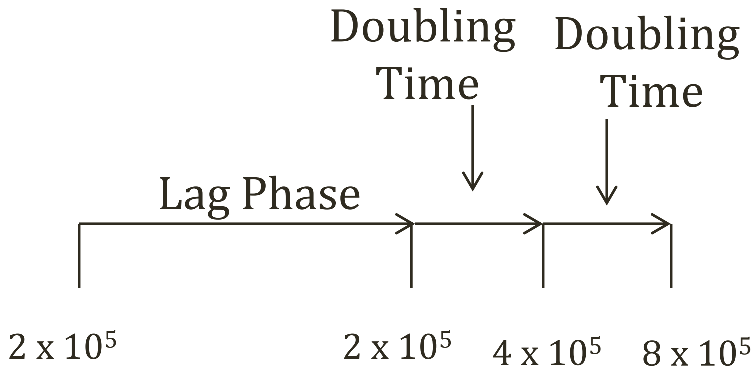
<u>Generation/doubling time</u>

Time for # cells to double

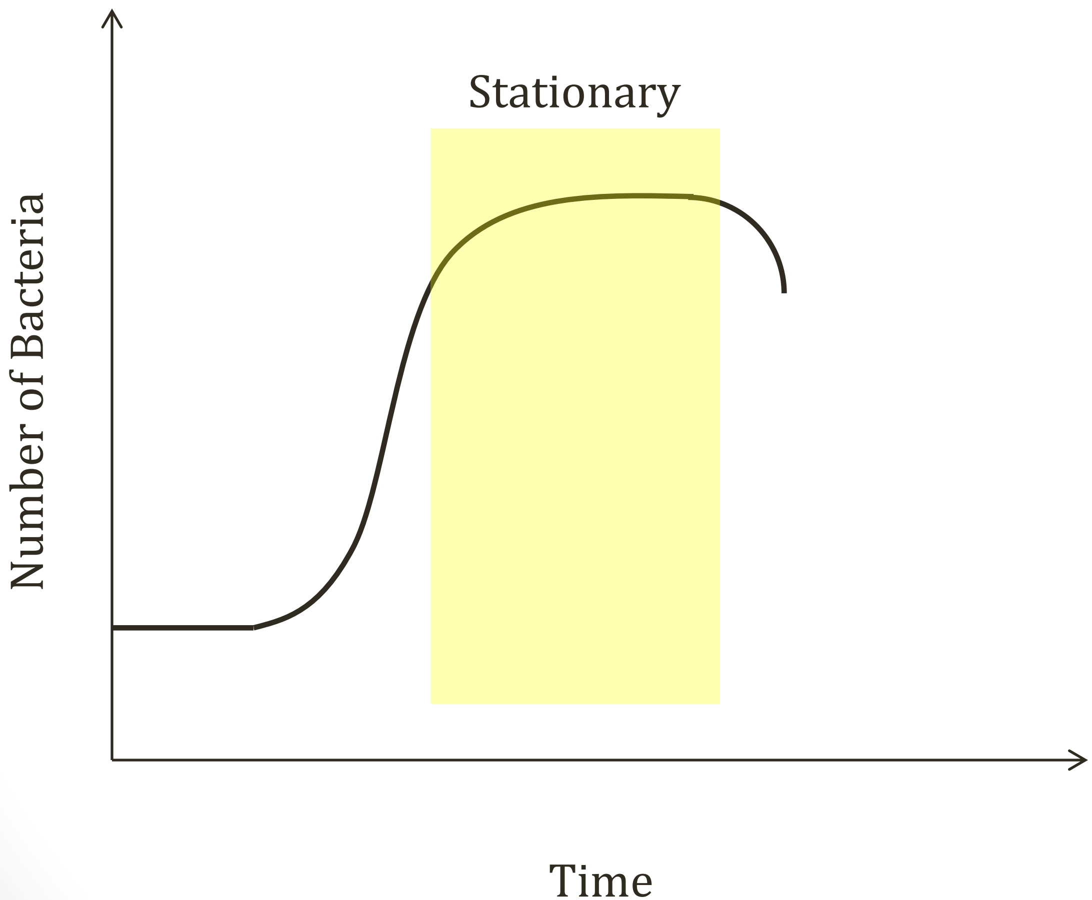
<u>Growth Phase</u>

Antibiotics

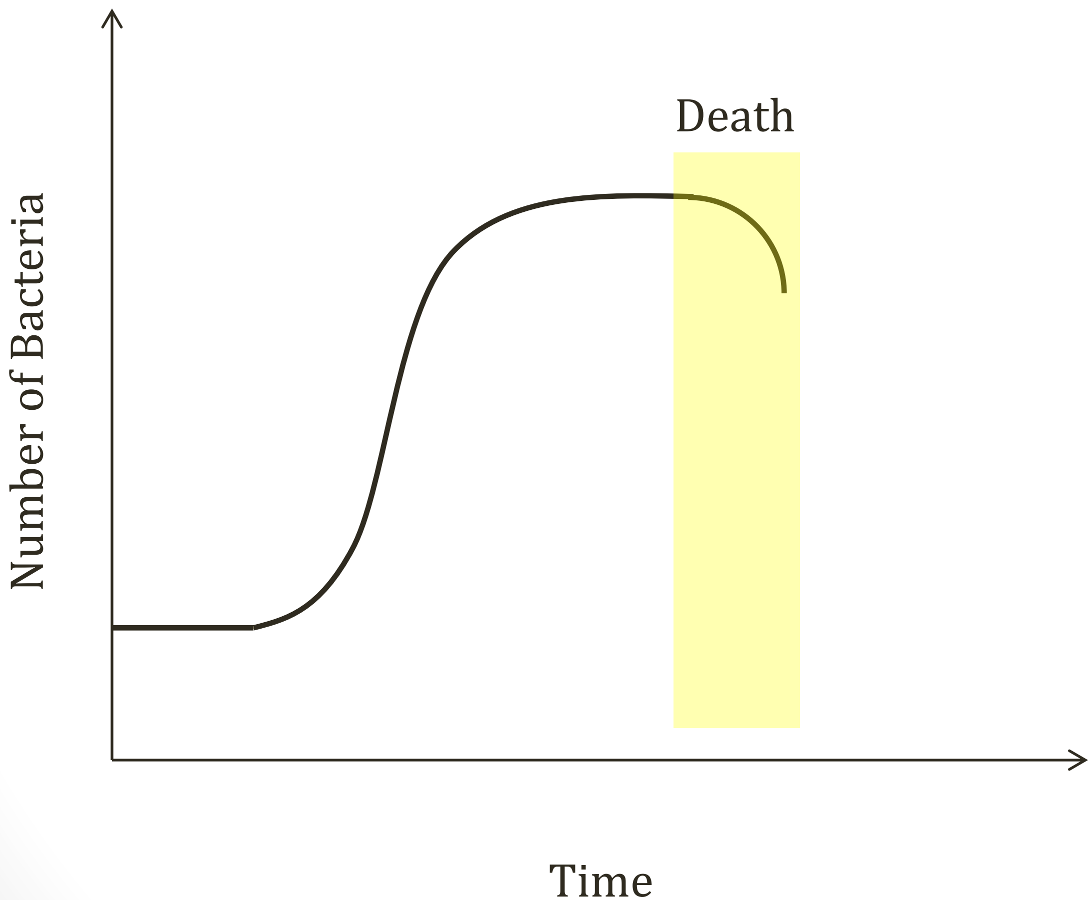
Bacterial Growth Curve



Bacterial Growth Curve



Bacterial Growth Curve



Gene Transfer

- Bacteria often transfer genetic material
- Key for evolution of antibiotic resistance
- Three key mechanisms:
  - Transformation
  - Conjugation
  - Transduction

Bacterial Transformation

- Direct uptake DNA from **surrounding environment**
- Allows for evolution of DNA over time
- Very useful technique in micro labs
- Introduce genes to bacteria for replication

Bacterial Conjugation

- Transfer from one cell to another via **pilus**
  - Physical contact of two organisms
- DNA transferred via plasmids

Plasmids

- Small DNA molecule within a cell
- Physically separated from chromosomal DNA
- Can replicate independently
- Can contain genes for antibiotic resistance, toxins
- Can be transferred one bacteria to another

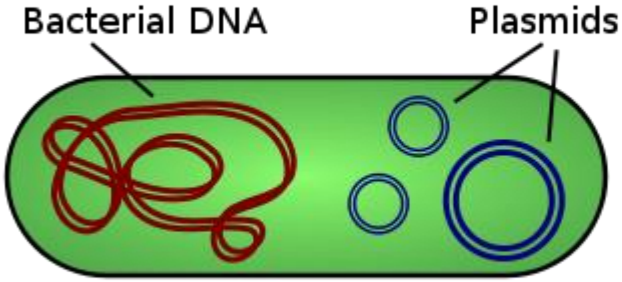


Image courtesy of Spaully/Wikipedia

Bacterial Conjugation

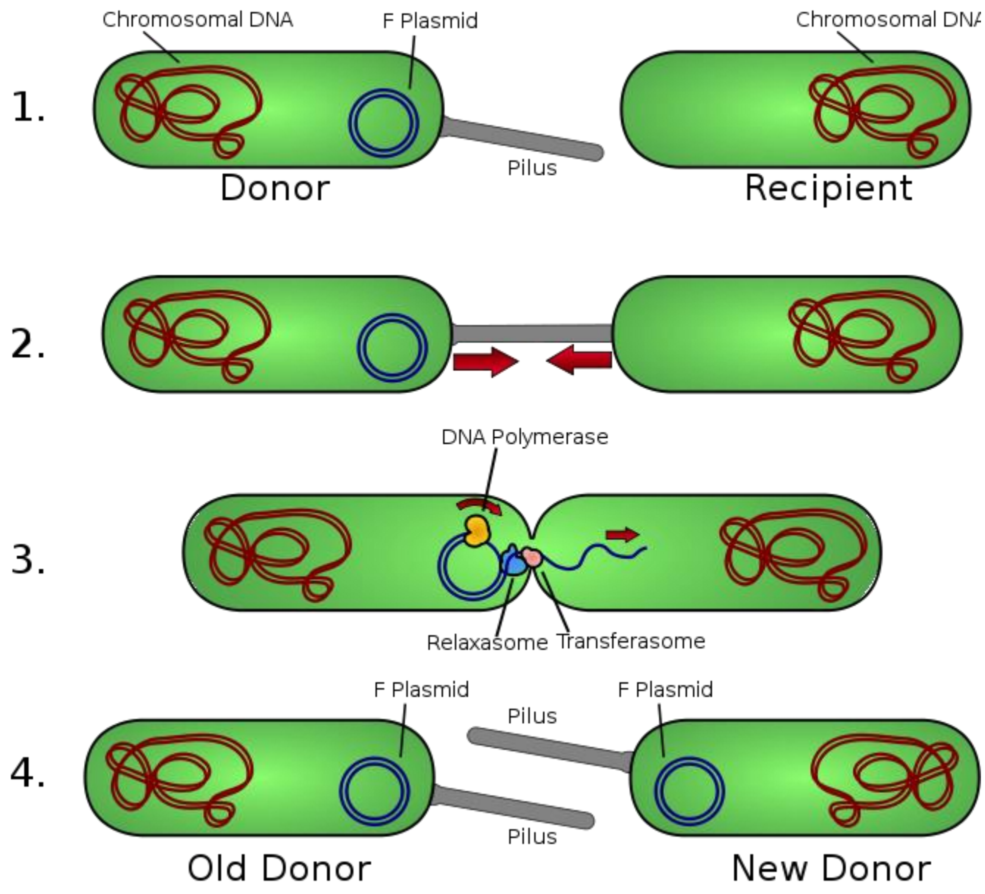
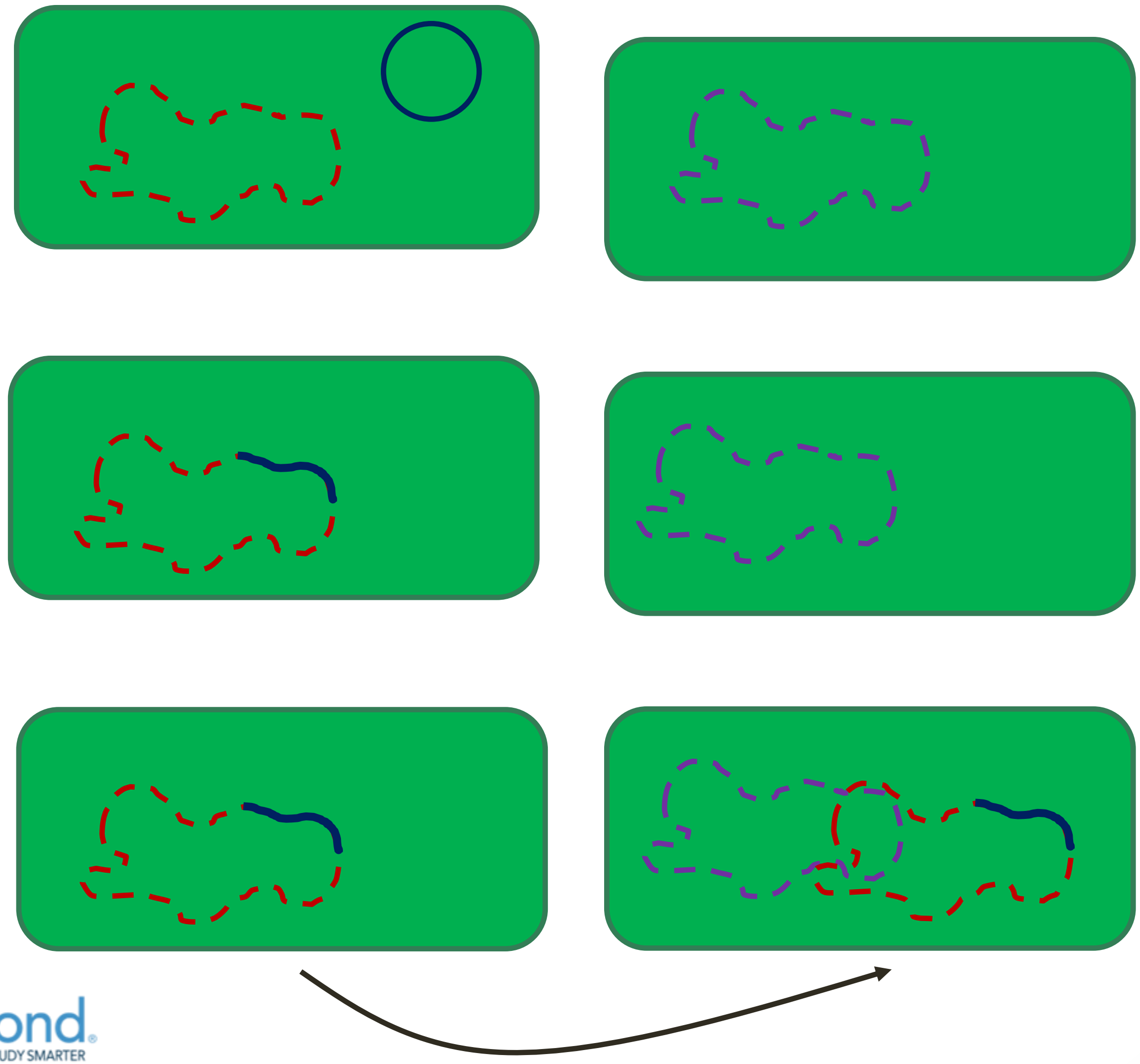


Image courtesy of Adenosine/Wikipedia

Transformation vs. Conjugation

- Classic scenario:
  - Strain A requires amino acid X for growth (does not need Y)
  - Strain B requires amino acid Y for growth (does not need X)
  - Strain A and Strain B grown together without X or Y
  - DNAase added to medium to degrade DNA
  - Bacteria grow!
  - Ability to grow without X/Y xferred between bacteria
  - Cannot be transformation
    - DNAase destroyed any leaked DNA
  - Must be conjugation

High Frequency Strains



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High Frequency Strains

- Used to map genes
- Process takes time
- Can interrupt at various time intervals
- See which genetic material has transferred
  - Plasmid site is origin of genetic transfer
  - Initial material transferred is that closest to plasmid
- With multiple experiments can make a map

Transduction

- Transfer of DNA via a **bacteriophage**
    - Virus that infects bacteria
- Virus picks up DNA, transfers to another bacteria

Transduction

- Generalized
  - Virus infects bacteria
  - Multiplies, randomly picks up host DNA
  - Host DNA transferred to other bacteria

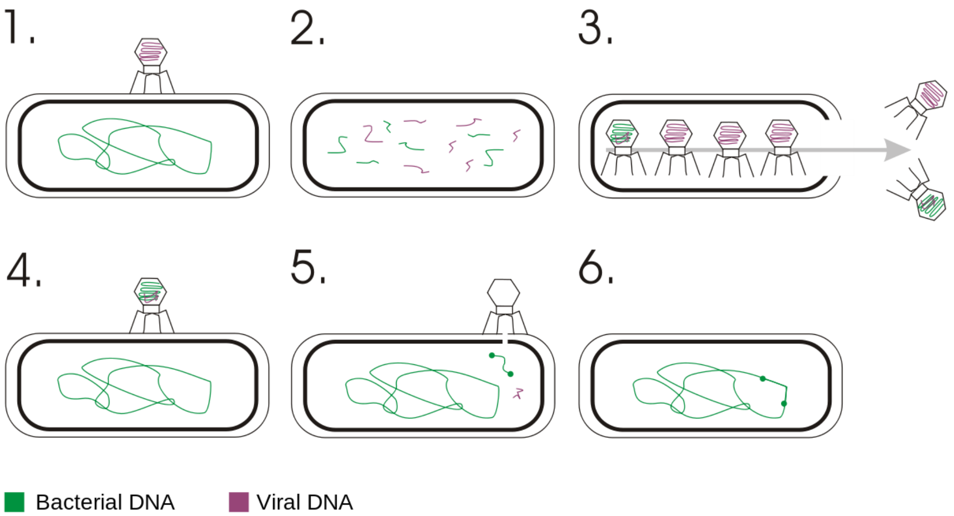


Image courtesy of Wikipedia/Public Domain

Transduction

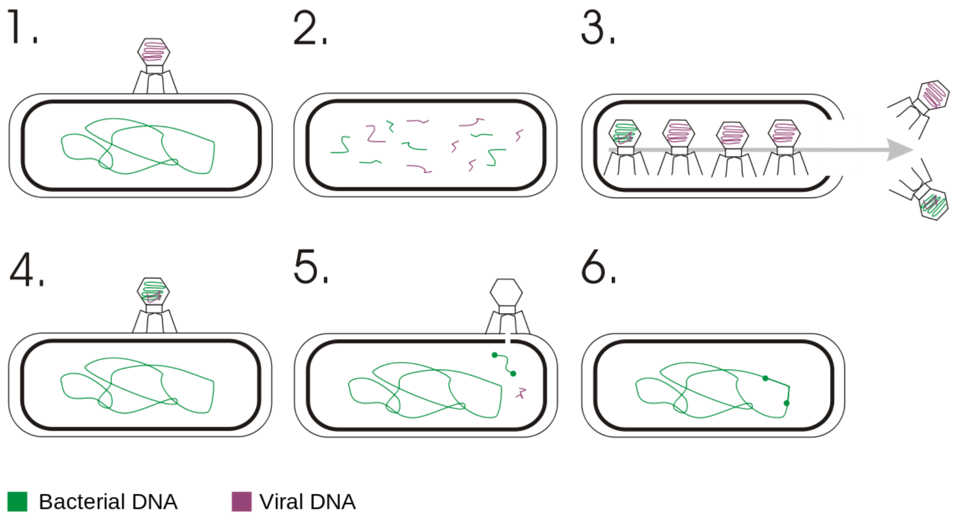
- Specialized
  - Transfer of specific genes
  - Virus DNA inserts into host DNA (lysogeny)
  - When bacteriophage DNA excised, packaged into virus with specific host DNA

Lytic vs. Lysogenic Phages

- Transduction happens in two ways
- Lytic cycle
  - Nuclear material enters bacteria
  - Multiplies, lyses cell
  - Releases progeny viruses
- Lysogenic cycle
  - Nuclear material enters cell
  - Incorporates in host DNA
  - May later become excised (enter lytic phase)
- Phages that replicate only via the lytic cycle: virulent
- Phages that replicate using both: temperate

Lytic Phages

- Virus infects bacteria
- Uses cellular machinery to reproduce
- Lyses cell
- Usually generalized gene transfer



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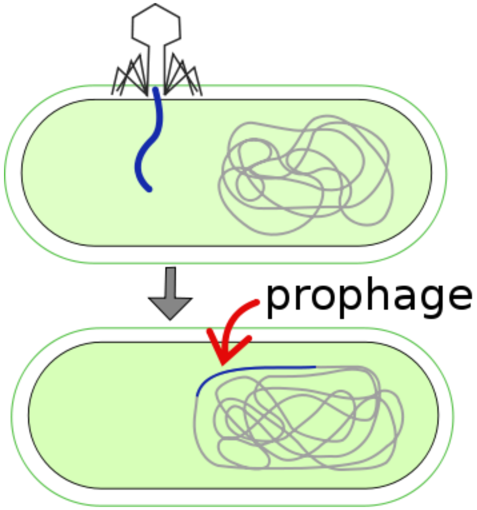
Lysogenic Phages

- Virus infects bacteria
- Incorporates phage DNA into bacterial DNA
- Can remain dormant for long periods of time
- Certain triggers (i.e. UV light) induce genome excision
- Results in a lytic cycle and release of phage particles



Asiela/Wikipedia

Why Lysogeny Matters

- Genes for some **bacterial toxins** are transferred to non-toxic strains via lysogeny
- Example:
    - Not all strains C. diphtheria are toxic
    - Gene for toxin is not part of bacteria's genome
    - Gene carried by a phage (corynephage)
    - Toxicity depends on infection with phage

Lysogenic Toxins

- Diphtheria toxin
- Erythrogenic toxin (S. pyogenes; Scarlet fever)
- Shiga-like toxin (E. Coli; EHEC)
- Cholera toxin
- Botulinum toxin

Source: Brussow, et al. Microbiol Mol Biol Rev. Sep 2004; 68(3): 560–602

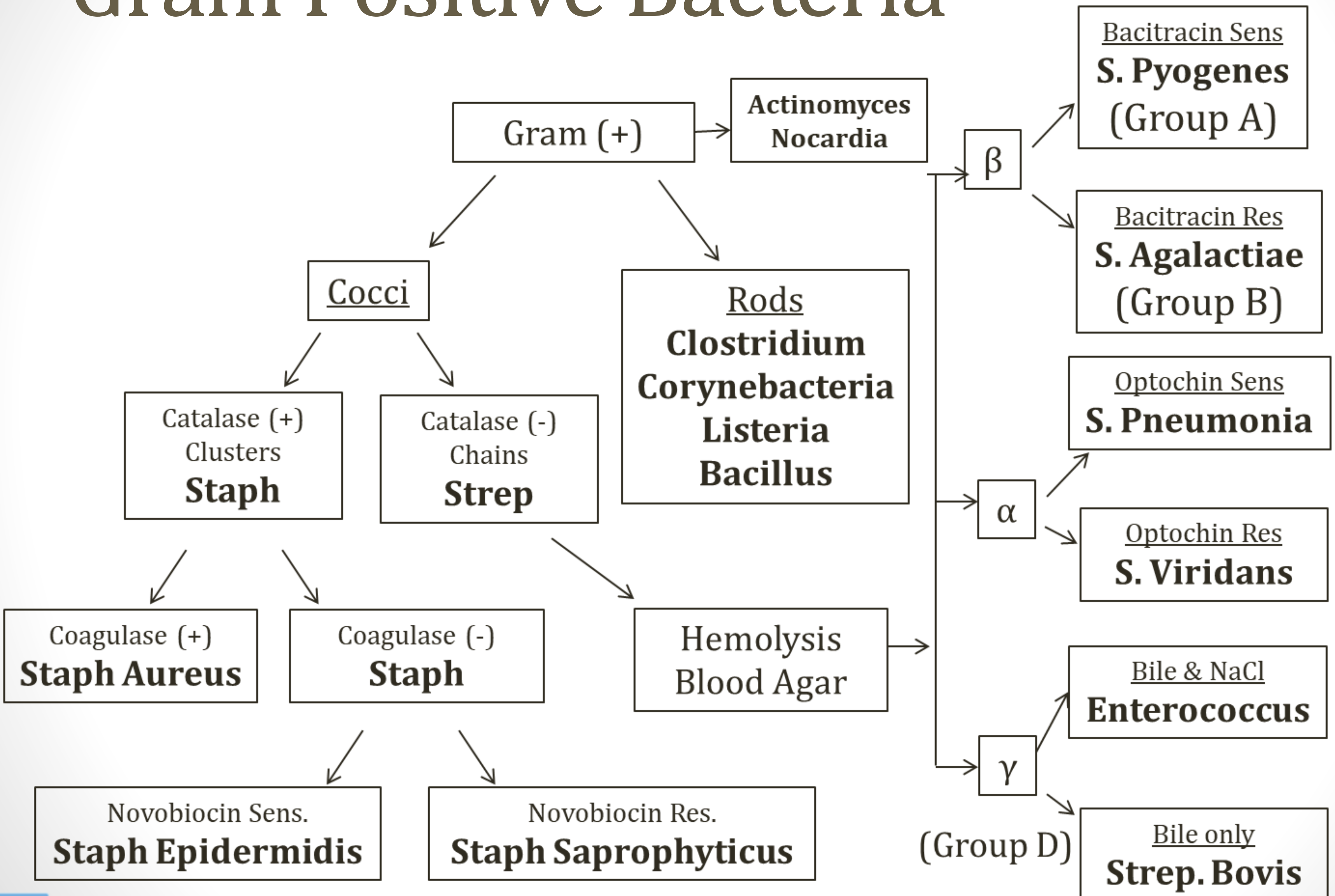
Transposition

- Transposons are DNA segments within bacterial DNA
- Can be excised and reintegrated in new locations in DNA
- Once excised, can also be moved to plasmid
- Mechanism of transfer of **resistance to antibiotics**
    - Bacteria #1 is resistant
    - Transposon segment carries resistance gene
    - Transposon moved to plasmid
    - Plasmid transferred to other bacteria

Bacterial Identification

Jason Ryan, MD, MPH

Gram Positive Bacteria



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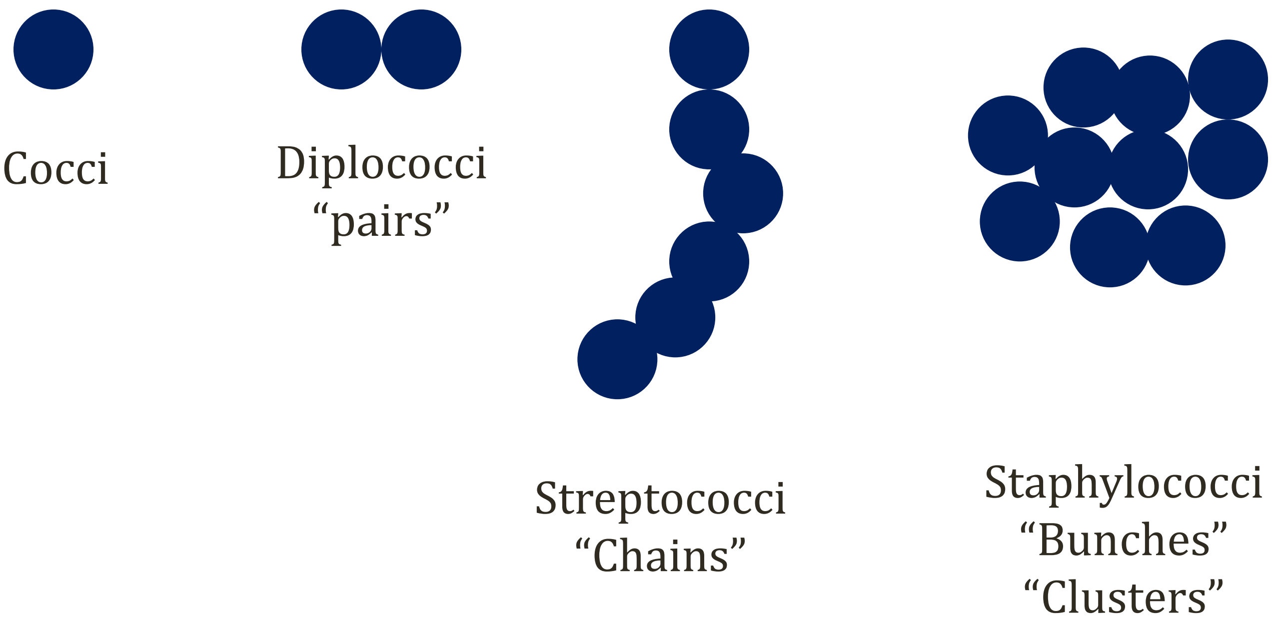
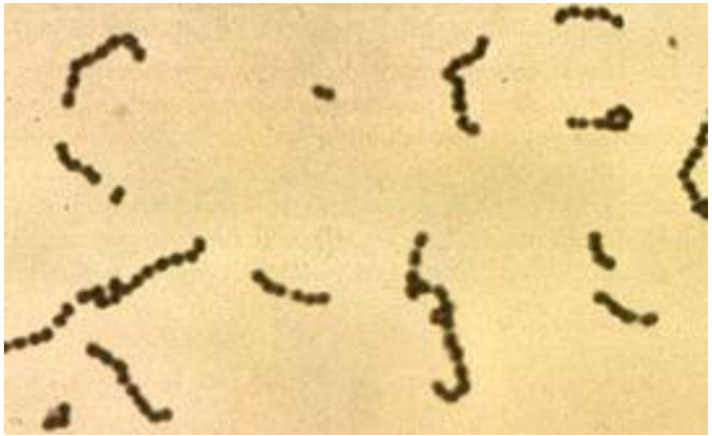
Lancefield Grouping

- System for classifying streptococci
- Based on “C carbohydrates” in the cell wall that allow agglutination with particular antisera
- Commercially available tests for different antigens
- Clinically relevant groups:
  - Group A: Strep Pyogenes
  - Group B: Strep Agalactiae
  - Group D: Enterococcus

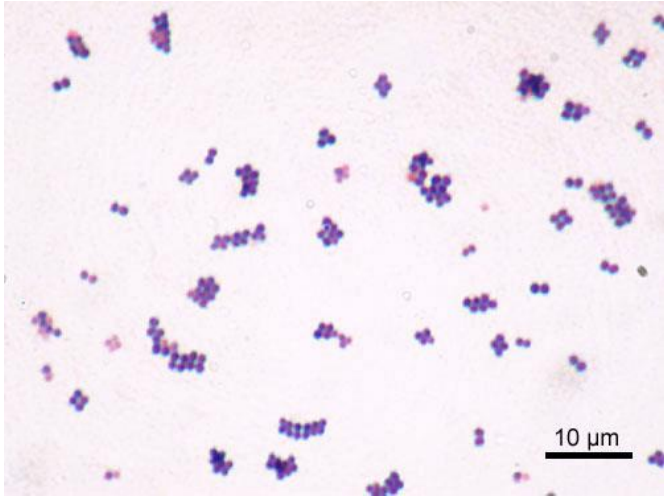
Cocci


Cocci
Diplococci
“pairs”
Streptococci
“Chains”
Staphylococci
“Bunches”
“Clusters”

Cocci



Streptocci
"Chains"



Staphlococci
"Bunches"
"Clusters"

Image courtesy GrahamColm/Wikipedia

Image courtesy Y Tambe/Wikipedia

Blood Agar

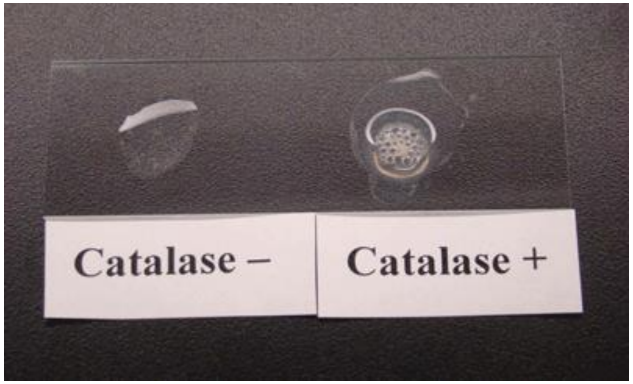
- Contain mammalian blood – usually 5% sheep blood
- Non-selective
- Enriched (blood)
- Differential by hemolysis pattern

<u>Hemolysis Patterns</u>
Beta = lysis
Alpha = partial
Gamma = no lysis

Image courtesy Y tambe/Wikipedia

Catalase Test

- Differentiates Staph from Strep
- Catalase enzyme produced by bacteria that use oxygen
- Breaks down H_2O_2 into H_2O and O_2 (makes bubbles)
- Hydrogen peroxide on slide
- Add bacteria
- Look for bubbles
- Catalase positive = bubbling
- Catalase negative = no bubbling



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CGD

Chronic Granulomatous Disease

- Phagocytes use NADPH oxidase
- Generate H_2O_2 from oxygen (respiratory burst)
- CGD = Loss of function of NADPH oxidase
  - Phagocytes cannot generate H_2O_2
- Catalase (-) bacteria generate their own H_2O_2 which phagocytes use despite enzyme deficiency
- Catalase (+) bacteria breakdown H_2O_2
  - Host cells have no H_2O_2 to use → recurrent infections
- Five organisms cause almost all CGD infections:
  - Staph aureus, Pseudomonas, Serratia, Nocardia, Aspergillus

Source: UpToDate

Coagulase Test

- Differentiates Staph Aureus from other Staph
- Rabbit plasma in tube, add bacteria
- Coagulase (cell surface) causes fibrin clot to form
- Coagulase positive = clumping
- Coagulase negative = no clumping

Novobiocin

- Differentiates S. saprophyticus from S. epidermidis
- Technique:
  - Plate bacteria on agar with Novobiocin "disk"
  - Measure clearance zone around disk
- Resistant = Growth near edge of disk
- Sensitive = Large zone of clearance around disk

CDC/Public Domain

Bacitracin

- Differentiates Group A strep from Group B strep
- Bacitracin: antibiotic that interferes with peptidoglycan synthesis
- Bacteria vary in their susceptibility
- Technique:
  - Plate bacteria on agar with bacitracin disk
  - Measure clearance zone around disk
- Resistant = Growth near edge of disk
- Sensitive = Large zone of clearance around disk

Optochin
ethylhydrocupreine

- Differentiates S. pneumonia from S. viridans strep
- S. pneumonia highly sensitive to Optochin
- Technique:
  - Plate bacteria on agar with optochin disk
  - Measure clearance zone around disk
- Resistant = Growth near edge of disk
- Sensitive = Large zone of clearance around disk

Bile Esculin Agar

- Selective for:
  - Group D strep (Enterococci and S. bovis)
- Bile salts inhibit most Gram-positive bacteria
- Esculin:
  - Hydrolyzed by Group D strep
  - Media turns dark brown/black

NaCl Media

- Differentiates Enterococcus from non-enterococcus Group D bacteria (S. bovis)
- Enterococcus is “salt tolerant”
- Can grow in high salt concentrations
- Inoculate bacteria on high NaCl media
- Watch for growth

Lancefield Group D

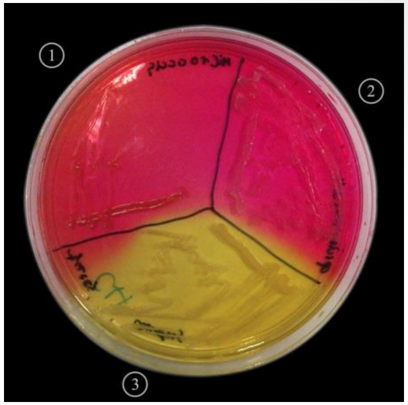
Bile Esculin Agar Turns Black
(positive result)

Group D Strep

<u>Grows on NaCl</u>
Enterococcus

<u>Does not grow on NaCl</u>
Strep Bovis

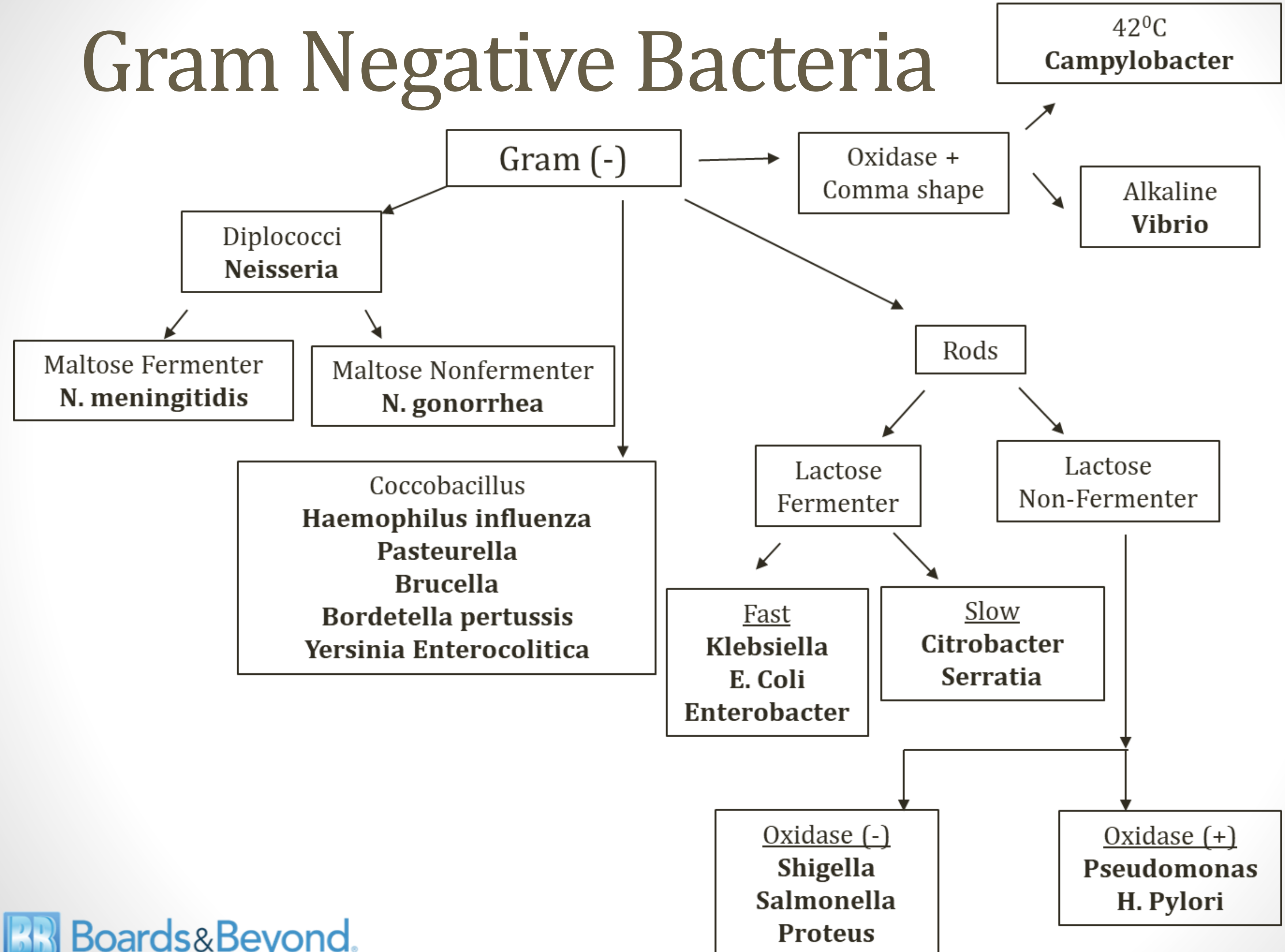
Mannitol Salt Agar



Navaho/Wikipedia

- Used to differentiate staph species
- Contains high concentration of salt (7.5%)
- Staph can tolerate high saline levels
- Contains mannitol and pH indicator (phenol red)
- Mannitol fermenters make acid
- Phenol red turns yellow
- Staph aureus ferments mannitol
- Most other staph do not
- **Growth on MSA with yellow color is Staph Aureus**

Gram Negative Bacteria



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Maltose

- Neisseria meningitidis can metabolize maltose
- Neisseria gonorrhoeae cannot
- Growth media with maltose used to differentiate

Lactose Fermentation

- MacConkey's Agar
- Selective media for gram (-) bacteria
- Contains bile salts as inhibitors of growth
- Inhibit Gram (+) bacteria
- Inhibits fastidious gram (-): Neisseria, Pasteurella
- Differential for lactose fermenters
  - Lactose fermentation produces acid → turns agar pink
  - Non-lactose fermenters are colorless

MacConkey's Agar

Image courtesy Wikipedia/Public Domain

Fast and Slow Fermenters

- Citrobacter and Serratia can initially appear as non-lactose fermenting due to slow growth
- Longer incubation will show growth

Oxidase

- Test for presence of cytochrome oxidase
- Bacterial colonies placed on paper discs with indicator present
- If oxidase is present, color change occurs

Campylobacter & Vibrio

- Oxidase (+) organisms that are "comma shaped" may be Campylobacter or Vibrio
- Campylobacter grows at 42^{o}C (Vibrio does not)
- Vibrio grows on alkaline media (Campy does not)

H_2S Production

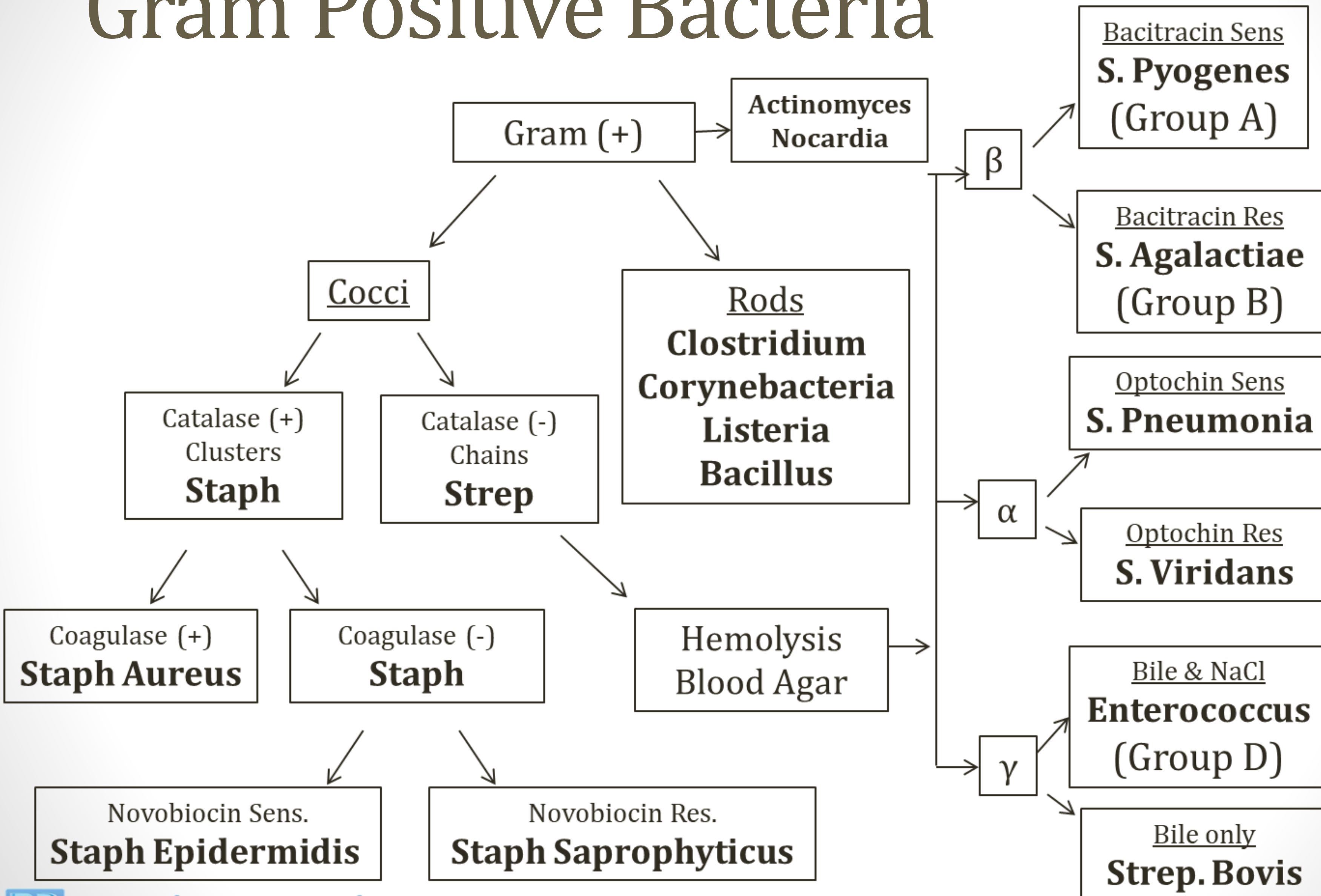
- Oxidase (-) organisms can be subdivided by H_2S
- Salmonella and proteus produce H_2S
- Shigella does NOT produce H_2S
- Triple Sugar Iron (TSI) test
  - Organisms that produce H_2S will turn TSI media black

Staphylococci

Jason Ryan, MD, MPH

Boards&Beyond
STUDY SMARTER

Gram Positive Bacteria



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Staphylococci

- Staph Aureus
- Staph Epidermidis
- Staph Saprophyticus
- All gram positive cocci
- All form clusters
- All catalase (+)

Staph Aureus
Special Features

1. Basic habitat is the nares (nose)
   - 30% of people carry the bacteria
2. Produces a yellow pigment (aureus = golden)
3. Beta-hemolytic
4. Coagulase (+)
   - Forms fibrin clot
5. Protein A virulence factor
   - Blocks Fc-IgG interaction
   - Prevents phagocytosis & complement activation
6. Produces several toxin-related diseases

Staph Aureus

Infections

- Toxin disease
  - Toxic Shock Syndrome (TSST-1)
  - Food poisoning (Staph aureus enterotoxin)
  - Scalded skin syndrome (Exfoliatin)
- Infectious diseases
  - Skin infections (Impetigo)
  - Pneumonia
  - Endocarditis
  - Osteomyelitis
  - Abscesses

Toxic Shock Syndrome

- Toxic Shock Syndrome Toxin (TSST-1)
- Fever, shock (hypotension), red rash
- Diffuse, red erythroderma (resembles sunburn)
- After weeks: desquamation of palms/soles
- Diarrhea is common
- Multi-organ system failure often results
- Classic scenarios (staph + packing):
  - Women using tampons
  - Surgical wound with packing

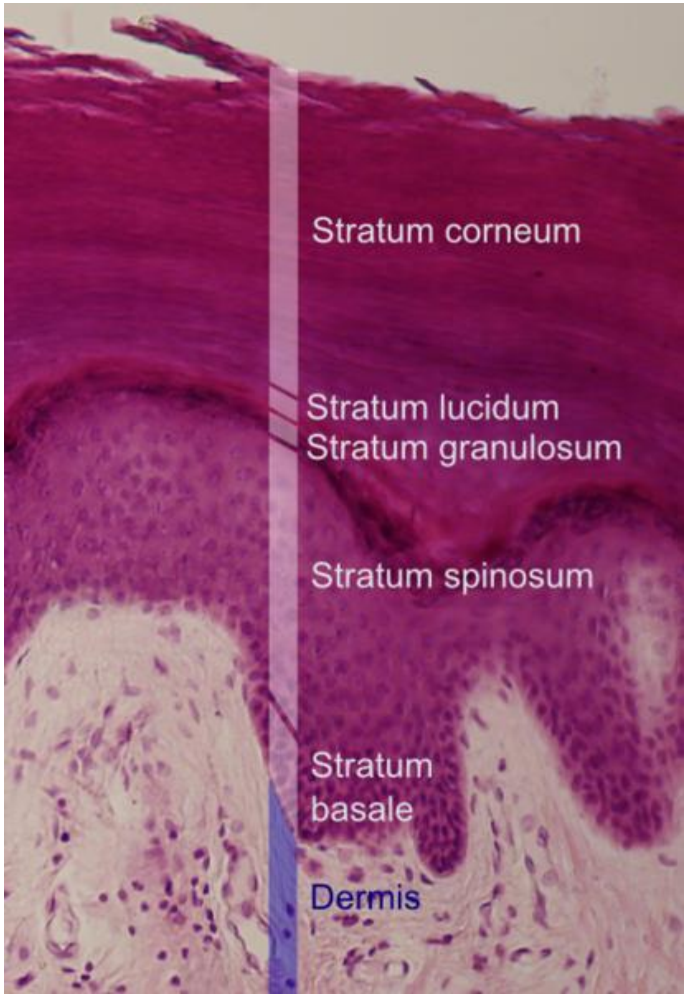
Staph Food Poisoning

- Food handler contaminates food
- Food left at room temperature several hours
  - Picnic is classic scenario
- Bacteria grow in food → produce enterotoxin
- Ingestion of preformed toxin causes disease
- GI illness develops ~3 to 6 hours later
  - Nausea, vomiting (diarrhea rare)
  - Abdominal cramps
- Look for multiple sick people after eating at a picnic
- Classic food is mayonnaise in potato or egg salad

Scalded Skin Syndrome

- Newborn disease
- Caused by S. Aureus exfoliative toxin (Exfoliatin)
- Classically occurs 3 to 7 days of age
- Fever, diffuse erythema starting at the mouth
- Sloughing of skin
- Toxin destroys keratinocyte attachments in stratum granulosum only
- Damage intraepidermal: Heals completely (no scar)
- Nikolsky's sign: skin slips off with gentle tug

Skin Layers



Mikael Häggström, /Wikipedia

Bullous Impetigo

- Impetigo = skin infection
  - Caused by Group A strep or Staph Aureus
  - Honey colored, crusted lesions
- Bullous impetigo = variant of impetigo with bullae
- Bullae = fluid-filled sacs similar to blisters
- Bullous impetigo caused by S. Aureus
- Classically occurs in children
- Easily spread one child to another
- S. Aureus exfoliative toxin strains

Image courtesy of Åsa Thörn/Wikipedia

Pneumonia

- Staph is rare cause of lobar pneumonia
- Classically occurs as “post-infectious”
  - Bacterial pneumonia following influenza

Endocarditis

- Classic cause of ACUTE endocarditis
  - Rapid onset of symptoms
  - Very ill patient
  - Often no pre-existing valve disease (i.e. mitral valve prolapse)
- Contrast with subacute → Strep Viridans
  - Slower onset of symptoms
  - Less sick patient
  - Prior valve abnormality

Intravascular devices

- "Central lines"
- Common cause of staph bacteremia
- Most important preventative measure is sterile technique:
  - Wash hands
  - Gloves
  - Sterile insertion practices

Osteomyelitis

- S. Aureus is common cause of osteomyelitis
- Children: Usually long bones (femur, tibia, fibula)
- Adults: Usually spine
- Mechanisms:
  - Hematogenous spread
  - Spread from skin/soft tissues
  - Trauma (surgery)
- Symptoms usually localized pain +/- fever
- Diagnosis made by imaging (CXR, CT scan, MRI)

Osteomyelitis

Classic Causes

- Child
  - Staph aureus (hematogenous spread)
- Sickle Cell patient
  - Salmonella (hematogenous spread)
- TB patient
  - Pott's disease (vertebrae/spine)
- Diabetic
  - Polymicrobial from foot ulcer
- Bedbound patients
  - Polymicrobial from pressure sores

Cellulitis

- Infection of deep dermis and subcutaneous fat
- Mostly caused by β-hemolytic streptococci
- S. Aureus can also cause
- Antibiotics must cover Staph

Image courtesy of Pshawnoah/Wikipedia

Abscesses

- Bacteria and inflammatory cells (pus)
- Walled off in deep tissues
- Skin abscesses commonly caused by S. Aureus
  - Furuncle = boil; infection of hair follicle
  - Carbuncle = multiple boils clustered together
- Tonsillar abscesses
- Mainstay of treatment is incision and drainage

Staph Aureus Antibiotics

- Most strains of Staph resistant to penicillin
- Produce beta-lactamases
- Antistaphylococcal penicillins
  - Dicloxacillin, Nafcillin, Oxacillin
- First generation cephalosporins
  - Cephalexin
- Beta lactam plus inhibitor
  - Amoxicillin/clavulanate

MRSA

Methicillin-resistant Staphylococcus aureus

- Resistant to all beta lactams
- Altered penicillin binding proteins (PBPs)
- Important hospital-acquired bacteria
  - Sometimes community acquired
- Vancomycin or daptomycin: antibiotics of choice
- Can also use Linezolid

Staph Epidermidis

- Normal skin flora; two clinical implications
- #1: Blood culture contaminant
  - Needle/IV contaminated by S. epi
- #2: Infects prosthetic materials in blood
  - Surface molecules aid in adherence
  - Bacteria produce biofilms
  - Catheter infections
  - Pacemaker infections
  - Prosthetic heart valves
  - Prosthetic joints
- Often methicillin resistant
- Treatment: Vancomycin

Staph Epidermidis

- Often methicillin resistant
  - Resistance to methicillin >80 percent
- Treatment: Vancomycin

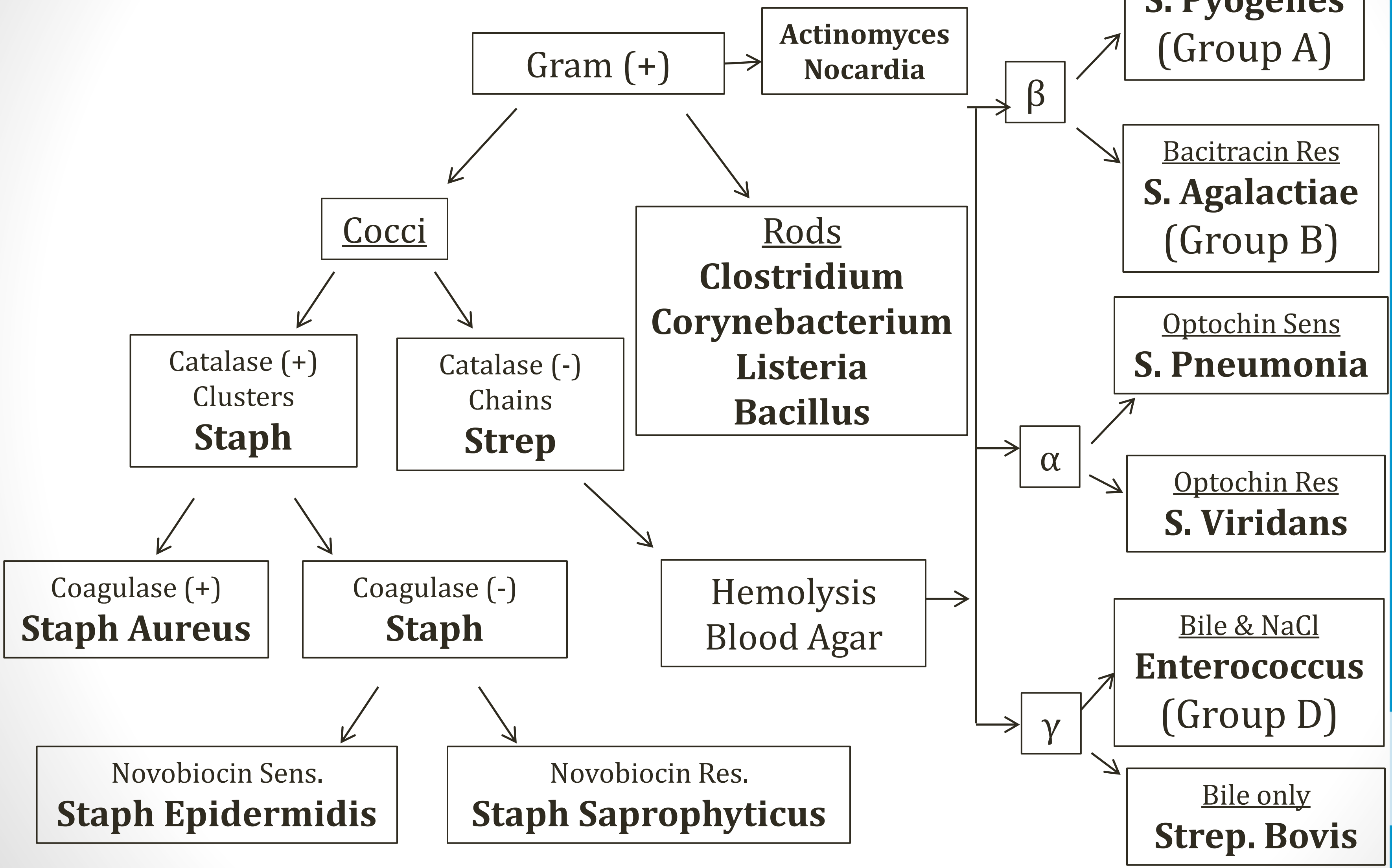
Staph Saprophyticus

- Cause of UTIs especially in sexually active women
  - Most caused by E. Coli (~90%)
  - Other bugs: Proteus, Klebsiella, S. Saprophyticus
- Key features:
  - Sexual activity (honeymooner's cystitis)
  - Nitrite negative on urine dipstick
- Treated by UTI antibiotics
  - Fluoroquinolones
  - SMX-TMP
  - Nitrofurantoin

Streptococci

Jason Ryan, MD, MPH

Gram Positive Bacteria



Streptococci

- Strep Pyogenes (Group A)
- Strep Agalactiae (Group B)
- Strep Pneumonia
- Strep Viridans
- Enterococcus (Group D)
- Strep Bovis
- All gram positive cocci
- All form chains
- All catalase (-)

Strep Pyogenes

Group A Strep

- Pyrrolidonyl arylamidase (PYR) positive
  - Substrate (L-naphthylamide-β-naphthylamide) hydrolyzed by bacterial enzyme to β-naphthylamide
  - Can be detected by color change with detection reagent
- M protein virulence factor
  - Inhibits phagocytosis

Strep Pyogenes

Group A Strep

- Cause of many different illnesses
- Infections
  - Pharyngitis (Strep throat)
  - Skin: Cellulitis/Impetigo
- Toxin-mediated disease
  - Scarlet fever
  - Necrotizing fasciitis
  - Toxic Shock Syndrome
- Immune disease
  - Rheumatic fever
  - Post-strep glomerulonephritis

Strep Pharyngitis

- 15-30% pharyngitis due to S. pyogenes
  - Many cases viral
- Important to identify and treat S. pyogenes
  - Prevent disease transmission
  - Limit symptoms, severity
  - Prevent rheumatic fever
- Diagnosis:
  - Throat culture
  - Rapid antigen test (useful if positive)
- Treatment: Penicillin, amoxicillin, cephalosporins

S. Pyogenes Skin Infections

- Cellulitis and Impetigo
- Both commonly caused by Strep but also S. Aureus
- Antibiotics need to cover Strep and Staph

Image courtesy of Pshawnoah/Wikipedia

Image courtesy of Åsa Thörn/Wikipedia

Scarlet Fever

- Rash following pharyngitis
- Skin reaction to erythrogenic toxin
- Gene for toxin transferred by lysogenic phage

Scarlet Fever

- Fever, sore throat, diffuse red rash
- Also, many small papules ("sandpaper" skin)
- Starts head/neck →expands to cover trunk
- Classic finding: Strawberry tongue
- Eventually skin desquamates
- Palms and soles are usually spared

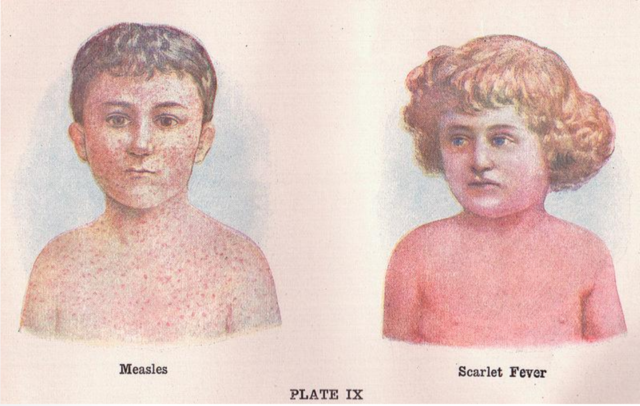


Image courtesy of Wikipedia/Public Domain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Necrotizing Fasciitis

- Infection of deep tissues
  - Muscle fascia/subcutaneous fat
  - Streptococcal pyrogenic exotoxin released
- Often fulminant and deadly
  - Infection spreads along muscle fascia
- Requires urgent surgical debridement

Necrotizing Fasciitis

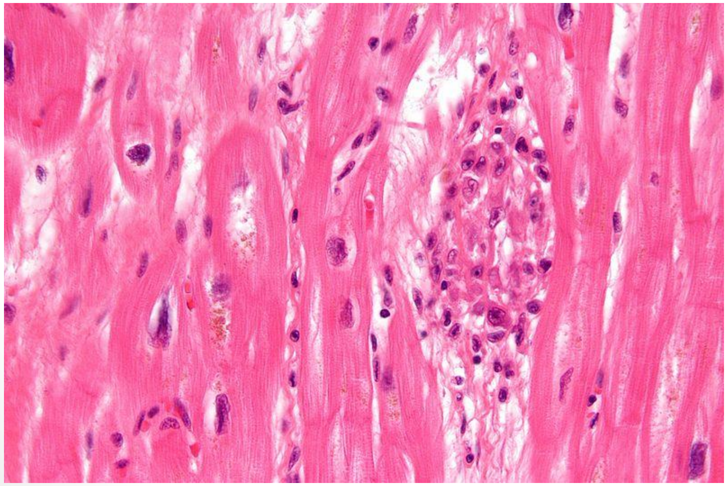
- Type 1:
  - Polymicrobial
  - Often anaerobes (Bacteroides, Clostridium, etc.)
  - Occurs in diabetics, immunocompromised, post surgery
- Type 2:
  - Group A strep (sometimes Staph)
  - Occurs in otherwise healthy people after skin injury
- Classic case:
  - Minor skin trauma
  - Redness/warmth (can be confused with cellulitis)
  - Pain out of proportion to exam
  - Fever, hypotension

Rheumatic Fever

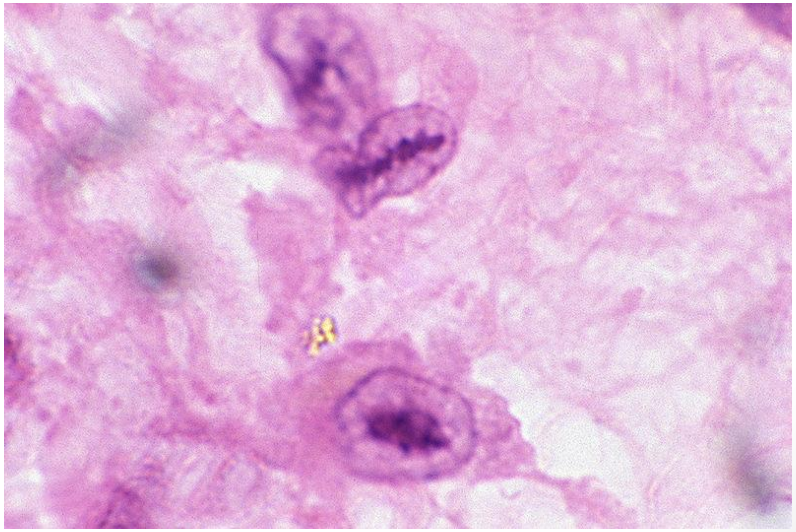
- Follows group A strep pharyngitis infection
- Streptococcus → anti-strep antibodies
- Cross react with tissue antigens
- Type II autoimmune reaction

Rheumatic Fever

- Aschoff bodies
  - Cardiac nodules with inflammatory cells (granulomas)
  - Pathognomonic for rheumatic carditis
- Anitschkow's cells
  - Macrophages with owl eye appearance
- Elevated ASO titers



Nephron/Wikipedia



Ed Uthman, MD/Wikipedia

Jones Criteria

Major	Minor
Carditis	Fever
Polyarthritis	Arthralgia
Chorea	Prior RF
Erythema marginatum	↑WBC, ESR, CRP
Subcutaneous nodules	Prolong PR interval

2 Major or 1 Major & 2 Minor
(Must have evidence of strep infection)

Rheumatic Fever

- Clues:
  - Sore throat or URI followed by joint pain, new murmur
- Treatment: Penicillin
- Cardiac involvement
  - Acute RF → severe valve disease, heart failure
  - Later → mitral stenosis (rarely aortic or tricuspid valves)

Post-streptococcal GN

- Nephritic syndrome 2-3 weeks after GAS infection
- Nephritogenic strains
  - Bacteria with certain M protein subtypes cause nephritis

Strep Agalactiae

Group B Strep

- Beta hemolytic (like GAS)
- Makes CAMP factor
  - Staph Aureus makes β-hemolysin
  - CAMP factor enhances lysis by β-hemolysis
- Hydrolyzes the compound hippurate
  - Will alter color of hippurate test

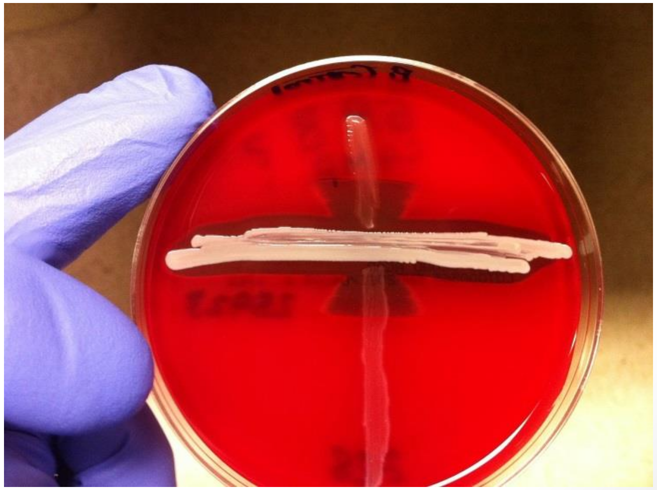


Image courtesy of Blueiridium/Wikipedia

Strep Agalactiae
Group B Strep

- Colonizes vagina
- Causes infections in newborns
  - Babies infected in utero or during birth
  - Pneumonia, meningitis, sepsis
- Pregnant women screened 35-37 weeks
  - Vaginal culture
- Women GBS (+) receive prophylaxis
  - Four hours prior to delivery
  - Penicillin, ampicillin, or cefazolin

Strep Pneumonia

- "Lancet shaped" gram (+) cocci
- IgA protease
- Key virulence factor: Polysaccharide capsule
  - Prevents phagocytosis
  - Basis of vaccine from capsular material
  - Asplenic patients at risk for sepsis
    - Splenectomy
    - Sickle cell anemia

Strep Pneumonia

- Lobar Pneumonia
- Meningitis
- Otitis Media
- Sinusitis

Viridans Group Strep

- Group of similar bacteria
- No Lancefield group (A, B, D)
- Normal mouth flora
- Cause dental carries (Strep Mutans)
- SUBACUTE endocarditis (Strep Sanguis)
    - Slow onset symptoms; less sick patient
    - Often affects ABNORMAL valves
    - Dextran → fibrin
    - Requires endothelial damage
    - Mitral valve prolapse
    - Pearl: Recent dental procedure

Enterococcus

- E. faecalis, E. faecium
- Normal colonic bacteria
- Lancefield group D
- Infections:
  - UTIs
  - Endocarditis (rare)
- Resistant to penicillin
- Vancomycin resistant enterococcus (VRE)
  - Dangerous hospital acquired infection

Enterococcus

- Relatively resistant to cell wall agents
  - Penicillin, ampicillin, and vancomycin
- Impermeable to aminoglycosides
- Bacteremia: Often use synergistic therapy
  - Vancomycin/gentamycin
  - Ampicillin/gentamycin
- Vancomycin resistant enterococcus (VRE)
  - Dangerous hospital acquired infection
  - Linezolid, Daptomycin
- Micro lab sensitivities very important for therapy

Enterococcus UTIs

- Often hospital acquired, associated with catheters
- Removal of catheter alone may cure infection
- Urinalysis: NEGATIVE for nitrites

Enterococcus Endocarditis

- Rare cause of endocarditis
- Usually after manipulation GU tract
  - TURP procedure, cystoscopy
- Vancomycin/gentamycin often used for empiric therapy before culture data available
- Synergistic effect of dual antibiotics

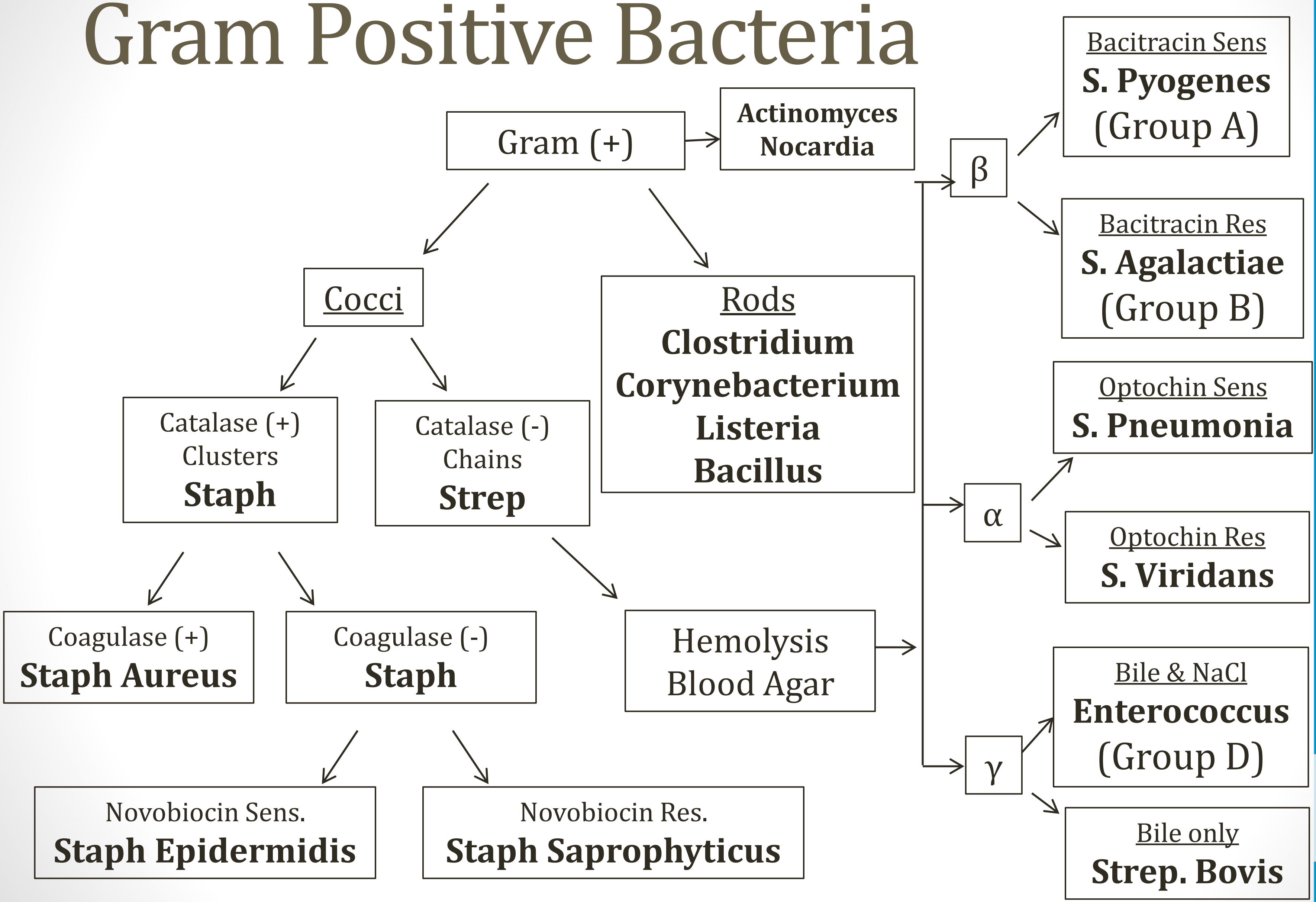
Strep Bovis

- Normal colonic bacteria
- Rare cause bacteremia/endocarditis
- Strongly associated with colon cancer

Other Gram Positives

Jason Ryan, MD, MPH

Gram Positive Bacteria



Boards&Beyond STUDY SMARTER

Clostridium

- Family of bacteria
  - All form spores
  - All obligate anaerobes
  - All form toxins
- C. tetani (tetanus)
- C. botulinum (botulism)
- C. perfringens (wound infections, food poisoning)
- C. difficile (diarrhea after antibiotic use)

Clostridium tetani

- Spores found in soil
- Enter body via penetrating injury
  - Classic scenario: barefoot on rusty/dirty nail or splinter
- Spores germinate into bacteria
- Tetanus toxin produced (tetanospasmin)
- Travels to spinal cord
- Blocks glycine and GABA release by inhibitory neurons
  - "Renshaw cells:" inhibitory spinal cord interneurons

Clostridium tetani

- Spasms, muscle contractions, rigidity
- Classic symptoms
  - Lockjaw (trismus)
  - Risus sardonicus (forced grin due to spastic facial muscles)

Clostridium tetani

- Treatment for tetanus
  - Wound debridement
  - Metronidazole
  - Tetanus immune globulin (binds circulating toxin)
  - Benzos or neuromuscular blockers until toxin wears off
- Tetanus toxoid used for vaccination

Clostridium botulinum

- Ubiquitous organisms
- Vegetables, fruits, seafood, soil
- Heat-resistant spores
  - Survive up to 100^{o}C
- Botulinum toxin
  - Works at neuromuscular junctions
  - Prevents Ach release (no muscle contraction)
  - Result: Floppy muscles (flaccid paralysis)
- Many different variants of toxin
- Some carried by bacteriophages

Botulism

- Three types: food, infant, wound
- Food (toxin ingestion; usually adults)
  - Undercooked food
  - Canned food: anaerobic environment promotes growth
  - Watch for multiple sick adults after a meal
- Infant (spores)
  - Ingestion of spores → growth in infant intestine
  - Watch for contaminated honey!
- Wound (bacterial growth)
  - Infection with C. botulinum

Botulism

- Symptoms: 12-48 hours after ingestion
- Symptoms: 3 D's
  - Diplopia, dysphagia, dysphonia
- Diagnosis:
  - Often clinical
  - Spores and toxins sometimes detected in stool
- Treatment:
  - Antitoxin blocks circulating toxin
  - Cannot block toxin already in nerves
  - Supportive care → toxin washout

Clostridium perfringens

- Widespread in nature, especially soil
- Infects dirty wounds & causes food poisoning
- Causes gas gangrene (clostridial myonecrosis)
  - Traumatic wound with vascular compromise
  - Favorable environment for anaerobic growth
- Alpha toxin
  - Destroys muscle tissue and causes hemolysis
  - Phospholipase that acts on lecithin (lecithinase)
  - Degrades phospholipids in cell membranes

Gas Gangrene

- Severe pain at injury site within 24 hours
- Skin tense and tender
- Systemic toxicity
  - Fever, Hypotension, Shock
- Diagnosis
  - Gas at injury site on imaging
  - Crepitus
- Treatment
  - Surgical debridement
  - Broad spectrum antibiotics

Image courtesy of Engelbert Schröpfer, Stephan Rauthe and Thomas Meyer/Wikipedia

Clostridium perfringens

- Food poisoning (undercooked meats)
  - Spores ingested → produce toxin
  - Late onset (8-22hrs) watery diarrhea
  - Contrast with S. aureus/B. cereus (preformed toxin)

Clostridium difficile

- Ubiquitous spores in nature including soil
- Ingestion not harmful with normal GI flora
  - Colonic flora prevent overgrowth of C. diff
- Causes antibiotic-associated colitis
  - Antibiotics alter normal gut flora
  - Favorable environment for C. diff growth

Clostridium difficile

- Not invasive: disease via toxins
- Two toxins
  - Toxin A: Enterotoxin → watery diarrhea
  - Toxin B: Cytotoxin → Cell necrosis/fibrin deposition
  - Both bind to GI cells and are internalized
  - Destroy cytoskeleton of GI cells → pseudomembrane

Clostridium difficile colitis

- Massive watery diarrhea
- On endoscopy (rarely done):
  - Pseudomembrane formation (white-yellow plaques)
  - Mucosal ulcerations, fibrin, inflammatory cells
- Diagnosis
  - Stool detection of toxin A and B

Clostridium difficile colitis

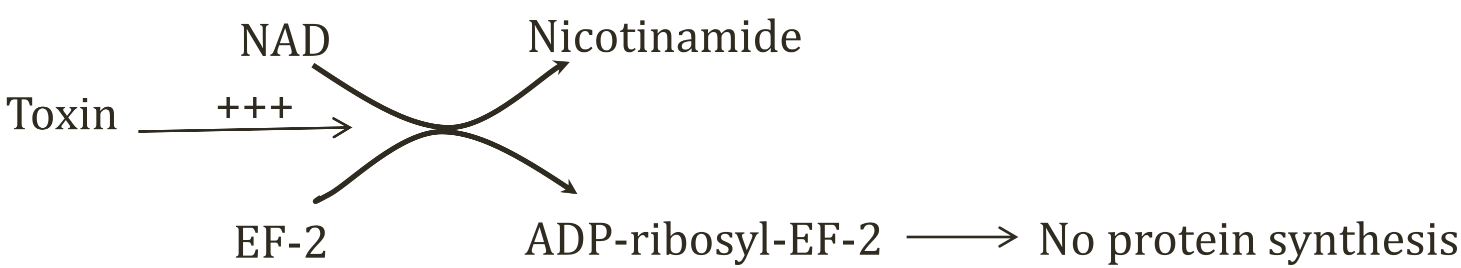
- Treatment:
  - Metronidazole
  - ORAL Vancomycin
- Other therapy for severe, recurrent disease
  - Surgery
  - Stool transplant

Corynebacterium diphtheria

- Causes diptheria
- Several special features of bacteria
  - Exotoxin
  - Unique lab diagnostic techniques

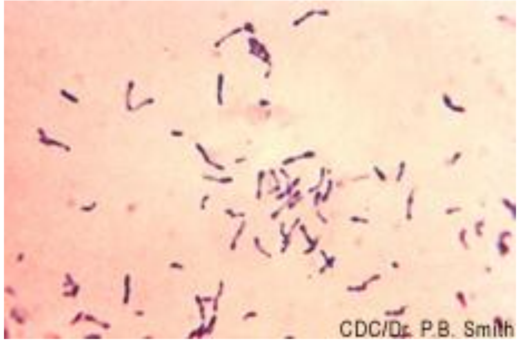
Diphtheria Exotoxin

- Not part of bacterial genome
- Carried by β-prophage
- “Lysogenic” phage → incorporates DNA into bacteria
- Inactivates elongation factor (EF-2)
- EF-2 necessary for protein synthesis (translation)



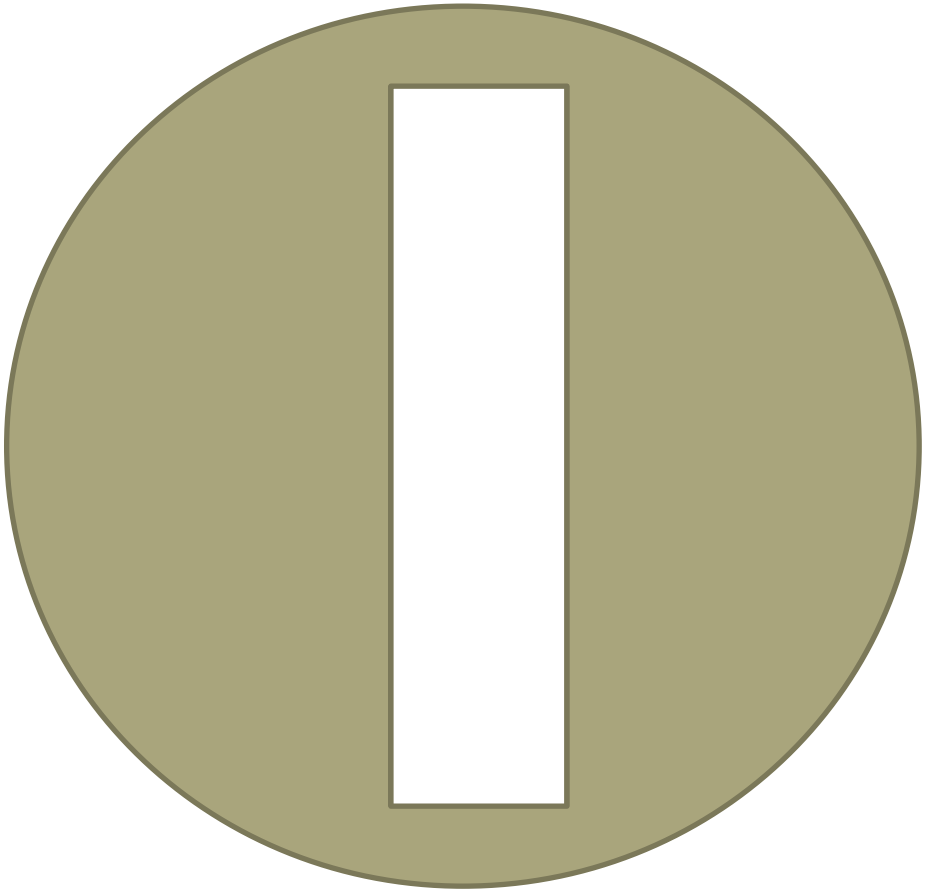
Corynebacterium Features

- Gram positive rods
  - Curved
  - "Chinese character" distribution
- Special culture media required
  - Loeffler's or Tinsdale (Tellurite plate)
  - Black colonies on Tinsdale media
  - Metachromatic (blue/red) granules on Loeffler's media
- Elek test for toxin detection (for diagnosis)
  - Antitoxin-impregnated filter paper under agar
  - Bacterial toxin precipitates and can be visualized



CDC/Public Domain

ELEK Test



Diphtheria

- Sore throat, fever, lymphadenopathy
- Gray-white membrane in pharynx
- Absorption/dissemination of toxin can cause:
  - Myocarditis (heart failure, arrhythmias, heart block)
  - CNS disease (neuropathies)
  - Renal disease (renal failure)

Diphtheria

- Rare due to vaccination with toxoid
- Treatment (acute infection):
  - Penicillin
  - Diphtheria antitoxin (passive immunization)
  - Diphtheria toxoid (active immunization)

Listeria

- Found in soil
- Facultative intracellular organism
- “Tumbling motility”
- Move from cell to cell to avoid extracellular response
- Polymerizes actin in cells to move (“actin rockets”)

Listeria

- Multiplies in cells with poor cell-mediated immunity
  - Neonates, HIV, organ transplant
- In adults, often from contaminated food
  - Undercooked meat, unwashed vegetables
  - Unpasteurized cheese/milk
  - Likes cold temperatures
- In neonates, transplacental or vaginal transmission

Listeria

- Gastroenteritis
  - Diarrhea, nausea, vomiting
  - Usually self limited
- Meningitis
  - Elderly or newborns
- Infection in pregnancy
  - Bacteremia in 3rd trimester
  - Flu-like illness (fever, chills)
  - Often resolves without treatment
  - Rarely can cause fetal demise or newborn infection

Granulomatosis Infantiseptica

- Severe in utero infection from Listeria
- Disseminated abscesses and/or granulomas
- Multiple organs: liver, spleen, lungs, kidneys, brain
- Skin lesions (papules, ulcers)
- Most babies stillborn or die soon after birth
- Placenta shows distinctive inflammation
  - Chorioamnionitis
  - Villitis
  - Abscess formation

Bacillus

- Bacillus anthracis
- Anthrax: Skin or pulmonary disease
    - Largely eradicated
    - Weapon of bioterrorism
- Bacillus cereus
    - Food poisoning

Bacillus Anthracis

- Only bacteria with a polypeptide capsule
  - Most are polysaccharide
  - B. Anthracis capsule contains D-glutamate
  - Limits/prevents phagocytosis
- Found in soil
- Infects cattle, sheep, horses (and humans)
  - Farm workers at risk
- Spores can be used as bioterrorism weapon
- Produces two toxins:
  - Edema toxin
  - Lethal toxin

Anthrax Toxins

- Edema toxin (contains edema factor)
  - Mimics adenylate cyclase
  - Increases cAMP → fluid secretion
- Lethal toxin (contains lethal factor)
  - Protease
  - Inhibits cell signaling
  - Causes apoptosis

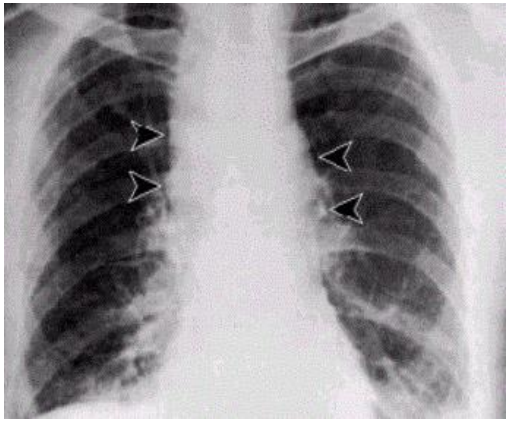
Anthrax

- Cutaneous disease
  - Spores enter skin through cuts/abrasions
  - Vegetate → bacteria grows
  - Painless black ulcers forms
  - Can progress to bacteremia and death
  - Edema surrounds black ulcer from edema factor
- Treatment: Ciprofloxacin, Doxycycline, Clindamycin

Image courtesy of Wikipedia/Public Domain

Anthrax

- Pulmonary disease
  - “Woolsorters’ disease”
  - Inhalation of spores
  - Flu symptoms that rapidly progress
  - Pulmonary hemorrhage, mediastinitis, shock, death
- Treatment: Multi-drug regimen, antitoxin



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Bacillus Cereus

- Food poisoning from enterotoxins
- Classically in undercooked/reheated rice
  - Bacteria frequently present in uncooked rice
  - Heat-resistant spores may survive cooking
  - Cooked rice at room temperature allow bacteria to multiply
  - “Reheated rice syndrome”

Bacillus Cereus

- Emetic type
  - Direct ingestion of toxin: Cereulide
  - Abdominal cramps, nausea, and vomiting (rarely diarrhea)
  - 1 to 5 hours after ingestion
  - Classically occurs in rice dishes
- Diarrheal type
  - Abdominal cramps and diarrhea (not vomiting)
  - 8 to 16 hours after ingestion
  - Caused by at several enterotoxins
  - Toxins are heat labile
  - Cooking food reduces risk of illness
  - Often from meats, vegetables, and sauces

Actinomyces

- Normal oral flora
- Also found in female genital tract
- Anaerobe
- Clusters into long filaments resembling fungi
- Causes head/neck abscesses
- In women, can cause IUD infections
- Classically preceded by dental work/orofacial trauma
  - Facial mass present on exam
  - Often yellow center (yellow "sulfur" granules)
  - Often draining puss
- Treatment: Penicillin +/- drainage

Nocardia

- Branching, filamentous (like Actinomyces)
- Acid fast
- Produces urease (can be used to identify bacteria)
- Obligate aerobe (loves lungs!)
- Found in soil

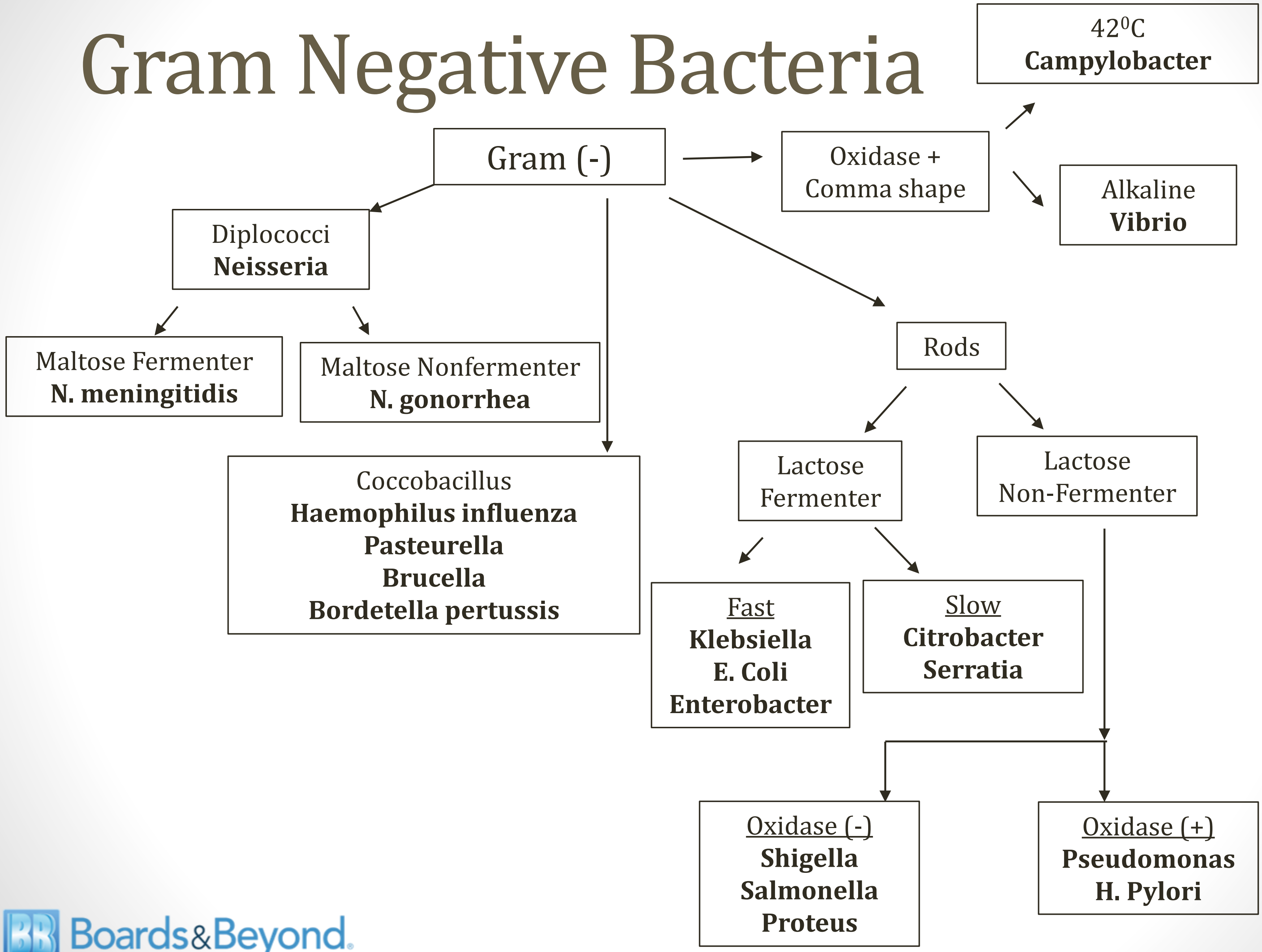
Nocardia

- Pneumonia
  - Immunocompromised patients
  - Inhalation of bacteria
  - Many radiology findings: nodules, masses, infiltrates, lobar consolidation, pleural effusions
- Skin infection
  - Immunocompetent patients
  - Often invades skin during gardening or farming
  - Lots of manifestations: ulcers, cellulitis, nodules, abscesses
- Rarely other infections: brain abscess, bacteremia
- Drug of choice: TMP-SMX

Gram Negative Rods

Jason Ryan, MD, MPH

Gram Negative Bacteria



Boards&Beyond
STUDY SMARTER

Gram Negative Rods

- Most are in the family: enterobacteriaceae
- Many are inhabitants of the normal GI flora
- Often cause diarrhea and UTIs
- Resistant to Penicillin and Vancomycin
- Outer membrane inhibits entry of drug

Klebsiella

- Intestinal flora
- Non-motile, capsular
- Infection with impaired host defenses
  - Alcoholics, diabetics, sick people (nosocomial)
- Infection with aspiration of GI contents
  - Aspiration pneumonia, Lung abscesses
- Often resistant to many antibiotics
- Treatment based on susceptibility testing

Klebsiella

- Klebsiella pneumonia
  - Lobar
  - Occurs in alcoholics or diabetics, often after aspiration
  - Classically results in red "currant jelly" sputum
- Lung abscess
  - Usually caused by mouth anaerobes
  - Peptostreptococcus, Fusobacterium, Prevotella, Bacteroides
  - Can also be due to Klebsiella
- Rare cause of UTIs (3-4%)
- Liver abscesses
  - Usually in patients with underlying liver disease or cholangitis

E. Coli

Special virulence factors

- Fimbriae (pili)
  - Attach to epithelial surfaces
  - May be specialized for surfaces (i.e. urinary tract)
- K capsule
  - K1 capsular antigen present in 75% meningitis cases (babies)
  - Inhibits phagocytosis, complement

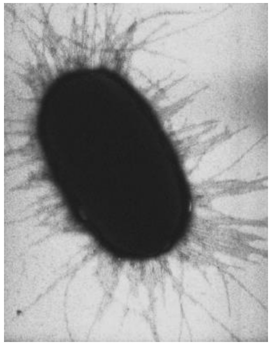


Image courtesy of Manu Forero/Wikipedia

E. Coli Diseases

- Watery diarrhea
- Bloody diarrhea (dysentery)
- UTI/pyelonephritis
  - E. Coli bacteremia/sepsis (rare), usually from UTI
- Meningitis in newborns

E. Coli Diarrheal Illnesses

- 4 different E. Coli diarrheal illnesses
- EnteroINVASIVE E. Coli (EIEC)
- EnteroTOXIGENIC E. Coli (ETEC)
- EnteroPATHOGENIC (EPEC)
- EnteroHEMORRHAGIC (EHEC)

E. Coli

- EnteroINVASIVE E. Coli (EIEC)
  - Invades intestinal mucosa
  - Necrosis, inflammation, bloody diarrhea
  - Clinically similar to Shigella (no toxins)
- EnteroTOXIGENIC E. Coli (ETEC)
  - Two toxins: Labile and Stable
  - Watery (traveler's) diarrhea (contaminated food/water)
  - No inflammation/invasion
- Enteropathogenic (EPEC)
  - No toxin, no inflammation
  - Blunt villi, prevent absorption
  - Diarrhea usually in children (p=pediatrics)

Enterohemorrhagic E. Coli

EHEC

- Does not ferment sorbitol (sorbitol-MacConkey agar)
- Classic serotype: E. coli O157:H7
- Does not invade host cells (toxin causes disease)
- Produces Shiga-like toxin → bloody diarrhea
    - Bacteriophage-encoded (lysogenic) toxin
- Usually from undercooked beef
- Toxin Effects
    - Endothelium swells → vessel lumens narrow
    - Deposition of fibrin/platelets in microvasculature
    - Hemolysis, inflammation

Hemolytic Uremic Syndrome

HUS

- Complicates ~10% EHEC cases
- Common in children
- Triad:
  - Hemolytic anemia
  - Thrombocytopenia
  - Acute renal failure (uremia)
- HUS + fever, mental status changes = TTP
  - Thrombotic thrombocytopenic purpura
- Usually occurs 5-7 days after diarrhea

E. Coli Treatment

- Most E. Coli diarrheas self-limited
  - Usual treatment is hydration
  - Antiperistaltic agents (Loperamide) not helpful
  - Antibiotics rarely used (may increase toxin release)

Gram Negative Sepsis

- Fever, tachycardia, hypotension
- Life-threatening
- Driven by endotoxin (LPS; Lipid A)
- Common scenario:
  - Elderly patient
  - UTI (catheter, BPH)
  - Gram negative sepsis (+ blood cultures)

Infectious Diarrhea

Bloody

- Campylobacter
- Salmonella enterica
- Shigella
- Yersinia enterocolitica
- EIEC
- Entamoeba histolytica
- EHEC

Watery

- ETEC
- Cholera
- C. difficile
- C. perfringens
- Giardia, Crypto
- Rotavirus, Norovirus

Fecal leukocytes, RBCs usually indicate invasive infection
Mucous, epithelial cells only seen in toxin-mediated disease
Stool ova and parasites seen in protozoal infections

Enterobacter

- Rare cause of nosocomial UTIs
- Resistant to many antibiotics
  - Extended-spectrum beta-lactamases (ESBL)
  - Resistance to most beta-lactams: penicillins, cephalosporins, and aztreonam
- Often treated with Carbapenems
  - Imipenem, Meropenem

Citrobacter & Serratia

- Slow lactose fermenters
- Not dominant pathogen for any clinical condition
- Often resistant to many antibiotics
- Citrobacter
  - Can be found in normal GI flora
  - Gram negative sepsis (with other GN bugs)
- Serratia
  - Produce distinctive red colonies (red pigment)
  - Catalase positive
  - Hospital outbreaks: contaminated water, soap, IV solutions
  - Sometimes osteomyelitis in IV drug users (also pseudomonas)

Salmonella

- Two general types
  - Salmonella typhi → typhoid fever
  - Non-typhoid strains → Enterica, enteritidis
- Non typhoid strains cause invasive gastroenteritis
  - Nausea, vomiting, cramps, bloody diarrhea
  - Ingestion of contaminated meat, eggs, poultry

Salmonella

- Flagellated and motile
- Encapsulated
- Disseminate through blood
  - Osteomyelitis in sickle cell patients
- Live in GI tract of mammals, birds, reptiles
- Produce hydrogen sulfide
  - Triple Sugar Iron (TSI) test → media turns black
  - Differentiates from Shigella
- Invades GI mucosa
- Cellular response: Largely monocytes

Typhoid Fever
Salmonella Typhi

- Fever, headache, abdominal pain, diarrhea
- Travelers to Asia, Africa, South America
- Classic feature #1: Rose spots
  - Faint salmon-colored macules
  - Trunk and abdomen
- Classic feature #2: Pulse-temperature dissociation
  - High fever → slow pulse
- Can remain in gall bladder (carrier state)
  - Endemic countries 1-4% people may be carriers
  - May be risk factor for carcinoma

Salmonella

- Diagnosis: Culture (stool, blood)
- Treatment gastroenteritis:
  - Fluids/electrolytes
  - Few data showing antibiotics are helpful (may prolong illness)
  - Difficult to treat: Lots of antibiotic resistance
  - Antibiotics used in severely ill patients only
  - Anti-peristalsis meds (Loperamide) contraindicated
- Typhoid fever: Ceftriaxone, Fluoroquinolones
- Typhoid vaccine available
  - Inactive variant of bacteria given orally
  - Used for traveler's to high risk areas

Shigella

- Nonmotile (no flagella)
- Invades mucosal cells (M cells in Peyer's patches)
  - Macropinocytosis
  - Induces apoptosis
- Spreads from cell to cell
  - Does not spread via bloodstream (like Salmonella)
- Releases Shiga toxin
  - But non-toxin strains still cause disease
  - Cellular invasion more important mechanisms of disease
- Very few bacteria can cause disease (few as 10!)
- Cellular response: Largely PMNs

Shigella

- Not normal GI flora
- Fecal-oral transmission
- Common in children
- Diagnosis: Stool Culture
- Treatment:
  - Fluids/electrolytes
  - Antibiotics improve symptoms, reduce shedding in stool
    - Can limit spread
  - Ceftriaxone or Ciprofloxacin

Salmonella and Shigella

Both GNRs, both cause bloody diarrhea, both invasive

Salmonella	Shigella
H2S (black on TSI)	No H2S
Monocytes	PMNs
Hematogenous spread	Cell to cell spread (Macropinocytosis)
No antibiotics	Yes antibiotics
Motile (flagella)	Nonmotile
--	Shiga toxin
--	Low infectious dose

Proteus

- Rare cause of UTIs
- "Swarm phenotype"
  - Long flagella
  - Facilitates urinary ascent
  - Bulls-eye on agar plates
- Produces urease
  - Converts urea to ammonia
- Associated with struvite kidney stones

Pseudomonas aeruginosa

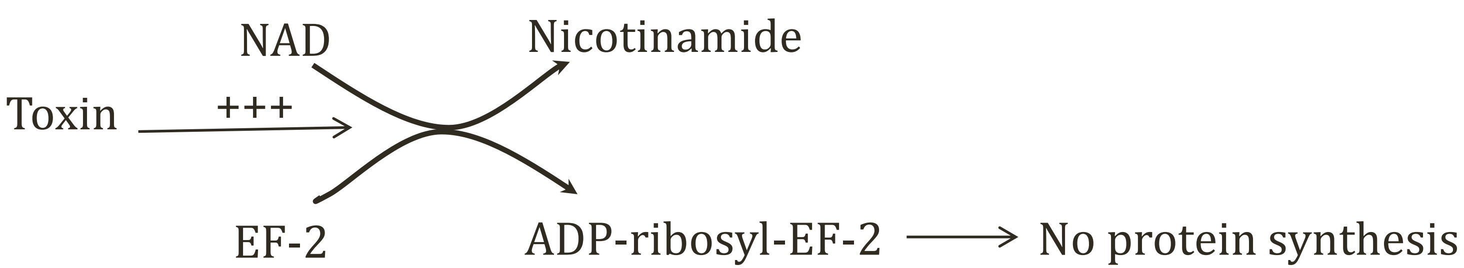
- Highly feared bacteria
  - Serious hospital acquired infections (i.e. VAP)
  - Resistant to many antibiotics ("anti-pseudomonal drugs")
- Many infections:
  - Pneumonia (nosocomial)
  - UTIs
  - Surgical wound infections
  - Bacteremia/sepsis
  - Osteomyelitis
  - Otitis externa

Pseudomonas aeruginosa

- Obligate aerobe
- Loves the water
  - Commonly found in environmental water sources
- Produces a blue-green pigment (pyocyanin)
  - Smooth, florescent green colonies on culture media
- Sweet, grape-like odor

Pseudomonas Toxins

- Endotoxin (LPS)
  - Can cause fever, shock
- Exotoxin A
  - Inactivates elongation factor (EF-2)
  - EF-2 necessary for protein synthesis



Pseudomonas Infections

- Pneumonia in cystic fibrosis
- Burn infections
- Hot tub folliculitis
  - Tender, itchy papules after using a hot tub or spa
- Otitis externa (Swimmer's ear)
  - Inflammation of the outer ear and ear canal
  - Painful ear with discharge

Pseudomonas Infections

- Osteomyelitis in IV drug users
- Ecthyma gangrenosum
  - Black, necrotic ulcers on skin with bacteremia
  - Invasion/destruction blood vessels by bacteria
  - Classic case is neutropenic cancer patient with fever, chills (bacteremia) who develops black lesions on chest/back

Burkholderia cepacia

- Gram negative rod similar to pseudomonas
- Oxidase positive
- Catalase positive
- Rare cause of infections:
    - Cystic fibrosis
    - Chronic granulomatous disease

H. Pylori

- Causes gastritis and ulcers (abdominal pain)
- Recently identified bacteria (1982!)
- Urease positive
  - Hydrolyzes urea to compounds that damage epithelium
  - Produces ammonium (alkaline)
  - Protects bacteria from stomach acid
- Urea breath test
  - Patients swallow urea with isotopes (carbon-14 or carbon-13)
  - Detection of isotope-labelled carbon dioxide in exhaled breath
  - Indicates urea was split (i.e. urease present)

H. Pylori

- Infection common in patients with ulcers
  - Majority of patients with duodenal ulcers
  - Many patients with gastric ulcers
- MALT lymphoma
  - Mucosal associated lymphoid tissue
  - B-cell cancer, usually in the stomach
  - HIGHLY associated with H. Pylori infection
- Diagnosis:
  - Biopsy
  - Urea breath test
  - Stool antigen

H. Pylori

- Treatment: “Triple therapy” for 7-10 days
  - Proton pump inhibitor
  - Clarithromycin
  - Amoxicillin/Metronidazole
- Testing often repeated to confirm eradication
  - Breath test, stool antigen, or biopsy
- Treatment failures ~20%
  - Alternate regimens can be tried

Legionella

- Does not gram stain well
- Silver stains used
- Special culture requirements
- Buffered charcoal yeast extract agar (BCYE)
- Iron and cysteine added for growth
- Supplemented with antibiotics and silver dyes
    - Antimicrobials prevent overgrowth by competing organisms
    - Dyes give distinctive color to Legionella

Legionella

- First identified at American Legion convention
- Infection from inhalation of aerosolized bacteria
  - Not airborne
- Outbreaks at hotels with contaminated water
- Can cause nosocomial pneumonia in nursing homes

Legionella

Symptoms

- Initially mild pneumonia symptoms
  - Fever; mild, slightly productive cough
- Can progress to severe pneumonia
- GI symptoms
  - Watery diarrhea, nausea, vomiting, and abdominal pain
- Hyponatremia (Na<130 meq/L) common
  - Can occur in any PNA but more common Legionella

Legionella

Diagnosis

- Classic Case
  - Mild cough
  - Watery diarrhea
  - Confusion (low Na)
  - Negative bacteria on gram stain
- Treatment: Fluoroquinolone or Macrolide

Pontiac Fever

- Mild form of Legionella infection
- Fever, malaise, chills, fatigue, and headache
- No respiratory complaints
- Chest radiograph usually normal

Bacteroides fragilis

- Gram (-) rod
- Anaerobic bacteria
- Normal GI flora
- Cause infection after breach of mucosal barrier

Bacteroides fragilis

- Rarely causes infections alone
- Usually part of polymicrobial infections from GI tract
  - Peritonitis (following perforation)
  - Intraabdominal abscess
  - Lung abscess (aspiration)
  - E. Coli/GNRs and B. Fragilis often components together
- Covered by metronidazole
- Common GI therapy: Cipro/Flagyl
  - Quinolone for E. Coli
  - Metronidazole for B. Fragilis

Other Gram Negatives

Jason Ryan, MD, MPH

Gram Negative Bacteria

- Gram (-)
  - Diplococci **Neisseria**
    - Maltose Fermenter **N. meningitidis**
    - Maltose Nonfermenter **N. gonorrhea**
  - Coccobacillus
    - **Haemophilus influenza**
    - **Pasteurella**
    - **Brucella**
    - **Bordetella pertussis**
    - **Yersinia Enterocolitica**
  - Oxidase + Comma shape
    - $42^{0}C$ **Campylobacter**
    - Alkaline **Vibrio**
  - Rods
    - Lactose Fermenter
      - Fast
        - **Klebsiella**
        - **E. Coli**
        - **Enterobacter**
      - Slow
        - **Citrobacter**
        - **Serratia**
    - Lactose Non-Fermenter
      - Oxidase (-)
        - **Shigella**
        - **Salmonella**
        - **Proteus**
      - Oxidase (+)
        - **Pseudomonas**
        - **H. Pylori**
        - **Campylobacter**

Moraxella catarrhalis

- Gram negative diplococci
- Colonizes airway
- Can cause otitis media, COPD exacerbations
- Usually treated empirically without micro diagnosis
- Not in most micro lab algorithms
  - Most labs will not speciate airway samples with gram (-) cocci
  - Non-virulent strains Neisseria normal airway flora

Neisseria

- Meningitidis and Gonorrhea
- Both gram negative cocci in pairs (diplococci)
- Both ferment glucose
- **M**eningococcus ferments **M**altose
- **G**onococcus ferments only **G**lucose
- Both produce IgA protease
- Ceftriaxone often used to treat both

Neisseria Meningitidis

- Causes meningitis and meningococcemia
- Transmitted by respiratory droplets
- Enters pharynx then bloodstream then CSF
- Many asymptomatic carriers

Neisseria Meningitidis

- Polysaccharide capsule prevents phagocytosis
- Lipooligosaccharide (LOS) outer membrane
  - Like LPS on enteric gram negative rods
  - Endotoxin → many toxic effects on body
  - Activates severe inflammatory response
- Vaccine available
  - Contains capsular polysaccharides → anti-capsule antibodies

Neisseria Meningitidis

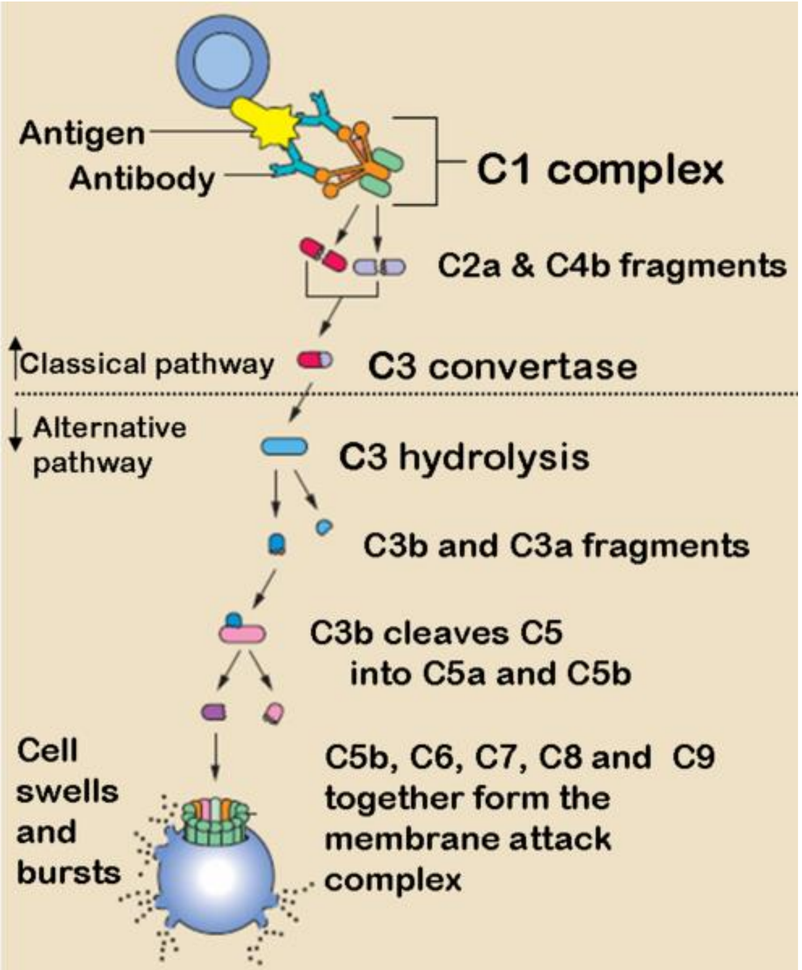
- Bacteremia can complicate meningitis
  - Meningococcemia
- Sepsis: fevers, chills, tachycardia
- Purpuric rash
- DIC
- Waterhouse-Friderichsen syndrome
  - Adrenal destruction from meningococcemia
- Life-threatening

Neisseria Meningitidis

- Can cause outbreaks
  - Dorms, barracks
- Can infect young, healthy people
  - College students in dorms
- Infected patients need droplet precautions
- Close contracts receive prophylaxis/vaccine
  - Rifampin
  - Also Ceftriaxone or Ciprofloxacin

Neisseria Meningitidis

Terminal complement pathway deficiency



<u>C5-C9 Deficiency</u>

Recurrent NM Infections

Most often meningitis

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Neisseria Gonorrhea

- Mainly causes gonorrhea (STD)
- Can also cause:
  - Pelvic inflammatory disease (PID)
  - Septic arthritis
  - Neonatal conjunctivitis
  - Fitz-Hugh-Curtis syndrome
- Key feature: antigenic variation of **pilus proteins**
  - No long term immunity after infection
  - Re-infection likely
  - No vaccine

Gonorrhea

- Most men/women with N. Gonorrhea asymptomatic
- N. Gonorrhea and Chlamydia often co-infect
  - Both can cause same symptoms
  - Treat for both (Ceftriaxone, Azithromycin/Doxycycline)
- Men: Urethritis
  - Dysuria, discharge
  - Can progress to or epididymitis/orchitis
- Women: Cervicitis
  - Itching, discharge from cervix
  - Not painful
  - Can progress to PID

Gonorrhea

- Pelvic inflammatory disease
  - Infection ascends (uterus, ducts, ovaries)
  - Pelvic/abdominal pain
  - Dyspareunia
  - Cervical motion tenderness on exam (chandelier sign)
  - High risk of subsequent **ectopic pregnancy, infertility**
- Fitz-Hugh-Curtis
  - Perihepatitis
  - Inflammation of Glisson's capsule around liver
  - Severe RUQ tenderness with pleuritic pain
  - "Violin string" adhesions of parietal peritoneum to liver

Septic Arthritis

- Disseminated gonococcal infection (0.5 to 3%)
- Septic arthritis
- Key scenario:
    - Sexually active young person
    - Swollen, warm and painful knee

Neonatal Conjunctivitis

- Ophthalmia neonatorum
- Can also be caused by Chlamydia
- Swelling and discharge from eye
- 5 to 14 days after birth
- Untreated can lead to visual impairment
- Prophylaxis: Erythromycin ophthalmic ointment
- Newborn prophylaxis mandated by many states

Chlamydia

- Obligate intracellular organisms
  - Cannot make their own ATP
- Cell wall lacks muramic acid
  - *N*-acetylmuramic acid (NAM) in peptidoglycan
  - Cell wall lacks peptidoglycan
- Do not gram stain well (technically gram negative)
- Giemsa stain

Chlamydia

- Penicillins do not work well
- Ceftriaxone (for Gonorrhea) ineffective
- Treatment of choice: azithromycin, doxycycline
  - Protein synthesis inhibitors

Chlamydia

- Two phases to life cycle
- #1: Elementary body (small, dense)
  - Enters cell via endocytosis
- #2: Reticulate body
  - Replicates in cells by fission
  - Can been seen in tissue culture
- Elementary bodies and reticular bodies grow, multiply, eventually rupture cell and disperse

Chlamydia

- Chlamydia trachomatis (sexually transmitted)
  - Nongonococcal urethritis
  - PID
  - Conjunctivitis
  - Reactive arthritis
- Chlamydophila pneumonia
  - Atypical pneumonia
  - Transmitted by aerosol
- Chlamydophila psittaci
  - Psittacosis (Parrot fever)
  - Infection from birds

Chlamydia trachomatis

- Sexually transmitted
- Often asymptomatic in men & women
- Women: Cervicitis
  - Discharge, post-coital bleeding
  - Can progress to PID, Fitz-Hugh-Curtiss
- Men:
  - Discharge, dysuria
- Treatment: Azithromycin/Doxycycline
  - Plus Ceftriaxone for N. Gonorrhea

Chlamydia trachomatis

Newborns

- Infection from passage through birth canal
- Conjunctivitis
  - Similar to Gonorrhea
- Pneumonia
  - 4-12 weeks old
  - Classic feature is "staccato cough"
  - Inspiration between each single cough
  - Often have a history of conjunctivitis

C. Trachomatis Diagnosis

- Nucleic acid amplification testing (NAAT)
  - PCR of Chlamydia DNA/RNA
  - Gold standard
- Culture and staining
  - No longer done routinely
  - Giemsa stain
  - Chlamydial inclusion bodies in cytoplasm of epithelial cells

Reactive Arthritis

- Autoimmune arthritis
- Triggered by infection
- Intestinal infections
  - Salmonella, Shigella, Campylobacter, Yersinia, C. Difficile
- Chlamydia trachomatis
- Classic triad (Reiter's syndrome)
  - Arthritis (often unilateral, lower extremities, knees, toes)
  - Conjunctivitis (red eye, discharge)
  - Urethritis (dysuria, frequency – noninfectious)
- Diagnosis: Classic features following typical infection
- Treatment: NSAIDs

Lymphogranuloma Venereum

- Chlamydia infection that enters lymphatics
- Different serotypes from those that cause urethritis
- Sexually transmitted
- Initially: Genital ulcer
  - Sometimes unnoticed; Resolves
- Later: Tender inguinal or femoral lymph nodes
- Treatment:
  - Drainage
  - Antibiotics

Herbert L. Fred, MD and Hendrik A. van Dijk

Trachoma

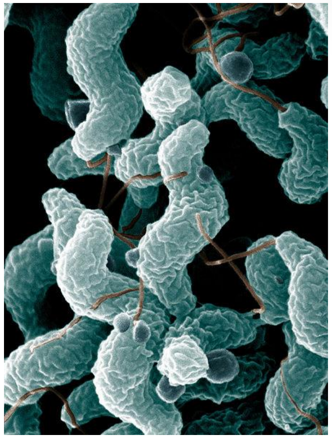
Chlamydia Eye Disease

- Caused by unique serotypes of C. Trachomatis
- Mostly in Africa and other developing parts of world
- Highly contagious
- Spread by contact with eye secretions
- Acutely causes conjunctivitis
- Repeated infections → Corneal scaring → blindness
- Leading cause of infectious blindness worldwide

C. Trachomatis Serotypes

Serotype	Infections
A, B, C	Trachoma, Blindness; Found in Africa
D through K	Urethritis, PID, neonatal pneumonia, neonatal conjunctivitis
L1, L2, L3	Lymphogranuloma venereum

Campylobacter



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- Usually C. jejuni, sometimes C. coli
- Faint, gram negative bacteria
  - Gram stain not sensitive
- Spiral shaped, curved rod (comma shaped)
- Oxidase positive
- Microaerophilic
  - Requires oxygen but lives best with low O2 levels

Campylobacter

- VERY common cause acute diarrhea in children
- A leading cause of acute diarrhea worldwide
- Fecal-oral transmission
  - Lives in animal intestines, especially poultry
  - Undercooked meat especially poultry
  - Unpasteurized milk
  - Can also contaminate drinking water
- Common trigger of Guillain-Barre
  - Demyelinating disease
  - Ascending weakness

Vibrio Cholera

- Toxin-mediated disease
- Toxin carried by bacteriophage (lysogenic)
- Permanently activates Gs → ↑cAMP
- Voluminous "rice-water" diarrhea

Vibrio Cholera

- Requires large “dose” of bacteria for infection
  - Acid kills small amounts of bacteria
  - Common in areas that lack clean water
  - Also can occur on acid suppression drugs (lowers dose req’d)
- Death from dehydration, electrolyte losses, shock
- Treatment: Aggressive volume repletion

V. vulnificus/parahaemolyticus

- Both cause food poisoning (diarrhea)
- Found in raw oysters
- V. vulnificus can infect wounds after swimming in contaminated water

Haemophilus influenza

- Colonizes nasopharynx
- Causes several respiratory diseases, meningitis
- Some have polysaccharide capsule some do not
  - "Capsular" bacteria are "typeable" into six serotypes (a to f)
  - Others are "nontypeable"
- Most disease caused by type B
  - Capsule consists of ribosyl and ribitol phosphate polymer
- Vaccine contains type B capsule (Hib)
  - Conjugated to a carrier protein (often tetanus toxoid)
  - Stronger T-cell response
  - Given before 7 months

Haemophilus influenza

Special Features

- IgA protease
- Grows on Chocolate agar
  - Factors V (NAD) and X (hematin) present
  - Will also grow with S. Aureus on blood agar

Haemophilus influenza

Infections

- Epiglottitis
  - Life-threatening (airway obstruction)
  - Unvaccinated children with fever, sore throat
  - Dysphagia, drooling
  - Epiglottis will appear “cherry red”
- Pneumonia
- Meningitis
- Otitis media, bronchitis, conjunctivitis
  - S. pneumoniae and non-typeable H. influenza
  - Vaccine not protective

Haemophilus ducreyi

- Causes chancroid
- Painful genital ulcer
- Contrast with chancre (syphilis): non-painful
- Sexually transmitted
- Treatment: Azithromycin/Ceftriaxone

Genital Ulcers

Disease	Feature
Syphilis	Painless chancre
H. Ducreyi	Painful chancroid
Herpes	Multiple vesicles/ulcers
Lymphogranuloma Venereum	Large, swollen lymph nodes (buboes)

Bordetella Pertussis

- Causes whooping cough
- URI with severe coughing
- Classic presentations
  - Paroxysms of coughing
  - Inspiratory “whoop”
  - Post-cough vomiting
  - Exhaustion from coughing
- Coughing fits can last weeks
- In China, pertussis known as the "100 day cough"

Bordetella Pertussis

- Transmitted by aerosolized droplets
- Pertussis toxin
  - Shown to inhibit Gi proteins
  - Allows over-activation of adenylate cyclase
  - ↑cAMP levels in cells in neutrophils
  - Result: impaired recruitment of neutrophils
- Toxin may not be cause of cough
  - Some species without toxin shown to cause symptoms

Bordetella Pertussis

- Infection rare due to vaccine
- Acellular pertussis vaccines used
- Contain purified pertussis antigens

Yersinia Enterocolitica

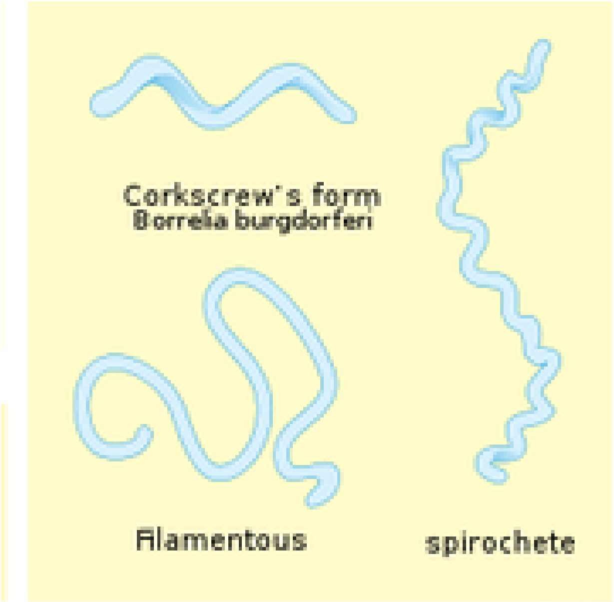
- Found in domesticated animals (dogs), pigs
- Often transmitted through contaminated pork
- Also from contaminated water or milk
- Fever, abdominal pain, nausea, vomiting
- Bloody diarrhea
- Can cause inflammation around appendix or in mesenteric lymph nodes (mesenteric adenitis)
  - May mimic Crohn's or appendicitis
- Don’t confuse with Yersinia pestis (plague)

Spirochetes

Jason Ryan, MD, MPH

Spirochetes

- Bacteria with long, corkscrew-shaped cells
- Difficult to grow/culture
- Serology usually used for diagnosis



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Spirochetes

- Leptospira (Leptospirosis)
- Borrelia (Lyme disease)
- Treponema (Syphilis)

Leptospira interrogans

- Causes Leptospirosis
- Lives in rodents → shed in urine
- Illness commonly from contaminated water
- Disease ranges asymptomatic → severe
- Flu-like illness: fever, rigors, myalgias, headache
- Conjunctival suffusion (red eyes)
- Aseptic meningitis
- Weil's disease (rare complication)
  - Liver damage (jaundice), renal failure, and bleeding

Leptospira interrogans

- Diagnosis:
  - Usually from classic history/exam
  - Serology (antibody) tests available
- Treatment: Doxycycline or Azithromycin
- Classic case:
  - Surfer or swimmer in Tropics
  - Flu-like illness
  - Conjunctival suffusion
  - Jaundice

Borrelia burgdorferi

- Causes Lyme disease
- Cause by tick bite (Ixodes scapularis)
  - Tick larvae feed on mice (reservoir for Borrelia)
  - Infected adult ticks feed on deer
- Ticks can bite humans → infection with Borrelia
- Tick must be attached ~48hrs to transmit bacteria
- Common in Northeast US (Lyme, Connecticut)

Lyme Disease

- Stage 1: Erythema chronicum migrans
  - Classic finding: expanding "Bulls-eye" rash
  - Flu-like symptoms
- Stage 2: Neurologic and cardiac
  - Facial nerve palsy
  - AV block

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Lyme Disease

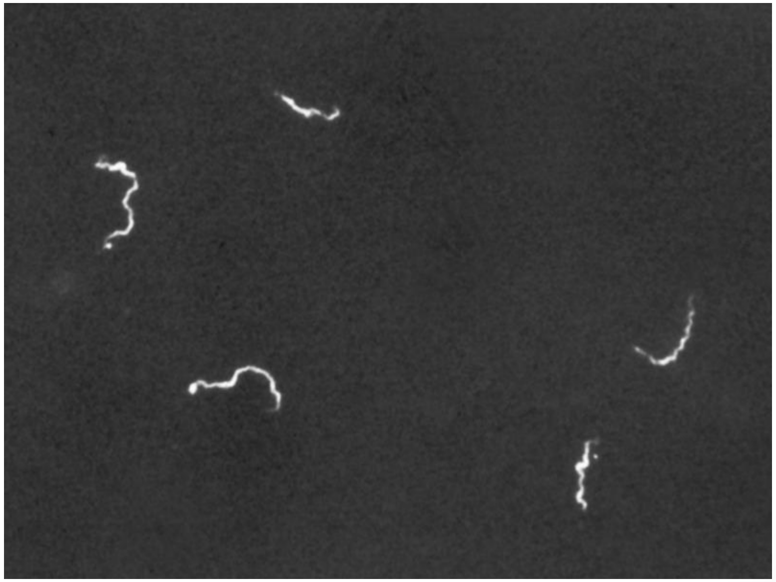
- Stage 3:
  - Arthritis (often knees)
  - Neuropathy (pain, paresthesias)
  - Encephalopathy (mild cognitive disturbance)
  - Rash: Blue-red discoloration
    - Acrodermatitis Chronica Atrophicans
    - More common in European Lyme
- Treatment: Doxycycline or Ceftriaxone

Relapsing Fever

- US: Borrelia hermsii and Borrelia turicatae
  - Transmitted by tick bites
- Developing world: Borrelia recurrentis
  - Transmitted by louse (insect)
  - Spread from person to person by louse (epidemics)
- Symptoms are relapsing fever (duh!)
- Antigenic variation causes recurrent fevers
- Spirochetes change major antigens on surface
- This evades immune response
  - Growth occurs
  - Fever returns

Treponema pallidum

- Causes syphilis
- Sexually transmitted disease
- Can see spirochete by dark field microscopy
- Disease: 1^o, 2^o, 3^o stages



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Primary Syphilis

- Two to three weeks after exposure
- Painless chancre (ulcer)
  - Classically on the penis
  - Usually 1-2cm
  - Raised
- Often unnoticed (painless) → disease progresses

Image courtesy of Wikipedia/Public Domain

Secondary Syphilis

- Rash
  - Classically maculopapular rash
  - Covers all extremities including palms/soles
- Flu-like symptoms
  - Fever, headache, malaise, sore throat, myalgias
- Condyloma lata
  - Large, raised, gray to white lesions
  - Moist areas: inside mouth, perineum
  - Often close to chancre; may reflect direct spread
- Treponema present in condyloma and chancre
  - Can visualize with dark-field microscopy

Palms and Soles

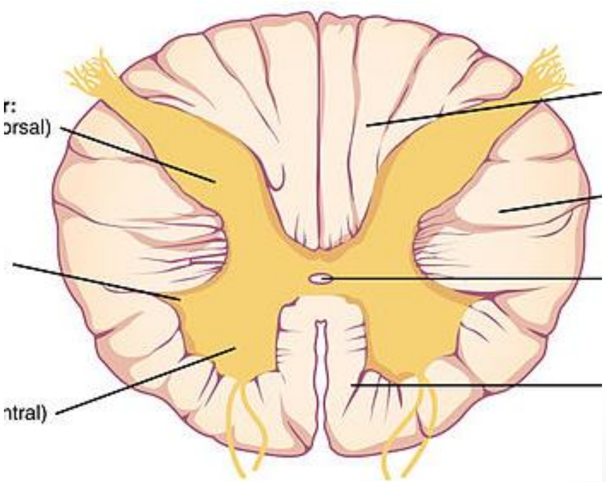
- Most maculopapular rashes spare palms/soles
- Three that don't:
  - Syphilis
  - Rock Mountain Spotted Fever
  - Coxsackie virus (hand, foot, mouth)

Tertiary Syphilis

- Gummas
  - Form of granuloma
  - Mass lesions that can appear anywhere: skin, liver
  - Often mistaken for tumors
- Aortitis
  - Vasa vasorum inflammation
  - Risk of aortic dissection
- Neurosyphilis
  - Many, many symptoms
  - Meningitis, dementia, nerve palsies

Tertiary Syphilis

- Argyll Robertson pupil
  - “Prostitute’s pupil”
  - Small pupils
  - Constrict to accommodation
  - Do not constrict to light
- Tabes Dorsalis
  - Demyelination of posterior columns
  - Wide-based gate
  - Ataxia (falls, loss of balance)



Syphilis Diagnosis

- VDRL
  - Venereal Disease Research Laboratory
  - "Non treponemal" test
  - Serum reacted with cardiolipin antigen (nonspecific)
- RPR
  - Rapid Plasma Reagin
- Syphilis patients' serum (antibodies) will react
  - Positive VDRL/RPR
- For neurosyphilis need to test CSF
  - Positive serum test does not necessarily indicate CNS disease
  - Many false negatives – difficult diagnosis

Syphilis Diagnosis

- Many false positives VDRL/RPR
  - Mononucleosis
  - Rheumatic fever
  - SLE
  - Leprosy
  - Pregnancy

Syphilis Diagnosis

- FTA-ABS
  - Fluorescent treponemal antibody absorption
  - “Treponemal test”
  - Detects antibodies against specific treponemal antigens
  - Very specific
- Test result: “Reactive” “Non-reactive”

Congenital Syphilis

- Spirochete transmitted from mother to fetus
- Can occur in 1st trimester
  - Mothers screened early in pregnancy
- Most often in mothers with no prenatal care
- Findings on baby can be early or late
  - Early (<2ys); Late (>2yrs)

Congenital Syphilis

Early Findings

- Hepatomegaly
- Runny nose
- Maculopapular rash
  - Small, red or pink spots
  - Often on back, buttocks, posterior thighs, and soles
- Abnormal long-bone radiographs
  - Many, many abnormalities reported

Congenital Syphilis
Late Findings

- Ears/nose
  - Saddle nose (no nasal bridge)
  - Hearing loss/deafness
- Teeth
  - Hutchinson teeth (notched, peg-shaped teeth)
  - Mulberry molars (maldevelopment of the molars)
- Legs
  - Saber shins (bowed legs)

Syphilis Treatment

- Penicillin G
- Jarisch-Herxheimer reaction
  - Flu-like syndrome after starting antibiotics
  - Killed bacteria cause immune response
  - Self-limited

Zoonotic Bacteria

Jason Ryan, MD, MPH

Zoonotic Bacteria

- All rare, all transmitted from animals to humans
- Almost all can be treated with Doxycycline
- Key is to recognize clinical syndromes

Animal Vector	Tick-Flea-Louse
Bartonella	Ehrlichia
Brucella	Borrelia
Chlamydophila psittaci	Rickettsia Rickettsia
Coxiella burnetii	Rickettsia Typhus
Leptospira	Rickettsia Prowazekii
Francisella tularensis	Yersinia pestis
Pasteurella	

Bartonella henselae

- Cats harbor fleas that carry Bartonella
- Cat Scratch Fever
  - Cat scratch (almost always a child)
  - Red, swollen area 3-10 days later
  - Regional lymphadenopathy (hallmark of disease)
    - Tender, red lymph nodes

Bartonella henselae

- Bacillary Angiomatosis (vascular lesions)
  - Diffuse skin papules in AIDS patients
  - Often mistaken for Kaposi Sarcoma
- Endocarditis (rare cause, culture negative)
- Treatment: Doxycycline, Azithromycin

Kaposi Sarcoma

OpenStax College/Wikipedia

- Raised, red/purple skin lesions
- Common in HIV/AIDS
- Angioproliferation
- Caused by HHV-8
- Can have similar appearance to Bacillary Angiomatosis
- Key differences
  - Kaposi Sarcoma: Lymphocytes
  - BA: Neutrophils/lymphocytes

Granulomatous Infections

- Tuberculosis
- Leprosy
- Fungal pneumonias (Histo, Blasto, Coccidio)
- Bartonella (cat scratch disease)
- Brucella
- Listeria in infants (Granulomatosis Infantiseptica)
- Schistosomiasis (worm)
- Syphilis (gummas)

Brucella

- Lives in cows, goats
- Infection from unpasteurized milk or animal exposure
- Classic patients:
  - Worker in meat packing plant
  - Traveler from Mexico who consumed milk/cheese
- Brucellosis (undulant fever)
  - Flu-like illness
  - High fever that rises and falls
  - Profuse sweating
- Treatment: Doxycycline + streptomycin/rifampin

Chlamydophila psittaci

Psittacosis

- Parrot fever
- Infection from inhalation dried feces
- Classic patient: Pet store employee
- Fever, headache, and dry cough
- Treatment: Doxycycline

Coxiella burnetii

Q fever

- Farm animals: cattle, goats, sheep
- Forms spores that get inhaled
- High concentrations in placenta of infected animals
- Symptoms
    - Pneumonia with flu symptoms (fever, headache, myalgias)
    - Endocarditis
- Diagnosis: Serology (antibodies)
- Treatment: Doxycycline

Culture Negative Endocarditis

- Evidence of endocarditis with sterile BCx
- Coxiella burnetii
  - Q fever
  - Farm animals (cattle, sheep, goats)
- Bartonella
  - Cat scratch fever
  - Cat fleas

Francisella tularensis

Tularemia (Rabbit fever)

- Important reservoirs: Ticks, deer flies, rabbits
- Occurs in animal handlers, especially rabbits
  - Also from tick bites
- Ulceroglandular tularemia (most common form)
  - Fever, chills malaise
  - Classically the fever abates for few days, returns
  - Skin ulcer at site of insect bite
  - Swollen, painful lymph nodes
- Treatment: Streptomycin (Doxycycline okay, too)

Pasteurella

- Lives in mouth of cats and dogs
- Infection: Cat/dog bites or scratches
- Key infections:
  - Cellulitis
  - Osteomyelitis
- Bite wounds usually polymicrobial (S. Aureus)
- Broad spectrum empiric therapy
  - Amoxicillin-clavulanate (oral)
  - Ampicillin-sulbactam (IV)
  - Piperacillin-tazobactam (IV)

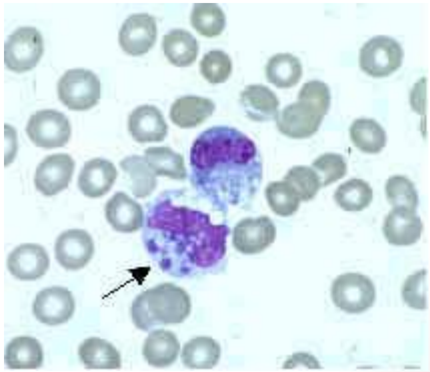
Leptospira interrogans

- Causes Leptospirosis
- Lives in rodents → shed in urine
- Illness commonly from contaminated water
  - Classic case is surfer or swimmer in tropics
- Treatment: Doxycycline or Azithromycin

Ehrlichia

Ehrlichiosis

- Tick-borne illness (Lone Star tick)
- White tail deer are principal reservoir
- Obligate intracellular bacteria
    - “Berry like” inclusions in monocytes (morulae)
- Symptoms
    - Flu-like illness
    - Leukopenia
    - Thrombocytopenia
- Diagnosis: Giemsa stain, serology
- Treatment: Doxycycline



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Anaplasma

Anaplasmosis

- Bacteria very similar to Ehrlichia
- Morula seen in granulocytes (not monocytes)
- Tick vector: Ixodes scapularis (not Lone Star tick)
  - Same vector as Lyme disease, Babesiosis
- Similar symptoms, treatments to Ehrlichiosis
  - Fever, joint pains
  - Low WBCs, platelets
  - Blood smear: granulocytes (not monocytes) with inclusions

Borrelia burgdorferi

- Causes Lyme disease
- Cause by tick bite (Ixodes scapularis)
  - Tick larvae feed on mice (reservoir for Borrelia)
  - Infected adult ticks feed on deer
- Ticks can bite humans → infection with Borrelia
- Common in Northeast US (Lyme, Connecticut)
- Treatment: Doxycycline or Ceftriaxone

Rickettsia and Chlamydia

- Similar types of bacteria
- Obligate intracellular bacteria
  - Use host ATP
  - Chlamydia cannot make ATP
  - Rickettsia can make some
- Cannot be cultured on common media
  - Inoculated into living cells (yolk sac of chicken embryos)
- Very small
  - Close to size of viruses
- Chlamydia: Person to person
- Rickettsia: Tick- or insect-borne illnesses

Rickettsia

- All infections occur from ticks-fleas-lice
- Three subtypes → different infections
  - R. rickettsii (Rocky Mountain Spotted Fever)
  - R. typhi (Murine typhus)
  - R. prowazekii (Epidemic typhus)

Typhus versus Typhoid

- Typhus = Greek word for smoky or hazy
  - Used by Hippocrates to describe state of mind
  - Typhus caused by Rickettsia sp.
  - Can cause plagues (R. prowazekii)
- Typhoid Fever
  - Caused by Salmonella typhi
  - Enteric disease
  - Fever, diarrhea, rose spots

Rocky Mountain Spotted Fever

Rickettsia rickettsii

- Occurs throughout US (despite name)
- Transmitted by tick bite
  - 1/3 may not recall/notice the bite
- Triad: Headache, fever, rash
- Headache, fever often come first
- Maculopapular rash
  - Starts wrists/ankles → spreads to trunk, palms, soles
- Rarely complications:
  - Encephalitis
  - Seizures
  - DIC
- Treatment: Doxycycline

Murine Typhus

Rickettsia typhi

- Also called “endemic” typhus
  - Endemic to certain populations (no epidemics)
- Reservoir: Rats
- Transmitted from rat fleas
- Common in developing world
- Flu-like illness
- Rash (<50%)
  - Maculopapular
  - Starts in trunk spreads out
- Treatment: Doxycycline

Epidemic Typhus

Rickettsia prowazekii

- Mostly historical
- Epidemics throughout history have killed millions
- Some outbreaks in Africa during civil wars
- Transmitted by body louse
  - Body louse lives on skin/clothes
  - Eggs laid on clothes and hatch
  - Larvae suck blood
  - During meal, louse defecates highly infective feces
  - Rickettsia in louse feces introduced to skin/membranes

Epidemic Typhus

Rickettsia prowazekii

- Fever, chills, headaches, malaise
- Maculopapular rash
  - Starts in trunk spreads out
- Confusion, seizures, coma
- Treatment: Doxycycline

Yersinia pestis

Bubonic Plague

- Reservoir: rats, sometimes squirrels or prairie dogs
- Humans get disease from rat flea bites
- Human to human spread via respiratory droplets
- Fever, chills, headache
- Intense pain/swelling of a lymph node area (bubo)
- Buboes:
  - Exquisite tenderness
  - Erythema and edema of overlying skin
  - Inguinal region most frequent ("bubo" = Greek word "groin")
- Treatment: Streptomycin (Doxycycline okay, too)

Tick-Flea-Louse

- Ehrlichia → Ehrlichiosis
- Borrelia → Lyme disease
    - ** Babesia (parasite) → same tick
- R. Rickettsia → Rocky Mountain Spotted Fever
- R. typhi → Murine typhus
- R. prowazekii → Epidemics/plague
- Y. Pestis → Bubonic plague

Mycobacteria

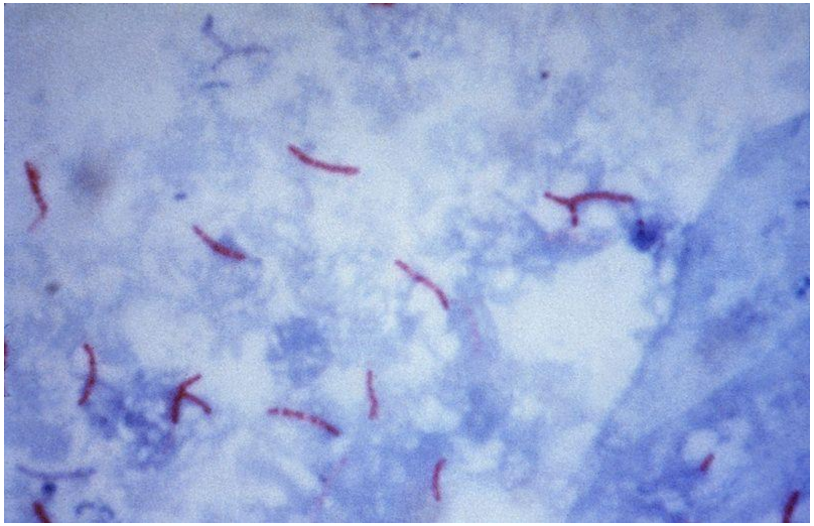
Jason Ryan, MD, MPH

Mycobacteria

- Mycolic acids in cell wall
- Lipid-rich cell wall that is "acid fast"
- Resistant to decolorization by acid after staining with carbolfuchsin
- Do not gram stain well (technically gram positive)

Ziehl-Neelsen

- The "acid fast" stain
- Contains carbolfuchsin
- Used to detect mycobacterium (especially TB)
- Also used for Nocardia



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Mycobacteria

- M. Tuberculosis
- M. avium complex (MAC)
- M. kansasii
- Mycobacterium leprae

MAC

Mycobacterium avium complex

- Most common non-TB mycobacterial infection
- Includes several bacteria:
  - M. avium, M. intracellulare
- Slow growing, acid-fast organisms

MAC

Mycobacterium avium complex

- Found in water and soil
- Inhaled or ingested
- Very rare cause of pulmonary disease in non-HIV
- HIV/AIDS: Disseminated disease
  - Very low CD4 count (<50)
  - Fever, sweats, abdominal pain, diarrhea, weight loss
  - Severe anemia
  - Hepatosplenomegaly
  - ↑ alk phos, ↑ LDH
  - Often no lung findings (if lung findings → it's TB)

MAC

Mycobacterium avium complex

- Diagnosis: Blood culture (takes 7 days or more)
- Treatment:
  - Clarithromycin plus Ethambutol
- Prophylaxis: Azithromycin

M. Kansasii

- Most frequent non-TB mycobacteria after MAC
- Environmental source not clear
- Similar pathology but less virulent than TB
  - Fever, sweats, cough, dyspnea
  - CXR infiltrates
- Treatment: Similar to TB

M. Leprae

Leprosy (Hansen's Disease)

- Obligate intracellular organism
- Grows very slowly - cannot be cultured
- Grows best at cool temps (27 to 33°C)
  - Infection involves skin
  - Extremities, face
- Reservoir is armadillos
- Mode of transmission unclear
- Causes granulomatous inflammation
- Mostly found in developing countries
- Most US cases occur in immigrants

M. Leprae

Leprosy (Hansen's Disease)

- Infects skin and superficial nerves
- Key signs/symptoms
  - Skin lesions
  - Loss of sensation

M. Leprae

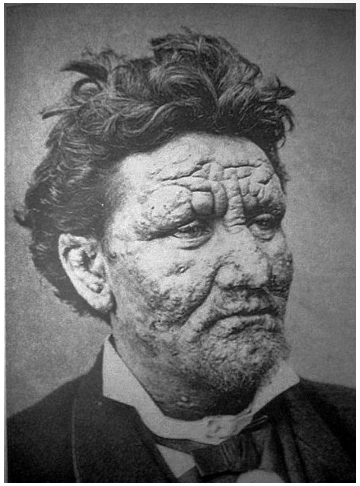
Leprosy (Hansen's Disease)

- Spectrum of disease
- Severity based on strength of cell-mediated response
- Tuberculoid leprosy - Milder disease
- Lepromatous leprosy – Severe disease

Tuberculoid Leprosy

- Patches of hypopigmented skin
- Loss of sensation over affected area
- Strong cell-mediated TH1 response contains infection
- Lesions show granulomas, few bacteria

Lepromatous Leprosy



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- Diffuse skin lesions
- Often deformed, thickened skin
- Hypopigmentation and hair loss
- Severe neuropathy (weakness, regional anesthesia)
- Th2 response
    - Humoral immunity
    - Depressed cell-mediated immunity
    - Antibodies cannot reach intracellular bacteria
- Lesions:
    - Multiple bacteria
    - No granulomas

M. Leprae

Leprosy (Hansen's Disease)

- Diagnosis:
  - Acid-fast organisms on skin biopsy
  - Note: False positive VRDL
- Treatment:
  - Tuberculoid: dapsone and rifampin (6 months)
  - Lepromatous: dapsone, rifampin, and clofazimine (years)

M. Leprae

Leprosy (Hansen's Disease)

- Rifampin
  - Tuberculosis drug
  - Blocks RNA synthesis
- Dapsone
  - Competes with bacterial para-aminobenzoic acid (PABA)
  - Inhibits dihydropteroate synthetase
  - Disrupts folic acid pathways (like sulfonamides)
  - Also used for pneumocystis jiroveci (like sulfonamides)
  - Hemolysis in G6PD (like sulfonamides)
  - Rarely can cause agranulocytosis (ANC=0)
- Clofazimine

IL-12 Receptor Deficiency

- IL-12 triggers differentiation T-cells to Th1 cells
- Activated TH1 cells produce IFN-γ
- Important for response to intracellular infections
- Children born with deficient receptors have a weak Th1 response and low levels IFN-γ
- Increased susceptibility:
  - Disseminated Salmonella
  - Disseminated nontuberculous mycobacterial (NTM)
  - Disseminated Bacillus Calmette-Guerin (BCG) after vaccine
- Treatment: IFN-γ

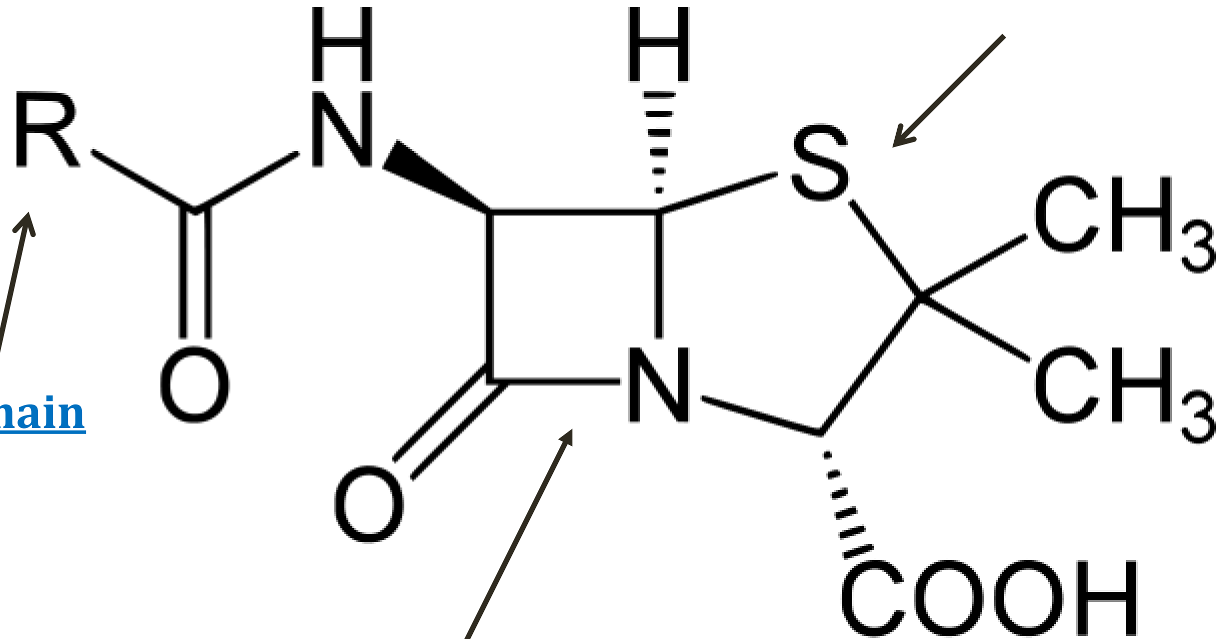
Penicillins

Jason Ryan, MD, MPH

Penicillins

Thiazolidine Ring
Penicillins

Side Chain



Beta Lactam Ring
Penicillins
Carbapenems
Aztreonam
Cephalosporins

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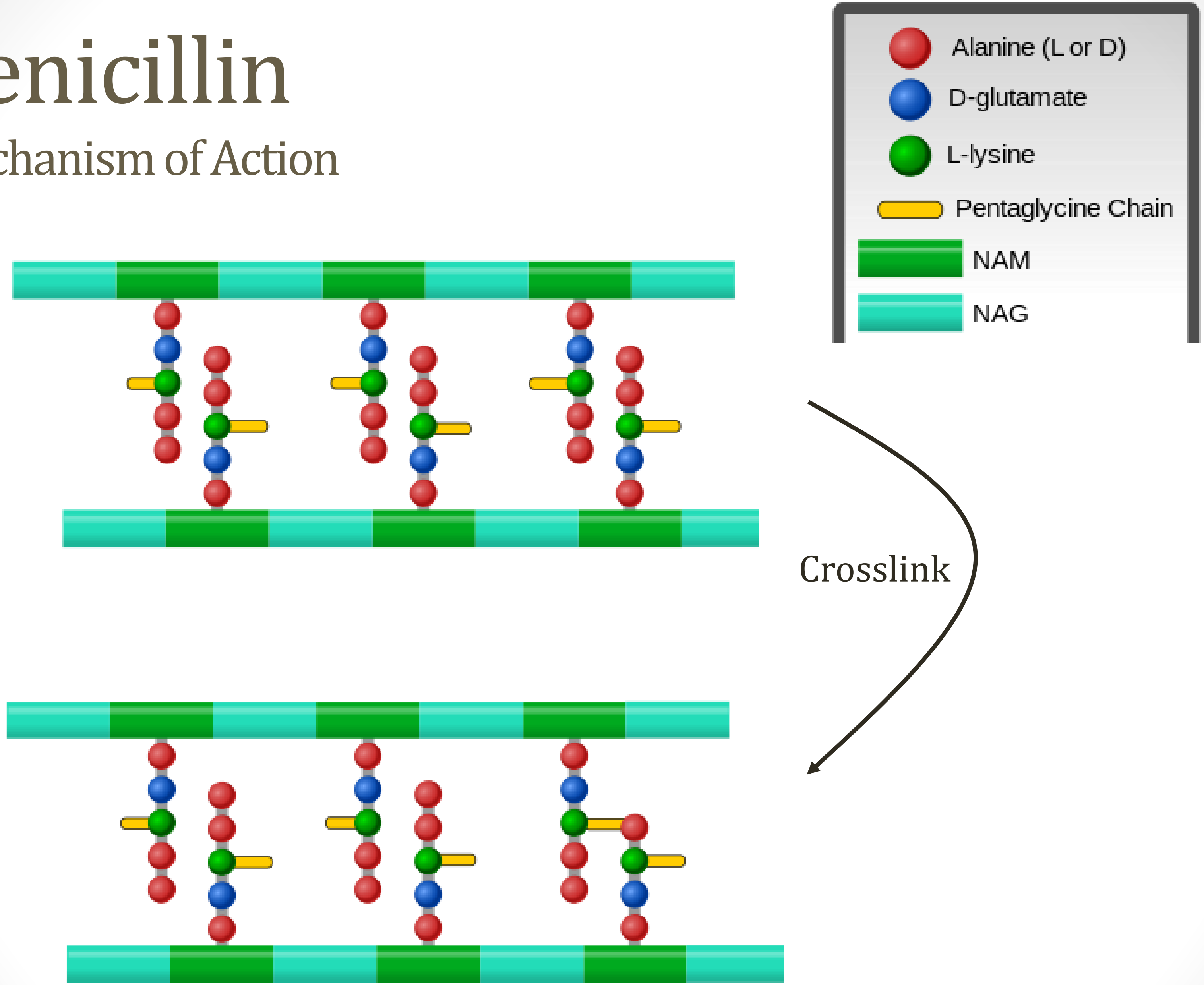
Penicillin

Mechanism of Action

- Bacteria constantly breaking down/remaking cell wall
- **Transpeptidases**
  - Cross link peptidoglycan in cell walls
  - Bind to **alanine** residues

Penicillin

Mechanism of Action



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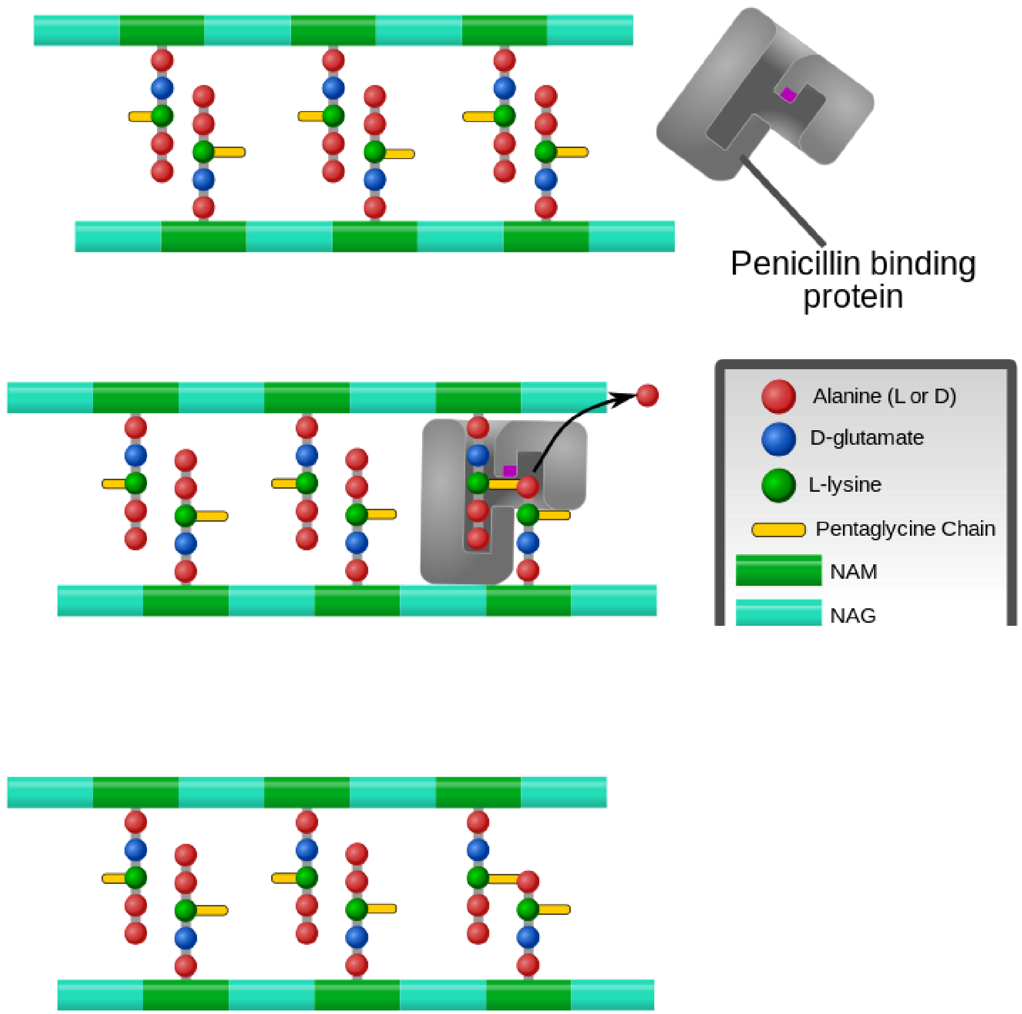
Penicillin

Mechanism of Action

Binds **ala-ala** residues
Links lysine-alanine



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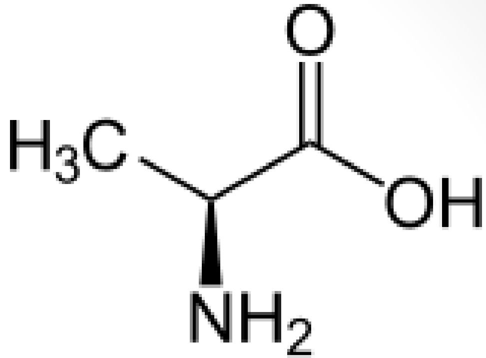
Penicillin

Mechanism of Action

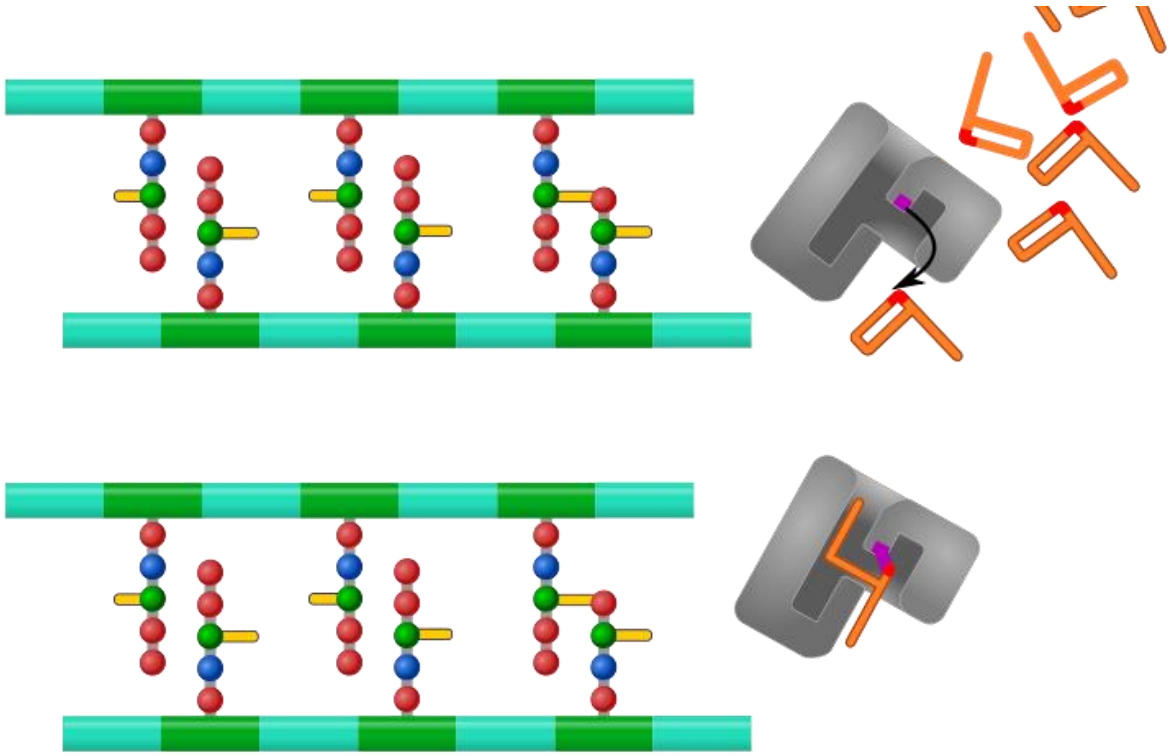


Alanine

- Penicillin binds to transpeptidases
  - "Penicillin binding proteins"
  - Mimics alanine ("D-alanyl-D-alanine") residues
  - **Inactivates enzymes**
- Wall breakdown > wall creation → **Autolysis**
  - Enzymes that hydrolyze cell wall continue to work
  - Cell death (bactericidal)
- All β-lactam antibiotics: similar mechanism

Penicillin

Mechanism of Action



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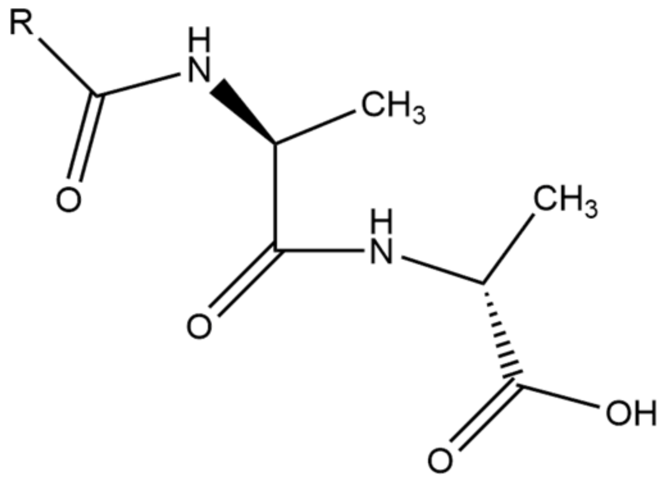
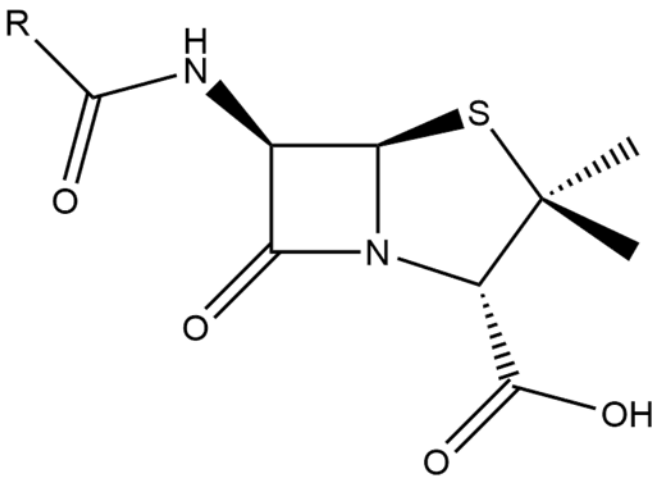
Penicillin

Mechanism of Action



D-Ala-D-Ala Terminus

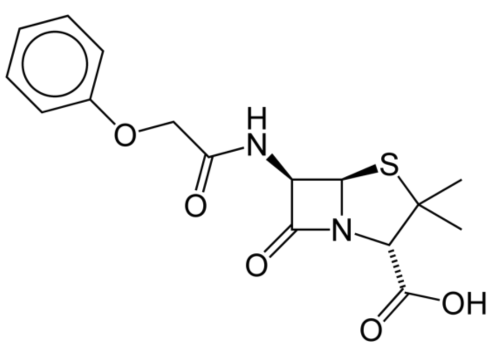


Penicillin

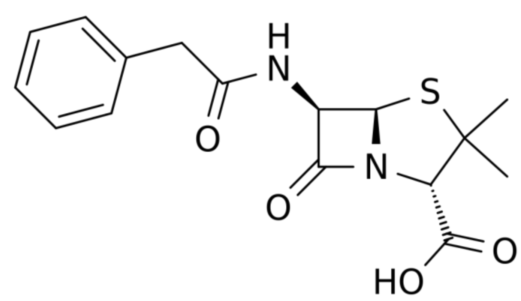
Omargs10/Wikipedia

Natural Penicillins

- Penicillin G (IM and IV)
- Penicillin VK (oral)
- **Probenecid**
  - Gout drug
  - Inhibits renal secretion PCN
  - Boosts PCN levels → co-administered in special circumstances



Penicillin G



Penicillin VK

Natural Penicillins

Resistance

- Modified **penicillin binding proteins**
  - May result from genetic mutations
  - Example: S. pneumonia often produces altered PBPs
- Reduced bacterial cell **penetration**
  - Gram negative bacteria: poor penetration
  - Porins: gram negative proteins that transport nutrients/waste
  - Bacteria may decrease number of porins
- Beta lactamase enzyme

Beta Lactamase

Penicillinase

- Bacterial enzymes
- Degrade beta lactam compounds
  - Penicillin G and VK
  - Some other penicillins
  - Some cephalosporins
- Many **gram negative bacteria**
- **Staphylococcus aureus**

Beta Lactamase

- Most **gram negative rods** have beta-lactamase gene
  - "Chromosomal beta lactamase"
  - Some express low levels
- Genes can also be transferred via **plasmids**
  - Extra-chromosomal genetic material
  - Self-reproducing
  - Transferrable

Beta Lactamase

- Gram negative bacteria
  - Beta lactamase found in **periplasm**
- Gram positive bacteria (S. Aureus)
  - No periplasm - Beta lactamase **secreted**
  - Generally produce more enzyme than GN

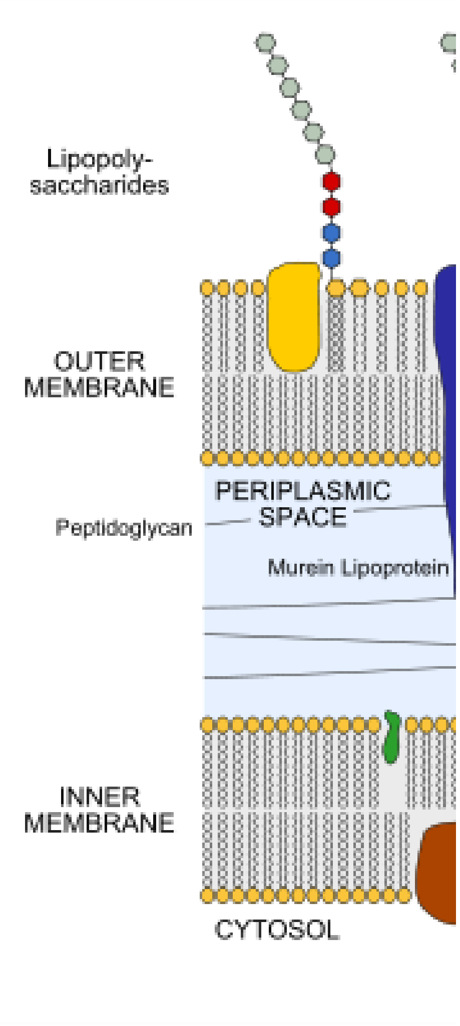


Image courtesy of Jeff Dahl/Wikipedia

β-Lactamase Inhibitors

Clavulanic Acid, Sulbactam, Tazobactam

- Inhibit bacterial β-lactamase
- Added to some penicillins to expand coverage
  - Aminopenicillins
  - Antistaphylococcal penicillins
- Little/no effect used alone

Penicillin G and VK

Clinical Uses

- Narrow spectrum – few specific modern uses
- Gram positives
  - Strep pyogenes (strep throat)
  - Actinomyces
- Treponema Pallidum (syphilis)
- Rare uses (only in susceptible isolates)
  - Neisseria meningitides
  - Strep. pneumonia

Penicillin Adverse Effects

Hypersensitivity (allergic) reactions

- Commonly leads to hypersensitivity (allergic reaction)
- 1st exposure: Sensitization
- 2nd exposure: Hypersensitivity reaction
- Symptoms resolve on stopping drug

Penicillin Adverse Effects

Hypersensitivity (allergic) reactions

- Acute ("immediate")
  - **Type I, IgE-mediated**
  - Usually **within 1 hour** of taking drug
  - Histamine release
  - Itching, urticaria
  - Bronchospasm
  - Anaphylaxis

James Heilman, MD

Penicillin Adverse Effects

Maculopapular Rash

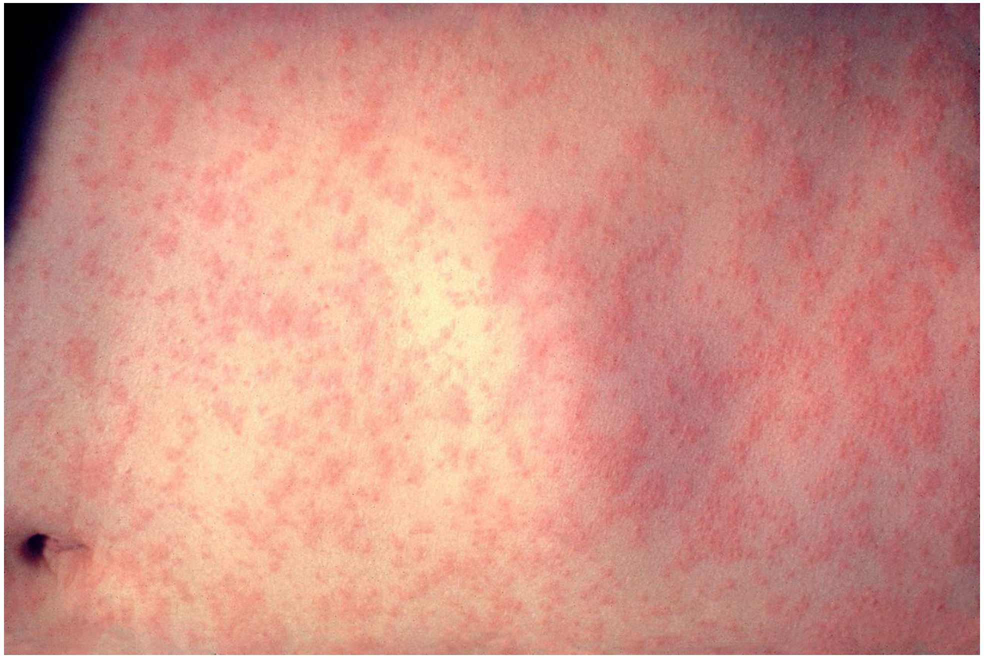
- "Non-immediate" reaction
- Most common with **aminopenicillins**
- Maculopapules
- Itchy or may be non-pruritic
- Absence of fever, wheezing, joint pain
- **Days or weeks** after starting drug
- **Type-IV (T-cell-mediated) mechanism**

Romano A et al. **Diagnosis of nonimmediate reactions to B-lactam antibiotics**. Allergy 2004

Penicillin Adverse Effects

Maculopapular Rash

- More common with viral infection
  - **EBV pharyngitis**
  - Amoxicillin given for pharyngitis → maculopapular rash
  - Mechanism not clear



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Penicillin Adverse Effects

Skin Reactions

- Stevens-Johnson Syndrome
  - Fever, necrosis
  - Sloughing of skin
  - Dermal-epidermal junction
  - Vesicles, blisters
- Toxic epidermal necrolysis
  - Severe form SJS (>30% skin)
- Mortality: SJS 1-5%; TEN 25-35%

Dr. Thomas Habif/Wikipedia

Penicillin Adverse Effects

Skin Reactions

- Immune mediated
  - CD8 T-cells play important roll
  - Re-challenge with drug can cause recurrence
- Antibiotic associations:
  - Sulfonamides (TMP-SMX)
  - **Aminopenicillins**
  - Cephalosporins

Penicillin Adverse Effects

Interstitial Nephritis

- Drug acts as hapten → immune response in kidneys
- Hypersensitivity (allergic) reaction
  - Complex mechanism
  - Considered a **Type IV hypersensitivity** reaction
  - T cells, Mast cells

Spanou Z et al. **Involvement of Drug-Specific T Cells in Acute Drug-Induced Interstitial Nephritis**. JASN Oct 2006

Penicillin Adverse Effects

Interstitial Nephritis

- Classic presentation
  - Fever
  - Oliguria
  - **Increased BUN/Cr**
  - **Eosinophils** in urine
  - White cells and **WBC casts** ("sterile pyuria")

Penicillin Adverse Effects

Hemolytic Anemia

- High doses can lead to extrinsic hemolytic anemia
- PCN binds to surface RBCs (hapten)
- Elicits immune response
- **Antibodies against PCN bound to RBCs**
- Direct Coombs test: positive
- Type II hypersensitivity

Penicillin Adverse Effects

Hypersensitivity (allergic) reactions

- Serum Sickness
  - Immune complex disorder (IgG)
  - **Days/weeks after exposure**
  - Complement activation
  - Type III hypersensitivity reaction
- Urticaria, fever, arthritis, lymphadenopathy

Tatum A et al. **Severe serum sickness-like reaction to oral penicillin drugs: three case reports**. Ann Allergy Asthma Ummunol 2001

Penicillin Immunology

Penicillin

Type I	Type II	Type III	Type IV
Acute	Hemolysis	Serum Sickness	T cells
IgE	IgG	IgG	Skin
Anaphylaxis		Fever	Nephritis
		Urticaria	
		Arthritis	

Penicillin Adverse Effects

C. Difficile Infection

- **Diarrhea** following antibiotic therapy
- Antibiotic depletes normal intestinal flora
- C. Difficile growth → **pseudomembranous colitis**
- May occur with any antibiotic
- Frequent associations
  - Clindamycin
  - Fluoroquinolones
  - Cephalosporins
  - **Penicillins**

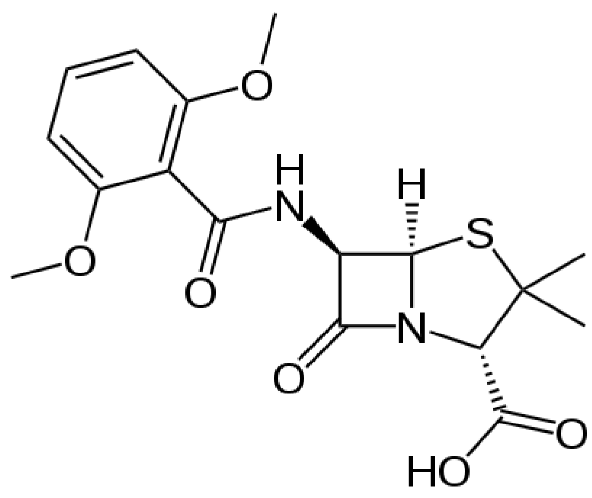
Jarisch-Herxheimer Reaction

- Occurs with **PCN therapy for spirochete infections**
- Classically occurs in **syphilis**
- Febrile syndrome
- Fever, chills, flushing, hyperventilation
- Usually ~2hrs after starting therapy
- Due to bacterial cell death → immune response

Antistaphylococcal Penicillins

Oxacillin, nafcillin, dicloxacillin

- Side chain protects β-lactam from **staph penicillinase**
- Prototype: Methicillin
  - No longer used
  - High frequency of adverse effects (interstitial nephritis)
- Covers Staph Aureus (non-MRSA) and most strep



Methicillin

Antistaphylococcal Penicillins

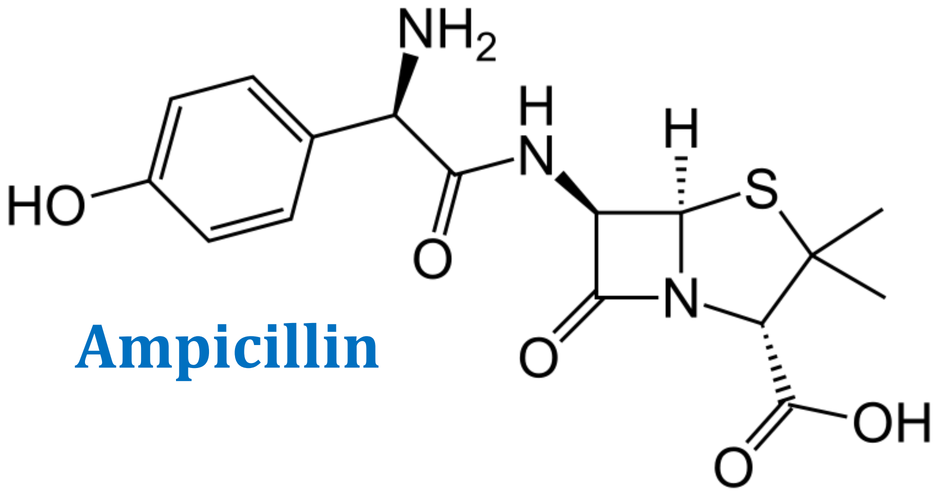
Oxacillin, nafcillin, dicloxacillin

- Common uses
  - Community acquired cellulitis
  - Impetigo
- Staph endocarditis based on culture data
- Side effects similar to penicillin

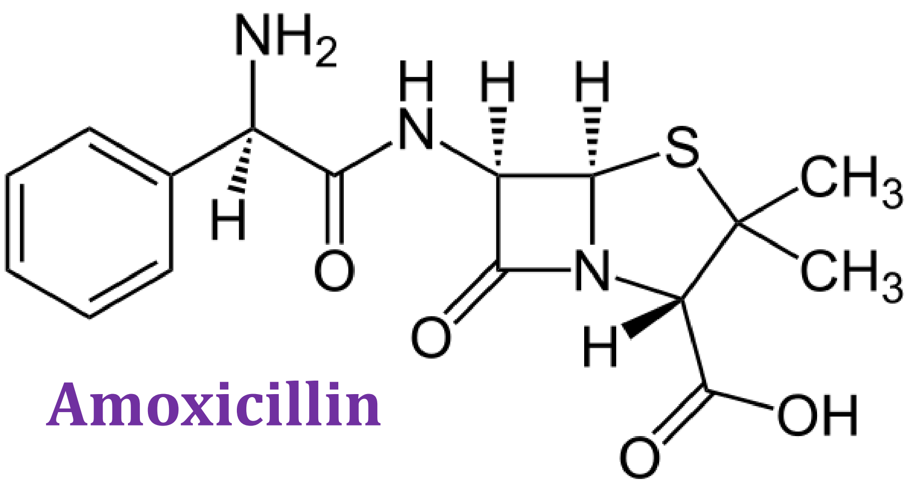
Åsa Thörn

Aminopenicillins

Amoxicillin/Ampicillin



Ampicillin



Amoxicillin

Aminopenicillins

Amoxicillin/Ampicillin

- Amoxicillin (oral)
- Ampicillin (IV)
  - Poor bioavailability when given orally
- **Penetrate porin channel of gram-negative bacteria**
- **Sensitive to beta lactamase enzymes**
- Covers penicillin bacteria plus some gram negatives

Aminopenicillins

Amoxicillin/Ampicillin

Bacteria

- **H. Influenza**
- E. Coli
- Proteus
- Salmonella
- Shigella
- **Listeria** (gram +)

Main Clinical Uses

- Otitis Media
- Bacterial sinusitis
- Meningitis
  - Newborns, elderly
  - Listeria coverage

Aminopenicillins

Maculopapular Rash

- Most common with aminopenicillins
- More common in viral infection
- Classic case
  - EBV infection with sore throat
  - Amoxicillin given for presumed bacterial pharyngitis
  - Maculopapular rash

Aminopenicillins

Skin Reactions

- Stevens-Johnson Syndrome
- Toxic epidermal necrolysis
- Antibiotic associations:
  - Sulfonamides (TMP-SMX)
  - **Aminopenicillins**
  - Cephalosporins

Dr. Thomas Habif/Wikipedia

β-Lactamase Inhibitors

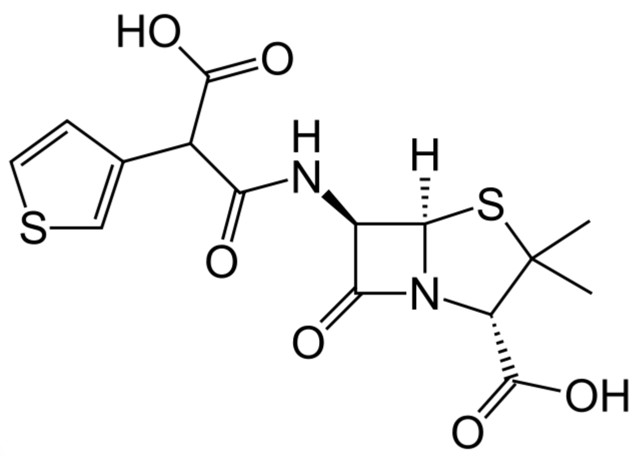
Clavulanic Acid, Sulbactam, Tazobactam

- Commonly used with aminopenicillins
  - Amoxicillin/Clavulanic acid (Augmentin)
  - Ampicillin/Sulbactam (Unasyn)
  - Increases activity against S. Aureus, H. flu
  - Also increases activity against anaerobes (B. fragilis)
- Common uses:
  - Otitis media/sinusitis (Broad-spectrum)
  - Bite wounds (Polymicrobial with anaerobes)

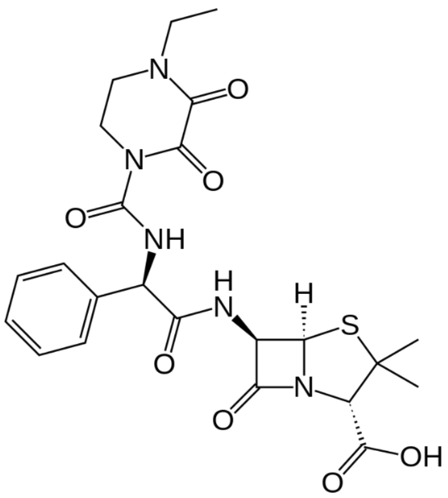
Antipseudomonal Penicillins

Ticarcillin, Piperacillin

- **Greater porin channel penetration**
- Effective against Pseudomonas aeruginosa
- More gram (-) coverage vs. aminopenicillins



Ticarcillin
(Carboxypenicillin)



Piperacillin
(Piperazine penicillin)

Antipseudomonal Penicillins

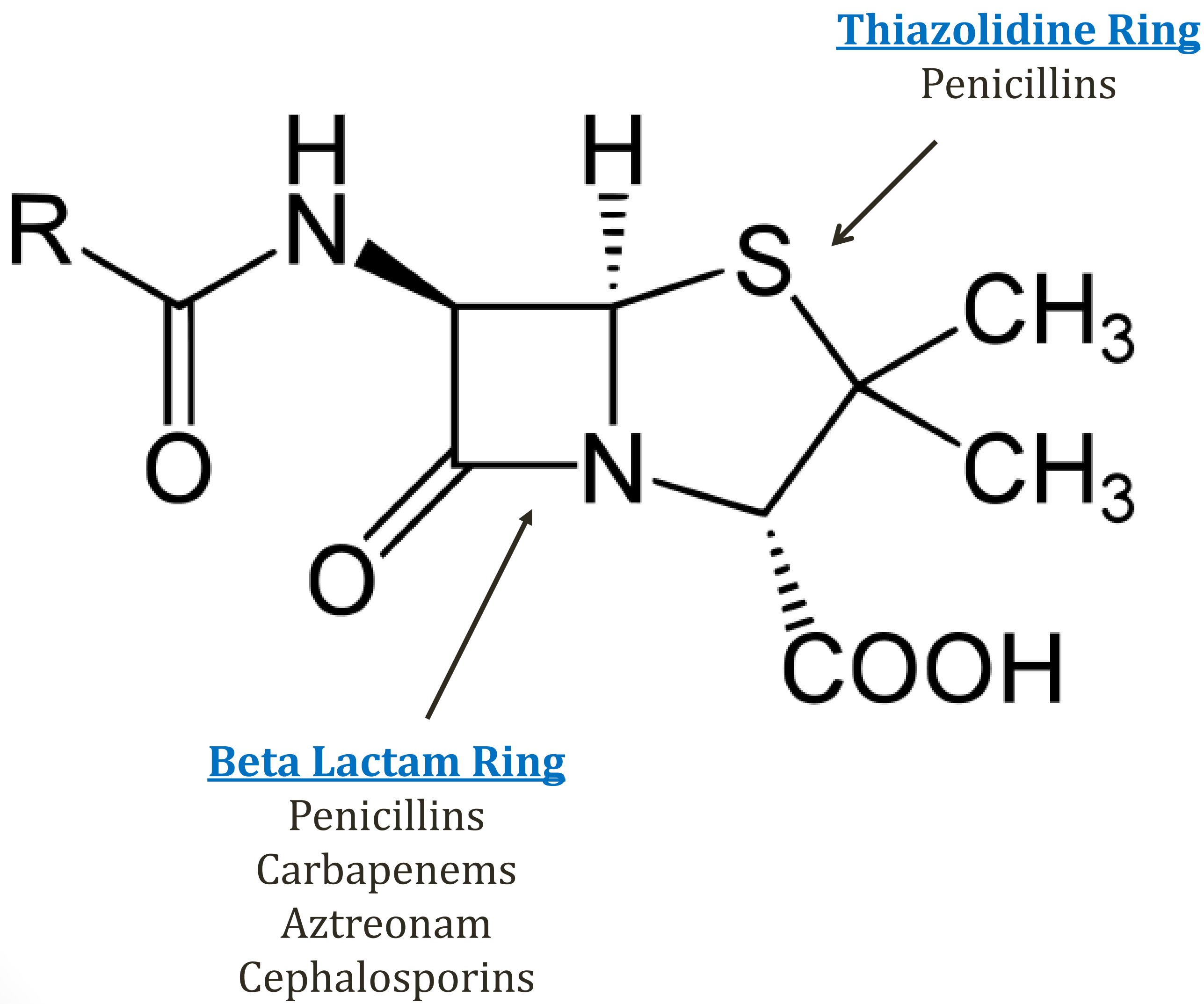
Ticarcillin, Piperacillin

- Susceptible to β-lactamases
- Given with β-lactamase inhibitor
  - Ticarcillin-clavulanate (Timentin)
  - Piperacillin-tazobactam (Zosyn)
- Broad-spectrum antibiotics
  - Most gram-positive (not MRSA)
  - More gram-negative (pseudomonas)
  - Most anaerobic bacteria
- Hospitalized patients with sepsis/PNA

β-Lactam Antibiotics

Jason Ryan, MD, MPH

Penicillin Structure



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Beta Lactam Antibiotics

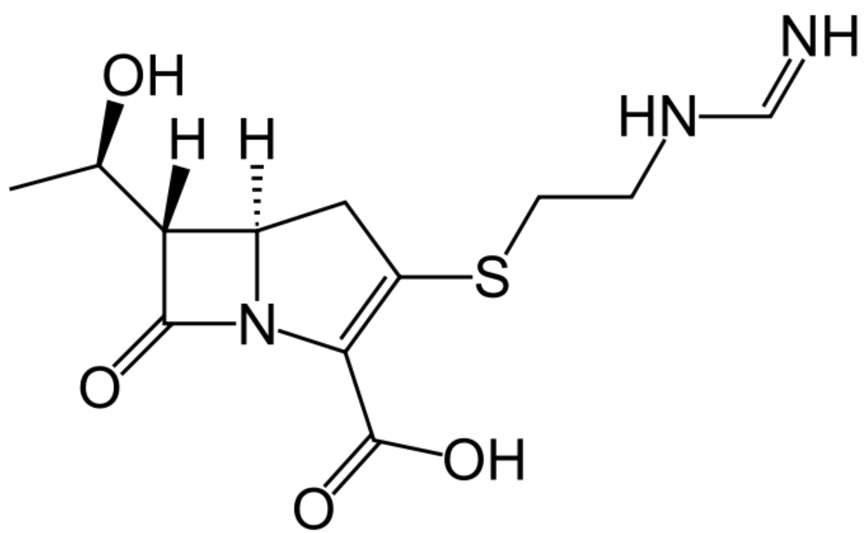
Carbapenems, Aztreonam, Cephalosporins

- Similar mechanism to penicillin
  - Bind transpeptidases (penicillin-binding proteins/PBPs)
  - Prevent peptidoglycan crosslinking
  - Autolysis
  - Usually **bactericidal**
- Potentially susceptible to beta lactamase

Carbapenems

Imipenem, meropenem, ertapenem, doripenem

- β-lactams (not penicillins)
- **Resistant to cleavage by most β-lactamase**



Imipenem

ESBL

Extended Spectrum Beta Lactamase

- Plasmid-mediated bacterial enzymes
- Confer resistance to most beta-lactam antibiotics
  - Penicillins, cephalosporins, aztreonam
- Found only in gram-negative bacteria
  - Pseudomonas
  - Klebsiella
  - E. coli
  - Enterobacter
  - Salmonella
  - Serratia
  - Shigella

Carbapenems

Imipenem, meropenem, ertapenem, doripenem

- Drug of choice for ESBL bacteria
- Broad spectrum:
  - Gram (+)
  - Gram (-) including pseudomonas, enterobacter
  - Anaerobes including B. fragilis
- Used in hospitalized patients

Imipenem

- First commercially available carbapenem
- Metabolized in kidneys
  - Loss of antibacterial effect
  - Nephrotoxic metabolites
- Proximal tubule enzyme: **dehydropeptidase I**
- Given with **cilastatin** (enzyme inhibitor)

Carbapenems

Imipenem, meropenem, ertapenem, doripenem

- Imipenem and meropenem
  - Older carbapenems
  - No important differences in efficacy
- Doripenem and ertapenem
  - Newer carbapenems
  - Doripenem: Similar to imipenem and meropenem
  - Ertapenem: Some resistance in ESBL bacteria
- Ertapenem
  - Once daily dosing
  - Weak activity against pseudomonas

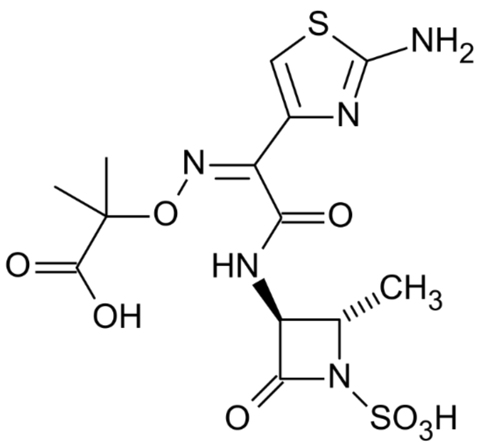
Carbapenems

Imipenem, meropenem, ertapenem, doripenem

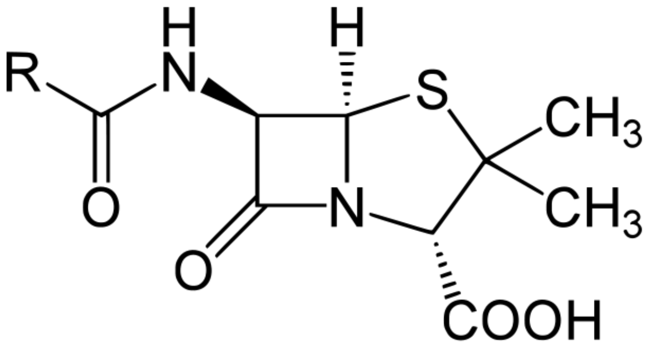
- Common side effects
  - Nausea, vomiting, diarrhea
  - Skin rash
- Neurotoxicity
  - **Seizures**
  - Inhibition of GABA receptors
  - Especially at high doses or with renal failure
  - Lower risk with **meropenem**

Aztreonam

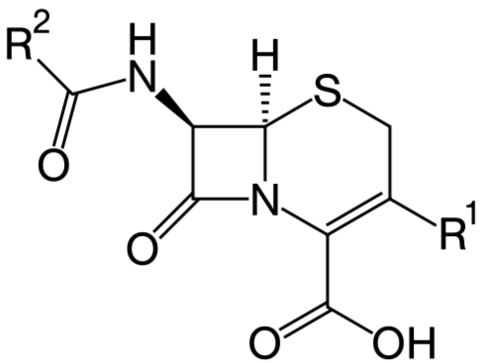
- Monobactam: β-lactam ring not fused to another ring



Aztreonam



Penicillins



Cephalosporins

Aztreonam

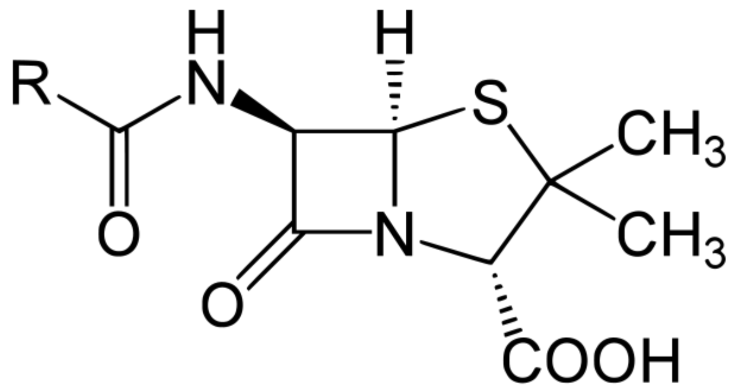
- Binds penicillin-binding protein 3 (PBP-3)
  - Found in **gram negative bacteria**
  - Prevents cross-linking of peptidoglycan
  - Bactericidal
- Limited susceptibility to β-lactamase
  - Some resistance in ESBL bacteria
- Only active against **gram (-) bacteria**
  - Does not bind PBP of gram (+) bacteria
  - No activity against gram (+) or anaerobes
  - Active against **pseudomonas**

Aztreonam

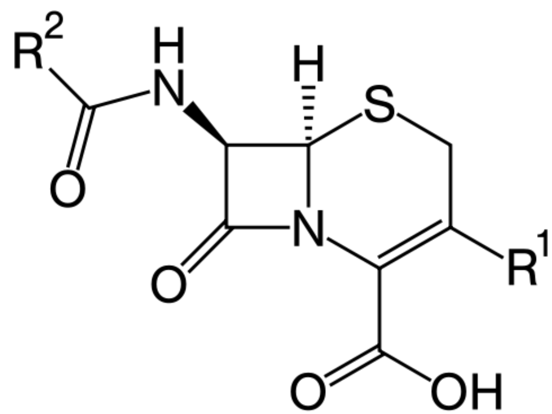
- Intravenous administration (hospitalized patients)
- Synergistic with **aminoglycosides**
- No cross reactivity in **penicillin allergic patients**
- Key niche: penicillin allergy

Cephalosporins

Penicillin



Cephalosporin



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Cephalosporins

- Divided into 1^{st} through 4^{th} generation
- 1^{st} generation: Mostly gram positive coverage
- Successive generations: increased gram (-) coverage

1st Generation Cephalosporins

- Cefazolin, cephalexin
- Developed to treat S. Aureus resistance to penicillin
- Covers many gram (+) including S. Aureus (not MRSA)
  - **Stable against S. Aureus beta lactamase**
  - Does not cover enterococcus or listeria
  - Susceptible to gram negative beta lactamases
- Main uses:
  - Surgical wound (skin) infections
  - Cefazolin given pre-op for prevention

2nd Generation Cephalosporins

Cefuroxime, Cefoxitin, Cefotetan

- Developed to treat amoxicillin-resistant infections
- Increased affinity for gram (-) PBPs
- **More resistant to beta lactamase**
- Increased gram (-)
  - H. influenza, Enterobacter, Proteus
  - E. coli, Klebsiella, Serratia, N. gonorrheae
- Increased anaerobic coverage (B. fragilis)

2nd Generation Cephalosporins

Cefuroxime, Cefoxitin, Cefotetan

- Cefuroxime (oral):
  - Otitis media (S. pneumonia, H. flu)
  - UTI in children (E. coli; no fluoroquinolones)
- Cefoxitin/cefotetan (IV):
  - PID (covers Neisseria; also give doxycycline for Chlamydia)
  - Pre-op in children with appendicitis
    - E. coli
    - Covers gram negatives and some anaerobes
    - Usually given with metronidazole

3rd Generation Cephalosporins

Ceftriaxone, Cefotaxime, Ceftazidime

- Broad gram (-) coverage
  - **More resistance to beta lactamase enzymes**
  - More gram (-) PBP affinity
- Ceftriaxone, Cefotaxime: Poor coverage pseudomonas
- Ceftazidime: Covers pseudomonas
  - Used in hospitalized patients with gram negative infections
  - Sepsis/pneumonia
- Most achieve **good CSF penetration** (meningitis)

Ceftriaxone

- Commonly used for N. gonorrhea
- Commonly used in meningitis
  - Active against S. pneumonia, N. meningitidis
  - Good CSF penetration

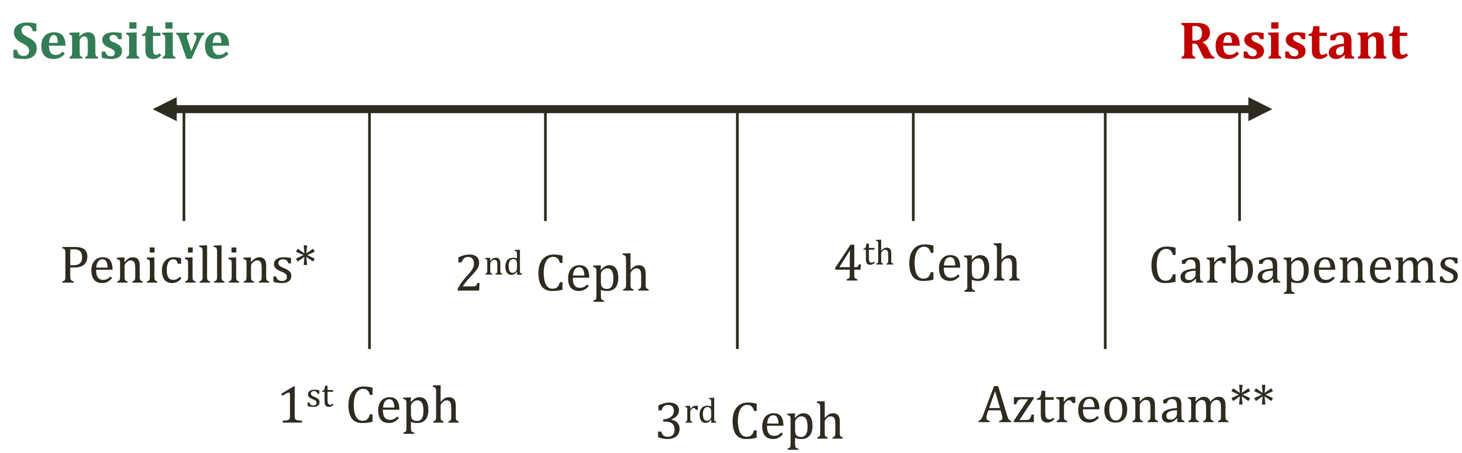
4th Generation Cephalosporins

Cefepime

- Broad spectrum (>3rd generation drugs)
  - MSSA
  - Many gram (+)'s
  - Many gram (-)'s including **pseudomonas**
- Resistant to some ESBL
- Hospitalized patients with gram (-) infections

β-lactamase Sensitivity

Based on side chain



* Anti-staphylococcal penicillins resist staph penicillinase

** Gram negatives only

5th Generation Cephalosporins

Ceftaroline

- Active against **MRSA**
- FDA approval 2010
- Prodrug converted to active metabolite
- Binds **PBP2a**
    - MRSA-specific PBP
    - Low affinity for most other beta-lactams
- Covers MRSA and VRSA
- Some gram negatives (not pseudomonas)
- Studied in skin infections and pneumonia

Cephalosporins

Resistance Mechanism

- Modified penicillin-binding proteins (PBPs)
- Altered cell permeability
- Beta lactamase

Cephalosporins

Adverse Reactions

- **Hypersensitivity Reactions** (similar to PCN)
  - Anaphylaxis
  - Maculopapular rash
  - Serum sickness (fever, rash, arthritis)
  - Hemolytic anemia (drug as hapten)
  - Interstitial nephritis
  - Stevens-Johnson Syndrome/Toxic epidermal necrolysis
- Some cross-reactivity with penicillins
  - Traditionally cited as 10%
  - Actual risk may be lower

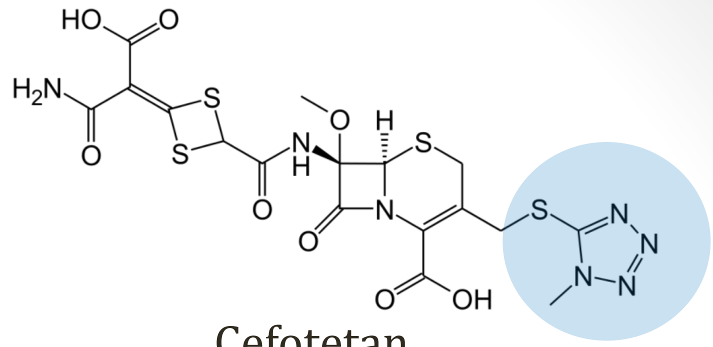
Cephalosporins

Adverse Reactions

- **Vitamin K deficiency**
  - Vitamin K1 from diet (green, leafy vegetables)
  - Vitamin K2 from GI bacteria
  - Antibiotics reduce bacterial vitamin K production
  - Result: Increased INR and potential bleeding
  - Commonly a problem for **patients on warfarin**
  - May be caused by any antibiotic

Cephalosporins

Adverse Reactions



Cefotetan

- **Hypoprothrombinemia**
  - Associated with N-methylthiotetrazole (NMTT) side chains
  - Cefotetan, cefazolin
  - Inhibits epoxide reductase (similar to warfarin)
  - ↓ hepatic synthesis of clotting factors
  - May prolong the PT/INR
  - Reversible with vitamin K
  - Most reports among malnourished patients

Shearer et al. **Mechanism of cephalosporin-induced hypoprothrombinemia: relation to cephalosporin side chain, vitamin K metabolism, and vitamin K status.** J Clin Pharmacol. 1988

Cephalosporins

Adverse Reactions

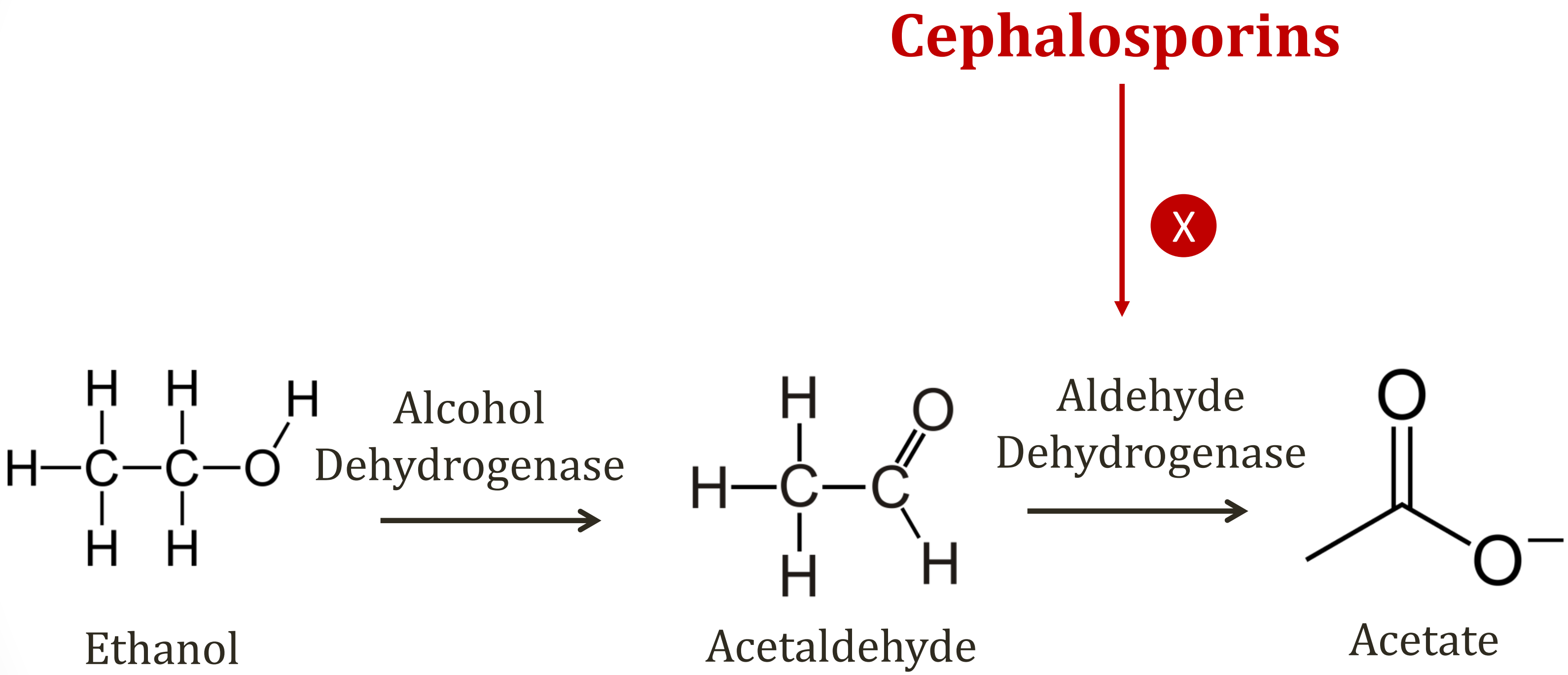
- Nephrotoxicity of aminoglycosides
  - Reports of increased risk with combination therapy

Cephalosporins

Adverse Reactions

- **Disulfiram reaction**
- Alcohol consumption with cephalosporins
- Warmth, flushing, sweating
- Inhibition of acetaldehyde dehydrogenase
- Accumulation of acetaldehyde
- Occurs with certain side chain structures
- Cefoperazone, cefamandole, and cefotetan

Ethanol Metabolism

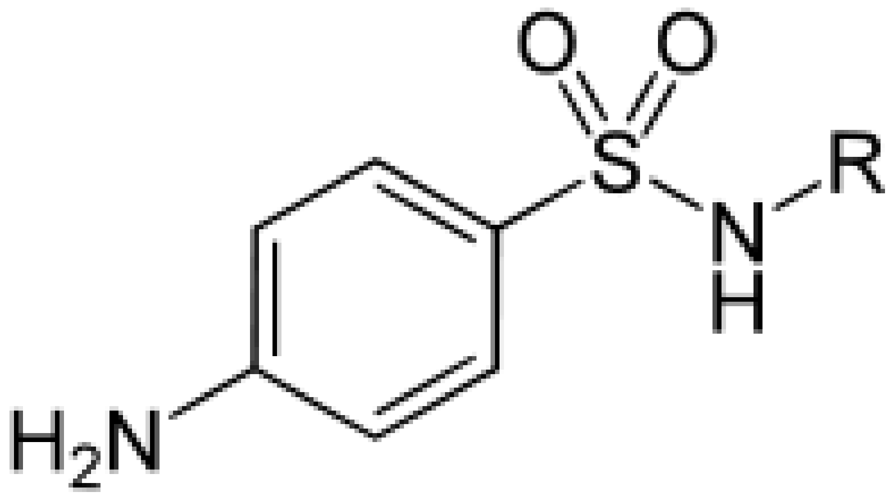


Sulfonamides

Jason Ryan, MD, MPH

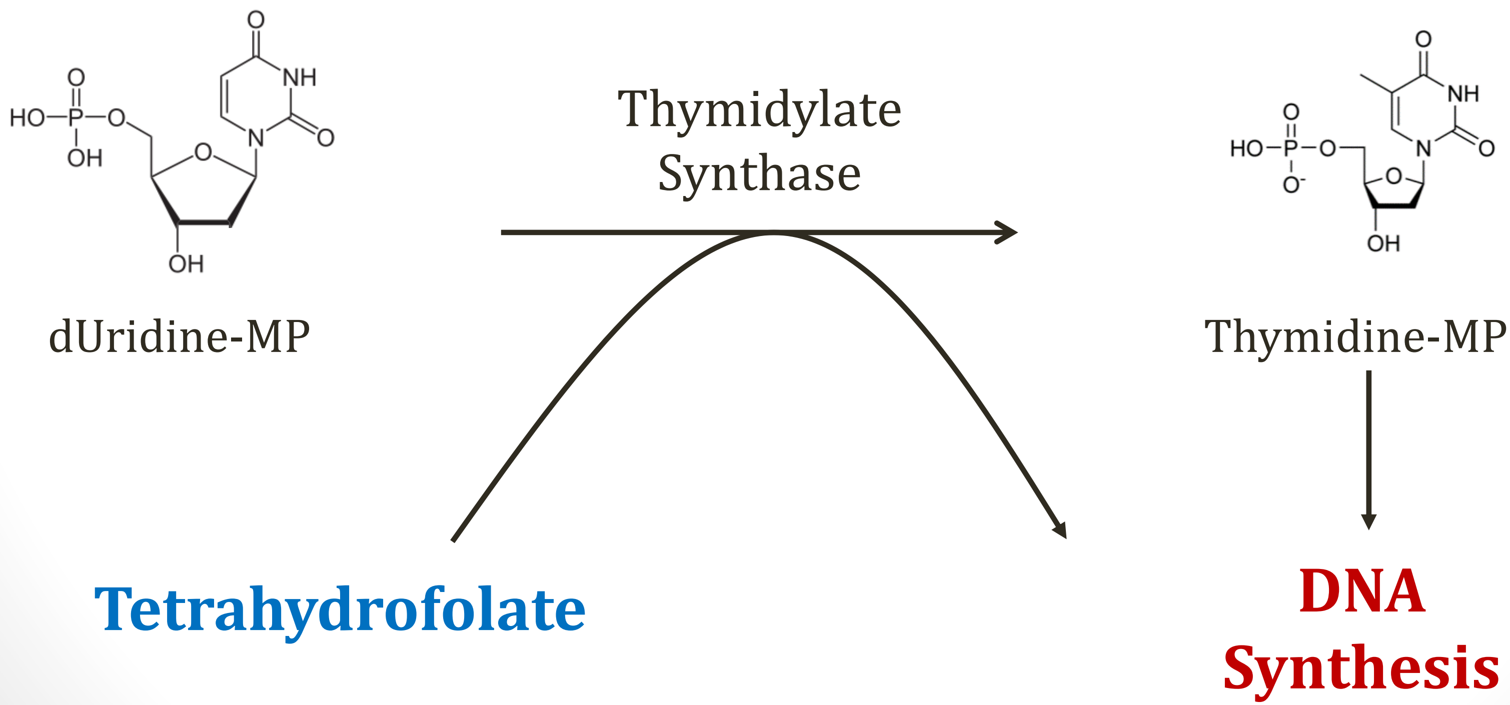
Sulfonamide Antibiotics

- Sulfonamide group = SO_2-N
- "Sulfa" drug = Contains sulfonamide group

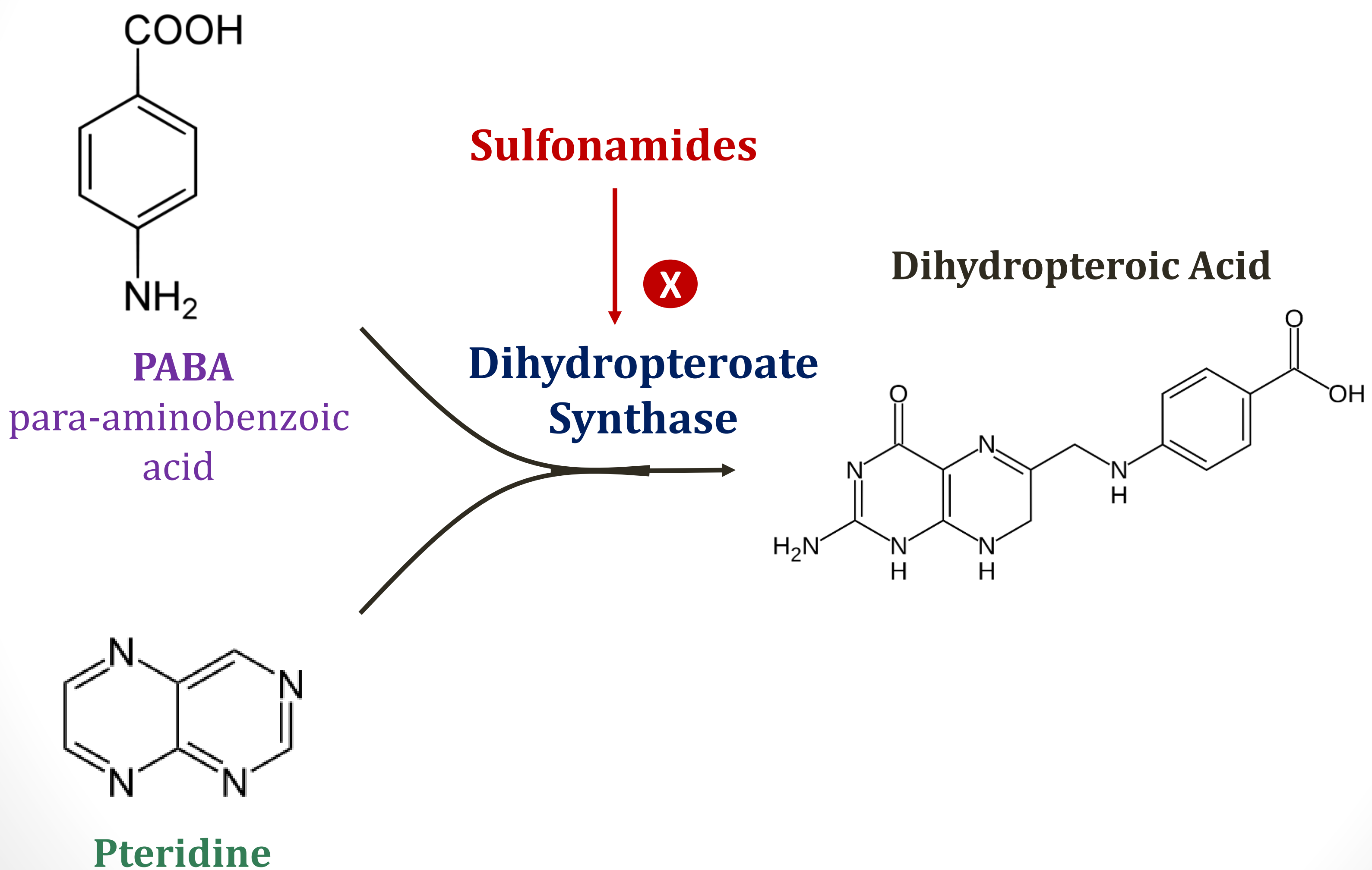


Bacterial Folate Synthesis

- Folate required for thymidine/DNA synthesis
- Mammalian cells: use exogenous folate (diet)
- Bacterial cells: no exogenous folate (must synthesize)

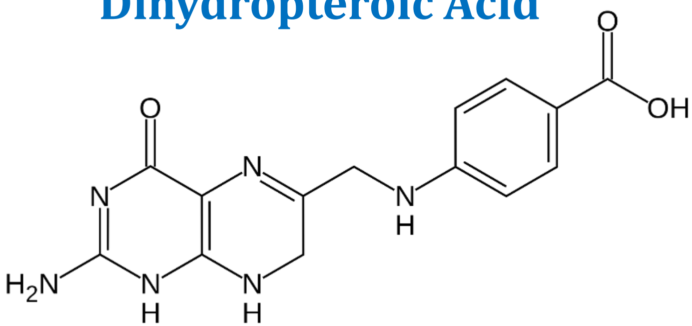


Bacterial Folate Synthesis

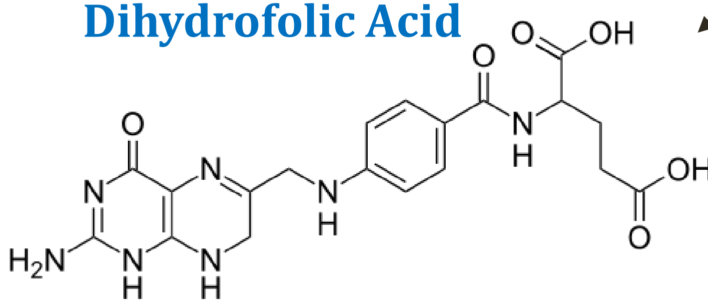


Bacterial Folate Synthesis

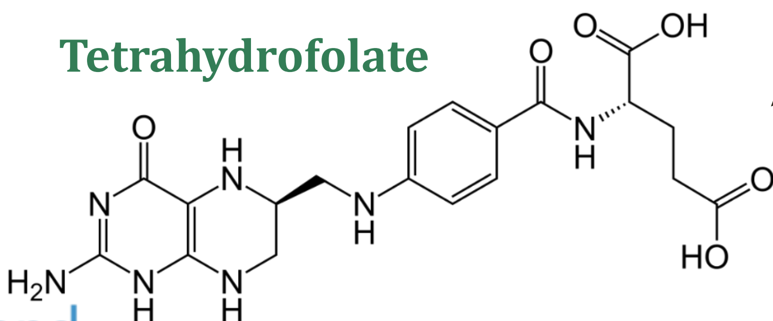
Dihydropteroic Acid



Dihydrofolic Acid



Tetrahydrofolate



Trimethoprim
Pyrimethamine

X

Dihydrofolate Reductase

Bacterial Folate Synthesis

PABA + Pteridine

↓ ~~Dihydropteroate Synthase~~ — Sulfonamides

Dihydropteroic Acid

↓

Dihydrofolic Acid

↓ ~~Dihydrofolate Reductase~~ — Trimethoprim, Pyrimethamine

THF

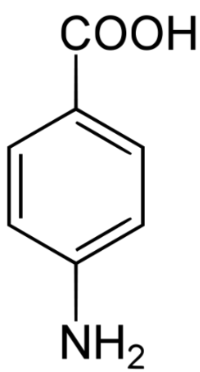
↓

DNA

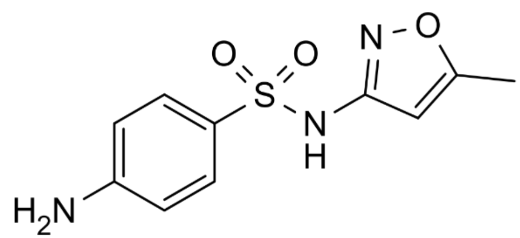
Sulfonamides

Sulfamethoxazole (SMX), sulfisoxazole, sulfadiazine

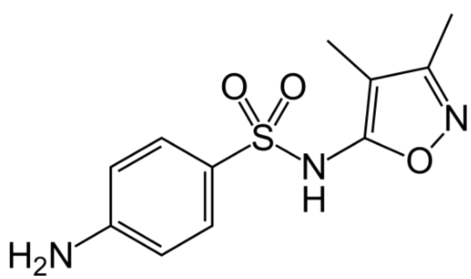
- Mimics of PABA
- Competitively inhibit dihydropteroate synthase



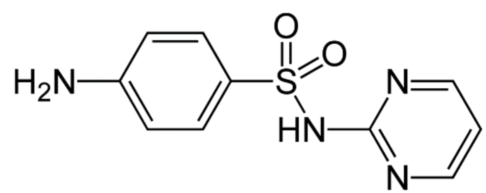
PABA



Sulfamethoxazole



Sulfisoxazole



Sulfadiazine

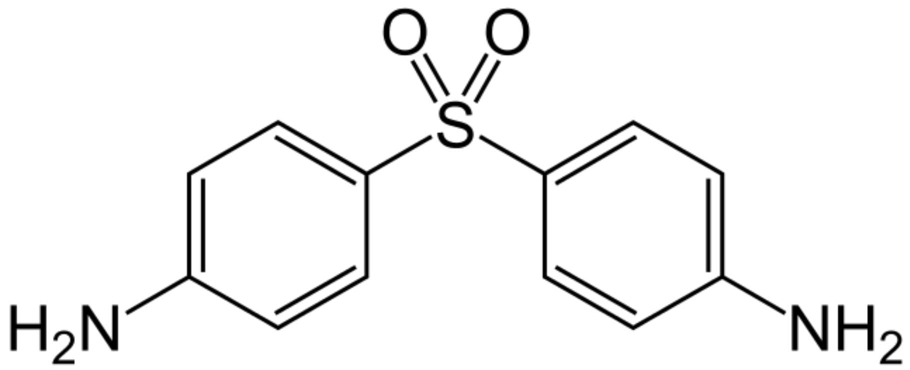
Sulfonamides

Resistance

- Increased PABA
- Altered dihydropteroate synthase
- Decreased uptake

Dapsone

- Not a sulfonamide
- Competes with PABA for dihydropteroate synthase
- Two main uses:
  - Mycobacterium leprae (leprosy)
  - Pneumocystis jiroveci



Sulfonamides

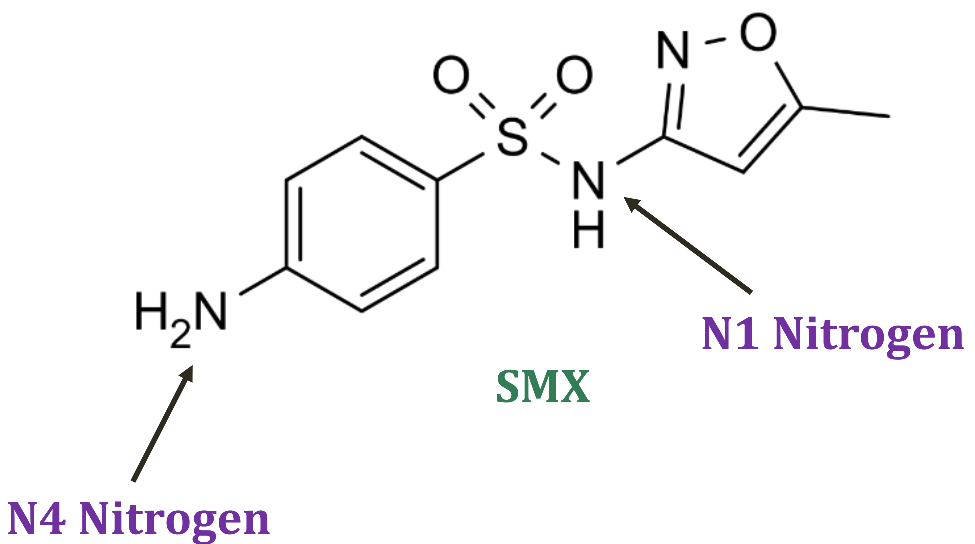
Sulfamethoxazole (SMX), sulfisoxazole, sulfadiazine

- Usually given with trimethoprim
  - TMP-SMX (Bactrim)
  - Sequential block of THF synthesis
- Sulfadiazine
  - Silver-sulfadiazine (cream) for burns
- Sulfadiazine and pyrimethamine
  - Also sequential block of THF synthesis
  - Used in toxoplasmosis (HIV)

Sulfonamides

Toxicity

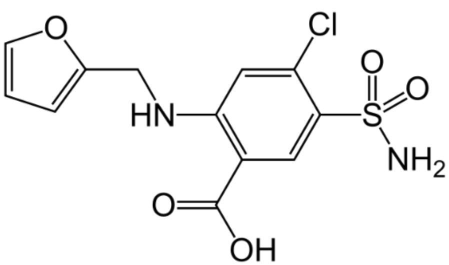
- Hypersensitivity reactions ~3% of patients
- Reactions linked to:
  - Arylamine (NH_2) at N4 position
  - Nitrogen ring attached to N1 nitrogen
- Only sulfonamide antibiotics contain both features



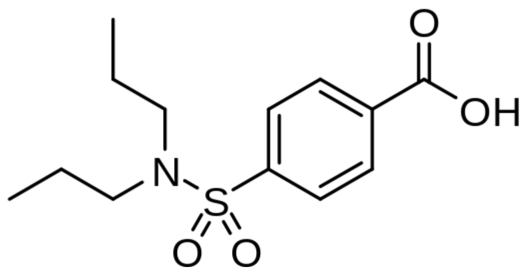
Sulfonamides

Toxicity

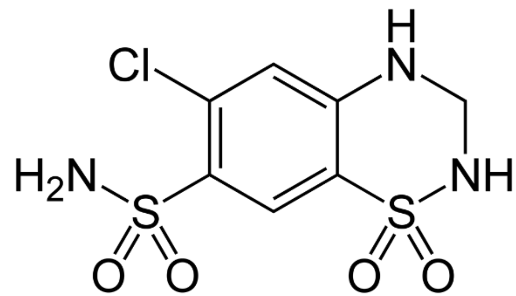
- Other sulfa drugs



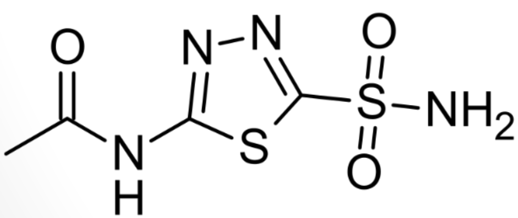
Furosemide (Loop Diuretic)



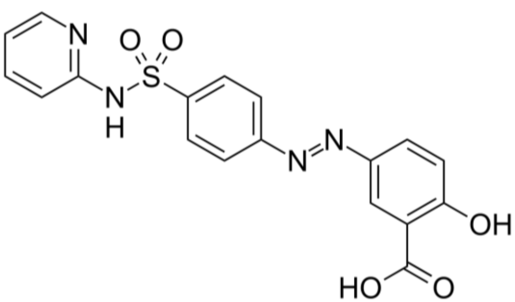
Probenicid (Gout)



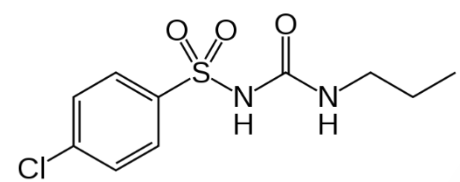
Hydrochlorothiazide (Thiazide diuretic)



Acetazolamide (Carbonic Anhydrase)



Sulfasalazine (IBD)



Sulfonylurea (Diabetes)

Sulfonamides

Hypersensitivity (allergic) reactions

- Similar to penicillin allergic reactions
- Anaphylaxis
- Maculopapular rash
- Serum sickness (fever, rash, arthritis)
- Interstitial nephritis
- **Stevens-Johnson Syndrome**
- **Toxic epidermal necrolysis**

Sulfonamides

Toxicity

- Photosensitivity
- Drug interaction with UV light
- Caused by many drugs
- Common drugs
  - Tetracycline
  - **Sulfonamides**
  - Amiodarone

Wikipedia/Public Domain

Sulfonamides

Toxicity

- Hemolysis in **G6PD deficient** patients
  - RBC susceptible to oxidative stress
  - Sulfonamides are oxidants - classic trigger for hemolysis
  - Other triggers: **Dapsone**

Databese Center for Life Science (DBCLS)

Sulfonamides

Toxicity

- Binds to **albumin**
- Displaces other bound substances
  - Bilirubin
  - Warfarin

Sulfonamides

Toxicity

- **Kernicterus** in infants
  - Sulfonamides → increased free bilirubin levels
  - Unconjugated bilirubin: neurotoxic
  - Basal ganglia, brainstem nuclei
- Permanent neurologic impairment
  - Movement disorder (chorea, tremor)
  - Hearing loss
  - Limited gaze

Sulfonamides

Toxicity

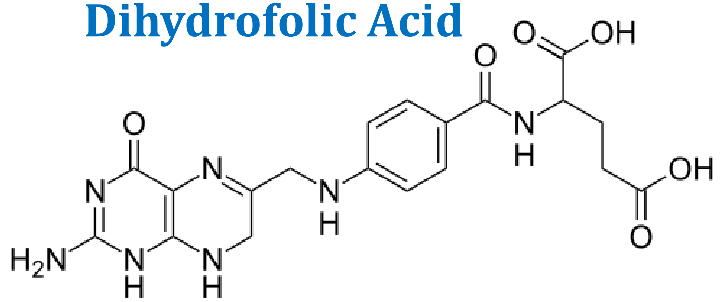
- Raise **warfarin** levels
  - Displaces warfarin from albumin
- INR level may rise in patients on warfarin therapy

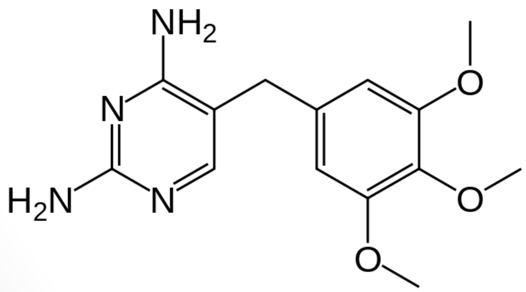
Trimethoprim/Pyrimethamine

Mechanism of Action

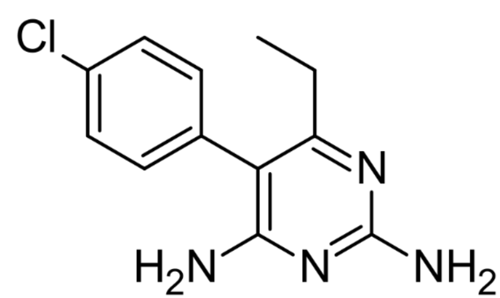
- Inhibit **dihydrofolate reductase**
- Similar structure to dihydrofolate

Dihydrofolic Acid





Trimethoprim



Pyrimethamine

Trimethoprim/Pyrimethamine

Toxicity

- Preferentially inhibits bacterial DHF reductase
- Some inhibition of human enzyme can occur
- Inhibits DNA synthesis of rapidly dividing cells

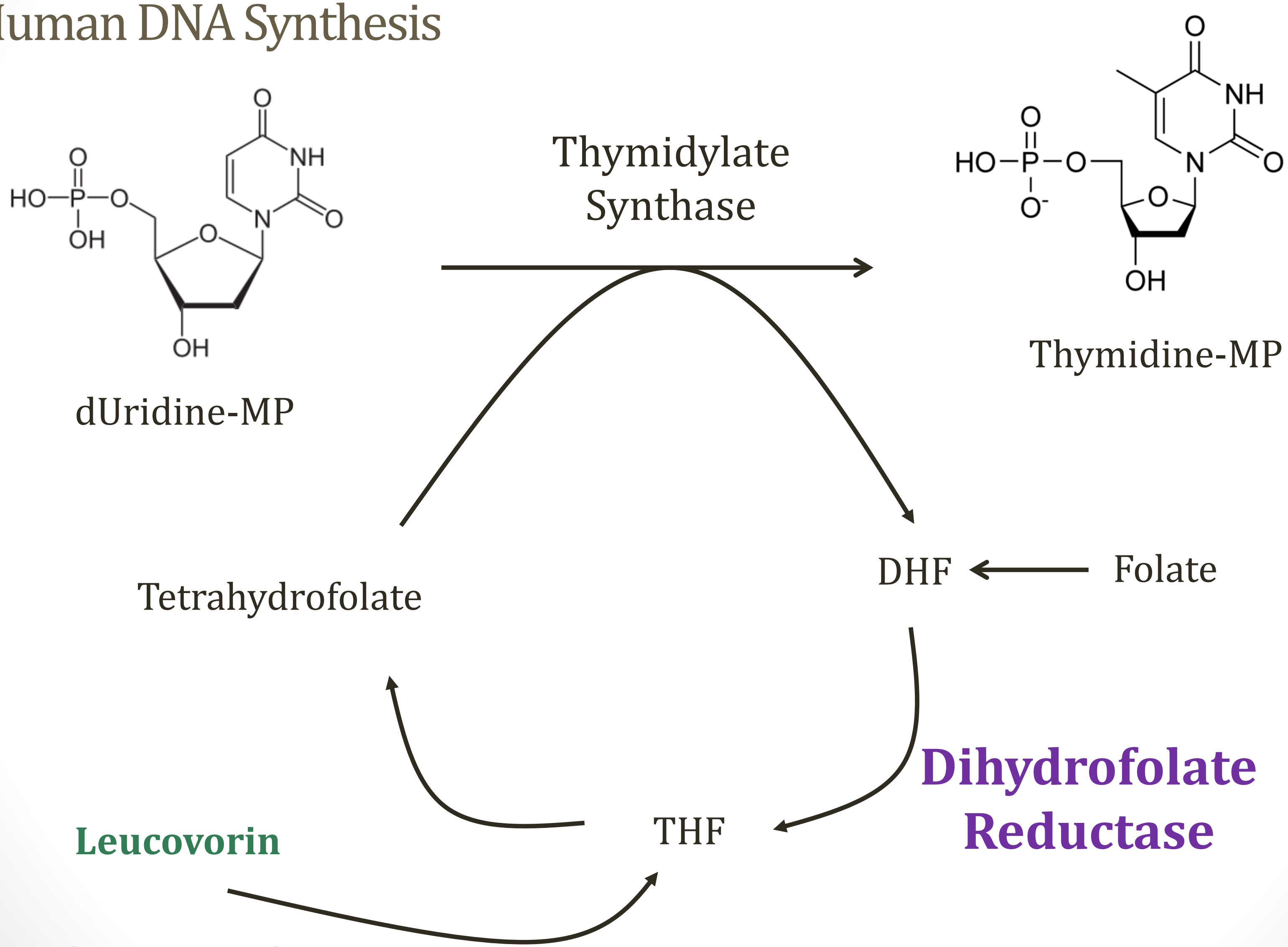
Trimethoprim/Pyrimethamine

Toxicity

- Bone marrow suppression
  - Pancytopenia: megaloblastic anemia, leukopenia, ↓platelets
- Can alleviate with **leucovorin (folinic acid)**
  - Converted to THF
  - Does not require dihydrofolate reductase
  - "Leucovorin rescue"

Dihydrofolate Reductase

Human DNA Synthesis



TMP-SMX

Bactrim

- Combination is **bactericidal**
- Covers many gram (+) and gram (-)
  - Does not cover pseudomonas
  - Does not cover B. fragilis (and most anaerobes)
- Covers some fungi and parasites
- Common uses:
  - Urinary tract infections (covers E. Coli well)
  - Pneumocystis pneumonia in HIV (treatment/prophylaxis)

TMP-SMX

Pregnancy

- Risk of **kernicterus**
- Disrupts **folic acid metabolism**

PCP

Pneumocystis jirovecii

- Opportunistic fungal infection
- Occurs in end stage HIV/AIDS
- Treatment of choice: TMP-SMX
- Hypersensitivity reactions: **6-25x higher in HIV**
- Alternative therapy often needed
    - Dapsone
    - Pentamidine
    - Atovaquone (malaria drug)

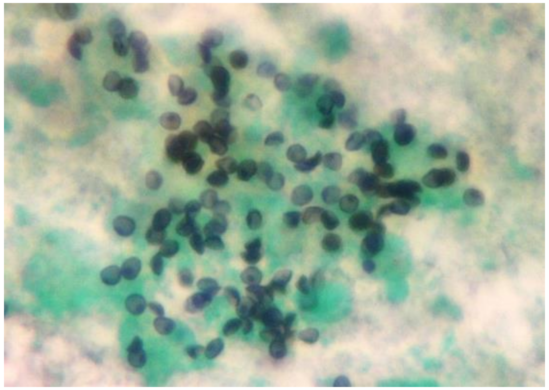


Image courtesy of Yale Rosen/Wikipedia

Protein Synthesis Inhibitors

Jason Ryan, MD, MPH

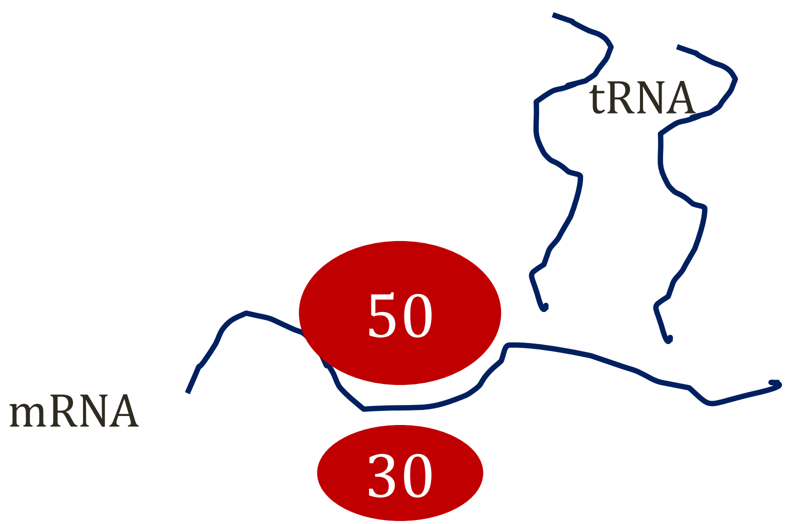
Protein Synthesis Inhibitors

- Aminoglycosides
- Macrolides
- Tetracyclines
- Chloramphenicol
- Clindamycin
- Linezolid
- Streptogramins

Bacterial Protein Synthesis

- DNA → Transcription → RNA
  - RNA polymerase
  - Target of Rifampin (tuberculosis)
- RNA → Translation → Protein

Bacterial Protein Synthesis



Aminoglycosides/Linezolid

~~1. Initiate Process~~ →

Tetracycline

~~2. Add tRNA~~ →

~~3. Add Peptides~~ →

~~Translocate~~

Chloramphenicol
Macrolides
Clindamycin

Aminoglycosides

Gentamicin, Neomycin, Amikacin, Tobramycin, Streptomycin

- Block initiation of protein synthesis
  - Primarily bind 30S
  - Misreading of genetic code
  - Bacteria cannot divide, produce cellular proteins
  - Cell death (bactericidal)
- Require O_2 for transport into cells
  - Not effective against anaerobes
- Do not effect eukaryotic cells (different ribosomes)
- Not transferred into eukaryotic cells
  - Not effective intracellular organisms (Rickettsia/Chlamydia)

Aminoglycosides

Gentamicin, Neomycin, Amikacin, Tobramycin, Streptomycin

- Used alone (rare) to treat serious gram (-) infections
- Streptomycin can be used for tuberculosis
  - Older agent
  - Used in combination with other drugs
- Neomycin given prior to bowel surgery
  - Poorly absorbed (stays in gut)
  - Often given with Erythromycin
  - Decrease colonic bacteria

Aminoglycosides

Gentamicin, Neomycin, Amikacin, Tobramycin, Streptomycin

- Often added to β-lactams
  - Synergistic effects
  - Combination more effective than sum of effects
- Vancomycin/gentamycin for endocarditis
- Ampicillin/gentamycin for newborn meningitis
- Pip/Tazo + tobramycin for CF patients (pseudomonas)

Aminoglycosides

Resistance

- Most common mechanism resistance:
  - "Aminoglycoside modifying enzymes"
  - Bacteria acquire enzymes that modify drug structure
  - Modified structure binds poorly to ribosomes
  - Phosphorylation (mediated by aminoglycoside kinases)
  - Adenylation/acetylation (mediated by transferases)

Aminoglycosides
Adverse Effects

- Ototoxicity
  - Toxic to 8th cranial nerve
  - Hearing loss, balance problems (falls)
  - Mechanism not clear
- Nephrotoxicity
  - Acute tubular necrosis
  - 5-10% of drug taken up by proximal tubular cells
  - Serum Cr will rise

Aminoglycosides

Adverse Effects

- Neuromuscular blockade
  - Rare side effect
  - Can block/limit release of ACh at neuromuscular junctions
  - Usually occurs when levels are high or pre-existing neuromuscular disease
- Pregnancy class D
  - Reports of renal and ototoxicity in fetus

Aminoglycosides

Monitoring

- Plasma levels sometimes monitored
  - Trough level: Just before next dose
  - Peak level: Short time after dose
- High trough = risk of toxicity
- Low peak = less effective therapy

Macrolides

Azithromycin , Clarithromycin, Erythromycin

- 50S ribosomal subunit
  - tRNA binds "A site"
  - Ribosome RNA catalyzes peptide bonds (peptidyl transferase)
  - Ribosome advances along mRNA
  - tRNA moves to "P site"
- Macrolides bind to P site:
  - Block tRNA movement to P site (translocation)
  - Promote tRNA dissociation
  - May also block peptidyl transferase

Source: Gaynor M., Mankin A. S. Macrolide Antibiotics: Binding Site, Mechanism of Action, Resistance. *Current Topics in Medicinal Chemistry* 2003, 3, 949-960

Macrolides

Azithromycin , Clarithromycin, Erythromycin

- Covers many gram (+) cocci, especially strep
- Some gram (-) coverage
- Concentrated inside macrophages, other cells
- Effective against intracellular pathogens
  - Chlamydia (obligate), Legionella (facultative)

Macrolides

Azithromycin , Clarithromycin, Erythromycin

- Community acquired pneumonia
  - Azithromycin covers Strep, H. flu, Atypicals
  - Good for penicillin allergic patients
- Chlamydia infection
  - Azithromycin (safe in pregnancy)
  - Often co-administered with Ceftriaxone (gonorrhea)

Macrolides

Azithromycin , Clarithromycin, Erythromycin

- Erythromycin
  - Binds to motilin receptors in GI tract
  - Stimulates smooth muscle contraction
  - Can be used in GI motility disorders
- Clarithromycin
  - Part of triple therapy for H. pylori

Macrolides

Resistance

- Resistance mechanism
  - 23S rRNA = component of 50S ribosome
  - Location of macrolide binding
  - Methylation of this site → resistance

Macrolides

Adverse Effects

- Nausea, diarrhea, abdominal pain (motility)
  - Erythromycin worst offender
- Prolonged QT on EKG
  - Erythromycin also worst offender
- Acute cholestatic hepatitis
  - ↑AST/ALT/Alk Phos/Bilirubin
  - Case reports in patients on Azithromycin
  - Contraindicated with history of cholestatic jaundice or hepatic dysfunction

Macrolides

Adverse Effects

- Rash
  - Maculopapular allergic reaction
- P450 Enzyme Inhibitors
  - Will raise serum levels of P450 metabolized drugs
  - Theophylline, Warfarin

Tetracyclines

Tetracycline, doxycycline, demeclocycline, minocycline

- Transported into bacterial cells
- Binds 30S ribosome
- Prevents attachment of tRNA
- Demeclocycline
  - Not used as an antibiotic
  - ADH antagonist
  - Given in SIADH
  - *Causes* nephrogenic DI to reverse SIADH

Doxycycline

- Most commonly used member tetracycline family
- Accumulates intracellularly
- Covers many unusual/atypical bacteria
  - Most zoonoses
  - Chlamydia
- Used to treat acne vulgaris (also minocycline)
  - Covers propionibacterium acnes within follicles

Tetracyclines

Tetracycline, doxycycline, demeclocycline, minocycline

- Absorption impaired by minerals and antacids
  - Calcium, magnesium (antacids)
  - Iron
  - Dairy including milk
- These substances are cations that chelate the drug
- Cannot be taken with antacids or milk

Tetracyclines

Resistance

- Decreasing influx or increasing efflux from cells
- Plasmid-encoded transport pumps
- Different from many other antibiotics:
    - No alteration of drug by bacteria

Tetracyclines

Adverse Effects

- GI distress (common)
  - Epigastric pain, nausea, vomiting and anorexia
- Photosensitivity
  - Red rash or blisters in sun exposed areas

Tetracyclines

Adverse Effects

- Discoloration of teeth
  - Brown-yellow discoloration of teeth
  - Children under the age of eight (does not occur in adults)
- Inhibition of bone growth in children
  - Deposit in bones
  - Chelate with calcium
- Contraindicated in pregnancy
  - Cross placenta
  - Can accumulate in fetal bone and teeth

Chloramphenicol

- Inhibits peptidyl transferase
- 50S ribosomal subunit
  - tRNA binds “A site”
  - Ribosome RNA catalyzes peptide bonds (peptidyl transferase)
  - Ribosome advances along mRNA
  - Moves tRNA to “P site”
- Chloramphenicol blocks peptidyl transferase

Chloramphenicol

- Rarely used in developed world:
  - Toxicity
  - Increasing resistance
- Used in developing world due to low cost

Chloramphenicol

- Broad coverage of gram (+), gram (-), atypicals
- Can be used in pregnancy instead of doxycycline
  - Rickettsia (RMSF), Ehrlichia
  - Only in 1st/2nd trimester
  - 3rd trimester risk of gray baby syndrome
- Can be used for meningitis (developing world)
  - Covers Neisseria
  - Less effective than alternative drugs

Chloramphenicol

Adverse effects

- Anemia
  - Bone marrow suppression
- Aplastic anemia
  - Idiosyncratic
  - Irreversible → often fatal
- Gray baby syndrome
  - Babies lack liver UDP-glucuronyl transferase
  - Required for metabolism/excretion of drug
  - Skin turns ashen, gray
  - Hypotension
  - Often fatal

Clindamycin

- 50S ribosome
  - 23S rRNA component
  - Prevents translocation
  - Same as macrolides
- Resistance mechanism
  - 23S rRNA = component of 50S ribosome
  - Location of macrolide binding
  - Methylation of this site → resistance
  - Same as macrolides

Clindamycin

- Covers some gram (+)
  - Staph, viridans strep, Strep pyogenes, and S. pneumoniae
- Covers many anaerobes
  - Clostridium perfringens
  - Mouth anaerobes: Fusobacterium, Prevotella, Peptostreptococcus

Clindamycin

- Main use is to cover anaerobes “above the diaphragm”
  - Aspiration pneumonia
  - Lung abscesses
  - Oral infections (mouth anaerobes)
- Lots of resistance to clindamycin in B. fragilis
  - Anaerobic infections “below the diaphragm”
  - Metronidazole

Clindamycin

Adverse Events

- Classic cause of C. difficile infection
    - Up to 10% of patients
    - Pseudomembranous colitis
    - C . difficile overgrowth
    - Massive, watery diarrhea
- Antibiotic-associated diarrhea
    - Milder than C. diff infection
    - Changes in GI flora
    - Less absorption of solutes → osmotic diarrhea
    - Stops when drug discontinued

Linezolid

- Binds to 50S Ribosome
- Blocks initiation
- Main use: Vancomycin-resistant enterococcus (VRE)
  - Epidemics in hospitals
  - Usually occurs in patients with prior antibiotic treatment

Linezolid

- Weak monoamine oxidase (MAO) inhibitor
- Can cause serotonin syndrome
- High risk when given with SSRIs
- Fever, confusion, agitation, hyperreflexia

Streptogramins

quinupristin/dalfopristin

- Block protein synthesis 50S ribosome
- Used together for sequential protein synthesis block
  - Synercid (quinupristin/dalfopristin)
- Used for vancomycin resistant bacteria
  - VRSA
  - VRE

Bacteriostatic vs. Bactericidal

Antibiotic Class	Action
Aminoglycosides	Bactericidal
Macrolides	Bacteriostatic
Tetracyclines	Bacteriostatic
Chloramphenicol	Bacteriostatic
Clindamycin	Bacteriostatic
Linezolid	Bacteriostatic (mostly)
Quinupristin/dalfopristin	Variable

Most protein synthesis inhibitors are bacteriostatic
Only aminoglycosides are bactericidal
Misread proteins travel to membrane and increase permeability

Source: Microbiol Rev. Sep 1987; 51(3): 341–350.

Other Antibiotics

Jason Ryan, MD, MPH

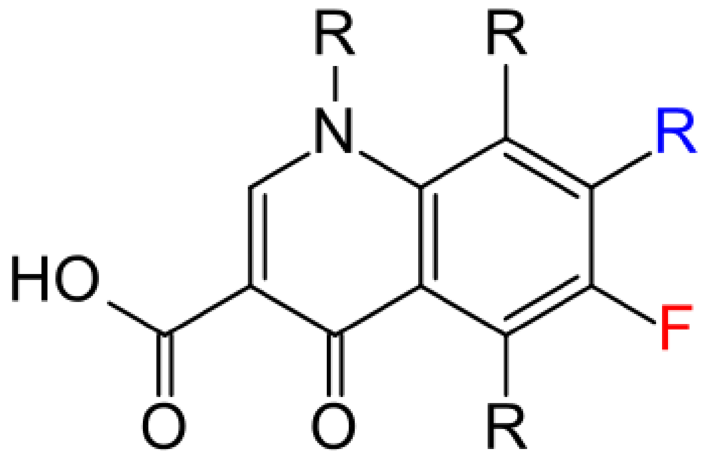
Other Antibiotics

- Quinolones
- Vancomycin
- Metronidazole
- Nitrofurantoin

Quinolones

Ciprofloxacin, Levofloxacin, Moxifloxacin, Norfloxacin

- Inhibit enzymes for bacterial **DNA synthesis**
- **DNA gyrase**
- **Topoisomerase IV**



Quinolones

Ciprofloxacin, Levofloxacin, Moxifloxacin, Norfloxacin

- Bacterial topoisomerase enzymes
- DNA Gyrase
  - Introduces double-stranded break
  - Repairs break
- Topoisomerase IV
  - Separates daughter chromosomes
  - "Decantenation"
- Inhibition → DNA damage → **cell death**

Quinolones

Resistance Mechanisms

- Alterations of **DNA gyrase** and **topoisomerase IV**
- Alteration in cell permeability
- Efflux of drug

Quinolones

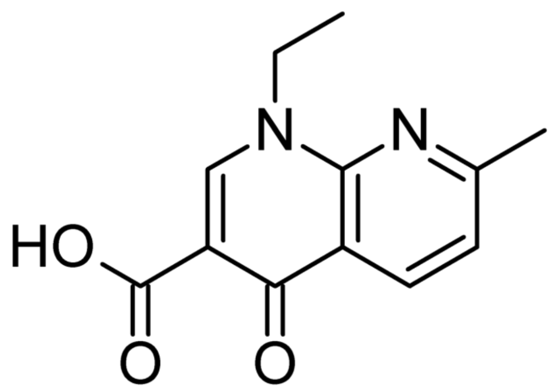
Ciprofloxacin, Levofloxacin, Moxifloxacin, Norfloxacin

- Many gram (+), gram (-), atypicals
- Common clinical uses (adults only)
  - UTIs (E. Coli, other enteric gram negatives)
  - Pneumonia (S. pneumo, H. flu, atypicals)
  - Abdominal infections (enteric gram negatives)

Quinolones

Early Drugs

- Nalidixic acid (not a fluoroquinolone), Norfloxacin
- Mostly gram negative coverage
- Limited/no gram positive coverage

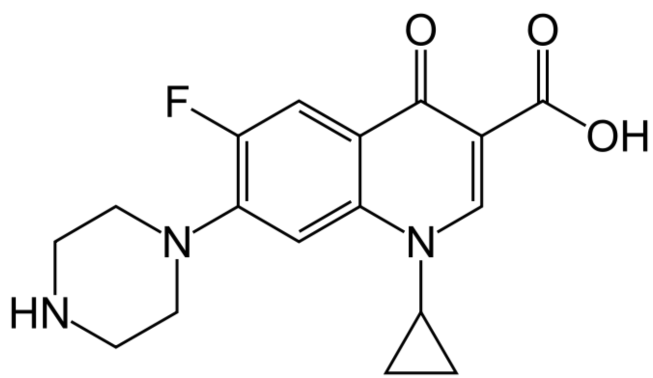


Nalidixic Acid

Quinolones

Ciprofloxacin

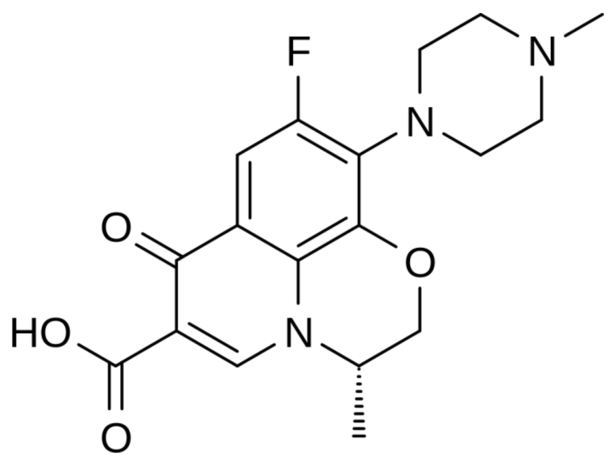
- Some gram positive coverage
  - Rarely used alone for gram positive coverage (resistance)
- Very good **gram negative coverage**
- Most reliable **pseudomonas** coverage
- Used in UTIs, GI infections
- Cipro ear drops for otitis externa



Quinolones

Levofloxacin

- More gram positive/atypical coverage than Cipro
  - Better strep pneumo coverage than Cipro
  - Covers most methicillin-susceptible Staph aureus
- Less effective against pseudomonas than Cipro
- Commonly used in pneumonia (strep, atypicals)



Quinolones

Gatifloxacin, Sparfloxacin, Moxifloxacin

- Better gram (+)/atypical coverage than Levofloxacin
- Less effective for pseudomonas than Levofloxacin
- Also used in pneumonia

Quinolones

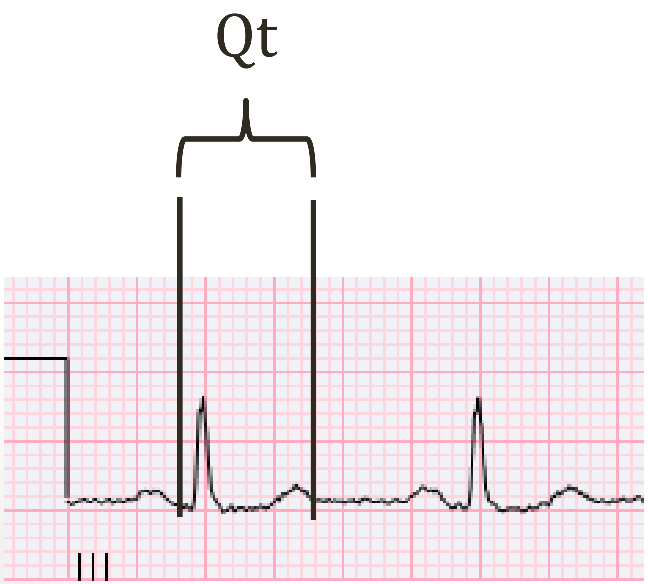
Adverse Reactions

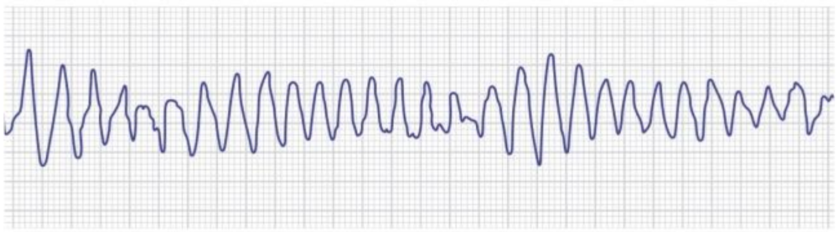
- **Gastrointestinal** upset
  - Anorexia, nausea, vomiting, and abdominal discomfort
  - Up to 17% of patients
- **Neurologic** side effects
  - Headache, dizziness
  - 2 to 6% of patients

Quinolones

Adverse Reactions

- QT prolongation on EKG
- Caused by blockade of K+ channels
- Can lead to torsade de pointes



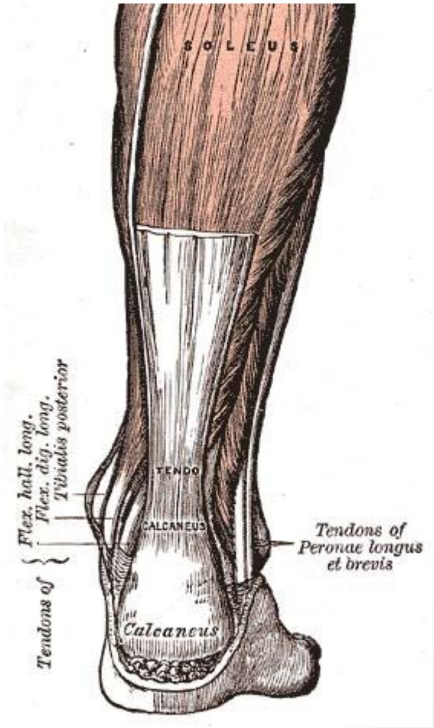


Boards&Beyond STUDY SMARTER

Quinolones

Adverse Reactions

- **Tendon rupture/tendonitis**
  - Most commonly Achilles
  - More common older patients (>60), people on steroids
- Cannot use in pregnancy/children
  - Toxic to developing cartilage in animal studies



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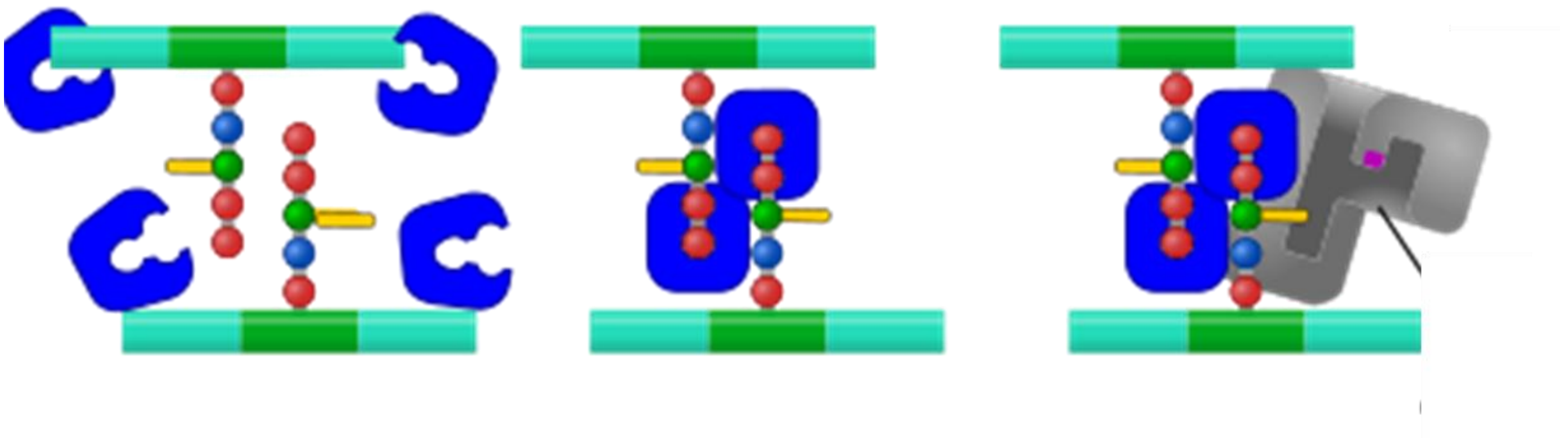
Antacids

- Disrupt absorption of many drugs
- Aluminum and magnesium hydroxide
- Sucralfate (contains aluminum)
- Key drugs
  - Tetracycline
  - **Fluoroquinolones**
  - Isoniazid
  - Iron supplements

Vancomycin

- Inhibits peptidoglycan formation (cell wall)
- Binds **D-alanyl-D-alanine peptides**
- Prevents crosslinking
- Cell wall breakdown>formation → **cell death**
- Same effect as beta lactams via different mechanism
  - Beta lactams: inhibit transpeptidases
  - Vancomycin: block transpeptidase binding

Vancomycin



Mcstrother/Wikipedia

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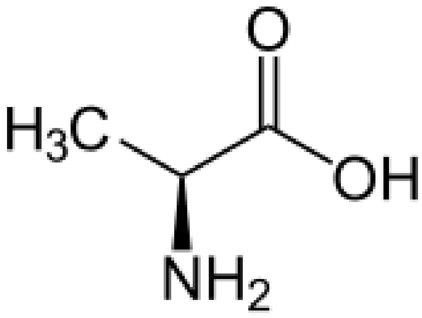
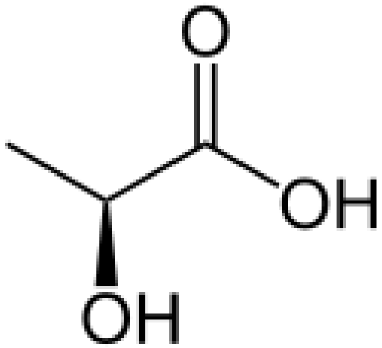
Vancomycin

- Resistance: terminal amino acids change
  - D-alanyl-D-alanine changed to **D-alanyl-D-lactate**
  - VRSA emerges



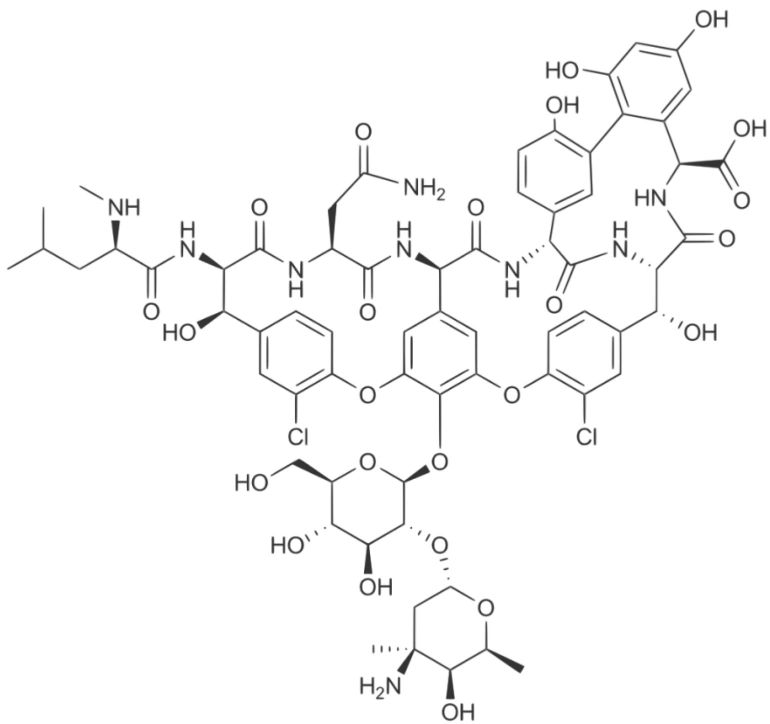
Alanine



Lactate

Vancomycin

- Only effective in gram (+)
- Too large to pass outer membrane gram negatives



Vancomycin

- Two common uses:
  - #1: Methicillin resistant Staph Aureus (MRSA)
  - #2: Oral therapy for C. difficile pseudomembranous colitis
- Often given empirically when MRSA is a concern
  - Endocarditis
  - Severe pneumonia/sepsis

Vancomycin

Adverse Effects

- Generally well tolerated
- Nephrotoxicity
  - Less common with modern preparations
  - Increased risk if **concomitant aminoglycoside therapy**
- Ototoxicity
  - Tinnitus, vertigo, and hearing loss reported (rare)

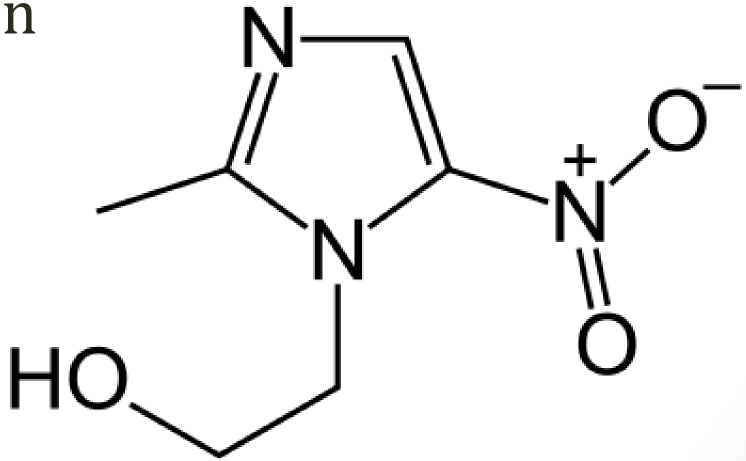
Vancomycin

Adverse Effects

- **Red man syndrome**
  - Flushing, erythema, itching
  - Usually affects upper body, neck, face more than lower body
  - Occurs 10-20 minutes after start of infusion
- Direct activation of mast cells → **histamine** release
  - "Pseudoallergic drug reaction"
- May develop with first administration
- Infusion related → slow infusion = no symptoms

Metronidazole

- Prodrug: Must be **reduced** to activate
- Only **anaerobic bacteria** capable of reduction
- Reduced metronidazole → more drug uptake
- Activated form generates free radicals
- Interact with DNA
- DNA breakage/destabilization
- Cell death



Metronidazole

Uses

- Good coverage of anaerobes "below the diaphragm"
  - **Bacteroides fragilis**
  - **Clostridium difficile**
- Peritonitis, abdominal abscesses, diverticulitis
- Often given with quinolone for anaerobic/GI gram(-)
- Cipro/Flagyl often used for diverticulitis

Metronidazole

Uses

- **H. pylori** and **Gardnerella vaginalis**
  - Facultative anaerobic bacteria
  - Susceptible to metronidazole
- Triple therapy for H. Pylori
- Treatment of bacterial vaginitis

Metronidazole

Uses

- Anaerobic protozoa (lack mitochondria)
  - **Trichomonas vaginalis**
  - **Entamoeba histolytica**
  - **Giardia lamblia**
- Covered by metronidazole

Metronidazole

Adverse Reactions

- Unpleasant metallic taste
- **GI**: Abdominal discomfort, nausea
- **Neuro**: Neuropathy, headache

Metronidazole

Adverse Reactions

- **Disulfiram-like reaction**
- Alcohol consumption with metronidazole
- Warmth, flushing, sweating
- Unclear mechanism
- Metronidazole may not inhibit alcohol metabolism
- Patients should **avoid alcohol**

$$\text{Ethanol} \longrightarrow \text{Acetaldehyde} \xrightarrow{\text{Aldehyde Dehydrogenase}} \text{Acetate}$$

Visapää JP. Lack of disulfiram-like reaction with metronidazole and ethanol. Ann Pharmacother. 2002. Jun;36(6):971-4.

Nitrofurantoin

- Rarely used antibiotic
- Exact mechanism incompletely understood
- Bactericidal drug
- Only use is **UTIs** (concentrates in urine)
- Two things to know about this drug:
  - Used for UTIs in **pregnancy** (avoid TMP-SMX, quinolones)
  - Can trigger **hemolysis in G6PD patients**

Fungal Pneumonias

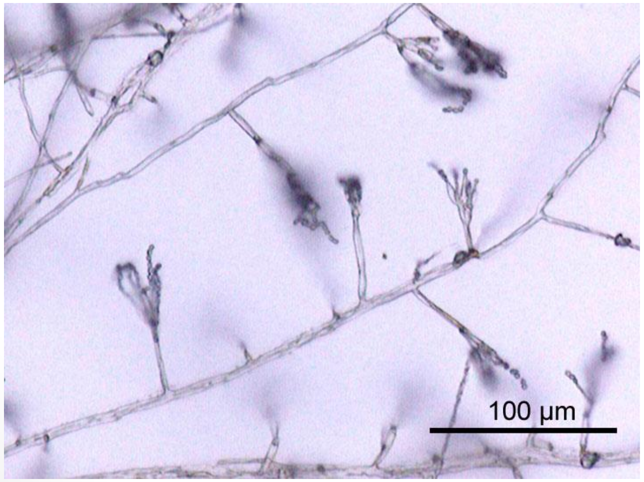
Jason Ryan, MD, MPH

Fungi

- Fungi are eukaryotes
  - Have a nucleus
  - Intracellular organelles
  - VERY different from bacteria
- Single celled: yeast
- Multicellular
  - Filamentous molds
  - Mushrooms
- Dimorphic = yeast or filamentous

Fungi

- Hyphae: long, branches of fungi
  - Often divided into multiple cells by septa (septate hyphae)
- Mycelium
  - Many hyphae together
- Spores (conidia)
  - Often formed on ends of hyphae (conidiophore)



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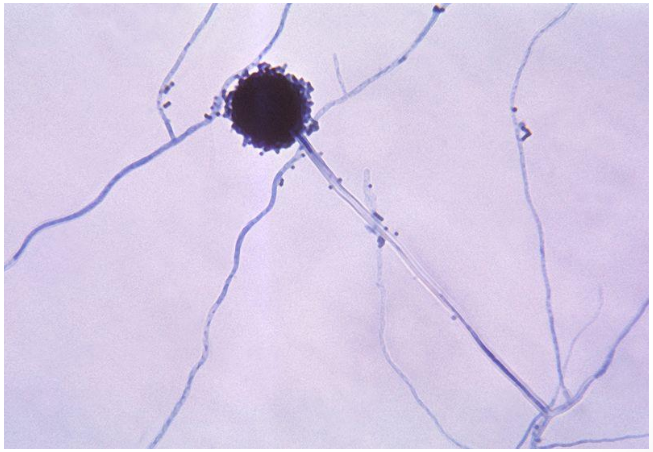

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Fungal Infections

- Pneumonia
  - Only in specific geographic areas
  - Histoplasmosis, Blastomycosis, Coccidioidomycosis
- Skin
  - Tinea versicolor, tinea pedis, sporothrix
- Opportunistic
  - Candida, Aspergillus, Cryptococcus, Mucormycosis, Pneumocystis

Pneumonia Fungal Infections

- Histoplasmosis
- Blastomycosis
- Coccidioidomycosis
- Paracoccidioidomycosis

Pneumonia Fungal Infections

Key features

- Cause pneumonia but can disseminate
- Dimorphic
- Cold temps = mold; warm temps (body) = yeast
- Disease from inhaling fungus
  - Not person to person spread
- All can cause granulomatous inflammation
  - Potential TB mimics
- Treatment:
  - Mild disease: Fluconazole/itraconazole
  - Severe/systemic: Amphotericin B

Granulomatous Infections

- Tuberculosis, Leprosy
- Fungal pneumonias (Histo, Blasto, Coccidio)
- Bartonella(cat scratch disease)
- Brucella
- Listeria in infants (Granulomatosis Infantiseptica)
- Schistosomiasis (worm)
- Syphilis (gummas)

Pneumonia Fungal Infections

- All have two distinct clues to diagnosis
  - Geography
  - Pathology

Geography

- Histoplasmosis
  - Ohio and Mississippi river valleys
- Blastomycosis
  - Ohio and Mississippi river valleys
  - Great Lakes
- Coccidioidomycosis
  - Southwest US
- Paracoccidioidomycosis
  - South/Central America

US Map

Boards&Beyond STUDY SMARTER

Image courtesy of Wikipedia/Public Domain

Geography

- Histoplasmosis/Blastomycosis
  - Ohio River/valley
  - Mississippi River/valley
  - “Midwest”
  - Great Lakes (Blastomycosis)
- Coccidioidomycosis
  - Arizona, New Mexico, California
- Paracoccidioidomycosis
  - South/Central America

Histoplasmosis

Histoplasmosis capsulatum

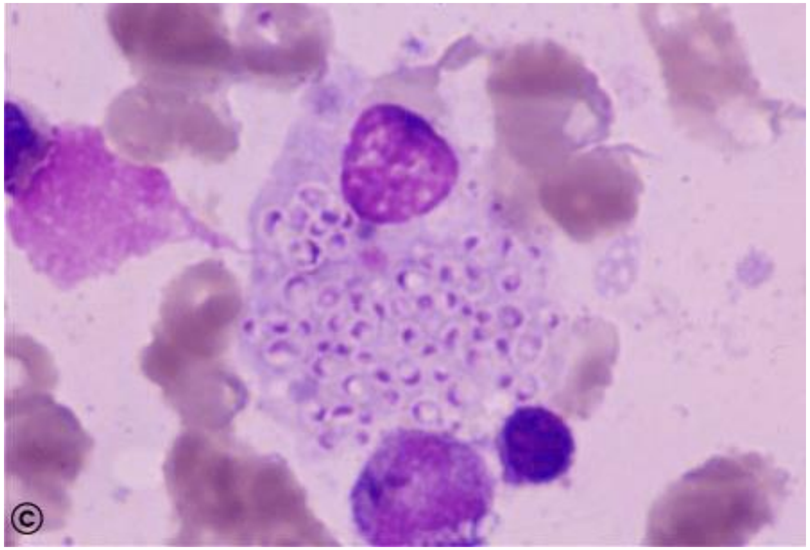
- Soil contaminated with bird or bat droppings
- Key site for infection: Caves
- Spores inhaled → yeast at body temperature
- Ingested by macrophages
- Survive/multiply in macrophages
  - Can be spread to others

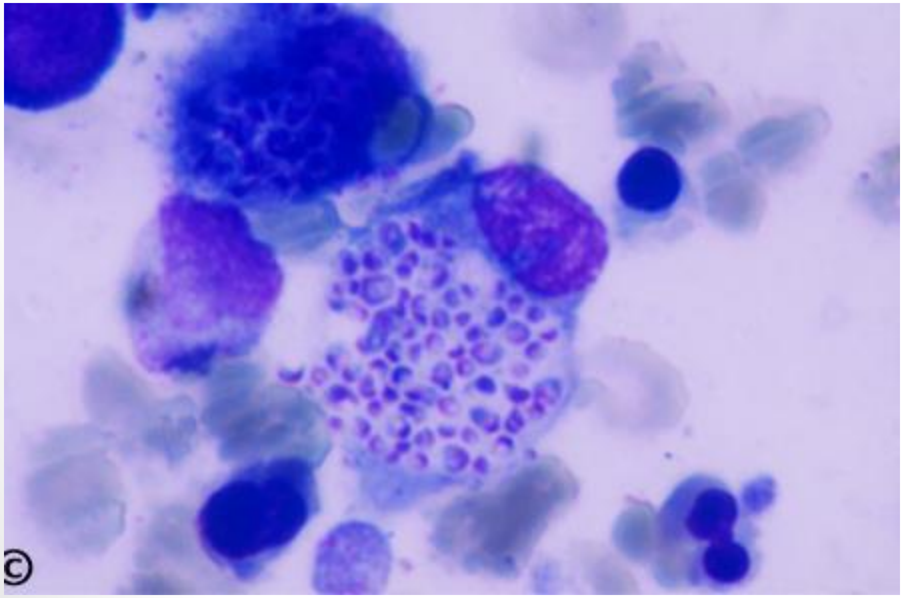
Histoplasmosis

Symptoms/Treatment

- Vast majority of people asymptomatic
- Most common symptoms are pulmonary
  - Slow onset over weeks
  - Mild pneumonia
  - Hilar lymphadenopathy
- Diagnosis: Antigen/antibody tests, biopsy
- Treatment:
  - Mild disease: Fluconazole/itraconazole
  - Severe/systemic: Amphotericin B

Histoplasmosis





Images courtesy of Nivaldo Medeiros, MD, www.hematologyatlas.com; Used with permission

Histoplasmosis

Disseminated disease

- Cell-mediated immunity clears infection
- Dissemination rare unless immunocompromised
  - HIV/AIDS
  - TNF-α inhibitors
- LOTS of symptoms: GI, CNS, anemia, lymph
- Some key features
  - Hepatosplenomegaly (abnormal LFTs)
  - Tongue, mouth ulcers
  - Pancytopenia (bone marrow involvement)
- Treatment is Amphotericin B

Blastomycosis

Blastomyces dermatitidis

- Inhaled conidia → yeast in the body (dimorphic)
- Many patients asymptomatic
- When symptomatic: slow onset PNA most common

Blastomycosis

- Extrapulmonary disease in ~20% of patients
- Skin is most common site
  - Verrucous (warts) lesions with irregular borders
- Bone (osteomyelitis) next most common
- Classic case:
  - Mississippi river exposure
  - Slow onset pneumonia
  - Skin lesions
  - Possibly bone pain

Blastomycosis

- Forms granulomas
- Classic path finding is "broad based budding yeast"
- Diagnosis by visualizing yeast
  - Sputum
  - Tissue
- Treatment:
  - Mild disease: Fluconazole/itraconazole
  - Severe/systemic: Amphotericin B

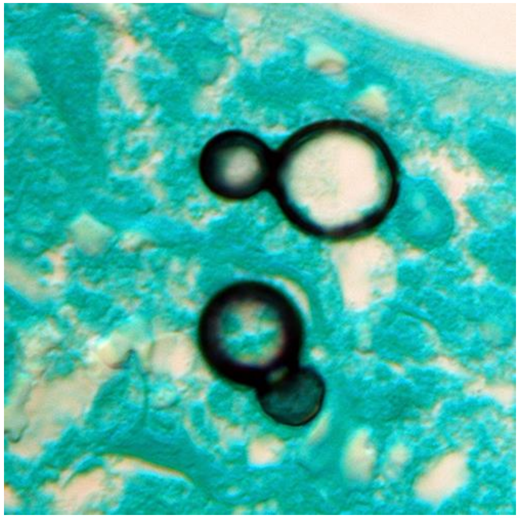


Image courtesy of Medmyco/Wikipedia

Coccidioidomycosis

- Mexico, Arizona, New Mexico, Texas, California
- Grows as mold beneath desert surface
- Dry conditions → Mold fractures into spores
- Infection by inhalation of a spores
- In lung, spore enlarges to spherule (not a yeast)
- Enlarging spherules produce endospores
- Mature spherules rupture, releasing endospores
- Each endospore can produce another spherule

Spherule

- Classic path finding: Spherule filled with endospores

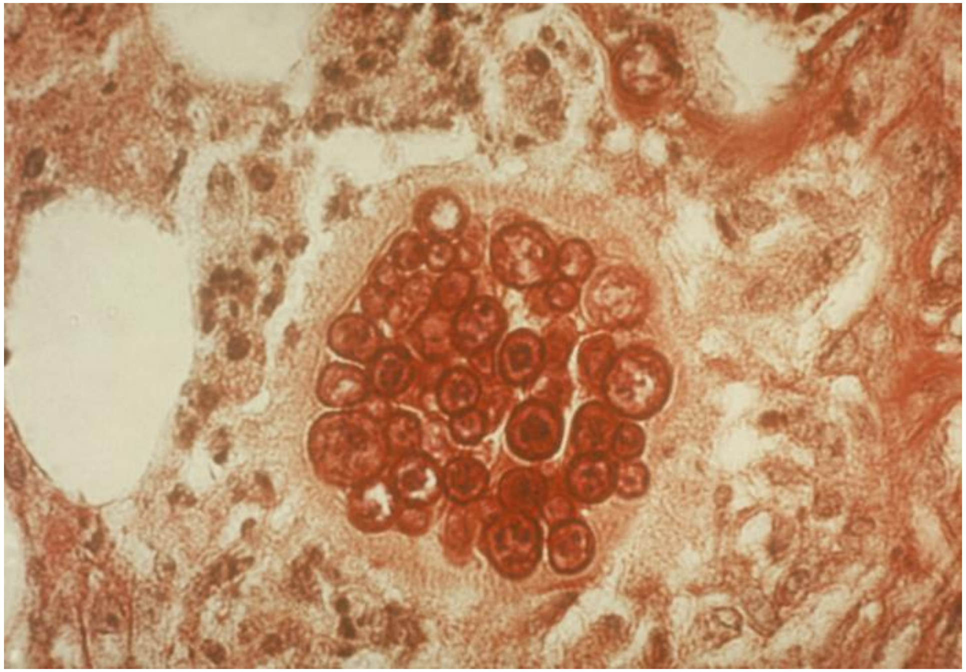


Image courtesy of Wikipedia/Public Domain

Coccidioidomycosis

- Most infections asymptomatic
- Symptoms: Valley Fever
  - Fever, malaise, cough
  - Arthralgias
  - Erythema nodosum
- Diagnosis: sputum Cx
- Rarely disseminates
- Feared result is meningitis
- Treatment:
  - Mild disease: Fluconazole/itraconazole
  - Severe/systemic: Amphotericin B

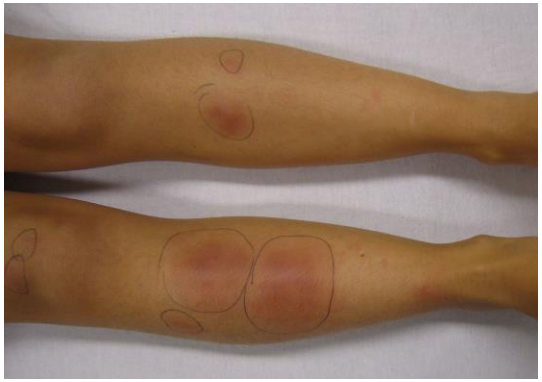
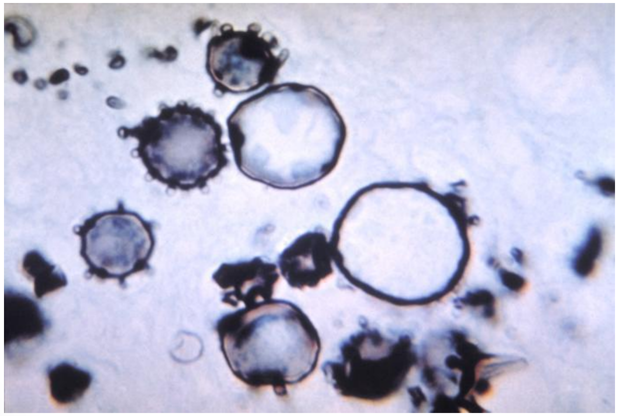


Image courtesy of James Heilman, MD

Paracoccidioidomycosis

- Central/South America
- Pulmonary symptoms (cough)
- In yeast form, mother cells buds off children
  - "Pilot's wheel"
  - "Mickey Mouse Head"



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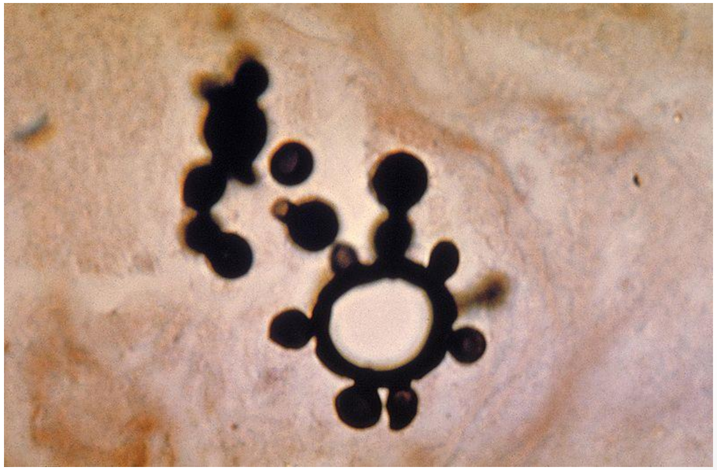

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Aspergillus

- Pneumonia in immunocompromised
  - HIV, Chemotherapy
- No specific geographic area
- Very sick patient
  - Fever, hemoptysis, pleuritic chest pain

Fungal Skin Infections

Jason Ryan, MD, MPH

Fungal Infections

- Pneumonia
  - Only in specific geographic areas
  - Histoplasmosis, Blastomycosis, Coccidioidomycosis
- Skin
  - Tinea versicolor, tinea pedis, sporothrix
- Opportunistic
  - Candida, Aspergillus, Cryptococcus, Mucormycosis, Pneumocystis

Skin and Nail Infections

- Dermatophyte infections
  - Tinea pedis
  - Tinea cruris
  - Tinea corporis
  - Tinea capitis
  - Tinea unguium
- Tinea versicolor
- Sporothrix schenckii

Terminology

- Tinea = fungal skin/nail infection
- Dermatophytes: fungi that require keratin for growth
- Most tinea infections caused by dermatophytes

Dermatophytes

- Majority of infections from 3 dermatophytes:
  - Epidermophyton
  - Trichophyton
  - Microsporum
- All consume keratin
- Exist only as molds with hyphae
- Most treated with topical antifungals
  - Clotrimazole, Miconazole (azoles)
  - Terbinafine
- Note: Nystatin not effective against dermatophytes
  - Only effective against cutaneous candida (diaper rash)

KOH Prep

- Potassium hydroxide (KOH)
- Used to identify fungal infections
- KOH dissolves epidermal keratinocytes
- Fungi visible in skin scrapings (hyphae)
- Used for:
  - Dermatophyte infections
  - Tinea versicolor
  - Candida

Tinea unguium
Onychomycosis

- Mostly a cosmetic problem
- Oral treatment often used:
  - Terbinafine
  - Itraconazole

Image courtesy of James Heilman/Wikipedia

Tinea pedis

Athlete's foot

- Fungal foot infection
- Itchy, red erosions between toes, on soles
- Untreated can lead to scaling
- Treatment: Topical antifungals
  - Clotrimazole, Miconazole
  - Terbinafine

Tinea corporis

Ringworm

- Itchy, circular or oval, red, scaling patch or plaque
- Spreads centrifugally
- Red border with central clearing (“ring”)
- Treatment: Topical antifungals
  - Clotrimazole, Miconazole
  - Terbinafine

Image courtesy of Dr. Lucille K. Georg/Wikipedia

Tinea capitis

- Dermatophyte infection of scalp
- Usually occurs in children
- Common in African-Americans
- Red, scaling patch on the scalp
- Spreads centrifugally
- Oral treatment often used:
  - Griseofulvin
  - Terbinafine
  - Itraconazole

Image courtesy of myself/Wikipedia

Tinea cruris

Jock itch

- More common in men
- Often occurs after physical activity with sweating
- Obesity increases risk
- Red patch on inner thigh
- Spreads centrifugally
- Red, sharply demarcated border
- Treatment: Topical antifungals
  - Clotrimazole, Miconazole
  - Terbinafine

Image courtesy of Robertgascoign/Wikipedia

Tinea Versicolor

Pityriasis versicolor

- Cause by *Malassezia* species
- Dimorphic fungi, normal skin flora
- Yeast can transform to mycelial form → disease
- Transformation triggers:
  - Hot, humid weather
  - Sweating
  - Topical skin oils

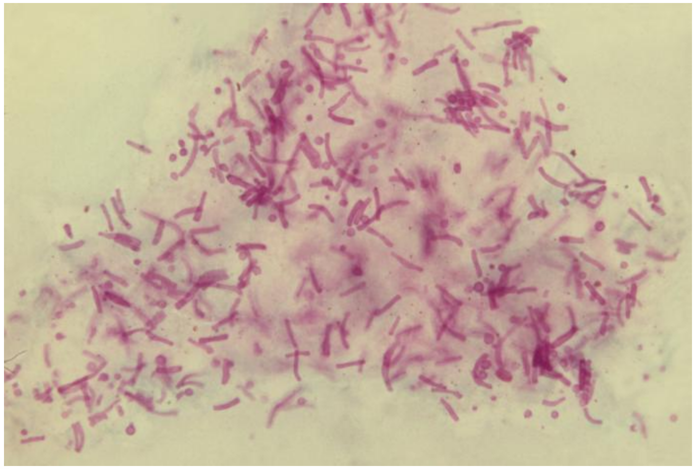
Tinea Versicolor

- Degradation of lipids → acids
- Damages melanocytes
- Hypopigmented skin
- Not a dermatophyte (does not consume keratin)

Image courtesy of Sarahrosenau/Wikipedia

Tinea Versicolor

- KOH prep shows hyphae AND yeast cells
- “Spaghetti and meatballs”
- Treatment: Topical azoles
- Also, selenium sulfide (topical)
  - Promotes shedding stratum corneum



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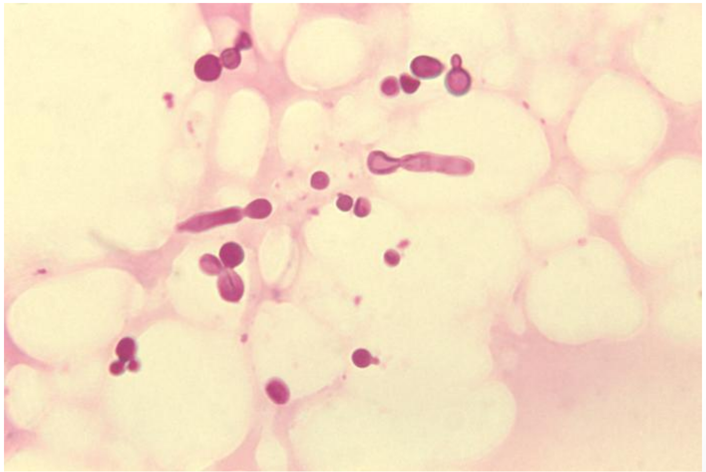

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Sporothrix schenckii

Sporotrichosis

- Dimorphic yeast that lives on plants
- Spores introduced skin of hands with trauma
  - “Rose gardener’s disease”
- Papule at site of trauma days to weeks later
- Travels up arm via lymphatics
  - “Ascending lymphangitis”
- Similar lesions occur along lymph channels

Sporothrix schenckii

Sporotrichosis

- Diagnosis: Fungal culture
- Treatment
  - Itraconazole (oral)
  - Saturated solution of potassium iodide (SSKI)

Opportunistic Fungal Infections

Jason Ryan, MD, MPH

Fungal Infections

- Pneumonia
  - Only in specific geographic areas
  - Histoplasmosis, Blastomycosis, Coccidioidomycosis
- Skin
  - Tinea versicolor, tinea pedis, sporothrix
- Opportunistic
  - Candida, Aspergillus, Cryptococcus, Mucormycosis, Pneumocystis

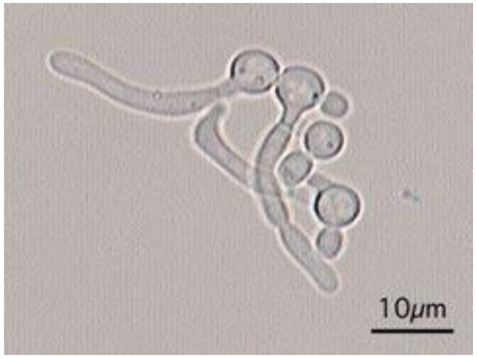
Candida Albicans

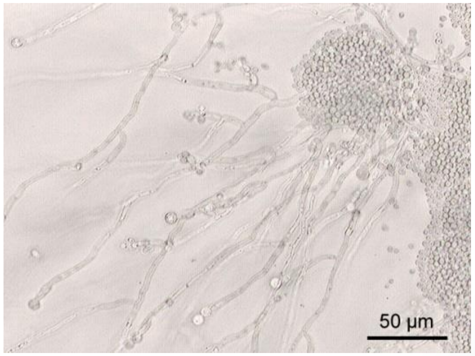
- Normal flora of mouth, intestine, skin, vagina
  - Common contaminant of sputum culture
- Overgrowth disease
  - Oral thrush
  - Esophagitis
  - Vulvovaginitis
  - Diaper rash
- Disseminated disease
  - Endocarditis
  - Disseminated candidiasis

Candida Albicans

- Dimorphic
- Forms pseudohyphae
  - Elongated, budding yeast cells
- Forms germ tubes (“germ tube test”)
  - Yeast with hyphae growing out
  - Differentiates candida

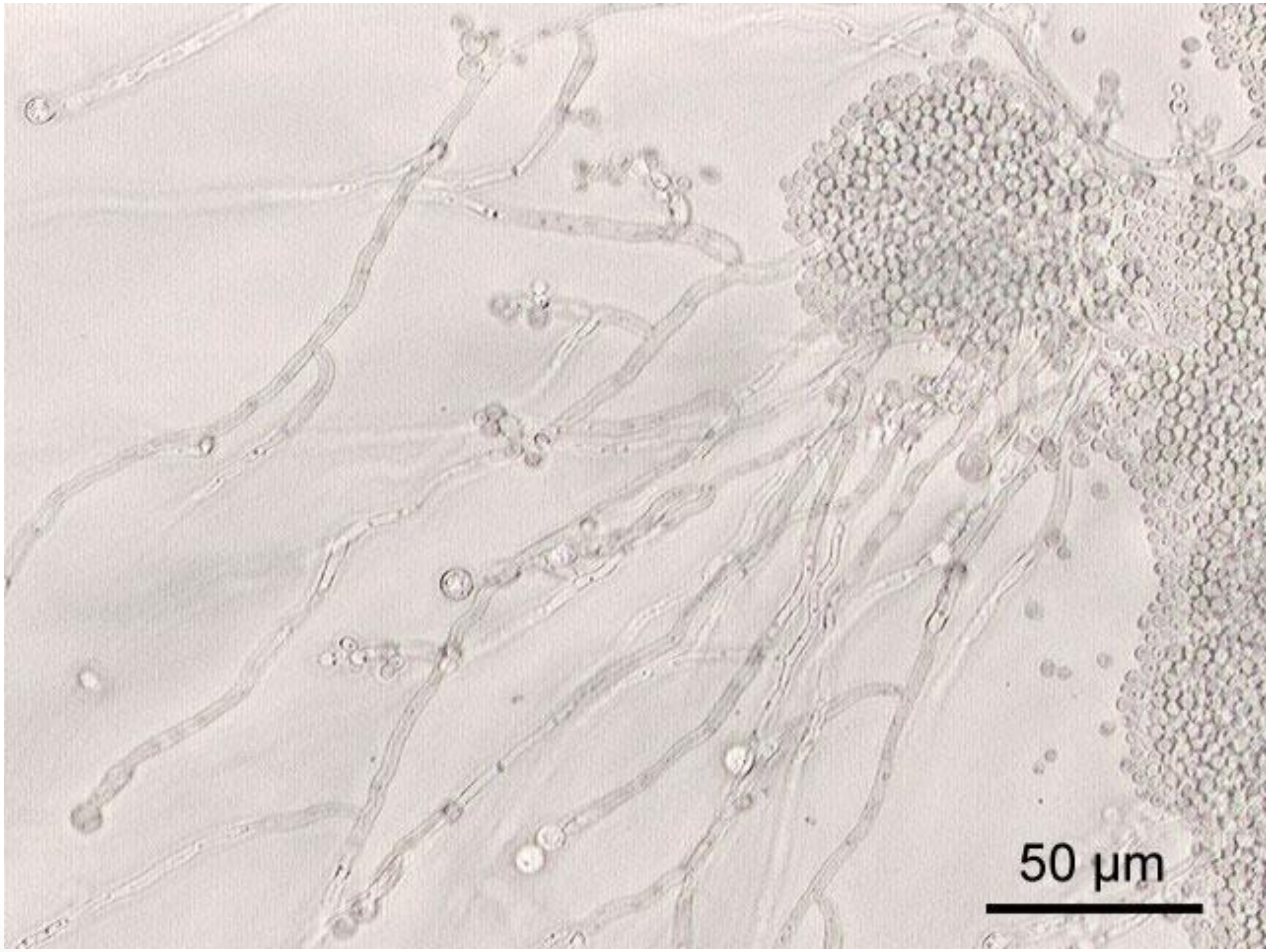
Germ Tubes





Images courtesy of Y Tambe/Wikipedia

Pseudohyphae



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Candida

Overgrowth Diseases

- Oral thrush
  - Inhaled steroid patients (asthma)
- Esophagitis
  - HIV/AIDS patients
  - White pseudomembrane on EGD
- Vulvovaginitis
  - "Yeast infection"
  - Itching, discharge ("cottage cheese" appearance)
  - Women taking antibiotics at risk (decreased normal flora)
- Diaper rash
  - Beefy, red plaques with satellite papules

James Heilman, MD/Wikipedia

Candida

Systemic Diseases

- Endocarditis (rare)
  - Almost always IV drug user
- Candidemia
  - From blood can spread to any organ system

Candidemia

- Immunosuppressed patients
  - Neutropenic patients from chemo
- Patients in the ICU
- Central lines
- Total parenteral nutrition (TPN)/Hyperalimentation
- IV drug users

Candida

Treatment

- Vaginal disease/diaper rash
  - Topical azole
- Oral thrush
  - Nystatin “swish and swallow”
  - Fluconazole
- Esophagitis
  - Fluconazole
  - Resistant cases: voriconazole, caspofungin
- Candidemia/endocarditis
  - Fluconazole (stable, not immunocompromised)
  - Caspofungin or Amphotericin B

Chronic mucocutaneous candidiasis

- Rare disorder
- Mutations in autoimmune regulator (AIRE) genes
- T-cell dysfunction
- T cells fail to react to candida antigens
- Chronic skin, mucous membrane candida infections
- Child with recurrent thrush, diaper rash

Candida Immunity

- T-cells important for mucosal defense
  - Example: HIV patients often get thrush (↓CD4)
- Neutrophils important for systemic defense
  - HIV patients rarely get candidemia
  - No candidemia in CMC
  - Chemo patients at risk for candidemia (neutropenia)

Pirofski L, Casadevall A; Rethinking T cell immunity in oropharyngeal candidiasis
J. Exp. Med. Vol. 206 No. 2 269-273

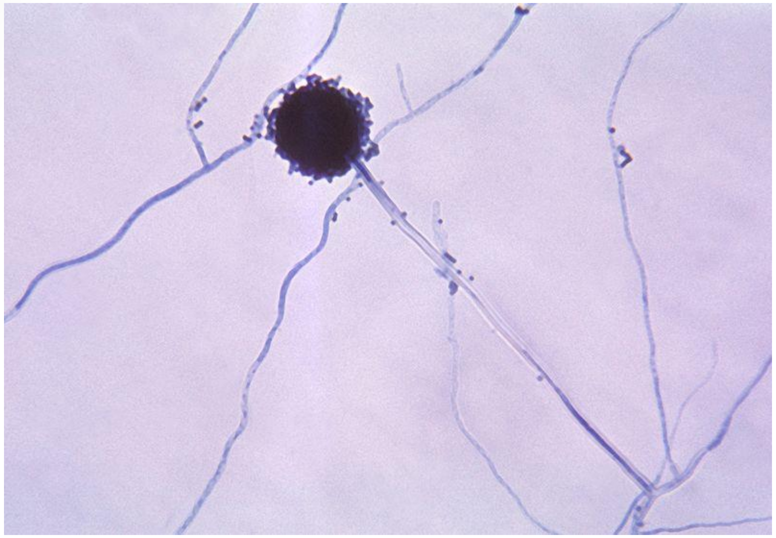
Aspergillus

- Aspergillus species ubiquitous in nature
  - A. fumigatus, A. flavus, and A. terreus
- Inhalation of spores (conidia) common
- Disease requires immunocompromise
- Usually chemo, stem cell transplant

Aspergillus

- Catalase positive
  - Common infection in chronic granulomatous disease
- Monomorphic fungi
  - Do not forms yeast cells
- Forms “branching septate hyphae”
  - V shaped branches
  - Visible septae
- Tips of some hyphae grow spores (conidiophore)

Aspergillus



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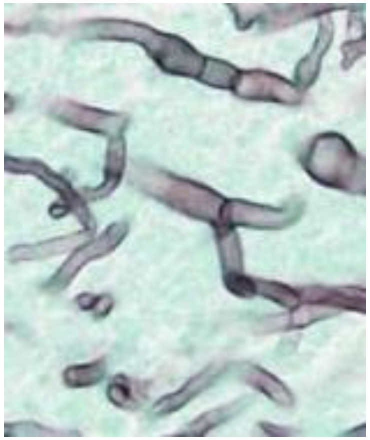

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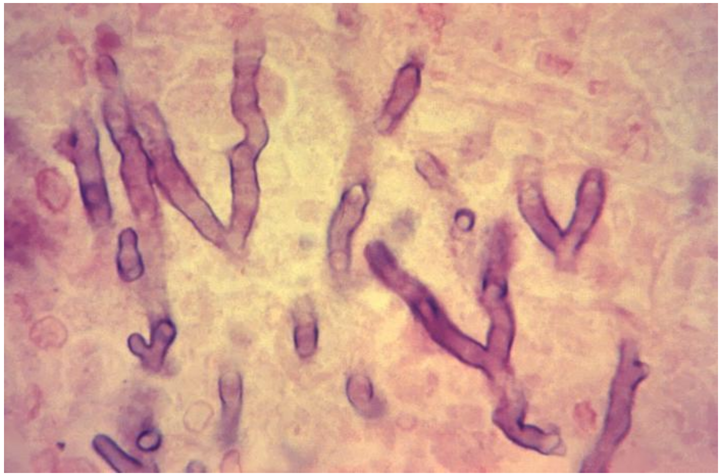

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Aspergillus Disease

- Aspergillosis
  - Lung disease that can progress to systemic illness
  - Neutropenic patients
- Allergic bronchopulmonary aspergillosis
  - Allergic reaction in CF/Asthma patients
- Aspergilloma
  - Fungus invades pre-formed cavities (TB)
- Hepatocellular carcinoma
  - Aflatoxins

Aspergillosis

- Severe lung disease
- Classic case:
  - Neutropenic patient
  - Fever, cough
  - Pleuritic chest pain
  - Hemoptysis
  - Multiple nodules/densities/infiltrates on imaging
- Can disseminate to any organ
  - Heart (endocarditis); Brain (abscesses; mycotic aneurysms)
- Treatment:
  - Voriconazole, Caspofungin, or Amphotericin B

ABPA

Allergic bronchopulmonary aspergillosis

- Hypersensitivity (allergic) reaction to aspergillus
  - Type I (IgE)
  - Type III
- Lungs become colonized with Aspergillus
- Occurs predominantly in asthma and CF patients
- ABPA patients:
  - Increases Th2 CD4+ cells
  - Synthesis interleukins (IL-4, IL-5)
  - Eosinophilia
  - IgE antibody production

ABPA

Allergic bronchopulmonary aspergillosis

- Classic case
    - Asthma or CF patient
    - Recurrent episodes cough, fever, malaise
    - Brownish mucus plugs, hemoptysis
    - Peripheral blood eosinophilia
    - High IgE level
- Diagnosis: Skin testing aspergillosis
- Treatment: Steroids

Aspergilloma

- Fungus ball
- Caused by Aspergillus fumigatus
- Grows in pre-formed cavities
- Pulmonary TB is most common association
- Often asymptomatic
- Can cause hemoptysis
- Diagnosis: Imaging plus sputum culture
- Treatment: Observation vs. surgery

Hepatocellular Carcinoma

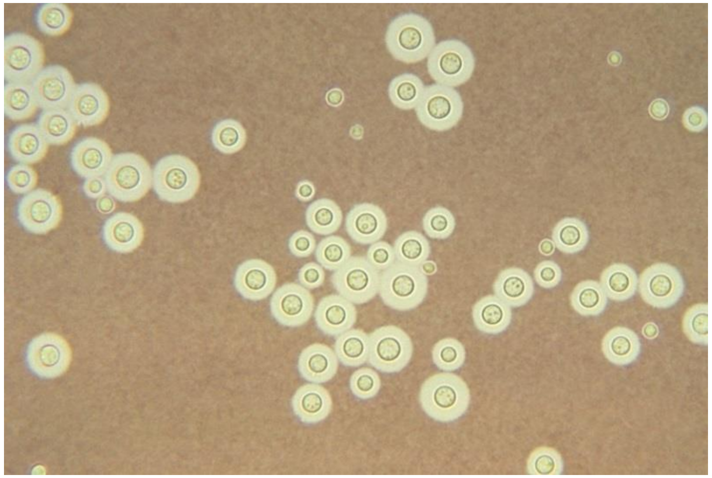
- Aflatoxin produced by aspergillus
- Can contaminate corn, soybeans, and peanuts
- High rates of dietary intake associated with HCC
- Industrialized countries screen for aflatoxin
- Exposure from:
  - Food from non-industrialized countries
  - Locally grown foods

Cryptococcus Neoformans

- Exists only as yeast
- Thick capsule
- Main disease is meningitis
  - HIV/AIDS
  - Immunocompromised (Chemo, post-transplant)
- Present in soil and pigeon droppings
- Inhaled → lungs → blood stream → meninges
- Rarely can cause pneumonia
- Rarely can spread to other tissues

Cryptococcus Neoformans

- Can be cultured on Sabouraud's agar
- India ink staining shows capsules as "halos"
- Latex agglutination test
  - Detects polysaccharide capsular antigen



India Ink stain shows yeast with "halos"

Image courtesy of Crisco 1492

Cryptococcal Meningitis

- Indolent symptoms over weeks
  - Fever, headache
- Can cause ↑ICP
- Risk of herniation with LP
- Must do CT or MRI
- Treatment:
  - Amphotericin B +/- Flucytosine
  - Fluconazole
- Sometimes intrathecal therapy used

Mucormycosis

- Rare fungal infection of nose, eyes, brain
- Caused by Rhizopus sp. and Mucor sp.
- Fungi have enzyme: ketone reductase
- Thrive in high glucose, ketoacidosis conditions
- Serum from DKA patients stimulates growth
- Risk factors:
  - Diabetes, especially DKA
  - Treatment with steroids
  - Leukemia
  - Stem cell transplant patients

Mucormycosis

- Disease from inhaled spores
- Enters nose or alveoli
- Angioinvasive fungus: Invades vessel walls
- Classically starts in sinuses
- Spreads to adjacent structures

Mucormycosis

Clinical features

- Severe sinusitis
  - Fever, discharge, congestion, sinus pain
- Necrosis of the palate
- Erythema/cyanosis of skin over sinuses
- Black eschars
- Orbital pain/swelling
- Facial numbness (cranial nerve damage)
- Cavernous sinus thrombosis

Mucormycosis

Clinical features

- Classic case:
  - Patient with DKA
  - Fever, headache, eye pain
- Diagnosis: mucosal biopsy
- Treatment:
  - Surgical debridement
  - Amphotericin B

Mucormycosis

- Broad hyphae
- Irregularly branched, rare septations
- Different from Aspergillus:
  - Narrow, regular (v-shaped) branching, many septations

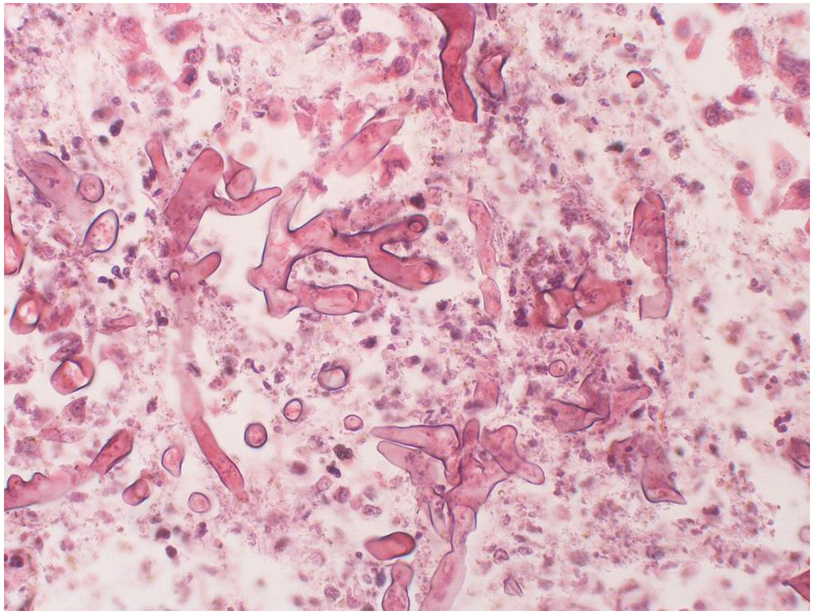


Image courtesy of Yale Rose/Flickr

PCP

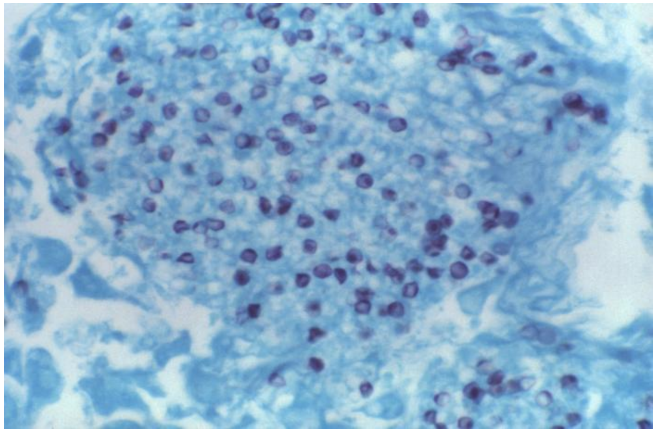
Pneumocystis jirovecii

- Causes diffuse interstitial pneumonia
- Requires immunocompromise
  - Classically HIV
  - AIDS-defining illness
- Yeast → inhaled
  - Usually no symptoms if immune system intact
- CXR will show diffuse, bilateral interstitial infiltrates

PCP

Pneumocystis jirovecii

- Diagnosed by microscopy
  - Sputum sample, BAL, or biopsy
  - Sent for staining or fluorescent antibody testing
- Staining required to visualize → cannot be cultured
- Special stains used
  - Silver stains often used



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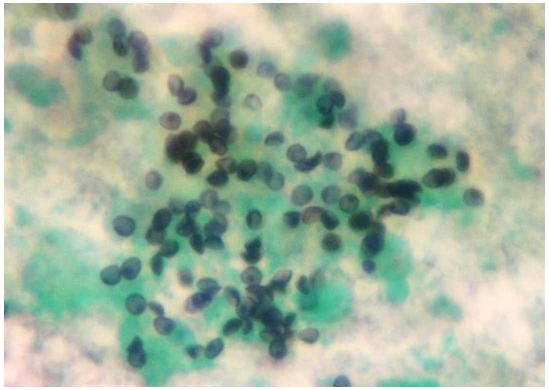


Image courtesy of Yale Rosen/Wikipedia

PCP

Pneumocystis jirovecii

- Treatments
  - TMP-SMX (first line)
  - Dapsone
  - Pentamidine
- Prophylaxis
  - TMP-SMX when CD4 <200cells/microL
  - High dose steroid or other immunosuppressed patients

Antifungal Drugs

Jason Ryan, MD, MPH

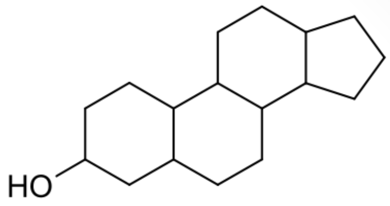
Antifungal Drugs

- Amphotericin B
- Nystatin
- Flucytosine
- Azoles (fluconazole, itraconazole, voriconazole)
- Echinocandins (caspofungin, micafungin)
- Terbinafine
- Griseofulvin

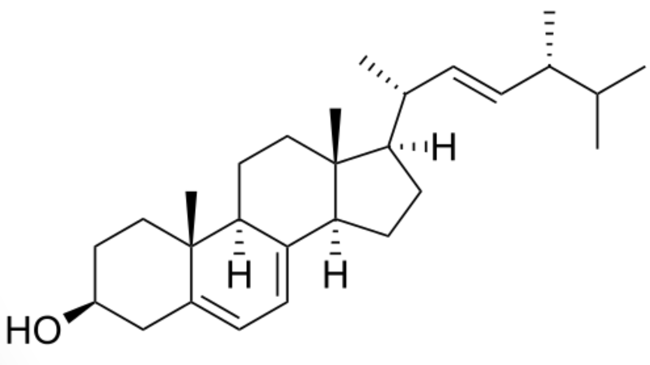
Antifungal Drugs

- Amphotericin drugs
  - Amphotericin B
  - Nystatin
  - Flucytosine
- Azoles (fluconazole, itraconazole, voriconazole)
- Echinocandins (caspofungin, micafungin)
- Tinea drugs
  - Terbinafine
  - Griseofulvin

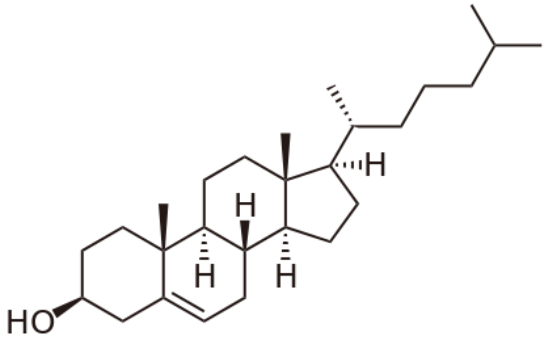
Sterols



- Steroids with alcohol groups present
- Cholesterol: animal cell walls
- Ergosterol: fungal cell walls



Ergosterol



Cholesterol

Amphotericin B

- Binds ergosterol
- Forms pores in membrane
- Electrolyte leakage → cell death
- Used for dangerous, systemic fungal infections
  - Candidemia
  - Mucormycosis
  - Cryptococcus
  - Systemic histoplasmosis, blastomyces, coccidiomycosis
- Usually given intravenously
- Intrathecal administration meningitis

Amphotericin B

- Several unique and important side effects
- Mechanisms not completely understood
- Many related to binding of cholesterol
- Fever, chills
  - "Shake and bake"
  - May be related to prostaglandin release
  - Minimize with Tylenol, NSAIDs, or diphenhydramine
- Phlebitis
  - Pain, inflammation of vein used for infusion
  - Avoided by using a central line
  - Sometimes hydrocortisone given with infusion
- Hypotension, arrhythmias

Amphotericin B

- Nephrotoxicity
  - Causes renal vasoconstriction/toxic to tubules
  - Can insert into cell membranes → create pores
  - Decrease GFR (Cr will rise)
  - Rarely ARF
  - Hydration reduces this complication
- Liposomal Amphotericin B
  - Amphotericin B dissolved in lipids
  - Developed based on animal studies
  - Reduced incidence of nephrotoxicity

Amphotericin B

- Hypomagnesemia, hypokalemia
  - Increased distal tubule permeability to Mg/K
  - Mg/K lost in urine
  - Need to replete Mg and K
- Anemia
  - Reversible, normocytic, normochromic anemia
  - Usually mild

Amphotericin B

- Distal (Type I) RTA
  - Non anion gap metabolic acidosis
  - Very low HCO_3^- (often <10meq/L)
  - Urine pH is high (pH>5.5)
- Nephrogenic diabetes insipidus
  - Hypernatremia

Nystatin

- Binds ergosterol (same mechanism Ampho B)
- Highly toxic when given IV
- Not used systemically
- "Swish and swallow" for thrush (candida)
- Diaper rash (candida)

Flucytosine

- Blocks fungal DNA/RNA synthesis
- Converted to 5-fluorouracil by cytosine deaminase
  - Cytosine deaminase only present in fungi
- Causes impaired DNA/RNA synthesis

Flucytosine

$$\text{dUMP} \xrightarrow{\text{Thymidylate synthase}} \text{dTMP}$$

Flucytosine

- High incidence resistance when used alone
- Used in combination with Amphotericin B
- Main use is **cryptococcal meningitis**
- Major side effect is bone marrow suppression
  - Some spontaneous conversion to 5-FU
  - Leukopenia, thrombocytopenia

Azoles

Fluconazole, itraconazole, voriconazole, clotrimazole, miconazole, ketoconazole

- Block ergosterol synthesis
- Inhibit P450 enzyme in fungi
- Enzyme converts lanosterol to ergosterol
- Side effects related to this mechanism:
  - Inhibits liver P450 system
  - Elevated levels of P450 meds (warfarin, theophylline)

Azoles

- Hepatotoxicity
  - Reported with all azoles
  - LFTs monitored in patients on these drugs (oral)
- Ketoconazole
  - Life-threatening hepatotoxicity reported
  - Rarely used any longer for this reason
  - Suppresses cortisol synthesis (can be used in Cushing's)
  - Suppresses testosterone synthesis (causes gynecomastia)

Azoles

- Itraconazole
  - Drug of choice for fungal pneumonias
  - Also Sporothrix
- Fluconazole
  - Excellent activity against Cryptococcus
  - Vulvovaginitis (Candida)
- Clotrimazole
  - Diaper rash
- Voriconazole
  - Severe, systemic fungal infections (Aspergillus)

Echinocandins

Caspofungin, micafungin

- Inhibit cell wall synthesis
- Block synthesis of β-glucans (polysaccharides)
- β-glucans account for 30-60% cell wall
- "Penicillin of antifungals"
- Used for severe, systemic infections
  - Aspergillus
  - Candidemia
- Few side effects
  - GI upset
  - Infusion-related histamine release (flushing)

Terbinafine

- Blocks squalene epoxidase
- Key enzyme for ergosterol synthesis
- Given orally to treat dermatophyte infections
  - Especially onychomycosis
- Side effects:
  - Headache (13% patients)
  - Hepatotoxicity (monitor LFTs)
  - Rarely blurry vision

Griseofulvin

- Blocks mitosis by interfering with **microtubules**
- Deposits in tissues with keratin
  - Binds to keratin → resistance to fungal invasion
- Oral therapy for skin/nail infections

Griseofulvin

- Side effects:
  - Induces P450 (warfarin, theophylline levels will fall)
- Teratogenic: not safe in pregnancy
- Carcinogenic
- Other adverse effects:
  - Liver toxicity
  - Photosensitivity
  - Porphyria attacks

Fungal Infections

Skin/Nail
Tinea

Griseofulvin
Terbinafine
Azoles

Serious Systemic
Aspergillus
Candidemia
Cryptococcus
Mucormycosis

Amphotericin B
Echinocandins
Voriconazole

Mild Local/Systemic
Histo
Blasto
Coccidio

Azoles

Malaria

Jason Ryan, MD, MPH

Malaria

- Protozoa infection of red blood cells and liver
- Occurs in tropics, subtropics
- Very rare in US, Europe
- Africa is most effected continent
- Transmitted by mosquito bite (female *Anopheles*)
- Caused by Plasmodium sp.
- Several species with distinct features:
  - P. vivax/P. ovale
  - P. malariae
  - P. falciparum

Malaria

Life cycle

- Bite of female mosquito → sporozoites to liver
- Asymptomatic for up to 1 month

Malaria

Life cycle

- Sporozoites invade hepatocytes
- Mature into multi-nucleated schizonts
  - "Pre-erythrocytic stage"

Malaria

Life cycle

- Schizonts rupture → release Merozoites
- Invasion of RBCs ("Erythrocytic stage")

Malaria
Life cycle

- Form trophozoites (ring form) in RBCs
- Inside RBCs mature to schizonts
  - Digest RBC proteins, especially hemoglobin
  - Breakdown products toxic to RBCs
- Merozoites formed (again) → RBC lysis
  - Occurs at regular intervals (48hr, 72hr)
  - Cyclic fevers can occur

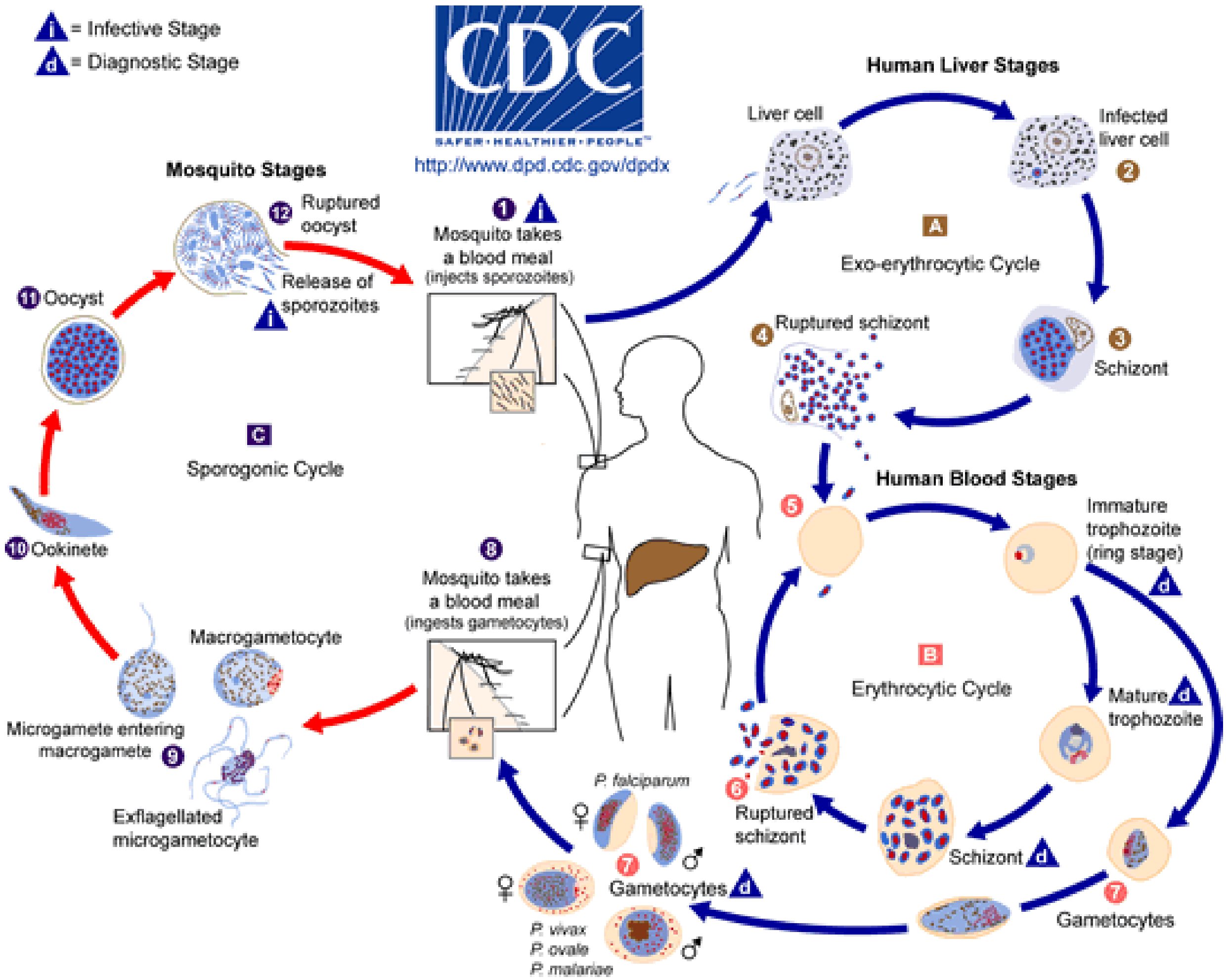
Malaria

Life cycle

- Key Points:
  - Protozoa goes to liver after mosquito bite
  - Sporozoites are the infective form
  - Incubation period occurs
  - Release of merozoites leads to RBC infection, symptoms
  - Plasmodium matures/grows in RBC
  - Eventually ruptures RBC → release of merozoites
  - Cycle of maturation/release → cyclical fevers

Malaria

Life cycle



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Malaria

Common symptoms

- Paroxysms of fever
  - Shivering and chills followed by high fever
  - Fever recurs at regular intervals (48hrs, 72hrs)
  - Variable by species of Plasmodium
- Anemia (RBC infection)
  - Severity varies by species of Plasmodium
  - Hemolytic: sometimes jaundice
- Splenomegaly
- Also nonspecific symptoms:
  - Sweating, fatigue, malaise, arthralgias, headache
  - Sometimes cough, vomiting, diarrhea

Malaria

Rare symptoms

- Altered consciousness (especially when febrile)
- Seizures
- "Blackwater fever"
  - Renal failure with hemoglobinuria
- Shock
- Severe symptoms usually due to P. falciparum

P. Vivax/Ovale

- Classically has a 48hr cycle of fevers
  - "Tertian" fever pattern
  - Fever day 1, day 3
  - No fever day 2, day 4
- Dormant form in liver
  - "Hypnozoites" form
  - Recurring infection months after resolution
- Primaquine treats P. vivax/ovale liver disease
  - Without this, relapses may occur

P. malariae

- Classically has a 72hr cycle of fevers
  - "Quartan" fever pattern
  - Fever day 1, day 4
  - No fever day 2, day 3

P. falciparum

- Most severe malarial infection
- Fever pattern is irregular
- Invades RBCs of any age
  - Other forms invade only reticulocytes

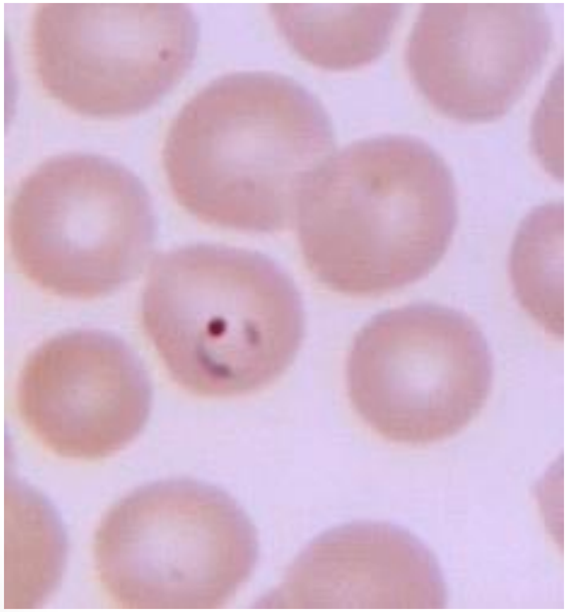
P. falciparum

- Induces sticky “knobs” on RBC surfaces
    - Knobs composed of parasite proteins
    - *P. falciparum* erythrocyte membrane protein 1 (PfEMP1)
- Knobs bind receptors on endothelial cells
- Result is occluded capillaries
    - Cerebral malaria (occluded vessels in brain)
        - Altered consciousness, delirium, coma
    - Renal failure (“blackwater fever”)

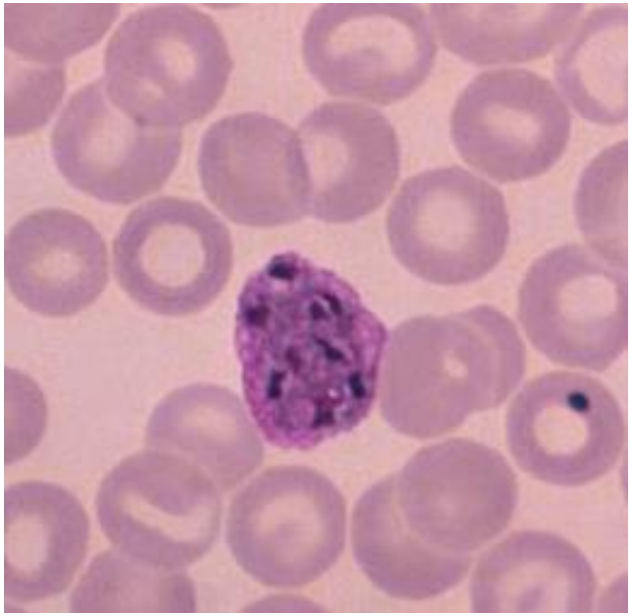
Malaria
Diagnosis

- Blood smear (Giemsa or Wright stains)

Trophozoite Ring



Schizont with merozoites



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Malaria Extras

- Duffy antigen
  - Necessary for P. vivax infection
  - Absence of Duffy → protective
- Sickle cell
  - May have evolved as protection from malaria
  - Children with HbS have lower risk of falciparum infection
- Thalassemia
  - Reduced parasite multiplication in P. falciparum infection

Malaria
Treatment

- Chloroquine
  - Weak base
  - Accumulates in food vacuoles (acidic) of RBC trophozoites
  - Blocks plasmodium **heme polymerase**
  - Heme portion of Hgb toxic to parasite
  - Plasmodium converts this to nontoxic form
- Lots of chloroquine resistance
- Used mainly in limited areas ("chloroquine sensitive")
- Not used for severe infections
- Only kills erythrocytic forms (not liver forms)
- Retinopathy associated with long-term use

Malaria

Treatment

- Severe infections
  - Artesunate (IV)
  - Quinidine (IV)
- Other drugs
  - Mefloquine (commonly used in chloroquine resistant areas)
  - Primaquine (liver phase only; not active against RBC phase)
  - Atovaquone

Immune Suppression

- Chloroquine and hydroxychloroquine
- Malaria drugs with immunosuppressive actions
  - Block TLRs in B-cells (↓activation)
  - Weak bases: ↑pH in immune cells → ↓ activity
  - Other actions
- Used in rheumatoid arthritis, SLE

G6PD Deficiency

- X-linked genetic disorder
- Hemolytic anemia triggered by various stressors
  - Infections
  - Fava beans
  - Drugs
- Many malaria drugs trigger anemia in G6PD
  - Quinidine
  - Primaquine
- Often test for G6PD deficiency prior to treatment:
  - Primaquine for P. vivax/ovale liver phase
  - IV Quinidine for life threatening P. Falciparum

Protozoa

Jason Ryan, MD, MPH

Protozoa

- Protozoa are eukaryotes
  - Have a nucleus
  - Intracellular organelles
  - VERY different from bacteria
- Unicellular
- Mobile
- Easily seen under microscope

Protozoa

- Exist in different stages
- Trophozoites
  - Feeding form
  - Vulnerable to environmental conditions
- Cysts
  - More durable form
  - Often present in feces → water → new infection

Protozoa Infections

- GI Illness
  - Giardia, Entamoeba, Cryptosporidium
- CNS Infections
  - Toxoplasma, Naegleria fowleri, Sleeping sickness
- Blood infections
  - Malaria, Babesia
- Others
  - Chagas disease, Leishmaniasis, Trichomonas

Protozoa

Transmission

- All GI protozoa transmit fecal → oral
  - Cysts in stool → water
  - Consumption of contaminated water
- Others transmitted by various methods
  - Direct (Trichomonas; STD)
  - Contact with cat feces (Toxoplasmosis)
  - Mosquito/fly (Malaria, Babesia)

Protozoa Drugs

- Metronidazole works for many infections
  - GI parasites: Giardia, Entamoeba
  - Trichomonas
- Most other drugs unique to one protozoa
  - Iodoquinol (Entamoeba)
  - Nitazoxanide (Cryptosporidium)
  - Suramin (Trypanosomes)
  - Melarsoprol (Trypanosomes)
  - Atovaquone (Babesia)
  - Nifurtimox (Chagas disease)
  - Sodium stibogluconate (Leishmania)

Giardia Lamblia

Giardiasis

- Cysts found in moist environments
- Classic source is water from a mountain stream
- Ingested cysts → trophozoite in intestine
- Affects small intestine
- Bloating, foul smelling, fatty diarrhea
- Steatorrhea
- Stools that float

Giardia

- Diagnosis:
  - Cysts in stool
  - Trophozoites in stool
  - ELISA for Giardia antigens in stool
- Classic case: Camper/hiker, diarrhea, flatulence
- Treatment: Metronidazole

Image courtesy of Joel Mills./Wikipedia

Image courtesy of Doc. RNDr. Josef Reischig, CSc./Wikipedia

IgA Deficiency

- IgA very important for defense against Giardia
- Lack of IgA → Recurrent/chronic giardia infection
- Bruton's Agammaglobulinemia
- Selective IgA deficiency

Langford TD et al. Central Importance of Immunoglobulin A in Host Defense against Giardia spp. Infect. Immun. **January 2002**vol. 70 no. 1 **11-18**

Entamoeba Histolytica

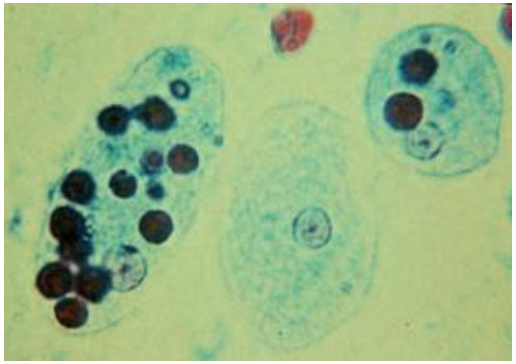
Amebiasis/Amebic dysentery

- Found worldwide
- Common in developing countries/poor sanitation
- Cysts ingested in contaminated water
- Form trophozoites in small intestine and invade tissue
- Causes bloody diarrhea (dysentery)
- Ascends portal system → liver
- Liver abscesses
  - RUQ pain
  - "Anchovy paste" exudate
- Traveler, bloody diarrhea, RUQ pain → Entamoeba

Entamoeba Histolytica

- Diagnosis:
  - Stool microscopy
  - Serology (antibodies to Entamoeba)
- Treatment:
  - Metronidazole
  - Iodoquinol (asymptomatic cysts carriers)

Trophozoite with ingested RBCs



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Cysts with multiple nuclei

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Entamoeba Histolytica

"Flask-shaped" ulcer on biopsy

CDC(Dr. Mae Melvin)/Public Domain

Entamoeba Histolytica

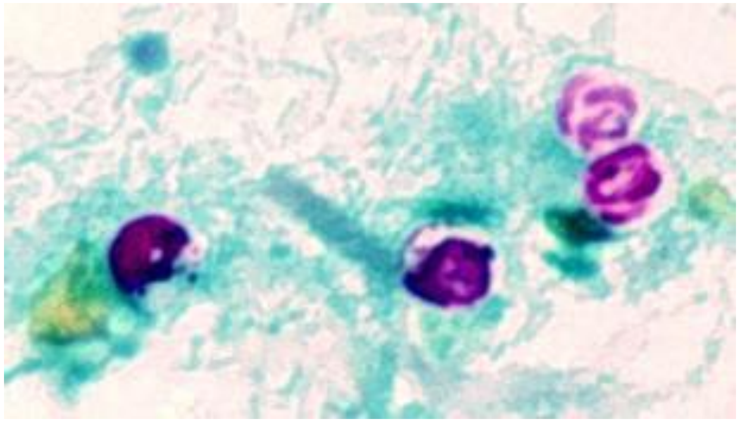
- Classic case
  - Patient in a developing country (or recent immigrant)
  - Bloody diarrhea developing over weeks
  - RUQ pain

Cryptosporidium

- Protozoa forms eggs (oocysts)
- Found in contaminated water
- Ingestion → infection
- Chlorination does not destroy oocysts
- Infection in swimming pools common
- Immunocompetent patients
  - Mild, watery diarrhea
  - Self-limited
- HIV/AIDS
  - Severe diarrhea

Cryptosporidium

- Diagnosis: Microscopy
  - Acid fast staining reveals oocysts
- Treatment:
  - Nitazoxanide (only in immunocompetent)
  - Anti-retroviral therapy for HIV patients
- Prevention is key
  - Wash hands
  - Filter water



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GI Protozoa

Contaminated Water Consumption

Hiker/Camper
Foul-smelling, greasy stools,
Cysts
Trophozoites/flagella

Giardia

Developing Country
Bloody diarrhea,
RUQ Pain
Cysts
Trophozoites/RBCs

Amebiasis

Watery diarrhea
HIV/AIDS
Acid fast oocysts

Cryptosporidium

Metronidazole

Toxoplasma gondii

Toxoplasmosis

- Commonly lives in cats (felines)
- Oocysts shed in stool
- Infection from ingested oocysts (soil)
- Also meat from contaminated animal (cysts)
- Invades intestine → disseminates
- May enter latent phase → reactivate later
- Two major disease processes
  - HIV CNS disease
  - Congenital toxoplasmosis

Toxoplasma gondii

Toxoplasmosis

- Significant CNS disease immunosuppressed
  - Usually HIV/AIDS (CD4 <100cells/mm3)
  - Sometimes "reactivates"
- Brain abscesses (fever, headache, nerve palsies)
- Multiple "ring-enhancing" lesions on imaging

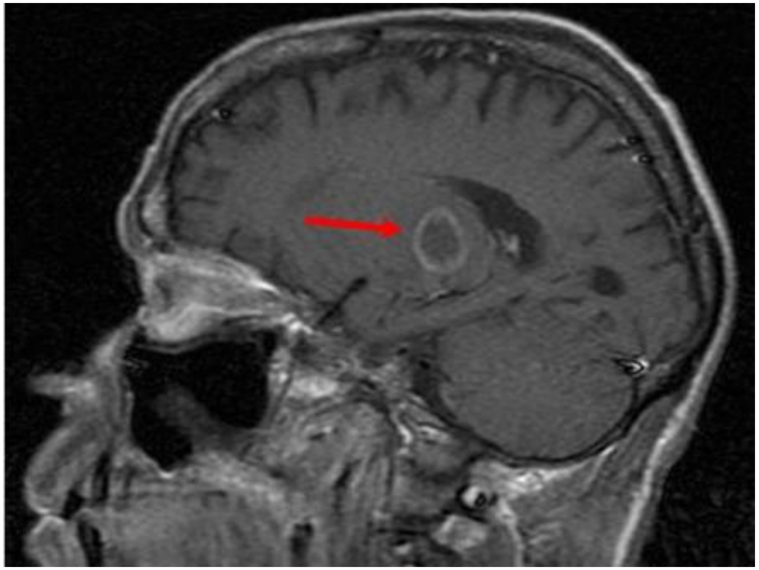


Image courtesy of LearningRadiology.com

Toxoplasma gondii

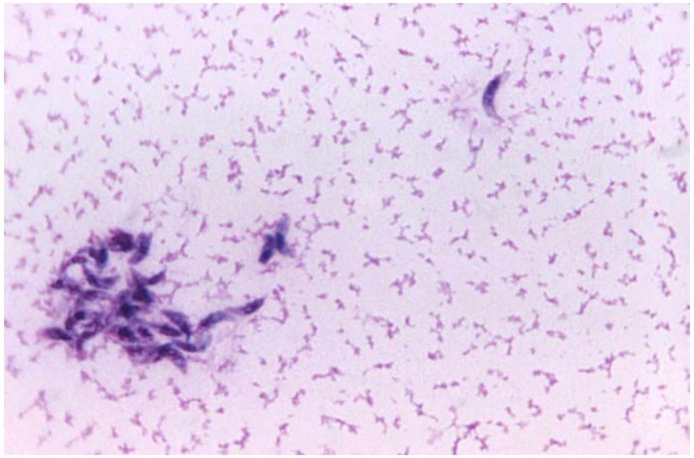
Toxoplasmosis

- Crosses the placenta
- Range of symptoms/signs in fetus
- Classic triad:
  - Chorioretinitis (inflammation of choroid in eye)
  - Hydrocephalus
  - Intracranial calcifications (seen on imaging)

Toxoplasma gondii
Diagnosis

- Serology
  - IgG or IgM antibodies to Toxoplasma
  - IgM antibodies appear within one week, rise, decline
  - IgG antibodies rise within two weeks, generally persist for life
- Biopsy

Tachyzoite (Giemsa stain)



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Toxoplasma gondii

Toxoplasmosis

- Treatment:
  - Sulfadiazine/pyrimethamine
- Blocks THF synthesis pathway
- Similar to TMP/SMX

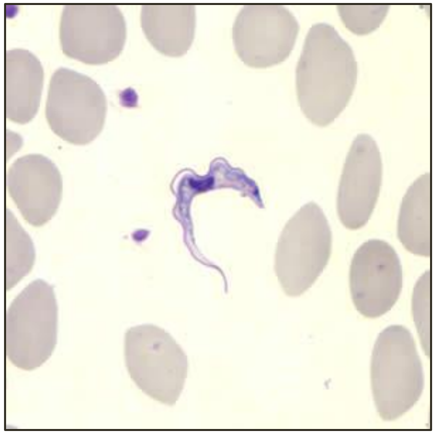
Naegleria fowleri

- Rare cause of fatal meningoencephalitis
  - 300 cases reported worldwide
- Found in freshwater lakes/ponds
- Contaminated water → nose → cribriform plate
- Classic case
  - Recent (4-5 days ago) swimming
  - Fever, confusion, stiff neck
  - Often fatal (99% in one series)

African trypanosomiasis

Trypanosoma brucei, T. gambiense, T. rhodesiense

- Protozoa infections from insect bite
- All occur in Africa
- All caused by tsetse fly
- "African sleeping sickness"
- Early and late features
  - Early: fever, arthralgias
  - Late: Somnolence, coma
- Organisms visible on blood smears



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African trypanosomiasis

Trypanosoma brucei, T. gambiense, T. rhodesiense

- Key feature: recurring fever
- Due to antigenic variation
- "Variant surface glycoproteins" (VSG)
  - Each trypanosome covered ~10million copies of one VSG
- Change VSG when host mounts immune response
- Waves of parasitemia
- Recurring fever

Babesia

Babesiosis

- Transmitted by Ixodes tick
- Same tick that transmits:
  - Borrelia (Lyme)
  - Anaplasma (Anaplasmosis)
  - Co-infection common
- Same geography as Lyme: Northeastern US
- Infects red blood cells
- Increased risk in asplenic patients
  - Spleen clears Babesia/infected RBCs

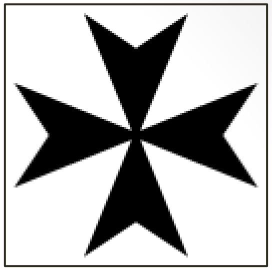
Babesia

Babesiosis

- Fever
- Hemolytic anemia
- Splenomegaly

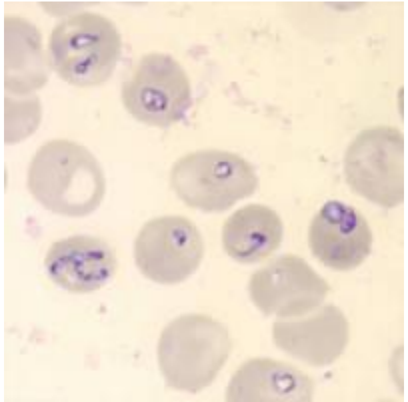
Babesia

Babesiosis



Maltese Cross

- Diagnosis:
  - Blood smear (ring forms; Maltese crosses)
  - PCR (amplification babesia RNA)
- Treatment:
  - Azithromycin (macrolide)
  - Atovaquone (malaria drug)



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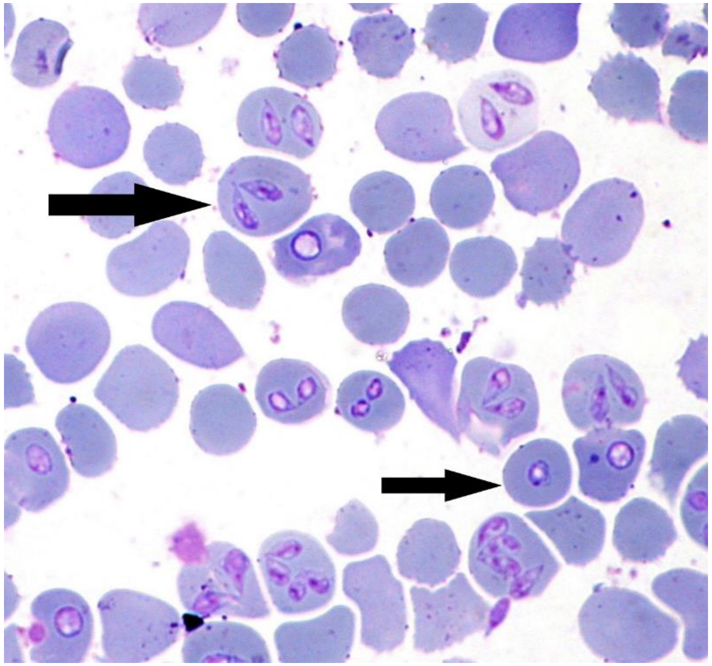

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Trypanosoma cruzi

Chagas' disease

- Transmitted by reduviid bug
- Found in South America
- Bugs nest in cracks/holes of housing
- Acute phase – nonspecific, febrile illness
- Chronic Chagas: heart, esophagus, colon

CDC/Public Domain

Trypanosoma cruzi

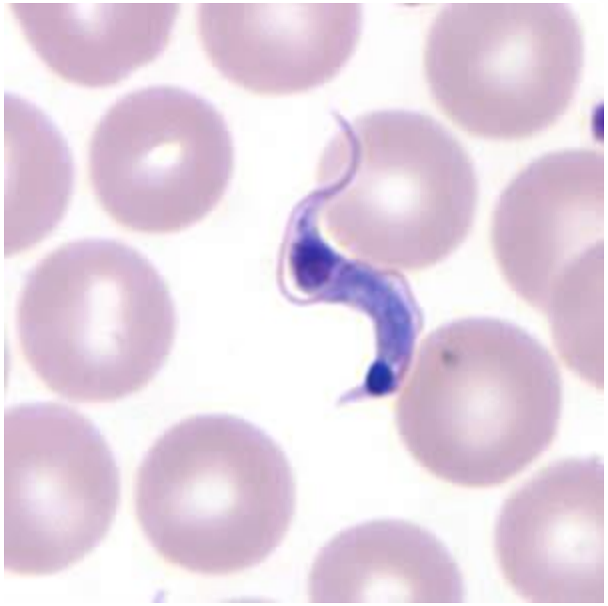
Chronic Chagas' disease

- Cardiac
  - Right and left heart failure
  - High prevalence ventricular thrombi
  - Pulmonary embolism/stroke
- Esophagus
  - Achalasia, megaesophagus (dilation)
- Colon
  - Megacolon (severe constipation)

Trypanosoma cruzi

Chagas' disease

- Acute phase: blood smear
  - Trypomastigotes visible
- Chronic phase
  - Serology (IgG antibodies)
- Treatment: Nifurtimox
  - Acute phase
  - Not effective with advanced disease



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Leishmania donovani

Leishmaniasis

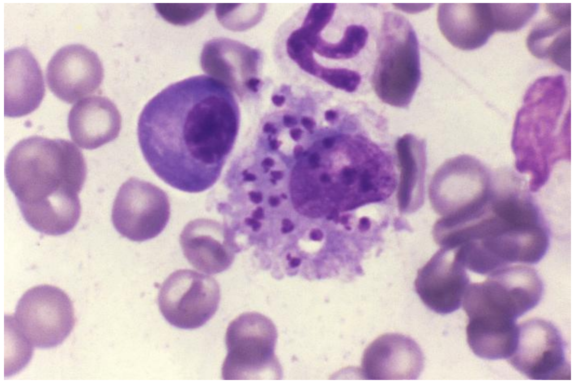
- Transmitted by sand fly
- Mostly Asia, Africa, South and Central America
- Protozoa infects macrophages
- Cutaneous leishmaniasis
  - Large ulcer with indurated borders
- Visceral leishmaniasis
  - Kala-azar (Hindi: “black fever”)
  - Fever
  - Painful splenomegaly
  - Pancytopenia

CDC/Public Domain

Leishmania donovani

Leishmaniasis

- Diagnosis by biopsy of affected organs
  - Usually bone marrow or spleen
- Amastigotes in macrophages
  - Small, round or oval bodies
- Treatment:
  - Amphotericin B
  - Sodium stibogluconate



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Trichomonas vaginalis

- Lives in urogenital tract
- Sexually transmitted (no cyst form)
- Men:
  - Usually asymptomatic
  - Can cause urethritis (discharge, dysuria)
- Women
  - About 50% asymptomatic
  - Vaginitis
  - Itching
  - Classically yellow-green, foul-smelling discharge

Trichomonas vaginalis

- Diagnosis:
  - Wet mount: motile trichomonads
  - pH >4.5 (normal 4-4.5)
- Treatment: Metronidazole
  - Patient and partner
- One of 3 main causes vaginitis
  - Bacterial vaginosis (Gardnerella vaginalis)
  - Candida (fungi)
  - Trichomonas (protozoa)

Motile Trichomonads

CDC/Public Domain

Clue Cell – Bacterial Vaginosis

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Vaginitis

	Bacterial vaginosis	Candida	Trichomonas
Discharge	Thin, off-white	Thick, White "Cottage Cheese"	Yellow-green
Odor	Fishy	None	Foul-smelling
Tissue	Normal	Vaginal erythema	Strawberry cervix
pH	>4.5	Normal (4-4.5)	>4.5
Other test	Whiff test	KOH Prep	Wet Mount
Treatment	Metronidazole	Fluconazole	Metronidazole

Whiff test: KOH yields fishy odor
KOH Prep: Shows pseudohyphae in candida
Wet mount: Motile trichomonads

Helminths

Jason Ryan, MD, MPH

Helminths

Worms

- Roundworms (nematodes)
- Flatworms
  - Tapeworms (cestodes): Ribbon-like
  - Flukes (trematodes): Look life leaves
- All have three stages
  - Eggs
  - Larvae
  - Adults

- **Helminths**
  - **Roundworms (Nematodes)**
    - Tissue
      - Dracunculus
      - Onchocerca
      - Loa Loa
      - Wuchereria
      - Toxocara
      - Diagnosis: Visualize worm (except Toxocara)
    - Intestinal
      - Enterobius
      - Ascaris
      - Trichinella
      - Strongyloides
      - Hookworms
      - Diagnosis: Stool (except Trichinella)
      - Treatment: Bendazoles or Pyrantel pamoate
  - **Tapeworms (Cestodes)**
    - Taenia
    - Diphyllobothrium
    - Echinococcus
  - **Flukes (Trematodes)**
    - Schistosoma
    - Clonorchis
    - Paragonimus

Tapeworms and Flukes:

- Diagnosis: Complex (Taenia: stool)
- Treatment: Praziquantel (exception: echinococcus)

Helminths

- Very rare in developed world
- Most cause eosinophilia
- Various modes of infection:
  - Ingestion of eggs
  - Penetration of skin

Helminths

- Many unique drugs used for therapy
- Bendazoles
  - Albendazole
  - Mebendazole
- Others:
  - Ivermectin
  - Pyrantel pamoate
  - Diethylcarbamazine
  - Praziquantel

Helminths

Things to know

- Name of organism
- Symptoms
- Mode of infection
- Diagnosis (often stool analysis)
- Treatment

Enterobius vermicularis

Pinworm

- Most common helminth infection US
- Common among children
- Eggs found in moist environments
- Child touches eggs, contaminates fingers
- Fingers touch food, mouth → ingestion of eggs
- Eggs hatch in small intestine
- Adults deposit eggs in perianal folds

Enterobius vermicularis

Pinworm

- Most infections asymptomatic
- Most common symptom: perianal itching
  - Inflammatory reaction to worms and eggs on skin
  - Occurs predominantly at night
- Diagnosis: Scotch tape test
  - Adhesive applied to perianal skin
  - Placed on glass slide
  - Eggs visualized under microscope
- Treatment:
  - Bendazoles (albendazole, mebendazole)
  - Pyrantel pamoate

Children, itchy anus, Scotch tape test

Ascaris lumbricoides

Giant roundworm

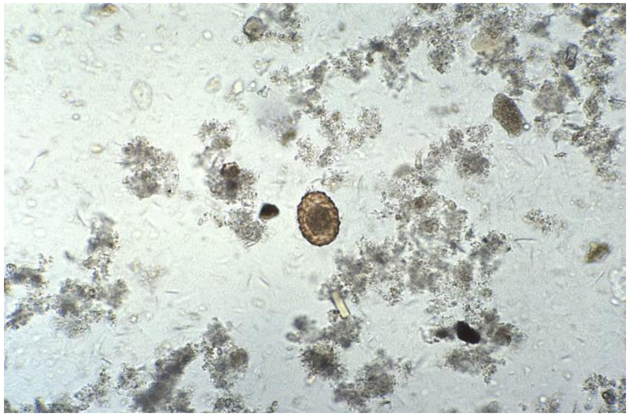
- Found in warm, tropical climates
- Common in children (vomiting worms!)
- Worms live in small intestine of infected patients
- Shed eggs in stool
- Eggs survive in environment
  - Fecal-oral transmission
- When ingested eggs hatch in small intestine
- Release larvae → penetrate intestinal wall
- Migrate via blood or lymphatics

Ascaris lumbricoides

Giant roundworm

- Most patients asymptomatic
- Intestinal symptoms
  - GI upset
  - Bowel obstruction
- Pulmonary symptoms
  - Loeffler's syndrome
  - Eosinophilic pneumonitis from worm migration to lungs
- Diagnosis: Eggs seen on stool examination
- Treatment:
  - Bendazoles (albendazole, mebendazole)
  - Pyrantel pamoate

Ascaris Egg



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Ascaris lumbricoides

Giant roundworm

- Classic case
  - Patient with recent travel
  - Abdominal pain
  - Wheezing, cough
  - Eosinophilia
  - Eggs seen on stool examination

Bowel obstruction, pneumonia, eggs in stool

Strongyloides stercoralis

- Larvae found in soil
- Penetrate skin
- Migrate via blood to lungs
  - Penetrate alveolar air sacs
- Ascend tracheobronchial tree → swallowed
- Mature into adults, burrow into duodenum/jejunum

Strongyloides stercoralis

- Skin reactions
  - Rash, often severe itching
- Pulmonary migration
  - Dry cough, throat irritation, dyspnea, wheezing, hemoptysis
- Duodenitis
  - Upper abdominal pain, diarrhea, anorexia, nausea, vomiting
- Diagnosis: Stool larvae or serology
- Treatment:
  - Albendazole
  - Ivermectin

Skin, belly pain, cough

Hookworms

Ancylostoma duodenale, Necator americanus

- Worms live in small intestine of infected patients
- Shed eggs in stool
- Eggs hatch in soil → larvae
- Larvae penetrate skin
- Migrate into blood, carried to lungs
- Ascend bronchial tree → swallowed
- Mature to adults in intestine

Hookworms

Ancylostoma duodenale, Necator americanus

- Major impact is on nutritional status
- Worms attached to intestinal mucosa
- Cause blood loss by ingesting blood
  - Facilitated by production of anticoagulants
- Daily losses of blood, iron, and albumin
- Result: Anemia, malnutrition
- Diagnosis: Stool exam for eggs
- Treatment:
  - Bendazoles (albendazole, mebendazole)
  - Pyrantel pamoate

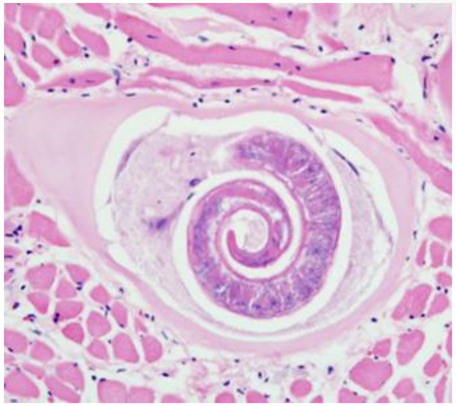
Skin, skinny, anemia

Trichinella

Trichinosis

- Cysts in undercooked meat
- Larvae invade small bowel → adults
- Migrate to striated muscles
- Symptoms: muscle weakness
- Diagnosis: serology, biopsy
- Treatment: Bendazoles

Larvae in tongue



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Meat, muscles

Intestinal Nematodes

Summary

- Ingested eggs: Enterobius, Ascaris, Trichinella (cysts)
- Skin penetration: Strongyloides, Hookworms
- Most diagnosed with stool examination
  - Exception: Pinworm (tape test)
- Most treated with bendazoles and pyrantel pamoate
  - Exception: Strongyloides (Ivermectin/albendazole)

Dracunculus medinensis

Guinea worm

- Consumption of unfiltered water
- Water contains copepods (small crustaceans)
- Copepod dies, spills larvae into intestine
- Female adults migrate to skin
- Up to a year later, worm migrates to surface of skin
- Painful papule develops
- Worm emerges → burning sensation
- Treatment: Extraction of worm slowly
  - Can take days or weeks!

Giant skin worm

Dracunculus medinensis

CDC/Public Domain

Onchocerca volvulus

River blindness

- Infection from female blackfly bite
- Deposits larvae into skin
- Mature into adults
- Adults produce offspring (microfilariae)
- Microfilariae move through tissues
  - Subcutaneous, dermal, ocular, lymph system
- Provoke a mild immune response while alive
- When they die, significant inflammatory response

Onchocerca volvulus

River blindness

- Skin symptoms
  - Generalized itching
  - Subcutaneous nodules ("onchocercoma")
  - Many other skin symptoms possible
- Eye
  - Keratitis, uveitis, blindness
- Diagnosis:
  - Skin biopsy ("skin snips")
  - Examined for microfilariae
- Treatment: Ivermectin

Itching, blindness, skin snips

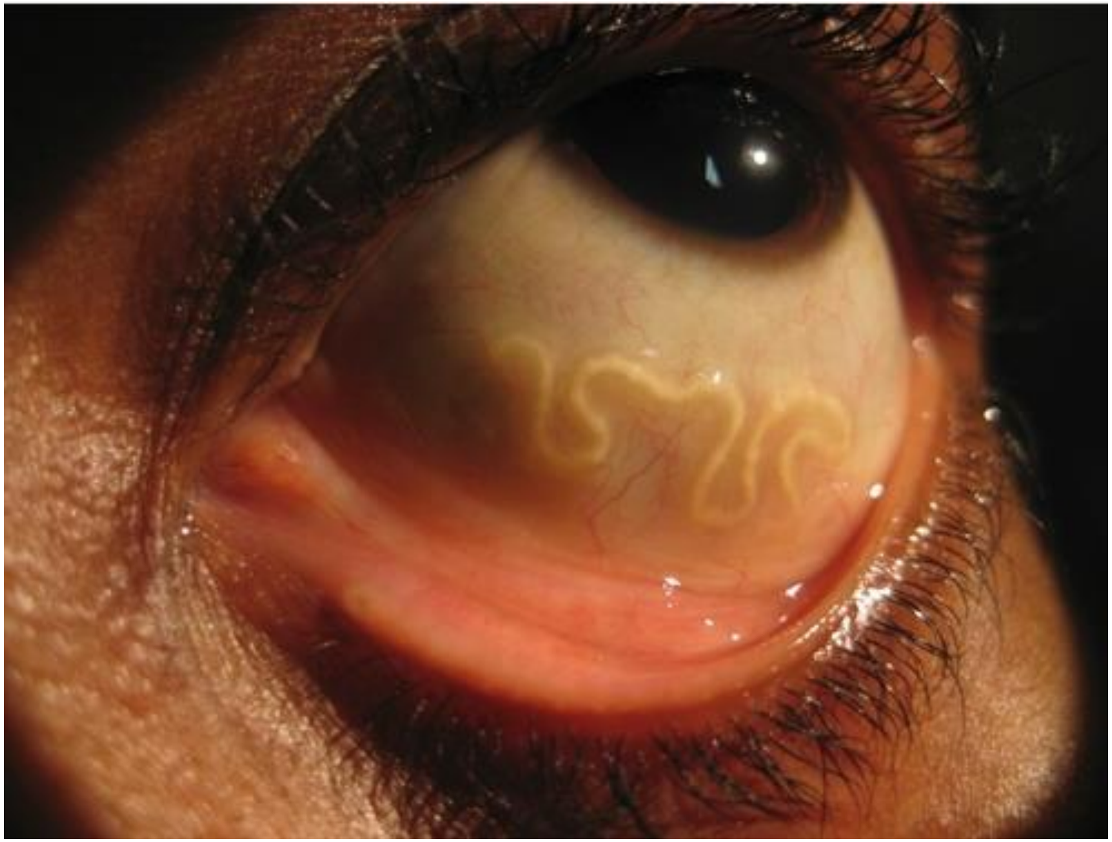
Loa Loa

Loiasis

- African eye worm
- Transmitted by biting deerflies (horse fly or deer fly)
- Fly introduces larvae to skin
- Larvae penetrate bite wound
- Mature into adult worms over months
- Adults live in the subcutaneous tissue
- Migrate to other areas, especially eye

Loa Loa

Loiasis



Lichtinger A, Caraza M, Halpert M – Am. J. Trop. Med. Hyg. (2011)
Open Access – Creative Commons

Loa Loa

Loiasis

- Most individuals asymptomatic
- Two main clinical manifestations:
  - Subcutaneous swellings (Calabar swellings)
  - Migration of worms across subconjunctiva of eye
- Worms measures 3 to 7 cm
- Can be visualized directly crossing the conjunctiva
  - Often takes 10 to 20 minutes!
- Diagnosis:
  - Visualizing adult worm: subcutaneous tissue or conjunctiva
    Blood smear: Detection of microfilariae
- Treatment: Diethylcarbamazine

Eye worm, skin swelling

Lymphatic Filariasis

Wuchereria bancrofti, Brugia malayi, Brugia timori

- Transmitted by mosquito bites
- Larvae migrate to lymphatic system
- Grow into adults over months (up to 1 year)
- Obstruct of lymphatic flow

Lymphatic Filariasis

Wuchereria bancrofti, Brugia malayi, Brugia timori

- Lymphedema/Elephantitis
  - Massive non-pitting edema
  - Hardening of tissues
  - Hyperpigmentation
- Major cause of disfigurement/disability
- Diagnosis: microfilariae seen on blood smear
- Key finding is eosinophilia
- Treatment: Diethylcarbamazine

Wikipedia/Public Domain

Elephantitis

Toxocara

Visceral larva migrans

- Not natural human parasites
  - Toxocara canis → dogs
  - Toxocara cati occurs in cats
- Disease of young children
  - Exposed to playgrounds/sandboxes contaminated by pet feces
- Hepatitis and pneumonitis
  - Larvae migrate to liver and lungs
- Key finding: eosinophilia
- Diagnosis: Serology
- Treatment: Bendazoles (albendazole, mebendazole)

Toxocara

Visceral larva migrans

- Classic case
  - Child who plays in sandbox, eats dirt
  - Mention of cat or dog exposure
  - Wheezing, dyspnea (often no history of asthma)
  - RUQ pain, hepatomegaly

Cats, dogs, kids, liver, lungs

Taenia solium

Taeniasis

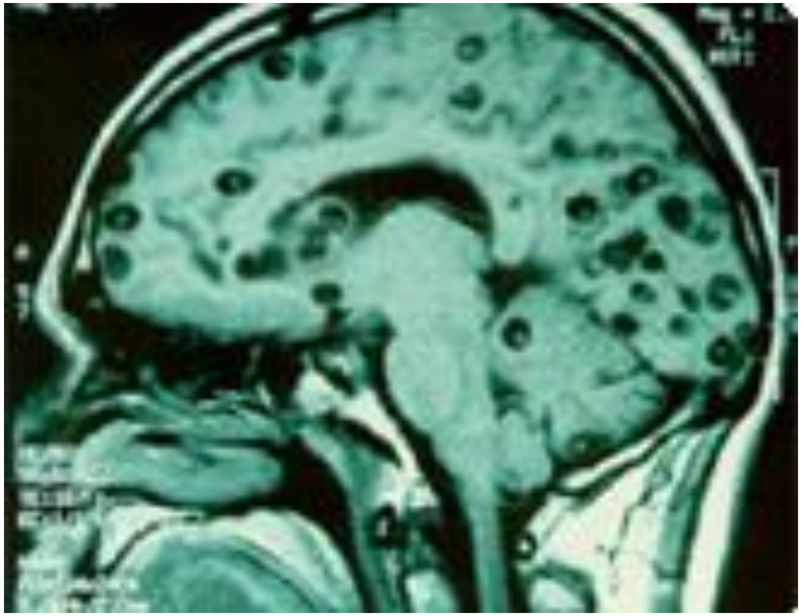
- Larval form (oncosphere) in raw, undercooked meat
- Ingested → matures into intestinal tapeworm
- Most infections asymptomatic
- Sometimes mild intestinal symptoms
  - Nausea, anorexia, epigastric pain
- Eosinophilia occurs
- Diagnosis:
  - Eggs or worms segments (proglottids) in stool
- Treatment: Praziquantel

Meat tapeworm in gut

Cysticercosis

- Caused by ***eggs*** of *Taenia solium*
- Not from undercooked pork
- Tapeworm carriers can shed eggs in stool
- Fecal-oral ingestion of eggs that hatch in intestine
  - Often another member in household with carrier
- Invade the bowel wall and disseminate
  - Brain, muscles, liver
- Over weeks, tissue forms (cysticerci) develop
  - Membranous walls filled with fluid
- Cysts in brain → neurocysticercosis
- Major cause of seizures in underdeveloped countries

Cysticercosis



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Eggs, brain cysts, seizures

Boards&Beyond STUDY SMARTER

Diphyllobothrium latum

- Tapeworm similar to Taenia solium
- Transmission from eating infected fish
- Classic unique feature: Anemia
  - D. latum has affinity for vitamin B12
  - Competes with host for vitamin
- Macrocytic, megaloblastic anemia
- Hypersegmented PMNs
- Neurologic symptoms
  - Paresthesias, subacute combined degeneration

B12 deficiency

Echinococcus granulosus

- Dogs are definitive host
- Eggs shed in dog stool
- Fecal-oral ingestion of eggs
- Eggs hatch, penetrate intestinal mucosa
- Enter blood/lymphatic system

Echinococcus granulosus

- Main clinical problem is liver cysts
- Can become massive (>10cm!)
- Hepatomegaly, RUQ pain
- Cysts may rupture → fever
    - May cause acute hypersensitivity reactions
    - Sometimes anaphylaxis
- Treatment: surgery
    - Pre-inject with agent to kill parasite
    - Hypertonic saline, ethanol
    - Adjunctive therapy with albendazole

Giant liver cysts

Schistosoma

Schistosomiasis

- Worms live in snails
  - Infectious form (cercariae)
  - Emerge from the snail, contaminate water
  - Cercariae penetrate skin of humans
- Over weeks, worms migrate through tissue and develop into adult worms inside blood vessels
- Mature worms produce eggs in bladder, intestine, spleen, liver
- Inflammation/scarring over years

Schistosoma

Schistosomiasis

- Acute infection
  - Swimmer's itch
  - Hypersensitivity (fever, urticaria and angioedema)

Schistosoma

Schistosomiasis

- Chronic infection: multisystem
  - GI, liver, spleen, GU, lungs, CNS
- GI
  - Abdominal pain, blood in stool
- GU:
  - Hematuria
  - Squamous cell carcinoma
- Liver/Spleen
  - Hepatosplenomegaly, Portal hypertension
- Granulomas
- Treatment: Praziquantel

Snails, skin, squamous cell, granulomas

Clonorchis sinensis

Chinese liver fluke

- Korea, Japan, Taiwan, and Southern China
- Infection from eating contaminated fish
  - Eggs hatch in snails, develop in cercariae
  - Cercariae released from snails to water
  - Penetrate flesh of fish
  - Humans eat fish → illness
- Flukes ascend and reside in biliary tract

Clonorchis sinensis

Chinese liver fluke

- Biliary tract inflammation and obstruction
  - Obstructive jaundice
  - Pancreatitis
- Two special complications:
  - Pigmented (bilirubin) gallstones
  - Cholangiocarcinoma
- Praziquantel

Fish in the gall bladder

Paragonimus westermani

- Raw or undercooked crayfish or crabs
- Fluke migrates to lungs
- Recurrent hemoptysis
  - Chocolate colored sputum (blood, inflammatory cells, eggs)
- Secondary bacterial infections common
- Diagnosis: Eggs in sputum or lavage
- Treatment: Praziquantel

Coughing crabs

Virus Structure

Jason Ryan, MD, MPH

Viruses

- Nucleic acids (either DNA or RNA)
- Surrounded by protein called a capsid
- Sometimes surrounded by envelope
- No metabolic activity

Virus Structure

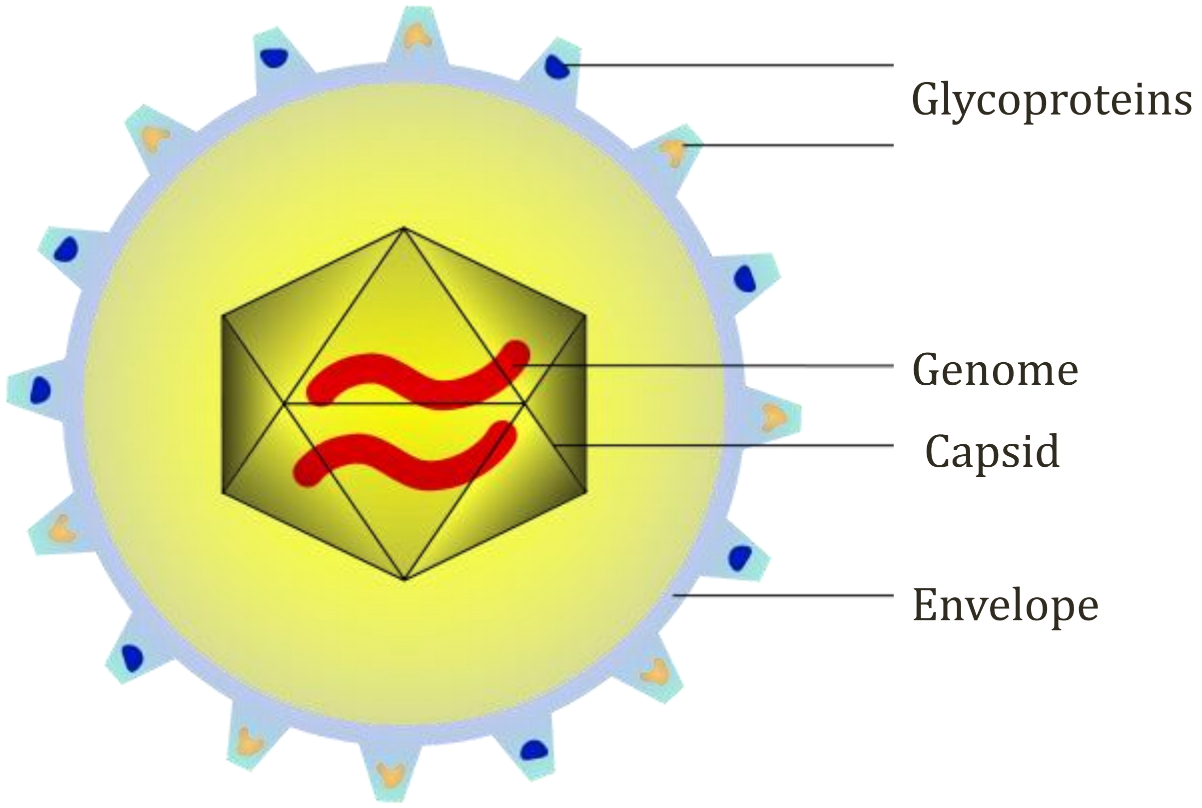
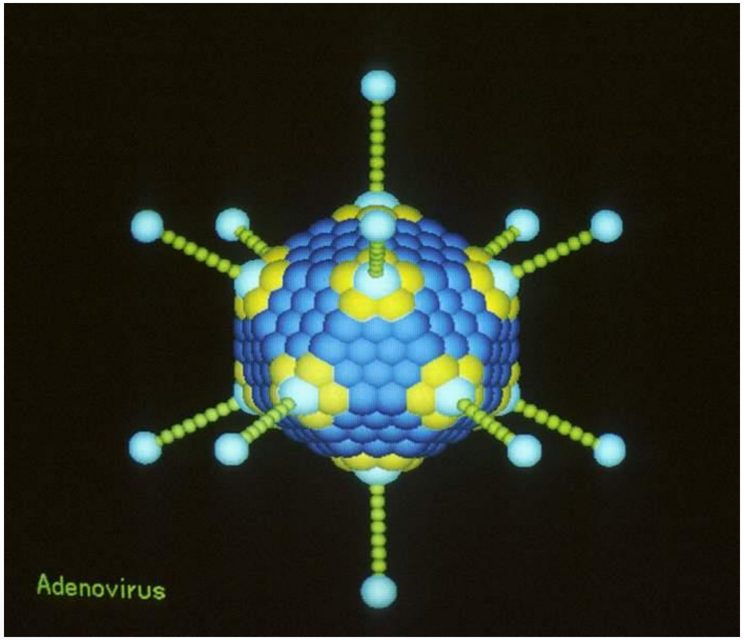


Image courtesy of Emmanuel Boutet/Wikipedia

Capsids

- Most capsids have one of two common shapes

Icosahedral



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Helical

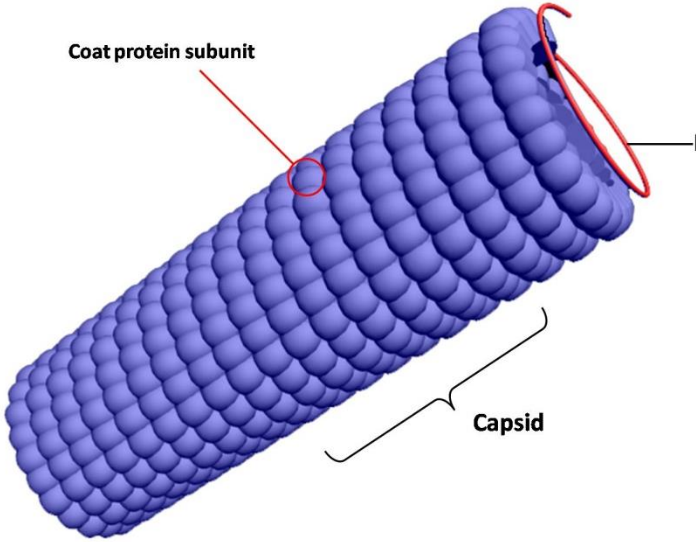

Image courtesy of Arionfx/Wikipedia

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Envelopes

- Viruses are "naked" or "enveloped"
- Envelope: lipid membrane acquired from host cell during assembly of the virus
  - Usually host cell plasma membrane
  - Sometimes nuclear membrane, endoplasmic reticulum
- Viral glycoproteins often embedded in membrane
  - Used for binding to host cells
  - Also antigens for immune system
- All naked viruses have icosahedral capsids
- Enveloped have icosahedral or helical

Envelopes

Enveloped	Naked
• Hepatitis B	• Adenovirus
• Herpes	• Rotavirus
• HIV	• Rhinovirus
	• Hepatitis A/E

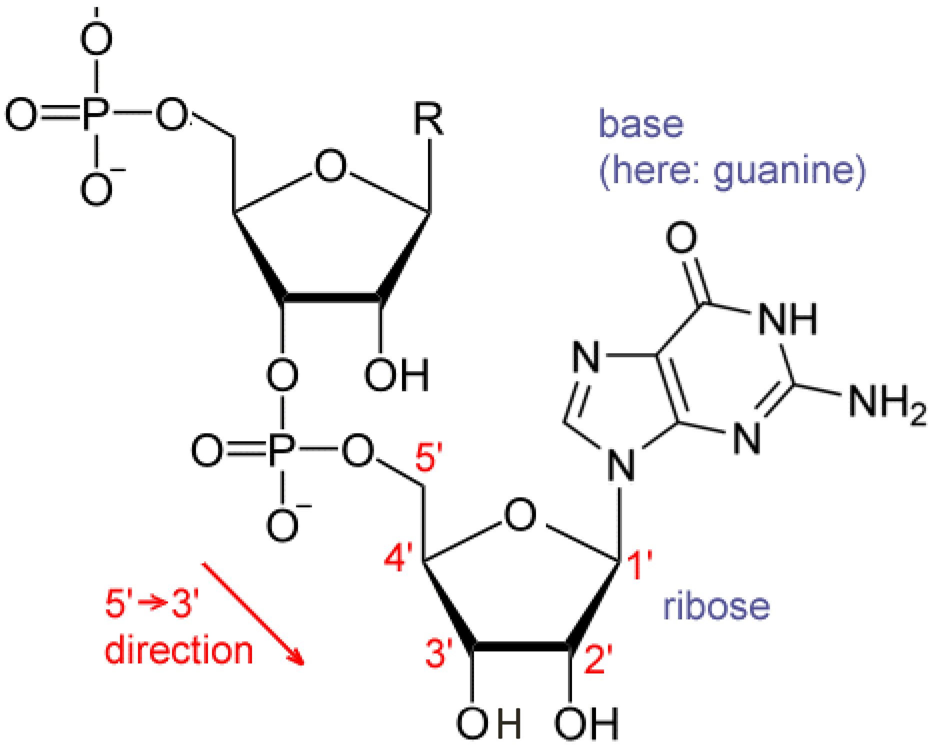
RNA Virus Genomes

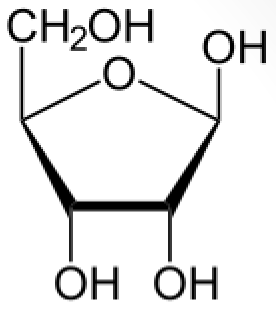
- Most are single stranded and linear
  - Exception: Reoviruses (ds RNA)
  - Exception: Retroviruses (single stands x 2)
  - Circular: Bunyaviruses, arenaviruses, delta virus (BAD)
- Most replicate in cytoplasm
  - Exception: Influenza, Retroviruses
  - Replicate in nucleus

RNA Virus Polarity

- Can be (+) sense or (-) sense (i.e. polarity)
- Positive stranded RNA
  - Structurally similar to mRNA
  - In cytoplasm, used for protein synthesis immediately
- Negative stranded RNA
  - Must be converted to (+) RNA first
  - Can then be used as template for protein
  - Virus must carry enzyme to convert (-) to (+) RNA

RNA Orientation





Ribose
(Wikipedia/Public Domain)

RNA Bases: Uracil, Guanine, Adenine, Cytosine

Narayanese/Wikipedia

RNA Virus Polarity

$C \rightarrow G$
$G \rightarrow C$
$A \rightarrow U$
$U \rightarrow A$

5’ CGAUCCGAU 3’ $\longrightarrow$ Proteins

3’ GCUAGGCUA 5’ $\not\longrightarrow$ Proteins

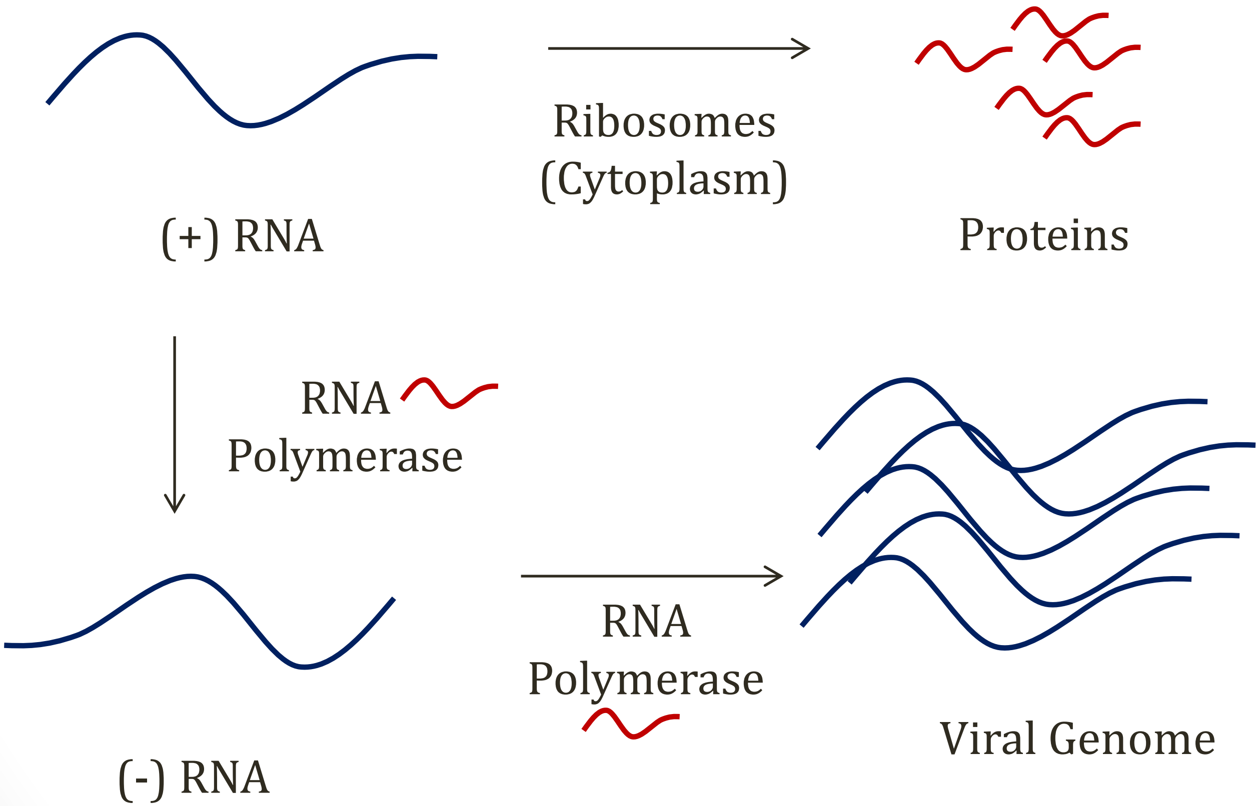
$\downarrow$ *RNA Polymerase*

5’ CGAUCCGAU 3’ $\longrightarrow$ Proteins

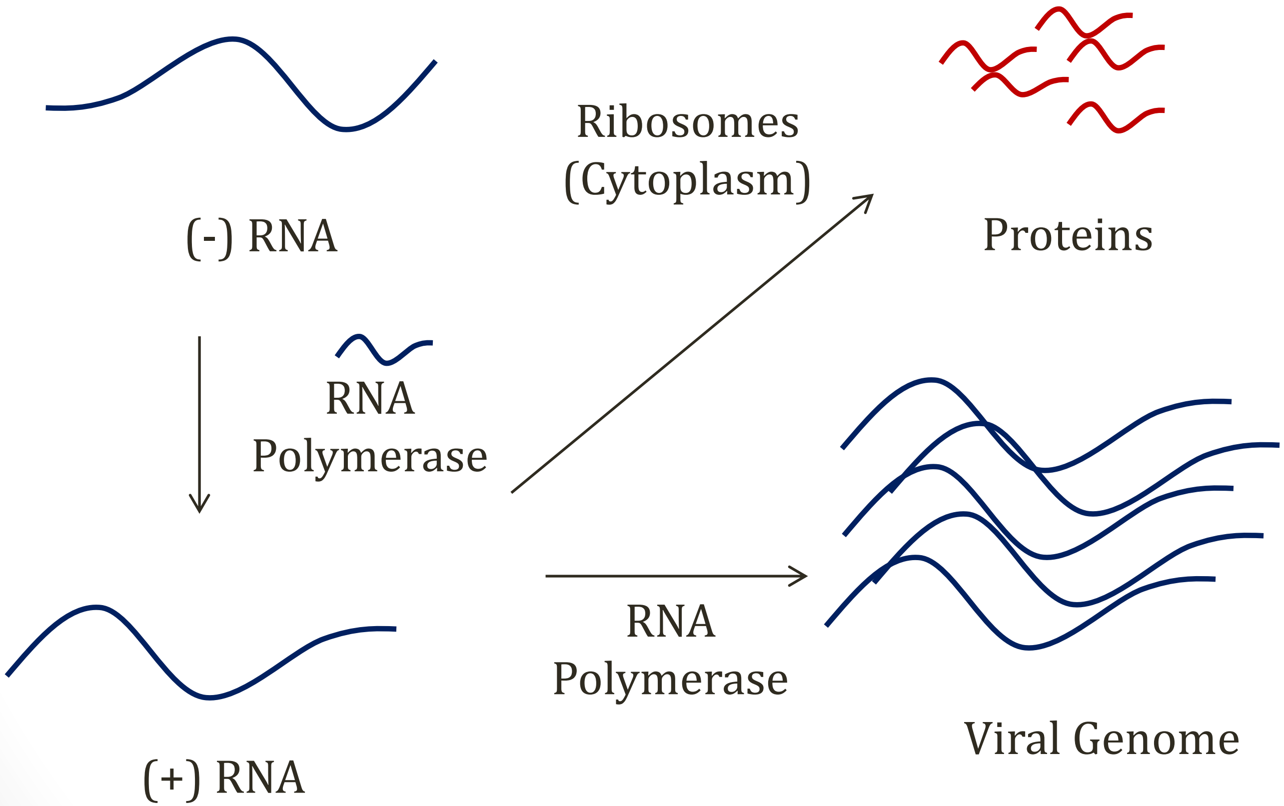
RNA Polymerase

- Human cells make RNA from DNA
  - Transcription
  - Enzyme: “DNA-dependent RNA polymerase”
- Viruses make RNA from RNA
  - Must synthesize their own enzyme
  - “RNA-dependent RNA polymerase”

RNA Virus Replication

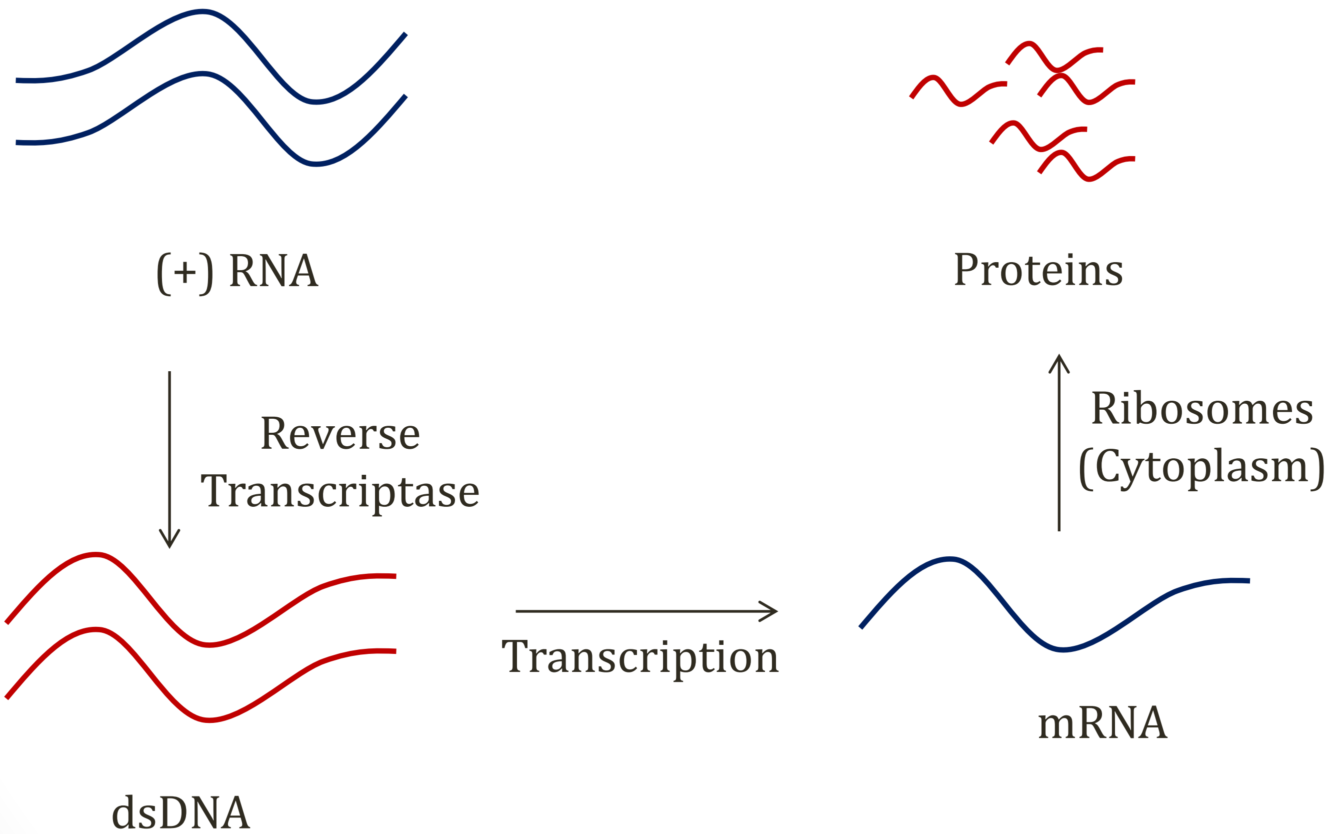


RNA Virus Replication



Retroviruses (RNA)

HIV, HTLV



DNA Virus Genomes

- Circular or linear DNA
- Most have double stranded DNA
  - Except **parvovirus** which is single stranded

Viral Genome Infectivity

- (+) RNA genomes: Infectious by themselves
  - Genetic material begins producing new proteins/nucleic acids on entry into cell
- dsDNA genomes :Infectious by themselves
- (-) RNA: NOT infectious by themselves
  - Require RNA-dependent RNA polymerase to reproduce

Segmented Genomes

- Many RNA viruses are segmented
- Multiple molecules of RNA ("segments") in virus
- Allows for re-assortment of RNA
  - Two viruses co-infect same cell
  - Mixing of segments into new virus
- Most important example is influenza virus
- BOAR
  - Bunyaviruses (California, Congo, Hanta)
  - Orthomyxovirus (Influenza)
  - Arenavirus (LCMV, Lassa)
  - Reovirus (Rotavirus, Coltivirus)

DNA Viruses

- DNA Viruses
  - Naked
    - Parvo → B19
    - Adeno
    - Papilloma → HPV
    - Polyoma → JC, BK
  - Enveloped
    - Hepadna → HBV
    - Herpes → HSV, EBV CMV, VZV, HHV
    - Pox → Small, Cow, Mol. Contagiosum

All DNA viruses (+) have icosahedral capsid except Pox
All DNA viruses replicate in nucleus except Pox

RNA Viruses

- RNA Viruses
  - (+) — Icosahedral
    - Naked →
      - Calici → Norwalk
      - Hepe → HEV
      - Reo → Rota, Colti
      - Picorna → PERCH (Polio, Echo, Rhino, Coxsacki, HAV)
    - Enveloped →
      - Corona* → Corona, SARS
      - Retro → HIV, HTLV
      - Flavi → HCV, Yellow, Dengue, StL, WNle
      - Toga → Rubella, EEEV, WEE
  - (-) — Helical
    - Enveloped →
      - Bunya → California, Congo,Hanta
      - Orthomyxo → Influenza
      - Arena → LCMV, Lassa
      - Delta → HDV
      - Paramyxo → Paraflu, RSV, Msls, Mumps
      - Rhabdo → Rabies
      - Filo → Ebola/Marburg

All ss except Reoviruses (ds)
All replicate in cytoplasm except influenza and retroviruses
All (+) are icosahedral except Coronavirus
All linear except BAD
All non-segmented except BOAR

Viral Vaccines

- Live, attenuated vaccines
  - Inactive strains
  - Rarely can produce clinical disease
  - Cannot give to immunocompromised
  - Long lasting protection (no boosters)
  - Smallpox, yellow fever, chickenpox (VZV)
  - Sabin's polio virus, MMR, Intranasal influenza
- Killed virus vaccines
  - No risk of infection
  - Less immune response (boosters often required)
  - Rabies , Injected influenza, Salk Polio, HAV

Viral Vaccines

- Recombinant vaccines
  - Vaccine protein gene inserted into a virus or cells in culture
  - When carrier virus or cell grows, vaccine protein created
  - Immune system will recognize the expressed protein
  - Hepatitis B vaccine: Recombinant HbsAg
  - HPV: Recombinant proteins types 6, 11 , 16, and 18

DNA Viruses

Jason Ryan, MD, MPH

DNA Viruses

DNA Viruses

- Naked → Parvo, Adeno, Papilloma, Polyoma
  - Parvo → B19
  - Adeno
  - Papilloma → HPV
  - Polyoma → JC, BK
- Enveloped → Hepadna, Herpes, Pox
  - Hepadna → HBV
  - Herpes → HSV, EBV, CMV, VZV, HHV
  - Pox → Small, Cow, Mol. Contagiosum

All DNA viruses (+) have icosahedral capsid except Pox
All DNA viruses replicate in nucleus except Pox
All DNA viruses are ds except Parvovirus (ss)
All DNA viruses are linear except middle 3

Parvovirus

- Very small virus
- Non-enveloped
- Single-stranded (-) DNA virus (only one!)
- B19 is predominant parvovirus in humans
- Four important syndromes
  - Aplastic crisis in sickle cell anemia
  - Hydrops fetalis
  - Fifth disease in children
  - Arthritis in adults

Aplastic Crisis

- B19 replicates in RBC progenitor cells
  - Only replicates in S phase (no S phase in mature RBCs)
  - Causes "S phase arrest"
- Bone marrow and blood → ↓erythropoiesis
- Healthy patients:
  - RBC production returns 10 to 14 days; mild/no anemia
- Sickle cell patients
  - Increased RBC turnover
  - Lack of erythropoiesis leads to severe anemia
  - Pallor, weakness, and lethargy

Aplastic Crisis

- Watch for a sickle cell patient with LOW retic count
  - Normal reticulocyte count 0.5 to 1.5%
  - Should be high in anemia
  - If low, think B19
- Symptoms of anemia: fatigue, dyspnea
- Treatment: Transfusions
- Infection resolves days → weeks

B19 in Pregnancy

- Fetus especially vulnerable to B19
  - Shortened RBC half-life
  - Expanding RBC volume
  - Immature immune system
- B19 infection in pregnancy: miscarriage, fetal death
- Hydrops fetalis
  - Fluid accumulation in fetus (ascites, pleural, etc.)
  - Diagnosed on ultrasound
  - "Immune hydrops" from Rh mismatch
  - Many non-immune causes including B19

Fifth Disease

Erythema infectiosum; slapped cheek disease

- Mild fever, rash in children
- Outbreaks among school aged children
- Fever, runny nose (due to viremia)
- Followed by rash (few days later)
    - Probably immune related
    - Viral infection has usually resolved
- Cheeks look like they have been slapped
- Face rash often followed later by rash on trunk/limbs
- No diagnostic test or treatment (self limited)
- Adults may catch this: mild arthralgia/arthritis

Arthritis

- B19 can cause acute arthritis
- Often in adults, usually women
- About 75% will have rash
  - Various rashes
  - Usually not slapped cheeks
- Symmetric, most frequently in small joints
  - Hands, wrists, knees, feet
- Joint stiffness is common (can mimic RA)
- Diagnosis: B19 antibodies in plasma
- Usually resolves in few weeks

Adenovirus

- Non-enveloped, icosahedral
- Double stranded DNA virus
- Important syndromes
  - Pharyngitis, Pneumonia
  - Pink eye (conjunctivitis)
  - Hemorrhagic cystitis
- Very stable - survive on surfaces
- Transmission:
  - Aerosol droplets
  - Fecal-oral
  - Contact with contaminated surfaces

Image courtesy of Joyhill09/Wikipedia

Acute Hemorrhagic Cystitis

- Cause by adenovirus
- Occurs in children
  - Watch for outbreaks at day care centers/schools
- Hematuria, sometimes gross
- Sometimes dysuria
- Usually no fever, other symptoms
- Self-limited

Papillomavirus

- Non-enveloped
- Double stranded, circular DNA virus
- Multiple subtypes: 1,2, 6, 11, 16, 18
- Clinical disease (depends on subtype):
  - Cutaneous warts
  - Genital warts
  - Cancer

Cutaneous Warts

- Caused by papillomavirus (1, 2, 3, 4, 7, 10)
- Treatment: salicylic acid or liquid nitrogen

Steven Fruitsmaak/Wikipedia

Anogenital Warts

Condylomata acuminata

- STD caused by papillomavirus (6, 11)
- Soft, tan, cauliflower-like lesions
- "Verrucous" = warts
- Penis, vulva, perianal area (rectal bleeding)
- Treatment:
  - Chemical agents
  - Surgical therapy
- Does not lead to cancer

SOA-AIDS Amsterdam/Wikipedia

HPV and Cancer

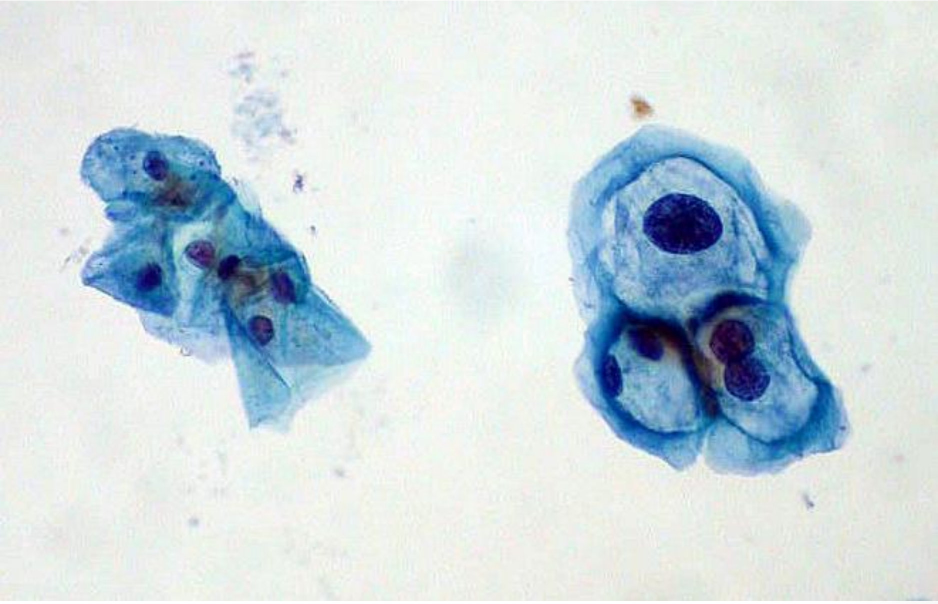
- Persistent infection over years can lead to cancer
- Malignancies associated with HPV infection:
  - Cervical
  - Anal, Penile
  - Oropharyngeal squamous cell cancers (mouth, throat)
- Usually types 16 and 18
  - Responsible for about 70 percent cases
- All more common in HIV/AIDS

Cervical Cancer

- High prevalence HPV among sexually active women
  - Most will clear infection
  - Some will have infection persist
- Vaccine available (capsid proteins)
  - Some target types 16/18
  - Others also target 11/6 (genital warts)
- Screening done with Pap smear

Koilocytes

- Seen on Pap smear
- Epithelial cell infected by HPV
- Large, darkened nuclei
- Perinuclear haloes



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Polyomavirus

- Non-enveloped
- Double stranded DNA virus
- Circular
- Disease in immunocompromised patients
- JC Virus: PML
  - Progressive multifocal leukoencephalopathy
  - CNS disease in HIV patients
- BK Virus
  - Classic disease in post-kidney transplant patients
  - Slowly progressive rise in creatinine

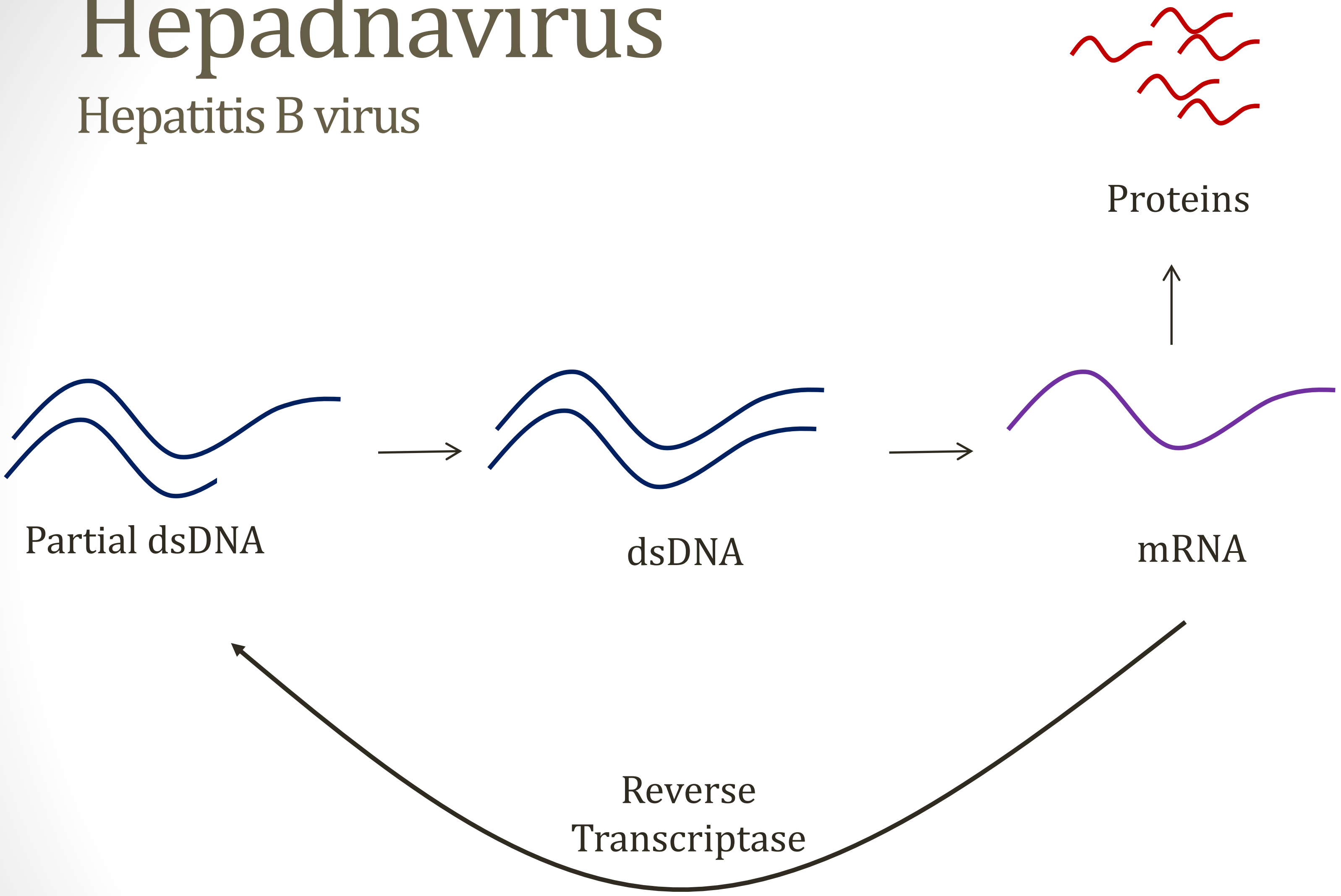
Hepadnavirus

Hepatitis B virus

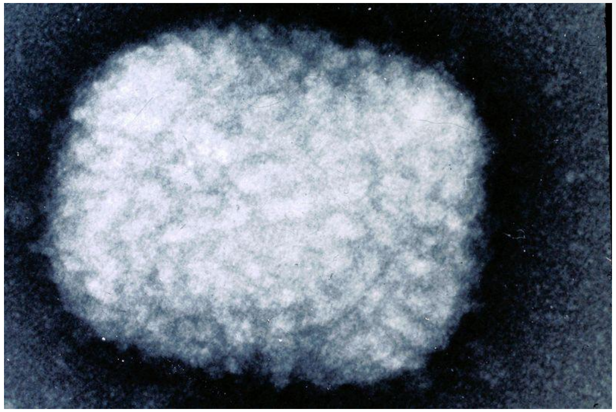
- Enveloped, Circular
- #1: Partially double stranded DNA virus
  - Genome enters hepatocytes → nucleus
  - DNA becomes fully double stranded
  - mRNA synthesized → cytoplasm
- #2: Reverse transcriptase synthesized
  - Viral mRNA → viral DNA
  - Packaged in capsid
- #3: Envelope from endoplasmic reticulum

Hepadnavirus

Hepatitis B virus



Poxvirus



Dr. Graham Beards/Wikipedia

- Enveloped
- Double stranded DNA virus
- Linear
- Capsid not icosahedral or helical
  - Complex shape: either an oval or brick-shape
- Large virus
- Replicates in cytoplasm (not nucleus!)
- Virus contains DNA-dependent RNA polymerase
- Makes RNA in cytoplasm
- Synthesis of proteins for replication

Poxvirus

- Relevant diseases:
  - Smallpox
  - Molluscum contagiosum

Smallpox

Variola virus

- Initially fevers, headache, malaise
- Skin rash erupts, goes through phases
- Macules → papules → raised pustules
- Eradicated by vaccination 1970s
- Concern for bioterrorism
  - Virus maintained US/Russian labs
  - Concern for release
  - Possible hidden stockpiles

CDC/Public Domain

Cowpox

Cowpox virus

- Causes pustules on cows
- Milkmaids often got small blisters on their hands
- Edward Jenner inoculated a boy with cowpox (1796)
- Then exposed him to smallpox → no infection

Vaccinia

Pox Virus

- DNA virus in the pox family
- Causes mild skin reaction
- Used to vaccinate against smallpox

Molluscum Contagiosum

Molluscum Contagiosum Virus

- Member of poxvirus family
- Skin infection common in children
- Spread by direct contact
- Spread by scratching (autoinfection; virus in lesions)
- “Flesh-colored dome” lesions
- Central dimple
- Sometimes itchy
- Usually self-limited
- Resolves weeks to months

E van Herk/Wikipedia

Herpes Viruses

Jason Ryan, MD, MPH

DNA Viruses

- DNA Viruses
  - Naked →
    - Parvo → B19
    - Adeno
    - Papilloma → HPV
    - Polyoma → JC, BK
  - Enveloped →
    - Hepadna → HBV
    - Herpes → HSV, EBV, CMV, VZV, HHV
    - Pox → Small, Cow, Mol. Contagiosum

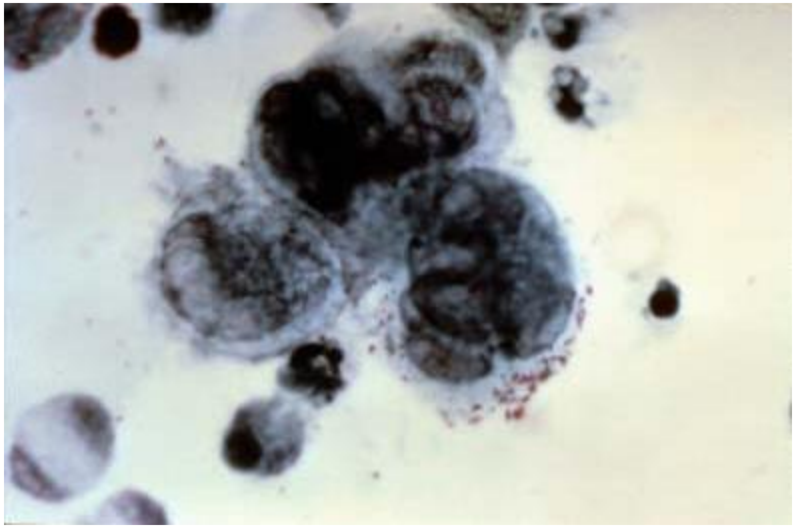
All DNA viruses (+) have icosahedral capsid except Pox
All DNA viruses replicate in nucleus except Pox

Herpes Viruses

- All enveloped, double stranded and linear
- All have icosahedral core
- Large viruses (only Pox is bigger)
- Replicate in nucleus
- Envelope from nucleus of cell (no cell membrane)
- Often cause latent infection
  - Acute disease followed by asymptomatic period
  - Virus may reactivate later

Herpes Viruses

- Four herpes viruses lead to giant cell formation
  - HSV1, HSV2, VZV, CMV
- Can be seen in Tzanck smear (HSV test)



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Herpes Viruses

- Many clinically important infections
  - Oral/genital herpes
  - Mono (EBV)
  - Chickenpox/Shingles (VZV)
  - Roseola
  - Kaposi Sarcoma
  - CMV infections

HSV1, HSV2, VZV

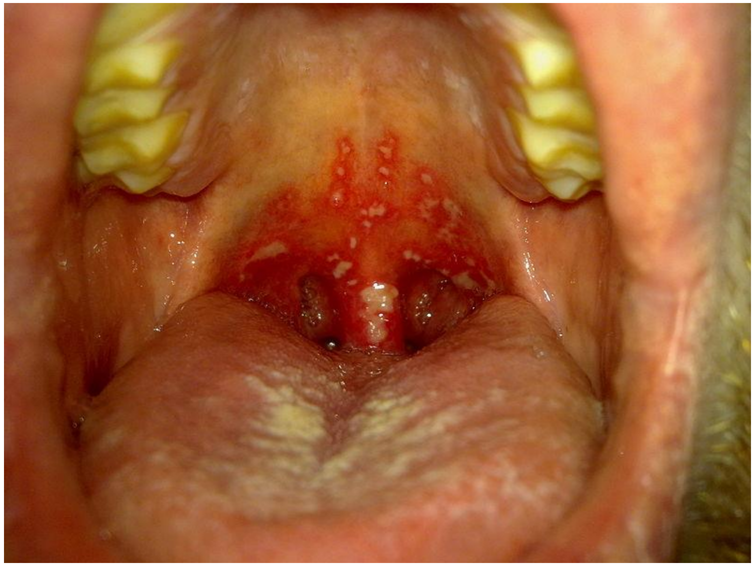
- HSV-1: Oral herpes, other infections
- HSV-2: Genital herpes, neonatal herpes, meningitis
- VZV: Chicken pox, Shingles
- Many similarities
  - Primary infection phase
  - Lay dormant in nerve ganglia
  - Can reactivate
  - Treatment: acyclovir, valacyclovir, famciclovir

HSV1

- Favors oral mucosa
- Transmitted in saliva
- Many primary infections asymptomatic
- Common initial infection: Gingivostomatitis
  - Severe sore throat
  - Painful vesicles on throat, pharynx
- Once infected, virus lives in latent state
  - Nerve cell bodies in ganglion neurons
  - Often trigeminal nerve ganglia
- Reactivation: Herpes labialis

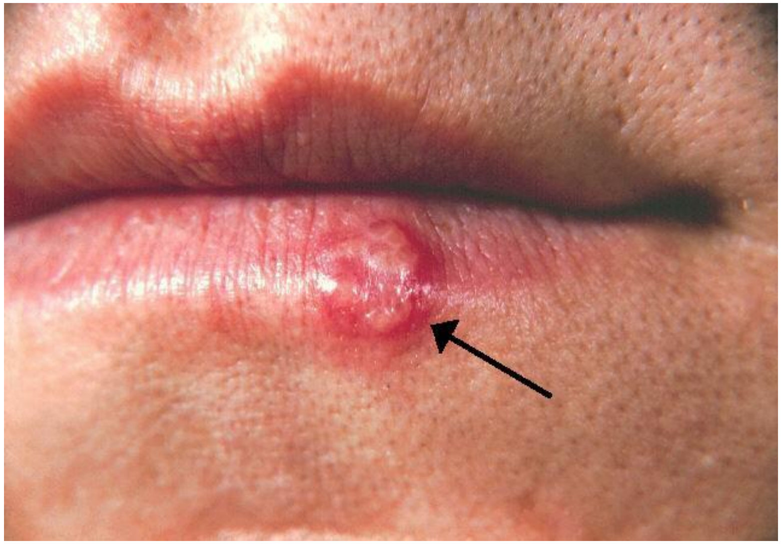
HSV1

Gingivostomatitis



Klaus D. Peter, Gummersbach, Germany/Wikipedia

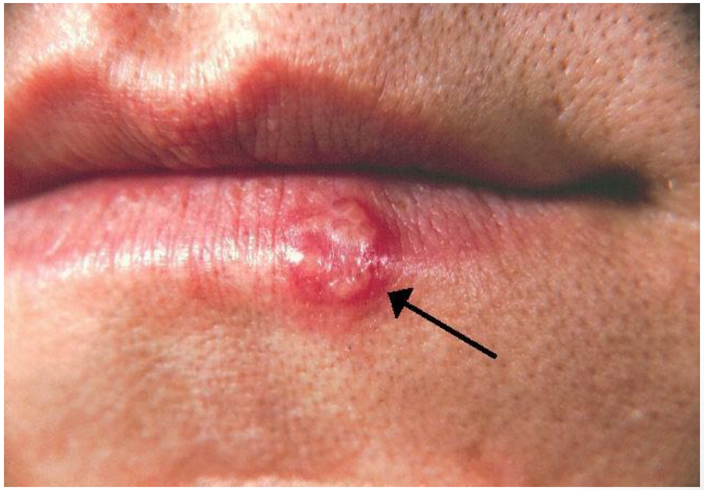
Herpes Labialis



CDC/Public Domain

Cold Sores

- Oral herpes often called "cold sores"
- Occur at vermillion border (edge of lips)
- Don't confuse with aphthous ulcers (canker sores)
  - Inner surfaces of lips, buccal mucosa
  - Not proceeded by vesicles
  - Not causes by infection
  - Immune related



CDC/Public Domain

HSV1

Other Infections

- Herpetic whitlow
  - Inoculation of virus into skin break in finger
  - Painful lesion on fingertip
- Keratoconjunctivitis
  - Infection of cornea/conjunctiva
  - Pain, redness, discharge
- Encephalitis (temporal lobes)

James Heilman, MD/Wikipedia

HSV2

- Favors genital mucosa
- Sexually transmitted
- Initial infection can be asymptomatic
- Classic symptoms: painful ulcers
- Virus enters latent phase in lumbar-sacral ganglia
- Recurrent eruptions of vesicles/ulcers
  - For frequent recurrences, suppressive Rx (acyclovir)
- Also can cause meningitis

Congenital Herpes

HSV2

- Newborn infection from infected mothers
- Serious infection more common when mother has primary infection
  - More virus replication
  - Fewer maternal antibodies
- Vesicular lesions on skin, eyes, mouth
- Can progress to CNS disease/encephalitis
- Seizures, poor feeding
- No congenital defects

Varicella Zoster

VZV

- Spread through air from infected persons
- Primary infection: Chicken pox
  - Highly contagious
  - Fever, sore throat
  - Diffuse (face, trunk, limbs) vesicular rash – very itchy
  - Classic progression: macules → papules → vesicles
  - Different stages in different parts of body
  - Eventually lesions crust, fall off
- Rare complications (often adults):
  - Encephalitis
  - Pneumonia

Varicella Zoster

VZV

- Reactivation of VZV: Herpes Zoster
- Virus will lay dormant in dorsal root ganglia
- Reactivated lesions classically follow dermatome
- Do not cross midline

Image courtesy of Fisle/Wikipedia

Varicella Zoster

VZV

- Pre-eruptive phase (1-10 days)
  - Sensory phenomena along dermatomes
  - Pain; less commonly itching or paresthesias
  - Other (rare) symptoms: malaise, myalgia, HA, photophobia
- Eruptive phase
  - Rash with pain
  - Most commonly a thoracic dermatome
  - Lymphadenopathy may be present

Post-Herpetic Neuralgia

- Can occur following resolution of zoster infection
- Constant or intermittent “stabbing” pain
- May last for months

Varicella Zoster
VZV

- Age is most important risk factor
  - Rare <50 years old
- Immune compromise
  - Transplant patients
  - Immunosuppressive drugs
- Special risk group: Inflammatory bowel disease

Varicella Zoster

VZV

- Rare complications:
  - Ophthalmic zoster (blindness)
  - Encephalitis
- Treatment:
  - Often supportive care only
  - Rarely steroids and acyclovir drugs

Diagnosis
HSV1, HSV2, VZV

- Modern tests of choice:
  - PCR (especially CSF for encephalitis)
  - Viral culture (1 to 3 days)
  - Serology (primary infection)
- Tzanck Smear
  - Used to diagnose HSV1, HSV2, or VZV
  - Microscopic exam of scraped ulcer
  - Stained with Giemsa or Wright stain
  - Positive if multinucleated giant cells seen
- Biopsy of infected tissue
  - Can see intranuclear inclusions
  - "Cowdry A inclusions"

EBV

- Causes mononucleosis ("mono")
- Spread by direct contact, saliva ("kissing disease")
- Virus infects and transforms B cells

EBV

- Envelope gp350/220 binds B-cell receptor CD21
  - Receptor for C3d fragment of complement
  - Also called C3d receptor, EBV receptor, CR2

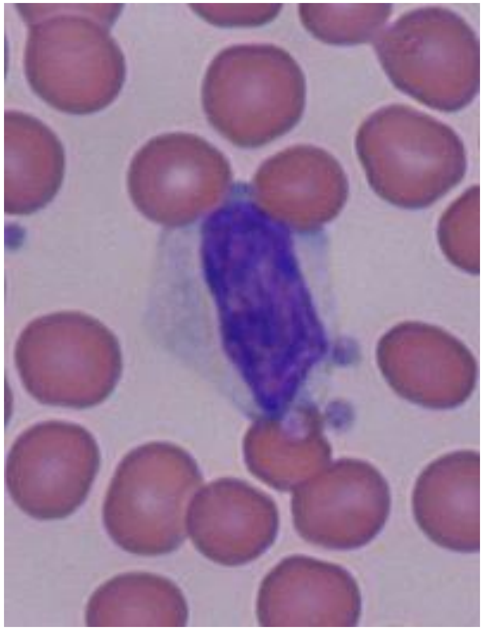
C3 → C3b → C3d

Infectious Mononucleosis

- Classic presentation
  - Age 15-20 (college student)
  - Fever
  - Hepatosplenomegaly (splenic rupture)
  - Pharyngitis
  - Posterior cervical lymphadenopathy
  - Atypical lymphocytes (T cells)
- No specific treatment
- Most symptoms resolve weeks
- Fatigue may last months

Atypical Lymphocyte

- Hallmark of infectious mononucleosis
- Majority are CD8+ T cells



Bobjgalindo/Wikipedia

Infectious Mononucleosis

Diagnosis

- Suggested by symptoms, lymphocytosis, atypical lymphocytes
- Heterophile antibodies ("Mono spot")
  - Heterophile antibodies agglutinate sheep or horse RBCs
  - Lab kits used
  - Sample of patient's blood (often finger stick)
  - Color change if heterophile antibodies present in plasma
  - Quick, highly specific
  - False negatives possible
- EBV-specific antibodies
  - Done when mono spot negative

EBV Extras

- Amoxicillin rash
  - Amoxicillin given to mono patient for sore throat
  - Diffuse maculopapular rash
  - Mechanism not understood
- VDRL false positive
  - Common cause false positive VRDL
  - Don't confuse with syphilis
- After primary infection can reactivate later
  - Reactivation common in new HIV/AIDS patients

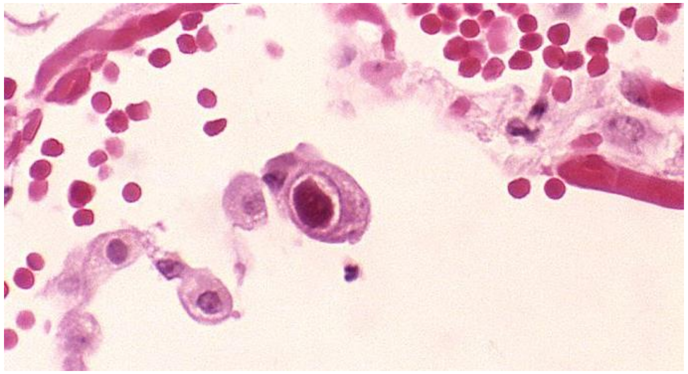
EBV

Other diseases

- Infection associated with many cancers
- Lymphomas
  - Burkitt, Hodgkin lymphoma, T-cell
- Nasopharyngeal carcinoma (especially China)
- Tumors in HIV patients
  - Non-Hodgkin lymphoma, Burkitt, CNS lymphoma
- Oral hairy leukoplakia
  - White plaques on tongue, cannot be scraped off
  - Classic finding in HIV patients with low CD4 count

Cytomegalovirus
CMV

- Ubiquitous virus
- Spread in multiple ways:
  - Sexually transmission
  - Direct contact (family, day care)
  - Blood or tissue exposure
  - Perinatal (in utero, during birth)
- Infected cells (biopsy): Owl's Eye nuclei
  - Large, dark inclusions from CMV infection
  - Perinuclear halo
- Can become latent in monocytes, marrow cells
- Treatments: Ganciclovir, Foscarnet, Cidofovir



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Dr. Edwin Ewing, Jr., CDC

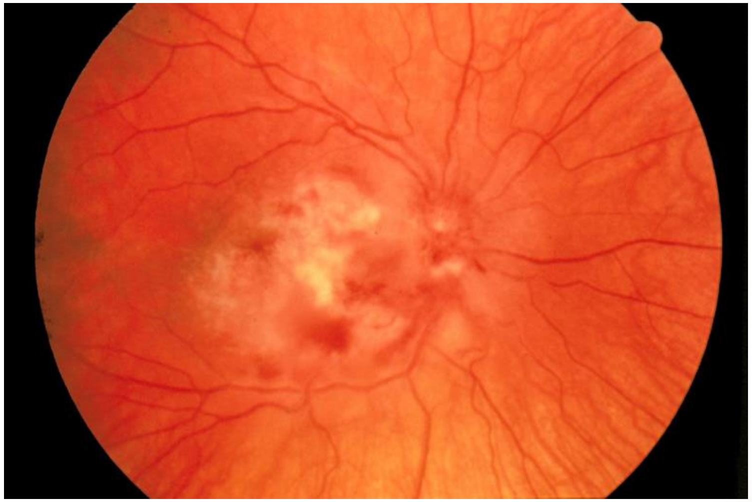
Cytomegalovirus

Infections

- Mostly affects immunocompromised
- Exception: CMV Mononucleosis
  - Similar to EBV infection
  - Monospot will be negative
  - Less lymphadenopathy, splenomegaly

Cytomegalovirus
Immunocompromised infections

- HIV, Transplant patients
- Pneumonia
  - Common after lung transplant
- Retinitis
  - Retinal edema/necrosis
  - Floaters, ↓vision
  - HIV: Low CD4 (50-100)



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Congenital CMV

- TORCH Infection
- Most infected newborns are asymptomatic
  - Some without symptoms will develop progressive hearing loss
- Potential findings
  - Small for gestational age, microcephaly
  - Hepatosplenomegaly
  - Rashes: “Blueberry muffin syndrome”
  - Seizures
  - Sensorineural hearing loss
- Defects more common if fetus infected 1st trimester
- Treatment: ganciclovir or valganciclovir

Newborn Deafness

CMV

- Blueberry muffin baby
- Seizures
- Hepatosplenomegaly

Rubella

- Blueberry muffin baby
- Cataracts
- Congenital heart disease

HHV-6

- Causes roseola infantum (sixth disease)
- Most often due to HHV-6 but can also be caused by HHV-7 and some other viruses
- Occurs sporadically, often no exposure

HHV-6

- Starts with febrile phase
  - High fever for several days
  - Irritable baby
  - Lymphadenopathy
  - Often confused with meningitis
- Rash
  - Fever breaks
  - Maculopapular rash
  - Starts neck and trunk
  - Spreads to face and limbs

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HHV-8

- Causes Kaposi's sarcoma (usually HIV patients)
- Transmitted unclear
- Infects/transforms endothelial cells
- Inactivates tumor suppressor genes
- Purplish plaques/nodules on skin
  - Sometimes mouth, GI tract, lungs

M. Sand, D. Sand, C. Thrandorf, V. Paech, P. Altmeyer, F. G. Bechara

RNA Viruses

Jason Ryan, MD, MPH

RNA Viruses

RNA Viruses

- Icosahedral (+)
  - Naked →
    - Calici → Norwalk
    - Hepe → HEV
    - Reo → Rota, Colti
    - Picorna → PERCH (Polio, Echo, Rhino, Coxsacki, HAV)
  - Enveloped →
    - Corona* → Corona, SARS
    - Retro → HIV, HTLV
    - Flavi → HCV, Yellow, Dengue, StL, WNle
    - Toga → Rubella, EEEV, WEE
- Helical (-)
  - Enveloped →
    - Bunya → California, Congo,Hanta
    - Arena → LCMV, Lassa
    - Delta → HDV
    - Paramyxo → Paraflu, RSV, Msls, Mumps
    - Rhabdo → Rabies
    - Orthomyxo → Influenza
    - Filo → Ebola/Marburg

All ss except Reoviruses (ds)
All replicate in cytoplasm except influenza and retroviruses
All (+) are icosahedral except Coronavirus
All linear except BAD
All non-segmented except BOAR

Caliciviruses

- Non-enveloped, (+) ssRNA, linear, icosahedral
- Norovirus genus (Norwalk virus)
- Viral gastroenteritis
  - Recall: Most gastroenteritis is VIRAL
  - 2-3 days of watery diarrhea, nausea, vomiting
  - Not inflammatory: non-bloody, no mucous, no fecal leukocytes

Caliciviruses

- Fecal-oral transmission
  - Often involves contaminated sea food
  - Low infectious dose, shed in stool for weeks after infection
- Commonly causes outbreaks
  - Schools (children), cruise ships, hospitals/nursing homes
- Usually diagnosed clinically, no specific treatment

Hepeviruses

- Non-enveloped, (+) ssRNA, linear, icosahedral
- Hepatitis E virus

Reoviruses

- Non-enveloped, dsRNA, icosahedral
- Segmented, linear viruses
- Contain RNA-dependent RNA polymerase
  - Required to make mRNA from dsRNA
- Coltivirus: Colorado tick fever
  - Transmitted by wood tick bite (*Dermacentor andersoni*)
  - Lives in rodents (squirrels, chipmunks) Rocky Mountains
  - Fever, chills, myalgias, headache
  - Self-limited
- Rotavirus

Rotavirus

- Causes gastroenteritis in children
  - Fecal-oral transmission
  - Infects mucosal cells
  - Excess secretion of fluids, electrolytes
- Watery diarrhea
  - No blood, mucous, few/no fecal leukocytes
- Diagnosis: virus in stool
- Vaccine available
  - Live, attenuated virus (oral)
  - Given to children prior to 6 months of age

Picornaviruses

Poliovirus, Echovirus, Rhinovirus, Coxsackievirus, Hepatitis A

- Non-enveloped, (+) ssRNA, linear, icosahedral
- Synthesize a large polypeptide
- Cleavage → viral proteins
- All transmitted fecal-oral
  - Enteroviruses
- Exception: Rhinovirus (common cold)
  - Cannot survive in stomach (acid-labile)
  - Transmitted directly via respiratory droplets

Poliovirus

- Polio (poliomyelitis)
  - Febrile illness followed by weakness/paralysis
- Inactivated poliovirus vaccine (IPV; Salk)
  - Cannot cause vaccine-associated polio
  - Only vaccine used in US
  - Preferred vaccine in developed countries
  - **Systemic** antibody response
- Live attenuated oral polio vaccine (OPV; Sabin)
  - Some advantages in developing world
  - Cheap, easy to administer (oral)
  - Fecal-oral transmission to some unimmunized contacts
  - Triggers **local immunity** in the GI mucosa

Picornaviruses

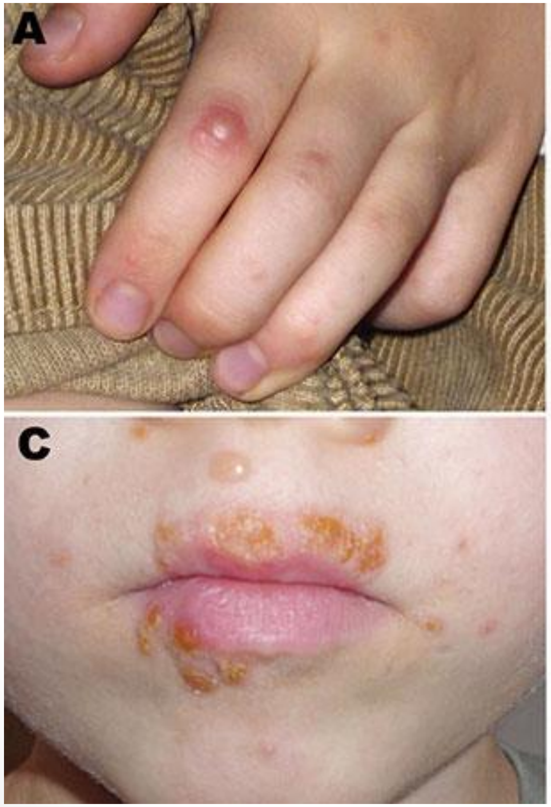
- Echovirus
  - Aseptic (viral) meningitis
  - 90% viral meningitis: coxsackievirus, echovirus
- Hepatitis A
- Rhinovirus
  - Viral upper respiratory illness (URI)
  - Most common virus associated with "cold" symptoms

Coxsackievirus

- Group A & B
- Aseptic meningitis (Group A &B)
- Hand, foot, and mouth syndrome (Group A)
  - Childhood illness
  - Sore throat, oral vesicles (buccal mucosa and tongue)
  - Rash: small lesions on **hands, feet**, buttocks
- Herpangina (Group A)
  - High fever, painful mouth blisters
  - Classically in children during summer
- Myocarditis, pericarditis (Group B)

Coxsackievirus

Hand, foot, mouth



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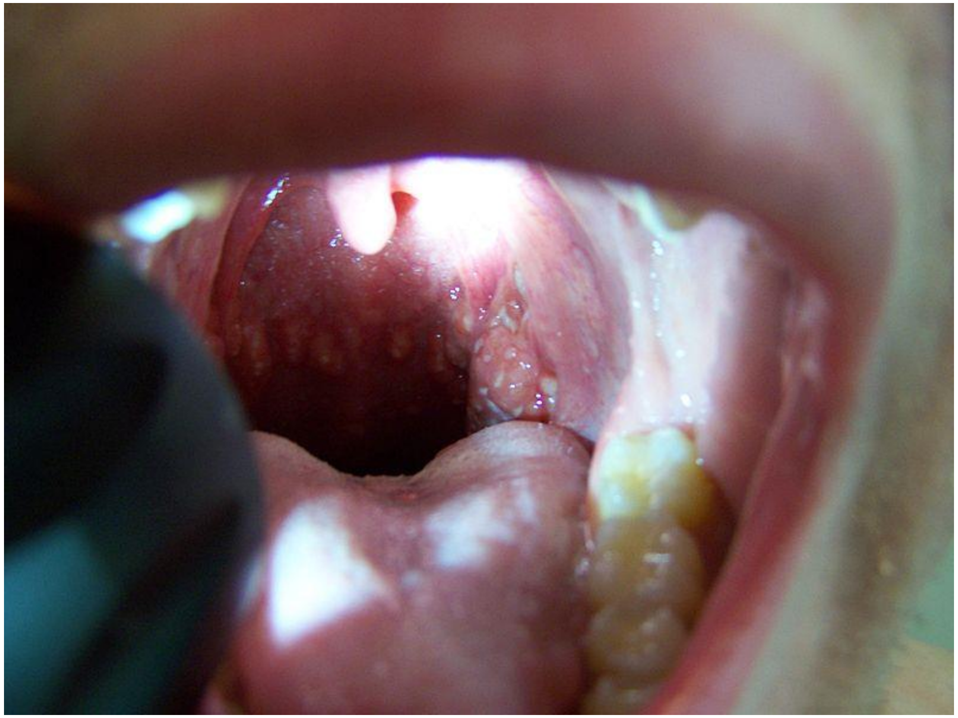
Herpangina



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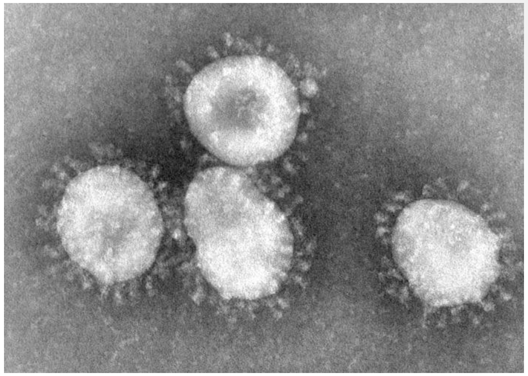
Coronavirus



CDC/Public Domain

- Enveloped, (+) ssRNA, linear, helical
- Upper respiratory infection ("cold")
- Severe acute respiratory syndrome (SARS)
- Worldwide outbreak in 2003
- Up to 1 week prodrome
  - Fever, malaise, headache, myalgias
- Cough, dyspnea
- Sometimes progressing to respiratory failure

Retroviruses

- Enveloped, ssRNA, linear
- Uses reverse transcriptase to convert RNA → DNA
- DNA replicates in nucleus
- Most important example is HIV
- Other example is human T- lymphotropic virus (HTLV)

Human T-lymphotropic virus

HTLV

- Two identical strands of (+) RNA
- Enters CD4 T-cells
- RNA genome reverse transcribed to DNA
- DNA product integrated into host cell genome
- T-cell proliferation and transformation
- Results: T-cell leukemia-lymphoma (NHL variant)

Human T-lymphotropic virus

HTLV

- Endemic outside US (Caribbean, Africa)
- Many in US infected by IV drug use
- Infects millions, few develop leukemia
- Uncommon in US

Flaviviruses

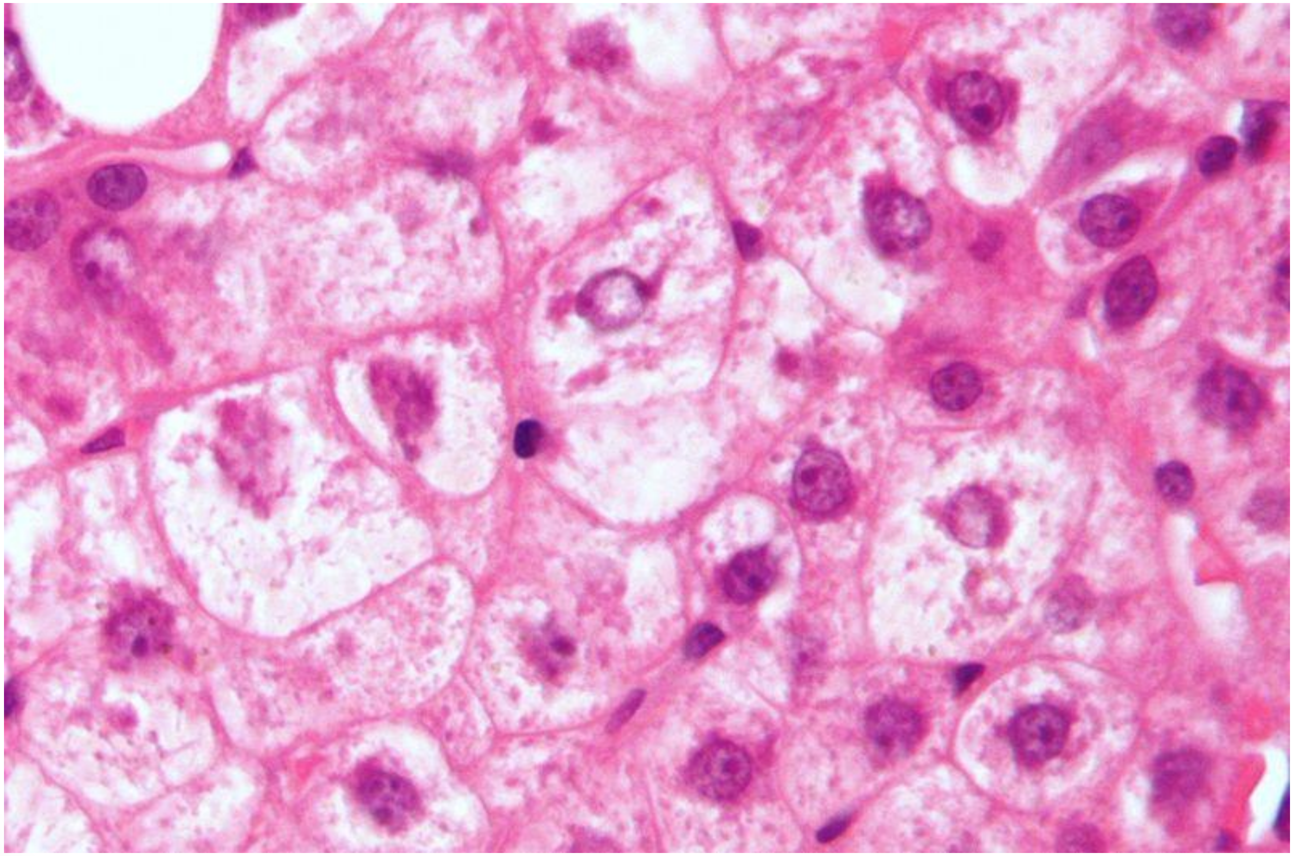
- Enveloped, (+) ssRNA, linear, icosahedral
- Hepatitis C
- Four mosquito illnesses
  - Yellow fever
  - Dengue fever
  - St. Louis encephalitis
  - West Nile virus

Yellow Fever

- Occurs in Africa, South America
- Virus can live in monkeys
- Arbovirus: transmitted by mosquito bite (Aedes)
- Infects liver (yellow for jaundice)
  - High fever, headache, jaundice, high bilirubin level
- Increased AST/ALT
  - Special feature: AST >> ALT
- Can cause hemorrhage ("black vomit")
  - Coffee-ground vomit, oozing from gums
- No specific treatment
- Vaccine available

Yellow Fever

- Councilman bodies in liver



Nephron/Wikipedia

Dengue Fever

- Occurs in Asia, South America
- Transmitted by mosquito bite
- "Break bone fever"
- Fever with headache and retro-orbital pain
- SEVERE muscle and joint pains
- Maculopapular rash
- Can rarely progress to hemorrhagic shock
- No specific therapy

St. Louis and West Nile

- Both transmitted by mosquito bites (arboviruses)
- Birds carry the virus
- Both cause encephalitis
  - Fever, altered mental status
  - Sometimes meningitis symptoms (stiff neck, photophobia)
- Most people asymptomatic
- St. Louis:
  - Widely distributed in the Americas
  - Few cases per year, sometimes outbreaks in US
- West Nile:
  - Widely distrusted across the globe
  - Outbreaks have occurred in US

Togaviruses

- Enveloped, (+) ssRNA, linear, icosahedral
- Rubella
- Eastern equine encephalitis
- Western equine encephalitis

Rubella

German measles; 3-day measles

- Childhood exanthem (rash)
- Acquired by inhalation of respiratory droplets
- Mild fever, lymphadenopathy
- Maculopapular rash (1-5 days after fever)
- Characteristic lymphadenopathy
  - Posterior cervical
  - Posterior auricular
- No specific treatment
- Vaccine: Live attenuated virus (MMR)

Congenital Rubella Syndrome

- ToRCHeS infection
- Mother acquires infection via respiratory droplets
  - Rash, fever, lymphadenopathy
- Classic triad in fetus:
  - Deafness
  - Cataracts
  - Cardiac disease

Congenital Rubella Syndrome

- Congenital heart disease
  - Patent ductus arteriosus (PDA)
  - Pulmonary artery stenosis
  - Many, many others
- Also petechiae/purpura ("blueberry muffin baby")
- Babies excrete virus for months
- Public health hazard
- Diagnosis:
  - IgM antibodies (recent infection)
  - Amniocentesis (virus in amniotic fluid)

Newborn Deafness

CMV

- Blueberry muffin baby
- Seizures
- Hepatosplenomegaly

Rubella

- Blueberry muffin baby
- Cataracts
- Congenital heart disease

Equine Encephalitis

- Eastern and Western Equine Encephalitis
- Both can infect humans and horses (equine)
- Found in North America
- Virus resides in birds
- Transmitted by mosquitos
- Most infections asymptomatic
- Can cause encephalitis
  - Fever, metal status changes

Bunyaviruses

- Enveloped, (-) ssRNA, helical
- Segmented (BOAR), circular genome (BAD)
- Result in rare infections
- California encephalitis
  - Mosquito-borne virus, causes encephalitis
  - Reservoir is rodents
- Hemorrhagic fever
  - Rift Valley fever
  - Crimean-Congo hemorrhagic fever
  - Hantavirus infection

Encephalitis Viruses

Mosquito-borne Arboviruses

- Flaviviruses (birds)
  - St. Louis
  - West Nile
- Togaviruses (birds)
  - Eastern Equine
  - Western Equine
- Bunyaviruses (rodents)
  - California

Hemorrhagic Fever

- Viral infections by enveloped RNA viruses
- Live in animals, usually birds
- Most transmitted in one of two way:
  - Mosquito or tick bites
  - Contact with infected animals
- Initial symptoms non-specific
  - Fever, headache, malaise
  - Often GI symptoms: vomiting, diarrhea
- Hemorrhage may occur
  - Petechiae, large hematomas, frank bleeding
- Can progress to respiratory failure, shock, death

Bunyaviruses

Hemorrhagic Fever

- Rift Valley fever
  - Mosquito-borne virus, East Africa
  - Transmitted by mosquito bite or contact infected animals
- Crimean-Congo hemorrhagic fever
  - Tick-borne virus, East Africa
  - Transmitted by ticks or contact infected livestock
- Hantavirus infection
  - Lives in rodents (mice)
  - Transmitted by rodent contact
  - Virus shed in rodent urine, feces, saliva
  - Often progresses: renal failure or respiratory failure

Filoviruses

- Enveloped, (-) ssRNA viruses, linear, helical
- Transmitted through contact with body fluid from infected person
- Ebola & Marburg
- Both cause hemorrhagic fever
- Both highly fatal

Arenaviruses

- Enveloped, (-) ssRNA, helical
- Segmented (BOAR), circular genome (BAD)
- Lassa fever
  - Hemorrhagic fever
  - Spread by urine from rats
  - Also through close contact with infected people
- Lymphocytic choriomeningitis virus (LCMV)
  - Rare cause of viral meningitis
  - Rats and mice shed virus in saliva, urine, feces
  - Children in poor conditions at higher risk exposure

Hemorrhagic Fever Viruses

- Bunyaviruses
  - Rift Valley Fever virus (mosquito)
  - Crimean-Congo hemorrhagic fever virus (tick)
  - Hanta virus (rodents)
- Filoviruses
  - Ebola/Marburg
- Arenaviruses
  - Lassa fever (rats)
- Sometimes flaviviruses
  - Yellow fever, dengue can progress

Rhabdoviruses

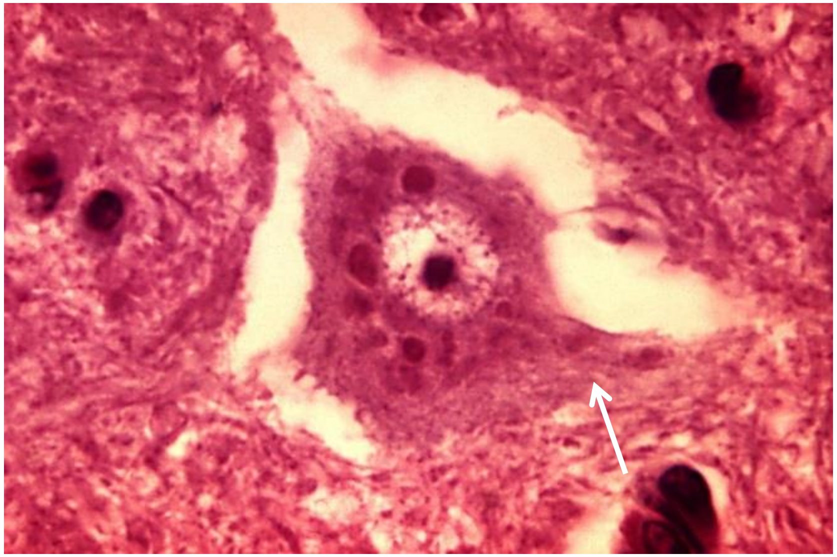
- Enveloped, (-) ssRNA, linear, helical
- Several rhabdo species cause rabies

Rabies

- Infection by bite of rabid animal
- Found in bats, raccoons, skunks, coyotes, wolves
- Classic transmission from dog bite
- Incubation period: 1 to 3 months after bite
- Prodrome: Fever, malaise, nausea, vomiting
- Rabies infection
  - Encephalitis
  - Painful pharyngeal spasms
  - Classically fear of water, agitation, salivation
- Progresses to paralysis, coma
- Virtually always fatal

Rhabdoviruses

- Special features of rabies viruses
  - Bullet shaped envelope
  - Forms “Negri bodies” in neurons/Purkinje cells
  - Viruses bind Ach receptors on peripheral nerves
  - Migrate to CNS



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Rabies

Management of Possible Infection

- Suspect rabies after:
  - Wild animal bite
  - Exposure to bats
- Important to clean bite wounds
- Vaccination: Inactivated virus vaccine
- Rabies immune globulin
  - Provides antibodies until protective antibodies generated from vaccination

Orthomyxoviruses

- Enveloped, (-) ssRNA, linear, helical
- Segmented genome (BOAR)
- Most important virus in influenza

Influenza Virus

- Causes acute respiratory illness (the flu)
- Occurs in winter months
- Transmitted by respiratory secretions
  - Infected person's cough, sneeze
- Fever, headache, myalgia, and malaise
- Cough, sore throat, runny nose
- Self-limited; improvement in days to weeks
- Rare complications
  - Pneumonia (viral or secondary bacterial)
  - S. pneumoniae most common; S. aureus 2nd most common

Influenza Virus

- Several subtypes (A, B, C)
- Influenza A most common
- Two key envelope glycoproteins
- Hemagglutinin
  - Binds to cells; assists in entry into cells
- Neuraminidase
  - Remove sialic acid from glycoproteins
  - Required for virus progeny to exit cell
- Virus replicates in nucleus

Influenza Virus

- Antigenic drifts
  - Minor changes in hemagglutinin and neuraminidase
  - Due to random mutation
  - Vary from year to year
  - Some previously infected not immune (epidemics)
- Antigenic shift
  - Segmented genome allows for high rates of reassortment when two viruses infect same cell
  - Often occur when animal/human virus infect same cell
  - Cause pandemics (US in 1918)
  - Can occur in other segmented viruses
  - BOAR: Bunyavirus, arenavirus, orthomyxovirus, reovirus

Influenza Vaccine

- Viruses grown in eggs
- WHO recommends strains for vaccine
  - Global surveillance of viruses at end of prior flu season
- Killed vaccine virus
  - Available each fall (prevents winter flu)
- Nasal spray
  - Live, temperature sensitive mutant
  - Replicates in nose, not lungs
  - Often used for children (cannot use >age 50)

Paramyxoviruses

- Enveloped, (-) ssRNA, helical
- All cause disease in children
- All contain F protein
  - Surface F (fusion) protein
  - Causes respiratory epithelial cell fusion
  - Palivizumab: monoclonal antibody against F protein
  - Used to treat RSV

Paramyxoviruses

- Parainfluenza
  - Croup
  - URI in children with “barking” cough (sounds like a seal)
  - Can cause respiratory distress (treat with steroids)
- RSV
  - Viral respiratory infection in infants
  - Treatment: Ribavirin, Palivizumab
- Measles
- Mumps

Measles

Rubeola

- Cough, Coryza, Conjunctivitis
- Classic maculopapular rash
  - Starts at head → spreads to feet
- Koplik spots
  - Small, white lesions in mouth
- Rare complications
  - Measles encephalitis
  - Subacute sclerosing panencephalitis (SSPE) – YEARS after
    - Personality changes, odd behavior, dementia
  - Giant cell pneumonia
    - Immunocompromised
    - Multinucleated giant cells in lung tissue

Measles

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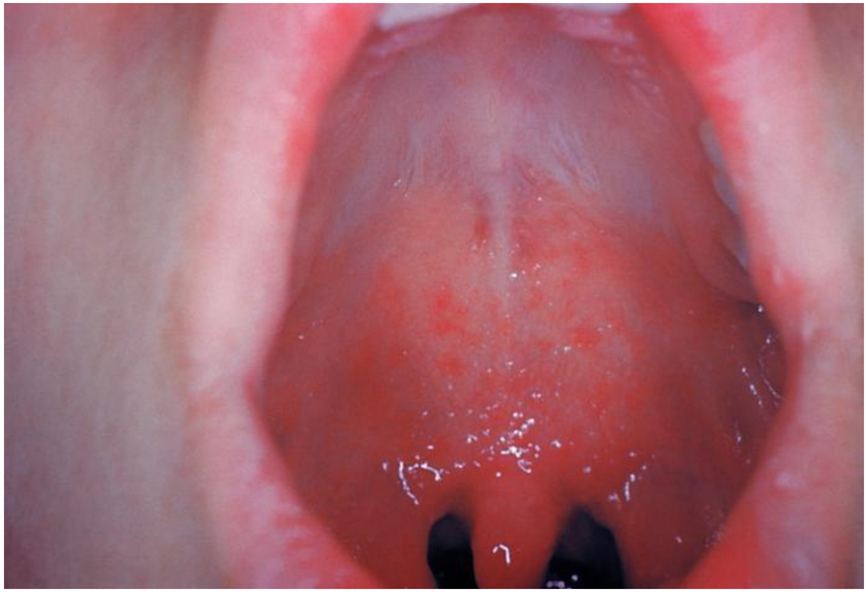

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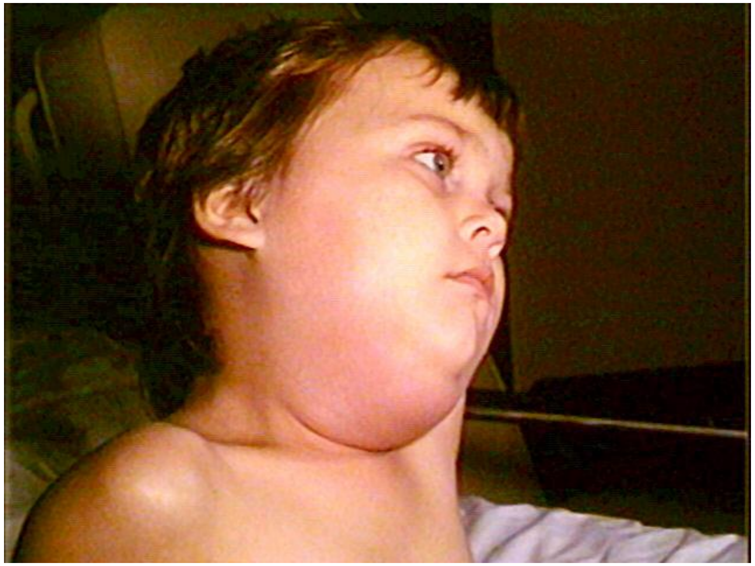
Measles

- 2014 outbreaks in US among unvaccinated children
- Can spread to vaccinated children
  - Vaccine 95% effective
- Test of choice:
  - Measles IgM
  - Not positive first few days of infection
- Possible therapies:
  - Vitamin A
  - Ribavirin

Mumps

- Prodrome of fever, malaise, headache, myalgias
- Parotitis
  - Inflammation of parotid glands (facial swelling)
- Orchitis
  - Testicular pain
  - Scrotal swelling
  - Can result in sterility
- Meningitis (aseptic)



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MMR Vaccine

- Measles, Mump, Rubella
- Live, attenuated vaccines
- Usually given after 1-year
- Prior to 1-year, maternal antibodies will kill vaccine
- Live, attenuated vaccine required:
  - Paramyxoviruses (measles, mumps) form "syncytia"
  - Move from cell to cell directly
  - No exposure to plasma (antibodies)
  - Need vigorous cell-mediated response to infection

Childhood Red Rashes

Virus	Features
Rubella (German Measles)	Head → Feet Postauricular LAD
Measles (Rubeola)	Head → Feet Cough, Coryza, Conjunctivitis Koplik spots
HHV-6 (Roseola)	Fever that breaks Neck/Trunk – Face/limbs Infants/Seizures
Parvovirus B19	Slapped cheek
Strep Pyogenes (Scarlet Fever)	Sore throat Sandpaper-like red rash Head/neck → Trunk

Viral Hepatitis

Jason Ryan, MD, MPH

Viral Hepatitis

- Hepatitis viruses (A, B, C, D, E)
- All cause liver inflammation
- Some cause chronic infection
- Can lead to cirrhosis or hepatocellular carcinoma

Viral Hepatitis

Acute Symptoms

- Many acute infections asymptomatic
- Fever, malaise, nausea, vomiting, anorexia
- RUQ pain
- Jaundice (yellow skin from bilirubin)
- Itching (bile salts in skin)
- Dark urine (bilirubin)
- Clay-colored stools (lack of bilirubin excretion)

Viral Hepatitis

Acute Symptoms

Conjugated Bilirubin $\xrightarrow[\text{Bacteria}]{}$ urobilinogen → stercobilin →

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Blood Tests

- Increased AST/ALT
  - ALT usually > AST
  - Contrast with alcoholic hepatitis (AST>ALT)
- Increased bilirubin (direct)
  - Liver can conjugate bilirubin in setting hepatitis
  - Cannot transport into bile
- False positive VDRL
  - Viral hepatitis is common cause of false positive VDRL
  - Don't confuse with syphilis

Hepatitis A

- Picornavirus (PERCH)
- Non-enveloped, (+) ssRNA, linear, icosahedral
- Synthesize a large polypeptide
- Cleavage → viral proteins

Hepatitis A

- Transmitted through:
  - Personal contact
  - Drinking contaminated water
  - Consumption of raw sea food
- Common in underdeveloped countries
  - Poor hygiene and sanitation
- Classic case: traveler to Mexico, Cental/South America
- Incubation period ~30 days

Hepatitis A

- Diagnosis:
  - Acute disease: Anti-HAV IgM antibodies plus symptoms
  - Prior disease: Anti-HAV IgG antibodies
- Self-limited; no specific therapy
- Acute disease only – no chronic infection
- Often asymptomatic
  - Antibody tests done later may show anti-HAV IgG
- Inactivated virus vaccine available (IM)
- Part of US routine childhood vaccination schedule

Hepatitis E

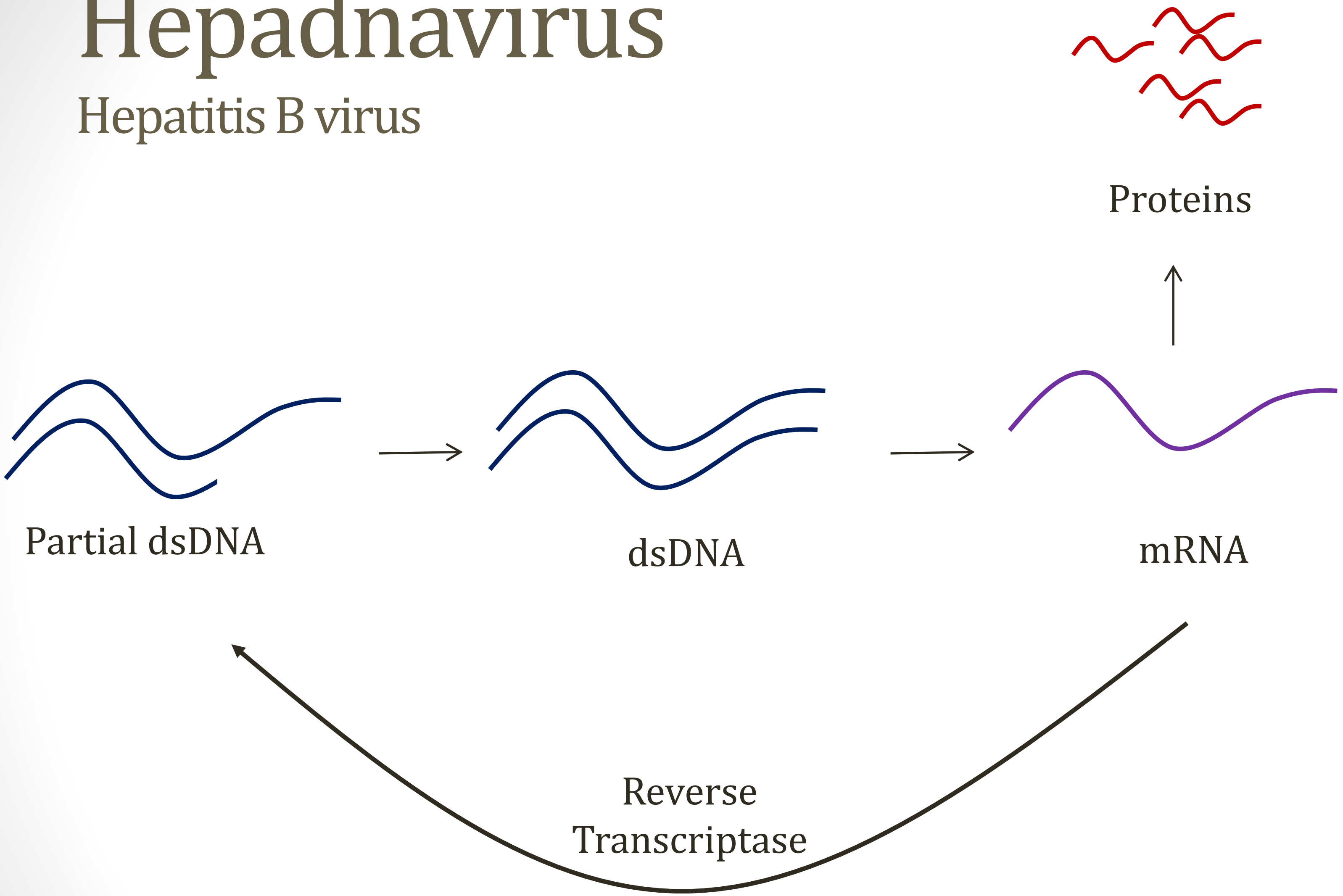
- Hepevirus
- Non-enveloped, (+) ssRNA, linear, icosahedral
- Outbreaks worldwide in resource-limited areas
- Infection from fecal contamination of water
- Self-limited acute infection - no chronic infection
- Diagnosis:
  - HEV genome in in serum or feces (PCR)
  - IgM antibodies to HEV
- Pregnancy
  - Hepatic failure more frequent during pregnancy
  - High mortality rate (15 to 25 %)

Hepatitis B

- Hepadnavirus family (DNA virus)
- Enveloped, circular, icosahedral capsid
- #1: Partially double stranded DNA virus
  - Genome enters hepatocytes → nucleus
  - DNA becomes fully double stranded
  - mRNA synthesized → cytoplasm
- #2: Reverse transcriptase synthesized
  - Viral mRNA → viral DNA
  - Packaged in capsid
- #3: Envelope from endoplasmic reticulum

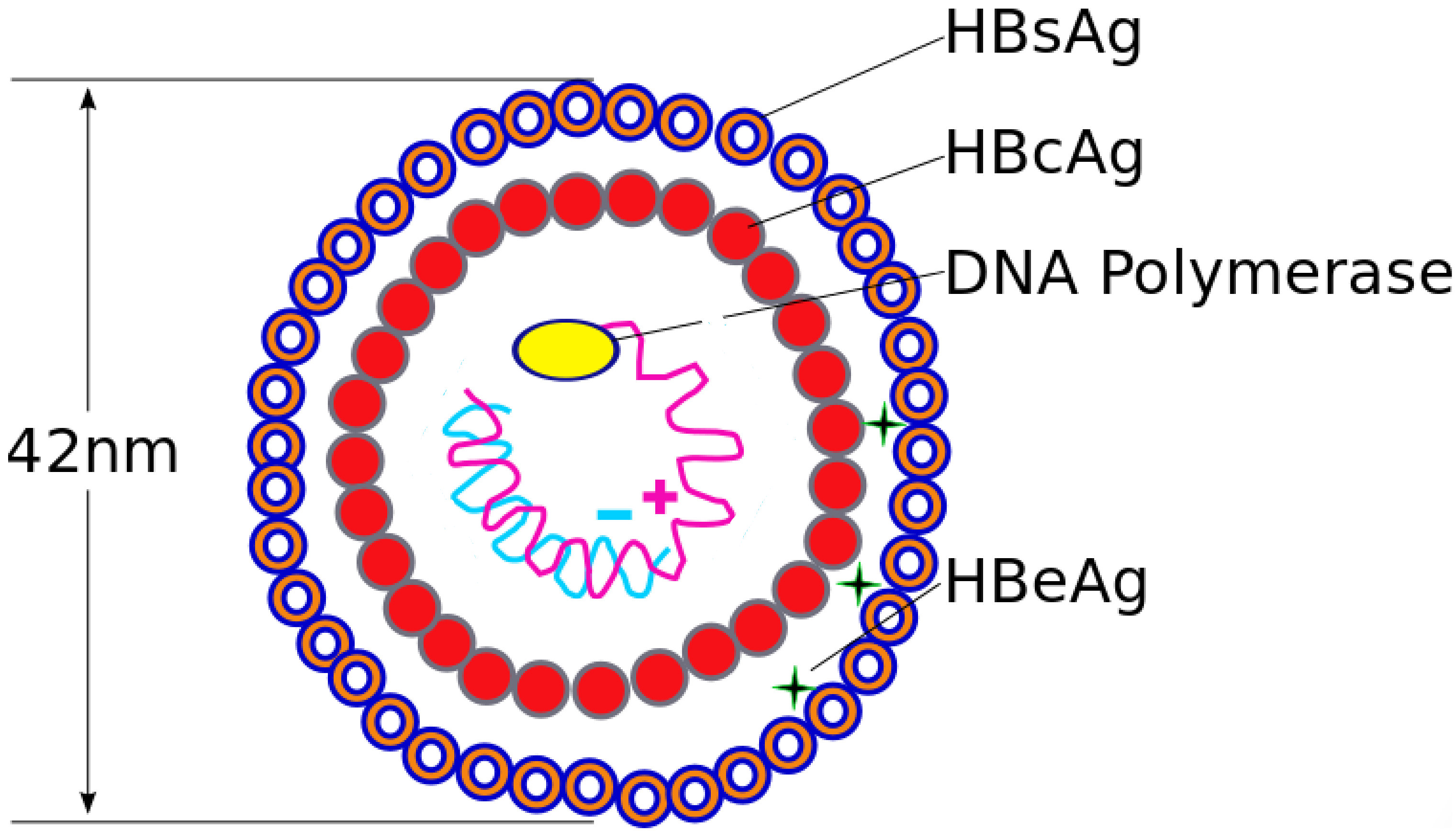
Hepadnavirus

Hepatitis B virus



Hepatitis B

Dane Particle



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Hepatitis B
Transmission

- Sexual contact
- IV (drug use, transfusion, needle stick)
- Maternal-fetal
  - Especially if mother gets acute disease 3rd trimester
  - Babies usually have minimal symptoms
  - Lots of viral replication in baby (immature immune system)
  - Babies at HIGH risk of progression to chronic disease
- Incubation of 1 to 4 months
- Acute infection
  - 70% have subclinical or mild hepatitis (anicteric)
  - 30% icteric hepatitis

Chronic Hepatitis B

- Progression to acute → chronic depends on age
  - 90% peri-natal
  - ~50% children
  - <5% adults
- Many chronic infections asymptomatic (carriers)
- Risk of progression to:
  - Cirrhosis
  - Liver failure
  - Hepatocellular carcinoma (viral DNA integrates into host)
  - Reactivation (acute hepatitis)

Immune Reconstitution

- If HIV is treated without treating Hep B it can cause severe liver damage
- HepB testing usually done prior to HIV therapy

Extrahepatic Manifestations

- Polyarteritis nodosa
  - Fevers, fatigue, arthralgias
  - Abdominal pain, melena
  - Neuropathy
  - Rash
- Glomerular disease
  - Most common is membranous nephropathy
  - Presents as proteinuria, nephrotic syndrome

Hepatitis B

Diagnosis

- Antigens
  - Hepatitis B surface antigen (HBsAg)
  - Hepatitis B e antigen (HBeAg)
- Antibodies
  - Anti-hepatitis B surface antigen (Anti-HBsAg)
  - Anti-hepatitis B e antigen (Anti-HBeAg)
  - Anti-hepatitis B core antigen (Anti-HBcAg)
- Antigens rise in acute disease, fall as infection resolves
- Antibodies rise as acute infection resolves

Hepatitis B Surface Antigen
HBsAg

- Hallmark of infection
- Glycoprotein that forms spheres and tubules (EM)
- From surface of envelope
- Detectable weeks after exposure, prior to symptoms

Hepatitis B Surface Antigen

HBsAg

- Recovery from acute hepatitis:
  - HBsAg becomes undetectable after four to six months
- Chronic infection
  - Persistence of HBsAg for more than six months
- Prior infection or vaccination:
  - Presence of anti-HBsAg antibodies without HBsAg
- Generally, when anti-HBsAg levels rise, HBsAg levels fall and infection clears

Hepatitis B Vaccine

- Contains recombinant HBsAg
- Vaccinated individuals will be (+) anti-HBsAg
- All other antibodies (HBc, HBe) should be negative

Hepatitis B Core Antigen

HBcAg

- Intracellular antigen (comes from within hepatocytes)
- Capsid core protein
- Expressed by infected hepatocytes
- NOT detectable in serum
- Anti-HBc can be detected
- Anti-HBc IgM rises in acute infection
- Anti-HBc IgG prior exposure or chronic infection

Window Period

- Brief period where:
  - HbsAg undetectable
  - Anti-HBsAg not yet detectable
- Can give false appearance of no infection
- SOLE marker of infection is anti-HBc (IgM)

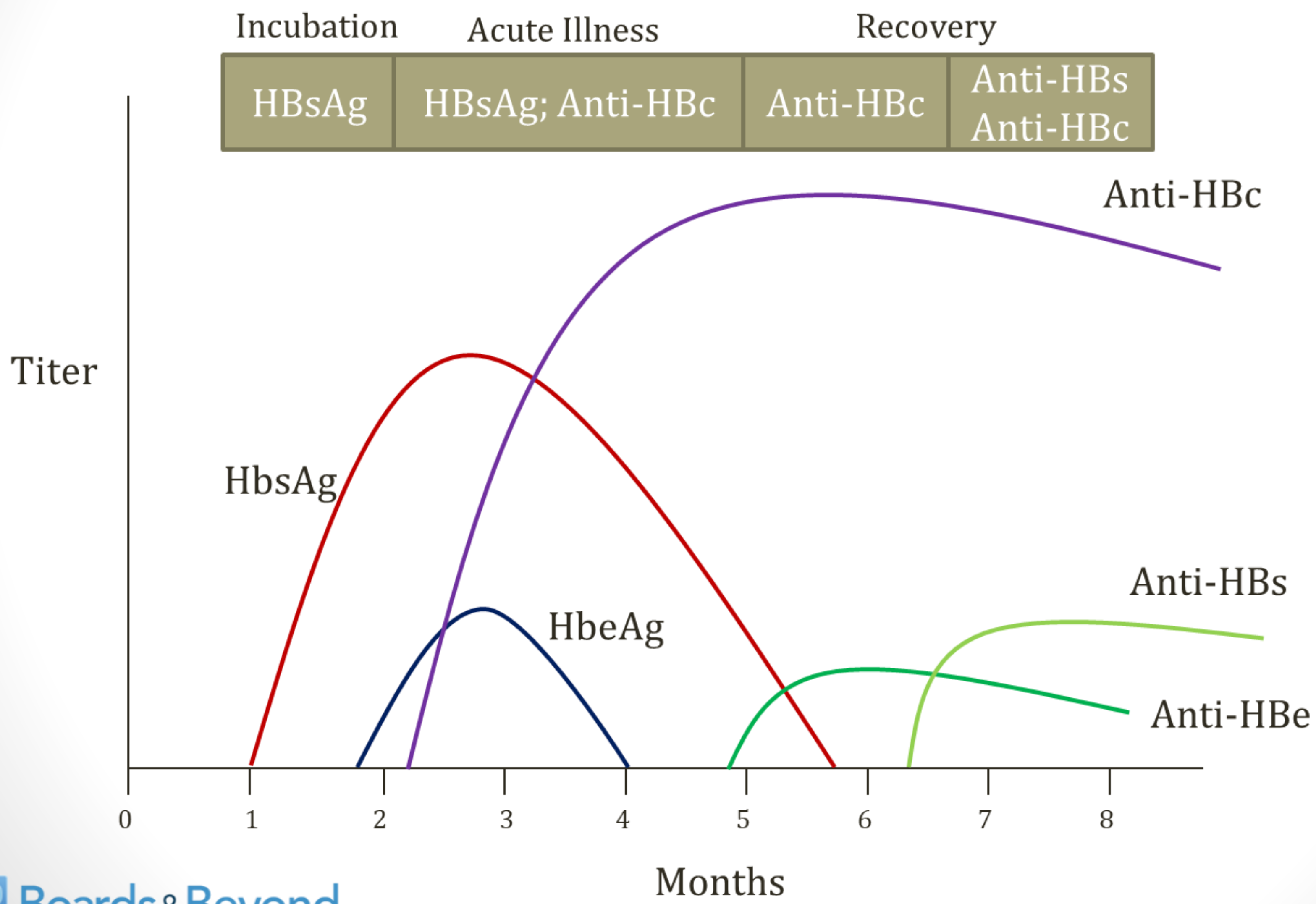
Hepatitis B e Antigen
HBeAg

- Viral protein secreted by infected cells
- Part of capsid core
- Indicates significant viral replication
  - Correlates well with levels of HBV DNA
  - HBsAg indicates presence of virus, not necessarily significant replication
- Elevated in patients who are **highly infectious**
- Seroconversion to Anti-HBeAg usually associated with fall in viral DNA production

Hepatitis B DNA

- Detectable with PCR
- Major role is for determining "viral load" for treatment

Hepatitis B Diagnosis



Hepatitis B Diagnosis

- Acute disease
  - HBsAg (except window)
  - IgM Anti-HBc (even during window)
  - HBeAg (indicates infectivity)
  - HBV DNA
- Recovery after acute disease
  - Anti-HBs; Anti-HBe; Anti-HBc (IgG)
  - Undetectable HBsAg
  - Absence of HBV DNA

Diagnosis of Hepatitis B

- Prior vaccination
  - Anti-HbsAg only
  - Not anti-HBc or anti-HBe
- Chronic infection
  - HBsAg positive
  - If HbeAg positive = high infectivity
  - Anti-HBc positive
  - Viral DNA may be high, low depending on viral load
- If HBsAg is positive = patient is infected
- If HBsAg is negative = patient is not infected

Treatment Chronic Hepatitis B

- Acute hepatitis B
  - Usually treated with supportive care
  - Immunocompetent adults <5% chance chronic disease
- Multiple treatments for chronic disease
  - Interferon
  - Lamivudine (NRTI)
  - Other antiviral drugs

Interferons

- Type I: Alpha, beta (most human cells)
- Type II: Gamma (T cells, NK cells)
  - Increase MHC expression, activates NK cells
- Activate interferon stimulated genes (ISGs)
  - Many, many cellular effects

Interferons

- Trigger cell production of RNAase L
  - Degrades viral and cellular RNA
- Production of protein kinase R
  - Inhibits translation of proteins
- Active only in presence dsRNA

Interferons

- Administered as drugs
- Antiviral: Hepatitis B, C (alpha)
- Leukemia, Lymphoma, Melanoma (alpha, beta)
- Multiple sclerosis (beta)
- Gamma:
  - Rare immune diseases
  - Chronic granulomatous disease (CGD)
  - IL-12 receptor deficiency

Hepatitis C

- Flavivirus (mostly mosquito illnesses)
- Enveloped, (+) ssRNA, linear, icosahedral
- High degree of antigenic variation
- Envelope glycoproteins
  - Contain a "hypervariable region"
  - High mutation rate in genome
  - Lack of proofreading by viral RNA polymerase
  - Result: prone to frequent mutations
- Difficult for immune system to eradicate effectively
- High rate of chronic disease

Hepatitis C

- Mostly acquired through IVDA or transfusion
  - Transfusion illness now rare due to screening
- Rare cases from needle sticks, sexual contact
- Acute illness
  - Usually asymptomatic
  - Usually leads to chronic disease
- Chronic infection
  - Usually asymptomatic or mild, nonspecific symptoms
  - Often incidental discovery of abnormal LFTs
  - Screening done for high risk patients (IVDA)

Hepatitis C
Diagnosis

- HCV RNA by PCR
  - Elevated soon after exposure
- Anti-HCV
  - Elevated by 12 weeks after exposure
- Both elevated in chronic disease (common)

Hepatitis C

- Chronic infection associated with:
  - Cirrhosis
  - Liver failure (common indication for transplant)
  - Hepatocellular carcinoma
- Treatment options:
  - Interferon
  - Ribavirin
  - Others

Hepatitis D
Delta Agent

- Small enveloped (-) RNA virus, circular genome
- "Defective virus"
- Lacks genes for envelope proteins
- Uses HbsAg for envelope protein
- Genome encodes one protein: delta antigen (HDAg)
- Virus particles carry HDAg

Hepatitis D

Delta Agent

- Pathogenesis:
  - Invades hepatocytes
  - Travels to nucleus to replicate
  - Uses HBV to provide envelope
  - Virus particle coated with HBsAg
  - Uses host cell RNA polymerase to replicate genome

Hepatitis D
Delta Agent

- Transmission:
  - Co-infected with HBV
  - HDV infection in setting of chronic HBV carrier state
  - Superinfection often leads to flare of hepatitis
- Diagnosis:
  - Serum HDAg
  - HDV RNA
  - Anti-HDV antibodies
- Hep B vaccine protects against Hep D

HIV

Jason Ryan, MD, MPH

HIV

Human Immunodeficiency Virus

- RNA retrovirus
- Uses reverse transcriptase: RNA → DNA
- Infects CD4+ T-helper cells
- Acquired immunodeficiency syndrome (AIDS)
- Susceptibility to unique opportunistic infections
- Natural host is humans

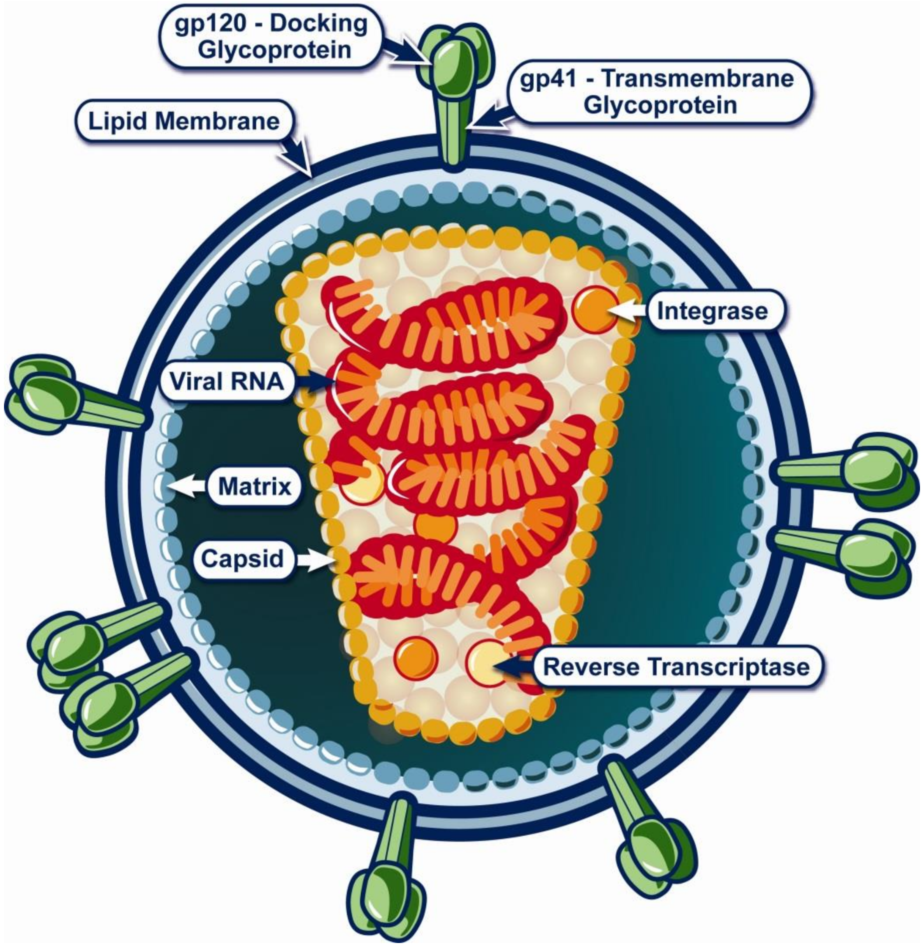
HIV

- Diploid: Carries two copies of (+) stranded RNA
- RNA tightly bound to key enzymes
  - Reverse transcriptase: Makes DNA from RNA
  - Aspartate protease: Cleavage of proteins
  - Integrase: Integrate DNA into host cell DNA
- Cone-shaped (conical) capsid
  - Multiple copies of p24 protein
  - Non-variable protein
  - Antibodies produced but do not neutralize virus

HIV

- Enveloped
  - Phospholipid from membrane of human cell
- Envelope contains Env protein
- Cap of env protein contains glycoproteins
  - gp120: Attachment to T-cells
  - gp41: Fusion and entry into T-cells
  - Both formed as single protein (gp160) and cleaved
- Gene for gp120 mutates rapidly (antigenic variation)
  - "V3 loop" portion is highly immunogenic
  - Varies significantly
  - Antibody neutralization difficult

HIV



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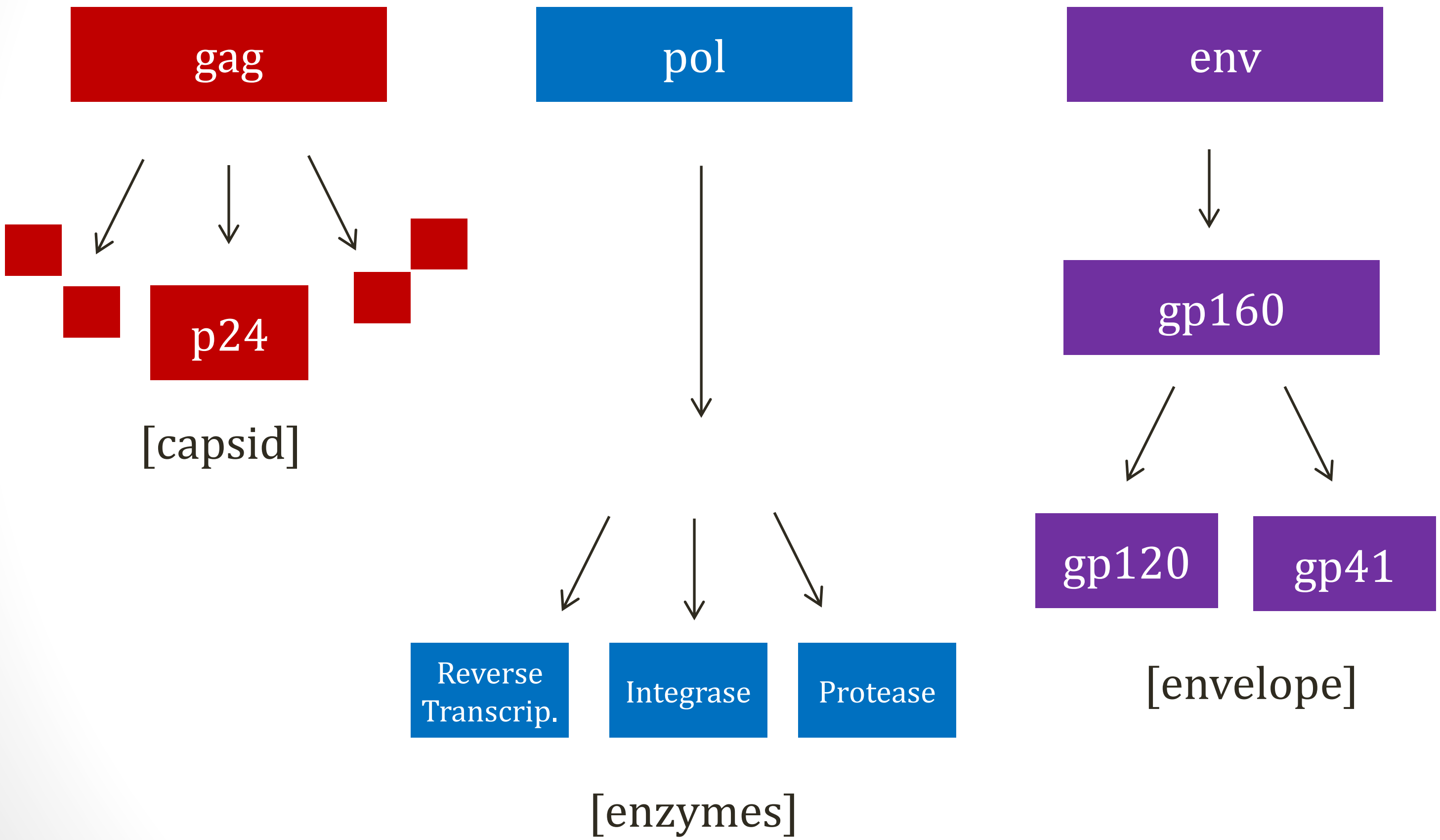
HIV Genome

- Three "main" genes encode major parts of virus
- Gag: nucleocapsid
- Pol: polymerase
- Env: envelope proteins

HIV Genes and Products



Other HIV Genes

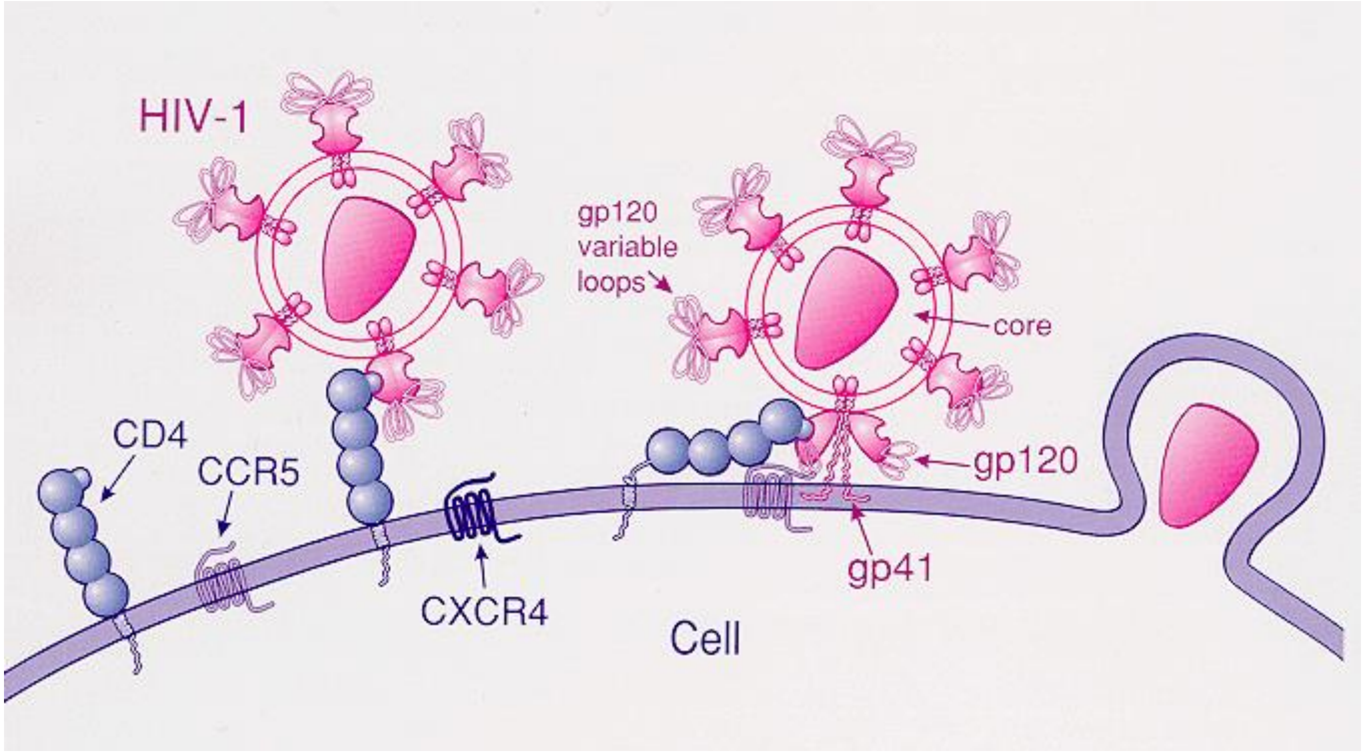
Regulatory and Auxiliary Genes

- Tat, Rev
  - Required for viral replication
  - Tat: Activates transcription of genes
  - Rev: Transports mRNA from nucleus to cytoplasm
- Nef, viv, vpr, vpu, vpx
  - Not required for replication (auxiliary)
  - Nef: ↓CD4 proteins and MHC I on T-cell surfaces

HIV Tropism

- CCR5 and CXCR4
  - Major lymphocyte receptors used by HIV to enter cells
- CCR5-tropic viruses
  - Replicate in monocytes/ macrophages (M-tropic)
  - Can also infect dendritic cells (trafficking to lymph nodes)
  - Occur early: Sexually transmitted to macrophages
- CXCR4-tropic viruses
  - Replicate more efficiently in T-cells (T-tropic)
  - Occur later after infection has developed
- Mutations in CCR5 gene associated with decreased susceptibility to HIV infection

Pathophysiology



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HIV-1 and HIV-2

- Two types of HIV (two viruses) cause infection
- HIV-1: Causes majority of infections worldwide
- HIV-2: Important cause of infection West Africa
- Both sexually transmitted
- Both can cause AIDS
- Some differences in progression, severity
- One drug class (NNRTIs) not effective HIV-2

HIV Transmissions

- Sexually transmitted
- Exposure to contaminated blood
- Perinatal transmission

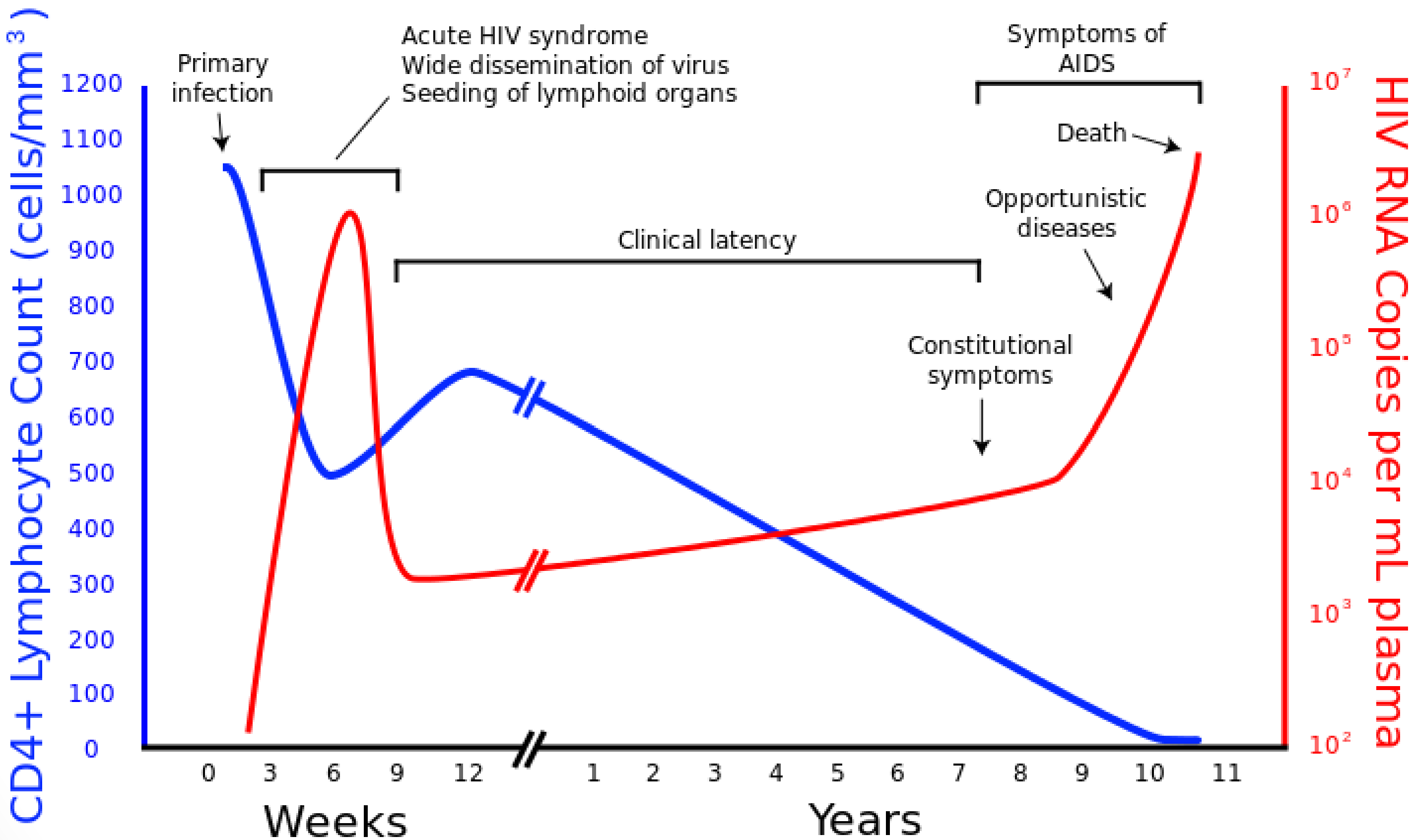
Markers of Infection

- CD4 T-cell count
  - Determined by flow cytometry
  - Normal ~1000 cells/mm^3
  - AIDS <200
  - Used to initiate prophylaxis against opportunistic infections
- Viral load
  - Quantification of HIV RNA
  - Used to monitor effect of drug therapy

HIV Symptoms

- Initial infection asymptomatic 10-60%
- Acute HIV syndrome
  - 2-4 weeks after exposure
  - Fever, myalgias, sore throat, cervical adenopathy
  - Sometimes maculopapular rash
  - Similar to mononucleosis
- Severe immunosuppression (AIDS)
  - Average time of 8 years from exposure
  - CD4 < 200cells/mm^3 or AIDS-defining infection
  - Symptoms from opportunistic infections

HIV Time Course



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Rare HIV Features

- Dementia
- Pulmonary hypertension
- Cardiomyopathy

HIV Diagnosis

- Older tests (antibody only)
  - ELISA: Screening (sensitive; many false positives)
  - Western blot: Confirmatory if positive ELISA (specific)
- Current CDC recommendations:
  - Combination antigen/antibody tests
  - "4th generation tests"
- Test for p24 antigen and HIV antibodies
- If positive, HIV1-HIV2 antibody differentiation assay

HIV Diagnosis

- Acute HIV
  - HIV RNA testing (viral load) will be high
- Perinatal HIV
  - Maternal HIV antibodies persist for months
  - Standard test is HIV PCR testing

Opportunistic Infections

- Pneumocystis (fungal) pneumonia
- CMV retinitis
- Cryptococcal (fungal) meningitis
- Toxoplasmosis (CNS protozoa infection)
- Cryptosporidium diarrhea (protozoa)
- Kaposi Sarcoma (HHV-8)
- Mycobacterium avium complex
- Thrush (Candida – fungus)

Opportunistic Infections

- Prophylaxis given based on CD4 count
- CD4 < 200
  - TMP-SMX: Pneumocystis pneumonia
- CD4 < 100
  - TMP-SMX: Pneumocystis and Toxoplasmosis
  - Itraconazole: Histoplasmosis (endemic areas)
- CD4 < 50
  - Azithromycin: Mycobacterium avium complex

HIV Treatment

- Older guidelines based on CD4 count
  - Treat patients <500cells/mm^3
- Newer guidelines recommended treating all patients
- Multi-drug therapy used (often different classes)
  - Highly active antiretroviral therapy (HAART)
- Gene mutations occur over time due to drugs
- Require altering medical regimen

IRIS

Immune Reconstitution Inflammatory Syndrome

- Treatment of HIV → flare of infectious symptoms
- Sometimes previously undiagnosed infection
- Leading agents:
  - Tuberculosis
  - Mycobacterium avium complex (MAC)
  - Cytomegalovirus (CMV)
  - Cryptococcal meningitis
  - Pneumocystis
  - HSV
  - Hepatitis B
  - HHV-8 (Kaposi Sarcoma)

HIV Drugs

Jason Ryan, MD, MPH

HIV Therapy

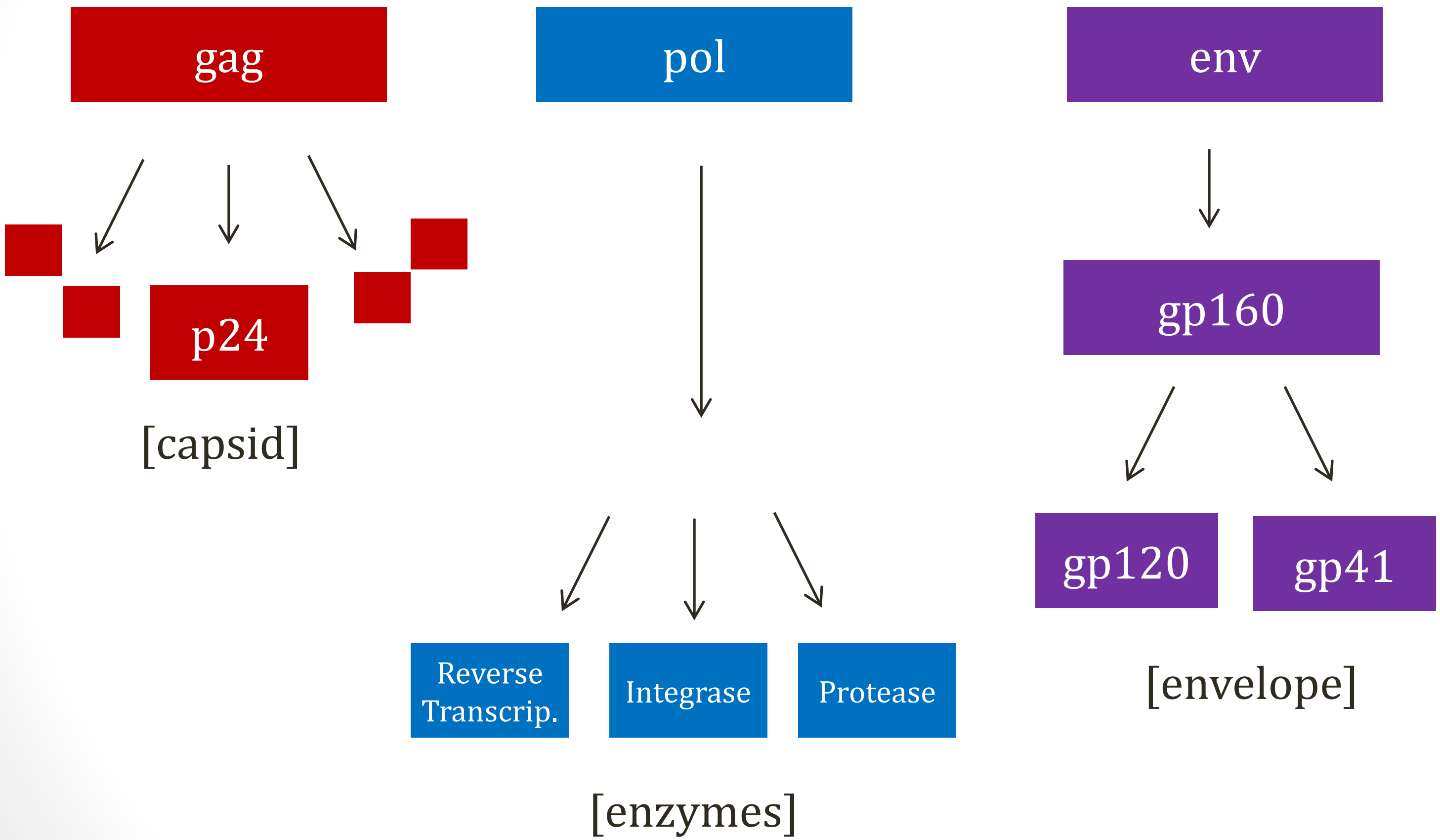
- Protease inhibitors
- Nucleoside reverse transcriptase inhibitors (NRTIs)
- Non-nucleoside rev. transcriptase inhibitors (NNRTIs)
- Other drugs

Protease Inhibitors

Lopinavir, Ritonavir, Indinavir

- Inhibit HIV protease
  - Product of pol gene
  - Cleaves polypeptides into smaller, functional units
  - Block production: reverse transcriptase, protease, integrase, structural proteins
- Viral particles cannot "mature"
- Become noninfectious

HIV Genes and Products



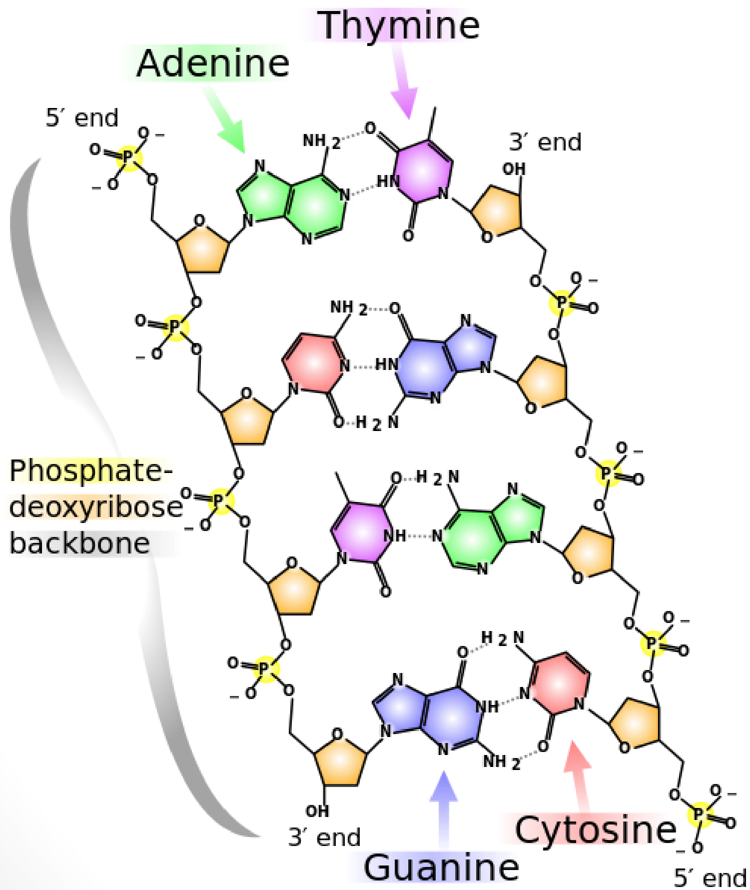
Protease Inhibitors

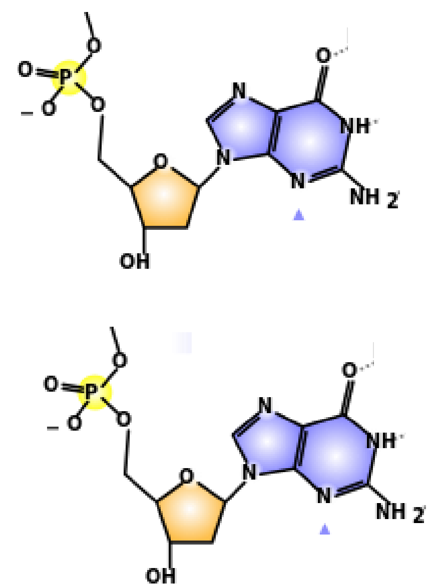
Lopinavir, Ritonavir, Indinavir

- Many side effects
  - Nausea, diarrhea
  - Hyperlipidemia, Hyperglycemia (insulin resistance)
  - Fat redistribution
- Indinavir
  - Kidney stones (hydration important)
- Ritonavir
  - Inhibits cytochrome p450 system
  - Low dose (less side effects) used to "boost" other PIs
  - Primary use of this drug is for boosting
  - Ritonavir/Lopinavir = Kaletra

NRTIs

Nucleoside reverse transcriptase inhibitors





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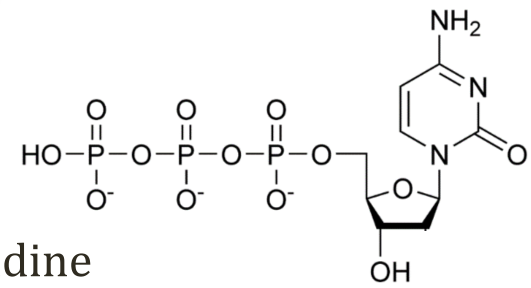
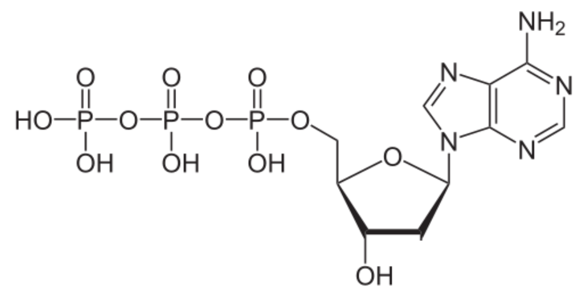
NRTIs

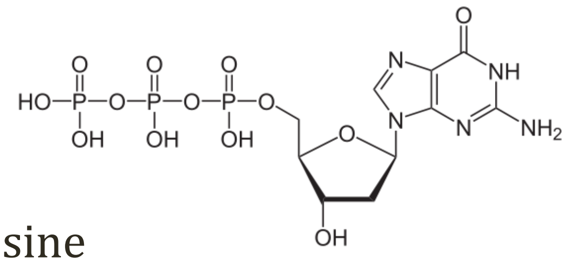
Nucleoside reverse transcriptase inhibitors



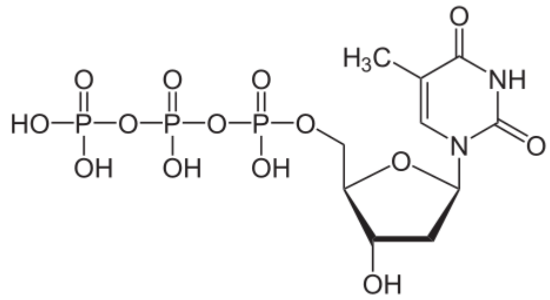
Cytidine



Adenosine



Guanosine



Thymidine

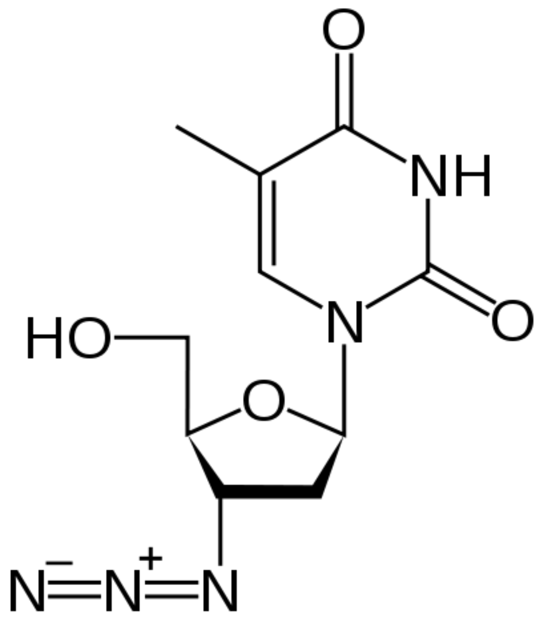
NRTIs

Nucleoside reverse transcriptase inhibitors

- Zidovudine, Lamivudine, Tenofovir, Didanosine
- Similar to nucleotides (ACGT)
- Lack –OH group: terminates DNA chain
- Inhibit reverse transcriptase

Zidovudine

Zidovudine



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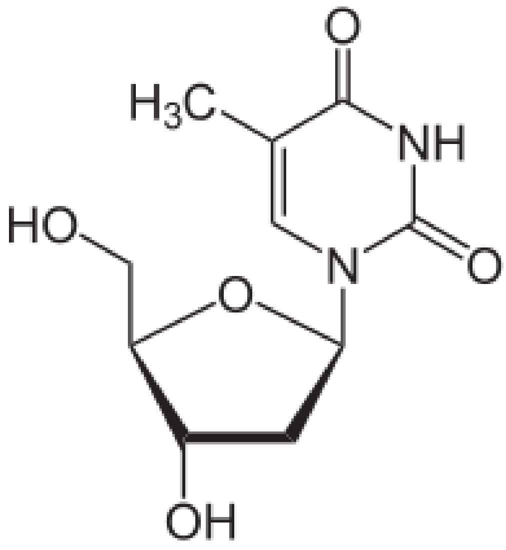
Thymidine



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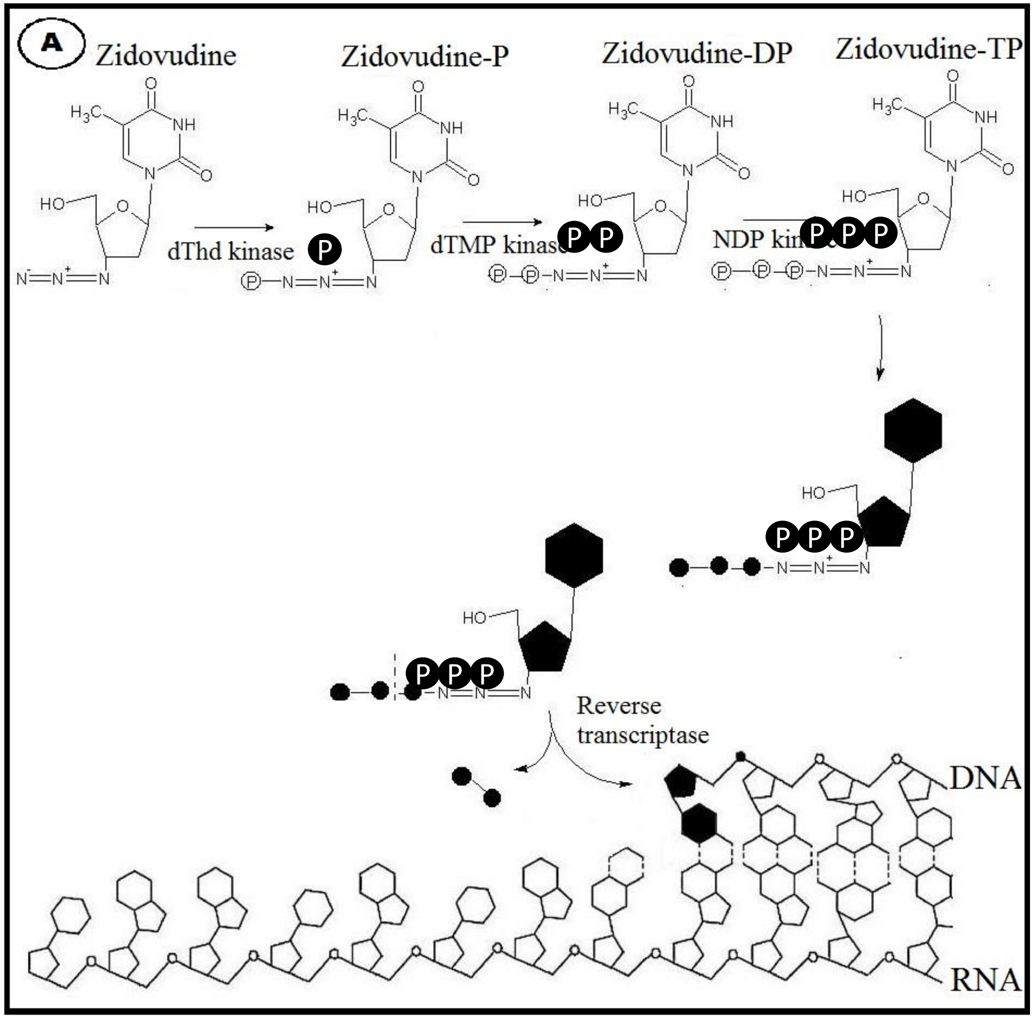
NRTIs

Nucleoside reverse transcriptase inhibitors



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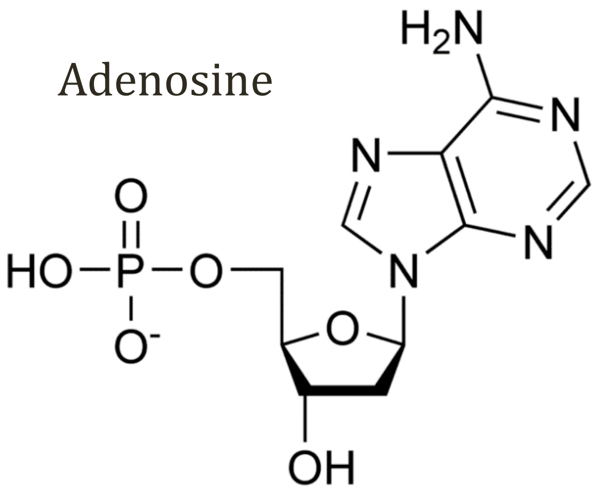
Nucleoside vs. Nucleotide

- Nucleotide
  - Nitrogenous base
  - Sugar
  - Phosphate group
- Nucleoside
  - Base and sugar
  - No phosphate group

Adenosine



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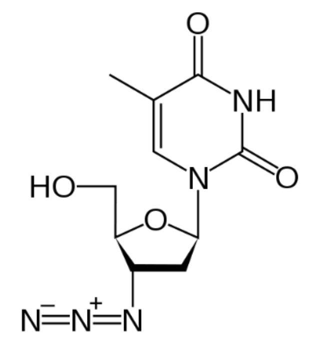
NRTIs

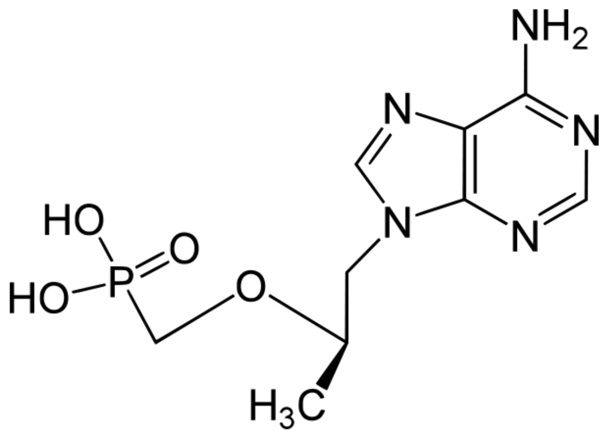
Nucleoside reverse transcriptase inhibitors

- Tenofovir
  - Nucleotide (contains 1 phosphate)
  - Becomes tri-phosphorylated
  - Inhibits RT as mimic of adenosine
- Zidovudine, Lamivudine, others
  - Nucleosides
  - Must be tri-phosphorylated

Zidovudine



Tenofovir



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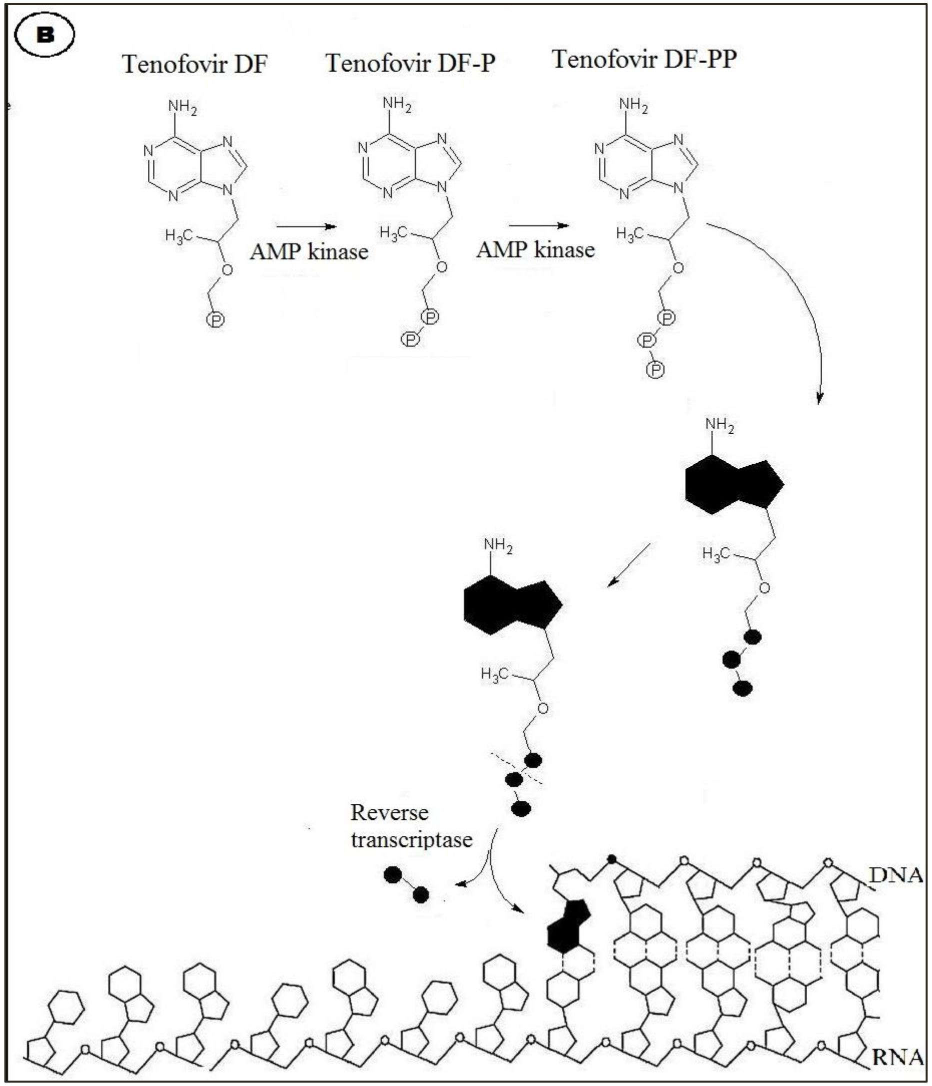
NRTIs

Nucleoside reverse transcriptase inhibitors



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NRTIs

Nucleoside reverse transcriptase inhibitors

- Mitochondrial toxicity
  - Adverse effect of NRTI class
  - DNA polymerase gamma inhibited (mitochondrial enzyme)
  - Loss of mitochondria
- Symptoms:
  - Peripheral neuropathy (pain, paresthesias)
  - Myopathy
  - Pancreatitis
  - Lactic acidosis

Source: Sex Transm Infect. Jun 2001; 77(3): 158–173.

Lactic Acidosis

- Inhibition of oxidative phosphorylation
- Anaerobic metabolism
- Lactic acidosis
- Cases of severe, life-threatening lactic acidosis reported with NRTIs

Zidovudine

- First antiretroviral medication used for HIV
- Bone marrow suppression
- Can be improved with G-CSF or EPO
- Can be given to prevent maternal-fetal infection
  - Prenatally to mothers
  - Also given to infant
  - New WHO guidelines recommend multi-drug combinations to prevent transmission

NRTIs

Nucleoside reverse transcriptase inhibitors

Drug	Nucleotide	Comments
Zidovudine (ZDV)	Thymidine	Bone marrow ↓
Emtricitabine (FTC)	Cytidine	
Abacavir	Guanosine	Fever, rash
Didanosine (ddI)	Adenosine	Pancreatitis
Stavudine (d4T)	Thymidine	Lipodystrophy
Lamivudine (3TC)	Cytidine	Least toxic; Hep B
Tenofovir	Adenosine	GI upset

NRTIs

Nucleoside reverse transcriptase inhibitors

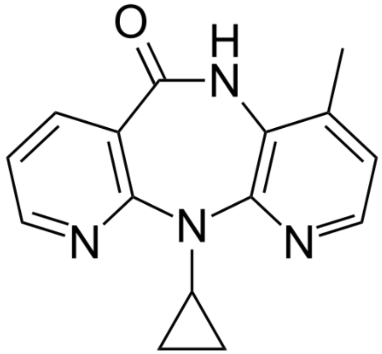
- Tenofovir
  - Fanconi syndrome
  - Loss of proximal tubule function
  - Proteinuria, urinary phosphate wasting, glycosuria
  - Metabolic acidosis, hypophosphatemia, hypokalemia
  - Polyuria, muscle weakness
- www.aidsinfo.nih.gov
  - Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

NNRTIs

Non-nucleoside reverse transcriptase inhibitors

- Nevirapine, Efavirenz, Delavirdine
- Inhibit reverse transcriptase (different site NRTIs)
- Do not require phosphorylation
- Do not suppress bone marrow (only effect RT)
- Not effective for HIV-2 (West Africa)

Nevirapine



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NNRTIs

Non-nucleoside reverse transcriptase inhibitors

- GI upset
- Skin rash (rarely severe SJS)
- Metabolized by P450 system
  - Nevirapine: Inducer
  - Delavirdine: Inhibitor
  - Efavirenz: Mixed

Other HIV Drugs

- Raltegravir
  - Integrase inhibitor
  - Integrase inserts viral DNA into cellular genome
  - Loss of activity disrupts viral life cycle
- Enfuvirtide
  - Binds gp41
  - Inhibits fusion/entry HIV
- Maraviroc
  - Blocks CCR5 on macrophages

Antivirals

Jason Ryan, MD, MPH

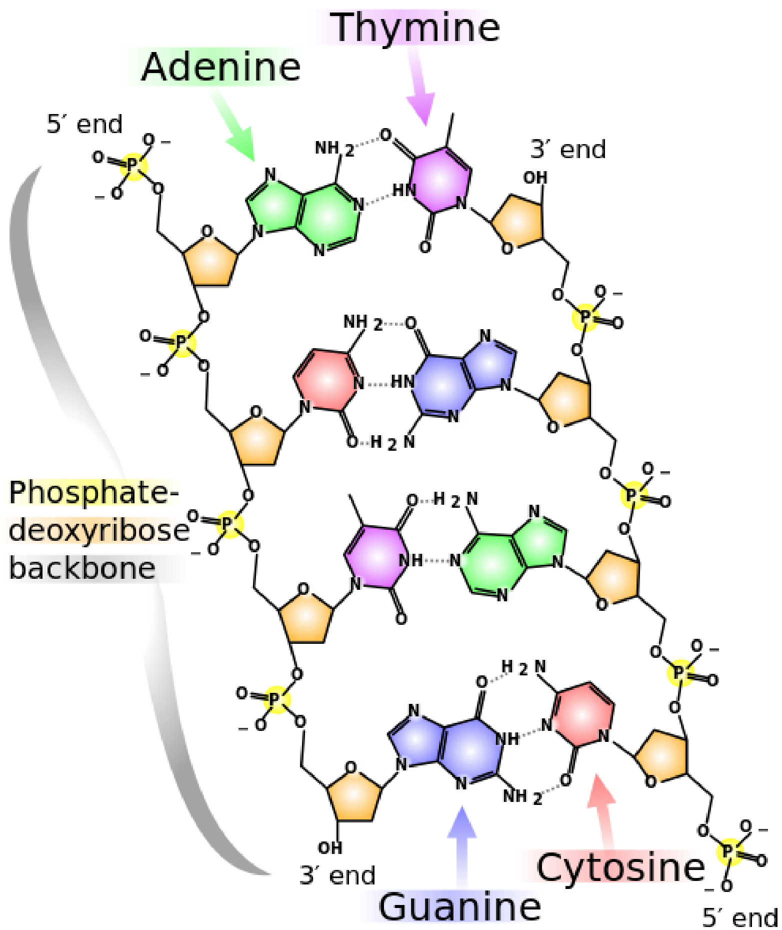
Antiviral Drugs

- Influenza drugs
  - Zanamivir, oseltamivir
- Ribavirin
  - RSV, Hepatitis C
- Acyclovir
  - Herpes viruses
- CMV Drugs
  - Ganciclovir
  - Foscarnet
  - Cidofovir
- Interferon

Zanamivir/Oseltamivir

- Used for treatment of influenza
- Inhibit neuraminidase
  - Enzyme that cleaves sialic acid from glycoproteins
  - Required step in exit from infected cells
- Efficacy only demonstrated 1st 48hrs of illness

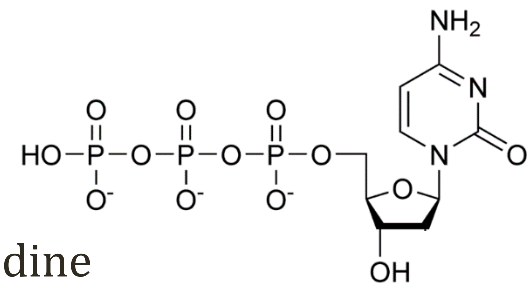
DNA/RNA Drugs
General Principles



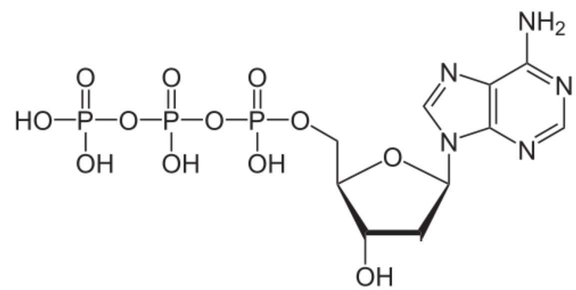
Madeleine Price Ball/Wikipedia

DNA/RNA Drugs

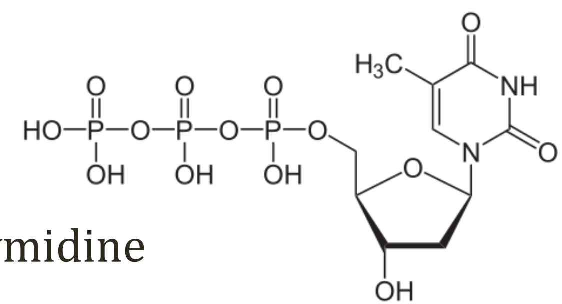
General Principles



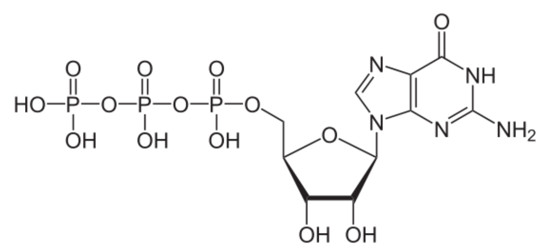
Cytidine



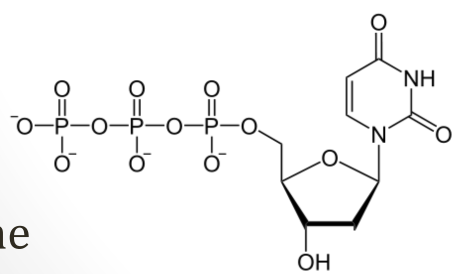
Adenosine



Thymidine



Guanosine



Uridine

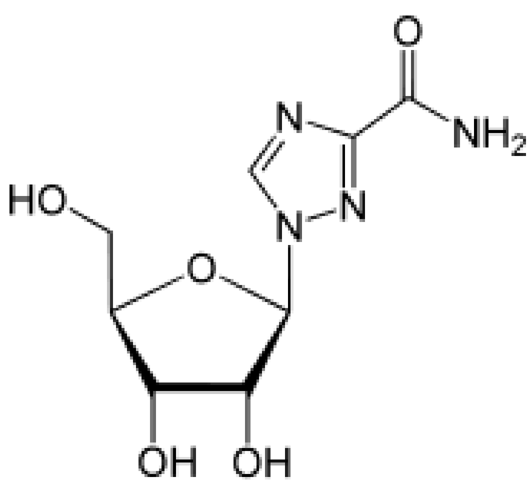
DNA/RNA Drugs

General Principles

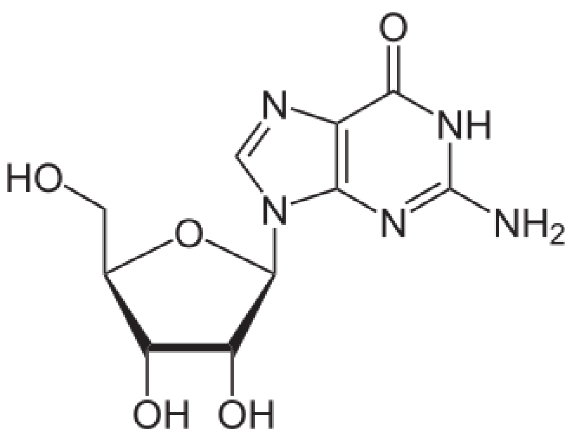
- Many antivirals mimic nucleotides (A, C, G, T)
  - Ribavirin, Acyclovir, Ganciclovir, Cidofovir
- Drug used by DNA or RNA polymerase
- Once used, chain terminates (inhibition)
- "Inhibitors" of RNA/DNA polymerase
- Drugs often need to become tri-phosphorylated
- Viral kinase and/or cellular kinases
- Mutations of viral kinases often lead to resistance

Ribavirin

- Inhibition of RNA polymerase
  - Triphosphorylated by cellular kinase enzymes
  - Binds RNA polymerase, prevents binding correct nucleotides
  - Result: ↓ in viral replication/production of defective virions



Ribavirin



Guanosine

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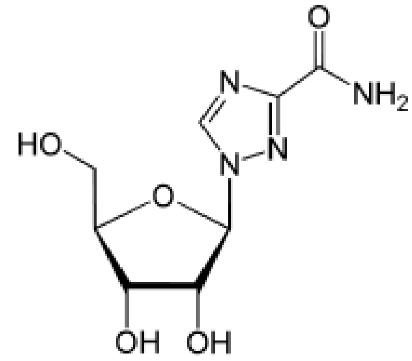
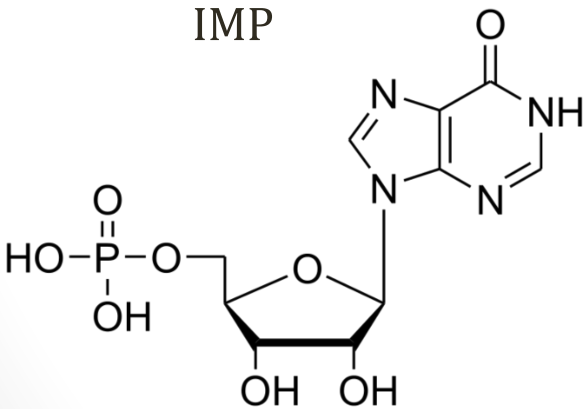
Ribavirin



Ribavirin

- Inhibits IMP dehydrogenase
  - Inosine monophosphate dehydrogenase
  - Used to synthesize guanine nucleotides
  - Inhibited by Ribavirin
  - Decreases pool of available guanine nucleotides

IMP



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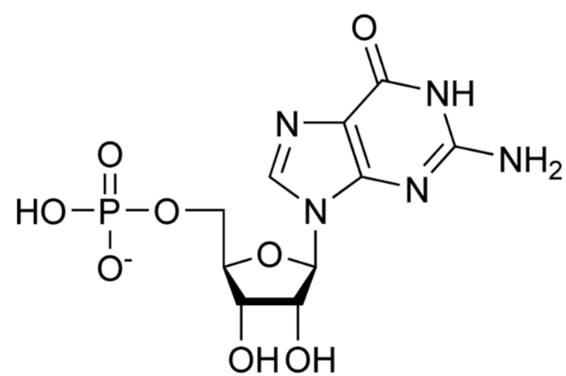
Guanosine Monophosphate



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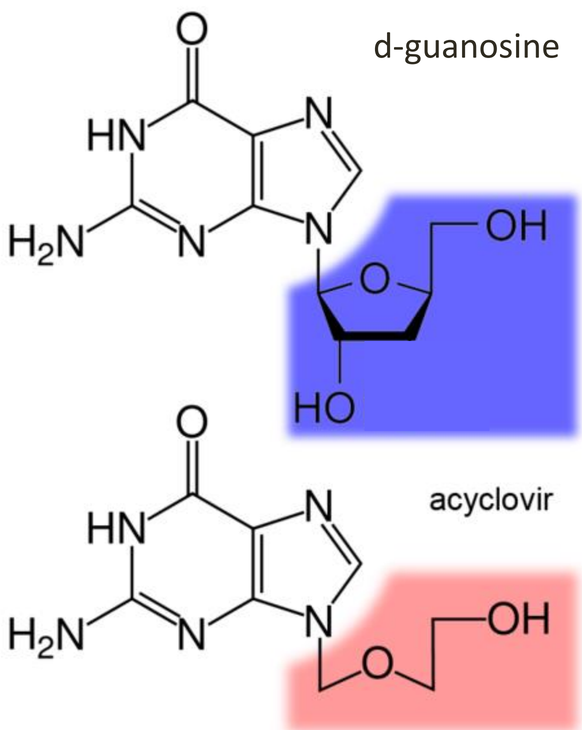
Ribavirin

- Two main modern uses
- RSV in children
- Hepatitis C
  - Often with interferon
- Key side effect: Hemolytic anemia
  - Drug accumulates in RBCs
  - Drug phosphorylation → relative ATP deficiency
  - Hemolytic anemia in ~10% patients
  - Can be severe
- Highly teratogenic

Acyclovir

- Inhibitor of herpes virus DNA polymerase
- Mimics guanosine → terminates chain growth



Self/Wikipedia

Acyclovir

- Phosphorylated by **herpes virus** thymidine kinase
  - Becomes acyclovir monophosphate
  - Only occurs in infected cells (targeted effect)
- Monophosphate → triphosphate by cellular enzymes
- Acts as analog to deoxyguanosine triphosphate (dGTP)
- Inhibits viral DNA polymerase
- Resistance:
  - ↓ viral thymidine kinase
  - Altered viral thymidine kinase
  - Altered viral DNA polymerase (↓ binding acyclovir triphos.)

Acyclovir

- Famciclovir: Similar mechanism
  - Longer half-life (lower dose can be used)
- Valacyclovir: Pro-drug, converted to acyclovir
  - Greater bioavailability (lower dose can be used)
- All 3 drugs generally well tolerated
- Acyclovir: Nephrotoxicity (IV form)
  - Crystalizes in urine
  - Given with IV fluids

Acyclovir

- Effective for HSV-1, HSV-2, and VZV
- Uses
  - Genital herpes
  - Herpes labials
  - Herpes encephalitis
  - Herpes zoster
- Sometimes given for “suppressive” therapy

CMV Drugs

- Used to treat CMV infections
  - HIV/AIDS
  - Transplant patients
- Three key drugs
  - Ganciclovir
  - Foscarnet
  - Cidofovir
- All interfere with CMV DNA polymerase

Ganciclovir

- Similar mechanism to acyclovir (analog to guanosine)
- Intracellular conversion by CMV viral kinase
  - Becomes ganciclovir 5'-monophosphate
- Monophosphate → triphosphate by cellular enzymes
- Acts as analog to deoxyguanosine triphosphate (dGTP)
- Incorporation terminates chain growth

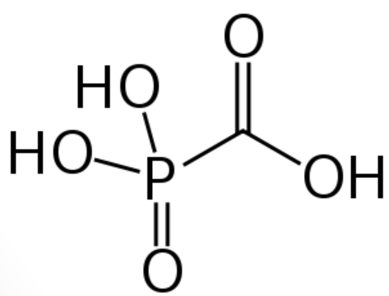
Ganciclovir

- Major toxicity:
  - Bone marrow suppression especially leukopenia
  - Inhibits bone marrow DNA polymerase
- Valganciclovir
  - Pro-drug
  - Converted to ganciclovir
  - Better bioavailability
- Ganciclovir given primarily IV (poor bioavailability)
- Oral valganciclovir preferred for oral dosing

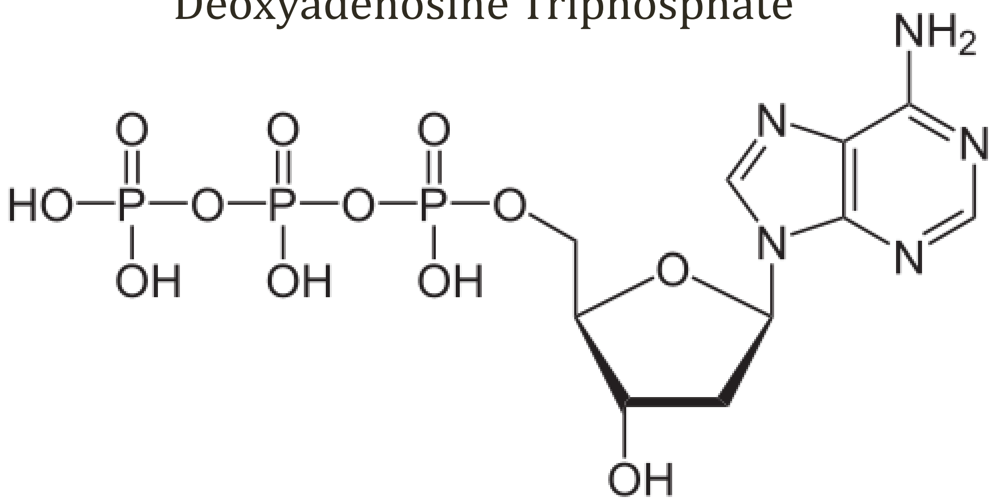
Foscarnet

- Pyrophosphate analog
- Binds/inhibits viral DNA polymerase
- Blocks cleavage pyrophosphate from triphosphates
- Stops DNA chain elongation

Foscarnet



Deoxyadenosine Triphosphate



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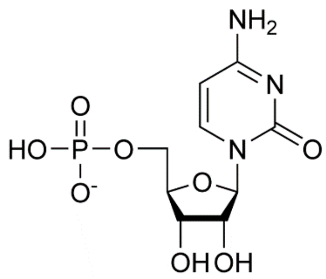
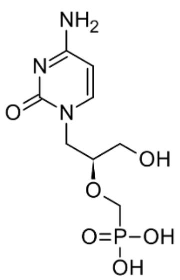
Foscarnet

- Uses:
  - CMV when Ganciclovir fails
  - Acyclovir-resistant HSV and VZV
- Side effects
  - Nephrotoxicity (limiting side effect)
  - Chelates calcium (hypocalcemia)
  - Induces renal wasting of magnesium (hypomagnesaemia)
  - Seizures (often related to electrolytes)

Cidofovir

- Nucleotide analog (cytidine)
- Cellular phosphorylation
  - No viral kinase required
- Inhibits viral DNA polymerase
- Main use is CMV retinitis
- Main toxicity is renal failure
  - Co-administer with saline
  - Probenecid (blocks renal tubular secretion of drug)





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Interferons

- Cytokines
- Glycoproteins synthesized by infected cells
- Numerous immunomodulatory effects
- Interferon α
  - Hepatitis B and C
  - Kaposi sarcoma (HHV-8)