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Review

Mechanisms and implications of antibiotic resistance in gram-positive bacterial strains

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Abstract

Antibiotics play a fundamental role in protecting millions of lives from infectious diseases. However, an important drawback of antibiotic treatment is that each advancement was followed by the development of resistance. This is due to the fact that the majority of pathogenic bacteria are capable of becoming resistant to a number of antimicrobial agents. There are a number of resistance mechanisms the microorganism may possess naturally or by acquisition from other microorganisms. The main mechanisms of resistance to a medication include altering its target, preventing its absorption, causing it to efflux actively, and rendering it inactive. Many types of gram-positive bacteria that cause serious infections in both the community and healthcare system are listed among the most dangerous bacteria according to the WHO's published list, which calls for the development of novel antibiotics to address the resistance issue. The following three strains, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus faecium*, and penicillin-resistant *Streptococcus pneumoniae*, are of special importance. Therefore, this review highlighted the main mechanisms and consequences of antibiotic resistance in Gram-positive bacterial strains.

Keywords: Antibiotics, Antimicrobial resistance, Gram-positive bacteria, Implications, Mechanisms of resistance

1. Introduction

The discovery of antimicrobial drugs, which are now used in both human and veterinary medicine as vital infection prevention and treatment, was one of the major turning events in the 20th century [1]. Thus, in order to restrict bacterial proliferation (by inhibiting its growth or enhancing cell degradation), a potent pharmaceutical compound known as antibiotics is frequently used globally [2]. Antibiotics play a fundamental role in controlling bacterial infection, which results in protecting human and animal lives, and for that reason, it is considered an important medical invention [3]. Antibiotics have also proved to be important for the development of sophisticated medical techniques, including solid organ transplantation, advanced surgical techniques, and cancer patient treatment [4].

Although antibiotics have proved to be important, currently serious health concerns have emerged with the overuse of antibiotics, including the emergence, spread, and expression of bacterial antibiotic resistance [5]. In the 21st century, antibiotic resistance, which is characterized by losing the antibiotic ability to treat targeted infectious illnesses, is distinguished as one of the biggest risks to human health [6].

Furthermore, antimicrobial resistance (AMR) has emerged as a significant problem that negatively impacts both human life and the economy. This was proved by a 2019 report by the World Health Organization (WHO), which claimed that AMR was the cause of 700,000 deaths, and it suggested that this number will reach 20 million deaths by 2050 [7]. It should be mentioned that the discovery of new antibiotics is always followed by the discovery of their resistance development [8]. Moreover, it was reported that the morbidity and mortality rates are directly impacted by the limitations in patients' treatment options as a consequence of increasing antibiotic resistance. Thus, purpose of this review is to give a summary of the mechanisms and consequences of antibiotic resistance in Gram-positive bacterial strains.

2. Origin of Antibiotic Resistance

Arsphenamine, which is a toxic organ arsenic compound, was a suitable treatment for syphilis until the beginning of the 20th century when the clinical application of antibiotics started. In 1938, penicillin took the place of arsphenamine therapy [9]. Moreover, in 1936, an inhibitor of dihydropteroate synthetase known as sulfonamides was

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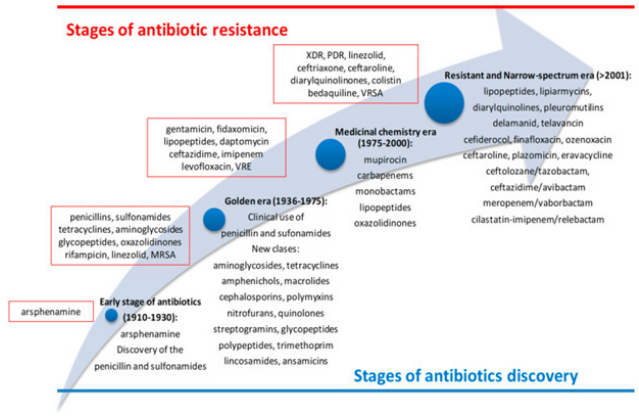

Fig. 1. The time line of antibiotic development and their resistance. (MRSA—methicillin-resistant *Staphylococcus aureus*, PDR—pan-drug-resistant, VRE—vancomycin-resistant enterococci, VRSA—vancomycin-resistant *S. aureus*, XDR—extensively drug-resistant) [10].

started to be used as antibiotic medication for the first time [8]. The most productive time in the history of antibiotics was during the period between 1936 and 1975. During this time, a wide range of antibiotic classes with distinct spectrums of activity and modes of action for clinical application were developed. As an example, these antibiotics: β-lactams (1938), aminoglycosides (1946), tetracyclines (1948), amphenichols (1949), polymyxins (1950), macrolides (1951), nitrofurans (1953), quinolones and trimethoprim (1962), lincosamides and ansamycins (1963), cephalosporins (1964), streptogramins (1965), phosphonates (1971), etc [10] (Fig. 1).

However, after a short time, the clinicians discovered a serious drawback of antibiotics, which is their inefficiency. This is clearly described by the term antimicrobial resistance (AMR), which means that an antimicrobial drug loses its ability to control the growth and spread of microorganisms. Consequently, Sir Alexander Fleming, the scientist who discovered penicillin, expressed concern about the widespread utilization of penicillin that could result in AMR [11]. Therefore, the need for more research in order to understand the AMR increased in the period between 1975 and 2000. During this period, many efforts were made to develop synthetic molecules with a wide range of activity, such as carbapenems and mupirocin, oxazolidinones, monobactams, and lipopeptides [12]. In addition to that, recently many groups of antibiotics have been developed, which include macrolactones, pleuromutilins, diarylquinolines, and catechol-substituted siderophores [13]. Antibiotic resistance development is mainly classified into two main categories, which are natural resistance and acquired resistance.

2.1. Natural Resistance

This type of resistance is further classified into two types: intrinsic or induced. Intrinsic resistance is a feature of bacterial species that is always present and is unaffected by prior antibiotic exposure. It is also present regardless of horizontal gene inheritance. On the other hand, the induced resistance corresponds to the naturally occurring genes whose expression is associated with exposure to antibiotics [7].

2.2. Acquired Resistance

Mainly, antibiotic resistance is known to be acquired. A certain microorganism develops this type of resistance when it becomes resistant to the effect of an antimicrobial drug that it used to be sensitive to [10]. There are several methods by which the resistance genetic material is transferred to the bacterial cells. These methods are known as horizontal gene transfer (HGT) and include transposition, transformation, and conjugation. In addition to that, the resistance genetic material could be acquired by the bacteria when mutations are acquired in its chromosomal DNA. It should be mentioned that bacteriophage-borne transfer of resistance genes is rather uncommon; instead, plasmid-mediated transmission is the most frequent way to acquire foreign genetic material. Additionally, all of these acquisition methods could be either long-term or short-term [14].

The minimum inhibitory concentration (MIC) is mainly used to determine the sensitivity and resistance of certain antibiotics. Due to the fact that some bacteria have been known to acquire resistance genes from other closely related microbes, the degree of resistance would be affected by the species and genes obtained. Thus, based on the MIC value, the bacterial intrinsic resistance to a certain drug is reported when the MIC value is high [15].

3. Antibiotic Mechanisms of Action

Based on the mechanism of action of antimicrobial agents they were categorized into various classes. Cell membrane depolarizing agents and inhibitors of cell wall production, nucleic acid and protein synthesis, and bacterial metabolic pathways are all the main classes of antimicrobial agents. An example of these agents is represented in Fig. 2 [16].

4. Mechanisms of Resistance

The resistance mechanisms to antibiotics undergo various changes during bacterial evolution. These resistance mechanisms are subdivided into four main groups, which are drug inactivation, active drug efflux, drug target change, and drug uptake restriction [17]. Drug inactivation, drug efflux, and limiting uptake are mainly the mechanisms of intrinsic resistance, while drug efflux, inactivation of drugs, and drug target modification are the mechanisms of acquired resistance [7].

4.1. Limiting Drug Uptake

Gram-positive bacteria are less likely to prevent medicine access because they lack an outer barrier. For example, aminoglycoside-related intrinsic resistance is accomplished in the *enterococci*; this is due to the fact that polar molecules couldn't penetrate the cell wall easily.

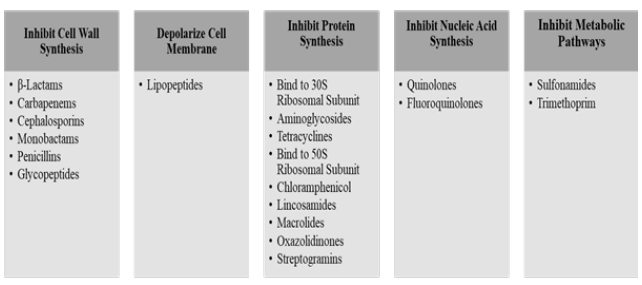

Fig. 2. Groups of Antimicrobial agent according to their mode of action [16].

Additionally, vancomycin resistance was reported recently in various types of gram-positive bacteria like *Staphylococcus aureus* [18]. Another defense mechanism against the antimicrobial is the development of biofilms that play a key role in bacterial colonization and consist of DNA, proteins, and polysaccharides [19].

On the other hand, in gram-negative bacteria, the intrinsic resistance that is accomplished by the outer membrane, which is mainly made of lipopolysaccharide (highly acylated glycolipid), restricts the movement of antibiotics through it [3]. A further factor that might cause acquired drug resistance is the alterations in the outer-membrane proteins' permeability, specifically porin proteins [20]. Hydrophilic antibiotics (β-lactams, tetracyclines, fluoroquinolones, and chloramphenicol) primary entry site is porins. The entry of these antibiotics into bacterial cells is influenced by the type and quantity of porin proteins present, which subsequently affects the bacteria's sensitivity to these antibiotics [21].

4.2. Drug Target Modification

The genes that encode the drug's target protein are subjected to a modification that is carried out by mutation. By this modification, the drug either fails to attach to the changed target or binds poorly to it. As an example, gram-positive and gram-negative bacteria acquire fluoroquinolone resistance as a result of mutation quinolone-resistance-determining region (QRDR) in the topoisomerase II and topoisomerase IV [22]. Another efficient method of this type of resistance is methylation. In which erm methylases in both gram-positive and gram-negative bacteria are directed against lincosamides, macrolides, and streptogramin B antibiotics [3].

4.3. Drug Inactivation

Bacteria can inactivate drugs in two primary manners: either by effectively breaking down the drug (using β-lactamases, which are drug hydrolyzing enzymes) or by adding a chemical group to it (like phosphoryl, acetyl, and adenyl groups) [23]. Numerous transferases have been identified, including those that target aminoglycosides by phosphorylation and adenylation as well as the widely utilized mechanism of acetylation (which is employed against aminoglycosides, chloramphenicol, streptogramins, and fluoroquinolones) [16].

4.4. Active Drug Efflux

A wide range of toxic materials are eliminated from the microorganism using efflux pumps. Thus, through this mechanism of resistance, the antibiotic failed to reach the intracellular concentration level, which is needed to kill the bacteria as a result of active drug efflux that inhibits the antibiotic accumulation. This mode of mechanism may be found in a variety of bacteria and helped it to develop resistance to a broad variety of antibiotics, like fluoroquinolones, aminoglycosides, and tetracycline [10].

5. Gram-Positive Bacteria

A worldwide priority pathogens list was released by the World Health Organization (WHO), which classified the pathogens as antibiotic-resistant bacteria as critical, high, and medium priority and that require immediate study and treatment development [24]. An example of this pathogen is Gram-positive bacteria, and especially multidrug-resistant (MDR) bacteria such as vancomycin-resistant *Enterococcus faecium* (VRE), Penicillin-Resistant *Streptococcus Pneumoniae*, and methicillin-resistant *S. aureus* (MRSA) are of particular concern and consideration as they can lead to serious infections [25].

The plasma membrane of Gram-positive bacteria (Fig. 3) is surrounded by a thick layer of peptidoglycan (PG), which shields it from the hostile environment in which it resides. It also helps in the identification of gram-positive from gram-negative bacteria [26]. The PG layer of gram-positive bacteria has the ability to retain the crystal violet dye that makes the bacteria produce a blue color under the microscope [27]. Many factors affect bacterial morphology and cell shape, such as PG thickness, degree of cross-linking, and chemical composition. Moreover, gram-positive bacteria can be found in various shapes, like rod-shaped (Bacillus subtilis), sphere-shaped (staphylococci and streptococci), as well as branching filament bacteria [28]. Moreover, the cell wall is made up of capsular polysaccharides that are covalently bound to PG, long anionic polymers known as teichoic acids, and membrane protein that serves as a sensor and channel to help in the transfer of various molecules [24].

5.1. Resistance of Gram-Positive Bacteria

The genetic ability of gram-positive bacteria to acquire and develop resistance to practically all antibiotics used in clinical settings is remarkable. So, in order to control this problem, measures should be carried out to avoid the resistance problem for the purpose of identifying new resistance mechanisms, optimizing the use of antibiotics, and creating solutions [25]. The two main resistance mechanisms of Gram-positive bacteria are breaking down the antibiotic enzymatically (by producing β-lactamases or by reducing the affinity and susceptibility of their target site) or the penicillin-binding protein (PBP) (by acquiring exogenous DNA or by altering the native PBP genes) (Fig. 4) [24].

5.1.1. Methicillin-Resistant *S. aureus* (MRSA)

In order to overcome the bacterial resistance mechanism, celbenin (which is known as methicillin semisynthetic penicillin) was developed in 1959. However, two years later, in the UK, the first methicillin-resistant *S. aureus* strain was discovered, and it was reported that it is resistant to all β-lactam antibiotics (cephalosporins and carbapenems) [29]. They also found that this resistance is due to PBP2a, which is encoded by genomic*A* that is obtained by *S. aureus* from unidentified heterologous sources. This PBP2a results in decreasing the bacterial sensitivity for penicillin and β-lactam antibiotics [24].

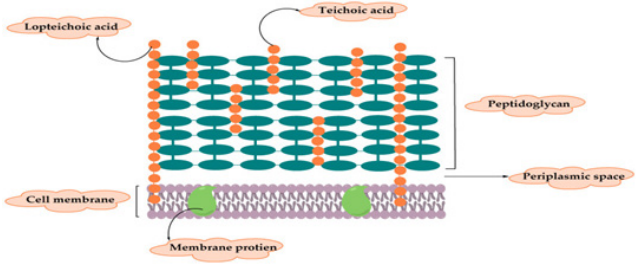

Fig. 3. The composition of the Gram-positive bacteria cell wall [24].

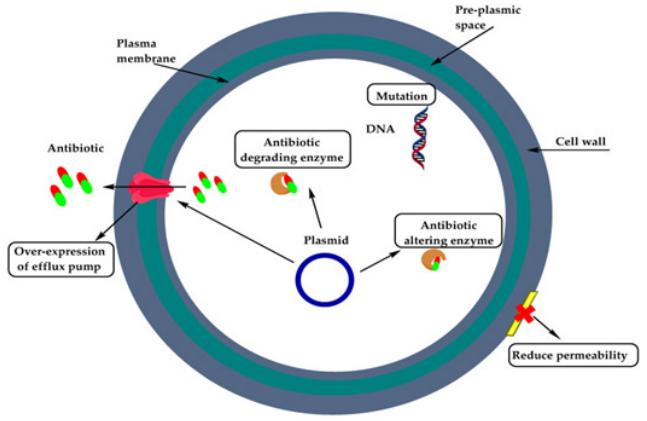

Fig. 4. The main resistance mechanisms of Gram-positive bacteria [24].

5.1.2. Vancomycin-resistant *E. faecium* (VRE)

Enterococcus faecalis and *E. faecium* are the only Enterococcus species that cause human infection, with about 80–90% of clinical isolates being caused by *E. faecalis* and 5–15% by *E. faecium*. Although *E. faecium* is considered normal gut flora in both humans and animals, it could lead to significant morbidity and death when it acts as an opportunistic pathogen in immunocompromised hosts [30]. Vancomycin was approved for the treatment of Enterococcus in the 1970s, but shortly after that, cases of vancomycin-resistant enterococci (VRE) began to emerge. In response to this growing issue, numerous preventative measures have been implemented to address VRE, which became a significant concern in the United States during the early 1990s [31].

The bacterial cell wall synthesis (peptidoglycan layer) is inhibited by the action of vancomycin. This is achieved by the binding of vancomycin to the D-alanyl-D-alanine (D-Ala-D-Ala) terminus. Thus, when this terminal chain is altered from D-Ala-D-Ala to D-alanyl-D-lactate termini, the antibiotic's ability to bind to this target is reduced, which will in turn cause the bacteria to become resistant to vancomycin. This alteration is achieved by the following gene cluster, which is known as the Vancomycin-resistance gene (VanA to VanG) [10].

5.1.3. Penicillin-Resistant *S. Pneumoniae*

There are six different PBP types in *S. pneumoniae*, and three of these mutations (PBP1A, PBP2X, and PBP2B) are linked to penicillin resistance. Penicillin resistance in *S. pneumoniae* (PRSP) is acquired through PBPs mutation. Following widespread treatment of bacterial infection with β-lactam antibiotics, these resistant pneumococci isolates persisted. Moreover, these isolates subsequently transformed as a result of spontaneous mutation accumulation as well as allele recombination from other β-lactam-resistant group streptococci [32].

6. Major Clinical Implications of Antimicrobial Resistance

The health of both humans and animals is directly impacted by the AMR problem. Drug-resistant strains of microorganisms are developed as a consequence of overuse and/or misuse of antibiotics in several fields, including veterinary medicine, agricultural practices, and healthcare facilities [33]. Moreover, the excessive use of antibiotics and the emergence of AMR strains affect the treatment efficacy and also may cause severe infections. Thus, in order to solve this problem, new antimicrobial drugs should be developed faster to overcome the fast emergence of resistance strains [34]. So, as a conclusion, the following clinical implications of AMR are among the major concerns [35]:

• The effective treatment of a wide range of illnesses that are linked to fungus, virus, and bacterial infection is directly impacted by antimicrobial resistance.

• Treatment for many common diseases, including flu, typhoid, urinary tract, and upper respiratory tract infections, is at risk as a result of the development and dissemination of novel resistance mechanisms, which could cause treatment failure, permanent impairment, and increase mortality.

• Without the presence of novel antimicrobial treatment, the success rate of the treatment of some serious health issues, such as organ transplantations or chemotherapy for cancer, as well as simple health issues like dental surgeries, would be negatively affected.

• Antibiotic-resistant patients require more expensive medications and longer-term therapy, and this contributes to raising the cost of healthcare.

7. Conclusion

Antibiotic-resistant bacteria have developed resistance to all of the agents that have been used. By having a fundamental grasp of the processes underlying resistance, the physician may more accurately identify and anticipate resistance patterns, even to antibiotics that are not included on the antibiogram, and choose the antibiotic that is most suited for the particular pathogen. Research on the causes of resistance and efforts to produce new antibiotics should be robust and ongoing since a thorough understanding of the processes is crucial for creating innovative ways to counter this danger.

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