

Antibiotics in SOM 208 are taught in a series of lectures. The first series addresses mechanism of action and resistance mechanisms. The second series focuses on side effects, bioavailability and metabolism. These notes combine the material from both series of lectures.



In choosing an antibiotic keep in mind the following:

- Does the patient have any drug allergies? Does the patient have any special circumstances that need to be considered in the choice of drugs (e.g., pregnancy, lactation, genetic conditions like G6PD deficiency, renal or hepatic insufficiency etc.)?
- Which is least toxic among the choices of effective drugs?
- Which has the least/ mildest side effects among the choices of effective drugs??
- Which is least costly among the choices of effective drugs??
- How is the drug administered? How often does it need to be given? Do blood levels need to be monitored?

Remember that since bacteria grow so rapidly, treatment will be started empirically. Remember to do Gram stains and get your cultures before you start antibiotics!



Yo! Go buy yourself a copy of Sanford, and keep it in the pocket of your white coat. And when in doubt, call an ID consult.

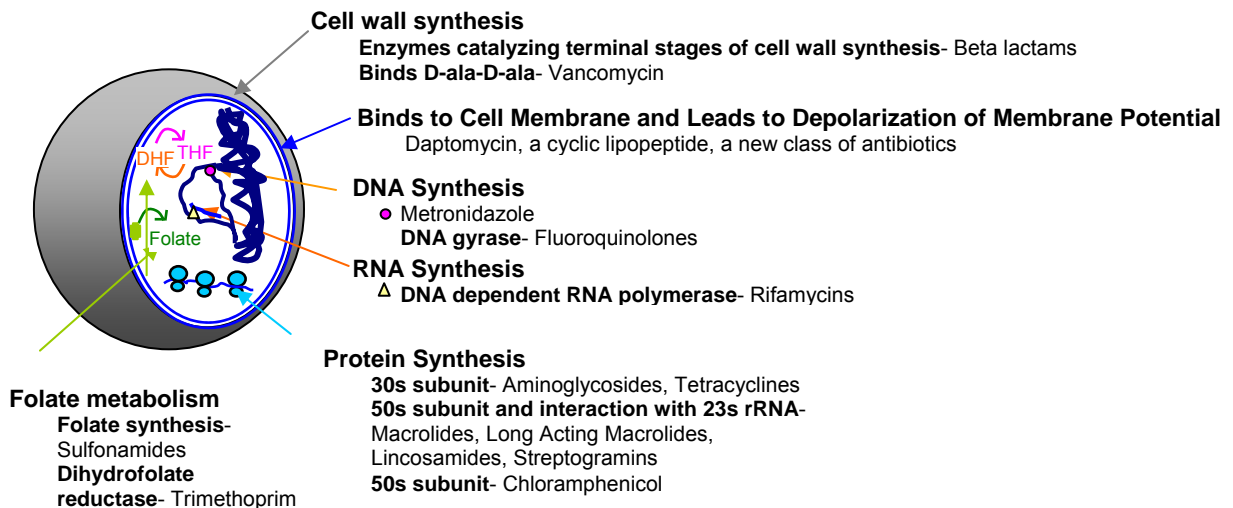
Antibiotics

Antibiotics are natural compounds that inhibit or kill bacteria. There are also synthetic compounds that have antimicrobial activity, and most people refer to them as antibiotics. In deciding which antibiotics to use in a particular situation, many factors must be considered including the safety and side effects of the antibiotic, the narrowest spectrum, the method of administration, and the cost of the therapy.



Most antibiotics target structures that are unique to prokaryotes. These include enzymes used in the synthesis of peptidoglycan, and enzymes or machinery used in the production of prokaryotic nucleic acids and proteins. Additionally, some antibiotics are used that function in a milieu unique to the targeted organism. A good example of this is metronidazole, which is toxic in a reducing environment.

Antibiotic Targets in the Prokaryotic Cell



I. Inhibitors of Cell Wall Synthesis:

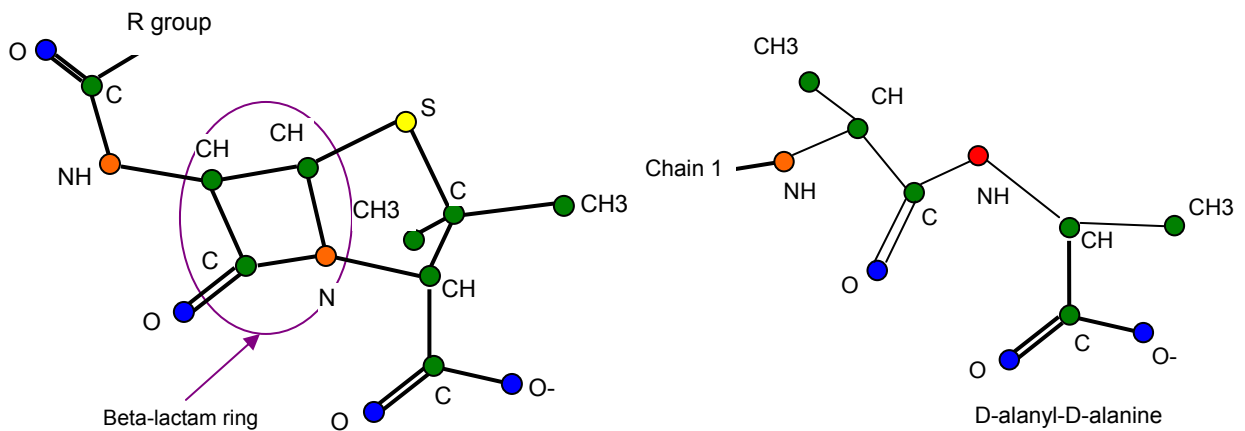
A. Beta-lactam Antibiotics (Penicillins (PCN), cephalosporins (CEPH), monobactams and carbapenems)

The beta lactam antibiotics are grouped together because they share a common structural feature, the beta lactam ring. They are some of the most commonly prescribed antibiotics, and since there are so many, they will be broken into functional groups based upon the spectrum of activity.



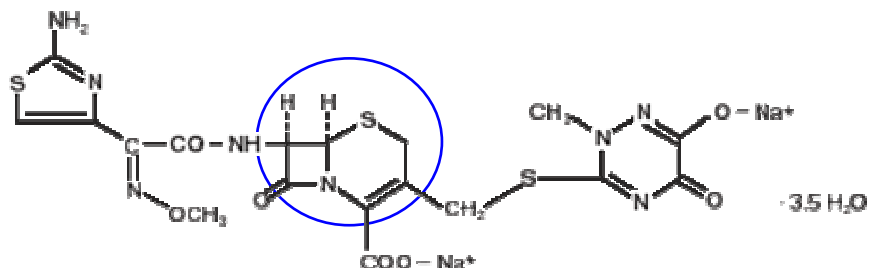
1. Mechanism of Beta-Lactam Antibiotics

Beta-lactam antibiotics inactivate a family of enzymes involved in the terminal stages of cell wall synthesis, and in shaping the cell. Members of this family of enzymes are called penicillin binding proteins (PBPs) because they are detected when they bind radiolabeled penicillin. Bacteria usually have 4 to 8 different penicillin binding proteins, and each is involved in a different aspect of cell wall synthesis. For example, *E. coli* has multiple PBPs, and three are essential to the cell for growth and survival. The most famous ones are PBP 1a and 1b, the transpeptidases. **Transpeptidase** is the enzyme that catalyzes cross-linking between linear chains of peptidoglycan. Without proper cross-linking, the cell wall is structurally unstable. Beta-lactam antibiotics are suicide inhibitors of **transpeptidase**. The beta-lactam ring is a structural analog of D-ala-D-ala, the substrate of transpeptidase. Once the enzyme binds the beta-lactam ring in its active site, the drug becomes covalently attached to the enzyme, resulting in permanent inactivation. Loss of PBP1 (transpeptidase) function leads to cells that can lyse, due to the high internal osmotic pressure found in bacteria. Lysis is facilitated, in many bacteria, by the activity of autolysins, enzymes that digest the existing cell wall. Other penicillin binding proteins have different functions. PBP2 is responsible for the characteristic rod shape of the *E. coli* cell. Beta-lactams that preferentially inhibit PBP2 lead to the formation of round cells. PBP3 is responsible for septum formation. Inhibition of PBP3 forms huge filamentous cells. **Although the various beta-lactam antibiotics interact with the PBPs to different degrees, it is extremely important to realize that any of the events that they mediate are lethal.** Beta lactams are generally bactericidal against growing bacteria with active autolysins. Important clinical situations in which the beta-lactams are not bactericidal include slow growing or dormant bacteria found in endocarditis and chronic osteomyelitis, and against certain bacteria such as enterococci that downregulate autolysin activity.



Penicillin

The four member beta lactam ring is attached to a five member ring. The R group will determine the spectrum of activity. The structure of D-alanyl-D-alanine is given for comparison.



Ceftriaxone, a cephalosporin

Note that the four member ring is attached to the 6 member ring.

The presence of an intact beta-lactam ring is the essential structural feature for all active beta-lactams. Bacteria may produce enzymes called beta-lactamases, that hydrolyze the beta-lactam ring and inactivate the antibiotic.

Susceptibility to beta-lactams:

- For **Gram-positive bacteria**, susceptibility is determined by the affinity of the drug for its target PBPs and whether the organism produces a beta-lactamase that can degrade the drug before it reaches its target.
- For **Gram-negative bacteria**, the same factors apply as for gram-positive, with the added consideration of the permeability of the outer membrane. Drugs that inhibit cell wall synthesis in Gram-negative bacteria must cross the outer membrane to gain access to the cell wall. The outer membranes of different Gram-negatives have specific properties that exclude antibiotics to different extents.

2. Penicillins

A. Uses

For convenience, the penicillins can be divided into 4 generations based on their spectrum of activity.

1st generation penicillins

- 1st generation penicillins are the naturally occurring penicillins.
- 1st generation penicillins work **best against susceptible Gram-positive organisms and certain other organism such as *Treponema pallidum*.**
- 1st generation penicillins are first line drugs for GAS infection, syphilis, and viridans streptococcal endocarditis.
- Members are **PCN G** and **PCN V**.
- Natural penicillins are **quickly metabolized** (if administered intravenously, the half-life about 30 minutes!). One trick to prolong blood levels is to administer them intermuscularly in a form that is slowly absorbed. **Procaine** can be injected with PCN G or **benzathine penicillin can be injected**. Both of these combinations are absorbed slowly, so the doses do not have to be given as frequently.

2nd Generation penicillins

- 2nd Generation penicillins were **made to resist inactivation by penicillinase (a beta-lactamase) from *Staphylococcus aureus* (MSSA).**
- 2nd Generation penicillins are stable when attacked by β -lactamases.
- 2nd Generation penicillins are **not active against Gram negative organisms and are generally less active than penicillin against Gram-positives that do not produce β -lactamases.**
- 2nd Generation penicillins' members include **methicillin, nafcillin, dicloxacillin and oxacillin.**
- When ***Staphylococcus aureus* are said to be methicillin resistant, they are resistant to all second-generation penicillins (in fact, to all beta-lactams), not just methicillin.**

3rd Generation Penicillins

- 3rd Generation Penicillins were **made to treat some Gram negative organisms that do not make beta lactamases.**
- They have some activity against Gram positives that lack penicillinase.
- Members include **amoxicillin and ampicillin.** They are also known as aminopenicillins.

4th Generation Penicillins

- 4th Generation Penicillins are big guns that were developed **against nasty Gram negative pathogens like *Pseudomonas*.** They have a broad spectrum of activity against many Gram-negative bacteria, but still can be inactivated by some beta-lactamases.
- 4th Generation Penicillins include **mezlocillin and piperacillin** (the ureidopenicillins), and **carbenicillin and ticarcillin** (carboxypenicillins).
- The ureidopenicillins can be used against Enterococci and a number of other Gram-positives, but not *S. aureus*.

B. Side Effects

- 2-4% of patients have **allergic reactions** to the PCNs. Since the reaction is precipitated by a breakdown product of the ring structure that is found in all of them, there is **cross allergenicity between PCNs.**
- **All can cause neutropenia due to the arrest of meta-myelocytes.**
- **Methicillin (2nd) can cause an allergic interstitial nephritis.**
- **Nafcillin (2nd) and Oxacillin (2nd) can cause hepatitis.**
- **Carbenicillin (4th) and Ticarcillin (4th) can cause a large salt load.**

C. Bioavailability

- They are most effective when the concentration of antibiotic at the site of infection is maintained at $\geq 4x$ MIC for 60-80% of the day.
- Different penicillins can be given IV, IM or orally. PCN G and V, dicloxacillin and amoxicillin are some example of penicillins that can be given orally. However, only amoxicillin can be given with food. It is much better absorbed than ampicillin.
- Penicillins are well distributed to all tissue except the CNS, prostate and eye.
- PCNs can cross inflamed meninges, so they can be used to treat meningitis.
- High CSF levels of PCN induce seizures, so do not inject them into CSF.

D. Metabolism

- Most penicillins have a short half-life.
- Penicillins are excreted unchanged by glomerular filtration and tubular secretion.
- Probenecid can be used to extend their half-life in the body because it blocks tubular secretion.
- Nafcillin (2nd), oxacillin (2nd) and the ureidopenicillins (piperacillin and mezlocillin) also have hepatic excretion.

3. Cephalosporins

A. Uses

There are lots of cephalosporins because it is very easy to modify their chemical structure. All the chemical names sound similar, so most practitioners use the distinctive brand names. For convenience, the cephalosporins can be divided into 4 generations based again on the spectrum of activity. Each successive generation is more active against Gram negatives and more resistant to β -lactamases. The trade off is that they lose activity against Gram positives.

1st generation cephalosporins

- 1st generation cephalosporins are good against methicillin sensitive *S. aureus*, streptococci and many Enterobacteriaceae.
- Members include: Cephalexin (Keflex), Cefazolin (Ancef), Cephapirin (Cefadyl) and Cephalothin (Keflin)

2nd Generation cephalosporins

- 2nd generation cephalosporins are more stable to Gram negative β -lactamase and less active against *S. aureus*.
- Members include: Cefuroxime (Ceftin [oral] and Zinacef), Cefotetan (Cefotan), and Cefoxitin (Mefoxin)

3rd Generation Cephalosporins

- 3rd generation cephalosporins have broader activity against Gram negatives.
- Members include: Cefdinir (Omnicef), Cefoperazone (Cefobid), Ceftazidime (Fortaz), and Ceftriaxone (Rocephin), and Cefotaxime (Claforan).

4th Generation Cephalosporins

- 4th Generation Cephalosporins are more resistant to destruction by chromosomal β -lactamases, but not completely resistant to the β -lactamases of *Serratia*, *Enterobacter* and *Pseudomonas*.
- Currently, there is one member, Cefepime (Maxipime).

B. Side Effects

- Allergy
- Antabuse reaction* associated with the MTT side chains of cefotetan, cefonicid, moxalactam and cefoperazone.
- This side chain also inhibits gamma-carboxylation of glutamic acid thus interfering with the action of vitamin K.

*Antabuse (Disulfiram) is designed to produce an adverse reaction when mixed with alcohol. This reaction may include throbbing in the head and neck, headache, nausea, and vomiting, and potentially more serious side effects.

C. Bioavailability

- Cephalosporins are most effective when the concentration of antibiotic at the site of infection is maintained at $\geq 4x$ MIC for 60-80% of the day.
- Cephalosporins can be given orally or parenterally depending upon the agent. Oral drugs are not first line for any serious infection.
- Cephalosporins have good tissue penetration. (The exception being the non inflamed meninges.)

D. Metabolism

- Cephalosporins are excreted by the kidneys using glomerular filtration and tubular secretion.
- **Cephalothin is deacylated by the liver.** Do not use it in meningitis because the deacylated form is less active and will compete with the active drug for transport into CSF. **Cefotaxime and cephapirin are also deacetylated by liver but have active metabolites.**
- **Ceftriaxone, Cefotetan and Cefoperazone** have some percent **excreted in bile**

4. Monobactams

A. Uses

- There is one member of the monobactams, **Aztreonam.**
- Aztreonam is active against facultative Gram negative bacteria.
- Aztreonam has no activity against Gram positive bacteria or obligate anaerobes.

B. Side Effects

- **The ring structure of Aztreonam is different from the penicillins, so there is no cross allergenicity.**
- There is a low incidence of side effects, chiefly diarrhea and rash.

C. Bioavailability

- Aztreonam is has parenteral administration.
- Aztreonam does not cross the meninges well. **Do not use it to treat meningitis.**

D. Metabolism

- Aztreonam has renal excretion.

E. Resistance

- Aztreonam is **resistant to many Gram negative β -lactamases** and a **poor inducer of the chromosomal β -lactamases.**
- Aztreonam is not resistant to some β -lactamases found in *Pseudomonas*, *Acinetobacter*, *Enterobacter* and some *Klebsiella* that have extended-spectrum beta-lactamase (ESBL) enzymes.

5. Carbapenems

A. Uses

- The carbapenems have three members: **Imipenem, Ertapenem and Meropenem.**
- Carbapenems are **active against almost everything.** Meropenem is more active against Gram negative rods (GNR) than imipenem and the latter is more active against Gram positive cocci (GPC). Ertapenem has less activity against *Pseudomonas* and *Enterococcus*. In general carbapenems can be used against:
 - All Gram positives, except MSRA.
 - All Gram negatives, except *Flavobacterium* sp., *B. cepacia*, and *S. maltophilia*.
- **Prepare for a fungal infection.**

B. Side Effects

- **Imipenem causes seizures.** Patients at increase risk of suffering a seizure include:
 - Those with renal insufficiency if the blood level of imipenem is too high.
 - Those already taking drugs such as theophylline, quinolones, metronidazole and cyclosporin.
- Imipenem must be **infused slowly or it causes nausea and vomiting.**
- It is unclear if there is cross allergenicity with penicillins.

C. Bioavailability

- Administration is parenteral.

D. Metabolism

- **Imipenem** is hydrolyzed by a dipeptidase on renal tubular cells. To overcome this, it is combined with **cilastatin**, a dipeptidase inhibitor.
- For all drugs, **reduce the dosage in patients with renal failure**.
- Ertapenem has a long half life and can be given once/day.

E. Resistance

- *Pseudomonas* can become resistant to carbapenems via a porin mutation.
- Novel beta lactamase resistance has been reported.
- In general, imipenem and meropenem are stable against all β -lactamases **except *S. maltophilia* and a rare isolate of *B. fragilis***

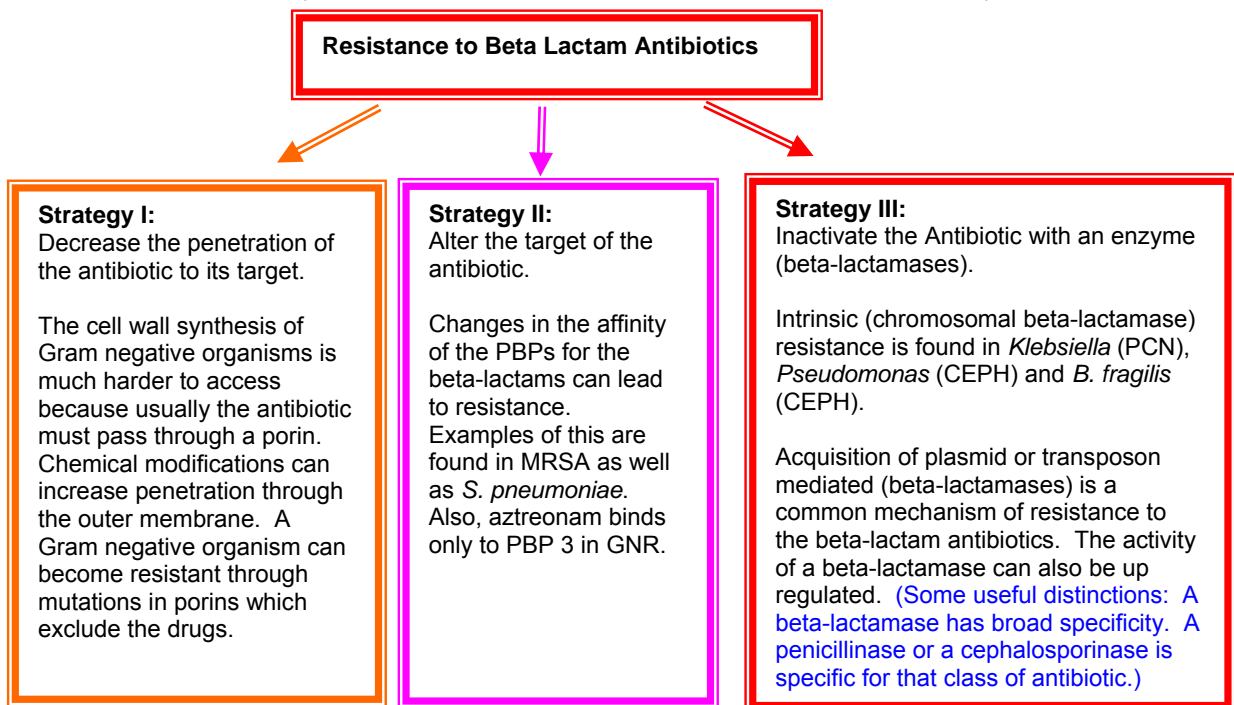
In general, there are three strategies used by bacteria to resist antibiotics:

1. Decreasing the penetration of the antibiotic to its target.
2. Altering the target of the antibiotic.
3. Inactivating the antibiotic via a bacterial enzyme.



6. Resistance to β -Lactam Antibiotics In General

Gram positives are intrinsically susceptible to most β -lactam antibiotics. Their PBPs are easily accessible.



One way to get around β -lactamases is to give a β -lactamase inhibitor in combination with the β -lactam antibiotic (e.g., Augmentin). There are three inhibitors in use, clavulanic acid, sulbactam and tazobactam. Although they have no antimicrobial activity, they are all suicide inhibitors of the β -lactamase. This allows the β -lactam antibiotic in the combination to bind transpeptidase and other PBPs without being degraded by β -lactamases.

These β -lactamase inhibitors, sulbactam, clavulanic acid and tazobactam, work against most Gram-negative β -lactamases and those found in *S. aureus*. They do not work against the chromosomally encoded β -lactamases of *Enterobacter*, *Citrobacter*, *Serratia* and *Pseudomonas* (class I β -lactamases).



B. Inhibitors of Cell Wall Synthesis: Vancomycin

1. Mechanism

- Vancomycin blocks the polymerization of the N-acetyl muramic acid-N-acetyl glucosamine backbone of the peptidoglycan (cell wall) by binding to D-ala –D-ala.
- This action is bacteriocidal.
- Don't confuse this mechanism with the way β -lactams work!

2. Uses

- Vancomycin can be used against **methicillin resistant *S. aureus* (MRSA)** and **penicillin (β -lactam) resistant pneumococci.**
- **It can be used for all Gram positive infections if patient is highly allergic to β -lactam antibiotics.**
- Vancomycin can be given **orally to treat *C. difficile* infections.**

3. Side Effects

- Rapid infusion of vancomycin causes **Red Man syndrome**. It is caused by **histamine release**, not allergy.
- Vancomycin is **ototoxic** (>80 micrograms/ml).
- Vancomycin is **nephrotoxic and/or ototoxic when given with aminoglycosides!**

4. Bioavailability

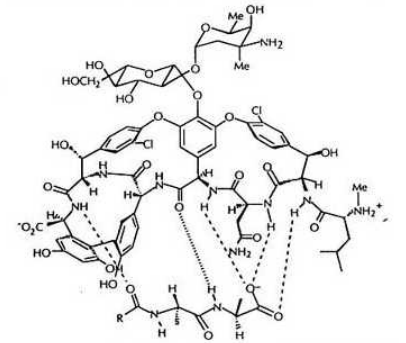
- Vancomycin can only be given by IV (except for oral treatment of *C. difficile* infection).

5. Metabolism

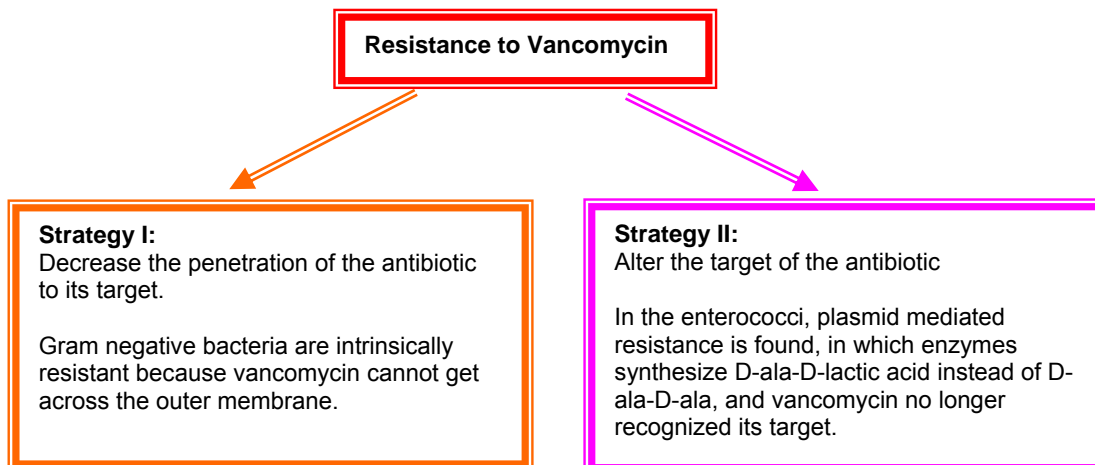
- Vancomycin is excreted only by glomerular filtration.
- **Vancomycin must be dose adjusted in renal failure.**
- **Vancomycin is not removed by peritoneal or hemodialysis.**

6. Resistance to Vancomycin

Vancomycin is one of the “big guns” against the Gram positives. With the increase in MRSA strains, vancomycin is the major drug to treat serious *S. aureus* infections. For many years, acquired resistance to vancomycin was never seen. However, several years ago, plasmid-mediated vancomycin resistance was found in the enterococci (called VRE strains). Genetic exchange of plasmids is well-known to occur between enterococci and staphylococci. The thought of plasmid-mediated resistance to vancomycin being passed from the enterococci to MRSA (methicillin resistant *Staphylococcus aureus*) is terrifying because of the lack of alternative treatments.



Vancomycin binding D-ala-D-ala



II. Inhibitors of Protein Synthesis

A. Inhibitors of Protein Synthesis: Aminoglycosides

1. Mechanism

Streptomycin, the prototype aminoglycoside, works by binding to a specific protein, S12, on the 30s ribosomal subunit. This blocks normal activation of the initiation complex. In general, aminoglycosides bind to the 30s ribosomal subunit. At low concentrations of the drugs, the mRNA is misread and the wrong amino acid is inserted. At higher concentrations, aminoglycosides inhibit translation. The action of aminoglycosides is bacteriocidal.

2. Representative Members and Their Uses

- Streptomycin is used to treat tuberculosis, and is sometimes used with a penicillin to treat enterococcal endocarditis. (Gentamicin would be the more typical choice.)
- Gentamicin, Tobramycin, and Amikacin are broad spectrum antibiotics. They are good against Gram negative rods and sometimes *Staphylococcus aureus*.
- Aminoglycosides and newer generation beta-lactams in combination are used to treat *Pseudomonas*.
- Overall, the aminoglycosides are pretty toxic drugs. When possible, less toxic alternatives are used.
- Efficacy is concentration dependant, so you want maximal peak levels.

3. Side Effects

- Streptomycin causes vestibular ototoxicity, but is not very nephrotoxic.
- All other aminoglycosides are nephrotoxic and ototoxic for the cochlea.
- Cochlear ototoxicity is irreversible because it is caused by the death of cochlear hair cells. It affects primarily high tones.
- Nephrotoxicity is usually reversible and resembles acute tubular necrosis. There is an increased chance of nephrotoxicity with high trough levels of the drug, hypotension, extended use and concurrent use of other nephrotoxic drugs (like vancomycin).
- Nephrotoxicity and ototoxicity are due to the binding of the drug to glycoprotein 330 (gp330) on the renal proximal tubules and on the epithelium in the cochlea and the endocytosis of the drugs.
- Very high concentrations of aminoglycosides cause neuromuscular blockade.

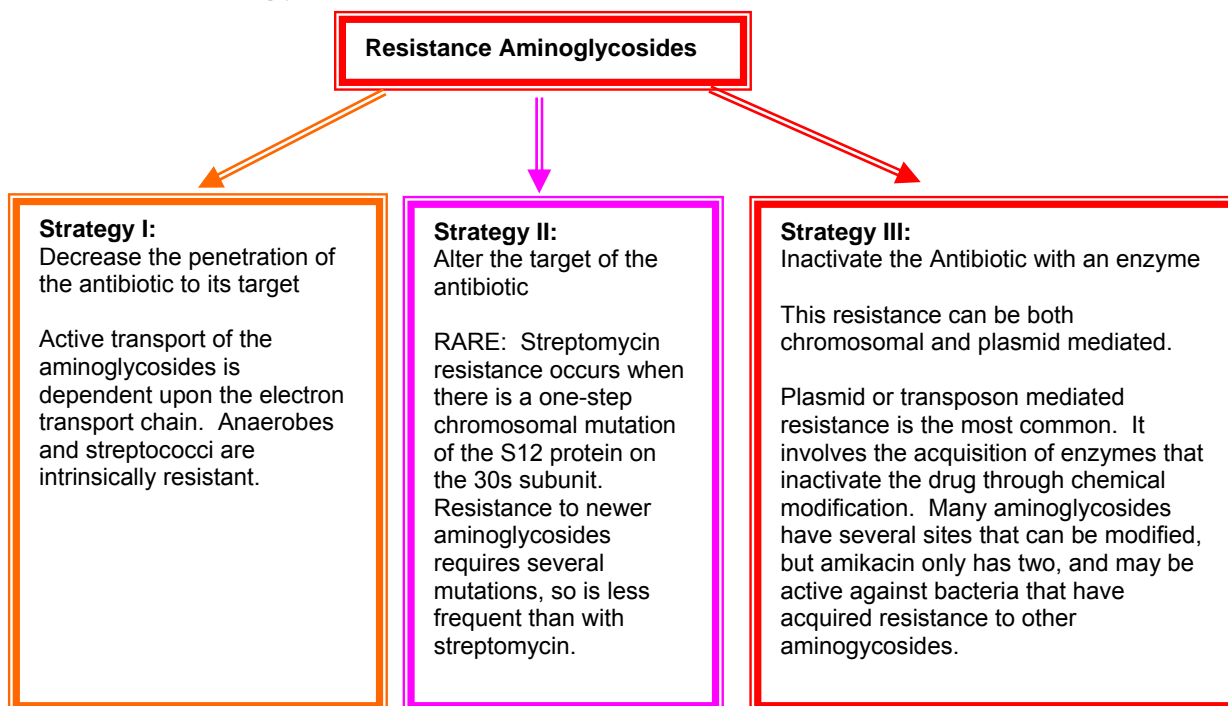
4. Bioavailability

- Aminoglycosides are administered by the IM or IV route. None of them are oral drugs.
- Aminoglycosides are very polar, so they do not enter the CSF, eye or bile. Do not use them against an intracellular pathogen.

5. Metabolism

- Aminoglycosides are excreted by glomerular filtration.
- The volume of distribution is close to that of extracellular fluid. If a patient has increased extracellular fluid, they will have lower than expected blood levels and because of this aminoglycosides should not be used in those patients.
- Aminoglycosides have a low toxic to therapeutic ratio. Blood levels need to be monitored to insure safety and efficacy.
- If the GFR falls below 70mL/min, the daily dose must be reduced to prevent toxicity.

6. Resistance to Aminoglycosides



B. Inhibitors of Protein Synthesis: Tetracyclines

1. Mechanism

Tetracyclines block tRNA binding to the ribosome by binding the 30s ribosomal subunit. Tetracyclines are almost always bacteriostatic.

2. Representative Members and Their Uses

- Tetracyclines that can be given via oral administration: **tetracycline, oxytetracycline, minocycline, and doxycycline.**
- **Demeclocycline** has oral administration only.
- **Tetracyclines are drugs of choice for *Chlamydia*, *M. pneumoniae*, *Rickettsia*, *Brucella*, and *Leptospira* and a lot of other organisms—get out your Sanford.**

3. Side Effects

- **Do not give to children or pregnant women.** Tetracyclines bind to newly synthesized bone and discolor teeth.
- Tetracyclines, especially **doxycycline**, can cause a **photosensitizing skin rash.**
- **Minocycline** causes **vertigo** if the blood level gets too high.
- Tetracyclines, in general, are anti-anabolic and raise BUN without hurting the kidneys.
- **Vaginal yeast infection commonly occurs** after a course of a tetracycline.



Tetracycline staining

4. Bioavailability

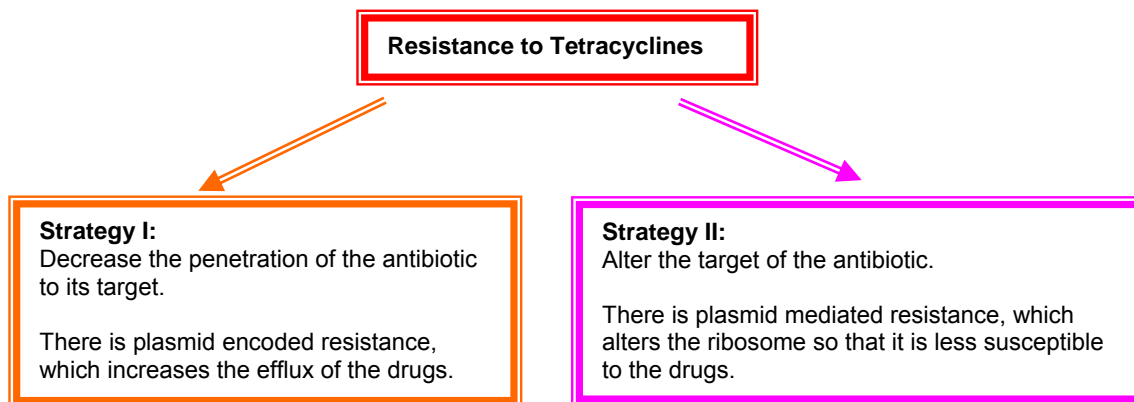
- **Antacids, milk and other dairy products inhibit absorption** of tetracyclines.
- Only doxycycline is good to give IV, because the others are too acidic and cause thrombophlebitis.

5. Metabolism

- Tetracyclines have renal and hepatic excretion.
- Doxycycline and minocycline have long half-lives, and have hepatic excretion.

6. Resistance to Tetracyclines

Resistance to one tetracycline means resistance to all tetracyclines. Unfortunately, acquired resistance to tetracyclines is very widespread, and is found in many medically important bacteria. This problem has severely limited the use of tetracyclines. However, certain bacteria that do not readily exchange genes, such as the *Chlamydia*, *Rickettsia*, and *Mycoplasma*, remain sensitive.



C. Inhibitors of Protein Synthesis: The MSL Group: Macrolides (Erythromycin), Long Acting Macrolides (Azithromycin) and Lincosamides (Clindamycin) and Streptogramins (Syneroid)

1. Mechanism

These antibiotics bind to the 50s ribosomal subunit and interact with the 23s ribosomal RNA. The overall effect is to block chain elongation. They can be bacteriocidal or bacteriostatic depending upon the organism.

2. Erythromycin

A. Uses for Erythromycin

- Erythromycin can be used against **Gram positive organisms**.
- Erythromycin can be used to treat GAS, *Legionella*, *Mycoplasma*, syphilis, diphtheria carriers and pertussis.
- Of the Gram negative rods, it is only active against *H. pylori*, *B.pertussis*, and *C. jejuni*. The outer membrane of many gram-negatives excludes erythromycin.
- Erythromycin is considered safe in pregnancy.

B. Side Effects Caused by Erythromycin

- **Erythromycin estolate causes cholestatic hepatitis (1/1000).**
- **Nausea and diarrhea are common, because erythromycin is a motilin agonist.**
- Erythromycin is **ototoxic in high doses**.
- Erythromycin **inhibits P-450 enzymes—so it changes the metabolism of numerous drugs including warfarin, cyclosporin and theophylline.**
- QT prolongation seen with IV administration of erythromycin.
 - Recent studies propose that the prolongation of the QT interval can lead to serious arrhythmias and even sudden cardiac death. This problem was originally seen with IV erythromycin, but oral erythromycin also increases the risk of sudden cardiac death. The risk increases when erythromycin is combined with drugs that inhibit its metabolism and boost erythromycin levels, such as diltiazem or verapamil. For more information, see N Engl J Med 2004;351:1053, 1089.

C. Bioavailability of Erythromycin

- Erythromycin can be given orally. The base is poorly absorbed, but the salts have better oral absorption.
- Erythromycin enters the prostate, crosses the placenta and enters milk, but does not get into the CSF.

D. Metabolism of Erythromycin

- Erythromycin is metabolized and excreted by liver.

- Erythromycin is not removed by dialysis.

3. Clarithromycin

A. Uses of the Long Acting Macrolide Clarithromycin

- The spectrum of clarithromycin is similar to erythromycin with the notable addition of some respiratory Gram-negative pathogens such as *Haemophilus*.
- Clarithromycin can be used for *H. pylori* and atypical mycobacteria infections.

B. Side Effects of the Long Acting Macrolide Clarithromycin

- Do not use clarithromycin in pregnant women; it might be teratogenic.
- Clarithromycin causes fewer GI problems than erythromycin.
- Clarithromycin is ototoxic in high doses.
- Clarithromycin inhibits cytochrome P-450 enzymes.

C. Bioavailability of the Long Acting Macrolides Clarithromycin

- Clarithromycin only needs to give twice daily. (Erythromycin is dosed 4 times a day!)
- Clarithromycin is well absorbed orally.

D. Metabolism of the Long Acting Macrolide Clarithromycin

- Clarithromycin is distributed into cells and concentrates into some organs like the lung.
- The dosage of clarithromycin must be adjusted in renal failure. Approximately 30% is renally excreted unchanged.

4. Azithromycin

A. Uses of the Long Acting Macrolide Azithromycin

- Azithromycin is active against many respiratory tract pathogens, including pneumococci, *Haemophilus*, *Moraxella*, *Mycoplasma*, and *Chlamydia*. However, resistance in pneumococci is increasing. Azithromycin is frequently used to treat respiratory infections and non-gonococcal urethritis. Its drawback is that it is expensive.
- Azithromycin is used to prevent MAC in AIDS.

B. Side Effects of the Long Acting Macrolide Azithromycin

- Allergic reactions are seen, and rarely epidermal necrolysis.

C. Bioavailability of the Long Acting Macrolide Azithromycin

- Azithromycin has once oral daily dosing.
- Azithromycin has prolonged tissue levels in many tissues including the lung, PMNs and macrophages so the course of therapy is shorter than with erythromycin or beta-lactam antibiotics.
- Antacids and food decrease absorption of Azithromycin.

D. Metabolism of the Long Acting Macrolide Azithromycin

- 75% of the dose is excreted unchanged in feces.
- 10% of the dose is renally excreted.

5. Clindamycin

A. Uses of the Lincosamide, Clindamycin

- Clindamycin is used against Gram positive cocci (but not *Enterococcus*) and anaerobes, both Gram-positive and Gram-negative (but not *C. difficile*), but not facultative Gram negative rods.

B. Side Effects of the Lincosamide, Clindamycin

- Clindamycin causes a significant risk of pseudomembranous colitis due to the overgrowth of *C. difficile*.

C. Bioavailability of the Lincosamide, Clindamycin

- Clindamycin is well absorbed orally. It can also be administered IM and IV.

D. Metabolism of the Lincosamide, Clindamycin

- Clindamycin has a mostly biliary excretion.
- Clindamycin is not removed by dialysis.

E. Resistance to the Lincosamide, Clindamycin

- Clindamycin resistant *Bacteroides* is becoming increasingly prevalent.

6. Streptogramins

A. Mechanism of Action of Streptogramins (Synercid)

- Streptogramins bind on the 50s ribosomal subunit near the macrolide binding site.

B. Uses of the Streptogramins (Quinupristin (streptogramin B)/Dalfopristin (streptogramin A))

- Synercid is the brand name of the fixed 3:7 combination of Quinupristin (streptogramin B)/Dalfopristin (streptogramin A).
- Quinupristin/ dalfopristin are bacteriocidal in combination for Gram positives (excluding *E. faecalis*). (They would be bacteriostatic as individual agents.)
- Quinupristin/ dalfopristin is used to treat VRE (*E. faecium*) and MRSA if vancomycin is contraindicated.
- Although Synercid was promoted for VRE and MRSA infections, in actual practice it is rarely used, and other agents, such as Linezolid, are more favorable.

C. Side Effects of the Streptogramins (Synercid)

- Quinupristin/ dalfopristin causes thrombophlebitis at infusion site.
- Quinupristin/ dalfopristin causes an increase in conjugated bilirubin.
- Quinupristin/ dalfopristin causes arthralgias and myalgias.
- Synercid's reaction with cytochrome P450 could increase the metabolism of many other drugs.

D. Bioavailability of the Streptogramins (Synercid)

- Quinupristin/ dalfopristin are only available in an IV form.

E. Metabolism of the Streptogramins (Synercid)

- Quinupristin/ dalfopristin are metabolized by the liver and excreted in bile.
- Quinupristin/ dalfopristin do not require dosage adjustment for renal failure.

F. Resistance to the Streptogramins (Synercid)

- Resistance can be mediated by the methylation of the binding site.
- Resistance can also be mediated by the acquisition of acetyltransferases.

7. Telithromycin (Ketek)—a Ketolide

A. Mechanism of Action of Telithromycin (Ketek)

- The mechanism of action of telithromycin is similar to that of macrolides, and is related to 50S-ribosomal subunit binding with inhibition of bacterial protein synthesis. Telithromycin, however, appears to have greater affinity for the ribosomal binding site than macrolides

B. Uses of the Telithromycin (Ketek)



- Telithromycin is approved for community-acquired pneumonia, exacerbations of chronic bronchitis, and sinusitis. **It should not be used as a first line drug.** Save telithromycin as an alternative to some quinolones for penicillin- and macrolide-resistant *S. pneumoniae*.

C. Side Effects of Telithromycin (Ketek)

- Telithromycin has many of the same problems as erythromycin including adverse GI effects, numerous drug interactions, and potential arrhythmias.
- Telithromycin is a strong inhibitor of CYP3A4 enzymes (like erythromycin and clarithromycin). It can **increase** levels of drugs metabolized by CYP3A4, such as simvastatin, lovastatin, atorvastatin, midazolam, and others.
 - Patients should discontinue taking simvastatin, lovastatin, or atorvastatin while taking telithromycin.
- Telithromycin is also metabolized by CYP3A4. Its levels can be increased by ketoconazole and other CYP3A4 inhibitors or decreased by rifampin and other CYP3A4 inducers.
- Telithromycin can prolong the QT interval. Do not give it to patients at risk for arrhythmias or taking certain antiarrhythmics.
- Telithromycin can exacerbate myasthenia gravis.
- Telithromycin can cause blurred vision or difficulty focusing.

D. Bioavailability of the Telithromycin (Ketek)

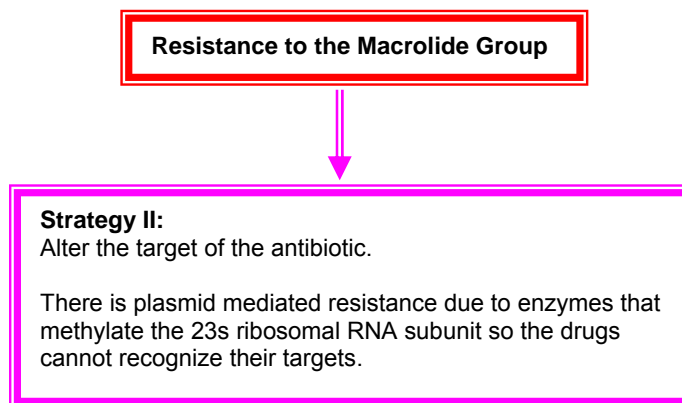
- Telithromycin is administered via the oral route. Absorption not affected by food

E. Metabolism of the Telithromycin (Ketek)

- Telithromycin is metabolized by the liver (37%) and excreted in bile. Approximately 50% is metabolized by CYP3A4 and the rest is non-P450 mediated

8. Resistance to The MSL Group (Macrolides (Erythromycin), Long Acting Macrolides (Azithromycin) and Lincosamides (Clindamycin) and Streptogramins (Syneroid))

- **Plasmid encoded resistance to one drug in this group means resistance to all.**
- **Resistance due to multidrug exporters affect macrolides but not clindamycin.**
- Chromosomal resistance to streptogramins is seen.



D. Inhibitors of Protein Synthesis: Chloramphenicol

1. Mechanism

Chloramphenicol binds the 50s ribosomal subunit and inhibits the translocation of the peptide chain from A site to P site. Chloramphenicol is bacteriostatic.

2. Uses

- Chloramphenicol is a broad spectrum antibiotic that is often used in underdeveloped countries. Due to side effects, it is no longer used in this country.

3. Side Effects

- Chloramphenicol causes aplastic anemia in 1/25,000 – 45,000 patients. This is irreversible!! (This is why it is uncommonly used in the US.) It also causes a reversible bone marrow suppression that is dose related.
- Chloramphenicol causes Gray baby syndrome in newborns, because the baby's liver is not able to glucuronidate it to metabolize it. This can lead to circulatory collapse and death.
- Chloramphenicol causes hemolysis in those with a G6PD deficiency.

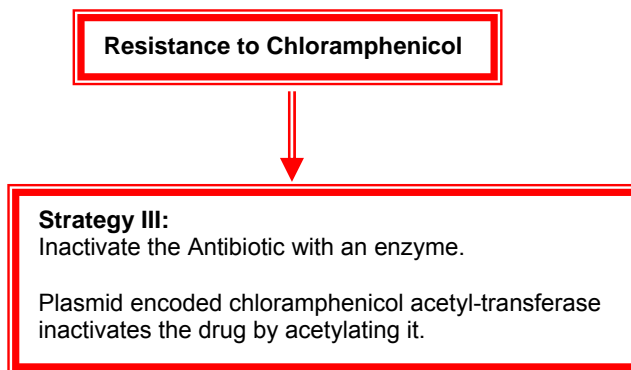
4. Bioavailability

- Chloramphenicol reaches good concentrations everywhere including the eyes and CSF.

5. Metabolism

- Chloramphenicol is glucuronidated in the liver and then renally excreted.

6. Resistance to Chloramphenicol



E. Inhibitors of Protein Synthesis: Oxazolidinones (Linezolid)

1. Mechanism of Action

Oxazolidinones (Linezolid) inhibits protein synthesis by binding to the 50S ribosomal subunit, blocking the peptide transfer activity.

2. Uses of Oxazolidinones (Linezolid)

- Linezolid is active against all Gram positive cocci and *P. multocida*.
- Linezolid is used to treat VRE, and is a potential agent for MRSA skin infections and beta-lactam resistant pneumococcal disease.

3. Side Effects of Oxazolidinones (Linezolid)

- Linezolid is a monoamine oxidase inhibitor, so high tyramine ingestion, and drugs such as pseudoephedrine need to be restricted. Tyramine is found in high concentrations in such foods as fermented cheeses, imported beer, some wines, such as Chianti and champagne, soy sauce, avocados, bananas, and fermented, smoked, or aged fish or meat.
- Thrombocytopenia occurs in ~ 3% of patients, usually after >2 weeks. Bone marrow suppression with prolonged use of linezolid has been seen in a small number of patients. Monitor the patient's CBC.

4. Bioavailability of Oxazolidinones (Linezolid)

- Linezolid is administered via the oral route. Absorption not affected by food and peak blood levels are equivalent to IV dosing.

5. Metabolism of Oxazolidinones (Linezolid)

- Linezolid is metabolized via renal and non renal routes.

6. Resistance

- Cross-resistance with other antibiotics is not seen, but resistance has developed slowly *in vitro*.

III. Inhibitors of DNA Synthesis

A. Inhibitors of DNA Synthesis: Quinolones (Ciprofloxacin, Levofloxacin, Trovafloxacin and others)

1. Mechanism

Quinolones interfere with the activity of DNA gyrase. They prevent winding of the DNA helix into the supercoiled form. Their actions are bacteriocidal. The newer agents are more accurately called fluoroquinolones.

2. Uses

- Fluoroquinolones are used against Enterobacteriaceae.
- Ciprofloxacin is most active against *Pseudomonas*.
- Newer fluoroquinolones (levofloxacin, gatifloxacin, moxifloxacin) have a very broad spectrum of activity, including Gram-positives, Gram-negatives, anaerobes, intracellular bacteria (*Chlamydia*), and *Mycoblasma*. Some fluoroquinolones are active against mycobacteria.
- Fluoroquinolones are used for UTIs, pneumonia, atypical pneumonia and bacterial gastroenteritis.

3. Side Effects

- **Trovafloxacin** can cause an **idiosyncratic hepatotoxicity**, which can be fatal.
- Fluoroquinolones that inhibit CYP-450 **raise blood levels of methyl-xanthines** (caffeine, theophylline), cyclosporin, and warfarin.
- **High drug levels are neurotoxic.**
- **Prolonged use leads to tendon damage (rupture of Achilles tendon).**
- **Fluoroquinolones are not approved for children** because studies on collie **dogs showed cartilage damage.**
- Safety in pregnancy is not established
- Do not give to lactating women.

4. Bioavailability

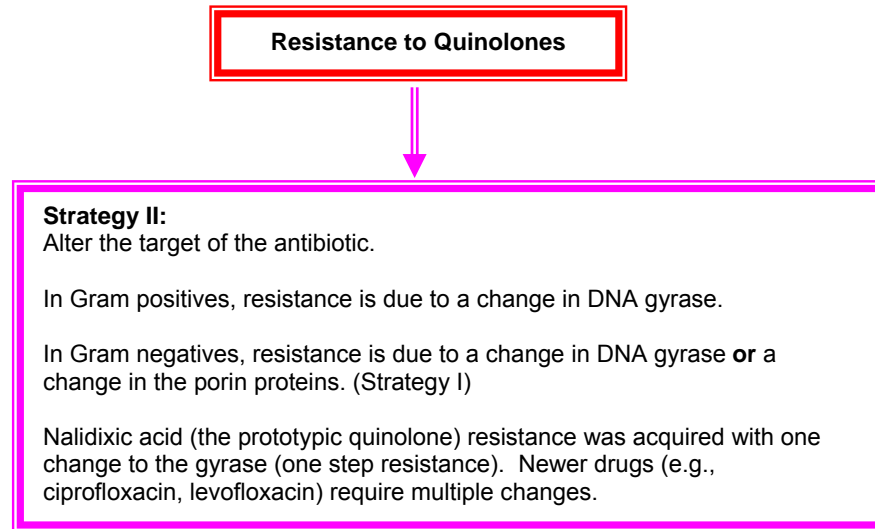
- Administration can be either oral and IV.
- **Antacids, iron and calcium will decrease their absorption.**
- **Food and histamine blockers delay absorption of fluoroquinolones.**
- Fluoroquinolones have good distribution into the prostate, CSF and eye.
- The completeness of absorption varies among the drugs.

5. Metabolism

- The route depends upon the drug.
- Renal excretion can be blocked with probenecid.
- **Grepafloxacin and trovafloxacin are eliminated by the liver.**
- Others must be dose adjusted in renal failure.

6. Resistance to the Quinolones

Plasmid or transposon-mediated resistance to quinolones is very rare (not well documented).



B. Inhibitors of DNA Synthesis: Metronidazole

1. Mechanism

In a reducing environment, metronidazole is reduced to a substance that inhibits bacterial DNA synthesis. Its action is bacteriocidal, but its use is limited to anaerobic organisms.

2. Uses

- Metronidazole can be used against obligate anaerobes other than *Actinomyces*, protozoa such as *Giardia* and *Entamoeba*, *Helicobacter pylori*, and the agent causing bacterial vaginosis.
- In some studies, it reduced disease activity in Crohn's disease.

3. Side Effects

- Metronidazole causes an **antabuse reaction**.
- Metronidazole produces a **metallic taste in the mouth**. (It tastes like you are chewing on tin foil).
- **Peripheral neuropathy, seizures and ataxia have been seen with prolonged use.**
- Metronidazole inhibits warfarin metabolism so it can increase the PT in patients taking it.

4. Bioavailability

- Administration can be oral or IV.
- Metronidazole gets into eye, and the CSF.

5. Metabolism

- Metronidazole is metabolized by the liver and excreted in urine.
- Reduce the dose in severe hepatic dysfunction.

6. Resistance to Metronidazole

- *Actinomyces* are intrinsically resistant.
- Acquired resistance to metronidazole is very unusual. However, very rare plasmid mediated resistance has been reported in *B. fragilis*.

IV. Inhibitors of RNA Synthesis

A. Inhibitors of RNA Synthesis: Rifamycins (Rifampin)

1. Mechanism

Rifamycins inhibit DNA dependent RNA polymerase by binding to the beta subunit and inhibiting initiation. This action is bacteriocidal. The drug in major use is rifampin, while rifabutin is used sporadically.

2. Uses

- Treatment of TB and other mycobacterial infections
- Rifampin is sometimes combined with other antibiotics in the treatment of selected refractory infections, but it is never used alone due to the development of resistance, as described below.

3. Side Effects

- Rifamycins turns urine, tears, and sweat orange.
- Starting and stopping the drug causes a flu like illness.
- Rifampin induces the P-450 enzymes so it reduces the blood levels of many drugs including warfarin, antiretrovirals, steroids etc. Rifabutin has less effect on P-450 enzymes than rifampin.
- Rifabutin causes uveitis and arthralgias with prolonged use.

Yo! Wear old clothes
and forget about the
contacts!



4. Bioavailability

- Both are oral and have once daily dosing.
- Rifamycins get into the CSF, prostate and eye.
- Rifabutin is only 15% bioavailable, so the blood levels are only 5% of rifampin.

5. Metabolism

- Rifamycins are excreted by liver.

6. Resistance

Plasmid mediated resistance has not been found.

Resistance to Rifamycins

Strategy II:

Alter the target of the antibiotic

Resistance occurs when the polymerase is altered. This resistance is chromosomally mediated, and occurs in one step. It is important not to use Rifampin alone.

V. Cell Membrane Toxins: The one drug in this class is Daptomycin.

1. Mechanism

Daptomycin is a cyclic lipopeptide antibiotic with activity limited to Gram positive pathogens. Antibacterial effects are mediated by disruption of multiple aspects of bacterial plasma membrane function, including peptidoglycan synthesis, lipoteichoic acid synthesis, and bacterial membrane potential; these effects occur with no penetration of the cytoplasm. The mechanism of binding is not known. Daptomycin exhibits concentration-dependant bacteriocidal activity.

2. Uses

- This drug is active only against aerobic Gram positive bacteria, and may be useful for treating MRSA and VRE infections as alternative to linezolid and Synercid. There is minimal published clinical experience with this drug.

3. Side effects

- High doses (4mg/kg b.i.d.) cause muscle weakness and elevated CPK.

4. Bioavailability

- Daptomycin is not absorbed orally. It is a highly protein bound, large molecule with a small volume of distribution. Dose must be reduced in renal insufficiency.
- The Half life of daptomycin is 7-10 hours.

5. Metabolism

- 80% is excreted in urine, 50% is unchanged; 5% in feces.

6. Resistance

- **Daptomycin does not penetrate outer membrane of Gram negative bacteria, so these organisms are intrinsically resistant.**
- **Since this drug has not been widely used, transferable genes encoding resistance have not been described.**

VI. Inhibitors of Folate Metabolism

A. Inhibitors of Folate Metabolism: Sulfonamides and Trimethoprim

1. Mechanism

Sulfonamides competitively inhibit folate synthesis. (Remember from BD, humans need an exogenous source of folate.) Trimethoprim competitively inhibits the bacterial dihydrofolate reductase, and is much less active toward the human enzyme. They are often given together because they act synergistically, and are bacteriocidal in combination.

2. Uses

- Sulfonamides and Trimethoprim are commonly used in combination to treat community acquired UTI. However,
- 20% of *E. coli* are now resistant.
- **Treatment of and Prophylaxis against PCP in AIDS patients.**

3. Side Effects

- They can cause an **allergic rash**.
- They can cause **megaloblastic anemia**.
- Reversible hepatitis has been seen in AIDS patients.
- **Sulfa drugs are contraindicated in newborns because they cause kernicterus.**
- They can cause hyperkalemia.

4. Bioavailability

- Sulfonamides and Trimethoprim can be given orally.

5. Metabolism

- Sulfonamides and Trimethoprim have renal excretion.
- Sulfonamides are metabolized in the liver.
- Dialysis removes sulfa drugs, but not metabolites, so they may accumulate and precipitate in the liver.

6. Resistance

Resistance to Inhibitors of Folate Metabolism



Strategy II:

Alter the target of the antibiotic.

Resistance to both sulfonamides and trimethoprim is due to the acquisition of genes encoding new enzymes that are not inhibited by the drugs. These enzymes are plasmid or transposon mediated.



Check out this great reference site for medications, drug interactions, etc. This link takes you to the UCSD access site. Click on Microdex Healthcare Series (#6)
http://libraries.ucsd.edu/sage/subjects//pharmacology_and_pharmacy.html