Antibiotics

An antibiotic was a substance, produced by one microorganism, which inhibited the growth of other microorganisms. The advent of synthetic methods has, however, resulted in a modification of this definition and an antibiotic now refers to a substance produced by a microorganism, or to a similar substance (produced wholly or partly by chemical synthesis), which in low concentrations inhibits the growth of other microorganisms. Chloramphenicol was an early example. Antimicrobial agents such as sulphonamides and the 4-quinolones, produced solely by synthetic means, are often referred to as antibiotics.

History of Antibiotics

Discovery of Penicillin

Fleming's contaminating mold was identified as belonging to the genus *Penicillium* ,which led to the name **penicillin** for the substance responsible for the antibacterial activity observed on the agar plate. Fleming published his work on penicillin in 1929, reporting that extracts of the mold were able to kill a number of gram positive pathogens in addition to the staphylococci and even the gram negative pathogen responsible for gonorrhea. Over the next 10 years, Fleming tried to progress penicillin further but was hampered by an inability to isolate and purify it. Early attempts to use crude penicillin topically in patients were not very successful, and Fleming did little further work on its clinical potential, focusing instead on its utility as bacteriological reagent. He never tested it in a model infection in mice! Meanwhile, Ernst Chain had taken on the task of isolating penicillin and solving its structure. The first results of this effort were published in 1940 , and by 1945, penicillin had

demonstrated its amazing curative properties in the clinic and was being produced and distributed on a large scale.

For their seminal work Florey, Chain, and Fleming were awarded the Nobel Prize in 1945. Over the ensuing years many generations of novel penicillins have been developed with improved spectrum, pharmaco-kinetics, and resistance to beta lactamase.

The Actinomycetes Take Center Stage

Fleming's discovery of penicillin in 1928 coupled with Rene Dubos' discovery of **tyrothricin** in 1939, led Selman Waksman to start investigating microbes found in the soil as a source of novel agents active against bacteria. Dubos' work that led to tyrothricin was very different from Fleming's fortuitous discovery of penicillin, as it resulted from the first deliberate search for compounds produced by soil microbes that were capable of killing pathogenic bacteria. He actually fed gram positive bacteria at intervals to a large sample of mixed soils, hoping initially to find microbes that were capable of destroying the bacteria. In reality, he discovered a bacterium that produced **an alcohol soluble compound capable of inhibiting the growth of gram-positive bacteria that he called tyrothricin.** The alcohol extract was actually a mixture of two compounds: **tyrocidin** and **gramicidin**. Although neither antibiotic proved to be of clinical utility, their discovery was a seminal event demonstrating the utility of screening soil microbes. Tyrocidin proved very toxic, and, although gramicidin was able to cure experimental infections in mice, it also was too toxic for systemic use in humans. Gramicidin is a complex of six related compounds and still has utility today as a topical treatment for superficial infections; it is one of three

constituents in **Neosporin ointment**. Natural products synthesized by soil microbes are frequently produced as a complex of related molecules.

Waksman's group started testing all three of the known types of microbe found in the soil (bacteria, fungi, and actinomycetes) for their ability to produce antibiotic activity. It quickly became apparent that the actinomycetes were the most fruitful source of this activity. The subsequent systematic screening of soil actinomycetes led to **actinomycin** and **streptothricin**, which, like tyrocidin and gramicidin, were too toxic for clinical use as antibacterials. Nonetheless a clear direction had been set in the quest for novel antibiotics.

The Discovery of Streptomycin

In 1943, Albert Schatz, a graduate in Waksman's lab found **Streptomycin**, which was active against gram negative bacteria and most importantly against *Mycobacterium tuberculosis* , the pathogen responsible for **TB (tuberculosis)**. It was quickly shown to be active in animal models of TB and then to be capable of curing the disease in actual patients by 1946.

Waksman was awarded the Nobel Prize in 1952 for his pioneering work with actinomycetes and for the discovery of streptomycin. His work led to the golden era of antibiotic discovery.

Definitions

The following terms are commonly employed in connection with antimicrobial agents and their uses:

A- Biocide: a chemical or physical agent, usually broad spectrum, which inactivates microorganisms. Chemical biocides include hydrogen peroxide and phenols while physical biocides include

heat and radiation. Biocides are generally broad spectrum, in contrast to anti-infectives, which have narrower range of antimicrobial activity.

B- Bacteriostatic: a specific term referring to the property by which a biocide is able to inhibit bacterial multiplication ; multiplication resumes upon removal of the agent. (The term "fungistatic" and "sporostatic" refer to biocides that inhibit the growth of fungi and spores, respectively).

C- Bactericidal: a specific term referring to the property by which a biocide is able to kill bacteria. Bactericidal action differs from bacteriostasis only in being irreversible ; i.e. the "killed" organism cannot longer reproduce, even after being removed from contact with the agent. In some cases, the agent causes lysis (dissolution) of the cells ; in other cases, the cells remain intact and may even continue to be metabolically active. (The terms "fungicidal", "sporicidal", and "virucidal" refer to the property whereby biocides are able to kill fungi, spores, and viruses, respectively).

D- Sterilization: a defined process used to render a surface of product free from viable organisms including bacterial spores.

E- Disinfectants: products or biocides used to reduce the number of viable microorganisms, or bio burden, on or in a product or surface to a level previously specified as appropriate for its intended further handling or use. Disinfectants are not necessarily sporicidal, but are sporostatic, inhibiting germination or outgrowth.

F- Septic: characterized by the presence of pathogenic microbes in living tissue.

G- Antiseptic: a biocide or product that destroys or inhibits the growth of microorganisms in or on living tissue (eg, skin).

H- Aseptic: free of, or using methods to keep free of, microorganisms.

I- Preservation: the prevention of multiplication of microorganisms in formulated products, including pharmaceuticals and foods.

J- Antibiotics: naturally occurring or synthetic organic compounds which inhibit or destroy selective bacteria, generally at low concentrations.

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.

Sources of Antibiotics

There are three major sources from which antibiotics are obtained:

1- Microorganisms. For example, bacitracin and polymyxin are obtained from some *Bacillus* species; streptomycin, tetracyclines, etc. from *Streptomyces* species; gentamicin from *Micromonospora purpurea;*

griseofulvin and some penicillins and cephalosporins from certain genera *(Penicillium, Acremonium)* of the family Aspergillaceae; and monobactams from *Pseudomonas acidophila* and *Gluconobacter* species. Most antibiotics in current use have been produced from *Streptomyces* spp.

2- Synthesis. Chloramphenicol is now usually produced by a synthetic process.

3- Semi synthesis. This means that part of the molecule is produced by a fermentation process using the appropriate microorganism and the product is then further modified by a chemical process. Many penicillins and cephalosporins are produced in this way.

Physical Agents

A- Heat: application of heat is the simplest means of sterilizing materials, provided the material is itself resistant to heat damage. A temperature of 100℃ will kill all but spore forms of bacteria within 2-3 minutes in laboratory-scale cultures ; a temperature of 121℃ for 15 minutes is utilized to kill spores. Steam is generally used, both because bacteria are more quickly killed when moist and because steam provides a means for distributing heat to all parts of the sterilizing vessel. At sea level, steam must be kept at a pressure of 15 Ib/sq in. (psi) in excess of atmospheric pressure to obtain a temperature of 121˚C ; autoclaves or pressure cookers are used for this purpose. At higher altitudes, the pressure would need to be higher than 15 psi to reach 121˚C. for sterilizing materials that must remain dry, circulating hot air electric oven are available, since heat is less effective on dry materials, it is customary to apply a temperature of 160 – 170˚C for 1 hour or more.

B- Radiation: ultraviolet light and ionizing radiations have various applications as sterilizing agents.

Chemical Agents

A- Alcohols: ethyl alcohol, isopropyl, and *n*-propanol exhibit rapid, broad-spectrum antimicrobial activity against vegetative bacteria, viruses, and fungi but not sporicidal. Activity is optimal when they are diluted to a concentration of 60 – 90 % with water.

B- Aldehydes: gluteraldehyde is used for low-temperature disinfection and sterilization of endoscopes and surgical equipment. It is normally used as a 2% solution to achieve sporicidal, and virucidal.

C- Biguanides: chlorohexidine is widely used in hand washing and oral products and as a disinfectant and preservative. Mycobacteria are generally highly resistant.

D- Bisphenols: the bisphenols are widely used in antiseptic soaps and hand rinses. In general, they are broad-spectrum but have little activity against *Psudomonas aeruginosa* and molds. **Triclosan** and **hexachlorophene** are bactericidal and sporostatic.

E- Halogen-Releasing Agents: the most important types of chlorine-releasing agents are sodium hypochlorite, chlorine dioxide, and sodium dichloroisocyanurate, which are oxidizing agents that destroy the cellular activity of proteins. Hypochlorous acid is the active compound responsible for the bactericidal and virucidal effect of these compounds. At higher concentrations, these compounds are sporicidal. Iodine is rapidly bactericidal, fungicidal, tuberculocidal, virucidal, and sporicidal. Iodophors (eg, **povidone-iodine**) are complexes of iodine and a solubilizing agent or carrier, which acts as a reservoir of the active I_2.

F- **Heavy Metal Derivatives:** silver sulfadiazine, a combination of two antibacterial agents, Ag^{+} and sulfadiazine, has a broad spectrum of activity. Binding to cell components such as DNA may be responsible for its inhibitory properties.

G- **Organic Acids:** are used as preservatives in the pharmaceutical and food industries. Benzoic acid is fungistatic ; propionic acid is both bacteriostatic and fungistatic.

H- **Peroxygens:** hydrogen peroxide has broad-spectrum activity against viruses, bacteria, yeasts, and bacterial spores. Sporicidal activity requires higher concentrations (10 – 30%) of H_2O_2 and longer contact times.

I- **Phenols:** phenol and many phenolic compounds have antiseptic, disinfectant, or preservative properties.

J- **Quaternary Ammonium Compounds:** these compounds have two region in their molecular structures, one a water-repelling (hydrophobic) group and the other a water-attracting (hydrophilic) group. Cationic detergents, as exemplified by quaternary ammonium compounds (QACs), are useful antiseptics and disinfectants. QACs have been used for a variety of clinical purposes (e.g. preoperative disinfection of unbroken skin) as well as for cleaning hard surfaces. They are sporostatic ; they inhibit the outgrowth of spores but not actual germination process. QACs are also mycobacteriostatic and have an effect on lipid-enveloped but not lipid-nonenveloped viruses.

K- **Vapor-Phase Sterilants:** heat-sensitive medical devices and surgical supplies can be effectively sterilized by vapor-phase systems employing ethylene oxide, formaldehyde, hydrogen peroxide, or peracetic acid.