Lec. 1 **PHARMACOLOGY** **Dr. Hanadi H. Al-Khafaji**

INTODUCTION TO ANTIMICROBIALS

Antibiotics: are chemical substances obtained from microorganisms that kill or suppress growth of other microorganisms at a very low concentration.

Bactericidal agents: They kill or destroy microorganisms.

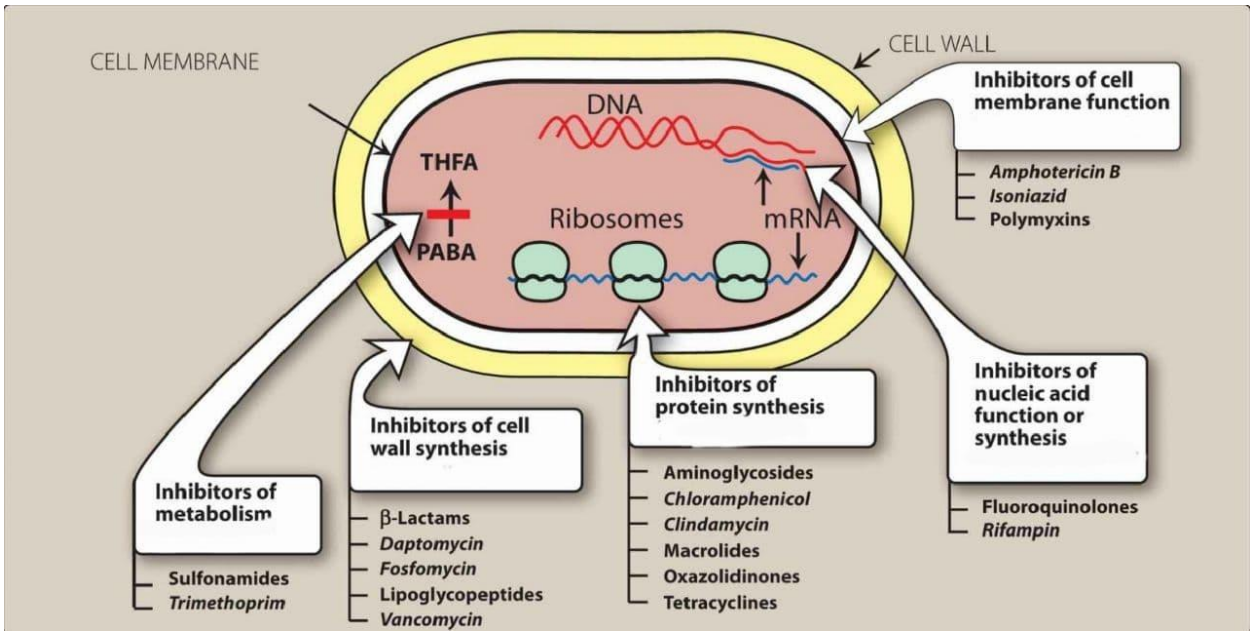
Bacteriostatic agents: They inhibit the growth and multiplication of microorganisms. At high concentration, some of the 'static' drugs may produce 'cidal' effect.

Antimicrobial agents: Antimicrobial agents are synthetic as well as naturally obtained drugs that act against microorganisms.

Resistance: is defined as the unresponsiveness of a microorganism to an antimicrobial agent. The resistance may be natural or acquired. The natural resistance is genetically determined. In acquired resistance, microbes that initially respond to an antimicrobial agent later develop resistance to the same agent by mutation or gene transfer.

Classification of Antimicrobial Agents by their site of action:

1. Cell wall inhibitors.
2. Protein synthesis inhibitors.
3. Cell membrane function inhibitors.
4. Metabolism inhibitors.
5. Nucleic acid function or synthesis inhibitors.



Cell Wall Inhibitors:

The bacterial cell wall is a rigid outer layer that completely surrounds the cytoplasmic membrane (the mammalian cells do not possess cell wall). Cell wall inhibitors selectively interfere with synthesis of the bacterial cell wall. The cell wall is composed of a polymer called peptidoglycan that consists of glycan units joined to each other by peptide cross-links Inhibitors of cell wall synthesis require actively proliferating microorganisms.

I. Penicillins:

#Mechanism of action: Penicillins interfere with the last step of bacterial cell wall synthesis, which is the cross-linking of adjacent peptidoglycan strands by a process known as transpeptidation. Since penicillins structurally resemble the terminal portion of the peptidoglycan strand, they compete for and bind to enzymes called penicillin-binding proteins (PBPs), which catalyze transpeptidase and facilitate cross-linking of the cell wall. The result is the formation of a weakened cell wall and ultimately cell death. For this reason, penicillins are regarded as bactericidal.(Bacteriostatics should not be taken with penicillins?)

- Natural penicillins:

Penicillin G (benzylpenicillin): It is destroyed by gastric acid (acid labile); hence penicillin G is usually given by IV route. It can also be administered by IM route but is painful. Penicillin G is widely distributed in body tissues, but poorly crosses the BBB; although during meningitis, adequate amount reaches the CSF. Penicillin G is rapidly excreted in urine mainly by active tubular secretion. Since renal function is not completely developed in infants and neonates, hence excretion of penicillins is slow. The action of penicillins can be augmented and prolonged by giving probenecid simultaneously

The duration of action of penicillin G is increased by combining it with poorly water-soluble compounds, such as procaine (procaine penicillin G) or benzathine (benzathine penicillin G) to yield aqueous suspensions. They are called depot penicillins.

Penicillin remains the drug of choice for the treatment of gas gangrene (Clostridium perfringens) and syphilis (Treponema pallidum).

Penicillin V: only available in oral formulation, has a spectrum similar to that of penicillin G, but it is not used for treatment of severe infections because of its limited oral absorption. Penicillin V is more acid stable than is penicillin G and is the oral agent employed in the treatment of less severe infections.

- Semisynthetic penicillins (aminopenicillins) or (extended spectrum penicillins)

They have broad antibacterial spectrum and are effective against both gram positive and gram negative organisms. They are hydrolysed by penicillinase.

Ampicillin and *amoxicillin* These extended-spectrum agents are also widely used in the treatment of respiratory infections, and amoxicillin is employed prophylactically by dentists in high-risk patients for the prevention of bacterial endocarditis.

These drugs are coformulated with β-lactamase inhibitors, such as clavulanic acid or sulbactam, to combat infections caused by β-lactamase–producing organisms.

- Penicillinase-resistant penicillins (Antistaphylococcal penicillins):

These penicillins are useful for the treatment of infections involving penicillinase-producing bacteria, such as Staphylococcus aureus or S. epidermidis.

Methicillin, the first antistaphylococcal penicillin to be developed, is no longer used clinically because of its toxicity (interstitial nephritis).

Oxacillin and *nafcillin* given by intermittent intravenous infusion are considered drugs of choice for serious staphylococcal infections such as endocarditis.

Dicloxacillin given orally is suitable for treatment of mild to moderate localized staphylococcal infections.

The penicillinase-resistant penicillins have minimal to no activity against gram-negative infections.

- Antipseudomonal penicillin: (-ve charged.drug interaction?)

Piperacillin is also referred to as an antipseudomonal penicillin because of its activity against Pseudomonas aeruginosa. Formulation of piperacillin with tazobactam (available only as parenteral preparation) extends the antimicrobial spectrum to include penicillinase-producing organisms.

#Adverse reactions to penicillins: Penicillins are among the safest drugs. However, adverse reactions may occur:

1. Hypersensitivity reactions range from rashes to angioedema (marked swelling of the lips, tongue, and periorbital area) and anaphylaxis. Cross-allergic reactions occur among the βlactam antibiotics. To determine whether treatment with a β-lactam is safe when an allergy is noted, patient history regarding severity of previous reaction is essential.
2. Diarrhea is a common problem that is caused by a disruption of the normal balance of intestinal microorganisms. It occurs to a greater extent with those agents that are incompletely absorbed and have an extended antibacterial spectrum. Pseudomembranous colitis from Clostridium difficile and other organisms may occur with penicillin use.
3. Nephritis: Penicillins, particularly methicillin, have the potential to cause acute interstitial nephritis. [Note: Methicillin is therefore no longer used clinically].
4. Neurotoxicity: The penicillins are irritating to neuronal tissue, and they can provoke seizures if injected intrathecally or if very high blood levels are reached.
5. Hematologic toxicities: Decreased coagulation may be observed with high doses of piperacillin and nafcillin (and, to some extent, with penicillin G). Cytopenias have been associated with therapy of greater than 2 weeks, and therefore, blood counts should be monitored weekly for such patients.

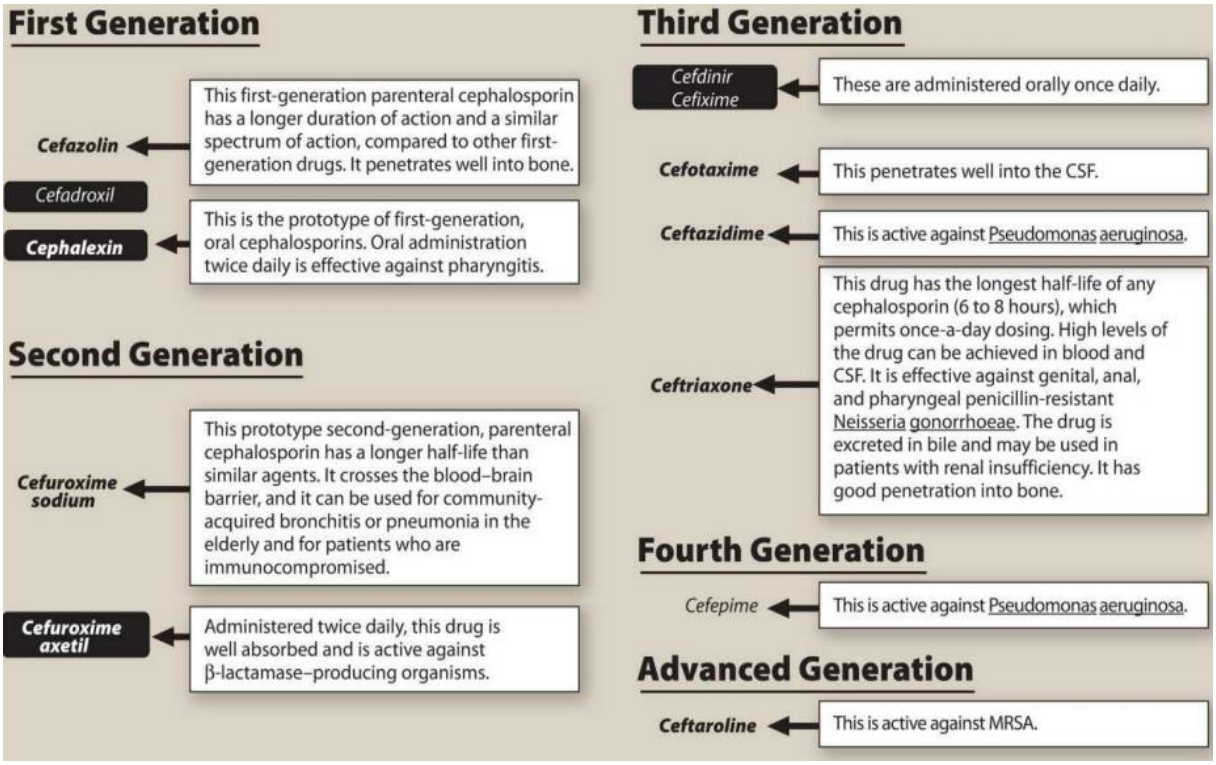
II. Cephalosporins:

The cephalosporins are β-lactam antibiotics closely related both structurally and functionally to penicillins. They tend to be more resistant than the penicillins to certain β-lactamases. Cephalosporins have been classified as first, second, third, fourth, and advanced generation, based largely on their bacterial susceptibility patterns and resistance to β-lactamases.

1. First generation: *cefazolin* and oral *cephalexin* act as penicillin G substitutes. They are resistant to the staphylococcal Penicillinase. They are the most active cephalosporins for Gram-positive bacterial infections
2. Second generation: *cefoxitin* and oral *cefuroxime* display greater activity against gram-negative organisms.
An important use of first- and second-generation cephalosporins is prophylaxis during surgery if an infection is likely to occur.
3. Third generation: These cephalosporins have assumed an important role in the treatment of infectious diseases. *Ceftriaxone* and *cefotaxime* have become agents of choice in the treatment of meningitis. *Cefixime* (Suprax) is an oral preparation.
4. Fourth generation: *Cefepime* must be administered parenterally. Cefepime has a wide antibacterial spectrum.
5. Advanced generation: *Ceftaroline* is a broad-spectrum, advanced-generation cephalosporin. The twice-daily dosing regimen also limits use outside of an institutional setting.

#Adverse effects:

Like the penicillins, the cephalosporins are generally well tolerated. However, allergic reactions are a concern.
Patients who have had an anaphylactic response, Stevens-Johnson syndrome, or toxic epidermal necrolysis to penicillins should not receive cephalosporins. Cephalosporins should be avoided or used with caution in individuals with penicillin allergy.
The highest rate of allergic cross-sensitivity is between penicillin and first-generation cephalosporins.



III. Other β-Lactam Antibiotics:

- Carbapenems: are synthetic β-lactam antibiotics that inhibit cell wall transpeptidation.

This results in bactericidal activity against most bacteria . *Imipenem, meropenem, doripenem,* and *ertapenem* are drugs in this group. Imipenem undergoes cleavage by a dehydropeptidase found in the brush border of the proximal renal tubule. Compounding imipenem with *cilastatin* protects the parent drug from renal dehydropeptidase and, thus, prolongs its activity in the body. The other carbapenems do not require coadministration of cilastatin.

- Monobactams: *Aztreonam*

1. It decreases cell wall formation and thus is bactericidal.
2. Only aerobic Gram-negative bacteria, especially Pseudomonas, are affected.

There is no activity against Gram-positive bacteria or anaerobes.

3. It is resistant to most β-lactamases.
4. Kinetics are similar to the penicillins, although it must be administered parenterally.
5. There is no cross-allergenicity with penicillins.

IV. β-Lactamase Inhibitors:

β-Lactamase inhibitors, such as clavulanic acid, sulbactam, and tazobactam, contain a β-lactam ring but, by themselves, do not have significant antibacterial activity or cause any significant adverse effects. They function by inactivating β-lactamases, thereby protecting the antibiotics that are normally substrates for these enzymes. The β-lactamase inhibitors are, therefore, formulated in combination with βlactamase–sensitive antibiotics, such as amoxicillin, ampicillin, and piperacillin.

V. Vancomycin:

Following cell entry, it binds to peptidoglycan precursors, disrupting polymerization and cross-linking required for maintenance of cell wall integrity. This interaction results in bactericidal activity.

Due to an increase in MRSA, vancomycin is commonly used in patients with skin and soft tissue infections, infective endocarditis, and nosocomial pneumonia.

Common adverse events include nephrotoxicity, infusion-related reactions (red man syndrome and phlebitis), and ototoxicity.

Vancomycin has poor absorption after oral administration, so use of the oral formulation is limited to the management of Clostridium difficile infection in the colon.

VI. Daptomycin:

Daptomycin is a bactericidal antibiotic. It is indicated for the treatment of complicated skin and skin structure infections and bacteremia caused by S. aureus, including those with right-sided infective endocarditis. Efficacy of treatment with daptomycin in left-sided endocarditis has not been demonstrated. Additionally, daptomycin is inactivated by pulmonary surfactants; thus, it should never be used in the treatment of pneumonia. Daptomycin is dosed IV once daily.

VII. Fosfomycin

Fosfomycin is a bactericidal synthetic derivative of phosphonic acid. It blocks cell wall synthesis by inhibiting the enzyme enolpyruvyl transferase, a key step in peptidoglycan synthesis. It is indicated for urinary tract infections caused by E. coli or E. faecalis and is considered first-line therapy for acute cystitis. Due to its unique structure and mechanism of action, cross-resistance with other antimicrobial agents is unlikely. Fosfomycin is rapidly absorbed after oral administration and distributes well to the kidneys, bladder, and prostate. The drug is excreted in its active form in the urine and maintains high concentrations over several days, allowing for a one-time dose.

The most commonly reported adverse effects include diarrhea, vaginitis, nausea, and headache.

VIII. Polymyxins

The polymyxins are cation polypeptides that bind to phospholipids on the bacterial cell membrane of gram-negative bacteria. They have a detergent-like effect that disrupts cell membrane integrity, leading to leakage of cellular components and cell death.

Only two forms of polymyxin are in clinical use today, polymyxin B
and colistin (polymyxin E). Polymyxin B is available in parenteral, ophthalmic, otic, and topical preparations.

Colistin is only available as a prodrug, colistimethate sodium, which is administered IV or inhaled via a nebulizer.

The use of these drugs has been limited due to the increased risk of nephrotoxicity and neurotoxicity (for example, slurred speech, muscle weakness) when used systemically. However, with increasing gram-negative resistance, they are now commonly used as salvage therapy for patients with multidrug-resistant infections.