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# Polymyxins: recent advances and challenges

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Antibiotic resistance is a pressing global health challenge, and polymyxins have emerged as the last line of defense against multidrug-resistant Gram-negative (MDR-GRN) bacterial infections. Despite the longstanding utility of colistin, the complexities surrounding polymyxins in terms of resistance mechanisms and pharmacological properties warrant critical attention. This review consolidates current literature, focusing on polymyxins antibacterial mechanisms, resistance pathways, and innovative strategies to mitigate resistance. We are also investigating the pharmacokinetics of polymyxins to elucidate factors that influence their *in vivo* behavior. A comprehensive understanding of these aspects is pivotal for developing next-generation antimicrobials and optimizing therapeutic regimens. We underscore the urgent need for advancing research on polymyxins to ensure their continued efficacy against formidable bacterial challenges.

KEYWORDS

**antibacterial mechanism, drug resistance mechanisms, nanotechnology, polymyxins, pharmacokinetics**

## 1 Introduction

Since the introduction of antibiotics in the last century, they have saved countless lives of patients with serious bacterial infections. In the past 50–60 years, doctors have come to expect that antibiotics would cure almost all patients with bacterial infections. However, due to the lack of early identification of the causative organisms and their antimicrobial susceptibility patterns in patients with bacteremia and severe infections in many healthcare facilities, broad-spectrum antibiotics have been heavily and mostly unnecessarily used since the 1990s (Akova, 2016). Consequently, this has led to the emergence of numerous drug-resistant bacteria and unregulated management of nosocomial infections, resulting in increased chances of transmission of drug-resistant bacteria, longer hospital stays, and higher mortality rates for patients (Akova, 2016). In 2017, the World Health Organization (WHO) added *Acinetobacter* baumannii, *Pseudomonas aeruginosa*, and *Enterobacter* species to the list of key pathogens in urgent need of new antibiotics (Mancuso et al., 2021). While medical institutions have conducted certain control and preliminary systematic evaluations of these pathogens (Tomczyk et al., 2019), the overuse and misuse of antibiotics in healthcare, agriculture, and livestock have contributed to a significant increase in antimicrobial resistance (Nadimpalli et al., 2020; Schrader et al., 2020). WHO and the U.S. Centers for Disease Control and Prevention (CDC) have recognized antimicrobial resistance as a worldwide threat. Without effective management and scaling up the supply of antibiotics, nearly 10 million people worldwide are expected to die from drug-resistant infections by 2050

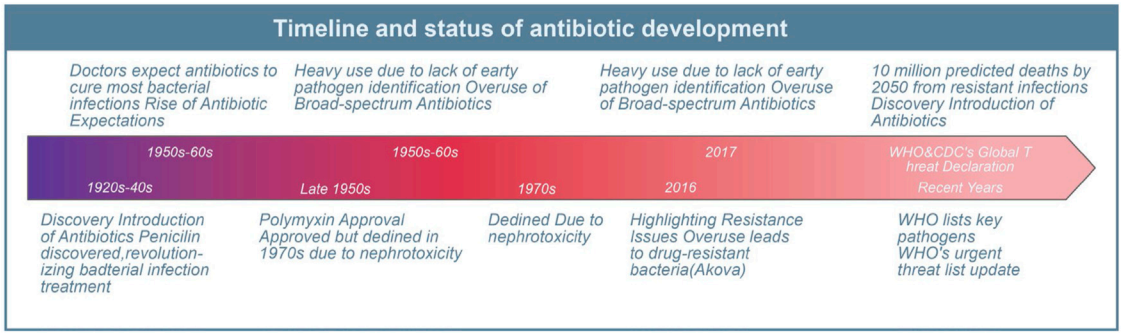


FIGURE 1
Antibiotic classification and current status of clinical resistance. This diagram illustrates the evolution and challenges of antibiotic use since its inception.

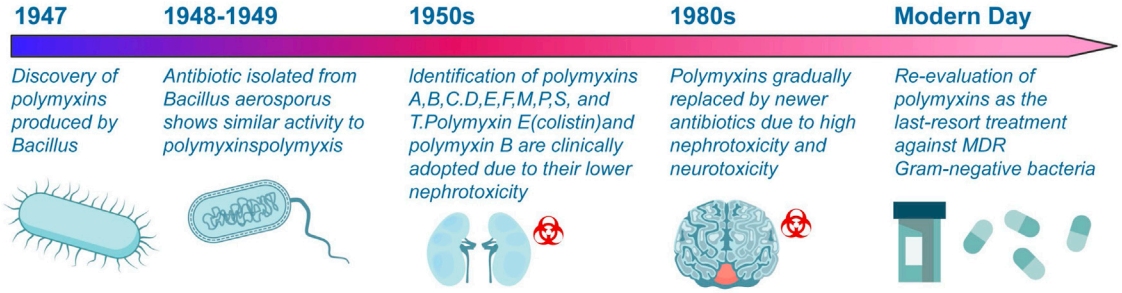


FIGURE 2
Evolution of polymyxin antibiotics. This illustration delineates the significant milestones in developing polymyxin antibiotics, from their discovery in 1947 to their contemporary relevance.

(Pulingam et al., 2022). Although the U.S. Food and Drug Administration (FDA) has approved several new antibiotics in recent years, the emergence of resistance has been reported (Abdallah et al., 2015; Giddins et al., 2018; Morrissey et al., 2020) (Figure 1). Therefore, there is an urgent global need for antimicrobials with innovative pharmacological activities and modes of action to combat the public health threat of antimicrobial resistance (Miethke et al., 2021).

Polymyxins have received increasing attention in recent years, as they are considered a potential weapon against Gram-negative drug-resistant bacteria. Polymyxin was approved in the late 1950s (Li et al., 2006). However, its usage rapidly declined in the 1970s due to its nephrotoxicity. Nevertheless, with carbapenem-resistant *Acinetobacter* baumannii (CRAB), *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* resistance rates increasing each year (Nang et al., 2021), polymyxins have been reintroduced into the clinic as a last-resort salvage treatment option for these resistant organisms (Cai et al., 2012; Doi et al., 2015). Over the past two decades, significant progress has been made in the study of polymyxins, including their chemical structure, activity/toxicity relationship, antimicrobial activity, and polymyxin resistance mechanisms. This review summarizes the history of polymyxin development and provides an overview of the mechanisms of drug resistance. Additionally, it focuses on the research conducted to overcome colistin resistance and highlights the development of new antimicrobials that have entered clinical trials. Furthermore, the review presents the latest research progress in overcoming polymyxin resistance and sheds light on the pharmacokinetic behavior of polymyxins to improve the standardization and safety of their global clinical application.

## 2 Polymyxins: from discovery to re-emergence in the era of superbugs

Polymyxins, discovered in 1947, are antimicrobial cationic polypeptides produced by *Bacillus* polymyxins (Benedict and Langlykke, 1947). Figure 2 provides a timeline highlighting the major milestones in the discovery, use, and resurgence of polymyxins. Brownlee and Bushby (1948) isolated an antibiotic from *Bacillus aerospore* that exhibited antibacterial activity against Gram-negative bacteria. In 1949, White et al. conducted a comparative study on the antibacterial activities of polymyxins and "Neosporin" and found no significant difference between them, suggesting that both substances belong to the polymyxins class of antibiotics. Consequently, a nomenclature system was established for the polymyxins family (Stansly and Brownlee, 1949). To date, polymyxin A (also known as Neosporin), B, C, D (polymyxin), E (also known as colistin), F, M, P, S, and T have been identified from *P. Polymysa* strains (Shoji et al., 1977; Niu et al., 2013). After their

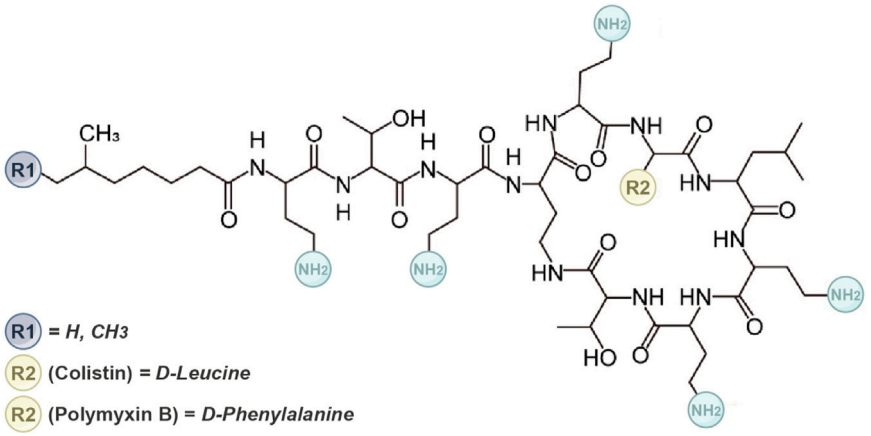


FIGURE 3
The molecular structure of the polymyxin. It outlines the structural distinctions between polymyxin B and colistin. Polymyxin B and colistin comprise five conserved L-α-γ-diaminobutyric acid (Dab) residues. These residues confer a net positive charge to polymyxin compounds at physiological pH. The cationic hydrophilicity of this macrocycle is pivotal for their antibacterial properties.

discovery, many polymyxins were found to have reversible nephrotoxicity, leading to the clinical use of colistin and polymyxin B due to their relatively low nephrotoxicity. The main market products are polymyxin B and polymyxin E, which exhibit similar antimicrobial activity (Storm et al., 1977). There are currently three polymyxin analogues for injection that have been marketed both domestically and internationally: colistin methanesulfonate (CMS) for injection, colistin sulfate and polymyxin B sulfate for injection. The blood-brain barrier passage rate of polymyxin is low, and it is difficult to achieve effective drug concentration by intravenous administration. Local applications such as intracerebroventricular or intrathecal administration have been increasingly adopted by the clinic in recent years, but there is a lack of relevant standardized operational guidelines (Yang et al., 2023). In addition, the nebulized inhalation method can significantly increase the lung tissue concentration of polymyxin while decreasing the systemic exposure level of the drug, thus achieving the goal of improving the efficacy and reducing systemic adverse effects (Tang et al., 2023). Currently, several domestic and international guidelines and consensus recommend nebulized inhalation of polymyxin as one of the important therapeutic methods for multidrug-resistant gram-negative (MDR-GRN) bacterial induced pneumonia (Lin et al., 2022).

Polymyxin is a cyclic lipopeptide compound composed of 10 amino acids, characterized by a cationic polypeptide consisting of a cyclic heptapeptide and a tripeptide side chain (Rutten et al., 1990; Falagas et al., 2010). The primary difference between PMB and colistin lies in the amino acid variation at position 6 (R2), where PMB contains phenylalanine and colistin contains leucine (Figure 3) (Velkov et al., 2010; Nation et al., 2014). They have similar antimicrobial effects. Compared to the parent antibiotics, sulfomethyl derivatives of polymyxins exhibit lower toxicity and similar *in vivo* antibacterial activity. Consequently, sulfonated derivative polymyxin E has been commercially available for clinical use in Japan, Europe, and the United States since the 1950s. Conversely, colistin methanesulfonate sodium, an antibacterial active component covered by sulfate, lacks inherent antibacterial activity and serves as a precursor drug that exhibits bactericidal effects. However, CMS was gradually replaced by newer antibacterial drugs in the 1980s due to its high nephrotoxicity and neurotoxicity. Importantly, commercial polymyxin B, CMS, and colistin products are mixtures (Govaerts et al., 2002), leading to batch-to-batch differences in the abundance of individual ingredients.

With limited antibiotic options available, the increasing bacterial resistance in clinical settings has necessitated the re-evaluation of "old" antibiotics, particularly polymyxin, which has shown effectiveness against many MDR Gram-negative bacteria. Polymyxins have been used in clinical practice for approximately 60 years, with polymyxin B and colistin now considered last-resort treatment options for infections caused by "superbugs."

## 3 Deciphering the multimodal antibacterial strategies of polymyxins

Understanding the mode of action of polymyxins is crucial for optimizing their use and developing new antibiotics. Polymyxin B and colistin, having similar chemical structures, exhibit comparable antibacterial mechanisms primarily against common Gram-negative bacteria (Kwa et al., 2007). Colistin demonstrates a narrow spectrum of antibiotics but shows activity against several clinically significant MDR Gram-negative bacteria, such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter*, and other enterobacteriaceae (Bialvaei and Samadi Kafil, 2015; Poirel et al., 2017; Doymaz and Karaaslan, 2019).

Both colistin and polymyxin B exert their effects on the bacterial membrane, causing damage. The outer membrane of Gram-negative bacteria serves as protection against various harmful substances, including antimicrobials. Extensive studies have demonstrated that polymyxins exerts its antibacterial effect by directly interacting with the lipid components of lipopolysaccharide (LPS), disrupting

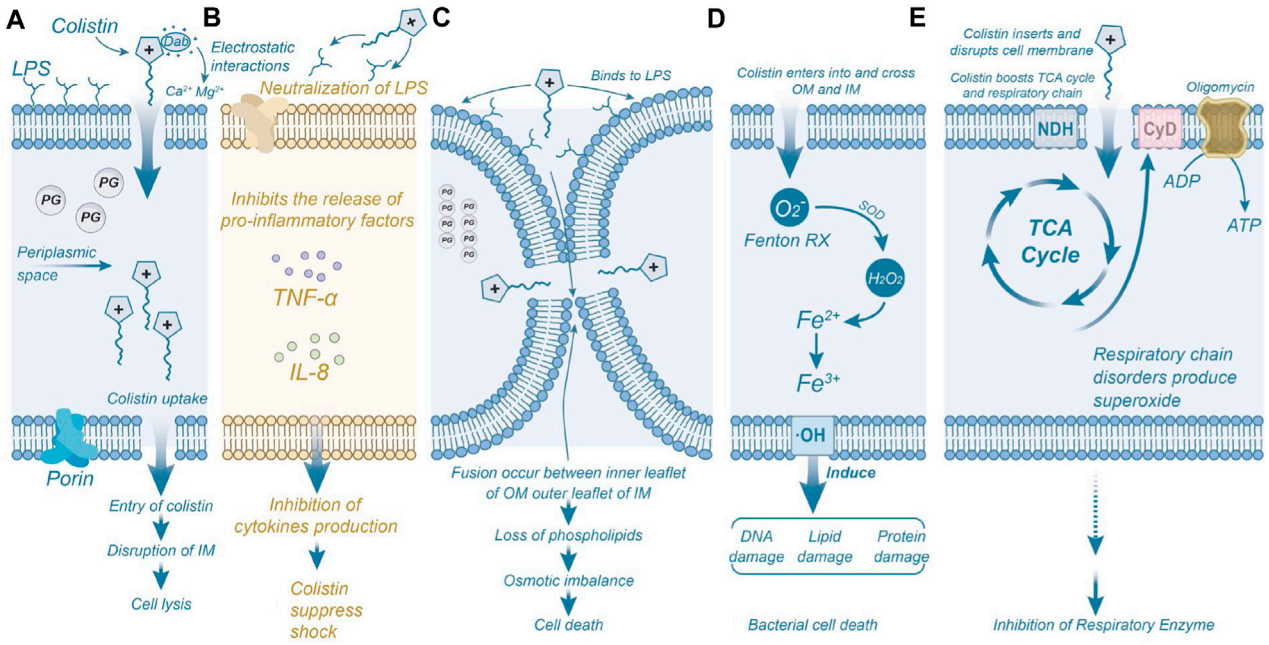


FIGURE 4
Mechanisms of Polymyxins-Induced Bacterial Inhibition and Death. **(A)** The Dab residue of colistin interacts electrostatically with the anionic phosphate group in the outer membrane of bacteria, resulting in structural disruption of the bacterial membrane. **(B)** Colistin neutralizes the activity of LPS molecules, inhibiting the induction of shock and consequent release of cytokines by immune cells, such as tumor necrosis factor-α and interleukin 8. **(C)** Colistin binds to phospholipids on the outer membrane of bacteria, causing depletion of phospholipids and leading to bacterial death. **(D)** Colistin triggers the production of reactive oxygen species (ROS) that damage DNA, lipids, and proteins, ultimately resulting in bacterial death. **(E)** Colistin inhibits the activity of respiratory enzymes. Permission to reproduce adapted from reference (El-Sayed Ahmed et al., 2020) has been obtained.

bacterial membranes (Nikaido, 2003). Electrostatic interactions occur between the positively charged α, γ-aminobutyric acid (Dab) residues of polymyxin and the phosphoric acid groups on the bacterial membrane, competitively displacing divalent cations ($Ca^{2+}$ and $Mg^{2+}$) through the negatively charged phosphoric acid groups in the lipid membrane (Dixon et al., 1986). In addition, polymyxins can neutralize endotoxins and inhibit the expression of cytokines such as TNF-α and IL-8, preventing tissue damage caused by excessive activation of inflammation (Schromm et al., 2021). Polymyxins binds to LPS through electrostatic and hydrophobic interactions (Velkov et al., 2010). Consequently, LPS becomes unstable, increasing bacterial membrane permeability, leading to the leakage of cytoplasmic contents and, ultimately, bacterial death (Schindler and Osborn, 1979; Falagas and Kasiakou, 2005). While the primary model for polymyxin's antimicrobial activity involves the destruction of the bacterial adventitia and intima, additional mechanisms have also been proposed (Figure 4).

Another mechanism of polymyxin action is the inhibition of type II NADH-quinone oxidoreductase (NDH-2) activity, a significant respiratory enzyme in the bacterial inner membrane (Deris et al., 2014). After entering the bacteria, polymyxin inhibits the respiratory enzymes of the tricarboxylic acid (TCA) cycle and consumes ATP, leading to bacterial death. Studies have demonstrated that polymyxins inhibits NDH-2 activity in a concentration-dependent manner in various Gram-negative bacteria, including *Escherichia coli*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii* (Mogi et al., 2009). These events are accompanied by activation of repair pathways and adventitial remodeling (Moffatt et al., 2019). Additionally, some researchers propose that most antibiotics induce bacterial death by perturbing bacterial metabolism, leading to increased production of reactive oxygen species (ROS), including superoxide ($O_2^-$), hydrogen peroxide ($H_2O_2$), and hydroxyl radicals (-OH), ultimately causing bacterial demise (Kohanski et al., 2007). Leveraging this property, many researchers have designed antimicrobial agents that promote bacterial death by stimulating the production of hydroxyl radicals through the Fenton reaction (Yeom et al., 2010). Elevated levels of hydroxyl radicals within bacteria can damage bacterial DNA, lipids, and protein synthesis, resulting in bacterial death (Dwyer et al., 2014). These findings indicate the importance of hydrophobic interaction in the antibacterial mechanism of polymyxin (Hancock, 1997).

## 4 Unraveling the complex web of polymyxin resistance: mechanisms, challenges, and countermeasures

The escalating issue of antibiotic resistance poses a significant threat to human health, particularly with the emergence of resistance in *Enterobacteriaceae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* against almost all available antibiotics. Such MDR bacteria are commonly found in intensive care units and among long-term hospitalized patients. Despite their potent bactericidal activity against many Gram-negative bacteria, the extensive use of polymyxins has led to the emergence of

TABLE 1 Bacteria resistant to polymyxins and their resistance gene.

| Bacteria | Resistance mechanisms | Gene | References |
|---|---|---|---|
| *A. baumannii* | Modifications of the LPS moiety | *pmr*A, *pmr*B, *pmrC*, *mcr* | Snitkin et al. (2013), Cheah et al. (2016), Lima et al. (2018) |
| *A. baumannii* | lipid A deficiency | *lpx*A, *lpx*C, and *lpx*D | Bojkovic et al. (2015), Jeannot et al. (2017), Sherry and Howden (2018) |
| A. baumannii | Changes in membrane permeability and Efflux pump systems | *lps*B, *lpt*D, and *vac*J | Hood et al. (2013), Whitfield and Trent (2014), Thi Khanh Nhu et al. (2016) |
| *Helicobacter pylori* | Modifications of the LPS moiety | *Cgt, ompD* | Sato et al. (2018) |
| *Neisseria meningitidis* | Efflux pumps | *por*B | Tzeng et al. (2005) |
| *Yersinia enterocolitica* | RosA/RosB efflux pump/potassium antiporter system | *RosA* and *RosB* | Bengoechea and Skurnik (2000) |
| *Pa. polymyxa* | Inactivates colistin | Unknown | Sampson et al. (2012), Deris et al. (2014) |
| *P. mirabilis* | LPS modification | *Proteus pmrI* gene | Jiang et al. (2010) |
| *S. marcescens* | LPS modification | *arn*B and *arn*C | Lin et al. (2014) |
| *K. pneumoniae* | Overexpression of PhoP/PhoQ, Inactivation of the *mgrB* gene | ColR/ColS, *blaCTX-M-15 ESBL* gene | Gutu et al. (2013), Cannatelli et al. (2014), Jayol et al. (2015a), Jayol et al. (2016), Nordmann et al. (2016) |
| *Klebsiella pneumoniae* | Reduces the affinity of antibiotics for cells | *mgrB* gene | Jayol et al. (2015b), Yap et al. (2022) |
| *Aeromonas spp* and *Escherichia coli* | *mcr*-variant of the plasmid-mediated | *mcr*-variant | Belaynehe et al. (2018), Gonzalez-Avila et al. (2021) |
| *P. aeruginosa* | LPS modification operon | *ParR/ParS* | Fernandez et al. (2010) |
| *V. cholera* | LPS biosynthesis and modification | *gspIEF, lpxN, vc0224/0239/1981* | Mlynarcik and Kolar (2019) |
| *Haemophilus influenza* | Lipooligosaccharide modifications | *lic1/2A, lpsA, lgtF, opsX* | Morey et al. (2013) |

polymyxin-resistant strains, including *Neisseria meningitidis*, *Proteus mirabilis*, and *Burkholderia* spp. (Tzeng et al., 2019). Notably, nosocomial infections caused by MDR *Pseudomonas aeruginosa*, *Acinetobacter baumannii,* and *Klebsiella pneumoniae* are closely associated with increased morbidity and mortality, and their resistance to polymyxins has attracted significant attention (Barbier et al., 2013; Bassetti et al., 2018).

In this section, we present a systematic review of recent discoveries on the mechanisms of polymyxin resistance. In recent years, antibiotic resistance genes have become one of the greatest threats to human health in the 21st century. *mcr*-1, the first plasmid-mediated polymyxin resistance gene, was discovered in China in 2015, indicating that the last line of defense has also been breached, further exacerbating the threat of bacterial resistance to public health. Table 1 summarized the resistant bacteria and resistance genes to polymyxins in recent years. Some of the more attention-grabbing, classical mechanisms of polymyxin resistance are summarized in Figure 5. The phosphoethanolamine (pEtN) transferase encoded by *mcr*-1 delivers pEtN from the cell membrane through modification of lipid A, leading to colistin resistance (Figure 5A). This modification reduces the affinity of polymyxin for lipopolysaccharides, as depicted in Figure 5B (Needham and Trent, 2013; Liu et al., 2016). In addition to colistin resistance, *mcr* mediates bacterial resistance to antimicrobial peptides (AMPs). The amphiphilic structure of AMPs enables them to penetrate bacterial cell membranes, forming pores and disrupting the integrity of the cell membrane, leading to lysis and death of the bacteria (Nang et al., 2021; Rodriguez-Santiago et al., 2021). The emergence of the plasmid-mediated colistin resistance gene *mcr*-1 has attracted global attention and prompted several countries to adjust their policies on the use of colistin in food and animals. Currently, researchers have conducted extensive studies on the distribution, function, mechanism of action, transmission vectors, and origin of *mcr*, as well as prevention and control strategies for *mcr*-positive bacteria (Liu et al., 2024). Some researchers have recently identified the problem of polymyxin resistance mediated by multiple *mcr* gene plasmids (Liu et al., 2016; Schwarz and Johnson, 2016). Certain environments, such as hospitals with a high potential for transmission of resistant bacteria through food or surfaces, as well as heavily contaminated surface water, can serve as reservoirs for various infections.

It has also been observed that the conditions of the medium influence the sensitivity of some bacteria to polymyxins. *Salmonella enterica* cells lacking carbon, nitrogen or phosphate ions, and serum and quiescence cells exhibit reduced sensitivity to polymyxin (Figure 5C) (McLeod and Spector, 1996). An alternative mechanism involves the activation of the *pmrA* genes in *Salmonella typhimurium*, triggered by low levels of $Mg^{2+}$ ions. It decreases the lipopolysaccharide molecule's negative charge and subsequently reduces polymyxin's binding affinity (Groisman et al., 1997), as depicted in Figure 5D.

Previous studies have demonstrated that the resistance mechanism in most Gram-negative bacteria is associated with structural changes in lipopolysaccharides (Moore et al., 1984; Pelletier et al., 2013). Bacteria can develop resistance to

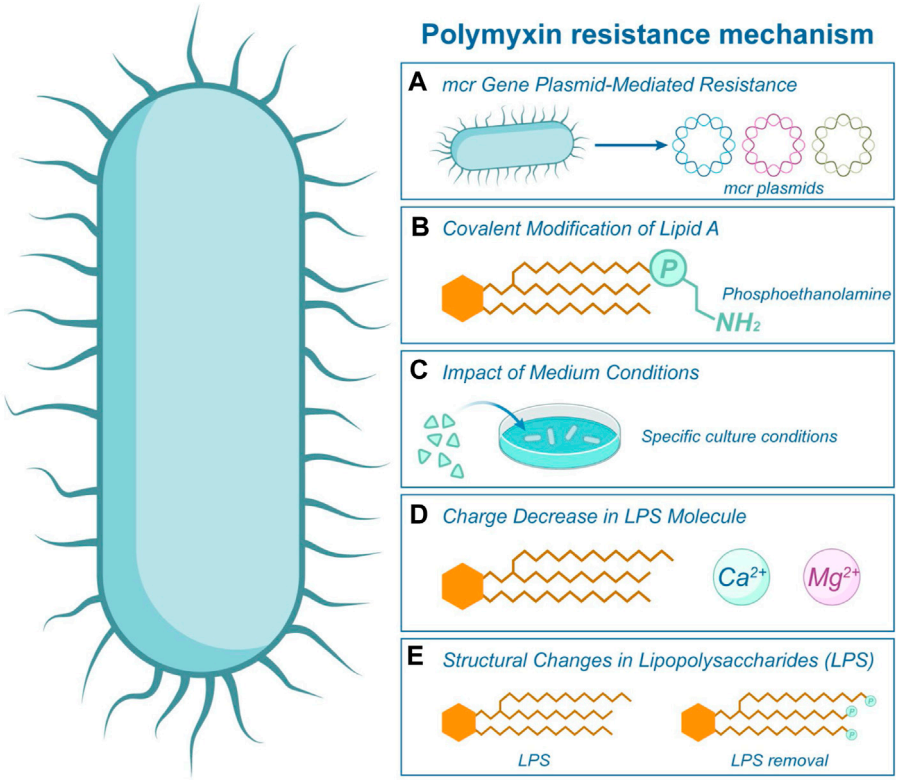


FIGURE 5
Polymyxin Resistance Mechanism. This illustration showcases the various mechanisms by which bacteria develop resistance to polymyxin. Central to this resistance is the structure of Lipopolysaccharide (LPS) present in the bacterial cell, as highlighted in figure. **(A)** The *mcr* gene on bacterial plasmids facilitates the primary resistance mechanism, as depicted by the label *mcr* in the image. Furthermore, resistance can arise from covalent modifications to Lipid A **(B)** or structural alterations in the LPS **(E)**. The efficacy of polymyxin is further diminished by the reduced charge on LPS **(D)**, especially when it interacts with cations such as $Mg^{2+}$. **(C)** The growth medium conditions in which bacteria reside can also influence their susceptibility to polymyxin.

polymyxin either by modifying the phosphate group of lipid A or by directly removing LPS (Moffatt et al., 2010; Olaitan et al., 2014), as depicted in Figure 5E. For instance, in the presence of high concentrations of polymyxin in *Pseudomonas aeruginosa*, the bacterial acidic phospholipids undergo conversion to neutral lipids, along with changes in proteins and carbohydrates, ultimately leading to the development of resistance (Gilleland and Lyle, 1979; Gilleland and Farley, 1982). Zhao et al. found that the increase of polymyxin concentration would affect the dynamics of genetic variants in the flora and lead to different degrees of evolution of resistance, and emphasized that during the use of polymyxin, the evolutionary findings were integrated into pharmacokinetics/pharmacodynamics to improve the antibacterial efficacy of patients (Zhao et al., 2022).

Antibiotic resistance has significantly compromised the effectiveness of antibiotics, leading to a substantial burden on medical care improvement and cost control. To address this issue, healthcare professionals must use antibiotics judiciously, preventing misuse and overuse, which can delay the emergence of resistance and reduce healthcare expenses for patients. Governments and medical institutions should also manage and optimize antibiotic use patterns, selecting the most suitable treatment plan based on recommended dosages and durations to achieve optimal clinical outcomes while minimizing toxicity and the risk of subsequent resistance. Furthermore, establishing an integrated and specialized antibiotic use monitoring system can help detect and prevent the emergence of antibiotic resistance in advance, addressing the problem at its source. Pharmaceutical researchers, in particular, should intensify their efforts in developing polymyxin antibiotics to counter emerging or potentially resistant bacteria in the future.

## 5 Innovative strategies in combating antibiotic resistance

Antibiotic resistance poses a significant challenge to global health, necessitating the exploration of diverse strategies to counteract its proliferation. Yan Zhu et al. proposed the combination of genome-scale metabolic modeling with multi-omics data elucidated the mechanisms by which A. baumannii cells respond to colistin treatment, including (i) upregulation of gluconeogenesis, pentose phosphate pathway, amino acid, and nucleotide biosynthesis fluxes; (ii) downregulation of TCA cycling, peptidoglycan, and lipopolysaccharide biogenesis; and (iii) alterations in respiratory chain fluxes. The findings elucidate the interaction of multiple metabolic pathways in A. baumannii when treated with colistin and provide key mechanistic insights for optimizing polymyxin combination therapy (Zhu et al., 2019). Li J et al. revealed the key pathways associated with the synergistic

activity of polymyxin B and rifampicin in combination against multidrug-resistant *Acinetobacter baumannii* by comparative metabolomics. They found that polymyxin B monotherapy significantly disrupted glycerophospholipid and fatty acid metabolism within 1 h, reflecting its activity against the bacterial outer membrane. Rifampicin monotherapy significantly disrupted glycerophospholipid, nucleotide, and amino acid metabolism, which was associated with inhibition of RNA synthesis, and with the combination, polymyxin B initially affected pathways associated with outer membrane biogenesis, whereas rifampicin affected them through inhibition of RNA synthesis, and the findings provide new mechanistic insights into optimizing this synergistic combination in patients (Zhao et al., 2021). As bacteria continue to evolve and resist conventional treatments, the scientific community has responded with vigor, delving deep into combination therapies, chemobiological innovations, and the potential of nanotechnology.

## 5.1 Polymyxin combination therapies: overcoming bacterial resistance

Combining polymyxin with sensitizing drugs represents a promising strategy to overcome polymyxin resistance and restore its sensitivity. Srisakul et al. proposed the combination of polymyxin and sulbactam as a means to overcome lipid A-mediated colistin resistance (Srisakul et al., 2022). Moreover, Chen et al. reported that Anthranilyl-CoA Synthetase PqsA effectively enhanced the activity of polymyxin B against MDR *Pseudomonas aeruginosa*-associated infections (Chen J. et al., 2022). In a study by Li et al., it was demonstrated that the combined use of the guanidine derivative isopropoxy benzene guanidine with low-level colistin enhanced the permeability of the bacterial outer membrane and increased the accumulation of reactive oxygen species, thereby combating MDR *Escherichia coli* (Li et al., 2023). Shein et al. suggested combining colistin and EDTA could overcome *mgrB*-mediated colistin resistance in carbapenem-resistant *Klebsiella pneumoniae* (Shein et al., 2022). Wang et al. showed that combination therapy using colistin and resveratrol improved the membrane permeability of bacteria and increased the sensitivity of *Pseudomonas aeruginosa* to colistin (Wang et al., 2023). The plasmid-mediated resistance gene *mcr*-1, a homolog of eptA, confers resistance by modifying lipid A through cationic phosphoethanolamine (Liu et al., 2016). MacNair et al. (2018) demonstrated that combining polymyxin with antibiotics targeting Gram-positive bacteria effectively treated infections caused by drug-resistant Gram-negative bacteria expressing *mcr*-1 (MacNair et al., 2018).

Additionally, combination therapy using melatonin and colistin has shown efficacy in eradicating *mcr*-positive pathogens and exhibits a favorable biosafety profile. The combined antibacterial mechanism of polymyxin and melatonin involves enhancing bacterial outer membrane permeability, promoting oxidative damage, and inhibiting the expression of bacterial efflux proteins. Liu et al. demonstrated that the combination of polymyxin and melatonin significantly restored the efficacy of colistin in three animal models of *E. coli* infection carrying *mcr*-1 (Liu et al., 2020). Table 2 presents an overview of clinical trials investigating polymyxin combination therapy to overcome drug resistance. Lindsey A Carfrae et al. proposed that the biotin biosynthesis inhibitor MAC13772 acted synergistically with colchicine, indirectly disrupting fatty acid synthesis (FAS) via MAC13772, leading to changes in phospholipid composition and restoring susceptibility to the antibiotic colchicine. In addition, the investigators propose that combination therapy using colchicine and the clinically relevant FabI inhibitor Debio1452-$NH_3$ is efficacious against systemic infections in mice with *mcr*-1-positive *Klebsiella pneumoniae* and colchicine-resistant *Escherichia coli*. We explored the mechanism of this interaction using chemogenomics, lipidomics, and transcriptomics (Carfrae et al., 2023).

## 5.2 Chemobiological advancements: enhancing antimicrobial efficacy against drug-resistant pathogens

Jonathan M. Stokes et al. found that pentamidine and its structural analogues sensitize Gram-negative pathogens to antibiotics and overcome acquired resistance to polymyxins (Stokes et al., 2017). Velkov and Li et al. optimized the structure of polymyxin by chemical biology and successfully developed a new lipopeptide, which has significant antibacterial activity against a variety of drug-resistant pathogens. The antimicrobial peptide has entered phase I clinical trials (Roberts et al., 2022). Zsolt Szűcs et al. prepared a vancomycin polycationic glycogen derivative with an n-decane side chain and 5 aminoethyl groups, which has a structure similar to that of polymyxin and can act synergistically against *Escherichia coli*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* by combining with teicoplanin (Szucs et al., 2022). Lindsey A. Carfrae et al. have found that the sensitivity of colistin therapy can be restored by inhibiting the synthesis of fatty acids in bacteria and finally changing the lipid composition of bacterial membranes (Carfrae et al., 2023).

## 5.3 Harnessing nanotechnology: a frontier in optimizing antibiotic delivery and performance

Nanomaterial-based therapy is a promising tool against refractory bacterial infections, characterized by the ability to evade the existing mechanisms related to acquired drug resistance and increase the activity of antimicrobials (Makabenta et al., 2021). Figure 6 summarizes some nanotechnologies to overcome antibiotic resistance. Nano-form metals, metal oxides, and other nano-drugs also have direct antibacterial effects (Lee et al., 2019; Elbourne et al., 2020; Zhang et al., 2022).

Nanotechnology represents a promising platform for drug delivery, particularly in the fight against antibiotic resistance. The key advantages of these nanocarriers lie in their ability to optimize and enhance the therapeutic effects of drugs (Figure 6). Nanocarriers greatly improve the stability of antibiotics in complex physiological and pathological environments. For example, nano-metals and metal oxides offer a protective barrier against threats such as hydrolysis, oxidation, pH fluctuations, and enzymatic attacks, thereby ensuring the preservation of their activity until they reach the intended target site (Elbourne et al., 2020). Moreover, nanocarriers, including gels and polymer nanofibers, facilitate the

TABLE 2 Clinical trial of polymyxin involved in drug resistance.

| Status | ClinicalTrials.gov identifier | Condition or disease | Drug | Combination of drugs |
|---|---|---|---|---|
| Phase 3 | NCT03159078 | Trauma | Polymyxin B | Carbapenem |
| | | Resistant Infection | | |
| | | Critical Illness | | |
| Phase 3 | NCT02134106 | Bacteremia | Polymyxin B | Doripenem |
| | | Healthcare-associated Pneumonia | | |
| | | Ventilator-associated Pneumonia | | |
| Completed | NCT00753558 | Carriage of Carbapemen-resistant *Klebsiella pneumoniae* | polymyxin E | Oral solution and buccal gel of gentamicin |
| Recruiting | NCT04839653 | Respiratory Tract Infections | polymyxin B | Gentamycin, amphotericine B |
| | | Critical Illness | | |
| Phase 4 | NCT04489459 | Blood Stream Infections Due to MDR *Klebsiella pneumoniae* | Colistin | Meropenem, Tigecycline |
| Completed | NCT01266499 | *Klebsiella Pneumoniae* Carbapenemase Resistant Associated Bacteremia or Pneumonia | Colistin | Garamycin |
| Early Phase 1 | NCT03950544 | Antibiotic-Resistant Infection | Polymyxin B | Fosfomycin, Tigecycline |
| Recruiting | NCT04202861 | Antibiotic Therapy | Polymyxins | Antibiotic combination |
| Phase 3 | NCT05258851 | Carbapenem-Resistant Enterobacteriaceae Infection | Colistin | Ceftazidime-avibactam |
| Phase 2 | NCT02472600 | Intestinal Colonization With MDR Bacteria | Colistin | Neomycin; Fecal microbiota transplantation; Omeprazole |

sustained release of antibiotics due to their unique design (Thapa et al., 2020). This feature ensures consistent drug concentrations and helps reduce dosing frequencies, thereby enhancing patient compliance. Furthermore, their small size allows nanocarriers to reside longer at damaged or infected sites, enabling effective infection control precisely where it is most needed (Mofazzal Jahromi et al., 2018; Liang et al., 2022). Significantly, these nanocarriers possess biodegradable and non-invasive properties, allowing for their safe breakdown and elimination from the body after fulfilling their purpose without causing any further harm (Ohnstedt et al., 2019). Moreover, nanocarriers provide a protective environment for drugs in the gastrointestinal tract, regulating their release. For instance, combining or encapsulating polymyxins with polymers and liposomes can protect drugs in the gastrointestinal tract, leading to enhanced drug absorption (Maher et al., 2016; Faustino and Pinheiro, 2020). Furthermore, the design of nanos and microparticles ensures targeted drug delivery, enabling drugs to be directed straight to the infection site. This precision allows for more accurate treatments, reduced drug dosages, and diminished risks of systemic side effects (Lee et al., 2019; Zigrayova et al., 2023). Additionally, when combined with the most effective antibiotics, nano preparations have exhibited synergistic effects and the potential to address the emerging global crisis of bacterial resistance (Lee et al., 2019; Zigrayova et al., 2023). Chengyuan Qin et al. Overcoming colistin resistance in bacterial infections by negatively charged polyethylene glycol functionalized liposomal co-delivery of curcumin and colistin. Liposomes restored the affinity of mucilage to the bacterial membrane and increased the uptake of curcumin, thereby decreasing efflux pump activity and realizing the synergistic effect of mucilage and curcumin. The liposome-loaded group did not exhibit any toxicity at effective antibacterial doses (Qin et al., 2023).

## 6 The critical role and complexities of polymyxins in modern medicine

Polymyxins, specifically Polymyxin B and Colistin (Polymyxin E), have emerged as pivotal agents in the fight against antibiotic-resistant bacterial infections. Polymyxin B is often available as a sulphate for injection, while colistin is available as polymyxin E sulphate for injection and colistin methane sulfonate for injection. CMS is a prodrug that is converted to colistin in the body after administration in order to exert antimicrobial activity. As the global medical community grapples with the challenges posed by multi-drug resistant Gram-negative bacteria (MDR-GNB), the significance and intricacies of these drugs have gained paramount importance. This article delves into the types, pharmacokinetic properties, differences, and the potential of personalized treatments with polymyxins. Additionally, it sheds light on the future research directions, emphasizing the need to further elucidate their behavior and interactions, especially in conjunction with contemporary medical treatments (Figure 7). CMS is a precursor drug that needs to be converted in the kidneys, and its conversion rate is affected by a number of factors, resulting in large individual variations in PK parameters, and blood concentrations are affected by renal function. PMB is mainly eliminated by non-renal routes and the total clearance has little correlation with renal function.

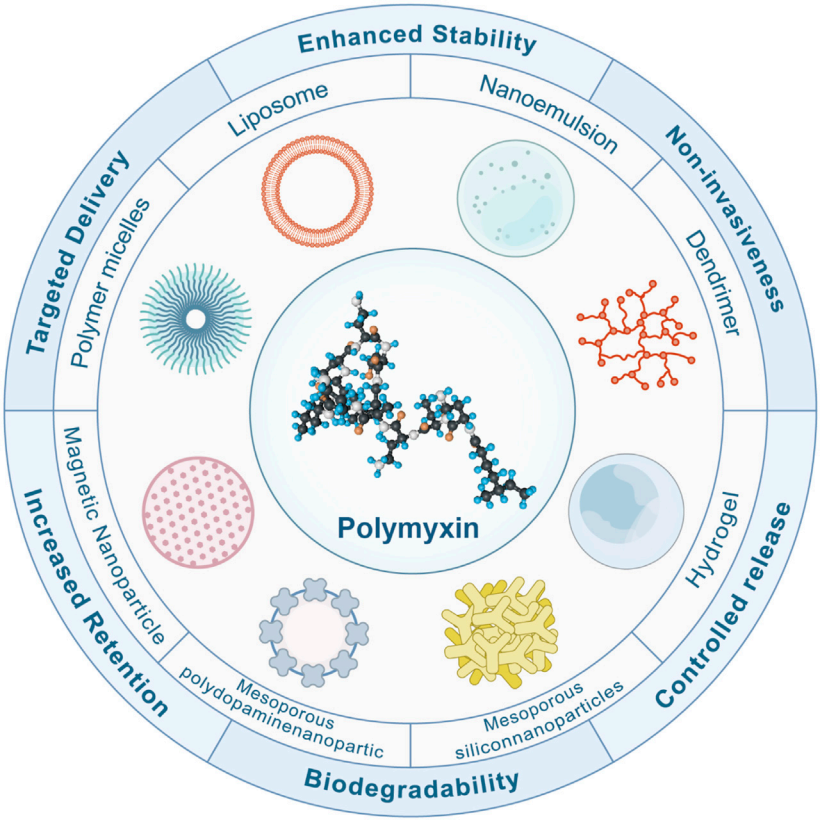


FIGURE 6
Features of Nanotechnology in Improving Polymyxin Resistance. Nanotechnology has emerged as a cornerstone in the battle against antibiotic resistance. Nano-carriers bolster the resilience of antibiotics amidst the intricacies of physiopathological landscapes. Harnessing the potential of gels and polymer nanofibers, the longevity of antibiotic release is notably augmented. Moreover, these carriers adeptly prolong the drug's residence at injury locales. Their biodegradable and non-invasive nature ensures a harmonious interaction with the human physiology. These nano-carriers deftly modulate drug release within the gastrointestinal milieu, optimizing absorption and maximizing bioavailability. Beyond that, the strategic design of nanoparticles and microparticles ensures a precision-guided delivery to infection epicentres, adeptly curbing side effects and magnifying therapeutic efficacy.

Dosage does not need to be adjusted according to renal function, and effective blood mass concentrations can be achieved rapidly and are less affected by renal function. Therefore, PMB is more suitable for bloodstream infections, whereas CMS is more suitable for urinary tract infections. The antimicrobial activity of different polymyxin E formulations varies, with CMS being less active than polymyxin E sulphate and less toxic, while polymyxin E sulphate is less commonly used due to toxicity and is mainly used for drug sensitivity testing (Infectious Diseases Society of China et al., 2021). Currently, there are fewer data from studies related to polymyxin E sulphate, and it is expected that more relevant studies will enrich the clinical options in the future.

## 6.1 Types and drug forms of polymyxins

In current clinical practice, Polymyxin B and Colistin are widely regarded as the two primary polymyxins, both boasting impressive antibacterial properties. Due to the rising antibiotic resistance of MDR-GNB globally, many previously effective antibiotics have become less effective against MDR Gram-negative pathogens (El-Sayed Ahmed et al., 2020). This resurgence of colistin in the mid-1990s emerged as a crucial weapon against MDR Gram-negative pathogens (El-Sayed Ahmed et al., 2020). Notably, *Klebsiella pneumoniae*, a common cause of healthcare-associated infections, often uses colistin as the treatment of choice (Uzairue et al., 2022). However, these two polymyxins differ in their modes and forms of administration. Polymyxin E is commonly administered intravenously as the prodrug colistin methanesulphonate, while PMB can be directly intravenously administered as its active form under physiological pH (Nation et al., 2015) (Figure 7). Alarmingly, with the clinical discovery of more and more carbapenem resistant *pseudomonas*, especially resistance to polymyxins has begun to appear (Qureshi et al., 2015).

## 6.2 Pharmacokinetic properties of polymyxin B

The administration of PMB is versatile, including intravenous, intrathecal, or nebulized inhalation routes. After intravenous administration, its steady-state distribution volume ranges from 12.7–34.3 L, with a half-life of about 9–11.5 h. This provides valuable guidance for clinicians on dose adjustments.

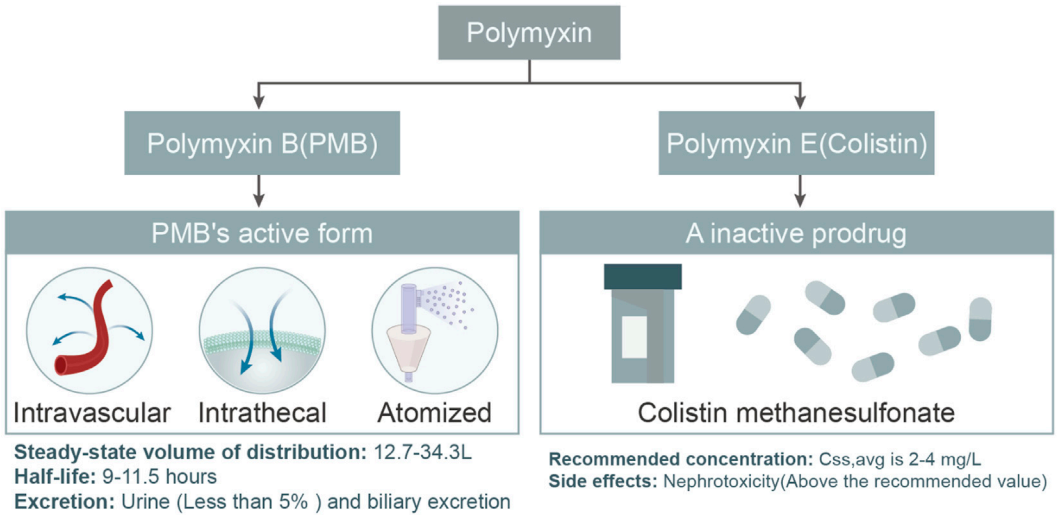


FIGURE 7
Comparative Pharmacokinetic Profiles of PMB and Colistin. This flowchart elucidates the distinct pharmacokinetic properties of PMB and Colistin. For PMB, the diagram underscores its distribution, half-life, and excretion pathways, notably the minimal renal excretion and a potential route through biliary excretion. In contrast, colistin is emphasized for its intravenous administration as the inactive prodrug, colistin methanesulphonate. The recommended concentrations for both drugs are depicted, with an accent on potential side effects, especially the heightened risk of nephrotoxicity when exceeding the advised levels.

Interestingly, in both animals and humans, less than 5% of PMB is excreted in the urine, indicating that the kidneys are not the primary route of elimination for PMB (Zavascki et al., 2008; Manchandani et al., 2016). Although biliary excretion might contribute to PMB's clearance, further studies are needed to identify other potential clearance mechanisms (Manchandani et al., 2016). It is worth noting that the intensity of concentration imposed by polymyxins affects the dynamics of genetic variation within the bacterial population, leading to different evolutionary outcomes of resistance. Jinxin Zhao et al. demonstrated that polymyxin B recurs at a critical threshold concentration (1 mg/L; i.e., 4× MIC) with low levels of resistance, but without fixed mutations, and that this resistance reverses upon removal of the antibiotic. This contrasts with the evolution of polymyxin B at ultra-MIC concentrations (≥4 × MIC), which drives the evolution of irreversible resistance, with molecular evolution occurring more rapidly at higher antibiotic concentrations. This study highlights the important role of combining evolutionary findings with pharmacokinetics/pharmacodynamics to optimize antibiotic use in patients (Zhao et al., 2022). V Aranzana-Climent et al. investigated a semi-mechanistic PK/PD model for the combination of polymyxin B and minocycline against polymyxin-resistant *Acinetobacter baumannii*. The combination effect was driven by minocycline, with PMB as an adjunct; simulations at clinically achievable concentrations indicated that 1.5 mg/L minocycline +0.2 mg/L PMB was expected to produce sustained killing for more than 30 h, whereas 0.3 mg/L minocycline +1 mg/L PMB was sufficient for bacterial regeneration. Interaction equations indicated that synergistic effects were maximized at PMB concentrations ≥0.1 mg/L and minocycline concentrations ≥1 mg/L. The possible mechanism is that PMB opens the bacterial membrane and increases the entry of minocycline into the cell, and the intracellular concentration of minocycline increased in bacteria treated with 0.5 mg/L PMB and minocycline in combination (Aranzana-Climent et al., 2020). Further studies on the protein binding rates of polymyxins and their combined antimicrobials in humans are necessary before any definitive recommendations can be issued. And, caution should be used in interpreting these modeling results based on *in vitro* results.

To provide the best treatment for each patient more accurately, researchers have begun to explore population pharmacokinetics (PPK). This method considers various physiological, pathological, and genetic factors that might influence drug efficacy and safety. Combined with pharmacodynamic (PD) metrics, this allows physicians to better adjust treatment strategies, achieving personalized treatment and enhancing therapeutic outcomes (van der Leeuw et al., 2014; Chen N. et al., 2022). Recent studies have assessed the pharmacokinetics/pharmacodynamics of Polymyxin B in patients with carbapenem-resistant *K. pneumoniae* bloodstream infections (Yu et al., 2022). Furthermore, for other drugs like paroxetine, population pharmacokinetic models have been successfully applied to guide personalized treatments (Li et al., 2022). These studies offer a framework for understanding how to leverage pharmacokinetic/pharmacodynamic principles to optimize polymyxin treatment strategies.

## 6.3 Metabolism, excretion of polymyxin B, and future research directions

While we have a certain understanding of many aspects of PMB, its metabolism and excretion mechanisms in the body remain somewhat elusive. Future research should focus more on these areas, especially considering the increasing bacterial resistance to conventional antibiotics. Additionally, with the advancements in medical technology, more patients now require continuous renal replacement therapy (CRRT) or extracorporeal membrane oxygenation (ECMO) support. These treatments might influence the pharmacokinetics of polymyxins, making it crucial to understand their interactions. A recent study reported a patient

with septic shock induced by severe acute pancreatitis who received life support through ECMO and CRRT and multiple anti-infective drug treatments. The study monitored the plasma concentration of Colistin sulfate during ECMO and CRRT, finding no significant difference before and after ECMO and CRRT (Peng et al., 2022), implying that ECMO and CRRT might not significantly influence the pharmacokinetics of Colistin sulfate. Moreover, different connection modes for ECMO and CRRT have shown that both modalities can achieve therapeutic goals without necessitating higher levels of anticoagulation therapy (Liu et al., 2021), providing important guidance for clinicians on the use of polymyxins in patients receiving ECMO and CRRT treatments. In conclusion, as our understanding of the behavior of polymyxins in the body deepens, future research should focus on their interactions with modern medical technologies, such as ECMO and CRRT, to optimize treatment strategies and improve therapeutic outcomes.

## 7 Conclusion

This review provides an overview of the latest discoveries and development history of polymyxins, as well as the mechanisms underlying multidrug resistance to polymyxins. Additionally, we discuss current research directions to overcome polymyxin resistance and highlight new antibiotics undergoing clinical research. Furthermore, we outline the future challenges and prospects of polymyxins in treating bacterial infectious diseases, particularly in relation to MDR bacterial infections. Over the past 5 years, numerous studies have explored the impact of the *mcr* gene on polymyxin resistance, revealing a much more complex mechanism of bacterial drug resistance than previously understood. Future research should focus on elucidating the causes of colistin resistance to enable the precise design and development of antibiotic drugs targeting drug-resistant bacteria and optimize drug administration strategies. These efforts are crucial to minimize the development of resistance and prolong the effectiveness of polymyxin as a last-line treatment.

Different forms of polymyxins exhibit significant differences in pharmacokinetics and toxicity, with some forms being more prone to induce nephrotoxicity or neurotoxicity. This necessitates a deep evaluation and careful consideration by physicians when selecting and using polymyxins (Nation et al., 2014). Specifically, Polymyxin B is seen as the last line of defense against carbapenem-resistant microbes, but its common side effects, such as neurotoxicity and nephrotoxicity, cannot be overlooked (Nation and Li, 2009; Yu et al., 2022). The toxicity observed in clinical settings stems from colistin's antibacterial mechanism, which involves the interaction and damage inflicted on bacterial bilayer membranes. When administered at high doses, this same mechanism can cause severe damage to the cell membranes of human organs, including the liver and kidneys. Toxicity is typically reversible upon discontinuation, and its severity is dose-dependent (Li et al., 2006). To address these issues, developing new polymyxin preparations must focus on reducing dosage, achieving targeted drug delivery, and controlling drug release. Using polymyxin-based nanoparticles, liposomes, microneedles, and composite nanomaterials necessitates collaborative efforts across disciplines such as chemistry, nanomedicine, and materials science to address polymyxin delivery, drug resistance, and toxicity challenges. Conjugation of polymyxin is also a promising approach that can enhance intestinal permeability and absorption while preventing microbial resistance. However, it is crucial to investigate the impact of molecular modifications on drug stability, antimicrobial activity, and the ability to overcome microbial drug resistance. The emergence of drug resistance poses a significant threat to the treatment of MDR-GNB infections since polymyxin serves as the last line of defense. Therefore, the future of antibiotic drug development lies in optimizing existing polymyxin drugs to reduce dosage, increase efficiency, mitigate toxicity, and overcome the emergence of drug resistance.

Addressing antibiotic resistance demands a comprehensive approach that includes political agendas, legislation, treatment development, and educational initiatives. Regular surveillance, policies, and the implementation of new medical therapies targeting resistant bacteria are essential for combating antibiotic resistance in human and agricultural contexts. Given the varying rates of resistance development across different antibiotics, multifaceted measures are necessary to ensure the sustainable development of healthcare. The increasing reliance on colistin as a last resort antimicrobial necessitates urgent exploration of its antimicrobial potential and the development of new, more effective antimicrobial agents to safeguard public health in the future. Looking ahead, there is growing interest in using new technological approaches to overcome polymyxin resistance. Continued advancements in analytical techniques for the identification and structural interpretation of natural products will likely lead to the discovery of novel polymyxin groups and new lipopeptide components within existing polymyxin groups.

## Author contributions

SY: Conceptualization, Formal Analysis, Validation, Visualization, Writing–original draft, Writing–review and editing. HW: Formal Analysis, Investigation, Validation, Visualization, Writing–review and editing. DZ: Investigation, Supervision, Validation, Visualization, Writing–review and editing. SZ: Formal Analysis, Investigation, Validation, Visualization, Writing–review and editing. CH: Conceptualization, Formal Analysis, Validation, Visualization, Writing–original draft, Writing–review and editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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