The Antimicrobial Block information is, unfortunately, Dr. Agarwal reorganizing the drug list. He has an order to his lectures and often includes multiple classes in one lecture. The LOs say something like “know the mechanism, pharmacokinetics, side effects, and indications for each class.” Sweet. That means “memorize the drug list.”

Instead of Lecture Objectives for most of the drugs, what we have attempted to do is organize the sections by classes. The hope is to give you some Tulane relevant material and then some high-yield stuff for the boards. The idea is that we leave the nit-picky detail out (since Clarkson includes that in his drug lists) and give you ways of remembering the content, or learning why a certain drug is what it is, making the memorization process easier.
1. **Define the terms: antibiotics, selective toxicity, therapeutic index, bacteriostatic and bactericidal.**

   - **Antibiotics** are chemicals that are produced by microorganisms and have the capacity to inhibit growth of or kill other microorganisms.
   
   - **Selective toxicity**: selectively toxic to microorganisms. You want to kill the bug without killing your own cells. You want them to “select” for the bacteria. An example is targeting the 50s ribosome, which humans don’t have (we have a 60s) or the cell wall of gram positive bacteria (human cells don’t have a cell wall). The danger comes from mitochondria, usually, which have very prokaryotic-like machinery.
   
   - **Therapeutic index** or therapeutic ratio is the ratio of maximum tolerated dose to minimum effective dose.
   
   - **Bacteriostatic**. Arrests the growth of, but does not kill, the bacteria. This stops the bacterial cells from growing, allowing the host immune system to take care of it. Obviously, immunocompromised patients will not be able to take care of anything, so bacteriostatic drugs won’t do anything from them.
   
   - **Bactericidal**. Kills the bacteria. This actively causes the death of the bacterial cells in a variety of ways. It doesn’t matter if the host is immune compromised or not. This drug will just destroy the bacteria. Of course, since these drugs are more toxic to bacteria, their risk for endogenous toxicity remains high.

2. **Understand the MIC and MBC values.**

   **MIC** = tube in which, in the presence of antibiotic, no bacterial cell growth can be found. Drug Serum levels should be above this concentration.

   **MBC** = tube in which, even after the antibiotic is removed, bacteria still do not grow (because they were killed off by the antibiotic).
3. Describe the terms synergism and antagonism.

- **Synergism**: When one drug helps out another so that the efficacy is greater than two drugs alone
  - **Enhanced drug permeability**: a cell wall synthesis inhibitor breaks down the cell wall allowing Aminoglycosides to penetrate and take effect
  - **Blocking successive steps in metabolic sequence**: sulfamethoxazole + Trimethoprim
  - **Using an inhibition of an enzyme capable of destroying a second drug**: β-lactamases can degrade β-lactam drugs. So, if you give a β-Lactamase-Inhibitor with the β-lactam, you allow the β-Lactam to function.

- **Antagonism**: When one drug intereferes with the action of another. Tetracycline + a penicillin (why would you give a bacteriostatic drug with a bacteriocidal drug?)

4. Discuss the classification of antimicrobial drugs based upon the mechanism of action. Includes 5 TONS of detail on mechanism of action in individual lectures
The following are listed in the order of the steps of translation that they interfere with.

**Aminoglycosides** bind the 30s subunit, preventing the formation of the initiation complex

**Tetracyclines** bind to the 30s subunit preventing the amino-acyl-tRNA from binding the ribosome.

**Chloramphenicol** binds the 50s subunit and prevents **transpeptidation**.

**Macrolides + Clindamycin** bind the 50s subunit preventing **translocation** (moving down along the RNA)

Agarwal did not go over the others, but you will. I include them here, but the details will be found in their respective letters.

6. **Define bacterial resistance and illustrate the mechanisms involved in acquiring bacterial resistance.**

   There are 3 themes you will see over and over again. However, you have to know the details in the box that follows.

   1. **Decreased Permeability** – either there are fewer porins (gram negative bacteria) or active efflux proteins that keeps the drugs out.

   2. **Metabolic Proteins** – proteins that degrade the drug (for example, β-Lactamases) can be acquired by plasmid vectors from other bacterial cells.

   3. **Alteration of Substrate** – the target of the drug is changed, reducing affinity for the drug. If the drug can’t bind, it can’t take effect.

**Mechanisms of Resistance to Antimicrobial Agents**

<table>
<thead>
<tr>
<th>Antimicrobial Agents</th>
<th>Primary Mechanism(s) of Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins and cephalosporins</td>
<td>Production of beta-lactamases, which cleave the beta-lactam ring structure; change in penicillin-binding proteins; change in porins</td>
</tr>
<tr>
<td>Aminoglycosides (gentamicin, streptomycin, amikacin, etc.)</td>
<td>Formation of enzymes that inactivate drugs via conjugation reactions that transfer acetyl, phosphoryl, or adenylyl groups</td>
</tr>
<tr>
<td>Macrolides (erythromycin, azithromycin, clarithromycin, etc.) and clindamycin</td>
<td>Formation of methyltransferases that alter drug binding sites on the 50S ribosomal subunit. Active transport out of cells</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Increased activity of transport systems that “pump” drugs out of the cell</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>Change in sensitivity to inhibition of target enzyme; increased formation of PABA; use of exogenous folic acid</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Change in sensitivity to inhibition of target enzymes; increased activity of transport systems that promote drug efflux</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Formation of inactivating acyltransferases</td>
</tr>
</tbody>
</table>
BEGIN CELL WALL INHIBITORS

Penicillins, Cephalosporins, β-Lactamase Inhibitors, Vancomycin, Imipenem, Meropenem, Aztreonam
Penicillins were a JITT session. This is a review of material to keep it straight for you. YOU MUST KNOW THE DRUG LIST AND THE SPECIFICS THEREIN. You will be tested on some nit-picky low-yield stuff in Tulane Pharm, but Clarkson usually underlines it, puts it in red, or bolds+underlines it for you.

The lactam structure. The general chemical structure of penicillin is shown. The four membered ring is a very unusual structure. Rings are usually 5 or 6 membered. A four membered ring is tense, and is fragile. That four membrane ring that is referred to as a Lactam Structure. Where the arrow is between the Nitrogen and the carbonyl group represents the weakest bond in the Lactam group, where bacteria attack the Lactams, cleaving the ring (they attack with Penicillinases also called β-Lactamases).

See the Sulfur? What bad can that do? Well, that sulfur makes these drugs prone to immune responses. They can be anaphylactic or they can be mild type IV rashes.

MOA:
Interacts with Penicillin Binding Proteins (PBP) that are part of the cell wall synthesis. When bound to PBPs, penicillin inhibits transpeptidation which therefore inhibits cross-linking of peptidoglycans blocking the formation of the cell wall. See biochemistry (peptidoglycan) for details and images.

Penicillins work very well on gram positive bacteria because their large cell wall is exposed to the aqueous environment. Gram negative bacteria, however, have an outer membrane, a periplasmic space, and a very small cell wall. In order to reach the peptidoglycans of the cell wall, the antibiotics must penetrate the outer cell wall (through porin proteins) then diffuse across the periplasmic space, and take their effect. To boot, the peptidoglycan layer is not a large component of cell survival; the outer membrane provides a large amount of protection as well.

Mechanisms of Resistance:
- Penicillinases – cleaving the Lactam ring breaks the molecule, preventing it from binding to PBPS.
- Change the structure of PBPs – if you change the PBP, ALL LACTAMS will be unable to bind. The classic example is Methicillin inducing Methicillin Resistant Staph Aureus (MRSA).
- Change in Porin Structure – relative to gram negative bacteria only. The outer membrane of the cell wall inhibits the free exchange of nutrients. Porins allow nutrients through. Lactams have been created that can fit through those channels. Well, if the bacteria wants to prevent the Lactams from getting in, it can simply reduce the number of porin channels there are.

Specifics of Subclasses of Penicillins

Because all the data is purely empirical, all you are left with is pure memorization of facts. This is the high-yield material for the BOARDS, which is often relevant on this pharm Tulane Exam. The approach we took is to explain why we have so many groups.
- **Narrow Spectrum, Beta-Lactamase Sensitive: Penicillin G and V**

These were the first of the penicillins found, made naturally from a fungus. These aren’t really used anymore because of resistance. These came out around WWII, and added about 20 years onto life expectancy. These are narrow-spectrum working mainly on gram positive bacteria. What are they still used for? Well, we usually use it for *treponema pallidum* the infectious agent of syphilis.

- **Very Narrow Spectrum, Beta-Lactamase Resistant: Nafcillin, Methicillin, Oxacillin**

So, you are a Drug company. You have Pen G and V and they worked great. But all the bugs they treat developed a Beta-Lactamase that rendered them useless. What do you do? Well, you design drugs that are Beta-Lactam Resistant. In doing so, the drug companies made them very narrow spectrum, so narrow that they only work on Staph. This is how we started treating Penicillin Resistant Staph, until of course, it became MRSA. So now we have a Beta-Lactamase secreting, PBP changed, resistant bug.

- **Broad Spectrum, aminopenicillins, Beta-Lactamase Sensitive: Ampicillin, Amoxicillin**

Alright, forget about Beta-Lactamase resistance, lets broaden the spectrum. These drugs have an amino group (thus the Am of Ampicillin and Amoxicillin) that makes them more water soluble. They have all the strengths of Penicillin G, all the weaknesses, but the added benefit of broadening their spectrum to include *E Coli, H. Influenzae, Listeria Monocytogenes* (amp), *Borrelia Burgdorfei* (amox). Because we know they are susceptible to Beta-Lactamases, they are often given together with Beta-Lactamase Inhibitors clavulonic acid, sulbactam, and Tazobactam.

- **Extended Spectrum, antipseudomonal, IV, drugs, Beta-Lactamase Sensitive: Ticarcillin, Piperacillin, Azlocillin, Carbencillin**

These are Board-tested as pseudomonal infections for in-hospital patients administering IV (parenteral) to a burn unit or cystic fibrosis patient. Like the broad spectrum antibiotics, they are often given with Beta-Lactamase Inhibitors. Note: Indanyl Carbenicillin is in your drug list as an orally effective treatment of UTIs. This will not be on the boards, but is bolded and underlined (so will be on your Tulane Exam).

**Pharmacokinetics**

Before we begin, let’s set some generalizations about antibiotics overall. If you just assume these to be true for all antibiotics (especially penicillins), and find the exceptions, your life will be made a lot easier.

1. Antibiotics are water soluble
2. Antibiotics are renally eliminated, and are therefore nephrotoxic

Naficillin and Oxacillins are the exceptions. Oxacillin is both water and lipid soluble. Naficillin is the highest-yield. Naficillin is lipid soluble and excreted in the bile. This means that Naficillin can cross the blood brain barrier, and does not have to be dose-adjusted for renal impairment.

There are Repository penicillins such as Procaine or Benzathine Pen G, which maintain levels for days.
**Side Effects**

More generalization of all antibiotics

(1) Antibiotics cause **allergic reactions** (all Types, I-IV). If you think about it, these antibiotics are made by fungus (protein of another organism) are **large** and contain **sulfur**. This screams possible allergic reaction.

(2) GI disturbances – you are killing organisms. You are killing cells. Your GI tract, in particular, with its high turnover of cells, is susceptible to unintentional destruction. Combine that with all the possible floral changes in the GI tract, and you’ve got a ripe situation for GI trouble. Take it for granted that all antibiotics cause GI upset.

What you want to take away is some fairly specific pieces of information.

Type I hypersensitivity (anaphylactic shock) is a major threat. If you have **anaphylactic reaction** to a penicillin, you will have **cross-reactivity** to other penicillins, so you avoid other penicillins. However, other cell wall inhibitors, especially those that are Lactams (like cephalosporins) may also have cross reactivity. **If you have an anaphylactic reaction to penicillin you will not use cephalosporins.**
1. Describe the structural differences between penicillins and cephalosporins.

Penicillins have a 5-membered ring, Cephalosporins have a 6 membered ring. Penicillins have one R group (on the left) while cephalosporins have 2 R groups (on the left and the right) which allows them to have a broader spectrum of action.

Really, the only difference between Penicillins and Cephalosporins is nitpicky details in the organisms they treat. Their mechanism of action, mechanism of resistance, and risks of side effects are essentially the same. These could actually be considered “subclasses” of penicillins.

However, because there are so many, as the Kaplan Videos say “When looking at Cephalosporins, sometimes our hippocampuses swell and we suffer an uncal herniation.” A joke that there is a lot… A LOT of memorization here.

2. Explain the mechanism of action AND resistance of cephalosporins.
Both are IDENTICAL to Penicillins. MOA = inhibition of transpeptidation by binding to penicillin binding proteins thereby inhibiting the cross-linking of the cell wall.

3. Describe the four generations of cephalosporins with specific examples, antimicrobial spectrum and pharmacokinetic properties.

1st Generation
- Basically its Penicillin G + PEcK = Proteus, E Coli, and Klebsiella
- Can be taken Orally
- Stable against Penicillinases (β-lactamases), which make these better than Penicillin
- Used in Surgical Prophylaxis

2nd Generation
- Basically its Penicillin G + HEN-PEcK = Haemophilus, Enterobacter, Neisseria
- Even more stable against penicillinase (β-Lactamase)
- No Drugs enter the CSF
- Cefoxatin, Cefaclor, Cefprozil

3rd Generation
- Decreased efficacy against gram positive cocci
- Increased efficacy against gram negative rods HEN-PEcK
- Even more stable against penicillinase (β-lactamase)
- Increased permeability to the Blood Brain Barrier (1st and 2nd are not permeable)
- Cefotaxime, Cefazidime, Ceftriaxone
- “Ceftriaxone treats meningitis in adults and children” – Agarwal
- Bugs they don’t work on are LAME – Listeria, Atypical, MRSA, Enterrococcal
Pharm: Cephalosporin and Vancomycin

4th Generation
- Cefepine = Broad Spectrum
- Much more potent (even less MIC than any of the other)
- Enterobacter and Psedomonas effective
- Not useful against MRSA or enterococcal organisms

Note: All Cephalosporins have renal clearance requiring dose modification in renal dysfunction. Cefoperazone and Ceftriaxone are largely eliminated in the bile.

4. Describe the adverse effects of the cephalosporins.
- Hypersensitivity. Hypersensitivity reactions. Just like Penicillin, these can cause a hypersensitivity reaction. If there is an anaphylactic reaction to penicillin, you will not give cephalosporins. However, if they have a mild reaction to penicillin, there is only a 1-3% risk of cross-sensitivity, and you CAN give a cephalosporin until a cephalosporin allergy is confirmed.
- Calcium. Mixing calcium with ceftriaxone
- Superinfections. When you give a broad-spectrum antibiotics, you kill off the normal flora. You then get an overgrowth of enterroccocal organisms that were NOT killed off by the antibiotics. Clostridium Difficile, Candida Albicans, and Enterobacter are good examples.

5. Explain the terms superinfection and cross-hypersensitivity.
Discussed in 4.

6. Discuss the mechanism of action of vancomycin.
Inhibits cell wall synthesis upon binding to D-alanyl-D-alanine and inhibits transglycosylase activity and preventing further elongation of peptidoglycan. This binds to the D-Ala-D-Ala, the target of the penicillin-binding proteins that penicillins inhibit. Resistance can develop by altering the binding site (D-Ala-D-Ala to D-Ala-D-Lactate)

7. Describe the pharmacokinetic properties of vancomycin.
Vancomycin cannot cross any barrier. It is not absorbed, it does not cross the Blood Brain Barrier. That means if you want to treat something in the GI, you give it orally, and it will stay only in the GI. If you have a systemic infection, you must give it IV, and it will not cross into the brain nor into the GI.

If you have a meningitis, you give ceftriaxone. If the patient has had an anaphylactic reaction to penicillin, you cannot give cephalosporins, so you give Vanco. If you give Vanco for meningitis, you must introduce it directly into the CSF.

You must give a slow dose of vanco IV in order to prevent hypotension & “red man syndrome”

8. Describe the main therapeutic indications and toxicities of vancomycin.
Clostridium Difficile causes psuedomembranous colitis after the use of broad-spectrum antibiotics that kills off everything else but the C Diff. You give Vancomycin to kill off the C Diff, while you stop the other antibiotics to give a chance of the organisms to come back.

MRSA is resistant to just about everything. Vancomycin is only of the only things left. Unfortunately, MRSA is now becoming Vancomycin resistant. We have to turn to other classes of drugs to take of this nasty. Vancomycin is usually used in gram positive organisms (Staph, Strep, Enterococcus)
These drugs are purely synthetic drugs that work on PBPs, work on transpeptidation, but are only given IV and are generally reserved for critical, in-hospital cases. All the drugs are cleared renally, and require dose alterations in renal impairment.

**Imipenem and Meropenem**

The mechanism of action is the same as penicillins and cephalosporins, but they are resistant to Beta-Lactamases. Of course, because they are PBP-related, MRSA is not a target. However, it has a huge spectrum including gram positive cocci, gram negative rods (Enterobacter, pseudomonas), and anaerobes (Bacteroides).

Imipenem only requires coadministration with cilastatin. This decreases the renal metabolism of imipenem via dehydropeptidase. Imipenem would have a very short half life if not administered with cilastatin. This is not the case with meropenem.

Both drugs can cross the BBB and develop seizures, particularly with imipenem.

**Aztreonam**

The mechanism of action is the same as penicillin and cephalosporins, but they are resistant to Beta-Lactamases.

This IV drug is used only against gram negative-rods (be careful when you read your stem, you want to use this on H. Influenzae, not Staph or Strep).

This drug has no cross-allergenicity with penicillins or cephalosporins, so is safe to give. A trick the boards may do is give you an infection, tell you there is an allergy to penicillin, and Macrolides / Vancomycin will NOT be present, and you must choose Aztreonam, so long as it is a gram negative infection.
Vancomycin

With all the Lactams there is a resistance, **Methicillin Resistance**, where there is an alteration of PBPs, so that NO cephalosporin, penicillin, or penicillin-like drug could work. This leaves us with very limited options. Vancomycin is also a **cell wall inhibitor**, but it is **not a penicillin**. Thus it retains its usefulness in treating gram positive cocci (like staph and strep) but gets around some of the resistances.

**Mechanism:**
Binding at the D-AlaD-Ala pentapeptide to sterically hinder the **transglycosylation** (NOT transpeptidation), inhibiting the elongation of peptidoglycan chains. The D-Ala-D-Ala is the substrate for PBPs.

**Resistance:**
Resistance is unfortunately becoming possible (VRSA or VRE). There is a change in the target, changing the D-Ala-D-Ala to **D-Ala-D-Lactate**, preventing binding of Vancomycin. What do we do with VRSA or VRE? Well, nothing. We are left with trying different types of brand new drugs like Streptogrammins.

**Pharmacokinetics:**
It does not cross any barrier. That means if you give it orally, it stays in the GI (to treat C. Diff pseudomembranous colitis). If you give it IV, it treats systemic infections, but does not get into the CSF. If you inject it into the CSF, you better be treating meningitis.

It is eliminated by the kidney and has a large half-life. In fact, it is usually given IV, **slowly**. Hypotension is common with rapid administration.

**Side Effects:**
- “Red Man Syndrome” a **maculopapular rash** from Type I hypersensitivity; anaphylaxis = IgE/Histamine. This is too much of a buzz word, so the Board’s will usually ask you WHY this happens, not what its called.
- **Ototoxicity** = one of many that can cause irreversable hearing issues. Usually it is an additive side effect to Aminoglycosides.
- **Nephrotoxicity** = it is excreted by the kidneys, so has a risk. Again, it is usually an additive side effect.

See the Cephalosporin lecture where the lecture objectives have been answered.
BEGIN PROTEIN SYNTHESIS INHIBITORS

Macrolides, Aminoglycosides, Tetracyclines, Clindamycin, Cephalosporin, Streptogramins, Oxazolidiones (Linezolid), Daptomycin
Notice that only one class of drugs is **bacteriocidal**. This is the Aminoglycosides and Linezolid. **Everything else is bacteriostatic.** So whether it binds to the 30s, 50s, or inhibits anything along translation, it will be bacteriostatic EXCEPT when Aminoglycosides/Linezolid causes a **misreading of codes** making aberrant proteins.
1. **Discuss the mechanism of action of aminoglycosides.**

Aminoglycosides are particularly useful against *gram-negative* bacteria. They use *porins* and *oxygen-dependent transport mechanisms* to get into the cell. There, they bind to the **30s ribosomal subunit**. This prevents the binding of the 30s and the 50s to form the 70s, which makes translation never even start. It can also cause a **completed 70s ribosome** to misread the genetic code, resulting in an aberrant protein.

It blocks the **initiation complex**, it is tightly bound (covalent), and is **bacteriosidal** (unique amongst protein inhibitors). It is **static** if it only blocks initiation and **cidal** if it causes aberrant proteins.

2. **Describe the pharmacokinetic properties of aminoglycosides. Explain the importance of peak and trough levels.**

Aminoglycosides are **highly polar, cationic structures**. This makes them completely unabsorbable with poor CNS distribution. They cannot cross any barriers because they are polar, charged molecules. However, polar cations are prime candidates for **glomerular filtration**, where they are rapidly excreted without being metabolized.

In addition, Aminoglycosides are **concentration-dependent**. Some drugs work by being around for a long time where concentration doesn’t really change much (time-dependent). Aminoglycosides **increase their killing power with increases in dose** (on a range of 4-64 times the MIC). That means you can give a **single large bolus** without having to worry about maintaining plasma levels over an extended period of time.

3. **Discuss the dose adjustment for aminoglycosides in patients with compromised renal function.**

Because there is **no metabolism** and the drug is excreted **renal-ly**, in the case of renal dysfunction, the drug is going to hang around a lot longer than it normally would. There is a significantly increased risk of toxicity, since there is no way to get rid of the drug. Give **less drug for renal compromised patients**.

4. **Explain the mechanism of acquired drug resistance due to Aminoglycosides**

   **Diffusion.** There is either a **decreased porin** concentration or a **decrease oxygen-dependent transport**, that limits the amount of drug that can get into the bacterial cell.
Aminoglycosides

**Inactivation.** Plasmid-coded inactivation enzymes can be acquired through plasmid transfer. These are generally very specific for each glycoside, so that cross-resistant is unlikely. These are acetylation, phosphorylation, or nucleotide transfer enzymes. Basically, what happens is that these enzymes make Aminoglycosides more water soluble.

5. **Describe the therapeutic indications of aminoglycosides**
You can use Aminoglycosides to treat either gram positive or gram negative organisms. They are usually not given for meningococcal (meningitis) or pneumococcal diseases.

Gram Positives - Only when you get synergy with a cell-wall synthesis inhibitors can you treat gram positive organisms like Staph, Strep (not S. Pneumonia, but we don’t know why), Viridans, etc.

Gram Negatives - **Aminoglycosides are great at killing gram negative** (Pseudomonas, Klebsiella, Proteus, Serattia).

6. **Explain the rational basis for combination therapy with an aminoglycoside and a cell wall synthesis inhibitor.**

   Imagine the cell wall as a castle wall, with the fair maiden (the ribosomes) inside. The Aminoglycoside is the evil dragon who wants to eat the fair maiden. The cell-wall synthesis inhibitor (such as Penicillin G) is that Orc from lord of the rings II with the dynamite. He runs at the castle wall, blows a giant hole in it, allowing the dragon to run through and eat the maiden.

   Cell-wall synthesis inhibitors clear the way for the Aminoglycosides by removing the barrier to diffusion, allowing the Aminoglycosides to have greater effect.
Aminoglycosides

Note that you would only combine **Cell Wall Synthesis Inhibitors** (bacteriocidal) with **Aminoglycosides** (bacteriocidal). All others Protein Synthesis Inhibitors are bacteriostatic, and would produce antagonism.

**7. Discuss the main toxicities of aminoglycosides.**

**Ototoxicity** is directly related to high peak plasma levels and the duration of treatment. It can cause deafness, may be irreversible, and can affect the fetus. It is worse when applied with other ototoxic drugs such as Furosemide. It causes ototoxicity by accumulating in the endo and perilymph where it destroys the hair cells of the organ of corti.

**Nephrotoxicity** reabsorption of Aminoglycosides in the proximal tubules disrupts calcium balance, leading to minor or severe renal failure. If you stop the drug, the renal damage is reversible.

**Neurmouscular Paralysis** is rare, but is more prevalent in patients with myasthenia gravis. If you give calcium, you fix it. This is rare, and doesn’t sound like a question.

Key Points:

- Bactericidal
- Uptake is O$_2$-dependent (only aerobes!)
- Gram Negative Rods
- Streptomycin, neomycin, gentamicin, tobramycin, amikacin,
- Synergy with Cell-Wall inhibitors (open the gate, both cidal)
- Streptomycin = drug of choice for bubonic plague and tularemia
- Polar, Cationic Compounds that do not cross barriers, are excreted by kidneys (no exceptions!)
- Nephrotoxic, Ototoxic, Neuromuscular Blockade
- Concentration-Dependent Killing = Once-Daily Dosing
- Resistance = Conjugating Enzyme, making it even more water soluble so that its elimination increases and its ability to enter the bacteria is reduced
Mechanism of Action
- Binds to the A-site of the 30s ribosome that prevents the attachment of an incoming aminoacyl-tRNA preventing translation.

Clinical Uses
- Tetracyclines are all bacteriostatic. They are “broad-spectrum” antibitoices, with good activity against a wide variety of bacteria, mostly gram negative. It is able to get at most of the bugs that avoid most antibiotics.
  - These includes, *H. Pylori, Rickettsia, Borrelia Burgdorfi, Brucella, Vibrio*, as well as the atypical bacteria (*Chlamydia* and *mycoplasma*)
  - Macrolides are also protein synthesis inhibitors that have similar spectrums. You can think “whatever I can hit with Tetracyclins I can also hit with Macrolides”

Pharmacokinetics
- Kidney for most (our assumption holds)
- Except Doxycycline which is lipid soluble penetrating the BBB into the CSF, and excreted by liver.

You have to know these two points for the exam
- You NEVER give tetracyclines to pregnant women or children under 8
- Tetracyclines are chelators binding up calcium and magnesium, which also destroys its antibiotic characteristics, which means:
  - Eating dairy or calcium with tetracyclines prevents its absorption
  - Deposits in the bones and teeth causing permanent discoloration and bone retardation

Resistance
- Pumping efflux. Rather than preventing the entry of the drug into the bacteria, the bacteria pumps it out, preventing its accumulation in the cytosol, preventing the effective dose inside the bacteria.
Chloramphenicol

<table>
<thead>
<tr>
<th>3. Formation of peptide bond</th>
<th>Chloramphenicol (50S)</th>
<th>Inhibit the activity of peptidyltransferase (-static)</th>
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Aminoglycosides inhibited initiation; Tetracyclines inhibited adding the next aminoacyl-tRNA. The next step is **transpeptidation** where the new amino acid attached to the tRNA is tagged onto the already made strand. The drug that does this is Chloramphenicol.

Before we begin, here is a little tid-bit from Kaplan: Anything that has “phen” in its name has an aromatic group, and is lipid soluble. So, **Chloramphenicol** is lipid soluble, and it is able to cross the BBB, is heptatically processed. The same is true of acetaminophen which exacts in anti-pyretic effects in the brain.

**Activity and clinical uses:**
It is a **bacteriostatic** with a wide spectrum. It is highly toxic, so is not used in the US. (This drug will most likely be a distracter on the Tulane and Board exams; it is a “wrong” answer choice because we no longer use it). We don’t use it because it is so toxic.

It is a backup drug for **Rickettsia**, **Salmonella**, and **Bacteroides** (intracellular and anaerobic), with out-of-the-US use for meningitis by H. influenzae.

**Pharmacokinetics**
- It has good tissue distribution and bioavailability, penetrating the CSF
- requires **glucuronidation** (conjugation) in order to be secreted by the liver. Thus, patients with decreased liver function require dose restrictions. The obvious patient is **liver dysfunction**, but what will probably be asked is the **neonate**, since they have insufficient enzymes.
  - **Inhibitors of Cytochrome P450**

**Side Effects**
- Dose dependent **bone marrow suppression**
- “Gray Baby Syndrome” because neonates lack the glucornyltransferase enzyme, the drug accumulates and displaces bilirubin, which is why there is no use in infants.
- **Aplastic Anemia** – which is 80% fatal. Agarwal states that this is the reason why we do not use it anymore. Even though 1/40,000 patients experience the condition, and only 80% are fatal, the risk is too great when there are alternatives.

This drug is usually asked in two ways on the Boards, if not just a distracter. There will be a question about H. Influenzae and babies (since Chloramphenicol is used to treat H Influenzae Meningitis) or there will be a question about Chloramphenicol’s drug interactions through the P450 system.
When identifying Macrolides, do not look at the –mycin ending; that is too abundant. What you want to for is the –thromycin suffix as in Erythromycin, Clarithromycin, and Azithromycin. This will help you differentiate the Macrolides from other drugs. Many questions on Tulane exams can be gotten correct just by knowing the general class information. The difficulty, therefore, is remembering which class a particular drug belongs to, since the drug names will be the answer choices.

**Mechanism Of Action**

Binds to the 50s ribosomal subunit and inhibits translocation. It is bacteriostatic.

**Treatment/Uses**

Macrolides are wide-spectrum antibiotics, following the Tetracycline spectrum

**Erythromycin:**
- It works on gram positive just as well as it does atypical bacteria
- It is classically used on the boards for Legionella Penumophilia (Legionnaire’s disease)
- must be taken as a salt (Erythromycin Estolate) to be adequately absorbed.

**Azithromycin:**
- Mycobacterium Avium Complex with a similar spectrum to Erythromycin
- Has the least drug interaction.

**Clarithromycin:**
- newest of the family that is also good at treating Mycobacterium Avium Complex.
- Classically associated with H.Pylori (it is the second drug of choice, first drug of choice if there are penicillin allergies)
- Causes least GI effect

**Pharmacokinetics**
- Macrolides are the exception to the rule about antibiotics. In general, Macrolides are large, lipid solubule, and metabolized by the liver. Because they are lipophilic, they are also not safe in pregnancy.
- Inhibits P450.
- Large amount of food-sensitivity; acid in the stomach destroys Macrolides. Eating with medication causes delayed gastric emptying, and more time for the pH of the stomach to destroy the Macrolides.
- Azithromycin is the exception to the exception, and is like other antibiotics: water soluble, renal excretion, safest of the Macrolides in pregnancy, and does not inhibit P450.
Macrolides and Clindamycin

**Side Effects**
- Macrolides stimulate motilin receptors, so have an additive GI upset (diarrhea) effect. Its an antibiotic, and all antibiotics cause GI problems. Macrolides make it worse.
- Erythromycin can cause cardiac dysrhythmias and prolonged QT syndrome

**Resistance**
- Bacteria methylate bases in the RNA. Macrolide must recognize RNA binding sites. If methylated by methyl transferases, the Macrolide cannot recognize its target and cannot bind appropriately.

CLINDAMYCIN

Clindamycin is not a Macrolide. However, its mechanism of action as well as the mechanism of resistance is identical.

What Clindamycin does differently is its narrow spectrum focusing on gram positive cocci and anerobes (strep, staph, and Bacteroides). Like the Macrolides, it can be used in patients with penicillin allergies.

- Tulane: Used for endocarditis prophylaxis over erythromycin for dental procedures (Viridans group).
- Boards: Used for staph aureus osteomyelitis (the most common cause of infectious osteomyelitis except in sickle cell salmonella osteomyelitis).
These are the newest agents. They bind to the 50s subunit either interfering with the initiation (Linezolid) or the elongation (Streptogrammins). Daptomycin has its own unique binding site and effect. The purpose of knowing these drugs is as an alternative to Vancomycin, when vancomycin resistance develops.

**LINEZOLID**

It inhibits the formation of initiation complex just like an Aminoglycoside, but does it from the 50s side. Because there is no resistance to it yet, the use of this drug is reserved for the treatment of Vancomycin resistant Staph and Enterococcus (which inherently means Methicillin resistant as well). This is an end-drug that we don’t want to have resistance develop for. That would be bad.

It causes **bone marrow suppression**.

The Boards love the mechanism

**STREPTOGRAMMINS (combination of Quinupristin and Dalfopristin)**

They bind to the 50s ribosome subunit and prevent the tRNA from interacting with the A site. If it’s already attached, it causes it to dissociate, effectively inhibiting elongation. It is bacteriostatic. It is used to treat VRE and VRSA.

**DAPTOMYCIN**

Has a unique mechanism of action which involves binding to and depolarizing cell membranes leading to lysis from electrolyte (K) disturbances. It is also used for the treatment of VRSA and VRE, but is indicated for complicated skin & soft tissue infections as well as right sided endocarditis.

You might say, “there’s not a lot here” and you would be right. They are new, sexy drugs that have very specific uses. Since we don’t know a lot about them, you don’t have to know a lot about them. They are very high-yield, which is good, because there is not a lot to know.
Interference with DNA: Indirect = Sulfonamides

There are two ways of interfering with screwing with nucleic acid synthesis. **Indirectly** through interference with Folic Acid (which is required for most nucleic acids) or **directly** with enzymes of transcription (RNA) or replication (DNA).

**Indirect route:**

Know this diagram. There has been this diagram on the boards. Clarkson has referred to it on practice quizzes. There are two enzymes that can be the target of drugs.

Folic acid is a vitamin for a human. Bacteria **can synthesize folic acid.** They do this by combining two molecules (Pteridine and PABA) via the enzyme **dihydropteroate synthetase** which is a **prokaryotic enzyme** that is targeted by sulfonamides.

Dihydropteroic Acid combines with Glutamate to eventually become Dihydrofolic Acid. The next conversion, via dihydrofolate reductase, should be familiar from Biochem. Humans **do possess this enzyme** as well as bacteria. Thus, inhibiting dihydrofolate reductase can effect human cells as well. There is an **anti-cancer drug, Methotrexate,** that selectively inhibits **eukaryotic DHF reductase.** Well, the drugs listed, **Trimethoprim** and **Pyrimethamine selectively inhibit prokaryotic DHF reductase.** They are not specific, they are selective.

When you have two drugs along a pathway, it makes sense to use them together. Using them in combination will obtain **synergy** and a **decreased resistance.**

**Uses**

You never used Sulfonamides by themselves. You always use them in conjunction. The most common is Trimethoprim-Sulfamethoxazole.

**Trimethoprim-Sulfamethoxazole** (called Bactrim) is the **drug of choice for nocardia,** for mycobacteria and gram-negative infections. However, we put a big red star next to and around **Pneumocystis Carinii Fungal Infections,** which is the hallmark opportunistic infection of AIDS.

**Pharmacokinetics**

- Acetylated in the liver and then renally excreted.
- Metabolism makes the drug **less water soluble,** which means the risk of developing **kidney stones** increases. If you **stay hydrated,** the risk of **crystalluria** is decreased.
- **High Protein Bonding.** Sulfonamides bind to plasma proteins (like **albumin**) displacing other proteins normally contained there. This is a particular problem for babies.
**Babies**

Neonates have two problems

1. They **cannot conjugate** well, their liver is poorly developed. Remember that for chloramphenicol? So if they cannot conjugate well, and acetylation is a conjugation step, then the Sulfonamides will accumulate in these kids.

2. When it does, **sulfonamides displace bilirubin** from albumin, causing an increased level of bilirubin free in the blood. This can cross the BBB and cause **kernicterus** (toxic encephalopathy).

Both Bilirubin and Sulfonamides compete for conjugation and albumin.

DON’T GIVE SULFONAMIDES TO KIDS!

**Side Effects**

- Hypersensitivity = **Steven-Johnson Syndrome** (Type IV hypersensitivity)
- **Hemolytic Anemia** in patients with **G-6-P Deficiency**. Only in the case of ingestion of free-radical inducing compounds (fava beans, quinilones from biochem) do these patients suffer bouts of hemolytic anemia. Well, **sulfa drugs** cause it too.
- Trimethoprim and Pyrimethamine effect human cells. This can cause problems with rapidly dividing cells (like the gut and the bones). This is low-yield Tulane, high-yield Boards.
Interference with DNA: Direct = Quinolones

Quinolones are easy to recognize, ending in -floxacin (norfloxacin, ciprofloxacin, ofloxacin)

**Mechanism of Action**
Quinolones basically prevent DNA replication from happening. They do this by inhibiting topoisomerase II (DNA Gyrase) and topoisomerase IV. DNA Gyrase is responsible for closure of DNA, so that inhibiting it leaves single-stranded DNA hanging around, which gets degraded. Destroying DNA = killing the cell, so these drugs are bactericidal.

**Clinical Uses**
By far, Cipro is used in UTIs (especially with sulfa allergies) and STDs (gonorrhea and Chlamydia can be treated with PO Cipro instead of IV 3rd generation Cephalosporin). In fact, if you got a UTI in undergrad, you were probably prescribed Cipro (more relevant for the ladies than the guys).

This can also be used against Methicillin resistant and Methicillin Susceptible strains of Staph.

Finally, this can be used to treat diarrhea caused by shigella and salmonella.

**Pharmacokinetics**
No surprises here, they are water soluble, renally excreted, and require dose adjustment for renal impairment.

**Side Effects**
You have a drug that inhibits replication that can go into bones and cartilage. What’s going to happen if you give it to kids? Well, you are going to get joint swelling and bone malformation. DON’T GIVE THIS TO KIDS OR PREGNANCIES. Usually you wait until after the growth spurt finishes to give Quinolones (even adults can have tendonitis and tendon rupture) but the technical age is 8 years old.

- All quinolones can cause increased QT intervals and arrhythmias.
Introduction to Antifungals

Until the advent of HIV there was not much need for systemic antifungals. Fungi usually infect immunocompromised patients. There can be the common topical infections (athlete’s foot, jock itch) but deep-seated systemic infections were fairly rare. Now with the ability to birth severely preterm neonates, and the spreading of HIV/AIDS, many patients are prone to infection with funguses.

A problem with treating fungi is that they are eukaryotes. That means that they are similar to humans both biochemically and structurally. It was much easier to be selective for bacteria than it is for fungus. So the goal is to identify the uniqueness in fungi and develop antimicrobial agents that exploits those differences. Alternatively, we can accept the risk of damaging human cells at the benefit of beating a nasty infection. That means toxicity and a limited repertoire.

There are 3 classes of drugs that effect the membrane. They do it either by interaction with or inhibition of ergosterol (the fungus version of cholesterol). (1) Allylamines (Terbinafine and Griseofulvin) along with (2) Azoles actually inhibit ergosterol synthesis while (3) Polyenes (Amphotericin B, Nystatin) interact with ergosterol to be fungicidal.

Flucytosine is in a class all of its own and is capable of disrupting RNA and DNA synthesis. This usually used with Amphotericin B.

Finally, which didn’t make the Kaplan cut but are found in BRS and your drug list, are the echinocandids. They are a new class of drug that targets cell wall synthesis. Yes, fungi have cell walls, humans don’t. Let’s kill the fungus and leave the mammalian cells with hardly any damage. This is great! Dead fungus with little side effects. Its new, so is Tulane Relevant, not so much for the Boards.
Polyenes

**Polyenes = Amphotericin B** is the prototype, and honorable mention **Nystatin**

| MOA: Binds ergosterol, makes pores |
| Resis: Decrease ergosterol in membrane, sterol switch |
| Use: Drug of choice for severe systemic infection |
| Pharm: No crossing BBB, IV administration, Water Soluble |
| SE: Severe Nephrotoxicity, acidosis, anemia |

Amphotericin B interacts with **Ergosterol**. Ergosterol is the fungal equivalent to Cholesterol. Just like we use cholesterol in our membranes, the fungus uses ergosterol. This is an interaction with ergosterol opposed to the inhibition of azoles. **Amphotericin B binds to ergosterol** creating pores in the membrane, leading to osmotic damage and fungal death. Kaplan made a big deal about this. Well, if ergosterol is the target, and the fungi are going to develop resistance, then the way they do it is by changing their ergosterol to **another sterol**. This is very similar to the Penicillin Binding Protein alteration of Methicillin Resistant Staph.

Amphotericin B has a wide fungicidal spectrum. Since **all fungi have ergosterol** in their membranes, **all fungi are susceptible to amphotericin B**. It has the widest antifungal action of all the antifungal medications. It is usually used as a **co-drug** (with flucytosine) to limit toxicity and resistance. It **remains the drug of choice** for severe infections caused by *Aspergillus, Candida, Cryptococcus*, and *Histoplasma*. These are the big guy fungi to know.

Remember the assumptions we made about pharmacokinetics way back in penicillins? Well it holds true for amphotericin. They are **water soluble**, ideal for administration via IV, and is excreted by the renal system. However, the down side is that **it does not cross the BBB**. Yet we can use it for cryptococcal meningitis by injecting amphotericin B **intrathecally**.

The **half-life** of amphotericin B is **two weeks**. Which means it’s going to work for a long time after one administration. Unfortunately, if it starts causing side effects, you are stuck with those side effects for a long time.

Of the side effects, we worry about the **dose dependent Nephrotoxicity**. If you wanted a drug that could mess up the patient’s kidneys, this is it. It causes a reduction in GFR and tubular necrosis. Tubular necrosis means electrolyte disturbances and pH imbalances (**acidosis** and **hypokalemia/magnesia**). So severe is the Nephrotoxicity it can actually cause an **anemia via downregulation of erythropoietin** (that renal hormone that caused RBC production)

**Amphotericin B** is the prototypical drug of the polyenes which interact with ergosterol forming pores leading to osmotic damage, but risk severe Nephrotoxicity.

Nystatin is a polyene. However, it is **too toxic** for use in systemic infections. Therefore, it is only used **topically** to treat **candida** in the **vagina or oral mucosa**
Azoles (Ketoconazole, Fluconazole, Itraconazole) Aptly named with “azole” as their suffix.

**Mechanism and Resistance**

These **interfere** with the **synthesis of ergosterol** by inhibiting **14α-demethylase**, a fungal P450 enzyme. It’s a P450 enzyme of the fungus which converts **lanosterol to ergosterol**. These are **fungistatic** but can be fungicidal at higher doses.

Resistance occurs via **decreased intracellular accumulation of azoles** (just like the tetracyclines). This occurs through **transporters** that **pump the drug out of cells**.

**Pharmacokinetics**

While these drugs are **effective orally**, they are **weak acids** and are very susceptible to Food and pH. When the pH goes up, the absorption goes down. Administration of **Antacids** or the **consumption of food decreases absorption**.

* Only **fluconazole** penetrates the BBB into CSF.

**Metabolism & Side Effects**

You inhibit a fungal P450. Funguses are eukaryotes. Humans are eukaryotes. Humans have P450. Ketoconazole and Itraconazole are both **metabolized by the liver** and **inhibit P450** in humans.

You inhibit fungal steroid synthesis (the ergosterol). Fungi are eukaryotes. Human are eukaryotes. Humans make steroids (from cholesterol). With azoles, we see a **decreased synthesis of steroids** (coritsol and aldosterone), the things that rely on cholesterol synthesis.

**As far as the drugs:**

**Ketoconazole** is important to know as the prototype. It can be injected systemically for fungal infections, but cannot penetrate the CSF. This is why you are better off focusing on Fluconazole.

**Fluconazole** is drug of choice for **most fungal infection**. It is **less toxic than amphotericin B** and is **able to penetrate the BBB**. So highly recommended is this drug that it is recommended for prophylaxis and suppression of cryptococcal meningitis.

**Itraconazole** blastomycoses and sporotrichoses. It does not cross the blood brain barrier.
Griseofulvin and Terbinafine

These drugs are administered systemically for topical infections. These drugs are low-yield Boards. This includes only the really high yield stuff; you have to know your drug list.

**Griseofulvin**

It is only active against dermatophytes and goes where keratin goes. This means hair, skin and nails is where you will find Griseofulvin. Makes sense that it effects dermatophytes… fungi of the skin.

It interferes with the microtubule structure required for mitosis and is therefore fungistatic.

It is an inducer of P450.

The distribution in keratin is the usually Board test point. Remember that it is taken orally, goes systemic, and treats topical infections.

**Terbinafine**

You’ll remember Terbinafine from those commercials. Don’t let Digger the Dermatophyte give you toe fungus! (ok, so not ALL high-yield only)

This is pretty much a better Griseofulvin; same target, different mechanism, less side effects.

Its mechanism is the inhibition of squalene epoxidase which decreases ergosterol synthesis. Unfortunately, it is only effective against dermatophytes (like Digger).

It is highly lipophililc and accumulates in the hair, skin, and nails. Even though this follows the same pattern as Griseofulvin, it does not follow keratin like Griseofulvin.

It belongs to the class of drugs called allylamines which neither Tulane nor Kaplan talked about.
Flucytosine and Echinocandids

**Flucytosine** (often Board tested related to its nucleotide biochemistry)

Flu-cytosine is a **fluorinated cytosine**. It is also a **prodrug**. It must be **deaminated to fluorouracil** before it can be effective. The resulting compound is 5-Flouro-Uracil (5-FU). Where else have you seen 5-FU? Yep, pharmacogenomics lecture as an **anticancer drug**. Well, if you can kill eukaryotic cancer cells, why can’t you kill eukaryotic fungal cells? Well, you can!

Flucytosine is activated by a **fungal cytosine deaminase** to form 5-FU. After **triphosphorylation** to a nucleotide it is incorporated into **fungal RNA** which prevents RNA synthesis.

5-FU is also going to interfere with thymine synthesis. It can form 5-fluorodeoxyuridine Monophosphate (5-Fd-UMP) which **inhibits thymidylate synthase reducing thymine**, interfering with DNA synthesis. So it screws up **both DNA and RNA synthesis**. Put a star next to thymidylate synthase.

It is used **coadministered with Amphotericin B for cryptococcal meningitis**. Unlike Amphotericin B, it is able to cross the BBB into the CSF. Use of Flucytosine on its own results in rapid resistance, **DON’T USE IT ON ITS OWN**!

Unfortunately, it works pretty well on humans, so is toxic to tissues with rapid turnover: the GI tract and Bones. It causes a **dose dependent bone marrow suppression**.

**Cell Wall Inhibitors (Echinocandins): Caspofungin**

Fungi have cell walls, just like bacteria. Humans don’t have cell walls. So, if we can target the fungus cell wall, we can kill it without having the drug effect mammalian cells. Great.

Fungal cell walls are maintained by **glucans**. The cross-linking of **1,6glucan** and **1,3glucan** stabilizes the cell wall. In the membrane is **1,3-Glucan Synthase**, a molecule that builds 1,3glucans. If you inhibit that enzyme, the cell wall falls apart, and the fungus succumbs to osmotic forces. This is like a penicillin for fungi!

They are finding use in against **Candida** and Fluconazole-Resistant **Aspergillus** and **Penumocystis Carinii**.

The pharmacokinetics are pretty beneficial. A **half life of 10 hrs** means once a day dosing. The clearance isn’t so well understood yet, but it definitely involves the liver.