Pharmacology

Theoretical

**الدكتور الصيدلاني:** **حسن عبد علي شبوط**

**L.13**

**Anti-infectives**

**Anti-infectives** are drugs that can either **kill** an infectious agent or inhibit it from spreading.

* Anti-infectives include antibiotics and antibacterials, antifungals, antivirals and antiproatozoans.

Antibiotics

* An antibiotic is an agent that either kills or inhibits the growth of a microorganism
* **antibiotic**: antibacterial drug obtained from other microorganisms.
* **antimicrobial:** antibacterial drugs obtained by chemical synthesis and not from other microorganisms.
* **bacteria**: single-celled microorganisms, some of which cause disease.
* **bacterial resistance:** ability of some bacteria to resist the actions of antibiotics.
* **bactericidal:** antibiotic that kills bacteria.
* **bacteriostatic:** antibiotic that inhibits the growth of, but does not kill, bacteria.
* **broad-spectrum:** drug that is effective against a wide variety of both gram-positive and gram-negative pathogenic bacteria.

Overview

* Antimicrobial therapy takes advantage of the biochemical differences that exist between microorganisms and human beings.
* Antimicrobial drugs are effective in the treatment of infections because of their selective toxicity; that is, they have the ability to injure or kill an invading microorganism without harming the cells of the host.

Selection of Antimicrobial Agents ------------------------------------

Selection of the most appropriate antimicrobial agent requires knowledge of

* 1) the organism's identity,
* 2) the organism's susceptibility to a particular agent,
* 3) the site of the infection,

* 4) patient factors,
* 5) the safety of the agent, and
* 6) the cost of therapy.

Combinations of Antimicrobial Drugs ---------------------

* It is therapeutically advisable to treat patients with the single agent that is most specific for the infecting organism.
* This strategy reduces the possibility of superinfection, decreases the emergence of resistant organisms and minimizes toxicity.
* However, situations in which combinations of drugs are employed do exist. For example, the treatment of tuberculosis benefits from drug combinations.
1. **Advantages of drug combinations**
* Certain combinations of antibiotics, such as beta-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, multiple drugs used in combination are only indicated in special situations for example, when an infection is of unknown origin.

**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 effect of penicillins and cephalosporins.

Drug Resistance ------------------------

* Bacteria are said to be resistant to an antibiotic if the maximal level of that antibiotic that can be tolerated by the host does not halt their growth.
* Some organisms are inherently resistant to an antibiotic. For example, gram-negative organisms are inherently resistant to vancomycin.
* However, microbial species that are normally responsive to a particular drug may develop more virulent, resistant strains through spontaneous mutation or acquired resistance and selection.
* Some of these strains may even become resistant to more than one antibiotic.

Prophylactic Antibiotics -------------------------

* Certain clinical situations require the use of antibiotics for the prevention rather than the treatment of infections . Because the indiscriminate use of antimicrobial agents can result in bacterial resistance and superinfection, prophylactic use is restricted to clinical situations in which the benefits outweigh the potential risks.
* The duration of prophylaxis is dictated by the duration of the risk of infection.

Hypersensitivity ---------------------------------

* Hypersensitivity reactions to antimicrobial drugs or their metabolic products frequently occur. For example, the penicillins, despite their almost absolute selective microbial toxicity, can cause serious hypersensitivity problems, ranging from urticaria (hives) to anaphylactic shock.

Superinfections ----------------------------------

* Drug therapy, particularly with broad-spectrum antimicrobials or combinations of agents, can lead to alterations of the normal microbial flora of the upper respiratory, intestinal, and genitourinary tracts, permitting the overgrowth of opportunistic organisms, especially fungi or resistant bacteria.
* These infections are often difficult to treat.

Class of antibiotic

* **Cell Wall Inhibitors**

Overview

* Some antimicrobial drugs selectively interfere with synthesis of the bacterial cell wall structure that mammalian cells do not possess.
* The cell wall is composed of a polymer called peptidoglycan that consists of glycan units joined to each other by peptide cross-links.
* To be maximally effective, inhibitors of cell wall synthesis require actively proliferating microorganisms; they have little or no effect on bacteria that are not growing and dividing.

**Penicillin ===============**

* The penicillins are among the most widely effective antibiotics and also the least toxic drugs known, but increased resistance has limited their use.

* Members of this family differ from one another in the R substituent attached to the 6-aminopenicillanic acid residue .
* The nature of this side chain affects the antimicrobial spectrum, stability to stomach acid, and susceptibility to bacterial degradative enzymes
* Penicillin is an antibiotic that disturbs the cell wall synthesis in bacteria.
* It was initially derived from the mold Penicillium rubrum. Since then, a number of naturally occurring penicillins have been derived e.g. penicillin G (benzylpenicillin) and penicillin V (phenoxymethylpenicillin).
* Other antibiotics obtained from penicillins include amoxicillin, ampicillin, flucloxacillin. These are classed as semisynthetic penicillins.
* Penicillins are bactericidal and mainly active against gram-positive bacteria.
* The most important side effect of penicillins is hypersensitivity, such as rashes or anaphylaxis. Patients who are allergic to one penicillin will be allergic to all.

Natural penicillins --------------------------

* Natural Penicillins were the first antibiotics used in clinical practice. They are based on the original penicillin- G structure. They inhibit bacterial cell wall synthesis and are generally bactericidal.
* Natural penicillins are effective against gram positive bacteria such as staphylococci, streptococci and gram negative bacteria such as meningococci, Treponema, Borrelia and Leptospira.

Penicillinase resistant penicillins -----------

* Penicillinase resistant penicillins are antibiotics, which are not inactivated by the penicillinase enzyme.
* Some bacteria produce the enzyme penicillinase that destroys the beta-lactam ring of the antibiotic, making the penicillin ineffective.
* Penicillinase resistant penicillins are used to treat resistant strains of staphylococci and other infections.

Ex : cloxacillin

Aminopenicillins -------------------------

* Aminopenicillins are bactericidal beta-lactam antibiotics, which work by inhibiting bacterial cell wall synthesis. They are chemically similar to penicillin but have a broader spectrum of activity than penicillin.
* Aminopenicillins are not deactivated by acid hydrolysis so they can be administered orally, they are however susceptible to hydrolysis by beta-lactamase and therefore are sometimes given with beta-lactamase inhibitors.
* Aminopenicillins are effective against most gram-positive bacterial infections and gram-negative infections such as E.coli and H.influenza.
* They are used to treat upper and lower respiratory tract infections, endocarditis urinary tract infections, skin infections, and so on.

Ex :Amoxicillin

 Ampicillin

Beta-lactamase inhibitors ----------------

* Beta-lactamase inhibitors block the activity of beta-lactamase enzymes.
* Some species of bacteria produce beta-lactamase enzymes, which cleave the beta-lactam group in antibiotics, such as penicillin, that have a beta-lactam ring in their structure. In doing so the beta-lactamase enzyme inactivates the antibiotic and becomes resistant to that antibiotic. To avoid development of resistance, beta-lactamase inhibitors are administered with the beta-lactam antibiotics so the action of beta-lactamase is inhibited. This tends to widen the spectrum of antibacterial activity.

**Ex : Amoxicillin and Clavulanate**

Antipseudomonal penicillins ---------------------

* Antipseudomonal penicillins are antimicrobial agents, which are used to treat pseudomonal infections.
* They have the activity of penicillins and aminopenicillins, and additional activity against Pseudomonas, Enterococcus and Klebsiella.
* Antipseudomonal penicillins are usually given with beta-lactamase inhibitors because like other penicillins they are susceptible to hydrolysis by beta-lactamases (therefore are not consistently active against Staphylococcus, some gram-negative rods and certain beta-lactamse producing gram-negative anaerobes).
* These penicillins when given with aminoglycosides work effectively and avoid development of resistance strains of bacteria.

**Ex : Piperacillin**

**Cephalosporins**

* Cephalosporins are a group of broad spectrum, semi-synthetic beta-lactam antibiotics derived from the mould Cephalosporium.
*
* The mechanism of action of cephalosporins is the same as penicillins. They interfere with bacterial cell wall synthesis.
* They are classified according to the chronological order in which they were produced.
* 10% of patients with allergic hypersensitivity to penicillins and/or carbapenems also having cross-reactivity with cephalosporins

First generation cephalosporins ------------

* First generation Cephalosporins, were the first lot of this class of antibiotics that were produced.

**Cephalexin ( Keflex cap )**

* Cephalexin is in a group of drugs called cephalosporin antibiotics and is used to fight bacteria in the body. It works by interfering with the bacteria's cell wall formation, causing it to rupture, and killing the bacteria.
* Cephalexin is used to treat infections caused by bacteria, including upper respiratory infections, ear infections, skin infections, and urinary tract infections.

Second generation cephalosporins ---------

* Second generation cephalosporins followed the first generation cephalosporins.
* Generic Name: **cefuroxime**
* Brand Name: Zinacef
* Third generation cephalosporins -------------
* **Ceftriaxone** (injectable powder for injection, intravenous solution)

 Like other third-generation cephalosporins, it has broad-spectrum activity against Gram-positive bacteria and expanded Gram-negative coverage compared to second-generation agents. In most cases, it is considered to be equivalent to cefotaxime in terms of safety and efficacy.

* Generic Name: **cefotaxime**
* Brand Name: Claforan (injectable powder for injection, intravenous solution)
* Generic Name: **cefixime**

 Brand Name: Suprax cap or suspension

* Fourth generation cephalosporins -------------
* **Cefepime**

 has an extended spectrum of activity against Gram-positive and Gram-negative bacteria, with greater activity against both Gram-negative and Gram-positive organisms than third-generation agents.

* Cefepime is a broad spectrum cephalosporin antibiotic and has been used to treat bacteria responsible for causing pneumonia and infections of the skin and urinary tract. Some of these bacteria include Pseudomonas, Escherichia, and Streptoccusspecies.

**Carbapenems**

* Carbapenems are a class of beta-lactam antibiotics. They have broad-spectrum antibacterial activity, being active against many aerobic and anaerobic gram-positive and gram-negative organisms.
* Carbapenems inhibit bacterial cell wall synthesis by binding to the penicillin binding proteins and interfering with cell wall formation. They are extremely resistant to beta-lactamase enzymes, making them very useful in treating bacterial infections where beta-lactamase is produced that makes other beta-lactam antibiotics ineffective.
* **Imipenem**

Mechanism of action

Imipenem acts as an antimicrobial through inhibiting cell wall synthesis of various Gram-positive and Gram-negative bacteria. It remains very stable in the presence of beta-lactamase (both penicillinase and cephalosporinase) produced by some bacteria, and is a strong inhibitor of beta-lactamases from some Gram-negative bacteria that are resistant to most beta-lactam antibiotics.

* **Meropenem**

Meropenem is an ultra-broad-spectrum injectable antibiotic used to treat a wide variety of infections.

**Vancomycin**

* Vancomycin is a tricyclic glycopeptide that has become increasingly important because of its effectiveness against multiple drug-resistant organisms, such as MRSA and enterococci. The medical community is presently concerned with emergence of vancomycin resistance in these organisms.
* is a mixture of polypeptides that also inhibits bacterial cell wall synthesis.
* It is active against a wide variety of gram-positive organisms. Its use is restricted to topical application because of its potential for nephrotoxicity with systemic use.
* \* MRSA ( Methicillin-resistant Staphylococcus epidermidis )
* Dose-related hearing loss has occurred in patients with renal failure who accumulate the drug.
* Ototoxicity and nephrotoxicity are more common when vancomycin is administered with another drug (for example, an aminoglycoside) that can also produce these effects.

Protein Synthesis Inhibitors

* A number of antibiotics exert their antimicrobial effects by targeting the bacterial ribosome, which has components that differ structurally from those of the mammalian cytoplasmic ribosome.

**Tetracyclines ==============**

* Tetracyclines are broad-spectrum antibiotics derived from cultures of Streptomyces bacteria, and work by inhibiting protein synthesis after uptake into susceptible organisms.
* They work by reversibly binding to the 30S ribosome of the microbial RNA and preventing the attachment of aminoacyl-tRNA with the acceptor site on the 70S ribosome. Their activity is bacteriostatic and not bacteriocidal.
* **Tetracycline**

It is commonly used to treat acne today, and, more recently, rosacea, and is historically important in reducing the number of deaths fromcholera.

* **Doxycycline**

Doxycycline is used to treat many different bacterial infections, such as urinary tract infections,acne, gonorrhea, and chlamydia, periodontitis (gum disease), and others.

Doxycycline is also used to treat blemishes, bumps, and acne-like lesions caused by rosacea. It will not treat facial redness caused by rosacea.

**Aminoglycosides =================**

* Aminoglycosides are a group of bactericidal antibiotics, which act by inhibiting bacterial protein synthesis. Their use is restricted because of potential side effects, as they can cause ear and kidney damage.
* All the aminoglycosides resemble each other in antibacterial activity, pharmacokinetics and toxicity.
* Aminoglycosides are not well absorbed when given orally, so need to be given intravenously for systemic infections.
* Aminoglycosides are used when other less toxic antibiotics are contraindicated or ineffective. They are mainly active against aerobic gram-negative bacilli, staphylococci and Mycobacterium tuberculosis, but lack activity against anaerobes.
* **Gentamicin**
* **Amikacin**

**Macrolides ==============**

* Macrolides are a class of antibiotics found in streptomycetes.
* Macrolides bind to the 50S subunit of the bacterial ribosome and inhibit ribosomal translocation, leading to inhibition of bacterial protein synthesis.
* Their action is primarily bacteriostatic but may be bactericidal at high concentrations, or depending on the type of microorganism.
* Macrolides mainly affect gram-positive cocci and intracellular pathogens such as mycoplasma, chlamydia, legionella.
* **Erythromycin**

Erythromycin is an antibiotic useful for the treatment of a number of bacterial infections. It is in the macrolide class and has an antimicrobial spectrum similar to or slightly wider than that of penicillin, and is often prescribed for people who have an allergy to penicillins.

* **Clarithromycin**

Clarithromycin is used to treat many different types of bacterial infections affecting the skin andrespiratory system. It is also used together with other medicines to treat stomach ulcers

* **Azithromycin**

**Chloramphenicol ===============**

* Chloramphenicol is active against a wide range of gram-positive and gram-negative organisms.
* However, because of its toxicity, its use is restricted to life-threatening infections for which no alternatives exist.

**Antituberculosis agents**

* Antituberculosis agents are drugs used to treat tuberculosis, an infectious disease caused by Mycobacterium tuberculosis.
* This infection mainly affects the lungs but can also affect many other organ systems. Many classes of drugs, with different mechanism of action have activity against Mycobacterium tuberculosis.
* Tuberculosis chemotherapy involves giving two to four drugs simultaneously. These drugs work differently so they target the organism in different ways and using a few types of drugs prevents drug resistant strains of Mycobacterium from evolving.
* **Isoniazid/ rifampin**
* **Isoniazid/ pyrazinamide/ rifampin**

**Quinolones**

* Quinolones are synthetic, bactericidal antibacterial agents with broad-spectrum activity.
* They inhibit the enzyme topoisomerase II, a DNA gyrase that is necessary for the replication of the microorganism. Topoisomerase II enzyme produces a negative supercoil on DNA, permitting transcription or replication so by inhibiting this enzyme DNA replication and transcription is blocked.
* **Ciprofloxacin**

- Ciprofloxacin is an antibiotic in a group of drugs called fluoroquinolones (flor-o-KWIN-o-lones). Ciprofloxacin fights bacteria in the body.

 - Ciprofloxacin is used to treat different types of bacterial infections. It is also used to treat people who have been exposed to anthrax.

**Sulfonamides**

* Sulphonamides (sulfa drugs) are one of a group of drugs derived from sulphanilamide that prevents the growth of bacteria.
* Sulphonamides compete with p-aminobenzoic acid (PABA) for the enzyme dihydropteroate synthetase, which is important in the formation of folic acid that is required by the bacteria.
* Folic acid is required for the synthesis of precursors of DNA and RNA both in bacteria and in mammals. Mammals obtain their folic acid in their diet but bacteria need to synthesize it.
* Sulphonamides inhibit the growth of bacteria but do not kill them i.e. their action is bacteriostatic.
* Many sulphonamides are rapidly excreted and very soluble in urine so they are used to treat infections of the urinary tract.
* **Sulfamethoxazole/ trimethoprim**