A REVIEW ON ANTIBIOTIC RESISTANCE IN BACTERIAL PATHOGENS

ABSTRACT

Human health has been greatly impacted by the use of antibiotics, which have become essential in modern medicine. The treatment of bacterial infections with antibiotics decreased childhood mortality and raised life expectancy. Global public health is seriously threatened by antibiotic resistance. The multi-drug resistance (MDR) pandemic has spread quickly throughout many nations, with some instances going untreated. This has led to greater mortality rates, longer hospital stays, increased medical expenditures, and more. The primary culprits behind nosocomial infections are thought to be a variety of multidrug-resistant (MDR) such as *A. baumannii, Pseudomonas aeruginosa, Enterobacteria* that produces extended-spectrum beta-lactamase (ESBL), and carbapenem-resistant CRE. The most prevalent bacterial pathogens have been identified as Methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE), according to recent reports. The primary factors in the development of antibiotic resistance are the subject of this review.

Key words: Multidrug resistance, antibiotic resistance, nosocomial infection, bacteria, genes.

1. INTRODUCTION

"Antibiotics have played a central role in modern medicine and their use has had a significant impact on human health. Their advancement has raised life expectancy, decreased childhood mortality, and given us a crucial tool for invasive surgery and the treatment of bacterial infections. One of the biggest threats to global public health is antibiotic resistance (AR). Antibiotic-resistant bacteria (ARB) infections are linked to higher rates of death, the need for hospitalisation, longer hospital stays, and greater medical expenses" [1].

"Water systems connect people at home, in hospitals, in agriculture, and on animal farms from their source to the stream. These systems take input from a variety of sources in a range of environmental circumstances" [2]. "They serve as networks for bacteria, plasmids, phages, antibiotic resistance genes (ARGs)" [3]. "The destiny of ARB and ARGs in the water systems is influenced by a number of factors, including temperature, the richness of organic matter, redox conditions, and the concentrations of metals, antibiotics, and biocides. These factors also affect the ecosystems and their habitats" [4]. "Mutations, horizontal gene transfer (HGT), and other genetic processes are the main factors facilitating the evolution of ARGs in aquatic environments. It is thought that conjugative transfer via mobile genetic elements—such

as plasmids and transposons, or ICE—is widespread and has the ability to spread ARGs to bacteria in unrelated phyla" [5]. Another significant mechanism that non-antibiotic medications and disinfectants can support is natural transformation [6,7].

Antibiotic Resistant Bacteria (ARB)

Genes or mutations that are beneficial to bacterial survival in the presence of antimicrobial drugs may be present in bacterial genomes. Bacteria that are susceptible to antibiotics can develop resistance through either de novo gene mutation or by obtaining resistance genes from other bacterial cells. Hence, selection pressure causes resistance to develop as a result of widespread misuse of antibiotics [8]. "Horizontal gene transfer (HGT) can result in the acquisition of antibiotic resistance in cells, even when those cells belong to different species or genera" [9]. "Nowadays, the release of a new antibiotic onto the market is nearly always accompanied by the rise of resistance bacterial strains. The creation of novel, potent antibiotics and antibacterial compounds depends on a thorough understanding of the mechanisms behind the emergence of drug resistance" [10].

"ARGs have been found in ancient DNA retrieved from both environmental and human ancestor samples, indicating that bacterial antibiotic resistance mechanisms predate human usage of antimicrobials" [11]. "The acquisition of ARGs may have been accelerated by resistance gene transfer and widespread use of antibiotics, as studies have also found higher numbers of ARGs in the genomes of contemporary strains of some bacteria (such as those belonging to the genera *Pseudomonas* and *Clostridium*) than in strains recovered from the microbiome of ancient human ancestors" [12].

Multidrug Resistance Bacteria (MDR)

Pathogenic organisms that exhibit resistance to several chemotherapeutic drugs are said to have multidrug resistance. MDR is a perfectly normal process that occurs in bacteria, but it is becoming more common for a variety of reasons, including the use of unidentified antimicrobial agents, unsanitary, unclean settings, and subpar healthcare facilities. Because antibiotic-resistant microorganisms are a constant threat, there aren't many antimicrobial medicines available to treat other illnesses [13,14]. "The quick spread of multi-drug resistance (MDR) in many nations, some of which lack a treatment option, is one particular cause for concern. Extensive drug resistance (XDR) denotes non-susceptibility to at least one agent in all but one or two antimicrobial classes, and pan-drug resistance (PDR) denotes non-

susceptibility to all agents in all available antimicrobial classes. MDR is defined as the acquired non-susceptibility to at least one agent among three or more antimicrobial classes" [15]. "Water, dirt, wastewater, sewage, plants (fruit, vegetables, herbs), raw meat, dairy products, the upper respiratory tract, the gastrointestinal tract, and human and animal skin are natural habitats and reservoirs for multi-drug resistance bacteria (MDRB). Another well-known source of MDRB is livestock, including pigs, cattle, and poultry. It is also feasible for MDRB to spread through food items and water. MDRB contamination of drinking water, milk, and meat products has been shown in numerous articles" [16].

2. Resistance evolution in the environment

Antibiotic resistance can result from foreign DNA absorption as well as alterations in the bacterium's pre-existing genome. In the patient or animal receiving the antibiotic, mutations easily develop and become fixed. Somewhere else, diseases are not subject to such a strong selection pressure. Furthermore, the process is not influenced by the genetic reservoir found in other species. Therefore, it is generally less expected that external factors will play a significant role in the mutation-based evolution of resistance that most infections experience. The variety of the human and domestic animal microbiota is far less than that of the gene pool found in water, soil, and other habitats with highly varying ecological niches when it comes to the uptake of novel resistance components [17,18]. The ambient microbiome is remarkably diverse, offering a multitude of genes that pathogens may acquire and utilise to counteract the effects of antibiotics. This is, in fact, its most remarkable characteristic [19]. At least some of the pathogens targeted by all licenced antibiotic classes to date—whether they are synthetic, semi-synthetic, or natural compounds—have developed resistance to them. According to this, unless we have a paradigm shift in the way we think about the design of antibiotics, external surroundings already include resistance elements for any antibiotics that will ever be discovered [20]. "Genes can be transferred into human infections, therefore their presence is concerning even although few studies have established the existence of ESBL, MRSA, and VRE producers in the environment, where they can operate as a reservoir of such resistance" [21]. "Numerous multidrug resistant (MDR) bacteria have been identified in hospital and municipal sewage systems, as well as in the soil surrounding animal farms and contaminated rivers. These findings raise the possibility that these bacteria could contribute to the spread of antibiotic resistance and develop into pathogens. Because of their increasing clinical significance and resistance to several medicines, they have begun to resemble both environmental and clinical microorganisms" [22,23].

3. Common antibiotic-resistant bacterial species

Globally, infections linked to health care increase rates of morbidity and mortality. Antimicrobial resistance, which restricts the use of antibiotics and makes it more challenging to treat infections brought on by multiresistant microbes, is directly linked to the rise in mortality. Infections with gram-negative bacteria that are resistant to carbapenem, primarily Enterobacteria, emerged as a significant public health concern at the start of the twenty-first century [24]. Nosocomial infections are thought to be mostly caused by MDR gram-negative bacteria, such as *A. baumannii, Pseudomonas aeruginosa, Enterobacteria* that produce extended-spectrum beta-lactamase (ESBL), and Enterobacteria that are resistant to carbapenem [25]. "The World Health Organization (WHO) has identified the genera *Pseudomonas, Acinetobacter* and *Enterobacter* as those belonging to the Gram-negative family of bacteria for which new and effective medications are desperately needed. They are used as "the last line of antibiotic defence" against resistant organisms because, among other things, they produce an extended spectrum of β-lactamases (ESBLs) that confer resistance to antimicrobials like cephalosporins, penicillins, and monobactams. Additionally, they include an increasing number of strains that are resistant to carbapenem" [26,27]. Concerningly, during the past 10 years, there has been a noticeable global rise in nosocomial CRB (carbapenem-resistant bacterium) infections; infections caused by *Acinetobacter* and *Pseudomonas* have been linked to 40–80% mortality in intensive care units [28,29].

According to current reports, the most prevalent bacterial diseases are vancomycin-resistant Enterococcus (VRE) and methicillin-resistant *S. aureus* (MRSA). Hospitals have also been shown to harbour animal products, water, and animals. Although some strains of MDR P. aeruginosa, Carbapenem-resistant Enterobacteriaceae, and *A. baumannii* have also been recovered from foods, animals, and water, clinical samples have been the primary source of these germs.

A large number of these organisms are opportunistic infections that contaminate the ill or immunocompromised. A lot of these bacteria seem to be found in large quantities in nature, and a contaminated environment can promote their proliferation. Public health is also greatly concerned about the Gram-positive methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) bacteria. It is well recognised that both have the capacity to spread epidemics [30].

The World Health Organization released the first-ever list of antibiotic-resistant "priority pathogens," which is a catalogue of 12 bacterial families that are the biggest threats to human health. According to how urgently new antibiotics are needed, the WHO list is split into three categories: critical, high, and medium priority [31].

Priority 1: CRITICAL

- *Acinetobacter baumannii*, carbapenem-resistant
- *Pseudomonas aeruginosa*, carbapenem-resistant
- *Enterobacteriaceae*, carbapenem-resistant, ESBL-producing

Priority 2: HIGH

- *Enterococcus faecium*, vancomycin-resistant
- *Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and resistant
- *Helicobacter pylori*, clarithromycin-resistant
- *Campylobacter* spp., fluoroquinolone-resistant
- *Salmonellae*, fluoroquinolone-resistant
- *Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

- *Streptococcus pneumoniae*, penicillin-non-susceptible
- *Haemophilus influenzae*, ampicillin-resistant
- *Shigella* spp., fluoroquinolone-resistant

3.1. What Mechanisms Bacteria Use to Adapt?

There is no one mechanism responsible for the fast spread of AMR throughout bacterial populations. Frequently, it is the outcome of intricate procedures. Therefore, before analysing the factors that cause resistance to these molecules, antibiotics must be divided into groups based on their distinct mechanisms of action. We have chosen to discuss the antibiotic classes that are most directly related to the development of antibiotic resistance in this review, despite the fact that there are many distinct classes of antibiotics. The modes of action and resistance of the major antibiotic families are presented in Table 1 the primary ways in which antimicrobial drugs function. Reduced drug uptake, altered drug targets, drug inactivation, and activation of drug efflux pumps are the primary causes of resistance [32, 33].

Table 1. Antibiotic resistance mechanisms and modes of action

Antimicrobial Groups	Mechanism of Action	Resistance Mechanism

β-Lactams Penicillins	Inhibits cell wall production	Beta-lactamase production Penicillinase
Cephalosporins Carbapenems		Cephalosporinase Carbapenemase
β-Lactamase inhibitors	Block the activity of beta-lactamase enzymes	Extended-spectrum beta-lactamase (ESBL)
Aminoglycosides, Chloramphenicol Macrolides, Tetracyclines	Inhibit ribosome assembly by binding to the bacterial 30S or 50S (inhibit protein synthesis)	Multifactorial (enzymatic modification, target site modification and efflux pumps)
Fluoroquinolone	Inhibit DNA replication	Multifactorial (target-site gene mutations, efflux pumps and modifying enzyme)
Sulfonamides and trimethoprim	Inhibit folic acid metabolism	Horizontal spread of resistance genes, mediated by transposons and plasmids, expressing drug-insensitive variants of the target enzymes.

3.2. Antibiotic-Resistant Pathogens

3.2.1. Acinetobacter baumannii

"Gram-negative aerobic bacillus *Acinetobacter baumannii* is a member of the group of pathogens known by the acronym ESKAPE (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumonia, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species*), which stands for the ability of these bacteria to evade the effects of antibiotic bactericidal activity" [34]. *A. baumannii* is an opportunistic pathogen that can become resistant to antibiotics through a variety of ways. It is a global cause of hospital-acquired infections.

The rapid evolution of this strain toward multi-resistance could be attributed to the creation of all four classes of β-lactamases (A, B, C, and D) by the integration of exogenous DNA into its genome [35]. Furthermore, genes encoding for ESBL (GES-11 and CTX-M) and narrow-spectrum β-lactamases (TEM-1, SCO-1, and CARB-4) have been found in Acinetobacter spp. [36]. With the exception of monobactams, class B β-lactamases are metallo-β-lactamases (MBLs) with a wide substrate range of inhibition [37]. A class of widely distributed enzymes known as class C β-lactamases is typically resistant to cephamycins (cefoxitin and cefotetan), penicillins, and cephalosporins [38]. Additionally, *A. baumannii* has Class D, or OXAs β-lactamases, which are capable of hydrolyzing carbapenems and extended range cephalosporins [39]. Additionally, AmpC cephalosporinase is inherent to *A. baumannii* [40].

"Efflux pumps have a role in *A. baumannii* bacterial resistance to many antibiotics from different chemical classes, including trimethoprim, aminoglycosides, tetracyclines, erythromycin, chloramphenicol, fluoroquinolones, and various beta-lactams" [41, 42].

"Three kinds of enzymes—phosphotransferases, adenylyl transferases, and acetyltransferases—are essential to *A. baumannii* resistance to aminoglycosides. Transposons and plasmids are two ways that the genes encoding for aminoglycoside-modifying enzymes can be transmitted" [43].

For the treatment of MDR *A. baumannii* bacteraemia, the combination of ampicillin, sulbactam, and carbapenem is the most effective [44]. Even while considerable rates of resistance have been reported, minocycline treatment is also beneficial [45]. Combining minocycline and colistin is the recommended treatment for *A. baumannii* infections that are resistant to minocycline, whereas colistin/rifampin is the most efficient treatment for *A. baumannii* infections that are resistant to colistin [46]. Moreover, carbapenem-resistant *A. baumannii* is quickly killed by trimethoprim-sulfamethoxazole in combination with colistin [47].

3.2.2. Methicillin-resistant *Staphylococcus aureus*

"S. aureus is the leading cause of nosocomial infections by gram-positive bacteria [48]. It is notoriously resistant to penicillin and many other antimicrobials" [49]. "Strains of *S. aureus* have developed resistance to many commonly used antimicrobial due to indiscriminate use. Staphylococcal resistance to penicillin is mediated by β-lactamase production. First report of a penicillin-resistant strain of *S. aureus* was published in 1945, revealing its association with β-lactamase enzyme produced by the bacteria. The methicillin resistant *staphylococcus aureus* (MRSA) is a specific strain of the *S. aureus* bacterium that has developed antimicrobial resistance to all penicillin 's, including methicillin and other narrow-spectrum β-lactamase-resistant penicillin antimicrobials" [50].

The first evidence of methicillin resistance was found in *Staphylococcus aureus* in 1961 as a result of widespread penicillin use. Penicillinase-producing *S. aureus* also became more prevalent after penicillin was introduced. While hospital-acquired methicillin-resistant *S. aureus* (HA-MRSA) is becoming less common, methicillin-resistant *S. aureus* (MRSA) is still a major burden in U.S. health care settings. In contrast to this discovery, there has been a notable rise in the frequency of community-acquired MRSA (CA-MRSA) infections within the

same area [51]. Due to the lack of the mecA gene, BORSA is not actually methicillin resistant or sensitive, and frequent misidentification puts patient treatment and outcomes at serious risk because severe infections may not respond to high oxacillin doses [52]. Overall, MRSA infections result in higher health care costs due to morbidity and length of hospital stay [53]. Methicillin resistance is independently linked to higher mortality, and the death rate after *S. aureus* blood stream infection surpasses 20 % [54,55].

3.2.3. Pseudomonas aeruginosa

"Aerobic gram-negative *P. aeruginosa* is a prevalent environmental pathogen that can cause a wide range of acute and chronic nosocomial infections, including severe respiratory infections in patients with compromised host defences" [56]. "*P. aeruginosa* is the third most frequent gram-negative bacterium in this environment that causes nosocomial bloodstream infections" [57]. "Due to several resistance mechanisms that are both intrinsic and acquired from other species, *P. aeruginosa* has demonstrated intrinsic resistance to a variety of antibiotics" [58]. "The overexpression of efflux pumps, a decrease in the permeability of the outer membrane, and the acquisition or mutation of resistance genes that encode for proteins that regulate the passive diffusion of antibiotics across the outer membrane are the key mechanisms of resistance" [59]. "Broad-spectrum antimicrobials with *P. aeruginosa* coverage, ceftazidime and cefepime, which belong to the third and fourth generations of cephalosporins, respectively, have been identified" [60]. "Numerous β-lactams, including imipenem and benzylpenicillin, can stimulate endogenous β-lactamase, such as AmpC β-lactamase. Furthermore, a gene mutation that results in the overexpression of AmpC β-lactamases can give *P. aeruginosa* resistance" [61]. "Transferable aminoglycoside modifying enzymes (AMEs), which reduce the binding affinity to their target in the bacterial cell, cause pseudomonas resistance to aminoglycosides" [62,63]. "Colistin is used in conjunction with an anti-pseudomonas medication such as imipenem, piperacillin, aztreonam, ceftazidime, or ciprofloxacin to treat MDR *P. aeruginosa"* [64].

2.3.4. Klebsiella pneumoniae

K. pneumoniae is a non-fastidious, frequently encapsulated, gram-negative bacillus that belongs to the Enterobacterales family [65]. Particularly in patients with impaired immune systems, *K. pneumoniae* can cause a variety of nosocomial and community-acquired infections, such as bloodstream infections, pneumonia, liver abscesses, urinary tract infections, and surgical site infections [66, 67]. Person-to-person contact is necessary to get a *Klebsiella*

infection because the germs cannot be transmitted through the air [68]. Because *Klebsiella* has acquired genes encoding enzymes like ESBLs and carbapenemases widely, the bacteria has developed a high level of resistance to antibiotics [69]. The most clinically significant strains of carbapenem-resistant Enterobacteriaceae (CRE) are *K. pneumoniae* strains that are resistant to the antibiotic [70]. Since carbapenems are frequently the last line of defence against gram-negative persistent infections, the rising number of *K. pneumoniae* (KPC) strains that produce the enzyme that codes for the blaKPC-3 gene poses a serious risk to public health [71,72].

2.3.5. E. coli

AMR *Escherichia coli* is known to be a major source of bloodstream infections and urinary tract infections (UTI) in both community and healthcare settings worldwide, despite not being officially recognised as a member of the ESKAPE group of pathogens [73]. One of the most typical signs of an *E. coli* UTI is sepsis. *E. coli* is the most common Gram-negative bacterial species identified from blood and urine cultures in Australian emergency rooms and inpatient settings [74]. A number of pandemic clones of MDR uropathogenic *E. coli*, including as ST131 and ST95, have spread around the world in the last ten years [75]. *E. coli* usually obtains resistance genes from other Enterobacterales members through horizontal gene transfer. All throughout Europe, there is a high prevalence of resistance to aminopenicillins, fluoroquinolones, aminoglycosides, and third-generation cephalosporins [76]. The general state of CRE, including *E. coli*, in Europe was demonstrated to deteriorate between 2010 and 2018, notwithstanding the rarity of carbapenem resistance in invasive strains of the bacteria [77]. Moreover, strains of *E. coli* obtained from Chinese pig farms were found to be resistant to colistin, the last-resort polymyxin, in 2016 [78]. One of the biggest clinical burdens on human and animal health at the moment is AMR *E. coli*.

There were comparatively many *E. coli* isolates resistant to tetracyclines, sulphonamides/trimethoprim, quinolones, and β-lactams. The proportion of *E. coli* isolates that responded to phenicol and aminoglycosides was low. Furthermore, the presence of resistance genes 592 in *E. coli* isolates suggested a higher likelihood that 593 of them carried bla-genes, tetA, qnrS, and sul2. Ampicillin (AMP), amoxicillin plus clavulanic acid (AMC), and sulfamethoxazole/trimethoprim were found to have the highest resistance rates (SXT). The antibiotics used as last resort, meropenem (MEM) and ertapenem (ETP), have the lowest rates of resistance [79]. Treated effluent samples included *E. coli* resistant to cefoxitin, ciprofloxacin, and cefotaxime (containing manufacturers of extended-spectrum beta-lactamases [ESBL] [80].

2.3.6. Anti-Regulators

The Gram-negative bacteria *Vibrio cholerae* is the cause of the cholera epidemic in humans. A toxin-coregulated pilus and cholera toxin (CT) are the two primary virulence factors in the pathophysiology of *V. cholerae* (TCP). An osmotic imbalance caused by the two subunits of CT, an ADP-ribosylating toxin, causes intestinal cells to produce more cAMP, which in turn causes diarrhoea [81]. When intestinal colonisation by *V. cholerae* occurs, TCP, a type IV bundle-forming pilus, is involved [82]. ToxT, the master regulator, controls the expression of TCP and CT [83]. In a mouse infection model, Hung et al. found that virstatin (4-[N-(1,8-naphthalimide)]-n-butyric acid) inhibits ToxT dimerization and lowers V. cholera colonisation [84]. ToxTazin, another small molecule inhibitor, decreases the pathogenicity of V. cholera by preventing the synthesis of an activator (TcpP) required for the expression of the toxT gene [85].

4. Conclusion

In Conclusion, antibiotic resistance poses a formidable threat to global public health, requiring urgent and concerted efforts from the scientific, medical, and policy-making communities. Antibiotic resistance could usher in a post-antibiotic era, where common infections and minor injuries become life-threatening. Addressing antibiotic resistance demands a multifaceted approach. First and foremost, there is an urgent need for global cooperation to curb the inappropriate use of antibiotics in human medicine, agriculture, and animal husbandry. Public awareness campaigns can play a crucial role in educating the public and healthcare professionals about responsible antibiotic use. Additionally, fostering the development of new antibiotics and alternative treatment strategies is essential to stay ahead of evolving bacterial resistance.

5. References

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