Unit 3 Lecture 7

Chemotherapeutics

Significant historical events that occurred in the area of chemotherapeutics include:

- Ehrlich used Compound 606 (Salvarsan) in 1909
- Domagk introduced Prontosil (Sulfa drug) in 1935
- Fleming observed antibacterial action of Penicillin in 1929
- Waksman used Penicillin in 1940
- Waksman discovered Streptomyces species. in 1943

Compare the characteristics of an “Ideal” Chemotherapeutic with that of the “ideal disinfectant." Do you see a similarity?

1. Low toxicity to host’s tissue
2. Lack of interference with body’s own defenses
3. Lack of allergenic properties
4. A -cidal property rather than a -static one
5. Action against many different pathogens
6. Lack of destruction of normal flora
7. Properties to which a pathogen cannot become resistant
8. Low cost

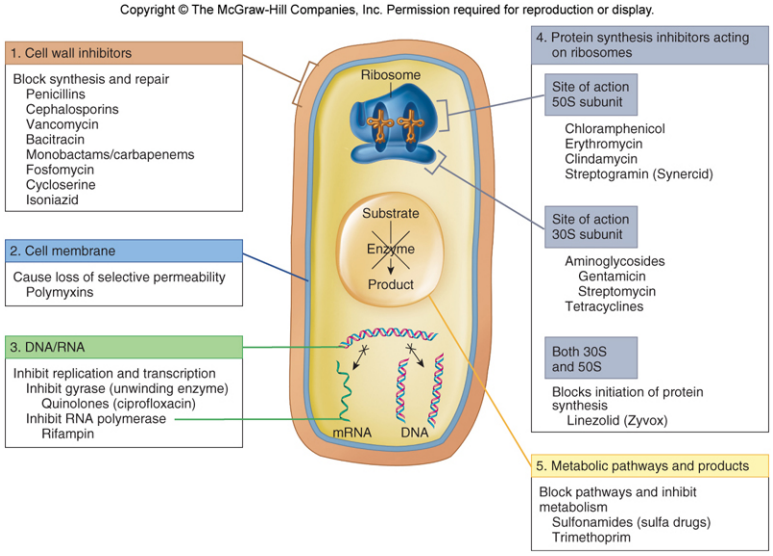
The body can recover from a majority of bacterial infections by itself as we will see in the next unit. Sometimes, however, the body needs help from antibiotics. Antibiotics are prepared naturally by microbes to kill or inhibit other microbes.

Classes of chemotherapeutics or antimicrobials that are used for treatment can be synthetic chemotherapeutics which are prepared exclusively from chemicals. Antibiotics, on the other hand must be produced by microbes. The sources are fungi (*Penicillium* and *Cephalosporium*), mold-like bacteria (*Streptomyces* species), or other bacteria (*Chromobacterium, Bacillus* species, *Micromonospora*). Some antibiotics are semi-synthetic. They start as a pure antibiotic but are chemically modified to make more effective. Other antibiotics are completely synthesized and are called synthetics.

Mechanism of Action

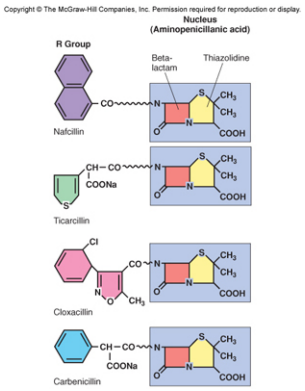
Their mechanisms of action vary just as the chemotherapeutics did. There are antibiotics that inhibit cell wall synthesis during cellular reproduction. They are generally cidal in nature and usually are very safe since human tissues have no cell walls as are found in bacteria. Examples of cell wall antagonists include penicillins, cephalosporins, bacitracin, and monobactams. There are those that interfere with ribosomal activity (most inhibit

translation). They are generally static in nature and are usually safe since prokaryotic ribosomes differ from human ribosomes. Examples of these are streptomycin, tetracycline, erythromycin, chloramphenicol, and, aminoglycosides. Some antibiotics alter permeability of cell membranes. These are generally cidal but have many side effects because of effect on human membranes. Examples of these antibiotics include polymyxins, Amphotericin B, and nystatin. Some antibiotics interfere with nucleic acid synthesis. They are generally cidal but are often too dangerous to use internally.



Rifampin and griseofulvin are examples of antibiotics utilizing this mode of action. Finally, some antibiotics compete for essential components of metabolism (metabolite analogs). These also are generally cidal and can be toxic to humans.

Major Drug Groups



Beta-lactams have a beta lactam ring. One of the beta lactams is the penicillin group. A characteristic of this group is found in their name; they end in -cillin. The spectrum of activity (how many types of organisms they affect) range from narrow spectrum penicillin (only a few cocci) and anti-staphylococcal penicillins (penicillinase-resistant) to broad or extended spectrum anti-pseudomonad (due to addition of various side chains to the molecular structure). Their mode of action is that they are cell wall antagonist which kills the organism (cidal). Another beta lactam group is the **Cephalosporin**. They have a similar structure to penicillins in that they have a beta lactam ring. They are usually safer than penicillins. As a result most antibiotics belong to this group. Newer generations expand coverage (become broader) by addition of side chains. You can tell a cephalosporin because they usually have cef-, kef-, or ceph- in the name. Other beta lactams include Monobactams (aztreonam) and the Carbapenems (imipenem). Their mode of action is like all others in this group, they inhibit cell wall synthesis.

An antibiotic that inhibits cell wall synthesis but is not in the beta-lactam group is vancomycin. This antibiotic is becoming very important today because it is one of the last antibiotics to treat some staphylococcal or enterococcal infections. If these organisms become resistant, there may not be any other class of antibiotics that can be used to treat the patient.

Aminoglycosides (such as gentamicin, tobramycin, streptomycin, kanamycin, and amikacin) affect protein synthesis. Their spectrum of activity varies with the antimicrobic. Often these drugs are very toxic requiring a monitoring of serum levels in the patient. Other antibiotics that affect protein synthesis include tetracycline, macrolids, erythromycin, and clindamycin.

Polymyxins affect permeability of the cell membrane and are therefore quite toxic.

A new class of antibiotic is the fluoroquinalones. Quinalones have -floxacin in their name. They inhibit DNA synthesis by inhibiting gyrases which cause the DNA molecule to unwind during replication.

Sulfonamides and trimethoprim mode of action is competitive inhibition. Nitrofurantoins are active in the urinary tract only.

Anti-Acid Fast drugs or anti-*Mycobacterium tuberculosis* include INH (Isonazid), PAS (para-aminosalicylic acid), and EMB (Ethambutol). An anti-leprosy synthetic drug is Dapsone.

Since fungi are eukaryotic organisms, antibiotics that work on bacteria will not affect fungi.

Griseofulvin, Nystatin, Amphotericin B, Flucytosine and the -azoles (Itraconazole, Miconazole, etc) are all anti-fungal drugs.

Parasites are also eukaryotic organisms. With the exception of one of the amoebocide's (Metronidazole), bacterial antibiotics will work on parasites. Anti-malarial drugs (quinine, chloroquine, primaquine) are used to treat malaria. Anti-helminth drugs immobilize, disintegrate, or inhibit the metabolism of a worm's life cycle.

The anti-viral drug, AZT, is used to treat AIDS. Acyclovir is used to treat herpes infections. Ribavarin, Amantadine and Rimantidine are used to treat some of the respiratory viruses. Their method of action may be to bar complete penetration of virus into host cell, or to block transcription and/or translation of viral molecules, or to prevent the maturation of viral particles.

Resistance

Resistance to antibiotics is based on one of five methods: drug inactivation due to enzyme production by the organism, decreased permeability to the

drug, activation of drug pumps, change in binding sites on or within the organism and use of an alternate metabolic pathway by the organism. R-factors are transferred by plasmids from one bacterium to another cause the synthesis of enzymes that inactivate the drug (beta-lactamase), cause a decrease in cell permeability and uptake of the drug by the bacterium, change in number of or affinity of drug receptor sites on the bacterium, or modify essential metabolic pathway. Natural selection of resistant strains has increased the amount of drug resistance. Microbes are the best example of Darwinian evolution: survival of the fittest.

Reasons for drug resistance on the rise is mainly due to drugs being prescribe inappropriately and drugs being used as “growth factors” in animal feeds. One of the questions everyone must ask themselves, “Is this drug necessary in the treatment of my illness, or can my body eliminate the organism by itself?”

Drawbacks or side effects of Chemotherapeutics

Taking drugs is not without risk. The patient may be “cured” of the infection but may die as a result of a toxic side reaction to the antibiotic. Blood forming cells may be susceptible to the antibiotic resulting in anemia (Chloramphenicol, Tetracycline, and Trimethoprim). There may be renal susceptibility resulting in hematuria (Trimethoprim, Sulfas, Polymyxins, Viomycin). There may be nervous system susceptibility causing a tinnitus (Streptomycin). Hypersensitivities may develop which may affect limited areas (skin rashes, GI distress) or may affect whole body (anaphylactic shock). Some antibiotics may inhibit normal body defenses, affect liver function (Tetracycline), or prevent antibody formation (treatment prevents memory).

One of the biggest problems is that antibiotics often do not know the difference between friend and foe, the good bacteria from the ones that are causing infection. These antibiotic treatments affect NORMAL FLORA. The role of normal flora in the body is briefly this; normal flora occupies niches so that pathogens cannot attach. A possible way to reestablish normal flora and to prevent further infection is the use of probiotics and prebiotics. These include the ingestion of live microorganisms to reestablish intestinal flora.

Other problems that can occur include improper use of the antibiotic may cause drug resistance. Drug-fastness is an acquired resistance to chemotherapeutic. Low doses of antibiotics allow R-plasmid transfer as well as allow mutation to bypass normal metabolism. The result is “super strains” of bacteria that antibiotics cannot treat (VRE or MRSA).

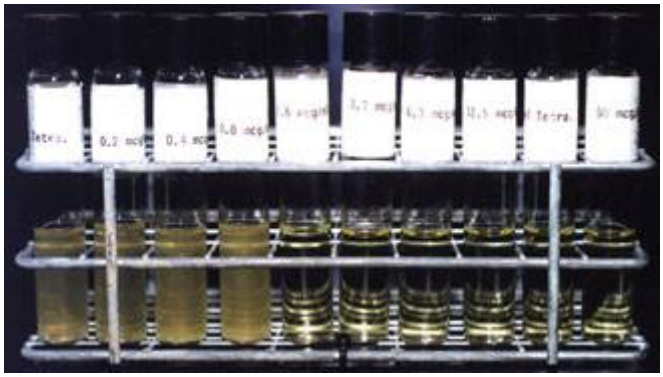
Effective Chemotherapy Requirements

- Identify the correct drug by sensitivity testing

- Prescribe and take the optimum dose till the drug is completely gone or till the physician tells you to stop.
- Beware of antagonistic forms prescribed together. Chemical antagonists react with one another. Therapeutic incompatibility interferes with desired reactions. Synergistic forms may be better. Synergism occurs when the sum of the results are greater than each drug alone. It allows for use of lower dose antibiotics that alone may be toxic in higher doses. Anti-tubercular combinations always given in combination e.g. INH, PAS, and Rifampin to prevent resistance from developing.

Susceptibility Testing

Susceptibility testing is used to establish effectiveness of a specific drug against a specific microbe. The goal of susceptibility testing is to give an accurate prediction of which antibiotics can help guide the patient to a favorable clinical outcome. Methods deployed in the laboratory include the Kirby-Bauer method (antibiotic diffusion into a medium from a disc. Activity *in vivo* may be complicated by factors not seen *in vitro.* MIC (Minimum Inhibitory Concentration) tests for the smallest dilution or concentration that will visually inhibit growth. A susceptible result of an organism to an antibiotic does not guarantee treatment success. There are many other factors that determine whether or not an antibiotic will be effective in a patient. Some patients on antibiotics, that are susceptible to the infective agent die, and some patients whose bacteria are resistant to the antibiotic they are on, survive. Generally speaking, there is a very strong correlation between a resistant result and treatment failure.



The first tube showing no growth (tube #4) is the MIC value or drug concentration needed at the site of the infection to eliminate the microorganism.