Critical Care

COMMENT

Open Access

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

Patrick M. Honore[1,2*], Emily Perriens[3], Sydney Blackman[4], Nathan De Lissnyder[5], Anaëlle Detournay[6], Salvatore Lucio Cutuli[7], Gennaro De Pascale[7,8] and Filippo Mariano[9,10]

Keywords Colistin, Continuous kidney replacement therapy (CKRT), Multidrug-resistant gram-negative bacteria, Pharmacodynamics, Nephrotoxicity, Neurotoxicity

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 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 Mg^{2+} and Ca^{2+}), 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 ~ 2 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 its global dissemination across Enterobacteriaceae,

*Correspondence:
Patrick M. Honore
patrick.honore@chuuclnamur.uclouvain.be
[1] CHU UCL Godinne Namur, UCL Louvain Medical School, Campus Godinne, Avenue G Thérasse 1, 5530 Yvoir (Namur), Belgium
[2] Faculty of Medicine and member of the Experimental Research Laboratory Institute of the Catholic Louvain Medical School, Brussels, Belgium
[3] ICU Brugmann University Hospital, ULB University, Brussels, Belgium
[4] Gynecology Department CHIREC Hospital, ULB University, Brussels, Belgium
[5] Vrije Universiteit Brussel, UZ Brussel, Brussels, Belgium
[6] CHU Brugmann, ULB, Brussels, Belgium
[7] Dipartimento di Scienze Dell'Emergenza, Anestesiologiche e della Rianimazione, Fondazione Policlinico Universitario A. Gemelli IRCCS, Cattolica del Sacro Cuore Largo A. Gemelli 8, 00168 Rome, Italy
[8] Dipartimento di Scienze Biotecnologiche di Base, Cliniche Intensivologiche e Perioperatorie, Università Cattolica del Sacro Cuore, Rome, Italy
[9] Department of Medical Sciences, University of Turin, Turin, Italy
[10] Nephrology, Dialysis and Transplantation U, City of Health and Science, CTO Hospital, Turin, Italy

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 veno-venous 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 high-dose 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 colistin-related 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.

Acknowledgements
None.

Funding
None.

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Received: 5 April 2025 Accepted: 9 April 2025
Published online: 08 May 2025

References

1. Rhouma M, Madec JY, Laxminarayan R. Colistin: from the shadows to a one health approach for addressing antimicrobial resistance. Int J Antimicrob Agents. 2023;61(2):106713. https://doi.org/10.1016/j.ijantimicag.2023.106713.
2. Falagas ME, Kyriakidou M, Voulgaris GL, Vokos F, Politi S, Kechagia KS. Clinical use of intravenous polymyxin B for the treatment of patients with multi-drug resistant Gram-negative infections: an evaluation of the current evidence. J Glob Antimicrob Resist. 2021;24:342–59.
3. Rhouma M, Letellier A. Extended-spectrum beta-lactamases, carbapenemases and the mcr-1 gene: is there a historical link? Int J Antimicrob Agents. 2017;49:269–71.
4. Liu YY, Wang Y, Walsh TR, et al. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. Lancet Infect Dis. 2016;16:161–8.
5. Mariano F, Malvasio V, Risso D, et al. Colistin therapy, survival and renal replacement therapy in burn patients: a 10-year single-center cohort study. Int J Gen Med. 2022;25(15):5211–21. https://doi.org/10.2147/IJGM.S357427.
6. Sun J, Zhang H, Liu YH, Feng Y. Towards understanding MCR-like colistin resistance. Trends Microbiol. 2018;26:794–808.
7. Gregoire N, Aranzana-Climent V, Magreault S, Marchand S, Couet W. Clinical pharmacokinetics and pharmacodynamics of colistin. Clin Pharmacokinet. 2017;56(12):1441–60.
8. Spapen HD, van Laethem J, Hites M, Verdoodt A, Diltoer M, Honoré PM. Treatment of ventilator-associated pneumonia with high-dose colistin under continuous veno-venous hemofiltration. J Transl Int Med. 2019;7(3):100–5. https://doi.org/10.2478/jtim-2019-0022.
9. Cutuli SL, Cascarano L, Lazzaro P, Tanzarella ES, Pintaudi G, Grieco DL, De Pascale G, Antonelli M. Antimicrobial exposure in critically Ill patients with sepsis-associated multi-organ dysfunction requiring extracorporeal organ support: a narrative review. Microorganisms. 2023;11(2):473. https://doi.org/10.3390/microorganisms11020473.
10. De Pascale G, Lisi L, Cutuli SL, Marinozzi C, Palladini A, Ferrando ES, et al. High-dose colistin pharmacokinetics in critically ill patients receiving continuous renal replacement therapy. Ann Intensive Care. 2024;14(1):152. https://doi.org/10.1186/s13613-024-01384-1.
11. Li J, Rayner CR, Nation RL, Deans R, et al. Pharmacokinetics of colistin methanesulfonate and colistin in a critically ill patient receiving continuous venovenous hemodiafiltration. Antimicrob Agents Chemother. 2005;49(11):4814–5.
12. Mariano F, Leporati M, Carignano P, Stella M, Vincenti M, Biancone L. Efficient removal of colistin A and B in critically ill patients undergoing CVVHDF and sorbent technologies. J Nephrol. 2015;28(5):623–31. https://doi.org/10.1007/s40620-014-0143-3.
13. Karaiskos I, Friberg LE, Galani L, et al. Challenge for higher colistin dosage in critically ill patients receiving continuous venovenous haemodiafiltration. Int J Antimicrob Agents. 2016;48(3):337–41.
14. Markou N, Fousteri M, Markantonis SL, et al. Colistin pharmacokinetics in intensive care unit patients on continuous venovenous haemodiafiltration: an observational study. J Antimicrob Chemother. 2012;67:2459–62.
15. De Pascale G, Pintaudi G, Lisi L, et al. Use of high-dose nebulized colistimethate in patients with colistin-only susceptible *Acinetobacter baumannii* VAP: clinical, pharmacokinetic and microbiome features. Antibiotics (Basel). 2023;12(1):125.
16. Boisson M, Jacobs M, Grégoire N, et al. Comparison of intrapulmonary and systemic pharmacokinetics of colistin methanesulfonate (CMS) and colistin after aerosol delivery and intravenous administration of CMS in critically ill patients. Antimicrob Agents Chemother. 2014;58(12):7331–9. https://doi.org/10.1128/AAC.03510-14.

Publisher's Note