International Journal of Applied and Natural Sciences (IJANS)
ISSN (P): 2319–4014; ISSN (E): 2319–4022
Vol. 14, Issue 2, Jul–Dec 2025; 11–26

International Academy of Science, Engineering and Technology
Connecting Researchers; Nurturing Innovations

ANTIMICROBIAL RESISTANCE: MECHANISMS, CLINICAL CHALLENGES, AND EMERGING THERAPEUTIC STRATEGIES

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ABSTRACT

Antimicrobial resistance (AMR) has become one of the toughest menaces to the overall health of people worldwide, undermining the effect of life-saving antibiotics and making it more difficult to clinically treat infectious diseases. The range of resistance mechanisms deployed by bacteria includes intrinsic, acquired, and adaptive mechanisms through degradation of the targets with enzymes, modification of targets, lowering of membrane permeability, and active efflux. These mechanisms are clinically demonstrated in such major pathogens as methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE), carbapenem-resistant Acinetobacter baumannii (CRAB), and the extended spectrum 8 -lactamase (ESBL)-producing Enterobacteriaceae. Such organisms highlight the need to implement novel therapeutic interventions urgently. However, new antibiotics (e.g., teixobactin, lefamulin, cefiderocol), bacteriophage-based therapies, engineered lysins, immune-modulatory agents, antibody-derived therapeutics, and nanotechnology-based antimicrobials are all recent developments. The therapeutic potential of the existing drugs is further enhanced by combination regimens and efflux pump inhibitors. This review outlines existing knowledge on bacterial resistance mechanisms and new treatment plans, with the crucial need of the world to be responsible in terms of stewardship, continuous innovation, and concerted effort to reduce AMR and maintain therapeutic effectiveness in the future.

***KEYWORDS**: Antimicrobial Resistance (AMR), Resistance Mechanisms, Multidrug-Resistant Pathogens, Novel Therapeutics, Antibiotic Stewardship, Infectious Disease Treatment*

Article History

***Received:** 24 Sep 2025 | **Revised:** 26 Sep 2025 | **Accepted:** 08 Oct 2025*

INTRODUCTION

Antibiotics have gained a place in modern medical practice; however, the populations of bacteria constantly develop mechanisms that help them survive in the presence of antibiotics. Antimicrobial resistance is now posing a threat to standard healthcare across the globe due to inherent phenotypic characteristics, the horizontal transmission of resistance determinants, and adaptive mechanisms associated with stress which reduces the impact of drugs (Blair et al., 2020). The major mechanisms of resistance include drug-inactivating enzymes, alterations of the target site, reduced membrane

permeability, and, most importantly, multidrug efflux pumps that lower the concentration of antibiotics in the cell and lead to cross-resistance (Nishino et al., 2021).

As a result, clinical implications are manifested in the fact that there are still hard-to-treat pathogens in the hospital and overall community. The resistance is preserved by the mecA-encoded penicillin-binding protein 2a of the Methicillin-resistant Staphylococcus aureus which helps the cell-wall synthesis even in the presence of β-lactam and the emergence of community lineages like USA300 (Rosado et al., 2025). *Pseudomonas aeruginosa* is a pathogen that proliferates in moist clinical conditions and develops strong biofilms and is the underlying cause of chronic infections and device-associated disease. Vancomycin-resistant enterococci (VRE) emerged together with the application of agricultural glycopeptides and became mostly nosocomitant, whereas community-acquired resistance within the Enterobacteriaceae is mediated by CTX-M extended-spectrum 2-lactamases, with the most significant E. coli ST131 clone (Ahmed et al., 2018; Chen et al., 2019; Liu et al., 2019). In parallel, the *Acinetobacterbaumannii* resistant to carbapenem has increased throughout Asia and has severely restricted the effective treatment options (Li et al., 2025).

To deal with this increasing crisis, there is a rising multidimensional approach. Recent antimicrobials including teixobactin and cefiderocol are able to restore activity against recalcitrant targets with novel binding modalities and Trojan-horse cellular entry mechanisms, respectively (Shukla et al., 2022; Viale et al., 2023). Phage- and lysin-based therapies bring in pathogen-specific modalities, but have stability and regulatory approval issues (Kline et al., 2025). The development of resistance, and to a certain extent, the selective antibiotic pressure are targeted by combination regimens and immunomodulatory interventions such as interferon-g and vaccinations (Casanova et al., 2024). Mechanically diverse nanotechnological tools against resistant organisms include nanoparticles of silver all the way up to targeted drug-carrier systems (Khalifa et al., 2025; Obeid et al., 2025).

RESISTANCE MECHANISMS OF BACTERIA TO ANTIBIOTICS

Bacteria are small living organisms that can cause disease in people. Doctors battle them with antibiotics. Unfortunately, bacteria have evolved several ways to withstand these medicines. Resistance is typically categorized into three major types according to scientists: intrinsic, acquired and adaptive resistance. Each variation reflects a different defence bacteria use to protect themselves (Blair et al., 2020).The natural resistance is a feature of bacteria which is the result of their genetics and the structure of the cell. It is linked to structural characteristics, including that the outer membrane of Gram-negative bacteria is impermeable and hinders penetration of antibiotics. There are also some bacterial species in which proteins of enzyme activity inactivate antibiotics before they can work most notably, beta-lactamases. Other systems include the use of so-called efflux pumps, nanoscale translocation tools that force cellular toxic entities out of the cell (Peterson and Kaur, 2022).

Equipped resistance is developed when bacteria take on alien genetic materials of related taxa. This horizontal gene transfer may be through conjugation (a direct exchange of DNA), transformation (adoption of the extracellular DNA) or transduction (DNA transfer by a virus). These processes are easy to disseminate the resistance determinants among different bacterial species (Van Duin and Paterson, 2020). The response to a stress caused by antibiotics is adaptive resistance, which is a response by bacterial populations. Instead of the lasting changes, the adaptive mechanisms offer short-term protection. These involve development of biofilms that impede drug penetration, modification of drug-binding sites and metabolic reprogramming that perpetuates the survival in the face of antibiotic attacks. The simultaneous effect of these measures makes bacterial cells extremely resistant, which causes infections that are very hard to eliminate (Sharma et

al., 2022).One of the most significant medical breakthroughs is antibiotics, which have significantly led to the decrease in the number of deaths resulting due to infectious diseases. However, bacteria being living organisms that are able to evolve as well as adapt, have come up with more advanced mechanisms of overcoming the effects of antibiotics. The set of defense mechanisms, also known as antibiotic resistance mechanisms, is one of the greatest threats to the modern population health (Munita& Arias, 2021).

Mechanisms of Antibiotic Resistance in Bacteria

Antibiotics are very strong medicines which have played a big role in helping to curb the death rates in the world. However, organisms known as bacteria have developed, over time, advanced mechanisms of avoiding these agents as they are able to be adapted. Such evasive mechanisms are the means of antibiotic resistance, and nowadays they are one of the most topical threats to the health of the world population (Du et al., 2018).

General Resistance Mechanisms

The bacteria populations have various mechanisms of reducing the effectiveness of antimicrobial agents. Certain isolates express certain enzymes that can break down or alter the drug, and therefore, override its pharmacological effects. Others preventing the binding of the antibiotic alter the molecular target inside the cytoplasm. The group of organisms also strengthens their cell envelope by decreasing membrane permeability, which in fact hinders the entry of drugs. Another very common approach is the use of efflux pumps, which are proteins that are located in the cytoplasm and are membrane bound, and their active function is to push antibiotics out of the cell before they have any chance to cause their fatal outcome. Horizontal gene transfer also promotes the spread of resistance determinants to bacterial communities in a short time (Nishino et al., 2021).Efflux pumps are one of such resistance mechanisms, which are of particular relevance. They can simultaneously eject a wide range of structurally diverse drugs and are powered by cellular energy sources, in particular, the proton motive force or ATP hydrolysis. As a result, efflux pumps became one of the key points of current antibiotic development and studies to avoid bacterial resistance (Fitzpatrick et al., 2017).

Families of Efflux Pumps

Efflux pumps are grouped into different families based on their structure and how they use energy. Various families of efflux pumps shown in **Figure 1**.

- ATP-Binding Cassette (ABC) transporters
- Major Facilitator Superfamily (MFS)
- Small Multidrug Resistance (SMR) family
- Multidrug and Toxic Compound Extrusion (MATE) family
- Proteobacterial Antimicrobial Compound Efflux (PACE) family
- Resistance-Nodulation-Division (RND) superfamily

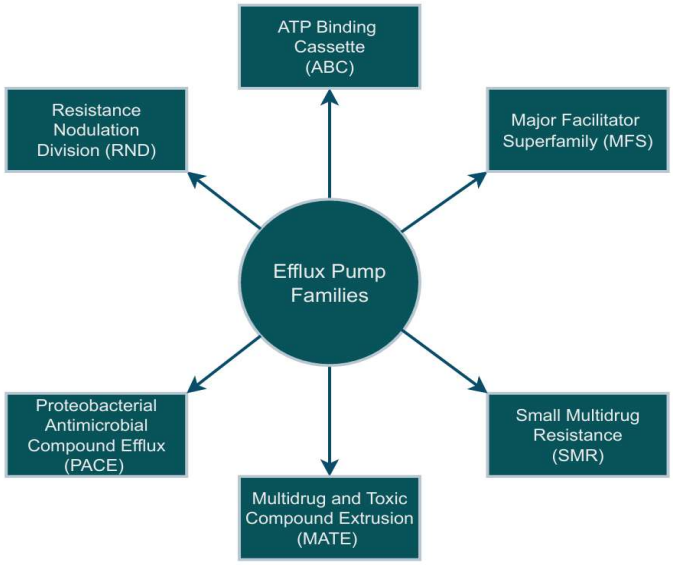

Figure 1: Families of Efflux Pumps

ATP-Binding Cassette (ABC) Transporters

One of the most common groups of proteins is the ABC transporters. They require the ATP and enable translocation of various substrates across cellular membranes. Bacteria nutrient uptake is achieved through the utilization of ABC transporters which coincidentally discharge xenobiotic compounds, e.g. antibiotics. One such example is the MacAB - TolC complex of Escherichia coli. The multifaceted facilitates the vulnerability of the bacterium to the macrolide antibiotics and also creates the chance to secrete the elements of virulence. The deletions in the abacus transporter genes play an important role in the antibiotic sensitivity of bacteria (Greene et al., 2018). Therefore the scientists have been striving to identify the inhibitors so that they can deactivate these efflux systems so as to restore the efficacy of antibiotics.

Major Facilitator Superfamily (MFS)

The largest as well as the most widely researched family of efflux pumps is MFS pumps. Instead of the ATP, they apply proton gradients. They extract every kind of compounds as sugar, amino acids and antibiotics. SA09310 Staphylococcus aureus also pumps tetracyclines and macrolides. The SCO4121 pump in Streptomyces coelicolor makes it resistant to ciprofloxacin. With the removal of these genes, these bacteria become noseblind (Islam et al., 2021). The multidrug resistance is largely due to MFS pumps due to their heterogeneity.

Small Multidrug Resistance (SMR) Family

There are many types of disinfectants and SMR pumps can be extremely small proteins.One well-studied member is EmrE in E. coli, which utilizes protons to pump drugs out. Such as, the A1S_0710 gene depletion in *Acinetobacter baumannii* decreases not only resistance but also motility, proving that SMR proteins influence survival more than just antibiotics (Burata et al., 2022).Multidrug and Toxic Compound Extrusion (MATE) Family These transport systems consist of 12 transmembrane domains with both the amino and carboxy termini located in the cytoplasm.Energy for MATE pumps is provided by a sodium or proton gradient. One prominent analogy is NorM of *N.gonorrhoeae* that actively effluxes fluoroquinolones and lethal agents(sentence).In Staphylococcus aureus, the MepA pump accounts for resistance to tigecycline, a last-resort antibiotic for resistant infections (Huang et al., 12072). Various MATE transporters function differently depending on the bacterial species indicating their versatile evolution (Yin et al., 2023).

PACE (Proteobacterial Antimicrobial Compound Efflux) Family

The PACE family is more recent, having been discovered about a decade ago. Such pumps are found in Proteobacteria including *Acinetobacter baumannii*, Klebsiella pneumoniae and Pseudomonas aeruginosa.Among the earliest characterized, AceI (in *A. baumannii*) confers tolerance to chlorhexidine, a widely used disinfectant in hospitals. Recent research also suggests that PACE pumps are resistant to dyes and antiseptics, further complicating infection control (Zhao et al., 2022).

Resistance-Nodulation-Division (RND) Superfamily

RND superfamily is specifically applicable in Gram-negative bacteria, including E. coli and Pseudomonas aeruginosa. These pumps are found as huge tripartite complexes that occur between the outer and inner membranes. A case in point is AcrAB-TolC of E. coli that forms a central part of multi-drug-resistance. Bacteria are also protected against the adverse conditions like acid in the stomach or bile salts in the intestines by RND pumps (Jang et al., 2023). Increasing research is carried out in such peptides, e.g., CASPs (capable of binding RND pumps and inactivating their activity) as a new therapeutic tool against such infections (Lyu et al., 2022).

Why Efflux Pumps Matter

Efflux pumps are also one of the most dominant factors that enable bacteria to be resistant to a multitude of drugs simultaneously. They can ensure that the drugs do not locate their target by keeping the concentration of drugs inside the cell low. This has led researchers to focus on efflux pump inhibitors (EPIs) which could be administered together with antibiotics. This co-formulation that regenerates the power of older drugs has potential to decelerate the onward transmission of resistance (Blair et al., 2020). Various bacterial species and their resistance mechanisms is show in **Table 1.**

Table 1: Mechanisms of Antibiotic Resistance

Bacterial Species	Resistance Mechanism	Antibiotics Affected	Reference
Escherichia coli	Efflux pump (AcrAB–TolC, RND family)	Fluoroquinolones, β-lactams, tetracyclines	Jang et al., 2023
Staphylococcus aureus	Efflux pump (MFS: SA09310)	Tetracyclines, macrolides, chloramphenicol	Islam et al., 2021
Klebsiella pneumoniae	Carbapenemase (KPC-type β-lactamase)	Carbapenems, cephalosporins	Du et al., 2018
Acinetobacter baumannii	PACE efflux (AceI protein)	Chlorhexidine, biocides	Zhao et al., 2022
Neisseria gonorrhoeae	Efflux pump (NorM, MATE family)	Fluoroquinolones, macrolides	Yin et al., 2023
Pseudomonas aeruginosa	RND efflux (MexAB–OprM)	Carbapenems, aminoglycosides, fluoroquinolones	Nishino et al., 2021
Enterobacter cloacae	AmpC β-lactamase	Penicillins, cephalosporins	Du et al., 2018
Mycobacterium tuberculosis	Target modification (rpoB mutation)	Rifampicin	Blair et al., 2020
Streptococcus pneumoniae	Target modification (altered PBPs)	Penicillin, cephalosporins	Blair et al., 2020
Salmonella enterica	Efflux pump (AcrAB–TolC, RND family)	Fluoroquinolones, tetracyclines	Du et al., 2018
Enterococcus faecium	VanA-mediated modification	Vancomycin	Blair et al., 2020
Clostridioides difficile	Efflux pump + ribosomal protection	Macrolides, fluoroquinolones	Nishino et al., 2021
Proteus mirabilis	Extended-spectrum β-lactamases (ESBLs)	Cephalosporins, penicillins	Du et al., 2018

Table 1: Contd.,

Helicobacter pylori	Efflux pumps + target mutation	Clarithromycin, metronidazole	Nishino et al., 2021
Serratia marcescens	MacAB–TolC (ABC transporter)	Macrolides, aminoglycosides	Greene et al., 2018
Campylobacter jejuni	Efflux pump (CmeABC, RND family)	Macrolides, fluoroquinolones	Du et al., 2018
Haemophilus influenzae	β-lactamase production	Ampicillin, amoxicillin	Blair et al., 2020
Legionella pneumophila	Efflux + decreased permeability	Macrolides, fluoroquinolones	Nishino et al., 2021
Shigella flexneri	Plasmid-mediated ESBLs + efflux	Cephalosporins, fluoroquinolones	Blair et al., 2020
Streptomyces coelicolor	MFS efflux (SCO4121)	Ciprofloxacin, chloramphenicol	Burata et al., 2022

ANTIBIOTIC RESISTANCE BACTERIA

MRSA

MRSA is a well-known "superbug" which is resistant to methicillin and many other antibiotics, and over time strains referred to as community-associated MRSA (CA-MRSA) have spread outside of hospitals, where in the USA a strain referred to as USA300 carrying SCCmec type IV and genes for PVL toxin has become dominant over older USA400 types (Garcia-Cobos et al., 2025) while in recent surveillance data CA-MRSA rates and PVL positivity have changed over time (Ding et al., 2024). On the other hand, Pseudomonas aeruginosa is predominantly a pathogen that is hospital-associated, thrives in moist environments such as sinks and respiratory equipment, and is a major cause of pneumonia or blood infections (Sathe et al., 2023), and in patients suffering from cystic fibrosis, it can form biofilms, which make it more difficult to kill it and cause multidrug resistance over time (Elfadadny et al., 2024). Community-acquired infections by *P. aeruginosa* are rare, but if they occur, many isolates are still sensitive to strong antibiotics such as high sensitivity to meropenem and ceftazidime (Esfahani et al., 2024).

Vancomycin-Resistant Enterococci (VRE)

Enterococci that are resistant to vancomycin (VRE) were first discovered in the late 1980s, and in large part this may be attributed to the application of avoparcin as livestock feed. In 1997, the European Union prohibited the use of an analog of vancomycin named avoparcin that subsequently led to a large reduction in VRE cases in livestock and human vectors (Simm et al., 2019). Contemporary epidemiology demonstrates that VRE are turned out to be mostly nosocomial, which is associated with the exposure to the antibiotics in the past, the presence of indwelling medical devices, malignancy, and immune suppression (Ahmed et al., 2018). Enterobacteriaceae having a long spectrum 2 -lactamase-positive organism pose one of the leading sources of antimicrobially resistant infections in the community. The most widely disseminated ESBL in the world is CTX-M genotype, and a ST131 E. coli clonal family has developed to be the most frequent to be linked with the community-acquired ESBL infections (Chen et al., 2019; Liu et al., 2019). ESBL producing E. coli has been a frequent etiologic agent of community infection particularly in Asia. This has seen the clinical usage of carbapenems that was initiated by the usage of a considerable portion of cephalosporin resistance exhibited by these organisms (Liu et al., 2019).

Carbapenem-Resistant Acinetobacter Baumannii (CRAB)

Acinetobacter baumannii (A. baumannii) is a Gram-negative bacterium, the probability of which is high to be involved in nosocomial infections, particularly those that happen in institutions with intensive units (Jiang et al., 2022). Consequently,

the rate of antimicrobial resistance in carbapenem-resistant A. baumannii strains (Carbapenem-Resistant A. baumannii, CRAB) is very high and it has been spreading as a pandemic in Asia and there is little effective treatment proposal of colistin or tigecycline (Li et al., 2025). The cases of A. baumannii of community origin are not very common but reported in tropical regions of Asia and in the North of Australia (Yassin et al., 2020).

The primary mechanisms of resistance are carbapenemases, e.g., OXA -2 -lactamases and (in some cases) metallo -lactamases (Quyen et al., 2025; Bae et al., 2024). A national survey conducted in China also reported that isolates of A. baumannii that cause community-onset pneumonia were not susceptible to imipenem and meropenem (Bae et al., 2024). On the other hand, carbapenem resistant Escherichia coli has been on the increase, and in particular, the ST131 clonal strain; it has been reported that approximately 20 percent of clinical E. coli isolates in India are metallo- beta -lactamase carriers such as bla NDM-1 independent of ST131 (Bonnin et al., 2012). The transmission of carbapenem resistance to the given organisms on cellular level is a serious problem that should be tackled immediately; one will have to take certain measures that will revolve around withstanding the bacteria and the introduction of the most powerful and efficient interventions.

Methicillin-Resistant Staphylococcus Aureus

Staphylococcus aureus is a Gram-positive round bacterium responsible for a variety of serious diseases: skin and soft tissue infection, pneumonia, blood stream infection and medical device infections. MRSA (methicillin-resistant S. aureus) is the designation given to strains which are resistant to many b-lactam antibiotics. Originally, resistance to penicillin in S. aureus developed in the oral bacteria by synthesizing penicillinase, thought to be an enzyme that breaks the b-lactam ring (Lade et al 2023). Methicillin (a penicillin derivative) was introduced to get around that, but MRSA strains acquired a new gene - mecA, which was carried on the SCCmec element. mecA encodes a modified penicillin-binding protein, PBP2a, that binds poorly to b-lactam antibiotics and helps the cell wall synthesis to continue even when b-lactam antibiotics are present (Rosado et al., 2025; Li et al., 2025). This change is so that the b-lactams can no longer stop S. aureus. Recent structural and dynamic studies are improving our understanding of how PBP2a functions and how it can be inhibited (Jiao et al., 2023; Adedeji-Olulana et al., 2024).

Ampicillin/Penicillin and Cephalosporin Resistance Enterococcus Faecium

Vancomycin-intermediate S. aureus (VISA) and vancomycin-resistant S. aureus (VRSA) are identified as a result of methicillin-resistant S. aureus (MRSA) through unique resistance mechanisms. Vancomycin resistant staphylococci (VISA) isolates usually have no exogenous resistance determinants; rather, they evolve thick cell walls that accumulate extra D-Al-D-Al residues that act as "decoy" binding sites that trap vancomycin before it can bind to the actual target sites (Gardete& Tomasz, 2014; Tawfeek et al., 2024).In contrast, VRSA resistance is associated with acquisition of the vanA gene cluster, which is presumably transferred from vancomycin-resistant Enterococci (VRE). The vanA operon further alters the terminal D-Ala-D-Ala of peptidoglycan precursors to D-Ala-D-Lac, which reduces by approximately 1,000-fold the affinity of binding to vancomycin (Gardete& Tomasz, 2014; Brdova et al., 2024).

VRSA remains an infrequent event but it does have the potential for horizontal spread which is of major concern (Tawfeek et al., 2024; Brdova et al., 2024).Enterococcus faecium is a Gram- positive cocci of family Enterococcaceae. Its resistance to the action of beta-lactam antibiotics, including the group of penicillins and cephalosporins is due mainly to the presence of a chromosomal gene pbp5, which encodes a class of beta-lactam penicillin-binding proteins (PBPs) 5,

which has a low affinity for beta-lactams, which allows these bacteria to survive despite the inhibition of other PBPs (Hunashal et al, 2023). Variants of PBP5 can develop mutations - insertions, deletions and rearrangements of DNA loops - that further reduce beta-lactam binding and consequently increase resistance levels (Hunashal et al., 2023).

Ampicillin/Penicillin and Cephalosporin Resistance Enterococcus Faecium

In addition, cephalosporin resistance is also contributed by regulatory systems. The CroRS two-component system detects cell wall stress and responds by activating defence mechanisms (Kellogg &Kristich, 2017). The serine/threonine kinase IreK and IreP (phosphatase) modulate the resistance to beta-lactam antibiotics through the phosphorylation of proteins involved in cell wall synthesis (Iannetta et al. 2021). Moreover, the protein GpsB is responsible for the signalling of IreK, thus increasing cephalosporin resistance (Minton et al., 2022). Recent genomic investigations confirm that both the sequence context of psr and pbp5 and associated regulatory elements modulate the extent of the beta-lactam resistance exhibited by E. faecium (Singh et al., 2013).

E. Faecium (Vancomycin-Resistant)

Enterococcus faecium is a gram-positive bacterium which carries an extrachromosomal genetic constituents, especially in the form of plasmids. These plasmids belong to different families, and most of the families have a transposon similar to Tn1546. Such elements are the basis of the ability of the bacterium to gain vancomycin resistance (Almeida-Santos et al., 2025; Kim et al., 2024).Vancomycin normally attaches to the end of peptidoglycan precursors containing D -alanine -D -alanine (D -Ala -D -Ala) motifs, thus blocking the cell-wall synthesis. VanA, vanB, vanD, vanM of the resistance determinants evade this blockade by substituting D -Ala -D -Ala with D -alanine -D -lactate (D -Ala -D -Lac). This biochemical replacement significantly lowers the binding affinity of vancomycin, lowering its antibacterial activity (Islam et al., 2023; Huang et al., 2024). The strongest resistance determinant that has beenseen to date is the vanA cluster that is often present on Tn1546-carrying plasmids (Huang et al., 2024).

LATEST STRATEGIES AGAINST DRUG-RESISTANT MICROORGANISMS

New Antibiotics

There is also active research on the development of new antibiotic agents against drug-resistant pathogenic bacteria. It was found in 2015 with one of them, Teixobactin. The effect of this compound on Gram-positive bacteria relies on the interaction with lipid precursors, which can be a component of cell-wall biosynthesis and disrupting the cytoplasmic membrane and reducing the risk of developmental resistance (Ling et al., 2015; Shukla et al., 2022). Lefamulin is an antibiotic of the pleuromutilin-class that was discovered in 2019 and applied to treat community-acquired pneumonia. The drug is reported to interact with the ribosomal subunit, and thereby, inhibit translational elongation and inhibit the amino acid incorporation using transfer RNA (Theuretzbacher et al., 2020).

Preclinical trials of Zoliflodacin are underway as a treatment of multidrug-resistant Neisseria gonorrhoeae. It interrupts the process of DNA replication and, therefore, offers a new treatment to the strains of gonococcal infection that are resistant to the usual antibiotics (Taylor et al., 2018). Cefiderocol is siderophore cephalosporin which exploits the bacterial iron- uptake systems to access Gram-negative pathogens and the medication subsequently destroys their peptidoglycan. The antibiotic has been demonstrated to be effective with regard to treating bacterial isolates which have become resistant to carbapenem (Wang et al., 2022; Viale et al., 2023). The viruses infecting bacteria are called bacteriophages and discharges the enzymes known as lysins (also known as endolysins) that cuts elements of bacterial cell

wall, thus, resulting in osmotic lysis and death (Kim et al., 2025). Recently, a bid to make these lysins more effective and strain or species-specific has ensued in a struggle to use them in some cases against bacteria that are resistant to some conventional antibiotics (Eghbalpoor et al., 2024; Shah et al., 2023). It should be mentioned that engineered lysins can be introduced into the market more quickly than conventional development pipelines on antibiotics (Pottie et al., 2024).

Bacteriophages

Phage therapy, a form of biotherapy that involves the use of intact bacteriophages to eliminate bacterial populations, takes advantage of the specificity of phages in which a single phage can target a specific bacterial strain and not the commensals. The empirical studies show that phage therapy has demonstrated positive results in situations where antibiotic resistance is a serious constraint (Kim et al., 2025).However, there are still a number of difficulties. The bacteria can also develop resistance against the lysins as well as phages. Furthermore, the erosion of big population of bacteria can lead to the simultaneous liberation of endotoxins, hence, triggering inflammatory events or other harmful outcomes (Turner et al., 2024).Other issues related to phage therapy are the selection of the best phage under a particular clinical scenario, phages stability and viability on the host and complex regulation mechanisms involving individual treatment measures (Kline et al., 2025; Youssef et al., 2025).A synergistic strategy is achieved through a combinatorial approach which includes antibiotics, bacteriophages and lysins, where each modality kills different components of bacteria and functions through different mechanisms, thus improving antibacterial action and preventing resistance development (Kim et al., 2025; Kocot et al., 2023).

Combination Therapy

The combination antibiotic therapy is the use of two or more antimicrobial agents the effects of which are mediated by various pharmacodynamic processes. This approach aims at attacking a variety of bacterial pathways simultaneously, and it is harder to develop resistance to pathogenic organisms (Sargianou et al., 2025). One such strategy is a combination of trimethoprim and sulfamethoxazole (TMPSMX) which is highly proven. Trimethoprim acts on dihydrofolate reductase and sulfamethoxazole on dihydropteroate synthase and the two medications inhibit two of the four steps in the folate biosynthetic pathway. TMP-SMX is frequently prescribed in the treatment of infections of the respiratory tract, urinary tract and other infectious pathogens, methicillin-resistant Staphylococcus aureus (MRSA), and some opportunistic bacteria (Nakamura et al., 2025). A second and more widely administered group is a 2-lactam antibiotic (ampicillin or piperacillin) in combination with a 2-lactamase inhibitor (clavulanic acid, sulbactam or tazobactam). The inhibitor inhibits hydrolysis of 2 -lactamases therefore preserving the chemical structure and antimicrobial activity of the 2 -lactam core. The presence of b -lactamase enzymes can also be treated using anti-bacterial agents such as ampicillin/sulbactam and piperacillin/tazobactam (Sargianou et al., 2025). Immune modulation denotes the enhancement of native host defence and hence, enhancement of extinction of bacterial infections. The particular relevance of such strategy is associated with the times of the rising opposition of antibiotics, which complicates therapeutic regimes. One of the mechanisms of action is the administration of immunomodulatory cytokine; interferon-7 (IFN -7) induces the activation of macrophages, which expands the capacity of this cell type to kill bacteria and the overall efficiency of the entire host immune system (Casanova et al., 2024). In the treatment of mycobacterial infections, including tuberculosis and non-tuberculous mycobacterial disease, IFN -7 has also been used in the adjunct treatment of the host immune system (Casanova et al., 2024).

Immune Modulation

Another intervention is the use of interventions based on vaccines. The antigens of specific bacteria are induced on the immune system in advance by the immunization programs before the disease takes place thereby preventing the disease. It has been associated with the decrease in the incidence of antibiotic-resistant pneumonia in different regions when vaccinated against Streptococcus pneumoniae (Zavaleta -Monestel et al., 2024). This means that the reduction of the burden of infections reduces the amount of antibiotics and halts the transmission of antimicrobial resistance as well (Johnson et al., 2023). The presence of immunostimulatory cytokines, including granulocyte -colony stimulating factor (G -CSF) enhances the growth of leukocytes. The multiplication in the figure of the immune effector cells may accumulate the immunity of the host to infectious complications. Despite the fact that these agents do not substitute the means of antibiotic therapy, they may reinforce immune reaction and decrease reliance on antimicrobials (Mezouar et al., 2020).

Antibody Therapy

The antibody therapies use engineered monoclonal antibodies (mAbs) or antibody-derived molecules to specifically bind and neutralize pathogenic bacteria. These agents work in a similar manner to precision-guided munitions, which may help reduce the use of broad-spectrum antibiotics. One of the bright examples of therapy success is bezlotoxumab human mAb that binds Clostridioides difficile toxin B and helps to avoid C. difficile infection recurrence (Johnson et al., 2019). It does not attack the microorganism, but its exotoxin, which saves the native microbiome and minimizes selection pressure against resistance (Denny et al., 2024). Regarding the case of the Staphylococcus aureus, specifically, the methicillin-resistant Staphylococcus ℕMRSA, researchers are developing antibody-fusion constructs that bind to multiple bacterial antigens, which enhances the host immune response and allows infection clearance (Multivalent mAb-centyrin fusion, 2023). The use of this type of multimodal designs is meant to overcome the antigenic heterogeneity of staphylococcal pathogens (Outsmarting pathogens with antibody engineering, 2023). Another approach is antibody -toxin conjugates, in which a monoclonal antibody is used to target a cytotoxic agent to pathogenic bacteria. An example is a new monoclonal antibody, WVDC-5244, that was effective in mouse models of infection with Pseudomonas aeruginosa, allowing the process of eliminating bacteria with the help of macrophages (Frontiers, 2023).

The lysibodies are engineered antibody constructs that have been designed to bind to conserved bacterial wall components by a wide range of taxa, thus increasing the breadth of targets, and retaining the high specificity (Outsmarting pathogens with antibody engineering, 2023). Though these antibody-based therapies have potential, they are facing numerous drawbacks: the target-site mutations can neutralize the efficacy, their potency can be neutralized by immune-mediated clearance of the therapeutic antibody, and the high cost of recombinant production is a major impediment to clinical implementation.

Nanotechnology

Nanotechnology in antimicrobial therapy uses very small particles (nanoparticles) to fight infections in new ways. Because they are tiny, they can directly damage bacterial cell membranes, causing the bacteria to burst (Khalifa et al., 2025). Some, like silver nanoparticles (AgNPs), also release silver ions that interfere with bacterial DNA, proteins, and enzyme systems (Rodrigues et al., 2024; Khalifa et al., 2025).Under light or in certain conditions, some nanoparticles produce reactive oxygen species (ROS)—highly reactive molecules that damage many parts of the microbe (Mondal et al., 2024). These ROS include singlet oxygen, hydroxyl radicals, and others.Nanoparticles can prevent or break apart biofilms—protective

layers that bacteria build. They may interfere with signaling (quorum sensing), block early attachment, or weaken the biofilm matrix (Parvin et al., 2025).

They are also used as drug delivery systems: loading antibiotics inside nanoparticles allows targeting delivery to infection sites, protecting the drug, and reducing side effects (Obeid et al., 2025).Advantages include broad-spectrum activity (against bacteria, fungi, viruses), multiple ways to kill microbes (making resistance harder), better delivery of poorly soluble drugs, and lower damage to healthy tissues. Challenges remain: ensuring nanoparticles are safe to human cells (biocompatible), expensive production, targeting specificity (so beneficial microbes are spared), regulatory approval, and possible environmental harm or unintended ecological impact (AlQurashi et al., 2025; Obeid et al., 2025).

CONCLUSION AND FUTURE PERSPECTIVES

AMR is a major menace to modern medicine that is enduring and threatening. The repertoire of resistance mechanisms that have been developed in bacterial populations such as intrinsic resistance and active efflux pumps undermine the therapeutic efficacy of first-line antimicrobial agents. Clinical implications of these mechanisms include the pathogenic potential of methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE), carbapenem-resistant Acinetobacter baumannii, extended-spectrum 2 -lactamase (ESBL)-producing Escherichia coli, and vancomycin-resistant Staphylococcus aureus. By depicting the international spread of multidrug resistance in both healthcare and the community, these organisms threaten the efficacy of the existing therapeutic modalities.Although these issues have been noted, there has been a positive but tentative news in the recent past. New antibiotics such as teixobactin, lefamulin, zoliflodacin and cefiderocol are the potential additions to the therapeutic armamentarium, as they have novel mechanisms which can delay the development of resistance. In addition to the traditional pharmacotherapy, new approaches like bacteriophage therapy, lysins, antibody-based therapeutics, immune modulation and nanotechnology-based interventions provide target and complementary approaches. The combination therapy and efflux pump inhibitors do not lose their relevance as the methods to renew the effectiveness of the already existing antibiotics.Forward planning suggests that effective AMR management will require the use of a multi-dimensional approach. To begin with, studies should continue to look into the next-generation antimicrobials and resistance-modifying adjuvants. Second, the development of rapid diagnostic means will make it possible to use the personalized therapy in order to decrease the misuse of antibiotics. Third, greater adoption of non-traditional strategies, such as vaccines, immunostimulants, and precision biologic, will enable the withdrawal of the significant dependence on antibiotics. Lastly, international surveillance, stewardship programs and aligned policy actions are still important to track the trends in resistance, curb misuse and equitable access of new therapies. In the end, the prevention of AMR will not only rely on the scientific development but also on the long-term international cooperation on the clinical, agricultural and environmental levels. The medical community can slow the development of resistance and save the antibiotics to the next generation by aligning new therapeutic interventions with stewardship and prevention, as well.

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