

Antibacterial Agents

- Antibacterial agents are a group chemical compound that fight against pathogenic bacteria.
- Thus, by killing or reducing the metabolic activity of bacteria, their pathogenic effect in the biological environments will be minimized.
- Antibacterial, which are a subclass of antibiotics, have been classified earlier in several ways; however, to make it more easily understandable, this can classify into five groups: type of action, source, spectrum of activity, chemical structure, and function.

Classification based on type of action

- Generally, antibacterial can be classified on the basis of type of action:

1. **Bacteriostatic** and

2. **Bactericidal.**

- Antibacterial, which destroy bacteria by targeting the cell wall or cell membrane of the bacteria, are termed bactericidal and those that slow or inhibit the growth of bacteria are referred to as bacteriostatic.
- Actually, the inhibition phenomenon of bacteriostatic agents involves inhibition of protein synthesis or some bacterial metabolic pathways.
- As bacteriostatic agents just prevent the growth of the pathogenic bacteria, sometimes it is difficult to mark a clear boundary between bacteriostatic and bactericidal, especially when high concentrations of some bacteriostatic agents are used then they may work as bactericidal.

Classification based on source of antibacterial agents

- Antibacterials are the subclass of antibiotics, which can be naturally obtained from fungal sources, semi-synthetic members which are chemically altered natural product and or synthetic.
- Cephalosporins, cefamycins, benzylpenicillin, and gentamicin are well-known examples of natural antibiotics/antibacterials.
- Natural antibiotics/antibacterials often exhibit high toxicity than synthetic antibacterials.
- Ampicillin and amikacin are semi-synthetic antibiotics, which were developed to show low toxicity and increase effectiveness.
- Synthetic antibiotics are also designed to have even greater effectiveness and less toxicity and, thus, have an advantage over the natural antibiotics that the bacteria are not exposed to the compounds until they are released.
- Moxifloxacin and norfloxacin are promising synthetic antibiotics

Classification based on spectrum of activity

- The classification of antibacterial agents based on their target specification and they are basically of two types – **narrow spectrum antibacterial and broad spectrum antibacterial**.
- The narrow spectrum antibacterials are considered to be those which can work on a narrow range of microorganisms, that is, they act against Gram-positive only or Gram-negative only bacteria.
- The broad spectrum antibacterial affects a wide range of pathogenic bacteria, including both Gram-positive and Gram-negative bacteria.
- Usually, the narrow spectrum antibacterials are considered ideal antibacterials and are preferred over the broad-spectrum antibacterials.
- The reason is that the narrow-spectrum antibiotics do not kill as many of the normal microorganisms in the body as the broad-spectrum antibiotics and thus has less ability to cause superinfection.
- Also, the narrow-spectrum antibiotic will cause less resistance of the bacteria as it will deal with only specific bacteria

Classification based on chemical structure

- Different skeleton-containing antibiotics display different therapeutic behaviour; therefore, it is an ultimate need to classify antibacterials on the basis of their chemical structure.
- This classification is also very important as similar structural units have similar patterns of toxicity, effectiveness, and other related properties.
- Usually on a structural basis, antibacterials have been classified into two groups: group A (β -lactams) and group B (aminoglycosides).
- However, in a more elaborated way, the antibacterials can be classified into β -lactams, β -lactam/ β -lactamase inhibitor combinations, aminoglycoside, macrolides, quinolones, and flouoroquinolones.

1. β -Lactams

Beta-lactams are a popular class of drugs, having a four-membered lactam ring, known as β -lactam ring; however, they vary by side chain attached or additional cycles. Penicillin derivatives, cephalosporins, monobactams, and carbapenems, e.g. imipenems, all belong to this class.

2. Aminoglycoside

In compounds of this group, two aminosugars joined by glycosidic bond to an aminocyclitol. Commonly used aminoglycosides are streptomycin, gentamicin, sisomicin, netilmicin, kanamycin, amikacin, neomycin, tobramycin, toframycin, spectinomycin, and paromomycin.

3. Macrolides

Macrolides belong to the polyketide class of natural products. Structurally, macrolides are antibiotics that consist of a macrocyclic lactone ring, usually 14-, 15-, or 16-member to which one or more deoxy sugars, usually cladinose and desosamine, may be attached. Some well-known examples of macrolides are erythromycin and roxithromycin etc.

4. Quinolones and flouroquinolones

Quinolones are quinine-derived structural units and have been proved to be potent synthetic antibacterial agents.

- The addition of flourine at position 6 is called flouroquinolone.
- In the bicyclic ring, the variation at positions 1-, 5-, 6-, 7-, and 8- exerts key effect on the therapeutic behaviour of these drugs. Usually, such structural alteration has led to enhanced coverage and potency of antibacterial activity and pharmacokinetics, e.g. improved anti-Gram-positive activity of moxifloxacin and garenoxacin.
- However, some of these modifications are associated with definite adverse effects.
- Some well-known examples of quinolone include nalidixic acid (first generation), ciprofloxacin (second generation), levofloxacin (third generation), and trovafloxacin (fourth generation).
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5. Streptogramin antibiotics

- Streptogramin antibiotics are a unique class of antibacterials consisting of two groups of structurally unrelated molecules: group A streptogramins (polyunsaturated macrolactones) and group B streptogramins (cyclic hexadepsipeptides).
- Dalfopristin and quinopristin are representative example of the streptogramin A and streptogramin B groups, respectively.

6. Sulphonamides

- Sulphonamides are one of the important class of synthetic organic compounds with great medicinal importance having a sulphonamide functional group ($R_1-SO_2-NR_2R_3$) in their structures. Some compounds belonging to this group also show antibacterial properties such as sulfadiazine.
- The original antibacterial sulphonamides are synthetic antimicrobial agents that contain the sulphonamide group.
- Some others are sulfonyleureas and thiazide diuretics which proved to be newer drug groups based on the antibacterial sulphonamides

7. Tetracyclines

- Tetracyclines are four rings hydrocarbon containing compounds, which can be defined also as “a subclass of polyketides having an octahydrotetracene-2-carboxamide skeleton.” These antimicrobial agents were originally derived from *Streptomyces* bacteria, but the newer derivatives are semi-synthetic.
- Some promising examples of this group are oxytetracycline and doxycycline.

8. Nitroimidazoles

- Nitroimidazoles are a group of compounds that contain a basic imidazole ring.
- The most commonly used example is metronidazole.
- Nitroimidazoles vary by the location of the nitro functional group.
- Most of the drugs of this class have their nitro group at position 6, such as metronidazole, and/or at position 2, such as benznidazole.

Function-based classification of antibacterial drugs

- Function means how a drug works or what is its mode of action.
- This is one of the most important factors related to each antibacterial.
- The major processes or functions, which are responsible for bacterial growth, are cell wall synthesis, cell membrane function, protein synthesis, nucleic acid synthesis, and so on.
- All such processes are targets for antibiotics; therefore, antibacterials, which interfere or disturb these processes in different ways, can be subdivided into four groups: such as cell wall synthesis inhibitors, inhibitors of membrane function, inhibitors of protein synthesis, and inhibitors of nucleic acid synthesis.
- All these groups are discussed briefly hereafter.

Cell wall synthesis inhibitors

- Structurally, the bacterial cell wall is different from that of all other organisms by the presence of polysaccharide backbone, called peptidoglycan, which is composed of alternating *N*-acetylmuramic acid and *N*-acetylglucosamine residues in equal amounts and most of eubacteria have peptidoglycan-based cell walls except the mammalian cell.
- Like all other organisms, the bacterial cell wall offers structural completion to the cell; therefore, the most important process for avoiding bacterial growth is to stop cell wall synthesis by inhibiting the peptidoglycan layer of bacterial cell walls.
- The agents used to work against this function are called cell wall synthesis inhibitors and the cell wall of new bacteria growing in the presence of these agents is deprived of peptidoglycan.

Inhibitors of membrane function

- The cytoplasmic membrane, which covers the cytoplasm, serves as a selective barrier and controls the internal composition of the cell.
- Whenever these functional roles of the cytoplasmic membrane get disturbed, macromolecules and ions will outflow, which will result in cell destruction or death.
- Selectivity of the agents is necessary to carry out this chemotherapy as the agents are aimed to target the bacterial cell membrane.
- Polymyxins are active antibacterial agents, which are cyclic peptides, having a long hydrophobic tail. Polymyxins are found in the form of A, B, C, D, E, where B and E can be used therapeutically.
- Polymyxins show their specificity for polysaccharide molecules, which are present in the outer membrane of many Gram-negative bacteria; therefore, polymyxins are considered to be selectively toxic for Gram-negative bacteria.

Protein synthesis inhibitors

- Protein synthesis is one of the most important functions in the bacterial cell and higher animal as well.
- Therefore, to cure infectious disease caused by pathogenic bacteria, it is the most important target for the drugs, which are called protein synthesis inhibitor antibiotics.
- Since both animal and bacterial cells synthesize proteins, due to the slow synthesis of animal proteins, it has remained a comfortable task for the development of the selective antibiotics.
- Only the side effects from toxicity and resistance phenomenon are taken seriously during antibiotic development.

- Mechanistically, protein synthesis inhibitors act to disturb any stage of the protein synthesis such as initiation and elongation stages (aminoacyl tRNA entry, proofreading, peptidyl transfer, ribosomal translocation and termination).

Inhibition of nucleic acid synthesis

- One of the most important targets for antibiotic to cure infectious diseases is nucleic acid synthesis, and the antibiotics used are called nucleic acid synthesis inhibitors.
- The antibacterials of this class can be subdivided into DNA inhibitors and RNA inhibitors.
- RNA inhibitors interfere with the bacterial transcription process in which messenger RNA transcripts of genetic material are produced for later transformation into proteins.

- RNA inhibitors such as rifampin, a well-known example of the rifamycins family, bind to DNA-dependent RNA polymerase, thereby creating a wall that inhibits elongation of RNA.
- Such a situation prevents gene transcription which affects the normal function of bacteria that results in cell death.
- Like all other biological polymerization processes, DNA synthesis is also achieved by initiation, elongation, and termination stages; therefore, antibacterial drugs target any one of these processes to inhibit DNA synthesis.
- Quinolones, including nalidixic acid and ciprofloxacin, work as DNA inhibitors.