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ANTIBIOTIC: A REVIEW

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Keywords:

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ABSTRACT

Antibiotics are the most active chemotherapeutics among drugs; they exert their therapeutic effect by antagonizing the growth of bacteria. Since 1910 many antibiotics have been developed with different mechanisms of action including: Inhibition of bacteria's cell wall synthesis; this class of antibiotics includes vancomycin and Beta-lactamantibiotics such as penicillins, cephalosporins and carbapenems, Inhibition of protein synthesis including tetracyclines, aminoglycosides, macrolides, and chloramphenicol DNA synthesis inhibitors such as fluoroquinolones and sulfonamides that inhibit folic acid synthesis. In this chapter we describe the three antibiotics classes, their mechanism of action, clinical uses, side effects, and their resistance by different bacteria.

INTRODUCTION:

Infections were the major cause of death during the 19th century. The introductions of antibiotics not only help in the treatment of infections but also have a major role in decreasing mortality and morbidity. In 1910 Paul Ehrlich developed the first antimicrobial salvarsan for the treatment of syphilis, a disease that was almost incurable back then. In 1932 prontosil, a sulfonamide antibiotic was discovered and since it was cheap, many companies were encouraged to mass produced many derivatives of prontosil. During the second half of the nineteenth century and before the important discovery of Fleming many researchers recorded observations regarding the antibacterial properties of penicillium fungi. In 1929, Alexander Fleming introduced "penicillin" as a compound with antibacterial properties, when he observed that a bacterial growth was terminated by a mold, however, because prontosil was available there was not much interest in penicillin. Till 1941, the purity of extracted penicillin was only 0.3 to 7% which was not sufficient to be clinically used. In 1945, Dorothy (Crowfoot),Hodgkin and Barbara low used X-ray crystallography to determine the chemical structure of penicillin and in 1950 penicillin was chemically synthesized. The isolation of 6-aminopenicillanic acid. In 1958 led to the semisynthesis of new penicillins such as ampicillin,methicillin and carbenicillin. Few years later, ticarcillin (1971) and piperacillin (1977) were synthesized and in 1989 the combination of piperacillin-tazobactam was introduced and was widely used because of its high activity against gram positive bacteria.

ANTIBIOTICS

Definition of antibiotics

It can be defined as any of a large group of chemical substances, as penicillin or streptomycin, produced by various microorganisms and fungi, having the capacity in dilute solutions to inhibit the growth of or to destroy bacteria and other microorganisms, used chiefly in the treatment of infectious diseases. In other words, it is a drug used to treat infections caused by bacteria and other microorganisms.

Antibiotic are substances produced by micro-organisms which suppress the growth and multiplication or kill other microorganisms at very low concentrations. The term antibiotic is now extended to include chemically related substances produced wholly or partially by chemical synthesis.

Originally, an antibiotic was a substance produced by one microorganism that selectively inhibits the growth of another. Synthetic antibiotics, usually chemically related to natural antibiotics, have since been produced that accomplish comparable tasks.

The successful use of any therapeutic agent is compromised by the potential development of tolerance or resistance to that compound from the time it is first employed. This is true for agents used in the treatment of bacterial, fungal, parasitic, and viral infections and for treatment of chronic diseases such as cancer and diabetes; it applies to ailments caused or suffered by any living organisms, including humans, animals, fish, plants, insects, etc. A wide range of biochemical and physiological mechanisms may be responsible for resistance. In the specific case of antimicrobial agents, the complexity of the processes that contribute to emergence and dissemination of resistance cannot be overemphasized, and the lack of basic knowledge on this topics in one of the primary reasons that there has been so little significant achievement in the effective prevention and control of resistance development. Most international, national, and local agencies recognized this serious problem. Many resolutions and recommendations have been propounded, and numerous reports have been written, but to no avail: the development of antibiotic resistance is relentless. The most striking examples, and probably the most costly in terms of morbidity and mortality, concern bacteria. The discovery of these infectious agents in the late 19^{th} century stimulated the search for appropriate preventative and therapeutic regimens; however, successful treatment came only with the discovery and introduction of antibiotics half a century later.

Antibiotics have revolutionized medicines in many respects, and countless lives have been saved; their discovery was a turning point in human history. Regrettably, the use of these wonder drugs has been accompanied by the rapid appearances of resistance strains. Medical pundits are now warning of a return to the preantibiotic era; a recent database lists the existence of more than 20,000 potential resistance genes (r genes) of nearly 400 different types, predicted in the main from available bacterial genome sequences (85). Fortunately, the number existing as functional resistance determinants in pathogens is much smaller.

Classification of antibiotics on the basis of their molecular structure

1. Beta-lactam antibiotics; Penicillins, Cephalosporins
2. Tetracyclines and Chloramphenicol (Broad-spectrum antibiotics)

3. Aminoglycoside antibiotics; Streptomycin, Kanamycin, Neomycin, Gentamicin, Tobramycin, Amikacin, Netilmicin
4. Macrolide antibiotics; Erythromycin, Clarithromycin, Azithromycin
5. Polypeptide antibiotics; Polymyxin, Colistin, Bacitracin
6. Miscellaneous antibiotics; Clindamycin, Novabiocin, Lincomycin, Vancomycin

Table 1: Schematic diagram of year and development and antimicrobial agents

Years	Development of antimicrobial agents
1928	Discovery of penicillin
1935	Discovery of sulfonamide
1940	Clinical application of penicillin
1950	Discovery of aminoglycoside, chloramphenicol, tetracycline and macrolide
1956	Discovery of vancomycin
1960	Synthesis of methicillin
1962	Synthesis of nalicixic
1967	Development of first generation cephems Development of second generation cephems Development of third generation cephems
1983	Development of carbapenem and monobactam increased use of third generation cephem, carbapenem, oral cephem and new quinolone antimicrobials
2000	(Decrease in newly develop antimicrobial agents)

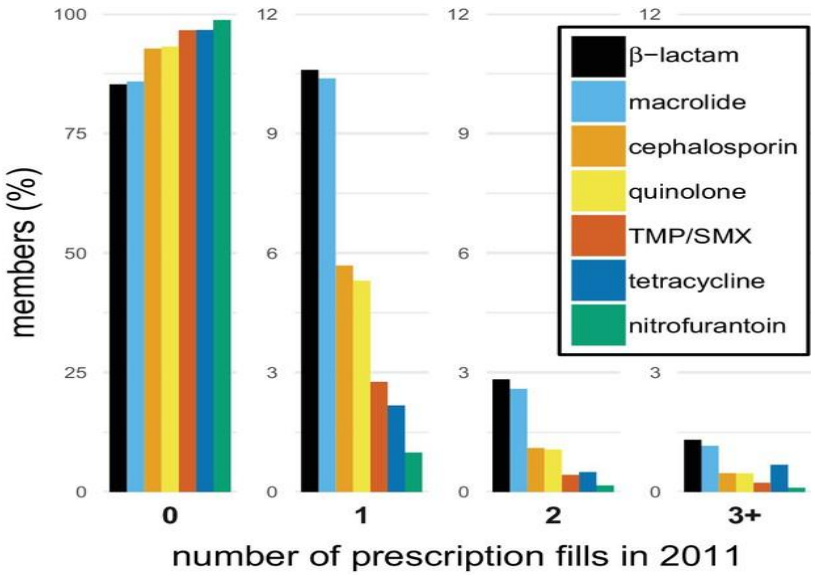

Fig.1: Statistical data of Antibiotic

Mechanisms of action and resistance of antibiotics:

The mechanisms of action of antimicrobial agents can be categorised based on the function that is affected by the agents, these generally included the following: inhibition of the cell wall synthesis, or nucleic acid synthesis, inhibition of ribosome function, or cell membrane function and inhibition of folate metabolism. Antimicrobials are one of the most successful forms of therapy in medicine, however the efficiency of antimicrobials is compromised by a growing number of antibiotic resistant pathogens. Resistance can be described in two ways:

(A) **Intrinsic resistance** whereby microorganisms naturally do not poses target sites for the antimicrobials and the antimicrobial does not effect them.

(B) **Acquired resistance** whereby a naturally susceptible microorganisms acquires mechanisms to not be affected by the antimicrobial. Mechanisms of acquired resistance include: the presence of an enzyme that inactivates the antimicrobial agent, post- transcriptional or post-translation modification of antimicrobial agent's target, reduced uptake to the antimicrobial agent and active efflux of the antimicrobial agent. Both the mechanisms of action and resistance of the mostly commonly used antimicrobial classes.

Classification based on mode of action

1. **Inhibition of cell wall synthesis**:

Beta-lactams:

Beta-lactam antibiotics have wide spectrum of activity and low toxicity because the drug targets bacterial cell wall that has no analogues in higher organisms.

Mechanism of action

The inhibition of cell wall synthesis leads to loss of osmotic support and eventually cell lysis. The last step in cell wall synthesis is the cross linking of peptidoglycans between the carboxyl of D-alanine in one peptidoglycan chain and an amino group in the next chain, this reaction is catalyzed by transpeptidase. The cross linking of the adjacent glycan chains causes the rigidity of the cell wall. Binding of penicillin to the transpeptidase enzyme forms an acyl enzyme complex via the penicillin beta-lactam ring cleavage, which leads to transpeptidase enzyme inaetivation and eventually cell lysis. Few novel antibacterial drugs were synthesized in the past few years. Some of these drugs are inhibitors of peptidoglycan synthesis such as MurA inhibitors; MurA is an enzyme that catalyses the first step in peptidoglycan synthesis, the natural fosfomycin is an irreversible inhibitor of this enzyme. Inhibitors of MurB, MurC, MurD and MurE were developed as well.

Penicillins :

Penicillins are group of antibiotic. It includes penicillin G and penicillin V.

Cephalosporins: The cephalosporins are the class of beta-lactam antibiotics originally derived from the fungus Acremonium, which was previously known as "cephalosporium".

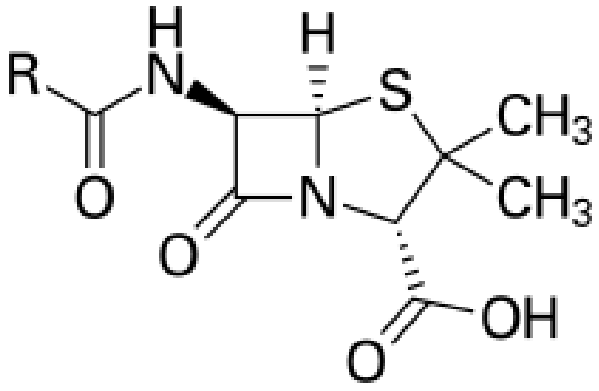

Fig. 2: Penicillin

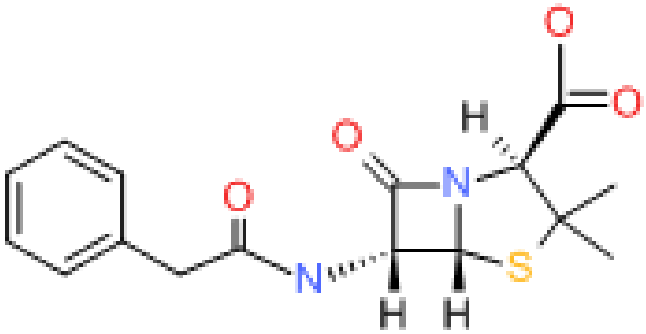

Fig. 3: Penicillin G

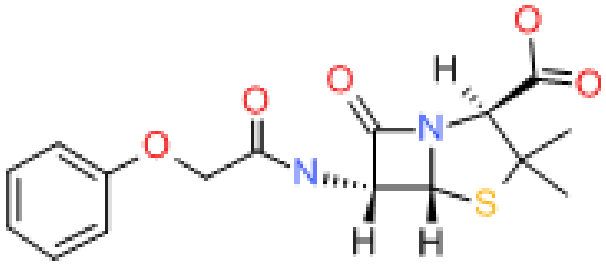

Fig. 4: Penicillin V

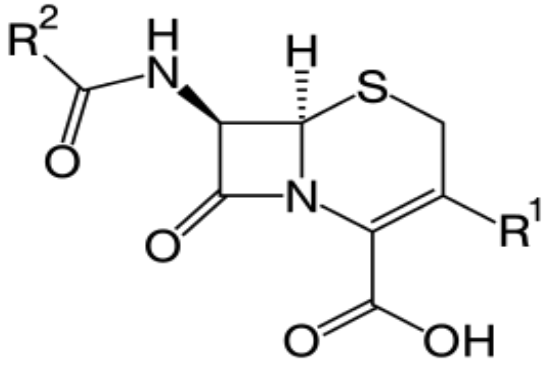

Fig. 5: Cephalosporins

Other categories of beta-lactams

Carbepenems:

Carbapenem antibiotics or Carbapenems are a class of broad-spectrum beta-lactam antibiotics. They are effective against a number of pathogenic bacteria from both Gram-positive and Gram-negative groups as opposed to narrow-spectrum antibiotic which work only against Gram-positive or Gram-negative bacteria but not both.

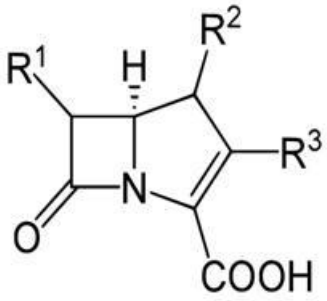

Fig. 6: Cabepenem

e.g.Imipenem: Developed in 1980 by Merck, Impenem is a broad-spectrum Carbapenem antibiotic that is effective against both Gram-positive and Gram-negative bacteria.

Monobactams:

Monobactam is the monocyclic beta-lactam ring . Only monobactam available in USA. Spectrum of activity is similar to ceftazidime.

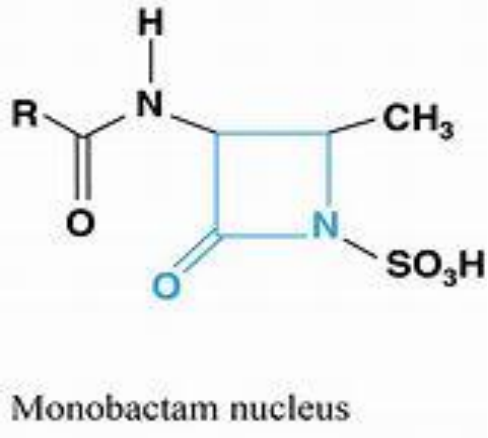

Fig. 7: Monobactam

Clinical Uses:

1. Pneumonia
2. Urinary tract infections

Adverse Effects:

1. Skin rashes
2. Occasionally Abnormal liver function test

e.g. aztreonam (Azactam): Aztreonam is similar action to penicillin. Azetronam binds the penicillin binding proteins of Gram-positive and anaerobic bacteria very poorly and is largely ineffective against them.[12]

Beta-lactamase inhibitors e.g. clavulanic acid

Other inhibitors of cell wall synthesis include- vancomycin and teicoplanin

2. **Inhibition of protein synthesis** : Aminoglycosides. Those derived by Streptomyces end in "mycin" e.g. tobramycin. Others like gentamicin from micromonospora purpurea which is not a fungus, hence 'micin' and semisynthetic drug e.g. amikacin.

- **Tetracyclines:**Tetracycline, sold under the brand name Sumycin among others, is an antibiotic used to treat a number of infections. This includes acne, cholera, plague, malaria, etc. It is taken by mouth.

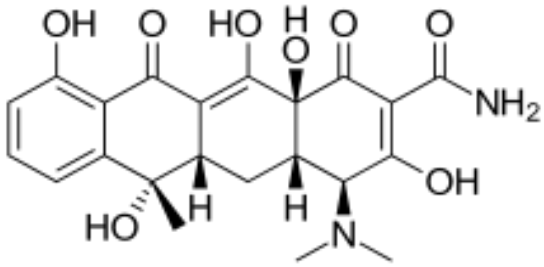

Fig. 8: Tetracycline

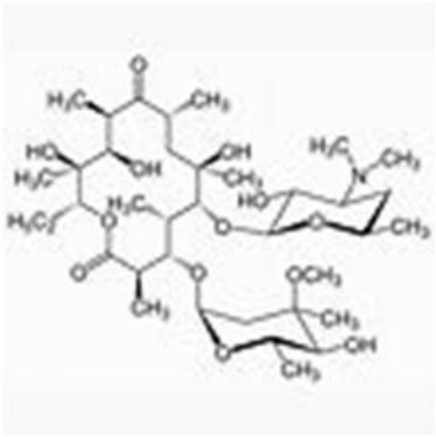

Fig. 9: Macrolides

Macrolides: e.g. erythromycin, clindamycin

3. **Inhibition of Nucleic acid synthesis**: Sulphonamides. These drugs and trimethoprim with which these drugs are combined inhibit synthesis of nucleic acid precursors.
4. **Quinolone**, e.g. ciprofloxacin. They act by preventing DNA replication.

Fig.10: Quinolone

5. **Azoles**, e.g. metronidazole, they act by the production of short- lived intermediate compounds which are toxic to DNA of sensitive organisms. Rifampicin inhibits bacterial DNA-dependant RNA polymerase.

Different groups of antimicrobial

Penicillin G, the most popularly used antibiotic because it is the cheapest, safest, and most effective antibacterial treatments available. Penicillin G and V remains the drugs of choice for treating many Gram-positive bacterial infections. Penicillin G and V are used to treat infections caused by Gram positive Staphylococcus pyogenes (strep throat), and streptococcus pneumoniae (respiratory tract infections, otitis media). Methicillin was the first penicillin to have activity against the staphylococcus strains that were resistant to penicillin G. Ampicillin and amoxicillin have broader spectrum of activity than earlier penicillins. It is active against common Gram-negative bacteria as well as Gram positive bacteria. But they are not active against Gram-negative bacteria as well as Gram positive bacteria. But they are not active against the Gram negative bacterium Escherichia coli, haemophilus influenzae and Salmonella typhi. Carbenicillin was the first penicillin synthesized to possess useful activity against Pseudomonas aeruginosa. This bacterium is normally only responsible for infections in hospitalized patients and had proved particularly difficult to treat. Cephalosporins are generally broad spectrum. The mode of action is bactericidal and that are restricted to hospital use for the treatment of serious infections. Tetracycline is bacteriostatic broad-spectrum antibiotic that has been used to treat a wide range range of infections. Erythromycin (Macrolide group) is a very safe antibiotic, it is effective orally, bacteriostatic, and active against Gram-positive infections, especially those of the respiratory tract caused by streptococci. For certain patients unable to tolerate penicillins, erythromycin has provided a valuable alternative. Quinolones are broad spectrum antibiotics that are bactericidal in action. It's been increasingly used because of their relative safety, their availability both orally and parentally and their favorable. 1^{st} generation quinolones (nalidixic acid) limited to Gram negative enteric bacteria however 2^{nd} and 3^{rd} generation fluoroquinolones (norfloxacin, ciprofloxacin) have improved activity against Gram positives e.g. staphylococci and pneumococci, also has activity against mycoplasma and legionella. Aminoglycosides Group is highly active against Gram-negative bacteria, it is only effective by injection, and is bactericidal. Streptomycin was the first member of this group to be used widely, but it has now been largely replaced by newer aminoglycosides, such as gentamicin.

Aminoglycosides group has a potential to damage the kidneys and cause hearing impairment. Chloramphenicol is a broad-spectrum, orally effective, bacteriostatic antibiotic. Chloramphenicol is an important alternative for treating typhoid fever and bacterial meningitis because of its ability to penetrate the central nervous system efficiently. The use of these antibiotics in most countries has declined because of concerns about its ability to cause a very rare but fatal anemia and because of the availability of other safer drugs. Florfenicol, fluorinated chloramphenicol derivative, is a broad spectrum antimicrobial agent active against wide range of Gram-positive and negative bacteria.

Current research

Several researches have been conducted throughout the globe to understand the existing and emerging antimicrobial resistance in microbes of different environmental niches (in table no 2). Through the finding of the research it has been well understood that antimicrobial resistance mechanisms are highly influenced by the way antibiotic are used locally and because of the different mechanism discussed above microbes can efficiently transfer the resistance either by horizontal or vertical route. Microbes from far geographical distance and different unrelated niches have been found to have similar mechanisms of antimicrobial resistance. Thus once the resistance mechanism has emerged for any antibiotics, similar mechanisms can be predicted in other region even at the low or short duration of selection pressure imposed by the use of any antibiotics. The resistance to penicillin emerged in *Staphylococcusaureus* shortly after the discovery and use of penicillin for therapeutics purpose.

Table 2: Years indicating the emergence of drug resistance bacteria

Years	Emergence of drug-resistance bacteria
1940- 1961	Emergence of penicillinase- producing *Staphylococcus aureus* Emergence and spread of multidrug-resistance S. aureus
1961	Emergence of MRSA
1967	Emergence of PISP
1974	Emergence of penicillinase- producing H. influenzae
1977	Emergence of PRSP
1980	Emergence of BLNAR H. influnzae
1983	Emergence ESBL- producing Gram-negative bacilli
1986	Emergence of VRE
1990	Increased infections with MRSA, PRSP, BLNAR etc. Increase of registant gonococci

CONCLUSION:

In conclusion, the importance and value of antibiotics cannot be overestimated; we are totally dependent on them for the treatment of infectious diseases, and they should never be considered mere commodities. Antibiotic are the critical to the success of advanced surgical procedure, including organ and prosthetic transplants.

Antibiotic are the contributed over years in bacterial infections control. These drug have an important role in the rise of life expectancy. The development of new antibiotic have slowed and since 1970 only three new class of antibiotic have been marketed. Resistance to antibiotics is caused by many mechanisms including decrease in antibiotic diffusion through the glycocalyx diffusion layer, that act like a bacterial barrier to the antimicrobial agents, enzymatic degradation of the antibiotic such as beta-lactamases that hydrolyze the beta-lactam ring of penicillins, cephalosporins and related drug.

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