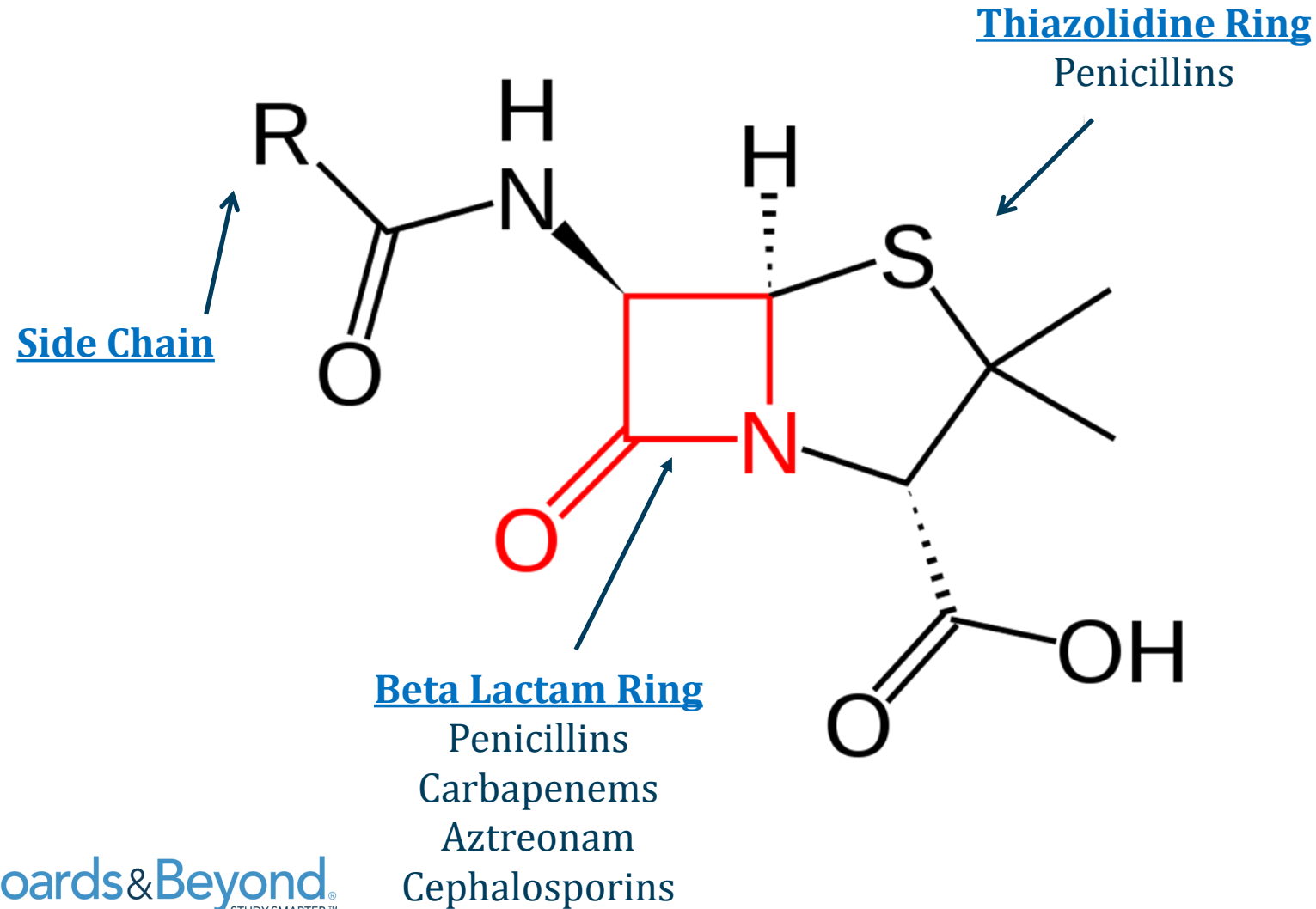


# Penicillins

Jason Ryan, MD, MPH



# Penicillins

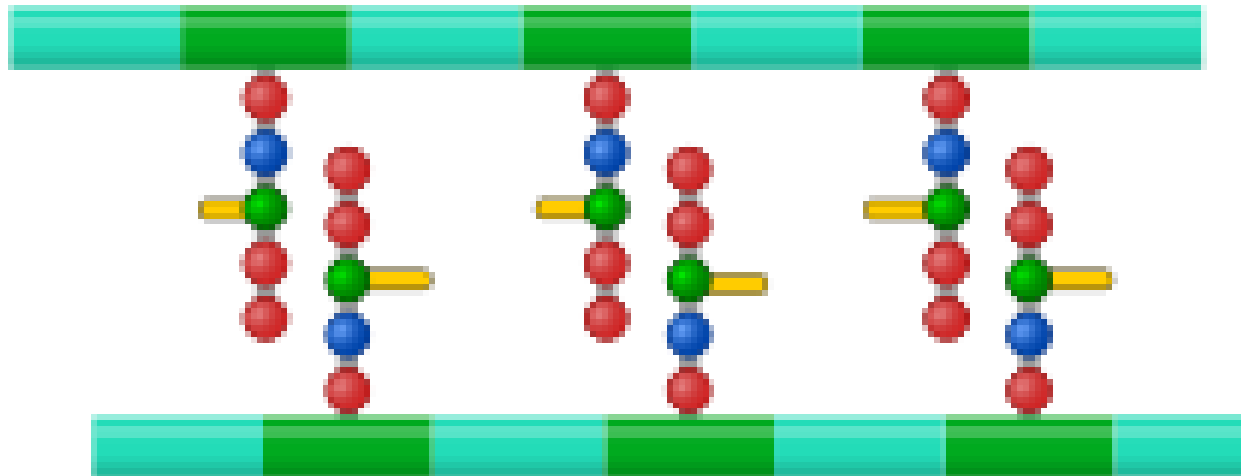


# Penicillins

## Mechanism of Action

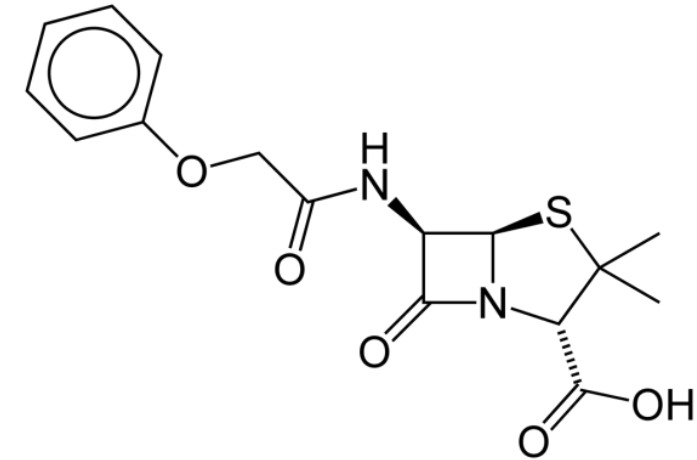
- Inactivates bacterial **transpeptidases**
- Inability to crosslink cell walls
- Wall breakdown → **autolysis**
- All  $\beta$ -lactam antibiotics: similar mechanism

Bacterial Cell Wall

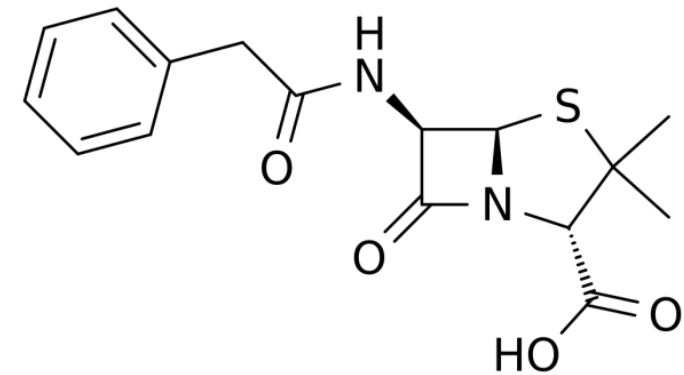


# Natural Penicillins

- Penicillin G (IM and IV)
- Penicillin VK (oral)
- Few modern uses due to resistance
- Inactivated by bacterial **beta lactamase enzymes**
  - Degrade beta lactam compounds
  - Found in many gram negative bacteria
  - Also Staphylococcus aureus (gram positive)



Penicillin G



Penicillin VK

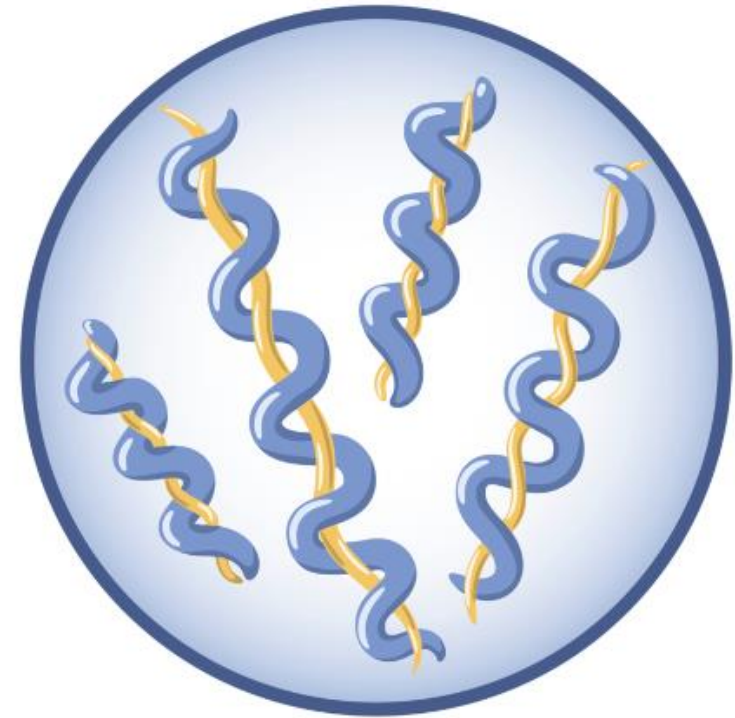


# Penicillin G and VK

## Clinical Uses

- **Treponema pallidum (syphilis)**
- Sickle cell disease
  - Prophylaxis in children against pneumococcal infection
- Rheumatic fever
  - Secondary prophylaxis against recurrent attacks
  - Pen G every 21 to 28 days

Treponema pallidum



# Penicillin G and VK

## Clinical Uses

- Actinomyces (gram positive rod)
  - Neck or facial mass often after dental work
- Strep pharyngitis
  - Group A strep sensitive to penicillin
- Pregnancy
  - Intrapartum prophylaxis for group B strep

## Actinomyces

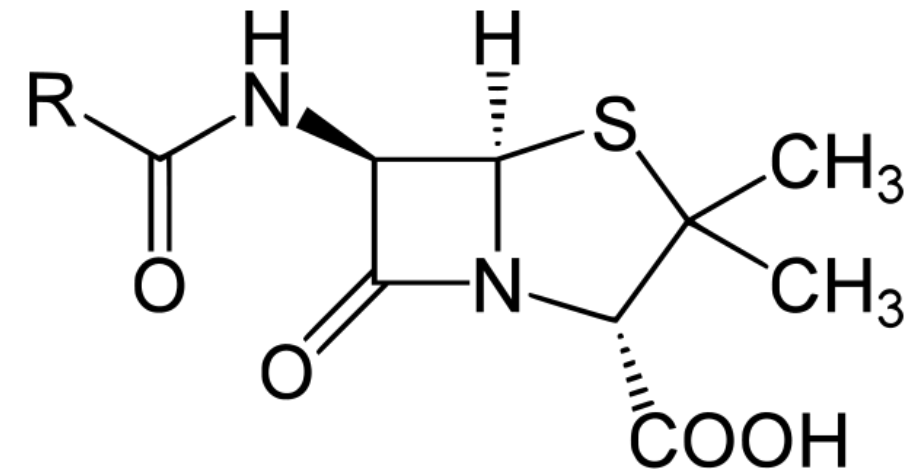


# Group B Strep Infection

## Intrapartum Antibiotic Prophylaxis

- Administer at least 4 hours prior to delivery
- First-line: **penicillin** or **ampicillin**
  - Rapidly accumulate in amniotic fluid
- Penicillin allergy with low anaphylaxis risk (rash): **cefazolin**
- High anaphylaxis risk allergy: **GBS isolate testing**
  - Determine clindamycin sensitivity
  - Clindamycin for sensitive isolates
  - GBS resistant to clindamycin: vancomycin
- Avoid fetal scalp electrode if possible

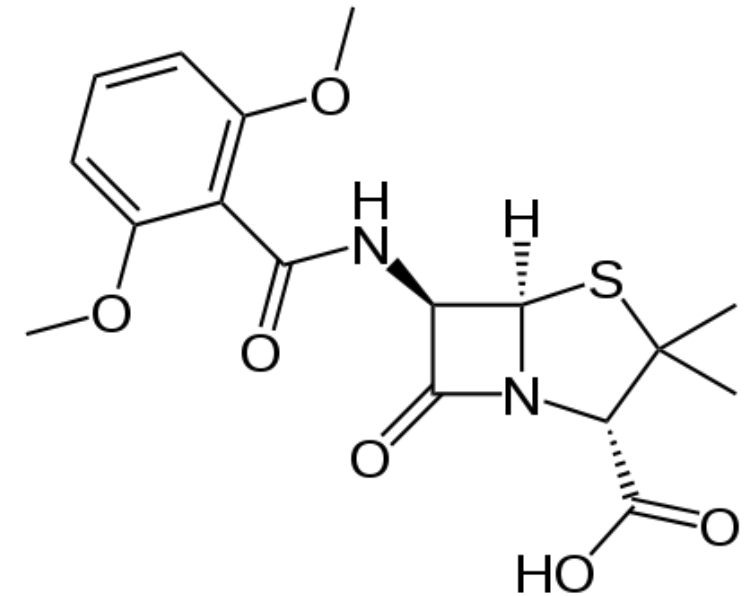
Penicillin



# Antistaphylococcal Penicillins

Oxacillin, nafcillin, dicloxacillin

- Dicloxacillin (oral)
- Nafcillin and oxacillin (intravenous)
- Side chain protects from **staphylococcal beta lactamase**
- Prototype: methicillin
  - No longer used
  - High frequency of adverse effects (interstitial nephritis)
- Covers **methicillin-sensitive staph aureus (MSSA)**
  - Also most streptococci
  - Good “gram positive coverage”



Methicillin

# MSSA versus MRSA

- **MSSA:** Methicillin-sensitive staph aureus
  - Treated with 1<sup>st</sup> generation cephalosporins or antistaphylococcal penicillins
- **MRSA:** Methicillin-resistant staph aureus
  - Treated with vancomycin or alternative drugs
- New staph infection: **methicillin sensitivity unknown**
  - All blood stream or serious infections: presumed MRSA until blood culture results known
  - Cellulitis or impetigo: presumed MSSA in mild cases unless MRSA risk factors present
  - Prior MRSA infection, hospital-acquired infection, long-term care resident



# Antistaphylococcal Penicillins

Oxacillin, nafcillin, dicloxacillin – common uses

- **Community acquired cellulitis**
  - Alternative: first generation cephalosporin
- **Impetigo**
  - Cephalosporins or dicloxacillin
- Other infections based on culture data

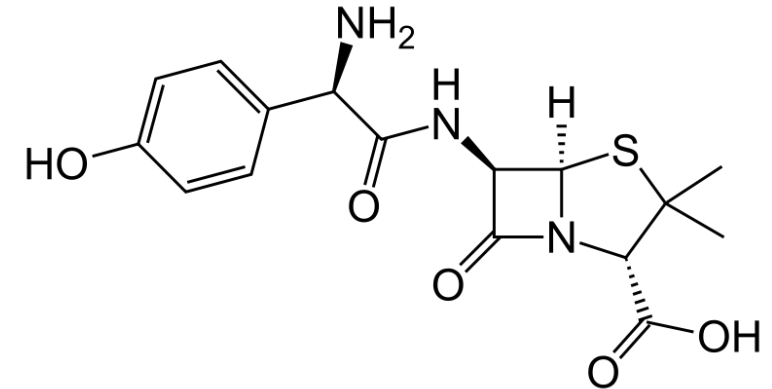
Impetigo



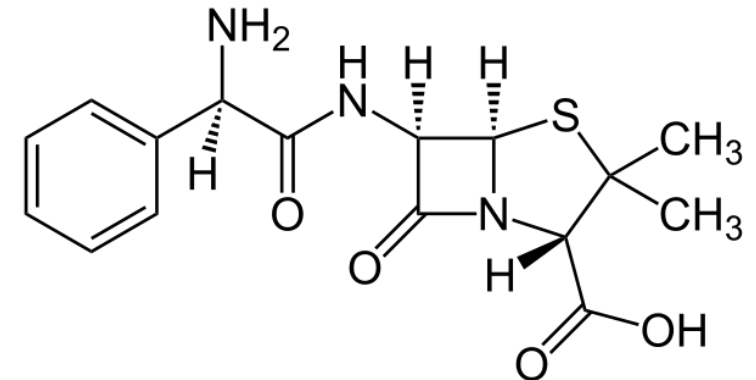
# Aminopenicillins

## Amoxicillin/Ampicillin

- Amoxicillin (oral)
- Ampicillin (IV)
- Penetrate gram negative bacterial porin channels
- Increased activity against **gram-negative bacteria**
  - Especially H. influenzae
- Also covers gram positive bacteria (not MRSA)
- Sensitive to beta lactamase enzymes



Ampicillin



Amoxicillin



# Aminopenicillins

Amoxicillin/Ampicillin

- **Otitis media**
  - *S. pneumoniae*, non-typeable *H. influenzae*, and *Moraxella catarrhalis*
  - Amoxicillin used unless risk factors present for *H. influenzae* resistance (beta lactamase)
- **Listeria gastroenteritis**
  - Febrile, diarrheal illness
  - Caused by contaminated food (uncooked meat, unpasteurized milk)
  - No treatment for immunocompetent, non-pregnant adults age < 65
  - Treated with amoxicillin or ampicillin (pregnancy, age > 65)

**Otitis Media**



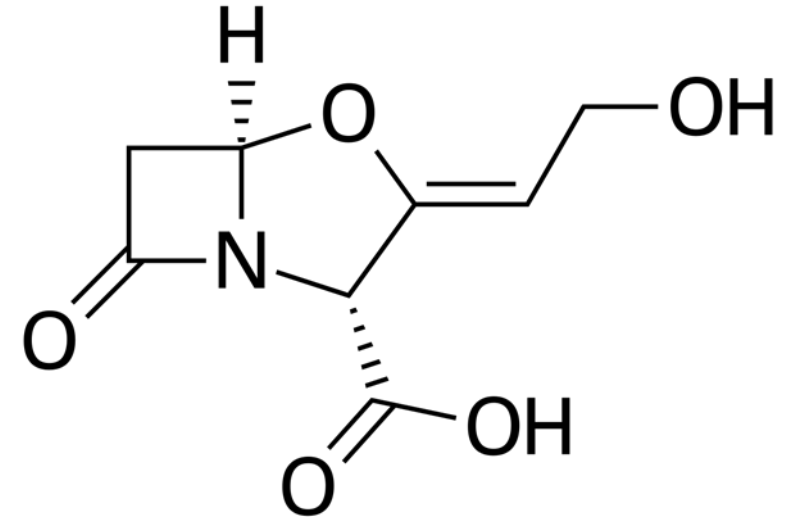
Michael Hawke MD/Wikipedia



# $\beta$ -Lactamase Inhibitors

Clavulanic acid, sulbactam, tazobactam

- Inhibit bacterial  $\beta$ -lactamase
- Added to some penicillins to expand coverage
- Little or no effect used alone
- Combination drugs: “broad spectrum” antibiotics
  - Gram positives
  - Gram negatives



Clavulanic Acid

# Aminopenicillins

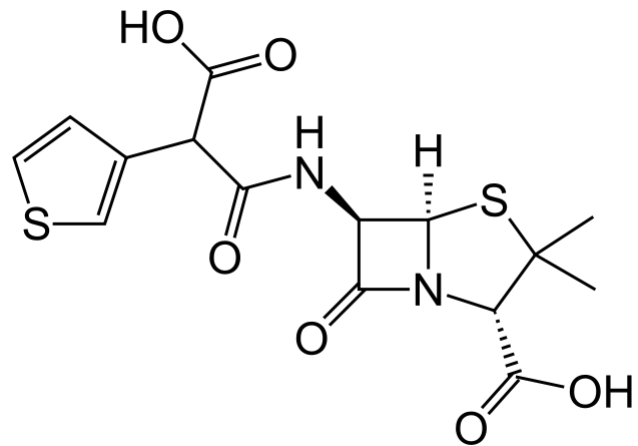
## Combination antibiotics

- Amoxicillin-clavulanic acid (Augmentin; oral)
- Ampicillin-sulbactam (Unasyn; intravenous)
- Increased activity against *S. aureus* and *H. influenzae*
- Increased activity against anaerobes (*B. fragilis*)
- Not effective against *Pseudomonas aeruginosa* or MRSA
- Severe otitis media/sinusitis (↑ effectiveness against *H. influenza*)
- Bite wounds (polymicrobial with anaerobes)

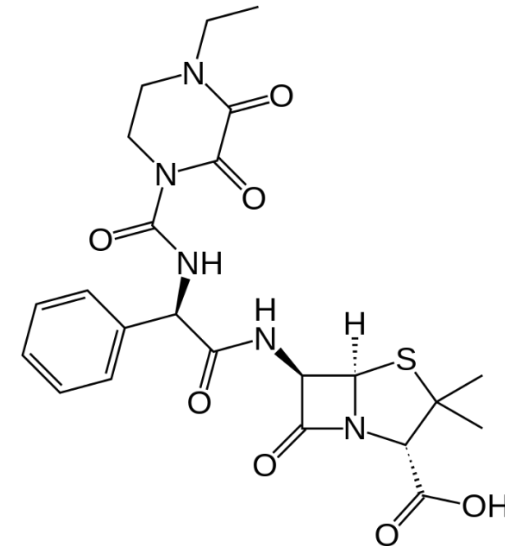
# Antipseudomonal Penicillins

Ticarcillin, piperacillin

- Greater gram negative efficacy
- Effective against *Pseudomonas aeruginosa*
- More gram (-) coverage compared to aminopenicillins



Ticarcillin

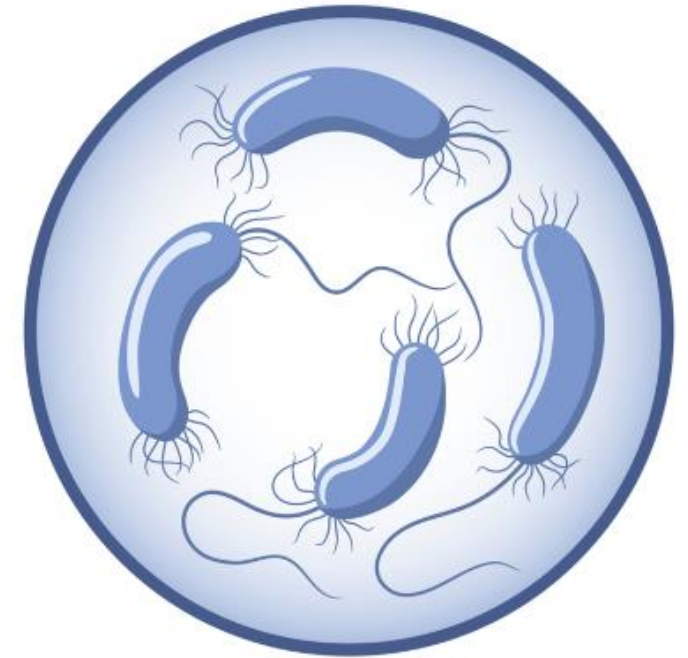


Piperacillin

# Pseudomonas Aeruginosa

- Gram negative rod
- Resistant to many classes of antibiotics
- Sepsis, pneumonia and urinary infections
- Respiratory infection in cystic fibrosis
- Wound infections in burn patients
- Otitis externa (swimmer's ear)

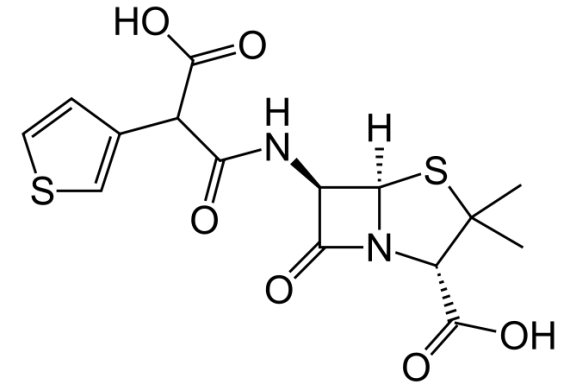
*Pseudomonas aeruginosa*



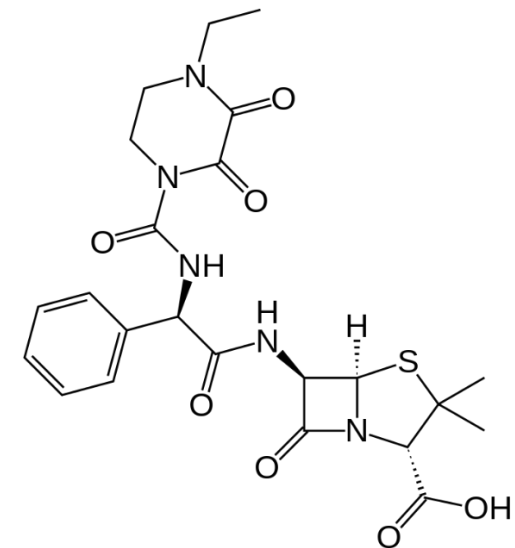
# Antipseudomonal Penicillins

Ticarcillin, piperacillin

- Susceptible to  $\beta$ -lactamases
- **Given with  $\beta$ -lactamase inhibitor**
  - Ticarcillin-clavulanate (Timentin)
  - Piperacillin-tazobactam (Zosyn)
- Broad-spectrum antibiotics
  - Most gram-positive (not MRSA)
  - Most gram-negative (pseudomonas)
  - Most anaerobic bacteria
- Hospitalized patients with sepsis or critical illness



Ticarcillin



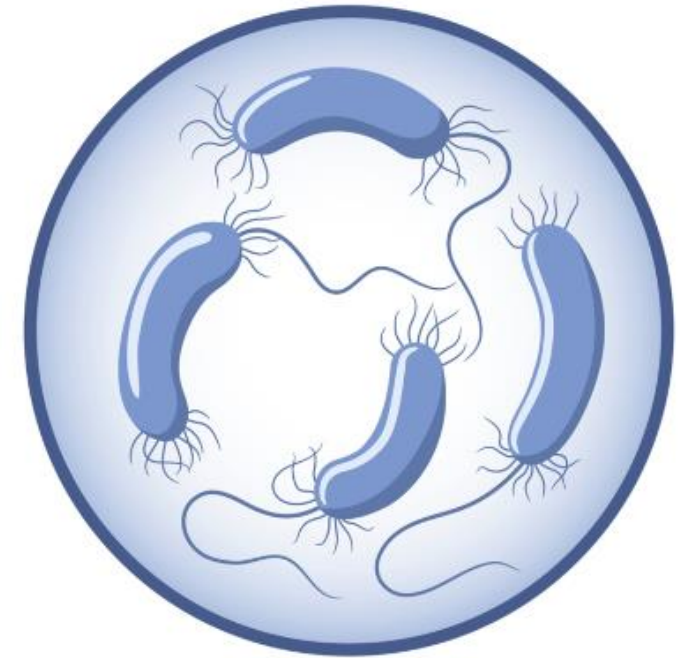
Piperacillin

# Pseudomonas Aeruginosa

## Anti-Pseudomonal antibiotics

- Ticarcillin-clavulanate
- Piperacillin-tazobactam
- Cephalosporins
  - Ceftazidime
  - Cefepime
- Aztreonam (monobactam)
- Fluoroquinolones: ciprofloxacin
- Carbapenems: meropenem and doripenem

Pseudomonas aeruginosa



# Penicillin Adverse Effects

## Hypersensitivity reactions

- Allergic reaction common with penicillins
- 1<sup>st</sup> exposure: sensitization
- 2<sup>nd</sup> exposure: hypersensitivity reaction
- Symptoms resolve on stopping drug
- Mainstay of treatment: avoidance of offending drug

# Penicillin Adverse Effects

## Hypersensitivity reactions

- **Immediate reactions**
  - Usually within **first hour** after receiving drug
  - Usually type I hypersensitivity
  - IgE-mediated through histamine release
- **Delayed (non-immediate) reactions**
  - Occur after multiple doses
  - Often develop days into treatment



# Penicillin Adverse Effects

## Immediate reactions

- Urticaria and itching
- Bronchospasm
- Anaphylaxis
- Diagnosis: clinical or skin testing
- Treatment based on severity of symptoms



# Penicillin Adverse Effects

Delayed reactions - maculopapular rash

- Cell-mediated (not IgE)
- Most common with **aminopenicillins**
- Maculopapules
- Itchy or may be non-pruritic
- Absence of fever, wheezing, joint pain
- **Days or weeks** after starting drug

Maculopapular Rash

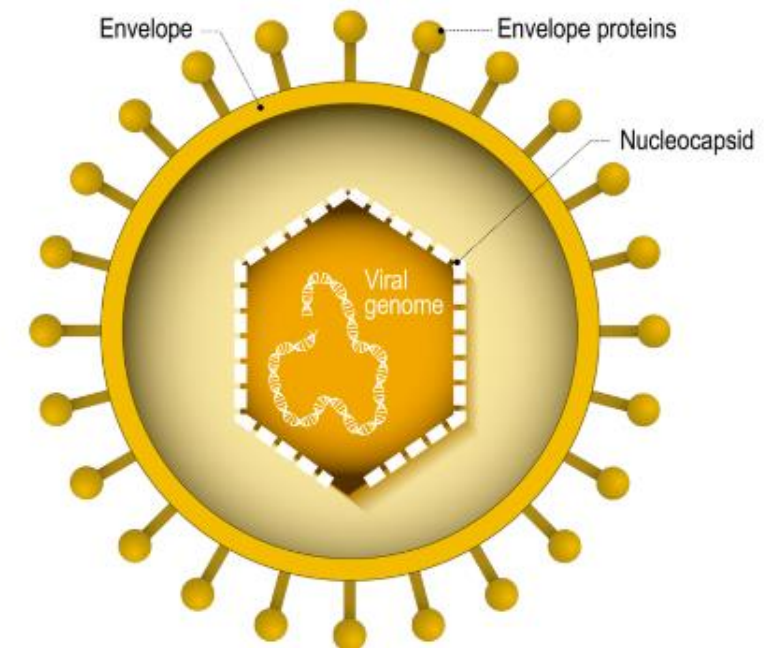


# Penicillin Adverse Effects

Delayed reactions - maculopapular rash

- More common in patient with viral infections
- Classically occur with **EBV pharyngitis**
- Aminopenicillin given for pharyngitis → maculopapular rash
- Mechanism not clear

**EBV**  
Epstein-Barr virus



# Penicillin Adverse Effects

## Delayed reactions – mucocutaneous reactions

- Stevens-Johnson syndrome
  - Necrosis and detachment of epidermis
  - Fever
  - Sloughing of skin
  - Vesicles, blisters
- Toxic epidermal necrolysis (>30% skin)
- Mortality: SJS 1-5%; TEN 25-35%
- Antibiotic associations:
  - Sulfonamides (TMP-SMX)
  - Aminopenicillins
  - Cephalosporins

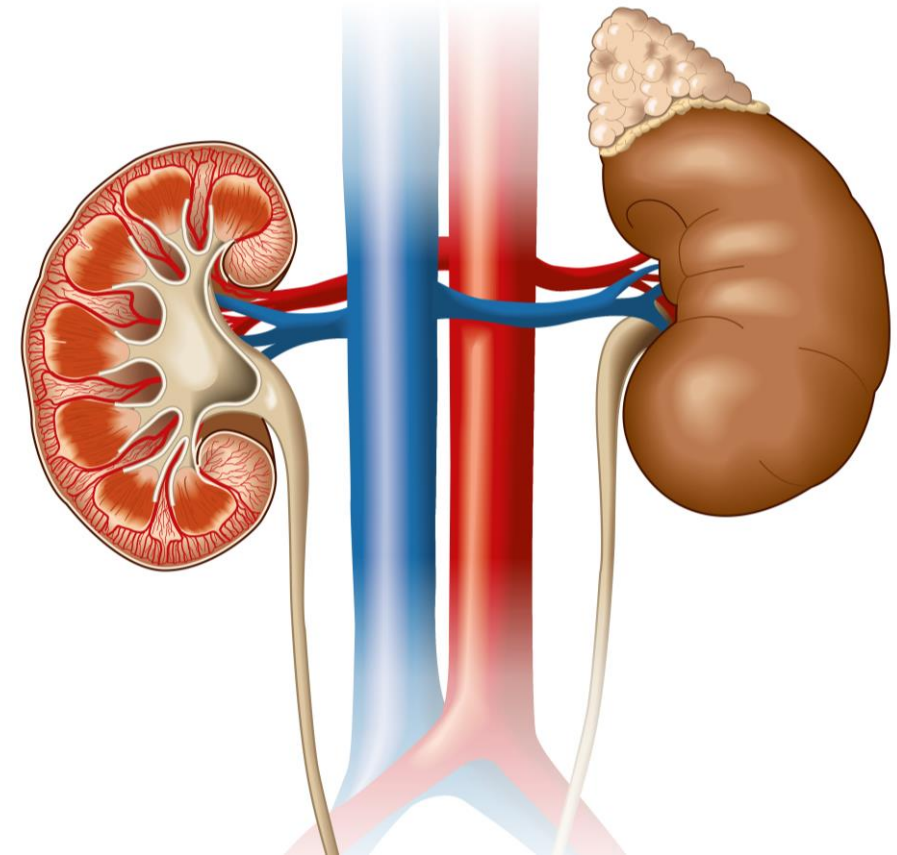




# Penicillin Adverse Effects

Delayed reactions – interstitial nephritis

- Drug acts as hapten → immune response in kidneys
- Fever
- Oliguria
- Increased BUN/Cr
- Eosinophils in urine
- Urinary white cells and WBC casts (“sterile pyuria”)



# Penicillin Adverse Effects

## Delayed reactions – cytopenias

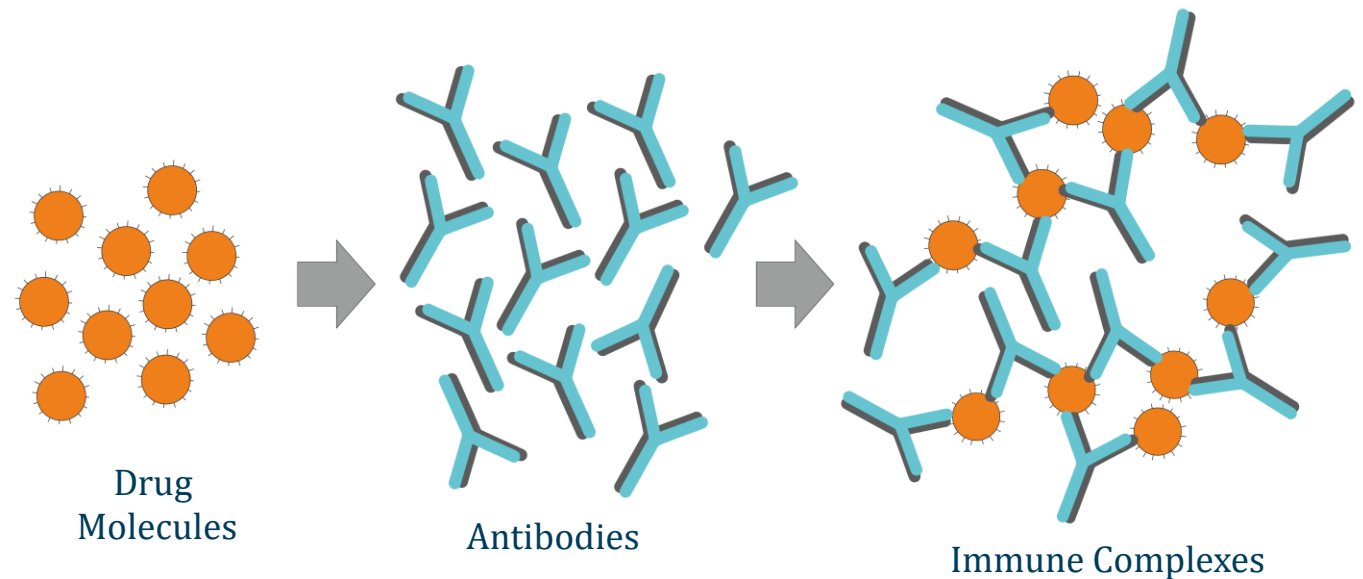
- High doses of PCN can lead to **autoimmune hemolytic anemia**
  - PCN binds to surface RBCs (hapten)
  - Elicits immune response
  - Antibodies against PCN bound to RBCs
  - Direct Coombs test positive
- Thrombocytopenia, neutropenia also reported with some penicillins



# Penicillin Adverse Effects

Delayed reactions – serum sickness

- **Immune complex disorder**
  - Circulating immune complexes form (IgG antibody-drug molecules)
  - Wide-spread deposition in tissues and organs
- Fever
- Arthritis
- Urticaria
- Lymphadenopathy

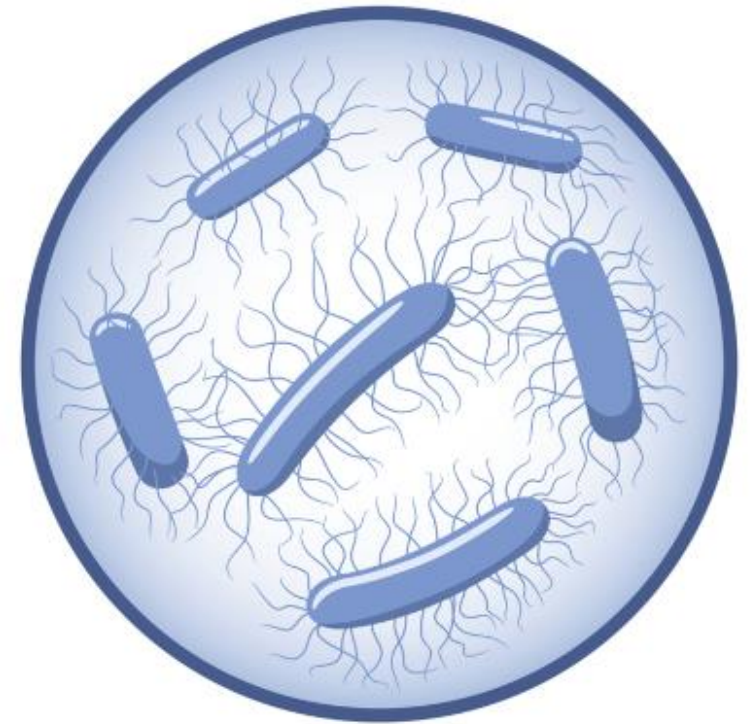


# Penicillin Adverse Effects

## C. difficile infection

- Diarrhea following antibiotic therapy
- Antibiotic depletes normal intestinal flora
- C. difficile growth → pseudomembranous colitis
- May occur with any antibiotic
- Frequent associations
  - 3rd and 4th generation cephalosporins
  - Broad spectrum penicillins
  - Clindamycin
  - Fluoroquinolones

## Clostridium difficile





# Jarisch-Herxheimer Reaction

- Occurs with penicillin therapy for spirochete infections
- Classically occurs in **syphilis**
- Febrile syndrome
- Fever, chills, flushing, hyperventilation
- Rash of syphilis may worsen
- Usually starts ~2 hours after starting therapy
- Due to bacterial cell death → immune response
- Transient syndrome: resolves 24 to 48 hours

Syphilis

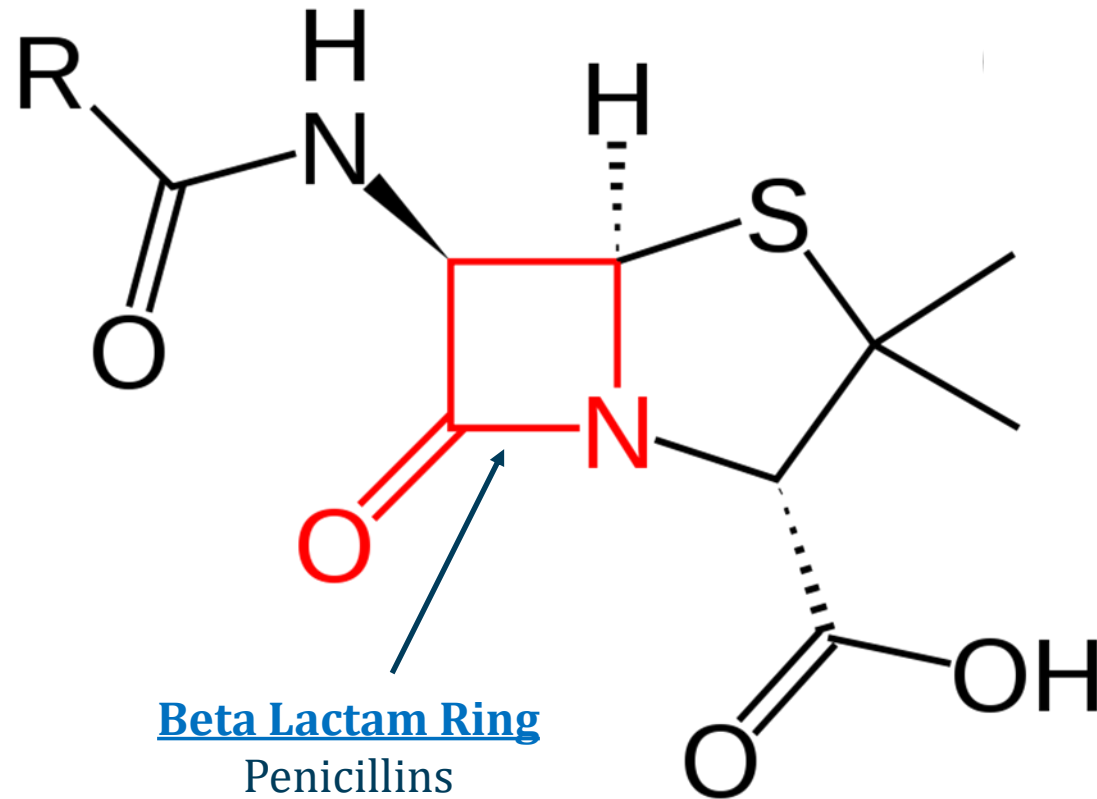


# Beta Lactams

Jason Ryan, MD, MPH



# Penicillin Structure



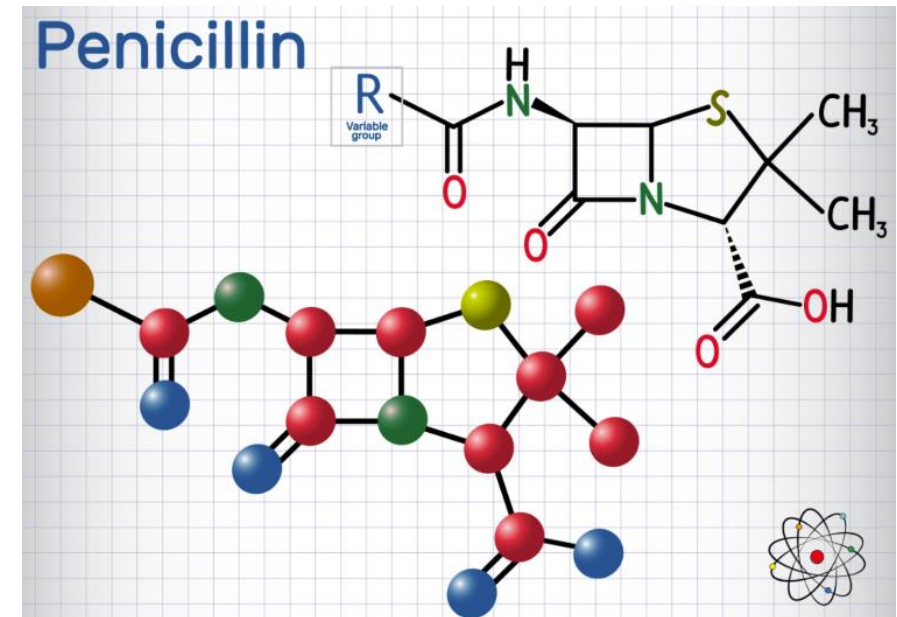
Beta Lactam Ring

Penicillins  
Carbapenems  
Aztreonam  
Cephalosporins

# Beta Lactam Antibiotics

Carbapenems, Aztreonam, Cephalosporins

- Similar mechanism to penicillin
  - Bind transpeptidases
  - Prevent peptidoglycan crosslinking in cell wall
  - Autolysis
- Potentially susceptible to beta lactamase enzymes



# Carbapenems

Imipenem, meropenem, ertapenem, doripenem

- $\beta$ -lactam drugs resistant to cleavage by most  $\beta$ -lactamase
- Effective against **ESBL-producing bacteria**
  - Extended Spectrum Beta Lactamase
  - Found only in gram-negative bacteria (e.g., pseudomonas)
  - Bacteria **highly-resistant to many antibiotics**



# Carbapenems

Imipenem, meropenem, ertapenem, doripenem

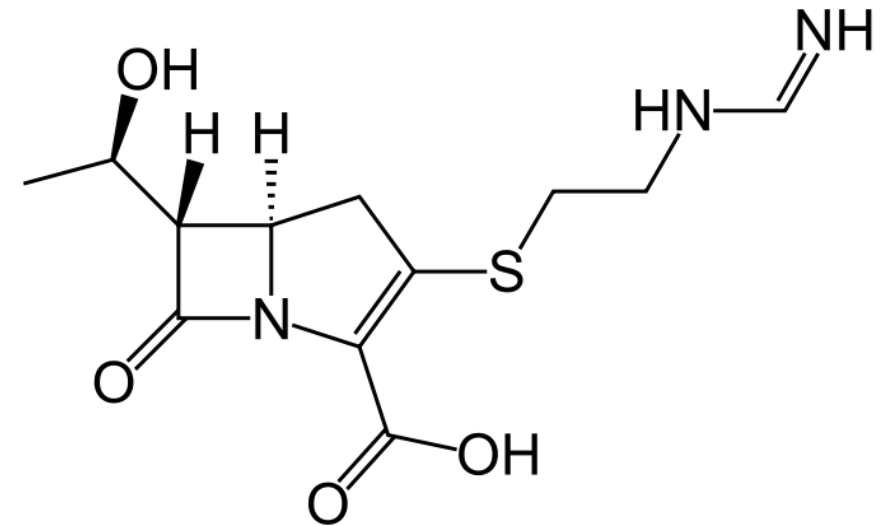
- Drug of choice for ESBL bacteria
- Key drug for **enterobacter** which is resistant to many drugs
- Broad spectrum:
  - Gram positive
  - Gram negative including most pseudomonas
  - Anaerobes including B. fragilis
- Used in hospitalized patients
  - Sepsis or pneumonia
  - Meningitis
  - Intra-abdominal infections

Enterobacter Colonies



# Imipenem

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

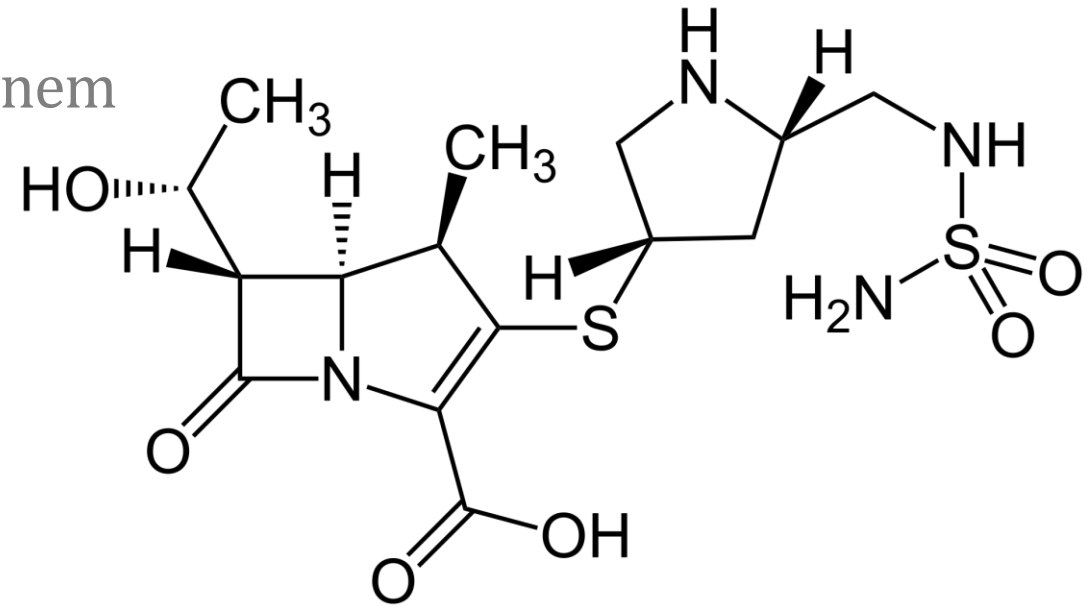


Imipenem

# 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: once daily dosing
  - Some resistance in ESBL bacteria
  - Weaker activity against pseudomonas



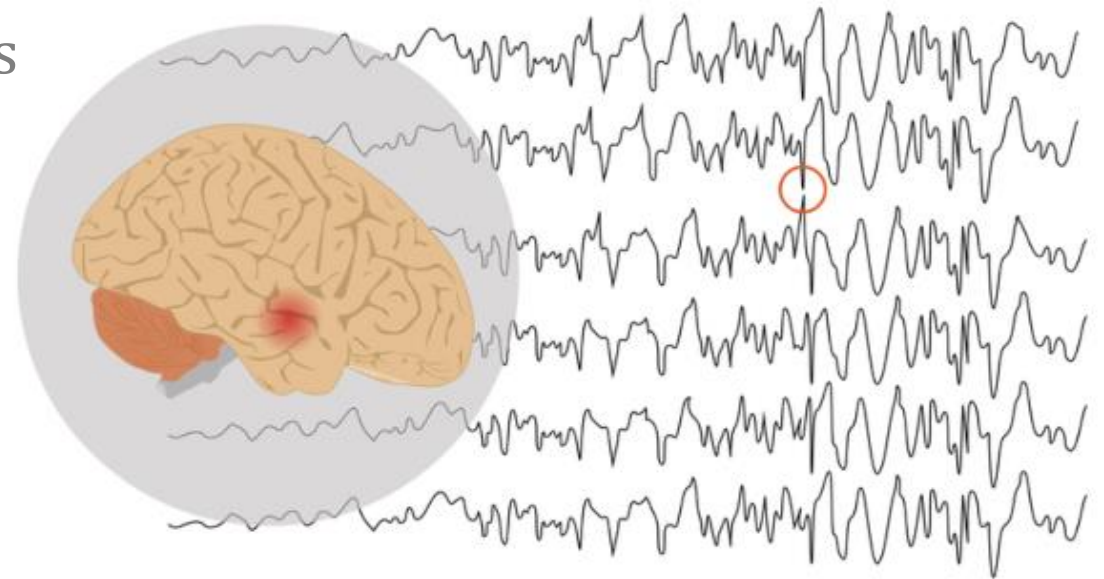
Doripenem



# Carbapenems

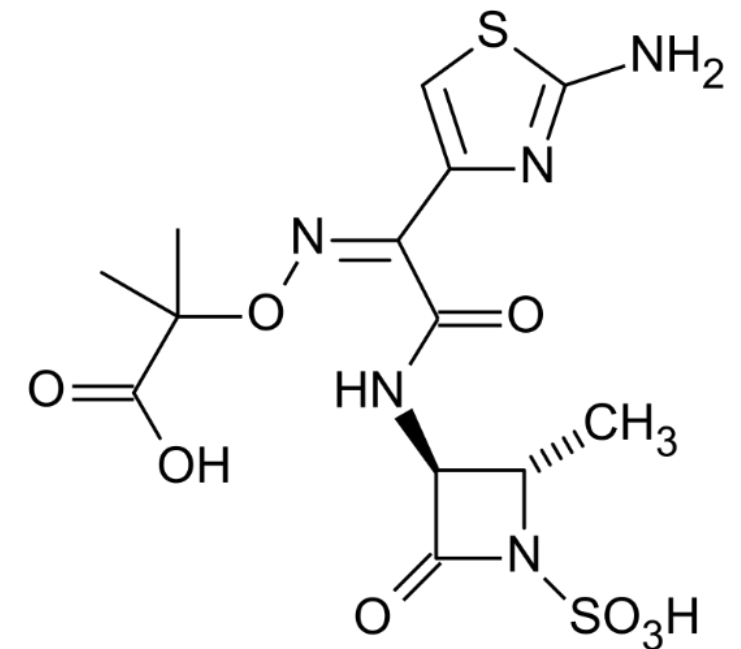
Imipenem, meropenem, ertapenem, doripenem

- Risk of central nervous system toxicity
- May cause **seizures**
  - Especially at high doses or with renal failure
  - Best described for imipenem (not used for meningitis)
  - Lower risk with **meropenem**
- Also change in mental status or myoclonus



# Aztreonam

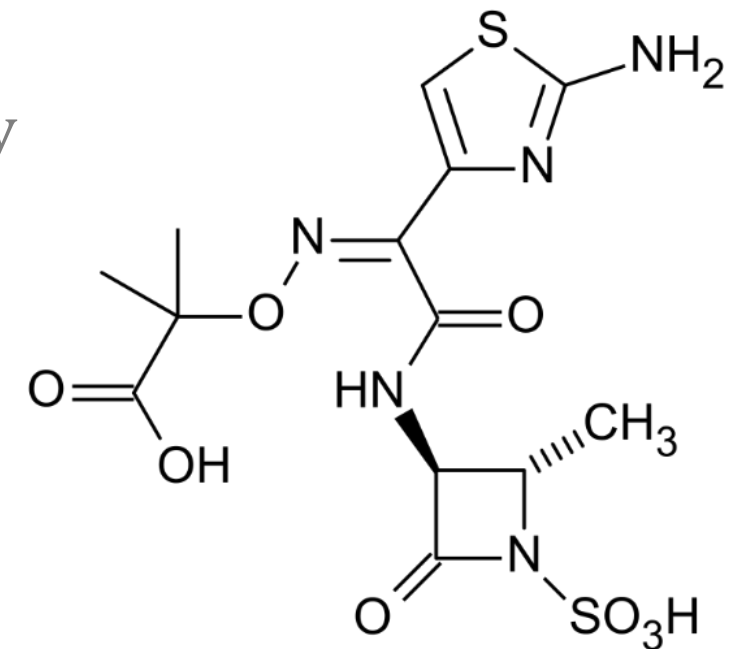
- Monobactam:  $\beta$ -lactam ring not fused to another ring
- Limited susceptibility to  $\beta$ -lactamase enzymes
- Binds penicillin-binding protein 3 (PBP-3)
  - Found in gram negative bacteria
- Only active against **gram (-) bacteria**
- Active against **pseudomonas**
- No activity against gram positive bacteria or anaerobes



Aztreonam

# Aztreonam

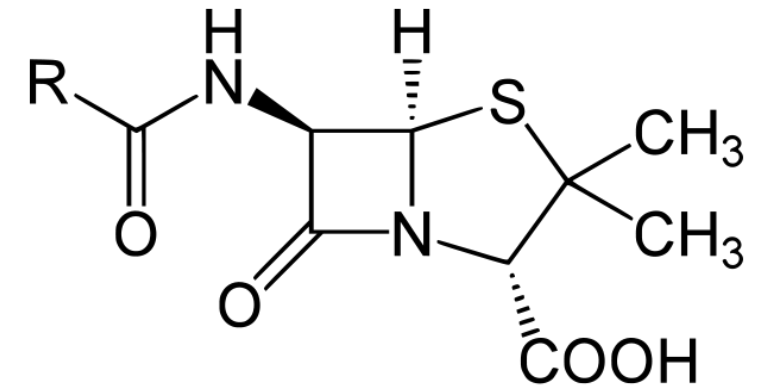
- Intravenous administration (hospitalized patients)
- Synergistic with **aminoglycosides**
- No cross reactivity in **penicillin allergic patients**
- Can be used in patients with prior severe hypersensitivity



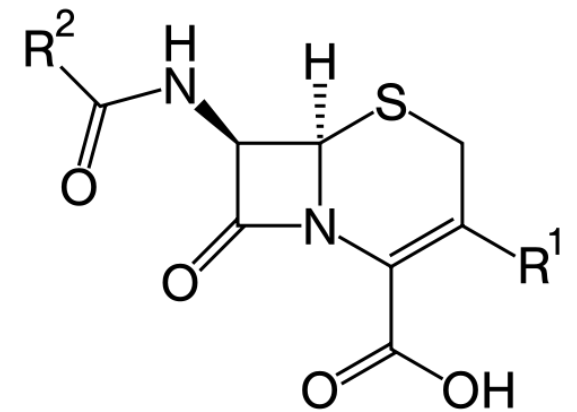
Aztreonam

# Cephalosporins

- Class of beta lactam antibiotics
- Divided into generations
- 1<sup>st</sup> generation: mostly gram positive coverage
- Successive generations: increased gram (-) coverage
- All named Cef- or Cep-



Penicillin



Cephalosporin

# First Generation Cephalosporins

## Cefazolin

- Developed to treat *S. aureus* resistant to penicillin
- Only cefazolin available in US
- Covers many **gram positives** including **methicillin-sensitive *S. aureus* (MSSA)**
  - Does not treat MRSA
- Some limited gram negative and anaerobic coverage
- Often used against **skin flora**
  - Nonpurulent cellulitis
  - Surgical wound (skin) infections
  - Pre-op for prevention of skin infections



# Second Generation Cephalosporins

Cefuroxime, cefaclor, cefprozil, cefoxitin, cefotetan

- Developed to treat amoxicillin-resistant infections
- Increased **gram negative coverage**
  - H. influenzae, Enterobacter, Proteus
  - E. coli, Klebsiella, Serratia, N. gonorrhoeae
- Increased **anaerobic coverage** (B. fragilis)
- Gram positive coverage but less active against S. aureus
- Cefoxitin and cefotetan: cephamycins
  - Different structure from cephalosporins
  - Classified as second generation agents



# Third Generation Cephalosporins

Cefotaxime, ceftazidime, ceftriaxone

- Broad gram negative coverage
- Less gram positive activity
- Ceftriaxone and cefotaxime: poor coverage of pseudomonas
- **Ceftazidime**: covers pseudomonas
  - Used in hospitalized patients with gram negative infections
  - Ceftazidime-avibactam: ESBL and carbapenem-resistant bacteria
- Most cross the blood-brain barrier
- Often used in **meningitis (ceftriaxone)**
  - Coverage of *S. pneumoniae*, *N. meningitidis*





# Pelvic Inflammatory Disease

## Management

- **Antibiotics:** usually **cephalosporin plus doxycycline**
- *N. gonorrhoeae* and *C. trachomatis*
- Inpatient: cefoxitin IV plus doxycycline PO
- Outpatient: ceftriaxone IM plus doxycycline PO





# Typical CAP

## Community Acquired Pneumonia

- Comorbidities (e.g., COPD)
  - Outpatient oral therapy
  - Fluoroquinolone (levofloxacin)
  - B-lactam (amoxicillin) plus azithromycin
- Inpatient
  - Fluoroquinolone (levofloxacin)
  - B-lactam (ceftriaxone) plus azithromycin



RUL Consolidation

# Fourth Generation Cephalosporins

## Cefepime

- Broad spectrum (more than 3<sup>rd</sup> generation drugs)
  - MSSA
  - Many gram positives
  - Many gram negatives including **pseudomonas**
- Effective against some ESBL bacteria
- Hospitalized patients with gram negative infections



# Fifth Generation Cephalosporins

## Ceftaroline

- Active against **MRSA**
- FDA approval 2010
- Binds MRSA-specific binding protein
- Studied in skin infections and pneumonia



# Fifth Generation Cephalosporins

## Ceftolozane-Tazobactam

- Ceftolozane: novel cephalosporin
- Combined with tazobactam (beta lactamase inhibitor)
- FDA approval in 2014
- Gram-negative activity including pseudomonas and ESBL bacteria



# Cephalosporins

## Adverse Reactions

- **Hypersensitivity reactions** (similar to PCN)
  - Anaphylaxis or urticaria
  - 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
- Used in patients with **low risk PCN allergies**

Urticaria





# Cephalosporins

## Vitamin K deficiency

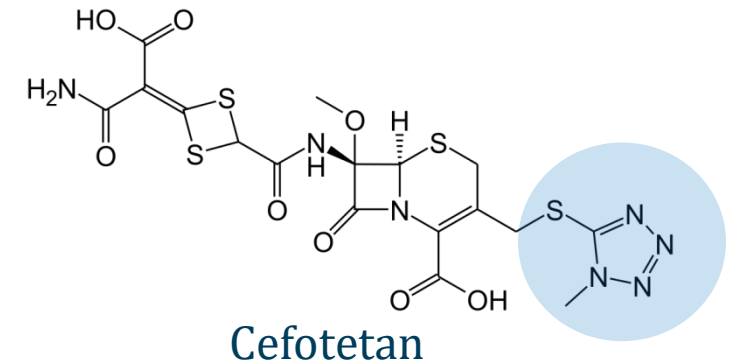
- Vitamin K1 from diet (green, leafy vegetables)
- Vitamin K2 from GI bacteria
- Antibiotics reduce bacterial vitamin K production
- Result: increased INR and potential bleeding
- Commonly a problem for **patients on warfarin**
- May be caused by any antibiotic



# Cephalosporins

## Hypoprothrombinemia

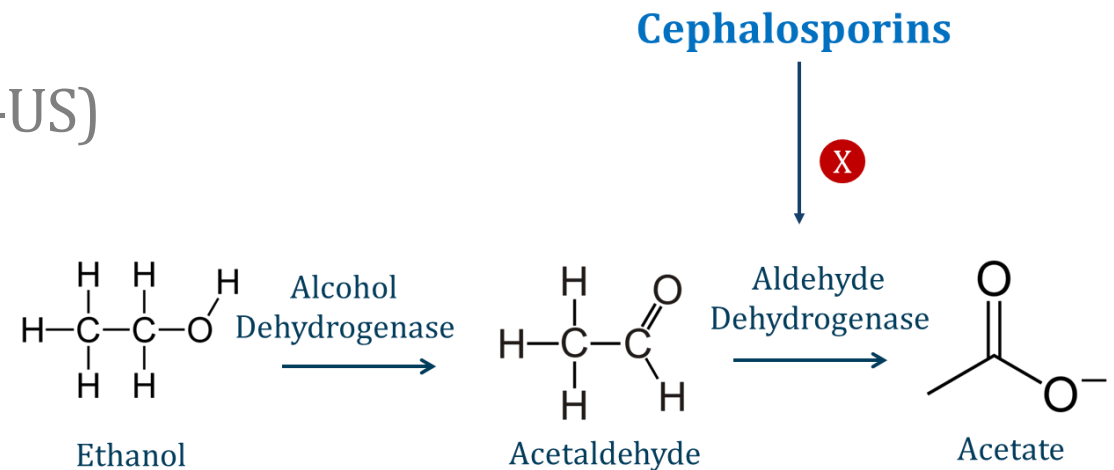
- Associated with N-methylthiotetrazole (NMTT) side chains
- Cefotetan and cefazolin
- Inhibits epoxide reductase (similar to warfarin)
- ↓ hepatic synthesis of clotting factors
- May prolong the PT/INR
- Reversible with vitamin K
- Most reports among malnourished patients



# Cephalosporins

## Disulfiram reaction

- Alcohol consumption with cephalosporins
- Warmth, flushing, sweating
- Inhibition of acetaldehyde dehydrogenase
- Accumulation of acetaldehyde
- Occurs with certain side chain structures
- Seen with cefotetan (2<sup>nd</sup> generation)
- Also cefoperazone and cefamandole (non-US)





# Protein Synthesis Inhibitors

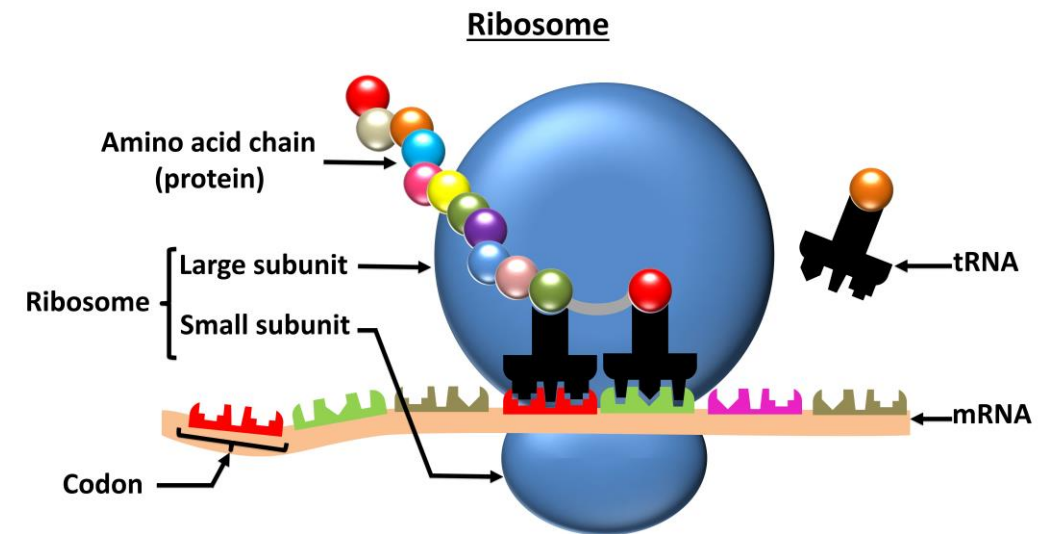
Jason Ryan, MD, MPH



# Aminoglycosides

Gentamicin, neomycin, amikacin, tobramycin, streptomycin

- Block protein synthesis at 30S ribosomal subunit
- Require O<sub>2</sub> for transport into cells
- Not effective against anaerobes
- Not transferred into eukaryotic cells
- Not effective against intracellular organisms
- Limited gram positive coverage alone
- Major use: **aerobic gram negative bacteria**



# Aminoglycosides

Gentamicin, neomycin, amikacin, tobramycin, streptomycin

- Enterobacteriaceae: Salmonella, E. coli, Klebsiella, Shigella
- **Often added to other antibiotics**
- Increases coverage and effectiveness of combination
- Vancomycin-gentamicin for sepsis
- Ampicillin-gentamicin for endocarditis



# Aminoglycosides

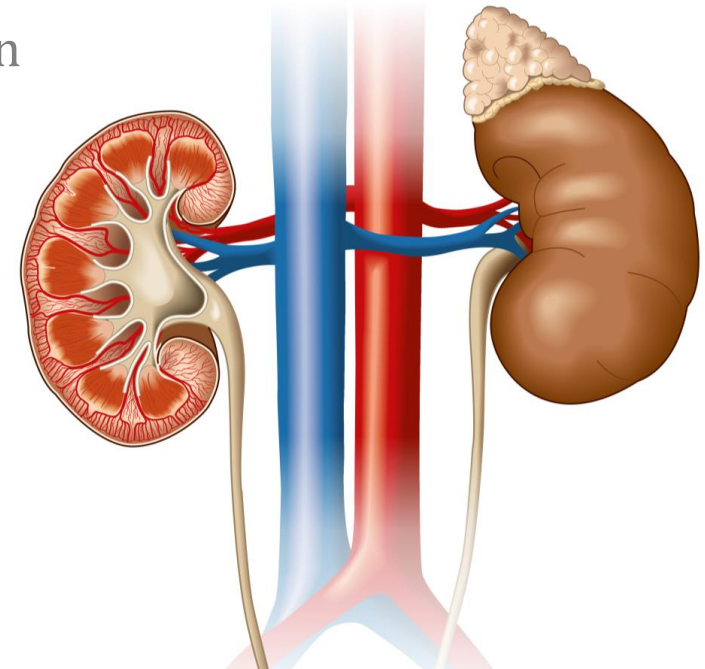
## Adverse effects

- **Nephrotoxicity**

- Acute kidney injury
- Affects 10 to 20% of patients
- Serum antibiotic levels monitored to limit toxicity
- Risk: gentamicin > tobramycin > amikacin > netilmicin > streptomycin

- **Ototoxicity**

- Toxic to 8<sup>th</sup> cranial nerve
- Hearing loss, balance problems (falls)

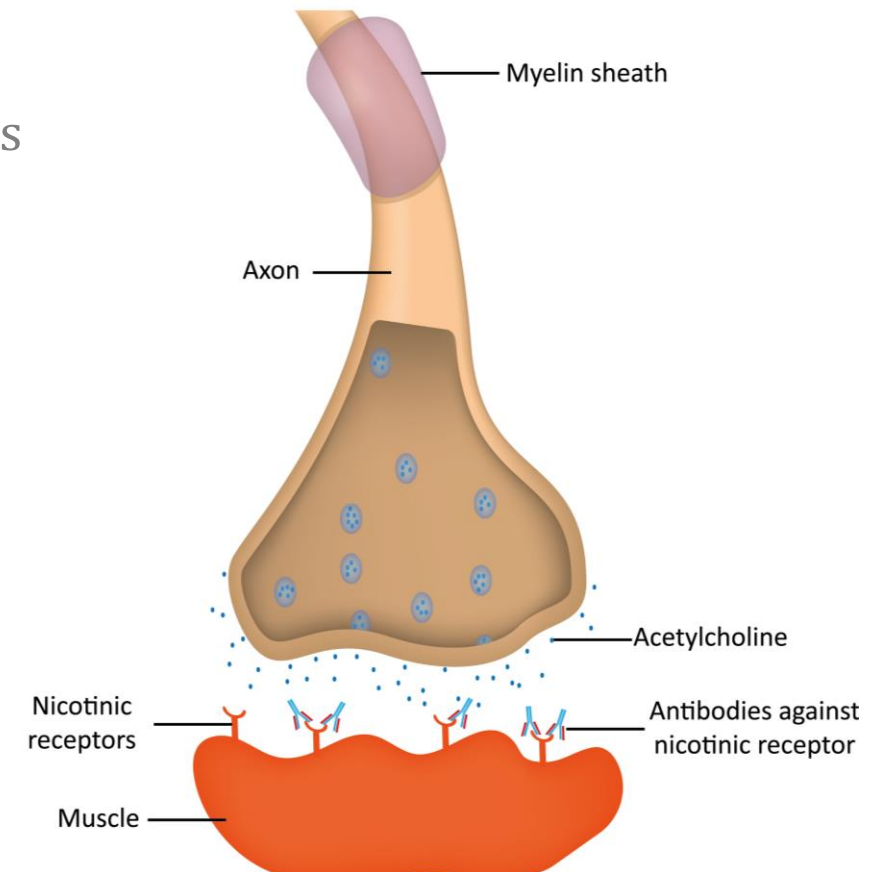


# Aminoglycosides

## Adverse effects

- **Neuromuscular blockade**
  - Rare adverse effect
  - Can block/limit release of ACh at neuromuscular junctions
  - Avoided in patients with **myasthenia gravis**
- Pregnancy class D
  - Reports of renal and ototoxicity in fetus

## Myasthenia Gravis

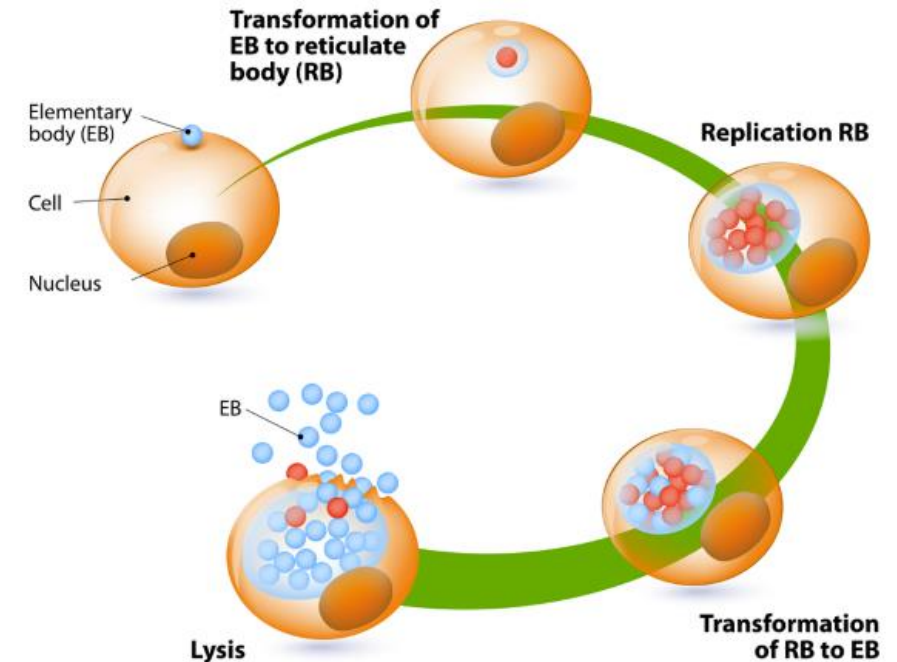


# Macrolides

Azithromycin, clarithromycin, erythromycin

- Block protein synthesis at 50S ribosome subunit
- Concentrated inside macrophages and other cells
- Effective against **intracellular pathogens**
  - Chlamydia, legionella, etc.
- Covers *Strep pneumoniae*
  - Although resistance high in some areas
- MSSA usually resistant
- Some gram negative coverage
- Can be used in **penicillin allergic patients**

## LIFE CYCLE OF THE CHLAMYDIA



# Macrolides

Azithromycin, clarithromycin, erythromycin

- Good coverage of **respiratory pathogens**
  - Community acquired pneumonia (Azithromycin)
  - Strep pneumoniae, H. influenza, Moraxella catarrhalis
  - Atypicals: Legionella, Chlamydia, Mycoplasma
- Used in **sexually-transmitted infections**
  - Azithromycin: Chlamydia (intracellular bacteria)
- Mycobacterium avium complex (MAC)
- Preferred treatment of Bordetella pertussis

RUL Pneumonia





# Macrolides

## Special uses

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

H. Pylori

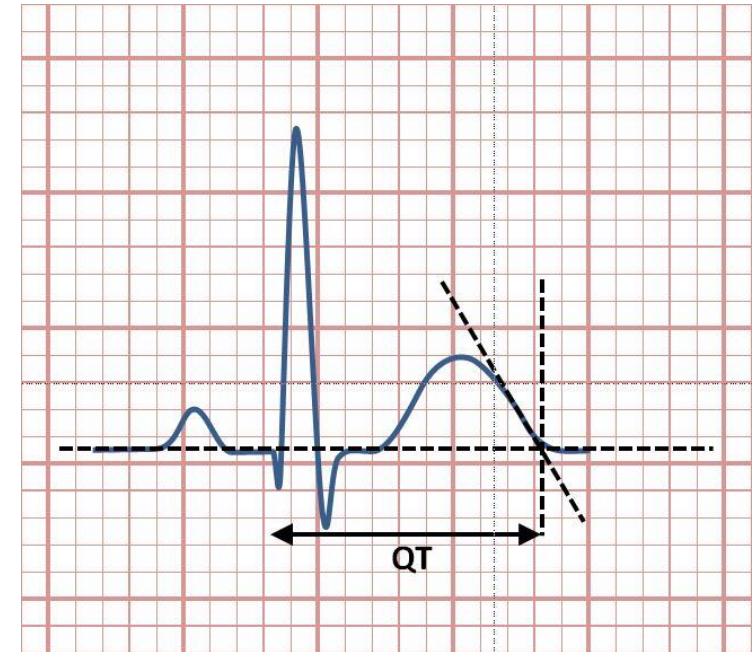




# Macrolides

## Adverse effects

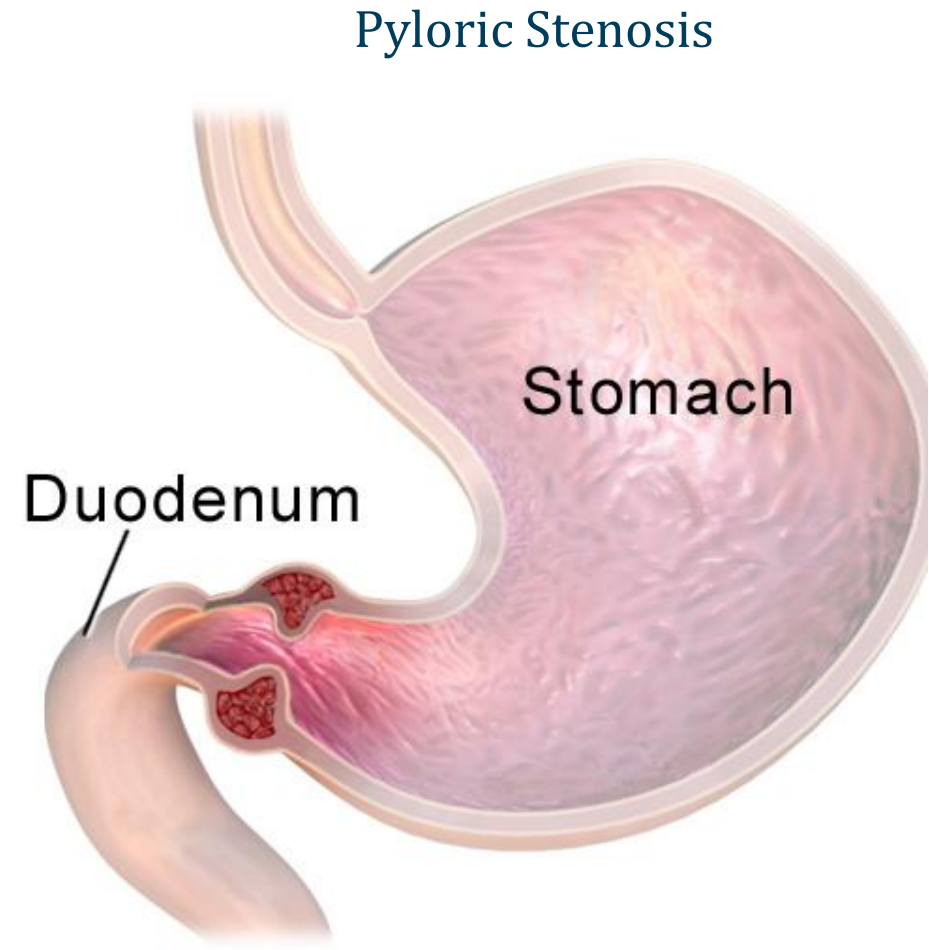
- Nausea, diarrhea, abdominal pain (motility – erythromycin worst offender)
- **Prolonged QT on EKG**
  - Erythromycin also worst offender
- **Acute cholestatic hepatitis**
  - ↑AST/ALT/Alk Phos/Bilirubin
  - Case reports in patients on Azithromycin
  - Contraindicated if prior cholestatic jaundice or liver dysfunction
- **P450 enzyme inhibition**
  - Will raise serum levels of P450 metabolized drugs
  - Theophylline and warfarin



# Macrolides

## Adverse effects

- **Infantile pyloric stenosis**
  - Erythromycin and azithromycin
  - Avoided in children < 2 weeks old



# Tetracyclines

Doxycycline, tetracycline, minocycline

- Inhibit protein synthesis at 30S ribosome
- Most commonly used drug in class: **doxycycline**
- **Effective against atypical pathogens**
  - Especially tick-borne or zoonotic infections
  - Rickettsia (Rocky Mountain spotted fever)
  - Borrelia (Lyme disease)
  - Coxiella burnetii (Q fever)
  - Brucella (brucellosis)
  - Propionibacterium (acne)
  - Chlamydia



# Tetracyclines

## Intestinal absorption

- **Impaired by minerals and antacids**
  - Calcium, magnesium (antacids)
  - Also iron or dairy products including milk
  - These substances are cations that chelate the drug
  - Cannot be taken with antacids or milk
- Oral tetracycline: absorption reduced with food
  - Absorption reduced by 50% with food
  - Doxycycline not affected by food



# 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
- Contraindicated in pregnancy
  - Cross placenta
  - Can accumulate in fetal bone and teeth



# Clindamycin

- Blocks protein synthesis at 50S ribosomal subunit
- Covers some gram positives
  - Staph, viridans strep, Strep pyogenes, and S. pneumoniae
- Covers many **anaerobes**
  - Clostridium perfringens
  - Mouth anaerobes: Fusobacterium, Prevotella, Peptostreptococcus
  - Limited effectiveness against B. fragilis
  - Used for anaerobes “above the diaphragm” (e.g., aspiration pneumonia)
- Often a second line agent

# Clindamycin

- Post-partum endometritis
  - Gentamycin + clindamycin
- Group B strep infection in pregnancy
  - Women with severe penicillin allergy



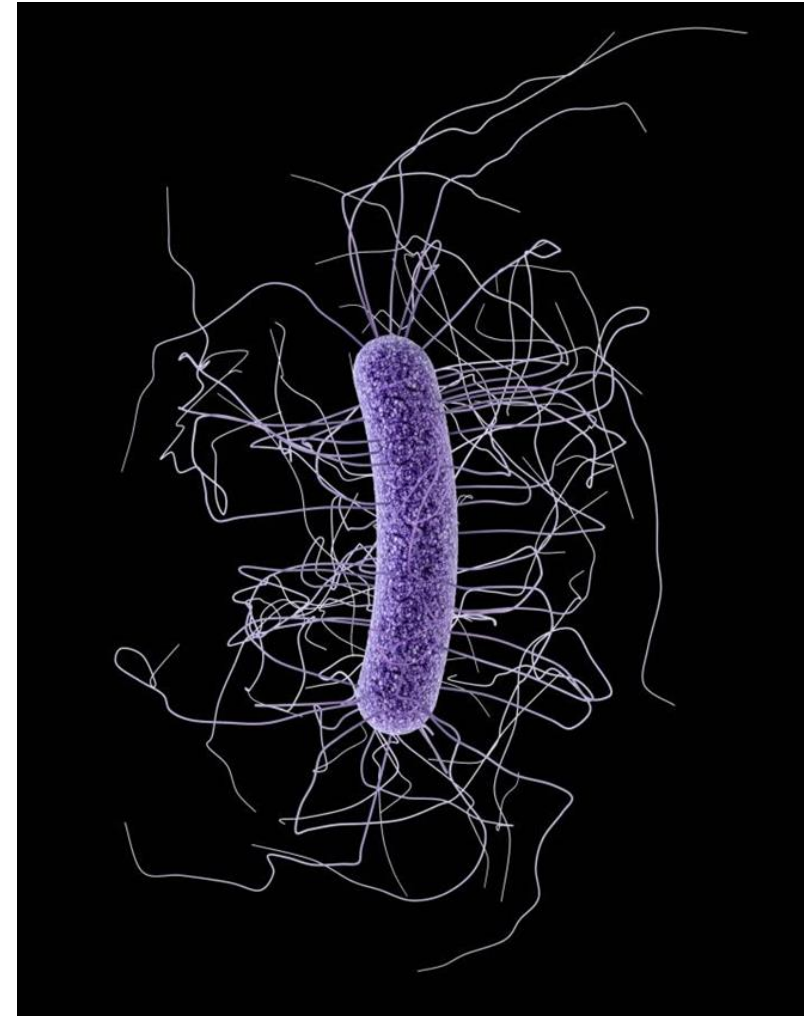


# Clindamycin

## Adverse effects

- Classic cause of **C. difficile infection**
  - Up to 10% of patients
  - Pseudomembranous colitis
  - C. difficile overgrowth
  - Massive, watery diarrhea

C. difficile



# Linezolid

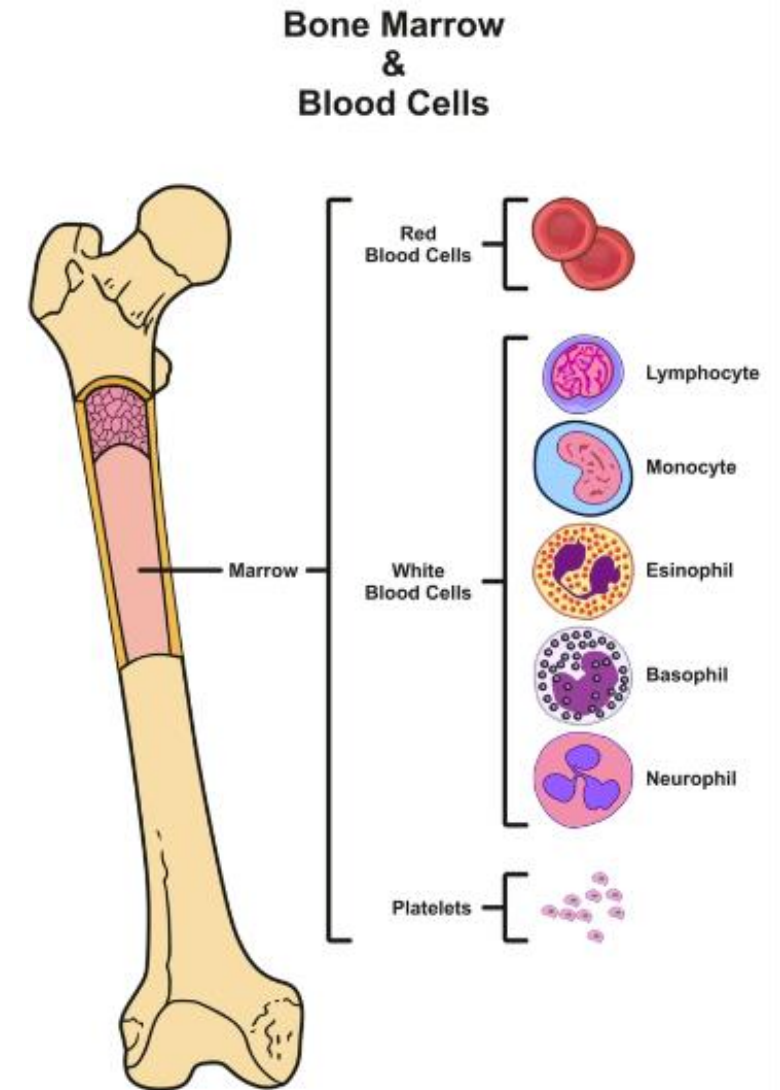
- Blocks protein synthesis at 50S ribosome
- Vancomycin-resistant enterococcus (VRE)
- Methicillin-resistant *S. aureus* (MRSA)



# Linezolid

## Adverse effects

- **Myelosuppression**
  - Usually mild and reversible
  - Thrombocytopenia most common
- **Peripheral and optic neuropathy**
  - “Glove and stocking” loss of sensation
  - Decreased visual acuity with optic neuropathy
- Can cause **serotonin syndrome**
  - Weak monoamine oxidase (MAO) inhibitor
  - High risk when given with SSRIs
  - Fever, confusion, agitation, hyperreflexia



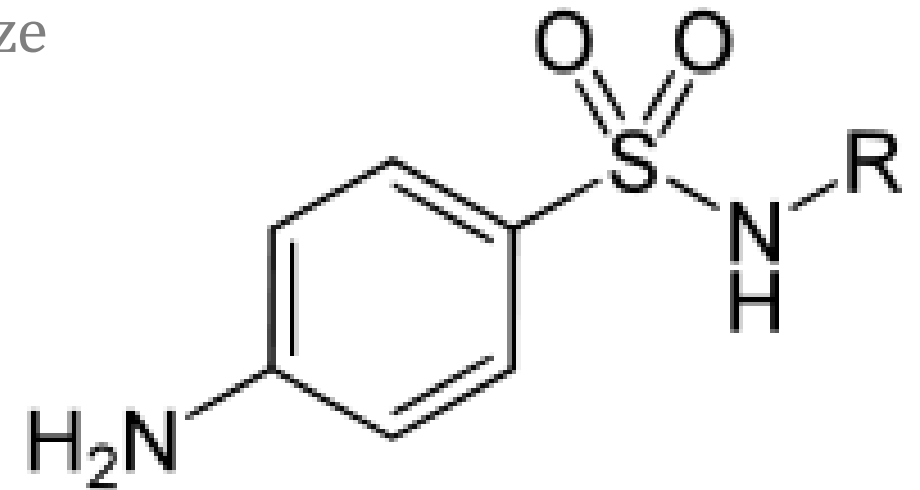
# Other Antibiotics

Jason Ryan, MD, MPH



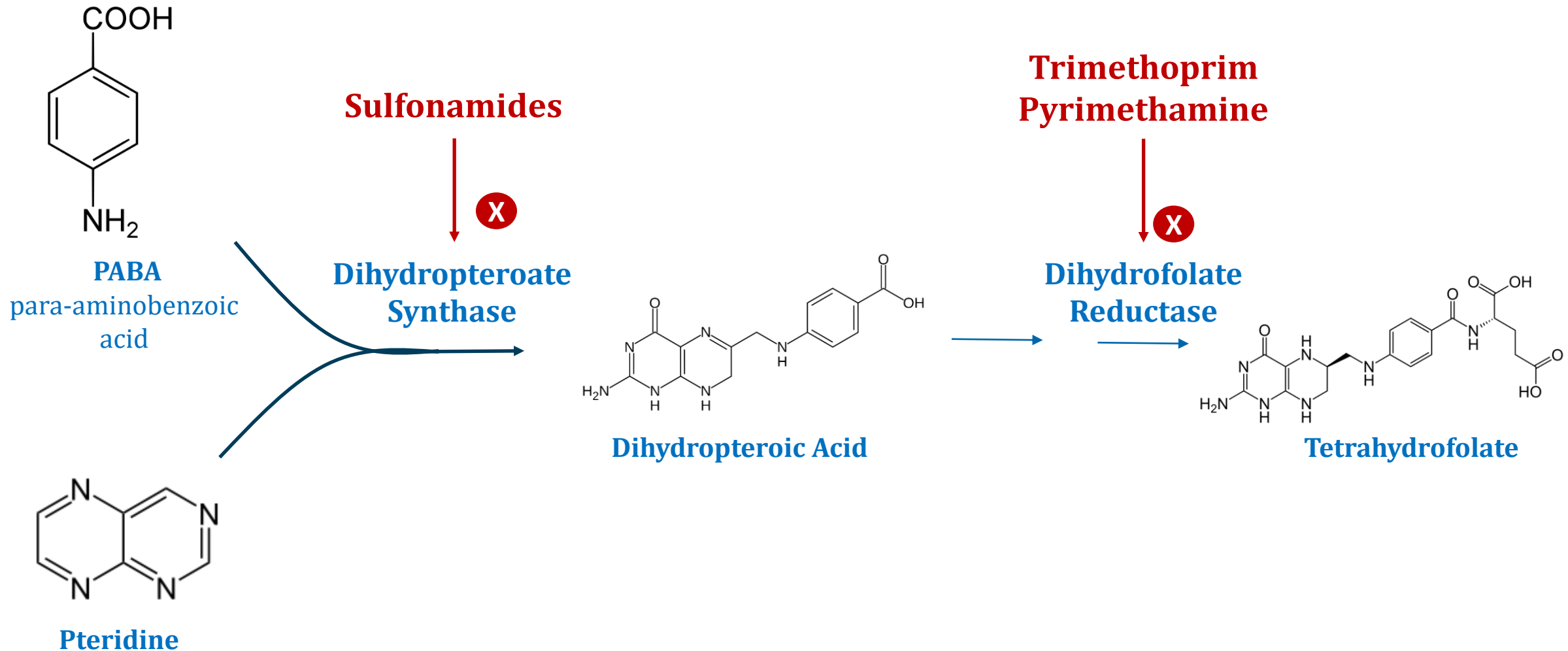
# Sulfonamide Antibiotics

- Sulfonamide group =  $\text{SO}_2\text{-N}$
- “Sulfa” drug = contains sulfonamide group
- Sulfonamide antibiotics inhibit bacterial synthesis of **folate**
- Folate required for **thymidine/DNA synthesis**
- Mammalian cells: exogenous folate from diet
- Bacterial cells: no exogenous folate - must synthesize



Sulfonamide Antibiotic Structure

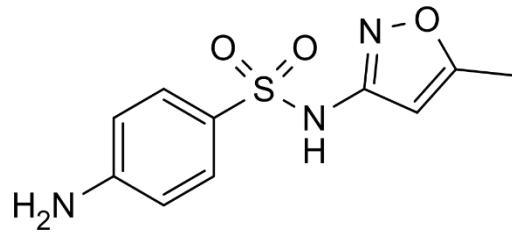
# Bacterial Folate Synthesis



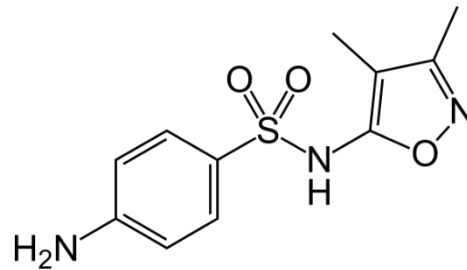
# Sulfonamides

Sulfamethoxazole (SMX), sulfisoxazole, sulfadiazine

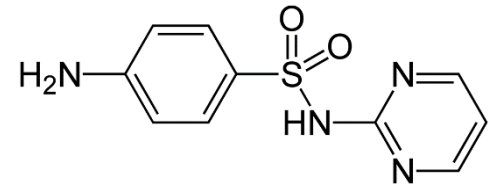
- Mimics of PABA
- Competitively inhibit dihydropteroate synthase
- Sulfamethoxazole commonly given with trimethoprim as TMP-SMX
- Sequential block of THF synthesis



**Sulfamethoxazole**



**Sulfisoxazole**



**Sulfadiazine**

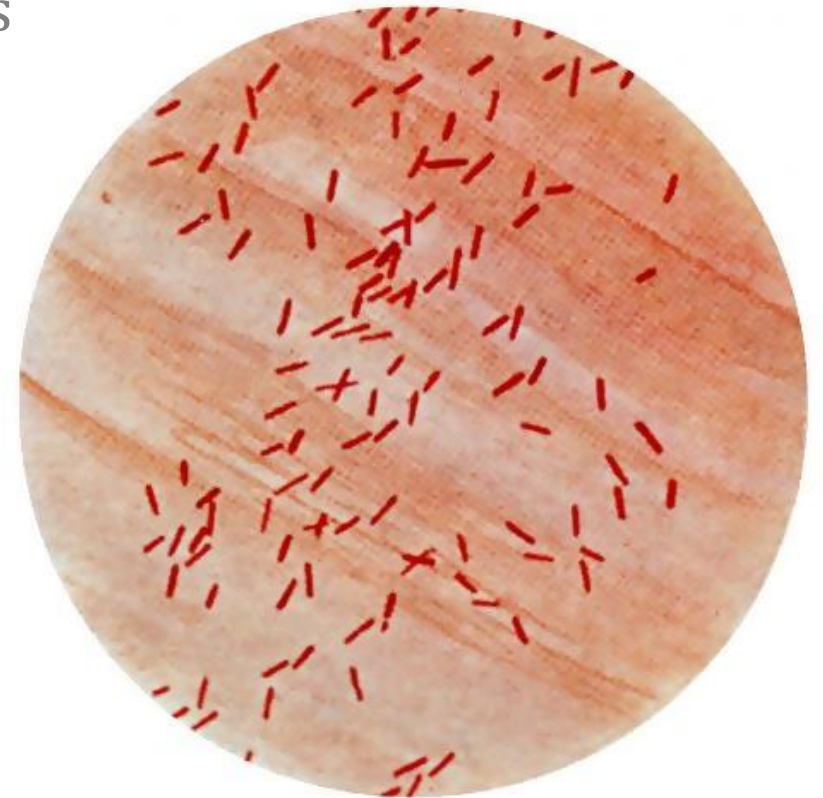


# Trimethoprim-Sulfamethoxazole

## TMP-SMX

- Gram positive bacteria including **most MRSA strains**
- Ineffective against most anaerobes including B fragilis
- Gram negative bacteria but not pseudomonas
- **Uncomplicated urinary tract infections**
  - Usually covers E. coli and Proteus
  - Some strains of E. coli may be resistant
- **Pneumocystis pneumonia (PCP)**
  - Treatment of choice
  - Prophylaxis

E. Coli

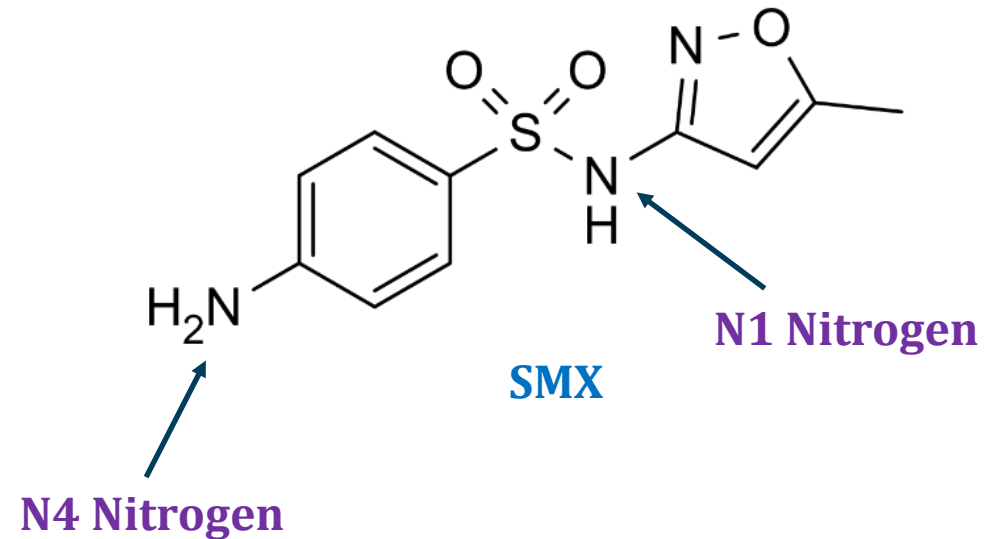


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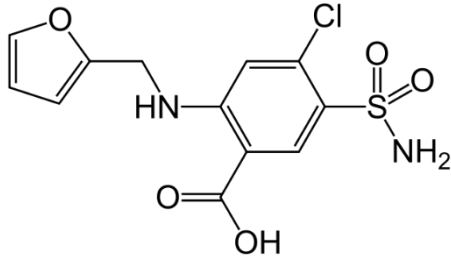
# Sulfonamides

## Toxicity

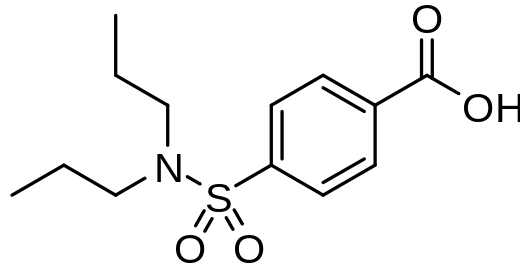
- Hypersensitivity reactions ~3% of patients
- Reactions linked to specific drug molecule features
  - Aromatic ring attached to N4 position
  - Nitrogen ring attached to N1 nitrogen
- Only sulfonamide antibiotics contain both features



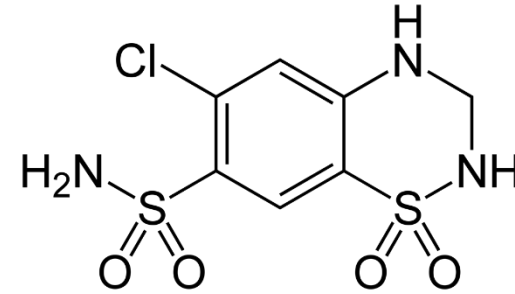
# Other Sulfa Drugs



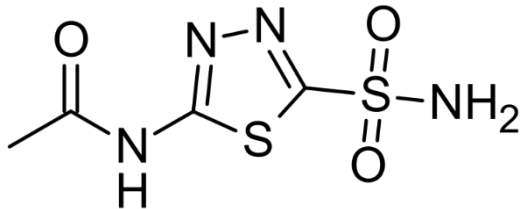
**Furosemide**  
(Loop Diuretic)



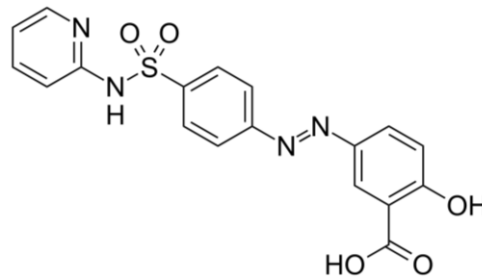
**Probenecid**  
(Gout)



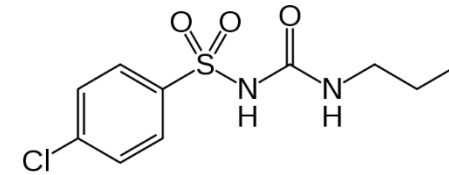
**Hydrochlorothiazide**  
(Thiazide diuretic)



**Acetazolamide**  
(Carbonic Anhydrase)



**Sulfasalazine**  
(IBD)



**Sulfonylurea**  
(Diabetes)

# Sulfonamides

## Hypersensitivity (allergic) reactions

- Similar to penicillin allergic reactions
- Anaphylaxis
- Maculopapular rash
- Serum sickness (fever, rash, arthritis)
- **Stevens-Johnson Syndrome**
- **Toxic epidermal necrolysis**
- Adverse reaction rate higher in HIV
  - 25 to 50% in some studies

## Mucosal Desquamation Stevens-Johnson Syndrome



# Sulfonamides

## Toxicity

- Nephrotoxicity
  - Interstitial nephritis
- Photosensitivity
  - Drug interaction with UV light
- Hemolysis in **G6PD deficiency**
  - Sulfonamides are oxidants - classic trigger for hemolysis
- Bind to **albumin**
  - Displaces other bound substances
  - Bilirubin – kernicterus in newborns (contraindicated)
  - Warfarin – may increase INR

## Photosensitivity



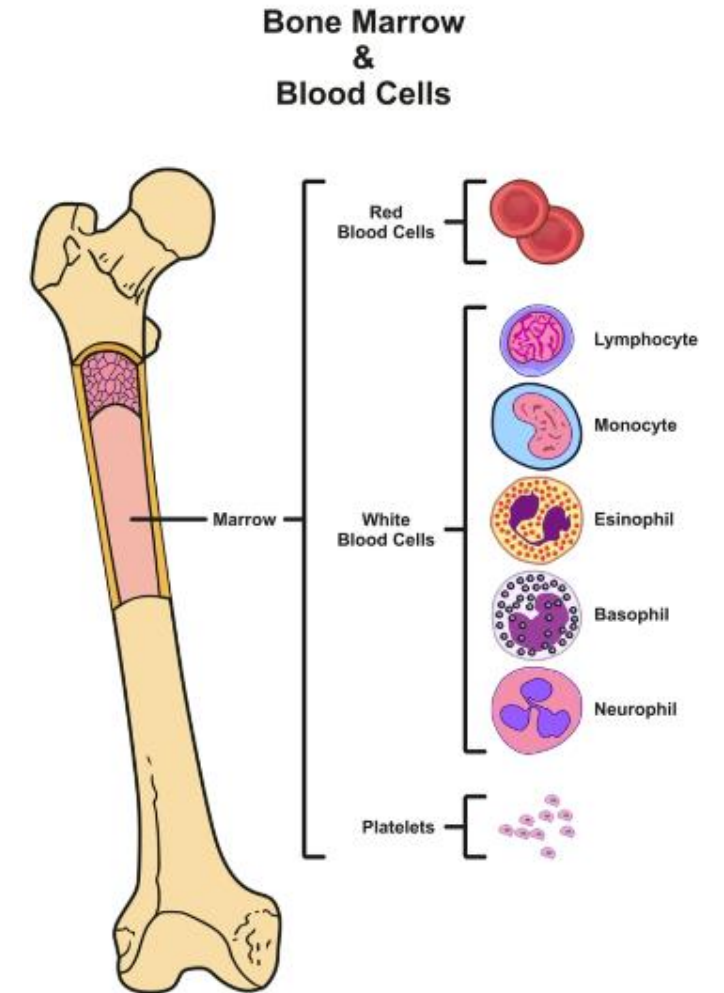
Wikipedia/Public Domain



# Trimethoprim

## Toxicity

- Preferentially inhibits bacterial dihydrofolate reductase
- Some inhibition of human enzyme can occur
- Inhibits DNA synthesis of rapidly dividing cells
- **Bone marrow suppression**
  - Pancytopenia: megaloblastic anemia, leukopenia, ↓platelets
- Can alleviate with folate supplementation
- Avoided in pregnancy (↑ folate demand)

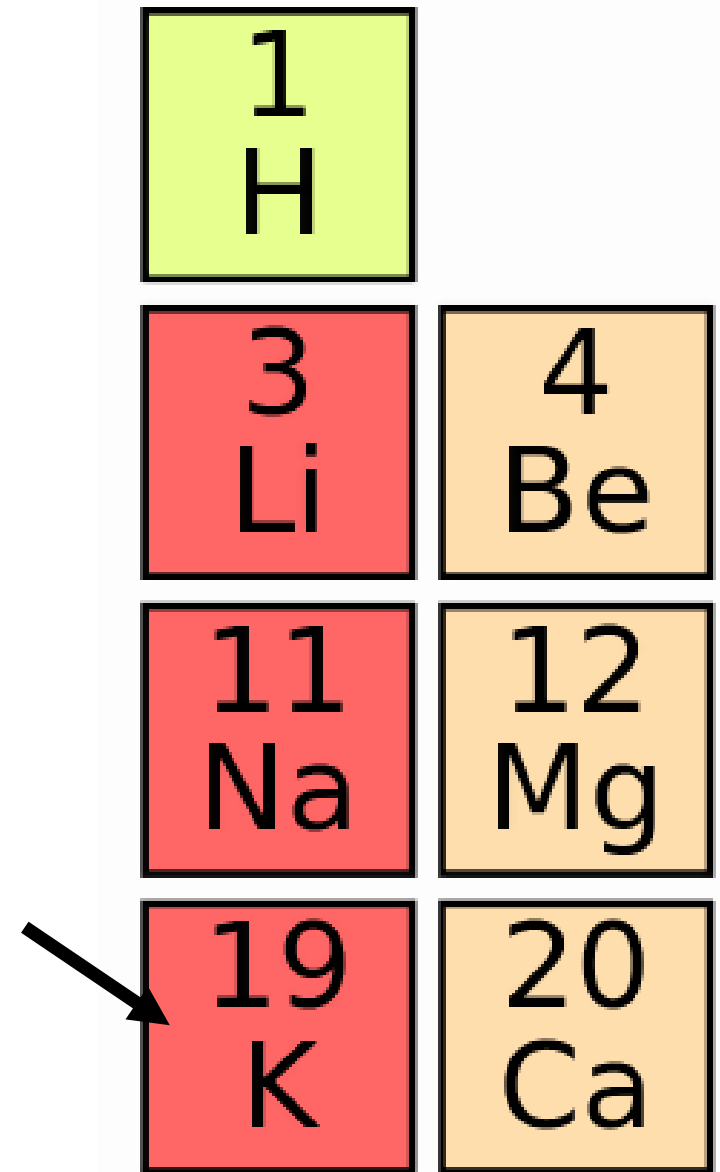


# Trimethoprim

## Toxicity

- **Hyperkalemia**
  - Blockade of epithelial sodium channel (ENAC)
  - Blocks secretion of potassium into urine
  - Similar effect to amiloride (potassium-sparing diuretic)
  - May be life-threatening
- Caution if patients on other drugs
  - ACE inhibitors
  - Angiotensin receptor blockers
  - Aldosterone antagonists

1 H	
3 Li	4 Be
11 Na	12 Mg
19 K	20 Ca



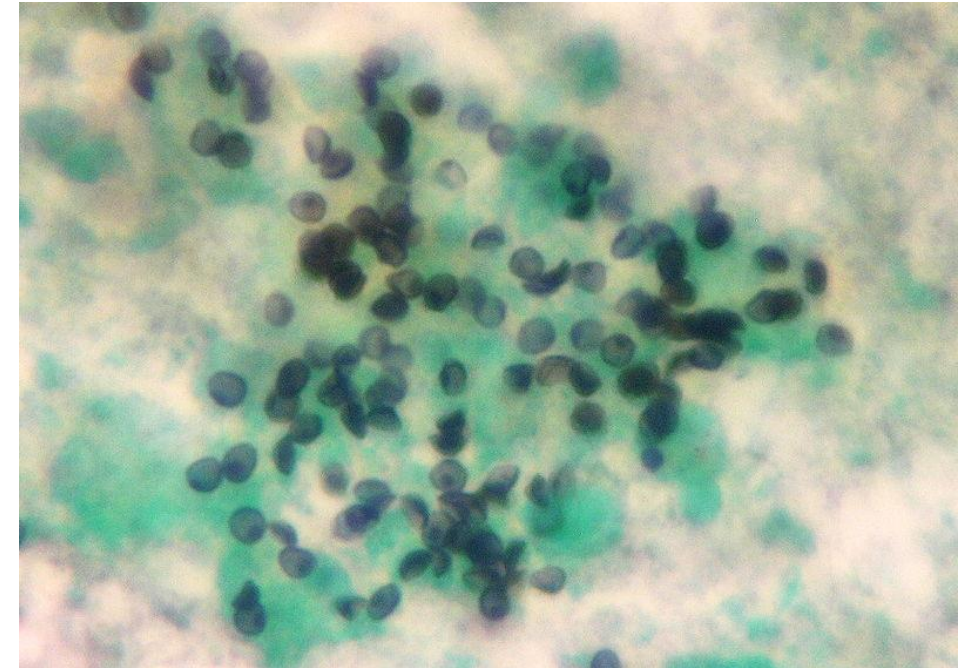


# Pneumocystis Pneumonia

## PCP

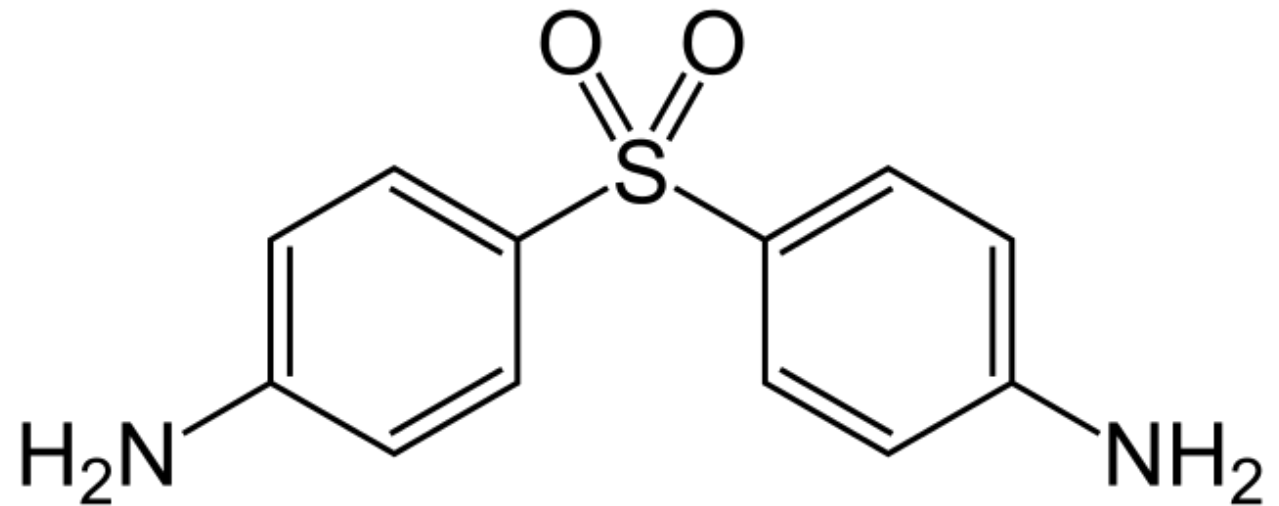
- Opportunistic fungal infection
- Occurs in end-stage HIV/AIDS
- Treatment of choice: **TMP-SMX**
- Hypersensitivity reactions more common
- Alternative therapy often needed
  - Dapsone
  - Pentamidine
  - Atovaquone (malaria drug)

Pneumocystis jirovecii



# Dapsone

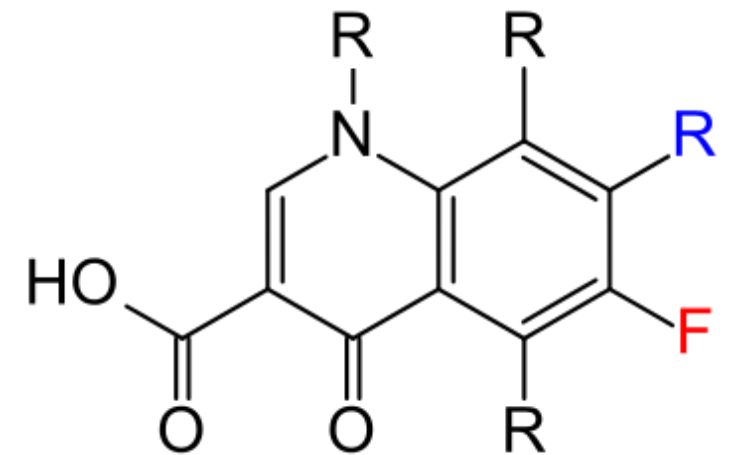
- Not a sulfonamide
- Competes with PABA for dihydropteroate synthase
- PCP pneumonia
- *Mycobacterium leprae* (leprosy)



# Fluoroquinolones

Ciprofloxacin, levofloxacin, moxifloxacin

- Inhibit enzymes for bacterial **DNA synthesis**
  - DNA gyrase
  - Topoisomerase IV
- Cover many gram positives, gram negatives and atypical bacteria
- Generally poor coverage of anaerobes except moxifloxacin
- UTIs (E. Coli, other gram negatives)
- Pneumonia (S. pneumo, H. flu, atypicals)
- Abdominal infections (enteric gram negatives)

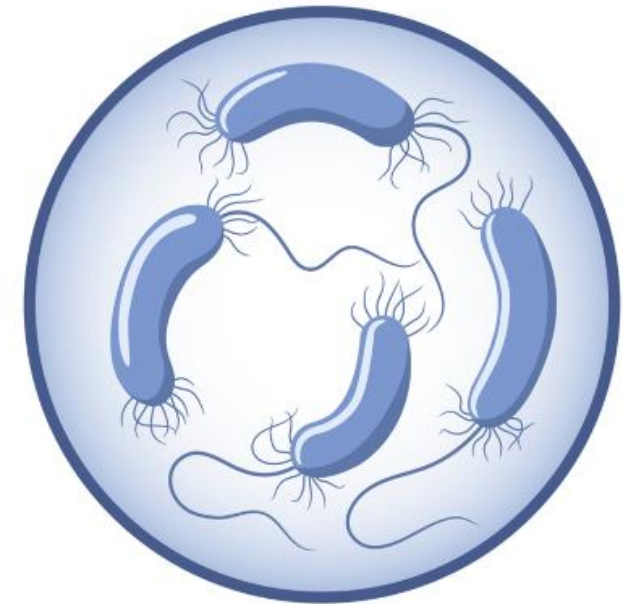


# Fluoroquinolones

## Ciprofloxacin

- Some gram positive coverage
- Rarely used alone for gram positive coverage due to resistance
- Very good **gram negative coverage**
- Most reliable fluoroquinolone **pseudomonas coverage**
- Gastrointestinal infections
  - Enterobacteriaceae including E. coli, Klebsiella
  - Often together with an anaerobic drug (metronidazole)
- Urinary tract infections
- Otitis externa (ear drops)

*Pseudomonas aeruginosa*

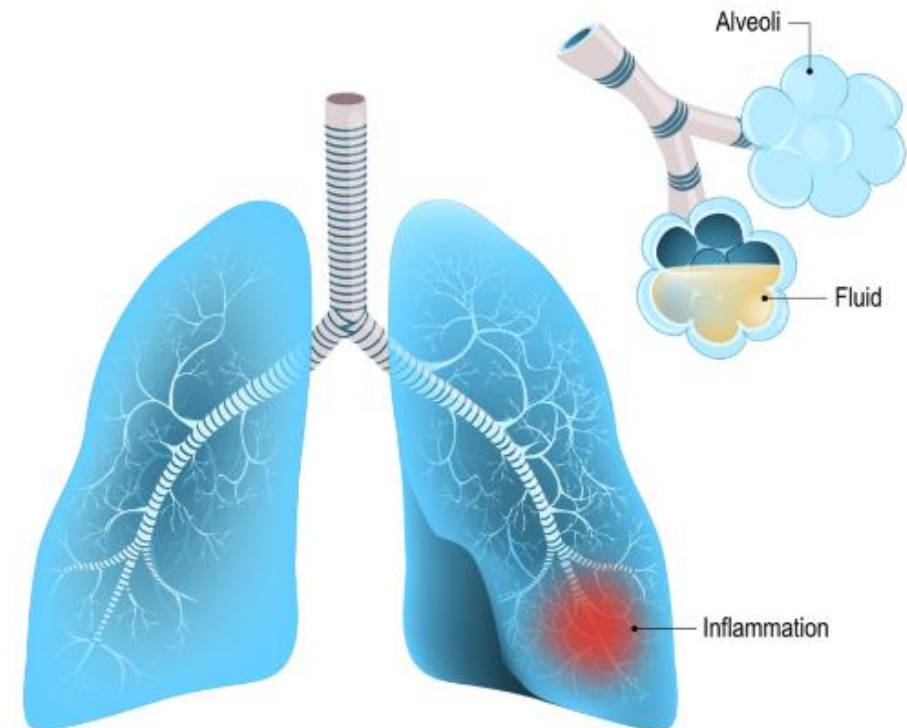


# Fluoroquinolones

## Levofloxacin and moxifloxacin

- More gram positive and atypical coverage than ciprofloxacin
  - Better strep pneumo coverage
  - Covers most methicillin-susceptible Staph aureus
- Less effective against pseudomonas
- Commonly used in **pneumonia**
  - Strep pneumonia, H. influenzae, M. catarrhalis
  - Atypical bacteria

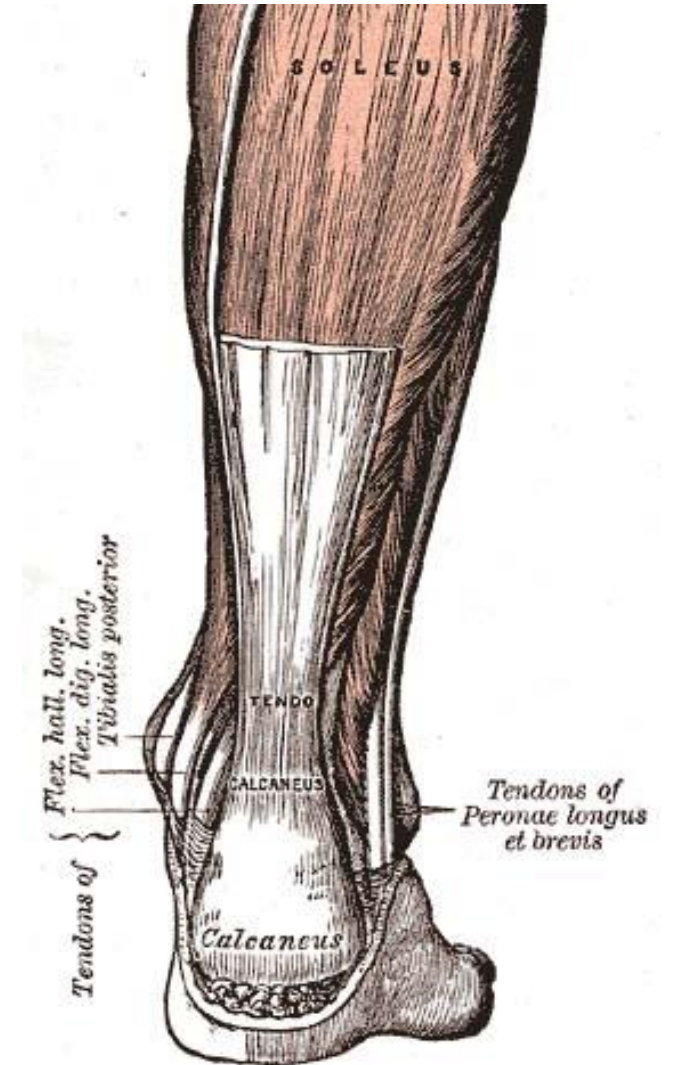
### PNEUMONIA



# Fluoroquinolones

## Adverse effects

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

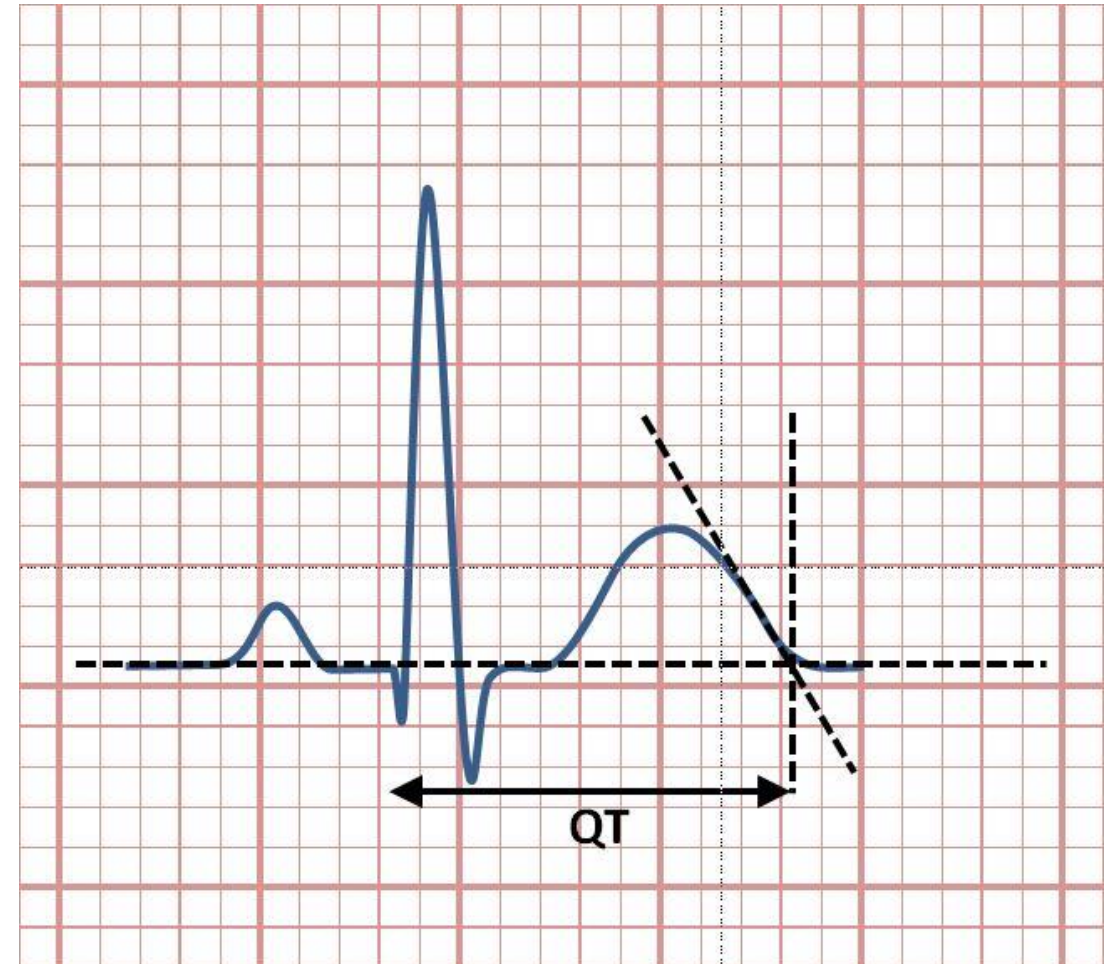




# Fluoroquinolones

## Adverse effects

- **Neurologic side effects**
  - Headache, dizziness, insomnia
  - Rarely confusion or delirium
- QT prolongation on EKG





# Fluoroquinolones

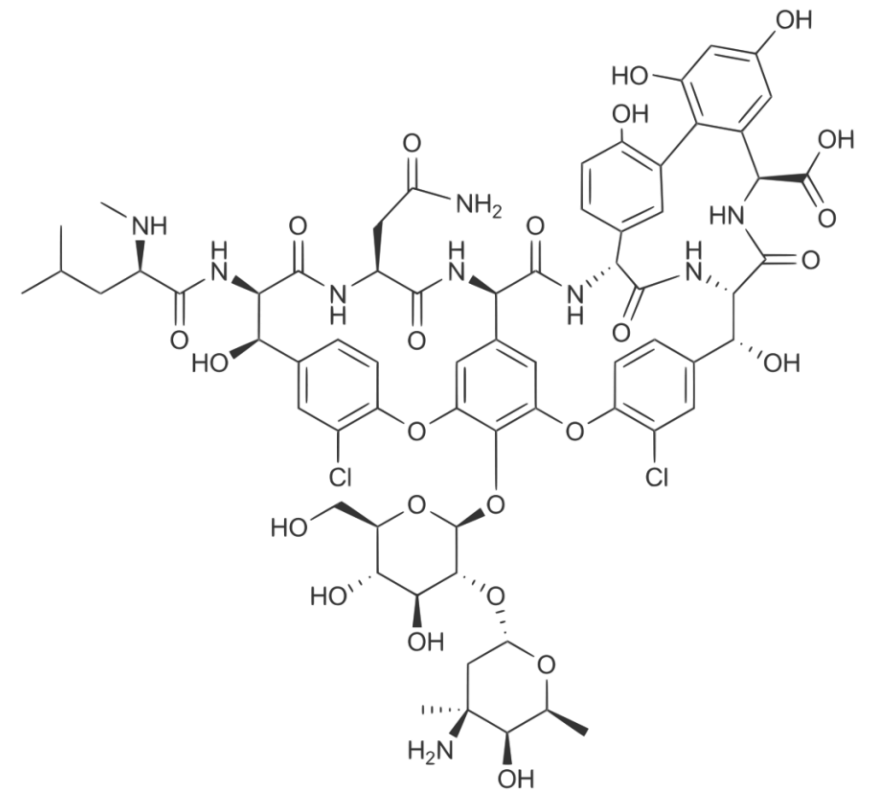
## Antacids

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



# Vancomycin

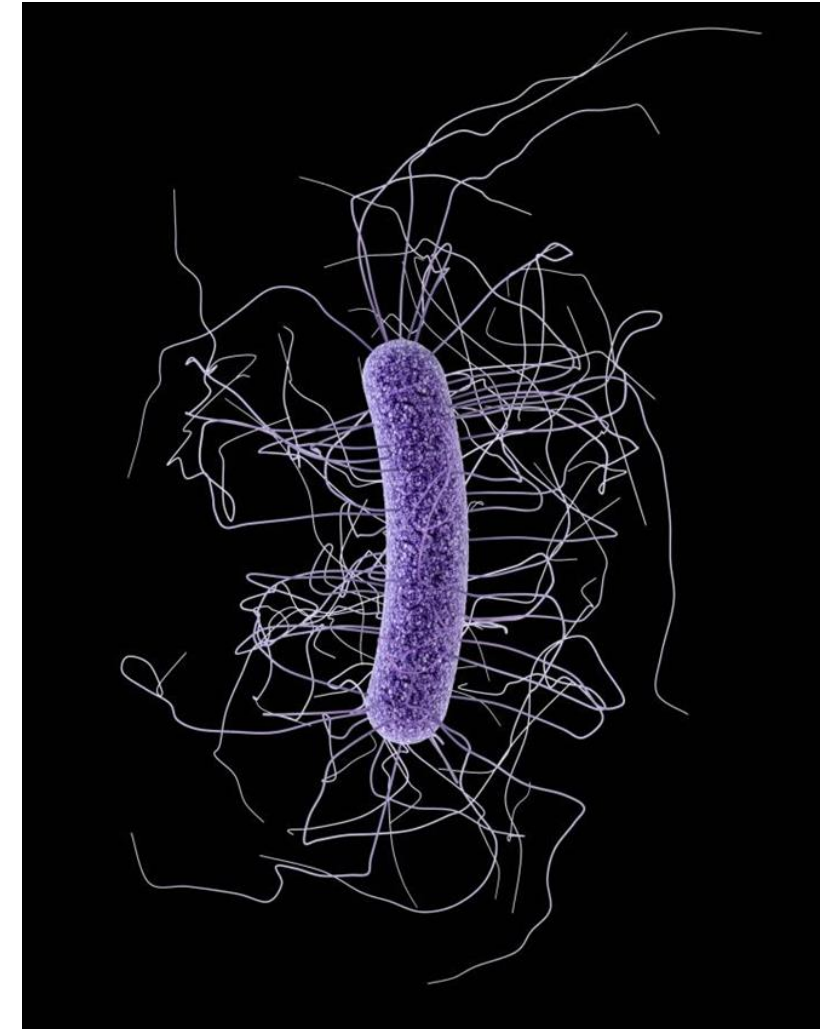
- **Inhibits cell wall synthesis**
  - Binds D-alanyl-D-alanine peptides
  - Prevents crosslinking
  - Cell wall breakdown → cell death
- Only effective against **gram positive bacteria**
- Too large to pass outer membrane gram negatives



# Vancomycin

- **Methicillin resistant Staph Aureus (MRSA)**
  - Intravenous administration
  - Often given empirically when MRSA is a concern
  - Endocarditis
  - Severe pneumonia/sepsis
- **C. difficile pseudomembranous colitis**
  - Oral therapy
  - Not absorbed → intestinal activity only
- **Penicillin-resistant S. pneumoniae**
  - Empiric therapy for meningitis

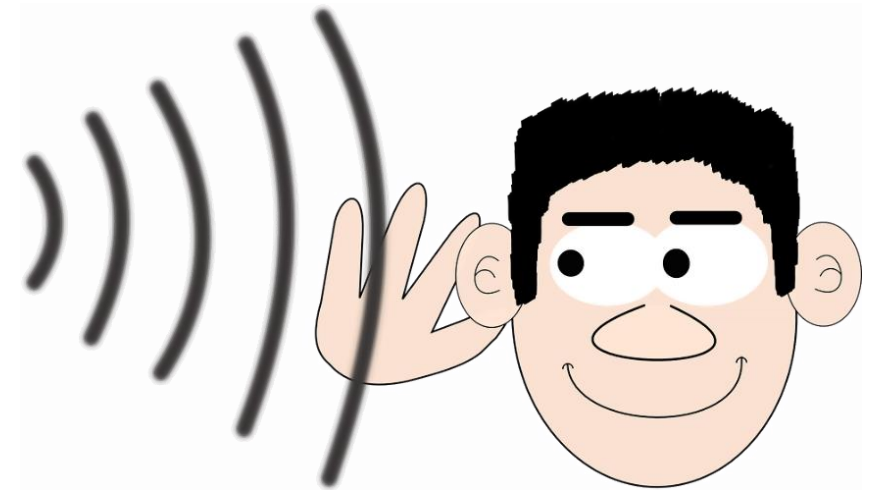
C. difficile



# Vancomycin

## Adverse effects

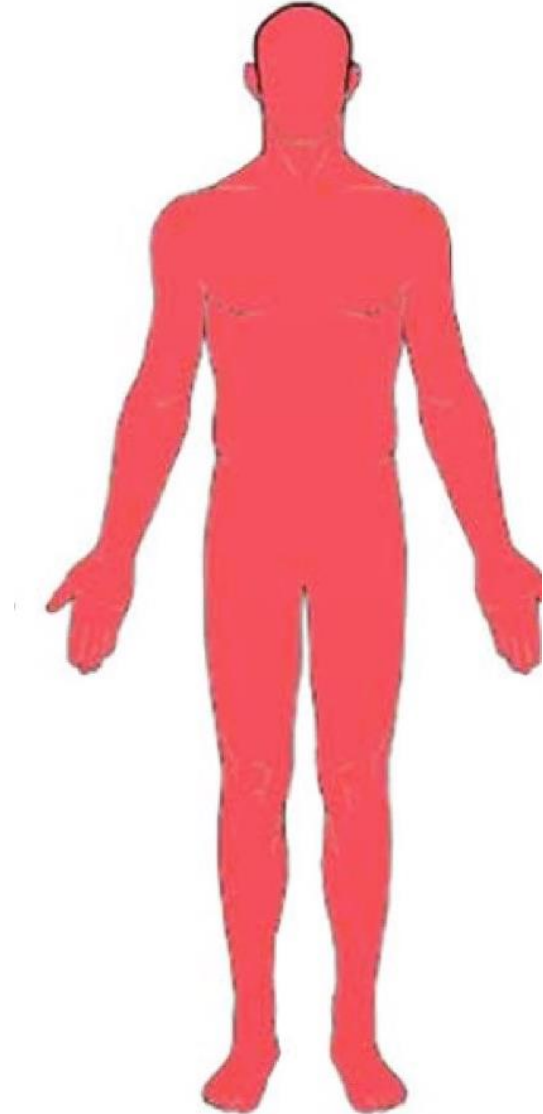
- **Nephrotoxicity**
  - Less common with modern preparations
  - Increased risk if concomitant aminoglycoside therapy
- **Ototoxicity**
  - Tinnitus, vertigo, and hearing loss reported (rare)



# Vancomycin

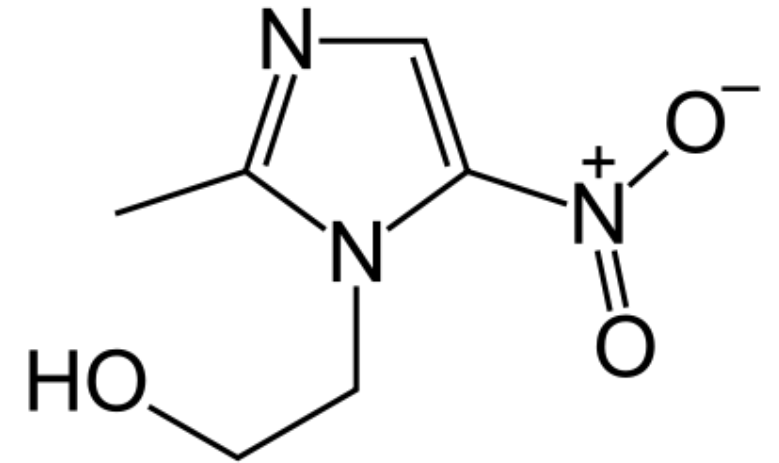
## Adverse effects

- **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

- Causes DNA breakage/destabilization → cell death
- Prodrug that must be reduced to activate
- Only **anaerobic bacteria** capable of reduction
- Good coverage of anaerobes “below the diaphragm”
  - Bacteroides fragilis
  - C. difficile
- Peritonitis, abdominal abscesses, diverticulitis
- Often given with quinolone for gram negatives
- Ciprofloxacin + metronidazole often used for diverticulitis

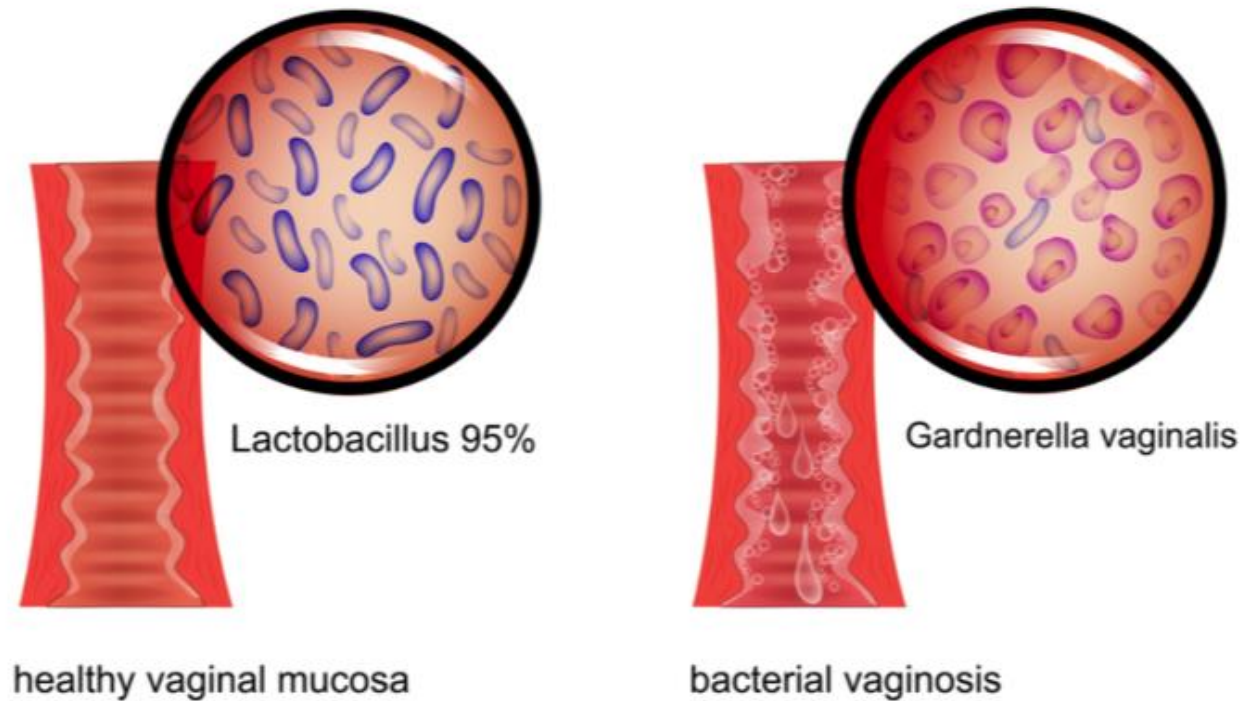


# Metronidazole

## Uses

- **H. Pylori**
  - Part of triple therapy
- **Bacterial vaginosis**
  - Treats *Gardnerella vaginalis*
- **Anaerobic protozoa**
  - *Trichomonas vaginalis*
  - *Entamoeba histolytica*
  - *Giardia lamblia*

## BACTERIAL VAGINOSIS





# Metronidazole

## Adverse Reactions

- Unpleasant **metallic taste**
- GI: abdominal discomfort, nausea
- **Disulfiram-like reaction**
  - Alcohol consumption with metronidazole
  - Warmth, flushing, sweating
  - Patients should **avoid alcohol**



# Nitrofurantoin

- Complex, incompletely-understood mechanism
- Major use is **uncomplicated urinary tract infections**
  - Concentrates in urine
  - Safe in pregnancy (avoid TMP-SMX, quinolones)
- Can trigger **hemolysis in G6PD patients**



# Fungal Infections

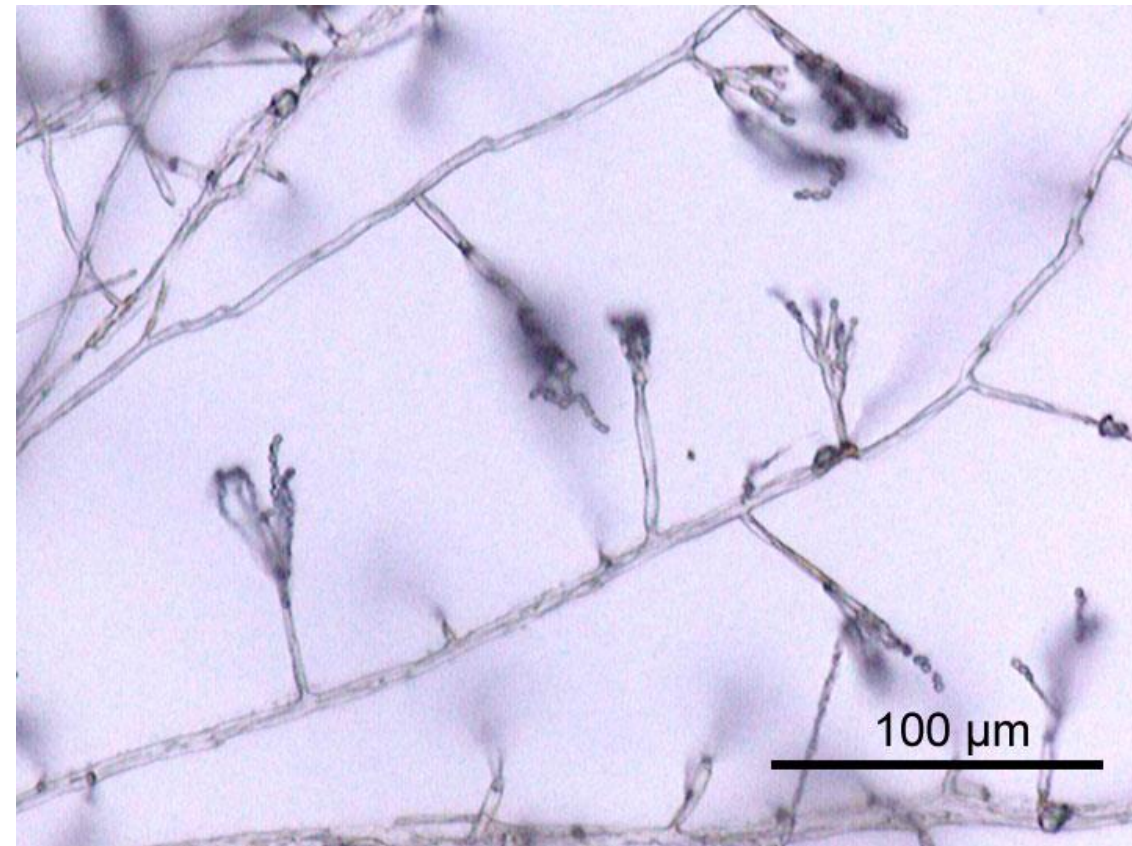
Jason Ryan, MD, MPH



# Fungi

- Fungi are eukaryotes
  - Have a nucleus and intracellular organelles
  - Different from bacteria (prokaryotes)
- **Yeast:** microscopic, single-celled fungus
- **Filamentous mold:** multicellular fungus
  - May form hyphae - long branches
- Dimorphic: yeast or filamentous
- Molds may produce **spores (conidia)**
- Spores develop into fungi

Hyphae



# Fungal Infections

## Mycoses

- **Systemic**
  - Only in specific endemic geographic areas
  - Histoplasmosis, blastomycosis, coccidioidomycosis
- **Opportunistic**
  - Occur in immunocompromised states
  - Candida, Aspergillus, Cryptococcus, Mucor
- **Cutaneous**
  - Tinea versicolor, tinea pedis, Sporothrix

# Systemic Mycoses

Histoplasmosis, blastomycosis, coccidiomycosis

- Caused by **dimorphic fungi**
- Mold forms found in soil
  - Cold temps = mold with spores
  - Warm temps (body) = yeast
- Inhalation of spores → disease
- May cause **lung infections**
- Often asymptomatic or mild
- Rarely leads to disseminated disease



# FUNGI

# Systemic Mycoses

Histoplasmosis, blastomycosis, coccidiomycosis

- All cause **granulomatous inflammation**
- Can mimic **tuberculosis or sarcoidosis**
  - Granulomas in lung
  - Hilar lymphadenopathy
- Mild disease: itraconazole
- Severe/systemic: amphotericin B
- Treatment with steroids → worsening symptoms

Hilar Lymphadenopathy



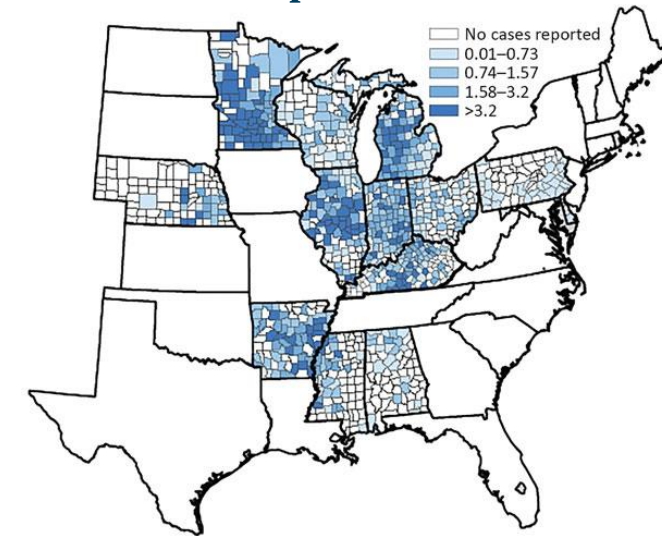


# Systemic Mycoses

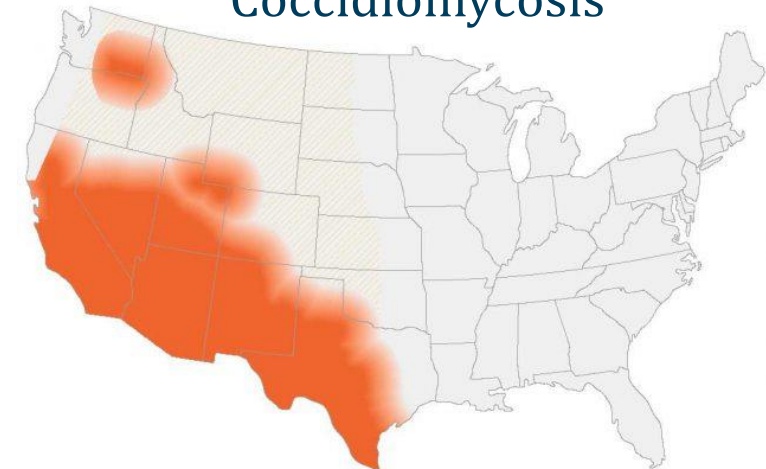
## Endemic areas

- Histoplasmosis/blastomycosis
  - Generally similar geographic areas
  - Ohio and Mississippi river valley
  - “Midwest”
- Coccidioidomycosis
  - Southwestern US
  - Arizona, New Mexico, California

Histoplasmosis



Coccidiomycosis



# Histoplasmosis

## Histoplasmosis capsulatum

- Soil contaminated with **bird or bat droppings**
- Key site for infection: **caves**
- Also chicken coops or farms with bird droppings
- Spores inhaled → yeast at body temperature

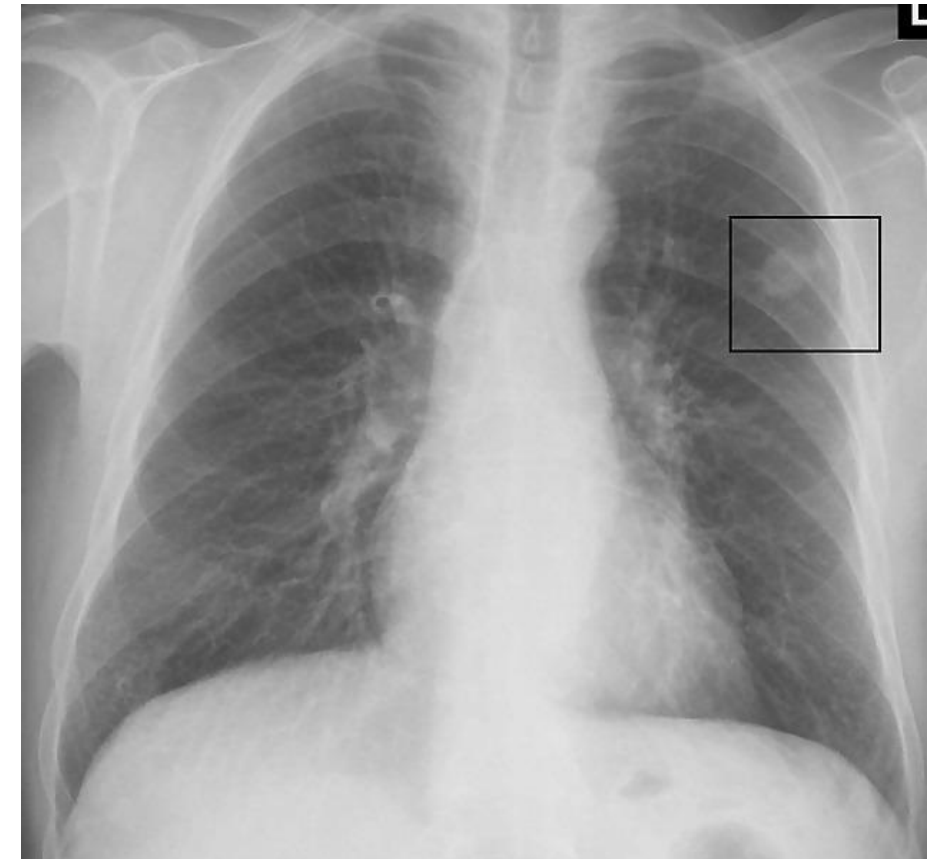


# Histoplasmosis

## Clinical features

- Vast majority of cases **asymptomatic**
- Most common symptoms are **pulmonary**
  - Slow onset over weeks of mild pneumonia
  - Hilar lymphadenopathy
- After healing may cause **pulmonary nodule**
  - Biopsy shows granuloma

Pulmonary Nodule



# Histoplasmosis

## Disseminated disease

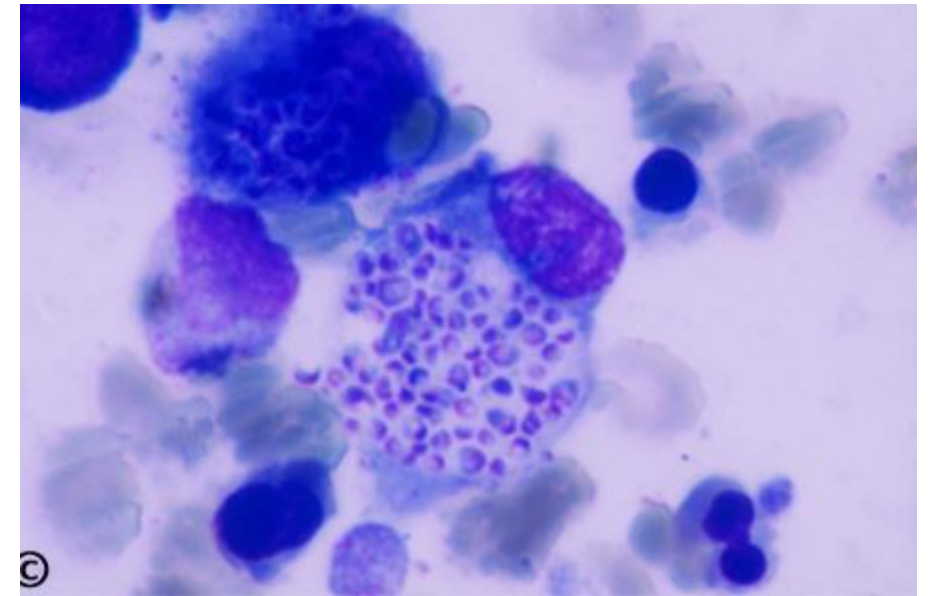
- Rare unless **immunocompromised**
  - HIV/AIDS, TNF- $\alpha$  inhibitors, solid-organ transplant
- Diffuse clinical features in many systems
  - Lymphadenopathy
  - Hepatosplenomegaly (abnormal LFTs)
  - Tongue, mouth ulcers
  - Pancytopenia (bone marrow involvement)
  - Skin lesion (nodules, plaques, others)
  - Pulmonary infiltrates (don't confuse with PCP)
- Treatment: amphotericin B



# Histoplasmosis

## Diagnostic testing

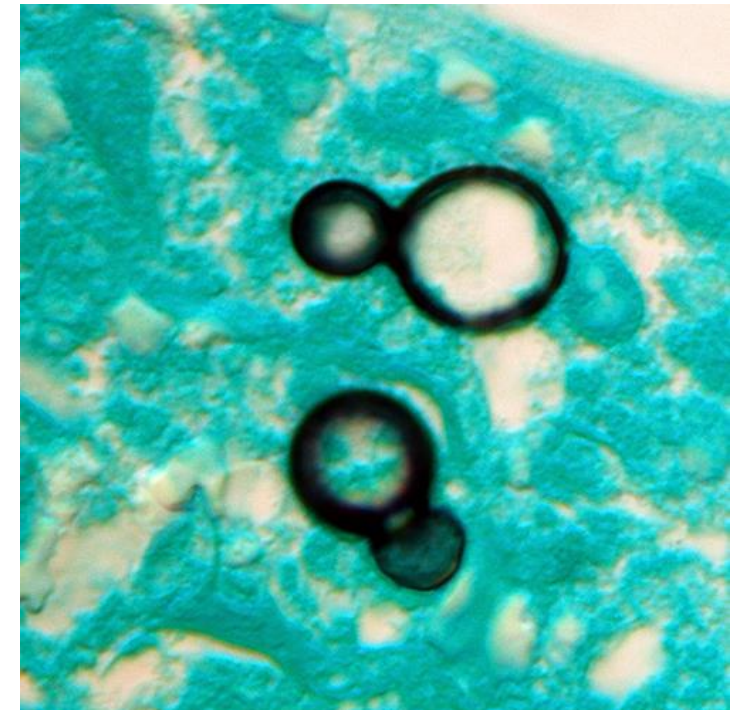
- All tests have limitations
- Positive tests less likely if recent exposure or mild disease
- Histoplasma antigen testing (urine, blood or BAL)
- Serologic tests for antibodies
- Fungal cultures
- Tissue biopsy: yeast within macrophages



# Blastomycosis

## Blastomyces dermatitidis

- Inhaled spores → yeast in the body
- Many patients asymptomatic
- When symptomatic: **chronic pneumonia** most common
  - Slow, insidious onset of pulmonary symptoms
- Presumptive diagnosis: visualization of yeast
  - Sputum, BAL
  - “Broad based budding yeast”
- Definitive diagnosis: sputum culture





# Blastomycosis

## Blastomyces dermatitidis

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



McKeen, et al. Cutaneous Blastomycosis: A case report and review of the literature

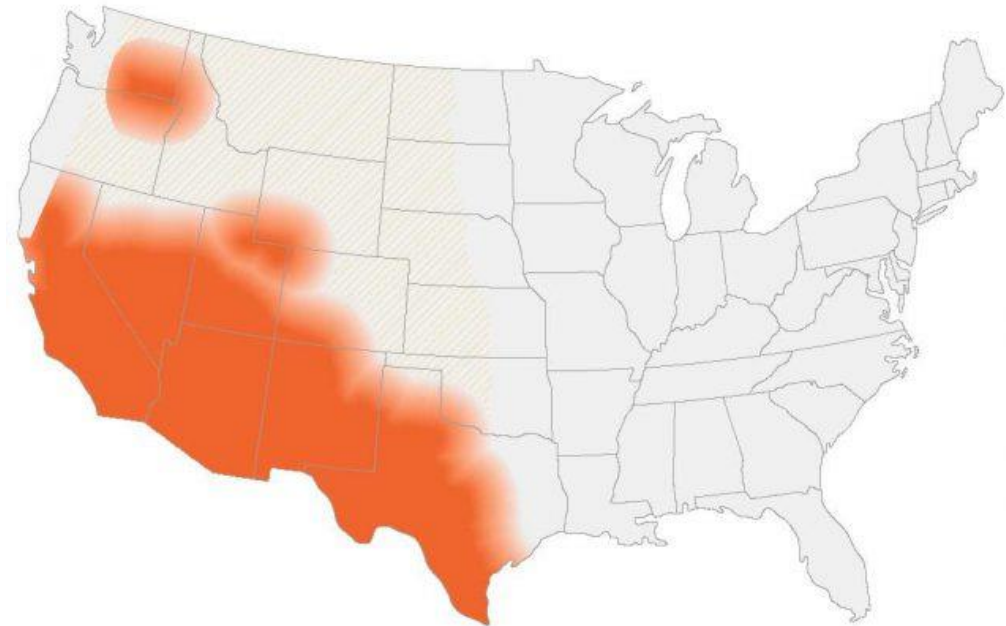


# Coccidioidomycosis

## Coccidioides

- Mexico, Arizona, New Mexico, Texas, California
- Grows as mold beneath desert surface
- Dry conditions → mold fractures into spores
- Infection by inhalation of a spores

Coccidiomycosis

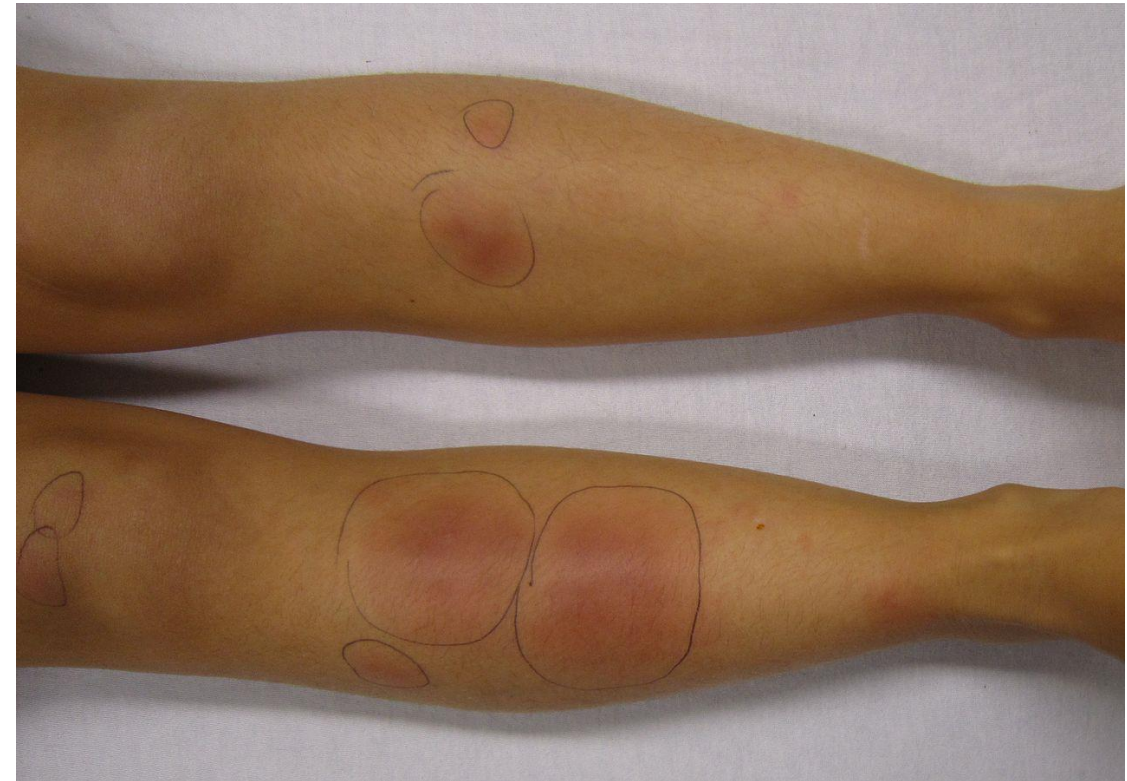


# Coccidioidomycosis

## Clinical features

- Most infections asymptomatic
- **Valley Fever**
  - Similar to community-acquired pneumonia
  - Fever, malaise, cough
  - **Arthralgias**
  - **Erythema nodosum**
- Diagnosis: **serologic testing**
  - Coccidioidal IgG and IgM antibodies
  - May be negative early after exposure
  - Alternative tests (culture) sometimes required

Erythema Nodosum



# Candida

- Normal flora of mouth, intestine, skin, vagina
- Impaired immune defenses → overgrowth disease
  - Oral thrush
  - Esophagitis
  - Vulvovaginitis
  - Diaper rash
- Disseminated disease (candida in blood cultures)
  - Endocarditis
  - Disseminated candidiasis

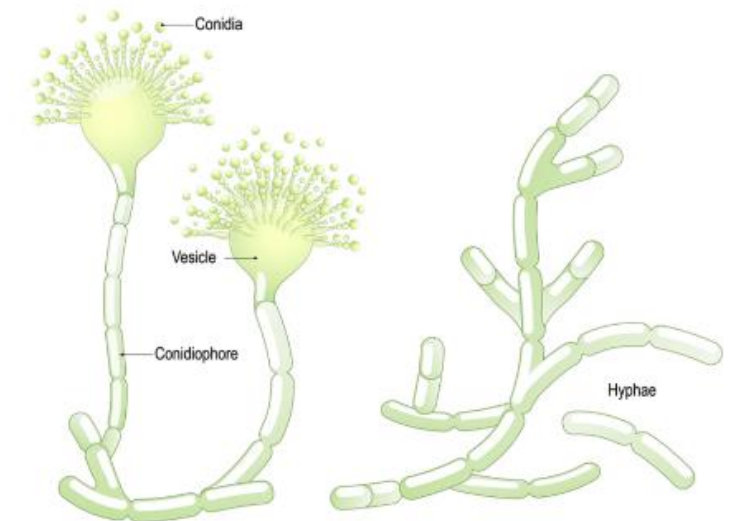
Oral Thrush



# Aspergillus

- Aspergillus species ubiquitous in nature
  - A. fumigatus, A. flavus, A. terreus
  - Inhalation of spores common
- Disease with abnormal lung function or immunocompromise
- **Allergic bronchopulmonary aspergillosis (APBA)**
  - Occurs in chronic lung disease
  - Leads to bronchiectasis
- **Chronic pulmonary aspergillosis**
- **Invasive aspergillosis**

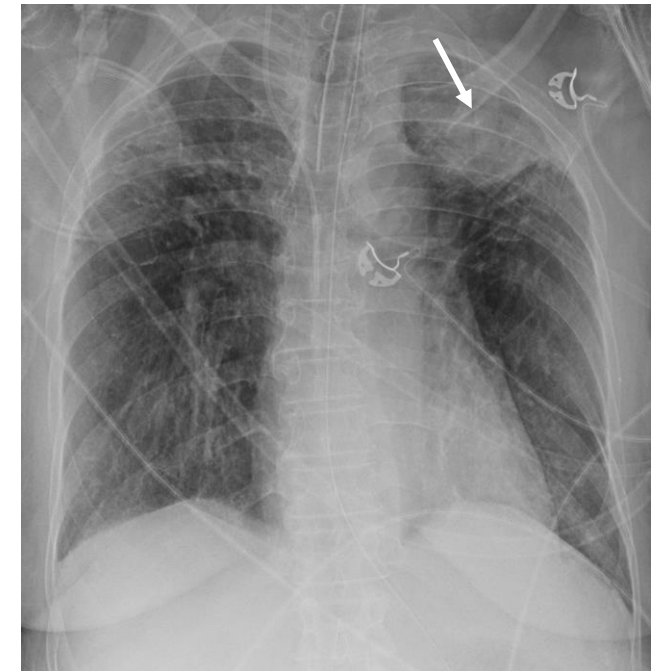
*Aspergillus fumigatus*



# Chronic Pulmonary Aspergillosis

- Usually occurs in patients with underlying **pulmonary tuberculosis**
- Pre-existing cavity → aspergillus colonization
- Slow onset weight loss, chronic cough, hemoptysis
- Negative tuberculosis testing
- **Positive aspergillus IgG antibody test**
  - Sputum culture often negative
- **Aspergilloma**
  - “Fungus ball”
  - Upper lobe cavitory lesion on imaging
  - Treatment: surgical resection

Aspergilloma

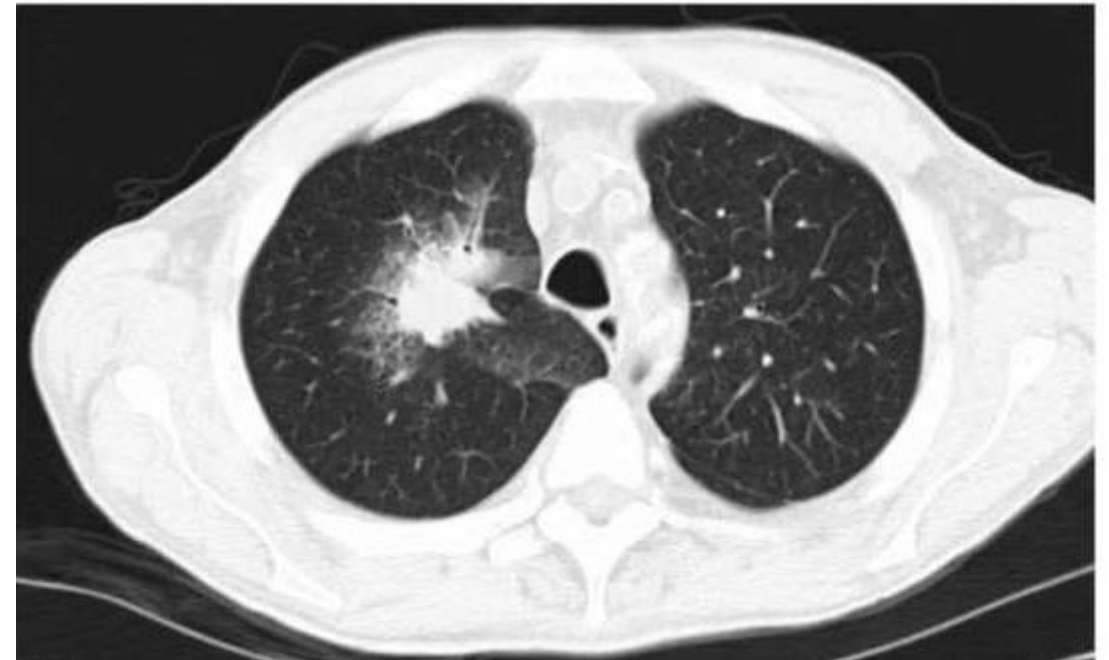




# Invasive Aspergillosis

- Lung disease that can progress to systemic illness
- Requires **immunocompromise**
  - Occurs with neutropenia
  - Also high doses of glucocorticoids
- Fever, chest pain, cough, hemoptysis
- Chest x-ray: nodules and infiltrates
- **Halo sign** on CT scan
  - Nodules surrounded by ground-glass infiltrates

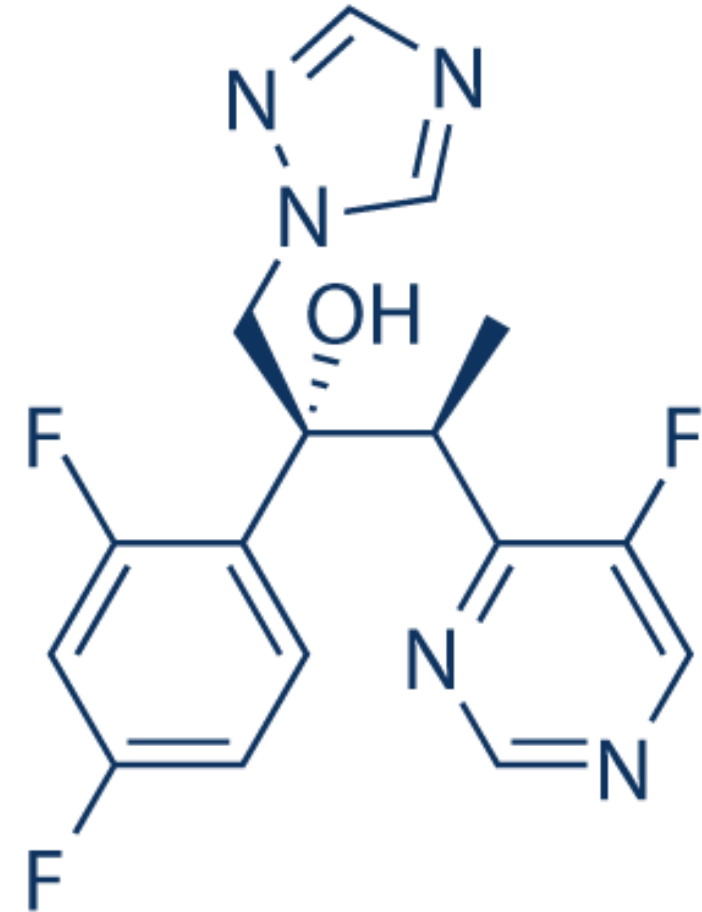
Halo Sign



## Diagnosis and treatment

- **Serum biomarkers**
  - Galactomannan and beta-D-glucan assays
  - Components of aspergillus
- Sputum for **fungal staining and culture**
- Biopsy required in some cases
- Treatment for most patients: **voriconazole**

# Voriconazole





# Cryptococcus Neoformans

- Exists only as yeast with a thick capsule (not dimorphic )
- Main disease is **meningitis** especially in HIV/AIDS
- Present in soil and **pigeon droppings**
- Inhaled → lungs → blood stream → meninges
- Rarely can cause pneumonia or other infections

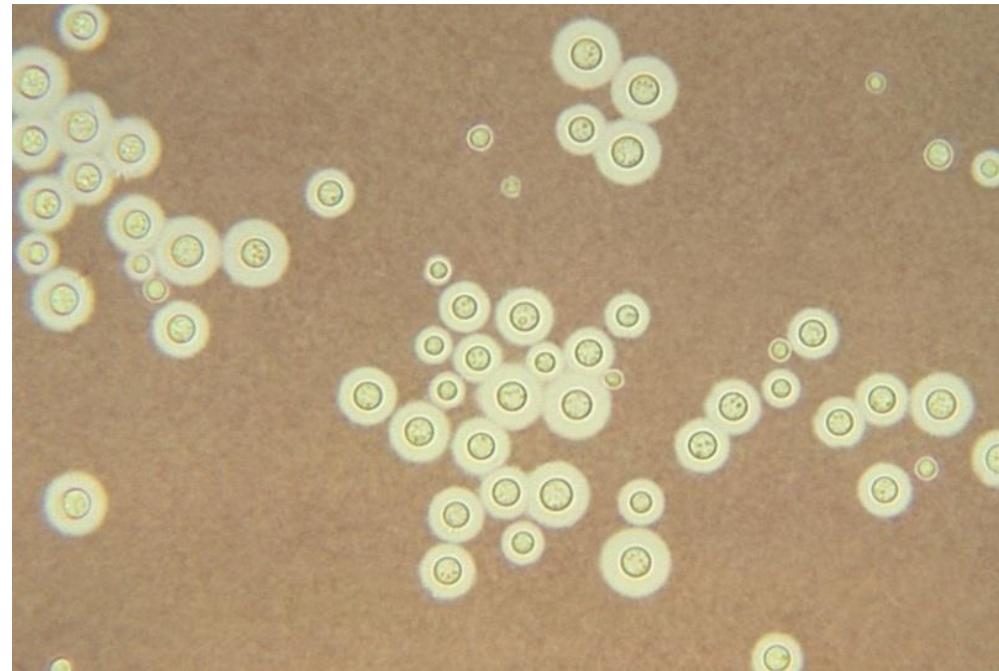
Pigeon



# Cryptococcal Meningitis

- Indolent symptoms over weeks
- Fever, headache
- Diagnosis: **lumbar puncture**
  - India ink staining of CSF (yeast with halos)
  - Cryptococcal antigen (latex agglutination or ELISA)
  - Culture
- Neuroimaging often done before LP
  - CT or MRI
  - May detect CNS mass or ↑ ICP

India Ink stain shows yeast with “halos”



# Cryptococcal Meningitis

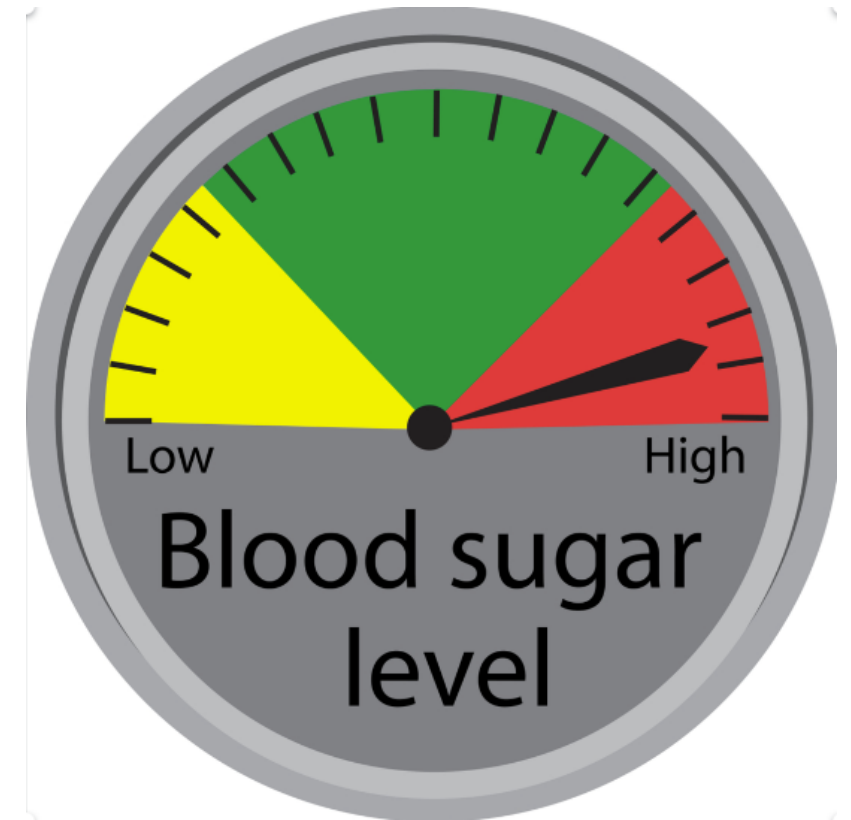
## Treatment

- Prolonged treatment required
- Induction: **amphotericin B plus flucytosine**
  - Usually for 2 weeks or more
- Consolidation therapy with **oral fluconazole**
  - Usually for 8 weeks
- Maintenance therapy with oral fluconazole (lower dose)
  - Up to 1 year



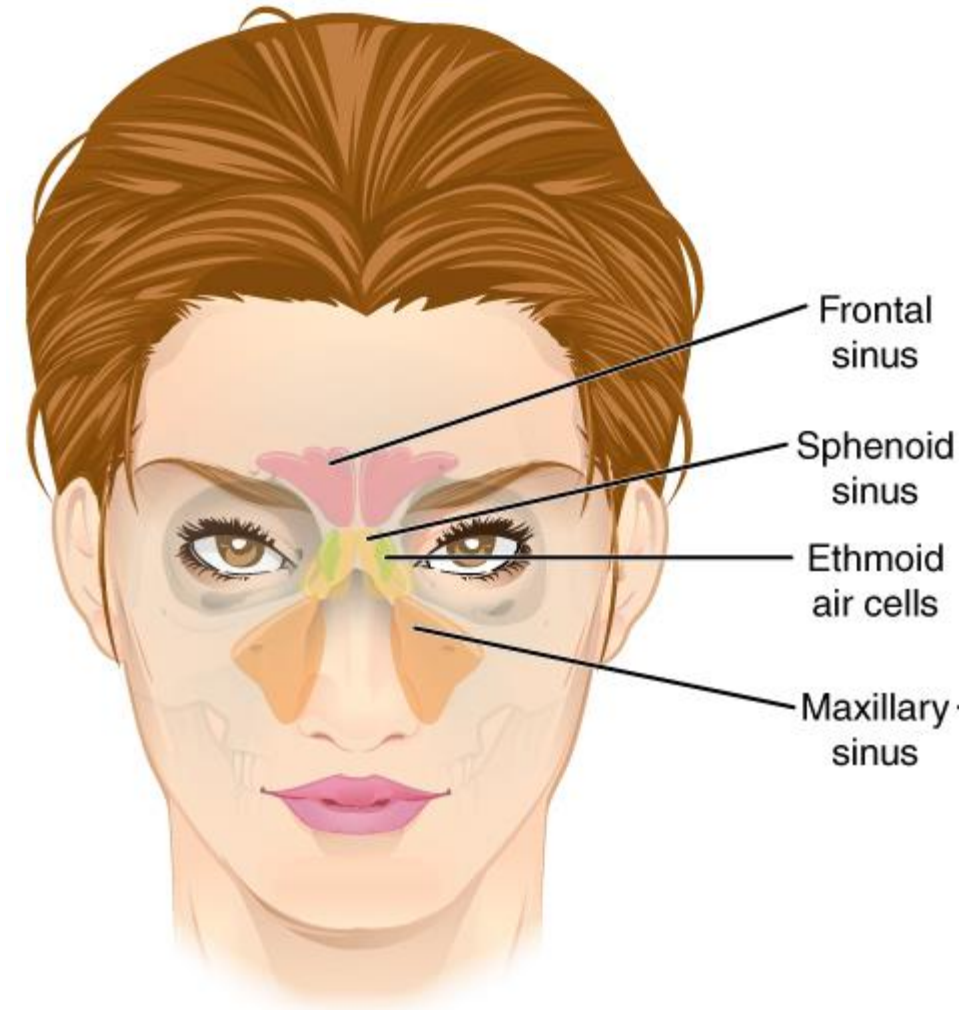
# Mucormycosis

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



# 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
- Erythema and cyanosis of skin over sinuses
- Necrosis of the palate
- Black eschars
- Orbital pain and swelling
- Facial numbness (cranial nerve damage)

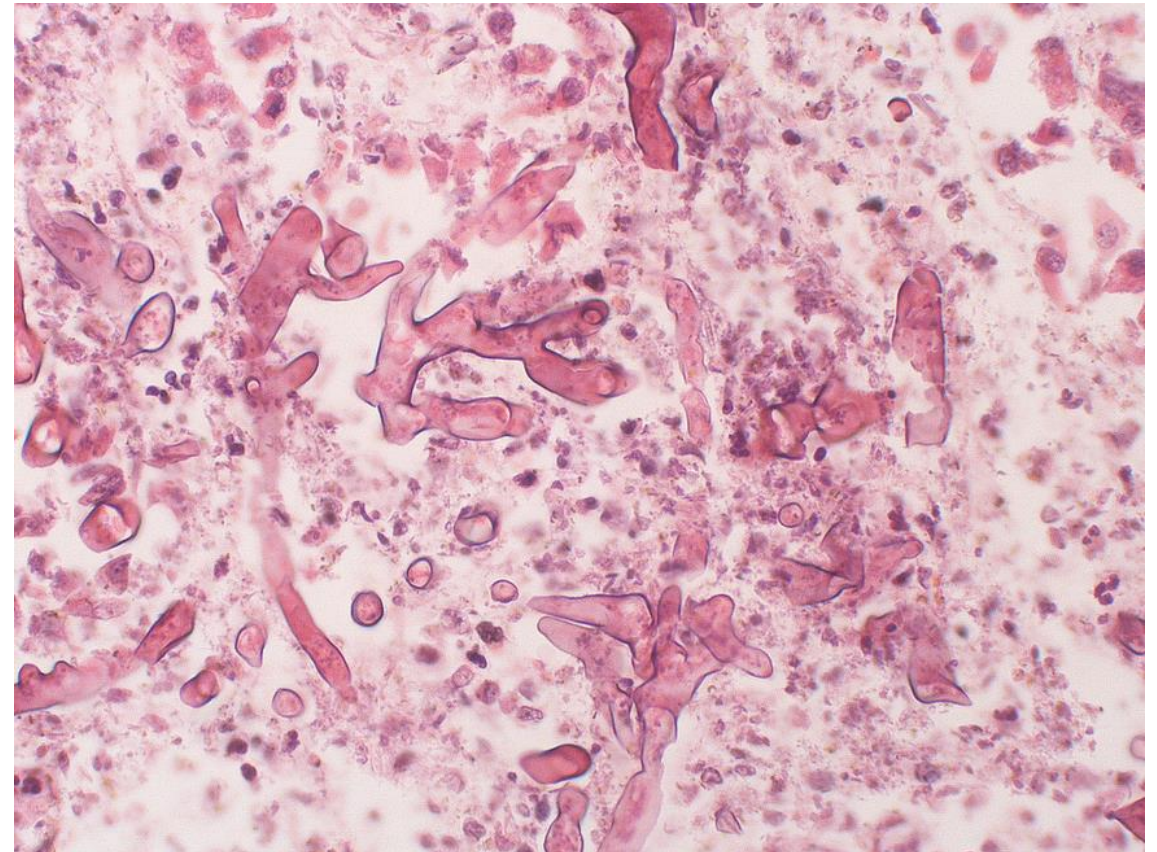


# Mucormycosis

## Diagnosis and treatment

- Classic case:
  - Patient with DKA
  - Fever, headache, eye pain
- Diagnosis: **mucosal biopsy**
  - Endoscopic sinus evaluation
  - Broad hyphae with irregular branching
- Treatment:
  - Surgical debridement
  - Amphotericin B

Mucormycosis





# Antifungal Drugs

Jason Ryan, MD, MPH



# Antifungal Drugs

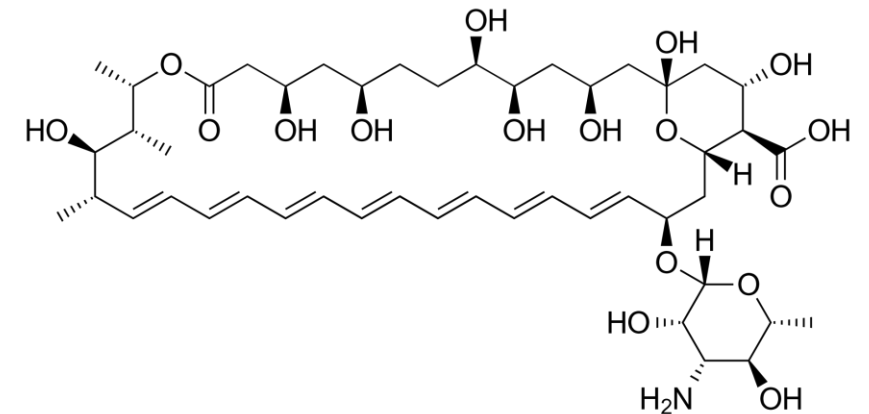
- Amphotericin drugs
  - Amphotericin B
  - Nystatin
  - Flucytosine
- Azoles
  - Fluconazole, itraconazole, voriconazole
- Echinocandins
  - Caspofungin, micafungin
- Tinea drugs
  - Terbinafine
  - Griseofulvin



FUNGI

# Amphotericin B

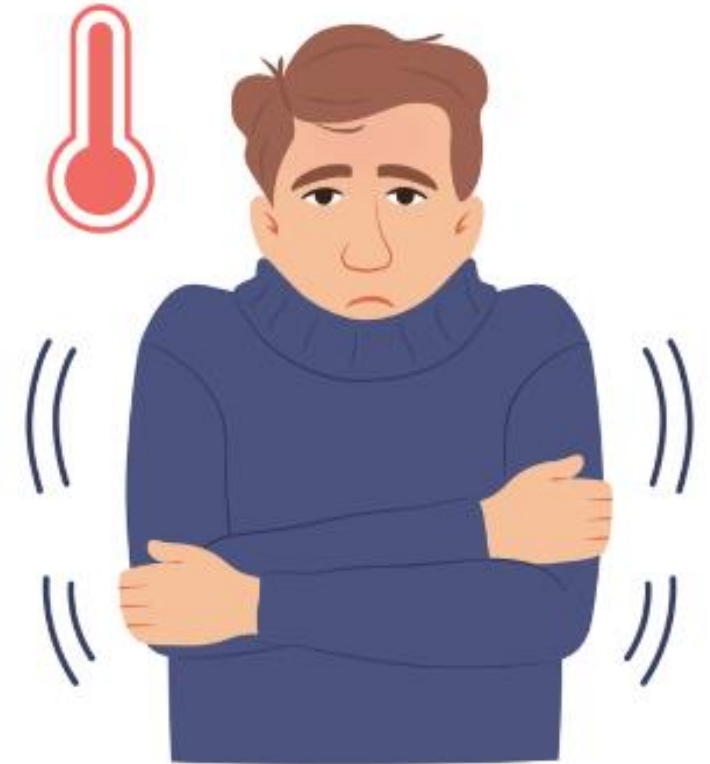
- Binds ergosterol → creates pores in fungal cell walls
- Used for **severe, invasive fungal infections**
- Poor oral absorption
- Usually given intravenously
- Standard formulation: amphotericin B deoxycholate
- In US, always given as **lipid-based amphotericin B**
  - Lower risk of nephrotoxicity
  - Conventional amphotericin generally not used



# Amphotericin B

## Adverse effects

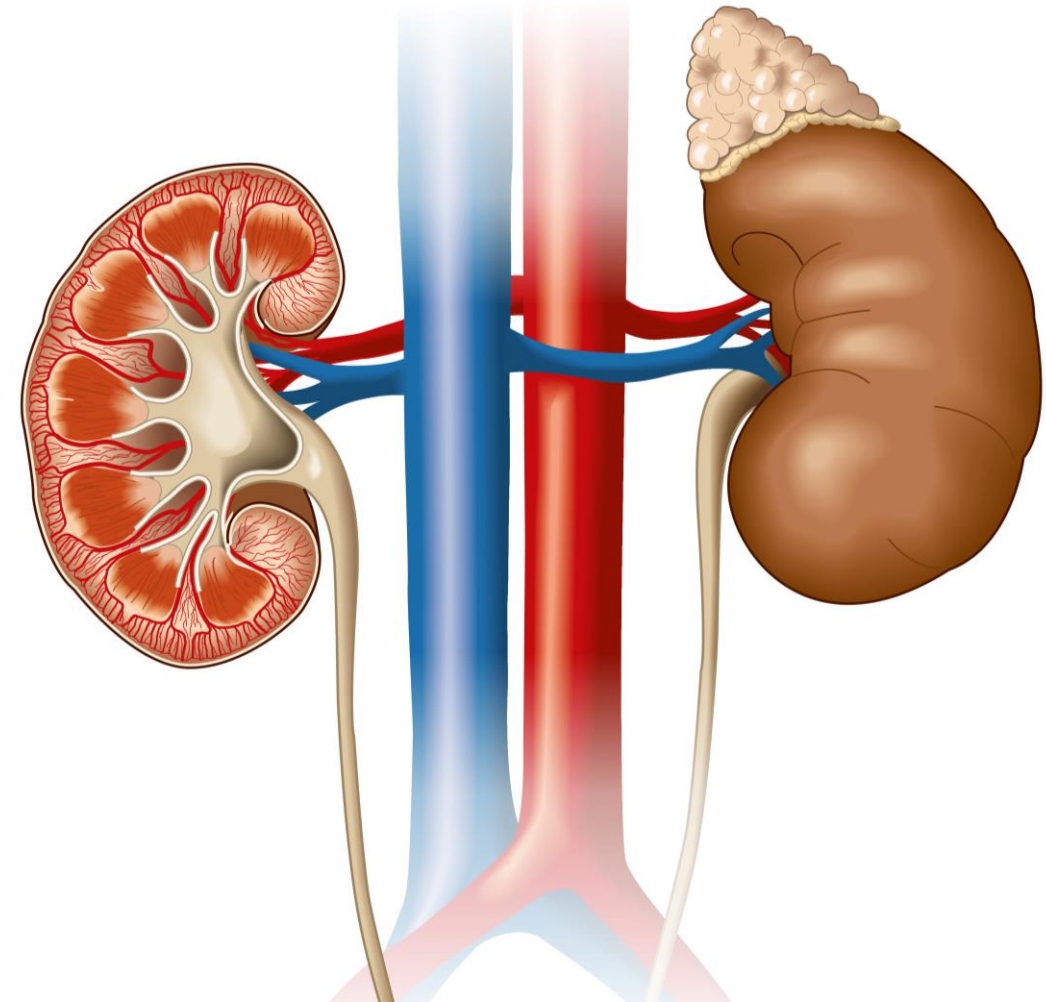
- **Fever and chills**
  - “Shake and bake”
  - May be related to prostaglandin release
  - Minimized with acetaminophen, NSAIDs, or diphenhydramine
- **Phlebitis**
  - Pain and inflammation of vein used for infusion
  - Avoided by using a central line
  - Sometimes hydrocortisone given with infusion



# Amphotericin B

## Adverse effects

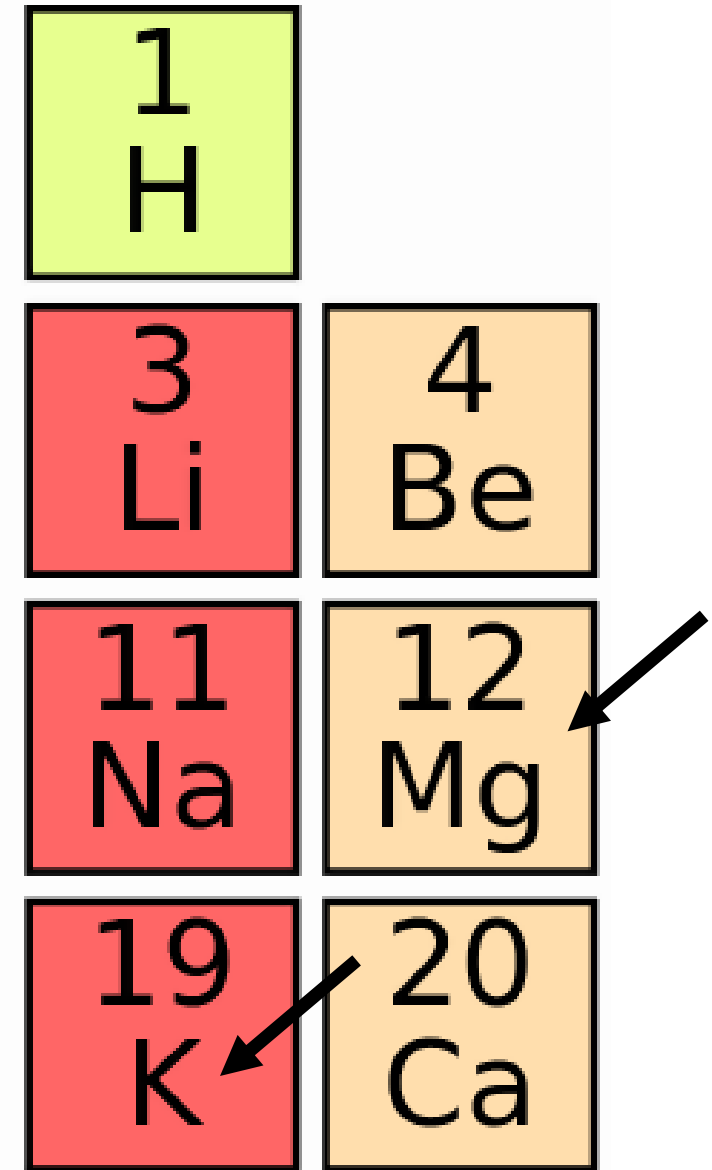
- **Nephrotoxicity**
  - Causes renal vasoconstriction/toxic to tubules
  - Decrease GFR (Cr will rise)
  - Rarely acute kidney injury
  - Saline infusion may reduce this complication
- **Liposomal amphotericin B**
  - Amphotericin B dissolved in lipids
  - Developed based on animal studies
  - Reduced incidence of nephrotoxicity



# Amphotericin B

- **Hypomagnesemia and 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

1 H	
3 Li	4 Be
11 Na	12 Mg
19 K	20 Ca

A diagram of the periodic table showing elements 1, 3, 4, 11, 12, 19, and 20. The elements are arranged in a grid: 1 (H) is in the top left; 3 (Li) and 4 (Be) are in the second row; 11 (Na) and 12 (Mg) are in the third row; 19 (K) and 20 (Ca) are in the fourth row. Arrows point to Magnesium (Mg) and Potassium (K).

# Amphotericin B

## Monitoring

- BUN and creatinine
- Electrolytes (Mg and K)
- CBC





# Nystatin

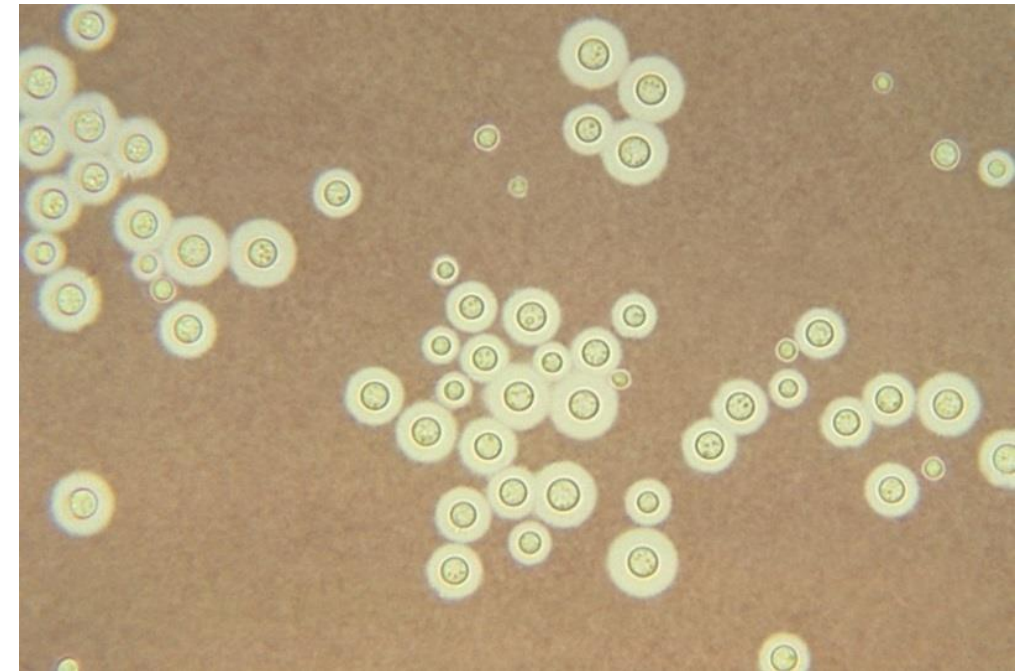
- Binds ergosterol
- Same mechanism amphotericin
- Highly toxic when given intravenously
- Not used systemically
- “Swish and swallow” for thrush (candida)
- Diaper rash (candida)



# Flucytosine

- Converted to 5-fluorouracil in fungi
- Blocks fungal DNA and RNA synthesis
- High incidence of 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

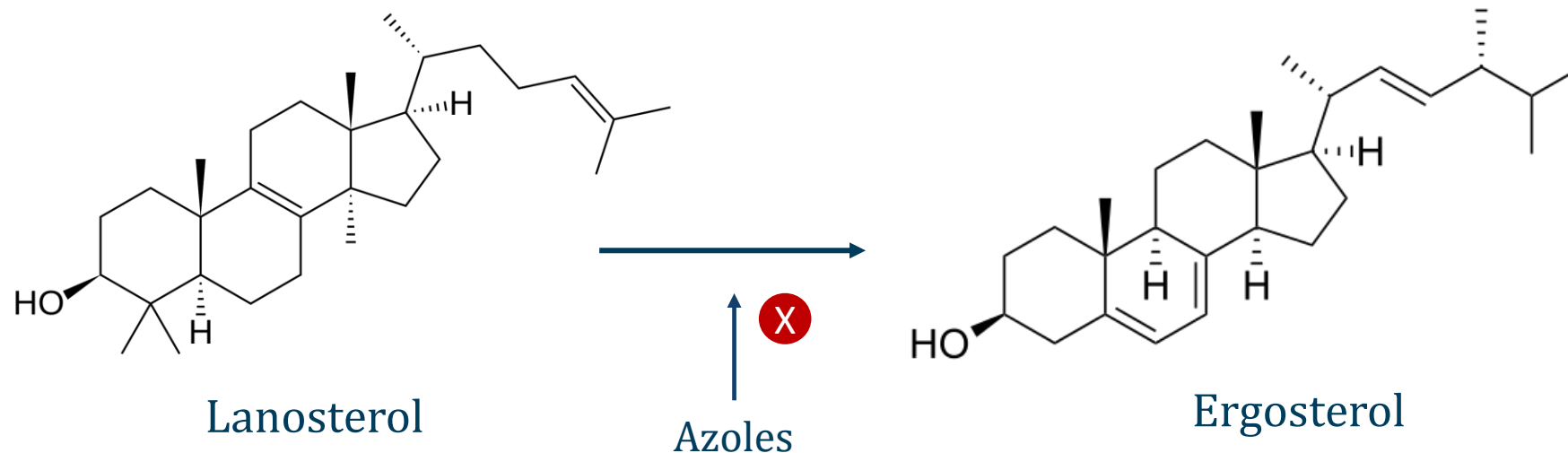
Cryptococcus - India Ink stain



# Azoles

Fluconazole, itraconazole, voriconazole, clotrimazole, miconazole, ketoconazole

- Block ergosterol synthesis
- Inhibit P450 enzyme in fungi that converts lanosterol to ergosterol
- Used in treatment of many fungal infections



# Azoles

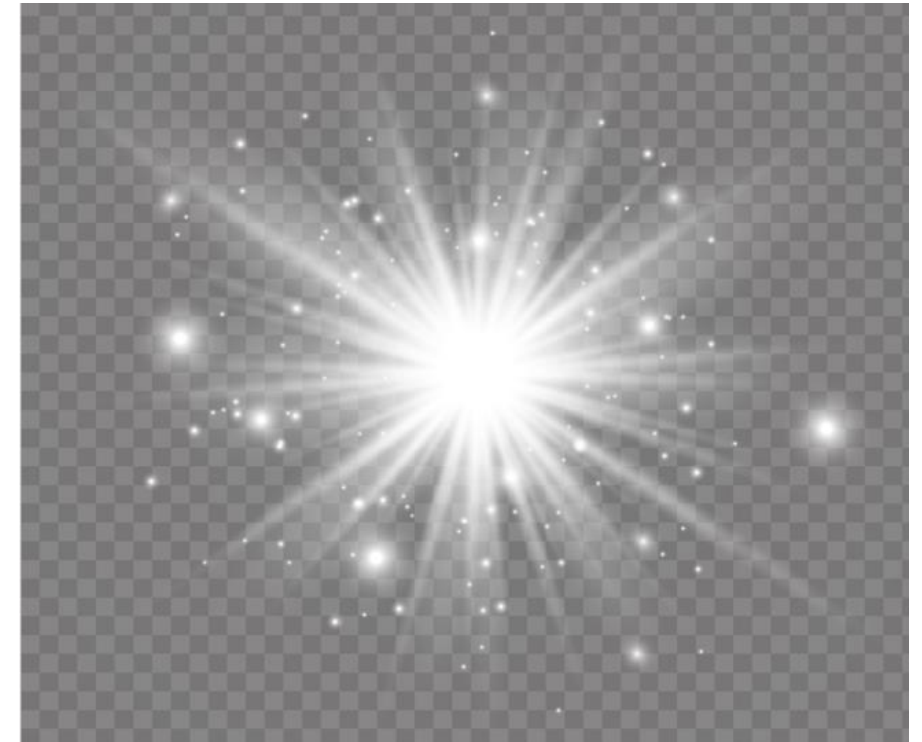
## Adverse effects

- **Inhibit human liver P450 system**
  - Elevated levels of P450 meds
  - Warfarin, theophylline
- **Hepatotoxicity**
  - Reported with all azoles
  - LFTs monitored in patients on these drugs
- **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)



# Voriconazole, Posaconazole, Isavuconazole

- Used for severe, systemic fungal infections (aspergillus)
- Several unique adverse effects
- **Transient vision changes**
  - Photopsia (flashes of light)
  - Photophobia
- **Visual hallucinations**
- Photosensitivity (skin rash)
- Alopecia
- Second generation: posaconazole, isavuconazole
  - Better side effect profile than voriconazole

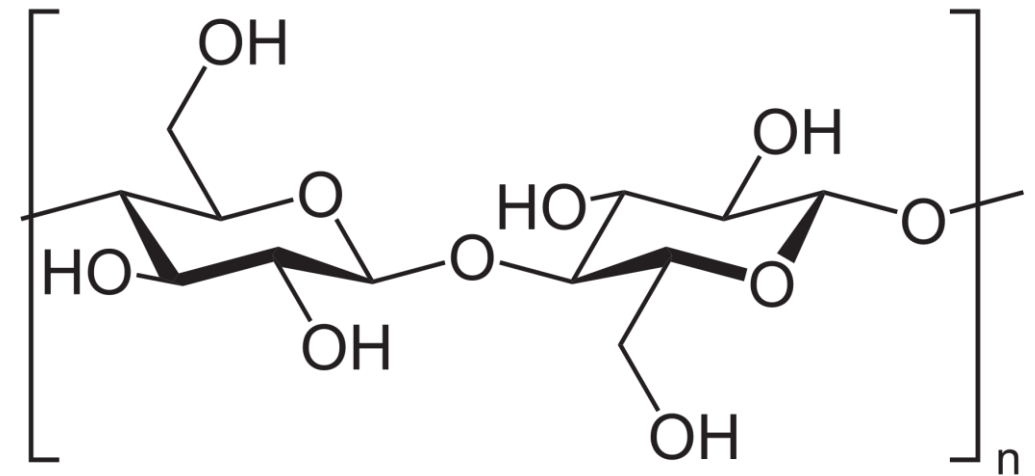


# Echinocandins

Caspofungin, micafungin

- Inhibit cell wall synthesis
- Block synthesis of  **$\beta$ -glucan polysaccharides**
- “Penicillin of antifungals”
- Used for severe, systemic infections
  - Aspergillus
  - Candidemia
- Few side effects
  - GI upset
  - Infusion-related histamine release (flushing)

Beta-Glucan Unit



# Terbinafine

- Inhibits **squalene epoxidase**
- Key enzyme for ergosterol synthesis
- Given orally or topically to treat **dermatophyte infections**
  - Especially onychomycosis
- Adverse effects:
  - Headache (13% patients)
  - Hepatotoxicity (monitor LFTs with oral forms)
  - Reports of taste changes or loss of taste

Onychomycosis

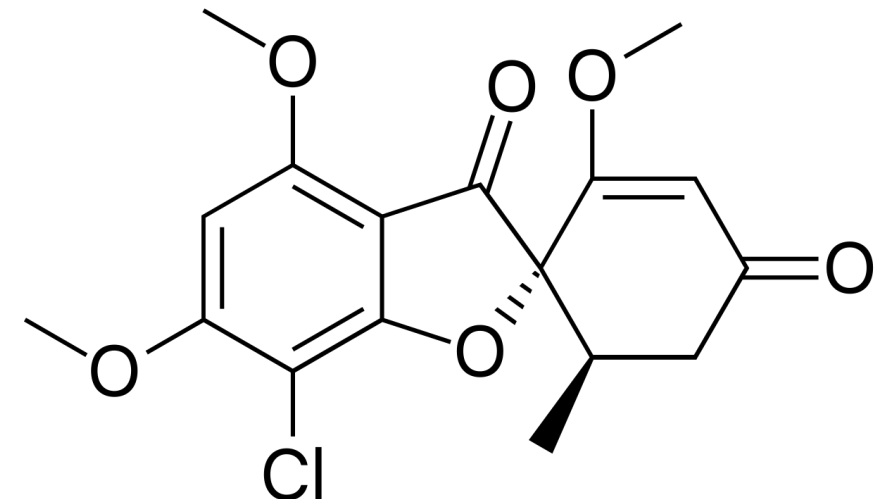




# Griseofulvin

- Blocks mitosis by interfering with microtubules
- Deposits in tissues with keratin
- Binds to keratin → tissues resist fungal invasion
- Oral therapy for **fungal skin and nail infections**
- Induces P450 (warfarin/theophylline levels will fall)
- Teratogenic: not safe in pregnancy

Griseofulvin



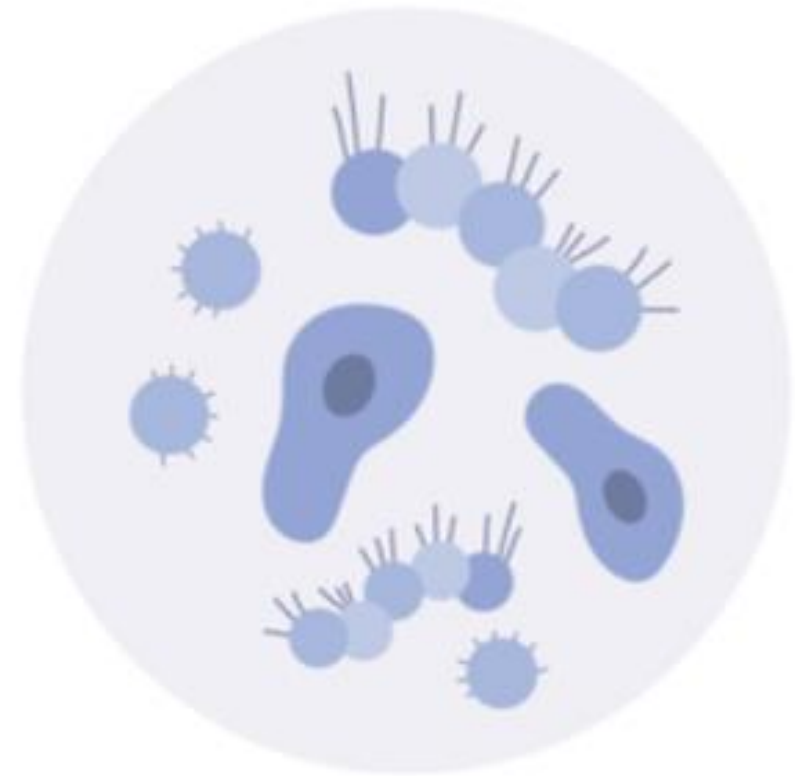
# Protozoal Infections

Jason Ryan, MD, MPH



# Protozoa

- Type of parasite along with helminths
- Unicellular, mobile organisms
- Exist in different stages
- **Trophozoites**
  - Motile, feeding and reproducing form
  - Vulnerable to environmental conditions
- **Cysts**
  - More durable form
  - Often present in feces → water → infection



PROTOZOA

# Giardiasis

## Giardia lamblia

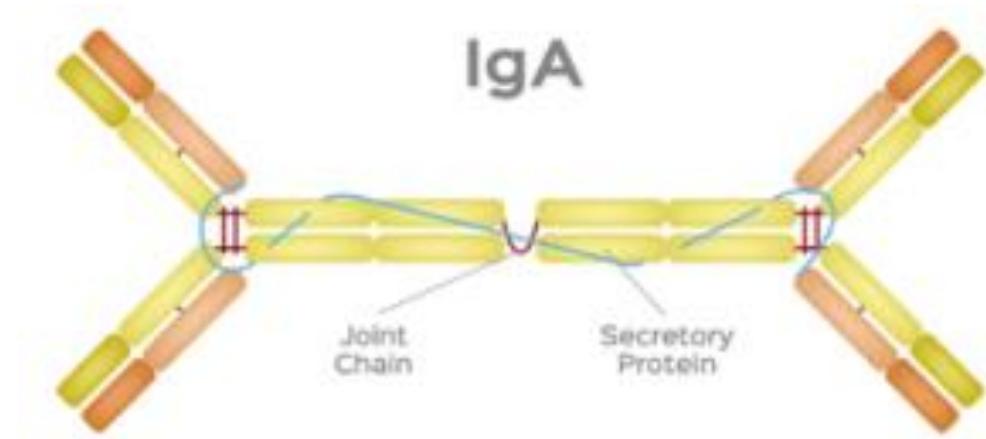
- Cysts found in moist environments
- Classic source is **water from a mountain stream**
- Outbreaks may occur with contaminated water
- Ingested cysts → trophozoite in intestine
- Do not invade – bloody diarrhea uncommon
- Affects small intestine → steatorrhea
- Bloating, foul smelling, fatty diarrhea
- Stools that float



# Giardiasis

## IgA deficiency

- IgA antibodies found in GI mucosa
- Critical for defense against Giardia
- Lack of IgA → recurrent/chronic giardia infection
- Bruton's Agammaglobulinemia
- Selective IgA deficiency



# Giardiasis

## Diagnosis and treatment

- Diagnosis: **stool ova and parasites**
  - Cysts and trophozoites in stool
  - ELISA for Giardia antigens in stool
- Classic case: camper/hiker, diarrhea, flatulence
- Treatment: **metronidazole**

Cyst



Trophozoites



# Entamoeba Histolytica

## Amebiasis/Amebic dysentery

- Common in regions with poor sanitation
- Cysts ingested in **contaminated water**
- Form trophozoites in small intestine
- Invade tissue → **bloody diarrhea**
  - Dysentery = bloody diarrhea with mucous
- Ascends portal system → liver
- **Liver abscesses**
  - Aspiration → brownish-yellow pus (“anchovy paste”)
- Traveler, bloody diarrhea, RUQ pain

Liver Abscess





# Entamoeba Histolytica

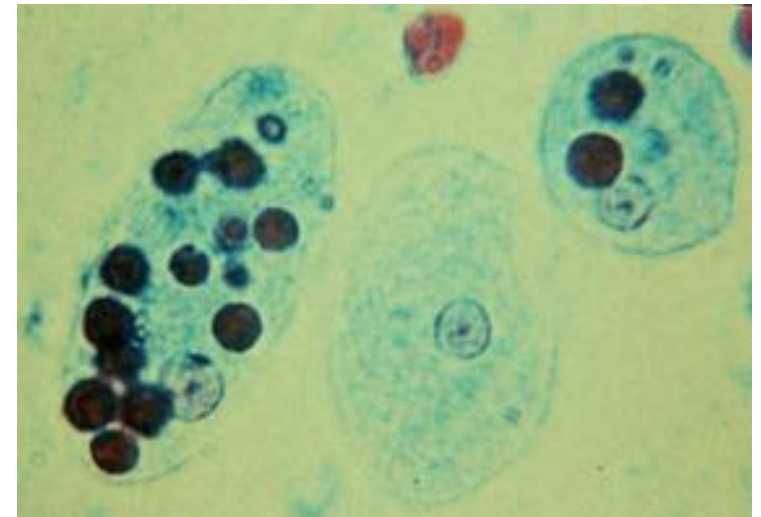
## Diagnosis

- Diagnosis: **stool ova and parasites**
  - Cysts and trophozoites
  - False negatives common – usually multiple specimens tested
- Antigen and antibody testing
  - Stool or blood

Cysts



Trophozoite with ingested RBCs



# Entamoeba Histolytica

## Treatment

- **Metronidazole**
  - Treatment for invasive diarrhea
  - Alternative: tinidazole
  - May not reliably eliminate cyst forms
- **“Luminal agents”**
  - Eliminate cysts to prevent transmission
  - Often given with treatment for invasive diarrhea
  - Paromomycin



# Cryptosporidiosis

## Cryptosporidium

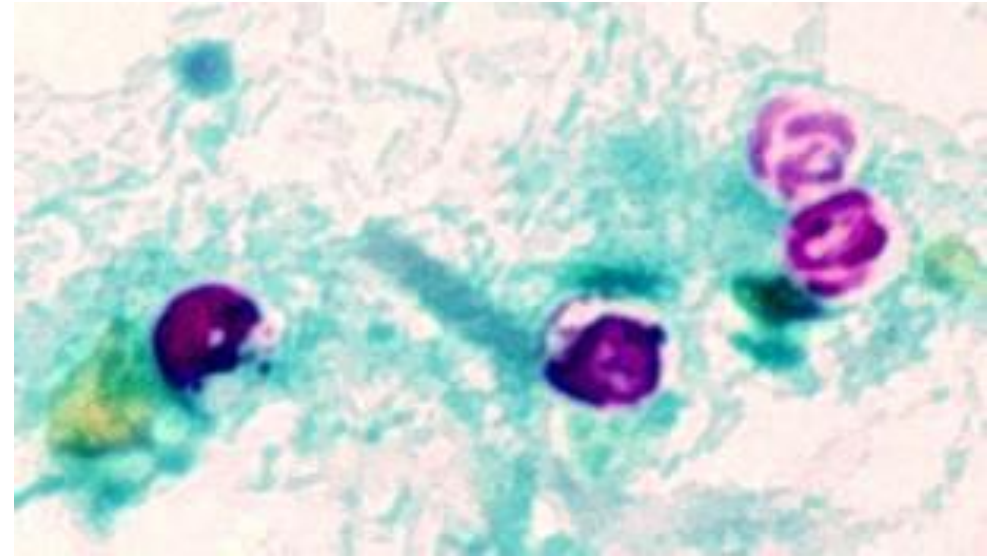
- Protozoa that forms eggs (oocysts)
- Found in contaminated water
- Contaminated water ingestion → infection
- Infection in **swimming pools** can occur
  - Chlorination does not destroy oocysts
- May also infect **horses or cattle**
- Immunocompetent patients
  - Self-limited, mild, watery diarrhea
- **Immunocompromise (HIV/AIDS)**
  - Chronic, severe, watery (non-bloody) diarrhea



# Cryptosporidiosis

## Cryptosporidium

- Diagnosis: **stool microscopy**
  - Acid fast staining reveals oocysts
  - Stool antigen testing also available
- Supportive therapy (fluids, electrolytes)
- **Nitazoxanide**
  - Severe symptoms only in immunocompetent patients
  - Limited efficacy in HIV/AIDS
- Anti-retroviral therapy for HIV patients
- Prevention is key
  - Avoid sources of contaminated water



# Toxoplasmosis

## Toxoplasma gondii

- Commonly found in cats (felines)
- Oocysts shed in stool
- Infection from ingested oocysts (soil)
- Also meat from infected animals
- Invades intestine → disseminates
- May enter **latent phase** in brain or muscle
- Infection controlled by immune system
- **Reactivation disease** may occur later





# Toxoplasmosis

## Clinical features

- Most primary infections asymptomatic
- Can cause **mononucleosis-like illness**
  - Fever, cervical lymphadenopathy
  - Negative heterophile antibodies
- **Congenital toxoplasmosis**
  - Occurs with primary maternal infection
  - Fetal chorioretinitis (blindness), intracranial calcification

Chorioretinitis

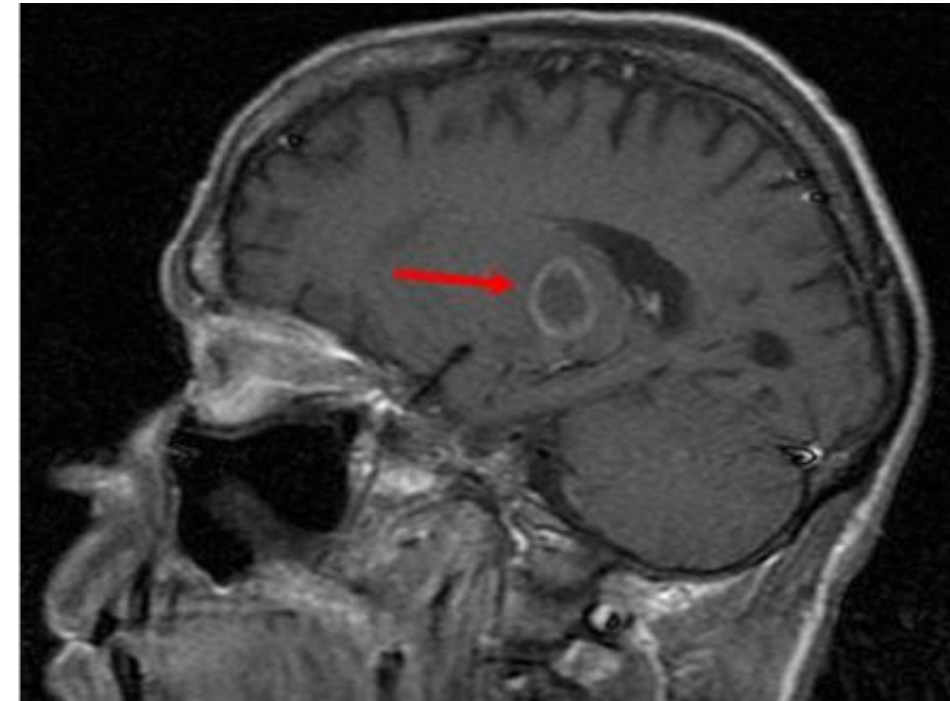


# Toxoplasmosis

## Clinical features

- Severe **reactivation disease** with **immunocompromise**
  - Usually HIV/AIDS (CD4 < 100cells/mm<sup>3</sup>)
  - Fever, headache, confusion, neurologic defects
  - Multiple “ring-enhancing” lesions with edema
  - Contrast forms ring around lesion
- Ring-enhancing lesions HIV
  - Toxoplasmosis
  - Primary CNS lymphoma

**Ring-enhancing Lesion**



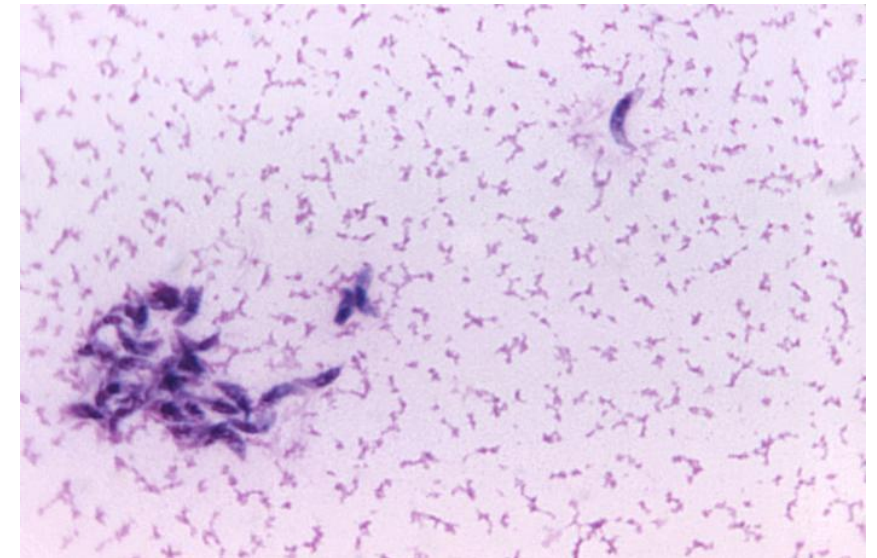


# Toxoplasmosis

## Diagnosis

- **Patients with HIV**
  - Presumptive diagnosis based on clinical findings
  - Clinical features (low CD4 count, headache, neuro deficits)
  - Imaging finding (ring-enhancing lesion)
  - Positive toxoplasma IgG antibodies
- **Immunocompetent patients**
  - Usually testing in patients with mono-like illness
  - Toxoplasmosis IgM and IgG antibodies
  - IgM indicates recent exposure
- Definitive diagnosis: brain biopsy (rarely done)

Tachyzoite on tissue biopsy



# Toxoplasmosis

## Treatment

- Usually no treatment in immunocompetent patients
  - Symptoms usually self-limited
  - Treatment only for prolonged or severe symptoms
- **HIV: sulfadiazine and pyrimethamine**
  - Blocks folate synthesis pathway
  - Similar to TMP-SMX (alternative option)
  - May suppress folate metabolism in bone marrow cells
  - Leucovorin added to prevent megaloblastic anemia

# 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
  - CSF negative for bacteria, viruses
  - Motile trophozoites in CSF
  - Often fatal (99% in one series)



# Chagas Disease

*Trypanosoma cruzi*

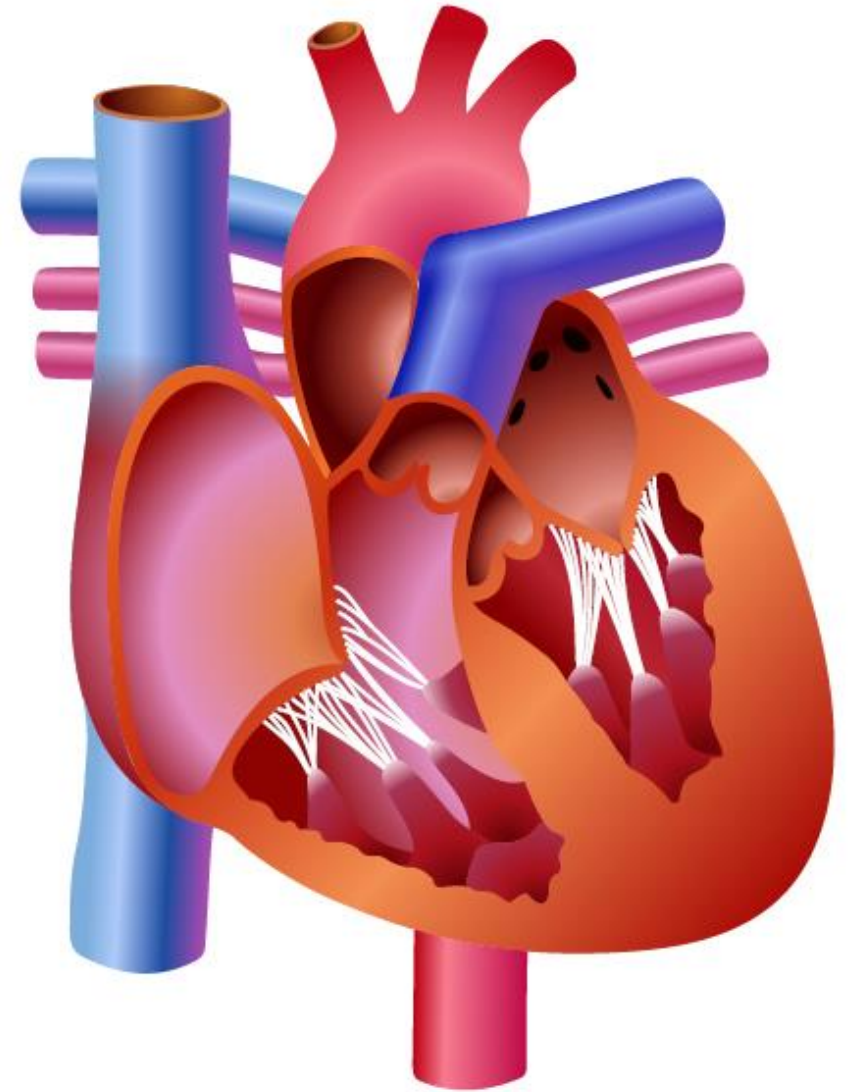
- Transmitted by **reduviid bug**
- Found primarily in Central and South America
- Bugs nest in cracks or holes of housing
- Acute phase – nonspecific, febrile illness
  - Fever, lymphadenopathy
  - Chagoma: nodule at site of bug bite
  - Romaña's sign: unilateral eyelid edema
  - Resolves over ~ 2 months
- Chronic form: heart, esophagus, colon

Romaña's sign



# Chronic Chagas Disease

- **Heart – most commonly involved organ**
  - Right and left heart failure
  - High prevalence ventricular thrombi
  - Pulmonary embolism/stroke
  - Common cause of death
- Esophagus and colon
  - Nerve damage
  - Achalasia, megaesophagus (dilation)
  - Megacolon (severe constipation)



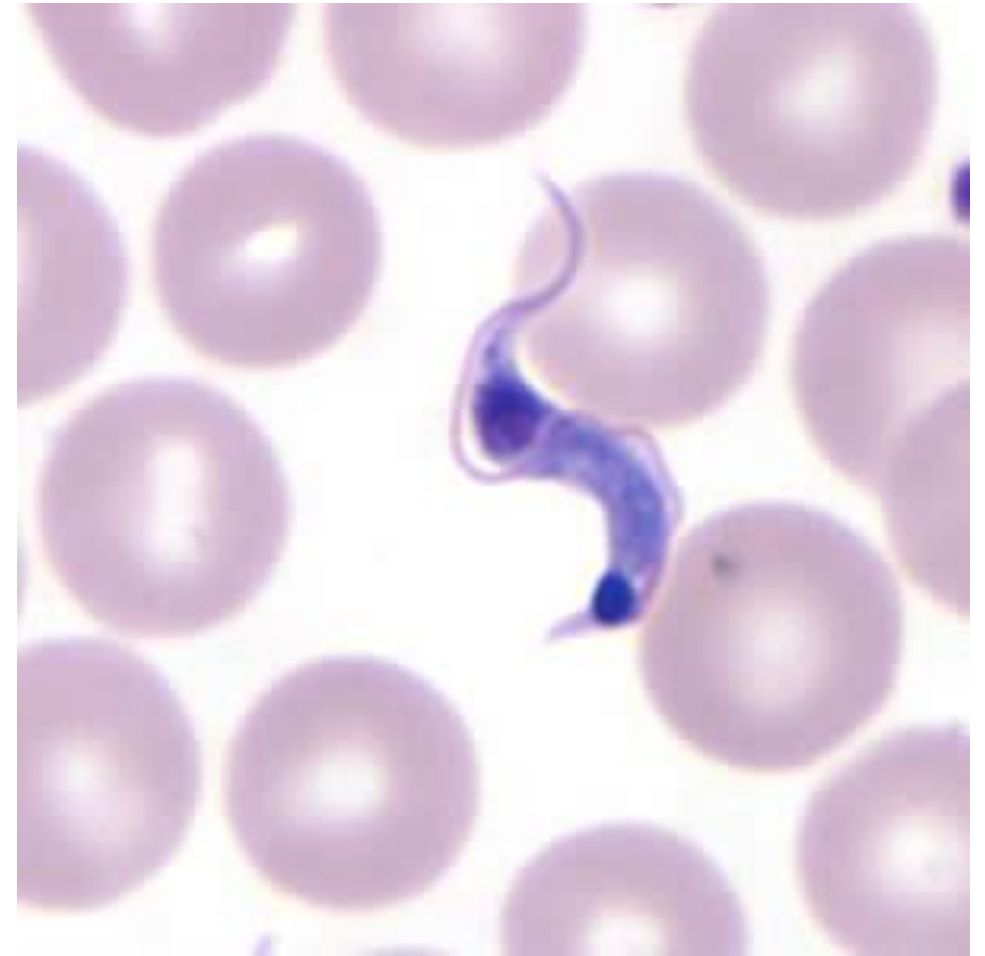


# Chagas Disease

## Diagnosis and treatment

- Acute phase: **blood smear**
  - Trypomastigotes visible
  - PCR testing also available
- Chronic phase
  - Serology (IgG antibodies to *T. cruzi*)
- Treatment: **nifurtimox or benznidazole**
  - Effective for acute phase
  - Used in chronic Chagas
  - Limited effectiveness with advanced disease

Trypomastigotes



# African Trypanosomiasis

*Trypanosoma brucei*

- Two subtypes: *T. gambiense* and *T. rhodesiense*
- Protozoa infections from **tsetse fly** bite
- Endemic to Africa
- Causes **sleeping sickness**

Tsetse fly





# African Trypanosomiasis

*Trypanosoma brucei*

- Tsetse fly bite: indurated skin ulcer (“trypanosomal chancre”)
- Cervical lymphadenopathy
- Key feature: **recurring fever**
  - Due to antigenic variation
  - Waves of parasitemia → remission → recurrence
- May cause **encephalitis**
  - Headache, somnolence, coma
- *T. gambiense*: low-grade, chronic illness for years
- *T. rhodesiense*: acute, rapidly-progressive illness

Trypanosomal chancre



# African Trypanosomiasis

## Trypanosoma brucei

- Peripheral blood: trypomastigotes
  - Also present in chancre or lymph nodes
- Early stage treatment: **suramin**
  - Not effective for encephalitis
  - Does not cross blood-brain barrier
- Encephalitis treatment: **melarsoprol**

Trypomastigotes



# Visceral Leishmaniasis

Leishmania Donovanii

- Transmitted by **sand fly**
- South Asia (India, Bangladesh and Nepal) and East Africa
- Infects macrophages
- Spleen, liver and bone marrow
- Fever
- **Painful splenomegaly**
- **Pancytopenia**
- Skin may darken (rare)
- Kala-azar (“black fever”)

Sand Fly

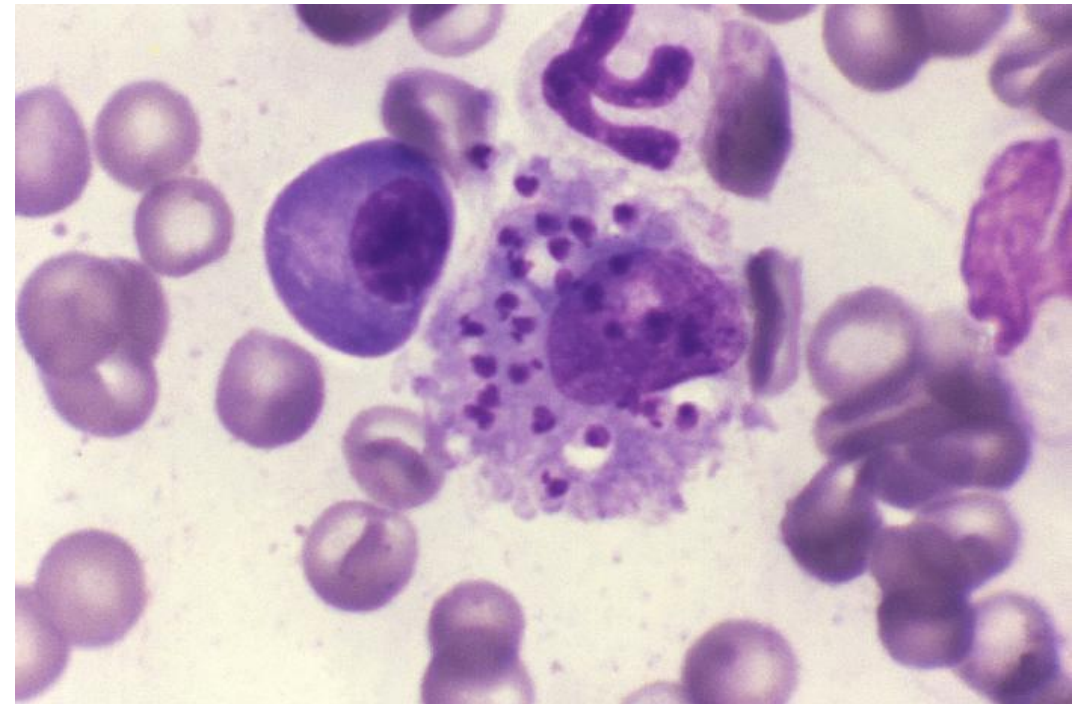


# Visceral Leishmaniasis

## Diagnosis and treatment

- Biopsy of involved organs
  - Usually bone marrow or spleen
  - Amastigotes in macrophages
  - Small, round or oval bodies
- Treatment:
  - Amphotericin B
  - Sodium stibogluconate

Amastigotes in macrophage



# Cutaneous Leishmaniasis

- Caused by other protozoa of genus *Leishmania*
- *L. tropica*, *L. mexicana*, *L. braziliensis*
- Also transmitted by sand fly
- Large ulcer with indurated borders
- Often treated topically
- Stibogluconate or paromomycin



# Malaria

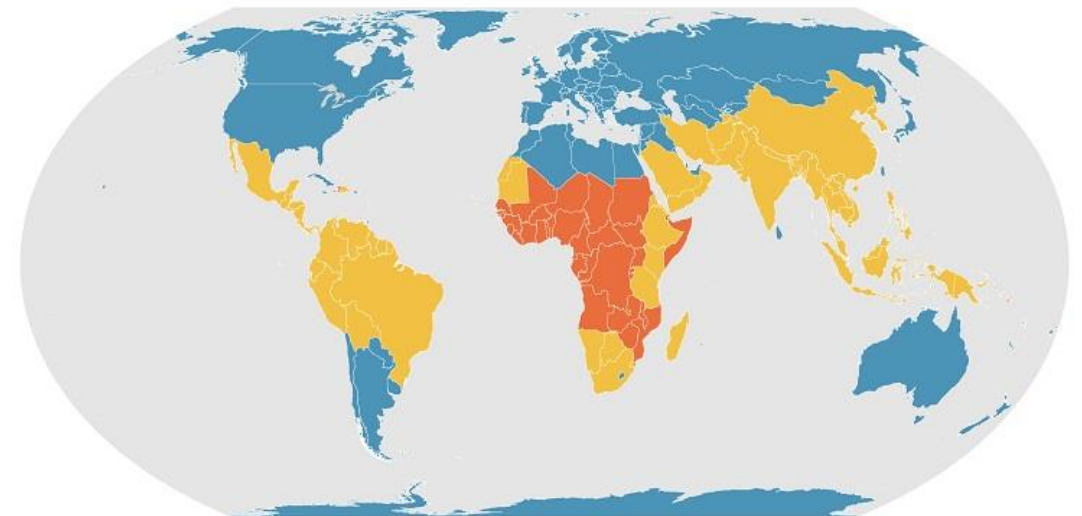
Jason Ryan, MD, MPH





# Malaria

- Protozoal infection of **red blood cells** and **liver**
- Transmitted by mosquito bite (female Anopheles)
- Occurs in regions surrounding equator
- Rare in US and Europe
- Africa is most affected continent
- Caused by species of **plasmodium**
  - P. falciparum (most common)
  - P. vivax
  - P. malariae
  - P. ovale



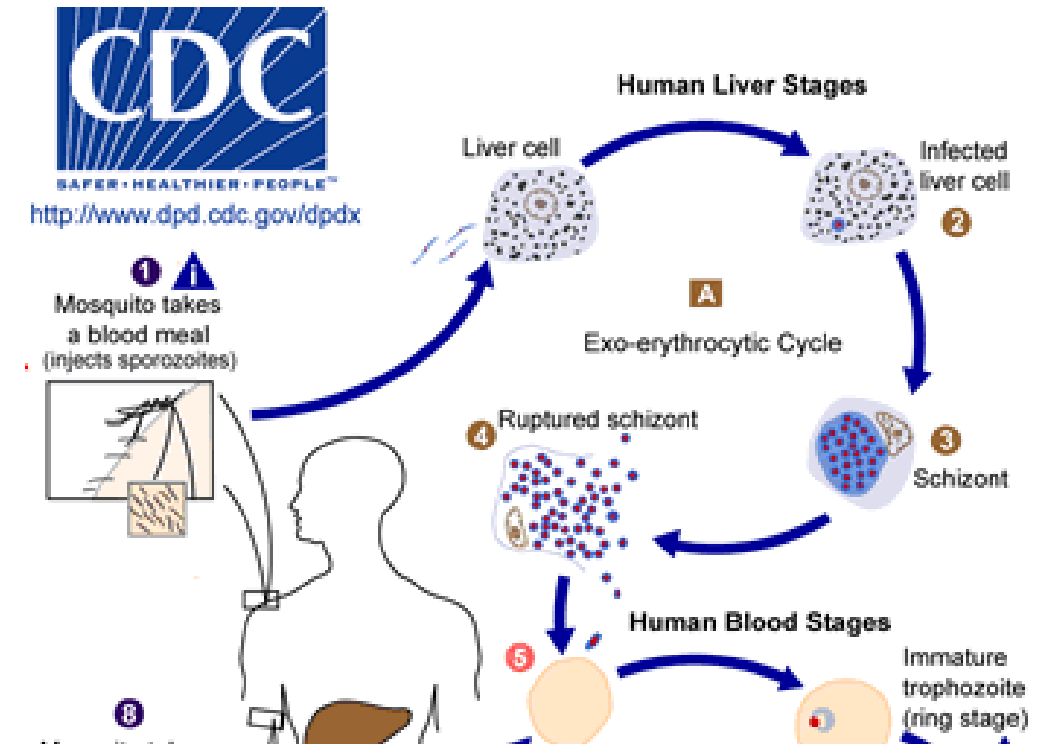
- Malaria transmission is not known to occur
- Malaria transmission occurs in some places
- Malaria transmission occurs throughout



# Malaria

## Life cycle

- Complex life cycle with various forms of plasmodium
- Bite of female mosquito → **sporozoites** to liver
- Pre-erythrocytic stage
  - Asymptomatic for up to 1 month
  - Sporozoites invade hepatocytes
  - Develop into **merozoites** → released from liver
  - Infect red blood cells

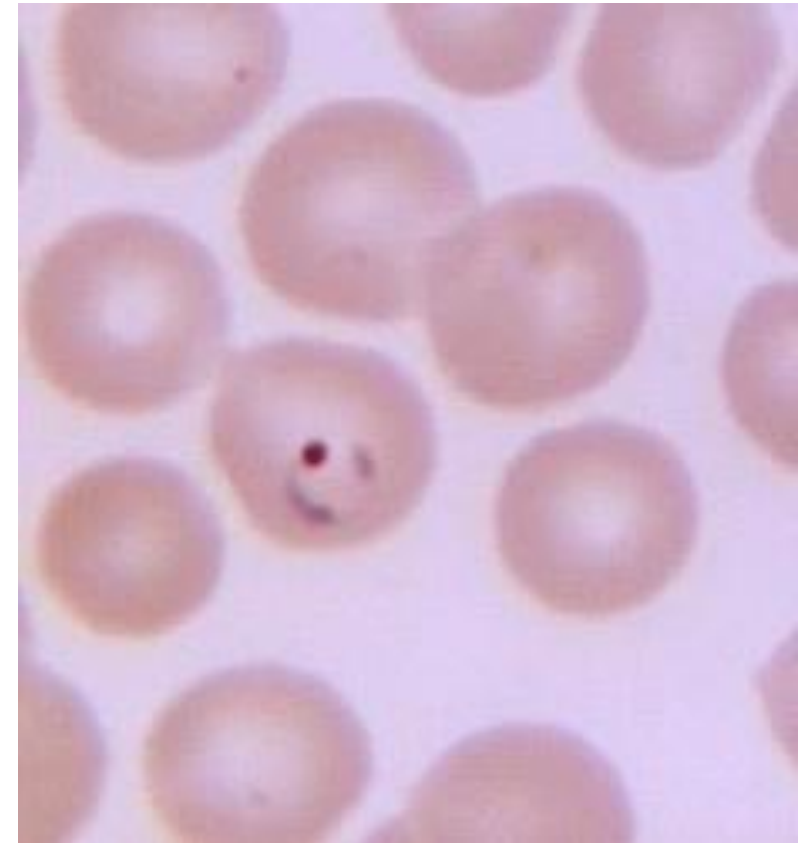


# Malaria

## Life cycle

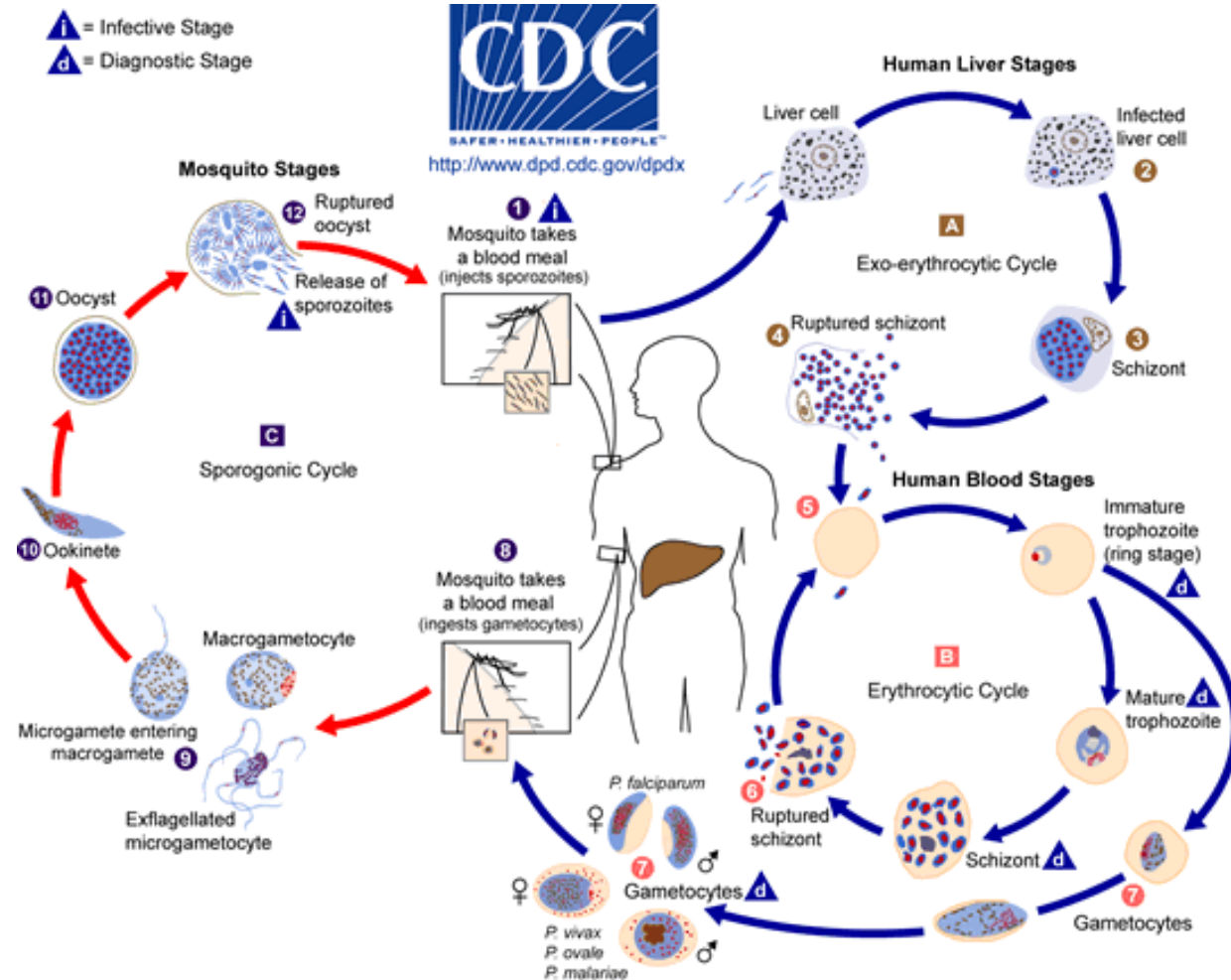
- Erythrocytic stage
  - Merozoites invaded RBCs
  - Form **trophozoites (ring form)** in RBCs
- Merozoites formed (again) → red cell lysis
  - Occurs at regular intervals (48hr, 72hr)
  - Hemolysis and jaundice
  - **Cyclic fevers** can occur

Trophozoite Ring Forms



# Malaria

## Life cycle



# Malaria

## Clinical features

- **Paroxysms of fever**
  - Fever spike with shivering and chills
  - Fever followed by drenching sweats
  - Fever recurs at regular intervals (48hrs, 72hrs)
  - Variable by species of Plasmodium
- Hemolytic anemia with jaundice
- Splenomegaly (clearance of red cells)
- Fatigue, malaise, arthralgias, headache



# Malaria

## Plasmodium Vivax and Ovale

- Classically has a **48 hour cycle of fevers**
  - “Tertian” fever pattern – every second day
  - Fever days 1 and 3; no fever days 2 and 4
- Produce **hypnozoites** in liver
  - Latent form
  - Recurring infection months after resolution
- **Primaquine** added to other therapy
  - Treats latent liver disease
  - Without this, relapses may occur



# Malaria

## Plasmodium Malariae

- Classically has a **72 hour cycle of fevers**
  - “Quartan” fever pattern – every third day
  - Fever days 1 and 4; no fevers day 2 and 3



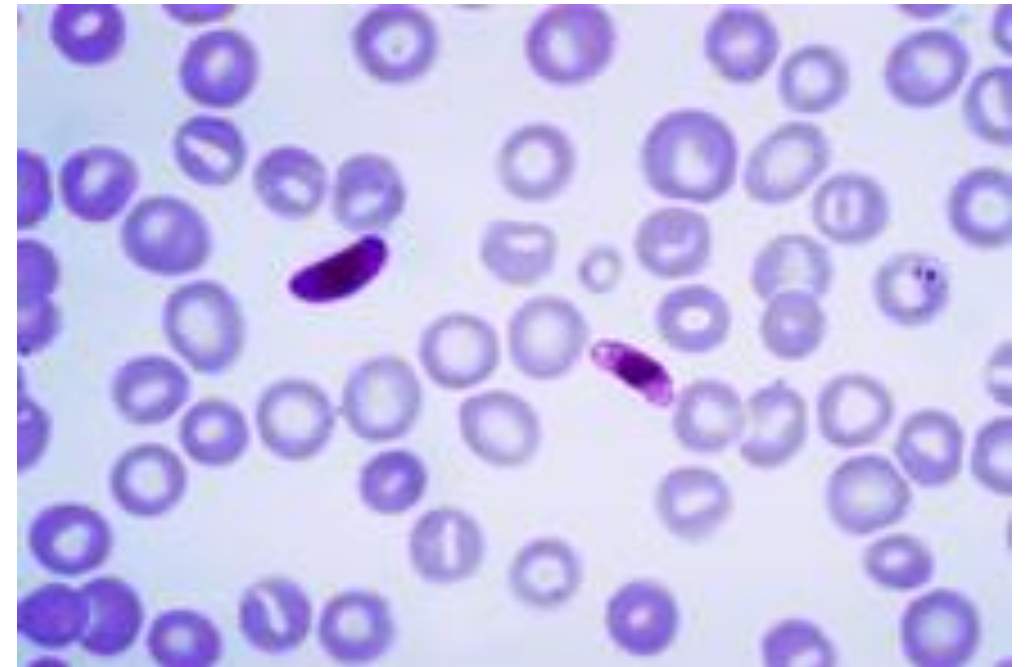


# Malaria

## Plasmodium Falciparum

- **Most severe malarial infection**
- Fever pattern is irregular
- Invades **more RBCs than other forms**
  - Can infect red cells of all ages
  - P. vivax: only reticulocytes
  - P. malariae: only mature red cells
- Infected red cells **occlude capillaries**
- Forms “banana-shaped gametocytes”

Banana-shaped Gametocytes P. Falciparum



# Malaria

## Complications

- **Cerebral malaria**
  - Encephalopathy - altered consciousness, delirium, seizures
- **Blackwater fever**
  - Extensive hemolysis → hemoglobinuria (dark urine)
  - May cause acute kidney injury
- Hypoglycemia
  - Decreased liver production, increased consumption
- Acidosis
  - Microvascular ischemia
- ARDS (pulmonary edema)

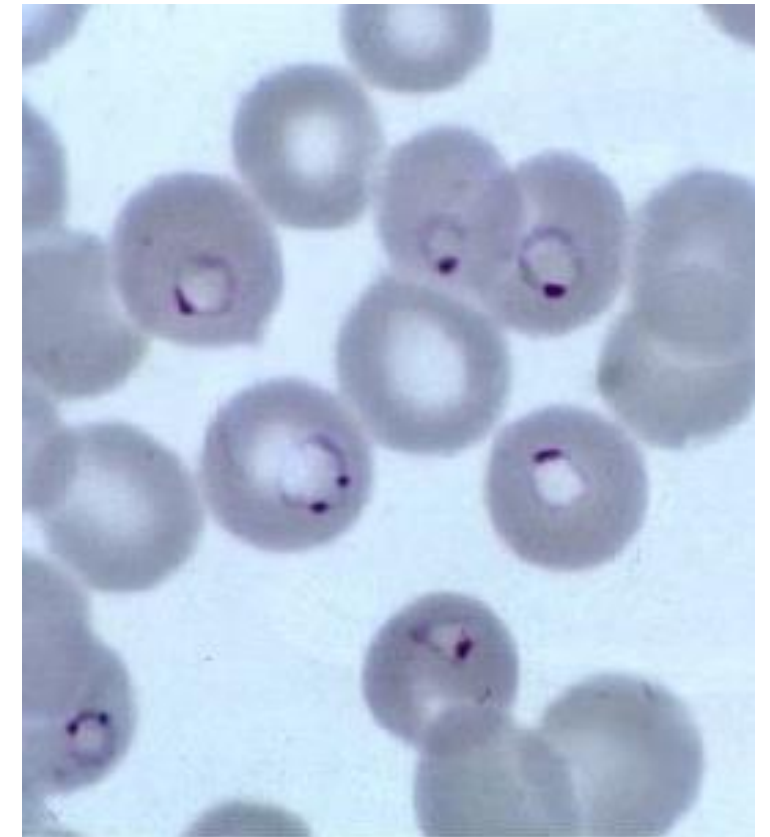


# Malaria

## Diagnosis

- **Thick and thin blood smears**
  - Light microscopy using **Giemsa stain**
  - Can distinguish plasmodium species
  - Can determine parasite load
  - More than 5% infected RBCs usually indicates *P. falciparum*
- Rapid diagnostic tests
  - Detect plasmodium species antigens
  - Useful in resource-limited settings

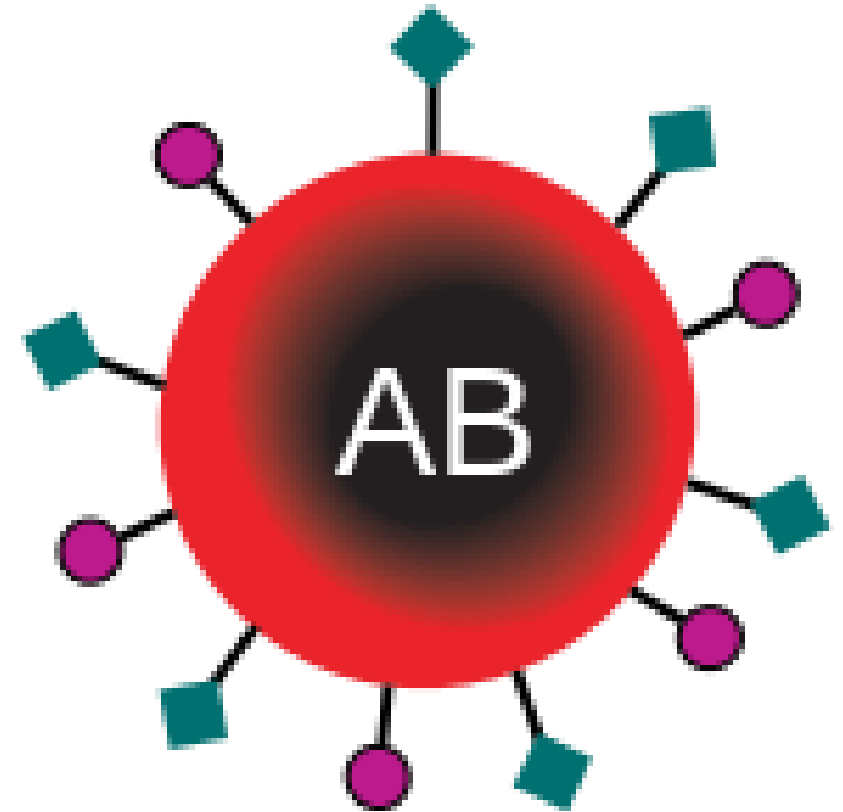
Trophozoite Ring



# Malaria

## Special features

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



# Malaria

## Special features

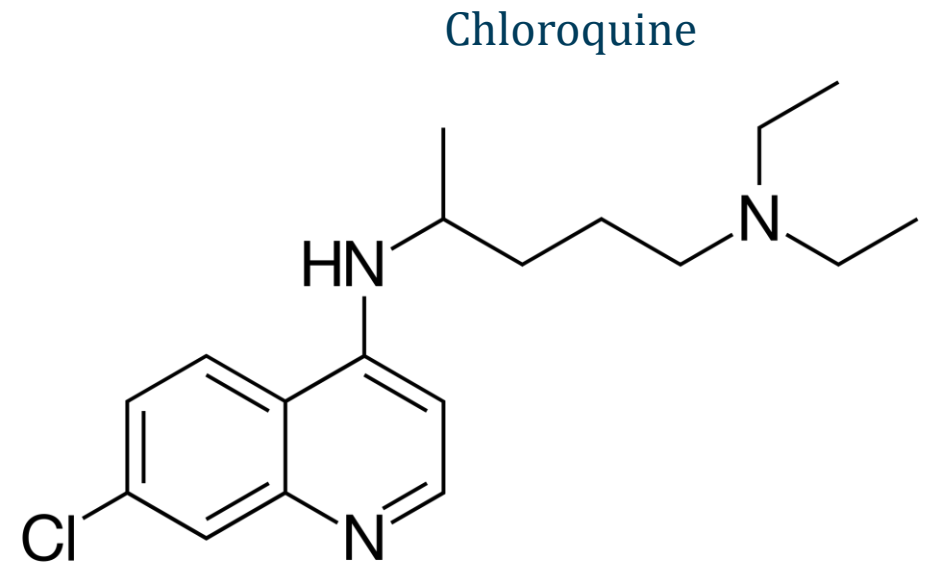
- **Premunition**
  - Naturally-acquired immunity against *P. falciparum*
  - Caused by prior infection
  - Present in many endemic areas
  - Limits development or severity of infection
- Not present in travelers to endemic regions
- Travelers at risk for severe, life-threatening disease



# Malaria

## Treatment

- **Chloroquine and hydroxychloroquine**
  - Accumulate in red cells
  - Block plasmodium **heme polymerase**
  - Heme portion of Hgb toxic to parasite
  - Plasmodium converts this to nontoxic form
- Chloroquine resistance very common
- Used in limited chloroquine-sensitive regions
- Also have immunosuppressive properties



# Malaria

## Treatment

- Many drugs and drug classes used
- **Artemisinin combination therapy (ACT)**
  - Artemisinin: plant extract
  - Artemisinins: group of rapid-acting anti-parasitic drugs
  - ACT: artemisinin combined with drug of different mechanism
  - Limits development of artemisinin resistance
  - Severe malaria: IV artesunate
  - Others: artemether, dihydroartemisinin
- Primaquine (liver phase only; not active against RBC phase)
- Mefloquine
- Atovaquone

Artemisia annua





# Malaria

## Prevention for travelers

- Travelers to endemic regions
- Basic prevention: insect repellent, window screens and mosquito netting
  - Sleeping quarters important: mosquitoes feed at night
- Chemoprophylaxis based on **region of travel**
  - Various options
  - Atovaquone-proguanil
  - Mefloquine
  - Doxycycline
- Usually started before travel
- Usually continued for several weeks after return



# HIV Infection

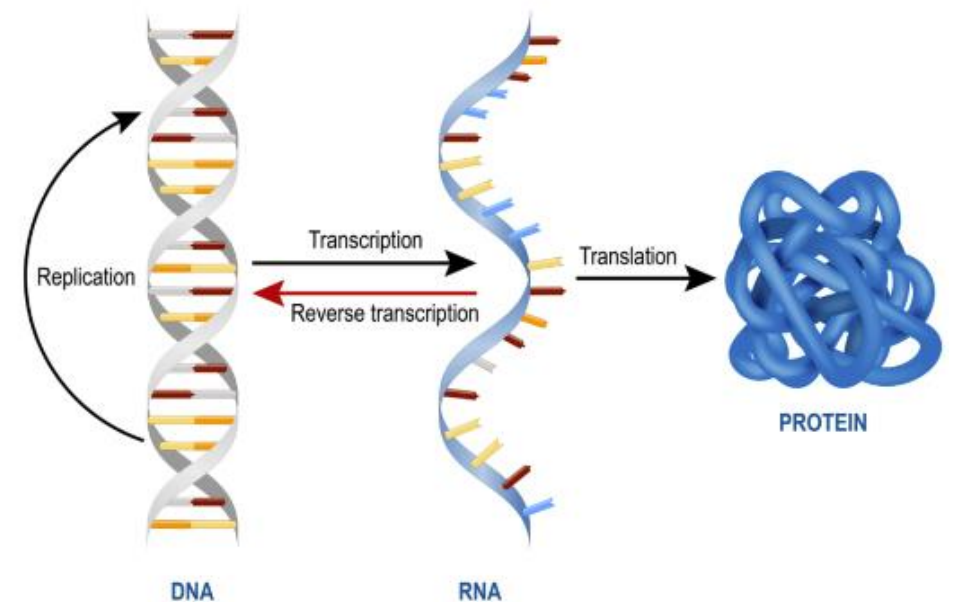
Jason Ryan, MD, MPH



# HIV

## Human Immunodeficiency Virus

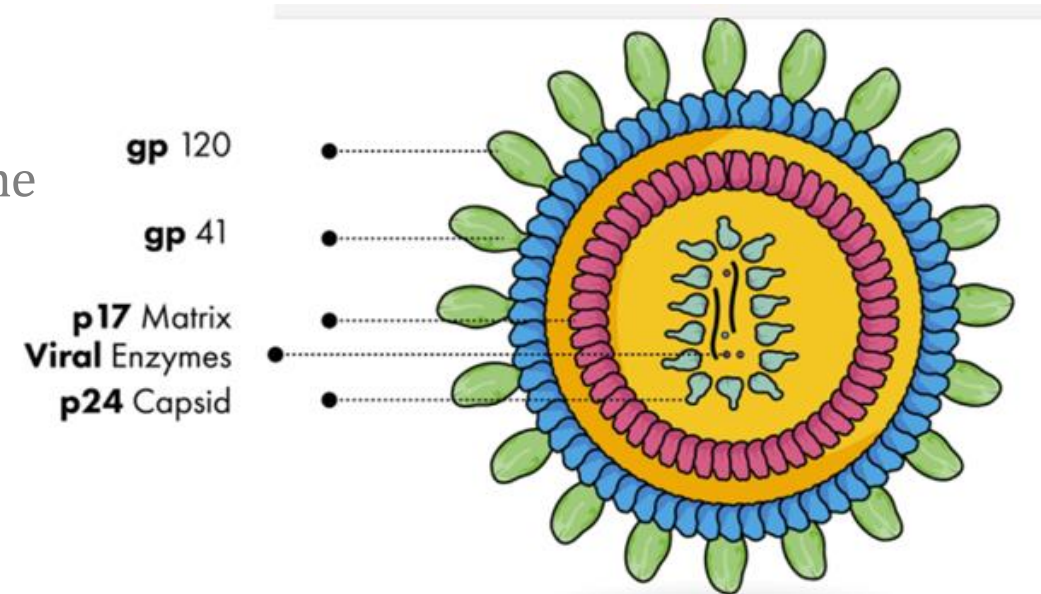
- Sexually-transmitted infection
- RNA retrovirus
- Uses reverse transcriptase: RNA → DNA → more virus
- Infects **CD4<sup>+</sup> T-cells** and macrophages
- Acquired immunodeficiency syndrome (AIDS)
- Susceptibility to unique opportunistic infections



# HIV

## Viral anatomy

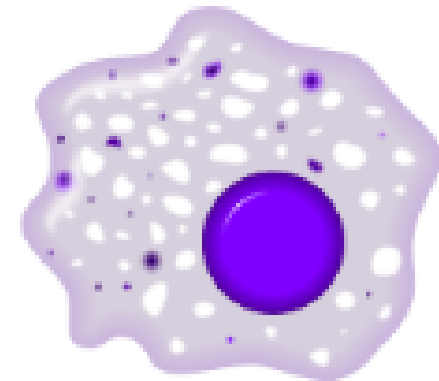
- Protein core (capsid) surrounded by lipid envelope
- **Viral p24 protein**: major capsid protein
- **Viral p17 protein**: matrix protein
- **Virus gp120 envelope protein**
  - Binds CD4 protein on T cells or macrophages
- **Virus gp41 protein**
  - Mediates fusion of viral envelope with cell membrane
  - Allows virus to enter cells



# HIV

## Human cellular targets

- Virus initially infects **macrophages** after exposure
  - Binds to **CCR5** on macrophages
  - Used by HIV to enter cells
- Later infects CD4+ T-cells

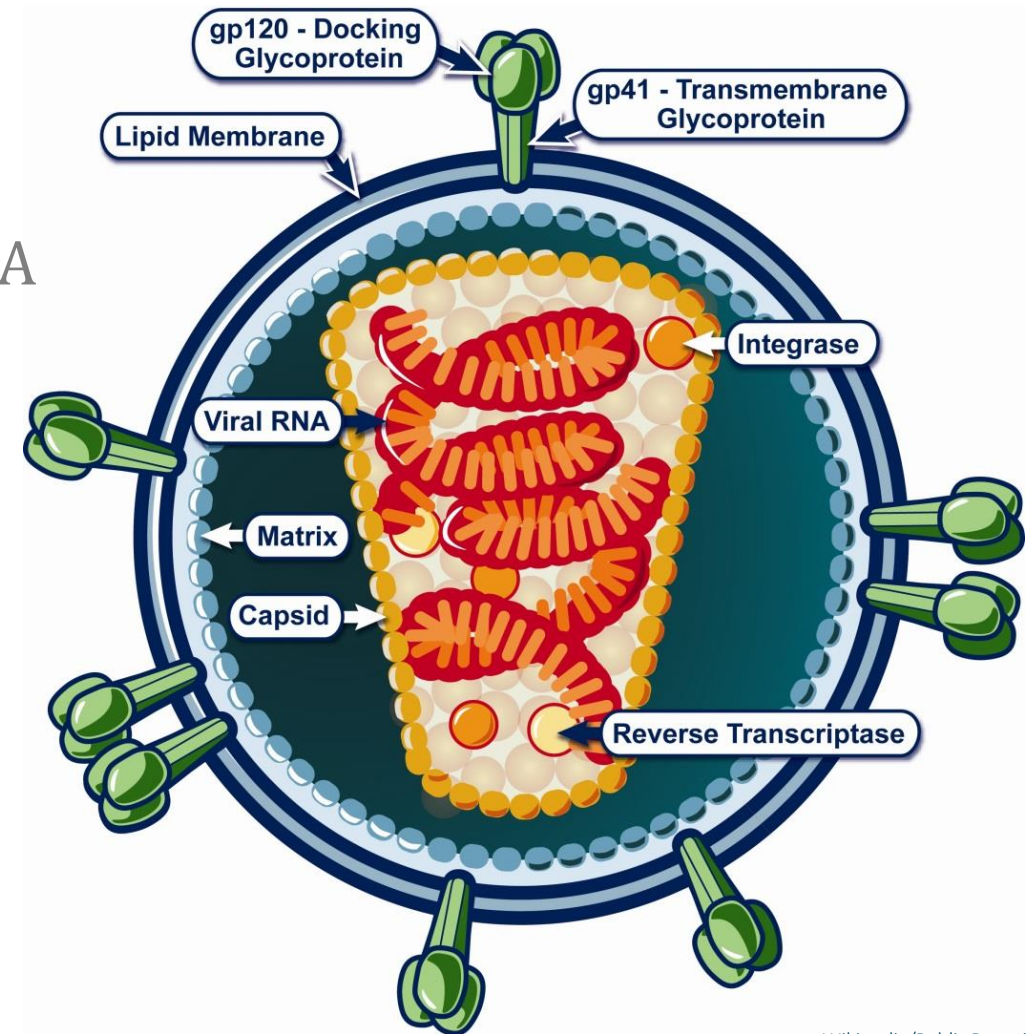


Macrophage

# HIV

## Key viral enzymes

- **Reverse transcriptase:** makes DNA from RNA
- **Aspartate protease:** cleaves proteins
- **Integrase:** integrate HIV DNA into host cell DNA

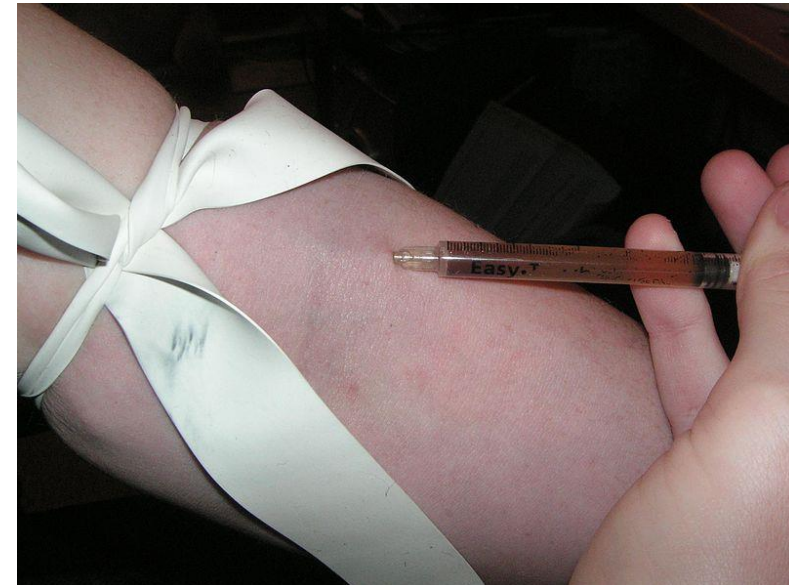




# HIV

## Transmission

- **Sexual contact**
  - Higher risk of acquisition among uncircumcised males
- **Exposure to contaminated blood**
  - Blood transfusion
  - Shared needles
  - Needle stick
- **Perinatal transmission**
  - HIV mother → baby
- Higher viral load in source patient = ↑ risk transmission





# HIV

## Markers of disease progression

- **CD4<sup>+</sup> T-cell count**
  - Determined by flow cytometry
  - Normal ~1000 cells/mm<sup>3</sup>
  - AIDS < 200
- **Viral load**
  - Determined by RT-PCR testing
  - Quantification of HIV RNA

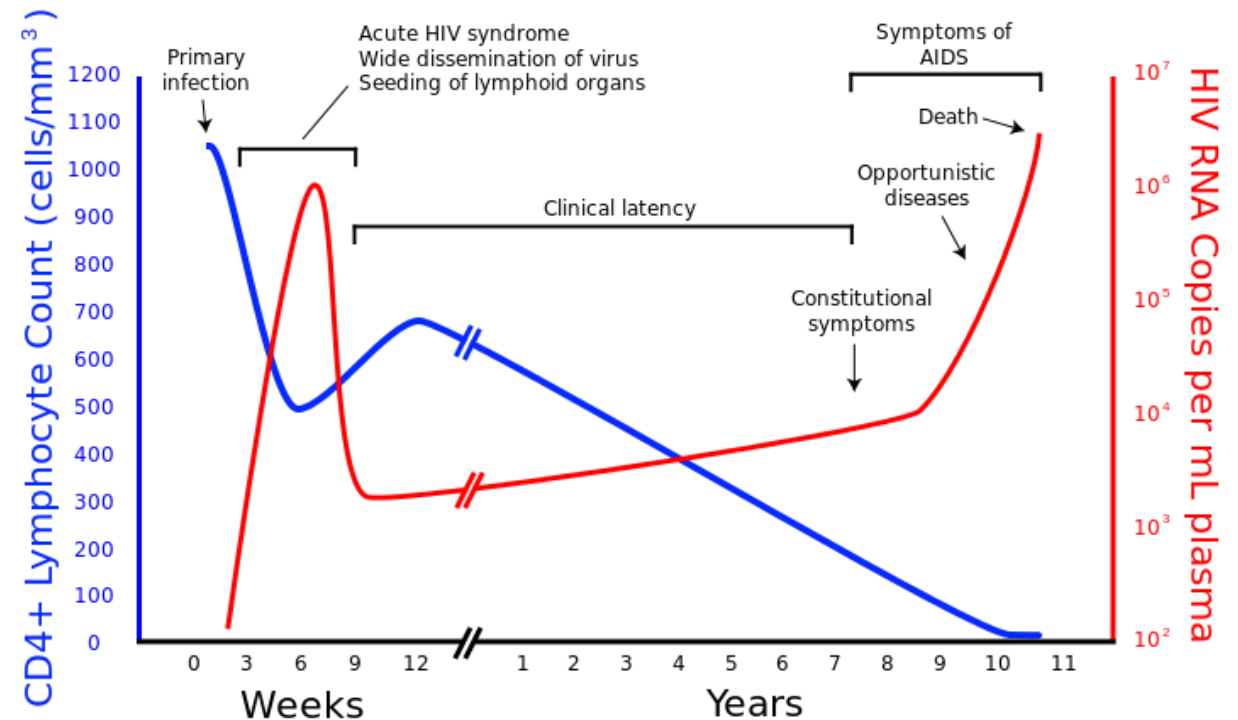
## T-cell



# HIV

## Clinical features

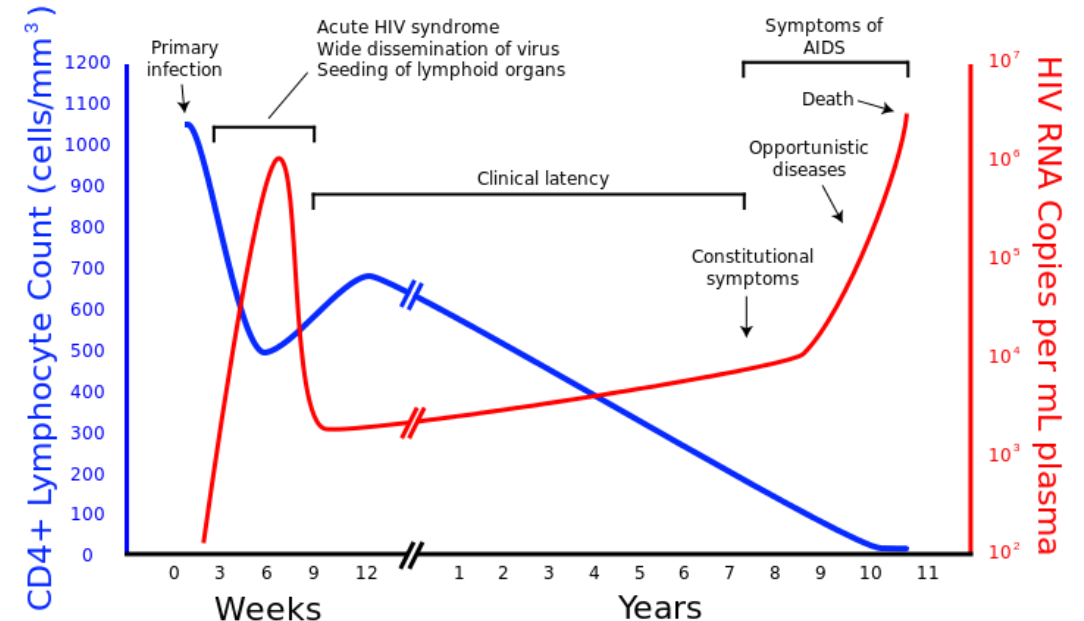
- **Acute HIV infection**
  - Shortly after exposure
  - Rapid increase in viral RNA
- **Chronic HIV infection**
  - Slowly decreasing T cell count
  - Lasts many years
- **AIDS**
  - Acquired immunodeficiency syndrome



# HIV

## Acute infection

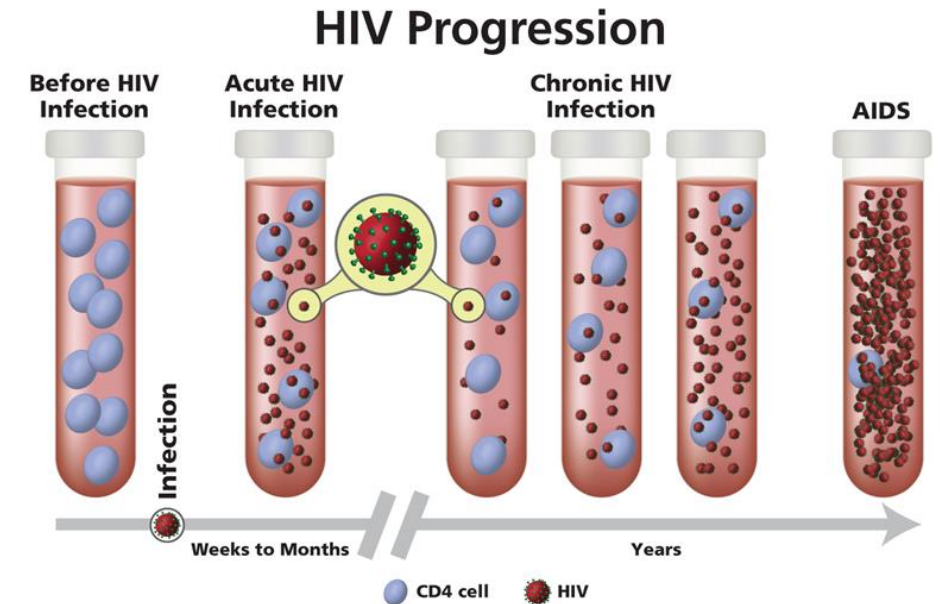
- Initial infection asymptomatic 10 to 60% cases
- **Acute HIV syndrome**
  - 2 to 4 weeks after exposure
  - Fever, myalgias, sore throat, cervical lymphadenopathy
  - Sometimes maculopapular rash
  - Similar to mononucleosis



# HIV

## Chronic infection

- Viral load stabilizes
- Slowly falling **CD4<sup>+</sup> T-cell count**
- Lasts about 8 to 10 years without treatment
- Possible persistent diffuse lymphadenopathy
- Some patients have fatigue, malaise
- Candida infections may occur (thrush, vaginitis)
- Seborrheic dermatitis common



# AIDS

Acquired immunodeficiency syndrome

- Severe immunosuppression
- Average time of 8 years from exposure
- $CD4 < 200$  cells/microL or AIDS-defining infection
- Clinical features due to **opportunistic infections**



# HIV Diagnosis

- **Combination antigen/antibody test**
  - “4<sup>th</sup> generation test”
  - Identifies **p24 antigen** and **anti-HIV antibodies**
  - Result is “positive” if antigen or antibodies identified
  - Can identify virus ~ 2 weeks after infection
- **HIV1-HIV2 antibody differentiation assay**
  - Confirmatory test after positive combination test
  - HIV-1: more prevalent, found worldwide
  - HIV-2: mostly confined to West Africa
- Early HIV: combination test **plus viral load**



# HIV Diagnosis

## Perinatal HIV

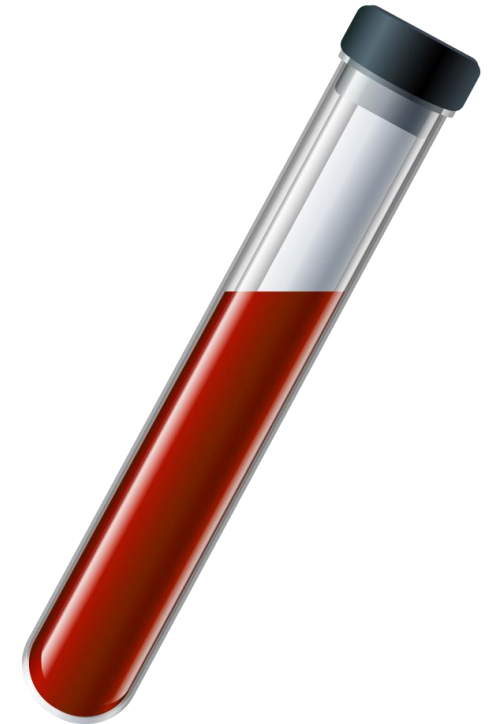
- Maternal HIV antibodies → newborn
- Antibody-based tests will be positive
- **HIV virologic tests** used
- Detect HIV RNA or DNA
- “Nucleic acid tests” or NATs





# HIV Screening

- All adolescents and adults **aged 15 to 65 years**
  - USPSTF recommendation
  - One-time screening with combined test
- **Annual screening if increased risk**
  - CDC guidelines
  - Injection-drug users and their partners
  - Persons who exchange sex for money or drugs
  - Sex partners of HIV-infected persons
  - Men who have sex with men (MSM)
  - Heterosexual persons with more than one partner since last HIV test



# HIV Treatment

- **Antiretroviral therapy (ART)**
- Older guidelines initiated treatment based on CD4 count
- Newer guidelines recommended treating all patients
- Multi-drug therapy used
- Often a mix of different drug classes
- Gene mutations occur over time due to drugs
- Require altering medical regimen



# Opportunistic Infections

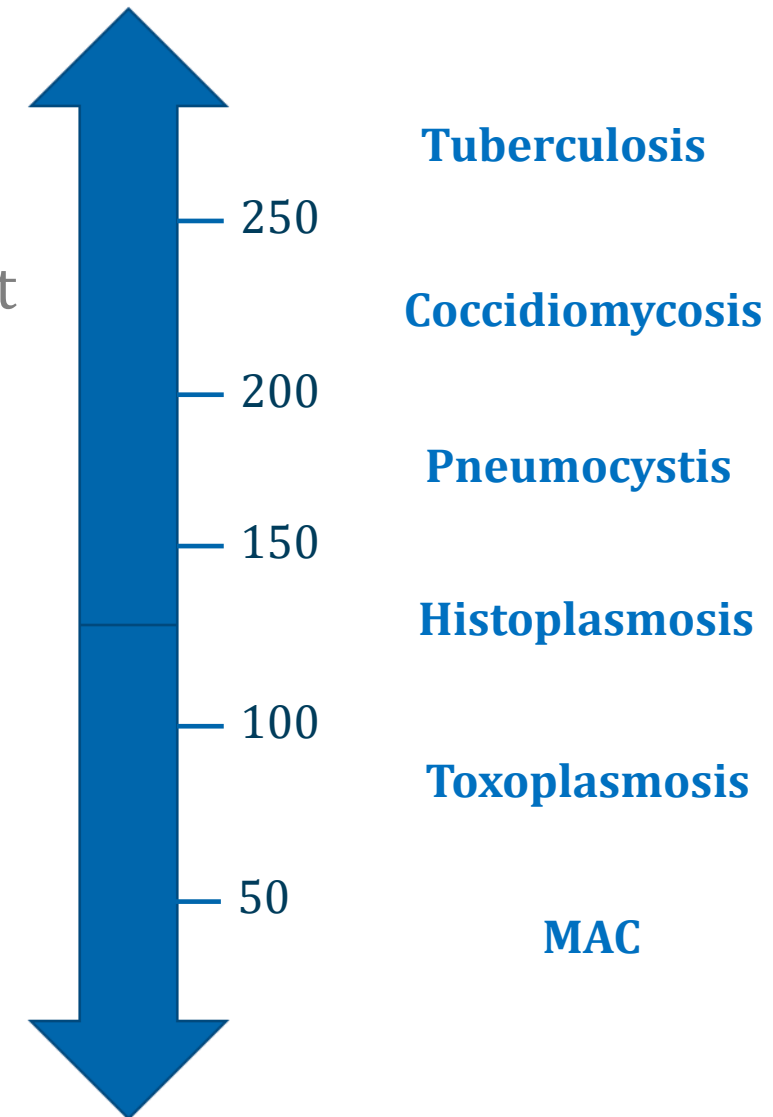
- More common or more severe among patients with advanced HIV
- Pneumocystis pneumonia
- Cryptococcal meningitis
- Toxoplasmosis
- Many others



# Opportunistic Infections

## Prophylaxis

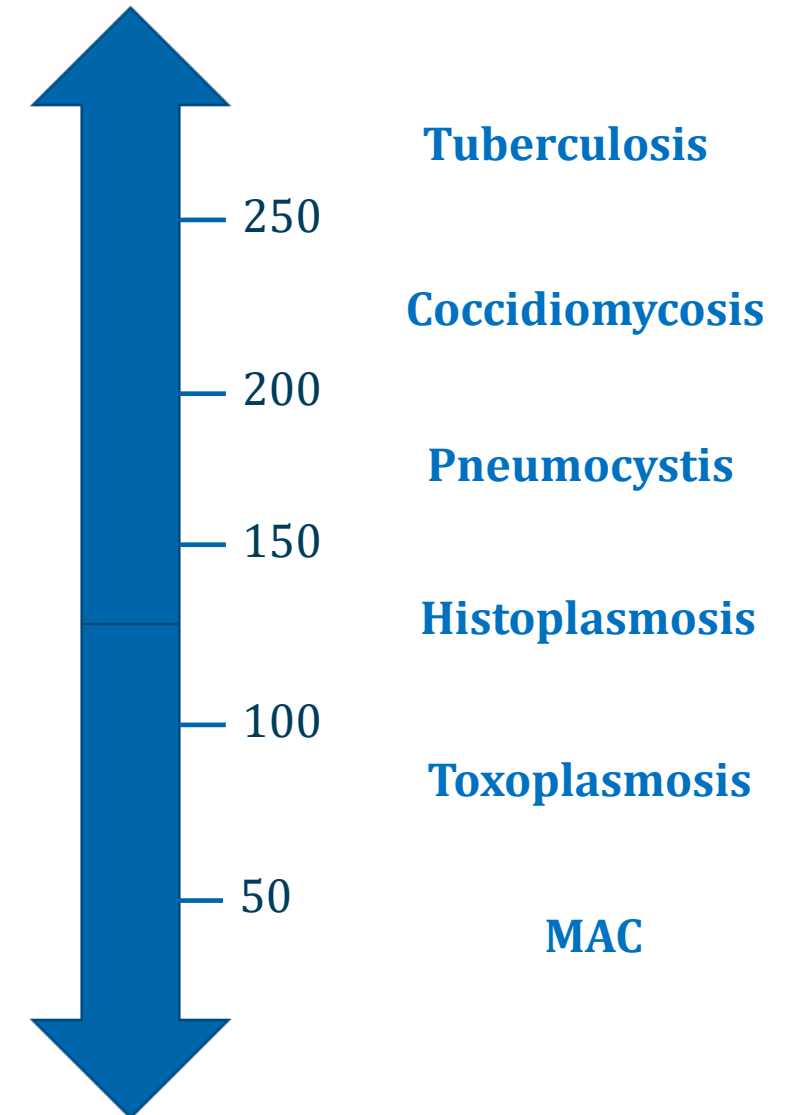
- Best prevention is ART to maintain CD4<sup>+</sup> T cell count
- Prophylaxis for some OIs administered based on CD4 count
- **All CD4<sup>+</sup> T cell counts**
  - Screen for latent tuberculosis infection
  - PPD test or Interferon-gamma release assays (IGRAs)
  - Treatment if positive
- **CD4<sup>+</sup> T cell counts < 250**
  - Coccidiomycosis IgG and IgM
  - Only done in endemic areas (e.g., Arizona or California)
  - Fluconazole if newly positive



# Opportunistic Infections

## Prophylaxis

- **CD4 < 200**
  - TMP-SMX: pneumocystis pneumonia
  - Allergy: dapsone, atovaquone, pentamidine
- **CD4 < 150**
  - Itraconazole: histoplasmosis (endemic areas)
- **CD4 < 100**
  - Test for toxoplasmosis IgG
  - If positive, TMP-SMX for toxoplasmosis
- **CD4 < 50**
  - Azithromycin: Mycobacterium avium complex
  - Only if not taking ART (low risk on ART)



# HIV

## Vaccinations

- Live vaccines avoided if CD4 count < 200
  - MMR, Zoster, Varicella
- Vaccines indicated in adults with HIV
  - Pneumococcal
  - Meningococcal
  - Hepatitis A virus
  - Hepatitis B virus
- All other standard adult vaccines administered
- Patients with HIV can receive COVID-19 vaccine



# Pre-Exposure Prophylaxis

- Tenofovir-emtricitabine (TDF-FTC) can limit transmission
  - Trade name Truvada
- Indicated in HIV negative patients deemed at high risk





# Post-Exposure Prophylaxis

- ART can reduce likelihood of infection after possible exposure
- Usually a 3 drug regimen for 28 days
  - Tenofovir
  - Emtricitabine
  - Integrase inhibitor
- HIV testing at start
- Repeat usually at 6 weeks and 3 months



# Post-Exposure Prophylaxis

## Indications

- Sexual contact with known HIV carrier
- Condomless sex with possible HIV exposure
- Intravenous drug use with shared needles
- Healthcare workers with **needle stick injuries**
  - Exposed to bodily fluid of a known HIV patient
  - Blood, semen, vaginal fluid
  - Not urine, saliva or sweat
  - Exposure to mucous membrane or non-intact skin

# INDICATIONS

# HIV Drugs

Jason Ryan, MD, MPH



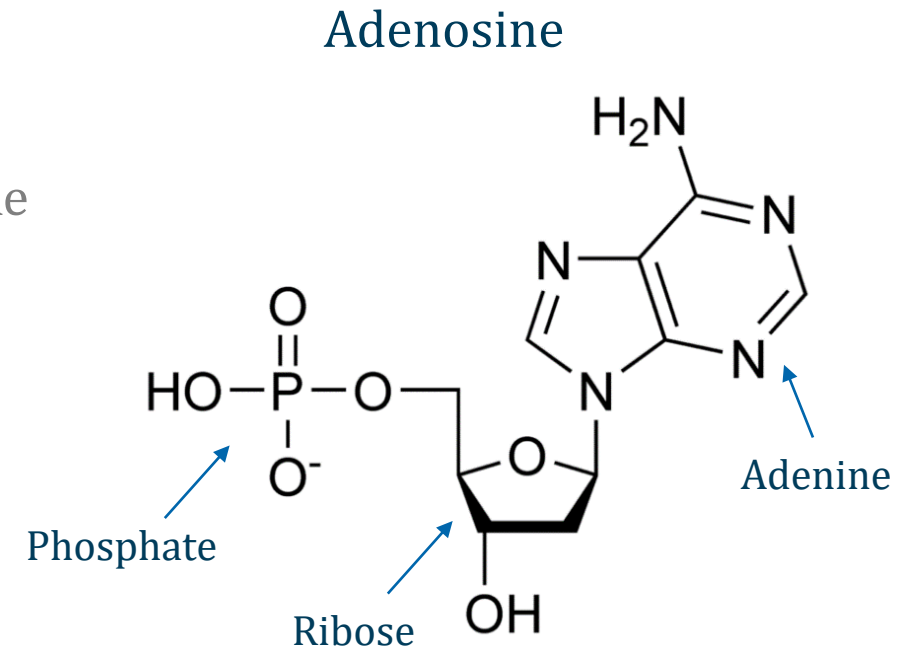
# HIV Therapy

- Nucleoside reverse transcriptase inhibitors (NRTIs)
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Integrase strand transfer inhibitors (INSTIs)
- Protease inhibitors (PIs)
- Other agents

# NRTIs

## Nucleoside/Nucleotide reverse transcriptase inhibitors

- **Reverse transcriptase**
  - HIV enzyme
  - Synthesizes DNA from viral RNA strands
  - DNA → more viral particles (replication)
- Uses **nucleotides** to build DNA molecules
  - Nucleotide = base + ribose + phosphate
  - DNA nucleotides: adenosine, guanosine, cytidine, thymidine
  - Bases: adenine, guanine, cytosine, thymine
- Nucleoside = nucleotide without phosphate

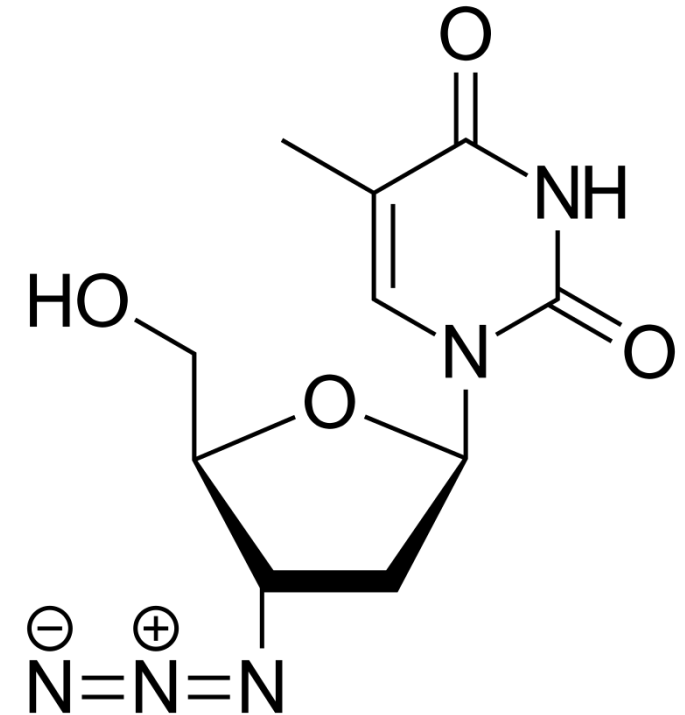


# NRTIs

Zidovudine, lamivudine, abacavir, didanosine, stavudine, tenofovir, emtricitabine

- Mimic structure of nucleosides or nucleotides
- Taken up by reverse transcriptase
- Incorporated into DNA strands
- Terminate growth of strands

Zidovudine (AZT)

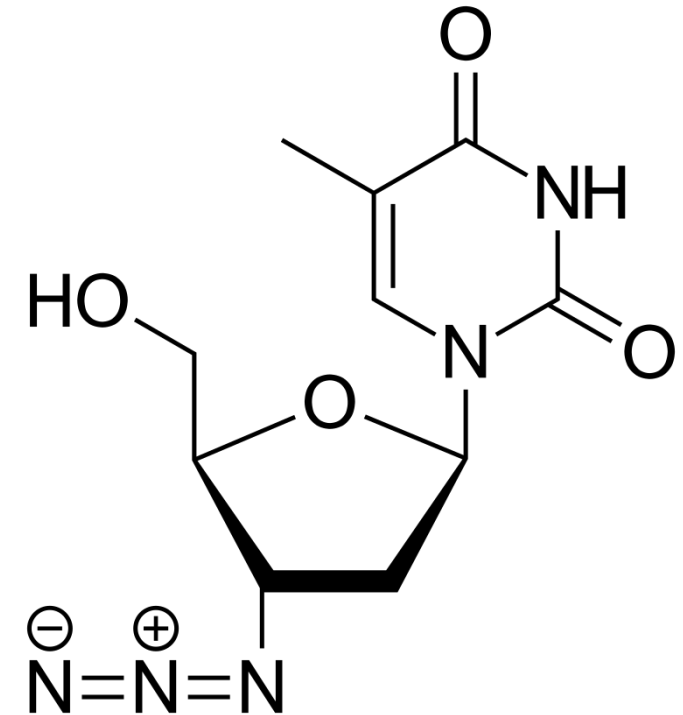


# NRTIs

Zidovudine, lamivudine, abacavir, didanosine, stavudine, tenofovir, emtricitabine

- Often have secondary name based on chemical structure
  - Stavudine = d4T (structure similar to thymidine)
  - Didanosine = ddI
  - Lamivudine = 3TC
- Usually given in pairs (tenofovir-emtricitabine)
  - Increased effectiveness

Zidovudine (AZT)



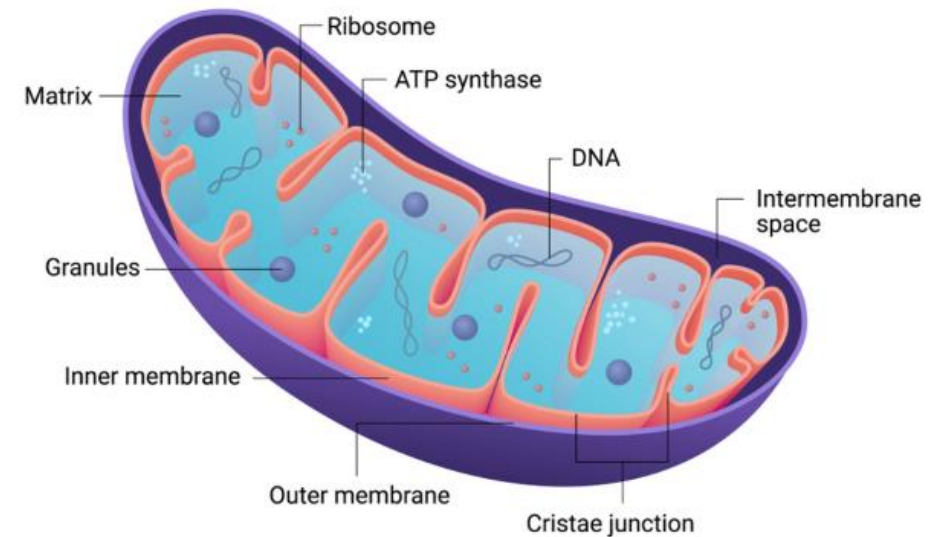


# NRTIs

## Adverse effects

- **Mitochondrial toxicity**
  - Adverse effect of NRTI class
  - DNA polymerase gamma inhibited
  - Replicates mitochondrial DNA
- **Lactic acidosis**
- Myopathy – weakness, elevated CK level
- Peripheral neuropathy - pain, paresthesias
- Pancreatitis
- Lipoatrophy
- Hepatic steatosis

## MITOCHONDRIA



# NRTIs

## Adverse effects

- **Lipoatrophy**
  - Loss of adipose tissue
  - Often involves face
  - Associated with use of NRTIs
  - Especially stavudine (d4T)
- **Hepatotoxicity**
  - Liver failure and steatosis may occur
- **Tenofovir**
  - Renal dysfunction

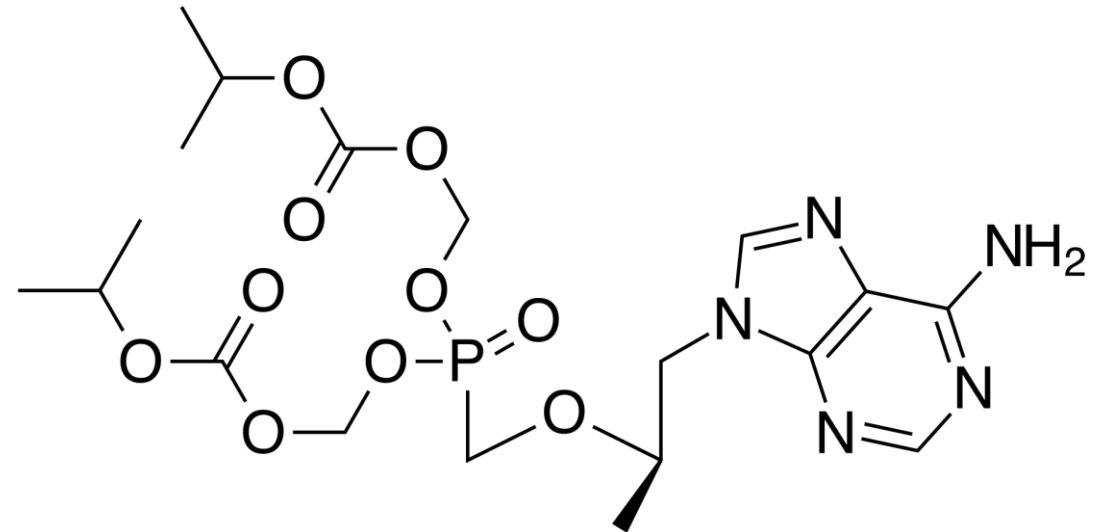
Lipoatrophy



# Tenofovir

- Often combined with emtricitabine
- Long term risks: **kidney injury** and **bone loss**
- Two oral formulations
  - Tenofovir disoproxil fumarate (TDF)
  - Tenofovir alafenamide (TAF)
- Lower rates of adverse effects with TAF

Tenofovir



# Zidovudine

- First antiretroviral medication used for HIV
- Bone marrow suppression
- Used to limit maternal-fetal infection
- **Newborns of mothers with HIV**

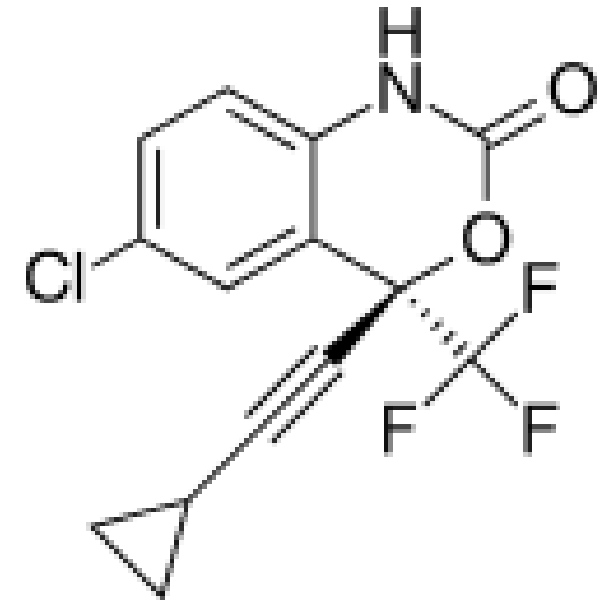


# NNRTIs

## Non-nucleoside reverse transcriptase inhibitors

- Efavirenz, rilpivirine, doravirine
- Inhibit reverse transcriptase
- Do not mimic nucleotides
- Bind to a different site NRTIs → inhibition of enzyme
- Adverse effect vary by specific drug
- Efavirenz and rilpivirine: **CNS toxicity**
  - Vivid dreams
  - Confusion
  - Mood changes and depression

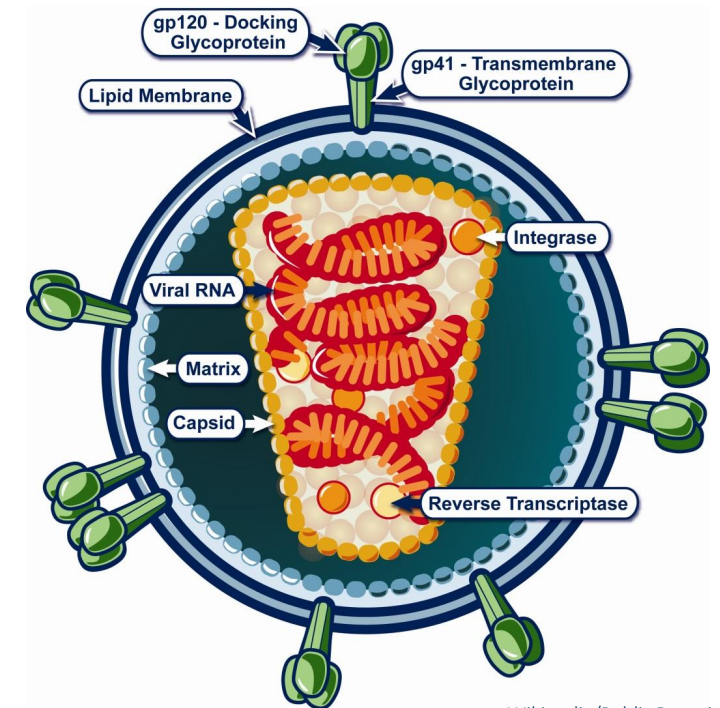
Efavirenz



# Integrase Strand Transfer Inhibitors

## INSTIs

- Raltegravir, elvitegravir, dolutegravir, bictegravir
- Integrase: HIV enzyme
  - Integrates viral DNA (from RNA) into host cell DNA
  - Viral DNA → more viral particles
- INSTIs prevent integration of viral DNA into host cell DNA
  - Inhibit strand transfer step of viral DNA integration

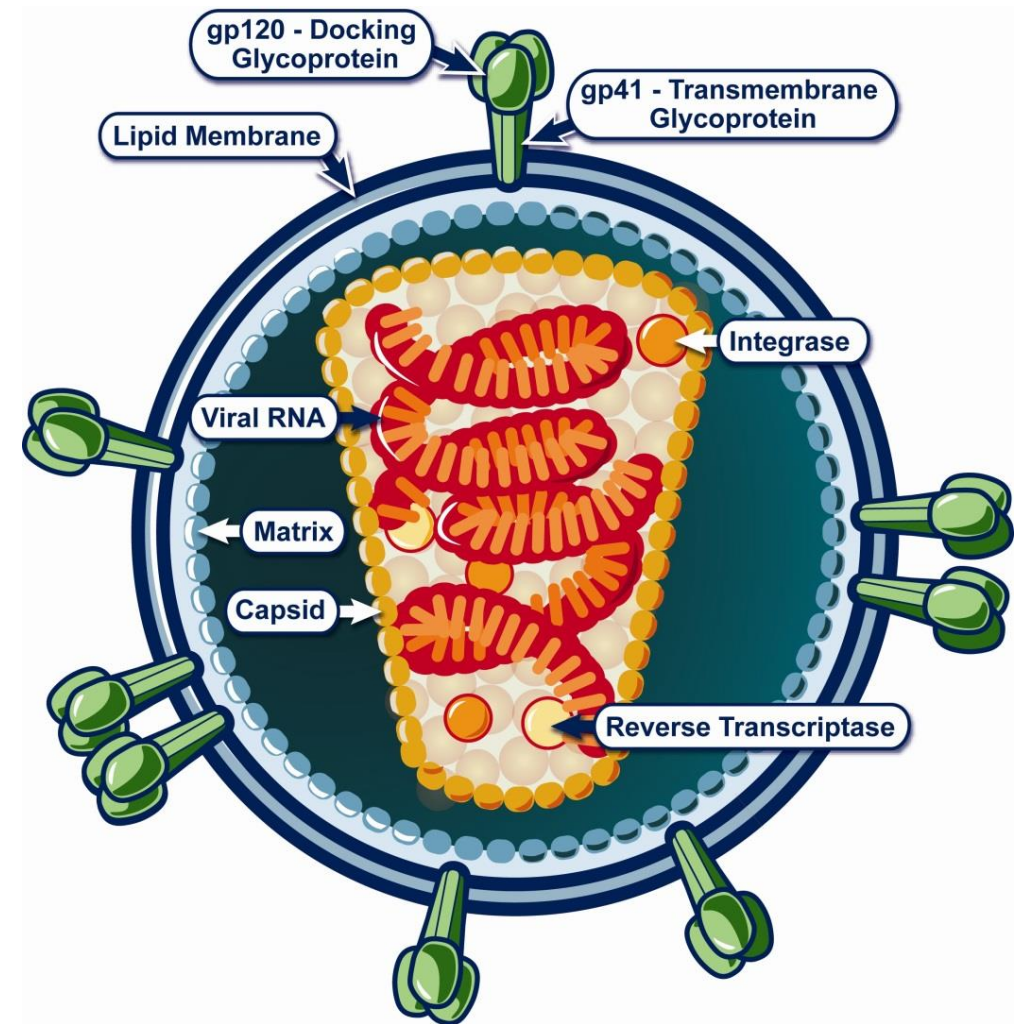




# Integrase Strand Transfer Inhibitors

## Adverse effects

- Usually well-tolerated
- Adverse effects vary by specific drug
- Elvitegravir given with **cobicistat**
  - Inhibitor of CYP3A
  - Increases drug levels and effectiveness





# Protease Inhibitors

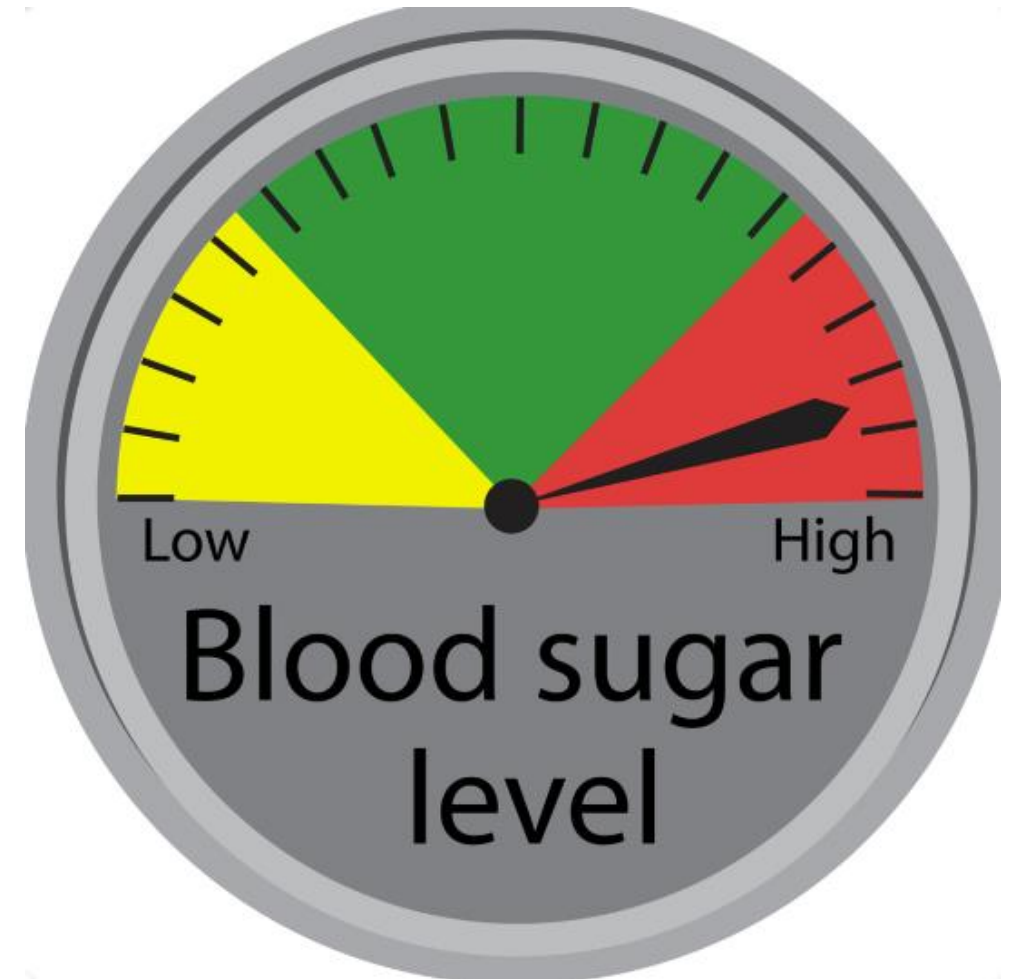
Lopinavir, ritonavir, indinavir

- Inhibit **HIV protease**
  - Cleaves polypeptides into smaller, functional units
  - Block production of many enzymes needed for viral replication
  - Reverse transcriptase, protease, integrase, structural proteins
- Viral particles cannot “mature” → become noninfectious

# Protease Inhibitors

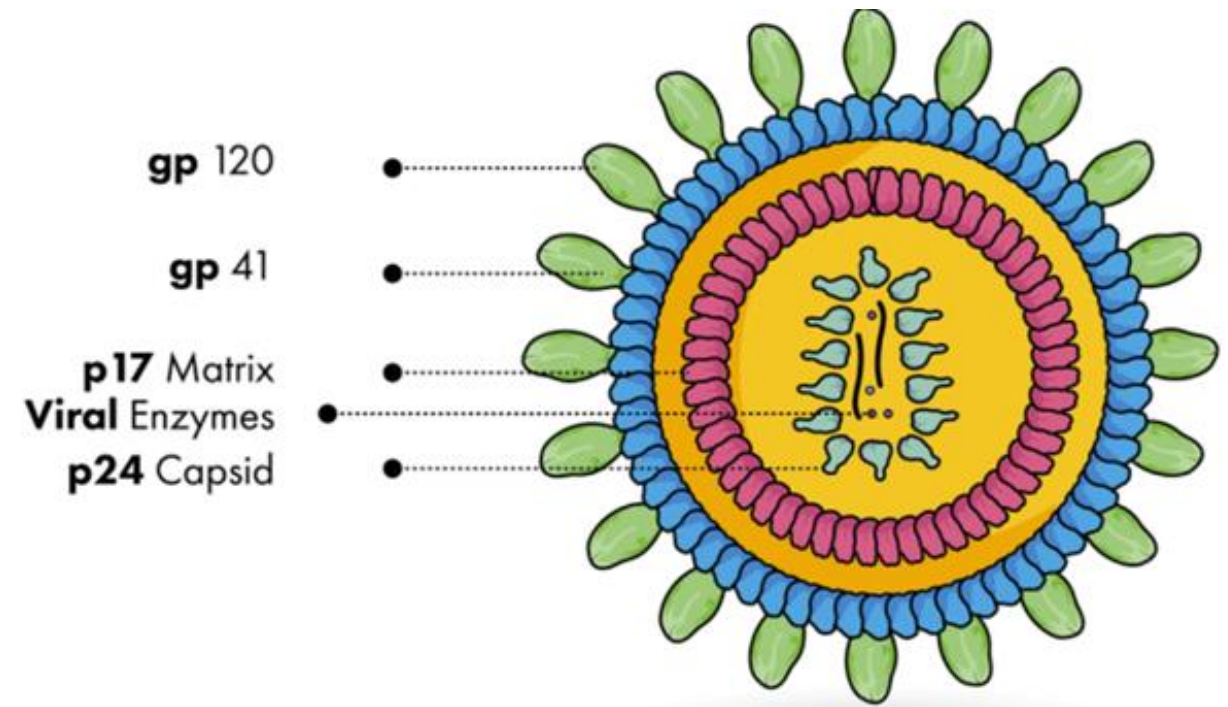
Lopinavir, ritonavir, indinavir

- Many class-specific adverse effects
  - Insulin resistance and hyperglycemia
  - Hyperlipidemia
  - Lipodystrophy (fat redistribution to back/abdomen)
  - Hepatotoxicity
- 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
  - Can also use cobicistat



# Other HIV Drugs

- **Enfuvirtide**
  - Binds gp41 on HIV surface
  - Inhibits fusion/entry HIV
- **Maraviroc**
  - Blocks CCR5 on macrophages
  - Impairs viral ability to bind macrophages



# HIV Therapy

## Treatment-naïve patients

- Many options for therapy
- Usually **multi-drug regimens used**
- Often 2 NRTIs plus INSTI
  - NRTI “backbone” of two drugs
  - Often emtricitabine-tenofovir
  - INSTI: dolutegravir or bictegravir
- Drugs modified over time based on viral resistance profile

# HIV Complications

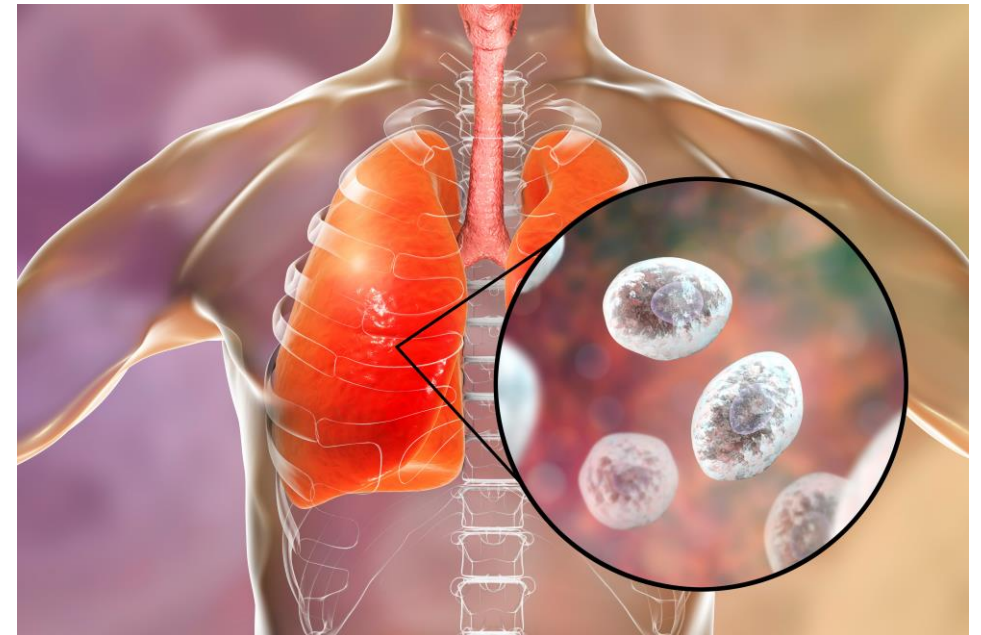
Jason Ryan, MD, MPH



# Pneumocystis Pneumonia

## PCP

- Fungal infection due to **Pneumocystis jirovecii**
- Causes diffuse interstitial pneumonia
- Requires immunocompromise
  - Classically HIV but can occur in other circumstances
  - Usually occurs with **CD4 < 200 cells/microL**
  - AIDS-defining illness
- Yeast → inhaled → pulmonary infection
- Usually no symptoms if immune system intact



# Pneumocystis Pneumonia

## Clinical features

- **Slow onset over weeks**
  - Can present more rapidly, often in non-HIV patients
- Fever, cough, dyspnea, hypoxemia
- Classic chest X-ray finding: **bilateral, diffuse infiltrates**
  - Can initially be normal; other findings possible
- Elevated serum LDH level
- Presumptive diagnosis often made clinically
- Definitive diagnosis: sputum, lavage or biopsy
  - Direct visualization of organism on microscopy
  - Cannot be cultured





# Pneumocystis Pneumonia

## Treatment

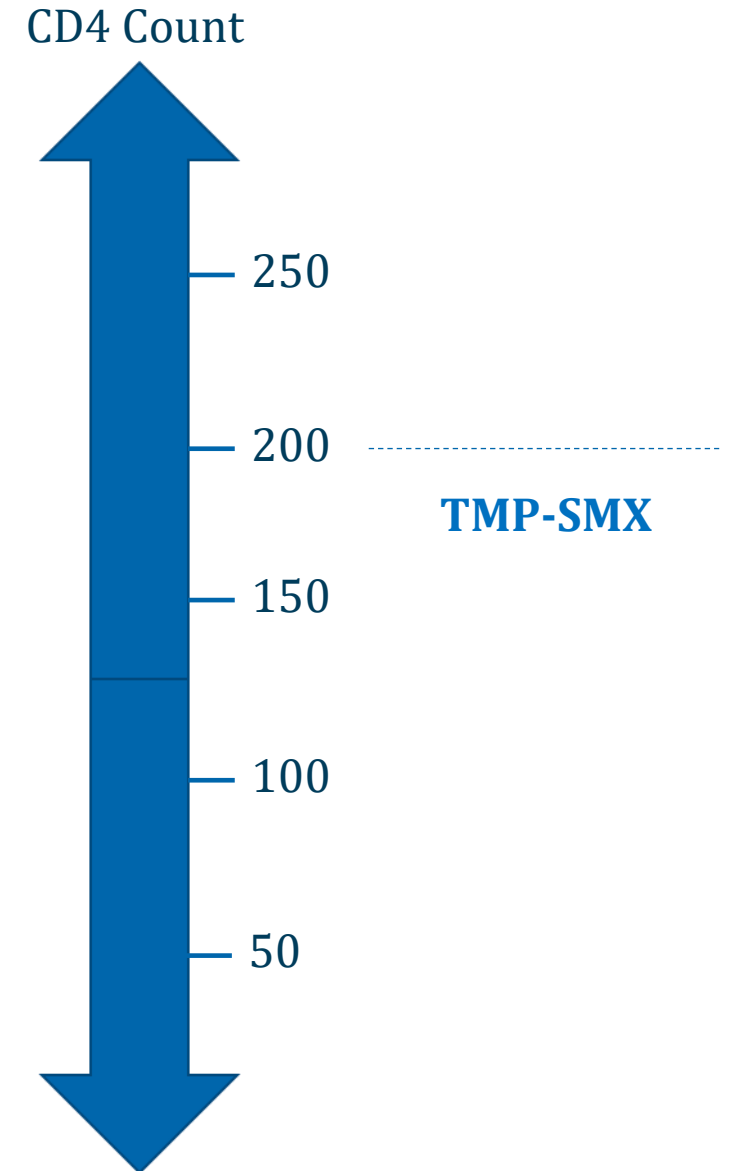
- First line therapy: **TMP-SMX**
  - Oral or intravenous for severe disease
  - Adverse reactions common
  - Rash, bone marrow suppression, hyperkalemia
- Many alternatives available
  - Dapsone, pentamidine, clindamycin, atovaquone
- **Glucocorticoids**
  - Added to treatment for moderate to severe PCP only
  - PaO<sub>2</sub> <70 mmHg on room air
  - Or alveolar-arterial (A-a) gradient ≥35 mmHg

# TMP-SMX

# Pneumocystis Pneumonia

## Prophylaxis

- Best prevention is antiretroviral therapy (ART)
- CD4 count <200 cells/microL: **TMP-SMX**
- Other possible indications for prophylaxis
  - High dose glucocorticoids
  - Certain immunosuppressive medications
  - Stem cell transplant recipients

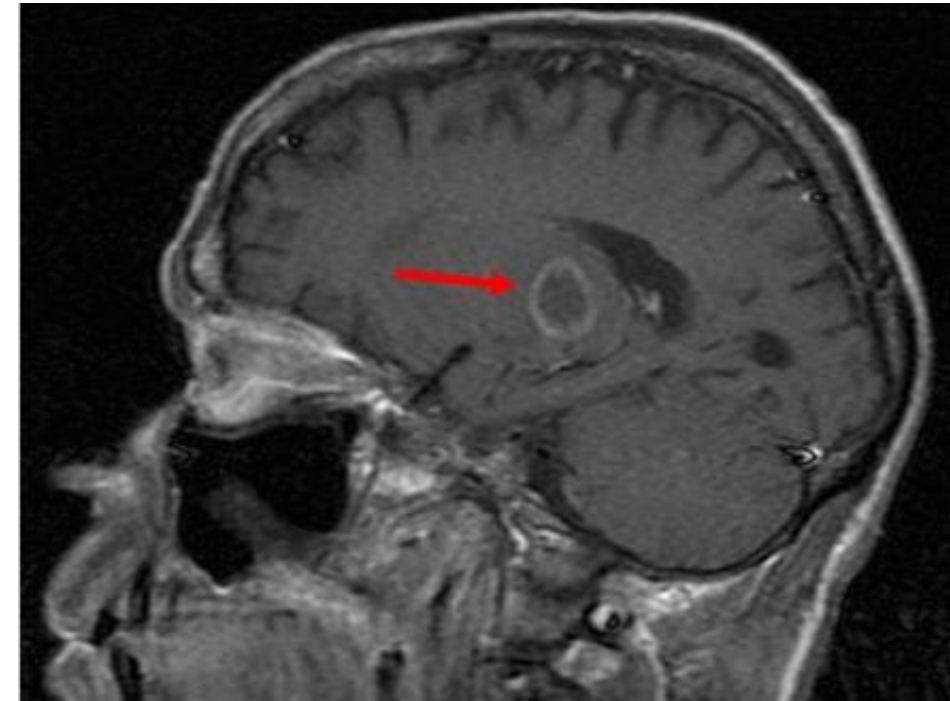


# Toxoplasmosis

## Clinical features

- Protozoal CNS infection with *Toxoplasma gondii*
- Severe **reactivation disease** in HIV/AIDS
  - Usually CD4 < 100cells/microL
  - Fever, headache, confusion, neurologic defects
- Diagnosis: MRI
  - Multiple “ring-enhancing” lesions with edema
- Treatment: **sulfadiazine and pyrimethamine**
- Ring-enhancing lesions HIV:
  - Toxoplasmosis
  - Primary CNS lymphoma

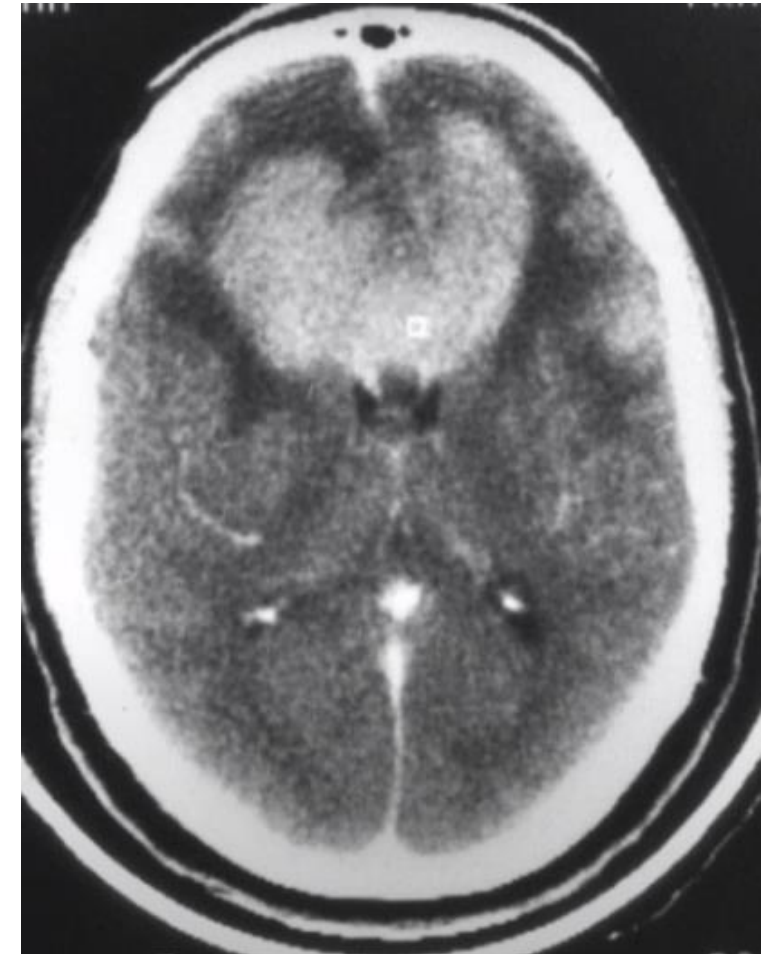
**Ring-enhancing Lesion**



# Primary CNS Lymphoma

- Non-Hodgkin lymphoma
- Usually diffuse large B cell lymphoma
- Related to Epstein-Barr virus (EBV) infection
- Confusion, memory loss, hemiparesis, aphasia, seizures
- Imaging: **usually (~70%) solitary lesion**
  - **Contrast-enhancing mass** on CT/MRI
  - Ring enhancement may be seen
  - May cross corpus callosum (“butterfly lesion”)

Primary CNS Lymphoma



# Primary CNS Lymphoma

- Definitive diagnosis: brain biopsy
- Lumbar puncture: CSF cytology or flow cytometry
  - May identify malignant lymphoid cells
- Treatment: chemotherapy and ART
  - Methotrexate-based therapy often used

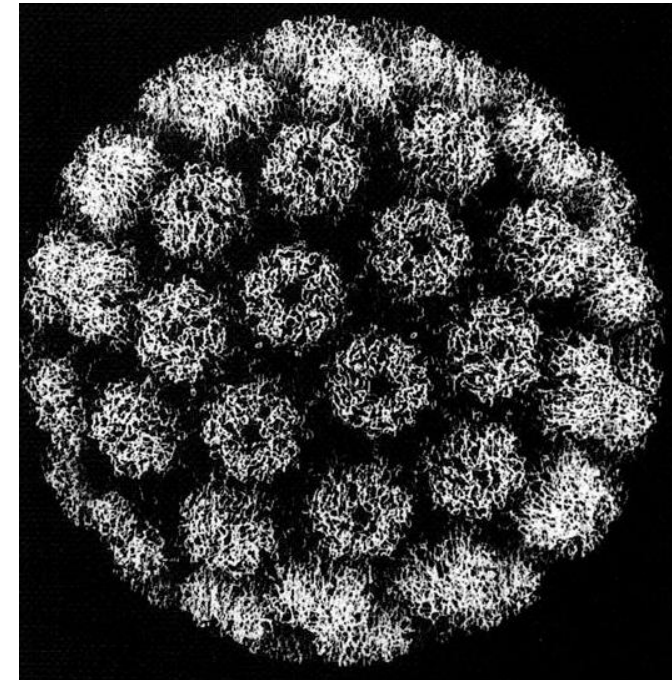


# PML

## Progressive Multifocal Leukoencephalopathy

- Inflammatory central demyelinating disorder
- Reactivation of a **latent JC virus**
- Viral destruction of oligodendrocytes
- Occurs with immunosuppression
  - HIV
  - Leukemia/lymphoma
  - Natalizumab (MS antibody treatment)

JC Virus

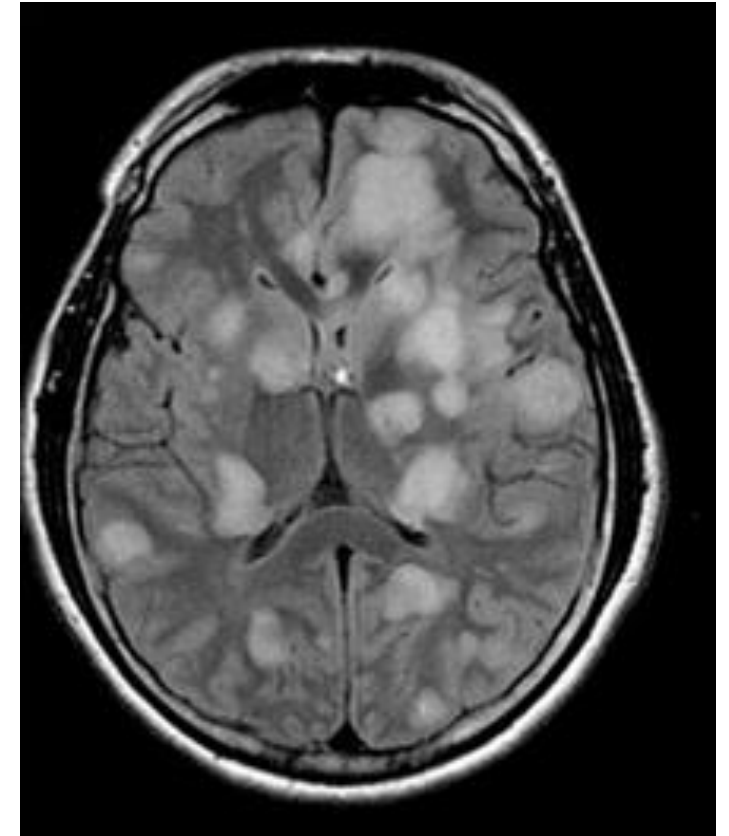




# PML

## Progressive Multifocal Leukoencephalopathy

- **Subacute (slow-onset) focal neurologic deficits**
  - Motor or sensory
  - Encephalopathy (confusion)
- Imaging: **multifocal white matter lesions**
  - **No enhancement**
  - Also no mass effect or edema
- CSF: JC virus IgG
- Definitive diagnosis: brain biopsy (rarely done)
- No effective therapy
- Treatment: **resolve immunosuppression**



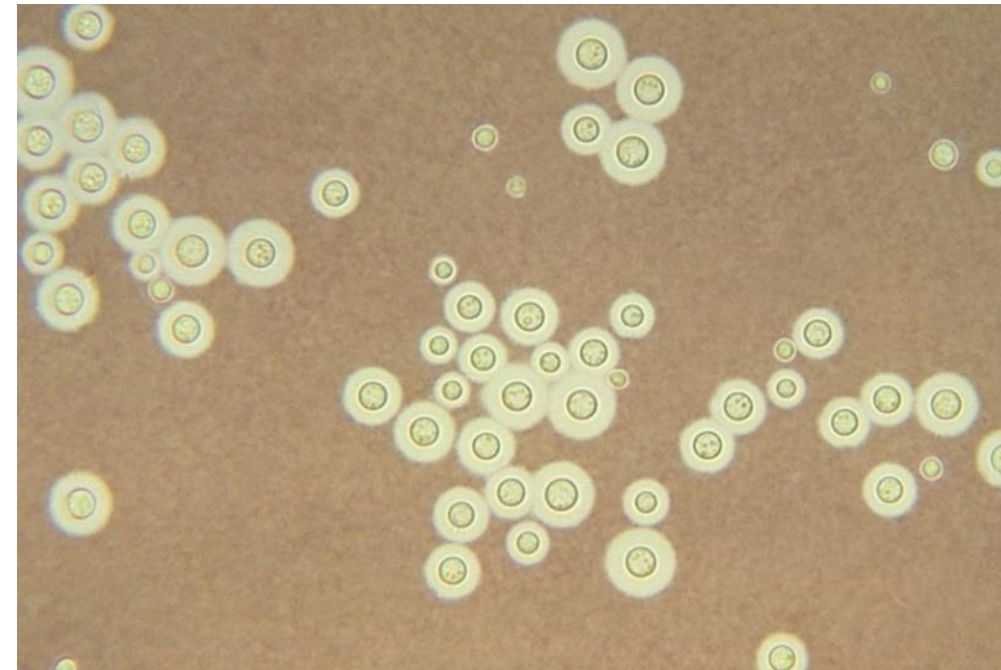
SILVA, Roberta Oliveira de Paula e et al . Progressive multifocal leukoencephalopathy as an AIDS-defining condition in a patient with high CD4+ T-lymphocyte count.  
**Rev. Soc. Bras. Med. Trop.**



# Cryptococcal Meningitis

- Fungal infection with **cryptococcus neoformans**
- Causes meningitis in patients with HIV/AIDS
- Diagnosis: **lumbar puncture**
- India ink staining of CSF
- Treatment: **amphotericin B plus flucytosine**
- Followed by **oral fluconazole** for up to 1 year

India Ink stain shows yeast with “halos”



# HIV Dementia

- Occurs in advanced HIV
- Limited attention, memory, concentration
- Diagnosis of exclusion
  - Neuroimaging, lumbar puncture often done
  - Lab testing for infections, anemia, thyroid disease
- Treatment: ART

DEMENTIA



# HIV

## Diarrhea

- Common complication of advanced HIV
- Large differential diagnosis
- Key causes of chronic diarrhea:
  - Cryptosporidium
  - Microsporidium/isospora
  - Mycobacterium avium complex
  - Cytomegalovirus

# Cryptosporidiosis

## Cryptosporidium

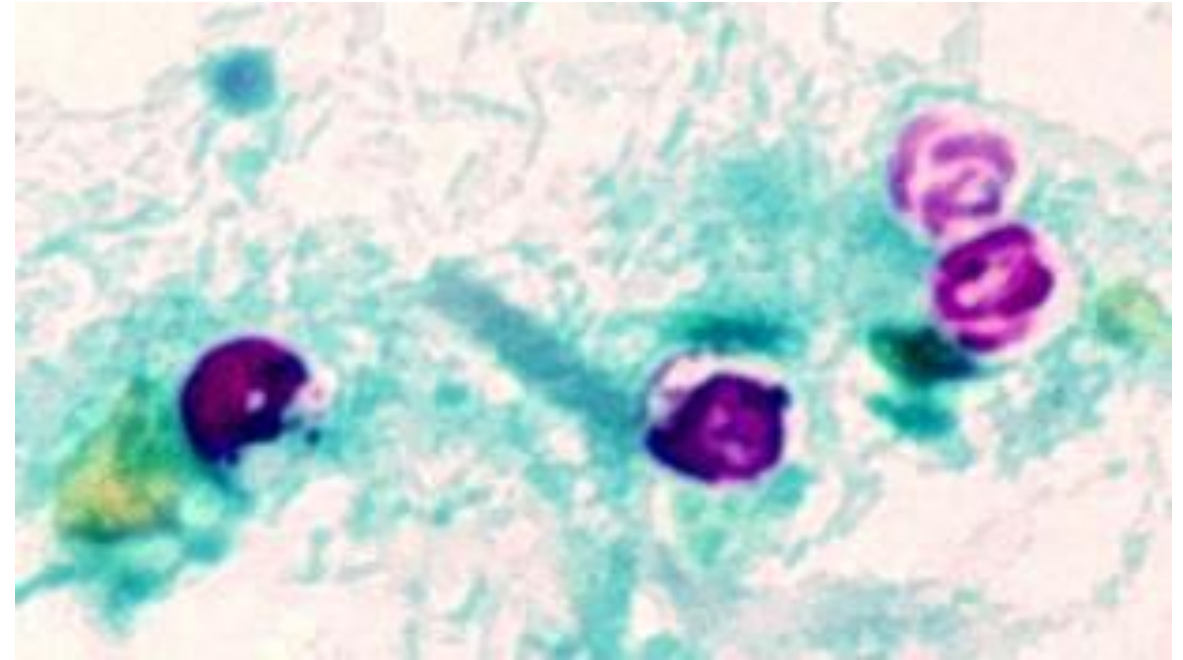
- Protozoa found in contaminated water
- May also infect **horses or cattle**
- Contaminated water ingestion → infection
- Infection in **swimming pools** can occur
  - Chlorination does not destroy oocysts
- Causes diarrhea in advanced HIV
  - Often with CD4 < 100
  - Chronic, severe, **watery (non-bloody)** diarrhea
  - Usually **low grade or no fever**



# Cryptosporidiosis

## Cryptosporidium

- Diagnosis: **stool microscopy**
  - Acid fast staining reveals oocysts
  - Stool antigen testing also available
- Supportive therapy (volume, electrolytes)
- Anti-retroviral therapy for HIV patients



# Microsporidia and Isospora

- Minor protozoal pathogens
- Fecal-oral transmission
- **Chronic, profuse, watery diarrhea**
  - Similar to cryptosporidium but usually no fever
- Diagnosis: stool examination
  - Microsporidia: spores
  - Isospora: oocysts
- Treatment:
  - Microsporidia: albendazole
  - Isospora: TMP-SMX



# MAC

## Mycobacterium avium complex

- Most common non-tuberculosis mycobacterial infection
- Includes several bacteria: *M. avium*, *M. intracellulare*
- Slow growing, acid-fast organisms
- Found in water and soil
- Inhaled or ingested
- Very rare cause of pulmonary disease in non-HIV





# MAC

## Mycobacterium avium complex

- In HIV may cause **disseminated disease**
- Usually occurs with very low CD4 count ( $<50$ )
- **High fever** and sweats
- Abdominal pain, **watery diarrhea**, weight loss
- Diffuse lymphadenopathy
- Hepatosplenomegaly
- Classic lab findings: anemia and  $\uparrow$  alk phos
- Often no lung findings
- If lung findings are prominent  $\rightarrow$  TB most likely



# MAC

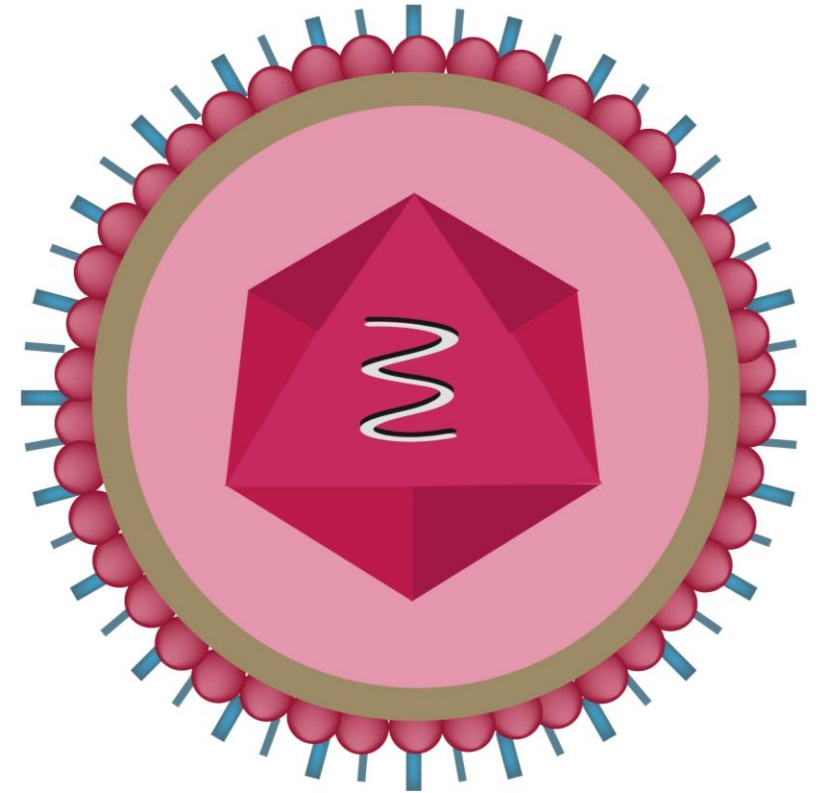
## Mycobacterium avium complex

- Diagnosis: blood culture or tissue biopsy
- Treatment: **clarithromycin plus ethambutol**
- Prophylaxis: azithromycin
  - Only with CD4 < 50 and not receiving ART

# CMV

## Cytomegalovirus

- Reactivation may occur with  $CD4 < 50$
- May infect the **CNS and retina**
  - CMV retinitis is most common manifestation
- May infect the **gastrointestinal tract**
  - Esophagus, stomach or bowel
  - CMV colitis (large bowel) most common



**Cytomegalovirus**

# CMV

## Retinitis

- Retinal edema and necrosis
- Blurry vision
- Scotomata or floaters
- Photopsia - flashing lights
- Diagnosis: fundoscopy
  - Fluffy, yellow-white retinal lesions with hemorrhage
- Treatment: ganciclovir (oral or intravitreal)
  - Alternatives: foscarnet or valganciclovir
  - Also ART

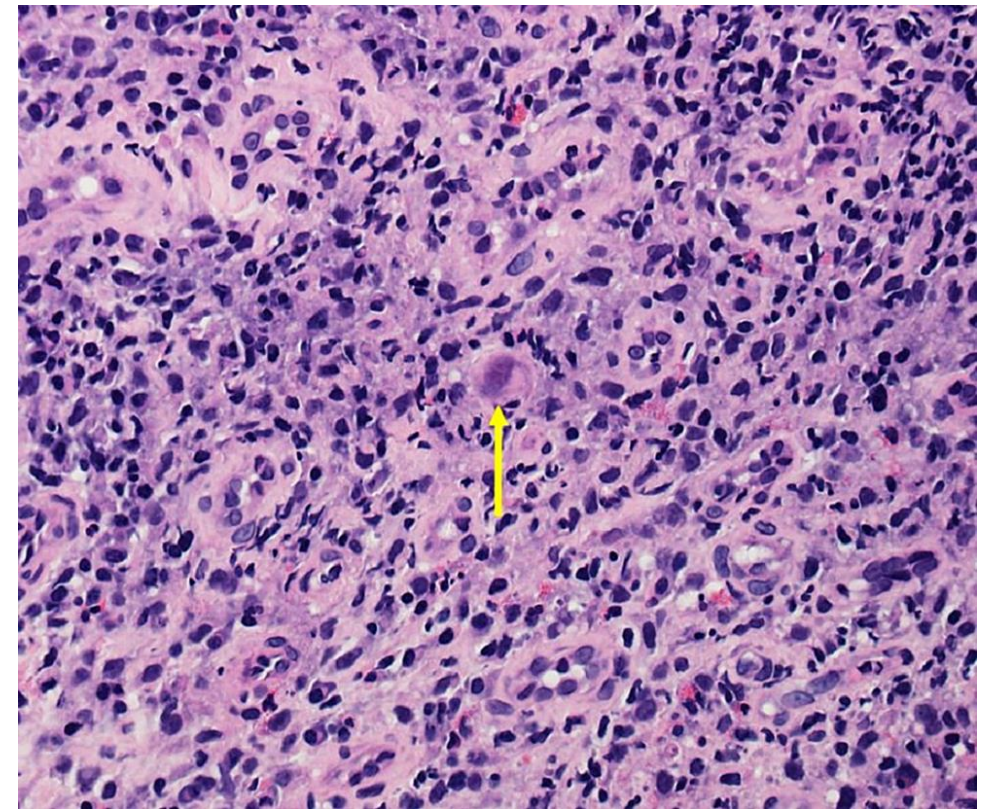


# CMV

## Colitis

- Low grade fever and abdominal pain
- **Frequent, small-volume diarrhea**
- Hematochezia and **bloody stools**
- Diagnosis: **colonoscopy**
  - Mucosal ulcerations
  - Biopsy: intranuclear and intracytoplasmic inclusions
- Treatment: **ganciclovir or valganciclovir**

CMV Colitis



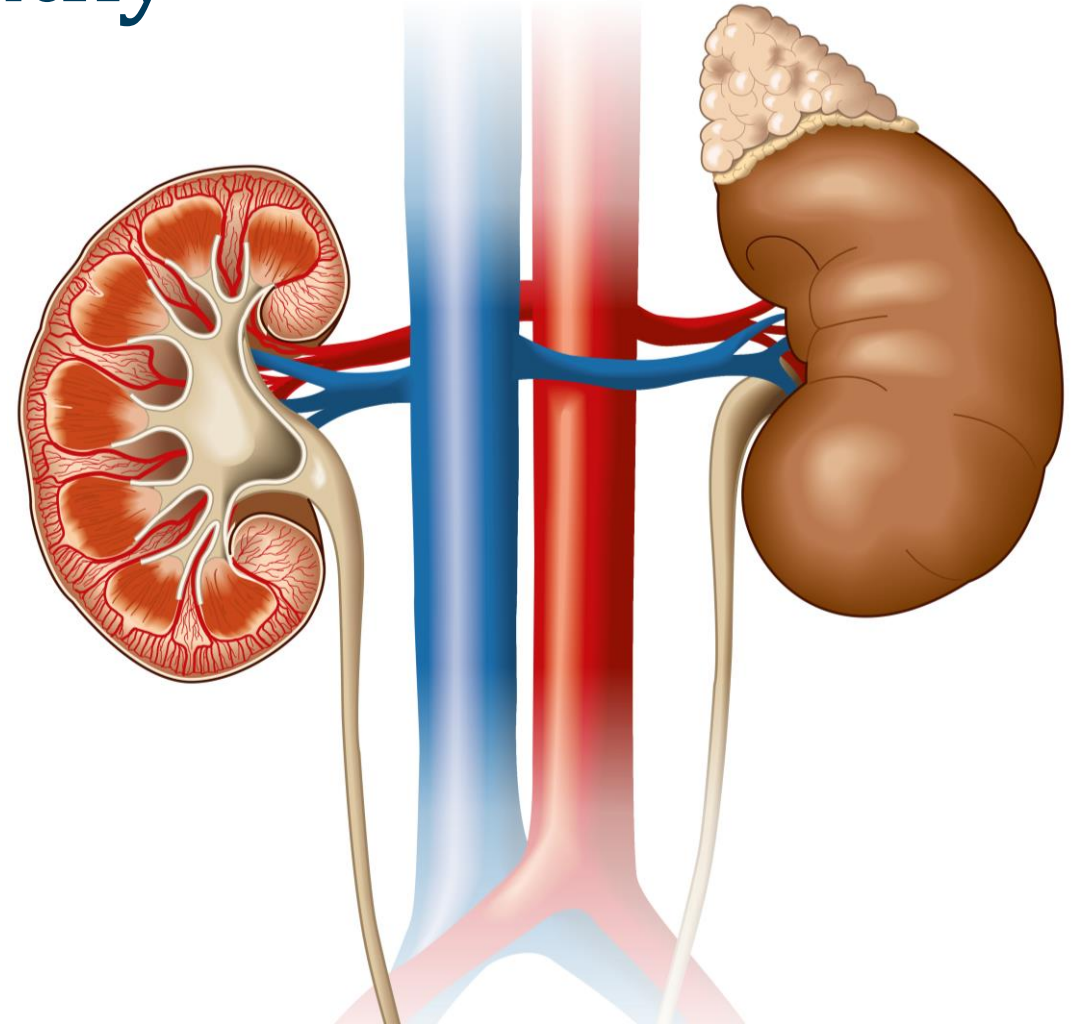
Inayat F, Hussain Q, Shafique K, et al. (November 08, 2016) Cytomegalovirus Colitis in Immunocompetent Patients. Cureus 8(11): e869. doi:10.7759/cureus.869



# HIV-Associated Nephropathy

## HIVAN

- Classic renal complication of HIV
- Usually occurs in advanced HIV
- Most cases CD4 < 200
- **Proteinuria** - often nephrotic range
- **Renal insufficiency (↑BUN and Cr)**
- Diagnosis: renal biopsy
  - Focal segmental glomerulosclerosis (FSGS)
- Treatment: **ART plus ACEi/ARB**



# Oral Thrush

## Oropharyngeal Candidiasis

- **Most common HIV opportunistic infection**
  - Classic presenting feature of HIV
- Usually occurs with  $CD4 < 200$
- White plaques on buccal mucosa, tongue
- Clinical diagnosis
- If no risk factors → test for HIV
- Treatment: topical agents
  - Clotrimazole, miconazole, nystatin
- Oral fluconazole





# Oral Hairy Leukoplakia

- Epstein-Barr virus lesion
- Classically affects lateral tongue in patients with HIV
- **White painless plaques**
  - Often “corrugated” (folded)
- **Cannot be scraped off**
  - Contrast with Candida which scrapes off
- Often no treatment required
  - Benign, painless



# Bacillary Angiomatosis

- Caused by **Bartonella henselae**
  - Gram-negative rod
- Fever, chills, malaise
- **Vascular lesions**
  - Raised, cherry-red vascular lesions
  - Most common in the skin
  - May also occur in organs (lungs, GI tract)
- Diagnosis: **biopsy**
  - Vascular proliferation with neutrophils
  - Bacteria visualized with modified silver stain
- Treatment: **erythromycin or doxycycline**



Helleberg M. Bacillary angiomatosis in a solid organ transplant recipient. *IDCases*. 2019;18:e00649. Published 2019 Oct 31. doi:10.1016/j.idcr.2019.e00649

# Kaposi Sarcoma

- Caused by **HHV-8** in advanced HIV
- Raised, red-purple skin lesions
- May have similar appearance to bacillary angiomatosis
- Diagnosis: **biopsy**
  - Spindle-shaped cells with lymphocytes
  - Evidence of HHV-8 DNA/RNA
- Treatment: ART
- Chemotherapy for severe cases
- Does not respond to antibiotics



# IRIS

## Immune Reconstitution Inflammatory Syndrome

- Treatment of HIV → **flare of infectious symptoms**
  - Caused by known or unknown opportunistic infection
  - Occurs despite falling viral load and increasing CD4 count
- Usually one week to a few months after starting ART
- Treatment aimed at underlying opportunistic infection
- Initiation of ART sometimes delayed for OI treatment
  - Goal is to prevent IRIS

# Tick-borne Illness

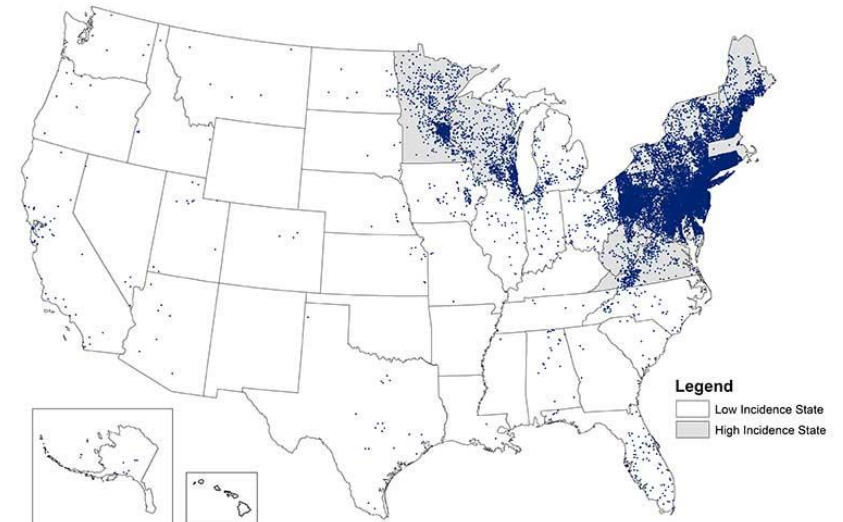
Jason Ryan, MD, MPH



# Lyme Disease

- Common in Northeast US (Lyme, Connecticut)
  - Especially New York, Connecticut, New Jersey, Pennsylvania, and Massachusetts
- Caused by **Borrelia burgdorferi**
  - Spirochete – spiral-shaped bacteria
- Transmitted by bite from **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 ~48 hours for transmission

Reported Cases of Lyme Disease  
United States, 2018





# Lyme Disease

## Stage 1

- **Erythema chronicum migrans**
  - Days after tick bite
  - Bacteria spread through skin
  - Classic finding: expanding “Bulls-eye” rash (painless)
- Flu-like symptoms
- Arthralgias may also occur (not arthritis)





# Lyme Disease

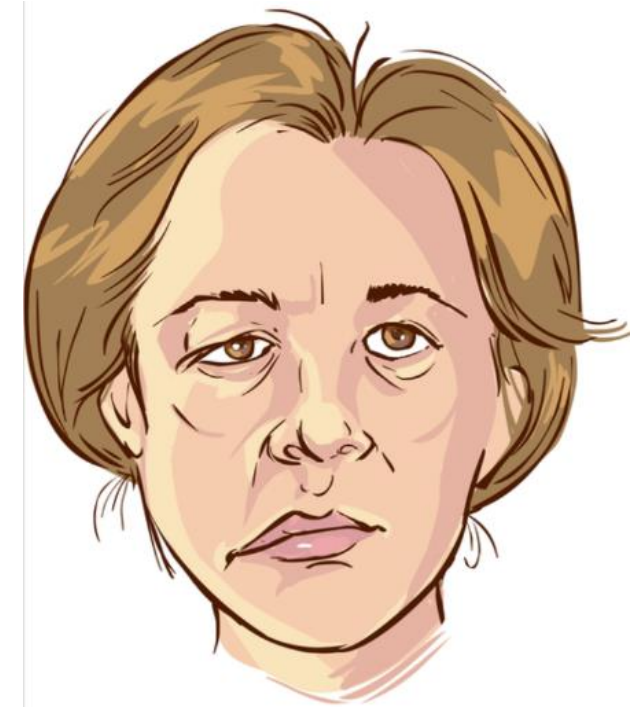
## Stage 2

- Early disseminated disease: **neurologic and cardiac symptoms**
  - Weeks to months after tick bite
  - Facial nerve palsy (may be bilateral)
  - Myocarditis → **AV block**

3<sup>rd</sup> Degree AV Block



Facial Nerve Palsy



# Lyme Disease

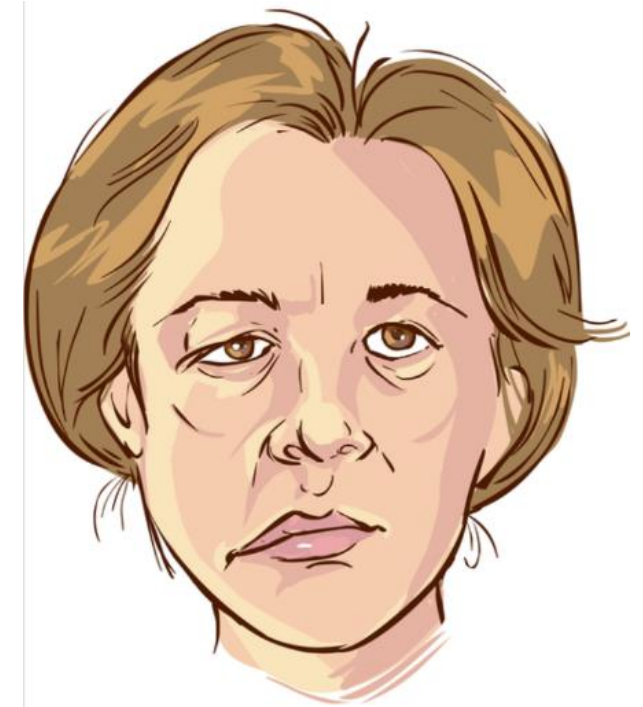
## Stage 2

- Early disseminated disease: **neurologic and cardiac symptoms**
  - Weeks to months after tick bite
  - Facial nerve palsy (may be bilateral)
  - Myocarditis → **AV block**

3<sup>rd</sup> Degree AV Block



Facial Nerve Palsy



# Lyme Disease

## Stage 3

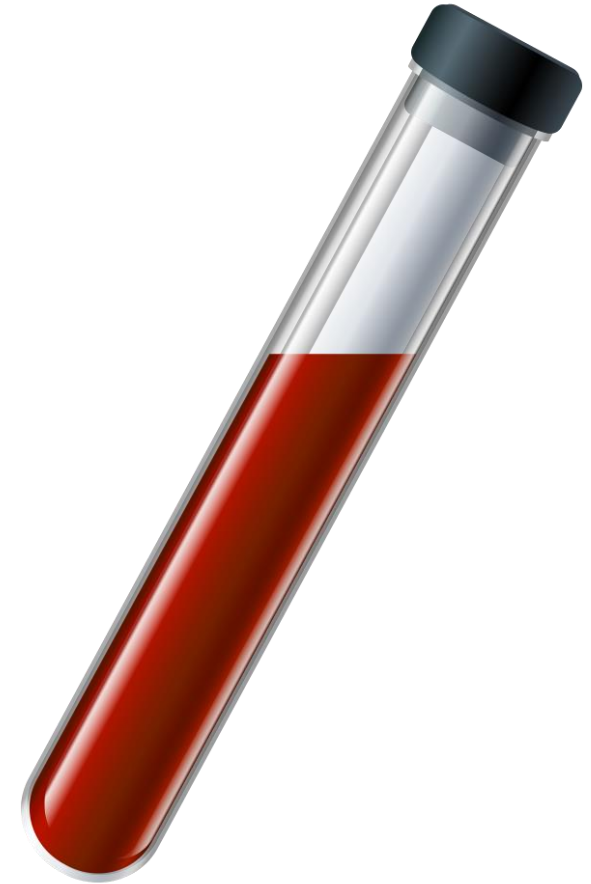
- **Late disseminated disease**
- Arthritis
  - Commonly monoarthritis at knee (warmth, swelling)
  - Possible initial presentation
  - Fluid WBC usually 10,000 to 25,000 (inflammatory)
- Encephalopathy
  - Mild cognitive disturbance



# Lyme Disease

## Diagnosis

- Difficult to culture
- Stage 1: **clinical diagnosis (classic rash)**
  - Serologic testing usually gives false negative result
- Stages 2 or 3: **serology for IgM and IgG antibodies**
  - Enzyme-linked immunosorbent assays (ELISA)
  - Many false positives due to similar antibodies
  - Positive test followed with **Western blot**
  - Confirmatory - also detects antibodies
  - Patient must have clinical features
  - Positive serology alone only indicates exposure



# Lyme Disease

## Treatment

- Stage 1 or mild disease: **oral doxycycline or amoxicillin**
  - EM rash
  - Arthritis without neurologic disease
  - Isolated facial nerve palsy
  - Mild, asymptomatic forms of AV block
- Late stage or severe disease: **IV ceftriaxone**
  - Encephalitis, high degree AV block, persistent arthritis
  - High degree AV block: hospitalization, monitoring, ceftriaxone
- Pregnancy: **amoxicillin**
  - Doxycycline avoided

# Lyme Disease

## Tick bite management

- Borrelia not transmitted within first 48 to 72 hours of attachment
- Remove ticks with tweezers or gloved fingers
- Pull straight up with even pressure
- Antibiotic prophylaxis: **single-dose doxycycline**
- Prophylaxis criteria:
  - Tick estimated to have been attached for  **$\geq 36$  hours**
  - Prophylaxis **begins within 72 hours** of tick removal
  - Local rate of infection of ticks with Borrelia  $\geq 20$  percent
  - Doxycycline not contraindicated (e.g., pregnancy)
- Can also observe for development of EM rash then treat



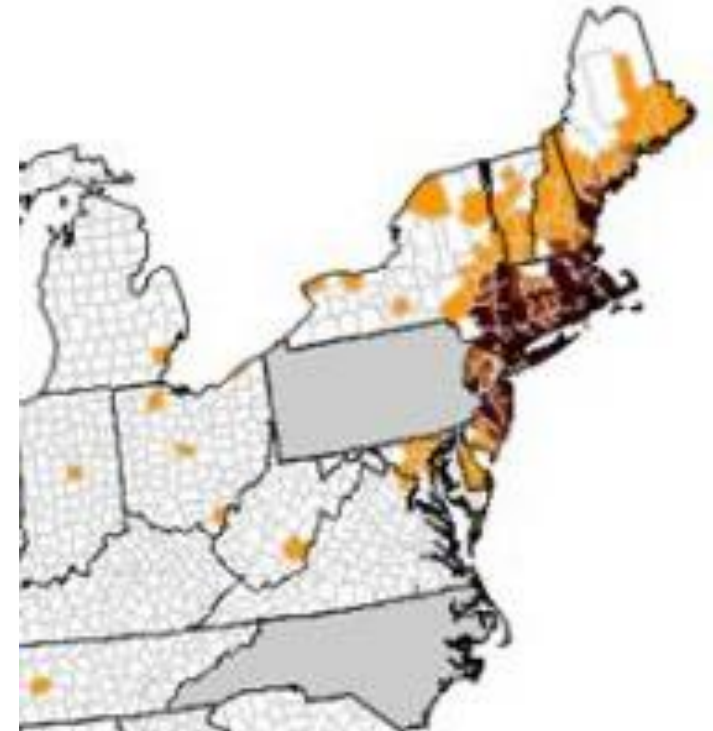


# Babesiosis

*Babesia microti*

- Protozoal infection transmitted by **Ixodes tick**
  - Same tick that transmits borrelia (Lyme)
  - Also Anaplasma (Anaplasmosis)
  - Co-infection common
- Similar geography to Lyme: **northeastern US**
  - Especially Nantucket Island and Martha's Vineyard

Babesiosis Cases 2018

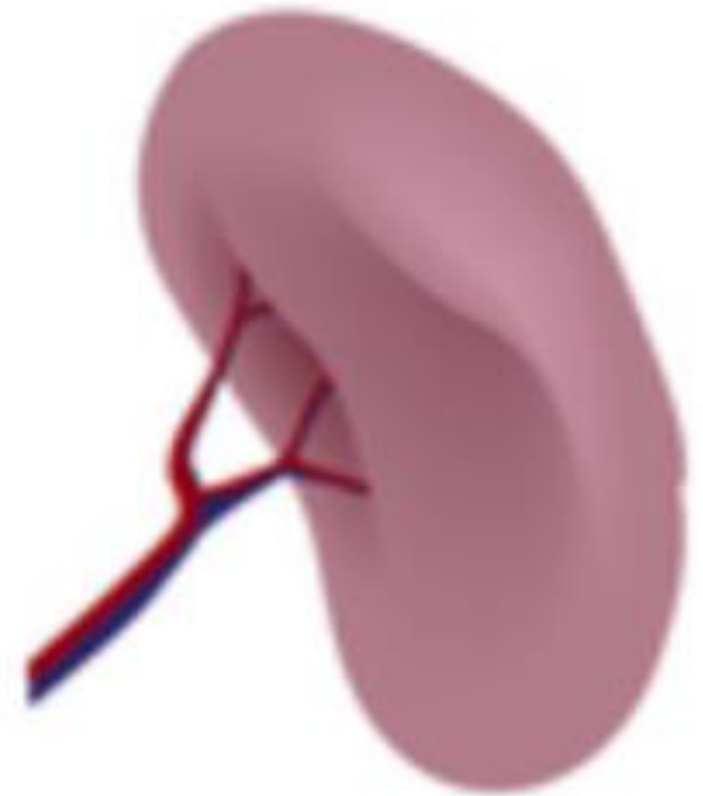


# Babesiosis

## Babesia microti

- Infects red blood cells → **hemolysis**
  - Similar to malaria
  - But no liver (non-red cell) phase
- Fever
- Hemolytic anemia
- Splenomegaly
- Infection may be asymptomatic or mild
- Severe features may occur in **asplenic patients**
  - Spleen clears Babesia-infected red cells

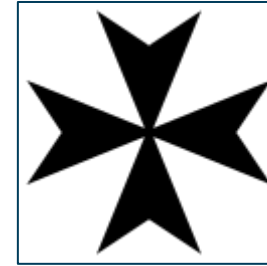
Spleen



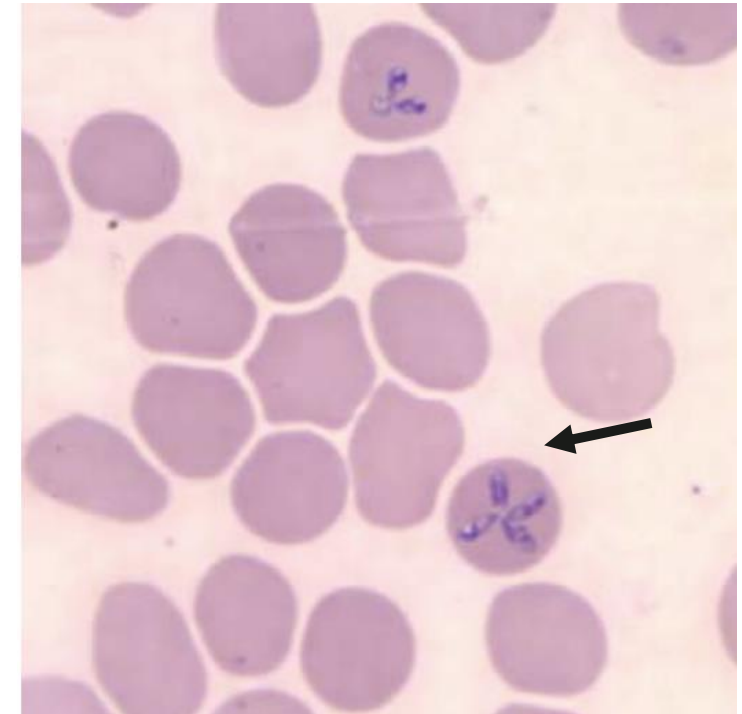
# Babesiosis

## Babesia

- Diagnosis: **Giemsa-stained blood smear**
  - Ring forms that can resemble plasmodium
  - Parasites may form **Maltese crosses**
- PCR for amplification Babesia DNA
- Treatment: **azithromycin plus atovaquone**
  - Azithromycin: macrolide antibiotic
  - Atovaquone: antimalarial drug



Maltese Cross

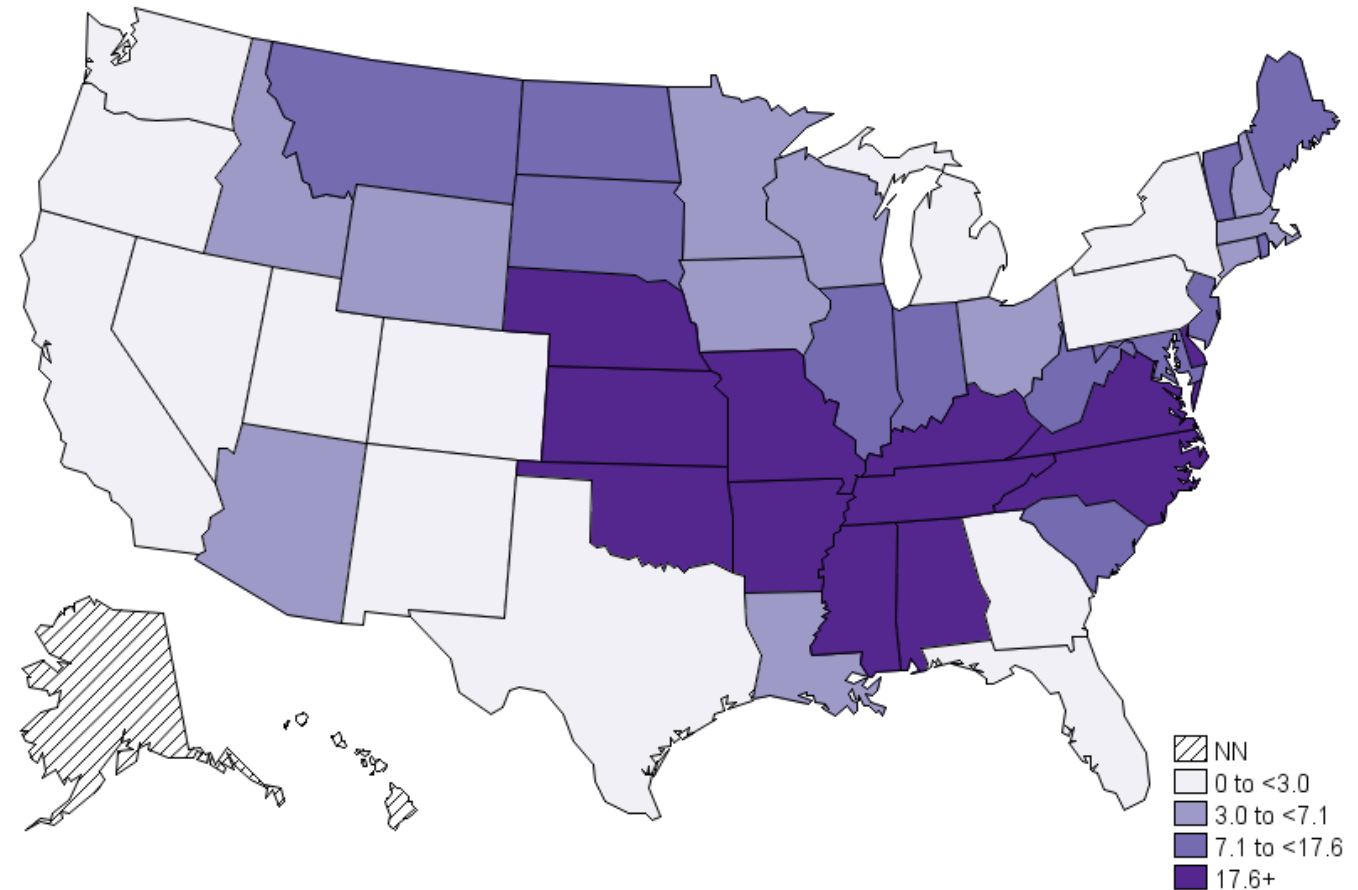


# Rocky Mountain Spotted Fever

*Rickettsia rickettsii*

- Obligate intracellular organism
- Infects endothelial cells
- Occurs in Eastern United States
- Name is a misnomer
- Transmitted by **tick bite**
- Different ticks based on region

Annual incidence Rickettsia cases 2018



# Rocky Mountain Spotted Fever

## Clinical features

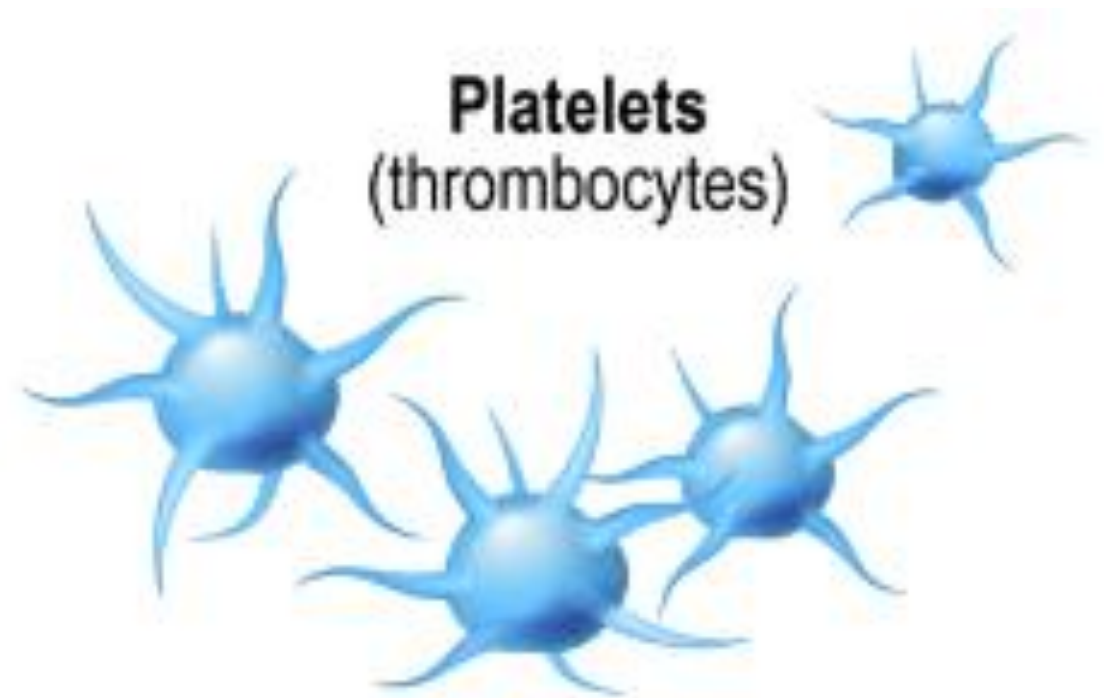
- Days after tick bite: **headache and fever**
- Days later: **maculopapular rash**
  - Begins on ankles and wrists
  - Spreads to trunk
  - Classically involves palms and soles
  - **Petechiae** develop over time



# Rocky Mountain Spotted Fever

## Clinical features

- Classic lab finding: **thrombocytopenia**
  - Platelet destruction at sites of endothelial damage
  - Often a helpful clinical clue in patient with rash
- Also may cause **hyponatremia**
  - Especially if CNS involvement occurs
- Mild elevations of AST/ALT





# Rocky Mountain Spotted Fever

## Clinical features

- Must differentiate from bacterial meningitis
- Also can cause fever, headache, rash
- Key test: **lumbar puncture and CSF analysis**

Common CSF Findings

	Bacterial Meningitis	RMSF
White count	Marked elevation (>1000)	Mild elevation (<100)
Predominance	PMNs	PMNs or lymphocytes
Protein	Increased	Minimal increase
Glucose	Low	Normal

# Rocky Mountain Spotted Fever

## Major complications

- Encephalitis
- Non-cardiogenic pulmonary edema
- Seizures
- Coagulopathy

Pulmonary Edema

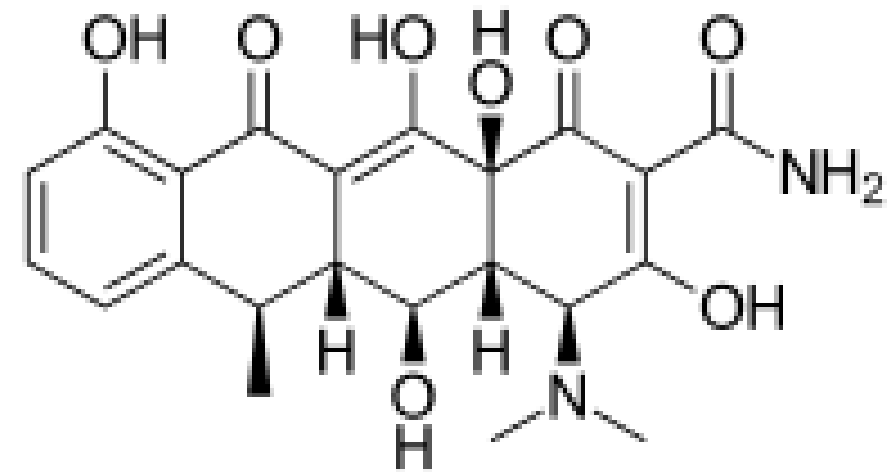


# Rocky Mountain Spotted Fever

## Diagnosis and treatment

- Presumptive diagnosis can be made **clinically**
- Early initiation of treatment improve outcomes
- Serologic testing for antibodies available
- Treatment: **doxycycline**
  - Alternative: chloramphenicol
  - Doxycycline often used in pregnancy

Doxycycline

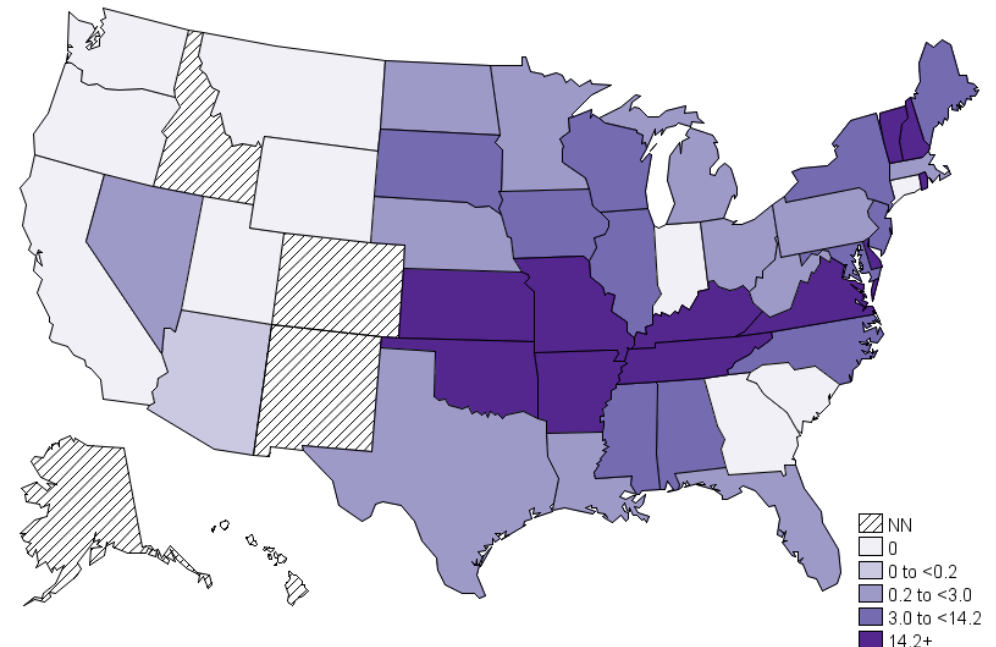


# Human Monocytic Ehrlichiosis

## *Ehrlichia chaffeensis*

- Member of Rickettsia family of bacteria
- Transmitted by Lone Star tick
- Common in Southern US
- Obligate intracellular bacteria - infect monocytes
- Infection common in spring and summer
- Similar features to **RMSF but no rash**
- Causes a flu-like illness
- Often causes leukopenia and thrombocytopenia
- Elevated AST/ALT may occur

Annual incidence of *E. chaffeensis* 2018

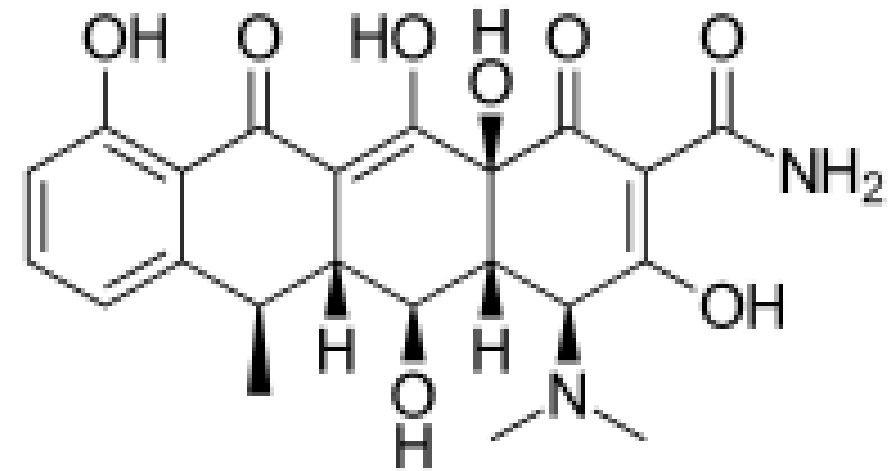


# Human Monocytic Ehrlichiosis

## Diagnosis and treatment

- Diagnosis often made clinically
  - Tick bite in endemic area
  - Typical clinical features
- Serology testing for antibodies
- Treatment: doxycycline

Doxycycline



# Anaplasmosis

*Anaplasma phagocytophilum*

- Member of Rickettsia family of bacteria
- Clinical features indistinguishable from Ehrlichia
- Infects granulocytes (not monocytes)
- Tick vector: Ixodes scapularis (not Lone Star tick)
  - Same vector as Lyme disease, Babesiosis
- Similar symptoms and treatment to Ehrlichiosis
  - Fever, joint pains
  - Low WBCs, platelets
  - Doxycycline



# Sexually-Transmitted Infections

Jason Ryan, MD, MPH



# Chlamydia

- **Special cell walls - lacks peptidoglycan**
  - Don't respond to many antibiotics
  - Treatments of choice: azithromycin, doxycycline
- **Do not gram stain well**
  - Obligate intracellular organisms
  - Cannot make their own ATP
  - Technically gram negative
  - Special stains (Giemsa) for visualization
  - Nucleic acid amplification tests (NAATs)

CHLAMYDIA



# Chlamydia

## Subtypes

- **C. trachomatis**
  - Most common sexually-transmitted infection
  - Eye infections and pneumonia in newborns
  - Lymphogranuloma venereum and trachoma
- C. pneumoniae
  - Atypical pneumonia
  - Transmitted by aerosol
- C. psittaci
  - Psittacosis (Parrot fever)
  - Infection from birds
  - Headache, fever and cough



# Chlamydia Trachomatis

## Clinical features

- Sexually-transmitted infection
- Often asymptomatic
- Women: **cervicitis**
  - Discharge, post-coital bleeding
  - Can progress to PID, Fitz-Hugh-Curtis
- Men: **urethritis, epididymitis or prostatitis**
  - May lead to discharge or dysuria
  - May also cause proctitis (rectal inflammation)

Chlamydia Cervicitis



# Chlamydia Trachomatis

## Diagnosis

- **Nucleic acid amplification testing (NAAT)**
  - Vaginal or cervical swab
  - Or urine
  - PCR of Chlamydia DNA/RNA
- Microscopy of discharge: leukocytes without bacteria
  - Gram stain not useful



# Chlamydia Trachomatis

## Treatment

- **Azithromycin or doxycycline**
  - Different regimens based on specific type of infection
  - Azithromycin preferred in pregnancy
- Co-infection common with *N. gonorrhoeae*
  - Also test for *N. gonorrhoeae*
- Must **treat partners** or reinfection may occur



# Chlamydia Trachomatis

## Newborns

- Infection from passage through birth canal
- Conjunctivitis
- Pneumonia





# C. Trachomatis

## Serotypes

Serotype	Infections
D through K	Urethritis, cervicitis, neonatal infection
L1, L2, L3	Lymphogranuloma venereum
A, B, C	Trachoma and blindness Remote, resource-limited areas

# Lymphogranuloma Venereum

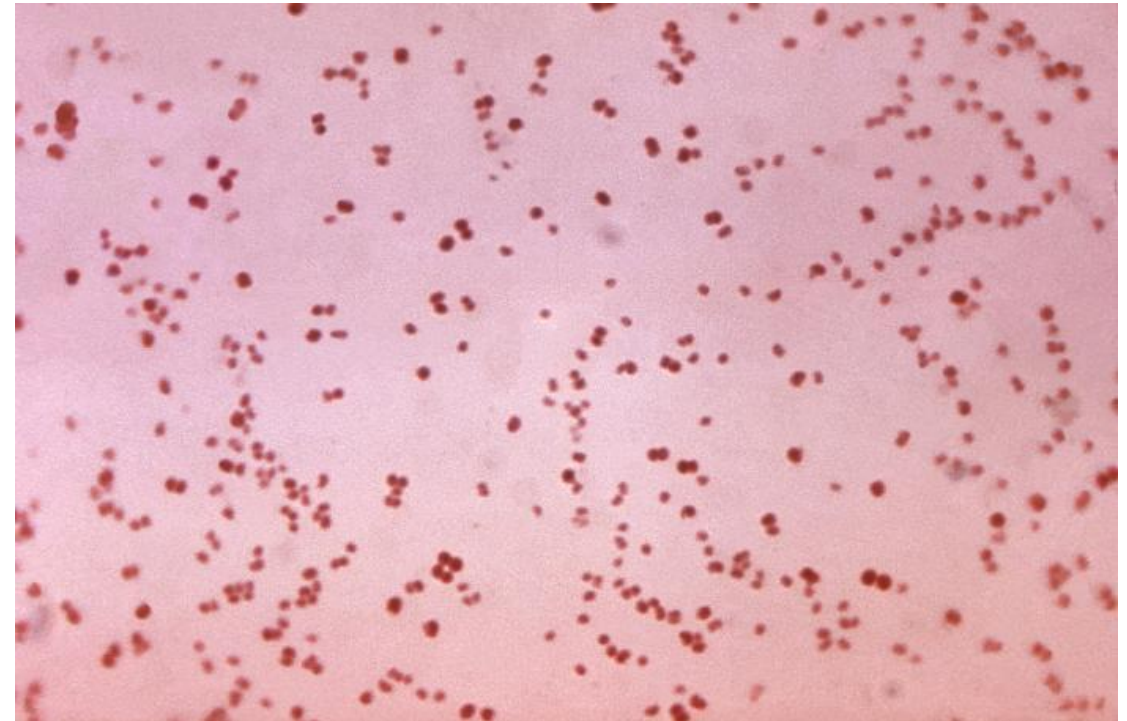
- Sexually-transmitted chlamydia infection that enters lymphatics
- L1, L2 and L3 serotypes
- Initially: **painless genital ulcer**
  - Sometimes unnoticed; resolves
- Later: tender inguinal or femoral **lymph nodes**
  - “Buboes:” swollen inflamed lymph nodes
- Diagnosis: NAAT
- Treatment: drainage of buboes and antibiotics
  - Doxycycline or azithromycin



# Neisseria Gonorrhoeae

- Neisseria: **gram-negative diplococci**
  - N. meningitidis: meningitis
  - N. gonorrhoeae: sexually-transmitted infection
- **Gonorrhea**
  - Second most common STI
  - Urethritis and cervicitis
  - Extragenital infection: proctitis, pharyngitis
  - Can disseminate → arthritis

N. Gonorrhoeae



# Gonorrhea

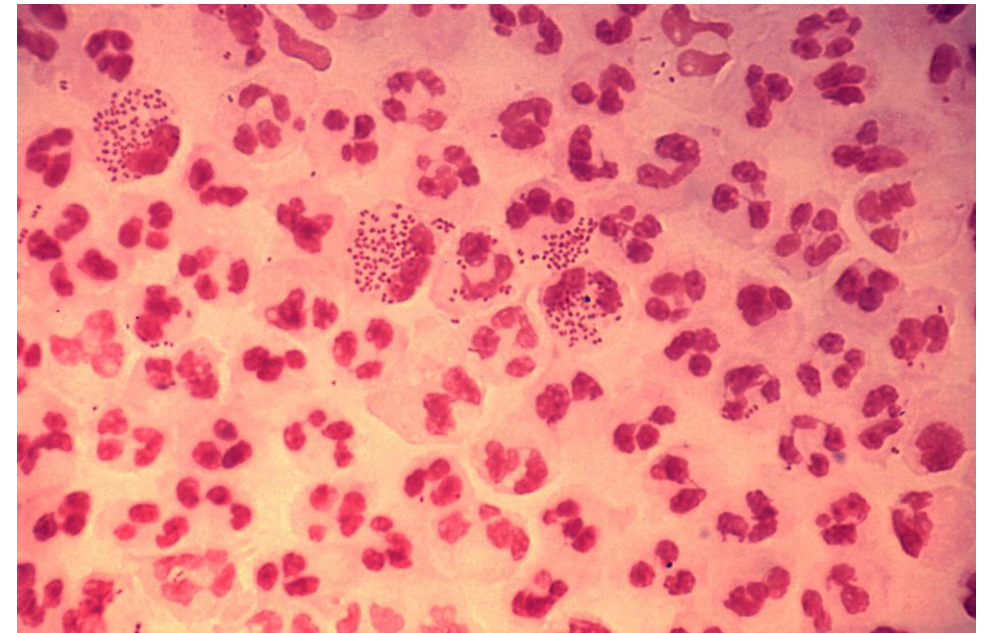
## Clinical features

- Often asymptomatic
- **Men: urethritis and epididymitis**
  - Dysuria, discharge
- **Women: cervicitis**
  - Itching, discharge from cervix
  - Not painful
  - Can progress to PID

# Gonorrhea

## Diagnosis

- **Nucleic acid amplification testing (NAAT)**
  - Men: urine or urethral swab
  - Women: vaginal or cervical swab or urine
- Gram stain
  - Mainly used on urethral swab in men
  - Low specificity in women
  - PMNs with intracellular gram-negative diplococci
- Culture
  - Used when antibiotic resistance is a concern



# Gonorrhea

## Treatment

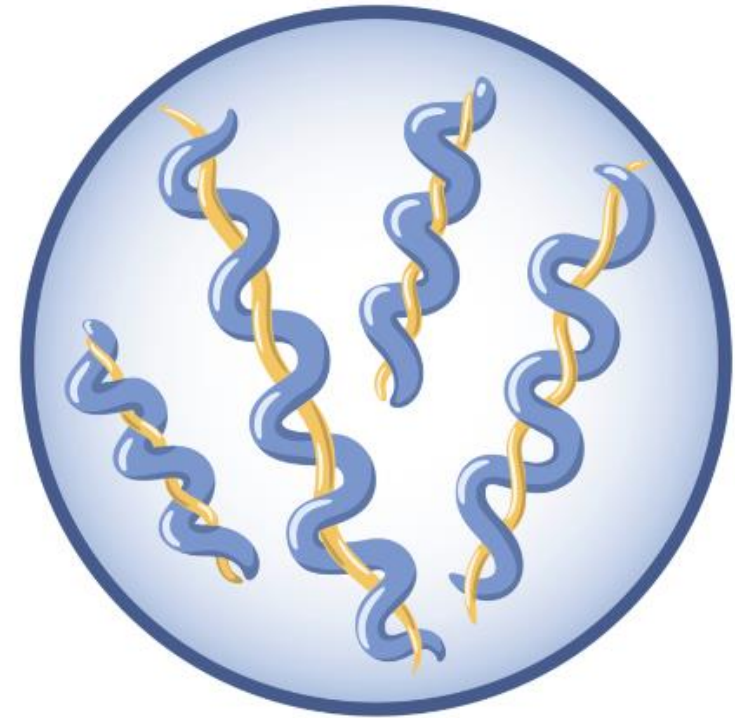
- **Ceftriaxone**
  - Lowest frequency of treatment failure
  - Can be given as a single IM dose
- Co-infection common with Chlamydia
  - Also test or treat for Chlamydia
- Evaluate and treat sexual partners



# Syphilis

- Caused by **Treponema pallidum**
- Spirochete (spiral-shaped bacteria)
- Sexually-transmitted infection
- May also infect newborns (congenital syphilis)
- Primary, secondary and tertiary stages

Treponema pallidum





# Primary Syphilis

- Two to three weeks after exposure
- **Painless chancre**
  - Ulcer
  - Classically on the penis
  - Usually 1 to 2 cm
  - Raised
- Often unnoticed
- Resolves spontaneously over weeks



# Secondary Syphilis

- Occurs in ~25% of untreated patients
- Weeks to months after chancre
- **Flu-like symptoms**
  - Fever, headache, malaise, sore throat, myalgias
- **Rash**
  - Classically maculopapular rash
  - Covers all extremities including palms/soles
- Resolves spontaneously



# Secondary Syphilis

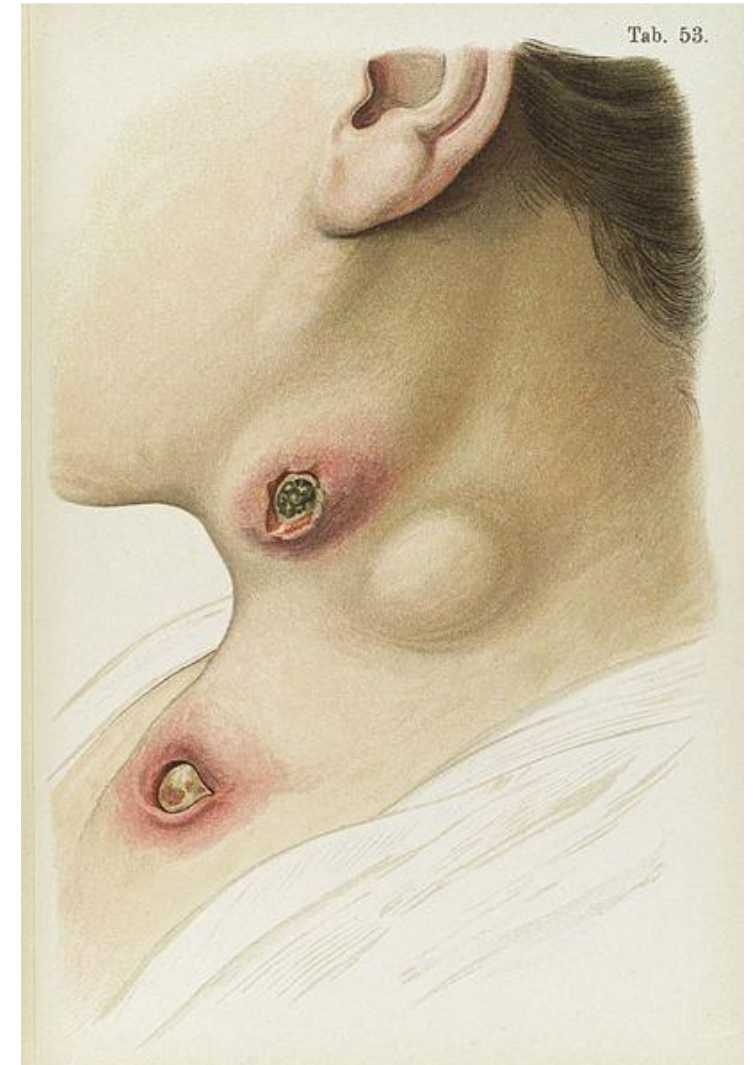
- **Diffuse lymphadenopathy**
  - Cervical, axillary, inguinal, or femoral
  - Classically involve **epitrochlear nodes (elbow)**
  - “Sailor’s handshake”
- **Condylomata lata**
  - Large, raised, gray to white lesions
  - Moist areas: inside mouth, perineum

Condylomata lata



# Late Syphilis

- Occurs years after initial infection
- Follows “latent syphilis:” period from 2<sup>0</sup> to late disease
- **Tertiary syphilis**
  - Aortitis – aortic dilation and dissection
  - Gummas – nodules/ulcers in skin, bones or other organs
- **Neurosyphilis**
  - Many possible features





# Neurosyphilis

- Meningitis
- Progressive dementia
- **Tabes dorsalis**
  - Demyelination of posterior columns
  - Wide-based gait
  - Ataxia - falls, loss of balance
- **Argyll Robertson pupil**
  - Small, irregular pupils
  - Do not constrict to light
  - Constrict to accommodation



Bilateral miotic and irregular pupils

Pupils do not react to light



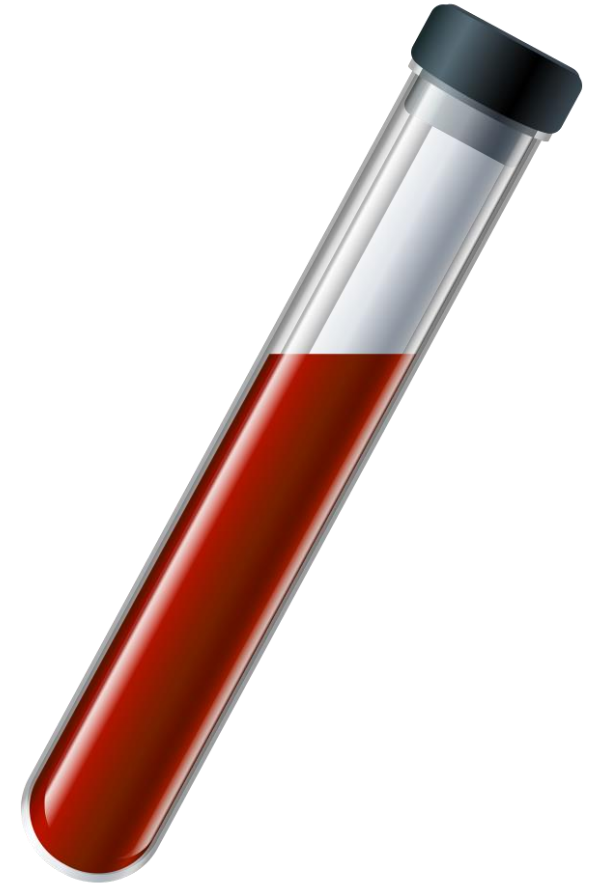
Pupils react briskly to accommodation



# Syphilis

## Diagnosis

- Treponema cannot be cultured
- **Non-treponemal serologic tests**
  - Tests for reaction of serum to cardiolipin antigen
  - If syphilis antibodies present → reaction
  - False positives may occur in lupus, viral infections, others
  - **Venereal Disease Research Laboratory (VDRL) test**
  - **Rapid Plasma Reagin (RPR) test**
  - Semi-quantitative results reported as titer



# Syphilis

## Diagnosis

- **Treponemal serologic tests**
  - Detects antibodies against specific treponemal antigens
  - Specific test
  - Fluorescent treponemal antibody absorption (FTA-ABS)
  - T. pallidum enzyme immunoassay (TP-EIA)
  - Results are “Reactive” or “Non-reactive”
  - Better test in primary disease (chancre)
- Neurosyphilis: **lumbar puncture**
  - Blood tests do not necessarily indicate CNS disease
  - CSF for VDRL is highly-specific

## Lumbar Puncture





# Syphilis

## Treatment

- **IM Penicillin G**
  - Primary, secondary, latent or tertiary disease
  - Alternative: doxycycline (used in penicillin allergy)
  - VDRL/RPR titers will fall with successful treatment
- Neurosyphilis: **penicillin G +/- probenecid**
  - Probenecid inhibits renal excretion penicillin
- **Jarisch-Herxheimer reaction**
  - Flu-like syndrome after starting antibiotics
  - Killed bacteria cause immune response
  - Self-limited



# Genital Herpes

- Sexually-transmitted infection due to **herpes simplex virus**
  - Usually HSV-2 but can be HSV-1 – clinically identical infections
- **Primary infection**
  - Can be asymptomatic
  - May lead to painful vesicles on an erythematous base
  - May cause fever and lymphadenopathy
  - Antibody testing is negative
- Virus enters **latent phase** in lumbar-sacral nerves
- **Recurrent eruptions** of vesicles and ulcers
  - Often less severe than primary infection
  - Antibody testing is positive in non-primary disease

Genital Herpes



# Genital Herpes

## Diagnosis

- Must distinguish from other genital ulcers
- Preferred test: **PCR for viral DNA**
  - Requires sample of vesicular fluid
  - Alternative: viral culture
- **Serologic antibody testing**
  - Useful when lesions have resolved
- Negative serology with (+) PCR = primary disease

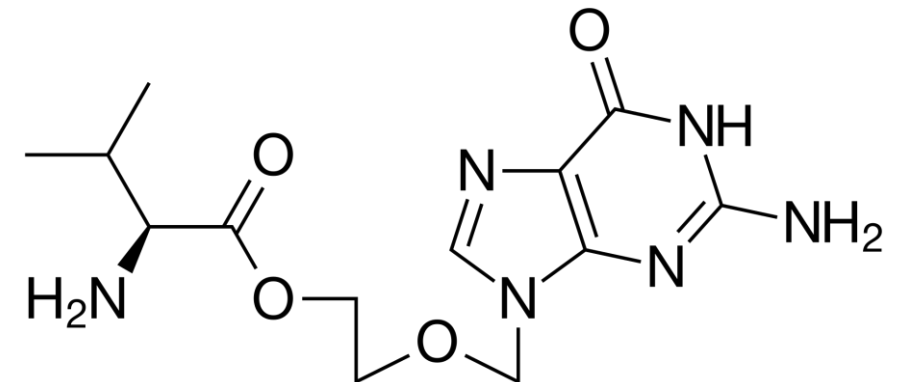


# Genital Herpes

## Treatment

- **Valacyclovir, acyclovir or famciclovir**
- Reduces frequency and severity of recurrence
- Does not eliminate latent viral infection
- Decreases but does not eliminate viral shedding
- Sexual transmission may occur even when asymptomatic

Valacyclovir



# Genital Herpes

## Treatment

- Primary infection almost always treated to avoid severe disease
- Recurrent disease: episodic treatment
  - Based on patient preference
  - Mild or infrequent symptoms do not require treatment
- Frequent recurrences: chronic suppressive therapy
  - Usually  $\geq 6$  episodes per year

# Chancroid

- Rare, sexually-transmitted infection due to **Haemophilus ducreyi**
- Small gram-negative rod
- **Painful genital ulcer**
- May cause painful inguinal lymphadenitis
- Clinical diagnosis
  - Laboratory testing not commonly available
  - Negative testing for HSV
- Treatment: azithromycin or ceftriaxone

# Genital Ulcers

Painful Ulcers	Painless Ulcers
Herpes (multiple vesicles) Chancroid	Syphilis (chancre) Lymphogranuloma venereum



# Anogenital Warts

## Condylomata acuminata

- Sexually-transmitted infection caused by **papillomavirus (6, 11)**
- Soft, tan, cauliflower-like lesions
  - “Verrucous” = warts
- Penis, vulva, perianal area
  - May cause rectal bleeding
- Treatment:
  - Chemical agents
  - Surgical therapy
- HPV 6 and 11: low-risk for cancer



# Sexually-Transmitted Infections

## Screening

- **Patients diagnosed with one STI usually tested for other STIs**
- HIV
- Syphilis
- N. gonorrhoeae and chlamydia
- Others



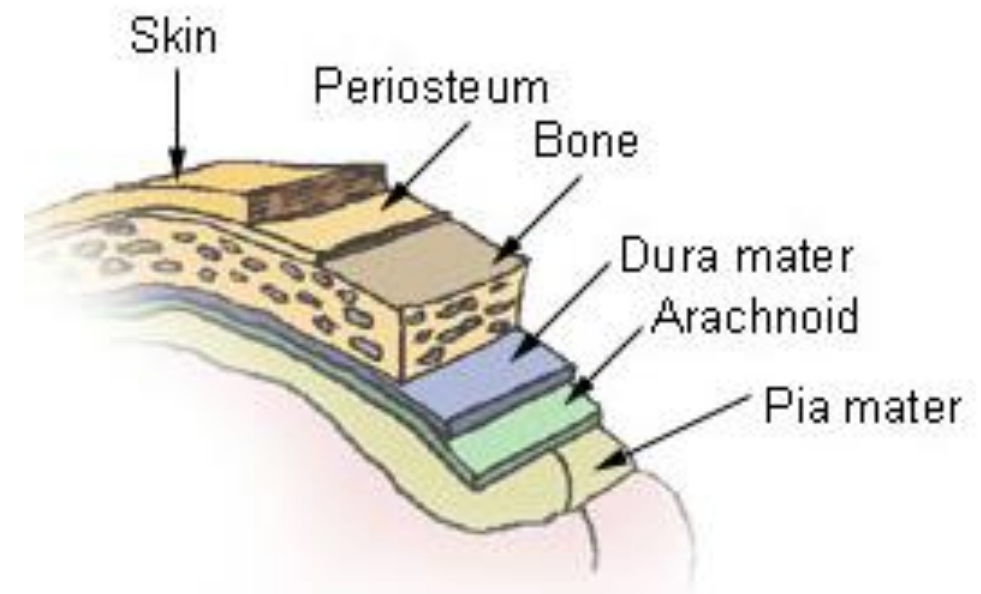
# Meningitis

Jason Ryan, MD, MPH



# Meningitis

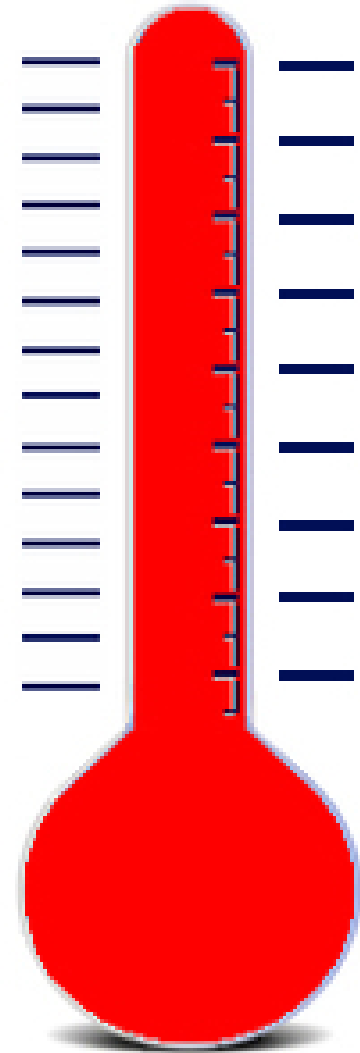
- Inflammation of the **leptomeninges**
  - Meninges: three membranes surrounding brain and spinal cord
  - Leptomeninges: inner two meninges - arachnoid, pia mater
- Involves **CSF in subarachnoid space**
- Usually infectious: viral, bacterial, fungal
- Rarely cancer, sarcoid, inflammatory diseases



# Meningitis

## Clinical features

- **Fever, headache, photophobia**
- Lethargy but intact sensorium
  - Contrast with encephalitis
- **Nuchal rigidity**
  - Nape = back of neck
  - Nuchal = related to nape
  - Nuchal rigidity = hurts to move back of neck



# Meningitis

## Clinical features

- **Kernig sign**
  - Thigh bent at hip with knee at 90 degrees
  - Subsequent extension of knee is painful (resistance)
- **Brudzinski sign**
  - Lie patient flat
  - Lift head off table
  - Involuntary lifting of legs
- Both signs of **meningismus**
  - Usually meningitis
  - Also subarachnoid hemorrhage

# Meningitis

## Clinical features

- **Infants may have non-specific signs**
  - Fever
  - Lethargy
  - Poor feeding
  - Inconsolable crying
- Must consider meningitis





# Meningitis

## Clinical features

- **Petechial rash**
- Classic finding in **meningococcal meningitis**
- Infection due to *Neisseria meningitidis*
- Indicates meningococemia and thrombocytopenia



# Meningitis

## Complications

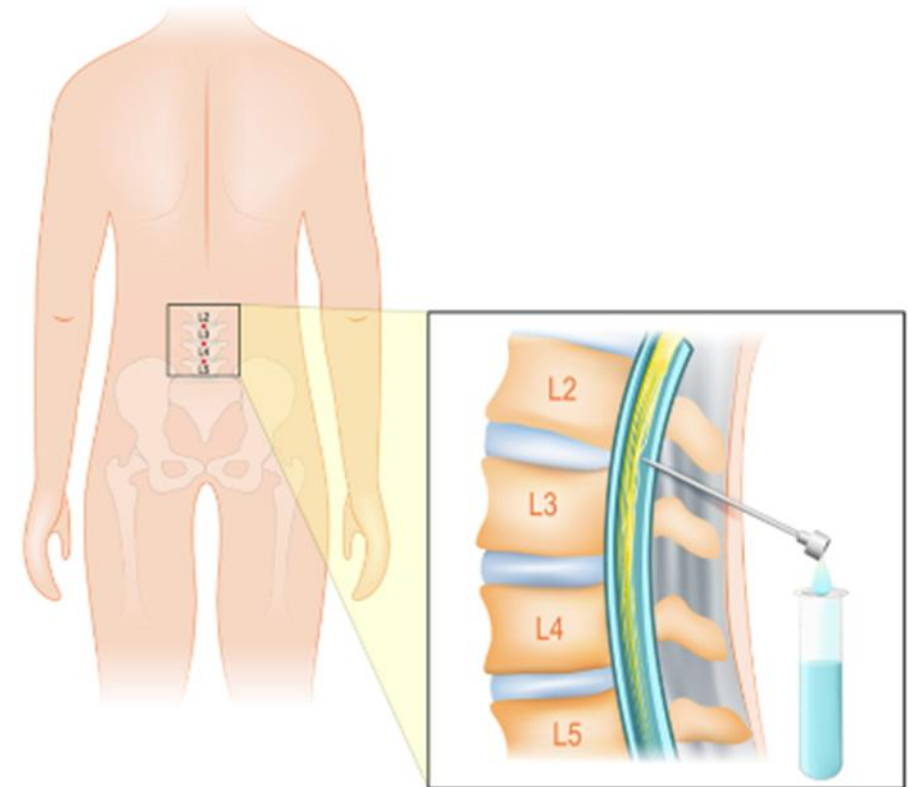
- Hydrocephalus
- Hearing loss
- Seizures
- Death
- Most from bacterial meningitis

# Meningitis

## Diagnosis

- Suggestive signs and symptoms
- **Lumbar puncture** to obtain **CSF sample**

### Lumbar puncture procedure



# Meningitis

## Spinal fluid testing

- Cell count and differential, glucose, protein, gram stain and culture
- Exceptions may occur (especially PMN or lymphocyte differential)

	WBCs	Diff	Glucose	Protein
Normal	< 5	--	50-75*	< 60
Bacterial**	> 1000	PMNs	↓	↑
Viral	5 to 500	Lymphocytes	Normal	Normal or ↑
Fungal/TB	Variable	Lymphocytes	↓	↑

\* two-thirds serum glucose (~100)

\*\* gram stain positive in bacterial

# Meningitis

## CT Scanning

- May be performed prior to lumbar puncture
- Used to exclude **mass or increased intracranial pressure**
- Not routinely performed
- Major indications
  - Immunocompromised state (e.g., HIV)
  - History of mass lesion
  - New onset seizures
  - Papilledema
  - Abnormal level of consciousness
  - Focal neurologic deficits



# Aseptic Meningitis

- Meningeal inflammation **without evidence of bacterial infection**
- Usually caused by **enteroviruses** especially **Coxsackievirus**
  - Most transmitted by fecal-oral route
- Suspected based on CSF results
  - Cell count < 500/microL
  - > 50% lymphocytes
  - Normal glucose
  - Negative Gram stain
- Antibiotics often given until cultures are negative
- Treatment: supportive care, usually self-limited

# Herpes Simplex Meningitis

- **Primary HSV infection** can lead to aseptic meningitis
  - Usually due to **HSV-2**
  - HSV-1 often causes encephalitis
- **Genital lesions** present in most patients
- Treatment: **acyclovir**

Genital Herpes





# Bacterial Meningitis

- Suspected based on CSF results
  - Cell count > 1000/microL
  - > 80% neutrophils (PMNs)
  - ↓ glucose and ↑ protein
  - Positive Gram stain
- Treatment: **antibiotics**
  - Culture takes days
  - Cannot wait for culture to drive choice of drug
  - **Empiric antibiotics administered**
  - Therapy modified based on culture results

# Bacterial Meningitis

Common causes and empiric antibiotics

	Newborn 0-1 Month	Children > 1 Month	Adults < 50	Adults > 50
Bacteria	GBS E. Coli Listeria	S. Pneumo N. Meningitidis	S. Pneumo N. Meningitidis	S. Pneumo N. Meningitidis Listeria
Empiric Antibiotics	Ampicillin Gentamycin Extended Ceph	Vancomycin 3 <sup>rd</sup> Gen Ceph	Vancomycin 3 <sup>rd</sup> Gen Ceph	Vancomycin 3 <sup>rd</sup> Gen Ceph Ampicillin

Extended-spectrum cephalosporins: ceftriaxone, cefotaxime or cefepime  
3<sup>rd</sup> generation cephalosporins: ceftriaxone or cefotaxime

# Bacterial Meningitis

Common causes and empiric antibiotics

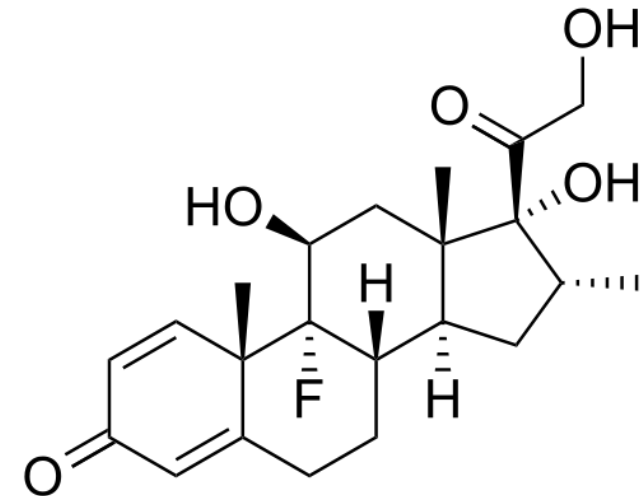
	Immunocompromise	Trauma/ Neurosurgery/ Health-care Associated
Bacteria	S. Pneumo N. Meningitidis Listeria Gram negative rods	MRSA Gram negative rods S. Epidermis
Empiric Antibiotics	Vancomycin Cefepime* Ampicillin	Vancomycin Cefepime*

\*Can also use ceftazidime or meropenem

# Bacterial Meningitis

## Corticosteroids

- **Dexamethasone**
- May decrease rate of hearing loss and neurologic complications
- **Adults**
  - Given empirically **prior to antibiotics**
  - Continued only if **S. pneumoniae** is causative agent
  - Clinical studies showed benefit limited to this group
- Controversial in children
  - Greatest benefit with HIB meningitis (rare due to vaccination)



Dexamethasone

# Bacterial Meningitis

## *Streptococcus pneumoniae*

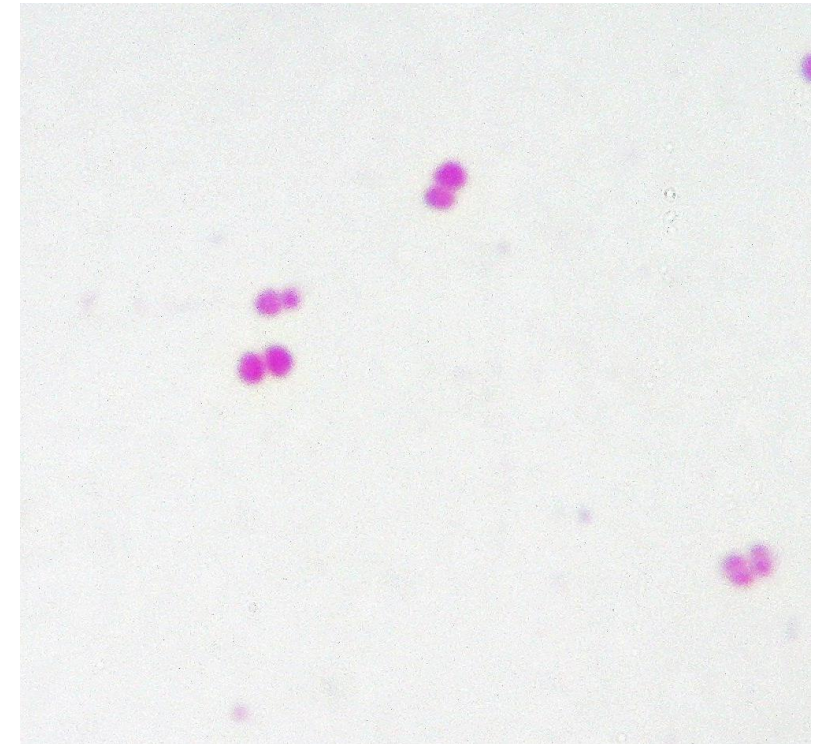
- Most common cause meningitis in adults
- Gram positive lancet-shaped cocci in pairs (diplococci)
- Most strains susceptible to ceftriaxone and 3<sup>rd</sup> generation cephalosporins
- Beta-lactam-resistant organisms possible
- Vancomycin added to empiric therapy
- Increased risk if **splenic dysfunction**



# Bacterial Meningitis

## Neisseria meningitidis

- Gram negative cocci in pairs (diplococci)
- May cause a petechial rash
- Transmitted by **respiratory droplets**
- Hospitalized patients need **droplet precautions**
  - Usually for 24 hours after start of antibiotics
- Can cause outbreaks
  - Close contacts receive **prophylaxis**
  - Usually rifampin, ciprofloxacin or ceftriaxone
- Vaccine available



# Bacterial Meningitis

## Haemophilus influenzae

- Small, gram negative rod
- **Haemophilus influenzae type B (HIB)**
  - Most pathogenic subtype
  - Vaccine given in infancy
  - HIB once most common cause bacterial meningitis
  - H. Flu meningitis almost always occurs in unimmunized children





# Bacterial Meningitis

## Listeria

- Gram positive rod
- Thrives with **poor cell-mediated immunity**
  - HIV, organ transplant and pregnancy
- In adults, exposure often from **contaminated food**
  - Undercooked meat, unwashed vegetables
  - Unpasteurized cheese/milk
  - Can cause GI illness (listeriosis)
- May colonize female genital tract
- Neonates: **transplacental or vaginal transmission**

# Neonatal Meningitis

- **Group B Streptococci (*Strep agalactiae*)**
  - Gram positive cocci in chains
  - May colonize genital tract in women
  - Most common cause meningitis in newborns
  - Antibiotics during labor used for prevention
- ***Escherichia coli***
  - Motile, gram-negative rod
  - Second most common meningitis cause neonates
  - Acquired from birth canal at delivery
- *Listeria*



# Viral Encephalitis

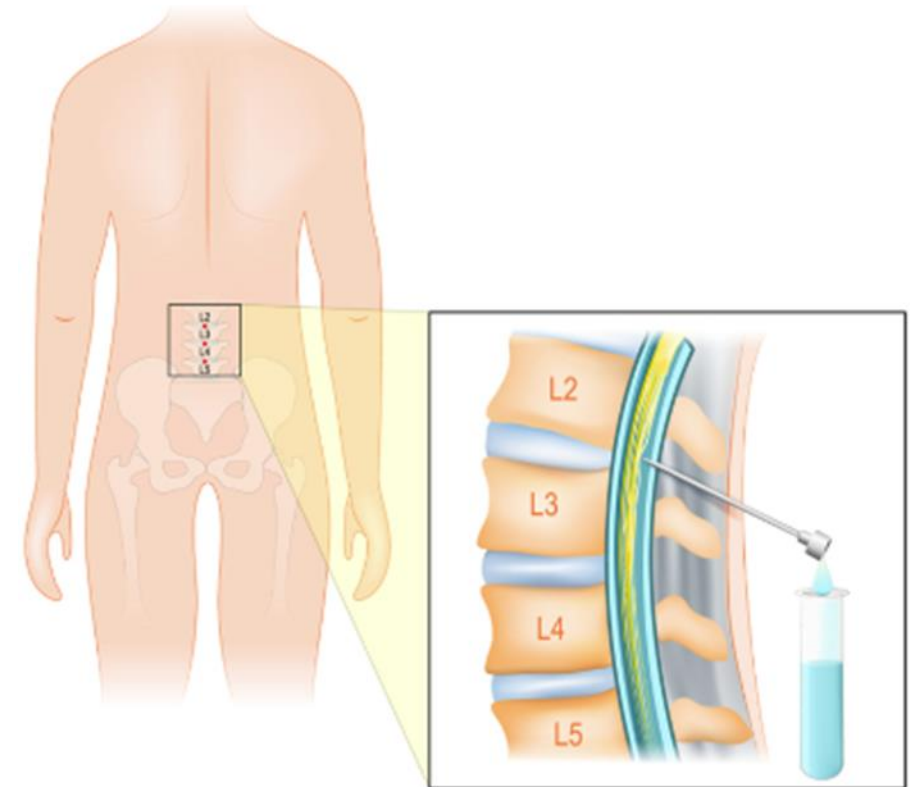
- Viral CNS infections may cause aseptic meningitis or encephalitis
  - Encephalitis = brain inflammation
  - Patients may have meningoencephalitis
- Fever
- **Altered mental status**
- **Seizures**
- May cause motor or sensory deficits



# Viral Encephalitis

- MRI imaging often performed
  - Exclude mass lesions or abscess
  - May shows areas of edema
- Diagnosis: **CSF analysis**
  - WBC < 500, lymphocyte predominance
  - Glucose normal, protein normal or increased
  - CSF PCR testing for HSV and other viruses

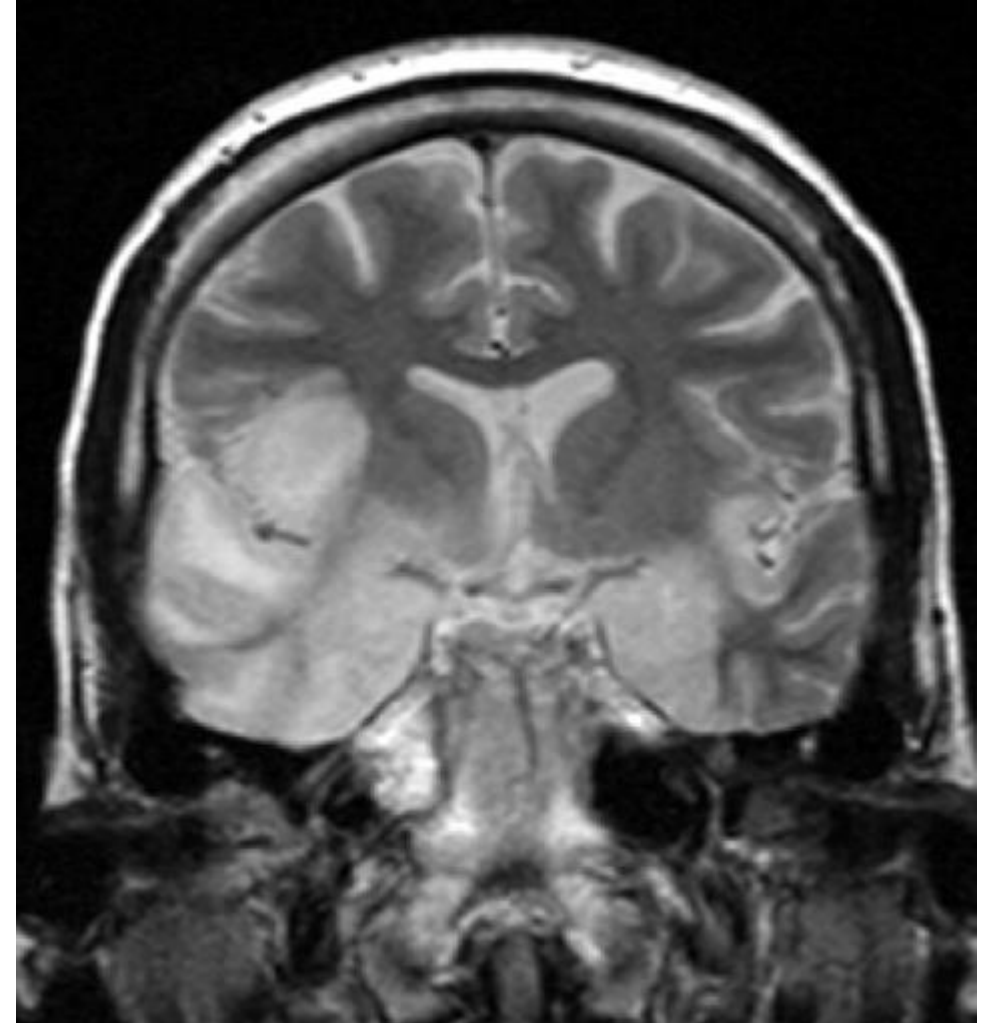
## Lumbar puncture procedure



# Viral Encephalitis

## HSV-1

- Most important etiology to identify
- Often fatal without early treatment
- May cause **red cells in CSF**
- MRI: **temporal lobe edema**
  - Classic finding in HSV (many other findings possible)
- Often re-activation of latent HSV-1
  - Antibodies present in serum
- Treatment: **acyclovir**
  - Given empirically until CSF negative for HSV



# Encephalitis

## Other causes

- **Mosquito viruses**
  - St. Louis encephalitis virus
  - Eastern equine encephalitis
  - West Nile virus
  - California encephalitis virus
- Rabies
- Mumps
- HIV



# Tuberculosis

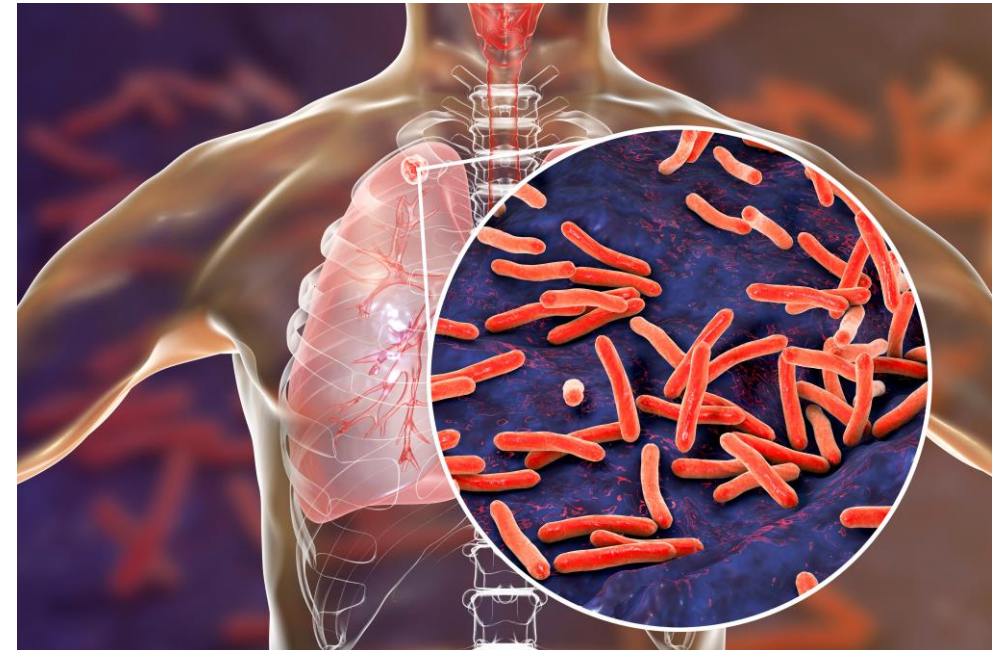
Jason Ryan, MD, MPH





# Tuberculosis

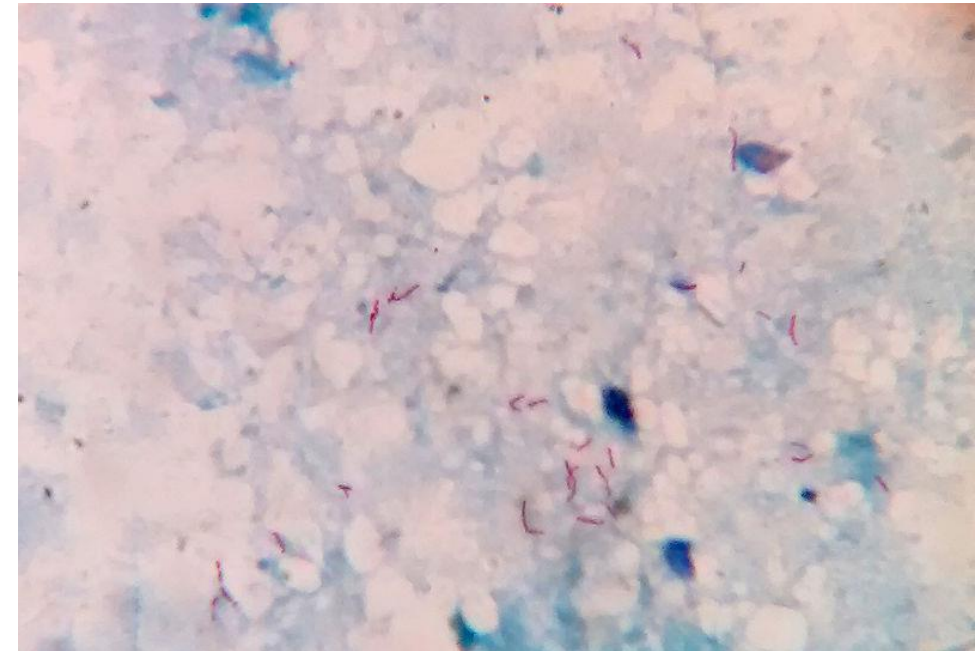
- Ancient disease: found in mummies!
- Old name: consumption
- Tubercle = round nodule
- Tuberculosis = multiple round nodules
- Caused by **Mycobacterium tuberculosis**
- Pulmonary disease
- May disseminate to other organs



# Mycobacterium Tuberculosis

- Mycobacteria: cell walls contain **mycolic acid**
- Slow growing and difficult to culture
  - Takes weeks to grow on special growth media
- Does not stain well with Gram stain
- **Acid-fast bacilli (rods)**
  - Stains with special dyes
  - TB resists decolorization with acid solvents (“acid-fast”)
  - Some other bacteria (Nocardia) also do this

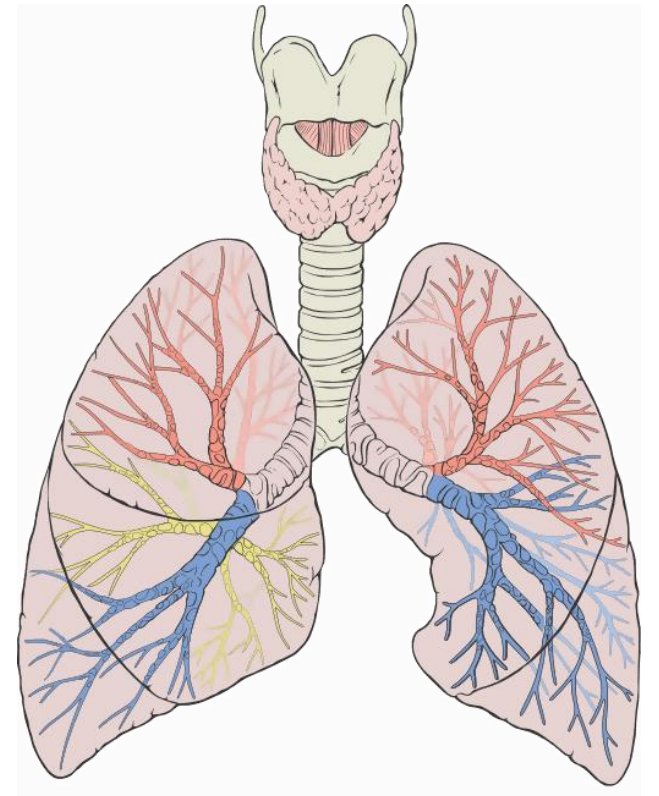
Acid Fast Bacilli



# Mycobacterium Tuberculosis

## Transmission

- **Respiratory spread** via aerosol droplets
- Commonly infects **lungs**
- Especially upper lobes (highest O<sub>2</sub> content)
- Aerosols generated by cough, sneeze, etc.
- Droplets inhaled by uninfected person
- Can spread rapidly in crowded areas
- Hospitalized patients: **airborne (respiratory) precautions**



# Mycobacterium Tuberculosis

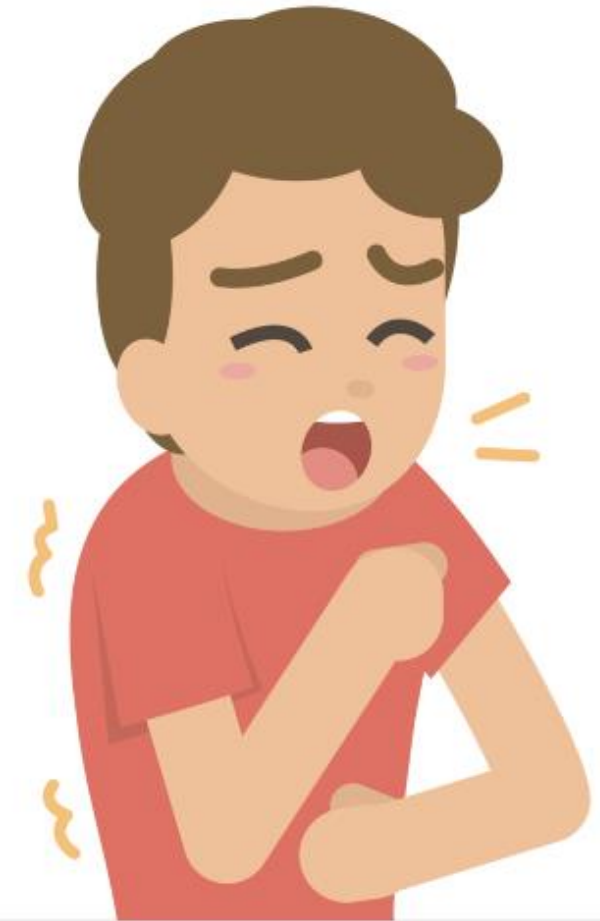
## Types of infection

- **Primary**
  - Infection on exposure
  - May be asymptomatic
  - Some patients will clear infection
- **Latent**
  - Asymptomatic chronic infection
  - Infection controlled by immune response
  - Identified through screening
  - Can be treated
- **Reactivation (active disease)**

# Primary Tuberculosis

## Clinical features

- **New infection** in a previously uninfected patient
- Often **asymptomatic** but may cause symptoms
- Symptoms mainly in children or immunosuppressed
- Gradual onset over weeks
- Fever and cough
- Pleuritic chest pain
- Fatigue, arthralgias



# Primary Tuberculosis

## Clinical features

- Chest x-ray often normal
- Classic finding is **hilar lymphadenopathy**
  - Also seen in reactivation
- Symptoms as early as 1 week after infection
- Resolves slowly over months to years

Hilar Lymphadenopathy



# Primary Tuberculosis

## Clinical features

- Most (90%) patients control infection
  - Disease heals leaving fibrosis
  - Sometimes completely clears
  - Usually enters latent phase (“walled off”)
  - Immunity develops
  - Screening tests will be positive for latent disease
- Rare (10%) patients have disseminated illness
  - More common with impaired immune response



# Disseminated Tuberculosis

- Hematogenous spread of *Mycobacterium tuberculosis*
- “Miliary:” named for appearance of “millet seeds” in lungs
- Occurs with progressive primary infection or reactivation
- Nearly any organ system can be involved
  - Bones
  - Joints
  - Liver
  - Central nervous system
  - Adrenal glands

Miliary Tuberculosis



# Disseminated Tuberculosis

## Special features

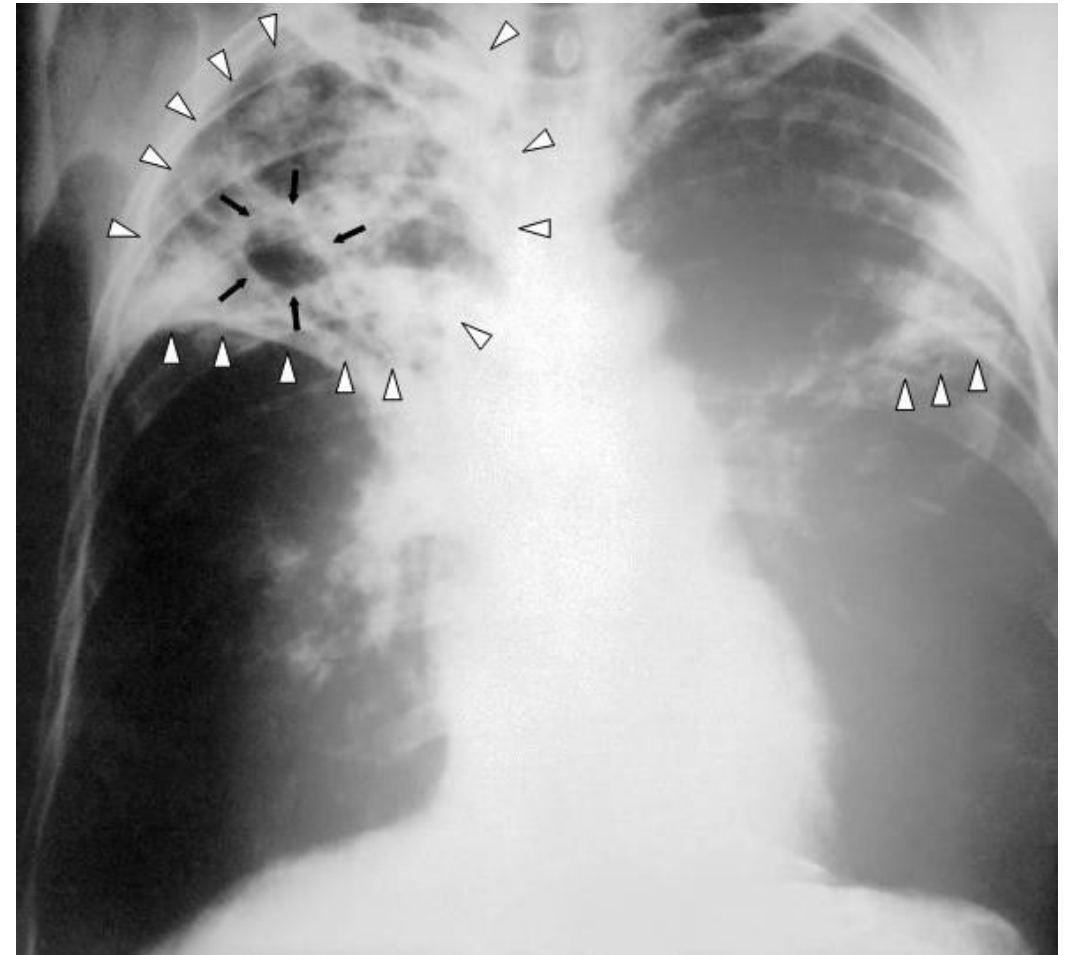
- **Pott's disease**
  - Spine infection (osteomyelitis)
  - Back pain, fever, night sweats, weight loss
- **Constrictive pericarditis**



# Reactivation Tuberculosis

- Majority of adult cases are reactivation
- Cough, weight loss, fatigue
- Fever, night sweats
- Hemoptysis
- Most cases have abnormal chest X-ray
- Upper lung lobes frequently involved
- Often lung cavitation (necrosis of tissue)
- Hilar lymphadenopathy may occur
- Disseminated disease possible

Cavitary Tuberculosis

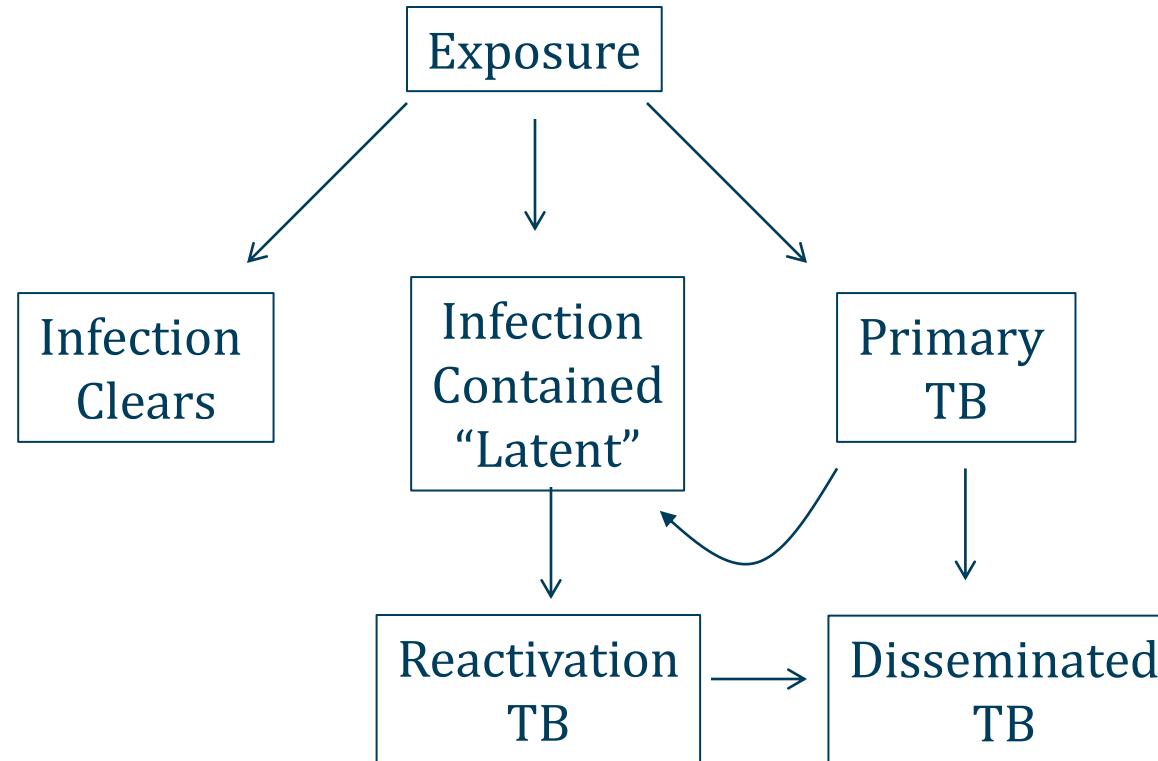


# Reactivation Tuberculosis

- Can occur in any patient with latent infection
- Increased risk with **immune compromise**
- HIV infection
- TNF- $\alpha$  inhibitors (etanercept, infliximab)
- Patients on dialysis

# Tuberculosis

## Infection summary



# Active Pulmonary Tuberculosis

## Diagnosis

- Suspicion of active disease: **obtain chest X-ray**
  - Upper lobe disease, cavitation, hilar lymphadenopathy
- Usually **three sputum samples**
- **Acid-fast smear**
- **Nucleic acid amplification (NAA) testing**
  - Highly specific (helpful if positive)
  - Lack sensitivity (false negatives)
- Mycobacterial culture
  - Takes up to 8 weeks



# Active Pulmonary Tuberculosis

## Diagnosis

- Not necessary to hospitalize solely for TB suspicion
- Outpatients: remain at home, avoid visitors, wear mask
- Inpatients: **respiratory isolation**
  - Private room
  - Negative air pressure
  - Persons entering must wear a respirator
  - Tight seal over the nose and mouth





# Active Tuberculosis

## Treatment

- Requires multi-drug regimens
- Depends on drug resistance of infection
- Drug-susceptible versus drug-resistant strains
- Initial treatment often with two months of **RIPE**
  - Rifampin
  - Isoniazid
  - Pyrazinamide
  - Ethambutol
- Followed by several months of **isoniazid and rifampin**

# Latent Tuberculosis

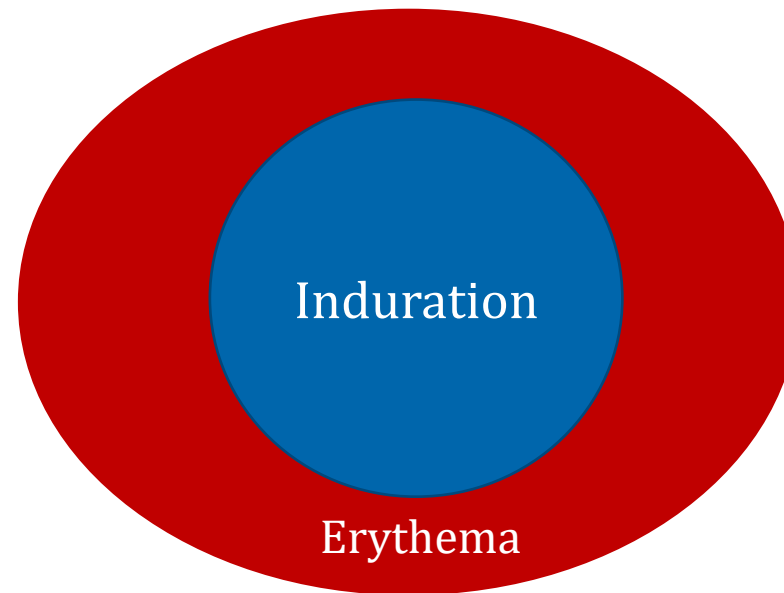
## Diagnosis

- **Tuberculin skin testing (TST)**
  - Skin injection of purified protein derivative (PPD)
  - Bacterial proteins combined with wax
  - Elicits hypersensitivity reaction in skin
  - Injection → wait 48 hours → measure diameter of skin reaction
- **Interferon-γ release assay (IGRA)**
  - Patient blood cells exposed to M. tuberculosis antigens
  - Amount of interferon-γ release measured
  - Preferred test when available
- Either test positive + negative CXR = latent disease

# Latent Tuberculosis

## PPD Interpretation

- Measure **area of induration** not surrounding erythema
- Positive test based on width of induration and patient factors



# Latent Tuberculosis

## PPD Interpretation

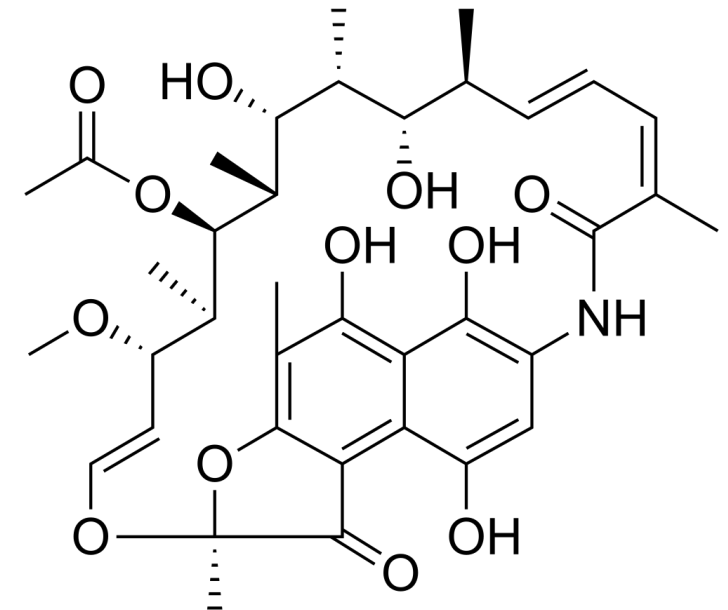
Induration	Positive Criteria
$\geq 5\text{mm}$	HIV Immunosuppressed: TNF-alpha drugs, chemo, organ transplant, glucocorticoids Recent known TB contact CXR consistent with prior TB
$\geq 10\text{ mm}$	Children < 4 Recent immigrants (< 5 years) from TB endemic areas Injection drug use Mycobacterial lab worker High risk settings: prison, nursing home, hospital, homeless shelter High risk patients: diabetes, dialysis, some malignancies, chronic malabsorption
$\geq 15\text{ mm}$	Most healthy adults and children > 4

# Latent Tuberculosis

## Treatment

- Reduce risk of reactivation
- Prior standard therapy: isoniazid (INH) daily for 9 months
- **Rifamycin-based regimens preferred**
  - Include rifampin (RIF) or rifapentine (RPT)
  - RIF daily for four months
  - INH and RIF daily for three months
  - INH and RPT weekly for three months

Rifamycin SV



# Latent Tuberculosis

## Treatment

- **Pyridoxine (b6) supplementation**
  - Given with isoniazid in some patients
  - Prevents **peripheral neuropathy**
- Further PPD testing not indicated
  - Will remain positive for life

Peripheral Neuropathy



# BCG Vaccine

- Bacille Calmette-Guérin
- Live strain of *Mycobacterium bovis*
- Used in children in areas with high prevalence of TB
- Less effective in adults
- Can create a **false positive PPD**
- IGRAs not affected by BCG vaccination
- Also used to treat **bladder cancer**





# Adult Vaccinations

Jason Ryan, MD, MPH



**Table 1** Recommended Adult Immunization Schedule by Age Group, United States, 2021

Vaccine	19–26 years	27–49 years	50–64 years	≥65 years
Influenza inactivated (IIV) or Influenza recombinant (RIV4)	1 dose annually			
Influenza live, attenuated (LAIV4)	1 dose annually			
Tetanus, diphtheria, pertussis (Tdap or Td)	1 dose Tdap each pregnancy; 1 dose Td/Tdap for wound management (see notes)			
	1 dose Tdap, then Td or Tdap booster every 10 years			
Measles, mumps, rubella (MMR)	1 or 2 doses depending on indication (if born in 1957 or later)			
Varicella (VAR)	2 doses (if born in 1980 or later)		2 doses	
Zoster recombinant (RZV)			2 doses	
Human papillomavirus (HPV)	2 or 3 doses depending on age at initial vaccination or condition	27 through 45 years		
Pneumococcal conjugate (PCV13)	1 dose			1 dose
Pneumococcal polysaccharide (PPSV23)	1 or 2 doses depending on indication			1 dose
Hepatitis A (HepA)	2 or 3 doses depending on vaccine			
Hepatitis B (HepB)	2 or 3 doses depending on vaccine			
Meningococcal A, C, W, Y (MenACWY)	1 or 2 doses depending on indication, see notes for booster recommendations			
Meningococcal B (MenB)	2 or 3 doses depending on vaccine and indication, see notes for booster recommendations			
	19 through 23 years			
Haemophilus influenzae type b (Hib)	1 or 3 doses depending on indication			

# Major Types of Vaccines

- Toxoid vaccines
- Conjugate vaccines
- Killed (inactivated) viral vaccines
- **Live, attenuated viral vaccines**
  - Weakened viral vaccines
  - Replicate poorly inside the body
  - MMR, varicella, rotavirus
  - Others: oral polio, intranasal influenza
  - **Cannot be given to immunocompromised**
  - **Not used in pregnancy**

**Rs are Alive**  
**Varicella**  
**Intranasal Flu**

# Influenza Vaccine

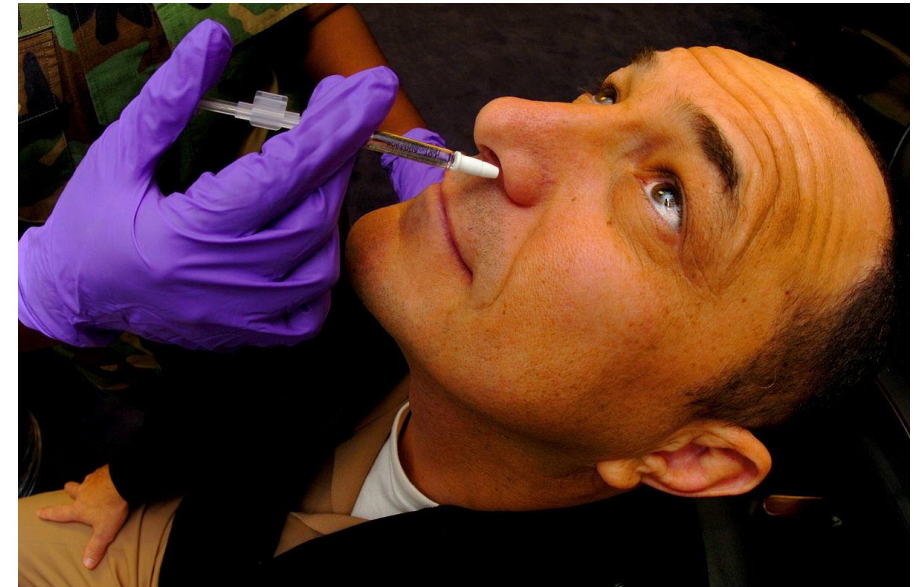
- Influenza A and B viruses
- Most are quadrivalent
  - Two strains of influenza A and two strains of influenza B
- Updated each year with new strains
  - Contain strains expected in flu season (fall/winter)
- Given annually to children  $\geq 6$  months old
- **All adults should receive each year**



Public Domain

# Influenza Vaccine

- **Inactivated influenza vaccines (IIV)**
  - Intramuscular or intradermal injection
  - Only contraindication: prior severe allergic reaction to vaccine
- **Live attenuated influenza vaccine (LAIV)**
  - Licensed in 2012
  - Administered intranasally
  - Must be healthy and nonpregnant
  - Only ages 2 through 49
  - No thimerosal
  - May contain residual amounts of egg protein



Public Domain

# Influenza Vaccine

## Cautions

- **Sensitivity to thimerosal**
  - Preservative used in multi-dose vials
  - Can use single-dose vials without thimerosal
- Eggs
  - Most flu vaccines manufactured using eggs
  - Contain small amounts of egg protein ovalbumin
  - Amount of egg proteins very low in modern vaccines
  - Studies indicate severe allergic reactions unlikely
  - Patients with allergies **can receive influenza vaccine**



Public Domain

# Tetanus Immunization

- DTaP given to children
  - Vaccination against tetanus, diphtheria and pertussis
  - Contains DT: tetanus and diphtheria toxoid
  - Also acellular pertussis (aP)
- **Adults: TdaP or Td**
  - Td = tetanus toxoid with reduced diphtheria toxoid
  - Used as a booster
  - Recommended at 10-year intervals throughout life



# Tetanus Immunization

## Puncture wounds

- **Clean, minor wound**
  - Td or TdaP if last dose  $\geq 10$  years ago
- **Dirty or severe wound**
  - Td or TdaP if last dose  $\geq 5$  years ago
- **Tetanus immune globulin**
  - Dirty or severe wounds
  - If  $\leq 3$  doses or unknown immunization status



# Varicella

- Prevents chickenpox caused by varicella-zoster virus
- **Live, attenuated virus vaccine** licensed in 1995
- Given to children at 12 months and 4 years
- Indicated in adults **without evidence of immunity**
  - Not immunized as children and did not have chickenpox
  - Lab testing for immunity may be performed
- Post-exposure prophylaxis in non-immune: **vaccination**
  - Early post-exposure vaccination reduces risk of illness

Chickenpox



# Herpes Zoster

## Shingles

- Reactivation of latent varicella-zoster virus
  - Painful vesicular rash along dermatomes
  - Common in older patients (↓ immunity)
- Vaccine limits risk of reactivation and severity of symptoms
- Indicated in **adults age  $\geq 50$  years**
- Zoster vaccine live (ZVL)
  - Contraindicated in some patients
- Recombinant zoster vaccine (RZV)



# HPV Vaccine

## Human Papilloma Virus

- Sexually-transmitted infection
- HPV types 16 and 18: most cervical cancers
- HPV types 6 and 11: anogenital warts
- 9-valent vaccine available since 2016 in US
  - Types 6, 11, 16, 18, 31, 33, 45, 52, and 58
- ACIP Guidelines
  - **Ages 11 to 12 years**
  - Females (1A) and males (1B)

## HPV

### Cervical intraepithelial neoplasia



Lee, Makin, Mtengezo, and Malata

# HPV Vaccine

## Catch up vaccination

- Can be administered up to **age 45**
  - Stronger recommendation up to age 26 per CDC
  - Ages 27 to 45 based on risk of HPV infection
- **If start before age 15 years**
  - Two doses at 0 and 6 to 12 months
- **If start age 15 or later**
  - Three doses at 0, 2 and 6 months



# Pneumococcal Vaccination

- Streptococcus pneumoniae
- PCV13
  - Polysaccharides from 13 serotypes
  - Effective in infants and young children
- **PPSV23**
  - Contains 23 pneumococcal polysaccharides
  - Does not elicit immune response in children under 2
  - Used in adults

Pneumonia



# Pneumococcal Vaccination

## Major Indications

- PPSV23 given to **all adults  $\geq 65$  years**
- PCV13:  $\geq 65$  with risk factors for severe disease
  - Immunocompromise (HIV, advanced CKD)
  - Splenic removal or dysfunction
  - Cochlear implant or CSF leak ( $\uparrow$  risk meningitis)
  - Prior pneumococcal meningitis



# Pneumococcal Vaccination

Ages 19 to 64 years

- Certain high risk groups: **single dose PPSV23**
  - Chronic heart, lung or liver disease
  - Poorly controlled diabetes
  - Current cigarette smoking
  - Alcohol use disorder
- PCV13 followed by PPSV23
  - Risk of severe infection
  - Same groups as  $\geq 65$

# Meningitis Vaccination

- *Neisseria meningitidis*
- **MenACWY vaccine**
  - Quadrivalent vaccine: types A, C, W, and Y
  - Routine for children ages 11 to 12
- **MenB**
  - Monovalent vaccine against type B
  - Newer vaccine
  - Given to certain high risk groups



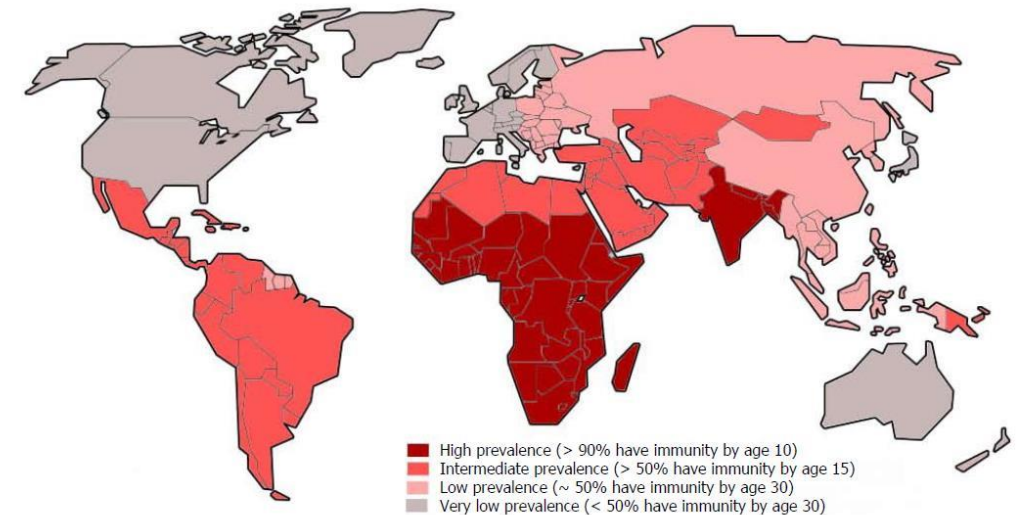
# Meningitis Vaccination

## Adult booster doses

- **MenACWY vaccine** – usually every 5 years while at risk
  - Splenic dysfunction
  - HIV
  - At risk due to outbreak
  - First-year college students living in residence halls
  - Military recruits
  - Travel to endemic areas
  - Microbiologists
- **MenB vaccine** - 1 year after series completion then every 2 to 3 years
  - Splenic dysfunction and complement deficiencies
  - Microbiologists
  - Exposed during outbreak

# Hepatitis A Vaccination

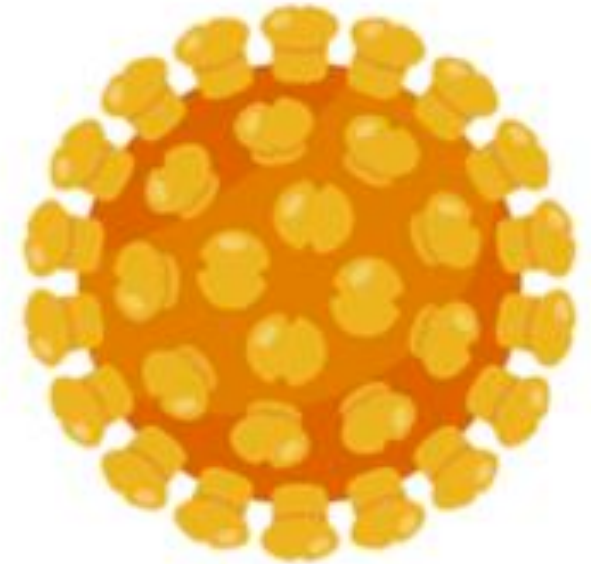
- Self-limited viral hepatitis
- More common outside US
- Routine vaccination in children
- Adult vaccination if not vaccinated as a child
  - Chronic liver disease
  - HIV
  - Travel to certain geographic areas
  - Persons experiencing homelessness
  - Persons who use injection drugs
  - Men who have sex with men (MSM)
  - Occupational risk for infection



Source: Jacobsen KH. Globalization and the Changing Epidemiology of Hepatitis A Virus. Cold Spring Harb Perspect Med 2018 Mar 2 PMID: 29500305  
Prevalence of hepatitis A

# Hepatitis B Vaccination

- May cause acute or chronic hepatitis
- Recombinant vaccine
  - Hepatitis B surface antigen (HBsAg)
  - Produced through recombinant DNA in yeast cells
- Routine vaccination for children
- Adult vaccination if not vaccinated as a child
  - At risk for infection by sexual exposure or injection drugs
  - Advanced chronic kidney disease
  - Chronic liver disease
  - HIV



**Hepatitis B**