**ANTIBIOTICS**

Definition: usually defined as a chemical produced by one microorganism that is capable of killing or inhibiting the growth of other microorganisms.

4 genera capable of producing natural antibiotics:
- **Penicillium** - terrestrial mold
- **Cephalosporium** - marine mold
- **Bacillus** - bacteria
- **Streptomyces** - bacteria

General considerations concerning antibiotics:

1. Making new and effective antibiotics to deal with the challenge of resistant organisms is becoming very difficult. Bacterial evolution has out-paced the ability of researchers to produce effective antibiotics to deal with the new strains. Some strains of *Staphylococcus aureus* are resistant to all antibiotics. Medical procedures and surgeries that have been somewhat routine are now threatened with the possibility of infection with resistant organisms.

2. Testing *in vitro* may not always have the desired *in vivo* effects.

3. When using antibiotics it is important to take the medication for the appropriate time frame. Not doing so, may select for resistant strains.

4. Culture and sensitivity testing should be performed to identify the infecting organism and to appropriately select the correct antibiotic. Indiscriminate usage of broad spectrum antibiotics should be avoided as much as possible. Keep statistics and collected data and share information with local health facilities.

5. Some antibiotics are incompatible in solution with certain interfering agents. For example, tetracyclines, when mixed with the anti-coagulant heparin, will cause the antibiotic to precipitate out of solution. This destroys the medication that was intended to help the patient. Sometimes, drug/drug interactions can produce detrimental consequences. For example, the antibiotic group known as the aminoglycosides combined with certain muscle relaxants can potentiate the competitive neuromuscular blockade.

6. Route of administration and ultimate blood level concentration should be considered. There are three major routes; I.V(intravenous), I.M(intramuscular), or oral.
7. Consideration should be given as to how the antibiotic is cleared from the body. Clearance is through the kidneys (renal) or the liver (hepatic) or both. Major management problems can arise with regard to choice and dose of antibiotics. If the patient has a urinary tract infection use an antibiotic that is cleared through the kidneys. If the patient suffers from renal insufficiency there may be interference with the clearing of an antibiotic. If the patient has a bile tract infection, use an antibiotic that is cleared by the liver. If the patient has a condition which keeps the liver from functioning, this has to be considered.

8. Consideration should be given as to when to use a bactericidal agent vs. a bacteriostatic agent. Since bacteriostatic agents require an intact immune system, they should not be used in patients with impaired host defense mechanisms such as those with leukemias, lymphomas or those that are receiving corticosteroids etc.

9. Why not consider the cost of therapy if an alternative and less expensive antibiotic works as well as a more expensive one.
**Antibiotic Groups**

1. **Penicillins** - at least 10,000 biosynthetic and semi-synthetic penicillins have been made. Only a few of clinical value. Effective, least toxic. From *Penicillium*.
   - A. Are bactericidal-interfere with cell wall synthesis
   - B. Rapidly cleared by the kidney. Can use Probenamide (Probenecid) to slow down clearance and increase blood levels to achieve appropriate concentration.
   - C. Can have allergic reactions that can cause rashes, fever and anaphylactic shock.
   - D. Some are acid labile and cannot be given orally. Penicillin G is hydrolyzed by stomach acid. Give acid labile antibiotics either I.M. or I.V.
   - E. Some bacteria make the enzyme penicillinase (B-lactamase). This cleaves the B-lactam ring of penicillin. These bacteria are resistant to penicillin. However, some penicillins have been developed that are resistant to penicillinase others are still sensitive to penicillinase.
     1. Penicillinase sensitive penicillins include:
        a. ampicillin
        b. carbenicillin (note: carbenicillin combined with aminoglycosides such as gentamycin, tobramycin and amikacin work synergistically on organisms such as *Pseudomonas aeruginosa*.
     2. Penicillinase resistant penicillins include:
        a. methicillin (note: have side chains to protect the beta lactam rings. Also, are acid labile.

2. **Cephalosporins** - From *Cephalosporium*
   - A. Are bactericidal. Extended Gram negative and Gram positive activity over the penicillins. If one is allergic to penicillin, or one is infected with a penicillinase producing bacteria, there is a 50% chance that cephalosporins will cause allergy and a 50% chance that penicillinase will destroy the cephalosporins. So therefore there exists a cross reactivity between the penicillins and the cephalosporins. Also more expensive then the penicllins. Several generations of cephalosporins have been developed.
     1. 1*- Include cephalothin
     2. 2*-Include cefamandole-expanded Gram negative activity
     3. 3*-Include cephalexime- good for bacillary meningitis
     4. 4*-Include cefepime-good for Gram neg. in urinary tract.
Note: A group of antibiotics derived from *Streptomyces* called the carbapenems, which have broad spectrum antibacterial activity, also have this beta lactam ring. Originally highly resistant to beta lactamase, the carbapenems are now showing susceptibility to a new beta lactamase produced by resistant strains of *Escherichia* and *Klebsiella*.

3. Erythromycin/Clindamycin-have similar biological effects and are categorized together. However, their chemical configurations are not similar. From *Streptomyces*.

A. Are bacteriostatic and interfere with protein synthesis at the ribosome.
   1. Erythromycin- drug of choice for Legionnaires’ Disease caused by *Legionella pneumophila* (a small gram negative rod). Also used for primary atypical pneumonia caused by *Mycoplasma pneumoniae*.
   2. Clindamycin-good for some Gram negative anaerobes. Can cause an imbalance in anaerobe populations when used allowing for *Clostridium difficile* to proliferate. This can cause pseudomembranous enterocolitis.

4. Vancomycin-From *Streptomyces*
   A. Are bactericidal against Gram positive cocci. Also, can be used against *Clostridium difficile*. Use for Staphylococcus that is resistant to methicillin and patients who are allergic to penicillins or cephalosporins.
   B. Cannot give orally as it doesn’t absorb into the G.I. Cannot give I.M. as it causes pain and necrosis. Must administer I.V. but very slowly to avoid burning of the vein.
   C. Can be nephrotoxic and ototoxic.
   D. Expensive therapy.

5. Tetracycline-From *Streptomyces*- First truly broad spectrum antibiotic.
   A. Are bacteriostatic against both Gram positive and Gram negative organisms. Works against *Rickettsia* and *Chlamydia*.
   B. Good against *Yersinia pestis* (causes plague) and *Brucella spp.* (small Gram negative rod that favors intracellular growth-causes undulant fever).
   C. Also works against *Entamoeba histolytica* a protozoan.
   D. Most valuable in mixed infections.
   E. Problems with tetracycline usage.
      1. Can get a suprainfection with yeast.
      2. Tetracyclines can cause pigmentation in the enamel of developing teeth. The yellow pigment undergoes photooxidation to a brown color to discolor teeth.
      3. Many pathogens have developed resistance to tetracyclines due to
the indiscriminate usage of this antibiotic. Widespread usage in agricultural feeds has contributed to this resistance.

4. Can lead to skin photosensitivity.
5. Can cause a fatty degeneration of the liver during pregnancy.
6. Cannot be consumed with dairy products. Tetracyclines bind to calcium and absorption would not occur properly
6. Chloramphenical (Chloromycetin)-From *Streptomyces*
   A. Are bacteriostatic.
   B. Good against *Salmonella typhi* (causes typhoid fever).
   C. Good against *Hemophilus influenzae*.
   D. Can result in erythropoietic depression. This can lead to an aplastic anemia. The antibiotic can poison the bone marrow.

7. Aminoglycosides-From *Streptomyces*
   A. Are bactericidal against a wide range of Gram positives and negatives.
   B. When considering the following aminoglycosides; streptomycin, kanamycin, gentamycin and neomycin, activity and toxicity increases in the order listed. Streptomycin is not very active and displays the least toxicity. It is mostly considered useless and many bacteria have become resistant. Kanamycin at 10X the therapeutic dose is toxic. Gentamycin at 10X the therapeutic dose is toxic. However, neomycin at only 2 or 3X the therapeutic dose is toxic. Neomycin is rarely used except topically because of toxicity. Toxic reactions include ototoxicity and nephrotoxicity.
   C. Aminoglycosides when used in combination with the penicillin drug carbenicillin, have a synergistic effect and work against both *Pseudomonas aeruginosa* and *Serratia spp*.
   D. Other aminoglycosides include tobramycin and amikacin.

8. Sulfonamides(sometimes referred to as the sulfonilamides)-Are pure synthetics
   A. Bacteriostatic. The sulfonamides competitively interfere with the bacterial cells utilization of essential metabolites like p-amino-benzoic acid (PABA). Bacteria need PABA to make folic acid. Therefore bacterial cells cannot make the coenzyme folic acid in the presence of sulfonamides.
   B. The sulfonamide called sulfisoxazole (Gantrisin) is used in treating urinary tract infections.
   C. 10% of those using these antibiotics suffer from side effects including vomiting, dizziness, photosensitivity and rashes.

9. Trimethoprim and sulfamethoxazole- Two pure synthetics used together (1 part trimethoprim to 5 parts sulfamethoxazole). Called Bactrim or Septra.
   A. Trimethoprim alone is bacteriostatic.
   B. Sulfamethoxazole alone is a sulfonamide and is therefore bacteriostatic.
   C. Together in the appropriate ratio they work in a bactericidal fashion. In fact, they are 20X more effective when used together.
   D. Fairly good broad spectrum activity. They are used against both bacteria and protozoa.
   A. Bacteriostatic in low concentrations and bactericidal in higher concentrations.
   B. Furadantin-Can be used systemically. Activity against some Gram negatives and positives. Also can be used against some protozoans. Used in urinary tract infections.
   C. Furacin-can be used topically on severe burn victims and graft patients.

11. Polypeptides-From Bacillus
   A. Bactericidal, prevents cell wall synthesis.
   B. Bacitracin – Inhibits many Gram positives and Neisseria spp. Best used topically as an ointment. Can be nephrotoxic.
   C. Polymyxin B- Can be used against Pseudomonas. Best used topically.
   D. Neosporin ointment contains these two polypeptides.

12. Quinolones and Fluoroquinolones
    Broad-spectrum synthetic antibiotics from the drug nalidixic acid. Most in medical use are the fluoroquinolones which contain fluorine.
    - Bactericidal in activity
    - Inhibit DNA replication and transcription
    - Can enter cells and target intracellular pathogens such as Legionella pneumophila.
    - Side-effects can be mild to severe and include:
      - Nerve damage
      - Tendon damage
      - Kidney stones
      - Can affect the development of cartilage in children
    - Many pathogens including Staphylococcus aureus, Streptococcus pyogenes and Enterococcus faecalis exhibit resistance
    - Divided into generations, where the early generation drugs have a more narrow spectrum
      - Examples:
        1st-cinoxacin
        2nd-ciprofloxacin (Cipro)
        3rd-balofloxacin (Baloxin)
        4th-clinafloxacin
ANTIBIOTICS AND DRUGS FOR SPECIAL CATEGORIES

1. Rickettsial diseases- Tetracyclines work best if infection is caught in the early stages.

2. Tuberculosis-caused by *Mycobacterium tuberculosis* (a weakly Gram positive beaded rod). Drugs are toxic and the bacterium has developed resistance to many. The treatment includes the usage of multiple drugs in lower concentrations. In addition, the combination of drugs is varied periodically. Drugs include:
   A. INH (isonicotinic acid hydrazide)-A synthetic, interferes with mycolic acid synthesis. Side effects include nephrotoxicity and neurotoxicity.
   B. PAS (para-amino-salicylic acid)-A synthetic, resembles sulfonamides and interferes with metabolites. Also toxic and used in low doses.
   C. Rifampin- From *Streptomyces*. Bactericidal, penetrates walled off tissues to reach bacteria. Side effects include liver disturbances.
   D. Ethambutol- A synthetic that interferes with mycolic acid synthesis. Side effects include blindness.

3. Antiprotozoan/Antihelminthic-Eucaryotic cells are targeted. Medications can be very toxic. First antiprotozoans:
   A. Metronidazole (Flagyl)- used against *Trichomonas vaginalis* (causes trichomoniasis, a venereal disease) This flagellate may cause a mild infection in the vagina of females, and less often an infection of the prostate in males. Metronidazole can be carcinogenic and can have side reactions that interfere with alcohol (acts like antibuse).
   B. Quinine- used against the protozoan (*Plasmodium*) that causes malaria. This drug interferes with RNA and DNA synthesis.
   C. Chloroquine- a chlorinated form of quinine. Now in use world wide against malaria.
   D. Emetine- Blocks protein synthesis good against amoeba.
   E. Pentamididine-used in early trypanosomiasis and used to treat pneumocystic pneumonia. Binds DNA. Now some antihelminthics:
      A. Niclosamide- inhibits ATP under anaerobic conditions. Good against tapeworms.
      B. Praziquantel- mechanism unknown. Good against the tapeworm and the blood fluke that causes schistosomiasis.
      C. Mebendazole- interferes with the worms capability for generating ATP. Good against ascariasis and pinworms.
4. Antimycotic (Antifungal)- Eucaryotic cells are targeted. Medications can be very toxic.  
   A. Polyene Drugs- cause damage to fungal plasma membranes. Membranes become too permeable.  
      1. Amphotericin B- can be used systemically for various mycoses. A metallic taste in the mouth sometimes develops when using this drug. Can cause anemia and cardiac arrest.  
      2. Nystatin- used topically for local infections of the skin and vagina.  
   B. Griseofulvin- taken orally for ringworm infections. Derived from Penicillium yet is active against fungi. Inhibits mitosis.  
   C. Imidazoles- cause injury to the plasma membrane. Can be toxic to liver. Includes: clotrimazole, miconazole (topical usage in athletes foot powder) and ketoconazole (can be used systemically for yeast infections).  
   D. Flucytosine- good against candidiasis. Can be used systemically. Can cause G.I. distress, leukopenia, loss of hair and impaired liver function. Interferes with nucleic acid replication.  
5. Antiviral  
   A. Amantadine-1st antiviral licensed for systemic use in the U.S. Prevents the Virus from entering the cell (may prevent uncoating in some). Can be used to prevent the spreading of flu in hospitals. May be teratogenic.  
   B. 5-ido-2-deoxyuridine (5-IDU) – This is a synthetic nucleotide subunit. Most antivirals in use today are nucleic acid analogs(base analogs) like 5-IDU. These base analogs were born out of cancer research. Placing the wrong nucleotide into the viral nucleic acid during replication will hinder the process of making virions.  
   C. Cytosine-arabinoside-another nucleic acid (base) analog. Can be used against herpes.  
   D. Adenine-arabinoside-another nucleic acid analog. Can be given I.V. for treatment of viral encephalitis caused by herpes and also in immunocompromised patients who suffer from varicella-zoster infections. Can be used topically for herpes eye infections.  
   E. Acycloguanosine (Acyclovir)- another analog. Used as an ointment for genital herpes. Systemic use to reduce severity and duration of herpes.  
   F. Azidothymidine (AZT)- Blocks reverse transcriptase and therefore viral DNA synthesis. For AIDS patients, to forestall the decline in the immune system.  
   G. Protease inhibitors- Block protease activity. Protease normally will cleave viral proteins to subunits of appropriate size. Protease inhibitors impede this activity.  
   H. Receptor blockers-Drugs that seek to block adsorption of the virus and therefore preventing viral replication.