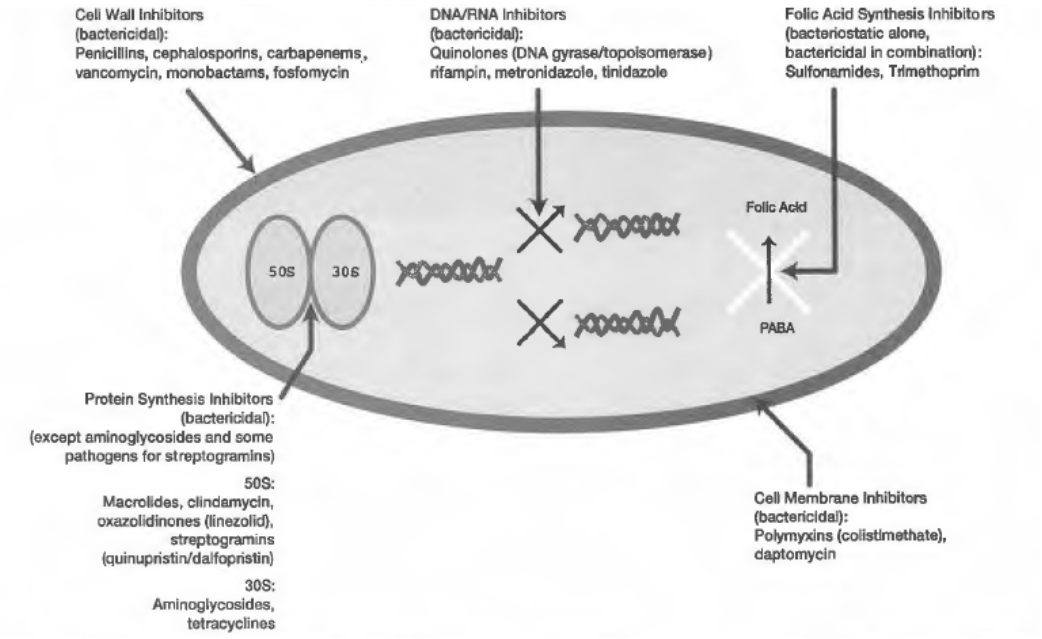
Infectious Disease Review

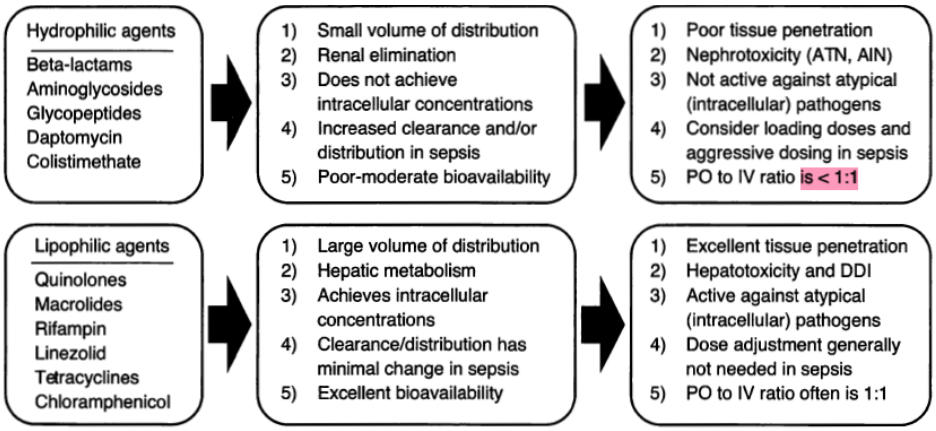
- Gram stain is the first thing to do

○ Gram +: thick cell wall, purple stain ■ Staph ■ Strep ■ Viridans ■ Enterococcus ■ Bacillus ■ Listeria ■ Clostridium ■ Lactobacillus	○ Gram -: thin cell wall, pink or reddish stain ■ Neisseria ■ Acinetobacter ■ E coli ■ Klebsiella ■ Proteus ■ Pseudomonas ■ H influenzae ■ Anaerobes (bacteroides, prevotella, fusobacterium) ■ Atypicals (chlamydia, mycoplasma, Tb)

- Most common bugs and sites:
  - CNS/Meningitis: S pneumo, neisseria, H influenzae
    - Kiddos: Strep/E coli, listeria
  - URI: Moraxella, H influenzae, Strep
  - Bone & Joint: S aureus, S epidermidis, strep, neisseria, gram neg rods
  - Mouth/ENT: Mouth flora (pepto, actinomyces), anaerobic GNR, H influenzae
  - SSTI: Staph, pasteurella
    - DM: aerobic/anaerobic GNR
  - Intra-abdominal: E coli, proteus, klebsiella, enterococci, strep, bacteroides
  - CAP: Strep, H influenzae, Atypicals
    - Alcoholics, IC, HCA: PEK
  - HAP: PEK, strep, pseudomonas, enterobacter, S aureus (including MRSA)
  - UTI": PEK, staph, enterococci/streptococci
- Types of Resistance:
  - ESBL: beta-lactamases can break down all PCN and some ceph
    - **Treat with carbapenems or newer cephs/beta lactamase inhibitors**
  - Carbapenem-resistant enterobacteriaceae: group of MDR gram neg mostly found in Klebsiella
    - **Treat with combo abx typically with polymyxin or Avycaz $$$**
  - MRSA
  - VRE (E faecalis or E faecium)
  - Acinetobacter baumannii
  - Pseudomonas
- Collateral damage:
  - Altered GI flora→ C diff
    - **Clindamycin has a BBW for C diff**
- Concepts:
  - MIC: lowest drug concentration that prevents microbial growth
  - Breakpoint: MIC where a drug is susceptible or resistant
  - Synergy: two or more agents combine for better power
  - Bactericidal: kills bacteria
  - Bacteriostatic: inhibits growth

- Antimicrobial Stewardship:
  - 1. Discontinuation or de-escalation
  - 2. IV to PO
  - 3. Restriction





- Pharmacodynamics:
  - Beta-lactam: maximize efficacy by more frequent dosing, extending infusion time, CIVI→ creates greater TIME above MIC

Note: Penicillins, Cephalosporins, and Carbapenems all have time dependent, bactericidal killing by inhibiting bacterial cell wall synthesis. Other similarities include:

- Monitoring: renal function, signs of anaphylaxis with first dose, CBCs and LFTs
- Probenecid inc levels by dec renal excretion
- All Preg Cat B except imipenem

Penicillins:

Class	Coverage	Warnings
Penicillins	Mainly gram + cocci (enterococcus + anaerobes). Little gram neg	-Pen G benzathine: NOT for IV use→ cardiorespiratory arrest and death

Aminopenicillins	Expanded coverage to include HNPEK	-Augmentin/Unasyn: CI for cholestatic jaundice or hepatic dysfunction, CrCL <30 -**Main SE:** GI upset, diarrhea, rash -**Amoxicillin is DOC for ear infections, H pylori, and ppx for endocarditis** -Some chewable tabs have phenylalanine. DO NOT use in pts with phenylketonuria
Beta lactamase inhibitor PCN	Expanded coverage to MSSA, more resistant strains of HNPEK, and B fragilis	
Extended spectrum PCN, Zosyn, and Timentin	Expanded coverage to include CAPES & Pseudomonas	
Nafcillin, oxacillin, and dicloxacillin	MSSA but not enterococcus	

- PCN Clinical Pearls:
    - Decreasing the clavulanate component in Augmentin dec diarrhea
    - Ampicillin on empty stomach 1 hour before or 2 hours after meals
    - Extended infusion of Zosyn is over 4 hours
    - Nafcillin is a vesicant→ use cold packs or hyaluronidase infections if extravasation occurs. Central line preferred.
    - PCNs work best against actively growing bacteria
- PCN Drug Interactions:
    - Tetracyclines and other bacteriostatic agents dec effectiveness by slowing bacterial growth
    - PCNs can inc MTX
    - PCNs dec serum concentrations of active metabs of mycophenolate due to impaired enterohepatic recirculation
    - Nafcillin is a moderate CYP3A4 inducer
    - Dicloxacillin and nafcillin dec INR by inc metab of warfarin
    - Other PCNs inc INR

Cephalosporins:

Class	Coverage	Warnings
First generation (cefadroxil, cefazolin, keflex)	Gram positive cocci with some PEK **Preferred for MSSA**	-Ceftriaxone is CI in hyperbilirubinemic neonates (causes biliary sludging when used with Ca containing IV products in neonates < 28 days old) -**Main SE:** GI upset, diarrhea, rash, seizures with accumulation
Cephamycin second generation (cefotetan and cefoxitin) Other (cefaclor, cefprozil, cefuroxime)	Added anaerobic coverage (B fragilis)	
Third gen (ceftriaxone, cefotaxime, cefdinir, cefditoren, cefixime, cefpodoxime, ceftibuten, ceftazidime)	More resistant streptococci along with enhanced gram negative coverage + CAPES	
Other third gen (Avycaz or Zerbaxa)	Lack gram positive activity but covers Pseudomonas **Added activity MDR Pseudomonas and other gram neg rods**	
Fourth gen (cefepime)	Broad gram neg including Pseudomonas and gram + activity similar to Ceftriaxone, covers MRSA	

Fifth gen (Ceftaroline)	Broadest gram positive, covers MRSA, gram neg activity similar to Ceftriaxone, no Pseudomonas	

- Cephalosporin Clinical Pearls:
  - Some agents may inc INR
  - <10% cross reactivity with PCN allergy→ DO NOT USE in pts with type 1 PCN allergy
  - Cefotetan has an NMTT or 1-MTT side chain which can inc bleeding and disulfiram reaction
  - Ceftriaxone= no renal dose
  - Cefixime: chewable tablet
- Cephalosporin Drug Interactions:
  - Drugs that dec stomach acid dec bioavailability of some ceph
    - Separate cefuroxime,cefpodoxime, cefdinir, and cefditoren by 2 hours or antacids
    - AVOID H2RAs and PPIs

Carbapenems:

Class	Coverage	Warnings
Doripenem, Imipenem/cilastatin (primaxin), Meropenem	**Very broad spectrum reserved for MDR gram neg (including ESBL), most gram pos, anaerobes.** NO atypical, MRSA, VRE, C diff, and stenotrophomonas	-Associated with CNS AE including confusional states and seizures -DO NOT use Dori for HAP/VAP -PCN cross reactivity ~50%, do not use in PCN allergy **Main SE:** diarrhea, rash, seizures with higher doses, BM suppression with prolonged use, inc LFTs
Ertapenem	Same as above, but NO activity against Pseudomonas, Acinetobacter, or Enterococcus **Common for ESBL and DM foot**	

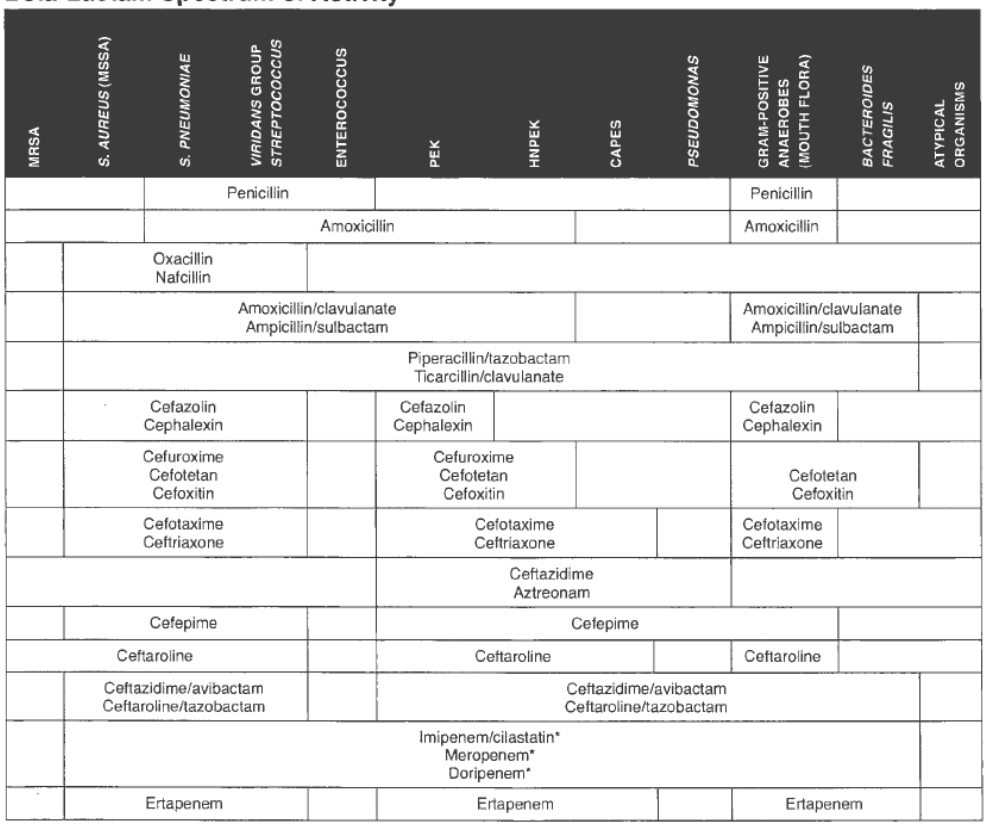
- Carbapenems Clinical Pearls:
  - Impairs renal function (mainly imipenem)
  - Imipenem is combined with cilastatin to prevent drug degradation by renal tubular dehydropeptidase
  - Common uses: ESBL, Pseudomonas, broad spectrum empiric coverage
- Carbapenem Drug Interactions:
  - Can dec VPA concentrations leading to loss of seizure control
  - Use with caution in pts with risk for seizures or with drugs that lower seizure threshold

Monobactam:

Class	Coverage	Warnings
Aztreonam	More resistant streptococci along with enhanced gram negative coverage + CAPES; includes Pseudomonas **NO GRAM POS**	-SE similar to PCN including rash, NVD, inc LFTs

- Aztreonam Clinical Pearls
  - Used for beta lactam allergy
  - CrCL: 10-30→ inc dose by 50% after first dose
  - CrCL: <10→ dec dose by 75% after first dose

Beta-Lactam Spectrum of Activity



Aminoglycosides: Bind to 30S and 50S ribosomal subunits to make a defective bacterial cell membrane; concentration dependent killing, with a post antibiotic effect

- Extended interval dosing allows higher doses that are needed to achieve desired peak (≥10x MIC) for gram neg while preventing accumulation which can lead to toxicity
    - Random level drawn after first dose to determine appropriate dosing interval
    - Dosing interval is ALWAYS rounded up to prevent toxicity
        - Dec nephrotoxicity
        - Dec cost
        - Inc bactericidal activity
        - NOT clinically superior to traditional dosing

Class	Coverage	Warnings
Gentamicin, tobramycin, and amikacin	Mainly gram negative including Pseudomonas **Gentamicin and streptomycin are used for synergy when treating gram pos (staphylococci and enterococcus in endocarditis) in combo with beta-lactam or vanco** Streptomycin and amikacin are second line therapy for mycobacterial infections	-**Boxed warnings:** nephrotoxicity, ototoxicity, neuromuscular blockade, and respiratory paralysis -CAUTION with impaired renal function and elderly **Main SE:** boxed warnings + vestibular toxicity -Monitoring: renal function, urine output, hearing tests, drug levels

- AG Clinical Pearls:
    - Tobramycin is bad for pregnancy
    - Traditional dosing: draw trough level right before 4th dose, draw peak levels ½ hour after the end of drug infusion of the 4th dose
    - Extended interval: draw random level per timing on nomogram
    - Amikacin has broadest spectrum of activity

- If underweight use actual BW
- If normal weight, use actual body weight or IBW
- If obese, use adjusted body weight
- Do not use extended interval dosing nomograms in:
  - Pregnancy
  - Ascites
  - Burns
  - CF
  - CrCL <30 mL/min
  - Or when using in synergy with gram pos infections

Traditional Dosing Target Drug Concentrations

DRUG	PEAK	TROUGH
Gentamicin		
Gram-negative infection:	5-10 mcg/mL	< 2 mcg/mL
Gram-positive infection:	3-4 mcg/mL	< 1 mcg/mL
Tobramycin	5-10 mcg/mL	< 2 mcg/mL
Amikacin	20-30 mcg/mL	< 5 mcg/mL

Quinolones: Inhibit bacterial DNA topoisomerase IV and inhibit DNA gyrase (topo II) which prevents supercoiling of DNA and promotes breakage of double stranded DNA; concentration dependent, bactericidal

- Generally AVOIDED for MRSA because of high resistance rates

Class	Coverage	Warnings
Respiratory quinolones (gemi, levo, and moxi)	Enhanced s pneumo and atypicals	-Boxed warnings: tendon rupture, inc risk with concurrent systemic steroid use, organ transplant, and >60 YO -May exacerbate muscle weakness related to myasthenia gravis -Cipro CI with tizanidine -Avoid use with QT prolongation and Class I and II antiarrhythmics (esp with moxi) -**Warnings:** PN, CNS effects (esp seizures), glycemic probs, inc LFTs, photosensitivity -AVOID USE in children due to musculoskeletal toxicity -**Main SE:** GI upset/diarrhea
Cipro and levo	Enhanced gram neg including pseudomonas (typically with a beta lactam)	
Moxi	Enhanced gram pos and anaerobic (mixed infections such as intra-abdominal)	

- Quinolone Clinical Pearls
  - DO NOT give cipro oral suspension through feeding tubes because oil makes it adhere
    - DO NOT refrigerate
    - Crush tablets and give through tube instead
  - Most need renal dose adjustments except moxi
- Quinolone Drug Interactions:
  - Antacids, didanosine, sucralfate, bile acid resins, Mg, Al, Ca, Fe, Zn, MUVI or any product containing multivalent cations can chelate and inhibit absorption
    - Give cipro 2 hours before or 6 hours after
    - Give levo 2 hours before or after
    - Give moxi 4 hours before or 8 hours after
  - Avoid dairy foods because risk of chelation
  - Lanthanum and sevelamer can dec serum concentration, take FQ 2 hrs before
  - Can inc effects of warfarin, sulfonylureas/insulin, and QT prolonging drugs

- Probenecid and NSAIDs inc levels
- Cipro has the most interactions (Pgp substrate, strong 1A2 inhibitor and weak 3A4 inhibitor)

Macrolides: Bind to the 50S ribosomal unit, resulting in inhibition of RNA-dependent protein synthesis with **bacteriostatic** activity related to the total exposure of the drug (AUC/MIC)

Class	Coverage	Warnings
Azithromycin, Clarithromycin, Erythromycin	Good atypical coverage and Haemophilus **Good for CA U/LRI and certain STDs**	-CI: history of hepatic dysfunction with prior use -Clarith: CI with colchicine in patients with renal or hepatic impairment, history of QT prolongation or ventricular arrhythmia -Caution with QT prolongation and hepatotoxicity **Main SE:** GI upset, taste perversion, and inc LFTs

- Macrolide Clinical Pearls
  - AzaSite: viscous solution for ophthalmic use; store at cold temps makes it more viscous
  - Azith ER suspension is not bioequivalent to Zithromax and cannot be interchanged
- Macrolide Drug Interactions:
  - Clarith and eryth with pimozide, ergotamine or dihydroergotamine, lovastatin or simvastatin
  - Erythromycin and clarith are substrates of 3A4 (major) and 3A4 inhibitors (moderate/strong)
  - Azith is a substrate of 3A4 and inhibitor of 1A2 and P-gp
  - ALL macrolides: do not use with agents that can prolong QT

Tetracyclines: Bind to the 50S ribosomal unit, resulting in inhibition of RNA-dependent protein synthesis with **bacteriostatic** activity related to the total exposure of the drug (AUC/MIC)

- Drug has a lot of utility in RTI, tick-borne/rickettsial diseases, spirochetes and chlamydia infections
- Tx MRSA in mild skin infections
- Tx VRE in UTI

Class	Coverage	Warnings
Doxycycline and Minocycline	Many gram positive bacteria including staph, strep, entero, nocardia, bacillus, and propionibacterium, gram neg and other unique pathogens **Mino has enhanced gram pos coverage→ preferred in SSTI**	-Children <8YO, PG, or breastfeeding: Preg Cat D-suppressed bone growth and skeletal development -Drug rash with eosinophilia and systemic sx syndrome, exfoliative dermatitis -Inc BUN, photosensitivity -Minocycline can induce lupus **Main SE:** NVD, rash

- Tetracyclines Clinical Pearls
  - Monitor: LFTs, renal function, CBC
  - Take with food to dec stomach upset and do not take with milk (chelation)
- Tetracycline Drug Interactions:
  - Impaired by antacids and other meds that contain divalent cations such as Fe containing, sucralfate, bile acid resins, or pepto
    - Take doses 1-2 hours before or 4 hours after
  - Lanthanum can dec concentrations, take 2 hours before or after
  - Major 3A4 substrate and moderate inhibitor

- Doxy is a weak 3A4 inhibitor
- Can inc INR
- Can enhance effects of neuromuscular blocking agents
- Can dec effectiveness of PCN by slowing growth of bacteria (PCN work on fast bacteria)

Sulfonamides: Interfere with bacterial folic acid synthesis by inhibiting DHF acid formation from para-aminobenzoic acid and TMP inhibits DHF acid reduction to THF→ ultimately inhibiting folic acid pathway

- Individually bacteriostatic, but together bactericidal

Class	Coverage	Warnings
Bactrim	Gram positive (including staph and MRSA, active against many gram neg and includes opportunistic pathogens **No Pseudomonas, enterococci, or anaerobic coverage**	-CI in sulfa allergy, PG, breastfeeding, anemia due to folate def, marked renal or hepatic disease, infants < 2 MO -Warnings: blood dyscrasias, SJS, TENs, TTP, G6PD deficiency -**Main SE:** NVD, allergic skin crystalluria, photosensitivity, inc K, hypoglycemia, dec folate, Coombs test

- Sulfas Clinical Pearls
  - Dose is based on TMP component
  - Sulfa:TMP is always a 5:1 ratio
  - Monitoring: renal function, LFTs, electrolytes, CBC
  - PG Cat C or D
- Sulfas Drug Interactions:
  - Sulfonamides are 2C8/9 inhibitors
  - Can inc INR, caution with concurrent use of warfarin
  - Can inc levels of sulfonylureas, metformin, fosphenytoin/phenytoin, dofetilide, azathioprine, MTX, and mercaptopurine
  - Levels of SMX/TMP can be dec by 2C8/9 inducers and therapeutic effects diminished by leucovorin
  - ACE,

Vancomycin: Inhibits bacterial cell wall synthesis

Class	Coverage	Warnings
Vancomycin	Gram positive including MRSA, streptococci, enterococci (not VRE) and c diff	-Caution with the use of other nephrotoxic or ototoxic drugs **Main SE:** infusion reaction/red man syndrome, nephrotoxicity -**Monitoring:** renal function, WBC, trough concentration at steady state (generally before 4th dose) Target troughs: 15-20 mcg/mL: pneumonia, endocarditis, osteomyelitis, meningitis, bacteremia -Target troughs: 10-15 mcg/mL: for other infections **First line tx for MRSA** -Consider alternative agent when MRSA MIC ≥ 2 mcg/mL

- Vancomycin Clinical Pearls
  - Dosed on actual body weight
  - CrCL: 20-40 mL/min → Q24H
  - CrCL <20 mL/min: give loading dose then dose per levels
  - Infuse peripheral IV at a concentration not to exceed 5 mg/mL
- Vancomycin Drug Interactions:

- Vancomycin can increase the toxicity of nephrotoxic and ototoxic drugs

Lipoglycopeptides: Inhibit bacterial cell wall synthesis by:

- Blocking polymerization and cross linking of peptidoglycan by binding to the D-Ala-D-Ala portion of the cell wall
- Disrupting bacterial membrane potential and changing cell permeability due to presence of lipophilic side chain moiety
- Concentration dependent killing, bactericidal

Class	Coverage	Warnings
Telavancin	Gram positive including MRSA, streptococci, enterococci (not VRE) and c diff **Approved for complicated SSTI & HAP**	-**BBW: REMS, nephrotoxicity, inc mortality with patients with existing moderate to severe renal impairment** -**Warnings:** can falsely increase PT/INR but drug does not increase bleeding risk -Rapid IV admin can cause red man syndrome. Infuse over 60 min to prevent it. **Main SE:** metallic taste, inc SCr, QT prolongation, red man syndrome
Oritavancin (**Single dose regimen because of extremely long t 1/2)** Dalbavancin (same coverage as orita except no enterococci; two dose regimen; infused over 30 min)	Gram positive including MRSA, streptococci, enterococci (not VRE) **Approved for SSTI**	-**CI: DO NOT use with heparin because it will interfere with aPTT lab results** **-Warnings:** may inc risk of bleeding in patients on warfarin. Can cause falsely inc INR/PT up to 24 hrs after or aPTT for up to 48 hours after a dose **Main SE:** N/V/D, HA, rash, red man's syndrome **Monitoring:** signs of osteomyelitis (oritavancin), LFTs, renal function

- Telavancin Clinical Pearls
  - Avoid in patients with congenital long QT syndrome or uncompensated HF
- Oritavancin Clinical Pearls:
  - Weak 2C9 and 2C19 inhibitor and weak inducer of 3A4 and 2D6

Daptomycin: Binds to the cell membrane components causing rapid depolarization, inhibiting all intracellular replication processes including protein synthesis.

- Concentration dependent, bactericidal activity

Class	Coverage	Warnings
Daptomycin	Gram positive including MRSA, streptococci, enterococci **(including VRE)** Approved for complicated SSTI and MRSA, bloodstream infections, including right sided endocarditis **Extend dosing interval to Q48H if CrCL <30	-**Warnings:** eosinophilic pneumonia: gradually develops after 2-4 weeks after therapy initiation -Myopathy: discontinue in patients with s/sx along with inc in CPK >1000 units (5x ULN) or in asx patients with CPK ≥ 2000 units/L (10x ULN) **Main SE:** inc CPK & myopathy **Monitoring:** CPK weekly (more frequently if taking a statin) muscle pain/weakness -Can falsely inc INR but does not inc bleeding risk

		Compatible with NS and LR only **DO NOT use to tx pneumonia because drug is inactivated in the lungs by surfactant**

Oxazolidinones: Binds to 50S subunit of the bacterial ribosome inhibiting bacterial translation and protein synthesis

- Bacteriostatic

Class	Coverage	Warnings
Linezolid or Tedizolid (approved for SSTI; infuse over 1 hour, stable in NS)	Gram positive including MRSA, streptococci, enterococci **(including VRE)**	-**Contraindications:** concurrent use or within 2 weeks of MAOi **Warnings:** duration related myelosuppression, peripheral or optic neuropathy when tx >28 days, serotonin syndrome, hypoglycemia **Tedizolid: consider alt options for patients with neutropenia** **Main SE:** myelosuppression, anemia, thrombocytopenia, HA, N/D **Monitoring:** weekly CBC, visual function Tedi has less myelotoxicity and GI problems No adjustments in renal impairment DO NOT shake linezolid suspension

- Drug Interactions: (tedi < SS than line)
  - Weak MAO inhibitor
  - Avoid tyramine containing foods and serotonergic drugs
  - Linezolid can exacerbate hypoglycemic episodes, caution in patients receiving insulin or oral hypoglycemic agents