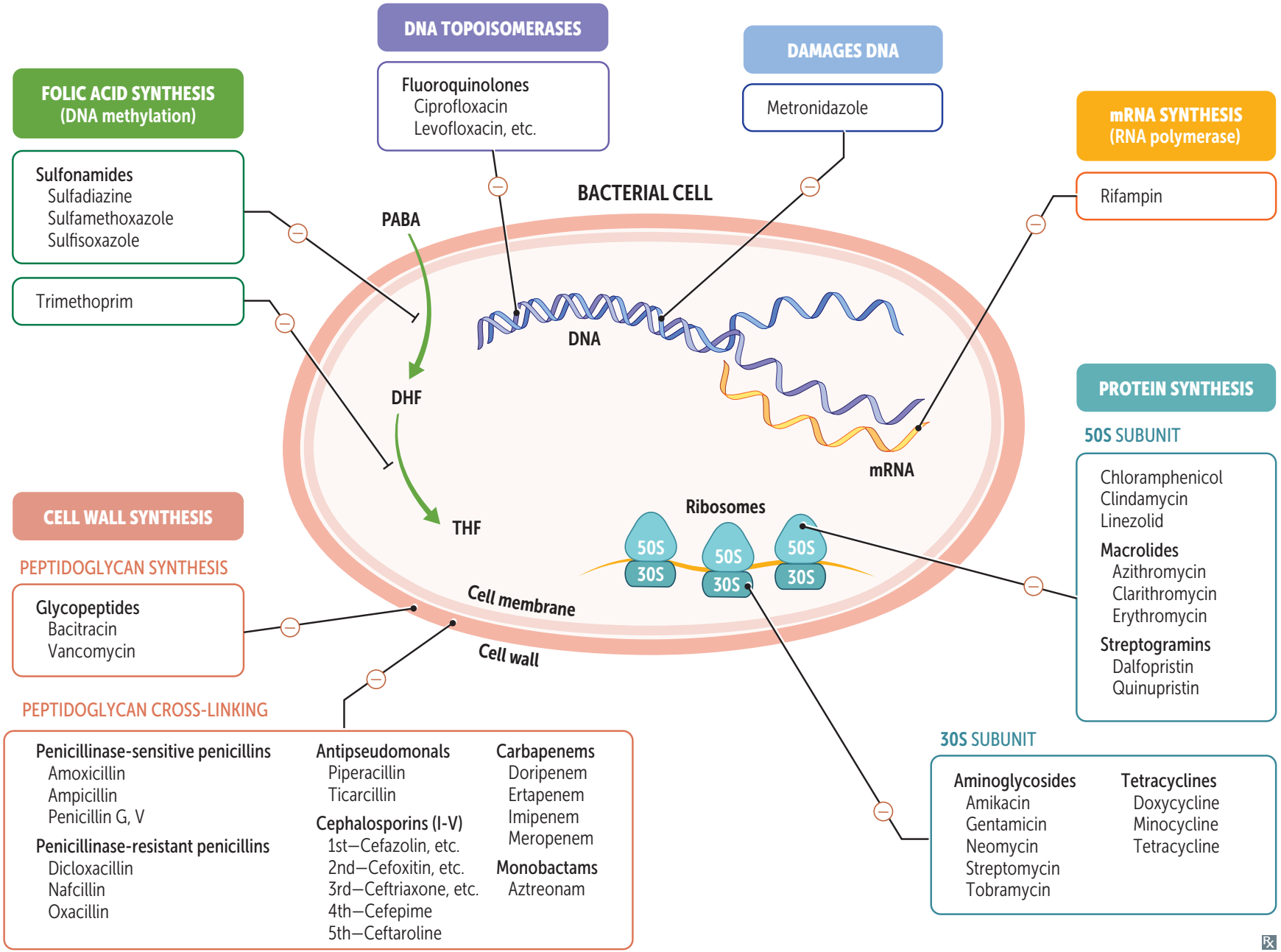
Antimicrobial therapy



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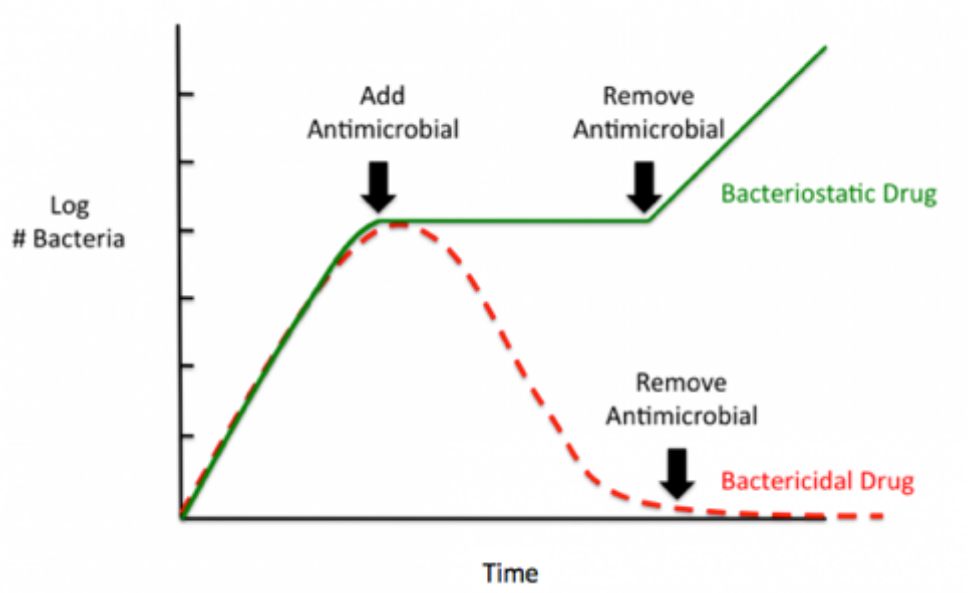
BACTERIOSTATIC AGENTS	BACTERICIDAL AGENTS
– **Inhibit bacterial growth** at drug serum levels achievable in patient – Intact cellular immunity is required to get rid of the static bacteria – *Not preferred in immunocompromisde patients, as bacteria will resurface* – **Examples:** Sulfonamides, Tetracyclines, Erythromycin (Macrolides), Chloramphenicol, Trimethoprim	– **KILL the bacteria** at drug serum levels achievable in patients – Most effective when cells are actively dividing/synthesizing cell wall – Preferred for quick action (in seriously ill patients) & in **immunocompromised patients** – *Most show Post-Antibiotic Effect (PAE) against susceptible organisms* – **Examples:** (All cell wall synthesis inhibitors) Penicillin, Cephalosporins, Aminoglycosides, Fluoroquinolones



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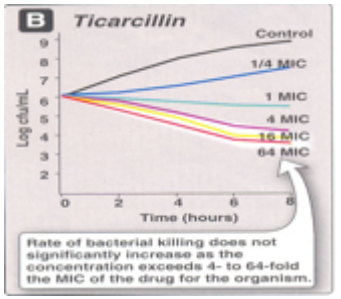
CONCENTRATION & TIME-DEPENDENT EFFECTS OF ANTIBIOTICS



MINIMUM INHIBITORY CONCENTRATION (MIC)

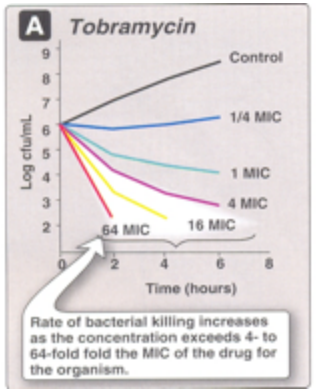
- Lowest concentration of drug that inhibits bacterial growth
- Based on the **MIC**, a particular strain of bacteria can be classified as **susceptible or resistant** to a particular drug
- *For some antimicrobial agents, increasing the concentration above MIC does not result in proportionate increase in kiling* **(i.e. Penicillins)**
- Killing continues as long as concentrations are above MIC
    - *So consideration should be given to maintain antiimicrobial concentration above MIC for the entire dosage interval* (graph)

MINIMUM BACTERICIDAL CONCENTRATION (MBC)

- Lowest concentration of antibiotic that kills 99.9% of bacteria after overnight incubation

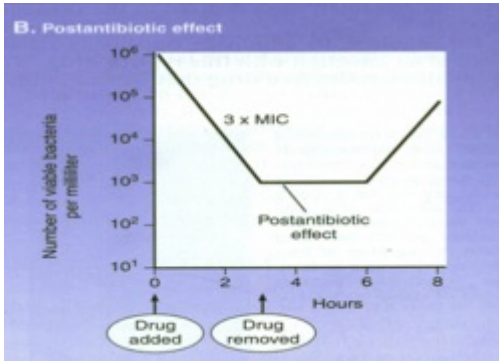
CONCENTRATION-DEPENDENT KILLING RATE (CDKR)

- **Aminoglycosides** (i.e. tobramycin – graph) **& Fluoroquinolones** exhibit a CDKR against a large group of gram-negative bacteria (*P. aeruginosa* & *Enterobacteriaceae*)
- **Penicillins & other β-lactams do NOT exhibit CDKR**



POST-ANTIBIOTIC EFFECT (PAE)

- *A prolonged period before bactria resumt growth after antibiotics decline to subinhibitory concentrations*
- After an antibacterial drug is removed from bacterial culture, if the antibacterial effect still persists on bacteria growth – *that is called PAE*
- **Most bactericidal antibiotics** show PAE against susceptible pathogens
    - PCNs show PAE against gram-positive cocci
    - AGs show PAE against gram-negative bacilli
- Prevents any remaining bacteria from replicating for several hours after the drug has been eliminated from the body



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COMBINATION ANTIMICROBIAL THERAPY

Clinical Indications: *empirical therapy, treat polymicrobial infection, enhance antimicrobial activity, prevent emergence of resistance*

SYNERGISTIC EFFECT

- Additive effect or Supra-additive effect
- When 2 drugs are given at the same time & togther produce an effect that is greater than the sum of the 2 drug's individual effects
- **β-Lactams + Aminoglycosides (againsts pseudomonal & enterococcal species) – *both are bactericidal!***
  - *Aminoglycosides are protein synthesis inhibitors; thus, they must reach the ribosome. It needs Penicillin's cell-wall inhibitor effects in order to enter the cell & inhibit protein synthesis.*

ANTAGONISTIC EFFECT

- Antimicrobials acting at different targets may enhance or impair overall antimicrobial activity

BACTERIAL RESISTANCE

Consequences of Resistance: *inactivation of the drug by microbial enzymes, decreased accumulation of drug in microbes (decreased uptake or increased efflux), reduced affinity of target macromolecule for the drug, altered metabolic pathways*

- **INNATE RESISTANCE**
- **ACQUIRED RESISTANCE:** the bacteria was sensitive to that antibiotic, but then becomes insensitive due to *mutation, transfer of genetic material (plasmids) that confer drug resistance, etc.*
- **MULTI-DRUG RESISTANCE:** *i.e. MDR tuberculosis*

SUPERINFECTION

*The appearance of bacteriological & clinical evidence of a **new infection** during the chemotherapy of a primary infection.*

- Use of **broad-spectrum antibiotics** or **combination** of agents:
  - Can lead to **alterations of normal microbial flora** of URT, GT, GUT
  - Permitting the **overgrowth of opportunistic organisms**, especially fungi or resistance bacteria
- Example: **PSEUDOMEMBRANOUS COLITIS** (*C. diff) – Candida infection*

ANTI-MICROBIALS: Bacterial Cell Wall Synthesis Inhibitors

β-LACTAMS: *Penicillins, Cephalosporins, Carbapenems, Monobactam; inhibit cell wall synthesis; bind PBP; bactericidal*

***ADMINISTERED WITH AMINOGLYCOSIDES FOR SYNERGISTIC EFFECT & PREVENTION OF RESISTANCE**

DRUG	MECHANISM	DISTRIBUTION/ RESISTANCE	INDICATION	ADVERSE EFFECTS
PENICILLINS	5-member *sulfur-containing thiazolidine ring* R-group side change alters β-lactamase resistance **MOA OF ALL LACTAMS:** **Interfere with cell wall synthesis:** **Binding to PBP**, inhibit cell wall **transpeptidation**, inhibit of **peptidoglycan** synthesis, breakdown of cell wall → cell death	**NATURAL RESISTANCE**: gram negative or lack cell well (***mycoplasma***) **ACQUIRED RESISTANCE:** plasmids **MOST COMMON:** β-lactamase (**Staph**) **PBP CHANGE:** MRSA, pneumococci, enterococci (Strep) **PORIN CHANGE:** ↓permeability in gram negatives (*pseudomonas*) **EFFLUX PUMP:** gram negatives	***Safe to use in pregnancy*** Should be given 1 hr before meal (except Amoxicillin*)	**Hypersensitivity: utricaria,** angioedema, anaphylaxis **CROSS-ALLERGIC REACTIONS:** *you can desensitize if necessary (neurogenic syphilis)* **NEUROTOXICITY**: **high** doses → **seizures & convulsions** (intrathecal or renal failure pts) *(High TI = generally well tolerated)*

NATURAL PENICILLINS: Narrow spectrum, β-lactamase/penicillinase **sensitive**

***Spectrum**: Streptococci, Meningococci (Neisseria meningitidis), Treponema pallidum*

DRUG	MECHANISM	DISTRIBUTION/ RESISTANCE	INDICATION	ADVERSE EFFECTS
PENICILLIN G **Crystal Benzyl Penicillin** *IV (acid-labile)* ***Procaine** & **Benzathine**:* *IM/Depot form;* ***Longer-acting***	1 International Unit (IU) of Crystalline PenG = 0.6μg (1g of benzyl penicillin = 1.6 million IU) Half-life Benzyl Penicillin G = 30 minutes Half-life Benzathine Penicillin G = 2 weeks 90% Excreted in **urine** via ***active tubular secretion*** ***PROBENECID inhibits tubular secretion to ↑plasma concentration**	**Extracellular distribution** *(Only crosses BBB in inflammation, i.e. meningitis)* ****95% of staphylococci are resistant to Penicillin G***	***High # of resistance strains*** **DRUG OF CHOICE:** **Syphilis *(Treponem pallidum)*** **ACTINOMYCOSIS** *Clostridium tetanus/perfringens* (w/ Clindamycin) **DIPTHERIA** **PROPHYLAXIS:** **RHD/RF** (Benzathine) **Gonorrhea, Syphilis** **Pregnant GBS carrier**	Hypersensitivity *Hemolytic anemia* **Jarisch-Herxheimer Reaction** in treatment of Syphilis – severe immunologic response due to death of spirochetes (release of proteins); fever, malaise, joint pain, exacerbation of lesions, hypotension
PENICILLIN V Phenoxymethyl Penicillin *PO (acid stable)*	Relatively poor bioavailability Must be taken QID Narrow antibacterial spectrum **Amoxicillin used instead.**		Minor infections	

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ANTI-STAPHYLOCOCCAL PENICILLINS: Very narrow spectrum, β-lactamase **resistant**

Spectrum**: Known or suspected Staphylococci ***NOT effective against MRSA

DRUG	MECHANISM	DISTRIBUTION/ RESISTANCE	INDICATION	ADVERSE EFFECTS
METHICILLIN (IV)	*NOT USED.*	**ALTERED PBPs = MRSA**		**NEPHROTOXICITY** (Interstitial Nephritis, Tubular Necrosis): NO LONGER USED
NAFICILLIN (IV)	Primarily excreted in **BILE** **Crosses BBB**		**DOC: non-MRSA *S. aureus*** ***"NAF for STAPH"***	***Can be given in renal impairment!*** **NEUTROPENIA**
OXACILLIN			**DOC: non-MRSA *S. aureus***	
CLOXACILLIN DICLOXAXILLIN				

AMINOPENICILLINS: Broad spectrum; β-lactamase **sensitive**

***Spectrum**: Gram-Positive Cocci (STREP – S. pyogenes, S. pneumo), E. coli, H. influenzae, Listeria, Borrelia burgdorferi* (Lyme Disease), *H. pylori*

*Combine w/ β-lactamase inhibitors **(Clavulanic Acid+Amoxicillin, Sulbactam+Ampicillin):** protects them from hydrolysis by β-lactamase

DRUG	MECHANISM	DISTRIBUTION/ RESISTANCE	INDICATION	ADVERSE EFFECTS
AMPICILLIN	Acid-stable, but **food interferes w/ absorption** **Excreted in Bile:** **ENTEROHEPATIC CIRCULATION**	*Penicillinase producing E. coli & H. influenza*	**DOC: *Listeria monocytogenes*** **(Meningitis in IC patients)** **+AMINOGLYCOSIDES** *(Ampicillin + Vanc + 3rd gen Cephalosporin for empiric TX)* **NON-β-lactamase *H. influenza*** Salmonella typhi carriers + SALMONELLA GASTROENTERITIS Shigellosis	**SEVERE DIARRHEA** **PSEUDOMEMBRANOUS COLITIS*** **Vaginal Candidiasis**
AMOXICILLIN *Better Oral bioavailability*	Food does NOT interfere with absorption		**DOC: UTI (pregnancy) + URT** ****PROPHYLAXIS:** DENTAL sx in pts w/ abnormal heart valves	NO diarrhea, NO pseudomembranous colitis

ANTI-PSEUDOMONAL PENICILLINS: Extended spectrum; β-lactamase **sensitive**

Spectrum**: Increased activity against Gram-Negative Rods (Pseudomonas aeruoginosa) – **Hospitals, Oxidase+

*Combine w/ β-lactamase inhibitors **(Clavulanic Acid+Ticarcillin & Tazobactam+Pipercillin):** protects them from hydrolysis by β-lactamase

DRUG	MECHANISM	DISTRIBUTION/ RESISTANCE	INDICATION	ADVERSE EFFECTS
CARBOXYPENICILLINS: **TICARCILLIN**			**DOC: *P. aeruoginosa: BURN & CF pts***	****BLEEDING** –platelet dysfunction**
UREIDOPENICILLINS: **PIPERCILLIN**	*P. aeruginosa, Enterobacter, Klebsiella*	**AVOID RESISTANCE**: Combine w/ **AMINOGLYCOSIDE** or **FLUROQUINOLONE** for Pseudomonas infections **outside the urinary tract**		

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ANTI-MICROBIALS: Bacterial Cell Wall Synthesis Inhibitors

β-LACTAMS: *Penicillins, Cephalosporins, Carbapenems, Monobactam; inhibit cell wall synthesis; bactericidal*

DRUG	MECHANISM	DISTRIBUTION/ RESISTANCE	INDICATION	ADVERSE EFFECTS
CEPHALOSPORINS *MOST given IV/IM* (poor oral absorption)	***More stable*** than PCNs to many bacterial β-lactamases = broader spectrum --Semi-synthetic by chemical attachment of **7-AMINOCEPHALOSPORANIC ACID** (obtained from **fungi**)	**Distribute into body fluids** **Resistance same as PCN**	****NOT ACTIVE AGAINST ***LAME*:** **L**isteria, **A**typical *(chlamyd/mycoplasma)*, **M**RSA, **E**nterococci ***Contraindicated*** in PCN allergy	– **HYPERSENSITIVITY RXNs** ***Use Macrolide or Aztreonam*** – **COMPLETE CROSS-ALLERGINICITY** between cephalosporins – **PARTIAL CROSS-ALLERGINICTY** w/ penicillins – Pain at injection site – Diarrhea – NEPHROTOXICITY: Cephaloridine, withdrawn ****MTT side chain** in **Cefoperazone** (3rd), Cefamanadole, Cefotetan, Cefmetazole (2nd)** 1. **BLEEDING due to HYPOPROTHROMBINEMIA**: TREAT WITH VITAMIN K 2. **DISULFIRAM**-like reaction **1ST: 'ph', LIN, THIN, XIN** **2ND: M, TAN, FUR, FOX, FAC** **3RD: CEFT; *Cef* +/- any vowel + P/D/T** **4TH: PI** **5TH: RO** **These acronyms are kind of a stretch… but better than nothing! ☺*
1st GENERATION: **CEFAZOLIN,** CEPHALOTHIN (IV) **CEPHALEXIN,** CEPHRADINE, CEFRADROXIL (PO) **LIN, THIN, XIN, 'PH'**	**Highly active against Gram-Pos Cocci**** Active against Gram-Neg **PEcK*** *(Proteus mirabilis, E. coli, Klebsiella)* Eliminated through **glomerular filtration & tubular secretion** ***PROBENECID* inhibits tubular secretion to ↑ plasma concentration**	Doesn't enter CNS, water soluble Resistant to Staph penicillinase	**CEFAZOLIN:** 1. **surgical prophylaxis** against Gram+ & penicillinase producing *S. aureus* 2. orthopedic surgery (penetrate bone) CEPHALEXIN: 1. URT infections 2. PCN & Sulfonamide-resistant UTI	
2nd GENERATION: **CEFOXITIN, CEFOTETAN, CEFMETAZOLE** (IV) CEFACLOR, CEFUROXIME AXETIL, CEFPROZIL (PO) **M, TAN, FUR, FOX, FAC**	More activity against **Gram-Neg** + anaerobes **HEN PEcK*** *(H. influenza, Enterobacter aerogenes, N. meningitides, + PEcK)* Cefamandole, Cefuroxime, Cefaclor: *H. influenzae*	*Cefuroxime crosses BBB**	**UPPER & LOWER RTIs:** Sinusitis, OM by β-lactamase H. *influ & Moraxella catarrhalis*) **ANAEROBIC INFECTIONS: Peritonitis, Diverticulitis, PID (BACTEROIDES): *CEFOTETAN, CEFOXITIN, CEFMETAZOLE*** **CAP:** β-lactamase H. influ: **CEFUROXINE**	
3rd GENERATION: **CEFTRIAXONE, CEFTAZIDIME, CEFOPERAZONE,** CEFOTAXIME, CEFTIZOXIME (IV) CEFIXIME, CEFDINIR, CEFDITOREN PIVOXIL, CEFIBUTEN, CEFPODOXIME (PO) **CEFT*;** ***Cef* + A/E/I/O/U + P/D/T**	**Highly active againsts many Gram-Pos Cocci** *(inferior to 1st generation)*, Gram-Neg Cocci, + Gram-Neg Bacilli (**HEN PEcK, PSEDUOMONAS, Serratia**) Excretion of **Cefoperazone & Ceftriaxone** mainly through **BILE *so safe in renal failure*** *(all others excreted by KIDNEY & **contraindicated** in renal disease)*	*Only generation of Cephalosporins that enter CNS ***(not Cefoperazone)*** **Resistant to most lactamases** **ADEQUATE THERAPEUTIC LEVELS IN CSF** (regardless of inflammation) **ACHIEVED ONLY BY 3RD GENERATION**** **BROADEST SPECTRUM OF CEPH. & RESISTANT TO β-LACTAMASE**	**CEFTAZIDIME – Empiric treatment** of **SEPSIS/MENINGITIS** of unknown cause *(ampicillin, vanc, 3rd gen ceph)* **CEFTAZIDIME – DOC *P. aeruginosa*** **CEFTRIAXONE – DOC: MENINGITIS + GONORRHEA + ACUTE OM** **CEFIXIME** – UTI TYPHOID FEVER: 2ND DOC	
4th GENERATION: PI **CEFEPIME,** CEFPIROME	Gram-Positive of 1st + Gram-Negative of 2nd Good activity against *pseudomonas, enterobacteriaceae, S. aureus, & S. pneumo* **Highly active against Hemophilis + Neiserria**			
5TH: CEFTAROLINE	**Pro-drug** of an active metabolite ceftaroline		Against MRSA: CAP + skin infection	

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ANTI-MICROBIALS: Bacterial Cell Wall Synthesis Inhibitors

β-LACTAMS: *Penicillins, Cephalosporins, Carbapenems, Monobactam; inhibit cell wall synthesis; bactericidal*

DRUG	MECHANISM	DISTRIBUTION/ RESISTANCE	INDICATION	ADVERSE EFFECTS
CARBAPENEMS **MEROPENAM,** Doripenem, Ertapenem	MOA same as PCN + Cephalosporins **MOST POTENT + WIDEST SPECTRUM LACTAMS** **Active against Gram-Pos Cocci + Gram-Neg Rods (Enterobacter, Pseudomonas-*except Ertapenem*), & Anaerobes** **Renal excretion**	β-lactamase resistant, but **Carbapenemases & metallo-β-lactamase susceptible**	**Empiric use in SEVERE LIFE-THREATENING INFECTIONS (Nosicomial infections)** **DOC: ENTEROBACTER** Febrile, neutropenic patients in ICU +/- aminoglycosides	**GI distress (NVD)** **DRUG FEVER:** Partial cross-allergenicity w/ PCN
Imipenem	Used with **CILASTATIN** to inhibit renal dehydropeptidase → **toxic metabolites**	Hydrolyzed by dehydropeptidase of brush border tubular cells of kidney		**SEIZURES (50%)** **Nephrotoxic (toxic metabolites)**

DRUG	MECHANISM	DISTRIBUTION/ RESISTANCE	INDICATION	ADVERSE EFFECTS
MONOBACTAM **Aztreonam** *Only used IV*	MOA same as PCN + Cephalosporins **ONLY active against AEROBIC Gram-Negative Rods** **(*H. influ, Pseudomonas, Enterbacteriaceae*)**	Resistant to β-lactamases	**PSEUDOMONAS IN PCN ALLERGIC PTS**** **Hospital acquired infections**	**NO CROSS REACTIVITY WITH PCN OR CEPHALOSPORINS**

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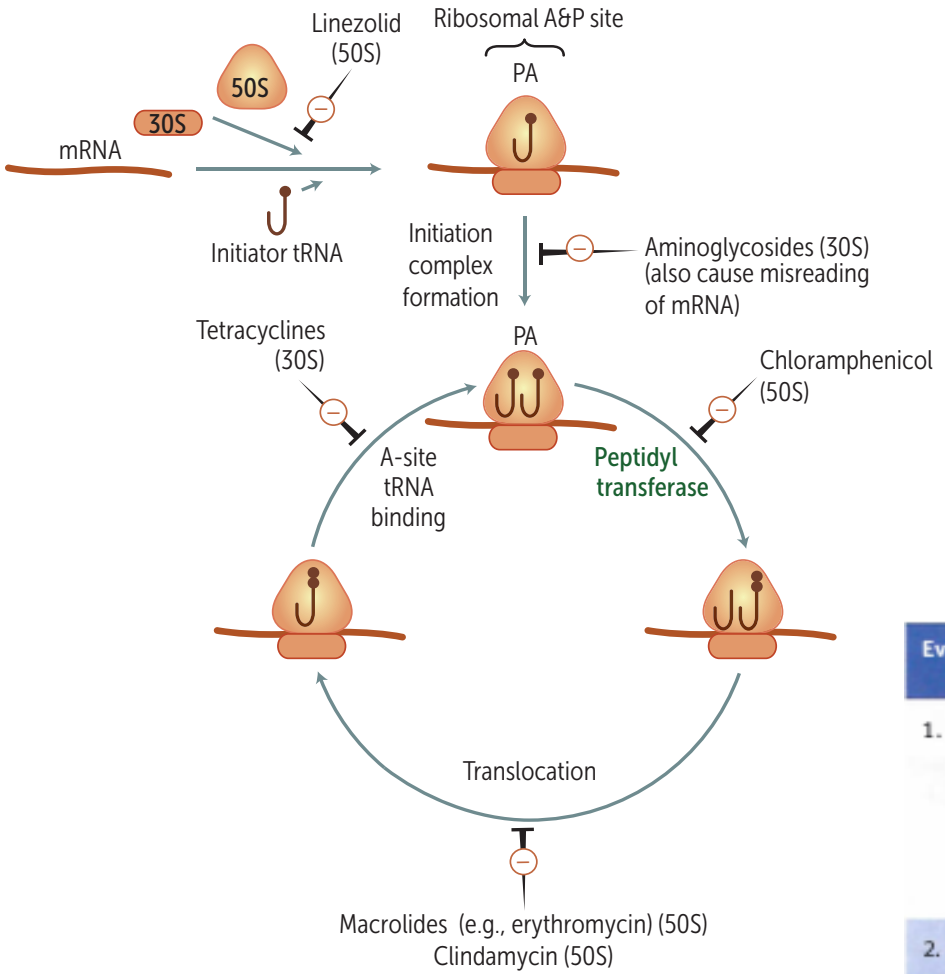
ANTI-MICROBIALS: NON-β-Lactam Cell Wall Synthesis Inhibitors

DRUG	MECHANISM	DISTRIBUTION/ RESISTANCE	INDICATION	ADVERSE EFFECTS
VANCOMYCIN *Poor oral absorption* *Slow IV infusion**	**GLYCOPEPTIDE ANTIBIOTIC** **BACTERICIDAL** Inhibition of synthesis of peptidoglycan: **Binds D-Ala-D-Ala & inhibits transglycosylation by** prevents elongation & crosslinking **Active only against Gram-Positive Bacteria** **90%** Excreted by **glomerular filtration –** *important to **decrease dose in renal dysfunction***	Distributes to most tissues, but not CNS (unless inflammated, i.e. meningitis) Resistance is rare, but VRSA & VRE are emerging (in surgical & burn wards) Resistance involves **decreased affinity for binding site due to replacement of terminal D-Ala by D-LACTATE****	**DOC: MRSA Staph aureus*** **2nd DOC: Enterococci Endocarditis** in PCN allergy **Penicillin-resistant pneumonoccus** (meningitis) **ALTERNATIVE**: ***C. diff enterocolitis*** (given orally)	**RED NECK SYNDROME**: Type I HSR** (flushing, pruritis, erythema of head & upper body, hypotension – due to **histamine release** after rapid IV injection) OTOTOXICITY: usually permanent, additive w/ other drugs NEPHROTOXICITY: mild but additive w/ other drugs
BACITRACIN	**POLYPEPTIDES** **Active against various Gram-Positive bacteria**		"Triple Antibiotic" **– topical** ointment	
FOSFOMYCIN	Analog of PEP – *inhibits the 1st enzymatic step in the synthesis of peptidoglycan* **Active against both Gram-Pos & Gram-Neg**		***Safe in pregnancy*** **Uncomplicated lower UTI**	
CYCLOSERINE	Structural **analog of D-Alanine** **Inhibits D-Ala into peptidoglycan pentapeptide**		2ND line therapy in resistant TB	**Dose-related CNS toxicity:** HAs, tremors, acute psychosis, convulsions
DAPTOMYCIN	Similar to Vancomycin Binds to cell membrane via Ca^{2+}-dependent **insertion of its lipid tail → depolarization** of cell membrane with K^+ efflux & rapid cell death		VRSA & VRE: Skin & soft tissue infections, bacteremia, endocarditis ***Contraindicated in pneumonia***	**Myopathy & Allergic Pneumonitis**

Protein synthesis inhibitors



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

30S inhibitors

A = **A**minoglycosides [bactericidal]
T = **T**etracyclines [bacteriostatic]

50S inhibitors

C = **C**hloramphenicol, **C**lindamycin [bacteriostatic]
E = **E**rythromycin (macrolides) [bacteriostatic]
L = **L**inezolid [variable]
"Buy **AT 30**, **CCEL** (sell) at **50**."

Event	Antibiotic(s) and Binding Site(s)	Mechanism(s)
1. Formation of initiation complex	Aminoglycosides (30S) Linezolid (50S)	Interfere with initiation codon functions—block association of 50S ribosomal subunit with mRNA-30S (static); misreading of code (aminoglycosides only)—incorporation of wrong amino acid (–cidal)
2. Amino-acid incorporation	Tetracyclines (30S) Dalfopristin/ quinupristin (50S)	Block the attachment of aminoacyl tRNA to acceptor site (–static)
3. Formation of peptide bond	Chloramphenicol (50S)	Inhibit the activity of peptidyltransferase (–static)
4. Translocation	Macrolides and clindamycin (50S)	Inhibit translocation of peptidyl-tRNA from acceptor to donor site (–static)

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ANTI-MICROBIALS: Bacterial Protein Synthesis Inhibitors – *Bacteriostatic (except AGs)*

DRUG	MECHANISM	DISTRIBUTION/ RESISTANCE	INDICATION	ADVERSE EFFECTS
AMINOGLYCOSIDES *Poor oral absorption* *IM/IV ADMINISTRATION* **SINGLE DAILY DOSE**	**BACTERICIDAL** for **Gram-Neg Aerobic Rods** **IRREVERSIBLY** bind **30S** subunit – Interfere w/ Initiation Complex formation by blocking 50S from mRNA-30S – ***Misreading of mRNA****: incorporation of incorrect AAs into the peptide → non-functional or* ***toxic protein*** **O_2DEPENDENT** TRANSPORT Transport enhanced w/ **PCN or Vanc** ***CDKR + PAE**	**INNATE**: Anaerobes (cytoplasm) **INACTIVATED BY ACETYLATION, ADENYLATION, PHOSPHORYLATION** – **PLASMID-MEDIATED** synthesis of inactivating enzymes **IMPAIRED ENTRY INTO THE CELL** **MUTATION OF RECEPTOR PROTEIN ON 30S RIBOSOME**	**EFFECT AGAINST P. AERUGINOSA: TAG Tobramycin > Amikacin > Gentamycin** ***CAUTION in Myasthenia Gravis***	*Narrow TI* **OTOTOXICITY:** auditory hair cell damage → tinnitus, hearing loss, vestibular damage (vertigo & ataxia) ***Enhanced by Loop Diuretics*** **NEPHROTOXICITY:** Acute Tubular Necrosis → ↓GFR, proteinuria, hypokalemia, acidosis; ***Enhanced by Vanc, Amphoter B, Cisplatin, Cyclosporin*** **NEUROMUSCULAR BLOCKADE:** Curare-like w/ **respiratory paralysis** **Treat w/ NEOSTIGMINE + Ca^2 Gluconates**
STREPTOMYCIN			**DRUG OF CHOICE:** **BUBONIC PLAGUE** (+ Doxycycline) **TULAREMIA, 2nd LINE FOR TB** Endocarditis: Streptomycin + PCN	***Contraindicated*** *in pregnant (deafness in newborn)*
GENTAMYCIN	**Active against P. AERUOGINOSA,** Klebsiella, Proteus, Serratia, E. coli, Enterobacter	Streptococci & Enterococci are relatively resistant due to failure of drug to penetrate into cell – *Given w/ Vanc or Penicillin*	**BRUCELLOSIS** (+ Doxycycline) TULAREMIA	
TOBRAMYCIN			**P. AERUGINOSA**	
PAROMOMYCIN	Only AG active against **Protozoan Infections**		*Entamoeba histolytica* Cryptosporidium parvum Visceral leishmaniasis Tapeworms (taenia solium)	
NEOMYCIN	Topical use only Kills ammonium producing bacteria		Minor soft-tissue infections: **Triple Abx: Neomycin + Bacitracin + Polymyxin** **Hepatic Encephalopathy** **Prep for bowel surgery w/ Erythromucin**	***Not used anymore because nephrotoxicity & deafness*** **Contact Dermatitis**
SEMISYNTHETIC: **AMIKACIN**	**More potent against P. AERUOGINOSA than Gentamycin**	**LESS VULNERABLE TO INACTIVATING ENZYMES MENTIONED ABOVE!****	**2nd LINE FOR MDR TB** Gentamycin-resistant bacteria	
SPECTINOMYCIN **AMINOCYCLITOL**	Structurally similar to AGs Binds **30S** subunit		**ALTERNATIVE for GONORRHEA in PENICILLIN-ALLERGIC PATIENTS**	

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ANTI-MICROBIALS: Bacterial Protein Synthesis Inhibitors – *Bacteriostatic (except AGs)*

DRUG	MECHANISM	DISTRIBUTION/ RESISTANCE	INDICATION	ADVERSE EFFECTS
TETRACYCLINES *Oral or IV ADMINISTRATION* ***(NOT IM – Pain + Inflammation)***	**BACTERIOSTATIC;** Broad spectrum antibiotics **REVERSIBLY** bind 30S subunit – Blocking aminoacyl tRNA attachment at A site – Inhibits elongation **Gram-Positive:** Streptococcus **Gram-Neg:** *Neisseria, H. pylori, H. ducrei, V. cholera* **Protozoa:** *plasmodium falciparum, entamoeba histolytica* **Anaerobes:** *C. perfringenes, C. tetani* **Oral Absorption is IMPAIRED by:** chelation w/ Ca^{2+}, Mg^{2+}, Fe^{2+}, Al^{3+} & dairy foods & antacids	Enter CSF but levels are insufficient for therapeutic efficacy (*except Minocycline)* **Plasmid-mediated decreased intraceullar accumulation of drug:** **EFFLUX PUMP (P-GLYCOPROTEIN)**	Chloroquine-resistant Malaria **Acne prophylaxis** Chronic Bronchitis Plague/Tularemia (DOC: Streptomycin) ***Contraindicated** in pregnancy (**bone deformities & tooth dysplasia**)*, pre-pubertal children (<8yrs), hepatic or renal disease*	**SUPERINFECTIONS** *(C. diff, P. aeruginosa, Proteus, Yeast)* higher than in other antibiotics: **PSEUDOMEMBRANOUS COLITIS** **GI upset *most common** **Tooth enamel dysplasia + ↓bone growth in children!** **RENAL: *Fanconi Syndrome** w/ outdated preparations **HEPATOTOXICITY especially in pregnancy & hx of liver disease**
DOXYCYCLINE* *Complete oral absorption*	Eliminated by **LIVER/BILE** – ***safe in renal patients***		**DOC: Chlamydia (Atypical), Rickettsiae (RMSF), Mycoplasma, LYME DISEASE, Cholera** **ALTERNATIVE FOR TULAREMIA**	**Phototoxicity** ***Vestibular Toxicity***
TETRACYCLINE				**Phototoxicity**
DEMECLOCYCLINE	Blocks ADH receptor in collecting ducts		**DOC: SIADH**	**Diabetes Insipidus** **Phototoxicity**
MINOCYCLINE *Complete oral absorption*		**ONLY TETRACYCLINE THAT REACHES THERAPETIC LEVELS IN CSF**	2nd: Eradication of **Meningococcal Carrier State**	***Vestibular Toxicity***
TIGECYCLINE *Slow IV infusion*	**GLYCYLCYCLINE** **BACTERIOSTATIC** Binds to 30S & blocks entry of aminoacyl t-RNA to A site Eliminated by **BILE/FECAL** – *safe in renal failure patients*		**MRSA, MDR *S. pneumo, VRE*** Treatment of skin infections, intra-abdominal infections, & CAP	

ANTI-MICROBIALS: Bacterial Protein Synthesis Inhibitors – *Bacteriostatic (except AGs)*

DRUG	MECHANISM	DISTRIBUTION/ RESISTANCE	INDICATION	ADVERSE EFFECTS
MACROLIDES	**BACTERIOSTATIC** **IRREVERSIBLY** binds to **50S** subunit & inhibits **translocation**	1. **↓affinity of 50S subunit** (methylation prevents binding of drug) 2. **Plasmid associated erythromycin esterase**** 3. **Inability to penetrate/↑efflux**	****PENICILLIN ALLERGY PATIENTS**** ***Contraindicated in liver failure***	**GIT problems (anorexia, NVD)** **Most common side effects* **MACRO**: GI **M**otility, **A**rrhythmia (QT), **C**holestatic hepatitis, **R**ash, e**O**sinophilia
ERYTHROMYCIN *Acid labile* *Poor bioavailability* *Given with **enteric coating***	Excreted in **BILE – *safe in renal patients***	Distributes will to all body fluids, *except the brain & CSF*; ****ACCUMULATES IN MACROPHAGES**	*Alternative for ATYPICAL microbes* **DOC: PERTUSSIS*** **DOC: PREGNANCY CHLAMYDIA & MYCOPLASMA** **DIPTHERIA Eradicate Carrier State** ***PCN-ALLERGIC PATIENTS: Syphilis, Staph/Strep/Pneumococcal** **SAFE IN PREGNANCY**	**Inhibits many CYP450 enzymes:** ↑ levels of *theophylline, warfarin, cyclosporine, methylprednisone* ***DIGOXIN TOXICITY*** **Long QT** ***CHOLESTATIC JAUNDICE* (with *ESTOLATE Erythromycin*): fever, jaundice, impaired liver function, hypersensitivity reactions
CLARITHROMYCIN *Acid-stable* *Good oral absorption*	*Longer half-life than Erythromycin* Excreted in **BILE – *safe in renal patients***	Erythromycin-resistant streptococci & staphylococci are also resistant to Clarithromycin	**DOC: *H. pylori*** ***M. leprae*, *Toxoplasma gondii***	**Inhibits many CYP450 enzymes:** ↑ levels of *theophylline, warfarin, cyclosporine, methylprednisone* ***DIGOXIN TOXICITY***
AZITHROMYCIN *Acid-stable* *Good oral absorption*	*Longer half-life than Erythromycin* Penetrates phagocytic cells extremely well Excreted by the **KIDNEY**		Respiratory Infections** *H. influenza*** **DOC: Legionella, *Myco. avium*** **2nd choice: CHLAMYDIA (pregnancy)**	***Free of drug interactions* ☺** ***Use this instead of Erythromycin if patient's drugs metabolized by CYP450***
KETOLIDES	Similar to Macrolides		**Patients allergic to β-lactams**	

CLINDAMYCIN **Treats Anaerobic infections ABOVE diaphragm	Not a macrolide, but has same mechanism of action & resistance	1. **↓affinity of 50S subunit** (ribosomal protection) 2. **Plasmid associated erythromycin esterase**** 3. **Inability to penetrate/↑efflux** ***C. difficle is resistant to clinda!***	**DOC: *C. TETANI & PERFRINGINS* (+ PCN)** **Anaerobic: *Bacteroides fragilis*** **PROPHYLAXIS: Endocarditis in valve disease (DENTAL SURGERY IN PCN-ALLERGY)*** Clinda+**Primaquine**: alternative to SXT for *P jiroveci* pneumonia (AIDS) **Clinda+Pyrimethamine**: (AIDS) *Toxoplasmosis* of brain	**Nausea, diarrhea, skin rash** **PSEUDOMEMBRANOUS COLITIS** **Impaired liver function** **Neutropenia**

Green = Kaplan, Deja. First Aid, or Tulane

ANTI-MICROBIALS: Bacterial Protein Synthesis Inhibitors – *Bacteriostatic (except AGs)*

DRUG	MECHANISM	DISTRIBUTION/ RESISTANCE	INDICATION	ADVERSE EFFECTS
CHLORAMPHENICOL **Chloramphenicol Palmitate:** PO **Chloramphenical Succinate:** Parenterally*	**BACTERIOSTATIC,** broad-spectrum abx Binds **REVERSIBLY** to the 50S subunit & prevents **peptidyltransferase enzyme** Metabolized by **GLUCURONIDE CONJUGATE** by the **LIVER** & excreted in urine ***Can antagonize 14nfluenza14al drugs, i.e. PCN & Ags***	Distributes to most tissues & secretions; **CROSSES BBB** Production of **acetyltransferase** capable of inactivating the drugs allows for resistance	***ALTERNATIVE DRUG FOR:*** **Meningococcal meningitis (β-lactam allergy)** **RICKETTSIAE** *(DOC: doxycycline)* **Bacteroides** with penicillin – *brain injection* **Typhoid Fever** *(DOC: azithromycin)* ***H. 14nfluenza*** ****NOT EFFECTIVE IN CHLAMYDIA*** ***Contraindicated in premature neonates*** *(lack glucuronide conjugation & detoxification)* – **GREY BABY SYNDROME**	**Inhibits CYP450 enzymes** GI: NVD BONE MARROW SUPPRESSION **&** **APLASTIC ANEMIA** (dose dependent) **ORAL or VAGINAL CANDIDIASIS**

DRUG	MECHANISM	DISTRIBUTION/ RESISTANCE	INDICATION	ADVERSE EFFECTS
STREPTOGRAMINS **QUINUPRISTIN-DALFOPRISTIN**	**BACTERIOCIDAL** Each part binds to a separate site on 50S ribosome & synergistically interrupts protein synthesis		**DOC: VRSA & VRE** ***(faecium)***	**Infusion related events:** pain & **Arthralgia-Myalgia Syndrome**

DRUG	MECHANISM	DISTRIBUTION/ RESISTANCE	INDICATION	ADVERSE EFFECTS
LINEZOLID	**BACTERIOSTATIC** Binds 50S subunit & inhibits formation of **70S initiation complex** Metabolized in LIVER Excreted in KIDNEY	Point mutation of rRNA: ↓affinity	**DOC: VRSA, VRE, MDR-Tb** Drug-resistant pneumococci	Thrombocytopenia, Anemia, Neutropenia **Serotonin Syndrome** *if given w/ SSRIs*

ANTI-MICROBIALS: Nucleic Acid Synthesis Inhibitors – *Bacteriocidal*

DRUG	MECHANISM	DISTRIBUTION/ RESISTANCE	INDICATION	ADVERSE EFFECTS
QUINOLONES	Synthetic; primarily against Gram-Neg			
NALIDIXIC ACID	**BACTERIOCIDAL**: Inhibits DNA gyrase (Top2) High concentration in urine		*Urinary anti-septic & lower UTIs*	Neurological toxicity: seizures Hemolysis in G6PD Deficiency
FLUORO-QUINOLONES *Good oral absorption*	**BACTERIOCIDAL** Synthetic fluorinated analogs of Nalidixic Acid Inhibit **Topoisomerase 2 & 4** – inhibits releasing → cell death by DNA cleavage **CDKR & PAE** Metabolized in the **LIVER.** Excreted by KIDNEY. **(Inhibited by PROBENECID)** ****CHELATORS**	High tissue penetration: *bone, prostate & phagocytes > plasma* 1. Mutation in Topo 2 & 4 2. Aminoglycoside acetyltransferase (inactivation)	**DOC:** **OSTEOMYELITIS** (except Norfloxacin) ALTERNATIVE FOR: LEGIONELLA, MDR-Tb ***Contraindicated in pregnancy & under 18***	Phototoxicity: rashes GI: NVD **CARTILAGE DAMAGE, TENDONITIS** ****Rupture of Achille's Tendon** Insomnia, dizziness, HA, seizures Prolonged QT **NSAIDs enhances the CNS toxicity of FQs – *seizures***
CIPROFLOXACIN	**BACTERIOCIDAL & Highly Potent**		**DOC: ANTHRAX, COMPLICATED UTI, PYELONEPHRITIS, TYPHOID FEVER, GASTROENTERITIS** (*Shigella, Salmonella, E. coli)* RTIs unresponsive to β-lactams **ALTERNATIVE FOR GONORRHEA**	**Inhibits CYP450 enzyme**
LEVOFLOXACIN			**DOC: TYPHOID FEVER** **COMMUNITY ACQUIRED PNEUMO*** **Prostatitis – E. coli & STD** (*except Syphilis)*	
GATIFLOXACIN			RTI due to *S. pneumoniae*	Not used in USA due to toxicity
MOXIFLOXACIN			Gram-Pos & Anaerobes (*B. fragilis)* *Poor activity against P. aeruginosa*	
NORFLOXACIN	***Not effective in systemic infections*		Compicated/Uncomplicated UTI Prostatitis	

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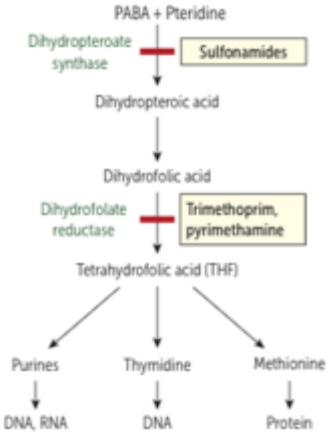
ANTI-MICROBIALS: Folic Acid Synthesis Inhibitors



DRUG	MECHANISM	DISTRIBUTION/ RESISTANCE	INDICATION	ADVERSE EFFECTS
SULFONAMIDES *Well-absorbed in GIT* ***Many are used in combo w/ other drugs due to ↑resistance***	**BACTERIOSTATIC** ***Structural analogs of PABA*** (competitive) Inhibits **DIHYDROPTEROATE SYNTHASE*** Metabolized by **acetylation & glucuronidation** in the liver	Penetrates CSF	***Contraindicated in late pregnancy – kernicterus*** *in newborns*	**Phototoxicity** **CRYSTALLURIA**, hematuria, renal failure **Hypersensitivity:** Stevens-Johnson, fever, exfoliative dermatitis ****HEMOLYSIS in G6PD DEFICIENCY**
SULFADOXINE + PYRIMETHAMINE			MALARIA	
SULFADIAZINE + PYRIMETHAMINE			**DOC: TOXOPLASMOSIS**	
SULFAPYRIDINE + 5-ASA (Sulfasalazine)			ULCERATIVE COLITIS & RHEUMATOID ARTHRITIS	
SULFACETAMINDE	*Topical*		**Bacterial conjunctivitis**	
SILVER SULFADIAZINE	*Topical;* **Releases silver ions**		**Burn dressings + ulcers**	
TRIMETHOPRIM	**BACTERIOSTATIC** Inhibits **DIHYDROFOLATE REDUCTASE**, prevents conversion of DHF to THF & prevents synthesis of purines	**TRIMETHOPRIM** 1. ↓permeability 2. Overproduction of DHFR 3. **Production of altered reductase & ↓affinity**	**Acute UTI** **Prostatitis** *Concentrates in* ***prostatic fluid & vaginal fluid***	**TMP: Treats Marrow Poorly** **Bone marrow suppression** **Enterocolitis**
SULFAMETHOXAZOLE + TRIMETHOPRIM (Cotrimoxazole)	**BACTERIOCIDAL*** Causes the sequential blockage of folate metabolism 5S:1T dose ratio → plasma conc. of 20:1	**SULFAMETHOXAZOLE:** 1. Overproduction of PABA 2. **Production of folic acid synthesizing enzyme w/ ↓affinity** 3. Impair permeability	**DOC: *P. jiroveci* in AIDS, NOCARDIA, PERTUSSIS** (in Macrolide allergeric pt), **UNCOMPLICATED UTI** **ALTERNATIVE FOR LISTERIA**	

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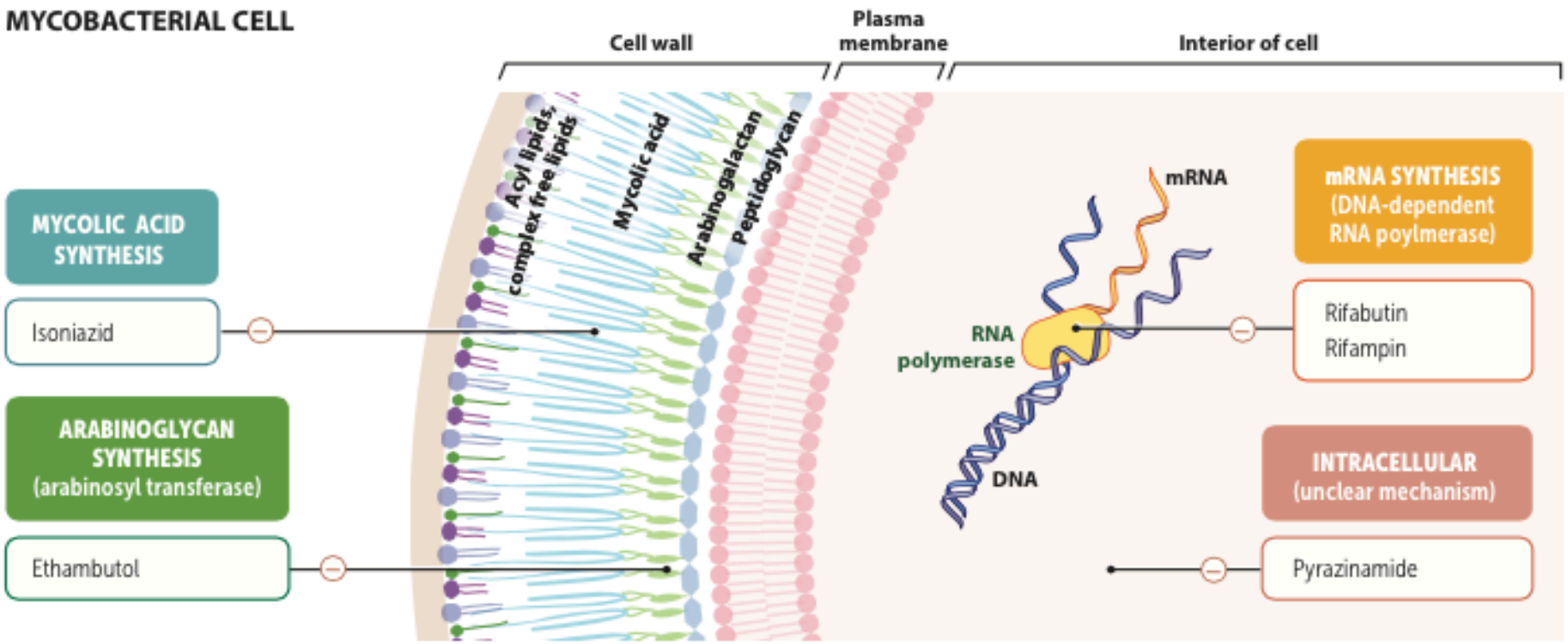

Active Tb Treatment:

- **INITIAL PHASE: Empiric 4 drug regimen**
  - **RIPE x2 months**
- **CONTINUATION PHASE: 3 drug regiment**
  - **RI+P (or E w/ liver disease) x6 months**

RESISTANCE IN Tb INFECTION:

- **PRIMARY RESISTANCE:** infection w/ resistant organisms
- **ACQUIRED RESISTANCE:** develops during Tb therapy
- **MDR-RB:** Tb resistant to Isoniazid & Rifampin;
  - **Treat w/ combo of 2nd line drugs** *for ~2 years*

Latent Tb Treatment:

- **Isoniazid x9 months**
- *Alternative: Isoniazid + Rifapentine (DOT) weekly x9 months*

MDR Latent Tb Treatment:

- **Combo of 2 drugs** (Pyrazinamide + Ethanmutol or FQ) **x9-12 months**

XDR TB:

- Resisnt to INH & RIF + any FQ + at least one of the other injectable Tb drugs (amikacin, kanamycin, capreomycin)
- *Needs up to 2 years of extensive drug treatment*

ANTI-MYCOBACTERIAL DRUGS: Tuberculosis

1st LINE DRUGS FOR TUBERCULOSIS: '*RIPE*' – *Rifampin, Isoniazid, Pyrazinamide, Ethambutol*

DRUG	MECHANISM	DISTRIBUTION/ RESISTANCE	INDICATION	ADVERSE EFFECTS
RIFAMPIN **R**ifampin's **4 R's:** **R**NA pol inhibitor **R**amps up CYP450 **R**ed/orange body fluids **R**apid resistance, *if used alone*	**BACTERIOCIDAL** **Rapidly growing & semi-dormant** Binds to **β subunit** & **inhibits DNA-dependent RNA polymerase**	Resistance from point mutations in **rpoB**	**DOC: Eradication of Meningococcal Carrier State** ***Contraindicated in HIV*** ***Use RIFABUTIN/RIFAPENTINE**	**HEPATOTOXICITY → Hepatitis** Pruritis, rash, fever, flu-like sympoms **Thrombocytopenia** **ORANGE DISCOLORATION OF FLUIDS** **ENZYME INDUCER: (CYP450)** ↓serum levels of oral contraceptives, **WARFARIN**, etc.
ISONIAZID	**BACTERIOCIDAL** **Rapidly dividing** **PRO-DRUG** activated by *Mycobacterial catalase-peroxidase* ***(katG*)*** Irreversibly binds to AcpM & KasA to **block mycolic acid synthesis**	1. Mutation of ***katG**** 2. Mutation in *kasA* gene 3. Overexpression of InhA **low level resistance & cross-resistance to ethionamide* 4. Overexpression of ahpC, protection from oxidative stress		**HEPATITIS*** **PERIPHERAL NEUROPATHY** **Prophylaxis w/ Vitamin B6* **RED-ORANGE URINE**: ***monitor compliance*** Drug-induced SLE
PYRAZINAMIDE	**BACTERIOSTATIC** **DORMANT organisms in macrophages;** Inhibits mycobacterial FA synthesis by targeting **FATTY ACID SYNTHASE I** *interrupting cell membrane*			Hepatotoxicity Hyperuricemia – ***monitoring*** Asymptomatic (most) or **GOUT** (rare)
ETHAMBUTOL	**BACTERIOSTATIC at low doses** **BACTERIOCIDAL at high doses** **Rapidly growing** Inhibits formation of **arabinogalactan polysaccharide layer**		***Prevent growth of drug-resistance***	**Retrobulbar neuritis** **Use for monitoring: visual acuity test & color discrimination*

ANTI-MYCOBACTERIAL DRUGS: Tuberculosis

2nd LINE DRUGS FOR TUBERCULOSIS:

DRUG	MECHANISM	DISTRIBUTION/ RESISTANCE	INDICATION	ADVERSE EFFECTS
STREPTOMYCIN	*Aminoglycoside*	Point mutation in either rpsL gene encoding S12 ribosomal protein or the rrs gene encoding 16s rRNA		
AMIKACIN, KANAMYCIN	*Aminoglycosides*			
CAPREOMYCIN	*Cyclic glycopeptide* Inhibit RNA synthesis via formation of **30S** subunit initiation complex & blockage of tRNA translocation from the A to the P site	***Aminoglycoside cross-resistance***	***3rd line drug***	Ototoxicity, Nephrotoxicity (↑BUN), ↑Neuromuscular block effects of severealdrugs, Electrolyte disturbances
LEVOFLOXACIN, CIPRO-, MOXIFLOXACIN	*Fluoroquinolones* Target DNA gyrase		**Drug-resistant Tb**	Nausea, bloating Cutaneous: rash & photosensitivity
THIONAMIDES: Ethionamide, Prothionamide	Inhibit mycolic acid synthesis	***Cross-resistance with INH via inhA mutation***		GI upset (poorly tolerated) **Hepatotoxicity** Neuropathy (Prophylaxis: Vitamin B6) **Hypothyroidism**
CYCLOSERINE	**BACTERIOSTATIC** *Analog of D-alanine* Blocks peptide formation	Wide distribution + **CSF*** *No cross-resistance with any other Tb drug!**		**CNS effects** (psychiatric + seizres) **Worse with Ethioamide & Isoniazid* ***↑ seizures w/ ETOH* ↑Phenytoin levels **Vitamin B2 decreases CNS side effects**
PAS: Para-aminosalicylic acid	Folate synthesis antagonist			Nausea, vomiting Hepatotoxicity Malabsorption (steatorrhea, low folate level) Hypothyroidism **Coagulopathy (Doubles PT time)**
BEDAQUILINE	Inhibits ATP synthase in mycobacteria **Replicating & non-replicating**	*No cross-resistance with any other Tb drug!**	**Lab-confirmed MDR-Tb** *With 3+ others x 24weeks*	

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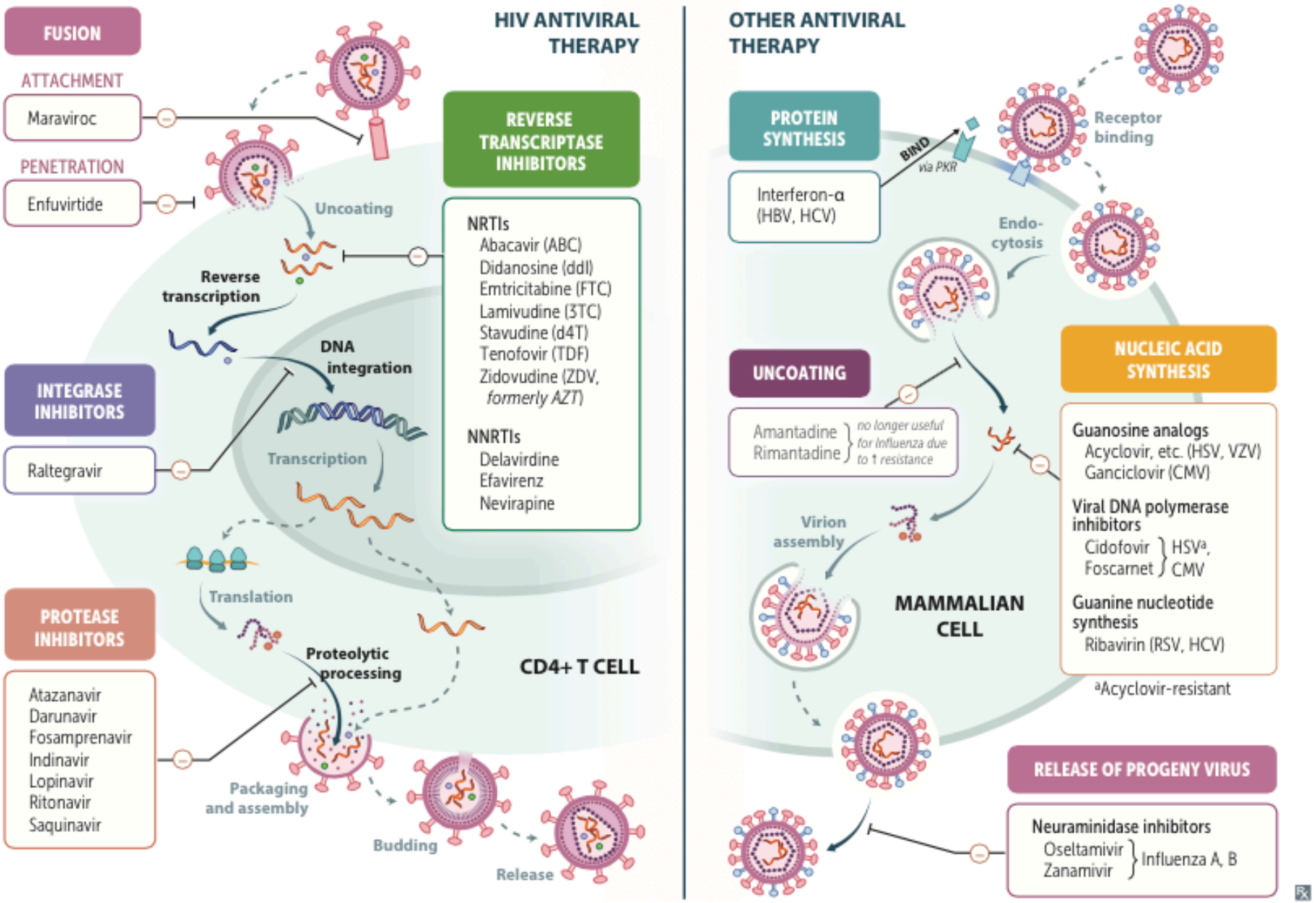
ANTI-MYCOBACTERIAL DRUGS: Leprosy

MULTIBACILLARY (BM) PATIENTS: *Rifampicin + Clofazimine + Dapsone*
PAUCIBACILLARY (PB) PATIENTS: *Rifampicin + Dapsone*

DRUG	MECHANISM	ADVERSE EFFECTS
RIFAMPIN	**ONLY DRUG HIGHLY BACTERICIDAL AGAINST M. LEPRAE** Given one a month	**RED URINE**
DAPSONE (+ Iron)	*Sulfone drug* ***folate synthesis antagonist*** Weakly bactericidal against *M. leprae*	**Hemolytic anemia**, Hepatitis Neuropathy, Agranulocytosis **DAPSONE SYNDROME:** *fever, enlarged LN, exfoliative dermatitis, hepatitis, MP rash*
CLOFAZIMINE	Anti-leprosy & anti-inflammatory properties Suppresses & prevents reactions **BACTERIOCIDAL** **Binds to bacterial DNA guanine bases** ↑Activity of bacterial PLA2 → release & accumulation of lsophospholiids (toxic to bacteria)	
Ofloxacin	FQ effective in Leprosy	Rare & generally mild
Minocycline	Moderately active against leprosy at 100 mg qd	

Antiviral therapy



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ANTI-VIRALS DRUGS: Herpes Virus Infections (HSV, VZV)

DRUG	MECHANISM	DISTRIBUTION/ RESISTANCE	INDICATION	ADVERSE EFFECTS
ACYCLOVIR *Poor oral absorption*	*Guanine analog* Sequentially activated by **viral thymidine kinase** & then by **host cellular kinase** to *acyclovir-TP* *Competes with dGTP for viral DNA polymerase* → → ***terminates chain elongation*** Cleared by **GRF & tubular secretion** (Half life depends on *renal function*)	Resistances in HSV or VZV: 1. **Mutation in thymidine kinase** 2. **↓thymidine kinase activity → cross-resistnce with all clovirs** 3. DNA pol mutation CMV is resistant	**HSV1 & HSV-2 Tx & Prophylaxis** **Genital Herpes (HSV II)** **Mucocutaneous (HSV I – lips/gums)** **H. Simplex Keratitis (HSV I)** **Herpes zoster (VZV) – SHINGLES CHICKEN POX (VZV)**	**RENAL DYSFUNCTION** NVD CNS: tremors, lethargy **Crystalline Nephropathy** w/ IV
VALACYCLOVIR	**Pro-drug** metabolized to Acyclovir *Prolonged release of acyclovir*		**HSV, VZV**	
FAMCICLOVIR	Pro-drug metabolized to Penciclovir		**HSV1 & HSV-2**	
PENCICLOVIR *Not absorbed orally*	Similar activity to Acyclovir when given IV *Not chain terminating, but achieves **higher intracellular levels than Acyclovir***		**HSV1 & HSV-2**	
DOCOSANOL (ABREVA)	Aliphatic alcohol; **inhibits fusion** between **host cell plasma membrane** & **HSV envelope**		Topical agent for HSV	
IDOXURIDINE **TRIFLURIDINE**	*Thymidine analogs* Triphosphorylated to active drugs that inhibit DNA polymerase		Topical agent for HSV *Useful for acyclovir-resistant HSV infections*	
FOSCARNET *IV only*	*Pyrofosphate (PPi) analog* Specifically inhibits **DNA polymerase, RNA polymerase, & HIV RT** by competing for the PP binding site	Mutation in DNA polymerase	**Acyclovir-resistant HSV or VSV** **Alternative: CMV retinitis (DOC: ganciclovir)**	**Nephrotoxicity** **Hypocalcemia** (tetany) **Hypokalemia & hypomagnesemia**

ANTI-VIRALS DRUGS: Herpes Virus Infections (CMV)

DRUG	MECHANISM	DISTRIBUTION/ RESISTANCE	INDICATION	ADVERSE EFFECTS
GANCICLOVIR *Poor oral absorption* *IV, Intraocular implant*	*Guanosine analog* Activated via phosphorylation by virus-specified protein kinase then by host kinase **Terminates viral DNA elongation**		**DOC: CMV RETINITIS**	
VALFANCICLOVIR *Oral only*	Pro-drug metabolized to Ganciclovir *Higher bioavailability*		**DOC: CMV RETINITIS** **CMV prophylaxis (transplant pts)**	
CIDOFOVIR			**CMV retinitis + Adenovirus**	

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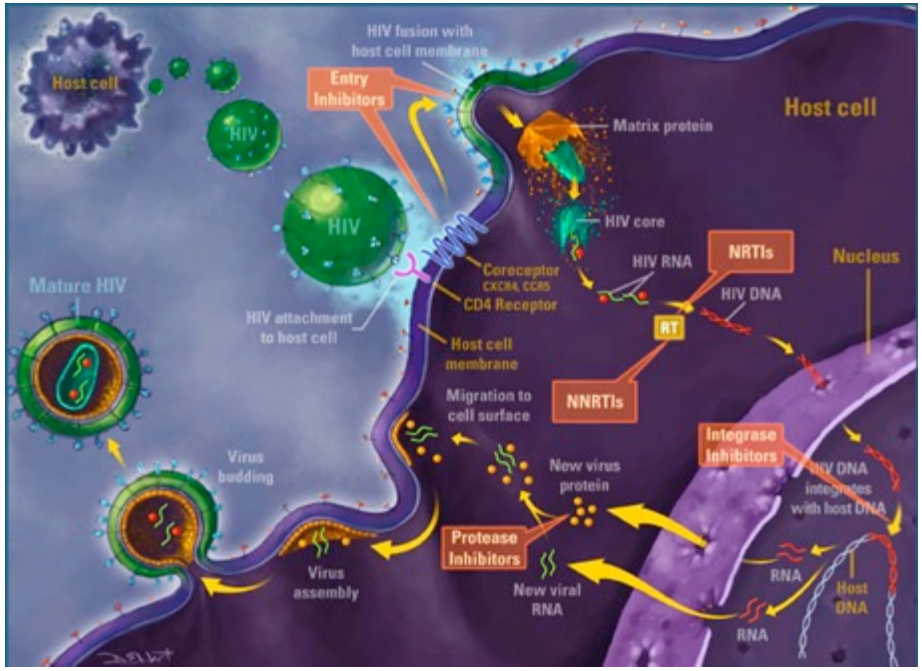
ANTI-VIRALS DRUGS: Influenza Virus Infections

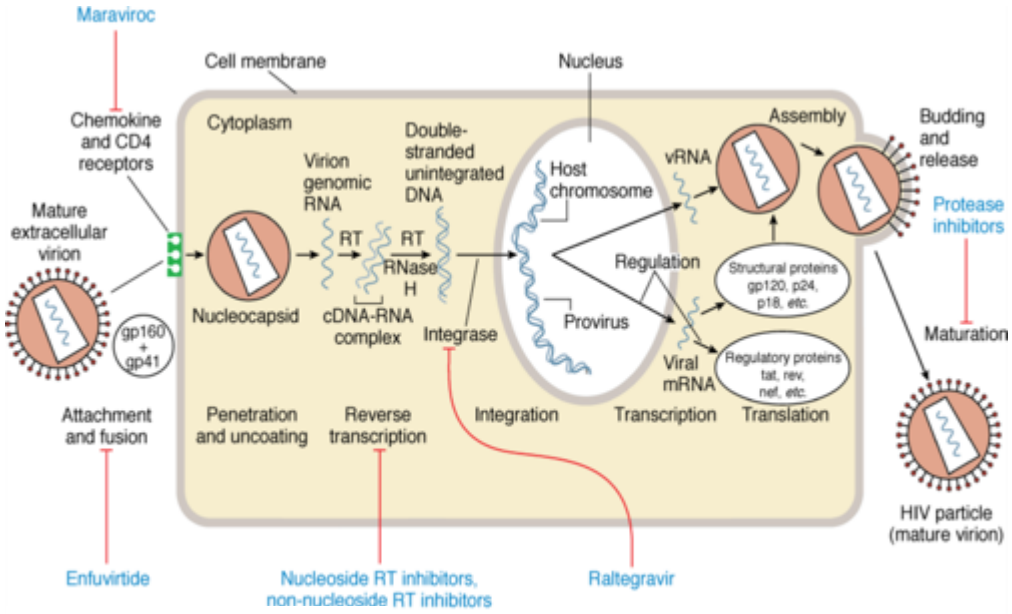
DRUG	MECHANISM	DISTRIBUTION/ RESISTANCE	INDICATION	ADVERSE EFFECTS
AMANTANDINE RIMANTADINE	Prevent uncoating of Influenza A by binding to M2 PROTEIN – *affect maturation of influenza HA glycoprotein in trans-golgi network*	Mutations in M2 protein	INFLUENZA A Prophylaxis & Early Tx	Nausea, llightheadedness, insomnia
OSELTAMIVIR *(Pro-drug)* **ZANAMIVIR** ***Inhalation***	Selectively inhibit viral **neuraminidases** of Influenza A & B, including H1N1 & H5N1 → **prevents virion release**	Neuraminidase mutations	**INFLUENZA A & B**	Oseltamivir: GI disturbance Zanamivir: bronchospasm

ANTI-VIRALS DRUGS: Viral Hepatitis Infections

DRUG	MECHANISM	DISTRIBUTION/ RESISTANCE	INDICATION	ADVERSE EFFECTS
INTERFERON *Parenteral routes*	*Glycoproteins* produced ***naturally*** by cells in immune system after exposure to viruses Binds cell surface-R & induces expression of **Translation Inhibitory Protein (TIP)** → Binds ribosome, **inhibits expression of viral proteins**	Broad-spectrum anti-viral	**IFNα-2b – Chronic Active HBV** (HBeAg+) **IFNα-2b + Ribavirin – Chronic Active HCV** HSV1&2, VZV, HPV Breast ca, lung ca, Kaposi sarcoma	Flu-like symptoms (HA, fatigue, asthenia, myalgia, arthralgia, fever) Neuropsychiatric (depression) ALOPECIA **Thyroiditis: *can mask or exacerbate***
LAMIVUDINE	***Cytosine*** *nucleoside analog* **Inhibits HBV DNA polymerase** (also HIV RT)	*Rapid emergence of drug resistance*	**HBV**	Well-tolerated
ADEFOVIR DIPIVOXIL	***Adenine*** *nucleotide analog* Phosphorylated by active diphosphate metabolite **Competitively inhibits HBV DNA pol** & causes **chain termination after incorpation into vDNA**	*In vitro broad*-spectrum	**Lamivudine-resistant HBV** HIV & HSV	
ENTECAVIR *Oral bioavailability 100%*	***Guanosine*** *nucleoside analog* **Competitively inhibits all 3 functions of HBV:** 1. **DNA polymerase** 2. Reverse Transcriptase 3. Synthesis of + strand of HBV DNA		**Alternative: HBV** Successful response results in: – Disappearance of HBsAg, HBV-DNA – **Seroconversion to HBeAg**	
TELAPREVIR	Inhibits HBV DNA polymerase			
RIBAVIRIN	***Guanosine*** *analog* Phosphorylated by host cell to **ACTIVE DRUG** Interferes with synthesis of GTP; **Inhibits viral RNA-dependent DNA polymerase & capping of viral mRNA** Triphosphate inhibits replication of wide-range		**Chronic HCV** (In combination w/ IFN) **RSV**	
Pegylated IFNα *SubQ*			**Chronic HCV**	

Anti-HIV Drugs





HIV INFECTION & REPLICATION

1. Viral transmission
2. Primary HIV infection
3. Sero-conversion (Flu-like)
4. Asymptomatic chronic infection w/ or w/out persistent generalized lymphadenopathy
5. Sympatomatic HIV infection
6. **AIDS** (presence of AIDS indicator conditions or CD4 cell count <200/mL)
7. **Advanced HIV infection (CD4 cell count <50/mL)**

Opportunistic infections: *toxoplasma, P. jiroveci, Shingles, thrush, Tb*

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HIV therapy

Highly active antiretroviral therapy (HAART): often initiated at the time of HIV diagnosis. Strongest indication for patients presenting with AIDS-defining illness, low CD4+ cell counts (< 500 cells/mm^3), or high viral load. Regimen consists of 3 drugs to prevent resistance: 2 NRTIs *and* 1 of the following: NNRTI *or* protease inhibitor *or* integrase inhibitor.

DRUG	MECHANISM	TOXICITY
Protease inhibitors		
Atazanavir Darunavir Fosamprenavir Indinavir Lopinavir Ritonavir Saquinavir	Assembly of virions depends on HIV-1 protease (*pol* gene), which cleaves the polypeptide products of HIV mRNA into their functional parts. Thus, protease inhibitors prevent maturation of new viruses. Ritonavir can "boost" other drug concentrations by inhibiting cytochrome P-450. All protease inhibitors end in *-navir*. Navir (never) tease a protease.	Hyperglycemia, GI intolerance (nausea, diarrhea), lipodystrophy. Nephropathy, hematuria (indinavir). Rifampin (a potent CYP/UGT inducer) contraindicated with protease inhibitors because it can decrease protease inhibitor concentration.
NRTIs		
Abacavir (ABC) Didanosine (ddI) Emtricitabine (FTC) Lamivudine (3TC) Stavudine (d4T) Tenofovir (TDF) Zidovudine (ZDV, formerly AZT)	Competitively inhibit nucleotide binding to reverse transcriptase and terminate the DNA chain (lack a 3′ OH group). Tenofovir is a nucleoTide; the others are nucleosides and need to be phosphorylated to be active. ZDV is used for general prophylaxis and during pregnancy to ↓ risk of fetal transmission. Have you dined (vudine) with my nuclear (nucleosides) family?	Bone marrow suppression (can be reversed with granulocyte colony-stimulating factor [G-CSF] and erythropoietin), peripheral neuropathy, lactic acidosis (nucleosides), anemia (ZDV), pancreatitis (didanosine).
NNRTIs		
Delavirdine Efavirenz Nevirapine	Bind to reverse transcriptase at site different from NRTIs. Do not require phosphorylation to be active or compete with nucleotides.	Rash and hepatotoxicity are common to all NNRTIs. Vivid dreams and CNS symptoms are common with efavirenz. Delavirdine and efavirenz are contraindicated in pregnancy.
Integrase inhibitors		
Raltegravir	Inhibits HIV genome integration into host cell chromosome by reversibly inhibiting HIV integrase.	↑ creatine kinase.
Fusion inhibitors		
Enfuvirtide	Binds gp41, inhibiting viral entry.	Skin reaction at injection sites.
Maraviroc	Binds CCR-5 on surface of T cells/monocytes, inhibiting interaction with gp120.	

ANTI-HIV DRUGS: Nucloside & Nucleotide Reverse Transcriptase Inhibitors (NRTIs)

DRUG	MECHANISM	DISTRIBUTION/ RESISTANCE	INDICATION	ADVERSE EFFECTS
Competitive Inhibitors of RT	**Nucleosides:** Phosphorylated to active metabolites that compete with endogenous nucleosides for incorporation into viral DNA; *competitive inhibitor HIV RT & **terminate** synthesis of DNA chains* *Nucleoside analogs triphosphorylated inside cells to active; incorporated into growing DNA by RT *RAPID RESISTANCE WHEN NUCLEOSIDE ADMINISTERED IS A SINGLE AGENT **Nucleotides:** *competitive inhibitor HIV RT, but **do not require initial phosphorylation*** *Nucleotide analogs do not need to be tri-phosphorylated, only diphosphorylated to active compound **RENAL EXCRETION:** *reduce dose in renal function*			***LACTIC ACIDOSIS** **Hepatomegaly + Steatosis** Hepatitis, Pancreatitis BM suppression (anemia)
ZIDOVUDINE (AZT, AZIDOTHYMIDINE) *Active orally*	*Nucleoside analog*	Wide distribution Resistance: **RT mutations**	**NRTI DOC: PEDS + PREGNANCY** **Prevents vertical transmission*	Peripheral neuropathy **MYOPATHY, CARDIOMYOPATHY** **LIPODYSTROPHY**
LAMIVUDINE (3TC)	*Nucleoside analog*		*Used for HBV*	Well-tolerated
EMTRICITABINE (FTC)	*Nucleoside analog*		*Used for HBV*	Well-tolerated
DIDANOSINE (dDI-**A**)	*Nucleoside analog*			**PANCREATITIS + PERIPHERAL NEUROPATHY**
STAVUDINE (d4T)	*Nucleoside analog*			**PERIPHERAL NEUROPATHY +PANCREATITIS** **LIPODYSTROPHY***
ABACAVIR (ABC-G)	*Nucleoside analog* Hepatic metabolism by ETOH-DH & glucuronyl trans			**HYPERSENSITIITY**
TENOFOVIR* (TDF-A)	***NucleoTide *PRO-DRUG***		*Used for HBV*	**RENAL TOXICITY**

COMBO DRUGS	TENOFOVIR + EMTRICITABINE + NNRTI + Protease inhibitor + Ritonavir OR Raltegravir **Most common*	NRTIs: COMBIVIR (COM) Lamivudine + Zidovudine – C + T **Given to healthcare workers after HIV needle stick*	NRTIs: TRIZIVIR (TZV) Abacavir + Lamivudine + Zidvudine – G + C + T

ANTI-HIV DRUGS: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

DRUG	MECHANISM	CYP450 METABOLISM	INDICATION	ADVERSE EFFECTS
Non-competitive Inhibitors of RT	Allosteric binding site alteration			**RASH**
DELAVIRDINE (DLV)	*3A4 substrate*	**CYP3A INHIBITOR**	***AVOID IN PREGNANCY**	*Not used much*
EFAVIRENZ	*3A4, 2B6 substrate* *Less effective when combined with PI*	**CYP3A, 2B6 INDUCER**		Vivid dreams, SJ, **DYSLIPIDEMIA**
NEVIRAPINE (NVP)	*2B6, 3A4 substrate*	**CYP3A INDUCER**	**PREGNANCY CLASS B: *SAFE**	Hepatotoxicity

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ANTI-HIV DRUGS: Fusion Inhibitors

DRUG	MECHANISM	DISTRIBUTION/ RESISTANCE	INDICATION	ADVERSE EFFECTS
ENFUVIRTIDE	***Entry Inhibitor*** Prevents gp120 from deforming, **blocking gp41** from entering cell	Resistance: changes in gp41	**SALVAGE THERAPY: MDR HIV**	Injection site reactions HSR (uncommon)
MARAVIROC	***Entry Inhibitor*** Interferes with binding of HIV to receptors; **Blocks CCR5**	**Trofile Assay:** HIV tropism test to see if drug will be effective		

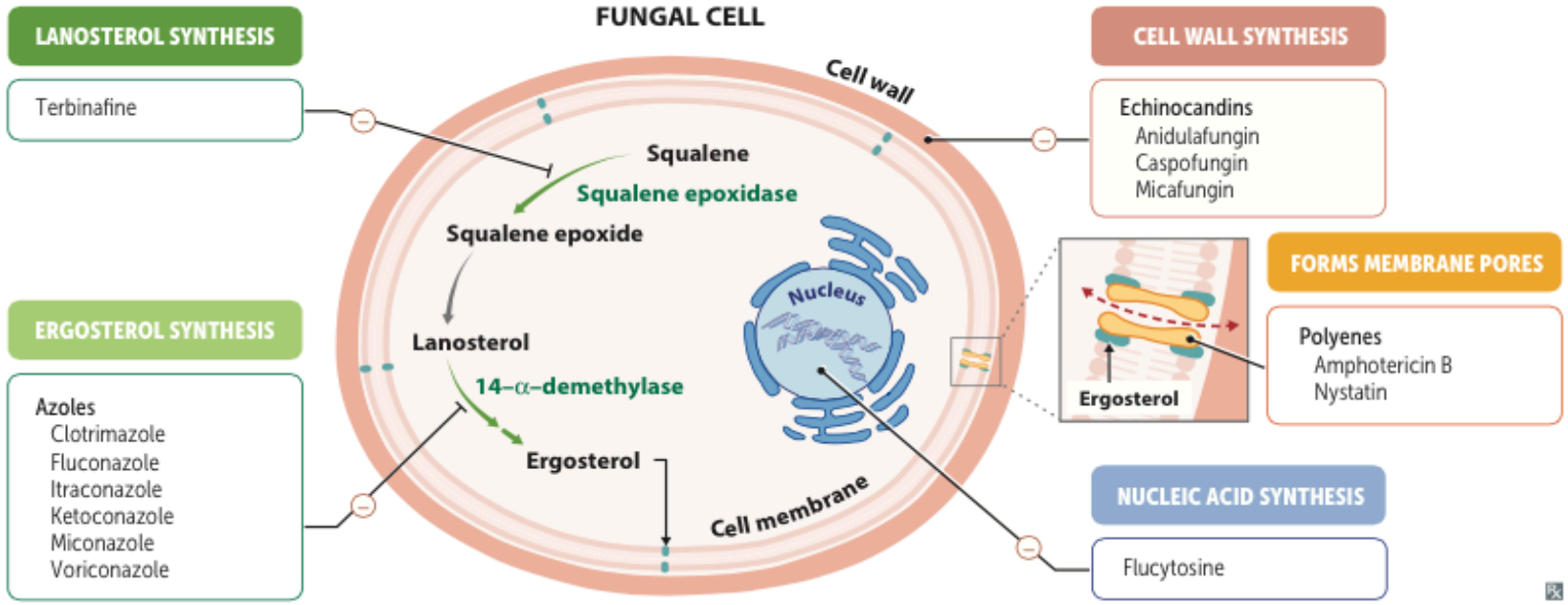
ANTI-HIV DRUGS: Integrase Inhibitors

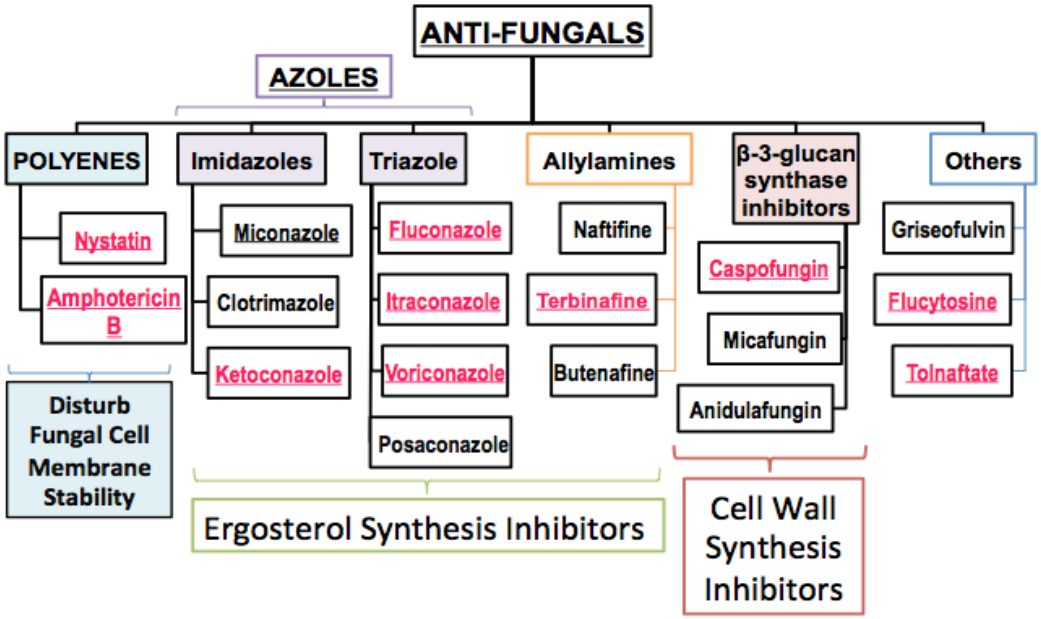
DRUG	MECHANISM	DISTRIBUTION/ RESISTANCE	INDICATION	ADVERSE EFFECTS
RALTEGRAVIR ELBITEGRAVIR	Nuclear action → **Block incorporation of viral DNA into host DNA for replication by integrase**	**Glucuronidation metabolism**		Myopathy Rhabdomyolysis

ANTI-HIV DRUGS: Protease Inhibitors

DRUG	MECHANISM	INDICATION	ADVERSE EFFECTS
3A4 Inhibitors (Competitive)	**Block the active site of viral protease** *Used in combination therapy w/ NRTI + NNRTI* **Resistance**: protease mutation		
RITONAVIR *Good bioavailability*	Protease inhibitor + **CYP450 inhibitor*** **LOW DOSE: "boost" serum levels & half life of other PIs** → *allows use of lower doses & ↓toxicity*	**1st line when combined w/ other PIs**	GI, especially bad taste **HYPERTRIGLYCERIDEMIA** *Multiple drug interactions**
LOPINAVIR	Co-formulated with Ritonavir in order to take advantage of P450 inhibition → ↑ **antiviral effect**	**1st line when combined w/ Ritonavir***	Well tolerated w/ some GI toxicity & hyperlipdiemia
FOSAMPRENAVIR (FPV) & DARUNAVIR	Contain moiety	**1st line when combined w/ Ritonavir*** ***Therapeutic failure seen when "unboosted"***	**Stevens Johnson Syndrome** + HA ***Fosamprenavir: transaminase elevation, hyperglycemia, hyperlipidemia***
ATAZANAVIR	Sensitive to gastric pH	**1st line when combined w/ Ritonavir*** ***Contraindicated with Nevirapine***	Cardiac, Hyperlipidemia, Nephrolithasis *Multiple drug interactions*

Antifungal therapy





Drug	Mechanism	Systemic infections				Superficial infections	
		Asperg	*Crypto*	*Blasto Coccidio Histo*	*Candida*	Dermato-phytes	*Candida*
Amphotericin[a]	Binds ergosterol	⊕	⊕	⊕	⊕		
Nystatin	Binds ergosterol						⊕
Flucytosine	Antimetabolite		⊕[b]		+		
Azoles	Block ergosterol synthesis						
Miconazole						⊕	⊕
Ketoconazole				+	+	⊕	⊕
Itraconzole		+[c]		⊕	+		
Fluconazole			⊕[b]	±	+		⊕
Griseofulvin	Disrupts mitotic spindles					⊕	

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ANTI-FUNGAL DRUGS: POLYENES

DRUG	MECHANISM	DISTRIBUTION/ RESISTANCE	INDICATION	ADVERSE EFFECTS
POLYENES	**Disturb fungal cell membrane stability** **Binds to ergosterol** → forms **PORES** → ↑permeability to proteins & ions (K+) → Cell death **Attach with high affinity to **ergosterol-containing membranes** than cholesterol containing membranes (as in humans)*			
AMPHOTERICIN B *IV*	**9**5% protein-binding; Half-life = 24 hours	**Resistance**: 1. ↓Ergosterol biosynthesis 2. Synthesis of **alternative sterols** that lessen the affinity	**DOC: SYSTEMIC INFECTIONS – *Asperg, Crypto*, Blasto, Coccido, Histo, Candida*** ***Pregnancy Class B (safe)***	**NEPHROTOXICITY**, **Hypokalemia** **INFUSION RXN:** Oxidative damage to fungal cells → **release of host inflammatory cytokines** → ***fever, chills, rigor, arthralgias***
NYSTATIN *PO, Topical*			**DOC: SUPERFICIAL – *Candida*** ***Oral, intestine, vaginal Candidiasis*** ***Contraindicated in hypersensitivity, vaginal application in pregnancy***	PO: anorexia, NVD, rash Vag: rash, burning sensation

Crypto Treatment: Initial Rx-Amphotericin B**, Adjuvant Rx-**Flucytosine**, & Completion Rx-**Fluconazole***

ANTI-FUNGAL DRUGS: AZOLES

DRUG	MECHANISM	DISTRIBUTION/ RESISTANCE	INDICATION	ADVERSE EFFECTS
AZOLES	**Ergosterol synthesis Inhibitors** **Inhibit CYP450-dependent *Lanosterol 14-α-demythylase*** → depletion of ergosterol in fungal cell membrane Impairs fungal ATPase function ****All CYP450 Inhibitors***			
FLUCONAZOLE *Rapid absorption* *>90% bioavailability*	***Triazole*** **>90% RENAL EXCRETION**	**Penetrates CSF**	**DOC: SYSTEMIC *Crypto* meningitis*, SUPERFICIAL *Candida*** **ALTERNATIVE: Systemic *Candida***	**Well-tolerated** GI, reversible ↑transaminase
VORICONAZOLE	***Triazole***	*Only ionized at low pH*	**FUNGICIDAL *in vitro against Aspergillus*** **FUNGISTATIC *in vitro against Candida***	**Visual disturbances** ↑Liver function tests, **Skin reactions**
ITRACONAZOLE	***Triazole*** **EXTENSIVELY METABOLIZED IN THE LIVER**		**DOC: SYSTEMIC – *Blasto, Coccido, Histo*** **ALTERNATIVE: Systemic *Asperg*, *Candida*** ***Paracoccidiodomycosis, Sporotrichosis*** ***PBHSCA***	**HEPATOTOXICITY** **Negative inotrope** **Serum levels ↓by Rifampin & other Inducers**
KETOCONAZOLE	***Imidazole***		**DOC: SUPERFIC – *Dermatophytes, Candida*** **ALTERNATIVE: SYSTEMIC *Blasto, Coccido, Histo, Candida***	Inhibits mammalian CYP450 enzymes & mammalian steroid synthesis → **GYNECOMASTIA** **Serum levels ↓by Rifampin & other Inducers**

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ANTI-FUNGAL DRUGS: ALLYAMINES, ECHINOCANDINS, OTHERS

DRUG	MECHANISM	INDICATION	ADVERSE EFFECTS
ALLYAMINES	**Ergosterol synthesis Inhibitors** **Inhibit squalene 2,3-epoxidase** → squalene accumulation **(FUNGICIDAL)**		
TERBINAFINE	Metabolized/excreted in urine Extensively distributed to **hair follicle**, nail, sebum-rich skin	Oral **Dermatophytes**: *Asperg, Candida, Pityrosporum* **FUNGISTATIC** against *Candida* (2-4wk cure)	*Alcohol & hepatotoxic meds ↑risk of liver damage* Potentiates effects of caffeine/theophylline ****SUBSTRATE of CYP1A2, 2C9/19, 3A4** – **Cimetidine** ↓clearance by 33% – **Rifampin** ↑ clearance by 100% ****INHIBITOR OR CYP-2D6** – ↑ **Levels of TCA** **Avoid combination or adjust dosages*
NAFTIFINE, BUTENAFINE		**Topical only**	No clinically significant interactions

DRUG	MECHANISM	DISTRIBUTION/ RESISTANCE	INDICATION	ADVERSE EFFECTS
ECHINOCANDINS	**Cell wall synthesis inhibitors** **IRREVERSIBLLY inhibit β-1,3-D glucan synthase (FUNGICIDAL)**		Invasive ***Aspergillosis* & *Candida***	
CASPOFUNGIN	**Spontaneous degradation, hydrolysis, N-acetylation**	Extensive tissue distribution		
MICAFUNGIN	Spontaneous degradation, hydrolysis, N-acetylation			
ANIDULAFUNGIN	Chemically degraded			

DRUG	MECHANISM	DISTRIBUTION/ RESISTANCE	INDICATION	ADVERSE EFFECTS
FLUCYTOSINE (5-FC) *Pro-drug* *Oral dosing only*	**ANTIMETABOLITE: PYRIMIDINE ANALOG** Deaminated to **5-FU** **Blocks Thymidylate Synthase** **Inhibits RNA, DNA, protein synthesis** Excreted via **GFR** – *Adjust dose in RF*	Distributes to **CSF** **Resistance**: 1. **Point mutation: loss of permease** 2. ↓UMP pyrophosphorylase or cytosine deaminase 3. ↑Synthesis of pyrimidines	**DOC: SYSTEMIC – *Crypto**** **ALTERNATIVE: Systemic Candida** ***ONLY used in combo therapy w/ amphotericin B to minimize resistance**	**BM SUPRESSION** **NVD**
GRISEOFULVIN *Oral*	**FUNGISTATIC** **Binds to keratin precursor making cells resistant to fungal invasion – *Disrupts mitotic spindles*** Hepatic metabolism		**DOC: SUPERFICIAL – *Dermatophytes*** ***ATHELETES FOOT**	**ANTABUSE (DISULFIRAM) RXN** ***Peripheral neuropathy*** ***Photosensitivity*** **Weak inducer of CYP450*** **↓effectiveness of cyclosporine,** estrogens, Warfarin **Phenobarb & Omeprazole ↓absorption**

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ANTI-PARASITIC DRUGS: Anti-Helminthic

DRUG	MECHANISM	DISTRIBUTION/ RESISTANCE	INDICATION	ADVERSE EFFECTS
BENZIMIDAZOLES	Inhibit tubulin polymerization Inhibit mt fumarate reductase: ↓glucose transport		Broad-spectrum anti-nematodes & anti-cestodes	Mild/transient: GI upset, HA, dizziness, lethargy, insomnia **Chronic therapy → reversible hepatic effects, alopecia, anemia**
ALBENDAZOLE *Fatty meals increase absorption*	**LARVICIDAL/OVICIDAL** Immobile intestinal parasites **PRO-DRUG:** metabolized to **Albendazole Sulfoxide** in the liver	Distributes well to tissues & enters **bile, CSF, & hydatid cysts**	*Anti-cestode (broad spectrum)* **DRUG OF CHOICE:** – **Cysticerosis (pork tapeworm)** ***HYDATID CYST** *(+corticosteroids)* – **Larvae Migrans** – **Ascaris** – **Nectar americanus: Hookworm** – **Trichuris trichuria: whipworm** – **Trichinella spiralis**	
MEBENDAZOLE	Synthetic benzimidazole **-CIDAL**		*Anti-nematode** **DRUG OF CHOICE:** – **Pin worm** – **Ascaris** – Nectar americanus: Hookworm – Trichuris trichuria: Whipworm	*Low incidence of adverse effects*
THIABENDAZOLE	**Chelator** of metal ions (NOT Ca^{2+}) Completely metabolized in liver & excreted in urine		*Anti-nematode:* ***roundworm***	**IRREVERSIBLE LIVER FAILURE** **FATAL STEVENS-JOHNSON**
PYRANTEL PAMOATE	**Prolonged activation of excitatory nACh** receptors on body wall muscle **NEUROMUSCULAR BLOCKADE:** Paralysis of worms	****Not effective against migratory stages in tissues or against ova***	*Anti-nematode (**Pinworm**, Ascaris)* **Trichostrongylus**	
PIPERAZINE	Paralysis of Ascaris: blocking acetylcholine at myoneural junction: live worms then expelled by normal peristalsis		Ascariasis ONLY (ALTERNATIVE) ***Contraindicated in Epilepsy, chronic neurologic diseases, liver or kidney disease, & PREGNANCY***	GI, NEUROTOXICITY, Allergic rxn
DIETHYLCARBAMAZINE	Immobilize microfilariae & **alters surface structure,** displacing them from tissue → *susceptible to destruction by host defense mechanisms*		*Anti-nematode* **DOC: Filariasis, Tropical Eosinophilia (Loa Loa)** ***Contraindicated in HTN, renal disease, patients with lymphangitis***	**MAZZOTTI'S RXN** **Occurs within 7 days of treatment in patients w/* ***ONCHOCERCIASIS***

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ANTI-PARASITIC DRUGS: Anti-Helminthic

DRUG	MECHANISM	DISTRIBUTION/ RESISTANCE	INDICATION	ADVERSE EFFECTS
IVERMECTIN	Acts on **parasite's Glutamate-gated Cl^- channel (GABA) R:** ↑Cl^- influx causing **hyperpolarization** ***Paralysis** by intensifying GABA-mediated transmission of signals in peripheral nerves	Does not cross BBB	*Anti-nematode* **DRUG OF CHOICE:** – **Onchocerciasis (River blindness)** – **Strongyloides** – **Larvae Migrans** *Also used for scabies & lice* ***Contraindicated in concomitant use with other drugs that enhance GABA, MENINGITIS IN CHILDREN <5 Y/O, PREGNANCY (C)***	**Fatigue, dizziness, GI** **Corneal opacities + eye lesions** **MAZZOTTI'S RXN:** rash, fever, lymphadenopathy, eosinophilia, arthralgia, tachycardia, hypotension, edema, abdominal pain
NICLOSAMIDE	Inhibits oxidative phosphorylation **(-CIDAL)**		*Anti-cestode: tapeworms* ***(2nd line)***	
PRAZIQUANTEL	Disrupts membrane of schistosome causing rapid influx of Ca^{2+} into parasite → muscular tetany	No reported resistance	**DOC: Schistosomiasis*** *Anti-cestode:* ***tapeworms*** **(Dwarf tapeworm)** *Anti-trematodes:* ***flukes***	**VIRTUALLY NO SIDE EFFECTS**
OXAMINIQUINE			Intestinal schistomiasis ***(S. mansoni)***	
METRIFONATE			Urinary schistomiasis (*S. hematobium*)	

***Schistosomiasis ('Snail Fever'):** *caused by trematodes; occurs in developing countries where people cannot afford proper water & sanitation*

- **Urinary schistosomiasis**: *hematuria, chronic infection, obstruction*
- **Hepatosplenic schistosomiasis**: ***portal HTN*** → *ascites, varices, splenomegaly, abnormal hepatic function*

ANTI-PARASITIC DRUGS: Amebicides

DRUG	MECHANISM	INDICATION	ADVERSE EFFECTS
METRONIDAZOLE TINIDAZOLE *Oral*	**Reductive bioactivation** of nitro group by **ferredoxin** (*found in anaerobic parasites*) to form **reactive cytotoxic products** Hepatic metabolism	**DOC:** Severe intestinal wall disease & hepatic abscess & extra-intestinal amebic disease **Used with luminal amebicide **Diloxanide*** **Trichomoniasis, Giardiasis,** *Gardnerella vaginalis,* Anaerobes (*B. fragilic,* ***C. diff***) **Triple Therapy for *H.pylori***	**GI irritation, HA, dark coloration of urine** **DISULFIRAM-LIKE REACTION** Leuopenia, dizziness, ataxia
NITAZOXANIDE	Inhibits pyruvate-ferredoxin oxidoreductase pathway	Giardia lamblia + Cryptosporidium parvum	
DILOXANIDE FUROATE	Luminal Amebicides	**Asymptomatic amebiasis**	
IODOQUINOL			
PAROMYCIN (AG)		Cryptosporidium in AIDS	

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MALARIA

- Plasmodia protozoa: *P. falciparum, vivax, ovale, malariae, knowlesi*
  - ***P. falciparum:*** most severe form; can infect RBCs of all ages causing high levels of **parasitemia** → End organ disease: CNS, lung, kidney
    - Symptoms: hypoglycemia, lactic acidosis, severe anemia, multi-organ dysfunction due to hypoxia
    - **Untreated**: kidney failure, seizures, mental confusion, coma, death
    - (*P. knowlesi causes severe disease similar to this)*
  - *P. vivax + P. ovale:* infect only young RBCs → Benign Tertian Fever (*fever every 3rd day)*
  - *P. malariae:* Quartan Malaria (*fever every 4th day*)
- **DRUG CLASSIFICATION:**
  - **Tissue schizonticides: ELIMINATE** developing or dormant **(hypnozoite) liver** forms
  - **Blood schizonticides:** act on **erythrocytic** parasites
  - **Gametocides:** kill sexual stages & **prevent transmission to mosquitoes**

ANTI-MALARIAL DRUGS

	DRUG	MECHANISM	DISTRIBUTION/ RESISTANCE	INDICATION	ADVERSE EFFECTS
QUINOLONES	**CHLOROQUINE** **HYDROXYCHLOROQUINE** *Use loading dose to rapidly achieve effective conc.*	***Blood schizonticide*** *Plasmodium accumulates chloroquine in food vacuoles* Drug incorporates into DNA → inhibits proliferation Prevents proliferation of Heme into Hemozoin → **Build up of Free Heme: TOXIC to parasite**	**Resistance:** ↑Ability o excrete drug faster *Common in *P. falciparum*	Sensitive *P. falciparum* Tx + Prophylaxis **+ DOC$_1$ FOR Tx in PREGNANT PATIENTS** **Chloroquine + Primaquine: *radical cure*** of *P. vivax & P. ovale*	Immunosuppressive actions **Pruritus** **Hemolysis in G6PD-deficiency**
	QUININE *Parenterally*	***Blood schizonticide*** Complexes with dsDNA to prevent separation → Block DNA replication & transcription Rapidly absorbed & metabolized before renal excretion		**DOC: Chloroquine-*resistant P. falciparum*** **(NON-US)** ESPECIALLY FOR CEREBRAL MALARIA **Used w/ doxy or clinda* ***Contraindicated in pregnancy***	***CINCHONISM**: GI, HA, vertigo, blurred vision, tinnitus* – Hypotension + arrhythmia – **Hemolysis in G6PD-deficiency** – **BLACKWATER FEVER:** hemoglobinuria
	QUINIDINE *Parenterally*			**DOC: Chloroquine-*resistant P. falciparum*** **(US)** ***Contraindicated in pregnancy***	
	MEFLOQUINE *Orally*			**DOC: Prophylaxis Chloroquine-*resistant P falciparum*** **+ DOC$_1$ FOR Tx in PREGNANT PATIENTS**	**Psychiatric, neurologic, seizures**
	PRIMAQUINE	***Tissue schizonticide + Gametocide*** Forms quinolone-quinone metabolites **Interferes with electron-transferring redox cmpds** **(cellular oxidants)**		**DOC: Prophylaxis *P. vivax*** **Chloroquine + Primaquine: *radical cure*** of *P. vivax & P. ovale* *ERADICATES LIVER STAGES ***Contraindicated in pregnancy***	Usually well-tolerated **Pruritus**, HA, metHb **Hemolysis in G6PD-deficiency**

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ANTI-MALARIAL DRUGS

	DRUG	MECHANISM	DISTRIBUTION/ RESISTANCE	INDICATION	ADVERSE EFFECTS
	LUMEFANTRINE	MOA unknown		Active against **erythrocytic stages** of all 4 species, including *chloriquine-resistant falciparum*	**CARDIOTOXICITY (Long QT)** **Not used for chemoprophylaxis* Embryoxicity
	ARTEMISININS: **ARTESUNATE & ARTEMETHER**	***Blood schizonticide*** Metabolized in the food vacuole of the parasite to **free radicals** Alkylate heme via Free Radical Formation		**MDR *P. falciparum***	
ARTEMISININ COMBOS	**ARTESUNATE-MEFLOQUINE**			**MDR *P. falciparum*** **DOC in SE Asia & S. America**	
	ARTESUNATE-AMODIAQUINE			**DOC: Uncomplicated *falciparum* in Africa**	
	COARTEM: **ARTEMETHER-LUMEFANTRINE**			**DOC_2: Chloroquine-resistant *P. falciparum* (USA)**	
	DIHYDROARTEMISININ-PIPERAQUINE			**DOC: *falciparum* in Vietnam**	
	ATOVAQUONE *Used orally + food*	*Unclear*	**Resistance:** mutations in cytochrome B	**Malaria, PCP, Babesia** ***Contraindicated in patients with hx of cardiac conduction defects, psychiatric disorders, or seizures***	Rash, cough, NVD, fever, abnormal liver function test
	SULFONAMIDES & SULFONES	Inhibits Dihydropteroate Synthetase *(Malaria synthesizes folate & hosts do not)*			
	PROGUANIL & PYRIMETHAMINE	Inhibits Dihydrofolate Reductase Blocks THF formation → block nucleic acid synthesis ***Only inhibit plasmodia in exo-erythrocytic stage***		***Always used in combo w/ other drugs**	
COMBOS	FANSIDAR: SULFADOXINE + PYRIMETHAMINE				
	MALARONE: **ATOVAQUONE + PROGUANIL**			**DOC_1: Any resistant *P. falciparum*** **Treatment & Chemoprophylaxis** **(Chloroquine-resistant + undetermined)**	
	QUININE (QUINIDINE) **+ DOXY or TETRACYCLINE** (OR CLINDAMYCIN)			**DOC_3: Chloroquine-resistant *P. falciparum*** ****Tetracycline contraindicated in kids***	
	QUININE + CLINDAMYCIN			**DOC_2: Chloroquine-resistant *P. falciparum* FOR PREGNANT PATIENTS**	

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MALARIA TREATMENT RECAP

Treatment of Chloroquine-resistant *P. falciparum*

1. **Malarone** (Atovaquone-Proguanil)
2. **Coartem** (Artemether-Lumefantrine)
3. **Quinine sulfate + Doxycycline or Tetracycline** (or Clindamycin)

Malaria Treatment in Pregnancy – *miscarriage, premature delivery, low birth weight, congenital infection, +/- perinatal death*

Uncomplicated Malaria: *P. malariae, P. vivax, P. ovale, chloroquine-sensitive P. falciparum* = CHLOROQUINE

Alternative: hydroxychloroquine

Chloroquine-resistant *P. falciparum*: MELFLOQUINE or **Quinine sulfate + Clindamycin**

Complicated Malaria Treatment – *Metabolic acidosis, renal failure, Blackwater fever (hemoglobinuria), hypoglycemia*

1. Artesunate IM or IV
2. Artemether IM
3. Quinine IV or IM
4. Full course of **Artemisinin-based combination therapy (ACT)** or **Quinine + Clindamycin or Doxycycline** if can tolerate PO

Chemoprophylaxis:

- Chloroquine: Sensitive *P. falciparum* (weekly)
- **Malarone**: Chloroquine-resistant *P. falciparum* (daily; begin 2 days before depature + continue 1 week after leaving)
- Mefloquine: Chloroquine-resistant *P. falciparum* (weekly)
- Doxycycline: MDR *P. falciparum* (daily; begin 2 days before depature + continue 4 weeks after leaving)
- Primaquine: terminal prophylaxis of *P. vivax & P. ovale*; alternative for primary preventation

**All chemoprophylactic recommendations involve taking the medication before, during, AND after travel to an area with malaria*