



(REVIEW ARTICLE)



## A review on antibiotic resistance and way of combating antimicrobial resistance

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GSC Biological and Pharmaceutical Sciences, 2021, 14(02), 087–097

Publication history: Received on 13 January 2021; revised on 07 February 2021; accepted on 09 February 2021

Article DOI: <https://doi.org/10.30574/gscbps.2021.14.2.0037>

### Abstract

Antibiotics are widely used most effective medication since the twentieth century against bacterial infections (Tetanus, Strep Throat, Urinary Tract Infections, etc.) and thus save one's life. Before 20th-century infectious disease played the main role in the death. Thus, antibiotics opened a revolutionary era in the field of medication. These cannot fight against viral infections. Antibiotics are also known as an antibacterial that kill or slow down bacterial growth and prohibit the bacteria to harm. Resistance comes as a curse with antibiotics that occurs when bacteria change in some way that reduces or eliminates the effectiveness of drugs, chemicals or other agents designed to cure or prevent infections. It is now a significant threat to public health that is affecting humans worldwide outside the environment of the hospital. When a bacterium once become resistant to antibiotic then the bacterial infections cannot be cured with that antibiotic. Thus, the emergence of antibiotic-resistance among the most important bacterial pathogens causing more harm. In this context, the classification of antibiotics, mode of action of antibiotics, and mechanism of resistance and the process of overcoming antibiotic resistance are discussed broadly.

**Keywords:** Antibiotic; Classification of antibiotic; Mode of action; Resistance mechanism

### 1. Introduction

Antibiotics are widely used most effective medication since the twentieth century against bacterial infections. In 1928, Alexander Fleming discovered Penicillin as the first natural antibiotic. He observed that *Penicillium* molds produced a diffusible extract that had antibacterial activity against *Staphylococci* (Silverman and Holladay, 2014). S.A. Waksman defined an antibiotic as “a chemical substance, produced by micro-organisms, which can inhibit the growth of and even to destroy bacteria and other micro-organisms” (Bud, 2007). Antibiotics can be prepared by either naturally or synthetically. Antibiotics inhibit bacterial growth by targeting essential cellular processes such as the synthesis of the bacterial cell wall, DNA/RNA, and proteins and retard growth and cause cell death (Mohr, 2016).

Resistance comes as a curse with antibiotics that occurs when bacteria change in some way that reduces or eliminates the effectiveness of drugs, chemicals or other agents designed to cure or prevent infections. Most of the antibiotics on the market were discovered in the mid to late 20th century. Thus, there is a limited arsenal of drugs to high resistance bacteria and bacteria can be resistant to multiple drugs at a time (Richardson, 2017). Bacteria evolve rapidly so the mechanism of developing resistance grows fast. Antibiotic consumption continues to rise among the low- and middle-income countries in recent years (Kleinet al., 2018). World Health Organization has named antibiotic resistance as one of the three most important public health threats of the 21st century (WHO, 2014). It has been reported by the Centers

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for Disease Control and Prevention (CDC) estimated more than 2.8 million antibiotic resistance infections occurred in the U.S each year, and more than 35,000 people die as a result (Soltaniet al., 2019). Thus, the number is increasing alarmingly.

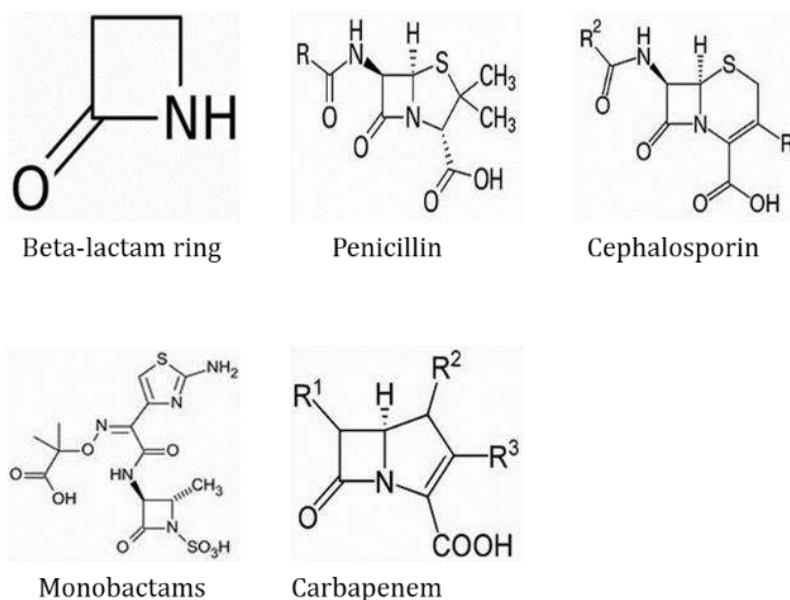
Antibiotic resistance spread over due to overuse of antibiotics. So, if however, bacteria are exposed to drugs below the dose required to kill all bacteria in a population (the minimum bacterial concentration or MBC), they can mutate and resist antibiotic treatment via natural selection for resistance-conferring mutations (Richardson, 2017). In this review, it is briefly discussed about the antibiotics, their classifications, mode of action, resistance mechanism, and possible overcome methods of antibiotic resistance.

## 2. Classification of antibiotics

The most common classification of antibiotics is based on their molecular structures, mode of action, route of administration (injectable, oral, and topical), and spectrum of activity (Etebu and Ariekpar, 2016). Antibiotics are shown similar effectiveness, toxicity and allergic activity having the same chemical structure. The most common classes of antibiotics are Beta-lactams, Macrolides, Tetracyclines, Quinolones, Aminoglycosides based on chemical or molecular structures (Etebu and Ariekpar, 2016; van Hoek et al., 2011; Frank and Tacconelli, 2012; Adzitey, 2015).

### 2.1. Beta-lactams

The beta-lactam groups are mostly prescribed groups of antibiotics. The most prominent members of the beta-lactam class include Penicillins, Cephalosporins, Monobactams and Carbapenems (Etebu and Ariekpar, 2016). All members belong to beta-lactam groups are containing beta-lactam ring. The chemical structure of beta-lactam, penicillin, cephalosporin, monobactams, and carbapenems are shown in Figure 1



**Figure 1** The chemical structures of the member of beta-lactam antibiotic groups.

The highly reactive beta-lactam ring contains 3-carbon and 1-nitrogen in the ring, and this ring disrupts protein synthesis of bacterial cell wall and thus leading cell death or inhibits their growth. However, this ring also interferes with the synthesis of peptidoglycan in the cell wall of bacteria by blocking a penicillin-binding protein (PBP), resulting in the cell lysis and death (Smithet al., 2018).

The penicillin was the first antibiotic discovered at St. Mary's Hospital in London by Alexander Fleming in 1928 (Petri, 2011; McGeeret al., 2001). Penicillin consists of a Thiazolidine ring, o beta-lactam ring which is attached to side chains (Figure 1). Penicillin originally isolated from the mold *Penicillium notatum*. Penicillin G, Penicillin V, Oxacillin (dicloxacillin), Methicillin, Nafcillin, Ampicillin, Amoxicillin, Carbenicillin, Piperacillin, Mezlocillin and Ticarcillin are the most common members in Penicillin class (Etebu and Ariekpar, 2016; Petri, 2011). The production of antibiotics using biochemical microbial fermentation is more cost-effective than synthesizing from raw materials (Talaro and Chess, 2018).

Cephalosporin is a member of the beta-lactam group antibiotic having a similar structure and mode of action of penicillin (Figure 1). It has been isolated from the mold *Cephalosporium acremonium* by GuiseppaBrotzu in 1945 (Petri, 2011). It contains a 7-aminocephalosporanic acid nucleus and side-chain containing 3,6-dihydro-2 H-1,3-thiazane rings (Figure 1). Cephalosporins are most commonly classified by their chemical structure, clinical pharmacology, resistance to beta-lactamase, antimicrobial spectrum, and generations. The classification of cephalosporins by generations is important and it has been done based on the features of antimicrobial activity (Mandlleet *et al.*, 2005). The cephalosporins group of antibiotics is subdivided into 1<sup>st</sup> to 5<sup>th</sup> generations based on their target organism. The 5<sup>th</sup> generation Cephalosporins are more effective against Gram-negative bacteria. Cephalosporins are most commonly used in the treatment of bacterial infections and diseases arising from Penicillinase-producing, Methicillin-susceptible *Staphylococci* and *Streptococci*, *Proteus mirabilis*, some *Escherichia coli*, *Klebsiella Pneumoniae*, *Haemophilus influenzae*, *Enterobacter aerogenes* and some *Neisseria* (Etebu and Arikekpar, 2016; Pegler and Healy, 2007).

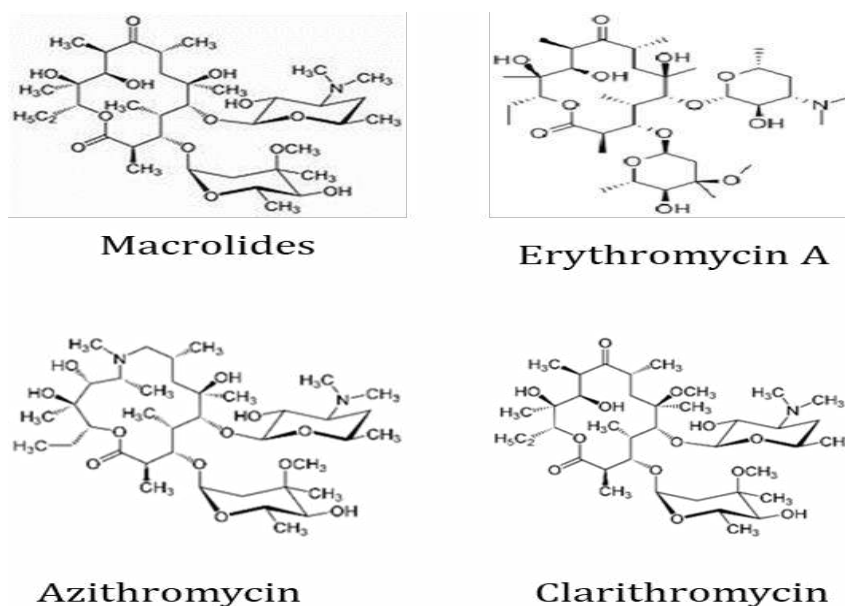
Monobactams are monocyclic  $\beta$ -lactam agents having a 2-oxoazetidine-1-sulfonic acid moiety (Figure1). Aztreonam is a commercially available monobactam antibiotic approved by the FDA, Aztreonam has a narrow spectrum activity (Mandlleet *et al.*, 2005). Aztreonam was isolated from Gram-negative bacteria *Chromobacterium violaceum*. It has broad-spectrum activity against Gram-negative bacteria such as *Neisseria* and *Pseudomonas*. It has been used for treating

pneumonia, septicemia and urinary tract infections caused by these groups of bacteria (Mandlleet *et al.*, 2005; Sykes *et al.*, 1981).

Carbapenems are widely used antibiotics for clinical uses in the United States. Carbapenems showed broad-spectrum activity against both Gram-positive and Gram-negative bacteria. There are four carbapenems that are most commonly referred such as imipenem, meropenem, ertapenem, and doripenem. Carbapenems can easily penetrate bacteria through the bacterial outer membrane, show a high affinity for multiple penicillin-binding proteins (PBPs) (Mandlleet *et al.*, 2005). They are often called “antibiotic of last resort” and it is prescribed when the patients are suspected of harboring resistant bacteria or became gravely ill (Torres *et al.*, 2007).

## 2.2. Macrolides

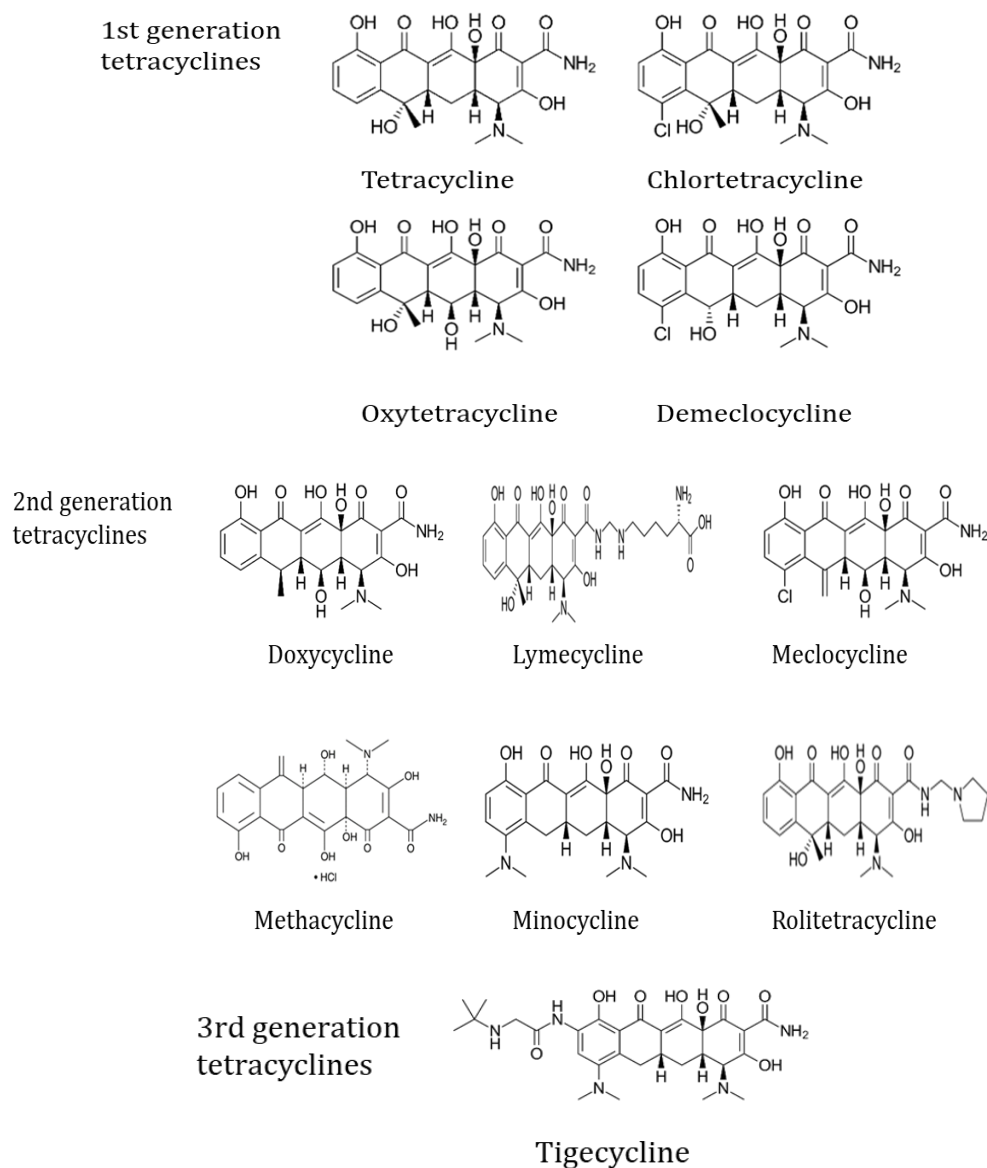
Erythromycin A was the first macrolides discovered and isolated in 1952 by J. M. McGuire from soil-inhabiting fungus *Saccharopolyspora erythraea* (Etebu and Arikekpar, 2016; Zhanelet *et al.*, 2001). It is a broad-spectrum antibiotic and primarily used for respiratory, skin and soft tissue infections. Demonstrated as broad-spectrum antimicrobial activity and was used primarily for respiratory and skin and soft tissue infections. The members of Macrolides are erythromycin, azithromycin, and clarithromycin (Figure 2) (Aminov, 2017; Zhanelet *et al.*, 2001). Macrolides can reversibly bind to the 23S rRNA of bacteria and thus, inhibit protein synthesis by blocking elongation (Zhanelet *et al.*, 2001)



**Figure 2** The chemical structure of the members of the macrolides group of antibiotics.

### 2.3. Tetracyclines

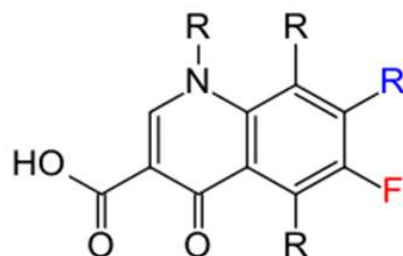
Tetracycline was discovered by Benjamin Duggar in 1945 from a bacterium *Streptomyces* (Sánchez *et al.*, 2004). The chlorotetracycline was the first member of this class. The tetracyclines can be sub-divided into different generations (1<sup>st</sup> to 3<sup>rd</sup>) based on the synthesis method. The members of first generation tetracyclines are tetracycline, chlortetracycline, oxytetracycline and demeclocycline derived from biosynthesis. The second-generation tetracyclines are doxycycline, lymecycline, meclocycline, methacycline, minocycline, and rolitetracycline those are semi-synthetic. The 3<sup>rd</sup> generation tetracyclines are total synthetic (e.g., tigecycline) (Fuoco, 2012). These classes of antibiotics target to attack bacterial ribosome by disrupting amino acids to polypeptide chains during protein synthesis. Tetracyclines are used in treating malaria, elephantiasis, amoebic parasites and rickettsia (Sánchez *et al.*, 2004). The chemical structure of tetracyclines are shown in Figure 3



**Figure 3** The chemical structure of the members of the tetracyclines group of antibiotics.

### 2.4. Quinolones

Quinolones class of antibiotics was discovered by chemists when Leshner accidentally discovered nalidixic acid as a by-product of the synthesis of the anti malarial compound chloroquine in 1962 (Andriole, 2005). The chemical structure of quinolone is shown in Figure 4. They consist of two rings, though recent generations of quinolones have more rings in the parent structure to increase their spectrum of antimicrobial activity.

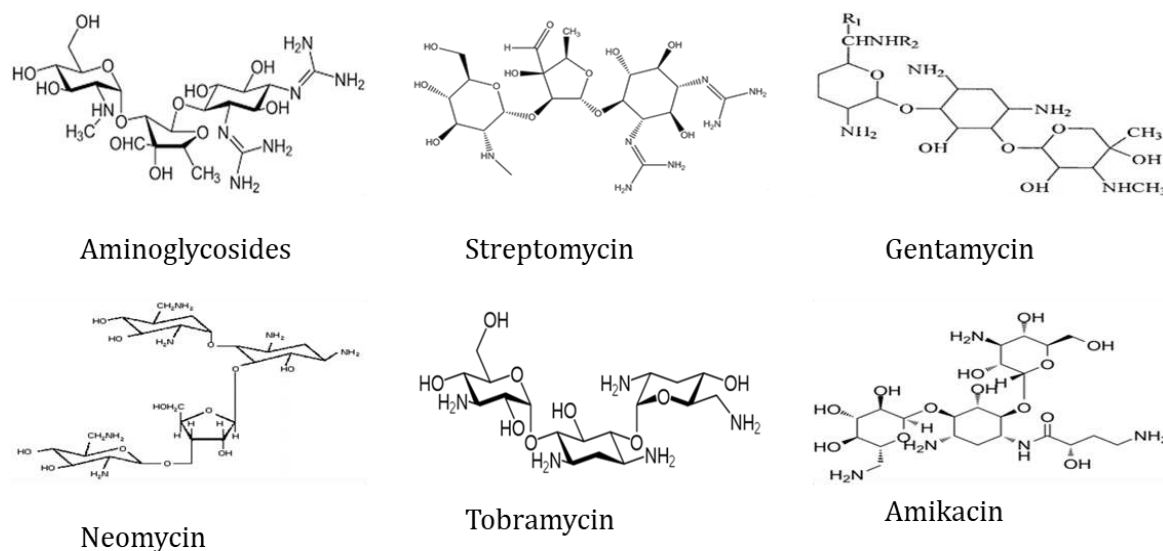


**Figure 4** The chemical structure of quinolones.

The members of quinolones are commonly cinoxacin, norfloxacin, ofloxacin, ciprofloxacin, temafloxacin, sparfloxacin, nalidixic acid, enoxacin (Domagala, 1994). The quinolones class of antibiotics can interfere with DNA replication and transcription in bacteria. These classes of antibiotics are used in the treatment of urinary, systemic and respiratory tract infections (Etebu and Arikekpar, 2016).

## 2.5. Aminoglycosides

Streptomycin was the 1st drug of aminoglycosides class of antibiotics which was isolated from soil Actinomycetes in 1943. Drug to be discovered among members of this class of antibiotics was streptomycin, first isolated in 1943 (Mahajan and Balachandran, 2012). The chemical structure of the members of aminoglycosides classes are shown in Figure 5



**Figure 5** The chemical structure of the members of aminoglycosides class antibiotics.

Other members of the aminoglycosides class of antibiotics are gentamicin, neomycin, tobramycin, and amikacin. The aminoglycosides class of antibiotics possess broad-spectrum antimicrobial activity. These classes of antibiotics can bind ribosomal subunits and thus, inhibit the protein synthesis in bacteria (Peterson, 2008). They are widely used in treating bubonic plague, tularemia, and tuberculosis (Talaro and Chess, 2018).

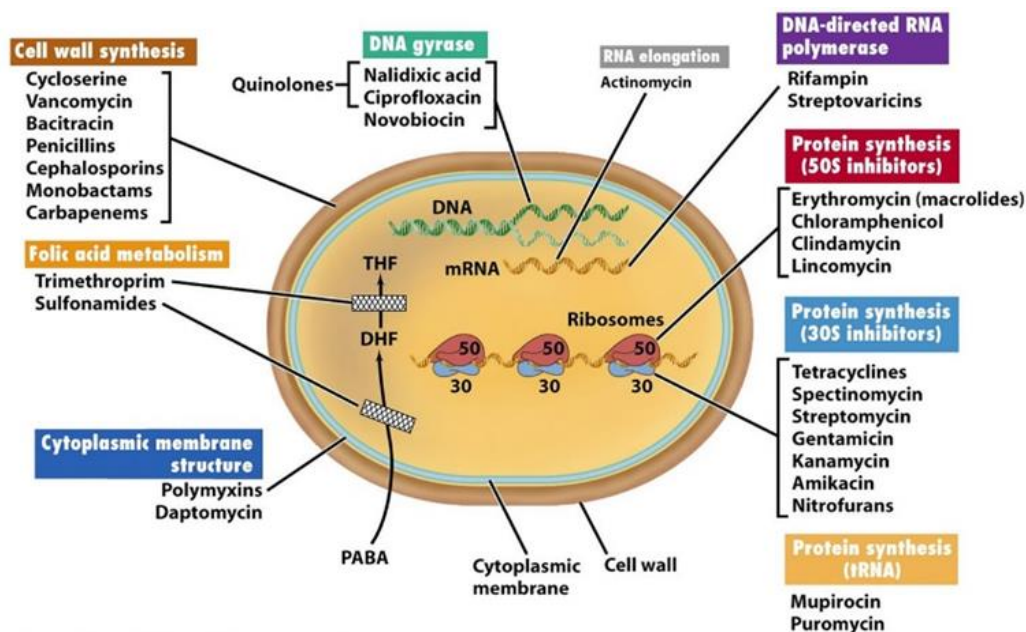
## 3. Mode of action of antibiotics

An antibiotic becomes functional by killing the bacteria. Antibiotics block the fundamental functions that took place in bacteria or stop them from multiplying which helps the immune system to fight against the bacterial infection. The antibiotics that affect a wide range of bacteria are known as broad-spectrum antibiotics. Some affect only a few types of bacteria known as narrow-spectrum antibiotics.

The mechanism of antibiotic actions is:

- bacterial cell wall synthesis inhibition,
- cell membrane structure and function breakdown,
- Disrupts the structure and function of nucleic acids,
- Disrupts protein synthesis,
- Key metabolic pathways blockage (Etebu and Ariekpar, 2016; Talaro and Chess, 2018; Madigan and Martinko, 2006; Wright, 2010).

The target site of antibiotics in bacteria is shown in Figure 6



**Figure 6** Major target sites of antimicrobial agents (Adopted from Madigan and Martinko, 2006).

The structural feature of bacteria or their unique metabolic processes make potent the antibiotics of different classes to those bacteria. Thus, the targets are directed, and the modes of actions are described as follows:

### 3.1. Inhibition of cell wall synthesis

Humans and animals do not have cell walls in their cell while the bacterial cells are surrounded by a rigid layer of peptidoglycan (PG), this structure is critical for the life and survival of bacterial species. The antibiotics (e.g., penicillins, cephalosporins, bacitracin, and vancomycin) target cell walls of bacteria and can selectively kill or inhibit bacterial organisms (Etebu and Ariekpar, 2016; Josephine et al., 2004; Park and Uehara, 2008).

### 3.2. Inhibition of cell membrane function

Intra- and extracellular flow of substances are regulated and segregated through the cell membrane. If somehow this important barrier becomes disrupted or damaged, then the essential solutes leaked which helps in cell survival. Because this structure is found in both eukaryotic and prokaryotic cells, the action of this class of antibiotic are often poorly selective and can often be toxic for systemic use in the mammalian host. Most clinical usage is therefore limited to topical applications. Examples: polymixin B and colistin (Falagas et al., 2010).

### 3.3. Inhibition of protein synthesis

Protein synthesis is a fundamental process for the multiplication and survival of all bacterial cells as enzymes and cellular structures are primarily made of proteins. Proteins are responsible for structural composition, metabolic and physiological processes, and response to adverse conditions. Several types of antibacterial agents target bacterial protein synthesis by binding to either the 30S or 50S subunits of the intracellular ribosomes. This activity then results in the disruption of the normal cellular metabolism of the bacteria and consequently leads to the death of the organism or the inhibition of its growth and multiplication. Examples: Aminoglycosides, macrolides, lincosamides, streptogramins, chloramphenicol, tetracyclines (Hong et al., 2014; Etebu, 2013; Nissen et al., 2000).

### 3.4. Inhibition of nucleic acid synthesis

Nucleic acid (DNA and RNA) synthesis is an essential process for all living organisms including bacteria. Some antibiotics work by binding to components involved in the process of DNA or RNA synthesis, which causes interference of the normal cellular processes which will ultimately compromise bacterial multiplication and survival. Examples: quinolones, metronidazole, and rifampin (Etebu and Arikekpar, 2016).

### 3.5. Inhibitors of other metabolic processes

Other antibiotics act on selected cellular processes essential for the survival of the bacterial pathogens. For example, both sulfonamides and trimethoprim disrupt the folic acid pathway, which is a necessary step for bacteria to produce precursors important for DNA synthesis. Sulfonamides target and bind to dihydropteroate synthase, trimethoprim inhibit dihydrofolate reductase; both enzymes are essential to produce folic acid, a vitamin synthesized by bacteria, but not humans (Talaro and Chess, 2018; Etebu and Arikekpar, 2016).

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## 4. Mechanism of antibiotic resistance

The three-fundamental mechanisms of antibiotic resistance are:

- Enzymatic degradation of antibacterial drugs
- Alteration of bacterial proteins that are antimicrobial targets
- Change in the membrane permeability to antibiotics (Maryet al., 2019; Etebu and Arikekpar, 2016).

Bacteria commonly use a mechanism to minimize the effects of antibiotics is the expression of drug efflux pumps. Efflux pumps have been reported as one of the mechanisms responsible for the antimicrobial resistance in biofilm structures. Efflux pumps are transport proteins involved in the extrusion of toxic substrates (including virtually all classes of clinically relevant antibiotics) from within cells into the external environment. These proteins are found in both Gram-positive and -negative bacteria as well as in eukaryotic organisms (Webber and Piddock, 2003).

Few conceptions are closely connected with antibiotic resistance. First, the environment plays a role in the spread of clinically relevant antibiotic resistance. The pathways which are responsible for the release of resistance-driving chemicals into the environment are controlled by environmental regulator. Hence, environmental regulators contributing significantly to the development of global and national antimicrobial resistance (AMR) action plans (Qiao et al., 2018; Singer et al., 2016). Antimicrobial resistance is an expected result of the interaction of many organisms with their environment. As antibiotics are naturally-produced, so cohabiting bacteria have evolved mechanisms to overcome their actions to survive. Thus, these organisms are often considered to be “intrinsically” resistant to one or more antimicrobials.

Second, it is important to recognize that the concept of antimicrobial resistance/susceptibility in clinical practice is a relative phenomenon with many layers of complexity. The establishment of clinical susceptibility breakpoints (susceptible, intermediate and resistant) mainly relies on the in-vitro activity of an antibiotic against a sizeable bacterial sample, combined with some pharmacological parameters (e.g., blood and infection site concentrations of the antimicrobial, among others). Thus, when treating antibiotic-resistant bacteria, the interpretation of susceptibility patterns may vary according to the clinical scenario and the availability of treatment options. For instance, the concentration of gentamicin achieved in the urine may be sufficiently high to treat a lower urinary tract infection caused by an organism reported as gentamicin-resistant. Similarly, different penicillin breakpoints have been established for *Streptococcus pneumoniae* depending if the isolate is causing meningitis vs. other types of infections, considering the levels of the drug that reach the cerebrospinal fluid (Van et al., 2000). Besides, the in vivo susceptibility of an organism to the antibiotic may vary according to the size of the bacterial inoculum, a situation that has been well documented in *Staphylococcus aureus* infections with some cephalosporins. Indeed, there is evidence to suggest that some cephalosporins (e.g. cefazolin) may fail in the setting of high-inocula deep-seated infections caused by cephalosporin-susceptible *S. aureus* (Munita and Arias, 2016). Thus, in the following sections, we will focus on the molecular and biochemical mechanisms of bacterial resistance, illustrating specific situations that are often encountered in clinical practice.

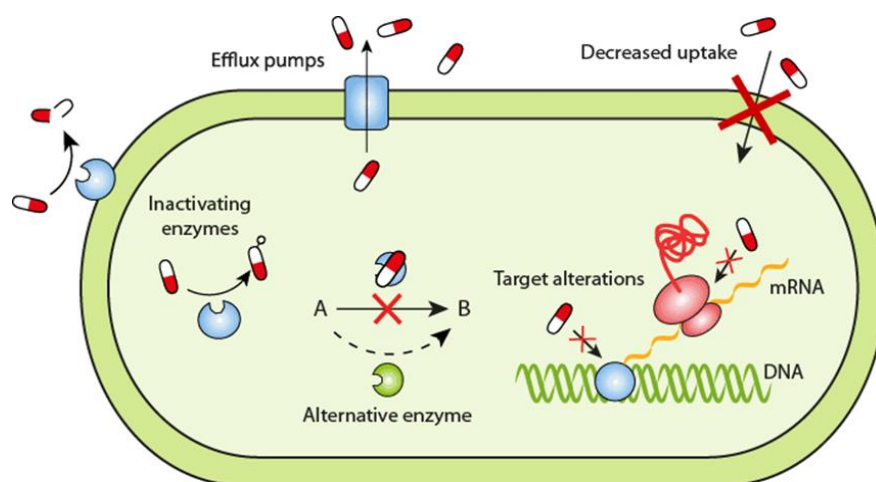
Bacteria can naturally produce an enzyme which inactivates antibiotics. Such an enzyme is  $\beta$ -lactamase.  $\beta$ -lactamase can destroy the active component (the  $\beta$ -lactam ring) of Penicillin. In later years, bacteria that produce extended-spectrum  $\beta$ -lactamases, so called Extended spectrum beta lactamase (ESBL)-producing bacteria, have become a major

problem. They can degrade a wide spectrum of  $\beta$ -lactam antibiotics, sometimes also the last resort drugs available for infections with these bacteria.

Bacterial resistance to  $\beta$ -lactam antibiotics can be achieved by any of three strategies:

- The production of  $\beta$ -lactam-hydrolyzing  $\beta$ -lactamase enzymes,
- the utilization of  $\beta$ -lactam-insensitive cell wall transpeptidases,
- and the active expulsion of  $\beta$ -lactam molecules from Gram-negative cells by way of efflux pumps.

In recent years, structural biology has contributed significantly to the understanding of these processes and should prove invaluable in the design of drugs to combat  $\beta$ -lactam resistance in the future (Wilke et al., 2005). Other enzymes produced by bacteria can add different chemical groups to antibiotics. This prohibits binding between the antibiotic and its target in the bacterial cell. Thus, resistance formed. The possible strategies of antibiotics resistance are shown in Figure 7



**Figure 7** Mechanism of antibiotic resistance (Adopted from E. Gullberg).

#### 4.1. Mutation

Mutation can occur in bacterial cell that changes in the composition or structure of the target in the bacterium (resulting from mutations in the bacterial DNA). Such changes can prohibit the antibiotic from interacting with the target.

#### 4.2. Express alternative proteins

Some bacteria can produce alternative proteins that can be used instead of the ones that are inhibited by the antibiotic. For example, the bacterium *Staphylococcus aureus* can acquire the resistance gene *mecA* and produce a new penicillin-binding protein. These proteins are needed for bacterial cell wall synthesis and are the targets of  $\beta$ -lactam antibiotics. The new penicillin-binding protein has a low affinity to  $\beta$ -lactam antibiotics and is thus resistant to the drugs, and the bacteria survive treatment. This type of resistance is the basis in MRSA (methicillin-resistant *Staphylococcus aureus*).

#### 4.3. Reprogram target

Sometimes bacteria can produce a different variant of a structure it needs. For example, Vancomycin-resistant bacteria make a different cell wall compared to susceptible bacteria. The antibiotic is not able to interact as well with this type of cell wall. Some bacteria are naturally resistant to certain antibiotics. Imagine for example an antibiotic that destroys the cell wall of the bacteria. If a bacterium does not have a cell wall, the antibiotic will not affect it. This phenomenon is called intrinsic resistance. When a bacterium that was previously susceptible to an antibiotic evolves resistance, it is called acquired resistance.

### 5. Strategies to overcome antibiotic resistance

More than 150 million prescriptions are written for antibiotics in the U.S. each year. Due to the spread of antibiotic resistance all over the world, it is the burning question now. In this case, self-awareness is a must to protect and fight against antibiotic resistance.



To protect oneself from antibiotic resistance some rules that must be followed-

- Over use of antibiotics and unnecessary use of them must be prohibited.
- The prescriber must be registered and concern during prescribing. For illnesses caused by viruses 'common colds, bronchitis, and many ear and sinus infections- they won't.
- The pills must be taken exactly as directed in the prescription and continue it even if after feeling better, otherwise, those bacteria are more likely to become drug-resistant.
- Immunization can protect oneself against some diseases (tetanus, whooping cough, etc.) that are treated with antibiotics. So, one should be vaccinated.
- The antibiotic-resistant bacteria are commonly found in hospitals, so cleanliness and proper sterilization must be performed, and surgical wounds must be free from infection.

The antibiotics are limited in our arsenal, so it is better to find ways of dosing and combining drugs to increase efficacy and decrease resistance. One method is using a sequential regimen. Sequential regimens alternate the use of two (or more) drugs over time. The design of sequential regimens can eliminate bacteria at doses that would normally lead to resistance and treatment (Fuentes-Hernandez et al., 2015). To combat bacterial resistance the main target is to enhance sensitivity to the second drug of an organism which develops resistance to one drug and avoids cross-resistance in which an organism that has developed resistance to one drug becomes less sensitive to the second drug.

Gram-positive bacteria lack the outer membrane whereas Gram-negative bacteria are surrounded by two membranes with a cell wall sandwiched in between. Gram-negative bacteria also have other defense systems- through efflux pumps. Knocking out efflux pumps is a promising strategy both to create new drugs and bring old antibiotics back to life, says physicist James C. Gumbart of the Georgia Institute of Technology (Richardson, 2017). The authors of a recent PLOS Biology article have shown that resistant bacteria can be re-sensitized by treating with a specifically designed anti-sense oligonucleotide. This oligonucleotide, a peptide-conjugated phosphorodiamidate morpholino oligomer (PPMO), acts as an antisense mRNA translation inhibitor and can be designed to target the mRNAs encoding resistance genes. They found that the most effective PPMOs target a constituent of the major drug efflux pump, and treatment with this PPMO can lead to a 2- to 40-fold increase in antibiotic efficacy.

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## 6. Conclusion

This review analyzes the importance of antibiotics, their classification, and mode of action, resistance mechanism and way to get rid of the current problem of antibiotic resistance. The antibiotics can be classified based on their molecular structures, mode of action, route of administration (injectable, oral, and topical), and spectrum of activity. Antibiotics help us to fight against infectious diseases. However, the improper use or over use of antibiotics helps to develop the emergence of bacterial resistance to all known antibiotics, which is an alarming concern now-a-days. If the bacteria once become resistant to the antibiotic, it is hard to cure the infectious disease using the antibiotic. Proper uses of antibiotics play an important role to minimize the antibiotic resistance. This review is delivering the knowledge about antibiotics, the proper use, and mode of action and resistance mechanism

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## Compliance with ethical standards

### *Acknowledgments*

The authors sincerely thank the staff of the Institute of Radiation and Polymer Technology, Atomic Energy Research Establishment, Savar, Dhaka, Bangladesh. This research work was supported by the Annual Development Project of Bangladesh. The title of the project is: "Strengthening of existing gamma source of Bangladesh Atomic Energy Commission". Special thanks to The Ministry of Science and Technology and The Ministry of Planning, Government of the People's Republic of Bangladesh.

### *Disclosure of conflict of interest*

All authors state that there is no conflict of interest.

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