Bacteria

- MDRB: Psuedomonas, Stenotrophomonas, Acinetobacter, VRE, MRSA
- Differentiation b/c colonization vs infection b/c colonized pathogens should not be treated
- most common organisms on skin: Coag Negative Staph (15 different species with the most common S. epidermidis, rarely cause problems), Staph aureus (is NOT normally on skin but may be present transiently inoculated from mucosa esp nares, axillae, perineum, etc 15% of pts have permanent colonization), Strep (GABHS), enteric GNR, fungi
- **bacteriostatic** (tetracyclines, macrolides, clindamycin, sulfonamides, trimethoprims, spectinomycin) vs **bacteriocidal** (beta-lactams, vanc, aminoglycosides, FQ, rifampin, metronidazole) = **endocarditis, meningitis, neutropenia**
- **CSF Penetration even w/o Inflammation:** FQ, Bactrim, Flagyl vs **CSF Penetration only w/ Inflammation:** PCN, 3rd Cephs, Vanc, Azactam, Imipenem, Clinda
- soap/water only removes unattached/transient bacteria NOT attached/resident bacteria hence you need antiseptics for skin and disinfectants for inanimate objects, alcohols (broad, rapid onset, short acting) vs iodine (broad, slow onset, long acting) vs chlorhexidine (narrow, fast acting, long acting), none sporicidal therefore must use gloves and scrub off w/ water
- Obligate Aerobe (require O2) vs Facultative Anaerobe (prefer O2 but can ferment) vs Microacrophilic (ferment but tolerate O2) vs Obligate Anaerobe (ferment and O2 is toxic)
- GP (purple) vs GN (red)
- **GPC** (virulence via secreted exotoxins)
    - **Staph** (+Catalase/Clusters) there are many species but only S. aureus is important the rest aka "CNS" are not important except in immunocompromised pts
        - ***S. aureus*** (+Coagulase) found on mucosa, pathogenic, >50% is MRSA, though the vanc MIC is rising there have been no cases of VRSA, most MRSA is colonized not infectious, MRSA is divided into CA (community acquired, less resistant) vs HA (hospital acquired, more resistant), MRSA is NOT more virulent than MSSA except for the CA-MRSA PVL+ strain (Panton-Valentine Leukocidin), colonization (1° nares 2° skin) lasts days to years hence isolation
            - IV: vanc → linezolid → daptomycin / tigecycline / quinoptistin+dalfopristin → New Abx: --avancins, iclaprim, etc
            - PO: bactrim / tetracyclines / linezolid / clindamycin (NB clinda only good for true CA-MRSA as HA-MRSA has inducible resistance to clinda but to be sure check "D-Test")
            - although ineffective as a single agent rifampin and gentamycin when combined with above abx provides synergism to these agents when MRSA is sensitive to it
            - Syndromes 2/2 Toxins: Staph Scalded Skin Syndrome (desquamating erythema in newborns), Toxic Shock Syndrome - TSS (sepsis + desquamating rash involving palms/soles + MOF, seen in women who use tampons, any pt w/ a wound, post-op w/ new hardware, etc Dx: -BCx unlike Strep TSS which has +BCx, Tx: penicillin + clinda/IVIG (to inhibit/clear toxins)), Staph Food Poisoning, Scarlet Fever
            - MSSA is usually Tx w/ oxacillin/nafcillin
            - MRSA is difficult to eradicate but you can try with nasal topical Bactroban and oral Rifampin
        - ***S. epidermis, S. saprophyticus,* etc** (-Coagulase) found on skin, non-pathogenic, usually a contaminant except for saprophyticus which causes UTIs, if NOT contaminant then Tx like Staph aureus
    - **Strep** (-Catalase/Chains or Pairs)
        - (alpha-hemolytic)
            - ***S. pneumoniae*** (many infections, beta-lactam resistance is emerging hence use ceftriaxone AND vanc until for serious infections until sensitivities are back), ***S. viridans*** (endocarditis), etc
        - (beta-hemolytic)
            - Group A: ***S. pyogenes*** aka "GABHS"
                - Pharyngitis & Impetigo 2/2 actual infection
                - Scarlet Fever & Toxic Shock Syndrome 2/2 toxin mediated (similar to Staph)
                - Complications: Rheumatic Fever (3wks after Pharyngitis ONLY, Tx does prevent RF) & GN (3wks after Pharyngitis OR Impetigo, Tx does NOT prevent GN) 2/2 IC mediated
            - Group B: ***S. agalectiae*** (normally found in GI and female GU tract, Bacteremia/PNA/Meningitis in very young/old pts)
            - Group C: no human pathogens
            - Group D: NB most of these species are now reclassified as Enterococci except ***S. bovis*** (IE and CRC)
        - (non-hemolytic) no human pathogens
    - **Enterococcus** (?) there are many species but only ***E. faecalis*** (85%, usually sensitive "s is for sensitive", more common) / ***feacium*** (15%, usually resistant aka VRE, less common), come from GI/GU tract
        - Abx: amp/pcn (only inhibitory therefore must add aminoglycoside), vanc (high r/o resistance), zyvox, quinopristin+dalfopristin, doxycycline, chloramphenicol, nitrofurantoin
- **GPR**

    - Spore Forming
        - ***Bacillus anthraxis*** (Anthrax), ***cereus*** (Gastroenteritis)
        - ***Clostridium tetani*** (Tetanus), ***botulinum*** (Botulism), ***perfringens*** (Food Poisoning), ***difficile*** (AAC), ***septicum*** (Sepsis associated w/ GI malignancy) NB Gas Gangrene can occur from any species
    - Non-Spore Forming
        - ***Corynebacterium diphtheria*** (Diphtheria) ***jeikeim*** (sepsis in neutropenic pts but in general it is part of skin flora and usually a contaminant if +BCx)
        - ***Listeria monocytogenes*** (associated w/ consumption of contaminated milk products, causes meningitis/bacteremia in elderly/neonates/immunosuppressed/pregnant pts, Tx: pcn/amp + aminoglycosides, resistance to cephalosporins)
        - ***Bifiobacterium, Proprionobacterum, Peptococci, Peptostreptococci***
- **GNC** (virulence from endotoxins aka LPS in membrane)
    - ***Neisseria meningitidis*** (normally found in pharynx and our body constantly fights bacteremia w/ complement but when there is MAC deficiency pts develop meningitis, meningococcemic sepsis w/ purpura fulminans, Water-House Friderichsen syndrome), Tx: penicillin, Px: rifampin/FQ b/c they concentrate in pharynx, ***gonorrhea*** (GU) Tx: ceftriaxone
    - ***Moraxella catarrhalis*** (URTI)
- **GNR**
    - ***Psuedomonas aeruginosa*** (high r/o acquiring resistance acutely hence double coverage when psuedomonal bacteremia/pneumonia otherwise just use single coverage as for UTI, etc, IVDU endocarditis/osteomyelitis, CF pneumonia, nail puncture thru shoe, diabetic otitis externa, ecthyma gangrenosum skin lesion, hot tub rash, folliculitis, cellulitis, etc)
        - Abx: 4th Pen, 4th Ceph, Monobactams, Carbapenems, Aminoglycosides, FQ
    - ***Haemophilus influenza***
    - ***Helicobacter pylori***
    - **Enterobacteriaceae** (large group of GNR that are part of normal colonic flora): ***Bacteroides, Fusobacterium, Prevotella, Vibrio, Burkholderia, Aeromonas, Actinobacillus, Acinetobacter, Escherichia, Enterobacter, Salmonella, Yersinia, Shigella, Citrobacter, Klebsiella, etc***
    - **The Unusuals**
- **Anaerobes**
    - foul smelling, gas producing infection in a location that has low oxygen esp deep soft tissue infections, abscesses and necrotic tissue but that is near mucosa/skin b/c these bacteria normally live on mucosa/skin and become infectious when they move into low oxygen tension environments
    - ***bacteria*** above that are underlined are anearobic
    - it takes awhile for Cx to grow
    - Abx: 1st/3rd/4th generation penicillins, carbapenems, clindamycin, metronidazole
- **Atypicals**
    - **Spirochetes (*Treponema, Borrellia, Leptospirosis*)**
    - **No Shape (*Myco/Ureaplasma*)**
    - **Weak GN (*Mycobacteria, Legionella*)**
    - **Obligate Intracellular Parasites (*Coxiella, Ehrlichia, Rickettsia, Chlamydia)***
    - **Fungus Like (*Actinomyces, Nocardia*)**

I. Cell Wall Synthesis Inhibitors

Beta-Lactams

- Mechanism
    (1) differ from one another in the R substituent
    (2) bacteria create a pentapeptide-disaccharide unit (peptidoglycan) in the cytoplasm, transfer it to a lipid on membrane which then flips into periplasm; a glycosidic linkage is formed between these units followed by peptide bond cross-linking using transpeptidases (aka penicillin binding proteins – PBP) creating a cell wall; other transpeptidases remodel the cell wall during cell growth and division; beta-lactams resemble the D-alanine-D-alanine terminal of the pentapeptide that transpeptidase recognizes therefore they competitively bind irreversibly to this enzyme inactivating it thus beta-lactams interfere with cell wall production and remodeling (maximally effective when bacteria are actively proliferating) resulting in a bacteriostatic effect
    (3) bacteria contain autolysins (aka penicillin binding proteins – PBP) which are enzymes that degrade the cell so that it can be remodeled; normally they are tightly regulated i.e. inhibited most of the time beta-lactams resemble inducers for the enzyme autolysin thus beta lactams activate autolysins resulting in cell wall breakdown and osmotic lysis of bacteria resulting in a bacteriocidal effect
    (4) both G+ and G- are susceptible to beta-lactams b/c they both possess a cell wall but G+ are more susceptible b/c they lack an LPS membrane that would prevent their entrance as seen in G-
    (5) beta-lactams and aminoglycosides work synergistically b/c penicillins increased bacterial permeability to intracellular antibiotics like aminoglycosides (but never give in the same infusion fluid b/c beta-lactams are negative while aminoglycosides are positive forming inactive neutral complexes)
    (6) Resistance
        - Inactivating Enzymes: beta-lactamases (hydrolyze ring)

        - Inhibitors: (clavulanate, sulbactam, tazobactam) contain a beta-lactam ring that irreversibly binds lactamases saturating the enzymes so that it can't cleave the antibiotic
        - Natural Resistance to Lactamases: Pen<Ceph< Carbapenems/Aztreonam
        - 95% of Staph are beta-lactamase + therefore can't use 1st gen pen
        - 65% of Staph are PBP + therefore can't use 2nd, 3rd, 4th gen pen must use other class entirely
    - Modified Cell Wall: decreased permeability
    - Modified PBP: lower affinity for beta-lactams
- Pharmacokinetics/dynamics
    (1) Administration
        - Variable (refer below)
    (2) Distribution
        - Throughout body except for CSF and bone unless inflamed (except ceftriaxone/cefotaxime)
        - Cross placenta but not teratogenic
    (3) Metabolism
        - Not metabolized just excreted
    (4) Excretion
        - Renal (all except nafcillin, ceftriaxone and cefoperazone therefore good in pts w/ renal dz) Secreted by organic acid pump at PCT which can be inhibited by probenicid thus increasing penicillin concentrations
        - Liver
- Side Effects / Drug Interactions
    (1) Hypersensitivity
        - Major Determinant (penicillin metabolites link w/ lysine residues creating haptens causing an allergy that is NOT life threatening, seen in 5% (penicillins) or 1% (cephalosporins) of patients ranging from rash to angioedema)
            - NB cephalosporins should be used w/ caution in pts sensitive to penicillins b/c there is ~10% cross-sensitivity
            - NB monobactams/carbapenems show no hypersensitivity at all
        - Minor Determinant (penicillin metabolites directly cause an allergy that is life threatening, seen in fewer patients causing anaphylaxis)

	GP	GN	AN	AT
<u>First Generation (Natural)</u> • NB made from mold, susceptible to beta-lactamases • SEs: Neurotoxicity (penicillins are irritating to neurons thus can provoke seizures especially if intrathecally injected, pt w/ h/o seizures, use of very high concentrations or injected in vessel instead of muscle during IM injection) • Major Uses: PO (Strep-Throat, Dental Infections) vs IV (Syphilis, Actinomyces, Meningococcemia) penicillin–V (Pen-Ve) PO penicillin–G (Pen-Gee) IV	X Strep Entero (not VRE)	Some (not Pseudo)	Some	Some
<u>Second Generation (AntiStaphylococcals)</u> • NB penicillinase resistant which is important in Staph infections b/c 95% of Staph now have beta-lactamases therefore use 2nd generation penicillins, but now many Staph infections have the *mecA* gene which encodes for a low affinity penicillin binding protein (PPBP2A) making it resistant to methicillin (MRSA) therefore must use different antibiotic mechanism entirely = vancomycin • SEs: acute hemorrhagic cystitis, hepatic dysfunction, AIN, leukopenia, neutropenia (NB methicillin is no longer available b/c of AIN but remember that the others can also cause it also) • Major Uses: MSSA infections only dicloxacillin (Dynapen), cloxacillin (Tegapen) PO oxacillin (Bactocill), nafcillin (Nallpen) IV	Staph (not MRSA) Strep X	-	-	-
<u>Third Generation (Amino-) aka Aminopenicillins</u> • NB susceptible to beta-lactamases, resistance is frequently seen in GNB which have obtained the beta-lactamase plasmid hence the addition of beta-lactamase inhibitors • SEs: +Coomb's, neutropenia/eosinophilia, rash esp in pts w/ Mono, w/ CLL, or on allopurinol, reversible cholestatic hepatitis and diarrhea with clavulanate • Major Uses: GI infections, URTIs, IE prophylaxis, UTIs, DM foot infection, bites, Listeria, Salmonella amoxicillin (Amoxil) PO, amoxicillin+clavulanate (Augmentin) PO ampicillin (Principen) IV, ampicillin+sulbactam (Unasyn) IV	Staph (not MRSA) Strep Entero (not VRE)	Some (not Psuedo)	All	-
<u>Fourth Generation (Carboxy-/Ureido-) aka Anti-Pseudomonals</u> • NB susceptible to beta-lactamases, resistance is frequently seen in GNB (Klebsiella) which have obtained the beta-lactamase plasmid hence the addition of beta-lactamase inhibitors • SEs: platelet dysfunction and sometimes (1% of the time) thrombocytopenia, renal dysfunction? (only for pipercillin), serum sickness, +Coomb's, neutropenia/eosinophilia, liver dysfunction, (NB ticarcillin (Ticar), ticarcillin+clavulanate (Timentin) is no longer available b/c of hypernatremia problems b/c you have to dissolve the abx in hypertonic saline) • Major Uses: BS abx pipercillin (Pipracil), pipercillin+tazobactam (Zosyn) IV	Staph (not MRSA) Strep Entero (not VRE)	Many Psuedo	All	-

Cephalosporins

- Different R2 group

	GP	GN	AN	AT
<u>First Generation</u> • Mainly used by surgeons esp orthopedists as a pre-op abx to kill any skin flora that might enter the body during surgery cephalexin (Keflex), cefadroxil (Duricef) PO cefazolin (Ancef) IV	Staph (not MRSA) Strep X	Few (not Psuedo)	-	-
<u>Second Generation</u> • Uses: out-pt simple URTIs, ab surgery, etc • Disulfiram-like reaction in cefotetan • Interaction w/ antiplatelets/heparin/coumadin cefuroxime (Ceftin), cefaclor (Ceclor), cefprozil (Cefzil) PO cefuroxime (Zinacef), cefoxitin (Mefoxin), cefotetan (Cefotan) IV	Staph (not MRSA) Strep X (but not as good as 1st generation cephs)	Some (not Psuedo)	Some	-
<u>Third Generation</u> • Mainly used in meningitis, endocarditis, pneumonia, intra-ab infection, etc • SEs: acute liver injury, cholelithiasis, diarrhea, eosinophilic pulmonary infiltrates cefdinir (Omnicef), cefpodoxime (Vantin), cefixime (Suprax), cefditoren (Spectracef) PO ceftriaxone (Rocephin), ceftazidime (Fortaz), cefotaxime (Claforan) IV	Staph (not MRSA) Strep X	Most (not Psuedo)	Some	-
<u>Fourth Generation</u> • Mainly used in severe infections esp neutropenic fever b/c it BS and has Psuedomonal coverage cefepime (Maxipime) IV	Staph (not MRSA) Strep X	All (+ Psuedo)	-	-
<u>Fifth Generation</u> • New drugs that is supposed to take place of Zyvox for MRSA infections ceftobiprolen (?) IV	Staph (+ MRSA)	?	?	?

Monobactams

- ring is unfused

aztreonam (Azactam) IV • relatively nontoxic causing only mild rash and mild abnl LFTs	GP	GN	AN	AT
	-	Most (+ Psued)	-	-

Carbapenems

- sulfur group replaced by carbon group
- each have slightly different antimicrobial profile
- no cross-sensitivity to penicillins therefore good in pen allergic pts

	GP	GN	AN	AT
imipenem+cilastin (Primaxin) IV • cilastatin inhibits renal dihydropeptidase which converts imipenem into a nephrotoxic metabolite • SEs: N/V/D, eosinophilia/neutropenia, LFTs, seizures (very important, seen in 2% of pts, higher if pre-existing r/o seizures or CNS problem, 2/2 cilastatin therefore the other carbapenems have no seizure) • NB Psuedomonas is developing resistance therefore try Merrem/Doribax meropenem (Merrem-$$$$$) IV • NB interferes w/ valproate ertapenem (Invanz-$$$$$) IV • NB mainly used for outpt IV therapy, doesn't cover pseudomonas/enterococcus/acinitobacter doripenem (Doribax)	Staph (not MRSA) Strep Entero (not VRE)	Most (+ Psued)	All	-

NON Beta-Lactams

- Mechanism
  (1) unlike beta-lactams which *resemble* D-alanine-D-alanine, vancomycin *binds* D-alanine-D-alanine preventing transpeptidases from cross-linking
  (2) Resistance: modified Cell Wall: some MRSA and *Enterococcus faecalis* have the vanA gene which modifies the D-ala-D-ala to D-ala-D-lactate making it intermediate or even resistant to vancomycin (VISA/VRSA and VIE/VRE), VRSA is a problem b/c the vanA gene is on a mobile transposon called Tn1546 that can easily transpose normal bacteria
- Pharmacokinetics
  (1) Administration
    - No oral absorption (only given PO for *C. difficile* infection)
    - dose (500-1250mg) based on weight while interval (BID-QOD) based on creatinine clearance
  (2) Distribution (throughout body except for CSF and bone unless inflamed)
  (3) Metabolism (not metabolized just excreted)
  (4) Excretion (renal)
  (5) Peak & Trough Monitoring (time dependent killing/toxicity therefore follow trough)
    - Peak (don't check)
    - Trough: 15 -20mcg/mL for mild-serious infections, therefore follow trough levels immediately before 4th dose
    - Dialysis pts get vanc Q5-7d
- Side Effects
  (1) Nephrotoxicity
    - Reversible
    - Rare unless COMBINED W/ AMINOGLYCOSIDES even though they have synergistic mechanisms
  (2) Oxotoxicity (high frequency first)
    - Reversible
    - Rare unless COMBINED W/ AMINOGLYCOSIDES even though they have synergistic mechanisms
  (3) Infusion Reaction ("Red Man Syndrome")
    - diffuse flushing, pruritus, tissue necrosis, hypoTN, eosinophilia, fever, chills
    - prevented by giving pretreatment antihistamine and slow infusion and adjusting for weight and creatinine clearance
  (4) Phlebitis
  (5) Neutropenia

Glycopeptides	GP	GN	AN	AT
vancomycin (Vancocin) IV	Staph (+MRSA) Strep Entero (not VRE)	-	Some • *C. diff* colitis when Flagyl has failed or colitis is life threatening	-

II. Protein Synthesis Inhibitors

Aminoglycosides

- Mechanism
  (1) Abx is pumped into bacteria using a pump that requires oxygen (therefore not effective against anaerobes) the abx then binds 30s and prevents formation of initiating complex (joining of 30s w/ 50s) but if for some reason the complex is formed the abx causes misreading of mRNA forming an abnormal protein that incorporates into bacterial membrane destabilizing it
  (2) If derived from Streptomyces spp. then end in "-m**y**cin"
  (3) If derived from Micromonospora spp. then end in "-mi**c**in)
  (4) beta-lactams and aminoglycosides work synergistically b/c penicillins increased bacterial permeability to intracellular antibiotics like aminoglycosides (but never give in the same infusion fluid b/c beta-lactams are negative while aminoglycosides are positive forming inactive neutral complexes)
  (5) Resistance: removal of pump, modified 30s, inactivating enzymes (acetyltransferases, nucleotoidyltransferases, phosphotransferases) cross-resistance fortunately does not exist b/t aminoglycosides
- Pharmacokinetics
  (1) Administration (IV except for neomycin which can be used to treat hepatic encephalopathy) dose based on ideal body weight (esp important in obese pts b/c there is no distribution into fat hence you might over dose if you dose based on actual BW)
  (2) Distribution throughout body except for fat and CSF and bone unless inflamed (NB accumulate in ear/kidney is the reason for SEs)
  (3) No Metabolism just excreted (don't have to adjust for liver failure)
  (4) Renal Elimination (adjust for CrCl)

(5) Peak & Trough ([ ] dependent killing/toxicity therefore follow peak therefore give a large dose a short period before HD and then dialyze off)
- Peak: peak levels are helpful when assessing aminoglocyside toxicity unlike vancomycin (obtain level 1/2-1hr after dose) exact goal peaks vary with exact aminoglycoside but typically are b/t 5-20 mcg/mL (concentration dependent killing aka use high dose w/ infrequent administration b/c less toxicity and more effective) vs Trough: trough levels need to be above the minimum inhibitory concentration (MIC) to be effective therefore follow trough levels after 1st dose and after 4th dose (obtain level immediately before next dose) exact goal troughs vary with exact aminoglycoside but typically are >1mcg/mL (check 6-14hrs after dose, <1 no change, 1-3 change to Q48hrs, >3 hold)
- Trough: (don't check)

- Side Effects
  (1) Nephrotoxicity 2/2 Tubulonecrosis (15%)
  - DO NOT COMBINE W/ VANCOMYCIN even though they have synergistic mechanisms
  - More common than ototoxicity but reversible
  (2) Oxotoxicity/Vestibulotoxicity (rare)
  - DO NOT COMBINE W/ VANCOMYCIN even though they have synergistic mechanisms
  - Oto: high frequency loss first (amikacyin) vs. Vestibulo: dizziness, vertigo (tobra/gent)
  - Less common than nephrotoxicity but irreversible but fortunately never really apparent to pt
  (3) Flaccid Paralysis (rare)
  - aminoglycosides block ACh release
  - rarely clinically apparent, only seen when you give intrapleural/peritoneal injections of aminoglycosides, when pt has myasthenia gravis or pt is on a non-depolarizing muscle relaxant
  (4) Toxicity RFs: old age, previous aminoglycoside exposure, renal disease, divided dosing instead of daily dosing, other nephrotoxic drugs (NB eventually everyone will develop toxicity)
  (5) Drug Interactions

Aminoglycosides				
gentamicin (Geramycin) amikacin (Amikin) IV • Common Uses: serious GN infections esp Psuedomonas • NB most potent b/c least vulnerable to inactivating enzymes (unlike gent/tobra) therefore good if bug is resistant to other aminoglycosides tobramycin (TOBI, Nebcin) INH • Uses: CF for airway Psuedomonal infections streptomycin (Tobricin) IM • Uses: AT esp TB, Yersina-Plague, Francisella-Tularemia neomycin/bacitracin/mupirocin Top/Ear/PO • neomycin (Neo-Fradin) PO (hepatic encephalopathy), polymixin + neomycin (Neosporin), polymixin + neomycin + bacitracin (Triple Abx Ointment), polymixin + neomycin + hydrocortisone (Cortisporin), polymixin + bacitracin (Polysporin), mupirocin (Bactroban), silver silfadiazine (Silvadene), mafenide (Sulfamylon)	GP	GN	AN	AT
	Staph (not MRSA) X Entero (not VRE)	Most (+ Psued)	-	Some

Tetracyclines "Cyclines" Tetra-Mino-Doxy

- Mechanism
  (1) Prevents joining of 30s & tRNA
  (2) Resistance via TetA Pump which pumps tetracyclines out of cells (cross-resistance unfortunately does exist between tetracyclines and very common accounting for its limited use)
- Pharmacokinetics
  (1) NB drugs are really identical only varying in pharmacokinetics: T→M→D = ↑absorption, distribution, duration of action
  (2) Administration: must NOT take with divalent cations like Ca^{++} (milk), Mg^{++} (antacids), and Fe^{++} (spinach) b/c they chelate tetracyclines preventing their absorption (problem b/c pts often treat the GI SEs of tetracyclines w/ antacids)
  (3) Distribution: throughout body esp in teeth/bone/liver/kidney/spleen (hence SEs) except for CSF and bone unless inflamed (except for minocycline which can penetrate the CNS even when not inflamed)
  (4) Metabolism: Liver (Conjugation)
  (5) Excretion: Biliary System (only doxycycline therefore good for RF pts) vs Renal (all except for doxycycline) liver metabolites are reabsorbed from GI and then filtered by kidney
- Side Effects (similar to quinolones but much MORE significant accounting for its limited use)
  (1) GI Distress: N, dyspepsia, D, esophagitis w/ strictures, therefore take with foods, chelates all bivalent cations (Ca, Mg, Fe, Al, Zn hence do not take w/ milk) and not at night
  (2) Teeth Discoloration/Hypoplasia and Bone Growth Inhibition b/c tetracyclines bind divalent cations (esp in children/pregnant women)
  (3) Hepatoxicity (esp in pregnant women)
  (4) Photosensitivity
  (5) CNS Problems: Psuedotumor Cerebri, Headache, Vestibulo/Ototoxicity (only minocycline)

(6) Blood Dyscrasia: Neutropenia, Eosinophilia, Thrombocytopenia
(7) Teratogenic
(8) Other: lupus like reaction, pericarditis, vasculititis, serum sickness ???

Tetracyclines				
• Uses: atypical infections and MRSA	GP	GN	AN	AT
tetra-cycline (Sumycin) PO mino-cycline (Minocin) IV/PO doxy-cycline (Adoxa, Vibramycin, Doryx, Oracea, Periostat) PO demeclo-cycline (Declomycin) PO • Mainly used for Tx SIADH	Staph (+MRSA) Strep X Entero	Most (not Psued)	All	Spirochetes No Shape Bacteria Oblig. Intracell. Parasites Fungi Like
tige-cycline (Tygacil) IV "The Tiger" • broad spectrum abx esp for intra-abdominal infections hence used a lot by surgeons • Some major holes in GN coverage including Psuedomonas, Burkholderia, Porteus, Serratia, Stenotrophomonas BUT good against MDR Acinetobacter/Klebsiella • Similar SEs to other tetracyclines but esp GI/CNS/HTN	Staph (+MRSA) Strep Entero (not VRE)	Most (not Psued)	+	+

Macrolids "ACE"

- Mechanism
  (1) Inhibits ribosomal translocation
  (2) Macrolides, ~Macrolides, and Chloramphenicol bind roughly at the same spot therefore never give together
  (3) Resistance Mechanism: modified ribosome decreasing macrolide affinity and inactivating enzyme esterase
- Pharmacokinetics (AC have better tissue penetration and longer half life)
  (1) Administration (A=Qd, C=BID, E=QID)
  (2) Distribution: throughout body except for CNS unless inflamed, macrolides accumulate in liver/prostate/macrophages (thus good for intracellular bugs)
  (3) Metabolism: Hepatic (P-450)
  (4) Excretion: Liver (AE: Biliary System) Kidney (C: Filtered)
- Side Effects (AC have much less SEs than E)
  (1) GI Distress (major cause of non-compliance esp E b/c E is structurally similar to Motilin hormone such that if given during 1st few weeks of like pts get pyloric stenosis)
  (2) Reversible Ototoxicity
  (3) Antibiotic Associated Colitis
  (4) Arrhythmias esp QT prolongation
  (5) Hepatobiliary Dz
  (6) Pancreatitis

Macrolides				
azithromyin (Zithromax) PO/IV • Uses: URIs and atypical CAP • Other SEs: cholestatic jaundice clarithromycin (Biaxin) PO • Use: *Mycobacterium avium* in AIDS pts • Other SEs: metallic taste erithromycin (Eryc, et al) PO/IV • Use: GI pro-kinetic never used as an abx • Other SEs: GI motility	GP	GN	AN	AT
	Staph (not MRSA) Strept X Entero	Few *Neisseria* spp *Haemophilus* spp *Morexella* spp (not Psued)	Most	Spirochetes No Shape Bacteria Weak GNR Obligate Intracellular Parasites

~ Macrolides				
Lincosamides				
clindamycin (Cleocin) PO/IV • SEs: AAC (b/c *C. diff* is resistant even though you would think that it would kill it because it is an anaerobe), injection rxn, photosensitivity, serum sickness, neutropenia, eosinophilia, thrombocytopenia, esophagitis, drug interaction w/ muscle relaxants • Uses: anaerobic infections, Toxo, PCP	Strep Staph (+ MRSA)	-	All first line: clinda (above diaphragm) second line: flagyl (below diaphragm) third line: chloramphenicol (CNS)	-
Chloramphenicol				
chloramphenicol (Chloromycetin) PO/IV • SEs: (significant accounting for its limited use): dose dependent G6PD deficiency anemia, dose independent aplastic anemia, neutropenia, thrombocytopenia, Gray Baby	Strep Staph (not MRSA) Entero (+VRE)	Most (not Psued)	All	No Shape Bacteria Obligate Intracell Parasites

Syndrome (premature infants lack UDP-glucuronyl transferase therefore they are unable to metabolize and then excrete the abx resulting in its accumulation w/ signs of FTT, poor feeding, depressed resp rate, hypoTN, flaccid, grey appearance, death), drug interactions, AAC, HA, optic neuritis, peripheral neuropathy, drug reactions • Uses: in general rarely used, sometimes in meningitis b/c excellent CNS penetration					
Streptogramins					
quinopristin + dalfopristin (Synercid) IV (given together b/c individually bacteriostatic while together bacteriocidal) • SEs: arthralgia/myalgia (very common and very pronounced), asymptomatic hyperbili injection rxn, HA, many others hence rarely used	All including Multidrug Resistant GP (VRSA,VRE)		Few (not Psued)	Some	-
Oxazolidinone					
linezolid (Zyvox) PO/IV (very high BA w/ PO = IV) • SEs: "Serotonin Rxn" similar to Cheese Reaction of MAOIs, irreversible peripheral neuropathy, reversible optic neuropathy, pancytopenia, lactic acidosis, HA	All including Multidrug Resistant GP (VRSA, VRE)		-	Some	-
Ketolides					
telithromycin (Ketek) • SEs: MG crisis, hepatoxicity, visual disturbances, loss of consciousness!!! Hence it is rarely used					

III. Folate Antagonists

Folate Synthesis Inhibitors

- Mechanism
  - (1) Discovered from the red dye (prontosil) in the 1930s
  - (2) Sulfonamides do not harm eukaryotic cells b/c they do not have the enzymes to synthesize THF (unlike bacteria) rather they have receptors so that they can acquire THF from diet (unlike bacteria)
  - (3) Sulfonamides (PABA analogue)

Pteridine + PABA
↓ (Dihydropteroate Synthase) X = Sulfonamides
Dihydropteroic Acid
↓ (?)
Diet → Dihydrofolic Acid
Eukaryotes → ↓ Prokaryotes (Dihydrofolate Reductase) X = Trimethoprims
Tetrahydrofolic Acid (THF)
↓
↓
↓
Cofactor for Many Processes
↓
(1) Pyrimidines/Purines → DNA/RNA
(2) Methionine, Glycine, f-met, tRNA → Proteins

  - (4) NB not effective when treating a purulent infection b/c the tissue breakdown products can provide enough thymines, purines, etc that bacteria do not need to make it
  - (5) Resistance (very common) w/ Modified Cell Membrane (decreased permeability), Modified Enzyme (lower affinity for sulfonamide), Increased PABA Synthesis
- Pharmacokinetics
  - (1) Administration
  - (2) Distribution throughout body even CSF, crosses placenta and breast milk
  - (3) Metabolism: Liver (Acetylation)
  - (4) Excretion: Renal (Filtration)
- Side Effects
  - (1) Hypersensitivity
  - (2) Myocarditis
  - (3) Pancytopenia: Anemia (Megaloblastic, G6PD Deficiency, Aplastic, Hemolytic), Thrombocytopenia, Leukopenia
  - (4) Nephrotoxicity w/ Hyperkalemia (important)
  - (5) Crystalluria (reversed with hydration and alkalinization)
  - (6) CNS (HA, vertigo, aseptic meningitis, psychosis)
  - (7) Hepatitis
  - (8) Drug Interactions
  - (9) Glossitis/Stomatitis esp in HIV pts taking it for prophylaxis
  - (10) GI

(11) "Big Pill" hence take ½ then ½ or in liquid form
(12) Pancreatitis

Folate Synthesis Inhibitors (Sulfonamides)				
sulfamethoxazole (SMX) sulfisoxazole (Gantrisin) PO sulfadiazine (?) PO • Toxoplasmosis mafenide (Sulfamylon) Top • applied to burned skin to prevent sepsis silver sulfadiazine (Silvadene) Top • applied to burned skin to prevent sepsis ethyl succinate + sulfathiazole (Pediazole) PO • Gastroenteritis (Salmonella/Shigella) (given PO b/c not absorbed) sulfasalazine • IBD (given PO b/c not absorbed) normal GI flora convert sulfasalzine into sulfapyridine and 5-aminosalicylate the latter which has anti-inflammatory effects	GP Staph (+MRSA) Entero (NOT VRE)	GN Most (not Psued)	AN -	AT <u>Obligate Intercell Parasites</u> (Nocardia)
Folate Reduction Inhibitors (Trimethoprims)				
trimethoprim (TMP, Primsol) PO	Staph (+MRSA)	Most (not Psued)	-	-
5 Sulfamethoxazole (SMX) + 1 Trimethoprim (TMP) = co-trimoxazole (Bactrim, Septra, Sulfatrim) PO, IV • Activity (1) Same + - *Pneumocystis carini* pneumonia - Ampicillin/Chloramphenicol Resistant *Salmonella* spp. - UTI				

IV. DNA Gyrase Inhibitors

Quinolones (very similar to tetracycline)

- Mechanism
  (1) Inhibits DNA gyrase (topoisomerase II – nicks DNA to allow for unwinding for replication/transcription)
  (2) Resistance (have been overused in past accounting for high resistance to GN bacteria esp for 1st/2nd generation): modified DNA gyrase that has decreased affinity and pumps t that pump quinolones out of cells
- Pharmacokinetics (similar to tetracyclines)
  (1) Administration: must NOT take with divalent cations like Ca^{++} (milk), Mg^{++} (antacids), and Fe^{++} (spinach) b/c they chelate FQs preventing their absorption (problem b/c pts often treat the GI SEs of FQs w/ antacids)
  (2) Distribution throughout body and bone except for CSF unless inflamed (except for oxfloxacin which can penetrate the CNS even when not inflamed)
  (3) Metabolism: Liver Conjugation
  (4) Excretion: Biliary (Moxi) vs Renal (All FQ except Moxi)
- Side Effects (b/c of the SEs below do not give to children or pregnant women)
  (1) GI Distress (take with foods not milk, etc)
  (2) CNS Problems esp HA, Dizziness, confusion, hallucinations, psychosis, seizures, increased ICP, peripheral neuropathy (hence take at night)
  (3) Tendon Rupture (1/10,000, primary Achilles, increased risk in elderly and on steroids, can occur after 1st dose or months after finishing course)
  (4) Prolonged QT

Fluorouinolones	GPC	GN	AN	AT
<u>First Generation</u> nalidixic acid (NO LONGER USED)	-	All (+ Psued)	-	<u>Weak GNR</u>
<u>Second Generation</u> nor-floxacin (Noroxin) PO lome-floxacin (Maxaquin) PO cipro-floxacin (Cipro) PO/IV o-floxacin (Floxin) PO/IV	Staph (not MRSA)	All (+ Psued)	Few	<u>Weak GNR</u> <u>Some Other ATs</u>
<u>Third Generation (Resp Quinolone)</u> levo-floxacin (Levaquin) PO/IV moxi-floxacin (Avelox) PO/IV	Strept Staph (not MRSA) Entero	All (+ Psued)	Some	<u>Weak GNR</u> <u>More Other ATs</u>
<u>Fourth Generation</u> (Resp Quinolone) None currently b/c there were SEs (liver)	Srept Staph (not MRSA) Entero	All (+ Psued)	All	<u>Weak GNR</u> <u>Many Other ATs</u>

Other

metronidazole (Flagyl) PO/IV
- Mechanism: converted into toxic metabolites which damage DNA and other macromolecules
- Use: anaerobes below diaphragm, C.diff, Protozoa, *H. pylori*, PID, BV, Giardia, Trich (no GP, no aerobic GN)
- SEs: AAC, dark brown urine, GI upset, disulfram-like reaction, reversible neutropenia, rash, vaginal/urethral burning, metallic dry taste, CNS (HA, seizures, encephalopathy, cerebellar dysfunction, peripheral neuropathy)

nitrofurantoin (Furandantin, Macrodantan, Macrobid) PO
- Mechanism: converted into toxic metabolite when in acidic environment (like urine) which damage DNA and other macromolecules
- Use: Strept, Staph (not MRSA), few GN esp E. coli
- SEs: turns urine brown, flu-like Sx, GI distress, acute pneumonitis → chronic ILD, CNS (HA, nystagmus, peripheral neuropathy, confused, depressed, vertigo, dizziness), G6PD anemia, pancreatitis, hepatitis, arrhythmias
- Methanamine (Hiprex, Mandelamine) is similar to nitrofurantoin but with other SEs: nephrotic syndrome, rash, ARF (can precipitate in tubules), react w/ sulfonamides

polymixin B (Poly-Rx) E (Colistin) INH
- Mechanism: bind to cell membranes of bacteria and disrupt their osmotic properties ("detergents')
- Use: some GN (+ Psued) used for MDR-Acinetobacter/Psuedomonas
- SEs: neurotoxicity, nephrotoxicity

daptomycin (Cubicin) IV
- Mechanism: similar to vanc
- Use: Strept, Staph (+MRSA), Enterococcus (+VRE)
- SEs: muscle toxicity w/ increased CPK (check Qwk, if myopathy Sx + >5xULN or if just >10xULN then stop), phlebitis, anemia, GI
- NB not effective in lungs b/c surfactant deactivates it

fosfomycin (Monurol) PO
- Mechanism: pyruryl transferase cell wall synthesis inhibitor
- Use: some GN esp E.coli
- SEs: asthma exac, hepatic necrosis, GI, vaginitis

rifaximin (Xifaxan) PO
- Mechanism: RNA polymerase inhibitor, derivative of rifampin, not absorbed by GI tract
- Use: traveler's diarrhea
- SEs: superinfection, HA, GI

dapsone (~sulfonamides) + clofazimine (inhibits DNA replication) + rifampin