REVIEW ARTICLE

Colistin resurgence: Revisiting an old antibiotic in the fight against resistant pathogens

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Abstract

The upsurge of colistin represents a pivotal juncture in the ongoing battle against antibiotic-resistant pathogens. The aim of the literature review was to delve into the resurgence of colistin, an erstwhile antibiotic, and its renewed prominence to overcome multidrug-resistant organisms. Through an exploration of recent literature, the review has been done to highlight the efficacy of colistin against gram-negative bacteria, especially those resistant to conventional antibiotics. Despite concerns regarding its toxicity and the potential for resistance development, colistin remains a critical therapeutic option to combat against the various infections caused by these extensively drug-resistant pathogens. Recent achievements in understanding colistin's pharmacodynamics, mechanisms of action, and resistance operations have revitalized interest in this old antibiotic. This review scrutinizes into the efficacy, mechanisms of action, and challenges related to the renewed employment of colistin among clinical settings. Employing a comprehensive literature search strategy, diverse databases such as PubMed, Google Scholar, and relevant academic databases were meticulously explored. Keywords were utilized to identify pertinent studies. Screening and selection criteria were applied to sift through articles, ensuring the inclusion of studies relevant to the topic. Furthermore, ongoing research endeavours aim to optimize colistin dosing regimens and explore combination therapies to increase potency while lowering the vulnerability of adverse reactions and the threat of resistance. The resurgence of colistin underscores the ever-evolving landscape of antimicrobial therapy and emphasizes the imperative of innovative measures to tackle antibiotic resistance effectively. By revisiting the function of colistin in the armamentarium against resistant pathogens, this review underscores the imperative for continued research and stewardship efforts to optimize its clinical utility while minimizing associated drawbacks

Keywords: Antimicrobial Resistance, Colistin, Multi-drug Resistance

Introduction

The increasing trend of Antimicrobial Resistance (AMR) among microorganisms has been a great threat for the medical fraternity in the today's world. [1]. Over the past decades, the medical community has witnessed the relentless evolution of resistant pathogens, rendering many once-effective treatments obsolete [2]. Colistin is being now increasingly employed in human medicine as a final option for infections which are being caused by Gram-Negative Bacteria (GNB) that resist multiple drugs, including carbapenemase-producing *Enterobacterales, Pseudomonas aeruginosa,* and *Acinetobacter baumannii* in these recent years [3].

Originally unveiled in the late 1940s, colistin (also referred to as polymyxin E), was initially employed primarily in veterinary medicine due to concerns about its nephrotoxicity and neurotoxicity in humans [4]. However, as antibiotic-resistance among GNB surged, the medical community revisited colistin to be the last available therapeutic option [5]. Furthermore, the surge of bacterial resistance to multiple antimicrobial treatments poses significant challenges in effectively managing infectious diseases, exacerbated by the limited antibiotics currently available [6]. Colistin has re-emerged as a final resort for Dealing with infections stemming from Multidrug-Resistant (MDR) GNB, notably *Acinetobacter baumannii, Pseudomonas aeruginosa,* and Enterobacterales. [7]. Despite its historical limitations, colistin was used because of its unique mechanism of action, targeting the lipopolysaccharide layer of GNB [8]. This mechanism makes colistin less susceptible to conventional resistance mechanisms, such as beta-lactamases and efflux pumps, which have rendered many other antibiotics ineffective [9].

Moreover, advancements in pharmacokinetic and pharmacodynamic understanding, coupled with the development of novel formulations and delivery methods, have addressed previous concerns regarding colistin's toxicity and suboptimal efficacy [10]. These innovations have revoked interest in colistin as a crucial inclusion in the synergistic treatment plan regimens aimed at combating severely drug-resistant infections caused by bacteria [11]. Furthermore, the expanding menace posed by healthcare-associated infections, particularly from Intensive Care Units (ICUs) and long-term care facilities, underscore the critical demand for potent antimicrobial therapies [12]. Its effectiveness against a broad array of gram-negative pathogens has positioned colistin as a valuable therapeutic option in settings where multidrug resistance is prevalent [13]. Due to evolving AMR and the limited pipeline of manufacturing of novel antibiotics, the resurgence of colistin represents a pivotal chapter in the ongoing struggle against drug-resistant pathogens [14].

This review aimed to provide a comprehensive overview of the resurgence of colistin, examining its historical context, mechanisms of action, pharmacological considerations, clinical efficacy, and future prospects in combating AMR.

Evolution of antibiotic resistance

The escalation of AMR on a global scale represents a formidable challenge to public health systems worldwide [15]. Over the past few years, among bacterial populations there has been a rising threat of AMR which is quite alarming; with MDR strains emerging as a particularly pressing concern [14]. These pathogens, adapt at evading the repercussions of multiple classes of antibiotics, pose significant challenges to infection control and treatment [16]. Factors which may be contributing to this phenomenon consist of overuse and misuse of antibiotics in many different sectors such as healthcare, agriculture and veterinary care [17]. The interdependence of modern civilization, influenced by global transportation and trade networks, facilitates further spread of resistant bacteria across global boundaries [17]. As many infections are frequently treated empirically without conducting antibiotic susceptibility testing, such practices substantially contribute to the growing resistance of bacteria to commonly used antibiotics. Hence, the selection of antimicrobial agents should be informed by the likely causative pathogen and the prevailing resistance patterns within the relevant geographic area [18]. Hence, the evolution and transmission of effective therapeutic options to combat antibiotic-resistant infections have become imperative [19]. Both urgent efforts should prioritize research and development into novel antibiotics and the enhancement of existing antimicrobial agents to ensure their efficacy against MDR pathogens [20]. Additionally, there is a growing recognition of the need of implementing stringent antimicrobial stewardship programs and infection control measures to mitigate the further spread of AMR [21]. Addressing the adaptation of AMR requires a multifaceted and concerted approach involving cooperation between healthcare professionals, policymakers, and researchers, and the public to preserve antibiotic effectiveness for future generations [22].

Scholarly research exploration approach on colistin resistance

A comprehensive review of the existing literature was conducted using a systematic approach from PubMed and Medline databases. The search was refined using the following keywords: "colistin resistance", "mechanisms of resistance", and "multi-drug resistant". Filters were applied to limit the selection to Randomized Controlled Trials (RCTs), systematic reviews, and meta-analyses published within the last 10 years.

This initial search yielded a total of 28 articles, without any duplications. The screening based on its title and abstract for relevance to the study's objectives was done. Upon screening, 5 articles were excluded due to mismatched inclusion criteria, inadequate sample size, or differences in primary or secondary outcomes. Further exploration accounted for the exclusion of 13 additional articles based on similar grounds. Ultimately, a total of 7 researches were eligible to be included in the systematic review. These articles were carefully analysed to synthesize existing knowledge on colistin resistance, identify gaps in research, and inform the framework of the existing study. The act of selecting is summarized in the Tabular form in Table 1 for transparency and reproducibility. This table delves into the key ethical considerations surrounding the emergence of colistin resistance, drawing insights from a range of scholarly sources [23-29]. By critically examining these ethical dimensions, we aimed to chart a course that ensures responsible management of colistin resistance, thereby safeguarding both patient welfare and the integrity of healthcare systems worldwide. Table 1 provides a comprehensive overview of the primary research studies informing our understanding of this critical issue.

Table 1: Scholarly research exploration approach results

Author	Research Focus	Conclusion	Observations
Ahmed MAEG, *et al*. (2020) [23]	Reviewing the historical and contemporary role of colistin in the context of antibiotic resistance.	Reinforcing the importance of colistin as a critical antibiotic in treating infections caused by resistant pathogens	Discussion of nephrotoxicity, neurotoxicity, and other adverse effects associated with colistin use, with insights into approaches aimed at lowering these hazards

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Li J., *et al*.(2019) [24]	Identifying the mechanisms underlying colistin resistance in these strains, including genetic mutations or mobile genetic elements like plasmids	Highlighting the genetic mechanisms responsible for colistin resistance and their potential impact on treatment strategies	Analysis of plasmid-mediated transmission of mcr genes and their role in disseminating resistance.
Fan Y. *et al.* (2020) [25]	Assessing the relationship between the concentration of colistin methanesulfonate in the body and its pharmacological effects.	Discussing the relationship between drug concentrations and antibacterial activity.	Analyzing correlations between drug concentrations and bacterial killing or resistance development.
Baig M., *et al*. (2018) [26]	Evaluating the effectiveness of intravenous colistin monotherapy versus combination therapy with colistin and meropenem in treating multidrug-resistant infections	Occurrence of antibiotic heteroresistance in clinical *Klebsiella pneumoniae* isolates and its importance in clinical outcomes.	Insights into current clinical practices with respect to the application of colistin monotherapy versus combination therapy with meropenem for multidrug-resistant infections
Stojowska-Swędrzyńska K., *et al.* (2020) [27]	Investigating the phenomenon of antibiotic heteroresistance in *Klebsiella pneumoniae*	Prevalence of antibiotic heteroresistance in clinical isolates of *Klebsiella pneumoniae* and its clinical significance.	Analysis of antibiotic resistance profiles and heteroresistance patterns across different clinical settings or geographic regions.
Slingerland CJ, *et al.* (2020) [28]	Development and synthesis of novel polymyxin compounds modified with reductively labile disulfide-linked lipids.	Reporting on the antibacterial potency of the modified polymyxins compared to standard polymyxin formulations.	Analysis of structure-activity relationships for the modified polymyxin derivatives, including correlations between chemical structure modifications and antibacterial efficacy.

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Binsker U, *et al.* (2020) [29]	Reviewing the worldwide use of colistin and its impact on the emerging resistance in Enterobacterales, focusing on epidemiological trends and patterns.	Highlighting the rapid emergence of colistin-resistant Enterobacterales globally and its implications for healthcare settings.	Analysis of genetic studies elucidating the molecular mechanisms of colistin resistance

Colistin has seen a resurgence as a crucial antibiotic in combating contemporary MDR bacteria, highlighting the pressing demand for improved strategies in antimicrobial use and innovative treatment strategies [30]. These interventions also play a role in reducing biases and build trust among stakeholders while respecting patient autonomy. We can ensure a unified approach to combating resistance and safeguarding the efficacy of colistin as a vital antimicrobial agent.

Initial decline and resurgence of colistin

The initial decline and subsequent resurgence of colistin in therapeutic practice reflect a complex interplay of factors spanning several decades. The resurgence of colistin highlights its critical role in treating infections caused by MDR bacteria, despite its historical decline due to concerns about toxicity and the availability of alternative antibiotics [31]. However, the rise of MDR bacterial pathogens has prompted exploration into revitalizing old medications previously withdrawn due to safety concerns [32]. Polymyxins exhibit strong inhibitory activity against GNB, making them a crucial option to address the challenge posed by pathogens that no longer respond to frontline antibiotics like β-lactams, aminoglycosides, and fluoroquinolones [33]. Recent research and clinical recommendations emphasize the critical need for careful administration of colistin, emphasizing tailored dosing protocols and rigorous monitoring to lower the risk of harm to the kidneys [34] Thus, the renewed use of colistin highlights the challenge of balancing therapeutic requirements with responsible antibiotic management in contemporary healthcare [35].

Mechanism of action

Colistin, included in the polymyxin category of antibacterial drugs, primarily exerts its bactericidal effect by disrupting the protective membrane structure of GNB. [36]. Colistin has a positive charge that enables it to electrostatically attach to the negatively charged phosphate groups of lipid A, which is part of the outer membrane in GNB [37]. Following its initial binding, colistin displaces the divalent calcium and magnesium ions that stabilize the three-dimensional structure of Lipopolysaccharides (LPS). As shown in figure 1, it subsequently embeds its hydrophobic fatty acid chain into the membrane, disrupting and increasing the permeability of the outer membrane. This disruption enables colistin to cross the outer barrier and damage the inner membrane's phospholipid bilayer, leading to leakage of cellular contents and ultimately bacterial cell death [38]. Notably, colistin is effective against a wide range of MDR GNB, such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and several members of the Enterobacteriaceae family [32]. It is a bactericidal agent with a narrow spectrum, targeting most GNB. However, it leaves unchanged gram-positive bacteria, anaerobic bacteria, or mycoplasmas [39]. Despite growing worries about bacterial resistance to colistin, frequently associated with mutations in regulatory genes such as those in two-component systems, colistin remains highly effective against many MDR bacteria. This effectiveness allows it to remain a vital option for treating serious infections when other treatments are unsuccessful [40].

In clinical settings, colistin is typically held in reserve as a last-line treatment for severe infections including Ventilator-Associated Pneumonia (VAP), bloodstream infections, and complex urinary tract infections especially in critically ill patients where other antibiotics have proven ineffective or unsuitable [36]. Additionally, colistin can be administered together with other antibiotics, such as carbapenems or tigecycline, to enhance efficacy and limit the emergence of resistance [43]. Even though colistin can cause significant kidney and nerve toxicity requiring vigilant monitoring and careful dose adjustments, it continues to be a vital option for treating life-threatening infections due to Extensively Drug-Resistant (XDR) GNB [31].

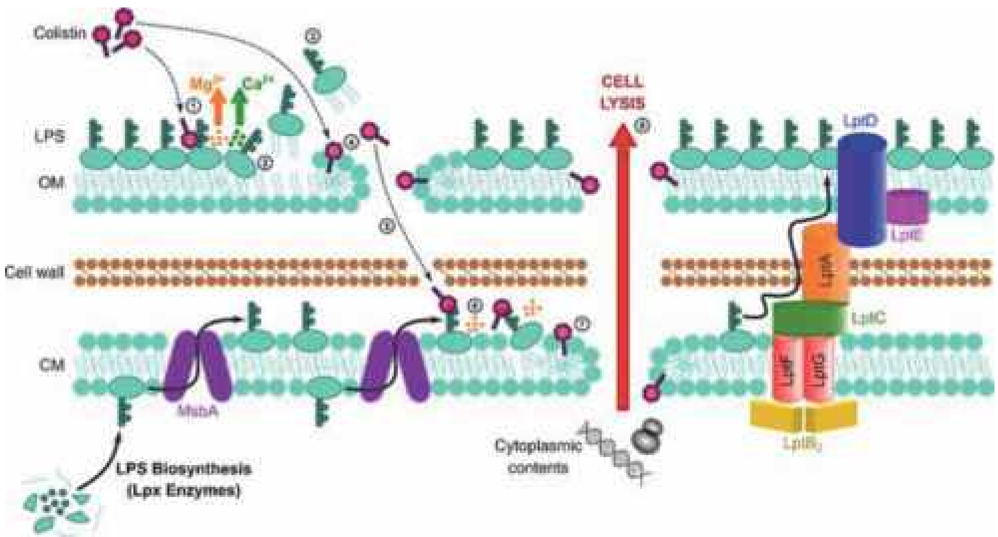

Figure 1: Colistin functions by acting on Lipopolysaccharide (LPS) found in both the outer membrane and Cytoplasmic Membrane (CM) of bacteria, resulting in the disruption of the cell envelope and eventual bacterial lysis. (Source: Sabnis *et al.*) [41]

Clinical applications

Colistin's clinical applications encompass a wide spectrum of infections, particularly those caused by extensively drug-resistant gram-negative organisms [33]. Colistin plays an essential role as a treatment option when typical antibiotics are either ineffective or unsuitable. It is especially indicated for managing infections caused by MDR, such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and certain Enterobacteriaceae, including *Klebsiella pneumoniae* and *Escherichia coli* [32]. These pathogens are well-known for their resistance to multiple classes of antibiotics, which significantly reduces the effectiveness of available treatments. [42].

Adverse effects and toxicity

Colistin proves effective against MDR GNB infections; however, neurotoxicity remains a fundamental dose-limiting factor for this treatment [44]. Colistin carries a risk of nephrotoxicity, though current diagnostic criteria may exaggerate the frequency of kidney injury. Nephrotoxicity itself correlates with lower rates of infection resolution and higher mortality [45]. The primary event in colistin-induced kidney injury is considered to be acute tubular damage of a necrotic nature affecting proximal tubule cells [46]. Neurotoxicity, another critical adverse effect, manifests as symptoms ranging from dizziness and confusion to more severe outcomes such as seizures and respiratory paralysis [47]. The neurotoxic effects of colistin are attributed to its ability to penetrate the blood-brain barrier, leading to neuronal damage and dysfunction [45]. To mitigate these risks, various strategies have been proposed. One approach involves optimizing dosing regimens to minimize peak serum concentrations, thereby reducing nephrotoxicity [48]. Neurotoxicity caused by colistin is dose-dependent and reversible. It can present as various symptoms such as paresthesia, peripheral neuropathy, ptosis, ophthalmoplegia, and in severe cases, neuromuscular blockade leading to respiratory paralysis, necessitating ventilator support. [49-50]. Furthermore, utilizing alternative antibiotics or combination therapy whenever feasible may help mitigate the credence on colistin and reduce the potential of adverse effects [50]. Comprehensive patient monitoring, including regular renal function tests and neurological assessments, is essential for early detection and management of adverse effects during colistin therapy. [51]. In summary, while colistin remains a crucial therapeutic option in combating drug-resistant infections, healthcare providers need to stay alert to the possible side effects and toxicities linked to its administration and implement suitable measures to reduce these risks, thereby promoting the best possible outcomes for patients.

Mechanisms of resistance

One common way bacteria resist antibiotics is by altering their outer membrane, reducing colistin's ability to bind and disrupt the membrane, typically mediated by alterations in lipid A biosynthesis pathways [52]. Another mechanism is the production of enzymes such as phosphoethanolamine transferases, which modify lipid A, decreasing colistin affinity [53]. Additionally, efflux pumps expel colistin from bacterial cells, diminishing its concentration intracellularly [54]. These mechanisms collectively confer resistance, rendering colistin less effective in treating bacterial infections. Consequently, clinicians face narrow range of options and an increased dependability on alternative antibiotics, which may have greater associated risks. Grasping how these mechanisms work is vital for creating effective approaches to counteract resistance. To ensure that colistin and other antibiotics remain effective in treating infections, it is important to use them responsibly and implement strategies that prevent the development of resistance (Figure 2).

Optimization of colistin use

Optimizing the colistin use in clinical settings necessitates a comprehensive strategy encompassing various approaches. Dosing strategies are crucial in maximizing efficacy while minimizing the risk of resistance and toxicity. Tailored dosing regimens based on pharmacokinetic and pharmacodynamic principles, including loading doses and prolonged infusions, have been proposed to enhance bacterial killing while ensuring safety [55]. Using colistin together with other antibiotics, like carbapenems or rifampicin, has become a promising strategy to overcome resistance and enhance the effectiveness of treatment. Such combinations often produce synergistic effects against MDR bacteria [56]. Furthermore, the implementation of antimicrobial stewardship programs plays a pivotal role in guiding appropriate colistin use. These programs promote judicious antibiotic prescribing, surveillance of resistance patterns, and interventions to prevent misuse or overuse of colistin, thereby preserving its efficacy for future use [56]. By integrating dosing optimization, combination therapies, and antimicrobial stewardship initiatives, healthcare facilities can effectively optimize colistin therapy and address the challenges associated with antimicrobial resistance.

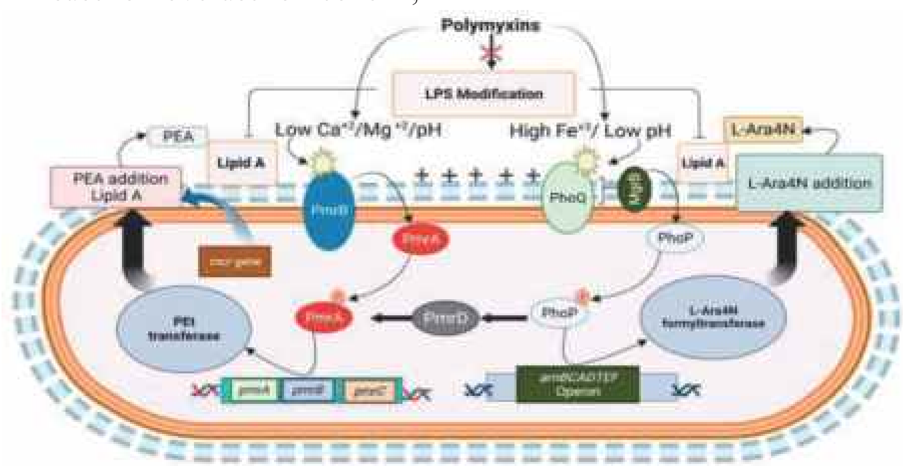

Figure 2: The mechanisms driving changes in Lipopolysaccharides (LPS) that contribute to polymyxin resistance among gram-negative bacteria involve multiple pathways. In species like *Salmonella*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, environmental stresses trigger responses mediated by histidine kinases such as PhoQ and PmrB. These stressors include exposure to cationic agents like polymyxins, low concentrations of Magnesium (Mg^{2+}) and Calcium (Ca^{2+}), acidic pH, and increased iron (Fe^{3+}) levels. The activation of the PhoP-PhoQ and PmrA-PmrB two-component regulatory systems is triggered by specific environmental cues. Once activated, these systems upregulate the expression of the arnBCADTEF and pmrCAB operons. This upregulation leads to modifications in lipid A: the arnBCADTEF operon facilitates the synthesis and attachment of 4-amino-4-deoxy-L-arabinose (L-Ara4N), while the pmrCAB operon enables the addition of phosphoethanolamine (PEA). These chemical modifications are executed by enzymes like phosphoethanolamine transferase and L-Ara4N formyltransferase. Moreover, the activation of PhoP-PhoQ can further enhance PmrA-PmrB activity via the PmrD protein, amplifying arnBCADTEF expression. Resistance to polymyxins is often linked to the inactivation of MgrB—a negative regulator of PhoP-PhoQ. Loss-of-function mutations or amino acid alterations in MgrB lead to unchecked PhoP-PhoQ activity, resulting in heightened expression of the pmrHFIJKLM operon, and consequently increased production of L-Ara4N, which contributes to antibiotic resistance (Source: Shahzad *et al.*) [56]

Future directions and challenges

In the continuous fight to curb antibiotic resistance, future directions in research and clinical practice are paramount to combat emerging challenges. One promising avenue lies in creating new antibiotics that work through unique and innovative mechanisms of action to overcome existing resistance mechanisms. This involves researching novel antimicrobial compounds obtained from various origins, such as natural substances and artificially created compounds [50]. Colistin-based combination therapies, integrating novel antibiotics or adjuvants, hold promise for overcoming resistance mechanisms in Gram-negative pathogens, paving the path toward optimizing treatment effectiveness against MCR infections. [59]. Additionally, advancements in technologies such as genomics, proteomics, and machine learning offer opportunities to identify novel drug targets, predict resistance mechanisms, and optimize treatment strategies [60]. However, substantial challenges persist, including regulatory hurdles, economic constraints, and the relentless evolution of resistance. Addressing these obstacles requires sustained investment, interdisciplinary collaboration, and global coordination to effectively manage antibiotic resistance in the years ahead.

Conclusion

The resurgence of colistin highlights the critical need to rely on older antibiotics in the fight against MDR GNB, as limited new antibiotics are available. Despite concerns about its toxicity, colistin remains an indispensable last-resort option in modern clinical practice to tackle severe infections caused by resistant pathogens. This renewed use underscores the importance of ongoing vigilance, monitoring, and stewardship to preserve its effectiveness. This resurgence highlights colistin's role as a last-resort treatment when other antibiotics fail to effectively combat infections caused by these resistant bacteria. While colistin continues to serve as a crucial last-resort antibiotic, its renewed use brings with it significant concerns about the potential emergence of resistance. This situation emphasizes the importance of careful management and stewardship practices in healthcare to ensure that colistin remains effective. The growing reliance on colistin draws attention to the must have requirement for responsible prescribing and the innovation of creative policies to prevent and control resistance. Understanding the mechanisms driving colistin resistance and implementing optimized dosing regimens and combination therapies are essential steps in preserving its efficacy. Additionally, the exploration of colistin-based combination therapies with novel antibiotics or adjuvants signifies a proactive approach to overcoming resistance mechanisms in GNB, potentially enhancing treatment efficacy against MDR infections. Moreover, the integration of genomics, proteomics, and machine learning presents opportunity for identifying new drug targets and predicting resistance patterns, thereby optimizing treatment strategies. Despite these advancements, formidable challenges such as regulatory complexities, economic constraints, and the persistent evolution of resistance continue to pose significant hurdles. Tackling these issues requires ongoing investment, interdisciplinary collaboration, and global coordination to safeguard the efficiency of antibiotics and ensure future generations have effective treatments against resistant infections.

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