Anti-infective Drugs

Anti-infective agents, or antimicrobials, are a special group of chemotherapeutic that kill or damage the pathogenic organisms.

Anti-infective agents are classified by their chemical structures or by their mechanisms of action. Some of these chemicals are made from other living microorganisms (such as the penicillins), and are classified as **antibiotics**. Other chemicals are **synthetics** (such as sulfonamides) or combinations of synthetic and naturally occurring microorganisms which called **semi-synthetics**.

Each new group of these drugs developed from other similar drugs is called a **generation**; the original drugs are referred to as **first-generation drugs**, and later groups are called **second-generation drugs**, **third-generation drugs**, and so on. With each new generation of drugs, certain advantages over the older drugs are usually present. The newer drugs may have improved effectiveness, fewer side effects, or a faster onset of action. They may have additional routes of administration. Because these drugs are new, they may often be more expensive.

An organism that causes infection is a pathogen. A variety of pathogenic organisms exists and may cause diseases in different ways. Bacteria, fungus, virus, parasite (protozoa, worm).

General Properties of Antimicrobial Agents

Antimicrobial agents share certain common properties. We can learn much about how these agents work and why they sometimes do not work by considering such properties as **selective toxicity**, **spectrum of activity**, **mode of action**, **side effects**, and **resistance of microorganisms** to them.

Selective Toxicity

The most fundamental characteristic that an antibiotic must possess is **selective toxicity**, which is the ability to kill or inhibit bacterial growth without harming the patient. Selective toxicity is achievable because the drug accumulates in a microbe at a higher level than in human cells.

Treatment of worm infections is especially difficult because what damages the parasite will also damage the host. In contrast, bacterial pathogens often can be treated by interfering with metabolic pathways not shared by the host. For example, penicillin interferes with cell wall synthesis; it is not toxic to human cells, which lack walls, though some patients are allergic to it.

The Spectrum of Activity

Each antibacterial drug is generally effective for only a limited number of pathogenic bacteria. These susceptible bacteria make up the **antibacterial spectrum** for that particular drug.

Some drugs are effective against a limited number of bacteria, for example, only some gram-positive or only some gram-negative bacteria. These drugs are characterized as having a **narrow antibacterial spectrum**.

Other drugs are effective against a wide spectrum of both gram-positive and gram-negative bacteria. These drugs are referred to as **broad-spectrum antibiotics**, an example is levofloxacin. A broad-spectrum drug is especially useful when a patient is seriously ill with an infection caused by an unidentified organism. Using such a drug increases the chance that the organism will be susceptible to it. However, if the identity of the organism is known, a narrow spectrum drug should be used. Using such a drug minimizes the destruction of the host's microflora, or normal flora, the indigenous microbes that naturally occur in or on the host that sometimes compete with and help destroy infectious organisms. The use of narrow-spectrum drugs also decreases the likelihood that organisms will develop drug resistance.

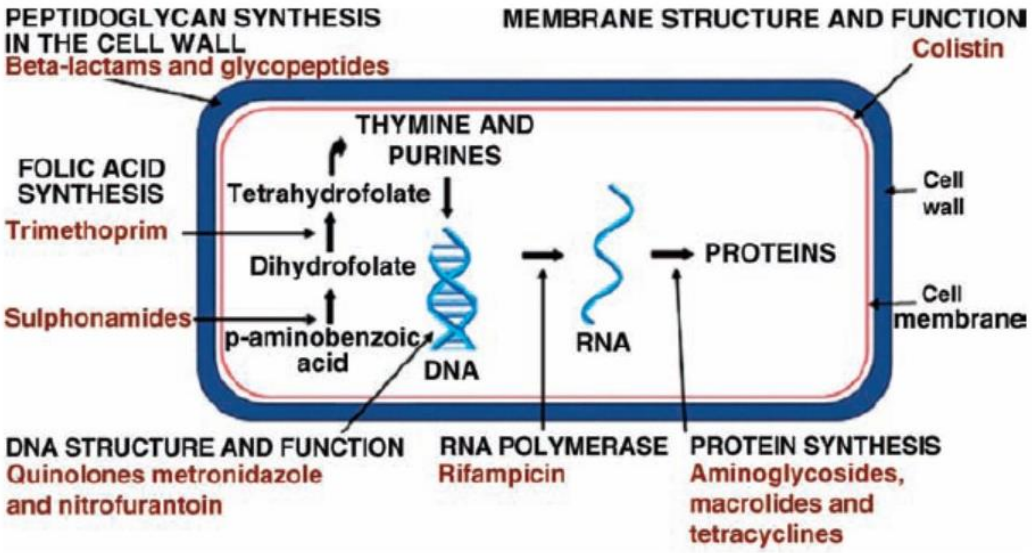
A specimen must be cultured and the antibiotic that is most effective against that particular organism is then determined through sensitivity testing. The correct antibiotics must be given to destroy the pathogen and to limit the adverse effects for the patient.

Bactericidal versus bacteriostatic action: When antimicrobial agents lead to the death of the susceptible microbe (e.g. bacteria) it is said have **bactericidal** action. These are particularly useful in situations in which the normal host defenses cannot be relied on to remove or destroy pathogens. But when it merely inhibits the growth it is said to have **bacteriostatic** action. These drugs depend on the normal host defenses to kill or eliminate the pathogen after its growth has been inhibited. For example, sulfa drugs, which are

frequently prescribed for urinary tract infections, inhibit the growth of bacteria in the bladder until they are eliminated by the body's defenses.

Modes of Action

Different modes of action of antimicrobials are discussed here: (1) inhibition of cell wall synthesis, (2) disruption of cell membrane function, (3) inhibition of protein synthesis, (4) inhibition of nucleic acid synthesis, and (5) Anti-metabolic activity.



Sites of antibiotic action in the bacterial cell.

Antimicrobial Side Effects

Antibiotics may cause adverse or negative reactions, including the following:

• **Allergy** (penicillin and sulfa products cause the most allergies). Allergic reactions can be limited to mild skin rashes and itching, or they can be life-threatening.
• Ototoxicity, nephrotoxicity, and hepatotoxicity (damage to the ears, kidneys, and liver, respectively, that may or may not be reversible if medication is stopped). Some antimicrobials have such severe potential side effects that cause life-threatening conditions. For example, in rare cases, chloramphenicol causes the potentially lethal condition **aplastic anemia,** in which the body is unable to make white and red blood cells. For this reason, chloramphenicol is usually used only when no other alternatives are available.
• Gastrointestinal (GI) distress so severe that it may require stopping the drug.

Antibiotics can also result in **superinfection**, when other organisms that are not sensitive to a prescribed antibiotic (for example, yeast) are able to multiply, overgrow, and get out of control because the antibiotic

also killed the normal bacteria, or normal flora, that would have kept them under control. **Pseudomembranous colitis** is a condition now commonly seen in hospitals and nursing homes that arises from superinfections

caused by ***Clostridium difficile***. A super infection may develop if an antibiotic is given unnecessarily, like prescribing penicillin for a viral infection. Penicillin cannot fight the viral infection but it may destroy the normal flora helping to maintain balance in the body.

Antibiotics are not effective against viral, parasitic, or fungal infections and other antimicrobials are required. However, it is common for a patient with a viral or fungal infection to also develop a bacterial infection, because the body's defenses are weakened. A secondary infection occurs when one infection follows another. In a mixed infection, both infections are present at the same time. For example, an individual may have a viral infection that produces a cold. Then, when the patient is weakened and ill, their body might become infected with a bacteria causing pneumonia, which is then a secondary infection.

RESISTANCE TO ANTIMICROBIALS

Just as humans are assembling a vast array of antimicrobial drugs, microorganisms have their own genetic toolbox of mechanisms to avoid their effects. In some cases, certain types of bacteria are inherently resistant to the effects of a particular drug; this is called **innate,** or **intrinsic, resistance.** Members of the genus *Mycoplasma* lack a cell wall, so, not surprisingly, they are resistant to any drug such as penicillin that exerts its action by interfering with cell wall synthesis. Many Gram-negative organisms are intrinsically resistant to certain drugs because the lipid bilayer of their outer membrane excludes entry of the drug. In other instances, previously sensitive organisms develop resistance through spontaneous mutation or the acquisition of new genetic information; this is called **acquired resistance.**

Genetic Basis of Resistance

1-Chromosome-Mediated Resistance

Chromosomal resistance is due to a mutation in the gene that codes for either the
target of the drug or the transport system in the membrane that controls the uptake of the drug. The frequency of spontaneous mutations which is much lower than the frequency of acquisition of resistance plasmids. Therefore, chromosomal resistance is less of a clinical problem than is plasmid-mediated resistance.

2-Plasmid-Mediated Resistance

Plasmid-mediated resistance is very important from a clinical point of view for three reasons: It occurs in many different species, especially gram-negative rods.

Plasmids frequently mediate resistance to multiple drugs. Plasmids have a high rate of transfer from one cell to another, usually by conjugation.

Resistance plasmids (resistance factors, R factors) are extrachromosomal, circular, double-stranded DNA molecules that carry the genes for a variety of enzymes that can degrade antibiotics and modify membrane transport systems.

3-Transposon-Mediated Resistance

Transposons are genes that are transferred either within or between larger pieces of DNA such as the bacterial chromosome and plasmids.

B-Non-genetic Basis of Resistance

1-Bacteria can be in a resting state, i.e., not growing; they are therefore insensitive to cell wall inhibitors such as penicillins and cephalosporins.

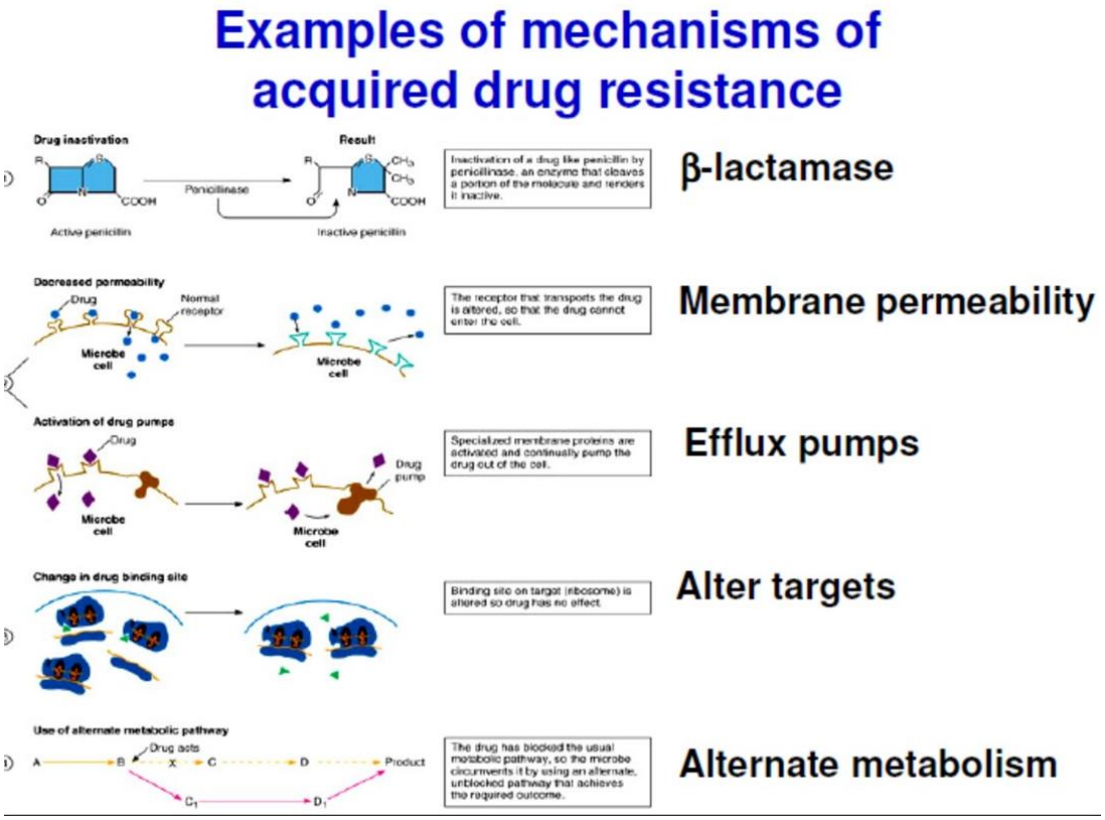
Similarly, *M. tuberculosis* can remain dormant in tissues for many years, during which time it is insensitive to drugs.

2-Under certain circumstances, organisms that would ordinarily be killed by penicillin can lose their cell walls, survive as protoplasts, and be insensitive to cell wall–active drugs.

Mechanisms of resistance to antibiotics:

1- Production of enzymes that inactivate the drug (eg. β -lactamase, which inactivates beta lactam antibiotics; acetyl transferases, which inactivate chloramphenicol; kinases and other enzymes, which inactivate aminoglycosides.

2- Alteration of Membrane Permeability- Change in the receptor that binds the drug.
3- Efflux pumps – Membrane proteins many Gram-negatives that pump out drug.
4- Alteration of Targets – usually affects ribosomes.
5- Alteration of Metabolic Pathway – Development of alternate pathway



Chemoprophylaxis refers to the use of antibiotics before bacterial infection has developed in order to prevent infection.

- Chemoprophylaxis is indicated before certain surgeries that carry a high risk for infection; for example, abdominal surgery.
- Individuals who are susceptible to certain infections (rheumatic fever, heart valve replacement, knee and hip replacement. These individuals should receive chemoprophylaxis before dental, respiratory, urinary, and other invasive medical procedures.
- In addition, individuals exposed to patients with tuberculosis, meningitis, and other contagious infections are often given chemoprophylaxis to prevent infection.

COMBINATIONS OF ANTIMICROBIAL DRUGS

It is therapeutically advisable to treat patients with a single agent that is most specific to the infecting organism. This strategy reduces the possibility of superinfections, decreases the emergence of resistant organisms, and minimizes toxicity. However, in some situations, combinations of antimicrobial drugs are advantageous or even required.

A. Advantages of drug combinations

Certain combinations of antibiotics, such as β-lactams and aminoglycosides, show synergism; that is, the combination is more effective than either of the drugs used separately. Because such synergism among antimicrobial agents is rare, synergistic combinations are only indicated in special situations (for example, in the treatment of enterococcal endocarditis). Combinations may also be used when an infection is of unknown origin or when there are organisms with variable sensitivity, such as when treating tuberculosis.

B. Disadvantages of drug combinations

A number of antibiotics act only when organisms are multiplying. Thus, coadministration of an agent that causes bacteriostasis plus a second agent that is bactericidal may result in the first drug interfering with the action of the second. For example, bacteriostatic tetracycline drugs may interfere with the bactericidal effects of penicillins and cephalosporins. Another concern is the risk of selection pressure and the development of antibiotic resistance by giving unnecessary combination therapy.