Antibiotics – Part 1

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Antibiotics – Outline and Goals

Antibiotics are probably the most important drug class – many of your patients will need antibiotics, you have taken several different antibiotics, and your family members will expect you to prescribe the correct ABx when needed! This is a difficulty topic, and you are not going to learn it all at once. The approach we will take is this:

1. This lecture covers antibiotics basics – what are ABx, how do they work, the major ABx classes, mechanisms of resistance, major side effects and typical applications.
2. After this lecture, you will have a series of lecture on specific pathogens, and each lecture will refer to specific ABx that can be used to treat the pathogen being discussed.
3. I will give an Antibiotics II lecture right before the exam – this will serve as a review
4. You will hear about ABx during the organ blocks next semester
5. You will have an infectious diseases course right before you hit the clinics, and this will have two ABx lectures.

This is what we want you to learn in this course:

- Know the major ABx classes
- Know the mechanisms by which ABx work
- What are the general uses of ABx classes?
- Drugs of choice: there are some pathogens for which there is one ABx that is almost always used – you need to learn these
- Major or unusual side effects
- Key resistance mechanisms
- The names – we won't expect you to know these in detail, but you should start learning these commonly used drugs – we will tell you which ABx are most commoly used at HUP.

Antibiotic Characteristics

- Antibiotics are substances produced by a micro-organism, typically a fungus or bacteria, that inhibits the growth of some other microorganism.
- These days, many antibacterials are based on a naturally occurring compound but they are chemically modified to extend their range of action, to improve potency and pharmacokinetics (penicillin G is inactivated by the low pH in the stomach, whereas penicillin V is acid-stable due to some chemical modifications and so can be taken by mouth), and to avoid resistance mechanisms.
- Antibiotics are low molecular weight compounds that have a specific spectrum of activity that is related to a specific mechanism of action. Due to this specificity, they are generally well tolerated by the host.
  - Narrow spectrum: specific against a few bacteria
  - Broad spectrum: active against many different bacterial types
- Therapeutic index: lowest dose that is toxic to the patient divided by the dose used to typically treat a patient – the larger the index, the better.

General types of adverse events

- Allergic reactions: hypersensitivity to a specific drug. The beta-lactams (penicillin is an example) are a good example of this.
- Toxic effects: can be drug specific. Gentamycin can be nephrotoxic, for example.

- Suppression of normal flora. The gut flora are important for human health, and the GI bacteria lecture will cover this. One reason to use narrow-spectrum antibiotics is to avoid disruption of normal flora, which can enable pathogens to take hold.

How do disinfectants differ from antibiotics?

Disinfectants (such as a detergent or a peroxide) have a nonspecific mechanism of action and so are broadly active - they are also not tolerated by the host. Usually need a higher concentration (relative to antibiotics) due to lack of specificity.

How do antibiotics kill bacteria or inhibit bacterial growth?

There are five major mechanisms by which antibiotics work:

1. Inhibit cell wall synthesis: this is the most common mechanism
2. Inhibition of protein synthesis: this is the second most common mechanism
3. Inhibition of nucleic acid function or production
4. Disrupting metabolic pathways, like folate metabolism
5. Disruption of the cell membrane (not the cell wall, but rather the membrane).

Knowing the mechanism gives you general clues as to usage:

- The bacterial cell wall is far more prominent (and exposed) in gram positive organisms. Thus, drugs that target the cell wall usually do a good job of hitting gram positives, and less effective at hitting gram negatives.
- Drugs that target the cell membrane typically inhibit gram negatives to a greater extent than gram positives as the membrane is on the outer surface of gram negatives.

The Basis for Antibiotic Selective Toxicity - 1. Absence of target from the host

Antibiotics are, by definition, selective. There are three major mechanisms that confer selectivity to antibiotics. The first is absence of the target from the host - our cells do not have a cell wall, so antibiotics that target the cell wall are selective and, in general, are very well tolerated. They have a high **therapeutic index.** Digoxin, which is used to treat heart failure, has a therapeutic index of 2 to 3, so you have to be very careful with dosing. Antibiotics often have therapeutic indices of 100 or more.

The Basis for Antibiotic Selective Toxicity - 2. Permeability differences

Some antibiotics are taken up by bacteria, but are taken up poorly by our cells. This results in selectivity, but also generally means that the drug needs to be given IV and not by mouth. Gentamycin is a good example (more on this later).

The Basis for Antibiotic Selective Toxicity - 3. Structural differences in the target

Bacterial ribosomes are sufficiently different from our ribosomes to make selectivity possible. Our ribosomes have two subunits, termed 40S and 60S (this is a measure of size). Prokaryotic ribosomes have 30S and 50S subunits (they are a bit smaller), and there are antibiotics that bind to each and inhibit their function.

Now that you have a specific drug, what happens?

Antibiotics can be **bacteriostatic**: they reversibly inhibit bacterial growth. Drugs that target metabolic processes typically fall in this category - they are competitive inhibitors with normal metabolites. In the example on the slide, bacterial growth rate is monitored over time. When penicillin is added, the bacteria die (it is bactericidal). When chloramphenicol is added, growth is arrested (this drug blocks protein synthesis). Growth resumes when the drug is removed.

Antibiotics can also be **bactericidal**: they kill bacteria. For a bactericidal effect, the bacteria typically need to be growing actively. This is a major issue with mycobacteria (they cause TB) because they grow very slowly.

Bacteriostatic vs. Bactericidal

In general, drugs that target the bacterial cell wall or membrane tend to be bactericidal, whereas those that target metabolic processes tend to be bacteriostatic. I would just keep this general principle in mind, since whether a drug is static or cidal depends on the organism and can depend on how rapidly it is growing. Bactericidal drugs are clearly more beneficial for certain situations, such as bacterial meningitis and endocarditis where you really need to treat aggressively.

Determination of Antimicrobial Activity – Susceptibility testing

As students, you will send patient samples to the clinical microbiology lab to see if they can culture an organism. If so, the lab will then test the organism for its sensitivity to various antibiotics. **Minimum Inhibitory Concentration** is the lowest concentration of an antibiotic that effectively inhibits growth of a microorganism. There are various ways to test susceptibility of bacteria to various antibiotics - I'll mention two.

- **Tube Dilution Assay for Antibiotic Sensitivities.** Bacteria are grown in small cultures in the presence of different concentrations of antibiotics - this tells you sensitivities of a given bacterial isolate to a range of drug concentrations.

- **Disc Diffusion Method.** The bacterial isolate is spread over a plate - over time, it will grow to form a 'bacterial lawn', which will turn the plate cloudy. Small, antibiotic impregnated discs are placed on the agar, and the drug diffuses into the agar. If the bacterial isolate is not sensitive to the antibiotic, it will continue to grow and you will see the cloudy area all around the disc. If the strain is sensitive, you see a clear area - the width of the clear area is related to the MIC. <u>This does not tell you if the drug is bacteriostatic of bactericidal.</u>

Situations Warranting Combined Antibiotic Therapy

Now that you have cultured a pathogenic bacteria from your patient and determined its antibiotic sensitivity, what do you do? Generally, you use one drug whenever possible, and you use the simplest drug possible to minimize the evolution of drug resistance; you also take into account things like side effects and tolerability. There are some cases where you might prescribe two or more antibiotics:

- Chronic infections. Using two or more drugs may limit the emergence of drug resistance
- Emergencies. You have a gravely ill patient, and you need to treat - you can't wait for culture results let alone drug sensitivities
- Mixed infections. Some infections, particularly wounds and abdominal infections, can be caused by mixed infections

- Drug synergies. With time, you will learn that certain drugs are more effective when used in combination than when used alone.

Drug-drug interactions

If you use more than one drug, you should be aware of possible drug interactions. Potentially, you can have four different outcomes:
Indifference: The two drugs have no effect on each other
Additive response: The response you achieve is the same as the sum of the two drugs used individually.
Synergistic Response: The response you achieve is greater than the sum of the two drugs used individually. Here are two practical examples:

Example of synergism: Bactrim is sulfamethoxazole used in combination with trimethoprim. Sulfamethoxazole inhibits the production of tetrahydrofolic acid, but does not prevent utilization of existing pools. Trimethoprim does not inhibit new synthesis of tetrahydrofolic acid, but does inhibit utilization of existing pools. Trimethoprim by itself has little to no antibacterial activity. However, the combination of sulfamethoxazole and trimethoprim together is synergistic.

Augmentin is a combination of amoxicillin, an extended spectrum penicillin, and the beta lactamase inhibitor clavulanic acid. On its own, clavulanic acid has no antibacterial activity. Amoxicillin in turn has no or little activity against a bacterial strain that produces an appropriate beta lactamase. Combining the two drugs makes for an effective combination.

Antagonistic response: The response you achieve is less than the sum of the two drugs used individually. This is relatively rare. A practical example is the use of penicillin (bactericidal) and erythromycin (bacteriostatic - this drug inhibits protein synthesis) in some cases. By slowing bacterial growth, erythromycin makes penicillin less effective: drugs like penicillin that disrupt the cell wall need bacterial growth in order to be effective. If erythromycin is used first, or gains access to the infected site first, it will make subsequent application of cell wall inhibitors less effective.

Sometimes treatment does not work - Factors that can limit successful antimicrobial therapy.

- Location: drug access can be an issue - many drugs fail to cross the blood-brain barrier that can limit drug access; some bacteria that you will learn about have an intracellular phase - some drugs may not penetrate eukaryotic cells.
- Abscess formation and necrosis - decreased circulation in the area of an abscess will limit drug concentrations; low nutrient levels may slow bacterial growth that makes some antibiotics less effective.

Example: Necrotizing pneumonia with abscess formation.

The slide shows a chest film, a CT scan, a slice of a lung and two micrographs showing a severe focus of pneumonia associated with necrosis (cell death) and abscess formation. It would be very hard to deliver effective concentrations of drug to the involved area.

Sometimes treatment does not work - Factors that can limit successful antimicrobial therapy.

- Presence of foreign bodies and obstructions. Some bacteria can adhere to artificial surfaces, such as catheter tips, and make a biofilm (recall Dr. Decatur's earlier lecture). Any foreign body can serve

as a nidus for infection, and some elicit their own inflammatory reactions that can limit drug access. These are often called foreign body granulomas, and are marked by the presence of multinucleated giant cells.

- The emergence of drug resistance - this is extremely important, and general mechanisms of resistance are listed on the slides to follow.

1. Enzymatic inactivation of the antibiotic. Many bacteria produce an enzyme called a beta lactamase that cleaves the beta-lactam ring present in penicillins, cephalosporins and carbapenems.

2. Inadequate or decreased uptake of the drug into the microbe. Drugs that inhibit metabolic functions need to gain entry into the bacterium, and often do so via porin proteins. These can be mutated.

3. Increased efflux of the antibiotic out of the microbe. Getting into a bacteria is just the first step - the drug needs to stay there. Bacteria can express multidrug efflux systems - protein complexes that form pores in the membrane and that actively (using energy) transport certain small molecules (like antibiotics) out of the cell.

4. Alteration of the drug target. Penicillins bind to penicillin binding proteins, which are the transpeptidases responsible for cross-linking the peptidoglycan layer. Mutations in PBPs can disrupt drug binding.

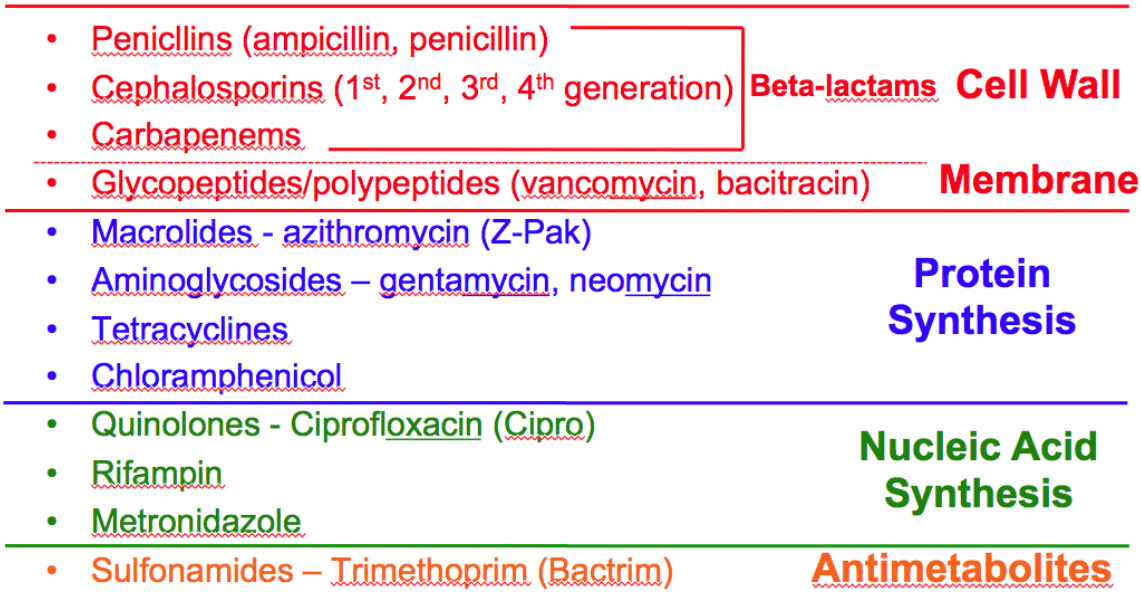
5. Altered metabolic pathways. New enzymes can be expressed or acquired that enable a bacteria to utilize an alternative metabolic pathway that enables it to escape the effects of a drug.

Questions you should always ask before prescribing antibiotics.

- Are antibiotics even needed? Not if it is a viral infection!
- Any allergies?
- Community or hospital acquired. If the later, chances of drug resistance are greater.
- Is the patient immunocompromised? If so, your differential diagnosis expands to more unusual organisms, and you have to treat more aggressively since the patient's immune system is compromised.
- Any positive cultures? If so, then you know what you are treating and what you should treat with – be as narrow-spectrum as possible.
- Is combination drug therapy needed? It is for mixed infections, chronic infections
- How serious is the infection? If life threatening, you need to treat more broadly since you can't run the risk of guessing wrong.
- Cost! Some newer ABx are very expensive

Bring on the drugs.

These are the drug classes that we will cover, broken down by mechanism of action. There are several other drug classes, but we will cover these 12:



Drugs commonly used at Penn

HUP has treatment guidelines for antimicrobial therapy with preferred drugs for certain drug classes and clinical situations. There are about 40 antibiotics listed, so one approach you can take is to study the drugs that you will encounter most frequently at Penn. **We will not expect you at this early stage to memorize the names of the cephalosporins – you should know the general properties of the 'generations', but not the specific names.** Of course, others are used, but the ID Division and Clinical Micro laboratory and infection control specialists have developed best practices for our physicians to follow. To limit the evolution of drug resistance, ABx need to be used with care. Those that are ***in bold and italics*** are controlled - i.e. you can't prescribe these without the OK of an ID specialist. Sometimes, this is due to side effect issues, but more commonly these are today's heavy-hitters - drugs that work against commonly encountered drug-resistant organisms. The last thing we want is for resistance to develop to these drugs, so their use her is carefully controlled.

The most commonly used anti-bacterials at UPenn
Drugs in bold/underline/italicized need ID approval before use

• Penicllins:	
– Natural	Penicillin
– Penicillinase-resistant	Oxacillin, naficillin, dicloxacillin
– Extended-spectrum	Amoxicillin, ampicillin, pipericillin
– With beta lactamase inhibitor	Amoxicillin/clavulanic acid, ampicillin/sublactam, pipericillin/tazobactam
• Cephalosporins	
– 1st generation	Cafadroxil, Cefazolin, Cephalexin
– 2nd generation	Cefuroxime
– 3rd generation	Cefixime, Cefotaxime, ***Ceftazidime***, Ceftriaxone
– 4th generation	Cefepime
• Carbapenems	***Meropenem***
• Glycopeptides/polypeptides	Vancomycin, ***Colistin***, ***daptomycin***
• Macrolides	Azithromycin, clarithromycin, erythromycin
• Aminoglycosides	Amikacin, gentamicin, streptomicin, tobramicin
• Tetracyclines	Tetracycline, doxycycline
• Chloramphenicol	***Chloramphenicol***
• Quinolones -	***Levofloxacin***, norfloxacin
• Rifampin	Rifabutin, Rifampin
• Metronidazole	Metronidazole
• Sulfonamides	Sulfadiazine, Trimethoprim-sulfamethoxazole

Review of gram negatives and gram positives

Gram positives have a thick, exposed peptidoglycan layer, while gram negatives have a thinner peptidoglycan layer that is beneath an outer membrane. From Amy Decatur's lecture, recall that the peptidoglycan wall has repeating units of disaccharides that are cross linked to each other via peptide bonds. A bacterial enzyme, **transpeptidase**, catalyzes formation of these cross-links.

Penicillins bind to transpeptidase, so these enzymes are also referred to as **penicillin binding proteins (PBPs)**.

How beta-lactam antibiotics work.

These antibiotics bind to transpeptidase and inhibit its function - they are competitive inhibitors. They do not destroy existing cross-links, but prevent formation of new ones. In general, these ABxs are more effective against Gram-positive bacteria because that wall is exposed. Some have activity against Gram-negatives, but for this they have to be able to cross the bacterial membrane. Beta-lactams are bactericidal, and work more effectively against rapidly growing bacteria.

Penicillins.

Very effective drugs that are very well tolerated - originally obtained from a mold, there are now three major classes of penicillins. They all share a common core structure, shown on the slide. The most significant feature is **the beta-lactam ring**, which is the four-sided ring with a nitrogen in it.

You should know what a beta-lactam ring is – penicellins, cephalosporins, carbapenems and monobactams (these are not covered here) all have this structure as well. The addition of different side groups (where the 'R' is) can alter the properties of the drug.

The penicillins, cephalosporins and carbepenems are drug classes that target the bacterial cell wall. They ALL contain a beta-lactam ring, and so are called beta-lactam antibiotics.

Penicillins - 3 classes.

Natural Penicillins:

Penicillin G - inactivated by low pH so is given IV

Penicillin V - acid stable, so can be taken PO

Penicillinase-resistant penicillins:

Methicillin, Oxacillin, Naficillin, Cloxacillin, Dicloxicillin

These are resistant to beta-lactamases, and were developed to combat Staph.

Extended Spectrum Penicillins:

Ampicillin, Amoxicillin, Carbenicillin, Pipericillin

Much improved activity against gram-negatives, but less effective against gram positives. Often used with beta lactamase inhibitors.

Side effects of penicillins

These are safe drugs with one significant side effect: hypersensitivity reactions. These can be severe, causing anaphylaxis, and can become more severe if a person is exposed to these drugs multiple times. Before administering a penicillin, you have to ask if there is a history of having taken these drugs before. Penicillin reactions can include hives, a skin rash that can be variable - it can be maculopapular like measles, or can be more raised (hives). Other common reactions can include itchy skin, wheezing, swollen lips. Any of these can occur quickly, but more commonly it takes a while, sometimes over a day or two.

Anaphylactic reactions to penicillin occur immediately, and include difficulty breathing, decreased blood pressure (which leads to rapid and weak pulse and dizziness), swelling of throat and tongue. Nausea and vomiting are NOT allergic reactions to the drug

Beta-Lactam Resistance – 3 Mechanisms:

1. Beta lactamases are produced that destroy the drug
2. Transpeptidase (the major PBP) acquires a mutation that prevents drug binding
3. Gram negatives: can have membrane pumps that remove the drug from the periplasmic space

Beta lactamase inhibitors

Little or no antimicrobial activity on their own, but can make beta lactam antibiotics more effective by binding to and inactivating beta lactamases. There are a number of these, including clavulanate, sulbactam and tazolbactram. Common combinations are:

Amoxicillin-clavulanate (a common trade name is Augmentin)
Ampicillin-sulbactam

Piperacillin-tazolbactam (Zosyn is a common trade name)
Ticarcillin-clavulanate (Timentin is a common trade name)

Natural Penicillins - Typical Uses

- Drug of choice for community-acquired Strep, pneumococci, meningococci,
- Treatment of choice for syphilis (a spirochete).
- Not effective against Staph due to drug resistance.

- Penicillin G: inactivated by acid, so given IV
- Penicillin V: acid stable, take PO

Beta-lactamase-resistant Penicillins - Oxacillin, Methicillin, Naficillin

Resistant to the beta lactamases produced by Staph; very narrow spectrum with no gram negative coverage. However, many strains of Staph are now resistant to these drugs. You have likely heard of MRSA (pronounced mersa) - many staph strains are now resistant to methicillin (they have picked up a new beta lactamase), and so **oxacillin is now used to treat staph.** However, resistance to this is also increasing.

Extended Spectrum

Ampicillin/Amoxicillin. These are rather similar to natural penicillins, but can cross the membranes of some gram negatives and inactivate their transpeptidase enzymes. **Often used for uncomplicated urinary tract infections, otitis media, and community acquired pneumonia, H. flu and Listeria meningitis.**

Ticarcillin, Mexlocillin, Piperacillin. These have very nice coverage of gram negatives, but at the expense of not hitting gram positives as effectively. They are still sensitive to beta lactamases, which is an issue.

Summary:

Natural penicillins: Good against strep, meningococci, spirochetes, most other gram-positive. NOT good for staph.

Penicillinase-resistant penicillins: Very similar to natural penicillins but are resistant to penicillinase and so were first line therapy against staph infections. But, presence of resistance to these drugs is increasing, aka methicillin-resistant staph.

Extended spectrum penicillins: Still pretty good against gram positives, but now with coverage of many gram negatives. UTIs, otitis media, community acquired pneumonia, H. flu, Listeria.

Penicillins that are coadministered with beta lactamase inhibitors. I referred to this when talking about drug synergism - a beta lactamase inhibitor is coadministered with an extended spectrum penicillin, giving the best coverage possible.

Cephalosporins

Same mechanism of action as penicillins (inhibit peptidoglycan synthesis via PBPs) with:

- –Wider antibacterial spectrum
- –Resistance to many beta-lactamases
- –Improved pharmacokinetics

- -Bactericidal
- They have a beta-lactam ring
- Adjoining ring differs from penicillins (this is sometimes asked on the boards)
- Different 'R' groups alter characteristics

Cephalosporins

- In general, are resistant to beta-lactamases produced by Staph and common gram-negatives
- Do not cover enterococci
- Described as "generations" from first generation (oldest) to fourth. Newer generations have better gram-negative coverage and poorer gram + coverage
- Can induce hypersensitivity reactions just like penicillins
- 5% of patients with penicillin reactions have reactions to cephalosporins as well

Cephalosporins - 1st generation

- Start with 'ceph' except for Cefazolin and Cefadroxil
- Very active against gram positives including staph (but not MRSA).
- Moderate against some gram negatives, esp. E. coli and Klebsiella
- Used for community acquired UTIs and respiratory infections
- Cefazolin is used for surgical prophylaxis

Cephalosporins - 2nd generation

Used for Otitis media in children
Increased activity, especially against gram negatives including *Haemophilus influenzae*
Respiratory infections, UTIs

Cephalosporins - 3rd generation

Less activity against Gram +, more effective Gram - coverage. Management of hospital-acquired gram-negative bacteremia, inpatient pneumonia and UTIs; some can penetrate CNS (unlike 1st and 2nd generation)

Single dose ceftriaxone is used for gonoccocal infections (to be covered in STD lecture)

Cefipime is the only licensed 4th generation cephalosporin in the U.S. Enhanced activity to enterobacter, can be used when resistance is seen to a 3rd generation drug.

Side Effects of Cephalosporins

•Overall relatively safe – in general, drugs that target the cell wall have a very high therapeutic index
•Hypersensitivity reactions just like penicillin
–Cross-allergy between penicillins and cephs about 5%
- Patients with significant PCN allergies should not be given cephalosporins, but if they have mild reactions one can risk it.
•Greater incidence of GI problems due to better gram negative coverage; can lead to *C. difficile* colonization and colitis

Resistance to Cephalosporins

Just like with penicillins! Same mechanisms.

Carbapenems
•Same mechanism of action as
•penicillins (inhibit PBPs) with:
–Wider antibacterial spectrum than other beta lactamases
–Resistance to beta-lactamases
–Improved pharmacokinetics
•Imipenem, meropenem, ertapenem, doripenem
•Bactericidal; usually given IV
•Highly active against Gram-positive, Gram-negative, aerobic, and anaerobic bacteria
•Often used as empiric therapy for critically ill patients; last resort for E. coli and Klebsiella infections
•Metabolized in kidney by dehydropeptidase. Blocked by cilastatin, which is sometimes coadministered.

These are powerful drugs - at Penn you need ID approval to use these, because if they are mis-used and resistance develops, we are in trouble. They are quite broad spectrum.

Beta lactam summary
•Common mechanism of action
•All have beta-lactam ring
•Generally more active against gram positives
•Variable coverage of gram negatives
•Common resistance mechanisms
•Generally well tolerated
•Hypersensitivity is major side effect, along with GI disturbances with more potent cephalosporins

Vancomycin
•Glycopeptide
•Interacts with the D-alanine-D-alanine termini of the pentapeptide side chains interfering with formation of bridges between the peptidoglycan chains. Thus, it works a step before the beta-lactams in preventing transpeptidation
•Thus, inhibits cell wall synthesis but does so differently from the beta-lactams; therefore, no cross-resistance with these drugs
•Usually given intravenously due to poor absorption from intestinal tract (unless you are treating a GI infection!). This makes sense, since peptides generally can't be taken by mouth - they are either degraded by peptidases in the GI tract or are poorly absorbed.

Vancomycin - Typical Uses
•Excellent Gram positive coverage (staph and strep)
•NO Gram negative coverage – vancomycin (a glycopeptide) is too big to pass through porins in the gram negative membranes
•Inferior to oxacillin against methicillin-sensitive *S. aureus (MRSA)*
•**Used for MRSA, and other beta-lactam resistant Gram positive organisms**
•Oral form used for *C. difficile* colitis

Can cause a hypersensitivity reaction; rarely this can be more severe, leading to what is called **Red Man Syndrome**, with a red rash on the face, neck and trunk.

Bacitracin

You have no doubt heard of, and probably used, Bacitracin. Like Vancomycin, this drug is a peptide - actually a mixture of peptides. It inhibits cell wall synthesis by preventing the transport of peptidoglycan precursors across the bacterial membrane. It is only used topically, and is mot effective against gram-positives.

Drugs that inhibit protein synthesis.

The second largest class of antibiotics is those that target protein synthesis, with most of these targeting the bacterial ribosome. Bacterial ribosomes are sufficiently different from our own that these drugs have good specificity. While our ribosomes have 60S and 40S subunits, prokaryotes have somewhat smaller ribosomes, with 50S and 30S subunits (S is a measure of size).

Drugs that target the bacterial ribosome

This cartoon from Microbiology Made Ridiculously Simple is useful: the top of home plate represents the larger 50S subunit, while the more narrow point of the plate represents the 30S subunit. The catcher makes a CLEan TAG. Chloramphenicol/Clindamycin, Linezolid and Erythromycin (and all macrolide ABx, so you have to remember that erythromycin is a macrolide) bind to the 50S subunit, while Tetracycline and AminoGlycosides bind to the 30S subunit.

Macrolides

This class of drugs includes the ever popular Azithromycin, which is marketed as a 'Z-Pak'.

•Reversibly binds to 50S ribosome
•Prevents protein elongation
•Bacteriostatic
•Broad activity against Gram + organisms; some Gram –
•Erythromycin largely replaced by azithromycin
•Community acquired pneumonia
•Skin infections not due to MRSA
•Upper resp. tract infections
•Atypical pathogens such as Legionella, Chlamydia and Mycoplasma
•Often drugs of choice for patients allergic to penicillin

These are well-tolerated drugs, with no unusual side effects to speak of. Resistance can entail a change in the drug binding site as well as hydrolysis of the drug and enhanced efflux of the drug.

Aminoglycosides

These target the smaller, 30S subunit of the ribosome and include:
Streptomycin
Gentamycin
Tobramycin
Amikacin

Neomycin - only used topically - I'm sure you have heard of this one.

These bind irreversibly to the 30S subunit, and so as a result they are typically bactericidal rather than bacteriostatic. Their transport through the bacterial cell membrane requires ATP hydrolysis (energy); **therefore they are not effective against anaerobes**. They can be used in conjunction with a beta-lactam drug - this damages the cell wall, and makes it easier for the aminoglycoside to enter the cell. This is a good example of synergy.

These drugs have good coverage against gram negatives, with use against Pseudomonas being particularly important. Toxicity issues can limit their use - they need to be monitored. Further, AGs are no absorbed from the gut, and so are delivered IV or IM. In practice, they tend to administered for serious gram negative infections:
Complicated UTIs
Pneumonia (often with a beta lactam)
Pseudomonas

Gentamicin at HUP is very frequently administered with a beta lactam.

As you will learn in the Lung Block in the spring, Pseudomonas colonization and infection is a serious problem for patients with Cystic Fibrosis. Once a day dosing with an AG can help keep this organism in check.

Aminoglycoside Resistance
The most common resistance mechanism is modification of the drug; the enzyme responsible for this is usually plasmid associated, and so can spread rather easily. Delivery of a drug-inactivating enzyme to a bacterium imparts high-level drug resistance (this is generally true, not just for AGs). Reduced uptake and an altered drug binding site have also been described - these usually afford intermediate levels of resistance, as uptake is not completely prevented, nor is binding.

Aminoglycoside Side Effects
There are two important side-effects:
Nephrotoxicity: quite common, and is associated with high trough levels (i.e. the lowest level of the drug seen in plasma). Toxicity is generally reversible, but if you have a patient on an AG, you will monitor drug levels (via blood draws) as well as renal function (via standard renal function tests).
Ototoxicity: This tends to be irreversible, and is associated with peak levels that are too high; can cause ringing in the ears (tinnitus) as well as outright hearing loss.

Tetracyclines.
These bind to the 30S subunit, prevent attachment of tRNA, and so block protein synthesis. This is an old drug class that is very commonly used for 'unusual' agents: mycoplasma, chlamydia, Lyme disease. Newer drugs in this class (doxycycline is the most commonly used) have better PK characteristics which allows for less frequent dosing. Also commonly used for Acne. Increased efflux from cells is most common resistance mechansism

Tetracyclines: Side Effects
•Discolored teeth in children – do not give to children or pregnant women

•GI upset
•Phototoxic dermatitis

Chloramphenicol
–Binds to 50S ribosomal subunit
•Prevents peptide bonds from forming and blocking proteins synthesis
–Effective against a **very** wide variety of organisms
–Due to rare but deadly side effects, used as drug of last resort for life-threatening infections. Used for meningitis if organism not known and patient has a penicillin allergy
–Young children and pregnant women with Rocky Mountain Spotted Fever (Amy Decatur's lecture) – usually you treat with tetracycline, but can't use this in children and pregnant women
–In under-developed countries, chloramphenicol is widely used because of its broad spectrum and very low cost
–Aplastic anemia – bone marrow wiped out; usually fatal; very rare)1 in 20 to 40 thousand)
–Neonates can't metabolize drug, resulting in very high levels and vasomotor collapse

Drugs that inhibit nucleic acid synthesis
There are three types:
Quniolones/fluroquinolones
Metronidazole
Rifamycins

Quinolones target DNA gyrase
If you want to unwind DNA to replicate it, or to coil it up, this creates tension - it is much like turning a rubber band. All cells have enzymes called gyrases that relieve this tension. Basically, they bind to the double helix, cut one strand while holding on to the other, let the molecule spin around, then reconnect the ends. Quinolones target this enzyme, and so they inhibit DNA replication.

Quinolones/Fluroquinolones
•Commonly used at Penn: levofloxacin, norfloxacin
•You may have heard of 'Cipro': Ciprofloxacin -made famous by the anthrax attack since it can kill this organism.
•Not good gram positives or anaerobes
•Good for gram negatives including:
  –Multi-drug resistant Pseudomonas (Cipro is best for this)
  –Enterics: E. coli, salmonella, shigella, campylobacter
  –Complicated UTIs (these are usually caused by gram negs)
  –GNR including pseudomonas
  –Gram positives (± enterococci)
•Levofloxacin active against many penicillin-resistant pneumocooci
•Safe
•Good PO
•Good tissue adsorption
•Resistance: due to mutations in drug binding site in gyrase
•Can disrupt normal gut flora, increasing chance of getting C. difficile

Metronidazole
You may have heard of 'Flagyl', which is metronidazole. It is a good anti-parasitic drug, and you'll hear more about this in the fall of year 2. This is one of those drugs that is activated by the host - when it enters a bacterium, its nitro group is reduced, and this makes the drug active. It appears to disupt DNA structure, leading to double-strand breaks and mutations. It is used for protozoans such as Trichomonas, Giardia, and various Amebic infections.
However, it is also good for <u>anaerobes</u> and for C. difficile (which can also be taken care of - usually - by vancomycin).

Antimetabolites: Sulfa drugs.
These are the only significant drugs that target bacterial metabolites, in this case folic acid synthesis. Historically, these were the very first antibiotics developed.

•Sulfonamides
–Group of related compounds
  •Collectively called sulfa drugs
–Inhibit growth of Gram + and Gram - organisms
  •Through competitive inhibition of enzyme that aids in production of folic acid
–Structurally similar to para-aminobenzoic acid
  •Substrate in folic acid pathway
–Human cells lack specific enzyme in folic acid pathway
  •Basis for selective toxicity
–Resistance due to plasmid
  •Plasmid codes for enzyme that has lower affinity to drug

Trimethoprim
–Inhibits folic acid production
  •Interferes with activity of enzyme following enzyme inhibited by sulfonamides
–Often used synergistically with sulfonamide
–Most common mechanism of resistance is plasmid encoded alternative enzyme
  •Genes encoding resistant to sulfonamide and trimethoprim are often carried on same plasmid

Trimethoprim/Sulfamethaxazole
Bactrim
No anaerobic coverage
Good for Strep and H. Flu (otitis media, sinusitis, bronchitis)
Also covers gram negatives that cause diarrhea: Shigella, Salmonella, E. coli
Good for pneumocystis (seen in AIDS patients)
Side effects: hypersensitivity; don't give to patients taking warfarin (a blood thinner) as it increases warfarin levels and can lead to bleeding.