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Bacterial Resistance to Antibiotics: A Review Article

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ABSTRACT: Antibacterial resistance (ABR) is nowadays considered as a public global health problem, with expected mortality rate of 10^6 yearly by 2050. ABR happens when pathogenic bacteria are not affected to antibacterial therapy, resulting in the spread of the pathogens inside the host. Antibacterial resistance in pathogenic bacteria is a significant concern that is correlated with high rates of deaths and illness. Bacterial resistance to many antibiotics in Gram- negative and - positive bacteria can't be treated easily and might not be irradicated by conventional antimicrobials. Resistance acquisition to antimicrobials by bacterial pathogens is one of the most critical issues that should be well studied, especially by the increasing data that indicated a very high rates, that may reach 100% of pathogenic bacteria that resist to many antibiotics in developing countries, principally in Asia and Africa. ABR has also been found that transfer of resistance genes is the main mechanism by which acquisition of resistance to antibiotics is mediated among many species of pathogenic bacteria.

1. INTRODUCTION

Antibacterial agents play a critical role in the control and treatment of infectious diseases. Antibiotics were not long in coming after the first antibacterial was found, but then rose the issue of antibiotic resistance. Antimicrobials act through different mechanisms to stifle bacterial pathogenesis— broadly they can be classified as either bacteriostatic or bactericidal. Among antimicrobial drugs are antibiotics which represent specific classes targeting various functions in bacteria due to diversification with numerous mechanisms continually being adopted by bacteria to counteract them (Abushaheen et al., 2020).

The primary antibacterial compound discovered happens to be penicillin, which is a β-lactam antibiotic. After this notable milestone, the era of antibiotics began where they were used to cure human infections; the first being sulfonamide and subsequently aminoglycoside antibiotics that included streptomycin and streptothricin. Today, there exist numerous classes of antibacterial agents identified by their mechanisms of action. For example some antibiotics impede protein synthesis— tetracyclines, streptothricin, macrolides, chloramphenicol and aminoglycosides while others interfere with DNA plus RNA synthesis such as quinolones and rifampin. Moreover some groups inhibit or cause damage to bacterial cell wall like glycopeptides and β-lactams whereas others (e.g., trimethoprim plus sulfonamides) alter energy metabolism in microbial cells (van Hoek et al., 2011).

Antibacterial resistance (ABR): this is the evolution of microorganisms, including bacteria, to develop resistance against antibacterial drugs that kill them; for example, antibiotics used to treat infections. ABR has risen as one of the most urgent global concerns in the 21st century— not only because of the fast-growing numbers of ABR infections but also due to the inadequacy of new antibacterial drugs developed to tackle this issue. An essential element that significantly contributes to this problem is antibiotic misuse or overuse across various sectors like clinical treatments — all aspects of agriculture and animal healthcare, as well as different parts of the food industry (Tang et al., 2023).

The swift worldwide dissemination of resistance genes paints a stark picture of the soaring escalation of an issue that falls squarely in the public health arena and thus calls for global efforts. The global figures depict deaths directly due to ABR surpassing 1.2 million in 2019; this death toll is forecasted to reach close to 10 million every year by 2050 if appropriate control measures are not adopted to rein in ABR. Public health has never faced such a grave situation: millions or even tens of millions people may die because antibiotic resistance is not controlled (O'Neill, 2016).

The process by which microorganisms are able to develop resistance to antibacterial drugs is further complicated, involving secondary resistance mechanisms. This type of resistance is extrachromosomal in nature, as the genes responsible for it are located on small circular DNA molecules called plasmids within the cytoplasm. It is noteworthy that one plasmid can carry resistance genes for multiple antibacterials. Plasmids mainly use conjugation and transduction for transfer; however, the latter method — via

saprophytic bacteria — poses specific challenges when transferred into pathogenic bacteria. Transduction refers to plasmid transfer from donor cell to recipient cell through bacteriophages: bacterial viruses (Węgleński et al., 2008).

MECHANISMS OF BACTERIAL RESISTANCE TO ANTIBIOTICS

In the realm of battling bacterial foes, resistance plays a central role. Pathogens can either possess innate resilience or evolve it over time against specific antibacterial classes. Resistance is developed through a multitude of mechanisms post exposure: mutations at a genetic level within bacterial cells leading to resistance against various antibiotics; gene exchange between bacteria facilitated by plasmids; promiscuous gene transmission involving transposons; delivery via bacteriophages and integrons — each harboring differing transference pathways. Upon acquiring these coveted genes for resistance, bacteria exhibit biochemical prowess in different dimensions: deactivating antibacterial agents (such as β-lactams and glycopeptides); modifying target proteins and nucleic acids (thus tetracyclines and macrolides for proteins, rifampin and fluoroquinolones for nucleic acids); tweaking cell wall permeability (to limit antibacterial influx like chloramphenicol and aminoglycosides); bypassing metabolic pathways (since trimethoprim-sulfamethoxazole disrupts bacterial metabolic processes). The evolution of resistance in bacteria reads like an elaborate spy novel where the enemy constantly adapts its defenses to evade annihilation (Giedraitienė et al., 2011).

Other mechanisms include: actively pumping the antibiotic out of the microbial cell, enzymatically modifying the antibiotic, degrading the antibacterial drugs, acquiring alternative metabolic pathways to bypass those inhibited by the drug, modifying antibiotic targets, and overproducing the target enzyme (van Hoek et al., 2011).

Changes in bacterial susceptibility can be either primary or secondary. Primary resistance occurs due to spontaneous mutations and can develop without drug exposure. This type of resistance is chromosomally encoded and not transmissible to other bacterial species. Although the occurrence of mutated bacteria is rare, they gain a survival advantage in the presence of antibiotics, outcompeting the susceptible population. These resistant bacteria can spread to different ecological niches within the same host or to other organisms. To defend against antibacterial agents, including antibiotics, bacteria have evolved various mechanisms to counteract these agents' effects. By acquiring resistance genes, bacteria can become partially or fully resistant to specific antibiotics through different effector mechanisms (Urban-Chmiel et al., 2022).

Based on numerous scientific studies conducted since the mid-20th century, several mechanisms have been proposed to explain bacterial resistance to antibiotics. Current understanding suggests that bacteria acquire resistance through active expulsion of antibiotics from cells, enzymatic modification of antibiotics, alterations in the components targeted by antibiotics, overproduction of enzymes targeted by antibiotics, changes in bacterial cell membrane permeability, development of alternative metabolic pathways, elevation of concentrations of antagonistic metabolites, reduction in enzyme levels or activity involved in activating antibiotic precursors, modifications in regulatory systems unrelated to the antibiotic's direct action, or decreased reliance on products from inhibited metabolic pathway (van Hoek et al., 2011).

HOW TO REDUCE DRUG RESISTANCE?

As part of efforts to combat drug resistance among microorganisms, it is crucial to enhance research efforts in several key areas. These include genetic enhancement of animals to identify markers linked to enhanced innate resistance to pathogens, exploration for novel antibacterial agents, and investigation into the role of bacteria in transmitting antibiotic resistance within human and animal microbial communities. Current strategies to address antibiotic resistance involve alternative approaches such as the use of bacteriophages or their enzymes, the development of next-generation vaccines, and the implementation of new feeding regimes for animals incorporating prebiotics, probiotics, and phytobiotics derived from bacterial subproducts. Additionally, there is considerable interest in exploring proteins and peptides with bactericidal properties synthesized by bacteria, plants, and various animals. This approach focuses on utilizing antibacterial peptides produced by safe microbial agents like Candida, Saccharomyces yeast, Micrococcus, Streptomyces, and Lactobacillus spp (Urban-Chmiel et ql., 2022). Given the correlation observed between excessive antibiotic use and the emergence of antibiotic resistance (ABR), reducing antibiotic consumption could be a valuable objective in combating antimicrobial resistance, particularly concerning the overuse of antibacterial agents (Tang et al., 2023).

ACQUISITION OF BACTERIAL RESISTANCE

The following are brief description about the mechanism of action by which bacterial pathogens develop their resistance to antibacterials.

AMINOGLYCOSIDE

Aminoglycosides are antibacterial agents that primarily inhibit protein synthesis and/or disrupt the integrity of bacterial cell membranes. They are predominantly isolated from Streptomyces or Micromonospora and exhibit a broad spectrum of antibacterial activity. Additionally, they often synergize effectively with other antibiotics, enhancing their utility as anti-infectives. The primary mechanism of resistance encountered with aminoglycosides involves the modification of enzymes. Other recognized resistance

mechanisms include inactivation of the drugs by aminoglycoside-modifying enzymes, alteration of ribosomes, reduced permeability of bacterial cells, and active expulsion of the drugs (Gebreyes & Altier, 2002 ; Poehlsgaard and Douthwaite, 2005).

B-LACTAM

In the past three decades, numerous new β-lactam antibiotics have been developed. All β-lactam antibiotics share a common feature: they contain a β-lactam nucleus in their molecular structure. This antibiotic family includes penicillins and their derivatives, cephalosporins, carbapenems, monobactams, and β-lactam inhibitors (Sun et al., 2014). β-lactam antibiotics function by inhibiting cell wall synthesis through binding to penicillin-binding proteins (PBPs) in bacteria. This interaction disrupts the structural cross-linking of peptidoglycans, thereby preventing terminal transpeptidation in the bacterial cell wall. Consequently, the bacterium's cell wall is weakened, leading to cytolysis or death due to osmotic pressure (Souza et al., 2020).

β-lactamase inhibitors are categorized as reversible or irreversible, with the latter being more effective because they permanently deactivate enzymatic activity. Clinical inhibitors such as tazobactam, sulbactam, and clavulanic acid are examples of irreversible β-lactamase inhibitors in use today (Drawz and Bonomo, 2010).

Currently, there is a notable and increasing prevalence of bacterial resistance to β-lactam antibiotics, posing a widespread challenge. Various mechanisms contribute to this resistance. The predominant and crucial mechanism involves bacteria producing β-lactamases, including extended-spectrum β-lactamases (ESBLs), plasmid-mediated AmpC enzymes, and carbapenem-hydrolyzing β-lactamases (Leverstein-van Hall et al., 2011).

GLYCOPEPTIDE

Vancomycin was the first glycopeptide introduced in clinical practice. Glycopeptides have a unique mechanism of action: instead of inhibiting an enzyme, they bind to a substrate. Specifically, these antibiotics target the d-alanyl–d-alanine terminus of the cell wall peptidoglycan precursor. Once bound, glycopeptides hinder the glycosyl transfer reaction through steric hindrance (Klare et al., 2003). Typically, when antibiotics are introduced clinically, bacterial resistance emerges fairly quickly. However, vancomycin was an exception as resistance to this glycopeptide was rare and clinically insignificant for nearly 30 years after its introduction. Currently, resistance to glycopeptides like teicoplanin and vancomycin has been detected in several Gram-positive bacterial pathogens, including Staphylococcus, Pediococcus, Leuconostoc, Lactobacillus, Erysipelothrix, and Enterococcus (van Hoek et al., 2011).

TETRACYCLINES

Regarding tetracyclines, staphylococci exhibit resistance through a reduction in their intracellular levels, achieved via a specific efflux mechanism linked to genes encoding membrane transporters. Inducible resistance to tetracyclines is mediated by small plasmids, whereas constitutive resistance is controlled by chromosomal factors. In constitutive resistance, there is no involvement of an efflux pump; rather, it involves actively shielding the ribosome from tetracycline binding (Emaneini et al., 2013).

CONCLUSION

Antibacterial resistance remains a significant global public health challenge in the twenty-one century. It is already receiving considerable attention from policymakers in developing nations and remains a prominent topic at numerous political conferences. The development of antibiotic resistance by bacteria poses one of the most critical issues in modern medicine. Of particular concern is the widespread occurrence of multi-drug resistant foodborne pathogens, reaching very high percentages, and in some cases, even 100%, especially in developing regions like Africa and Asia. Additionally, it has been observed that drug resistance in many bacterial species often involves the transfer of resistance genes between different species through mechanisms of resistance.

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