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Antibiotics

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Part1

Introduction

Antibiotics

An antibiotic is a substance or compound that kills bacteria or inhibits their growth. Antibiotics belong to the broader group of antimicrobial compounds, used to treat infections caused by microorganisms, including fungi and protozoa.

The term "antibiotic" was coined by Selman Waksman in 1942 to describe any substance produced by a microorganism that is antagonistic to the growth of other microorganisms in high dilution. This original definition excluded naturally occurring substances that kill bacteria but are not produced by microorganisms (such as gastric juice and hydrogen peroxide) and also excluded synthetic antibacterial compounds such as the sulfonamides. Many antibiotics are relatively small molecules with a molecular weight less than 2000 Da.

With advances in medicinal chemistry, most antibiotics are now semi synthetic modified chemically from original compounds found in nature, as is the case with beta-lactams (which include the penicillins, produced by fungi in the genus *Penicillium*, the cephalosporins, and the carbapenems). Some antibiotics are still produced and isolated from living organisms, such as the aminoglycosides, and others have been created through purely synthetic means: the sulfonamides, the quinolones, and the oxazolidinones. In addition to this origin-based classification into natural, semi synthetic, and synthetic, antibiotics may be divided into two broad groups according to their effect on microorganisms: Those that kill bacteria are bactericidal agents, whereas those that only impair bacterial growth are known as bacteriostatic agents.

History of Antibiotics

Penicillin, the first natural antibiotic discovered by Alexander Fleming in 1928. Many treatments for infections prior to the beginning of the twentieth century were based on medicinal folklore. Treatments for infection in ancient Chinese medicine using plants with antimicrobial properties were described over 2,500 years ago. Many other ancient cultures, including the ancient Egyptians and ancient Greeks used molds and plants to treat infections. The discovery of the natural antibiotics produced by microorganisms stemmed from earlier work on the observation of antibiosis between micro-organisms. Louis Pasteur observed that, it would offer the greatest hopes for therapeutics. Synthetic antibiotic chemotherapy as a science and the story of antibiotic development began in Germany with Paul Ehrlich, a German medical scientist in the late 1880s. Scientific endeavours to understand the science behind what caused these diseases, the development of synthetic antibiotic chemotherapy, and the isolation of the natural antibiotics marked milestones in antibiotic development.

Originally known as antibiosis, antibiotics were drugs that had actions against bacteria. The term antibiosis, which means "against life," was introduced by the French bacteriologist Vuillemin as a descriptive name of the phenomenon exhibited by these drugs. (Antibiosis was first described in 1877 in bacteria when Louis Pasteur and Robert Koch observed that an airborne bacillus could inhibit the growth of Bacillus anthracis). These drugs were later renamed antibiotics by Selman Waksman, an American microbiologist in 1942. Bacterial antagonism of Penicillium spp. were first described in England by John Tyndall in 1875.

The significance to antibiotic discovery was not realized until the work of Ehrlich on synthetic antibiotic chemotherapy, which marked the birth of the antibiotic revolution. Ehrlich noted that certain dyes would bind to and color human, animal, or bacterial cells, while others did not. He then extended the idea that it might be possible to make certain dyes or chemicals that would act as a magic bullet or selective drug that would bind to and kill bacteria while not harming the human host. After much experimentation, screening hundreds of dyes against various organisms, he discovered a medicinally useful drug, the man-made antibiotic, Salvarsan. In 1928 Fleming made an important observation concerning the antibiosis by penicillin. Fleming postulated that the effect was mediated by a yet-unidentified antibiotic-like compound that could be exploited. Although he initially characterized some of its antibiotic properties, he did not pursue its development. In the meantime, another synthetic antibacterial antibiotic Prontosil was developed and manufactured for commercial use by Domagk in 1932. Prontosil, the first commercially available antibacterial antibiotic, was developed by a research team led by Gerhard Domagk (who received the 1939 Nobel Prize for Medicine for his efforts) at the Bayer Laboratories of the IG Farben conglomerate in Germany. Prontosil had a relatively broad effect against Gram-positive cocci but not against enterobacteria. The discovery and development of this first sulfonamide drug opened the era of antibiotics. In 1939, discovery by Rene Dubos of the first naturally derived antibiotic-like substance named gramicidin from B. brevis. It was one of the first commercially manufactured antibiotics in use during World War II to prove highly effective in treating wounds and ulcers.[16] Florey and Chain succeeded in purifying penicillin.

The purified antibiotic displayed antibacterial activity against a wide range of bacteria. It also had low toxicity and could be taken without causing adverse effects. Furthermore, its activity was not inhibited by biological constituents such as pus, unlike the synthetic antibiotic class available at the time, the sulfonamides. The discovery of such a powerful antibiotic was unprecedented. The development of penicillin led to renewed interest in the search for antibiotic compounds with similar capabilities. Because of their discovery of penicillin Ernst Chain, Howard Florey and Alexander Fleming shared the 1945 Nobel Prize in Medicine. Florey credited Dubos with pioneering the approach of deliberately, systematically searching for antibacterial compounds. Such a methodology had led to the discovery of gramicidin, which revived Florey's research in penicillin.

Production of Antibiotics

Since the first pioneering efforts of Florey and Chain in 1939, the importance of antibiotics to medicine has led to much research into discovering and producing them. The process of production usually involves the screening of wide ranges of microorganisms, and their testing and modification. Production is carried out using fermentation, usually in strongly aerobic form. Antibiotics are small molecules whose synthesis often requires dozens of enzymes. Process of production can divided into two phases is:

1. Trophophase (feeding and growth phase) in which a rapid consumption of nutrients and growth occurred. A lot of new cells are produced and the growth rate can be monitored either by cell count or by measuring the increasing DNA content.

2. Idiophase (decrease of growth and increase production of antibiotics), it can be monitored by decrease RNA synthesis and drop in respiratory

activity. In bacterial cultures, the separation between trophophase and idiophase is clearly observing the growth throughout cell count, but in filamentous actinomycetes and fungi, there is no clear cut between the two phases. It can distinguish between the two phase in filamentous organisms by estimating the dry cell weight or by estimating DNA contents.

Side Effects

Although antibiotics are, in general, considered safe and well-tolerated, they have been associated with a wide range of adverse effects. Side-effects are many and varied, and can be very serious depending on the antibiotics used and the microbial organisms targeted. The safety profiles of newer medications may not be as well established as those that have been in use for many years. Adverse effects can range from fever and nausea to major allergic reactions including photodermatitis and anaphylaxis. One of the more common side-effects is diarrhea, sometimes caused by the anaerobic bacterium *Clostridium difficile*, which results from the antibiotic's disrupting the normal balance of the intestinal flora, Such overgrowth of pathogenic bacteria may be alleviated by ingesting probiotics during a course of antibiotics. An antibiotic-induced disruption of the population of the bacteria normally present as constituents of the normal vaginal flora may also occur, and may lead to overgrowth of yeast species of the genus *Candida* in the vulvo-vaginal area. Other side-effects can result from interaction with other drugs, such as elevated risk of tendon damage from administration of a quinolone antibiotic with a systemic corticosteroid. Certain antibiotics administered by IV (e.g.aminoglycosides, vacomycin) can cause significant permanent hearing loss.

Drug-Drug Interactions

It has been hypothesized that interference of some antibiotics with the efficiency of birth control pills is thought to occur in two ways. Modification of the intestinal flora may result in reduced absorption of estrogens. Second, induction of hepatic liver enzymes causing them to metabolize the pill's active ingredients faster may affect the pill's usefulness. However, the majority of studies indicate that antibiotics do not interfere with contraception. Even though a small percentage of women may experience decreased effectiveness of birth control pills while taking an antibiotic, the failure rate is comparable to the failure rate of those taking the pill. Moreover, there have been no studies that have conclusively demonstrated that disruption of the gut flora affects contraception. Interaction with the combined oral contraceptive pill through induction of hepatic enzymes by the broad-spectrum antibiotic rifampicin has been shown to occur. It is recommended that extra contraceptive measures are applied during antimicrobial therapy using these antimicrobials.

Alcohol

Interactions between alcohol and antibiotics vary depending on the specific antibiotic, and, in some cases, can cause severe side-effects and decrease effectiveness.

"It is sensible to avoid drinking alcohol when taking medication. However, it is unlikely that drinking alcohol in moderation will cause problems if you are taking most "common" antibiotics." However, there are specific types of antibiotics with which alcohol should be avoided completely, because of serious side-effects.

Because of the risks of side-effects and effectiveness, one should check the specific indications on the specific antibiotic, but there is no

categorical danger in mixing alcohol and [some] antibiotics. Despite the lack of a categorical counter indication, the belief that alcohol and antibiotics should never be mixed is widespread, as indicated in a survey in one British clinic.

Patients often assume that they should avoid alcohol when taking any antibiotics this belief has no foundation. One potential source of the myth is from STD clinics in the 1950s and 1960s. Doctors gave the advice for moral reasons as they were worried that alcohol would reduce the inhibitions of sufferers and lead to further spread of diseases such as gonorrhoea. It has been suggested, but not corroborated, that the origin of this myth centers on the fact that, during World War II, penicillin was in short supply and was recycled from urine; convalescing soldiers that drank beer produced a greater volume of urine, and, thus, were banned from drinking beer, leading to the belief that alcohol interacted poorly with antibiotics.

Specific Effects

By way of side-effects, certain antibiotics, including metronidazole, tinidazole, cephamandole, latamoxef, cefoperazone, cefmenoxime, and furazolidone, cause a disulfiram-like chemical reaction with alcohol by inhibiting metabolism by acetaldehyde dehydrogenase, leading to serious side-effects, which include severe vomiting, nausea, and shortness of breath. Alcohol consumption while taking such antibiotics is, therefore, prohibited.

Other effects of alcohol involve the activity of liver enzymes, which break down the antibiotics. In addition, serum levels of doxycycline and erythromycin succinate may, in certain circumstances, be significantly reduced by alcohol consumption.

Antibiotic Resistance

The emergence of antibiotic resistance is an evolutionary process that is based on selection for organisms that have enhanced ability to survive doses of antibiotics that would have previously been lethal. Antibiotics like Penicillin and Erythromycin, which used to be one-time miracle cures are now less effective because bacteria have become more resistant. Antibiotics themselves act as a selective pressure that allows the growth of resistant bacteria within a population and inhibits susceptible bacteria. Antibiotic selection of pre-existing antibiotic resistant mutants within bacterial populations was demonstrated in 1943 by the Luria Delbr experiment. Survival of bacteria often results from an inheritable resistance. Any antibiotic resistance may impose a biological cost. Spread of antibiotic-resistant bacteria may be hampered by reduced fitness associated with the resistance, which is disadvantageous for survival of the bacteria when antibiotic is not present. Additional mutations, however, may compensate for this fitness cost and aids the survival of these bacteria.

The underlying molecular mechanisms leading to antibiotic resistance can vary. Intrinsic resistance may naturally occur as a result of the bacteria's genetic makeup. The bacterial chromosome may fail to encode a protein that the antibiotic targets. Acquired resistance results from a mutation in the bacterial chromosome or the acquisition of extra-chromosomal DNA.

Antibiotic-producing bacteria have evolved resistance mechanisms that have been shown to be similar to, and may have been transferred to, Antibiotic-resistant strains. The spread of antibiotic resistance mechanisms occurs through vertical transmission of inherited mutations from previous generations and genetic recombination of DNA by horizontal genetic exchange.

Antibiotic resistance is exchanged between different bacteria by plasmids that carry genes that encode antibiotic resistance that may result in co-resistance to multiple antibiotics. These plasmids can carry different genes with diverse resistance mechanisms to unrelated antibiotics but because they are located on the same plasmid multiple antibiotic resistances to more than one antibiotic is transferred. On the other hand, cross-resistance to other antibiotics within the bacteria results when the same resistance mechanism is responsible for resistance to more than one antibiotic is selected for.

Antibiotic Misuse

This poster from the U.S. Centers for Disease Control and Prevention "Get Smart" campaign, intended for use in doctor's offices and other healthcare facilities, warns that antibiotics do not work for viral illnesses such as the common cold. The first rule of antibiotics is try not to use them, and the second rule is try not to use too many of them.

Inappropriate antibiotic treatment and overuse of antibiotics have been a contributing factor to the emergence of resistant bacteria. The problem is further exacerbated by self-prescribing of antibiotics by individuals without the guidelines of a qualified clinician and the non-therapeutic use of antibiotics as growth promoters in agriculture. Antibiotics are frequently prescribed for indications, in which their use is not warranted,

An incorrect or sub-optimal antibiotic is prescribed or in some cases for infections likely to resolve without treatment. The overuse of antibiotics like penicillin and erythromycin, which used to be one-time miracle cures, was associated with emerging resistance since the 1950s. Therapeutic usage of antibiotics in hospitals has been seen to be associated with increases in multi-antibiotic-resistant bacteria.

Common forms of antibiotic misuse include excessive use of prophylactic antibiotics in travelers, failure to take into account the patient's weight and history of prior antibiotic use when prescribing, since both can strongly affect the efficacy of an antibiotic prescription, failure to take the entire prescribed course of the antibiotic, failure to prescribe or take the course of treatment at fairly precise correct daily intervals (e.g., "every 8 hours" rather than merely "3x per day"), or failure to rest for sufficient recovery to allow clearance of the infecting organism. These practices may facilitate the development of bacterial populations with antibiotic resistance. Inappropriate antibiotic treatment is another common form of antibiotic misuse. A common example is the prescription and use of antibiotics to treat viral infections such as the common cold that have no effect. One study on respiratory tract infections found "physicians were more likely to prescribe antibiotics to patients who they believed expected them, although they correctly identified only about 1 in 4 of those patients". Multifactorial interventions aimed at both physicians and patients can reduce inappropriate prescribing of antibiotics. Delaying antibiotics for 48 hours while observing for spontaneous resolution of respiratory tract infections may reduce antibiotic usage; however, this strategy may reduce patient satisfaction.

Several organizations concerned with antimicrobial resistance are lobbying to improve the regulatory climate. Approaches to tackling the issues of misuse and overuse of antibiotics by the establishment of the U.S. Interagency Task Force on Antimicrobial Resistance, which aims to actively address the problem antimicrobial resistance, are being organised and coordinated by the US Centers for Disease Control and Prevention, the Food and Drug Administration (FDA), and the National Institutes of Health (NIH), as well as other federal agencies. An NGO campaign group is Keep Antibiotics Working. In France, an "Antibiotics are not

automatic" government campaign starting in 2002 led to a marked reduction of unnecessary antibiotic prescriptions, especially in children. In the United Kingdom, there are NHS posters in many doctors' surgeries indicating that 'no amount of antibiotics will get rid of your cold', with many patients specifically requesting antibiotics from their doctor inappropriately, believing they treat viral infections.

In agriculture, associated antibiotic resistance with the non-therapeutic use of antibiotics as growth promoters in animals resulted in their restricted use in the UK in the 1970 (Swann report 1969). At the current time, there is a EU-wide ban on the non-therapeutic use of antibiotics as growth promoters. It is estimated that greater than 70% of the antibiotics used in U.S. are given to feed animals (e.g., chickens, pigs, and cattle) in the absence of disease. Antibiotic use in food animal production has been associated with the emergence of antibiotic-resistant strains of bacteria including *Salmonella* spp., *Campylobacter* spp., *Escherichia coli*, and *Enterococcus* spp. Evidence from some US and European studies suggest that these resistant bacteria cause infections in humans that do not respond to commonly prescribed antibiotics. In response to these practices and attendant problems. However, delays in regulatory and legislative actions to limit the use of antibiotics are common, and may include resistance to these changes by industries using or selling antibiotics, as well as time spent on research to establish causal links between antibiotic use and emergence of untreatable bacterial diseases. Two federal bills (S.742 and H.R. 2562) aimed at phasing out non-therapeutic antibiotics in US food animal production were proposed but not passed. These bills were endorsed by public health and medical organizations including the American Holistic Nurses Association, the American Medical Association, and the American Public Health Association (APHA). The EU has banned the use of antibiotics as growth promotional agents since 2003.

Sources of Antibiotics

The antibiotics are produced by bacterial microorganisms. Although many antibiotics are chemically synthesized today, antibiotic substances are still being produced from microorganism's bacteria and mold such as *Penicillium chrysogenum* and soil organisms such as *Bacillus brevis* were grown to collect the first crude samples of antibiotics

Application of Antibiotics

Antibiotics are now widely used in many fields:

1.Human medicine (β-lactam compound especially penicillin and cephalosporine, aminoglycoside, sulfa drug, macrolids, antifungal antibiotics like nystatine, anticancer activity including actinomycine D and mitomycin C.

2. Veterinary medicine.

3. Animal feed.

4. Agriculture: insecticides, herbicides, growth regulators.

5. Food industry.

Isolation of Microorganisms

There are many types of microorganisms that can produce antibiotics; among them bacteria, fungi, actinomycetes, etc. each type needs specific conditions for appropriate growth. To grow and isolate certain type of microorganism we need to avoid the growth of other unwanted organisms.

1. To grow bacteria or actinomycetes, it grows in alkaline medium in which fungi cannot grow.

2. To grow fungi the medium must be acidic to prevent the growth of bacteria and actimomycetes.

3. To grow actinomycetes must add antibacterial agent to inhibit bacterial growth.

Structure of Antibiotics

A. Carbohydrate antibiotics

1. Pure saccharides like streptozotocin (an antibiotic use in medicine for treating certain cancer of thepancreatic islet cell).

2. Some antibiotic structure are (a compound containing amino sugars in glycoside linkage is mean they contain monosaccharides joined by glycosidic bond. This named aminoglycosides like streptomycin and neomycin).

3. Other glycosides its mean glycopeptides antibiotic like vancomycin.

B. Macrocyclic lactone (it contains 14-16 membered compounds have substituents which are linked to lactone ring and at least one sugar contains nitrogen like erythromycin.

C. β-Lactam antibiotics are the most important of this class such as penicillins, cephalosporin and cephamycins.

D- Heterocyclic antibiotics (nitrogen or oxygen containing).

E- Aromatic antibiotics such as chloramphenicol is extremely lipid soluble.

Antibiotics Pharmacodynamic

The assessment of the activity of an antibiotic is crucial to the successful outcome of antimicrobial therapy. Non-microbiological factors such as host defense mechanisms, the location of an infection, the underlying disease as well as the intrinsic pharmacokinetic and pharmacodynamic properties of the antibiotic. Fundamentally, antibiotics are classified as either having lethal (bactericidal) action against bacteria or are bacteriostatic, preventing bacterial growth. The bactericidal activity of antibiotics may be growth phase-dependent, and, in most but not all cases, the action of many bactericidal antibiotics requires ongoing cell activity and cell division for the drugs' killing activity. These classifications are based on laboratory behavior; in practice, both of these are capable of ending a bacterial infection. 'In vitro' characterisations of the action of antibiotics to evaluate activity measure the minimum inhibitory concentration and minimum bactericidal concentration of an antimicrobial and are excellent indicators of antimicrobial potency. However, in clinical practice, these measurements alone are insufficient to predict clinical outcome. By combining the pharmacokinetic profile of an antibiotic with the antimicrobial activity, several pharmacological parameters appear to be significant markers of drug efficacy.

The activity of antibiotics may be concentration-dependent and their characteristic antimicrobial activity increases with progressively higher antibiotic concentrations. They may also be time-dependent, where their antimicrobial activity does not increase with increasing antibiotic concentrations; however, it is critical that a minimum inhibitory serum concentration is maintained for a certain length of time. A laboratory evaluation of the killing kinetics of the antibiotic using kill curves is useful to determine the time- or concentration-dependence of.

Antibiotics Pharmacokinetics

Routs of Administration

1. Parenteral: intravenous IV, intramuscular IM and intraosseous (into bone marrow).
2. Topical: epicutanous ointment, gel, ear drop and nasal administration.
3. Enteral: by mouth as tablets, capsules and drop by gastric feeding tube.

Distribution

1. Central compartment: the central compartment includes the well-perfuse organs and tissues (heart, blood, liver, brain and liver) with which drug equilibrates rapidly.
2. Peripheral compartment: it includes those organs (adipose tissue and skeletal muscles) which are less well-perfued therefore equilibrating more slowly.
3. Special compartment: entry of drug into the cerebrospinal fluid (CSF) and central nervous system (CNS). Drug also has relatively poor access too thus making the treatment of infections in these regions difficult.

The passage of antibiotic molecules across cell membrane depends on:

1. The physicochemical nature of antibiotic (molecule size 900-2500), lipid soluble/water soluble) and the cell membrane.
2. Blood flow to organ or tissue.
3. pH difference between plasma and tissue.