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*Review Article*

# Combating carbapenem-resistant organisms with colistin-sparing regimens

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## ABSTRACT

The increase in carbapenem-resistant organisms (CROs) poses a public health threat and necessitates the investigation of alternative therapies to reduce colistin use. The aim of this review is to discuss sparing the use of colistin. There are many limitations to the use of colistin, including a higher risk of toxicity and the rapid development of resistance. The use of colistin-sparing combinations includes β-lactam/β-lactamase inhibitor combinations, carbapenem-aminoglycoside combinations, and carbapenem-fosfomycin combinations. In addition, monotherapy agents such as cefiderocol, a new siderophore cephalosporin with potential activity against CROs, and plazomicin, a next-generation aminoglycoside with a favourable safety profile and also some combination therapies that might spare the use of colistin. The review concludes by highlighting the urgent need to explore colistin-sparing regimens and develop new antimicrobial agents to ensure effective treatment options for multidrug-resistant infections.

**Keywords:** Carbapenem-resistant organisms, Colistin, Colistin-sparing regimens, Polymyxins

## INTRODUCTION

The rapid increase in antimicrobial resistance is a serious concern, and the need to explore new treatment options is crucial. One approach to manage this issue is by either upgrading existing antibiotics or using antibiotic combinations. In times, there has been an uptick in cases involving carbapenem-resistant bacteria in specialised healthcare settings.[1] While there is evidence supporting the use of combinations, these findings are often limited to experimental data or studies with small sample sizes. Furthermore, evidences are limited on antibiotic dosing protocols that are optimised based on the pharmacokinetic and pharmacodynamics parameters. Antibiotics are commonly combined under the assumption that their effectiveness remains consistent when used alone. However, there is evidence that using antibiotics in combinations has broadened the antimicrobial spectrum and combated the emergence of resistance.[2] Extensively used as a final treatment option for multidrug-resistant Gram-negative bacterial infections, Colistin is a cationic polypeptide belonging to the polymyxin class of antibiotics.[3] Polymyxins such as Polymyxin B (also known as colistin) act by disrupting the cell membranes, leading to their antibacterial potential. The growing prevalence of carbapenem-resistance organisms (CROs) poses challenges for healthcare providers that underscore the need for effective treatment strategies. CROs consist of four categories of Gram-negative Pathogens: (i) Carbapenem-resistant *Enterobacteriaceae* (CRE) have Class A Carbapenemase (e.g., *Klebsiella pneumoniae* carbapenemases [KPC]), Class B

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Carbapenemase (e.g., New Delhi metallo β-lactamases [NDM]), Class C Carbapenemase (e.g., oxacillinases [OXA-48]). (ii) carbapenem-resistant *Pseudomonas aeruginosa;* (iii) Carbapenem-resistant *Acinetobacter baumannii* (CRAB); and (iv) *Stenotrophomonas maltophilia*.[4,5]

Carbapenems exhibit broad-spectrum activity against both Gram-negative and Gram-positive bacteria, serving as a critical line of defence against the most persistent and challenging infections. Overuse of colistin is a result of the increasing carbapenem resistance over time.[6] Therefore, it is crucial to explore the treatments that can reduce the need for colistin while still effectively killing bacteria. To combat infections stemming from drug-resistant pathogens, particularly those in the 'Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter (ESKAPE)' group, clinicians often employ the combination therapy.[7] To combat the spread of these pathogens and minimise reliance on colistin, it is also crucial to evaluate new combinations that may delay resistance.[8] For instance, β-lactam antibiotics can synergise with various other types of antibiotics. The rationale for using colistin-sparing regimens for CROs will aim to preserve the efficacy of colistin and prolong the clinical utility of colistin as a last-line antibiotic. Colistin-sparing regimens discussed below would also minimise the risk associated with the drug. Also, using the alternative combination therapies can enhance antimicrobial activity and prevent the emergence of resistance in CROs. This approach aligns with the broader goal of preserving antibiotic efficacy and ensuring effective treatment options for multidrug-resistant infections.

This review aims to present a look at strategies for managing infections without relying heavily on colistin-covering approaches, such as creating new antimicrobial agents, combining antibiotics using additional therapies alongside medications and exploring alternative treatment methods. The focus will be on understanding how these approaches work, their effectiveness and potential obstacles they may face.

## EPIDEMIOLOGY AND GLOBAL BURDEN OF CROS

CROs have become a concern, as health is showing different levels of impact in various regions and healthcare settings. As per the Centres for Disease Control and Prevention, CRE infections lead to around 13,100 hospitalisations and 1,100 fatalities annually in the United States.[9] In Europe, the European Centre for Disease Prevention and Control stated that CRE caused 33,000 cases and 8,600 deaths in 2015.[10] The global challenge posed by CRAB is also worrisome, with prevalence rates reported between 5% and over 90% in areas.[11] In regions such as Asia, the Middle East, and Southern Europe, CRAB has emerged as a prominent cause of healthcare-associated infections. Various factors contribute to the spread of CROs, including spectrum antibiotic use, inadequate infection control measures, international travel movements, and patient transfers between medical facilities.[12] Furthermore, CROs' ability to survive in the environment and their potential transmission, through surfaces, medical devices and healthcare staff, play a role in their dissemination. A significant public health challenge arises from CROs, with key organisms of the *Enterobacteriaceae* family, along with *P. aeruginosa*, *A. baumannii*, and *Stenotrophomonas* species.[13]

## RESISTANCE MECHANISM OF CROs

CROs utilise the defence mechanisms that enable them to withstand the impact of carbapenems and other antibiotics. It is essential to comprehend these mechanisms to devise treatment plans and combat resistance. The main mechanism of carbapenem resistance includes diminished outer membrane permeability that bounds the penetration of antibiotics into the bacteria (altering the membrane protein or lipopolysaccharide), active efflux of carbapenems, modification in antibiotic binding site, and degradation of carbapenemase enzymes that can hydrolyse and deactivate carbapenems and other beta-lactam antibiotics.[14] The most clinically significant carbapenemases are KPC, NDM, and OXA-48, which have spread rapidly across different regions of the world.[15] The scarcity of effective treatments for carbapenem-resistant Gram-negative infections often necessitates resorting to antibiotics such as colistin, despite their increased toxicity, and remains among the few viable options. The combination of these resistance mechanisms and the capacity of CROs to attain and spread resistance genes through gene transfer presents obstacles in treating these pathogens with current therapies.

Bacteria develop resistance to colistin through mutations and adaptive processes. Various molecular mechanisms contribute to colistin resistance in Gram bacteria.[16] The most probable mechanism is *K. pneumoniae* resistance brought on by the changes in the gene as a result of insertion sequences or mutations. This gene encodes a regulator of the phoP/phoQ system that alters the bacterial membrane charge in response to magnesium levels, including exposure to polymyxins. Colistin resistance primarily occurs through modification, which is colistin's primary target, within the bacterial cells. Covalent modification of lipopolysaccharides in lipid A due to mutations that introduce groups such as 4-amino-4-deoxy-L-arabinose and phosphoethanolamine has been found to reduce the effectiveness of polymyxins.[17] It is also suggested that the resistance of colistin in strains may be due to a blend of alterations, in porins, increased activity of efflux pump mechanisms mediated by outer membrane protein OprH, and

by carbapenemase production.[12] Major factors that contribute to the increase in resistance to colistin are (i) overuse and misuse of antibiotics, (ii) inadequate infection control measures, and (iii) global movement of people and goods.

## INDICATIONS OF POLYMYXIN E (COLISTIN)

Colistin has received approval from the U.S. Food and Drug Administration (FDA) to treat infections caused by gram-negative bacteria, especially those resistant to other antibiotics.[18,19] The FDA-sanctioned uses of colistin include (i) Acute or chronic infections triggered by strains of Gram-negative bacteria [Figure 1] like *Acinetobacter* species, *Enterobacter* species, *Escherichia coli*, *Klebsiella* species, and *P. aeruginosa*. (ii) Meningitis caused by strains of Gram-negative bacteria, particularly in cases where patients are allergic to alternative antibiotics or when other treatments prove ineffective. (iii) Respiratory tract infections induced by strains of Gram-negative bacteria encompassing pneumonia, bronchitis, and bronchiectasis. (iv) Treating urinary tract infections caused by strains of Gram-negative bacteria.[20] Colistin is commonly used as the last option in treating infections caused by resistant Gram-negative bacteria, especially those like CRE and multidrug-resistant *P. aeruginosa,* when other antibiotics are not effective. It is crucial to be aware that colistin carries high toxicity risks and should only be used cautiously under the guidance of a healthcare provider.[21] Typically, it is reserved for infections where the benefits outweigh the risks, and it should only be administered following susceptibility testing.[22] The FDA has also approved the use of colistin for veterinary use, in treating bacterial infections in livestock and poultry. Nevertheless, there are concerns surrounding its use in animals due to the risk of developing and spreading colistin bacteria, which could further constrain treatment options for infections.[23]

## OFF-LABEL USE OF POLYMYXIN E (COLISTIN)

Colistin is used as an off-label drug to treat infections that are resistant to various other antibiotics. It is often utilised in treating lung infections caused by the types of bacteria. For patients with conditions such as fibrosis or ventilator-associated pneumonia, colistin proves effective by delivering doses directly to the lungs.[24] In some cases, it is used prophylactically for individuals who have undergone organ transplants or spent extended periods in hospitals exposed to hospital-acquired infections.[25] However, the widespread use of colistin beyond its approved indications could lead to the rise of bacteria that are resistant to this drug making treatment options scarcer. To address this concern, antimicrobial stewardship program focuses on the proper usage of colistin and minimizing the risk of resistance development.[26]

***Mostly Gram-negative organisms (Sensitive strains)***
- *Enterobacteriaceae*
- *Pseudomonas aeruginosa*
  *Acinetobacter baumannii*
- *Klebsiella species*
- *Escherichia coli*

**Figure 1:** Food and Drug Administration approved indications for use of Polymyxin E (colistin).

## THREATS OF CROs

The increased usage of colistin as a last resort remedy for CRO infections has resulted in the development of resistance to colistin. Organisms that are resistant to carbapenems (CROs) present a risk to public health. These bacteria are immune to carbapenem antibiotics, which are typically seen as a resort against infections caused by bacteria resistant to multiple drugs.[27] The appearance and dissemination of CROs have sparked worries among healthcare providers and public health authorities due to the treatment choices and the potential for widespread transmission. CROs have led to infections such as pneumonia, bloodstream infections, and urinary tract infections. Several factors contribute to the spread of CROs, including inappropriate antibiotic use, insufficient infection control measures, international travel, long hospital stays, high mortality rates, and patient transfers between medical facilities.[28] Furthermore, the emergence of elements such as plasmids and transposons carrying genes for carbapenem resistance has accelerated resistance dissemination among bacterial populations.[29] Moreover, global cooperation and sharing of information play a role in coordinating efforts to prevent and combat the spread of CROs beyond borders. International initiatives such as the Global Antimicrobial Resistance Surveillance System by the World Health Organisation aim to enhance surveillance and provide an understanding of resistance worldwide, including CROs.[30] The threat posed by CROs underscores the importance of actions to address antimicrobial resistance and promote responsible antibiotic usage. Neglecting this issue may lead us into an antibiotic era where common infections could become untreatable, endangering modern healthcare systems and posing a significant threat to public health on a global scale.[31]

## COLISTIN-SPARING COMBINATIONS FOR CROs

Combining antibiotics with different mechanisms of action can enhance the antimicrobial activity, prevent the emergence of resistance, and potentially achieve synergistic effects.[32] Examples of such synergistic combinations are (i) β-lactam/β-lactamase inhibitor combinations: Combinations of β-lactam

antibiotics (such as carbapenems or cephalosporins) with newer β-lactamase inhibitors have shown promising results in treating CRO infections. Examples include ceftazidime-avibactam, imipenem-relebactam, and meropenem-vaborbactam.[33,34] (ii) Carbapenem-aminoglycoside combinations: The combination of carbapenems (such as meropenem or doripenem) with aminoglycosides (such as amikacin or gentamicin) has demonstrated synergistic activity against CROs, including CRE and CRAB.[35] (iii) Carbapenem-fosfomycin combinations: The combination of carbapenems with fosfomycin, a broad-spectrum antibiotic with a unique mechanism of action, has shown promising results against CROs. Examples include meropenem-fosfomycin.[36] This combination can potentially overcome resistance mechanisms and enhance antimicrobial activity. The rationale for using these combinations is based on: the synergistic activity of the above-stated combinations in preclinical studies, prevention of resistance, expanding treatment options and limiting the use of colistin (Polymyxin) [Table 1].[37]

## SINGLE THERAPEUTIC AGENTS

Cefiderocol is a novel siderophore cephalosporin with a unique mechanism of action that allows it to bypass the outer membrane barriers of Gram-negative bacteria. It has demonstrated potent *in vitro* activity against CRE, CRAB, and other multidrug-resistant Gram-negative pathogens. A study reported by Bassetti *et al*. in 2021 stated that cefiderocol had good clinical and microbial efficacy in the heterogeneous patient population in infections that were caused by carbapenem-resistant Gram-negative bacteria.[38] A recent study by Sajib *et al*. also stated that the use of cefiderocol as a single monotherapy has similar benefits to that used in combination with other antibacterial agents.[39] Unlike colistin, which carries significant nephrotoxicity risks, cefiderocol has demonstrated a favourable safety profile.[40] Furthermore, cefiderocol exhibits potent *in vitro* activity against a wide range of CROs, including CRE and nonfermenting Gram-negative bacilli.[41] Clinical studies have shown high cure rates with cefiderocol in treating CRO infections, making it a potential first-line option over the more toxic colistin.

Plazomicin is a next-generation aminoglycoside and presents a promising alternative to colistin for treating infections caused by CROs. Plazomicin is a parenteral drug approved by the FDA for treating urinary tract infections, including pyelonephritis.[42] A recent study evaluated the effectiveness of Plazomicin and other aminoglycosides against various bacterial isolates, including those carrying $bla_{KPC}$ genes.[43] The combating antibiotic-resistant *Enterobacteriaceae* study conducted by McKinnell *et al*. provided evidence that plazomicin may be a more effective treatment option compared to Colistin for patients with CRE bloodstream infections, with improved clinical outcomes and higher rates of bacteremia clearance.[44]

Eravacycline, a synthetic fluorocycline antibiotic, new tetracycline derivative that acts on the 30s ribosomal subunit to inhibit bacterial protein synthesis.[45] Eravacycline shows effectiveness against a range of bacteria both Gram-positive and Gram-negative including drug-resistant strains. A meta-analysis confirms that eravacycline is effective in treating intra-abdominal infections.[46] Although gastrointestinal side effects are common, overall eravacycline is considered an option because of its favourable safety profile. Eravacycline has been approved by FDA in 2018 for treating intra-abdominal infections.[47]

Omadacycline, a novel aminomethylcycline antibiotic, is used in the treatment of acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia.[48] Omadacycline has *in vitro* activity against pathogens including *S. pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, and atypical pathogens (*Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*).[49,50] Results from the past study have shown that omadacycline has potent activity against multidrug-resistant strains, also.[51,52]

## DUAL DRUG COMBINATION

The search for effective treatments against carbapenem-resistant organisms (CROs) has led researchers to explore various dual-drug combinations. For instance, imipenem has demonstrated promising in vitro and in vivo activity when paired with agents such as amikacin,[53] tigecycline,[54] tobramycin,[54] rifampicin,[55] and relebactam.[56] Similarly, meropenem exhibits enhanced efficacy in combination with amikacin,[57] ertapenem,[58] gentamicin,[59] aztreonam,[60] vaborbactam,[61] and fosfomycin.[62] Doripenem also shows improved antimicrobial effects when used alongside sulbactam,[63] ertapenem,[64] or gentamicin.[65] Among cephalosporins, ceftazidime and ceftolozane have displayed synergistic effects with amikacin, aztreonam, and avibactam.[66-68] Additionally, cefepime has shown potential against CROs when combined with newer β-lactamase inhibitors like enmetazobactam and zidebactam.[69] Finally, the combination of tazobactam with amikacin has been validated as an effective strategy against resistant pathogens.[70] These findings highlight the importance of combination therapy in overcoming antimicrobial resistance for future clinical applications [Table 2].

## TRIPLE DRUG COMBINATION

A recent case study, by Hiraki *et al*., detailed the treatment of skin and soft-tissue infection caused by carbapenem *A. baumannii* using a combination of ampicillin-sulbactam and meropenem.[71] Another research study conducted by Khalili *et al*. demonstrated that the combination of meropenem with ampicillin sulbactam could serve as an option for combating

**Table 1:** List of available colistin-sparing regimens.

| Single-drug therapy[32-37] | Dual-combinations therapy[53-70] | Triple-combination therapy[71-76] |
|---|---|---|
| Cefiderocol | Imipenem plus Amikacin/Tigecycline/Tobramycin/ Rifampicin/Relebactam | Meropenem plus Ampicillin plus Sulbactam |
| Plazomicin | Tazobactam plus Amikacin | Tigecycline plus Ampicillin plus Sulbactam |
| Eravacycline | Ceftolozane plus Amikacin/Aztreonam | Ceftolozane plus Tazobactam plus Fosfomycin |
| Omadacycline | Doripenem plus Gentamicin/Amikacin/Sulbactam/Ertapenem | Ceftazidime plus Avibactam plus Aztreonam |
| | Meropenem plus Amikacin/Ertapenem/Gentamicin/ Aztreonam/Vaborabactam/Fosfomycin | Imipenem plus Cilastatin plus Relebactam |
| | Ceftazidime plus Amikacin/Aztreonam/Avibactam | |
| | Cefepime plus Enmetazobactam/Zidebactam | |

**Table 2:** Dual therapy combinations.

| Drug | Combination with |
|---|---|
| Imipenem | Amikacin[53] |
| | Tigecycline[54] |
| | Tobramycin[55] |
| | Rifampicin[55] |
| | Relebactam[56] |
| Meropenem | Amikacin[57] |
| | Ertapenem[58] |
| | Gentamicin[59] |
| | Aztreonam[60] |
| | Vaborabactam[61] |
| | Fosfomycin[62] |
| Doripenem | Sulbactam[63] |
| | Ertapenem[64] |
| | Gentamicin[65] |
| | Amikacin[63] |
| Ceftazidime | Amikacin[66] |
| | Aztreonam[67] |
| | Avibactam[67] |
| Ceftolozane | Amikacin[68] |
| | Aztreonam[68] |
| Cefepime | Enmetazobactam[69] |
| | Zidebactam[69] |
| Tazobactam | Amikacin[70] |

carbapenem organisms (CROs) while reducing the reliance on colistin.[72] The importance of reserving colistin usage and addressing colistin resistance highlights the necessity for exploring alternative treatment strategies. A case series published by Assimakopoulos *et al.* reported the treatment of ventilator-associated pneumonia caused by CRAB through triple drug combination therapy involving high dose ampicillin sulbactam with tigecycline.[73] Additionally, ceftolozane tazobactam and fosfomycin have shown promise as therapies against carbapenem organisms due to their synergistic effects observed in laboratory tests.[74] The combined use of ceftazidime-avibactam and aztreonam presents itself as an approach for managing moderate to severe *S. maltophilia* infections, leading to complete bacterial eradication and resistance suppression.[75] An approved triple drug combination is imipenem, cilastatin relebactam, designed to combat drug gram-negative bacteria effectively [Table 1].[76]

## LIMITATIONS OF CURRENT TREATMENT OPTIONS

The treatment of CRO infections has become increasingly challenging due to the limited number of effective antibiotics available and the associated risks of toxicity and adverse effects. The use of colistin is associated with several limitations, including nephrotoxicity, neurotoxicity, and the potential to develop resistance. The emergence of colistin-resistant CROs has further compromised its efficacy, underscoring the need for alternative treatment options. However, the above-listed combinations have been tested preclinically and have proven some efficacy and can be further explored to limit and spare the use of colistin.

## DISCUSSION

Prevention of developing colistin resistance is also essential to maintain the efficacy against multidrug-resistant bacteria by the robust implementation of an antibiotic stewardship program in healthcare settings. This must include the guidelines for appropriate prescribing and monitoring the antibiotic use. Adequate infection control measures must be taken to reduce the transmission of resistance in healthcare facilities. Further use of combination therapies and investigating new antibiotics or alternative therapies will reduce the reliance on colistin. Colistin-sparing regimens discussed above may vary in cost considerations. Single drug therapy may be available at a lower cost, but it may lead to treatment failures, whereas dual- or triple-drug therapy with a higher cost might be more effective than monotherapy, justifying the higher cost.

## CONCLUSION

Rapid spread of CROs and the rise of colistin resistance threaten to leave us without effective antibiotics to treat serious Gram-negative infections. Combination therapy and other colistin-sparing strategies hold promise to preserve the effectiveness of our last-line antibiotics while we work to develop new treatment options. Implementing these approaches will require a concerted global effort to combat this urgent public health threat. Additionally, the antimicrobial stewardship program plays a crucial role in promoting the judicious use of these combinations and minimising the development of further resistance.

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