ANTIBIOTICS

Topics from lectures Micro 1, 2, 3, and the beginning of 4:
Sulfonamides, Urinary Tract Infections (UTIs), Benign Prostatic Hypertrophy (BPH), Overactive Bladder Syndrome, Acne, Protein Synthesis Inhibitors, Cell Wall Synthesis Inhibitors, Tuberculosis (TB), and DNA Synthesis Inhibitors (quinolones).

5 fundamental sites of action for antibiotics

1. Interfere with a metabolic enzyme
2. Inhibit Protein Synthesis
3. Inhibit Cell Wall Synthesis
4. Inhibit DNA Synthesis and/or Repair
5. Alter membrane characteristics

Antibiotics are designed based upon selective or relative toxicity

Pick targets that are:

- Unique to the pathogen – for instance, the cell wall
- Similar, but different from the host – for instance protein synthesis
- Shared, but have less importance to host - for instance metabolic reactions that must occur in the pathogen, but are not critical in the host.

The DNA synthesis inhibitors are the quinolones. Quinolones include antibiotics and antiprotozoal drugs. We aren’t covering any membrane altering antibiotics.

Plasmids

Plasmids are a ring of “extra-chromosomal” DNA. This means they are in addition to the DNA normally in the bacteria. They are:

- Common in Gram-negative bacteria like E. coli.
- Frequently carry the genes coding for resistance factors to drugs (e.g., enzymes, pumps or altered drug binding sites).
- Easily swapped between bacteria (through conjugation), including bacteria of different species (by bacteriophages).
E. coli causes 70+% of UTIs

Other important bacteria causing UTIs include Staphylococcus saprophyticus (20%), Klebsiella species (sp.) (12%) and Enterococcus sp. (12%).

Acute, uncomplicated cystitis (a bladder infection with no other problems) is typically treated with the combination product Trimethoprim Sulfamethoxazole (Septra). However, resistance is so pervasive, other drugs including Ciprofloxacin (Cipro) or Nitrofurantoin (Macrobid) are used.

In complicated cystitis, Amoxicillin (Amoxicillin), Cipro, or a combination of Gentamicin with Amoxicillin may be used.

Antimycobacterial agents

Isoniazid (INH, Nydrazid) is a cell wall synthesis inhibitor used in combination therapy as a 1st line TB treatment, often along with Rifampin (Mycostat).

Dapsone (Aczone) is similar to sulfamethoxazole in that it inhibits folic acid metabolism. It is used to treat leprosy.

Getting UTIs

The bacteria enter the bladder by ASCENDING the urethra, the tube that takes urine from the bladder to the outside. Bacteria are ALWAYS normally present, especially near the opening of the urethra.

The host is more likely to get a UTI if they:

1. Are not producing enough urine,
2. Have an alteration of the chemistry of their urine,
3. Have an altered immune response or
4. Have had an alteration in the normal flora of the urethra and neighboring tissue.
5. For women, having sex and/or using a diaphragm increases the risk of UTI.

E. coli are particularly well suited to causing UTIs because they often have pili that allow attachment.

Conditions that may complicate UTIs...

- An abnormality or blockage (kidney stones for instance)
- Catheters
- Diabetes mellitus
- Immunosuppression
- Neurogenic bladder
- Bladder diverticuli (little pockets in the bladder wall that hold urine)
- Pregnancy

Urinary Antispasmodics

Urinary antispasmodics are antimuscarinic (anticholinergic) drugs used to treat incontinence or overactive bladder syndrome. They may have the normal side effects of anticholinergics including: dry mouth, lack of sweating, constipation, headache and so forth.

Solifenacin (VesiCare)
Non antibiotic drugs used in UTI therapeutics

Urine acidifiers are available OTC, usually in combination products. Methylene blue (Urolene Blue) is a dark blue biological dye, an anti-infective and a urine acidifier. It is a common ingredient in OTC products used to treat UTIs.

Phenazopyridine (Baridium) is also a dye, but in this case a dark, almost fluorescent orange. It stains EVERYTHING orange, clothes, toilets.... Phenazopyridine is an unusual OTC drug; it has a very strong anesthetic effect on the bladder mucosa. It SHOULD NEVER BE GIVEN WITHOUT AN ANTIBIOTIC, and should not be used for more than a couple days.

Pentosan Polysulfate Sodium (Elmiron) is like Teflon spray for the bladder. It is a heparin-like drug that sticks to the bladder mucosa and protects it from irritation. Unfortunately, like heparin it can cause thrombocytopenia and is an anticoagulant with fibrinolytic activity.

Acne

We are covering two retinoids used to treat acne. Isotretinoin, “Accutane,” is used for severe recalcitrant nodular acne and Adapalene, “Differin,” is for acne vulgaris. Both cause skin redness and drying resembling Vitamin A toxicity.

Isotretinoin is taken orally for 20 weeks. It is a POTENT teratogen and women patients must sign an “iPledge” agreement that requires periodic pregnancy testing and the use of two forms of birth control.

Adapalene is a topical and is not associated with teratogenicity, or fetotoxicity.

Another common use of retinoids is in cancer chemotherapy. Isotretinoin is used off label in the treatment of neuroblastoma in kids.

Benign Prostatic Hyperplasia

Alpha 1 blockers
- Doxazosin (Cardura) & Tamsulosin (Flomax)
5-alpha reductase inhibitor (androgen blocker)
- Finasteride (Proscar, Propecia)
Protein Synthesis Inhibitors

The **aminoglycosides** are an important group of antibiotics with serious side effects. They are neurotoxic and can damage the 8th cranial nerve (hearing/balance) and/or have neuromuscular junction blockade effects like curare. They are also toxic to the kidney. Like most older antibiotics, resistance is common.

**Gentamicin (Garamycin)** and **Streptomycin** (generics) are aminoglycosides and have a number of uses treating serious, mostly Gram-negative infections. Streptomycin is also a 4th line treatment for TB and can only be given IM.

**Chloramphenicol (Chloromycetin)** is a broad-spectrum antibiotic that can inhibit protein synthesis in our mitochondria leading to bone marrow suppression and the loss of RBCs and WBCs. Resistance is common. Chloramphenicol may cause **Gray Baby Syndrome** in neonates too young to metabolize the drug.

**Azithromycin (Zithromax)** and **Erythromycin (E-Mycin)** are **Macrolide** antibiotics. Azithromycin has a very long half-life and some indications require only one dose. Erythromycin is a strong prokinetic and potent P450 inhibitor. Both may aggravate or trigger Myasthenia Gravis.

**Clindamycin (Clindamax, Cleocin)** is a **Lincosamide** antibiotic that shouldn’t be taken with caffeine. It is usually reserved for penicillin-allergic patients and while resistance is common, there are lots of products available.

**Linezolid (Zyvox)** is the only oxazolidinone antibiotic currently on the market. Resistance is still relatively rare. Linezolid has MAOI activity.

**Synercid** is a fixed dose combination of **Quinupristin** and **Dalfopristin**, two Streptogramin antibiotics. The combo is bactericidal and resistance is relatively uncommon.

**Doxycycline (Adoxa, Vibramycin, Oracea) and Tetracycline (Sumycin)** are important very broad-spectrum Tetracycline antibiotics. The tetracyclines are potent photosensitizers and except for doxycycline, shouldn’t be taken with any divalent cation (e.g., any dairy product or antacid). Tetracyclines can be given chronically to treat acne (in low doses) or for malaria prophylaxis.

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**CDAD**

**Clostridium difficile Associated Diarrhea**

*C. difficile* is an anaerobic bacteria and a part of the normal flora of our GIT. When we are healthy, it is a minor constituent. When we take an oral antibiotic that reduces the numbers of dominant bacteria, the *C. difficile* is free to reproduce in large numbers. *C. difficile* also produces irritant, inflammatory metabolic products, potent toxins that trigger diarrhea and pseudomembranous colitis. Pseudomembranous colitis is a condition in which sheets of fibrin are deposited inside the GIT.

Patient education for all oral antibiotics should include instructions to report any diarrhea that occurs within a couple months of therapy.

**Metronidazole (Flagyl)** is used to treat *C. difficile* infections. **Vancomycin** may also be used.

The accidental discovery of penicillin by Sir Alexander Fleming is one of the most important developments ever in medicine. Fleming happened to find mold growing in a petri dish in 1928 and it wasn’t until the impetus of WW2 that extracts from the mold were isolated to produce the first commercially available penicillin antibiotic.

Penicillin contains a chemical ring structure called a beta lactam ring. Over the years, a number of additional beta lactam antibiotics have been developed including, Monobactams, Cephalosporins, and Carbapenems.

A standard penicillin is Penicillin G Procaine. One problem with this product is that some people are allergic to the PABA produced by procaine metabolism. The procaine reaction is a “fear of impending death” seen in 1 in 500 people.

Some bacteria produce beta-lactamase enzymes. Bacteria that produce these enzymes are resistant to the beta-lactam antibiotics. It is a little more complicated, of course, because there are many different beta-lactamases. So some bacteria are resistant to many beta-lactam antibiotics, while others are only resistant to one or the other. There is some cross-reactivity, but like many enzymes, these can be fairly specific. To increase the spectrum of beta-lactam antibiotics, a beta-lactamase inhibitor can be added.

Amoxicillin (Amoxil) can be combined with Clavulanic acid to make Augmentin. Unasyn is ampicillin with sulbactam, and Zosyn is piperacillin with tazobactam.

Another way to increase the effectiveness of a penicillin antibiotic is to combine it with Probenecid (Benuryl), which is indicated as an adjunct to extend the plasma half-life of various penicillins by blocking renal secretion.

There are many generations of cephalosporins. The 1st generation cephalosporin Cephalexin (Keflex) is a very commonly used antibiotic. Cefaclor (Ceclor) is a common 2nd generation and Cefepime (Maxipeme) is a 4th generation cephalosporin. Each subsequent generation has an improved spectrum.

The cephalosporins commonly cause problems with lab tests (Coomb’s, urine glucose), they often cause phlebitis if injected and they are tough on the kidneys.

The 1st monobactam was Aztreonam (Azactam, Cayston). Cayston is administered using a proprietary Altera nebulizer. Aztreonam has a similar spectrum to the aminoglycosides without all the neurotoxicity issues.

Carbapenems are the most potent of the beta-lactam antibiotics. Ertapenem (Invanz) is a restricted use antibiotic, a move intended to slow the development of resistance.

Vancomycin (Vancocin, Covane) is NOT a beta-lactam, but does inhibit cell wall synthesis. It is considered an antibiotic of last resort due to resistance problems. It also has a number of serious side effects.
SUPER INFECTIONS

Antibiotic therapy (and immunosuppression of any kind) often causes a SUPER INFECTION.

The most common kinds of super infections associated with oral antibiotics are:

1. *Clostridium difficile* associated diarrhea (CDAD) and/or pseudomembranous colitis caused by *C. difficile*.
2. *Candida albicans* (yeast infections, often of the mouth)

Ciprofloxacin (Cipro) inhibits enzymes that modulate DNA repair and synthesis. It is the antibiotic most likely to trigger a *C. difficile* super infection. It has a number of odd side effects; it can cause tendon rupture, for instance, especially in patients taking corticosteroids or who are more than 60 years old. It can trigger arrhythmias and like all the quinolones, may induce strangely vivid, or horrifying, dreams.

**Homework and Exercises**

1. Read the “START HERE” announcement in Laulima for updates and instructions.
2. Read about Antibiotics in Unit 8 of Adams & Urban, PHARMACOLOGY Connections to Nursing Practice. There are several chapters applicable to the material covered in these 4 lectures.
3. Review the Powerpoints and listen to the audio from the face-to-face lecture. You may opt to watch the appropriate videos for this lecture. Review any handouts available for this lecture in the Course Index.
4. Complete the SLO practice sets for Micro 1-3 in Tasks, Tests and Surveys.
5. Use “Chat,” “Discussions and Private Messages” or the lecture “Forum” to ask questions and find answers or to seek assistance.
6. Complete the online quiz in Laulima, Tasks, Tests and Surveys.

If you have any questions, email me at abeale@hawaii.edu