

Antibiotics/Antifungals/Antivirals:

Basic principles –some questions and concepts to think about while studying:

- Reasons why antibiotics are selective for bacteria, fungi, and viruses (SELECTIVE TOXICITY)
- Bactericidal versus bacteriostatic drug action
 - Why would the combination be antagonistic?
 - Are there issues to consider when treating an immunocompromised patient?
- Narrow spectrum versus broad spectrum antibiotics
 - Does the antibiotic target only gram negative or positive bacteria (narrow) or both (broad)?
 - Is an antibiotic specific for anaerobic or aerobic (require O₂) bacteria?
 - Does the antibiotic selectively target only a few types of bacteria (*e.g.* mycobacterium)?
 - Why do superinfections occur?
- What are the major mechanisms by which bacteria acquire resistance to a particular class of antibiotic?
 - Inactivation (destruction) of Drug
 - Modification of the Drug itself
 - Modification of Drug target
 - Mutation or overexpression of Drug target
 - Efflux pump
 - Lack of drug activation
- How can we prevent the emergence of drug resistance?
 - Don't treat viral infections with antibiotics
 - Why will choosing narrow spectrum over broad spectrum antibiotics reduce the chance of selecting drug resistant bacteria (and prevent superinfections)?
 - When is combination drug therapy appropriate (*e.g.* treating tuberculosis or HIV)?
- Some of the classes of antibiotics or prototypes highlighted in lecture are known to cause serious drug interactions or adverse effects:
 - Inhibitors or inducers of hepatic metabolism?
 - Allergic reactions, Nephrotoxicity, Cardiotoxicity, Ototoxicity, etc?
- What if a patient is suffering from renal failure, is pregnant or nursing, or immunocompromised?
 - How does this information affect choice of a specific antibiotic?

Use your textbook: Key points and summary of major nursing implications at the end of each chapter are great study guides!

Antimicrobial Resistance – here is a link to the Food and Drug Administration – Veterinary Medicine. You will find several movies to help 'image' the process of how drug resistance is transferred among bacteria:

<http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/ucm134359.htm>

Recent article on CA-MRSA

<http://www.consultantlive.com/infection/article/1145625/1393856>

The Centers for Disease control also has lots of useful information (including information about HA and CA-MRSA):

<http://www.cdc.gov/drugresistance/index.htm>

http://www.cdc.gov/ncidod/dhqp/ar_mrsa.html

A couple of links that teach about HIV and HIV drug resistance:

<http://www.cellsalive.com/hiv1.htm>

<http://www.hopkins-hivguide.org//tutorial/launch.html>

The CDC has up to date information on influenza vaccines and drugs

<http://www.cdc.gov/flu/index.htm>

What should I focus on?????

Note: I do not expect you to know which antibiotic is prescribed for which bacteria unless this was specifically highlighted in lecture. You should be able to choose the best antibiotic for a patient based on a description I give you of some hypothetical situation: *e.g.* pathogen X is an aerobic, gram negative bacteria causing severe pneumonia in an immunocompromised patient ... which of these five would be the best antibiotic for this patient? *i.e.* can you use your knowledge of the basic principles of antibiotic therapy and the general facts about each class of antibiotics to make the best choice for this patient.

Note: Be familiar with the PROTOTYPES for each drug class discussed in lecture (see following table). Understand the basic mechanisms of action (Cell wall synthesis inhibitor, DNA synthesis inhibitor, protein synthesis inhibitor, etc). In lecture, I went into a little more detail about mechanisms for some antibiotics. For example, both Amoxicillin and Vancomycin inhibit cell wall synthesis, however, their mechanisms differ. This is relevant in understanding why Vancomycin is still effective in treating a MRSA infection whereas all the β -lactams are totally ineffective. Expand upon these principles so that it is clear why some antibiotics are synergistic when combined and others are antagonistic (*e.g.* Erythromycin and Clindamycin bind to the same place on the bacterial ribosome responsible for protein synthesis and therefore the combination is antagonistic). Further expand the following prototype table I put together (below) by noting whether prototypes are bacteriostatic or bactericidal, narrow or broad spectrum, and if they are major causes of drug-drug interactions. When going through the material, envision yourself a patient caretaker who is on the frontline in recognizing serious adverse effects or signs of dangerous drug interactions when patients are taking antibiotics, especially with other drugs.

Regarding Cephalosporins – yes, there are a lot of them. Understand the major differences among the generations (narrow spectrum versus broad spectrum, β -lactamase sensitive versus resistant). I will not expect you to memorize which cephalosporin belongs to which class. Cephalexin (Keflex) and Cefdinir (Omnicef) are two of the most described antibiotics – be familiar with these two cephalosporins belonging to the 1st and 3rd generations, respectively. Do note that we discussed how three specific cephalosporins are associated with unique side effects.

PROTOTYPES
Summary of Antimicrobials

DRUG CLASS	PROTOTYPE	MECHANISM	RESISTANCE	MAJOR ADVERSE EFFECTS
Penicillins	Penicillin V, Amoxicillin	Cell wall synthesis inhibitors – inhibits transpeptidase – the enzyme responsible for cell wall crosslinking	Major: β -lactamase (destroys drug) Minor: reduced affinity of transpeptidase for Penicillin <i>e.g.</i> MRSA	Drug Allergy
Cephalosporins	Cephalexin, Cefdinir	Same as Penicillins	Same as Penicillins	Drug Allergy
Carbapenems	Imipenem	Same as Penicillins	Mutant PBP (resistant to most β -lactamases)	Superinfections
Vancomycin	Vancomycin	Cell wall synthesis inhibitor – different than Penicillins – inhibits cell wall crosslinking by binding peptidoglycan subunit (monomer)	Acquisition of a new pathway to synthesize peptidoglycan monomer (D-ala-D-ala \rightarrow D-ala-D-lac) This altered building block no longer binds Vancomycin	Ototoxicity Nephrotoxicity
Macrolides	Erythromycin, Azithromycin	Protein synthesis inhibitors	Modification of bacterial ribosome, drug efflux pumps	DRUG INTERACTIONS: erythromycin (Azithromycin does not inhibit p450!)
Clindamycin	Clindamycin	Protein synthesis inhibitor	Modification of bacterial ribosome	Drug allergy Superinfections/colitis

Tetracyclines	Doxycycline	Protein synthesis inhibitors	Drug efflux pumps	Bone and tooth development; Tooth staining; Photosensitivity
Aminoglycosides	Gentamicin	Protein synthesis inhibitor	Enzymatic Drug inactivation	Ototoxicity, Nephrotoxicity
Sulfonamides Trimethoprim	n/a	Antimetabolites: inhibit Folate synthesis	Overexpression or mutation of drug target	Drug allergy Photosensitivity
Fluoroquinolones	Ciprofloxacin	Inhibit DNA Gyrase leading to DNA synthesis inhibition	Drug efflux pumps Mutation of DNA Gyrase	Photosensitivity Tendon Rupture
Metronidazole	Metronidazole	Anaerobic bacteria metabolize (activate) drug to a DNA damaging agent	Decreased metabolic activation – aerobic bacteria are innately resistant	DRUG INTERACTIONS Classified as potentially mutagenic and contraindicated in pregnant and nursing women
Anti-Tuberculosis	Isoniazid	Mycobacterium Cell wall synthesis inhibitor	Mutation or lack of expression of enzyme needed to activate drug	DRUG INTERACTIONS Peripheral neuropathy Hepatotoxicity
Anti-Tuberculosis	Rifampin	Bacterial RNA polymerase inhibitor	Mutation in RNA polymerase	DRUG INTERACTIONS!!! Hepatotoxicity
Antifungal	Amphotericin B	Fungal cell wall disruptor	n/a	Nephrotoxicity Bone Marrow Suppression
Antifungal	Ketoconazole	Fungal cell wall synthesis inhibitor	n/a	Endocrine effects Drug Interactions

Summary of Antivirals

Antiviral (Influenza)	Oseltamivir (Tamiflu)	Inhibits viral neuraminidase – blocks release of virus	Mutation in viral neuraminidase	Few (delirium, confusion in teenagers?)
Antiviral (Herpes)	Acyclovir	Inhibits viral DNA synthesis	Lack of activation of drug by herpes thymidine kinase Mutation of viral DNA polymerase	few
Antiviral (Cytomegalovirus)	Ganciclovir	Inhibits DNA synthesis	Mutations in the enzyme needed to activate drug or viral DNA polymerase (target)	Bone marrow suppression
Anti-HIV NRTI	Zidovudine (AZT)	Inhibits HIV reverse transcriptase (RT)	Mutations in drug target (RT)	Anemia and Neutropenia
Anti-HIV NNRTI	Efavirenz	Inhibits HIV reverse transcriptase (RT)	Mutations in drug target (RT)	CNS effects Drug interactions
Anti-HIV Protease inhibitor	Ritonavir	Inhibits viral protease necessary for processing viral proteins and maturation of viral particles	Mutations in viral protease	Altered glucose and lipid metabolism DRUG INTERACTIONS!