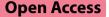
COMMENT



Optimizing colistin dosing in patients undergoing continuous kidney replacement therapy: critical considerations for intensivists

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Introduction

The limited availability of novel antimicrobials against multidrug-resistant Gram-negative bacteria (MDR-GNB) has necessitated the reevaluation of older antibiotics [1, 2]. Polymyxins, including colistin (polymyxin E) and polymyxin B, were first discovered in 1949 and subsequently reclassified by the World Health Organization (WHO) in 2012 as critically important agents for the treatment of MDR-GNB infections, leading to renewed clinical interest [3]. Colistin, a polycationic antimicrobial, interacts

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with negatively charged phosphate groups of lipid A subunits within the lipopolysaccharide layer of Gram-negative bacteria. This interaction disrupts the bacterial outer membrane by displacing cations (primarily Mg²⁺ and Ca²⁺), ultimately causing membrane leakage and bacterial death [4]. As a result, polymyxins remain crucial therapeutic options for MDR-GNB infections [5].

Colistin is administered as an inactive prodrug, colistin methanesulfonate (CMS) [5]. However, its clinical use is constrained by a narrow therapeutic window, with nephrotoxicity and neurotoxicity being the primary dose-limiting factors, both of which are concentration-dependent. Given its pharmacokinetic and pharmacodynamic characteristics-exhibiting both concentration- and time-dependent activity-colistin's primary pharmacodynamic target is the area under the plasma concentration-time curve (AUC), with a recommended 24-h steady-state AUC target of approximately 50 mg·h/L, corresponding to a steady-state mean plasma concentration of $\sim 2 \text{ mg/L}$ [5].

The emergence of colistin resistance, first reported in 2015, has been attributed to the plasmid-mediated mobile colistin resistance gene (mcr-1), which encodes phosphoethanolamine transferase, conferring resistance in certain Gram-negative bacteria. Initially detected in Escherichia coli isolates from farm animals, raw meat, and humans in China, subsequent studies confirmed global dissemination across Enterobacteriaceae, its



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highlighting the urgency of coordinated international efforts to combat resistance [6, 7].

Given these challenges, ensuring that colistin dosages exceed the minimal inhibitory concentration (MIC) is essential for optimizing therapeutic outcomes [8]. However, critically ill patients requiring continuous kidney replacement therapy (CKRT) are at risk of inadequate colistin exposure due to extracorporeal removal of the drug, as colistin pharmacokinetics is characterised by low volume of distribution (0.3–0.4 L/Kg) and wide free fraction ranging between 59 and 74% [9]Therefore, accurate dosing strategies are critical to balancing efficacy and toxicity [8].

Recent insights

A recent study by De Pascale et al. provided valuable insights into colistin dosing during CKRT. This study included all consecutive patients admitted to three Intensive Care Units (ICUs) who were treated with colistin for at least 48 h. Treatment consisted of a 9 MIU loading dose, followed by 6.75 MIU every 12 h (q12h), administered during CKRT [10]. Serial blood sampling was performed after the seventh dose over a 24-h period. A total of 20 patients with carbapenem-resistant Acinetobacter baumannii ventilator-associated pneumonia were enrolled [10].

This investigation focused on the pharmacodynamic parameter fAUC0-24/MIC (free AUC over 24 h divided by MIC), targeting a value \geq 12. The findings demonstrated 100% efficacy for MIC \leq 2 mcg/mL and 85% efficacy for MIC=4 mcg/mL. However, these doses exceeded the toxicity threshold, as the observed mean steady-state plasma concentration was higher than the recommended 3–4 mcg/mL [10].

The need for higher colistin doses during CKRT may be explained by the extensive carrier-mediated tubular reabsorption of colistin in the kidneys, a physiological mechanism not replicated by extracorporeal devices currently used in clinical practice [10]. Moreover, in patients with renal failure, plasma concentrations of colistimethate sodium—substantially removed during continuous venovenous hemodiafiltration (CVVHDF)—are significantly higher than active colistin concentrations due to reduced conversion efficiency [11].

Only the unbound fraction of colistin A and B (ranging from 30 to 60%) is dialyzable [8, 12]. Interindividual variability in colistin dosing requirements during CKRT may stem from factors such as the true unbound fraction of colistin, influenced by its primary carrier alpha-1-acid glycoprotein concentration, as well as dialysis efficiency parameters, including blood and dialysate flow rates [8, 13, 14]. Additionally, due to colistin's hydrophobic nature, some extracorporeal membranes (e.g., polymethacrylate and acrylonitrile) exhibit adsorption-mediated drug removal [8, 12–14].

In response to this variability, some researchers have proposed a pharmacokinetic model recommending a loading dose of 12 MIU, followed by a maintenance dose of 6.75–7.5 MIU every 12 h, to achieve a target steady-state plasma concentration of 2–3 mcg/mL [14]. Similar to pharmacodynamic-guided strategies, this approach necessitates measuring colistin levels in both plasma and dialysis effluent to minimize toxicity and underdosing risks [14].

Interestingly, De Pascale et al. also observed that steady-state colistin concentrations were significantly lower in patients who recovered renal function compared to those who did not. While this finding remains observational, it suggests a potential relationship between renal recovery and colistin pharmacokinetics [9, 10].

Another potential contributor to elevated colistin concentrations in CKRT patients may be the concurrent administration of high-dose nebulized CMS (5 MIU every 8 h) via vibrating mesh nebulizers. The study authors noted that this adjunctive therapy may have contributed to the unexpectedly high steady-state colistin levels, a strategy previously advocated by Boisson et al. [15, 16].

Conclusion

The study by De Pascale et al. concluded that highdose CMS administration in critically ill CKRT patients resulted in steady-state concentrations exceeding the MIC90 of commonly isolated bacteria but also surpassed safety thresholds. These findings suggest that, beyond the empirical treatment phase, lower CMS maintenance doses should be considered in clinical practice, particularly in the absence of therapeutic drug monitoring or alternative antimicrobial options.

Colistin dosing should account for both intravenous (IV) and nebulized administration, requiring careful monitoring of colistin levels in plasma and dialysis effluent to optimize efficacy while mitigating toxicity. A precise and individualized dosing approach is crucial to improving patient outcomes while minimizing colistinrelated adverse effects in critically ill CKRT patients.

Practical recommendations for clinicians

1. For IV colistin administration only:

- Loading dose: 12 MIU
- Maintenance dose: 6.75–7.5 MIU every 12 h
- Higher doses may be used mainly in the empirical phase due to the risk of overexposure
- Target steady-state concentration: 2–3 mcg/mL

- Therapeutic drug monitoring in plasma and dialysis effluent is essential to minimize toxicity and underdosing.
- 2. For combined IV and nebulized colistin administration:
 - · Loading dose: 9 MIU
 - Maintenance dose: 6.75 MIU every 12 h (q12)
 - High-dose nebulized CMS: 5 MIU every 8 h via vibrating mesh nebulizers
 - Close monitoring of systemic colistin levels is critical to prevent excessive drug accumulation.

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Availability of data and materials

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Declarations

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Consent for publication

Not applicable.

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