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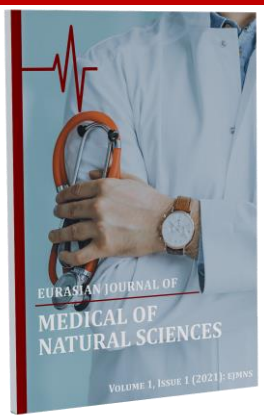

ANTIBIOTIC RESISTANCE IN BACTERIA: THE MOST DANGEROUS PATHOGENS

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ABSTRACT

Antibiotics have enabled the treatment of bacterial infections like meningitis and bacteraemia, which were once untreatable and often fatal. However, in recent decades, the overuse and misuse of antibiotics, along with various social and economic factors, have accelerated the spread of antibiotic-resistant bacteria, rendering many treatments ineffective. Today, antimicrobial resistance (AMR) claims at least 700,000 lives globally each year. The World Health Organization (WHO) warns this figure could soar to 10 million annually by 2050 if new, more effective treatments are not developed, emphasizing the urgent nature of this health crisis. In response to the growing threat of antibiotic resistance, the WHO released a list of priority pathogens in February 2017, including the ESKAPE group (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species), which pose the greatest danger to humans. Understanding the resistance mechanisms in these bacteria is crucial for developing new antimicrobial therapies. This review explores the modes of action and resistance mechanisms of widely used antimicrobials, as well as the current state of AMR in the most critical resistant bacteria identified by the WHO's global priority pathogens list.

Introduction

Although antimicrobial resistance (AMR) is a natural process, the current public health crisis stems largely from the overuse of antibiotics. Other significant factors, often called "socioeconomic determinants," also contribute to the growing prevalence of AMR. These include inadequate community hygiene, unsafe food practices, poor infection control in healthcare settings, the accumulation of antibiotics in the environment, and their widespread use in agriculture and the food industry. Bacterial resistance to antibiotics has been recognized for more than 50 years. By the late 1950s, for example, most isolates of *Staphylococcus aureus*

had developed resistance to penicillin, which had previously been effective in treating such infections. However, during the 1960s, the development of new drugs like vancomycin and methicillin gave the impression that resistance could be overcome through the creation of new antibiotic classes. Unfortunately, in the decades that followed, bacteria evolved numerous mechanisms to resist these drugs, causing antibiotic resistance to persist and intensify.

In 2017, the World Health Organization (WHO) published its first list of 12 bacterial families posing the greatest threats to human health. This list classified bacteria into three priority categories—critical, high, and medium—based on the urgency of the need for new antibiotics. The most critical group includes multidrug-resistant bacteria that threaten patients in hospitals, nursing homes, and those requiring medical devices like ventilators and blood catheters. These critical-priority bacteria include *Acinetobacter*, *Pseudomonas*, and certain *Enterobacteriaceae* such as *Klebsiella pneumoniae*, *E. coli*, and *Enterobacter* species. These pathogens, resistant to multiple antibiotics, can cause severe and often deadly infections such as pneumonia and bloodstream infections. The high-priority group includes bacteria like *Enterococcus faecium* and *Staphylococcus aureus*, which are resistant to antibiotics like vancomycin and fluoroquinolones. The medium-priority group includes bacteria like *Streptococcus pneumoniae* and *Shigella*, for which effective antibiotics are still available, though some resistance exists.

In 2019, due to its significant impact on human health, the WHO classified antimicrobial resistance as one of the top ten global health threats.

What Is Antimicrobial Resistance and How Does It Continue to Rise?

According to the World Health Organization (WHO), antimicrobial resistance (AMR) occurs when microorganisms no longer respond to antibiotics that were once effective in treating infections caused by them. This resistance makes infections harder, or even impossible, to treat, increasing the risk of severe infectious diseases and death. Describing AMR as merely a result of antibiotic overuse is insufficient, as AMR naturally develops over time through various mechanisms. However, the excessive use of antibiotics in humans and animals accelerates this process, fueling the spread of AMR.

While we often speak of bacteria becoming resistant to antibiotics, it's important to understand what this entails. There are two main types of resistance: natural (which includes intrinsic and induced resistance) and acquired. Intrinsic resistance refers to bacterial species that are inherently resistant to specific antibiotics, regardless of prior exposure (e.g., *Escherichia coli*'s resistance to vancomycin or *Pseudomonas aeruginosa*'s resistance to ampicillin and certain cephalosporins). Natural resistance can also be induced when bacterial genes are activated in response to exposure to clinical doses of antibiotics.

Acquired resistance, on the other hand, occurs through two processes: mutations during DNA replication or through DNA transfer. Mutant strains can pass the resistance mutation to their progeny through vertical gene transfer. Alternatively, bacteria can gain resistance through horizontal gene transfer, which occurs via three methods: transformation, transduction, and conjugation. In transformation, bacteria take up extracellular DNA from a donor; in transduction, DNA is delivered to a bacterium by a bacteriophage; and in conjugation, DNA is transferred directly between bacteria through mating.

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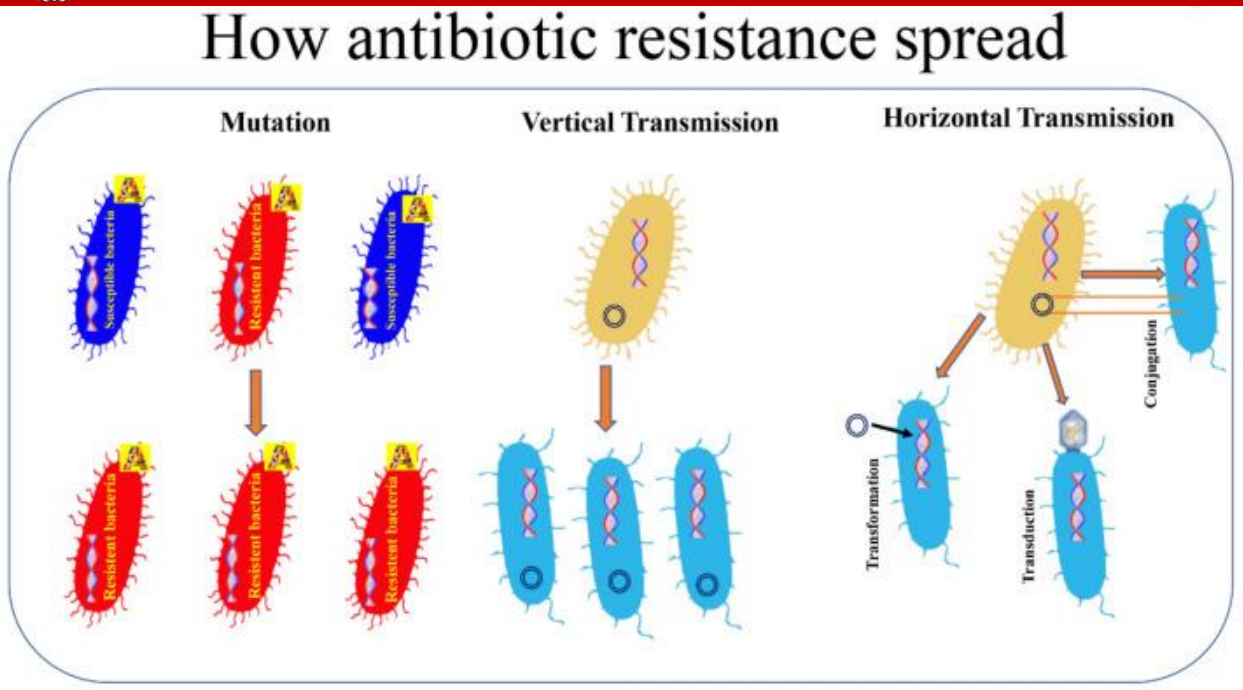

Figure 1

How antibiotic resistance spread. Bacterial resistance towards antibiotics can be natural, or acquired by vertical or horizontal transmission. A: antibiotic.

The antibiotic-resistant genetic material is subsequently transferred from resistant bacteria to non-resistant bacteria, making them resistant to antibiotics as well.

How Bacteria Acquire Resistance

The rapid spread of antimicrobial resistance (AMR) in bacterial populations cannot be attributed to a single mechanism. Instead, it results from complex processes. To understand these, antibiotics are typically classified based on their mechanisms of action before analyzing the factors contributing to resistance. While there are various antibiotic classes, this review focuses on those most closely associated with antibiotic resistance. Table 1 provides an overview of the mechanisms of action and resistance for the primary antibiotic groups. The main antimicrobial mechanisms involve inhibiting critical bacterial processes such as cell wall synthesis, protein production, nucleic acid synthesis, and metabolic pathways. Key resistance mechanisms include reduced drug uptake, alterations of drug targets, drug inactivation, and activation of drug efflux pumps (Figure 2).

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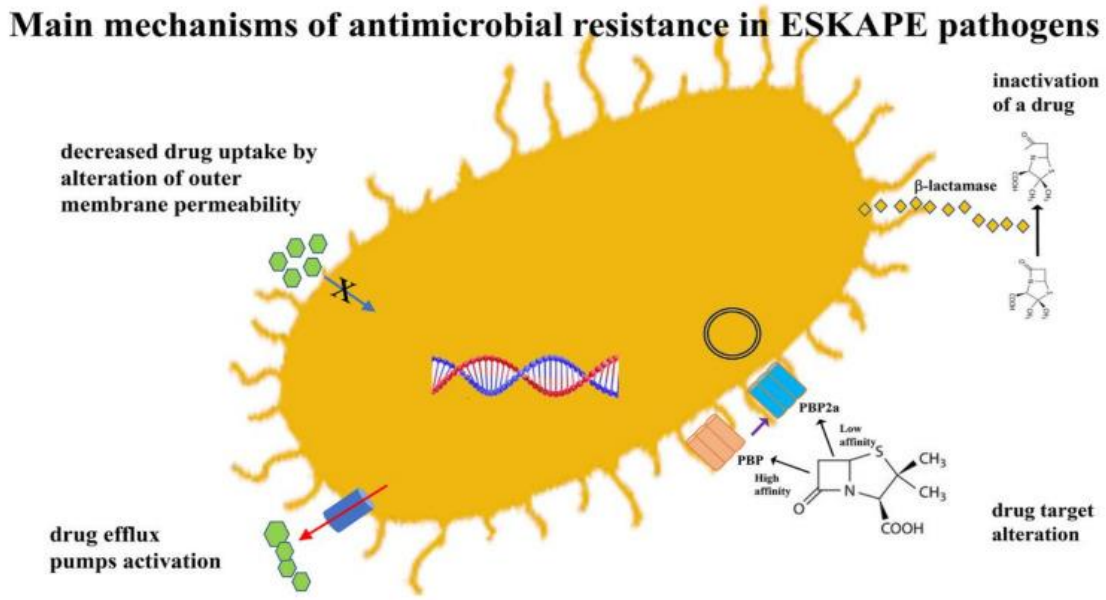

Figure 2. Mechanisms of antibiotic resistance in ESKAPE pathogens.

Table 1
Mode of action and resistance mechanisms of antibiotics.

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.

Since the mechanisms of action of antibiotics depend on their structure and their affinity for bacterial components, understanding these mechanisms is essential to comprehend how resistance develops.

This review discusses bacterial pathogen resistance based on the categories established by the World Health Organization (WHO).

The Major Antibiotic-Resistant Pathogens That Are Difficult to Treat

1. Acinetobacter baumannii

Acinetobacter baumannii is an aerobic, gram-negative bacillus that belongs to the ESKAPE group of pathogens (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species), named for their ability to "escape" the bactericidal effects of antibiotics. This opportunistic pathogen is a leading cause of hospital-acquired infections globally and develops resistance through several mechanisms:

1. **Production of β-lactamase enzymes**

A. baumannii produces all four classes of β-lactamases (A, B, C, and D) by acquiring foreign DNA, accelerating its evolution toward multidrug resistance. It carries genes for narrow-spectrum β-lactamases (e.g., TEM-1, SCO-1, CARB-4) and extended-spectrum β-lactamases (ESBLs) such as GES-11 and CTX-M. Class B β-lactamases, also known as metallo-β-lactamases (MBLs), have a wide substrate range and inhibit all β-lactams except monobactams. Class C β-lactamases confer resistance to cephamycins, penicillins, and cephalosporins, while Class D or OXA β-lactamases hydrolyze extended-spectrum cephalosporins and carbapenems. Additionally, *A. baumannii* has an intrinsic ampC cephalosporinase.

2. **Efflux pump expression:**

Efflux pumps in *A. baumannii* contribute to resistance against various antibiotics, including aminoglycosides, tetracyclines, erythromycin, chloramphenicol, trimethoprim, fluoroquinolones, and certain β-lactams. Research has identified four classes of efflux pumps linked to antimicrobial resistance in *A. baumannii*: the major facilitator superfamily (MFS), the resistance-nodulation-cell division (RND) superfamily, the multidrug and toxic compound extrusion (MATE) family, and the small multidrug resistance (SMR) family Overexpression of the AdeABC efflux pump, part of the RND family, has been associated with tigecycline resistance in *A. baumannii*.

3. **Enzymatic modification of aminoglycosides:**

The most common form of aminoglycoside resistance in *A. baumannii* is through enzymatic modification. Three classes of enzymes - acetyltransferases, adenylyltransferases, and phosphotransferases - play a critical role in modifying aminoglycosides and conferring resistance. The genes encoding these enzymes can be transferred via plasmids and transposons.

4. **Production of Modified Porins:**

Acinetobacter baumannii reduces the permeability of its outer membrane by producing altered porins, which decreases the transport of molecules and contributes to carbapenem resistance. The downregulation of porins, proteins responsible for allowing substances to pass through the outer membrane, is closely linked to this resistance. Additionally, *A. baumannii* can develop resistance to colistin, a polypeptide antibiotic that targets lipopolysaccharides (LPS), through mutations in the genes involved in LPS biosynthesis.

5. **Modification of Antibiotic Targets:**

Resistance in *A. baumannii* can also occur through modifications to the drug's target. This is achieved by the overexpression of penicillin-binding proteins, which leads to resistance

against imipenem, or by mutations in DNA gyrase, contributing to resistance against quinolones and tetracyclines.

Carbapenems, such as imipenem and meropenem, were once the most effective treatments for A. baumannii infections [48]. However, due to rising resistance, they were replaced by minocycline/tigecycline, until significant resistance to these agents also emerged [48,49]. Currently, a combination of ampicillin, sulbactam, and carbapenem is considered the most effective treatment for multidrug-resistant (MDR) A. baumannii bacteremia [50]. Minocycline is also used, though increasing resistance has been observed [48]. For minocycline-resistant infections, a combination of minocycline and colistin is employed, while colistin/rifampin is most effective against colistin-resistant strains. Additionally, trimethoprim-sulfamethoxazole, in combination with colistin, rapidly kills carbapenem-resistant A. baumannii. However, strains resistant to these treatments are also frequently identified. Therefore, it is crucial to develop new antibiotics capable of combating MDR A. baumannii.

2. Pseudomonas aeruginosa

Aerobic gram-negative P. aeruginosa is a widespread environmental pathogen that can cause a wide range of acute and chronic nosocomial infections, including severe respiratory infections in patients with weakened host defenses. P. aeruginosa is the third most frequent gram-negative bacteria in this environment that causes nosocomial bloodstream infections. 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. 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 fundamental mechanisms of resistance. Broad-spectrum antibiotics with P. aeruginosa coverage, ceftazidime and cefepime, which belong to the third and fourth generations of cephalosporins, respectively. All four major classes of β-lactamases (A, B, C, and D) have been found in P. aeruginosa, much like in A. baumanni. Several β-lactams, including imipenem and benzylpenicillin, can generate endogenous β-lactamase, like AmpC β-lactamase. Furthermore, AmpC β-lactamase overexpression due to a gene mutation can confer resistance in P. aeruginosa. Transferable aminoglycoside modifying enzymes (AMEs), which reduce the binding affinity to their target in the bacterial cell, mediate pseudomonas resistance to aminoglycosides. Colistin is used in conjunction with an anti-pseudomonas medication such as imipenem, piperacillin, aztreonam, ceftazidime, or ciprofloxacin to treat MDR P. aeruginosa. Penicillins, aminoglycosides, and cephalosporins combined with fosfomycin have been effective in treating drug-resistant P. aeruginosa.

3. Staphylococcus aureus

Staphylococcus aureus is a major human pathogen, a gram-positive, facultative anaerobe, and both catalase- and coagulase-positive. It typically forms irregular, grape-like clusters. This bacterium can cause a range of infections, from mild skin and soft tissue infections to life-threatening conditions such as bacterial endocarditis, pleuropulmonary infections, and device-related infections. Its importance as a pathogen lies not only in its contagious nature and ability to cause chronic infections but also in its remarkable capacity to develop resistance to both old

and new antibiotics. For instance, penicillin-resistant S. aureus strains, which carried plasmid-encoded beta-lactamases that degrade the β-lactam ring of penicillin, emerged just three years after penicillin was discovered. These resistance genes, often carried on transposable elements, were frequently co-located with genes conferring resistance to other antibiotics such as erythromycin and gentamicin. Methicillin, a semi-synthetic penicillin, was introduced in 1959 to combat penicillin-resistant strains, but by 1961, the first methicillin-resistant S. aureus (MRSA) strain had already been identified. Methicillin and other β-lactam antibiotics inhibit S. aureus by binding to penicillin-binding proteins (PBPs). MRSA strains acquired the mecA and mecC genes via horizontal gene transfer, which led to the production of PBP2a, an alternative PBP with low affinity for almost all β-lactam antibiotics, rendering methicillin ineffective.

For years, vancomycin was considered a last-resort antibiotic for treating severe MRSA and other resistant gram-positive infections. However, by the late 1980s, vancomycin resistance emerged in enterococci (VRE) and later in S. aureus (VRSA). The VRSA resistance mechanism is mediated by the VanA operon, which was acquired from vancomycin-resistant Enterococcus via the mobile genetic element Tn1546. In 1997, the first vancomycin-intermediate S. aureus (VISA) isolate was identified, showing reduced susceptibility to vancomycin at concentrations below 4–8 μg/mL. Vancomycin-resistant S. aureus (VRSA), however, requires concentrations of 16 μg/mL or more for inhibition. While both VISA and VRSA have evolved from MRSA, they do not progress from one another, as their resistance mechanisms differ.

According to the World Health Organization (WHO), the pathogenicity and antibiotic resistance patterns of S. aureus pose a significant threat to global health. MRSA, VISA, and VRSA are well-known hospital-acquired pathogens and are considered high-priority agents, as their resistance could lead to infections that are difficult or impossible to control. MRSA infections, in particular, are challenging to treat, and the use of various antibiotic classes over the years has contributed to the rise of multidrug-resistant (MDR) strains. In MRSA, resistance to multiple antibiotics arises through several mechanisms, including (1) mutations in target genes (e.g., fluoroquinolone resistance is due to mutations in the gyrA and gyrB genes of topoisomerase II), (2) target alterations, and (3) overexpression of efflux pumps like the NorA pump.

Daptomycin, a cyclic peptide antibiotic that binds to the bacterial cytoplasmic membrane in the presence of calcium ions, is a key alternative to vancomycin for treating MRSA infections [82]. Although daptomycin resistance in S. aureus is relatively rare, it is increasing due to mutations in various proteins, reducing drug binding to its target site. Additionally, S. aureus can develop resistance to other antibiotics, such as trimethoprim-sulfamethoxazole and tetracyclines, via similar mechanisms. Prolonged use of fusidic acid or rifampicin monotherapy has led to high resistance rates, making combination therapy a more effective option for treating S. aureus skin infections. Due to the rising incidence of MRSA infections, there has been renewed interest in macrolide-lincosamide-streptogramin (MLS) antibiotics for treatment. Among these, clindamycin—a lincosamide—has become a preferred option for treating serious infections due to its excellent pharmacokinetic properties, including good clearance, long half-life, and deep tissue penetration. However, resistance to clindamycin is also increasing in healthcare-associated MRSA strains.

MLS resistance in S. aureus occurs through three primary mechanisms: target modification, active efflux, and enzymatic inactivation. The most common mechanism is ribosomal target modification, mediated by erm genes (ermA, ermB, ermC, and ermF), which encode methyltransferases that modify the ribosomal binding site, blocking the antibiotic and conferring both constitutive and inducible resistance. Inducible resistance arises when a suitable macrolide inducer, such as erythromycin, activates the methyltransferases, resulting in resistance to erythromycin and false susceptibility to clindamycin in vitro. In these cases, clindamycin therapy may select for resistant mutants, leading to clinical treatment failure. Inducible clindamycin resistance can be detected through automated susceptibility testing or a double-disk diffusion test (D-test). Infections caused by MRSA strains with a positive D-test should not be treated with clindamycin.

4. Klebsiella pneumoniae

Klebsiella pneumoniae, a member of the Enterobacterales family, is a gram-negative bacillus that is typically encapsulated and non-fastidious. This bacterium can cause a variety of nosocomial and community-acquired infections, including urinary tract infections, pneumonia, liver abscesses, surgical site infections, and bloodstream infections, particularly in immunocompromised patients. Since Klebsiella does not spread through the air, direct person-to-person contact is required to contract an infection.

K. pneumoniae has developed significant antibiotic resistance, primarily through the acquisition of genes that encode enzymes like extended-spectrum beta-lactamases (ESBLs) and carbapenemases. Carbapenem-resistant *K. pneumoniae* strains are the most prominent among carbapenem-resistant Enterobacteriaceae (CRE). Since carbapenems are often considered the last line of defense against persistent gram-negative infections, the rising prevalence of carbapenemase-producing *K. pneumoniae* (KPC) strains, which carry the carbapenemase-encoding blaKPC-3 gene, poses a significant threat to public health.

5. Enterobacter Species

Enterobacter species are motile, aerobic, gram-negative bacilli belonging to the Enterobacteriaceae family. The Enterobacter cloacae complex (ECC) includes several pathogens, with Enterobacter cloacae and *Enterobacter aerogenes* being the most common. In 2019, E. aerogenes was reclassified as Klebsiella aerogenes due to its greater genetic similarity to the Klebsiella genus [96]. These bacteria are non-fastidious and sometimes encapsulated, often causing opportunistic infections in immunocompromised, hospitalized patients, and they have acquired multiple antibiotic resistance mechanisms.

Many Enterobacter strains produce extended-spectrum beta-lactamases (ESBLs) and carbapenemases, including VIM, OXA, metallo-β-lactamase-1, and KPC [34]. Additionally, the overexpression of ampC β-lactamases plays a key role in the development of antibiotic resistance, as these enzymes can be produced in high amounts, contributing to multidrug resistance (MDR). These MDR strains are resistant to nearly all available antibiotics, with the exception of tigecycline and colistin. However, recent reports indicate the emergence of pan-drug-resistant *K. aerogenes* strains, which show resistance even to colistin, a last-resort antibiotic. To make treatment even more challenging, *K. aerogenes* can harbor subpopulations of colistin-resistant bacteria that go undetected with current diagnostic tests.

6. Enterococci

Enterococci are gram-positive cocci, facultative anaerobes, and gastrointestinal commensals capable of surviving in a wide range of stressful environments. Although more than 50 species of Enterococci have been identified, two species cause the majority of human infections: *Enterococcus faecalis and Enterococcus faecium*. E. faecalis is more pathogenic, but E. faecium exhibits greater resistance to antimicrobial agents, causing severe morbidity and mortality, especially in immunocompromised patients. These microorganisms are generally harmless in healthy individuals, but in immunocompromised patients, they are implicated in hospital-acquired infections such as catheter-associated urinary tract infections, endocarditis, and bacteremia.

Enterococci are becoming increasingly resistant to antibiotics due to several factors:

1. The widespread use of broad-spectrum antibiotics (penicillins and cephalosporins) in hospitals promotes the intestinal colonization of E. faecium by significantly reducing the normal gram-negative intestinal flora. Mutations in PBPs (penicillin-binding proteins) and overexpression of β-lactamases result in high resistance to β-lactam antibiotics.
2. Enterococci have intrinsic resistance to many commonly used antibiotics.
3. These bacteria can acquire and spread antibiotic resistance genes.

In *E. faecium*, at least three distinct pathways contribute to cephalosporin resistance. In the 1970s, vancomycin was introduced to counter Enterococci resistant to third-generation cephalosporins. However, by the 1990s, the extensive use of vancomycin led to the emergence of vancomycin-resistant Enterococci (VRE), which became the second most common nosocomial pathogen. *E. faecium* can acquire resistance genes via mobile genetic elements such as plasmids and transposons; for instance, vancomycin resistance can be transferred by the vanA gene cluster on the transposon Tn1546. Vancomycin inhibits cell wall synthesis by targeting the D-alanyl-D-alanine terminus of peptidoglycan, but resistance is mediated by gene clusters like vanR, vanS, vanH, vanX, and vanZ, which replace the D-Ala-D-Ala terminus with D-alanyl-D-lactate. Vancomycin binds weakly to D-Ala-D-Lac, significantly reducing its effectiveness. The vanA gene cluster, the most common type of vancomycin resistance, is located on the Tn1546 transposon.

E. faecium is considered an MDR (multidrug-resistant) bacterium due to its intrinsic resistance to aminoglycosides like tobramycin, kanamycin, and gentamicin. It produces aminoglycoside-modifying enzymes (AMEs) such as aminoglycoside nucleotidyltransferases (ANTs), acetyltransferases (AACs), and phosphotransferases (APHs) [109]. Mutations in the rpsL gene, which encodes the ribosomal protein S12, can lead to high-level streptomycin resistance. Furthermore, high-level resistance to fluoroquinolones in E. faecium is commonly associated with point mutations in the gyrA and parC genes, which encode subunits of DNA gyrase and topoisomerase IV, or with the overexpression of the efflux pump NorA, which expels these drugs from the bacterial cell.

Conclusions

Antibiotic resistance refers to the ability of bacteria to withstand the effects of antibiotics designed to kill them or inhibit their growth. While this is a natural process resulting from genetic changes following antibiotic exposure, it is being significantly accelerated by the overuse and misuse of antibiotics. Excessive use of antibiotics kills susceptible bacteria, allowing drug-resistant strains to thrive. Factors such as poor sanitation, inadequate infection

control, and the use of antibiotics in livestock further contribute to the spread of antimicrobial resistance. Additionally, novel and often overlooked resistance mechanisms, such as heteroresistance (HR) and the mutant prevention concentration (MPC), play a crucial role. Heteroresistance occurs when a small subpopulation of resistant cells exists within a larger, susceptible bacterial population. These resistant cells rapidly proliferate when exposed to antibiotics, while the susceptible cells are killed. Recent studies have shown that heteroresistance is widespread across various bacterial species and antibiotic classes [110].

The MPC, on the other hand, is a threshold concentration above which the selection of resistant mutants is less likely to occur [111]. Traditionally, the minimum inhibitory concentration (MIC) has been used to gauge bacterial susceptibility to antibiotics, but MIC only represents one aspect of resistance. Even after treatment with antibiotics at MIC levels, resistant mutants can persist due to spontaneous mutations. The MPC represents the concentration needed to eliminate all mutants, essentially the MIC of the least-susceptible mutant [112]. Understanding the MPC/MIC ratio is critical to preventing the emergence of resistant mutants.

The ESKAPE pathogens, known for their rapidly growing multidrug resistance, pose a significant global health threat. Despite their genetic differences, these bacteria share common resistance mechanisms, including reduced drug uptake, target alteration, drug inactivation, and the activation of efflux pumps. To combat the spread of ESKAPE pathogens and antibiotic resistance in general, enhanced surveillance and stricter antimicrobial stewardship in both human healthcare and agriculture are essential. In addition to these measures, the development of new antibiotics and alternative approaches, such as inhibiting biofilm formation and bacteriophage therapy, are vital for slowing the spread of multidrug-resistant strains globally.

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