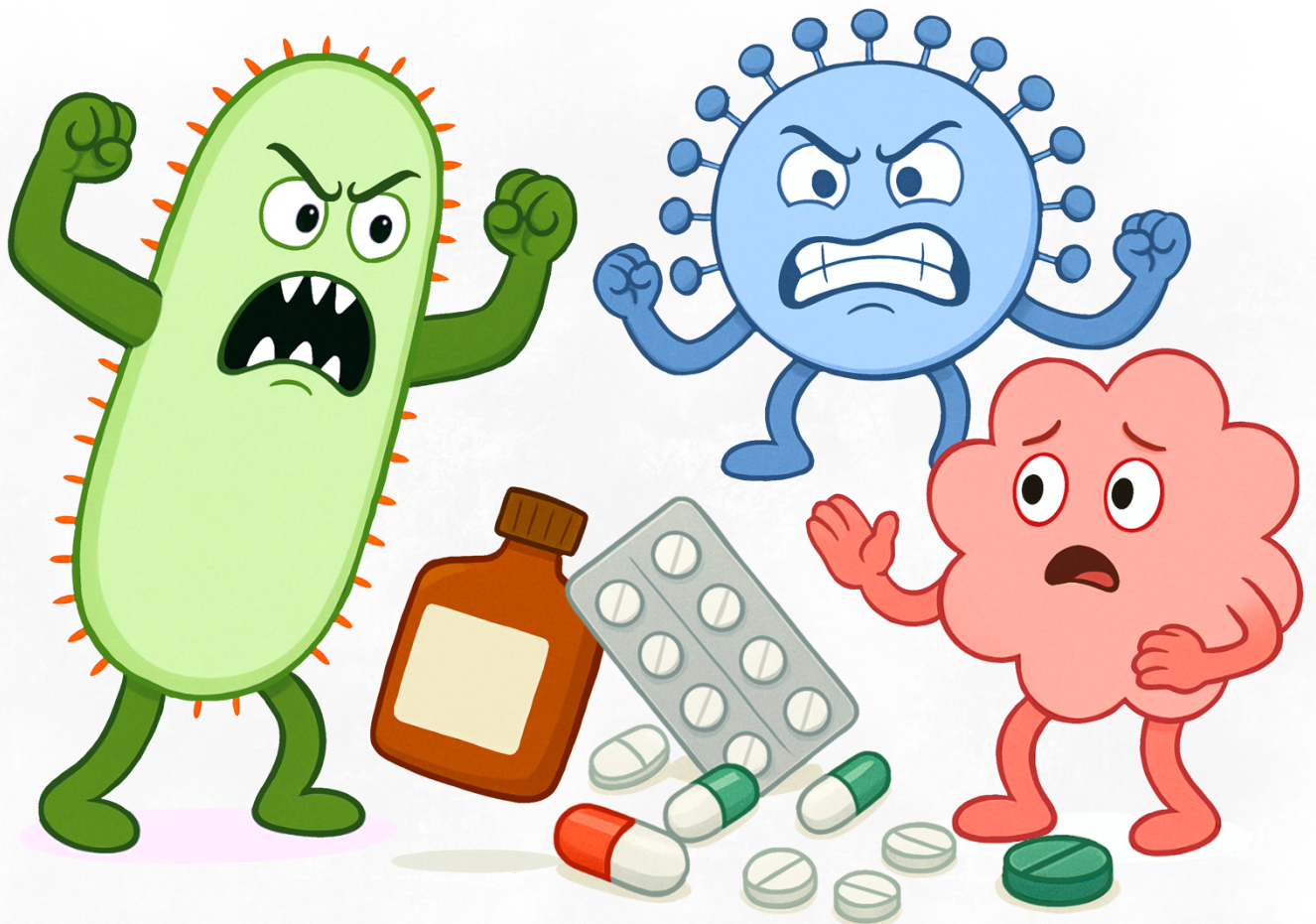




Pharmacology Exam 3

Anna Emilie Høifødt • Hanna Bentsen



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Authors

Anna Emilie Høifødt
Hanna Bentsen

Editors

Marie Rishovd
Anna Emilie Høifødt
Hanna Bentsen

Illustrator:

Anna Edine Lind Jodalen

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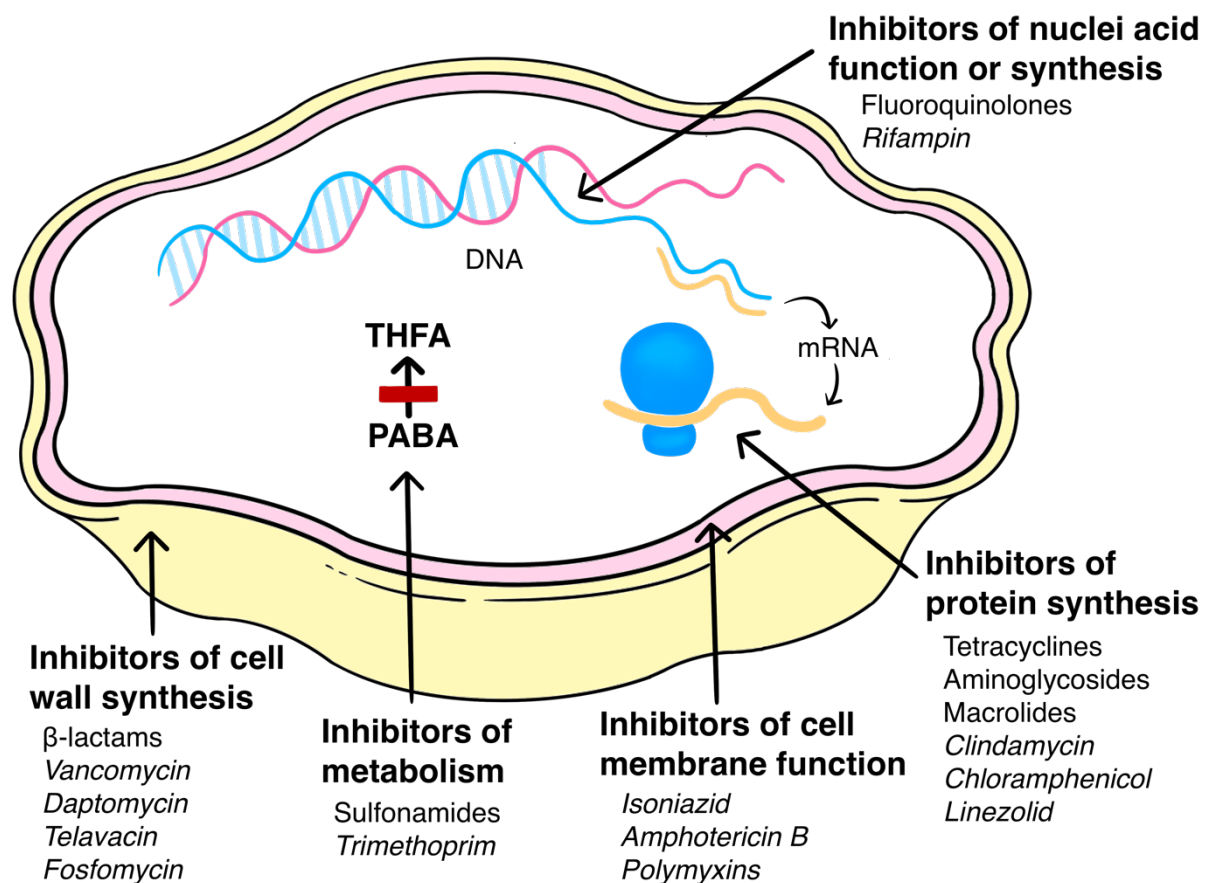
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Section 1 – Antibiotics

- 1.1 – General About Antibiotics
- 1.2 – Cell Wall Inhibitors
- 1.3 – Inhibitors of Bacterial Protein Synthesis
- 1.4 – Antifolate Drugs, Quinolones and Others
- 1.5 – Antimycobacterial Drugs
- 1.6 – Test Yourself

1.1 - General About Antibiotics

- Antibiotics are different drugs aimed at fighting bacterial infections
- Different types of antibiotics attack bacteria in different ways



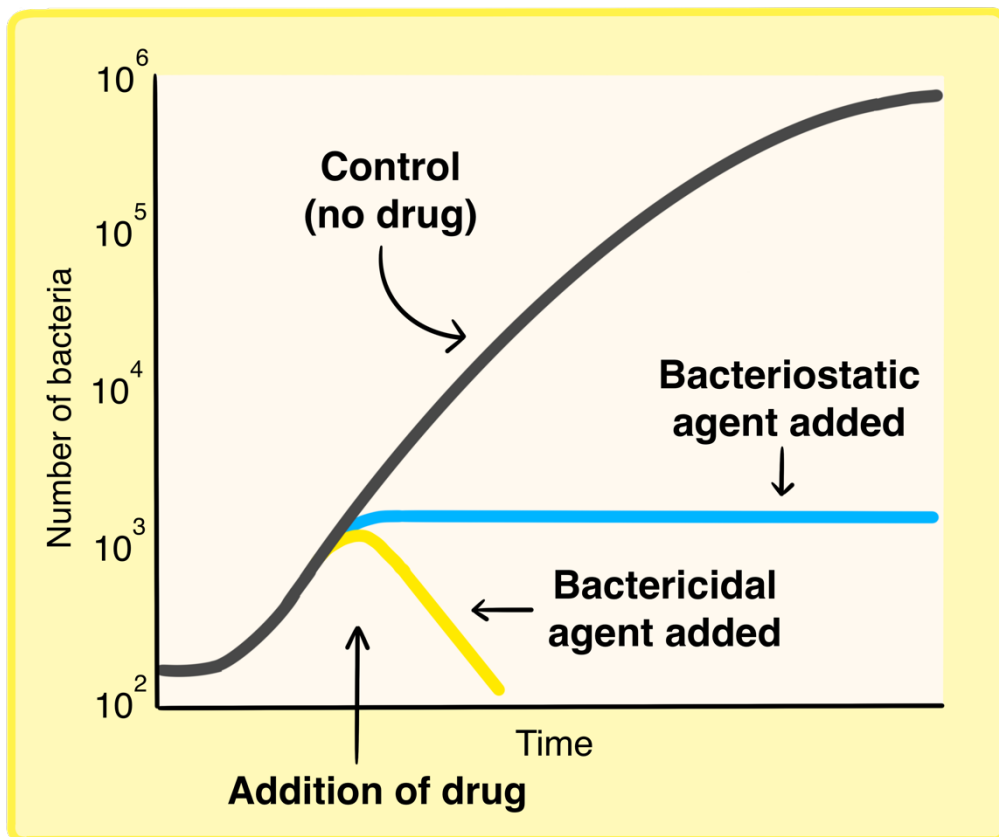
- Antibiotics are either bacteriostatic or bactericidal

Bacteriostatic drug

The drug prevents the growth of bacteria
i.e., keeps the bacteria in a stationary phase of growth

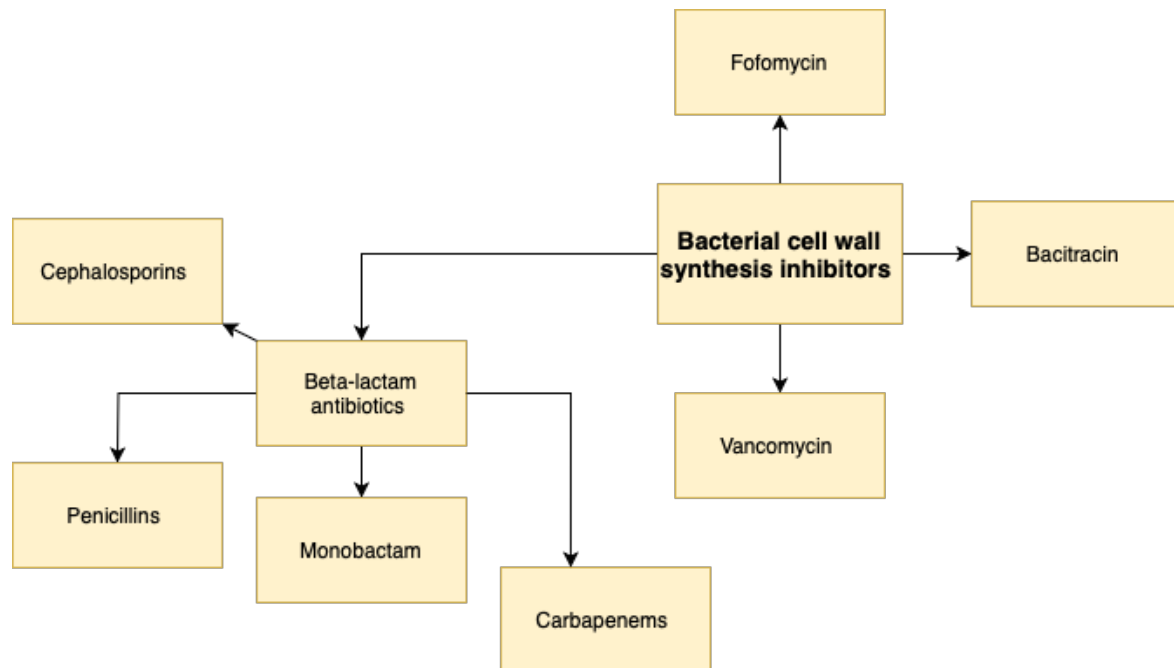
Bactericidal drug

The drug kills the bacteria



1.2 - Cell wall inhibitors

- Cell wall inhibitors work by inhibiting the penicillin-binding proteins (PBPs)
- PBPs are responsible for cross-bridging the bacterial cell wall peptidoglycans



1.2.1 - Penicillin

- Penicillins is a class of antibiotics that inhibit the bacterial cell wall synthesis
- They are beta-lactam antibiotics. This means that they inhibit the bacterial enzymes known as the penicillin-binding-proteins (PBPs)
- Penicillins can be grouped into their antimicrobial activity

I. Narrow spectrum antibiotics

- Are active against many gram-positive cocci
- Penicillin G is given by injection (IV or IM) because it is not stable in stomach acid
- Penicillin V is taken by mouth (oral) because it can survive stomach acid
- Both are used to treat similar bacterial infections, but the main difference is how they are given due to their stability in the stomach

Narrow-spectrum penicillin	Route of administration	Route of elimination	Infections	Major pathogens
Penicillin G (benzylpenicillin)	IM IV	Renal	Syphilis Endocarditis Meningitis Pneumonia Various others	Treponema pallidum Viridians streptococci, enterococci Meningococci Pneumococci Streptococci
Penicillin V (phenoxymethylpenicillin)	Oral	Renal	Pharyngitis	Streptococcus pyogenes

CLINICAL CORRELATION

- Penicillins are widely distributed throughout the body's organs and tissues, but they normally do not enter the CNS well
- However, when the meninges are inflamed, the blood-brain barrier becomes more permeable, allowing penicillin to penetrate the CSF
- In such cases, penicillin can be given IV to effectively treat bacterial meningitis

II. Penicillinase-resistant penicillins

- Some bacteria express beta-lactamase (penicillinase) which is an enzyme that inhibit beta-lactam antibiotics
- The first penicillinase-resistant antibiotic was called Methicillin
- Staphylococci that are resistant to these penicillins are called Methicillin-resistant Staphylococcal aureus (MRSA)

Penicillinase-resistant penicillins	Route of administration	Route of elimination	Infections	Major pathogens
Dicloxacillin	Oral	Renal	Osteomyelitis Endocarditis Pneumonia Skin and soft tissue infections	Staphylococcus aureus
Nafcillin	Oral Parenteral	Biliary		

CLINICAL CORRELATION

Cellulitis

- Dicloxacillin is the first-line antibiotic to treat cellulitis
- Cellulitis is an inflammation of the skin and the underlying tissues
- Dicloxacillin is often preferred because cellulitis is commonly caused by staphylococcus aureus

III. Extended spectrum penicillins

- Extended spectrum penicillins include aminopenicillins (amoxicillin and ampicillin) and antipseudomonal (piperacillin)

CLINICAL CORRELATION

Infectious COPD exacerbation

- Most COPD exacerbations are caused by respiratory tract infections
- Intravenous ampicillin is part of the first-line treatment for the infection, combined with prednisolone and ipratropium/salbutamol for symptom relief
- After hospitalization or in case of clinical improvement the antibiotic can be changed to oral treatment with amoxicillin or amoxicillin with clavulanate for severe cases

IV. Beta-lactamase inhibitors

- Clavulanate, sulbactam and tazobactam are all beta-lactamase inhibitors that can be added to the extended-spectrum penicillins to treat infections caused by organisms that produce penicillinase (beta-lactamase)
- These drugs have no antimicrobial activity by themselves

Extended spectrum penicillins	Route of administration	Route of elimination	Infections	Major pathogens
Amoxicillin ± clavulanate	Oral	Renal	Otitis URTI Pneumonia Skin and soft tissue infections Urinary tract infections	Pneumococci Streptococci Staphylococci Haemophilus influenzae Moraxella catarrhalis E. Coli
Ampicillin ± sulbactam	Oral Parenteral	Renal Biliary	Meningitis Decubitus and diabetic foot ulcers Endocarditis Lyme disease	Listeria Monocytogenes Gram-positive and anaerobic organisms Streptococci, enterococci Borrelia burgdorferi
Piperacillin ± tazobactam	Parenteral	Renal	Intraabdominal infections Skin and soft tissue infections Pneumonia	Aerobic and anaerobic organisms, including Pseudomonas aeruginosa

¹URTI = upper respiratory tract infection

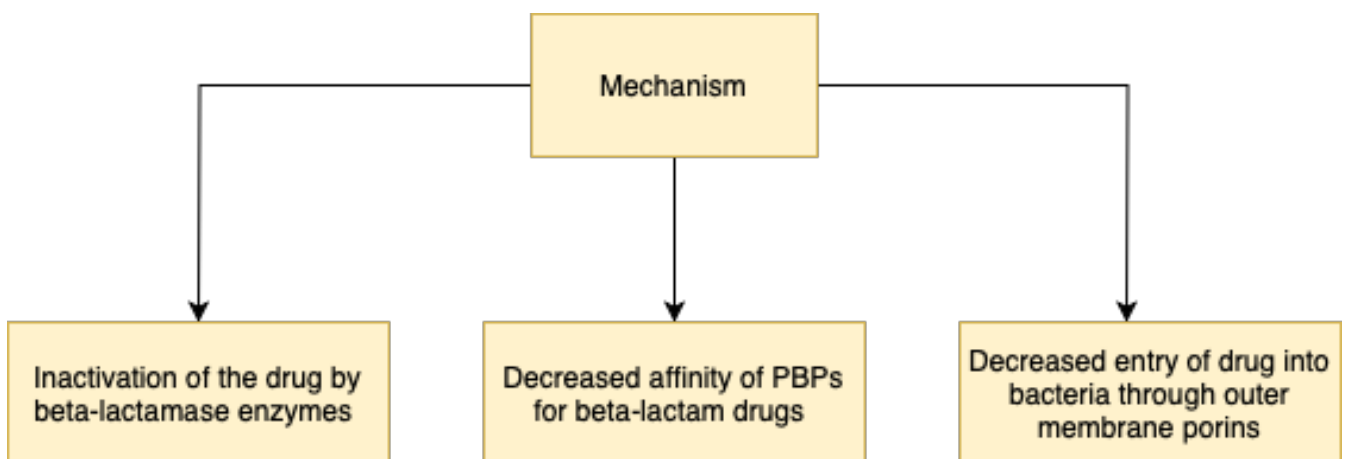
CLINICAL CORRELATION

Piperacillin + tazobactam

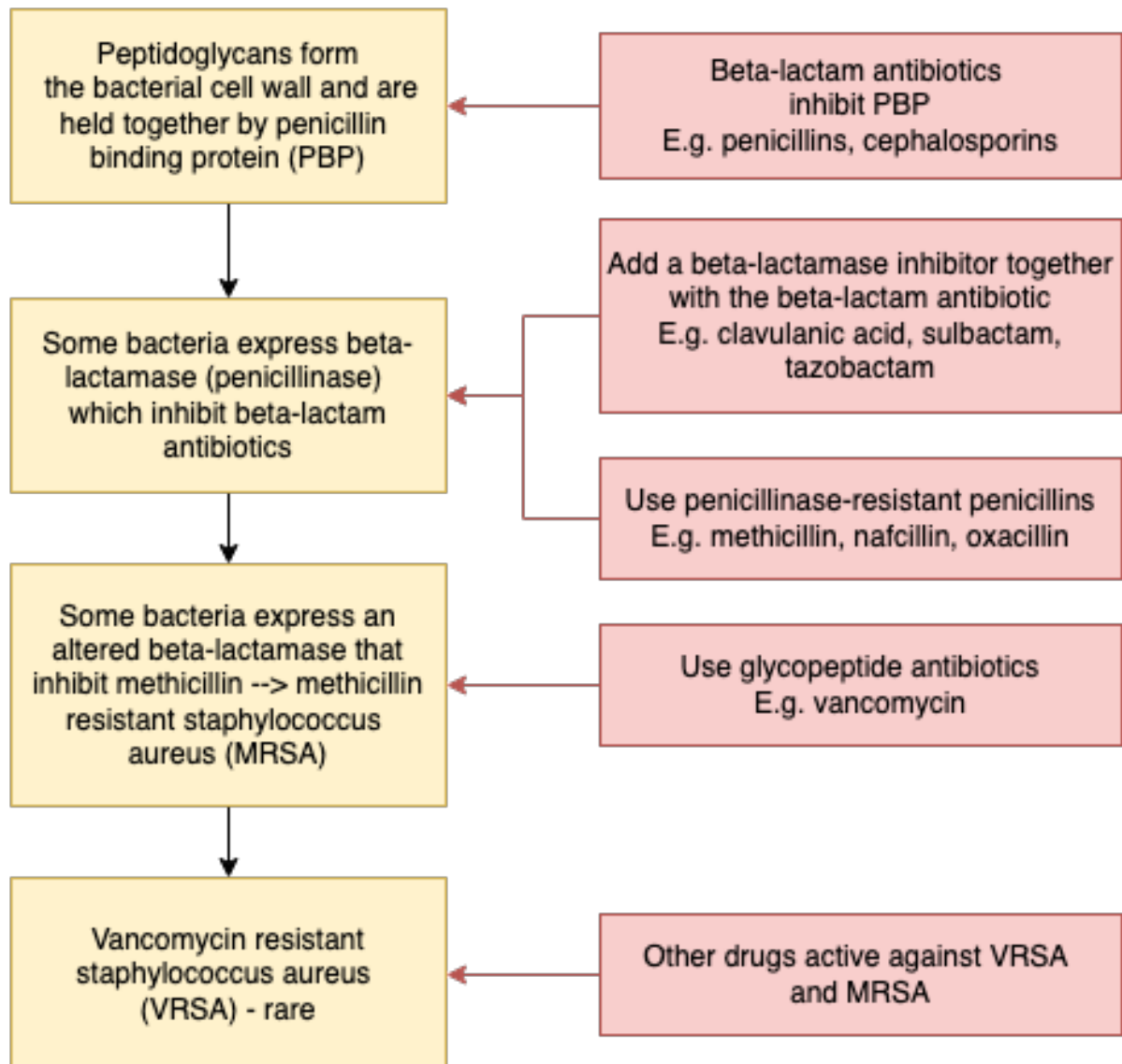
- This combination is often used in hospitals for severe infections that cannot be treated with regular penicillin or other antibiotics
- Piperacillin is rarely used alone

V. Bacterial resistance

- There are in general three different mechanisms in which bacteria exert bacterial resistance to beta-lactam antibiotics



- A clinical approach to bacterial resistance



VI. Side effects

- Penicillins are a common cause of drug-induced hypersensitivity reactions
- Drug-induced hypersensitivity reactions can occur when penicillin is degraded to penicilloic acid
- This can lead to hives or worst-case anaphylactic shock
- Ampicillin is known to cause a maculopapular rash in patients with certain viral illnesses such as mononucleosis

1.2.2 – Cephalosporins

- Cephalosporins are beta-lactam inhibitors
- Compared to penicillins, they exhibit greater resistance to beta-lactamases and has a broader antimicrobial spectrum
- Cephalosporins are divided into three different generations based on differences in their antimicrobial spectrum
- Subsequent generations of cephalosporins have increased activity against gram-negative bacilli and less activity against some species of gram-positive cocci

I. First-generation cephalosporins

First generation cephalosporins	Route of administration	Route of elimination	Infections	Major pathogens
Cefazolin	Parenteral	Renal	Perioperative prophylaxis	Staphylococci E. Coli
Cephalexin	Oral	Renal	Skin and soft tissue infections	Streptococci Staphylococci

CLINICAL CORRELATION

Prophylactic antibiotic treatment

- Cefazolin is commonly used as antibiotic prophylaxis prior to many abdominal surgeries.
- For example, a single intravenous dose of cefazolin is typically administered 30 minutes before a cesarean section to reduce the risk of postoperative infection.

II. Second-generation cephalosporins

Second-generation cephalosporins	Route of administration	Route of elimination	Infections	Major pathogens
Cefotetan	Parenteral	Renal	Intraabdominal, gynecological and biliary infections	Aerobic organisms Anaerobic organisms
Cefoxitin	Parenteral	Renal	Respiratory tract Skin and soft tissue	Pneumococci H. influenzae M. Catarrhalis
Cefprozil	Oral			
Cefuroxime	Oral Parenteral			

III. Third-generation cephalosporins

- Commonly used to treat infections caused by gram-negative bacteria

Third-generation cephalosporins	Route of administration	Route of elimination	Infections	Major pathogens
Ceftriaxone	Parenteral	Biliary	Gonorrhea UTIs Otitis Meningitis Pneumonia Lyme disease	Gonococci Pneumococci Meningococci B. burgdorferi H. influenzae Other gram-negative organisms
Ceftazidime	Parenteral	Renal	UTIs Pneumonia Others	P. aeruginosa Other gram-negative bacteria
Cefdinir	Oral	Renal	Similar to above mentioned	Similar to above mentioned

¹UTI = urinary tract infection

CLINICAL CORRELATION

Gonorrhea

A single intramuscular dose of 1 g ceftriaxone is administered for the treatment of gonorrhea

CLINICAL CORRELATION

Bacterial meningitis

- Cefotaxime is another third-generation cephalosporin used in the treatment of bacterial meningitis

VI. Fourth- and advanced generation cephalosporins

Advanced generation cephalosporins	Route of administration	Route of elimination	Infection	Major pathogens
Cefepime	Parenteral	Metabolized	Intraabdominal infections UTIs Pneumonia Skin and soft tissue infections	Drug-resistant gram-negative bacilli
Ceftaroline	Parenteral (IV)	Renal	Community-acquired pneumonia Skin and soft tissue infections	MRSA Drug-resistant pneumococci

VII. – Bacterial resistance and side effects

- Bacteria require resistance through the same three mechanisms as penicillins, but they are more resistant to beta-lactamases than penicillins
- Cephalosporins cause little toxicity, although some elicit hypersensitivity reactions
- The incidence of hypersensitivity reactions with cephalosporins is lower than with penicillin. However, there is some cross-reactivity to penicillin allergy

1.2.3 – Others

Drug	Route of administration	Route of elimination	Infection	Major pathogens	Side effects
Aztreonam (monobactam)	Parenteral	Metabolized	UTIs Gynecological, intraabdominal, skin, lung and other infections	Aerobic Gram-negative bacilli P. aeruginosa	Hypersensitivity reactions
Carbapenems	Parenteral	Renal	Intraabdominal infections Pneumonia Meningitis Febrile neutropenia Sepsis	Aerobic Anaerobic Drug-resistant gram-negative bacilli	Hypersensitivity reactions
Vancomycin	Oral Parenteral	Renal	Bone and joint Skin and soft tissue Pneumonia Sepsis Endocarditis	MRSA Enterococci	Nephrotoxicity Ototoxicity Vestibular dysfunction (ataxia, vertigo, nystagmus, and nausea)

Fosfomycin	Oral	Renal	Lower urinary tract infections	E. coli Enterococcus faecalis	Diarrhea
Bacitracin	Topical	Not applicable	Skin and eye infections	Staphylococci Streptococci	Nephrotoxic

CLINICAL CORRELATION

Carbapenems

- These are powerful, broad-spectrum beta-lactam antibiotics used when other antibiotics are not effective
- Used as a last resort against multi-drug-resistant infections

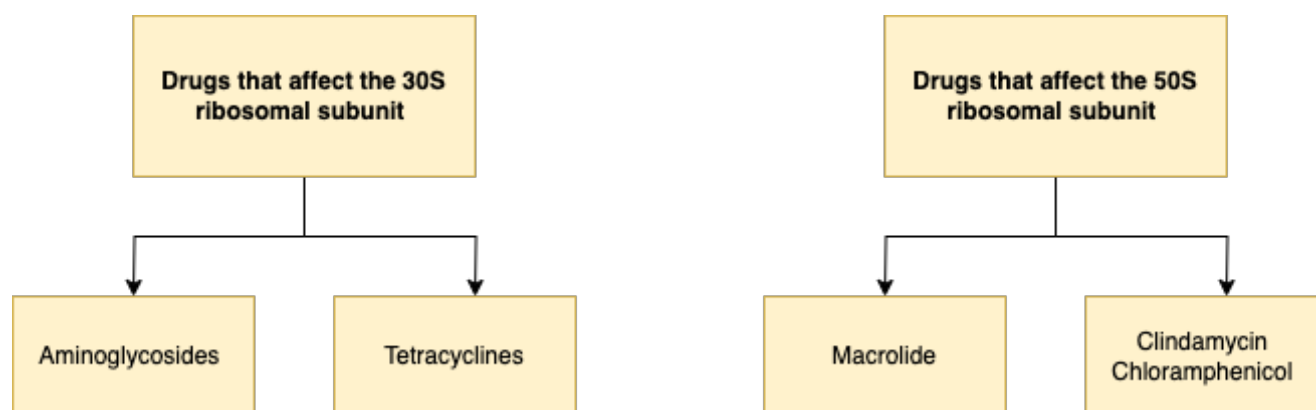
CLINICAL CORRELATION

Clostridium difficile

- Oral vancomycin is an antibiotic used to treat infections caused by clostridium difficile
- This infection causes severe diarrhea and abdominal pain, often associated with prior antibiotic treatment

1.3 – Bacterial protein synthesis inhibitors

- These antibiotics target the bacterial (prokaryotic) protein synthesis
 - The ribosome in prokaryotes is composed of a 30S subunit and a 50S subunit
 - In contrast, the ribosome in eukaryotes is composed of a 40S subunit and a 60S subunit.
- Therefore, these drugs have little effect on the protein synthesis of mammals and other animals



1.3.1 – Aminoglycosides

- Inhibit the 30S ribosomal subunit
- Aminoglycosides exhibit concentration-dependent killing. This means that the rate and extent of microorganism killing are a function of antibiotic concentration. The higher concentration of antibiotic the more killing of bacteria.
- These drugs also have a high post-antibiotic effect
- Hence, aminoglycosides are sometimes administered as a large single daily dose

Drugs	Route of administration	Route of elimination	Infection and major pathogens	Side effects
Amikacin	IV	Renal	Infective endocarditis Aerobic gram-negative bacilli Pseudomonas aeruginosa	Nephrotoxicity Ototoxicity
Gentamicin	IV Topical	Renal		
Tobramycin	IV Topical	Renal		
Neomycin	Topical	Not applicable	Superficial eye infections Otitis externa Skin infections	Same as above Most nephrotoxic of the aminoglycosides
Streptomycin	IM	Renal	Plague Tularemia Drug-resistant tuberculosis	Like the above mentioned

CLINICAL CORRELATION

Aminoglycosides

- The amino groups in this drug are ionized in bodily fluids
- For this reason, the aminoglycosides are poorly absorbed from the gut and must be administered parenterally
- Occasionally they are administered orally to treat neonatal necrotizing enterocolitis

CLINICAL CORRELATION

Gentamicin

- In case of suspected sepsis with unknown pathogen empirical antibiotics should be administered within 1 hour of admission
- In Norway, first-line is benzylpenicillin and a single dose of gentamicin IV
- If gentamicin should be administered more than once, a gentamicin serum level should be ordered to consider the next dosage
 - Be aware of kidney failure before administering this drug!

1.3.2 – Tetracyclines

- Inhibit the 30S ribosomal subunit
- Tetracyclines bind to divalent and trivalent cations such as calcium, aluminum, and iron. As a result, their bioavailability is reduced when taken with food or medications containing these ions

Drug	Route of administration	Route of elimination	Infection	Adverse effects
Doxycycline	Oral IV	Fecal Renal	Lyme disease Rocky mountain spotted fever Ehrlichiosis	Nephrotoxicity Hepatotoxicity Photosensitivity Discoloration of teeth in pregnant women and children <8 years
Minocycline	Oral IV	Biliary Renal	Granuloma inguinal Brucellosis Cholera	
Tetracycline	Oral	Renal	Relapsing fever Chlamydial urethritis Acne MRSA	
Tigecycline	IV	Biliary Fecal Renal	Skin and soft tissue infections with MRSA Intraabdominal infections Community acquired pneumonia	

CLINICAL CORRELATION

Chlamydial infection

Doxycycline is the first-line treatment for genital chlamydial infections

1.3.3 – Macrolides

- Inhibit the 50S ribosomal subunit
- Erythromycin and clarithromycin inhibit cytochrome P450 3A4. This can lead to increased plasma concentration of many drugs metabolized by this enzyme.

Drug	Route of administration	Route of elimination	Infection and major pathogens	Side effects
Azithromycin	Oral IV	Biliary	Respiratory tract infections Gonorrhea in combination with ceftriaxone	Stomatitis Heartburn Nausea Anorexia GI discomfort
Clarithromycin	Oral	Biliary Renal		
Erythromycin	Oral Topical	Biliary	Respiratory tract infections with strep, pneumococci, Legionella pneumophila, Mycoplasma pneumoniae, Chlamydia pneumonia	

¹Stomatitis = inflammation of the mouth

CLINICAL CORRELATION

Mycoplasma pneumonia

- Mycoplasma is a common cause of atypical pneumonia. It often presents with few symptoms and a dry cough
- First line treatment is oral clarithromycin

1.3.4 – Clindamycin, Chloramphenicol and Quinupristin-Dalfopristin

- Inhibit the 50S ribosomal subunit

Drug	Route of administration	Route of elimination	Infection and major pathogens	Side effects
Clindamycin	Oral IV Topical	Hepatic metabolism Renal, biliary and fecal excretion	Streptococcal and staphylococcal, and anaerobic infections	Superinfection with <i>C. difficile</i> → diarrhea
Chloramphenicol	IV	Hepatic metabolism Renal excretion	Meningitis Brain abscess	Aplastic anemia
Quinupristin-dalfopristin	IV	Hepatic metabolism Biliary excretion	Skin and soft tissue infections with staph or strep pyogenes Infections with enterococcus faecium	Inflammation of veins at infusion site Arthralgia Myalgia Diarrhea

CLINICAL CORRELATION

Bacterial conjunctivitis
Topical chloramphenicol is used to treat bacterial conjunctivitis

1.3.5 – Other protein synthesis inhibitors

Drug	Route of administration	Route of elimination	Infection or major pathogen	Side effects
Linezolid	Oral IV	Hepatic metabolism Renal excretion	Infections with vancomycin-resistant <i>E. faecium</i> , streptococci, and MRSA	Thrombocytopenia, neutropenia and anemia
Mupirocin	Topical	Not applicable	Impetigo from streptococci, staphylococci	

1.3.6 – Bacterial resistance

Mechanism of resistance	Example
Decreased accumulation of the drug by bacteria	Decreased uptake of aminoglycosides via porins in the bacterial membrane
Decreased binding of the drug	Decreased binding of macrolides to the 50S ribosomal subunit
Inactivation of the drug by bacterial enzymes	Inactivation aminoglycosides by adenyase, acetylase and phosphorylase enzymes

1.4 – Antifolate drugs

- These drugs are used to treat bacterial and protozoal infections, as well as some forms of cancer
- They do this by inhibiting the synthesis of folate in cells

Drug	Mechanism of action	Route of administration	Clinical use	
Silver sulfadiazine	Inhibits formation of dihydrofolate and subsequently the synthesis of folate	Topical	Burn infections, other skin infections	
Sulfacetamide		Topical ocular	Ocular infections	
Sulfamethoxazole		Oral		In combination: UTI Prostatitis
Trimethoprim	Inhibits dihydrofolate reductase and the formation of tetrahydrofolate	Oral	UTIs	Pulmonary infections caused by Pneumocystis Jiroveci and nocardia species

CLINICAL CORRELATION

Trimethoprim-sulfamethoxazole (Bactrim)

- This drug combination is commonly used to treat UTIs
- It is also used in high doses to treat Pneumocystis Jiroveci pneumonia, which can be seen in AIDS and immunocompromised patients

I. Side effects

Drug	Side effects
Sulfonamides (sulfadiazine, sulfacetamide, sulfamethoxazole)	Skin rash: Steven-Johnsen syndrome in severe cases Crystalluria GI upset Headaches Hepatitis In glucose-6-phosphate deficiency can cause hemolytic anemia
Trimethoprim-sulfamethoxazole	Skin rash GI upset Hepatitis Hematologic disorders

1.5 – Fluoroquinolones

- Ciprofloxacin is primarily active against gram-negative bacteria, but newer agents like levofloxacin are active against both gram-negative and gram-positive bacteria
- Fluoroquinolones exhibit concentration-dependent killing
- These drugs are bactericidal, meaning this drug kills bacteria

Drug	Mechanism	Route of administration	Route of elimination	Clinical uses	Side effects
Ciprofloxacin	Inhibition of DNA gyrase	Oral IV Topical	Renal excretion	Intraabdominal infections Bacterial diarrhea UTIs Infection of prostate, bone, joints and eyes Anthrax exposure	Tendonitis and tendon rupture Peripheral neuropathy Hypo- and hyperglycemia Seizures Phototoxicity QT interval elongation Restlessness, anxiety, headaches, nausea
Levofloxacin		Oral IV		Bronchitis Community-acquired-pneumonia Infections of urinary tract, prostate, skin and eye	
Norfloxacin		Oral		UTIs	
Moxifloxacin		Oral IV		Community-acquired pneumonia Sinusitis Bronchitis Tuberculosis	
Gemifloxacin		Oral			

Gatifloxacin		Topical ocular		Bacterial conjunctivitis	
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I. Pharmacokinetics and side effects

- The fluoroquinolones also bind to divalent and trivalent cations, like calcium, magnesium and iron, and should not be taken within 2 hours of ingesting foods and drinks with these cations
- Due to many side effects, these drugs should only be used when alternative drugs are not effective or available

1.6 – Other antibacterial drugs

- Nitrofurantoin is rapidly excreted in the urine and is therefore limited to treatment of lower urinary tract infections
- Rifaximin is not absorbed from the gut, and is therefore a suitable agent to treat traveler's diarrhea

Drug	Route of administration	Route of elimination	Clinical use	Side effects
Nitrofurantoin	Oral	Renal excretion	Lower urinary tract infections	Nausea, vomiting Diarrhea
Polymyxin B	IV Topical	Not applicable	Superficial infections of skin or mucus membranes	Nephrotoxicity Neurotoxicity
Daptomycin	IV	Renal excretion	Infections caused by methicillin- or vancomycin resistant staphylococci	Muscle toxicity
Rifaximin	Oral	Fecal	Traveler's diarrhea IBS	Not applicable

1.7 – Antimycobacterial drugs

Drugs for tuberculosis	Drugs for mycobacterium avium-intracellulare infections	Drugs for leprosy
Isoniazid Ethambutol Pyrazinamide Rifampin	Azithromycin Rifabutin	Dapsone Rifampin Clofazimine Thalidomide

1.7.1 – Drugs for tuberculosis

- Tuberculosis is a contagious bacterial infection that mainly affects the lungs and is caused by *Mycobacterium tuberculosis*.
- The main goals of tuberculosis chemotherapy are to quickly kill TB bacteria, eliminate dormant forms, and prevent relapse and transmission.
- Treatment should be based on drug susceptibility testing, especially at the start, if sputum remains positive, or if relapse occurs.
- Patients should be isolated until sputum cultures are negative.
- Isoniazid, a key TB drug, works by inhibiting mycolic acid synthesis, but resistance—often due to mutations in the *katG* gene—is becoming more common.

Drug	Mechanism	Spectrum	Pharmacokinetics	Clinical use
Isoniazid	Bactericidal; targets actively and dormant growing <i>M. tuberculosis</i>	Active against <i>M. tuberculosis</i> , some <i>M. kansasii</i> ; not effective against <i>M. avium-intracellulare</i> , <i>M. leprae</i>	Taken orally; metabolized in liver; excreted in urine	First-line TB drug; used in standard 4-drug regimen; typical duration 6–9 months; rifampin may replace if needed
Ethambutol	Bacteriostatic; inhibits arabinosyl transferase → disrupts mycobacterial cell wall	<i>M. tuberculosis</i> , <i>M. avium-intracellulare</i>	Oral administration; metabolized in liver; excreted in urine and feces	Used in combination TB therapy and for <i>M. avium-intracellulare</i> infections

Pyrazinamide	Bactericidal; exact mechanism unclear; active in acidic pH of macrophages	M. tuberculosis	Oral administration; metabolized in liver; excreted in urine	Part of initial TB regimen; shortens treatment duration to 6 months
Rifampin	Inhibits DNA transcription by binding RNA polymerase β subunit; selective for bacteria	Broad activity against <i>M. tuberculosis</i> and other mycobacteria	Widely distributed (lungs, CSF); excreted mainly in feces, also urine	Used in combination TB therapy; alternative to isoniazid in some regimens

Adverse effects	
Isoniazid	Hepatotoxicity Peripheral neuritis (due to vitamin B6 deficiency) Toxic encephalopathy Seizures Blood disorders
Ethambutol	Optic neuritis Impaired red-green color discrimination Hyperuricemia Gout Hepatitis Thrombocytopenia
Pyrazinamide	Arthralgia Hyperuricemia Gout Hematologic toxicity Fever Hepatitis
Rifampin	Hepatotoxicity Hypersensitivity reactions Discoloration of bodily fluids Renal disease Leukopenia and thrombocytopenia

1.7.2 - Drugs for leprosy

- Leprosy treatment involves long-term use of antimycobacterial drugs, ranging from several months to a lifetime.

Drug	Mechanism	Spectrum	Pharmacokinetics	Clinical use
Dapsone	Inhibits folic acid synthesis → bacteriostatic against <i>M. leprae</i>	Effective against <i>M. leprae</i>	Taken orally; metabolized by acetylation; excreted in urine	Used in combination therapy for leprosy
Clofazimine	Bactericidal for <i>M. tuberculosis</i> , bacteriostatic for <i>M. leprae</i>	Active against <i>M. leprae</i> , <i>M. avium-intracellulare</i> , and <i>M. tuberculosis</i>	Poor gut absorption (55% bioavailability); long half-life (~70 days); widely distributed	Used with dapsone and rifampin for lepromatous leprosy; treats erythema nodosum leprosum
Thalidomide	Immunomodulatory; may stimulate CD8+ T cells	Not antimicrobial; used for immune modulation	Variable absorption; concerns over teratogenicity	Treats erythema nodosum leprosum; contraindicated in pregnancy due to risk of birth defects (e.g., phocomelia)

Adverse effects	
Dapsone	GI upset Peripheral neuropathy Optic neuritis Proteinuria Lupus-like syndrome Hematologic toxicity
Clofazimine	GI upset Photosensitivity Discoloration of body fluids and skin Hepatotoxicity

1.8 - Test yourself

1) Name all the beta-lactam antibiotic groups:

2) A patient is treated with Vancomycin. Which side effect is most likely to occur with this drug?

- a) Diarrhea
- b) Ototoxicity
- c) Alopecia
- d) Hypertension

3) Clavulanate, sulbactam and tazobactam are examples of:

- a) Beta-lactam antibiotics
- b) Peptidoglycans
- c) Beta-lactam inhibitors
- d) Narrow-spectrum antibiotics

4) Name two different third-generation cephalosporins:

5) Penicillin G can be used to treat which disease:

- a) Syphilis
- b) Gonorrhea
- c) Lyme disease
- d) Mycoplasma

6) A woman is being treated for a chlamydial infection. She experiences severe erythema on her skin after she was outside in the sun. Which antibiotic is most likely responsible for this adverse effect?

- a) Mupirocin
- b) Clindamycin
- c) Doxycycline
- d) Azithromycin

7) Aminoglycosides exhibit concentration-dependent killing. What does this mean?

8) Clindamycin is active against gram-positive cocci and is useful in treating infections caused by gram-positive cocci and anaerobes resistant to penicillin and other drugs. It causes a higher rate of which condition?

- a) Pseudomembranous colitis
- b) Severe headache
- c) Erythema of the skin
- d) Liver failure

9) Route of administration of Mupirocin.

- a) Topical
- b) Oral
- c) Intravenous
- d) Intramuscular

10) A man is being treated for a bacterial infection and is experiencing severe pain in his right heel. He is found to have an inflamed Achilles tendon. Which antibiotic is most likely to give such an adverse effect?

- a) Trimethoprim
- b) Daptomycin
- c) Ciprofloxacin
- d) Rifaximin

11) A woman has been traveling in Asia and is experiencing severe diarrhea. She is given a drug that is not absorbed by the gut. Which agent is this woman probably taking?

- a) Trimethoprim
- b) Levofloxacin
- c) Nitrofurantoin
- d) Rifaximin

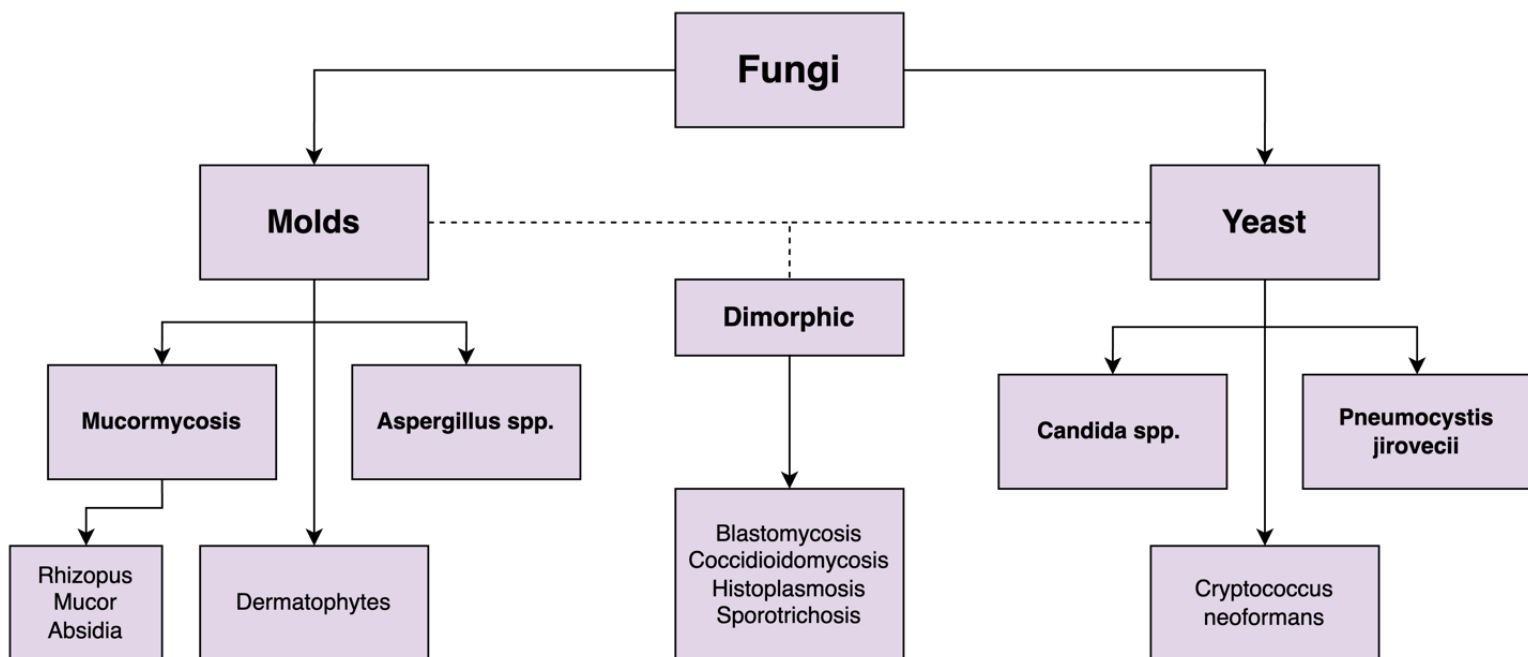
12) What is the mechanism of action of fluoroquinolones?

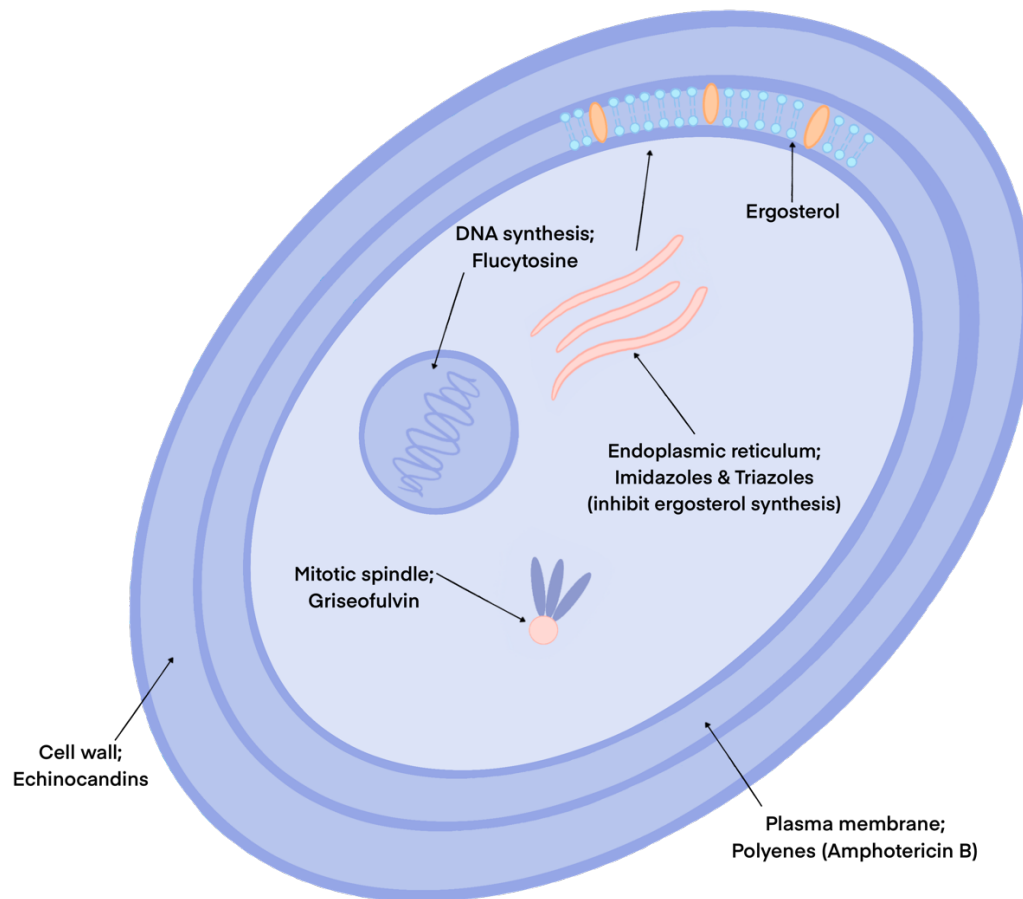
13) What is the mechanism of action of trimethoprim?

Section 2 – Antifungal Drugs

- 2.1 – General about Fungi
- 2.2 – Polyene Antibiotics
- 2.3 – Azole Derivatives
- 2.4 – Allylamine Drugs
- 2.5 – Echinocandin Drugs
- 2.6 – Other Antifungal Drugs
- 2.7 – Test Yourself

2.1 – General about Fungi





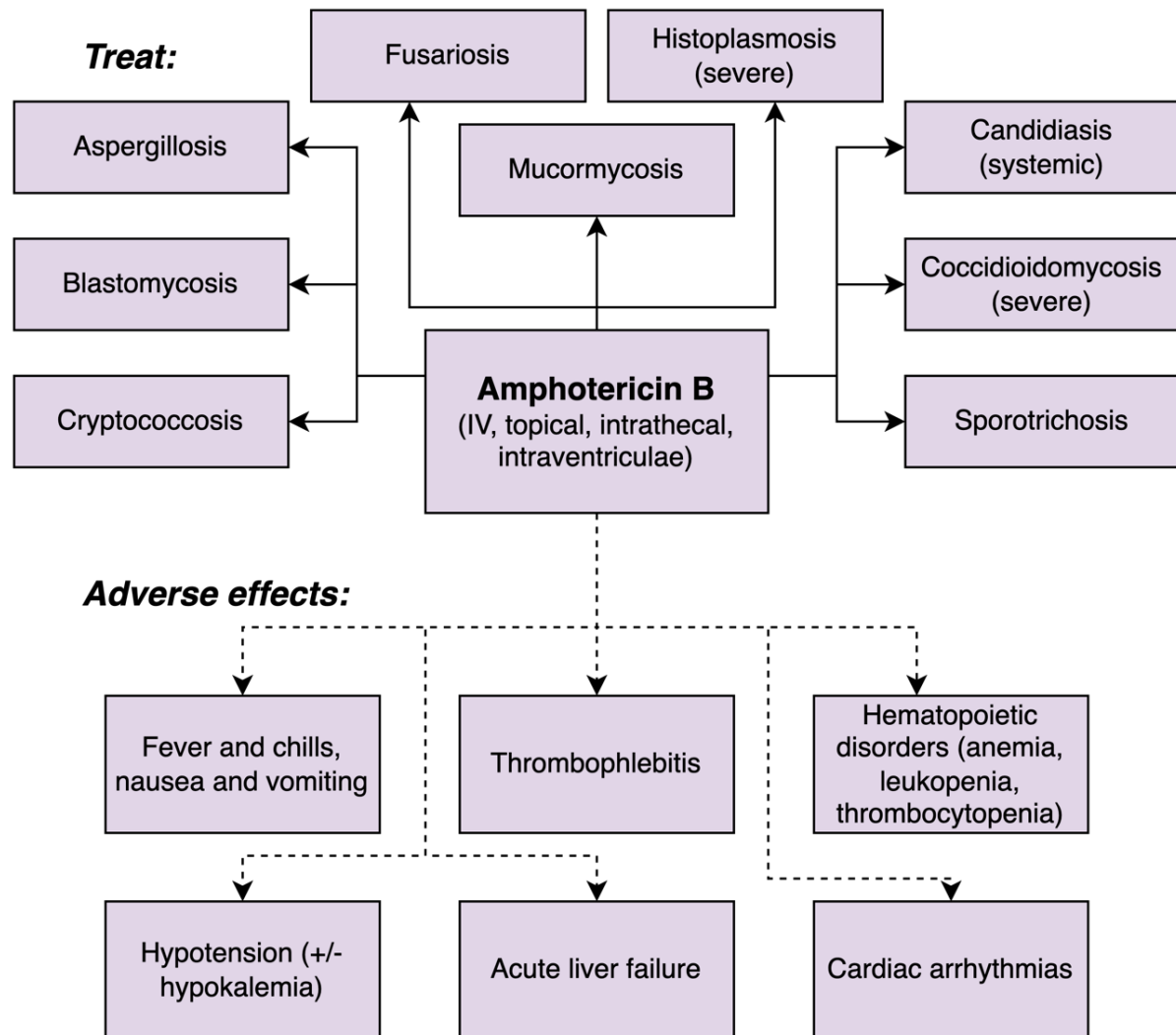
CLINICAL CORRELATION

Antibiotic + antifungal

- It is not uncommon for a fungal infection to appear during/after a long or strong antibiotic treatment.
(e.g. a vaginal yeast infection in women)
- Sometimes antifungals are therefore prescribed together with the antibiotic treatment.

2.2 – Polyene Antibiotics

- The polyene antibiotics are Amphotericin B, Natamycin and Nystatin. As seen in the illustration above, they bind to ergosterol in the cell membrane and increases the permeability.
- Except for Amphotericin B, the polyene antibiotics are used as a topical treatment for superficial and mucocutaneous mycoses.



	Natamycin	Nystatin
Type of fungi	Aspergillus, Candida, Fusarium, Penicillium	Candida species
Administration	Topical ocular	Oral or topical (for mucocutaneous and vaginal)

2.3 – Azole Derivatives

2.3.1 – Azole Derivatives

	Clotrimazole	Fluconazole	Itraconazole	Ketoconazole (Nizoral) ²	Efinaconazole
Type of fungi	Candida + M. Furfur + dermatophyte	Cryptococcal + coccidioidal meningitis ¹ , mucocutaneous and disseminated candidiasis	Blastomycosis + histoplasmosis + onychomycosis	Seborrheic dermatitis	Onychomycosis
Mechanism of action	Inhibit synthesis of ergosterol ⁴				
Administration	Topical	Oral or IV	Capsule or liquid (oral)	Oral or topical	Topical
Absorption	Well absorbed from the gut		Requires gastric acid		Well absorbed from the gut
Excretion	In urine and feces				
Adverse effects		- N&V - headache - skin rashes - hepatotoxicity ³	- N&V - rash - hypokalemia - hypertension - edema - headache - hepatotoxicity - negative inotropic effects		

¹ Because it crosses blood-brain barrier

² Not as much used anymore because of newer drugs available that cause fewer drug interactions and has a greater efficacy

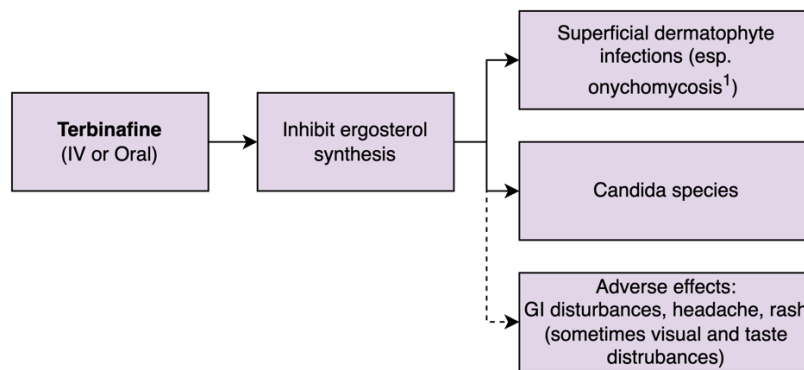
³ Fluconazole has fewer drug interactions than itraconazole and ketoconazole

⁴ Which disrupts the function and structure of the membrane leading to inhibition of fungal cell growth.

2.3.2 – Oxaborole Derivatives

- Tavaborole is a very new drug, which is closely related to the azole derivatives.
- It is used as a topical treatment (ointment) for onychomycosis of the toenails.

2.4 – Allylamine Drugs



¹ Requires a shorter duration of therapy and is more effective than itraconazole and griseofulvin.

2.5 – Echinocandin Drugs

	Caspofungin
Mechanism	Inhibit fungal cell wall synthesis
Type of fungi	Candida species (esophageal, oropharyngeal and invasive) Aspergillus species (invasive)
Administration	IV ¹
Adverse effects	Headache, phlebitis (at site of drug injection), fever and abnormal liver function tests.

¹ Because of poor bioavailability

2.6 – Other Antifungal Drugs

	Ciclopirox	Flucytosine ¹	Griseofulvin	Tolnaftate
Mechanism	Disrupt synthesis of fungal RNA, DNA and protein	Interferes with fungal protein synthesis by being incorporated into the fungal RNA	Disrupts microtubule function	Inhibit mycelial growth in susceptible fungi
Type of fungi	Dermatophytes; C. albicans and M. furfur (tinea versicolor and onychomycosis)	Candida and Cryptococcus species (pneumonia, septicemia, meningitis, endocarditis)	Trichophyton rubrum, T. tonsurans, T. verrucosum Microsporum audouinii, M. canis, M. gypseum Epidermophyton floccosum	Epidermophyton, Microsporum, Malassezia furfur
Administration	Topical	Oral	Oral	Topical
Adverse effects	Irritation, pain or discoloration of affected area	(usually mild) Cardiopulmonary arrest or hematologic toxicity	Insomnia, headache, dizziness, GI bleeding, hepatitis, skin rash, leukopenia	Mild itching, dryness and peeling of treated skin

¹ Because drug resistance is rapidly developed, flucytosine is always given together with amphotericin B

2.7 – Test Yourself

1) Place in correct box:

Yeast	Molds

Mucormycosis

Dermatophytes

Candida Spp.

Aspergillus spp.

Cryptococcus neoformans

Pneumocystis jirovecii

2) What are the adverse effects of Amphotericin B?

3) Match the route of administration with the correct azole derivative?

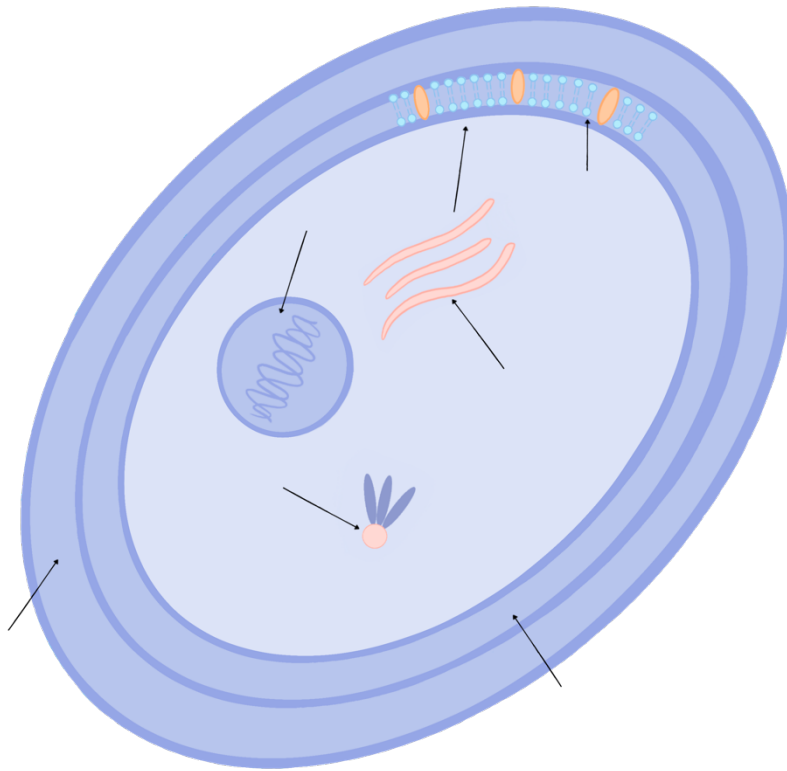
- | | |
|------------------|-----------------------------|
| 1) Clotrimazole | a) Oral or IV |
| 2) Fluconazole | b) Oral (capsule or liquid) |
| 3) Itraconazole | c) Topical |
| 4) Ketoconazole | d) Topical |
| 5) Efinaconazole | e) Oral or topical |

4) What is the mechanism of terbinafine?

- a) Inhibit ergosterol synthesis
- b) Inhibit mycelial growth
- c) Inhibit fungal cell wall synthesis
- d) Disrupt microtubule function

5) Why cannot caspofungin be administered orally?

6) Fill in the correct drug and where they inhibit the fungal cell, by the arrows.

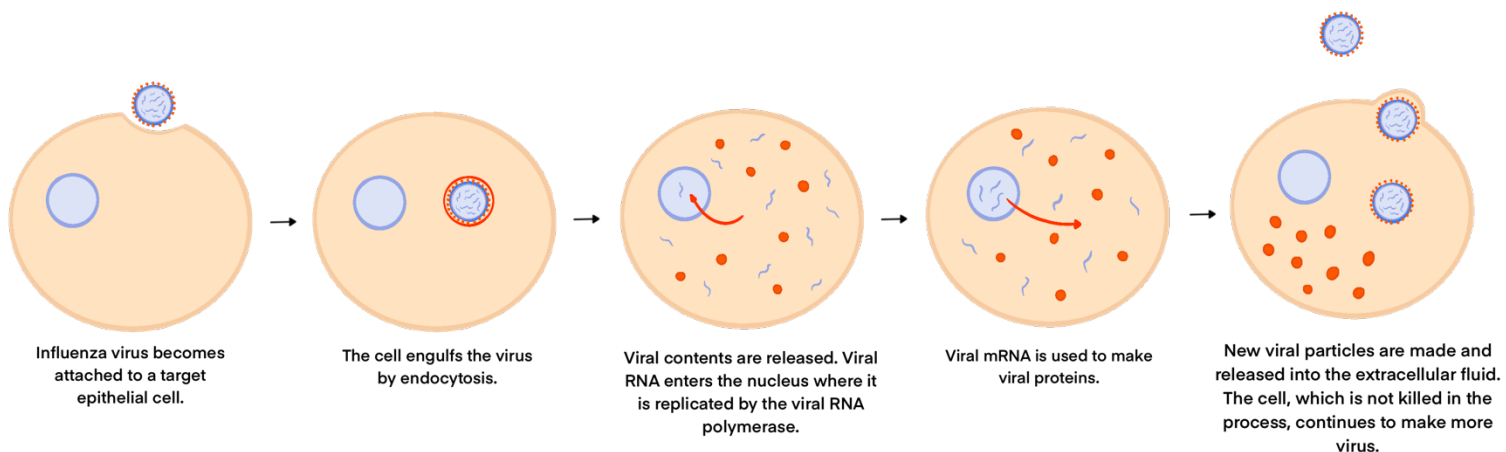


Section 3 – Antiviral Drugs

- 3.1 – General about Viruses
- 3.2 – Drugs for Herpesvirus Infection
- 3.3 – Drugs for HIV Infection
- 3.4 – Drugs for Influenza
- 3.5 – Drugs for Hepatitis C and Other Viral Infections
- 3.6 – Test Yourself

3.1 – General about Viruses

- Viruses are not able to reproduce by themselves. They consist of genetic material (DNA or RNA) that usually is surrounded by a protein coat. They depend on invading a host cell and using the metabolic pathway of the host cell for reproduction and spreading.
- Therefore, it is difficult to find drugs that prevent viral replication without harming the host cell.
- Examples of antiviral interference:
 1. In the synthesis of the viral nucleic acids
 2. Prevent entry of a virus
 3. Prevent release and spread of a virus
 4. Inhibit incorporation of viral nucleic acid into the host cell genome



3.2 – Drugs for Herpesvirus Infection

- Inhibit viral DNA polymerase and therefore the replication (except foscarnet).
- **Herpes simplex virus (HSV)** causes infection of the genitals, lips and mouth, and conjunctiva (very rarely cause fatal encephalitis).
- **Varicella-zoster virus (VZV)** cause chickenpox and shingles.
- **Cytomegalovirus (CMV)** usually presents as retinitis, esophagitis and colitis in immunocompromised patients.

CLINICAL CORRELATION

VZV

- Most people experience Varicella-zoster virus as chicken pox only once, usually as children.
- However, shingles is a reactivation of the latent Varicella-zoster, usually in older people/immunocompromised.
- Presents as a unilateral rash with a lot of pain and sometimes motor paralysis.

3.2.1 – Nucleoside Analogs

	Acyclovir ³	Famciclovir (Penciclovir – active metabolite)	Ganciclovir ⁴	Cidofovir
Pharmacokinetics²: <pre> graph LR Cidofovir --> Cidofovir_monophosphate[Cidofovir monophosphate] Cidofovir_monophosphate --> Cidofovir_diphosphate[Cidofovir diphosphate] Cidofovir_diphosphate --> Inhibit_viral_DNA_polymerase[Inhibit viral DNA polymerase] Acyclovir_Penciclovir_Ganciclovir[Acyclovir + Penciclovir + Ganciclovir] --> Monophosphates_of_previous[Monophosphates of previous] Monophosphates_of_previous --> Diphosphate_of_previous[Diphosphate of previous] Diphosphate_of_previous --> Triphosphate_of_previous[Triphosphate of previous] Triphosphate_of_previous --> Causes_DNA_chain_termination[Causes DNA chain termination¹] Valacyclovir_Famciclovir_Valganciclovir[Valacyclovir + Famciclovir + Valganciclovir] -.-> Prodrugs Acyclovir_Penciclovir_Ganciclovir subgraph Cell Cidofovir_monophosphate Cidofovir_diphosphate Monophosphates_of_previous Diphosphate_of_previous Triphosphate_of_previous end </pre>				
Type of infection	Mainly: HSV-1, HSV-2, VZV	HSV-1, HSV-2, VZV	Mainly CMV, also HSV-1 and HSV-2	CMV, HSV, VZV that are ganciclovir and acyclovir resistant
Administration	Oral: E.g. children with chickenpox IV: serious HSV and VZV Topical: mild mucocutaneous HSV	Oral (topical cream)	IV: CMV Ophthalmic gel: keratitis ⁵	IV
Toxicities	Oral: Occasional nausea, diarrhea, rash, headache. IV acyclovir: Renal side effects if not proper hydration		Myelosuppression, CNS toxicities, GI disturbances, retinal detachment	Nephrotoxicity, neutropenia, metabolic acidosis
Treating abilities	These drugs do not eliminate the virus, they are used for shorter periods to treat/shorten/prevent the recurring episodes of infection.			

¹ Only some, e.g. acyclovir and ganciclovir

² The nucleoside analogs are activated by viral thymidine and host cell kinases to inhibit viral DNA polymerase and cause DNA chain termination.

³ Valacyclovir is a prodrug of acyclovir. Used for VZV infection, and HSV and CMV prophylaxis in e.g. immunocompromised patients.

⁴ Valganciclovir is an oral prodrug of ganciclovir, used for less severe CMV infections.

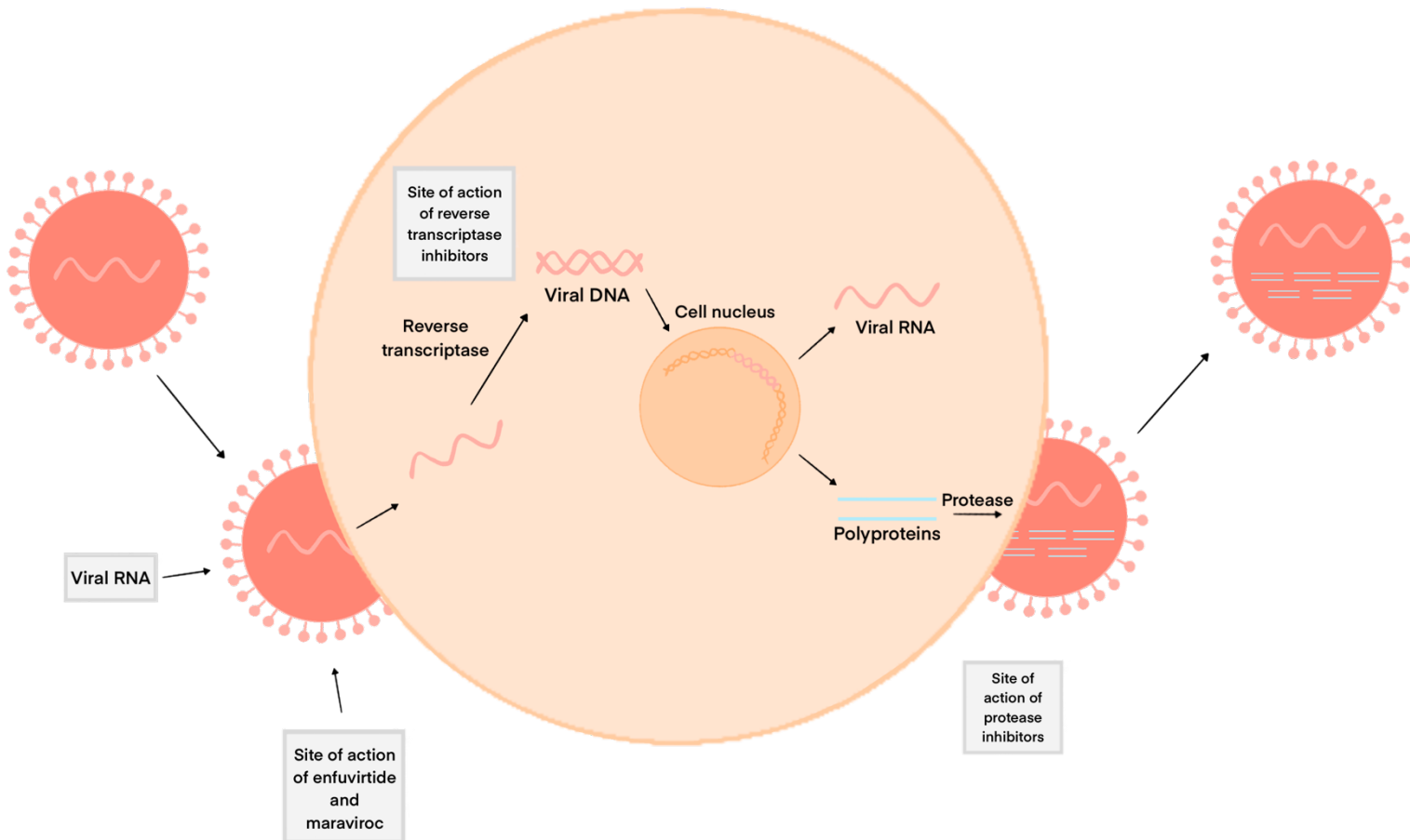
⁵ Trifluridine also treat this.

3.2.2 – Other Drugs

	Foscarnet
Pharmacokinetics	Pyrophosphate derivative, do not require activation by viral/cellular kinases.
Type of infection	CMV, VZV, HSV
Administration	IV: CMV in immunocompromised patients, or acyclovir resistant HSV or shingles.
Toxicities	Renal, cardiac, hematologic and pancreatic impairments, seizures

3.3 – Drugs for HIV Infection

- HIV spread by contact with body fluids, e.g. sexually transmitted or by blood contamination.
- The human immunodeficiency virus destroys cells of the human immune system and weakens the ability to fight off everyday infections and diseases.
- HAART – highly active antiretroviral therapy, is a multidrug treatment that improves survival in HIV-positive patients by combining drugs from the different classes.



3.3.1 – Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTIs)

- Included in most HIV treatment regimens, often in combination with an integrase strand inhibitor or a protease inhibitor.
- Combination therapy is necessary to prevent both HIV replication and resistance.
- NRTIs require metabolic activation by host cell kinases to inhibit reverse transcriptase.

	Abacavir	Emtricitabine	Lamivudine	Tenofovir	Zidovudine
Infection(s)	HIV	HIV + HBV		HIV	
Adverse effects	Lactic acidosis, hepatic steatosis, lipodystrophy				
	Hypersensitivity reactions (fever, rash, GI upset)	Headache, nausea, diarrhea, fatigue, insomnia, depression		Headache, GI intolerance	
				Renal impairment	Bone marrow suppression
Elimination	Metabolized by alcohol dehydrogenase + glucuronyl transferase	Renal excretion			

3.3.2 – Nonnucleoside Reverse Transcriptase Inhibitors

- NNRTIs directly inhibit reverse transcriptase. They are lipophilic and reach the CNS.
- Used as alternative drugs for the patients who do not respond to or tolerate the primary drugs.
- Always combined with other drugs to avoid resistance.

	Rilpivirine	Efavirenz	Nevirapine
Adverse effects	Rash, drug interactions		
	Insomnia & sleep disturbances	Teratogenic, neuropsychiatric reactions	Hepatotoxicity, increase metabolism of some drugs

3.3.3 – HIV Protease Inhibitor

- PIs inhibit the maturation of the virus by inhibiting the proteolytic activity which leads to an immature, noninfectious virus.

	Darunavir
Function	A part of initial treatment ¹ for HIV patients
Administration	Oral, should be taken with food.
Elimination	Metabolized by the CYP3A enzymes
Adverse effects	Nausea, vomiting, diarrhea, disturbances in glucose and lipid metabolism, fat redistribution. Rash ²

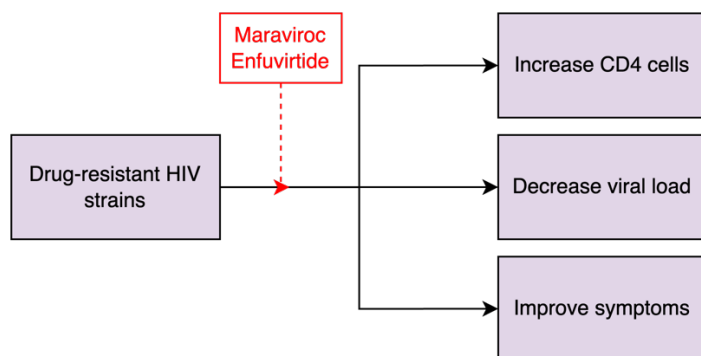
¹ Darunavir is always paired with ritonavir in initial treatment, because ritonavir acts as a booster.

² Only in darunavir, the others are general for PIs.

3.3.4 – Fusion and Entry Inhibitors

- Quite new drugs. Commonly used in HIV infections by drug-resistant strains.

	Maraviroc	Enfuvirtide
Function	Entry inhibitor	Fusion inhibitor
Administration	Oral	Subcutaneous
Elimination	Metabolized by CYP 450 liver enzymes	Metabolized via hydrolysis
Adverse effects	Cough, diarrhea, muscle and joint pains, possible hepatotoxicity	Injection site reaction, hypersensitivity, may increase risk of bacterial pneumonia



3.3.5 – Integrase Strand Transfer Inhibitors

- Raltegravir is the first integrase strand transfer inhibitor for HIV infections.
- Often included in initial treatment of HIV.

	Raltegravir
Function	Integrase strand inhibitor
Administration	Oral
Elimination	UGT metabolism ¹
Adverse effects	Headache, diarrhea, nausea, ↑CK

¹ UDP-glucuronosyltransferase (UGT)1A1-mediated glucuronidation. No interactions with CYP450 drugs

3.3.6 - Combination Drugs for HIV

I. PrEP (Pre Exposure Prophylaxis)

- Is an infection prevention for HIV negative individuals who are at high risk of infection.
- PrEP can be administered orally (Truvada, Descovy), as an intramuscular injection (can last for 2 months, Apretude) or an intravaginal ring.
- Contains two NRTI (**tenofovir and emtricitabine**)

II. Three-drug Combination Products

- Used in HIV infected patients over 12 y.o. and > 35kg
- **Emtricitabine** (NRTI) + **tenofovir** (NRTI) + **rilpivirine** (NNRTI) = Odefsey
- Increases the chances of the patient taking the medication correctly as it is all in one pill instead of several
- Lowers the cost of medication because there is only one pill

III. Four-drug Combination Products

- Used in HIV infected patients over 12 y.o. and > 35kg
- **Elvitegravir** (integrase strand transfer inhibitor) + **cobicistat** (CYP3A inhibitor) + **emtricitabine** (NRTI) + **tenofovir** (NRTI) = Genvoya
- Cobicistat is included here because it increases the plasma levels of elvitegravir

3.4 – Drugs for Influenza

- One of the most common causes of death due to infectious diseases.
- The primary mean of prevention is vaccination. Neuraminidase inhibitors are used to prevent complications and shorten outbreaks.

3.4.1 – Neuraminidase Inhibitors

	Oseltamivir	Zanamivir
Function	Inhibit neuraminidase in Influenza A and B viruses	
Administration	Oral (Treatment and prophylactically)	Intranasally ¹
Adverse effects	GI symptoms	Cough, throat discomfort ²

¹ Contraindicated in patients with underlying airways disease, due to it being intranasally.

² May induce bronchospasm in asthmatic patients.

CLINICAL CORRELATION

Tamiflu (Oseltamivir)

- Tamiflu is an antiviral drug used to reduce the severity and duration of influenza symptoms. May also reduce the risk of complications, especially in high-risk patients.
- Should be initiated within 48 hours of symptom onset for optimal effect. The earlier the treatment is initiated, the better the effect will be.
- Oseltamivir is eliminated through the kidneys, so dose adjustments are recommended for patients with impaired renal function <60 GFR.

3.5 – Drugs for Hepatitis and Other Viral Infections

3.5.1 – Drugs for Hepatitis B Infection

- HBV is spread by contact with body fluids, e.g. sexual transmission.
- Acute infection is usually self-limiting and does not require treatment. However, chronic HBV infection might cause liver failure and cirrhosis, and therefore requires life-long treatment.
- Drugs for HBV that all inhibit the formation of the DNA copy of the viral RNA: adefovir, entecavir, tenofovir, lamivudine and telbivudine.

	Entecavir
Mechanism	Inhibits HBV DNA polymerase
Administration	Oral (once daily)
Elimination	Renal excretion ¹
Adverse effects	Headache, dizziness, fatigue, nausea

¹ Entecavir is excreted unchanged in urine, but dose-adjustments are necessary in patients with renal dysfunction

3.5.2 – Drugs for Hepatitis C and Other Viral Infections

- HCV is spread by contact with contaminated blood, e.g. by needlestick injury
- HCV only presents as chronic condition in 75% of infected patients. They might experience no/mild symptoms beforehand. The chronic infection can lead to cirrhosis, liver cancer and liver failure.

	Ribavirin	Sofosbuvir	Peginterferon alfa	Palivizumab	Imiquimod
Mechanism	Inhibits RNA (and DNA) ¹ viral replication	Inhibits HCV RNA polymerase	Glycoprotein cytokine that interferes with the viral replication	Inhibit a fusion protein (RSV) and therefore the viral entry into the cells	Stimulate innate and cell-mediated immune system
Clinical use	Broad-spectrum antiviral drug ² , especially severe RSV virus + chronic HCV	Usually in combinations, for HCV	HCV and HBV ³	To prevent and treat RSV in children	Skin conditions (e.g. warts),
Administration	Oral (HCV) or aerosol (RSV in children)	Oral	S.C once a week	IM once a month	Topical
Adverse effects	Inhalation: Pulmonary and cardiovascular effects Oral: Hemolytic anemia (which can worsen cardiac issues) Teratogenic	Fatigue, rash, irritability, headache, nausea, dizziness, back pain, anemia	Hematologic toxicity, cardiac arrhythmias, altered BP, CNS dysfunction, GI distress, chills, fatigue, headache, myalgia	Hypersensitivity reactions	Dose-dependent local reactions.

¹ HCV is an RNV virus, but ribavirin can also inhibit DNA viruses.

² Adenovirus, Colorado tick virus, Hantaan virus, HBV, HCV, Crimean-Congo hemorrhagic fever virus, herpesvirus, Influenza A and B, Lassa virus, Measles virus, Mumps virus, Muerto Canyon virus, RSV (respiratory syncytial virus), Rift Valley fever virus and yellow fever virus.

³ Less used today because of development of newer drugs.

- **Epclusa** (sofosbuvir + velpatasvir) is the most recently approved drug combination for HCV, by the U.S. and Europe, for HCV.

	Epclusa	
	Sofosbuvir	Velpatasvir
Mechanism	Inhibits HCV RNA polymerase (NS5B)	Inhibits key activator of RNA polymerase (NS5A) + active against all 6 HCV genotypes
Adverse effects	Headache + fatigue ¹	

¹ Do not use with amiodarone as it may cause bradycardia.

3.6 – Test Yourself

1) What type of herpes virus cause the different infections?

_____ cause chickenpox and shingles.
 _____ causes infection of the genitals, lips and mouth, and conjunctiva (very rarely cause fatal encephalitis).
 _____ usually presents as retinitis, esophagitis and colitis in immunocompromised patients.

2) Match the herpes drug with the correct type of administration:

- | | |
|----------------|-------------------------|
| 1) Acyclovir | a) Oral (topical cream) |
| 2) Famciclovir | b) IV |
| 3) Ganciclovir | c) IV, Ophthalmic gel |
| 4) Cidofovir | d) Oral, IV, Topical |

3) Foscarnet:

- a) can treat CMV, VZV and HSV
- b) do not need activation by a cellular/viral kinase
- c) is administered IV
- d) all of the above

4) What is HAART an abbreviation for, and what does it mean?

5) What are the typical adverse effects if NRTIs?

- a) Metabolic alkalosis, headache, dizziness
- b) Weight loss, fever, dizziness
- c) Lactic acidosis, hepatic steatosis, lipodystrophy
- d) Headache, weakness, fever

6) Which drug is an HIV protease inhibitor?

- a) Darunavir
- b) Rilpivirine
- c) Efavirenz
- d) Nevirapine

7) What is PrEP and who should use it?

8) What is the drug combination in Epclusa?

- a) Sofosbuvir/Velpatasvir
- b) Sofosbuvir/Ribavirin
- c) Velpatasvir/Peginterferon alfa
- d) Peginterferon alfa/Ribavirin

Section 4 – Antiparasitic Drugs

4.1 – General about Parasites

4.2 – Drugs for Infections Caused by Lumen- and Tissue-Dwelling Protozoa

4.3 – Drugs for Infections Caused by Blood- and Tissue-Dwelling Protozoa

4.4 – Drugs for Helminth Infections

4.5 – Drugs for Ectoparasite Infestations

4.6 – Test Yourself

4.1 – General about Parasites

- **Parasitism** = A relationship between two species in which “the parasite” derive nutrients and other resources from “the host”.
- **Endoparasitic** infections = parasite lives within their host, helminths and protozoans.
- **Ectoparasitic** infections = parasite live on the skin, lice and mites.

4.2 – Drugs for Infections Caused by Lumen- and Tissue-Dwelling Protozoa

- Used for protozoan parasites that inhabit the intestines and other tissues of their human host.

I. Tissue amebicides

	Metronidazole	Tinidazole
Treat	Aerobic protozoa: Entamoeba histolytica (Amebiasis), Trichomonas vaginalis (STD), Giardia Lamblia (GI)	
	Anaerobic bacteria: Helicobacter pylori, Clostridium difficile, Bacteroides fragilis	
	Dracunculus medinensis (nematode in India, Pakistan and parts of Africa)	
Administration	Oral	
	IV in severe infections	
Excretion	Metabolized by CYP3A4 -> renal excretion	
Half-life	8h	13h
Adverse effects	- GI discomfort, metallic taste, leukopenia, thrombocytopenia - Teratogenic Disulfiram-like reaction with alcohol	

II. Luminal amebicides

	Iodoquinol	Paromomycin	Diloxanide	Nitazoxanide
Treat	Dientamoeba fragilis			Cryptosporidium parvum, Giardia lamblia ¹ Ascariasis
	Entamoeba histolytica ²			
Adverse effects	Rash, diarrhea, dose-related neurotoxicity	GI distress, diarrhea	GI distress, lethargy, headache	GI distress, headache, discolored urine

¹ In immunocompetent persons

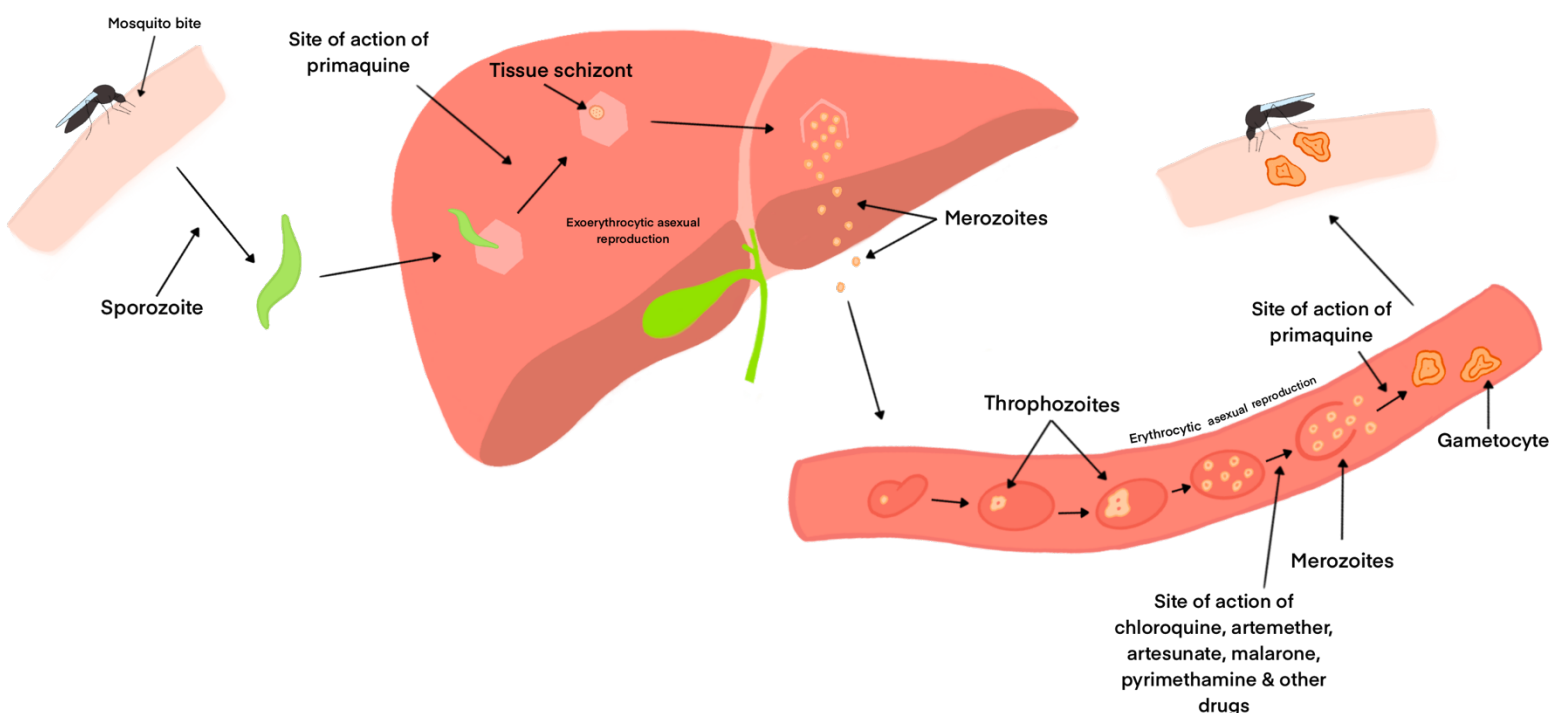
² Only act as a luminal amebicide (asymptomatic) , need to be combined with metronidazole/tinidazole (tissue amebicide) to treat symptoms.

4.3 – Drugs for Infections Caused by Blood- and Tissue-Dwelling Protozoa

- Infections caused by protozoan parasites that inhabit in the blood and tissues of humans.

4.3.1 – Drugs for Malaria

- Malaria is one of the most common infectious diseases in the world today, characterized by cyclic/episodic fever. It is transmitted by mosquito bites, mainly in tropical/subtropical areas.
- The different types are Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae and Plasmodium ovale. P. falciparum causes the most serious infections.



	Chloroquine	Primaquine	Artesunate & Artemether (Coartem) ¹
Treat	<i>P. falciparum</i> by itself, <i>P. vivax</i> , <i>P. ovale</i> (in combination w/primaquine)	<i>P. vivax</i> and <i>P. ovale</i> + transmission of all forms	Multidrug-resistant <i>P. falciparum</i> (+ <i>P. vivax</i>)
Mechanism	Prevent degradation of heme	Unclear, but exoerythrocytic tissue stage + destroy all gametocytic/sexual forms	Form free radicals that attack heme
Resistance	Most areas are very resistant, except the Caribbean Islands, parts of Central America, North Africa and the Middle East.		Emerging resistance, therefore, should not be used alone
Adverse effects	GI distress, N&V	Hemolytic anemia in G6PD deficiency	

¹ = artemether plus lumefantrine

CLINICAL CORRELATION

Primaquine

- When the erythrocytic (blood) form is eliminated, *P. vivax* and *P. ovale* may remain as exoerythrocytic form (in the liver).
- Primaquine is the only drug that removed *P. vivax* and *P. ovale* from the liver and prevent relapses.
- It should be used in conjunction with other drugs as it does not affect the erythrocytic stage of malaria (blood).

	Combination Drugs	
	Malarone (Atovaquone+Proguanil)	Fansidar (Pyrimethamine+sulfadoxine)
Treat	Chloroquine-resistant P.falciparum	P.falciparum, Toxoplasma Gondi
Mechanism	Inhibit electron transport, ATP and pyrimidine biosynthesis + prevent DNA synthesis	Inhibit steps in the synthesis of folic acid
Adverse effects	N&V, headache, dizziness, anorexia, diarrhea, abdominal pain	N&V, skin rashes, megaloblastic anemia

4.3.2 – Drugs for Toxoplasmosis

- Protozoan Toxoplasma Gondi is a very common infection in humans, it is transmitted through uncooked food/raw meat. It is also transmitted through cat feces.
- In healthy people the infection is usually asymptomatic. If there are symptoms, they usually are flu-like symptoms, muscle aches and pains, and swollen lymph nodes. In severe cases it can cause damage to the eyes, brain or other organs.

	Pyrimethamine¹ + Sulfadiazine	Spiramycin
Treat	Toxoplasma Gondi (except tissue cysts)	Fetal infection of T.gondi (from acute infection of mother during pregnancy)
Mechanism	Blocking folic acid synthesis (needed by t. gondi to live)	AB, macrolide
Adverse effects	Folate deficiency, hematologic abnormalities.	Stomach pain, N, V, D

¹ Quite commonly can cause hypersensitivity reactions, discontinue as soon as a rash appears.

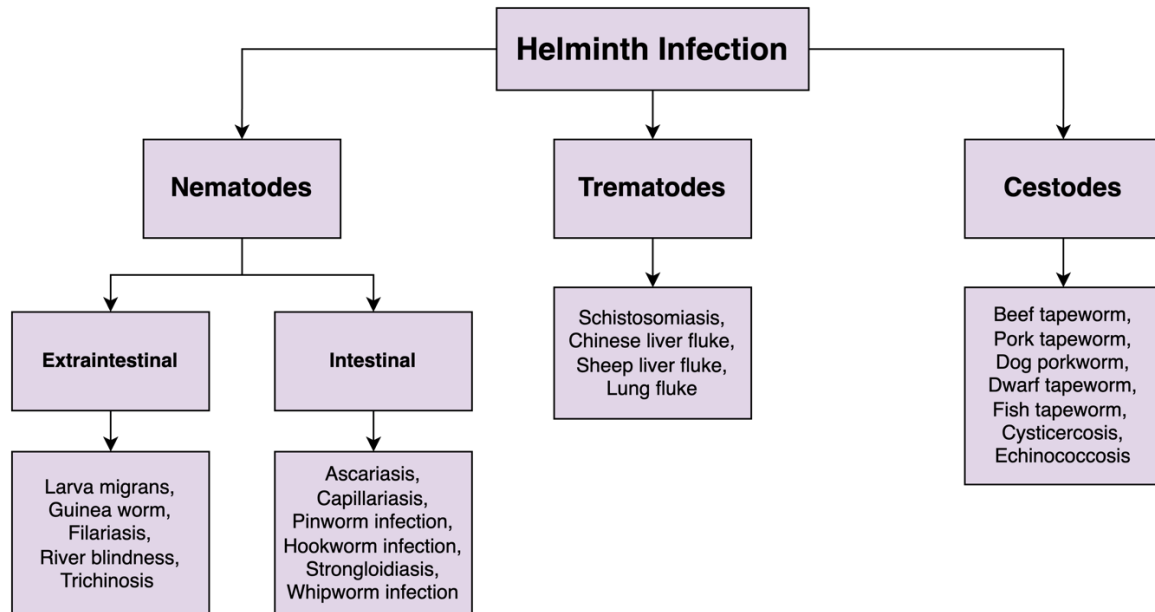
4.3.3 – Drugs for Other Protozoan Infections

	Pentamidine	Melarsoprol
Treat	- Pneumocystis jiroveci, - <u>EARLY</u> African trypanosomiasis brucei (sleeping sickness) - Leishmaniasis	<u>LATE</u> African trypanosomiasis brucei (sleeping sickness) ¹
Administration	P.jiroveci: <u>IV</u> /IM for treatment, nebulizer for prophylaxis Sleeping sickness: <u>IV</u> /IM	Slow IV
Mechanism of action	Interferes with the parasitic production of DNA, RNA, proteins and phospholipids.	Bind to thiol groups in key proteins, disrupting the parasite's metabolic processes.
Adverse effects	Hematologic toxicity, ventricular tachycardia, edema, pancreatitis, bronchospasm, Stevens-Johnson syndrome, DM	Irritate surrounding tissues (may cause hypersensitivity and febrile reactions), may cause reactive encephalopathy, peripheral neuropathy, hypertension, albuminuria,

¹ Only drug available for second stage-CNS manifestations of African trypanosomal infections.

4.4 – Drugs for Helminth Infections

- Different types of helminths are roundworms (nematodes), flukes (trematodes), and tapeworms (cestodes).
- Many infections go untreated because the cost of the drug treatment is so high



4.4.1 – Drugs for Nematode Infections

	Albendazole	Pyrantel pamoate	Ivermectin	Diethylcarbamazine (DEC)
Mechanism	Impairs glucose uptake	Produce a depolarizing neuromuscular blockade -> irreversible paralysis of nematode	Hyperpolarization that cause paralysis of the pharyngeal muscles in the helminths	Trigger exposure of antigens on parasites, making them vulnerable to an immune attack.
Treat	Intestinal nematode infections ¹ Cestode infections ²	Hookworm and pinworm infection	Broad-spectrum helminth ³	Microfilariae ⁴
Elimination	By metabolism and renal excretion	Partly metabolized in the liver ⁵	Excreted in feces	Primarily excreted in urine.
Adverse effects	GI discomfort, hepatic and hematologic toxicity. Teratogenic	Abdominal cramps, anorexia, diarrhea, vomiting.	Constipation, diarrhea, dizziness, vertigo, sedation.	Dizziness, vision disturbances.

¹ capillariasis, hookworm, ascariasis, pinworm, whipworm, trichinosis

² cysticercosis, echinococcosis, Microsporidiosis

³ Strongyloidiasis, onchocerciasis (river blindness), cutaneous larva migrans, Loa loa, B. malayi, W. bancrofti, recently scabies

⁴ E. bancrofti, B. malayi, Loa loa

⁵ 50% of oral dose is excreted unchanged in the feces

4.4.2 – Drugs for Trematode and Cestode Infections

	Praziquantel
Treat	Trematode: Chinese liver fluke, the lung fluke, Schistosomiasis Cestode: Pork, beef, fish, dog, and dwarf tapeworms.
Administration	Oral
Mechanism	Expose antigens that are hidden by an outer covering.
Adverse effects	Abdominal discomfort, dizziness, drowsiness, headache.

4.5 – Drugs for Ectoparasite Infestations

- Ectoparasites live on the skin of their animal host.

	Permethrin	Spinosad
Treat	- Pediculosis from lice - Scabies from mites	Head lice (>4.y.o.)
Mechanism of action	Block sodium current in neurons of the parasite, causing paralysis.	Activate nicotinic acetylcholine receptors, causing muscle contraction and paralysis in parasite.
Application	Pediculosis: Liquid preparation on hair/scalp for 10 minutes. (Need to remove eggs after) Scabies: A cream for 8hours.	Topical application on head/scalp.
Resistance	Increasing resistance	

4.6 – Test Yourself

1) What anaerobic bacteria can be treated by Metronidazole?

- a) Giardia Lamblia, Trichomonas vaginalis
- b) Helicobacter pylori, C. difficile, Bacteroides fragilis
- c) C. difficile, Giardia Lamblia, Cryptosporidium parvum
- d) None of the above

2) What is the mechanism of action of Chloroquine in treatment of malaria?

- a) Unclear
- b) Form free radicals that attack heme
- c) Destroy all gametocytic forms
- d) Prevent degradation of heme

3) What drugs should be used to treat Toxoplasmosis?

4) Choose the false match of drug and protozoan infection:

- a) Melarsoprol – Late African trypanosomiasis brucei (sleeping sickness)
- b) Melarsoprol – Leishmanias
- c) Pentamidine – Pneumocystis jiroveci
- d) Pentamidine – Early African trypanosomiasis brucei (sleeping sickness)

5) Why do a lot of helminth infections go untreated?

