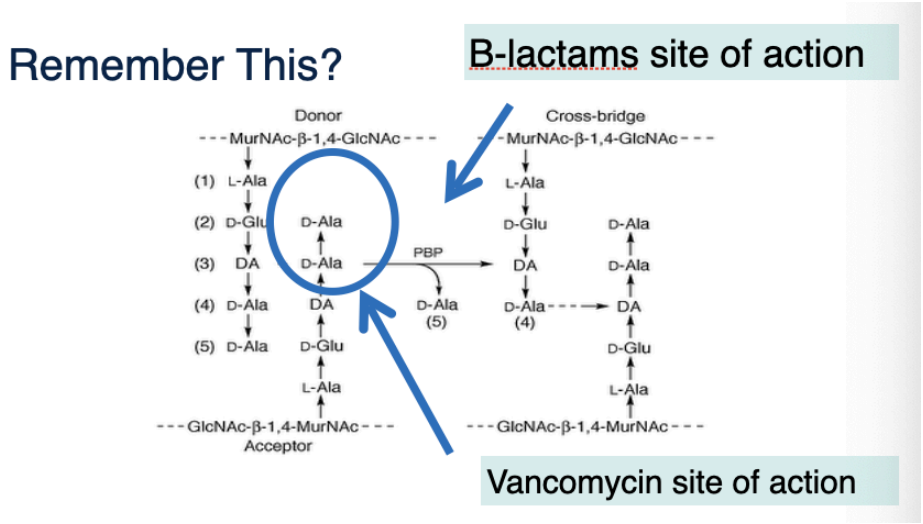
Module 15: Infectious Diseases Principles of ID, Pharm of selected Antibiotics Part 2

Drugs for Resistant Gram-Positive Infections

Vancomycin

- Until recently, the only commercially available antibiotic from the glycopeptide in the USA
- An antibiotic that is used a LOT (and way too frequently)
- Spectrum of activity
    - Gram (+) organisms only
        - Aerobic (most activity) > anaerobic (some activity)
- **MOA**
    - Binds to D-ala D-ala terminal portion of peptidoglycan precursors and prevents further cross linking
        - Considered "slowly bactericidal"
        - Weaker killing when compared to beta-lactams, and **outcomes are worse** when using vancomycin over an active beta-lactam
        - This is important, **while it is broader spectrum, it is a less effective agent,** therefore we only want to use when we must!



- Site of action
    - B-lactams site of action: inhibits PBP
    - Vancomycin site of action: binds to D-ala D-ala
    - We don't see cross-mutation between beta-lactams and vancomycin because they bind to different sites
- Pharmacokinetics
    - IV and PO formulations available
        - IV for systemic infections **(DOC MRSA)**
        - PO formulation not absorbed, **only appropriate clinically for *C. difficile* infection**
            - Because it is not absorbed systemically there ends up being a high concentration of the medication in the GI tract.
            - One of two drugs of choice for hospitalized patients
    - Renally eliminated
        - Dose adjustments needed in renal insufficiency
    - **Therapeutic drug monitoring** to ensure safe and effective exposures
        - Blood levels to evaluate for toxicity and if dose is at effective range
- Clinical Applications

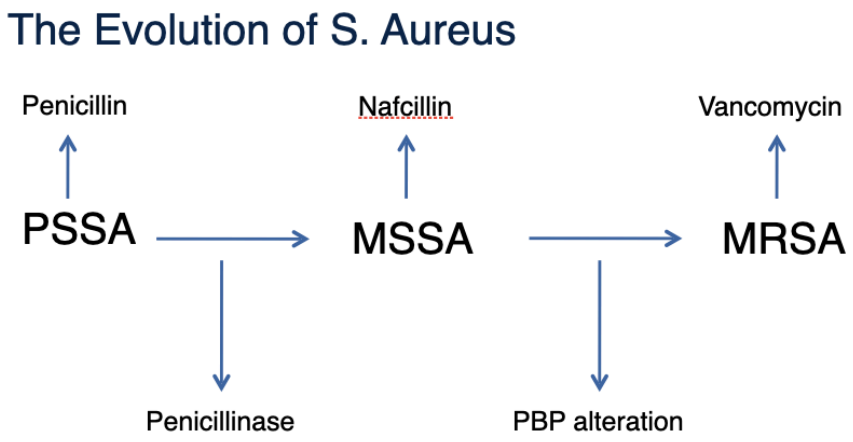
- **Used empirically (and definitively) for MRSA coverage**
  - Inferior to b-lactams for MSSA
- Patients with B-lactam allergy for Gram (+) coverage
- Vancomycin also has activity against strep and enterococcus as well but considered inferior to b-lactam based therapy
- **Think broader spectrum, but weaker killing**

MRSA

- What is MRSA?
  - Remember PBP alteration PBP2 ⟶ PBP2A
  - B-lactams will not bind to PBP2A* and this **b-lactams lack activity against MRSA**
- Continual problem in hospitals
  - Commonly 30-60% of staph aureus
- Growing problem in community as well
  - Now empirically covered in many skin infections (we will discuss this later) and other target populations

Vancomycin and MRSA

- Empiric regimens for many hospital acquired infections will frequently include vancomycin to cover MRSA
- Vancomycin has been the standard of care for MRSA for decades (a long time!!)
  - However, outcomes for invasive MRSA infections are suboptimal
- While many alternatives exist for MRSA infections (will discuss later), limited data suggest anything is better
  - Lots of controversy over optimal therapy



Vancomycin: ADRs

- **Nephrotoxicity**
  - Aggressive dosing regimens associated with rates of toxicity at 10 – 15%
    - Dependent on the presence/absence of risk factors
- Ototoxicity
  - More a book answer, extremely rare, limited concern
- Thrombocytopenia
  - Infrequent, but possible
- **Vancomycin infusion reaction**
  - **Not a true allergy, histamine response due to rapid infusion**

    - Can overcome by **slowing down infusion** (≤ 1 gram over 1 hour) and/or **premedicating with diphenhydramine**
    - Not a contraindication to giving vancomycin

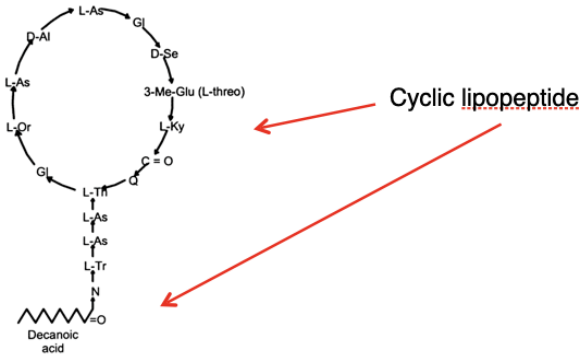
Telavancin

- Second generation glycopeptide (a LIPOglycopeptide)
- **MOA**
    - Same as vancomycin + direct binding to the bacterial membrane which disrupts membrane barrier function
- Enhanced activity against Gram (+) including lower MICs demonstrated in MRSA
- **Pharmacological issues** (this is why this medication isn't really used)
    - **Nephrotoxicity (higher than with vancomycin)**
    - **Interference with coagulation tests (significant)** → like with patients on heparin
    - **Teratogenicity in animal studies** → pregnancy test before prescribing
    - **Qt prolongation**

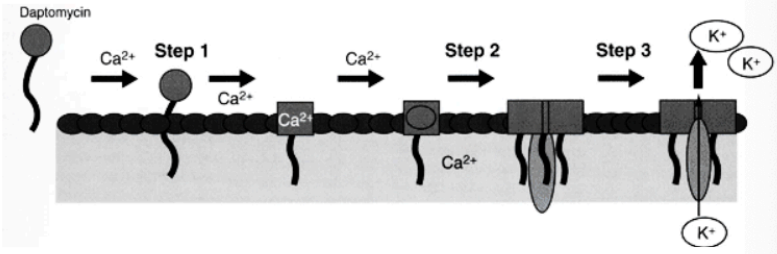
Dalbavancin and Oritavancin

- **Long-acting** lipoglycopeptides
- Half-life > 300 hours
- Allow **once weekly dosing** options
- Studied in skin infections
    - 1-2 doses for entire course of therapy
- High potential in future for outpatient therapy
    - Skin infections, but also complicated infections warranting longer courses of antibiotics

Daptomycin: The Only Cyclic Lipopeptide



Daptomycin MOA



- Daptomycin inserts itself into the inner cell membrane using calcium to do so. When several daptomycins do this, it bores a hole into the inner cell membrane of gram (+) organisms. This creates a potassium efflux core which shoots K+ out of the cell causing rapid depolarization of the cell and cell death.

Daptomycin: Things to Know!

- **IV only** (once daily dosing, no therapeutic dose monitoring required)
- Spectrum: **Gram (+) organisms only**
    - Staphylococcus (including MRSA), Streptococcus, Enterococcus (including VRE)
- Rapidly bactericidal
- Clinical applications
    - Major uses: **MRSA and VRE bloodstream infections, endocarditis, and soft tissue infections** (resistant gram + organisms)
    - Since going generic (and the price coming down a LOT) increased used in outpatient setting for MRSA (**once daily, no monitoring**)

Daptomycin Has some issues!

- Some cross-resistance can be seen with strains of MRSA that have elevated vancomycin MICs
    - The mechanism of vancomycin MIC increase is cell wall thickening
    - This can limit the amount of daptomycin that gets to the inner cell membrane
- Adverse event of concern
    - CPK elevations and rhabdomyolysis
    - Infrequent, caution with statins, high doses
- **Irreversible binding to pulmonary surfactant**
    - **Avoid pneumonia!**

Linezolid

- Until 2014, only available oxazolidinone
- **MOA**: inhibits protein synthesis by binding to the 50S ribosomal subunit
    - Bacteriostatic effect
- Spectrum of activity
    - **Gram (+) only** – including MRSA and VRE
    - Oddballs as well – mycobacterium, Nocardia (rare clinical application → do not focus on this)
- Pharmacokinetics
    - **Great absorption (~100%)**
    - **IV and PO dose the same**
        - Great oral medication option
    - Limited renal excretion
        - No dosage adjustment, BUT enough for lower UTI
            - But becoming more common for dose adjustments d/t links to toxicity
- Clinical applications
    - VRE infections
    - MRSA pneumonia
    - Outpatient oral option for skin infections
- Side effect of concern
    - **Thrombocytopenia** → usually seen with longer courses (~day 10-14 of therapy)
    - **Peripheral/optic neuropathy**
        - Optic neuritis of particular concern with long (≥ 28 days) courses
        - Can lead to irreversible blindness
- Drug interactions

- Linezolid is a weak MAOI
- **Concern for serotonin syndrome** with drug which work on serotonergic receptors (e.g., SSRIs)
  - Serotonin syndrome: fever, agitation, mental status changes
  - **Rare occurrence** – but be aware

Tedizolid

- Novel oxazolidinone that's been out for ~6 years
- Once daily!
- Approved as a 6-day course for skin infections
- Less thrombocytopenia?
- No SSRI concern?
- Many PK concerns/unknowns right now
- Not used a lot in clinical practice, more of a FYI drug

Vancomycin-Resistant Enterococcus (VRE)

- Common in e. faecium; occasionally occur in e.faecalis
  - In e. faecium, ampicillin resistance is also common
- **Treatment choices for VRE**
  - **Linezolid**
  - **Daptomycin**
  - **Tigecycline** (and some other tetracyclines)
    - Will discuss later
  - **Oritavancin**

Fluoroquinolones and Aminoglycosides

Fluoroquinolones

- **MOA**: Inhibit bacterial DNA replication (unique)
  - DNA gyrase and topoisomerase inhibition
  - Prevents unwinding of double helix
- Agents of clinical relevance
  - Levofloxacin
  - Moxifloxacin
  - Ciprofloxacin
  - Delafloxacin (?)
- Bactericidal, **concentration dependent** (AUC/MIC) killing
- **Excellent bioavailability**
  - Ciprofloxacin 80%; levofloxacin/moxifloxacin 100%
- Spectrum of Activity
  - Gram (+)
    - Levofloxacin (the best) > moxifloxacin >> ciprofloxacin (not the best)
    - Levofloxacin and moxifloxacin has some in vitro activity against *S. aureus* and enterococcus, but **should NOT be relied upon to treat these pathogens**
      - Simple, one step mutation to resistance
      - Concern for development on therapy
    - **Levofloxacin and moxifloxacin have excellent streptococcus coverage (including *S. pneumoniae*)**
      - This is important to remember
      - Notice ciprofloxacin is not
  - Gram (-)
    - Ciprofloxacin and levofloxacin have **anti-pseudomonal** therapy

        - All three have similar activity against **Enterobacteriaceae**
            - 20 – 30% resistance in target organisms, which means they are not relied on empirically
        - **Resistance high and increasing in Gram (-) organisms, due to overuse**
    - Anaerobic
        - **Only moxifloxacin has reliable activity** (including bacteroides)
- Clinically Relevant Spectrum of Activity
    - The **"respiratory fluoroquinolones"**
        - **Levofloxacin and moxifloxacin**
        - Excellent activity against all **CAP organisms**
            - ***S. pneumoniae* (cipro lacks this activity), *H. influenzae, M. catarrhalis,* atypical pathogens**
    - The **anti-pseudomonal fluoroquinolones**
        - **Ciprofloxacin and levofloxacin**
        - Coverage against **Gram (-)**, including ***P. aeruginosa***
    - **Anaerobic FQ**
        - **Moxifloxacin**
- Important PK Considerations
    - **Excellent bioavailability; IV = PO**
    - Highly lipophilic
        - Allows to be used for a wide array of infection types
    - **Renally eliminated (dose adjustment needed)**
        - Exception is moxifloxacin (this also has a UTI implication as well)
        - Because they are renally eliminated these drugs, exception of moxifloxacin, are useful in treatment of UTIs
- Side effects (there are a lot!)
    - Central nervous system toxicity
        - Headaches, dizziness, insomnia, seizures
        - Recent association with neuropsychiatric effects like anxiety
    - Potential damage to growing cartilage
        - Soft contraindication in pediatrics → avoid if you can
    - **Tendon rupture/tendonitis**
        - Aortic dissection/aneurysm (rare) by similar mechanism
    - Dysglycemias (hyperglycemia and hypoglycemia)
    - Cardiac arrhythmias and possible torsades → very low risk
        - Moxifloxacin highest risk
        - Minimal risk if given alone and not otherwise at risk
    - **C. difficile associated disease**
    - Recent FDA advisory advises against use for uncomplicated infections
- Drug Interactions
    - **Reduced oral absorption when taken with divalent cations**
        - Ca, Mg, Fe
        - Due to chelation in the GI tract → neither medication is absorbed and increases treatment failure
    - Ciprofloxacin inhibits CYP1A2 (concern for toxicity levels of CYP1A2 meds)
        - Theophylline, a few others impacted

Delafloxacin: FYI medication

- FDA approved in 2017

- Claim to fame is enhanced S. aureus activity over levofloxacin (including MRSA)
    - This has been said in the past for others too….
- Gram (-) spectrum similar to levo/cipro (including *P. aeruginosa*)
- I wont test you on this – just FYI

Aminoglycosides

- **MOA**: Bind to the 30S ribosomal subunit to cause a decrease in protein synthesis
    - **Requires active (oxygen dependent) transport into the bacterial cell to exert its action**
        - **No activity against anaerobes**
        - **Concerns for reduced activity at site of active infection**
- Bactericidal (rapidly!)
- Agents
    - IV: gentamicin, tobramycin, amikacin, streptomycin
    - PO/topical: Neomycin (topical creams, ointments)
- Spectrum of Activity
    - Gram (+)
        - Activity against staphylococcus and streptococcus
        - Only used for synergy against Gram (+) organisms (next slide)
    - Gram (-)
        - Active against many Gram (-) bacilli
        - Including resistant *Enterobacteriaceae* AND *P. aeruginosa*
            - Tobramycin the only one with reliable *P. aeruginosa* activity
    - Anaerobes
        - No activity (remember the mechanism)
- Synergy
    - Gram (+)
        - **Usually combined with B-lactam for synergistic effect**
        - **Cell wall disruption allows for enhanced entry into the cell**
        - Expands spectrum to include enterococcus
        - Only used in severe, invasive infections
            - Endocarditis, osteomyelitis
            - Fallen out of favor recently
    - Gram (-)
        - In vitro a similar synergistic effect is demonstrated
        - This has never translated into improved clinical outcomes
        - Some will give combination therapy for severe GN infections, but evidence to support that practice is lacking
- Clinical Applications
    - Gentamicin
        - Mostly used for synergy for severe staphylococcal or enterococcal infections (and sometimes strep)
            - **Falling out of favor** in a lot of these scenarios
        - Eye ointments (as well as tobramycin)
    - Tobramycin
        - **Used for empiric double coverage of nosocomial infections**
            - Remember the importance of active empiric therapy
            - Like in HAP or ventilator acquired pneumonia
        - Sometimes continued for definitive therapy
    - Amikacin has a role in some mycobacterial infections

    - Neomycin
        - **Orally to decontaminate the GI tract prior to surgery** (not absorbed PO so present in the GI tract to work)
        - Often in topical creams (NEOsporin)
    - Streptomycin (FYI, not tested on this)
        - Enterococcal infection when gentamicin resistance (for synergy)
        - Mycobacterial infections like TB
- Monotherapy
    - **Should be avoided for the most part for definitive monotherapy of Gram (-) infections**
        - Literature suggests failure rates are higher with AGs
        - **EXCEPTION: UTI's – excellent efficacy data as monotherapy for both lower and upper tract infections** (including those complicated by bacteremia)
- Important PK Considerations
    - Poor oral absorption
        - PO not used for systemic infections
    - Concentration dependent killing
        - **Optimize both Cmax/MIC and AUC/MIC for efficacy** (peak and total exposure)
    - Highly concentrated in the urine (and kidney)
        - **Good for UTI**
        - **Renal dosing needed**
        - **Toxicity concerns**
        - **Gentamicin, Tobramycin, and Amikacin can be used for UTIs**
    - Dose-optimization and therapeutic drug monitoring
        - High dose, extended interval dosing
        - Peak/trough targets to maximize efficacy and minimize toxicity
- Adverse effects
    - **Nephrotoxicity**
        - Most common and most serious ADE
        - Strategies to minimize
            - **Shorter durations**
            - **Once daily dosing** (saturable toxicity)
    - **Vestibular/ototoxicity** (balance and hearing issues)
        - Associated with total drug exposure (optimize PK)
        - Can be irreversible

Drugs with Antipseudomonal Activity

- Piperacillin, Piperacillin/Tazobactam
- Cefepime, Ceftazidime
- Ceftolozane/Tazobactam, Ceftazidime/avibactam
- Cefiderocol
- Imipenem, Meropenem, Doripenem
- Meropenem/Vaborbactam, Imipenem/relebactam
- Aztreonam
- **Ciprofloxacin, Levofloxacin (and delafloxacin)**
- **Tobramycin** (and plazomicin)

Macrolides and Tetracylines

Macrolides

- **MOA**: Bind to the 50 S subunit of the ribosome – block protein synthesis at the translation stage
- Bacteriostatic

- Agents of clinical relevance
    - Erythromycin (IV/PO)
    - Clarithromycin (PO)
    - Azithromycin (IV/PO)
- Spectrum of Activity
    - **The respiratory pathogens**
        - ***S. pneumoniae, H. influenzae, M. catarrhalis***
            - **Pneumococcus resistance is high!** Over 50%, so not a reliable option
            - Resistance is so high d/t overuse of macrolides and Zpacks.
        - Atypical pathogens
            - *Mycoplasma pneumoniae, Chlamydia pneumoniae, Legionella pneumophilia*
    - C. trachomatis
    - N. gonorrhea
    - Mycobacterium avium complex (MAC) → present in HIV infected populations
        - Clarithromycin, Azithromycin
    - Clarithromycin and *H. pylori*
- Side effects
    - **Biggest class concern: Nausea/Vomiting/Diarrhea**
        - **Worst with erythromycin** as it binds to the motilin receptor in the GI tract
            - Pearl: Erythromycin (PO) only real use today is as a promotility agent in hospital for patients with severe constipation
        - **Much less with Azithromycin**
    - **QT prolongation (pro-dysrhythmia)**
        - **Least common with azithromycin**
            - Controversy to degree of risk with azithromycin – but definitely the least common with this agent
        - Highest with erythromycin
- PK (generally given PO)
    - Azithromycin IV dose = PO dose
        - NOT related to bioavailability!!
    - **Azithromycin long half-life**
        - **~72 hours; initial reason behind shorter courses of the drug!**
    - Metabolism
        - **Inhibitors and substrates of CYP3A4**
        - Many drug interactions possible
            - Largely seen with Erythromycin/Clarithromycin
            - Limited concern with azithromycin (sound familiar?)
    - **No renal dose adjustment needed**
    - All of these reasons (including decrease ADE) why azithromycin is the workhorse for the class
- Clinical Uses
    - **Greatest use in respiratory tract infections (azithromycin)**
        - Part of commonly used combination therapy for CAP
            - **No longer monotherapy due to pneumococcal resistance** so we must add another pneumococcal drug
        - Also utilized in tracheobronchitis, COPD, exacerbations, etc.
            - When antibiotics are warranted…

    - Clarithromycin is part of the standard therapy for *H. pylori*
    - No longer recommended for *N. gonorrhea/C. Trachomatis*
        - Increased resistance in GC, superiority of doxycycline for *C. trachomatis*
    - Often part of mycobacterial regimens
        - Clarithromycin usually with best data, azithromycin comes in when drug-interaction concerns come up (happens a lot)

Tetracyclines

- **MOA**: another ribosomal (30S subunit) antibiotic
- Bacteriostatic
- Agents
    - Tetracycline (PO) → won't see this used a lot
    - Doxycycline and Minocycline (IV/PO) → commonly used
    - Demeclocycline (PO)
        - Used for SIADH because medication caused drug induced diabetes insipidus
    - Tigecycline, Eravacycline (IV)
    - Omadacycline (IV/PO)

Doxycycline and Minocycline

- Gram (+)
    - ***S. aureus* (including MRSA), *S. pneumoniae, enterococcus***
- Gram (-)
    - ***H. influenzae, M. catarrhalis***
    - Can have activity against Enterobacteriaceae
        - Including drug-resistant isolates
    - *A. baumannii* and *S. maltophilia*
        - Minocycline > Doxycycline
- Anaerobes
    - Variable activity
- Miscellaneous
    - Atypical pneumonia pathogens – especially with doxycycline
    - Organisms associated with animal bites, Lyme disease

Tetracyclines

- PK
    - Highly lipophilic
    - **Penetrates many sites well**
    - **Not highly renally eliminated** (except tetracycline)
- Adverse events
    - N/V/D (lessened with food)
    - **Binding into growing teeth and bones (avoid if < 8 y/o)**
    - **Photosensitization**
    - Minocycline and Tinnitus
- Drug-interactions
    - **Chelation with divalent/trivalent cations**
- Clinical Uses
    - Doxycycline and Minocycline most often used
        - **Respiratory tract infections, including CAP**
            - Monotherapy in target patients
        - Skin and soft tissue infections, particularly where CA-MRSA is a concern
            - Possible strep issues…..

        - Minocycline emerging as a potential treatment option for drug-resistant Gram (-) infections
            - Carbapenem-resistant *A. baumannii*
            - *S. maltophilia*

Tigecycline and Eravacycline

- **Tetracycline derivatives "glycylcyclines"**
- Both IV only
- **MOA**: Same; ribosomal
- Chemical modifications to side chains of tetracycline core affords the ability to overcome some of the tetracycline-resistance mechanisms
- Spectrum of Activity
    - Gram (+)
        - **Broad, including MRSA and enhanced VRE activity**
    - Gram (-)
        - Similar to tetracyclines, but includes **enhanced coverage against resistant Gram (-) organisms**
            - **ESBL, CRE, Acinetobacter**
        - Lacks activity against P. aeruginosa
    - Anaerobic
        - **Broad coverage**
    - Also **covers atypical pathogens seen in CAP**
- PK – like other tetracyclines – large volume of distribution
- Adverse events
    - **N/V – particularly with tigecycline (~20%)**
        - Lower (< 10%) with eravacycline
- Place in Therapy
    - **Last-line option for many resistant Gram (-) organisms**
        - Most notably, *A. baumannii* and CRE
            - Blood, lungs, urine → these medications don't get to these sites particularly well
        - **Limited by PK profile**
    - **Polymicrobial wounds that include MRSA or VRE** (like with diabetic ulcers)
    - Second line therapy for patients **with PCN allergies** for many disease states
        - Intra-abdominal infections

Omadacycline

- Latest tetracycline derivative approved
    - CAP and Skin infections
- **IV and PO** good oral option
- **Gram (+) activity excellent → especially gram (+) resistant**
    - Including MRSA and VRE (and resistant streptococcus)
- Gram (-) activity more like traditional tetracyclines
- Key benefit: oral option
- ADE of note: **N/V (high rates)**
- **Must be separated by food and dairy by 2-4 hours**
    - **Significantly decreased absorption**

Other Key Antibacterials

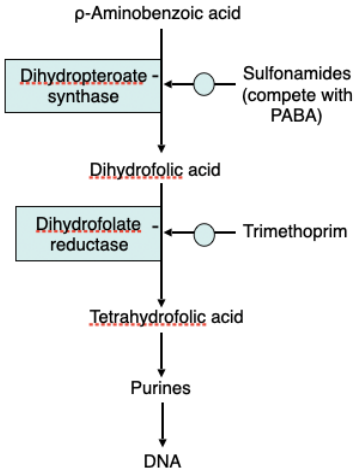
Clindamycin

- **MOA**: another 50 S ribosomal subunit acting drug

- Bacteriostatic
- Spectrum of activity
    - Gram (+) → can't reliably use this drug for gram (+)
        - *S. aureus* (including MRSA) and Streptococcus spp → **resistance increasing, no longer reliable! 25-30% rate of resistance**
- Gram (-)
    - No activity
- Anaerobes
    - Historically, activity seen, **but increasing resistance makes it unreliable here as well**
- Clinical pearl
    - **Toxin suppressing activity in necrotizing Gram (+) infections**
    - **Necrotizing fasciitis, toxic shock**
- Side effects
    - Nausea and Diarrhea (diarrhea common with clindamycin- both IV and PO)
    - ***C. difficile* diarrhea → One of highest associations**
- Clinical application
    - **Frankly, none,** given increasing resistance and evolving understanding of microbiology of various disease states
    - Historically
        - Skin infections due to MRSA and strep activity
        - Aspiration pneumonia due to the presumed role of anaerobes

Sulfonamides and Trimethoprim

- **Sulfonamide MOA**: structural analogs of p-aminobenzoic acid
- (PABA) that blocks production of dihydrofolic acid
    - Most commonly used agent is sulfamethoxazole
- **Trimethoprim MOA**: inhibitor of dihydrofolic acid reductase
- Stops DNA synthesis
- TMP + SMX = Bactrim, Septra
- Both individually are bacteriostatic
    - When combined bactericidal



- TMP/SMX: Spectrum of Activity
    - Gram (+)
        - **Good for *S. aureus* (including MRSA)**
        - **Also active against strep** (but limited clinical experience)

    - Gram (-)
        - Activity against enteric Gram (-) are variable
            - *Klebsiella, E. coli*, Proteus → check local epidemiology (20-30% resistance)
        - Enterobacter, Citrobacter, Serratia
            - Active, but limited clinical experience (not recommended for systemic infections)
        - No *P. aeruginosa* activity
    - Miscellaneous
        - Limited anaerobic activity (avoid clinically)
        - Listeria and Nocardia
        - **DOC: *P. jirovecii,* maybe *S. maltophilia***
- Side effects and Drug Interactions
    - **"Sulfa drugs" are the most common agents associated with hypersensitivity reactions**
        - ~3% of all patients
        - Can be as simple as a rash and as severe as SJS/TEN
    - **Trimethoprim and Hyperkalemia**
        - Most important ADE to know
        - Causes triamterene effect like K+ sparring diuretic results in decreased excretion of K+ and buildup of K+ systemically
    - Trimethoprim can also cause false rises in creatinine
        - **No AKI, but small rise (~0.3 – 0.5) in creatinine**
        - Older sulfonamides caused crystallization in urine, uncommon with sulfamethoxazole – but diagnoses can be muddied
    - Trimethoprim can cause anemia, leukopenia
    - **Increased INR when given with warfarin**
- Clinical Applications
    - **Common agent used for outpatient UTI's**
        - Be wary increasing resistance (really isn't reliable empirically)
    - Used for skin infections when MRSA is a concern
    - **DOC for many bad infections in vulnerable populations**
        - **PCP pneumonia, Nocardia, (maybe) *S. maltophilia***

Nitro-Imidazoles: **Metronidazole,** Tinidazole

- **MOA**: Poorly defined interaction with DNA causing helical structure loss, strand breaking, and cell death
- Spectrum of Activity
    - Antibacterial: **Anaerobes only, including *C. difficile***
    - **Some parasitic activity, most notable *T. vaginalis***
- Side effects
    - Nausea/vomiting (also metallic taste)
    - Peripheral neuropathies (rare, but cumulative) numbness/tingling
- PK
    - **100% bioavailability**, limited renal elimination
- Drug interactions
    - **Disulfiram interaction with ethanol; Increased INR with warfarin**
- Clinical application
    - **Empiric anaerobic activity**
    - Second-line *C. difficile* infection (vanco is superior)

    - **Trichomoniasis**

Rifampin

- **MOA**: inhibitor of DNA-dependent RNA polymerase, blocks RNA synthesis
- Spectrum of activity
    - Gram (+): ***S. aureus*** **(including MRSA) and streptococcus**
        - **Not used as monotherapy concern for rapid resistance development**
    - Gram (-): Limited activity alone, but can be used in synergy
    - **Mycobacterial infections → TB**
- Side effects
    - **Hepatotoxicity** (monitor LFTs)
    - **Discolored fluids** (urine, tears, sweat)
- PK
    - **100% bioavailability**, No renal dosing needed
- Drug interactions
    - **Strong inducer of multiple CYP450 enzymes → concern for subtherapeutic levels**
        - Most notable CYP 3A4, 2C9, 2C19
    - **Contraindicated with many HIV medications**
    - Significant interactions with many antifungals, anti-hypertensives, statins, amongst others
- Clinical applications
    - **Used in combination for severe staphylococcal infections with hardware**
        - Prosthetic valves and joints → rifampin able to penetrate biofilm and infections there
    - **Mycobacterial infections**

Nitrofurantoin

- MOA: inhibition of a variety of bacterial enzyme systems interfering with metabolism
- **Spectrum: Urinary tract organisms (Gram (+) and (-))**
    - **Notably active against E. coli**
- Use: Only used to treat **lower urinary tract infections**
- Side effects: Rare inflammatory lung process
- Debated efficacy if Clcr < 30 mL/min