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β-Lactams-Based Antibiotics Resistance: A Bottom-up Overview

Review Article

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Author Details

Anekpo Chijioke C[1], Okoloagu Nkiruka[2] and Ezenwa Adanma[3]*

[1]*Department of Otorhinolaryngology, Enugu State University of Science and Technology, Nigeria*
[2]*Department of Opthamology, Enugu State University of Science and Technology, Nigeria*
[3]*Department of Opthamology, Nnamdi Azikiwe University, Nigeria*

*Corresponding author

Anekpo Chijioke C, Department of Otorhinolaryngology, Enugu State University of Science and Technology, Nigeria

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Abstract

β -lactamase enzymes are an extensive group of hydrolyzing enzymes produced by bacteria as a common resistance mechanism against beta-lactam antibiotics. These enzymes hydrolyze the core beta-lactam ring and thus decrease the effectiveness of drug concentration, thereby conferring increased resistance. Currently, most infections pose difficulty in their treatment due to β-lactamate resistance. Among multidrug-resistant pathogens, extended-spectrum β-lactamase or Carbapenemase-Producing Enterobacteriaceae (CPE) is currently considered the main threat due to the scarcity of therapeutic options and their rapid spread around the globe. More evidence is emerging on the mechanisms bacteria use to resist β-lactam antibiotics. Moreover, due to several scientific innovations, different therapy has shown effectiveness in current cases of drug resistance due to β-lactamase enzymes produced by most bacteria. While it seems like the antibiotic crisis has brought to the limelight situation reminiscent of the pre-antibiotic era, our study showed that there is light at the end of the tunnel. Here, we discussed the recent updates on antimicrobial resistance due to β-lactamase enzyme production and the therapeutic options used in mitigating the spread of resistance due to β-lactamase enzyme.

Keywords: β-lactamase; β-lactamate antibiotics; Antimicrobial resistance; Bacteria

Introduction

Drug resistance is a major problem that limits the effectiveness of chemotherapies. Resistance to antimicrobial agents has become a major source of morbidity and mortality worldwide. When antibiotics were first introduced in the 1900s, it was thought that we had won the war against infectious microorganisms. It was soon discovered, however, that the microorganisms could develop resistance to any of the drugs used. Apparently, most pathogenic microorganisms have the capability of developing resistance to at least some antimicrobial agents. Antibiotics must first cross the cell envelopes before it inhibits bacterial growth. Some may then need to be activated, and all must reach their target at a concentration high enough to exert an effect. Antibiotic resistance leads to higher medical costs, prolonged hospital stays, and increased mortality. This results from the emergence of new resistance mechanisms, spreading globally and threatening the medical sector's ability to treat common infectious diseases. The resistance to β-lactam antibiotics is a severe threat to public health.

Bacteria and other infection-causing microbes have remarkably developed several ways to become resistant to antibiotics and other antimicrobial drugs [1]. The possibility of microorganisms resisting the effect of antibiotics has been the subject of intense investigation since the early days of the discovery of antibiotics. The main mechanisms of resistance are: limiting uptake of a drug, modification of a drug target, inactivation of a drug, and active efflux of a drug. These mechanisms may be native to the microorganisms or acquired from other microorganisms [2].

Beta-lactam antibiotics are the most frequently prescribed class of drugs worldwide [3]. The antibiotic inhibits bacterial cell wall synthesis, thus resulting in the lysis and deformation of the bacterium [4]. It is effective on both Gram-positive and negative bacteria. These antibiotics are characterized by a core of a beta-lactam ring and are classified by their moieties into four major families: Penicillin, cephalosporin, carbapenems, and monobactams [5,6]. β-lactam antibiotics inhibit the formation of a peptidoglycan layer. The final transpeptidation step in synthesizing the peptidoglycan is facilitated by PBPs which bind to

the D-Ala-D-Ala at the end of muropeptides (peptidoglycan precursors) to crosslink the peptidoglycan. Beta-lactam antibiotics mimic the D-Ala-D-Ala site, thereby irreversibly inhibiting PBP crosslinking of peptidoglycan.

Many members of the Enterobacteriaceae family of gram-negative bacteria possess chromosomal β-lactamase genes. Other gram-negative bacteria that possess these include Aeromonas spp., Acinetobacter spp., and Pseudomonas spp. Plasmid-carrying β-lactamase genes are most commonly found in the Enterobacteriaceae but may also be found in some species of gram-positive bacteria such as Staphylococcus aureus, Enterococcus faecalis, and Enterococcus faecium [7,8]. This review briefly summarized what is currently known about β-lactams resistance in bacterial pathogens. This understanding is crucial for developing novel treatment interventions and surveillance protocols for mitigating the spread of antimicrobial resistance infectious diseases due to the loss of function of β-lactams antibiotics.

Beta-Lactam Antibiotics: Back to History

This set of antibiotics constitutes a broad class of antibiotic agents that contain β-lactam rings in their molecular structure. The discovery of beta-lactam antibiotics dates back to 1921, when Alexander Fleming, a Scottish bacteriologist suffering from a common cold, decided to inoculate his nasal secretion on agar plates and observed the absence of colonies for several days. This observed abnormality was suggested as the presence of a diffusible substance in the nasal secretion that affected the ability to grow. Fleming later named the substance that could dissolve the cell wall and cause lysis in many gram-positive bacteria, Lysozyme. This discovery paved the part for the discovery of other antibiotics like Penicillin. Penicillin G was the first beta-lactam developed, which led the search for the synthesis of additional derivatives [9].

In the fall of 1928, Fleming studied the relationship between colony morphology of Staphylococcus and their virulence. Before leaving for vacation, he inoculated culture plates with Staphylococcus colonies and stacked the plates on the corner of his laboratory bench. When he returned, he found several cultures contaminated with molds. He discarded the contaminated plates into a Lysol basin. He worked with many cultures that day, and a few culture plates rested above the level of the liquid antiseptic, escaping the disinfectant. The next day, while describing his experiments to a colleague, Fleming dug up some previously discarded culture plates [9]. Upon re-examination, one of the plates contained a contaminating mold whose presence seemed to be influencing the morphology of the surrounding Staphylococcus colonies: colonies in proximity to the mold were transparent and seemed to be undergoing lysis. This observation was reminiscent of what Fleming had previously seen with Lysozyme and led him to realize that the mold contained an antagonistic microbial property. Fleming carefully sub-cultured and preserved the Penicillium notatum, which he originally described as Penicillium rubrum. The discovery of this first beta-lactam antibiotic resulted in further research into other beta-lactam antibiotics.

Classification of Beta-Lactam Antibiotics

Classification of β-lactamase enzymes is based on their molecular structure and/or functional characteristics. Two major types of beta-lactamases can be distinguished based on the method of hydrolysis: serine-based or metal (e.g., zinc) based [10]. Beta-lactamases have been categorized into four classes (Ambler classifications) known as A, B, C, and D. The hydrolysis of beta-lactams by the enzymes of classes A, C, and D relies on an active site serine residue, whereas those of class B are metalloenzymes that use one or two zinc ions to coordinate hydrolysis. While serine enzymes from different classes and may share some structural similarities, metalloenzymes are structurally dissimilar [11,12]. Given the differences in enzyme structure and binding sites, finding a single molecule that can inhibit both serine and Metallo-beta-lactamases has been a daunting challenge.

Class C beta-lactamases confer resistance to broad-spectrum cephalosporins, penicillins, and monobactams. Like other beta-lactamases, they are highly transferable and widespread among Gram-negative bacteria, especially in clinical isolates. Class C beta-lactamases catalyze the hydrolysis of the beta-lactam ring by a conserved catalytic Serine (Ser 64 in Escherichia coliBLAampC) and an activating conserved Tyrosine (Tyr 150) [13]. Gram-negative bacteria produce β-lactamases from all four structural groups (A, B, C, or D). The β-lactamases found in gram-positive bacteria are mainly from group A, with some from group B [14]. These enzymes may be innately found on the bacterial chromosome or may be acquired via a plasmid.

Mechanism of action of Beta-lactams Antibiotics and Resistant Mechanisms

Beta-lactam drugs must bind to specific targets located in the cytoplasmic membrane of bacteria to exert their inhibitory effect. These target proteins can be identified by their ability to covalently bind isotope-labeled Penicillin and are termed Penicillin-Binding Proteins (PBPs). The enzymatic functions of higher-molecular-weight PBPs are essential in cell wall peptidoglycan synthesis. Beta-lactams exert their initial bacteriostatic effect through the inhibition of these high-molecular-weight PBPs. The beta-lactam antibiotics inhibit the last step in peptidoglycan synthesis by acylating the transpeptidase involved in crosslinking peptides to form peptidoglycan. The binding of beta-lactam antibiotics to their target (PBPs) interrupts the terminal transpeptidation process and induces loss of viability and lysis [15].

Resistance can occur as a result of lower affinity PBPs in some microbes. For example, this has been demonstrated in a study involving S. aureus, where it was shown that a reduction in the presence of PBP2a leads to resistance [5,16]. Therefore, changes in the affinity or quantity of PBPs play a major role in the development of beta-lactam resistance among clinical isolates of bacteria. Reduced beta-lactam susceptibility mediated by PBPs can arise in several ways. It might be a manifestation of the reduction in affinity of normally occurring PBPs, a loss in quantity of a PBP, or the addition of low-affinity PBPs. In some Gram-positive bacteria, a combination of these events may occur to produce resistance. According to the study by Lienen et al. [5], the low-level β-lactam resistance in some gram-positive bacterial pathogens may be due to the presence of naturally occurring slow-reacting low-affinity PBPs.

Although other mechanisms such as efflux pumps, decreased permeability from porin channel mutations, and target site changes [17] play a role in gram-negative resistance to antibiotics, the production of β-lactamases is one of the more common resistance mechanisms. In gram-negative bacteria, the modification of PBP affinity has been shown to result in beta-lactam resistance. In other instances, there is evidence to suggest that a reduction in the permeation of beta-lactam antibiotics is also required to produce clinically significant levels of resistance. It also seems possible that minor changes in the affinity of PBPs for new poorly hydrolyzed β-lactam antibiotics contribute to resistance to these compounds in the face of slow rates of hydrolysis and species-related restriction of outer membrane permeation.

The PBP-inhibitory activity of Penicillin and other β-lactam antibiotics is based on the structural, geometric, and stereochemical similarities between the amide bonds of Penicillin and the enzyme-substrate (D-Ala-D-Ala dipeptide) [18,19]. Therefore, β-lactamases inactivate beta-lactam antibiotics by catalyzing the beta-lactam ring's hydrolysis, rendering it unable to exert its effect on its target PBPs.

β-lactams Resistance: Impact on Infection Progression and Treatment

The production of beta-lactamase enzyme and co-acquisition of other resistance mechanisms make treating infections by bacteria difficult [20]. Incidentally, the laboratory detection of ESBLs can be complex and is not routinely performed in most laboratories. Increasing

resistance of ESBL-producing bacteria to multiple types of antibiotics has led to an increase in the use of carbapenems [21], which, in response, has resulted in the emergence of carbapenemase-producing bacteria [22]. Carbapenemase enzymes produced by bacteria have the ability to hydrolyze all beta-lactams. The increasing distribution of beta-lactamase-producing bacteria and ESBL-producing bacteria in the community contributes substantially to the community burden of antimicrobial resistance [23]. The ESBL enzymes are encoded by transferable conjugative plasmids, which often code resistance determinants to other classes of antimicrobial agents and are also responsible for the dissemination of resistance to other bacteria in the community and in hospitals.

The selection of the most appropriate treatment is based on a combination of several criteria, which varies according to many parameters, including the targeted pathogen(s), clinical severity, and site of infection. The first clinically used β-lactamase inhibitors (clavulanic acid, sulbactam, and tazobactam) were discovered in the mid-to-late 1980s. A conserved similarity with these inhibitors is the shared β-lactam backbone. In addition, these inhibitors form stable intermediates with β-lactamases, thereby allowing β-lactam to effectively bind to a target penicillin-binding protein [24].

Ceftolozane/tazobactam, approved in 2014 by the United States Food and Drug Administration (USFDA), is considered the most active beta-lactam antibiotic against Pseudomonas aeruginosa [25,26]. Ceftolozane/tazobactam has no activity against strains producing Class A KPC carbapenemases or those with metallo-beta-lactamases. Most Class D (OXA) beta-lactamase-producing organisms, including OXA-48-like enzymes, are also resistant to ceftolozane/tazobactam [25]. In clinical practice, ceftolozane/tazobactam has demonstrated similar efficacy to meropenem in intra-abdominal infections [27].

Ceftazidime is also a widely distributed cephalosporin active against Gram-negative microorganisms, including Enterobacteriaceae and Pseudomonas aeruginosa. However, ceftazidime is highly vulnerable to ESBL-producing strains and is inactivated by carbapenemases. Avibactam, a novel non-BLBLI belonging to the diazabicyclooctane chemical class, restores activity against Enterobacteriaceae producing class A, class C (AmpC), and class D (OXA) beta-lactamases, including most OXA-48 carbapenemase-producing Enterobacteriaceae. Ceftazidime/avibactam has no activity against MBL-producing microorganisms. In addition, the drug has minimal activity against Acinetobacter spp., anaerobic and Gram-positive organisms. The ceftazidime/avibactam combination has potential bacteriocidal activity against ceftazidime-resistant P. aeruginosa strains in vitro [28,29]. Ceftazidime/avibactam has also demonstrated similar efficacy to carbapenems in intra-abdominal infections [30].

So far, a growing number of reports have demonstrated the value of ceftazidime/avibactam for the treatment of MDR and carbapenemase-producing Enterobacteriaceae in various conditions, including urinary tract, intraabdominal, pulmonary, and bacteremic infections [31-40]. The recently published British guidelines proposed ceftazidime/avibactam as an alternative to carbapenems to treat ESBL-producing and AmpC-producing Enterobacteriaceae infections [25]. On the basis of recent data, the experts suggest that ceftazidime/avibactam is effective against non-MBLs carbapenemase-producing organisms, but they underscore the need for further studies to define the optimal regimen.

Currently, the drugs of choice for treating infections caused by beta-lactamase-producing organisms are carbapenems [41]. The use of carbapenems, however, has also been associated with the emergence of carbapenem-resistant organisms. Colistin, polymyxin B, tigecycline, and fosfomycin have been shown to have substantial antimicrobial activity against ESBL-producing Enterobacteriaceae and merit further evaluation. Temocillin also has a very promising effect [42].

There are in vitro studies suggesting synergy between vancomycin and beta-lactams for Multi-resistant Staphylococcus aureus isolates, including those with decreased susceptibility to vancomycin [43,44]. Several other studies are available reporting the synergistic effect of these beta-lactams and other antibiotics [43,45,46]. However, the exact mechanisms of action remain largely elusive, although reports are emerging, shedding more light on this aspect. More studies are needed to understand and shed more light on the efficacy of the various treatment options.

Global Emergence and Spread of Extended-Spectrum β-lactamases

The prevalence of ESBLs is increasingly being reported worldwide, and it varies according to geographic location. It is also directly linked to the use and misuse of antibiotics. In Africa, ESBL-producing organisms have been reported in Egypt, Morocco, Tunisia, France, Italy, China, Senegal, Nigeria, and South Africa [47]. In Nigeria, prevalence rates range from 5% to 44.3%, as shown in several studies carried out in Ogun, Kano, Nnewi, Maiduguri, Zaria, and Benin [48-51]. In many parts of the world, 10%–40% of strains of E. coli and K. pneumoniae express ESBLs. Among the multidrug-resistant pathogens, extended-spectrum β-lactamase (ESBL-E) or Carbapenemase-Producing Enterobacteriaceae (CPE) is currently considered the main threat due to the scarcity of therapeutic options and their rapid spread around the globe.

Extended-Spectrum β-Lactamases (ESBL) are mutant forms of beta-lactamase enzymes that can hydrolyze various β-lactam antibiotics and thus mediate resistance to penicillins, 3rd, and 4th-generation cephalosporins. The genes encoding for those enzymes are commonly found both in the chromosomes and plasmids in different bacteria species such as Staphylococcus aureus, E. coli, and Klebsiella species [52,53]. ESBL-producing bacteria species cause severe human infections, even in countries with advanced public health and health care facilities. Most of the infections are associated with cross-contamination in hospital and clinic settings, while community-acquired infections have also been reported in several countries worldwide. ESBL-producing bacteria such as E. coli and Klebsiella species may be transmitted to meat if standard operating procedures and proper hygiene practices are not implemented in the farms and abattoirs, respectively. The impact of ESBL on public health is quite significant, with a more severe global impact predicted if an adequate effort is not shown to mitigate their spread. The frequent use of antibiotics to enhance animal productivity provides opportunities for bacteria that harbor resistance determinants to be released into the environment with severe epidemiological implications on humans.

Future Perspective and Recommendations

Drug resistance cases have increased exponentially in the last twenty (20) years [54]. This development is a result of different factors, such as drug abuse, change in weather conditions, and microbial interactions, which facilitate an increase in the exchange of genes through horizontal gene transfer. The increase in morbidity and mortality has a toll on the financial status of different households, especially those in developing countries. The increasing cases of antibiotic-resistant infectious diseases have prompted increased focus on alternative drug development. Currently, different alternative therapeutic options have shown effectiveness in current cases of drug resistance to infectious diseases. Some of these therapeutic options include antimicrobial peptides, bacteriophages (use of phages, phage proteins, and cocktails), nanomaterials, use of microbiota, phytochemicals) or a combination of any of the options) [55-58]. Usually, combination therapy is more effective than a single approach. This is because a bacterial pathogen that is resistant to one biomaterial may not resist the other.

Alternatively, the use of beta-lactamase inhibitors such as Avibactam, a combination of beta-lactamase inhibitors and beta-lactam

drugs, has shown to be very promising. Also, Carbapenems have shown to be effective against some infections caused by microbes producing beta-lactamase. The combination therapy, which utilizes the synergistic effect of combined drugs such as vancomycin and beta-lactam drugs, has also shown promises [59-62]. Over the past decades, several beta-lactam agents have been developed targeting resistant microbes, including those producing carbapenemases. Some of these agents include ceftazidine-avibactam, meropenam-vaborbactam, imipenem-relebactam and cefiderocol. These beta-lactam agents differ in their mechanisms of action [63]. Despite the research efforts so far, more remain to be learned on their exact mechanisms of action. These areas provide an avenue for further studies, especially the mechanisms of actions of combined therapy.

Due to the growing resistance to antibiotics by microbes, there is a need for the production of drug that is less sensitive to inhibition by beta-lactamase enzymes and has a greater spectrum of activity [64-66]. More studies to increase the efficacy of the already existing beta-lactam drugs are needed. Based on their importance to human health, the World Health Organization has placed third-generation cephalosporins (3GC, e.g., cefotaxime, ceftriaxone) into the "watch" group of antibiotics, i.e., drugs that are critically important to human medicine and should be prioritized as targets of antibiotic resistance monitoring and stewardship programs (World Health Organization, 2021). Approaches to predict the activities of these group of antibiotics against target pathogens is needed. Combining these priority antibiotics with other alternative therapeutic agents, as we have already outlined, will greatly increase their therapeutic value [67-69].

Overall, it is clear that changes in the affinity or quantity of PBPs play a major role in the development of beta-lactam resistance among clinical isolates of bacteria. In gram-positive bacteria, the beta-lactam affinity phenotype of PBPs appears to translate directly into the susceptibility phenotype for beta-lactam antibiotics. The reduced beta-lactam susceptibility mediated by PBPs can arise in several ways. It might be a manifestation of the reduction in affinity of normally occurring PBPs, a loss in quantity of a PBP, or the addition of low-affinity PBPs, which in some cases may be inducible. Therefore, more insight is needed into how the different β-lactams drugs interact with microbial cells and how these microbes resist beta-lactam drugs. This information is vital for optimizing the different treatment regimens to the level needed for obtaining a more reliable treatment efficacy [70,71].

Conclusion

The Public health challenges of drug resistance demand that all hands are on the desk to checkmate this issue. The importance of beta-lactamase in the response of a bacterial strain to a particular antibiotic is based on the capacity of the enzyme to complement the basic tolerance or compensate for its lack. The resistance to the different drugs has been shown to be a result of a cooperative and synergistic effect of different factors and also the diversities in microbial defense mechanisms contributing greatly to treatment difficulties. A drug that can work for a particular strain of bacterial pathogen might not work for another strain even though they belong to the same clonal group sharing the same lineage. This is because even in a particular lineage, diversities still exist.

Interestingly, for most pathogens, heteroresistance has been reported. Heteroresistance is a situation where the subpopulation of a pathogen that was initially susceptible to a certain antibiotic suddenly becomes resistant – this has been a significant challenge for several treatment efforts. Furthermore, other types of mutations can set in, leading to resistance acquisition. All these issues complicate treatment efforts against beta-lactam antibiotics and even other antibiotics classes. Therefore, more studies are needed to understand better the mechanisms of actions of β-lactam drugs and how bacterial pathogens respond to this class of antibiotics under different in vitro and in vivo conditions. Overall, all antimicrobial agents have their own strengths and caveats. Therefore, antimicrobial stewardship is crucial to ensure their rational use and prevent resistance development.

Conflict of Interest

The authors report no conflict of interest.

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