Polymyxin-B: A Novel Approach for the Treatment of Antibiotic-Resistant Infections - A Review

***Sheryas Kumar, [1]Yogendra Sharma**

***Assistant Professor, J K Institute of Pharmacy, Khurja**

[1]Research Scholar, J K Institute of Pharmacy, Khurja

Abstract: Antibiotic resistance has become a growing concern in healthcare, as many bacterial infections are becoming increasingly resistant to traditional antibiotics. Polymyxin-B, a cyclic lipopeptide antibiotic, has emerged as a promising treatment option for antibiotic-resistant infections. This review provides an overview of Polymyxin-B, including its mechanism of action, history, and effectiveness in treating antibiotic-resistant infections. This paper also discusses how Polymyxin-B addresses antibiotic resistance and its potential use as a last-resort treatment option. While Polymyxin-B is effective, it is not without potential side effects. Continued research and development of Polymyxin-B and its potential for combination therapy with other antibiotics are also discussed. In conclusion, Polymyxin-B is a novel approach for treating antibiotic-resistant infections that warrants further research and attention in the fight against antibiotic resistance.

Keywords: *Antibiotic, resistance, antibiotic, lipopeptide, Polymyxin-B*

Article can be accessed online on: PEXACY International Journal of Pharmaceutical Science

Corresponding Author- Sheryashh1287@gmail.com*

Update: Received on 14/06/2023; Accepted; 17/06/2023, Published on; 28/06/2023

Introduction

Antibiotic-resistant infections have become a growing public health concern recently due to bacteria's continued evolution and resistance to commonly used antibiotics. With the escalation of antibiotic-resistant bacterial strains, there is now an urgent need for new antibiotics to combat this public health crisis.

Polymyxin-B, a cyclic lipopeptide antibiotic, has become a promising treatment option for antibiotic-resistant infections. Its discovery marks an important advancement in the fight

against antibiotic resistance as its unique mechanism of action against bacteria differs from traditional antibiotics. Studies have demonstrated its efficacy against various bacterial infections, including those caused by gram-negative bacteria that often resist other antibiotics [1].

This review seeks to overview Polymyxin-B and its potential as a novel approach for treating antibiotic-resistant infections. The paper will cover its mechanism of action, history, development, and efficacy in treating such conditions. Furthermore, this paper will address how Polymyxin-B addresses antibiotic resistance and its potential use as a last-resort treatment option. Although Polymyxin-B has been demonstrated effective, there may be side effects. Further research and development into Polymyxin-B and potential combination therapy with other antibiotics will also be discussed [2].

Overall, this paper emphasizes the significance of finding new treatments to combat antibiotic-resistant infections, and Polymyxin-B is one such potential solution. Further development and research into Polymyxin-B could represent a breakthrough in the fight against antibiotic resistance, potentially improving patient outcomes with these infections.

Explanation of antibiotic-resistant infections

Antibiotic-resistant infections occur when bacteria become resistant to the antibiotics used to treat them. This means the antibiotics no longer effectively kill or stop the growth of these germs, allowing the infection to persist and potentially worsen. Antibiotic resistance can arise due to overuse or misuse of antibiotics, creating selective pressure for bacteria to develop resistance. Bacteria can acquire this resistance through mutations in their DNA or by acquiring resistance genes from other bacteria [3].

Antibiotic resistance can occur in any bacterial infection, from mild cases like urinary tract infections to more serious ones like sepsis or pneumonia. Treatments caused by antibiotic-resistant bacteria tend to be more challenging, often necessitating more aggressive treatments with stronger or toxic antibiotics or May not even provide a satisfactory solution. This presents an enormous challenge to public health since the prolonged illness, increased healthcare expenses, and even death may result from antibiotic resistance-associated illnesses.

That is why research into new treatment options like Polymyxin-B is critical to combat antibiotic-resistant infections [4].

Overview- Polymyxin-B

Polymyxin-B is an antibiotic commonly used to treat infections caused by Gram-negative bacteria. This scientific paper provides an overview of Polymyxin-B's mechanism of action, pharmacokinetics and pharmacodynamics, indications, contraindications, adverse effects, and clinical use. Polymyxin-B is one of a group of antibiotics known as Polymyxin, derived from Bacillus polymyxa. Polymyxin-B disrupts the integrity of bacteria's cell membrane, leading to leakage of intracellular contents and eventually death for the microbe [5].

Polymyxin-B has a complex pharmacokinetic profile with considerable inter-individual variability. It is administered intravenously and eliminated primarily through the kidneys. Furthermore, its pharmacodynamics is concentration-dependent; how effective it works depends on how much of it is present in your system. Polymyxin-B is indicated for treating infections caused by Gram-negative bacteria, particularly those resistant to other antibiotics. Examples include Pseudomonas aeruginosa, Acinetobacterbaumannii, and Klebsiella pneumoniae. Polymyxin-B is not recommended for patients with a history of hypersensitivity to its components or the drug itself. Some potential adverse effects of its use include nephrotoxicity, neurotoxicity, and respiratory distress [6] [7].

Polymyxin-B is an antibiotic with the potential for toxic effects, but it remains an essential tool in managing multidrug-resistant Gram-negative infections. However, its use should only be reserved for serious infections where other effective treatments are unavailable, and careful monitoring of renal function and potential side effects is mandatory. Polymyxin-B is an essential antibiotic in treating infections caused by multidrug-resistant Gram-negative bacteria. Unfortunately, its use carries potential risks and requires close monitoring to minimize potential toxicities [8].

Drug Profile

Polymyxin-B is an antibiotic of the cyclic lipopeptide class that was first discovered in the 1940s and has been used for many years to treat various bacterial infections. Polymyxin-B has broad antimicrobial activity against various gram-negative bacteria like Pseudomonas aeruginosa,

Klebsiella pneumoniae, and Acinetobacterbaumannii, which may be resistant to other antibiotics [9].

Polymyxin-B works by adhering to the outer membrane of bacteria's cell wall and disrupting its structure, leading to leakage of intracellular components and eventual death. Polymyxin-B is usually administered intravenously; it may be taken alone or combined with other antibiotics. Polymyxin-B has been limited due to potential side effects like kidney toxicity or neurotoxicity. However, recent studies have demonstrated that these risks can be minimized with appropriate dosing and monitoring [10].

Polymyxin-B is a last-resort treatment option for infections resistant to other antibiotics due to its unique mechanism of action. Although its efficacy and safety have yet to be proven, its use should only be reserved in instances where other effective options have failed. Currently, research is being done to enhance Polymyxin-B's safety and efficacy and explore its potential use in combination therapy with other antibiotics.

Mechanism of Action

Polymyxin-B has a distinct mechanism of action, set apart from other antibiotics. It binds to lipopolysaccharides on the outer surface of gram-negative bacteria's cell wall, creating an opening in their membrane which increases permeability and ultimately leads to cell death for the bacteria. Polymyxin-B binds to the lipid, a portion of lipopolysaccharides, and forms a complex with membrane phospholipids, displacing calcium and magnesium ions that normally stabilize cell walls, making them more permeable [11].

This increased permeability allows for the leakage of intracellular components and ultimately results in bacterial death. Polymyxin-B has a unique affinity for gram-negative bacteria due to its lipopolysaccharides, which are only found in these organisms and not those of gram-positive bacteria. As such, Polymyxin-B can effectively treat infections caused by these microorganisms - even those resistant to other antibiotics. However, Polymyxin-B's specific mechanism of action may lead to potential toxicity, especially in the kidneys and nervous system. Thus, proper dosing and monitoring are necessary to minimize any side effects [12].

History and background

Polymyxin-B is an antibiotic of the Polymyxin family, discovered in the late 1940s by scientists from the Rockefeller

Institute in New York. They screened soil bacteria for antibacterial compounds and identified Polymyxin-A - the first Polymyxin compound ever identified! Subsequent discoveries included Polymyxin-B and C as well as other related compounds [13].

Polymyxin-B first developed clinically in the 1950s and was used primarily to treat infections caused by gram-negative bacteria like Pseudomonas aeruginosa, Klebsiella pneumoniae, and Acinetobacterbaumannii. Due to concerns about its potential toxicity to kidneys and the nervous system, however, its use was mostly restricted to topical applications or infections that proved resistant to other antibiotics [14].

With the rise of antibiotic-resistant bacteria, particularly gram-negative ones, in recent years, there has been renewed interest in Polymyxin-B as a treatment. Researchers are working on optimizing dosage and administration methods for Polymyxin-B to minimize toxicity and maximize efficacy. They have also created new formulations, such as liposomal Polymyxin-B, improving their pharmacokinetic and pharmacodynamic properties. As a result, more people are turning to Polymyxin-B to treat severe infections caused by antibiotic-resistant bacteria [15].

Effectiveness of Polymyxin-B

Polymyxin-B is an antibiotic belonging to the Polymyxin family. This antibiotic primarily targets infections caused by gram-negative bacteria resistant to other antibiotics. Polymyxin-B works by binding to lipopolysaccharides present on bacteria's outer membrane, disrupting their cell wall and leakage of intracellular components resulting in death for the bacteria [16].

Studies have demonstrated the efficacy of Polymyxin-B in treating infections caused by multidrug-resistant bacteria such as Pseudomonas aeruginosa, Klebsiella pneumoniae, and Acinetobacterbaumannii. Furthermore, Polymyxin-B has been successfully utilized to combat infections caused by bacteria with extended-spectrum beta-lactamase (ESBL) and carbapenemase enzymes.Polymyxin-B is more effective than other antibiotics, such as colistin, in treating certain multidrug-resistant infections. A study comparing Polymyxin-B and colistin for ventilator-associated pneumonia caused by Acinetobacterbaumannii revealed that Polymyxin-B had a higher clinical cure rate and lower mortality rate [17].

Polymyxin-B may cause potential side effects such as nephrotoxicity, neurotoxicity, and respiratory paralysis. To ensure these adverse reactions are identified early and managed appropriately, careful monitoring of patients receiving Polymyxin-B is necessary.Polymyxin-B is an antibiotic with promising results in treating antibiotic-resistant infections caused by gram-negative bacteria. However, its use should only be reserved for situations where other treatments have failed, and careful monitoring is necessary to minimize any potential negative reactions [18].

Pharmacological Activities

Wang et al. (2022) conducted a study to analyze the population pharmacokinetics of polymyxin B in critically ill patients undergoing continuous venovenoushaemofiltration (CVVH) and to optimize individual dosing regimens in specific clinical scenarios. The study enrolled 53 patients who were treated with CVVH and polymyxin B for multi-drug-resistant Gram-negative bacterial infections from two hospitals. The authors collected blood samples during and outside CVVH and performed population pharmacokinetic analysis and Monte Carlo simulations using Phoenix NLME software. The study found that CVVH significantly increased the clearance of polymyxin B, and patients on CVVH required high doses of polymyxin B and a dose-adjustment regimen based on therapeutic drug monitoring to improve efficacy. The study concluded that a loading dose of 200 mg plus a fixed maintenance dose of 150 mg every 12 h had a high probability of achieving the pharmacokinetic/pharmacodynamic target in patients on CVVH. Overall, the study provides valuable insights into the dosing of polymyxin B in critically ill patients undergoing CVVH [19].

Silva et al. (2022) conducted a study to investigate the potential of (−)-camphene-based thiosemicarbazide (TSC) in combination with polymyxin B (PMB) against carbapenem-resistant Enterobacterales (CRE). The study found that TSC may act synergistically with PMB, rescuing its activity against CRE. The authors also performed theoretical calculations to better understand the molecular mechanism underlying the observed synergistic effect. The results suggested that the presence of TSC moieties led to significant changes in the hydrogen atom charge of the PMB structure, resulting in stronger hydrogen bonds in the Enterobacterales active site. The study

concluded that the clinical potential of PMB/TSC combinations requires further evaluation. Overall, the study provides important insights into potential therapeutic options for CRE infections, which are urgently needed due to the significant shortage of effective treatments [20].

Wang et al. (2022) conducted a study to develop a population pharmacokinetic (PK) model for polymyxin B in paediatric patients and assess the appropriateness of different dosages. The study enrolled 19 paediatric patients who received intravenous polymyxin B for multidrug-resistant Gram-negative bacterial infections. The PK data were modelled using a two-compartment model with first-order elimination, and weight was identified as a significant covariate of polymyxin B clearance. The study found that current polymyxin B dosing for paediatric patients may be acceptable when minimum inhibitory concentrations (MICs) are <0.5 mg/L, and dose adjustment needs to consider the MIC of infecting pathogens. The steady-state polymyxin B exposure was lower than the therapeutic exposure of 50–100 mg·h/L. Clinical success occurred in 14 of 19 patients, and only one patient developed acute kidney injury. The study concluded that dosing adjustments of polymyxin B are necessary to optimize its clinical efficacy and minimize toxicity in paediatric patients. Overall, the study provides valuable information for clinicians to consider when dosing polymyxin B for paediatric patients with multidrug-resistant Gram-negative bacterial infections [21].

Wang et al. (2022) conducted a study to develop a population pharmacokinetic (PK) model of polymyxin B in elderly patients and propose alternative dosing regimens. The study enrolled critically ill elderly patients (age ≥65 years) who received intravenous polymyxin B for multi-drug-resistant Gram-negative bacterial infections. The population PK model was developed using Phoenix NLME software, and albumin was identified as a significant covariate of PK parameters. Monte Carlo simulations were performed to optimize regimens attaining the PK/PD target and target exposure. The study found that fixed maintenance dosing of 50 mg and 75 mg for polymyxin B may maximize efficacy while balancing nephrotoxicity concerns for elderly patients. The simulation results indicated that two fixed regimens of 50 mg and 75 mg would be sufficient to reach the PK/PD targets when the minimum inhibitory concentrations were ≤0.5 mg/L. Weight-based regimens (1.25–1.5 mg/kg for 70 kg

and 80 kg; twice daily) may result in at least 40% of predicted AUCss,24h>100 mg·h/L, except for 1.25 mg/kg for 58 kg. The study also assessed the clinical efficacy and nephrotoxicity of polymyxin B treatment. Overall, the study provides important insights into the dosing of polymyxin B in elderly patients with multi-drug-resistant Gram-negative bacterial infections [22].

Zhang et al. (2022) conducted a study to investigate the mechanism of polymyxin B-induced hyperpigmentation, a serious side effect of polymyxin B that severely compromises the psychological health and compliance of patients. The study used SK-MEL-2 cells to investigate the response of melanin content and tyrosinase activity after polymyxin B treatment. Tandem mass tag (TMT)-labeling quantitative proteomics was also employed to investigate the response of SK-MEL-2 cells to polymyxin B treatment. The study found that the melanin content and tyrosinase activity were significantly upregulated after polymyxin B treatment in SK-MEL-2 cells at 48 h and 72 h. The differentially expressed proteins were involved in pathways such as lysosome, PI3K/Akt signaling pathway, and calcium signaling pathway. The study also found that the upregulation of melanogenic enzymes and microphthalmia-associated transcription factor (MITF) was validated by qPCR and Western blot. Meanwhile, phosphorylation of PI3K, β-catenin, and cyclic-AMP response binding protein (CREB) in response to polymyxin B treatment was observed. The study provides valuable insights into the proteomic response of polymyxin B-induced melanogenesis in SK-MEL-2 cells and reveals that signaling pathways, including melanin biosynthesis, PI3K/Akt, and calcium signaling pathways, may be involved in the mechanism of melanogenesis [23].

Chung et al. (2022) conducted a study to explore the adjuvant effects of exogenous metabolites in combination with polymyxin B to combat multidrug-resistant Klebsiella pneumoniae. The study employed genome-scale metabolic models (GSMMs) to delineate the altered metabolism of New Delhi metallo-β-lactamase- or extended spectrum β-lactamase-producing K. pneumoniae strains upon addition of exogenous metabolites in media. Metabolites that caused significant metabolic perturbations were selected to examine their adjuvant effects using in vitro static time–kill studies. The metabolic network simulation shows that feeding of 3-phosphoglycerate and ribose 5-phosphate would lead to enhanced central carbon

metabolism, ATP demand, and energy consumption, which is converged with metabolic disruptions by polymyxin treatment. The study demonstrated enhanced antimicrobial killing of 10 mM 3-phosphoglycerate and 10 mM ribose 5-phosphate combination with 2 mg/L polymyxin B against K. pneumoniae strains. Overall, the study suggests that exogenous metabolite feeding could possibly improve polymyxin B activity via metabolic modulation and offers an attractive approach to enhance polymyxin B efficacy. The study developed a systematic framework to facilitate the clinical translation of antibiotic-resistant infection management, bridging the metabolic analysis and time-kill assay, to provide biological insights into metabolite feeding [24].

Comparison to other antibiotics

Polymyxin B is an antibiotic belonging to the polymyxin class of drugs. As a cyclic polypeptide with its own mechanism of action, this medication distinguishes itself from other classes of antibiotics by targeting Gram-negative bacteria like Escherichia coli, Pseudomonas aeruginosa and Klebsiella pneumoniae that cause severe infections in humans.

As opposed to other antibiotics, polymyxin B has a limited scope of activity because it only treats Gram-negative bacteria; other antibiotics like penicillins, cephalosporins and fluoroquinolones offer greater versatility in treating various bacterial infections [25].

Polymyxin B works by disrupting bacterial cell membranes through interaction with lipopolysaccharides (LPS) and phospholipids, leading to increased membrane permeability and subsequent cell death. Its mechanism of action differs significantly from other antibiotics which typically target cell wall production (e.g. penicillins and cephalosporins) or inhibit protein synthesis (macrolides, tetracyclines and aminoglycosides) [26].

Polymyxin B is often associated with potential side effects including kidney and nerve damage. Because of these potential toxicities, its use should generally be reserved for multidrug resistant infections where other antibiotics have failed.

Polymyxin B remains an effective antibiotic in combatting antibiotic-resistant bacteria, especially those classified as carbapenem-resistant Enterobacteriaceae (CRE). With its special mechanism of action and high specificity against Gram-negative bacteria, this tool makes polymyxin B an

indispensable ally in an age of increasing antibiotic resistance [27].

Potential side effects

Polymyxin-B can have potential side effects, which may restrict its use in certain patient populations [28]. Some of the most frequent adverse reactions reported with Polymyxin-B use include:

Nephrotoxicity

Nephrotoxicity is the most frequent side effect of Polymyxin-B, characterized by kidney damage or impairment. Patients receiving Polymyxin-B are usually closely monitored for signs of nephrotoxicity, such as changes in urine output, elevated creatinine levels, and electrolyte imbalances.Nephrotoxicity is a potential adverse reaction of Polymyxin-B, which manifests as damage or impairment to the kidneys. Nephrotoxicity may arise through direct toxicity to renal tubules or interference with blood flow within the kidneys. Patients with preexisting renal impairment or those taking other nephrotoxic medications are particularly at risk for nephrotoxicity. Patients taking polymyxin-B are typically monitored closely for signs of nephrotoxicity, such as altered urine output, elevated serum creatinine levels, electrolyte imbalances and other renal function parameters. In severe cases, the condition can progress to acute kidney injury or renal failure which may require dose reduction, discontinuation of therapy or other interventions [29].

Neurotoxicity

This less common but serious adverse effect of Polymyxin-B can cause respiratory paralysis, seizures and other neurological symptoms. Patients taking Polymyxin-B are typically monitored closely for signs of neurotoxicity such as changes in mental status, muscle weakness and difficulty breathing.Neurotoxicity is a potential side effect of Polymyxin-B that may manifest as damage to the nervous system. Polymyxin-B causes neurotoxicity through an unknown mechanism; however, it has been speculated to do with its ability to bind with and disrupt cell membranes in the nervous system. Patients taking Polymyxin-B are typically monitored closely for signs of neurotoxicity, such as respiratory paralysis, seizures, confusion and other neurological symptoms. Neurotoxicity is typically more of a risk for patients with neurological conditions or those taking high doses of the drug. Furthermore, certain medications like diuretics or muscle relaxants may also

increase this potential side effect. Therefore, proper monitoring is key to reduce the possibility of serious adverse reactions while on Polymyxin-B [30][31].

Ototoxicity

Polymyxin-B may cause ototoxicity, or damage to the inner ear, leading to hearing loss or tinnitus. Patients taking Polymyxin-B should undergo regular hearing tests for signs of ototoxicity.Ototoxicity is a potential side effect of Polymyxin-B, which manifests as damage to the inner ear which may result in hearing loss or tinnitus. The exact mechanism by which Polymyxin-B causes ototoxicity remains uncertain; however, it could involve damage to hair cells responsible for detecting sound waves within the inner ear. Patients taking Polymyxin-B should undergo regular hearing tests to monitor for signs of ototoxicity; if present, medication should be discontinued or dose adjusted accordingly to prevent further hearing impairment [32].

Allergic Reactions

Although allergic reactions to Polymyxin-B are rare, they can occur and range in severity from mild rashes to severe anaphylactic reactions. Patients with a history of allergy to Polymyxin-B or other antibiotics should not be given Polymyxin-B. Symptoms of an allergic reaction to Polymyxin-B may include hives, swelling of the face or throat, difficulty breathing, and a sudden drop in blood pressure. In severe cases, anaphylaxis can occur, which can be life-threatening. Patients should be closely monitored for signs of an allergic reaction during the administration of Polymyxin-B, and healthcare providers should be prepared to intervene immediately in the event of a severe reaction [33].

Gastrointestinal Side Effects

Polymyxin-B can cause gastrointestinal side effects like nausea, vomiting and diarrhea that are relatively common; occurring in up to 20% of patients taking Polymyxin-B. Most cases are mild and self-limiting but in rare cases may become severe enough that treatment must be discontinued. It remains unclear exactly why Polymyxin-B causes these reactions but it's believed to be due to disruption to normal gut flora. To help alleviate these discomforts some individuals taking Polymyxin-B may receive probiotics or other supportive measures as needed in order to alleviate potential side effects from taking Polymyxin-B [34]. Electrolyte Imbalances:Polymyxin-B can cause electrolyte imbalances, leading to muscle

weakness, cardiac arrhythmias and seizures. Specifically, this substance affects sodium, potassium and calcium levels - essential minerals for normal cell functioning. These imbalances can arise as a result of changes in renal function, as Polymyxin-B is primarily eliminated through the kidneys. Patients taking Polymyxin-B should be closely monitored for signs of electrolyte imbalances and may require supplementation or adjustment of their electrolyte levels in order to avoid complications. It's essential to remember that electrolyte imbalances can happen rapidly and be life-threatening, thus the necessity for careful monitoring in patients taking Polymyxin-B [35].

It is essential to be aware that the incidence and severity of side effects associated with Polymyxin-B use may differ depending on a patient's age, underlying medical conditions, and other factors. Therefore, careful monitoring of patients receiving Polymyxin-B is necessary in order to detect potential issues early and manage them appropriately [36].

Polymyxin-B and Antibiotic Resistance

Polymyxin-B has seen a recent resurgence as an effective treatment for infections caused by antibiotic-resistant bacteria. This is likely due to its unique mechanism of action, which makes it effective against many multidrug resistant strains. Polymyxin-B targets the bacterial cell membrane, disrupting its integrity and leading to cell death - unlike many other antibiotics which target specific processes or components within cells [37].

However, overuse and misuse of Polymyxin-B can lead to resistance, decreasing its efficacy as a treatment option. Resistance is usually linked to mutations in bacteria's outer membrane that reduce their ability for antibiotics to bind and disrupt it. Healthcare settings are especially at risk for developing resistant bacteria due to multiple courses of antibiotic exposure that could put patients at greater risk for developing resistant infections.

To combat antibiotic resistance, researchers are working on developing new formulations of Polymyxin-B and finding drugs that can be combined with it for greater efficacy. Some studies have examined using Polymyxin-B in combination with other antibiotics like Carbapenem or tigecycline to enhance its activity against resistant bacteria. Other investigations have looked into using nanoparticles or other delivery systems in

order to enhance targeting and efficacy of Polymyxin-B [38].

In conclusion, Polymyxin-B is effective against many antibiotic-resistant bacteria; however, the potential risk of resistance development underscores the necessity for cautious usage of this antibiotic. Ongoing efforts to develop new treatments and combination therapies can help enhance Polymyxin-B's effectiveness while tackling the growing challenge of antibiotic resistance.

How Polymyxin-B addresses antibiotic resistance?

Polymyxin-B is an antibiotic that works by targeting the bacterial cell membrane. This unique mechanism of action makes Polymyxin-B effective against many multidrug resistant bacteria, even those resistant to other commonly used antibiotics.

Polymyxin-B works by attaching itself to and disrupting the outer membrane of bacterial cells, leading them to lyse and die. This mechanism differs from many other antibiotics which target specific processes or components within cells; thus, Polymyxin-B remains an important tool in combatting antibiotic resistance.One way Polymyxin-B combats antibiotic resistance is by offering an alternative treatment option for infections caused by multidrug-resistant bacteria. This is especially important in healthcare settings where patients may be more susceptible to infections and exposed to resistant strains of bacteria. By offering a treatment option effective against these germs, Polymyxin-B can help reduce their spread and improve patient outcomes [39].

Another way Polymyxin-B combats antibiotic resistance is by serving as a catalyst for developing new drugs and combination therapies. As researchers strive to find ways to enhance existing antibiotics' efficacy, Polymyxin-B serves as an invaluable starting point. By understanding how Polymyxin-B works and why it works against resistant bacteria, researchers can create drugs or combination therapies that build upon this understanding and increase treatment options for antibiotic-resistant infections [40].

In conclusion, Polymyxin-B addresses antibiotic resistance by providing an effective treatment option for infections caused by multidrug-resistant bacteria and serving as a platform for developing new drugs and combination therapies. Though resistance to Polymyxin-B is increasing, ongoing efforts to enhance existing

antibiotic effectiveness and develop new treatments can help address this challenge and ultimately improve patient outcomes.

Future Directions

Polymyxin-B has a bright future in the treatment of antibiotic-resistant infections, with ongoing research focused on several key areas.

Research is being done on new formulations and delivery systems for Polymyxin-B. For instance, researchers are exploring the use of nanoparticles and liposomes to better target and deliver Polymyxin-B, potentially decreasing resistance risks and improving patient outcomes. Other researchers are investigating combinations between Polymyxin-B with other antibiotics in order to enhance its activity against resistant bacteria [41].

Research is also focused on finding new compounds and drugs that can be combined with Polymyxin-B to combat resistance. These include beta-lactam antibiotics and other drugs which could enhance its efficacy against resistant bacteria. Other approaches involve using bacteriophages or phage-derived enzymes that target and disrupt bacteria's cell membrane, potentially increasing Polymyxin-B's activity [42].

In addition to these efforts, researchers are also researching strategies for preventing antibiotic resistance from spreading. This includes developing diagnostic tools and rapid tests that can identify resistant bacteria and guide treatment decisions. Other approaches involve employing infection control measures such as improved hand hygiene and personal protective equipment in order to reduce transmission risks and limit the spread of resistant bacteria.

In conclusion, the future of Polymyxin-B and its role in treating antibiotic-resistant infections looks promising, with ongoing research focused on developing new formulations, combination therapies, and infection control strategies. These efforts have the potential to enhance current treatments' efficacy while decreasing antibiotic resistance's spread - ultimately improving patient outcomes and alleviating antibiotic resistance's burden on global public health.

One promising area of research involves the application of artificial intelligence (AI) and machine learning (ML) to discover new drug candidates and optimize existing treatments. These approaches can sift through large datasets of genetic and phenotypic information to recognize patterns and

predict drug activity against specific pathogens. This could expedite development of novel drugs and combination therapies while decreasing resistance risks and improving patient outcomes [43].

One important area of research focuses on the microbiome and its role in modulating antibiotic resistance. Researchers are investigating ways to promote beneficial bacteria growth while decreasing exposure to antibiotic-resistant pathogens. Other approaches involve using faecal microbiota transplantation (FMT) as a way to restore balance within patients' gut microbiome that experience recurring or resistant infections [44].

Polymyxin-B's future in treating antibiotic-resistant infections depends on ongoing research to create new treatments, enhance existing ones, and prevent resistance from spreading. With continued investment in research and innovation, there is reason to be optimistic that these efforts will address the growing threat of antibiotic resistance while improving patient outcomes around the world [45].

Conclusion

Antibiotic resistance is a global public health crisis, with multidrug-resistant pathogens posing an increasingly daunting obstacle to effective treatment of bacterial infections. Polymyxin-B offers a novel solution to this problem; its unique mechanism of action targeting the bacterial cell membrane provides an effective remedy for many multidrug-resistant pathogens.

Though the rise of Polymyxin-B resistance is a cause for concern, ongoing efforts to develop new formulations, combination therapies and infection control measures are helping address this problem and improving patient outcomes. Utilizing AI/machine learning techniques, studying the microbiome, creating rapid diagnostic tools and tests all hold promise in furthering our understanding of antibiotic resistance while creating treatments to combat resistant pathogens.

It is essential to recognize the essential role antibiotics play in treating bacterial infections, and we must continue investing in research and innovation to combat the rising threat of antibiotic resistance. By working together to develop new treatments and infection control measures, we can guarantee patients receive quality care while decreasing antibiotic resistance's impact on global public health.

Polymyxin-B is an important tool in the fight against antibiotic-resistant infections, with ongoing research efforts helping to enhance its efficiency and create new treatments for this pressing public health concern.

References

1. Zakharova, A. A., Efimova, S. S., & Ostroumova, O. S. (2022). Lipid Microenvironment Modulates the Pore-Forming Ability of Polymyxin B. *Antibiotics*, *11*(10), 1445.

2. Hussein, M., Wong, L. J., Zhao, J., Rees, V. E., Allobawi, R., Sharma, R., ... & Velkov, T. (2022). Unique mechanistic insights into pathways associated with the synergistic activity of polymyxin B and caspofungin against multidrug-resistant Klebsiella pneumoniae. *Computational and Structural Biotechnology Journal*, *20*, 1077-1087.

3. Sib, E., Voigt, A. M., Wilbring, G., Schreiber, C., Faerber, H. A., Skutlarek, D., ... & Schmithausen, R. M. (2019). Antibiotic resistant bacteria and resistance genes in biofilms in clinical wastewater networks. *International journal of hygiene and environmental health*, *222*(4), 655-662.

4. Smith, N. M., Lenhard, J. R., Boissonneault, K. R., Landersdorfer, C. B., Bulitta, J. B., Holden, P. N., ... & Tsuji, B. T. (2020). Using machine learning to optimize antibiotic combinations: dosing strategies for meropenem and polymyxin B against carbapenem-resistant Acinetobacter baumannii. *Clinical Microbiology and Infection*, *26*(9), 1207-1213.

5. Smith, N. M., Lenhard, J. R., Boissonneault, K. R., Landersdorfer, C. B., Bulitta, J. B., Holden, P. N., ... & Tsuji, B. T. (2020). Using machine learning to optimize antibiotic combinations: dosing strategies for meropenem and polymyxin B against carbapenem-resistant Acinetobacter baumannii. *Clinical Microbiology and Infection*, *26*(9), 1207-1213.

6. Huang, T., Zeng, M., Fu, H., Zhao, K., Song, T., Guo, Y., ... & Chu, Y. (2022). A novel antibiotic combination of linezolid and polymyxin B octapeptide PBOP

against clinical Pseudomonas aeruginosa strains. *Annals of Clinical Microbiology and Antimicrobials*, *21*(1), 1-11.

7. Goossens, A., & Gonçalo, M. (2020). Contact allergy to topical drugs. In *Contact Dermatitis* (pp. 1019-1055). Cham: Springer International Publishing.

8. Falagas, M. E., Kyriakidou, M., Voulgaris, G. L., Vokos, F., Politi, S., & Kechagias, K. S. (2021). Clinical use of intravenous polymyxin B for the treatment of patients with multidrug-resistant Gram-negative bacterial infections: an evaluation of the current evidence. *Journal of Global Antimicrobial Resistance*, *24*, 342-359.

9. Chiu, S., Hancock, A. M., Schofner, B. W., Sniezek, K. J., Soto-Echevarria, N., Leon, G., ... & Brynildsen, M. P. (2022). Causes of polymyxin treatment failure and new derivatives to fill the gap. *The Journal of Antibiotics*, *75*(11), 593-609.

10. Nourbakhsh, F., Lotfalizadeh, M., Badpeyma, M., Shakeri, A., & Soheili, V. (2022). From plants to antimicrobials: Natural products against bacterial membranes. *Phytotherapy Research*, *36*(1), 33-52.

11. French, S., Farha, M., Ellis, M. J., Sameer, Z., Côté, J. P., Cotroneo, N., ... & Brown, E. D. (2019). Potentiation of antibiotics against Gram-negative bacteria by polymyxin B analogue SPR741 from unique perturbation of the outer membrane. *ACS Infectious Diseases*, *6*(6), 1405-1412.

12. Raman, A. P. S., Singh, M. B., Jain, P., Chaudhary, P., Bahadur, I., Lal, K., ... & Singh, P. (2022). An update on synthesis, properties, applications and toxicity of the ILs. *Journal of Molecular Liquids*, 119989.

13. Jangra, M., Kaur, P., Tambat, R., Raka, V., Mahey, N., Chandal, N., ... & Nandanwar, H. (2022). Recent Updates on Bacterial Secondary Metabolites to Overcome Antibiotic Resistance in Gram-Negative Superbugs: Encouragement or Discontinuation?. *Antimicrobial*

Resistance: Underlying Mechanisms and Therapeutic Approaches, 385-418.

14. Roberts, K. D., Zhu, Y., Azad, M. A., Han, M. L., Wang, J., Wang, L., ... & Li, J. (2022). A synthetic lipopeptide targeting top-priority multidrug-resistant Gram-negative pathogens. *Nature communications*, *13*(1), 1625.

15. Zhang, B., Li, X., Chen, Y., Chen, B., Cheng, Y., Lin, H., ... & Wu, C. (2023). Determination of polymyxin B in human plasma and epithelial lining fluid using LC-MS/MS and its clinical application in therapeutic drug monitoring. *Journal of Pharmaceutical and Biomedical Analysis*, *227*, 115291.

16. Fujimori, K., Tarasawa, K., & Fushimi, K. (2021). Effectiveness of polymyxin B hemoperfusion for sepsis depends on the baseline SOFA score: a nationwide observational study. *Annals of Intensive Care*, *11*, 1-9.

17. Tamma, P. D., Aitken, S. L., Bonomo, R. A., Mathers, A. J., Van Duin, D., & Clancy, C. J. (2021). Infectious Diseases Society of America guidance on the treatment of extended-spectrum β-lactamase producing Enterobacterales (ESBL-E), carbapenem-resistant Enterobacterales (CRE), and Pseudomonas aeruginosa with difficult-to-treat resistance (DTR-P. aeruginosa). *Clinical Infectious Diseases*, *72*(7), e169-e183.

18. Zhou, Y., Li, Y., Xie, X., Song, L., Lan, G., Sun, B., ... & Xu, P. (2022). Higher incidence of neurotoxicity and skin hyperpigmentation in renal transplant patients treated with polymyxin B. *British Journal of Clinical Pharmacology*, *88*(11), 4742-4750.

19. Wang, P., Xing, H., Zhang, F., Liu, S., Lu, Y., Zhang, X., ...& Sun, T. (2022). Population pharmacokinetics of polymyxin B in critically ill patients receiving continuous venovenoushaemofiltration. *International Journal of Antimicrobial Agents*, *60*(1), 106599.

20. Silva, B. R., Queiroz, P. A., Amaral, P. H. R. D., Freitas, B. C. D., Stocco, A. F., Sampiron, E. G., ... &Siqueira, V. L. D. (2022). Polymyxin B

Activity Rescue by (−)-Camphene-Based Thiosemicarbazide Against Carbapenem-Resistant Enterobacterales. *Microbial Drug Resistance*, *28*(10), 962-971.

21. Wang, P. L., Liu, P., Zhang, Q. W., Yuan, W. H., Wang, D., Zhang, X. J., & Yang, J. (2022). Population pharmacokinetics and clinical outcomes of polymyxin B in paediatric patients with multidrug-resistant Gram-negative bacterial infections. *Journal of Antimicrobial Chemotherapy*, *77*(11), 3000-3008

22. Wang, P., Liu, D., Sun, T., Zhang, X., & Yang, J. (2022). Pharmacokinetics and pharmacodynamics of polymyxin B and proposed dosing regimens in elderly patients with multi-drug-resistant Gram-negative bacterial infections. *International Journal of Antimicrobial Agents*, *60*(5-6), 106693.

23. Zhang, C., Liu, X., Wu, H., Wang, Y., Fan, Y., Guo, B., ...& Zhang, J. (2022). Proteomic Response Revealed Signaling Pathways Involving in the Mechanism of Polymyxin B-Induced Melanogenesis. *Microbiology Spectrum*, *10*(2), e02730-21.

24. Chung, W. Y., Rahim, N. A., Maifiah, M. H. M., Shivashekaregowda, N. K. H., Zhu, Y., & Wong, E. H. (2022). In silico genome-scale metabolic modeling and in vitro static time-kill studies of exogenous metabolites alone and with polymyxin B against Klebsiella pneumoniae. *Frontiers in Pharmacology*, *13*.

25. Tabcheh, J., Vergalli, J., Davin-Régli, A., Ghanem, N., Al-Bayssari, C., & Brunel, J. M. (2023). Rejuvenating the Activity of Usual Antibiotics on Resistant Gram-Negative Bacteria: Recent Issues and Perspectives. *International Journal of Molecular Sciences*, *24*(2), 1515.

26. Fu, L., Li, X., Zhang, S., Dong, Y., Fang, W., & Gao, L. (2022). Polymyxins induce lipid scrambling and disrupt the homeostasis of Gram-negative bacteria membrane. *Biophysical Journal*, *121*(18), 3486-3498.

27. Clancy, C. J., Potoski, B. A., Buehrle, D., & Nguyen, M. H.

(2019, August). Estimating the treatment of carbapenem-resistant Enterobacteriaceae infections in the United States using antibiotic prescription data. In *Open forum infectious diseases* (Vol. 6, No. 8, p. ofz344). US: Oxford University Press.

28. Xie, J., Roberts, J. A., Lipman, J., Cai, Y., Wang, H., Zhao, N., ... & Zhang, K. (2020). Pharmacokinetic/pharmacodynamic adequacy of polymyxin B against extensively drug-resistant Gram-negative bacteria in critically ill, general ward and cystic fibrosis patient populations. *International journal of antimicrobial agents*, *55*(6), 105943.

29. Li, Y., Deng, Y., Zhu, Z. Y., Liu, Y. P., Xu, P., Li, X., ... & Zhou, Y. G. (2021). Population pharmacokinetics of polymyxin B and dosage optimization in renal transplant patients. *Frontiers in Pharmacology*, *12*, 727170.

30. Payne, J. D. (2020). Texas Chapter American College of Physicians-Abstract supplement. *The Southwest Respiratory and Critical Care Chronicles*, *8*(32), 2-74.

31. Staff, N. P., Cavaletti, G., Islam, B., Lustberg, M., Psimaras, D., & Tamburin, S. (2019). Platinum-induced peripheral neurotoxicity: from pathogenesis to treatment. *Journal of the Peripheral Nervous System*, *24*, S26-S39.

32. Guo, J., Chai, R., Li, H., & Sun, S. (2019). Protection of hair cells from ototoxic drug-induced hearing loss. *Hearing loss: Mechanisms, prevention and cure*, 17-36.

33. Du, X., Tong, H., Jiang, Y., & Shao, B. (2022). A Retrospective Analysis of Polymyxin B Combined with Tigecycline in the Treatment of Multi-Drug Resistance Klebsiella pneumoniae Infection: Hypertension Increases the Incidence of Acute Kidney Injury. *Indian Journal of Pharmaceutical Sciences*, 103-110.

34. Djague, F., Lunga, P. K., Toghueo, K. R. M., Melogmo, D. Y. K., & Fekam, B. F. (2020). Garcinia kola (Heckel) and Alchornea cordifolia (Schumach. & Thonn.) Müll. Arg. from Cameroon possess potential

antisalmonellal and antioxidant properties. *PLoS One*, *15*(8), e0237076.

35. Parente, D. M., Cunha, C. B., & Lorenzo, M. (2020). Adverse Reactions to Antibiotics in the Critical Care Unit. In *Infectious Diseases and Antimicrobial Stewardship in Critical Care Medicine* (pp. 427-436). CRC Press.

36. Wang, P., Zhang, Q., Zhu, Z., Pei, H., Feng, M., Sun, T., ... & Zhang, X. (2021). Comparing the population pharmacokinetics of and acute kidney injury due to polymyxin B in Chinese patients with or without renal insufficiency. *Antimicrobial Agents and Chemotherapy*, *65*(2), e01900-20.

37. Nourbakhsh, F., Lotfalizadeh, M., Badpeyma, M., Shakeri, A., & Soheili, V. (2022). From plants to antimicrobials: Natural products against bacterial membranes. *Phytotherapy Research*, *36*(1), 33-52.

38. Thomas, V. M., Brown, R. M., Ashcraft, D. S., & Pankey, G. A. (2019). Synergistic effect between nisin and polymyxin B against pandrug-resistant and extensively drug-resistant Acinetobacter baumannii. *International journal of antimicrobial agents*, *53*(5), 663-668.

39. Kim, S. Y., Seo, H. W., Park, M. S., Park, C. M., Seo, J., Rho, J., ... & Ryu, C. M. (2023). Exploitation of a novel adjuvant for polymyxin B against multidrug-resistant Acinetobacter baumannii. *Journal of Antimicrobial Chemotherapy*, *78*(4), 923-932.

40. Rigatto, M. H., Falci, D. R., & Zavascki, A. P. (2019). Clinical use of polymyxin B. *Polymyxin Antibiotics: From Laboratory Bench to Bedside*, 197-218.

41. Krivic, H., Himbert, S., Sun, R., Feigis, M., & Rheinstädter, M. C. (2022). Erythro-PmBs: A Selective Polymyxin B Delivery System Using Antibody-Conjugated Hybrid Erythrocyte Liposomes. *ACS Infectious Diseases*, *8*(10), 2059-2072.

42. Huang, T., Zeng, M., Fu, H., Zhao, K., Song, T., Guo, Y., ... & Chu, Y.

(2022). A novel antibiotic combination of linezolid and polymyxin B octapeptide PBOP against clinical Pseudomonas aeruginosa strains. *Annals of Clinical Microbiology and Antimicrobials*, *21*(1), 1-11.

43. Lv, H., Shi, L., Berkenpas, J. W., Dao, F. Y., Zulfiqar, H., Ding, H., ... & Cao, R. (2021). Application of artificial intelligence and machine learning for COVID-19 drug discovery and vaccine design. *Briefings in Bioinformatics*, *22*(6), bbab320.

44. Chiu, C. W., Tsai, P. J., Lee, C. C., Ko, W. C., & Hung, Y. P. (2021). Application of microbiome management in therapy for Clostridioides difficile infections: from fecal microbiota transplantation to probiotics to microbiota-preserving antimicrobial agents. *Pathogens*, *10*(6), 649.

45. Marchant Gutiérrez, P. F. (2021). *Functional transfer of OMV-mediated polymyxin resistance: role of tolR and degS genes in altruistic antibiotic resistance* (Doctoral dissertation, Universidad Andrés Bello).