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Mechanisms of Antibiotic Resistance

Dr. Ashitha Ephrem[1], Jayakumar Sudha Sanjay[2]

[1]Assistant Professor, Department of Pharmacy Practice, Srinivas College of Pharmacy, Mangalore, India
[2]Pharm D Intern, Department of Pharmacy Practice, Srinivas College of Pharmacy, Mangalore, India

Corresponding Author: Jayakumar Sudha Sanjay

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ABSTRACT

Antibiotic therapy is one of the main approaches of modern medicine which is used to combat infections. The "golden era" of antibiotics ranged from 1930s to 1960s which gave rise to many antibiotics. Unfortunately, this era ended because researchers were unable to maintain the pace of antibiotic discovery in the face of emerging resistant pathogens. Persistent failure to develop new antibiotics and nonjudicious use of antibiotics are the predisposing factors associated with the emergence of antibiotic resistance. Antimicrobial resistance (AMR) is a serious global threat of growing concern to human, animal, and environment health. This is due to the emergence, spread, and persistence of multidrug-resistant (MDR) bacteria or the "superbugs." This review discusses the mechanisms underlying in the development of antibiotic resistance and the common organisms.

KEYWORDS: *Antibiotics, Resistance*

INTRODUCTION

Antibiotics represent one of the most successful forms of therapy in treating infectious diseases. But the efficiency of antibiotics is compromised by increasing number of antibiotic-resistant pathogens. Antibiotic resistance, which is implicated in elevated mortality and morbidity rates as well as in the increased treatment costs, it is considered to be one of the major global health threats and the magnitude of the problem recently prompted a number of international and national bodies to take actions to protect the public. [1]

The multidrug efflux systems contribute significantly to the increased resistance to multiple antibiotics in bacteria. [1] Resistance mechanisms in the bacteria have evolved rapidly, owing to the presence of selective pressures. Their defence mechanisms against antibiotics involve the production of antibiotic deactivating enzymes, such as the several classes of β-lactamases or aminoglycoside modifying enzymes, changes in antibiotic targets, and reduction of intracellular antibiotic concentration, either by limiting the entrance of the antibiotic or facilitating its expulsion. [2] Unfortunately, the marked increase in antimicrobial resistance among common bacterial pathogens is now threatening the therapeutic accomplishment, interrupting the successful outcomes of critically ill patients. In fact, the World Health Organization has announced antibiotic resistance as one of the three most important public health threats of the 21st century. [3]

MECHANISMS OF ANTIBIOTIC RESISTANCE

Some of the organisms are naturally resistant to particular antimicrobial agent, usually because they do not possess the molecular target of the drug or are impermeable to it. Whereas, acquired resistance occurs through mutation or the acquisition of new genetic material carried by mobile elements such as plasmids and transposons. The four major mechanisms for acquired resistance are drug inactivation,

target modification, reduced permeability and drug efflux pumps.

Drug Inactivation

Beta-lactamases are enzymes that hydrolyse the beta lactam ring. Penicillin contains beta lactam ring and is therefore inactivated by these enzymes. The first beta lactamase was discovered in S. aureus. [4] However, these enzymes more commonly produce resistance in Gram-negative pathogens. [5] Beta lactamase enzymes destroy the amide bond of the β-lactam ring, rendering the antimicrobial ineffective. To overcome this problem, new β-lactam compounds with a wider spectrum of activity and less susceptibility to penicillinases (such as ampicillin) were manufactured. [3]

Target Modification

A common pathway for bacteria to develop antimicrobial resistance is to avoid the action of the antibiotic by interfering with their target site. To achieve this, bacteria have evolved different tactics, including modifications of the target site that result in decreased affinity for the antibiotic molecule and protection of the target (preventing the antibiotic from reaching its binding site). One of the classic and best-studied examples of the target protection mechanism is the tetracycline resistance. The target changes may consist of (i) point mutations in the genes encoding the target site, (ii) enzymatic alterations of the binding site (e.g., addition of methyl groups), and/or (iii) replacement or bypass of the original target. Mutations of the target site: One of the classical examples of mutational resistance is the development of rifampin resistance. [3]

Reduced Permeability

Most of the antibiotics used in clinical practice have intracellular bacterial targets or, in the case of Gram negative bacteria, targets located in the cytoplasmic membrane. Hence, the compound must penetrate the outer and/or cytoplasmic membrane to exert its antimicrobial effect. Bacteria have developed mechanisms to prevent the antibiotic from reaching its intracellular or periplasmic target by decreasing the uptake of the antimicrobial molecule. [3] The relative impermeability of the outer membrane is one of the major causes of increased intrinsic drug resistance seen in opportunistic Gram-negative pathogens like S. maltophilia and P. aeruginosa. [5] Hydrophilic molecules such as tetracyclines, β-lactams, and some fluoroquinolones are particularly affected by changes in permeability of the outer membrane since they often use water-filled diffusion channels known as porins to cross this barrier. [6] The example of the efficiency of this natural barrier is the fact that vancomycin, a glycopeptide antibiotic, is not active against Gram-negative organisms due to the lack of penetration through the outer membrane. Several types of porins have been described, Among the best-characterized porins, the three major proteins produced by E. coli (known as OmpF, OmpC, and PhoE) and the P. aeruginosa OprD (also known as protein D2) are classical examples of porin-mediated antibiotic resistance. One classic example of porin-mediated resistance is the aberrant production of OprD in P. aeruginosa, which is normally used for the uptake of basic antibiotics and amino acids. [3]

Drug Efflux Pumps

Drug efflux is the energy-dependent process of production of complex bacterial machineries capable of extruding a toxic compound out of the cell can also result in antimicrobial resistance. The efflux system able to pump tetracycline out of the cytoplasm of E. coli dates from the early 1980s and was among the first to be described. [7] From then, many classes of efflux pumps have been characterized in both Gram-negative and Gram-positive pathogens. [3] The five major families of efflux pumps includes (i) the major facilitator superfamily, (ii) the small multidrug resistance family (SMR), (iii) the

resistance-nodulation cell-division family (RND), (iv) the ATP-binding cassette family, and (v) the multidrug and toxic compound extrusion family. These differ in terms of structural conformation, energy source, range of substrates they are able to extrude, and the type of bacterial organisms in which they are distributed. [3, 8] The majority of these pumps are preferentially found in Gram-negative organisms and the few exceptions that predominate in Gram-positive organisms.

MECHANISMS OF ANTIBIOTIC RESISTANCE IN STREPTOCOCCUS PNEUMONIAE

Streptococcus pneumoniae is a Gram-positive pathogen and one of the most common causes of community acquired diseases, such as pneumonia, otitis media, septicemia, bacterial meningitis and others. The morbidity and mortality of infections caused by S. pneumoniae remain high despite appropriate antibiotic therapy. [9]

Beta lactams

The mechanism of action of beta-lactam antibiotics is based on the binding of the antibiotic to cell wall synthesizing enzymes that is, the penicillin-binding proteins (PBPs), thereby interfering with the biosynthesis and remodeling of the bacterial peptidoglycan. Binding of beta-lactams to PBPs leads to a covalently deacylated complex removing the PBPs from the metabolically active pool. [10] The mechanism of penicillin resistance in clinical isolates of *Streptococcus pneumoniae* involves the alteration of PBPs so as to reduce their affinity for the antibiotic molecule. Mutations leading to resistance to penicillin are usually seen in the transpeptidase-penicillin-binding domain. [11]

Fluoroquinolones

Quinolones such as new fluoroquinolones, moxifloxacin and trovafloxacin, appeared as alternative therapeutic agents for the treatment of penicillin-resistant pneumococcal infections. In the clinical isolates of pneumococci, fluoroquinolone resistance is mediated by target modifications that involve mutations in the gyrase genes, *gyrA* and *gyrB*, and in the topoisomerase IV genes, *parC* and *parE*. Moreover, the in vitro studies indicated that some strains may use an efflux mechanism resulting in reduced intracellular accumulation of the antibiotic. [12,13]

Macrolide-lincosamide-streptogramins (MLS)

Even though MLS antibiotics are chemically distinct, they competitively interact while binding to the ribosomal 50S subunit, where only one molecule is able to bind. [14] Two mechanisms of resistance to MLS in clinical isolates of pneumococci have already been reported which includes modification of the target that results in co-resistance to MLS and efflux of the antibiotic that mediates resistance to 14-membered and 15-membered macrolides only resulting in a so-called M phenotype.

Chloramphenicol

Chloramphenicol acts by inhibiting bacterial protein synthesis which targets the peptidyl transferase during translation. [15] In pneumococci, resistance to chloramphenicol is due to the production of the chloramphenicol acetyltransferase enzyme catalyzing the conversion of chloramphenicol to derivatives that are unable to bind to the ribosomal 50S subunit and therefore are no longer capable of inactivating the peptidyl transferase.

Tetracycline

Tetracyclines exhibit bacteriostatic activity by binding to either the acceptor site (A-site) or the peptidyl-donor site (P-site) of the 30S subunit of the bacterial ribosome, thus preventing binding of the aminoacyl-tRNA to the A-site. Tetracyclines acquire resistance by Ribosomal protection mediated by the genes *tet*(M) and *tet*(O). [16]

Trimethoprim-sulfamethoxazole

The combination of trimethoprim with sulfamethoxazole (cotrimoxazole) has been used extensively for the treatment of lower respiratory tract infections. They interfere with the biosynthesis of folic acid. Trimethoprim selectively acts by inhibiting the bacterial dihydrofolate reductase (DHFR) thus preventing the reduction of dihydrofolate to tetrahydrofolate. Trimethoprim resistance in clinical isolates of *S. pneumoniae* results from substitution of single amino acids in the chromosomal-encoded DHFR. [17]

MECHANISMS OF ANTIBIOTIC RESISTANCE IN ENTEROCOCCI

Enterococci are gram-positive anaerobes shaped by the selective pressures of their competitive environment, these bacteria have evolved a diverse array of responses and genetic plasticity allowing them to thrive in the modern healthcare environment. Indeed, enterococci are leading causes of nosocomial infections and are second only to staphylococci as a cause of gram-positive nosocomial infections. [18, 19] Multidrug-resistant (MDR) enterococci are important nosocomial pathogens and a growing challenge in clinical setting. These organisms have developed resistance to nearly all antimicrobials currently used in clinical practice using a diverse number of genetic strategies. Due to the ability to recruit antibiotic resistance determinants, MDR enterococci display a wide range of antibiotic resistance mechanisms including modification of drug targets, inactivation of therapeutic agents, overexpression of efflux pumps and a sophisticated cell envelope adaptive response that promotes survival in the human host and the nosocomial environment. [18]

The discovery of antibacterial agents and the understanding of the microbiological basis of disease, the infection became a treatable with remarkable results. Moreover, clinicians realized that certain microorganisms appear to respond less to specific antimicrobial agents. It was later found that the addition of aminoglycosides with penicillin produced synergistic activity improving the cure rates for enterococcal infective endocarditis from 40 to 88%. [20] The synergistic effect was seen despite the fact that enterococci are also inherently less susceptible to aminoglycosides compared to other gram-positive bacteria. Hence, the combination of a cell-wall active agent (penicillin/ampicillin) with an aminoglycoside became the standard of care for deep-seated enterococcal infections and the combination is still used to the present day. [21]

The remarkable increase in the antimicrobial use in clinical medicine in the latter half of the 20th century provided the selective environment for these microorganisms to evolve by recruiting a variety of antibiotic resistance determinants. The most distinct example of the adaptability is the acquisition of the genes encoding vancomycin resistance. Its use is associated with the emergence and spread of methicillin-resistant Staphylococcus aureus (MRSA) in 1960s. Moreover, unlike MRSA, enterococci have been able to recruit and maintain a variety of gene clusters encoding the biochemical machinery for vancomycin resistance. Vancomycin-resistant enterococci (VRE) was first recognized in 1988. Even though, the availability of anti-gram-positive agents (linezolid, quinupristin/dalfopristin, daptomycin, tigecycline), enterococci have rapidly adapted the emergence of resistance to all these newer agents have been well documented. This phenomenon makes the treatment of MDR enterococcal infections a clinical challenge. [18]

Glycopeptide Resistance

Glycopeptides (vancomycin and teicoplanin) bind to the terminal D-alanine-D-alanine moiety of peptidoglycan precursors, preventing cross-linking of peptidoglycan chains and inhibiting synthesis of the cell wall. Resistance to these agents, typified by vancomycin, can be described as high-level (MIC >64 mg/ml)

or low-level (MIC between 4 and 32 mg/ml), both due to a change in the terminal amino acids of the peptidoglycan precursor from D-Ala-D-Ala to D-alanine-D-lactate (D-Ala- D-Lac) or less commonly, D-alanine-D-serine (D-Ala-D-Ser). [22] The type of amino acid change is relevant, as it determines the level of resistance.

Ampicillin/Penicillin Resistance

Ampicillin and penicillin are the most active b-lactams against enterococci that inhibits the synthesis of peptidoglycan, the basic structure of the bacterial cell wall and a critical component needed for bacterial viability Resistance to ampicillin in E. faecium is mediated by PBP5, a transpeptidase that functions in the presence of high concentrations of b-lactams. [23]

Cephalosporin Resistance

Though the resistance of enterococci to cephalosporins is a well-known feature, the molecular basis of this phenotype is not completely understood. One of the common observations is that intrinsic resistance is associated with a decrease in binding affinity of cephalosporins for the enterococcal PBPs, specifically Pbp5. [24, 25]

Dap Resistance

DAP is a lipopeptide antibiotic that targets the cell membrane (CM) and is related to many cationic antimicrobial peptides (CAMPs) that are produced by the innate immune system of eukaryotic organisms. Insertion of DAP in the CM requires the presence of calcium ions and appears to bind preferentially at the division septum plane. Once inside the membrane, DAP oligomerizes in the outer leaflet and the DAP complexes reach the inner leaflet of the cell membrane forming a 'pore' structure that disrupts the integrity and functionality of the cell membrane resulting in a variety of processes including leakage of ions that leads to cell death. [26]

Two main mechanisms postulated to mediate DAP resistance in enterococci include, the diversion of the antibiotic from the septum by redistribution of cardiolipin microdomains away from the division plane at the septum level. This mechanism, is characterized in Enterococcus faecalis only, initially mediated by substitutions in the LiaFSR signaling system that controls cell envelope homeostasis. Changes in phospholipid synthesis enzymes (cardiolipin synthase and possibly a glycerol-phosphodiester phosphodiesterase) complete the resistance phenotype. The second mechanism, seen in E. faecium, is electrostatic repulsion of the positively charged daptomycin or calcium complex from the cell membrane. Several other genes may be involved in this mechanism.

Oxazolidinones

Linezolid is a bacteriostatic agent having broad activity against gram-positive bacteria. It acts by binds to the 23S rRNA and disrupts the docking of the aminoacyl-tRNA in the A site of the ribosome, and inhibit the delivery of peptides and the subsequent elongation of the polypeptide chain. [27, 28] Mutations in genes encoding the 23S rRNA, is an important part of the drug-binding site at the ribosome, are the most common mechanisms of linezolid resistance.

Tetracyclines & Glycylcyclines

Tetracyclines are bacteriostatic agent that exert their antibacterial effect by binding to the ribosome and interfering with the docking of aminoacyl-tRNA. This process occurs via association with several loops of the 16S rRNA and the ribosomal protein S7. [29] Resistance is mediated by multiple genes, but follows two general strategies, efflux of the antibiotic and ribosomal protection.

Quinolones

Enterococci demonstrate low levels of intrinsic resistance to the quinolones, but also can acquire high-level resistance through several mechanisms. Mutations in QRDR alter drug binding. Externalization of antibiotics through efflux pumps is another

well-described mechanism of quinolone resistance. Third known mechanism of resistance, in E. faecalis, [30] is mediated by qnr and encodes for a protein with a series of pentapeptide repeats similar to the plasmid-borne quinolone resistance genes described in Enterobacteriaceae

Rifampicin

Rifampicin acts by inhibiting transcription of mRNA by binding to the b-subunit of the enterococcal DNA-dependent RNA polymerase. Resistance to these agents is widespread, occurring in 65.9% of E. faecium isolates. [31] Rifampicin resistance occurs from a variety of mutations in the rpoB gene that encodes for the b-subunit of the RNA polymerase.

MECHANISMS OF ANTIBIOTIC RESISTANCE IN STAPHYLOCOCCUS AUREUS

Staphylococcus aureus is a gram positive organism responsible for a wide spectrum of infections. S.aureus have shown remarkable ability to acquire resistance to a variety of antibiotics through, mutation and horizontal gene transfer. Resistance to vancomycin represents the most serious therapeutical challenge in the future years. It is essential to monitor the development of antibiotic resistance in staphylococcus aureus to both old and new antibiotics. To recognise the emergence and spread of new resistant traits it is important to detect the mechanisms and genetic determinants underlying resistant phenotypes. [32]

Resistance to beta-lactam antibiotics

S. aureus resistance to penicillin appeared very soon after the introduction of this antibiotics. Nowadays, more than 90% of S. aureus isolates are penicillin resistant, which is due to the production of penicillinase, an extracellular enzyme that hydrolyzes penicillin. The prototype of the antistaphylococcal penicillins called methicillin, was designed to resist the action of penicillinase. Moreover, S. aureus developed resistance to it. The Methicillin resistant staphylococcus aureus (MRSA) produces an altered penicillin binding protein, termed PBP2a which has reduced affinity for methicillin and can continue peptidoglycan synthesis in the presence of antibiotic. PBP2a is encoded by the mecA gene that is incorporated in a chromosomal genetic element designated staphylococcal chromosomal cassette (SCC) mec.

MRSA are resistant to all the beta lactams, including carbapenems and cephalosporins. They are typical nosocomial pathogens and are often multiresistant which is also resistant to other classes of antibiotics. Recently, MRSA strains causing serious infections termed as community acquired (CA-MRSA) have emerged. [35]

Resistance to Glycopeptides

Vancomycin is considered as one of the cornerstone of therapy in MRSA. But, at the end of the decade, strains are intermediately resistant (VISA) or fully resistant (VRSA) to vancomycin. Mechanism of resistance in VISA includes trapping of the antibiotics in a thickened cell wall, rich in residues that binds vancomycin. The antibiotic is hence prevented from reaching the true targets in the glycopeptide precursors at the inner layer of the cell wall. The mechanism of resistance in VRSA is similar to that of vancomycin-resistant enterococci (VRE). The vancomycin target D-Ala-D-Ala is replaced by Ala-D-Ala-Lac and this modification causes a dramatic reduction of affinity to vancomycin. [32]

Resistance to Fluoroquinolones

Fluoroquinolone resistance is widespread among MRSA and is due to mutations in the quinolone-resistance determining region (QRDR) of DNA gyrase and topoisomerase IV. Overexpression of the efflux pump NorA can also contribute to resistance.

MECHANISMS OF ANTIBIOTIC RESISTANCE IN BURKHOLDERIA PSEUDOMALLEI

Burkholderia pseudomallei is a Gram-negative bacterial pathogen that is a major

cause of bacterial sepsis and chronic disseminated infections (melioidosis) in humans. The mechanisms range from exclusion from the cell due to permeability issues bestowed by constituents of the bacterial cell envelope, enzymatic inactivation, efflux from the cell, altered target sites (which in rare instances may include target deletion), metabolic bypass of a susceptible enzyme with a resistant variant, target overproduction and drug sequestration. From these mechanisms, all except enzymatic modification, target overproduction, metabolic bypass and drug sequestration have been documented in B. pseudomallei. In many instances, bacterial antibiotic resistance is mediated by mobile elements, like plasmids, transposons or integrons. [33] Moreover, all resistance documented to date in *B. pseudomallei* is mediated by chromosomally encoded genes. [34]

Ceftazidime resistance

Ceftazidime resistance occurs by amino acid substitutions in PenA class A b-lactamase, upregulation (overproduction) of PenA b-lactamase and deletion of penicillin binding protein 3 BPSS1219 .

Resistance to clavulanic acid inhibition occurs by point mutations in PenA b-lactamase. Trimethoprim-sulfamethoxazole resistance by BpeEF–OprC efflux pump expression. Doxycycline resistance by BpeEF–OprC efflux pump expressions.

CONCLUSION

A significant proportion of patients find their hospital stay complicated due to infection. Nosocomial infections have an impact on morbidity and mortality, and leads to significant economic burden. In view of the rising levels of antibiotic resistance and increasing severity of the illness of hospital in-patients, this is a problem that is likely to worsen. Further, the discovery of new antimicrobials as well as finding strategies to expand the useful life of existing antibiotics is important to combat the ever-increasing antimicrobial resistance.

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