Principles of Antimicrobial Therapy

Antimicrobials are chemical substances that used for treatment of infectious disease caused by invading microbes; thus, they were classified according to the type of microorganism on which they act into: Antibacterial, Antifungal, Antimycobacterial, Antiprotozoal drugs, Anthelmintics and Antiviral.

Antibiotics: Biological Compounds produced from natural source (microorganisms), that used to Kill or inhibit the growth of other pathogens.

Antibacterial: All are synthetic chemical substances that used to kill or inhibit growth of invading bacteria by interfering with their growth or multiplication inside the host.

Selection of Antimicrobial Agents

1) the identity of the organism.
2) the susceptibility of the organism to a particular agent.
3) the site of the infection.
4) patient factors.
5) the safety and efficacy of the agent.
6) the cost of therapy. However, most patients require.

empiric therapy (immediate administration of drug(s) prior to bacterial identification and susceptibility testing).

- **The minimum inhibitory concentrations (MIC):** the lowest antimicrobial concentration that inhibit visible growth of microorganism after24 hrs. of incubation.

- **The minimum bactericidal concentrations (MBC):** lowest antimicrobial concentration that Kill 99.9% of colony count after overnight incubation in antimicrobial free broth dilution.

Bacteriostatic versus bactericidal drugs

o **Bacteriostatic:** Arrest growth & replication of bacteria, thus limit their spreading, then immune system attacks, and eliminate the pathogen.

o **Bactericidal:** effectively kill ≥99.9% within 18 to 24 hours of incubation under specific laboratory conditions. It is also possible for an antibiotic to be bacteriostatic for one organism and bactericidal for another. For example, linezolid is bacteriostatic against Staphylococcus aureus and enterococci, but is bactericidal against most strains of S. pneumoniae.

⊡ Chemotherapeutic Spectra

1- **Narrow-spectrum antibiotics:**

Chemotherapeutic agents acting only on a single or a limited group of microorganisms are said to have a narrow spectrum. For example, *isoniazid* is active only against Mycobacterium tuberculosis.

2- **Extended-spectrum antibiotics:**

antibiotics that are modified to be effective against gram positive organisms and also against number of gram-negative bacteria. For example, *ampicillin* is considered to have an extended spectrum.

3- **Broad-spectrum antibiotics:**

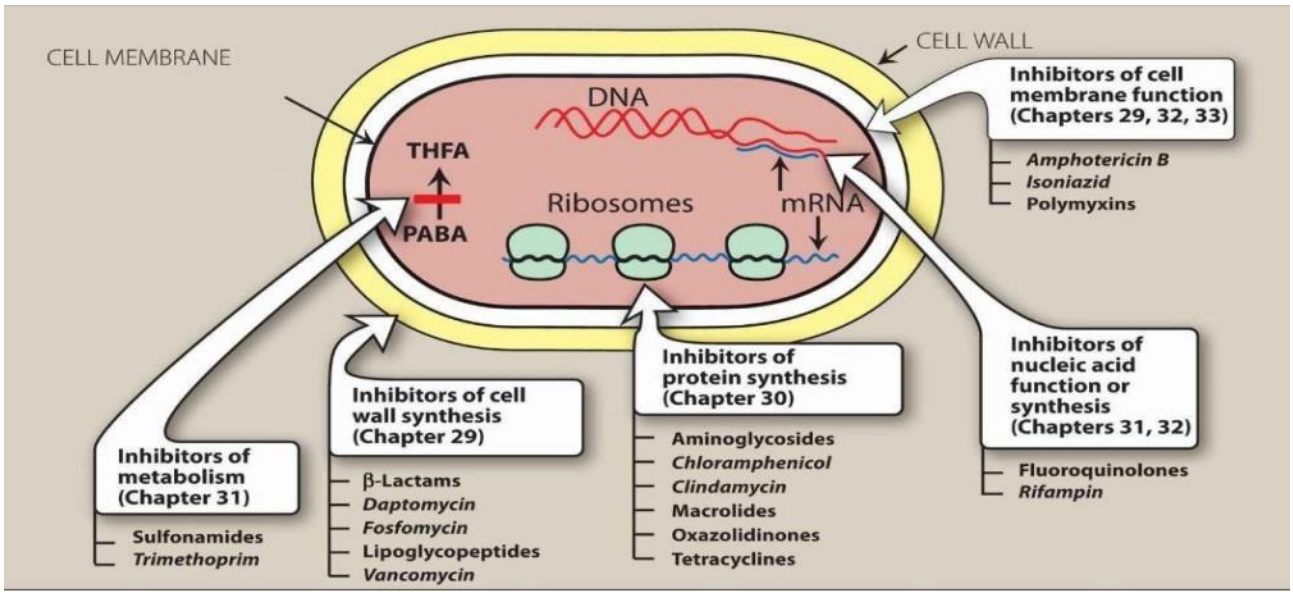
Drugs such as *tetracycline*, fluoroquinolones and carbapenems affect a wide variety of microbial species and are referred to as broad-spectrum antibiotics.

• Superinfections

Drug therapy, particularly with broad-spectrum antimicrobials or combinations of agents, can lead to alterations of the normal microbial flora permitting the overgrowth of opportunistic organisms. These infections usually more serious and require secondary treatments using specific anti-infective agents.

Sites of Antimicrobial Action

Antimicrobial drugs can be classified in a number of ways: 1) by their chemical structure (for example, β-lactams or aminoglycosides), 2) by their mechanism of action (for example, cell wall synthesis inhibitors), or 3) by their activity against particular types of organisms (for example, bacteria, fungi, or viruses).



Cell Wall Inhibitors

Some antimicrobial drugs selectively interfere with synthesis of the bacterial cell wall a 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.
Cell wall inhibitors are bactericidal drugs effective against actively proliferating microorganisms They are classified into:

1. Beta lactam drugs as: [Penicillin's, Cephalosporins, Carbapenem & Monobactam].
2. Combination of Beta lactamase inhibitors and Beta lactam drug.
3. Miscellaneous drugs (Vancomycin, Daptomycin, Fosfomycin, Telavancin & Polymyxin).

Beta lactam drugs

Penicillin's, Cephalosporins, Carbapenem & Monobactam

Mechanism of action:

They act by inhibiting the cross linking of peptidoglycan layers through inhibition of enzymes called penicillin-binding proteins (PBPs), as transpeptidase result in weak cell wall and lysis or death of the bacteria. For this reason, cell wall inhibitors are bactericidal drugs act on replicated microorganisms. Some drugs additionally activate the effect of autolysin to break down the cell wall. On other hand, some bacteria produce b-lactamase- enzyme that breaks the critical beta lactam ring and inactivate these drugs.

Penicillin's

penicillin's classified into the following groups:

1- Natural penicillin:

Penicillin G (benzyl penicillin), Penicillin V (Phenoxy methyl penicillin).

Penicillin G

• Its water soluble drug, acid sensitive cannot be given orally, available as solution for IM and IV injection. Its sensitive to beta lactamase and has short duration (4 hours), with narrow spectrum of activity including gram positive bacteria, spirochets and clostridium.

Indications: Used for treatment of pneumococcal infection, gonorrhea, syphilis, & gas gangrene.

• Long-acting forms of penicillin G
– Procaine Penicillin G (12 hrs.)
– Benzathine Penicillin G (3-4 weeks).

Pencillin V (Phenoxy-methyl penicillin)
Acid stable given orally, and less potent than penicillin G used for moderate infections.

2- Semisynthetic penicillin's (Anti staphylococcal penicillin):

Methicillin, Cloxacillin, Floxacillin, Nafcillin.

They are β-lactamase (penicillinase)-resistant penicillins. Used for infections caused by MSSA while ineffective against (Gram negative, anaerobic & enterococci).

Extended-Spectrum penicillin's:

Ampicillin, Amoxicillin:

• They are effective against gram positive and gram-negative bacteria including *E. coli, H. influenzae,* and *Salmonella typhi* but ineffective against pseudomonas and klebsiella infections.

• Ampicillin slowly absorbed from GIT, and absorption affected by food, and may cause diarrhea. While amoxicillin have better oral absorption

which not affected by food and given less frequently.
• Many bacterial β-lactamases are inhibited by clavulanic acid that combined with amoxicillin (co-amoxiclav) and such combination used for treatment of infections caused by penicillinase-producing organisms.

• Co-amoxiclav indicated for RTI and UTI which are confirmed to be resistant to amoxicillin.

Antipseudomonalpenicillin:

Carbencillin, Piperacillin, Ticarcillin.

• They are acid sensitive, given by injection and effective against Pseudomonas aeruginosa.
• Combination of piperacillin with tazobactam used against penicillinase-producing organisms. e,g Enterobacteriaceae & Bacteroides species.

☒ **Adverse reactions:** penicillins are among the safest drugs. However, adverse reactions may occur:

- **Hypersensitivity:** Approximately10% of patient's self-report allergy to penicillin. Reactions range from rashes to anaphylaxis. Cross-allergic reactions occur among the β- lactam antibiotics.

- **Diarrhea:** a common problem that is caused by a disruption of the normal balance of intestinal microorganisms.
- **Nephritis:** penicillin's particularly *methicillin*, have the potential to cause acute interstitial nephritis.
- **Neurotoxicity:** penicillin is irritating to neuronal tissue, and may induce seizures if injected intrathecally or if very high blood levels are reached. Epileptic patients are particularly at risk.

- **Hematologic toxicities:** Reduce blood coagulation with high doses of *piperacillin* and *nafcillin*. Cytopenia's have been associated with therapy of greater than 2 weeks.

⊡ Cephalosporins:

- They are semisynthetic drugs, have same mechanism of action and resistance to penicillin. They have wider spectrum, but ineffective against infections caused by MRSA, enterococci, clostridium and listeria species.

- Cephalosporins **classified** into generations according to their spectrum, ability to cross BBB and stability against beta lactamase.

- **1st Generation** more effective against **Gram +ve than Gram -ve**
e.g; **Cephalexin, Cefazolin.**

- **2nd Generation** have lower effect than first generation against Gram +ve with increased effect on Gram –ve effect.
e.g; **Cefdinir, Cefoxitin, Cefuroxime, Cefotetan.**

- **3rd Generation** more effective on Gram –ve, with few Gram +ve.
e.g; **Cefexim , Cefotaxime, Ceftriaxone, Cefperazone, Ceftazidime.**

- **4th Generation** (G+ve and G-ve)
e.g; Cefepime, Cefperom.

- **Advanced 5th generation e.g; Ceftaroline**.

Therapeutic Uses

- Pyogenic infection better than penicillin's: 1st, 2nd, 3rd, 4th MSSA.
- Advanced (new drugs) mainly used for severe infections by (MRSA).
- Enteritis (GIT) (pseudo., Klebsiella) Meningitis (3rd,4th).
- Gonorrhea (Cefixime from 3rd generation).
- Upper & Lower RTI.
- Prophylactic against surgical infection e.g; Cefazoline.

Adverse effects of Penicillins and Cephalosporins

Hypersensitivity reactions: urticaria, skin rash, angioedema, bronchospasm, and Anaphylaxis.

☒ Carbapenems

Carbapenems are synthetic β-lactam antibiotics include:
Imipenem, Meropenem, Doripenem…….. etc.

Spectrum of activity; They have broader spectrum than other beta lactams.
- active against β-lactamase–producing gram-positive and gram-negative organisms, anaerobes, and P. aeruginosa
- Anaerobic bacteria & Actinomyces, Nocardia spp.
- Stable against beta lactamase producing bacteria.
- Ineffective against MRSA & Enterococci

These agents are excreted by glomerular filtration.

Adverse effects:

Nausea, Vomiting, eosinophilia. High levels of imipenem may provoke seizures, Patients with penicillin allergy should use carbapenems cautiously because of possible cross-reactivity

⊡ Monobactams

e,g; Aztreonam

Has antimicrobial activity directed against **aerobic gram-negative** including the *Enterobacteriaceae* and *P. aeruginosa*. It lacks activity against gram-positive organisms and anaerobes.
can be used for treating patients who are allergic to other penicillins, cephalosporins, or carbapenems. Given by IV or IM and can accumulate in patients with renal failure.

⊡ β-Lactamase Inhibitors

These include *clavulanic acid*, *sulbactam* and *tazobactam*, by themselves, do not have significant antibacterial activity or cause any significant adverse effects.

β-Lactamase inhibitors **function by inactivating β-lactamases**, thereby protecting the antibiotics that are normally substrates for these enzymes. The β-lactamase inhibitors are, therefore, combined with β- lactamase–sensitive antibiotics, such as ***amoxicillin, ampicillin, Ticarcillin, piperacillin and Ceftazidime*** for the treatment of complicated infections.

⊡ Other cell wall inhibitors:

o Vancomycin

• Its **hydrophilic drug** , have large molecular weight , **not absorbed orally**, given by injection to treat systemic infections.

The use of the oral formulation is limited to the management of ***Clostridium difficile*** infection in the GIT.

• Vancomycin is active against **aerobic and anaerobic gram-positive bacteria,** including resistant strains of staph as MRSA, MRSE, in addition to Enterococcus spp., and Clostridium difficile. Its **bactericidal drug**, bind to peptidoglycan precursors disrupting polymerization and cross- linking required for maintenance of cell wall integrity.

• Used for pseudomembranous colitis (superinfection of the bowel caused by *Clostridium difficile*.

V*ancomycin* is commonly used in patients with skin and soft tissue infections, infective septicemia, endocarditis, and nosocomial pneumonia

• Frequencyof administration is dependent on renal function. Therefore, monitoring of creatinine clearance is required to optimize exposure and minimize toxicity.

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

o **Telavancin**

Semisynthetic antibiotics with activity **against gram-positive bacteria**. Has similar spectrum to vancomycin affecting primarily staphylococci, streptococci, and enterococci. Additionally, *telavancin* can disrupt membrane of bacteria, thus being less liable to resistance.

Used as alternative to vancomycin in treating Hospital Acquired Pneumonia (HAP) caused by resistant gram-positive organisms, including MRSA.

- **Adverse effect profile**, which includes nephrotoxicity, so prior to initiation, assessment of renal function, pregnancy status, and current medications is needed to ensure safe administration.

- Can interfere with phospholipid reagents used in assessing coagulation. Alternative therapy should be considered with concomitant *heparin* use.

o **Daptomycin**:

- Effective resistant gram-positive organisms, including MRSA and vancomycin resistant enterococci (VRE).
- Inactivated by pulmonary surfactants; thus, it should never be used in the treatment of pneumonia.

o **Fosfomycin:**

- It is a bactericidal synthetic drug, blocks cell wall synthesis.
- It is indicated for urinary tract infections caused by E. coli and is considered first line therapy for acute cystitis.
- Less likely to possess cross-resistance with other antimicrobial agents.
- The drug is excreted in its active form in the urine and maintains high concentrations over several days, allowing for a one-time dose.

o **Polymyxins:**

- The polymyxins 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.
- Have activity against most gram-negative bacteria, including P.aeruginosa, E.coli, K. pneumoniae, Acinetobacter spp., and Enterobacter spp.
- Two forms of polymyxin are used clinically ***polymyxin B*** **and** ***colistin*** **(*polymyxin E*)**. *Polymyxin B* is available in parenteral, ophthalmic, and topical preparations. *Colistin* is only available as a prodrug, *given by* IV or inhalation.
- They have nephrotoxic and neurotoxic adverse effects. Thus, need careful careful dosing and monitoring of adverse effects to maximize the safety and efficacy of these agents.