International Journal of Multidisciplinary Research and Growth Evaluation.

Antibiotics: A review

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Article Info

ISSN (online): 2582-7138
Volume: 03
Issue: 06
November-December 2022
Received: 01-10-2022
Accepted: 18-10-2022
Page No: 139-142

Abstract
The discovery of antibiotics has helped to save the lives of an uncountable number of people. Antibiotics have been grouped in different classes based on their origin, structure, and mechanism of action. An intrinsic and acquired mechanism of antimicrobial resistance has been identified in many bacterial strains that are of high clinical importance. This has seriously jeopardized the use of antibiotics and has also caused the spread of microbes that are resistant to effective first-choice, or "first-line" drugs. Thus, sensible use of antibiotics and the search for effective alternative measures are of high importance in order to minimize the effect due to existing and emerging antimicrobial resistant microbes.

Keywords: Antibiotics, Antibiotics resistance, Plasmids, Mutation, Beta-lactamases

Introduction
After the discovery of antibiotic substance penicillin from the fungus *Penicillium notatum* in 1928 by Sir Alexander Fleming, antimicrobial agents (antibiotics and related medicinal drugs), was followed by prontosil, the first sulfa drug, was discovered in 1935 by German chemist Gerhard Domagk (1895-1964). Fleming, Florey, and Chain shared the 1945 Nobel Prize for medicine for their work on penicillin [1-2]. Aminoglycosides, chloramphenicol, tetracycline and macrolides were discovered in the year 1950 (Table 1). These antibiotics effectively acted on both the Gram positive and negative bacteria and were drug of choice for several bacterial diseases. Later in the 1956 and 1960, vancomycin and methicilin were discovered that gave breakthrough in treating infectious disease (Table 1). It is highly effective in curing infection particularly due to notorious Gram positive bacteria. Nalidixic acid was discovered in the year 1962 and was introduced for clinical use in 1967 [3]. This is the first synthetic quinolone antibiotic effective for both the Gram positive and negative bacteria. These along with its recent subset of fluoroquinolones are very effectively used especially in the treatment of urinary tract infections caused by Gram negative bacteria. Development of first, second and third generation of cephalosporin in late 90's added to the armamentarium to fight against infection caused by both Gram positive and negative bacteria [3]. First-generation cephalosporins are predominantly active against Gram-positive bacteria, and successive generations have increased activity against Gram-negative bacteria [4-8]. These discoveries antimicrobial agents have saved the lives and eased the suffering of countless numbers of people. However, emerging antimicrobial resistance in microbes has now seriously jeopardized its use and has also caused the spread of microbes that are resistant to effective first-choice, or "first-line" drugs [9-15].

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. 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.

Table 1: Development of antimicrobial agents

Year	Development of Microbial agents
1928	Discovery of Penicillin
1935	Discovery of Sulfonamide
1940	Clinical Application
1950	Discovery of aminoglycoside, chloramphenicol, tetracycline and macrolide
1956	Discovery of vancomycin
1960	Synthesis of Methicillin
2000	Decrease in newly developed antimicrobial agents

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) [16]. 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 penicillin G-resistant staphylococci. Both are effective on oral administration and are active against the Gram-negative bacterium *Escherichia coli*, *Haemophilus influenzae* and *Salmonella typhi* [1]. 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 clinically important group of antimicrobial agents. Injectable forms of this group are generally broad-spectrum. The mode of action is bactericidal and that are restricted to hospital use for the treatment of serious infections [5]. Tetracycline is bacteriostatic broad-spectrum antibiotic that has been used to treat a wide range of infections [17]. 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 [14]. 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 parentrally and their favorable. 1st generation quinolones (nalidixic acid) limited to Gram negative enteric bacteria however 2nd and 3rd generation fluoroquinolones (norfloxacin, ciprofloxacin) have Improved activity against Gram positives *e.g*. staphylococci and pneumococci, also has activity against mycoplasma and legionella [3, 12]. Aminoglycoside 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 [3, 15]. 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 [18-19].

The antibacterial activity

Antibiotics targets and impair several essential mechanisms involved in bacterial metabolism, growth or multiplication. It also causes the bacterial lyses by distortion and damage to the cell membrane that cause leakage of vital cell materials and death [1-2, 21-23]. Polymyxins disrupt the bacterial cell membrane by interfering with phospholipids damaging the osmotic barrier. Resistance to colistin may occur via alteration of the lipid A binding site or by efflux pumps. One possible mechanism for colistin dependence may be a mutation of lipid A which results in a defective cell membrane and osmotic trauma in the absence of colistin. Inhibition of cell wall synthesis by binding to transpeptidases and inhibiting peptidoglycan formation is another important mechanism of antibiotic [1, 23]. These transpeptidase enzymes and some other bacterial proteins, to which penicillins bind, are collectively called penicillin-binding proteins (PBPs). The PBPs are different for Gram-positive and Gram-negative bacteria and in anaerobic species. β-lactams are only efficacious against actively dividing bacteria, since that is when a new cell wall is being created [1, 8, 11].

By interfering with protein synthesis taking place in the ribosome, several classes of antimicrobials are able to stop cell division. Certain antimicrobials bind to one or both subunits (30S, 50S) and cause misreading of the genetic code or formation of abnormal, nonfunctional protein complexes. Aminoglycosides (gentamicin, tobramycin, amikacin, streptomycin) act primarily by binding to the 30S subunit. Tetracylines are another biochemical class of antibiotic which also bind to the 30S ribosome [17]. Tetracylines are bacteriostatic rather than bactericidal, because their binding to the ribosome is transient. Several classes of antimicrobials inhibit the 50S ribosomal subunit. Macrolides (erythromycin), chloramphenicol and clindamycin are primarily bacteriostatic and attach reversibly to the 50S subunit and interfere with the linking of amino acids [14, 17, 19, 21, 23].

Inhibition of nucleic acid (DNA) replication is effectively enhanced by some antimicrobials (Table 2). They bind to the DNA molecule-gyrase complex, inhibiting its function and leading to bacterial cell death [12]. Quinolone such as naladixic acid, which only acts on aerobic Gram-negative species and newer fluoroquinolones, such as ciprofloxicin, norfloxacin, and ofloxacin that have a much broader spectrum of activity are important antimicrobial compounds [3, 12, 25]. Bacteria usually lack the ability to take up folic acid from the environment and must synthesize it internally. Trimethoprim and the sulfonamides interfere with folate metabolism by competitively blocking the synthesis of tetrahydrofolate. Trimethoprim and sulfonamides are usually administered together because trimethoprim potentiates sulfonamides [2].

Mechanisms of antimicrobial resistance

Antibiotic resistance is the ability of a bacterium or other microorganism to survive and reproduce in the presence of antibiotic doses that were previously thought effective against them. Different mechanisms are known to enhance

the antimicrobial resistance (Fig. 1). Microbes could be intrinsically resistant and may lack a target for the antibiotics [5]. Chlamydiae do not have peptidoglycan and are not susceptible to the action of penicillins. The antibiotic target may be inaccessible. Membrane changes block antibiotic entrance and penetration into the cell. Peptidoglycan in Gram-negative bacteria is inaccessible to penicillins that cannot penetrate the Gram-negative outer membrane. Efflux pumps can actively pump out antibiotics from cells. Gram-negative bacteria resist the activity of tetracyclines by this important mechanism [26].

The antibiotic target may be modified to prevent the action of the drug: Ribosomes become altered, mutated, and chemical-physical changes prevent antibiotic attachment to those ribosomes. By synthesis of a new metabolic pathway bacteria can produce a new enzyme that is not inhibited by the antimicrobial. Trimethoprim-sulfamethoxazole resistance is due to bacteria that produce a new dihydrofolate reductase not inhibited by trimethoprim and a new dihydropteroate synthetase not susceptible to sulfonamides. Quinolone resistance is affected by point mutations in the DNA gyrase, which prevent binding of the drug to its target [2, 12, 20, 22, 25-28].

The antibiotic may be chemically modified or destroyed

Enzymes degrade antibiotics, or inactivate them by reactions of: phosphorylation, adenylation, or to the alteration of the compound in the periplasmic space by bacterial enzymes that acetylate, phosphorylate or adenylate aminoglycosides (Table 2). This alteration of the compound leads to binding to the bacterial ribosomes and poor uptake into the cell. The genes coding for antibiotics altering enzymes are often found on transposons and have been identified in members of the Enterobacteriaceae and *P. aeruginosa*, *S. pneumoniae* and Gram-positive species such as *S. aureus*, *S. faecalis*, and *S. pyogenes*. Important examples include the huge range of β-lactamases [5, 11, 13, 23, 26].

Chloramphenicol resistance is due to the presence of an intracellular enzyme called chloramphenicol transacetylate. This enzyme acetylates hydroxyl groups on the chloramphenicol structure which causes decreased binding to the 50S ribosome. The first florfenicol resistance gene (pp-*flo*) that confers resistance to both chloramphenicol and florfenicol was found to be plasmid encoded from *Photobacterium piscicida*. Likewise, *flost* gene with 97% homology to the pp-*flo* gene was reported among *Salmonella enterica* serovar Typhimurium DT104. Since then *floR* gene has been reported in *Escherichia coli* and *Salmonella* spp in plasmid and chromosomal locus as well [18, 19, 30-32]. Though mode of action of florfenicol is similar to chloramphenicol, it is highly effective to variety of Gram positive and negative clinical bacterial isolates. Florfenicol has gained interest as the need of alternative microbial agents has become inevitable to decrease morbidity and mortality due to emergence of antibiotic-resistance microorganism. Description of florfenicol in multi-drug resistance *Salmonella enterica* serovar Typhimurium Phage type DT104 worldwide epidemic strains have also added its importance from the public health point of increase the chances for development of antibiotic-resistant bacteria [5].

Future direction for the research on antimicrobial

Based on these information available on antimicrobial compounds and resistance mechanism of the bacteria it is every evident that antimicrobial resistance is biological phenomenon that has existed in the microbes from early evolution and would continue till the existence of the microbial world. Thus, the most rational approach would be minimizing and optimum use of antimicrobial compounds that would help to control the emergence of resistant bacteria. Alternate approaches like probiotics and vaccine have been effective in prevention of infectious diseases. Likewise, bacteriophages or “phages” that disrupt bacterial metabolism and cause the bacterium to lyse could be another therapeutic option. Several reports on therapeutic use of lytic bacteriophages to treat pathogenic bacterial infections are made available for future research. Phage therapy may prove as an important alternative to antibiotics for treating multidrug resistant pathogens [91-93]. Similarly, researches on antimicrobial peptides have also shown that these components of innate immunity are potent, broad spectrum antibiotics which demonstrate potential as novel therapeutic agents. These peptides can act on both Gram negative and Gram positive bacteria, including mycobacteria, Mycobacterium tuberculosis, enveloped viruses, fungi and even transformed or cancerous cells. It may also be useful in enhancing immunity by functioning as immunomodulators. Development of new drugs by making use of bioactive phytochemicals and plants have an almost limitless ability to synthesize aromatic substances are targets of several ongoing research. Most of these compounds are phenols or their oxygen-substituted derivatives such as tannins. In many cases, these substances serve as plant defense mechanisms against predation by microorganisms, insects, and herbivores. Many of the herbs and spices used by humans to season food yield useful medicinal compounds including those having antibacterial activity. One of the major causes of antibiotic resistance is the decrease of effective drug concentration at their target place, due to the increased action of ABC transporters. Since ABC transporter blockers can be used in combination with current drugs to increase their effective intracellular concentration, the possible impact of ABC transporter inhibitors is of great clinical interest. ABC transporter blockers that may be useful to increase the efficacy of current drugs have entered clinical trials and are available to be used in therapeutic regimes the herbs and spices used by humans to season food yield useful medicinal compounds including those having antibacterial activity. One of the major causes of antibiotic resistance is the decrease of effective drug concentration at their target place, due to the increased action of ABC transporters. Since ABC transporter blockers can be used in combination with current drugs to increase their effective intracellular concentration, the possible impact of ABC transporter inhibitors is of great clinical interest. ABC transporter blockers that may be useful to increase the efficacy of current drugs have entered clinical trials and are available to be used in therapeutic regimes.

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