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LETTER TO THE EDITOR

Cost-effective analysis of low- versus high-dose colistin in the treatment of multi-drug resistant pneumonia in Saudi Arabia

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Dear Editor,

We have recently read with great interest the article by Cara et al. in which they reported that low-dose colistin (< 5 mg/kg/day colistin base activity [CBA]) was not inferior to high-dose colistin (> 5 mg/kg/day CBA) in terms of clinical cure and was associated with a lower incidence of nephrotoxicity resulting in significant cost avoidance [1]. Although the authors shed light on an area with very limited information, we believe that the authors' conclusions were perhaps misleading due to limitations in the study methodology.

The major limitation was in the underlying assumption that both high- and low-dose of colistin are acceptable for the treatment of multi-drug resistant pneumonia. While we concur with the authors that there are currently no definite dosing recommendations for colistin, several recently published studies have provided us with a better understanding of its pharmacokinetics and dosing strategies.

The doses evaluated in the study by Cara et al., high doses (average 5.7 mg/kg/day CBA) and low doses (average 3 mg/kg/day CBA) were within the range of doses recommended by the US Food and Drug Administration (FDA) for patients with normal renal function (2.5-5 mg/kg/day CBA) [2]. However, a pharmacokinetic study demonstrated that only 61% of the patients with creatinine clearance between 50 and 80 mL/min achieved clinically relevant plasma concentrations at FDA-recommended doses, while around 90% of the patients with creatinine clearance < 80 mL/min achieved the desired plasma concentrations at higher doses recommended by the European Medicines Agency (EMA) [3]. According to the EMA, the recommended dose of colistin for patients with normal renal function is 9 million units colistimethate sodium, which is approximately 300 mg CBA (about 5 mg/kg CBA for a 60 kg patient).

Another major limitation related to the dosing regimens evaluated in the study was the absence of a loading dose. Pharmacokinetic studies indicated that because of the slow rate of conversion of the prodrug colistimethate sodium to the active drug colistin and the long half-life of colistin, a loading dose is necessary to attain adequate concentrations more rapidly [4, 5]. Though the administration of colistin loading doses has not been evaluated in randomized controlled trials, the currently available clinical evidence supports the use of a loading dose [4]. In fact, Nation et al. recently reported the results of the largest population pharmacokinetic study conducted to-date and provided dosing algorithms of colistin in patients with a wide range of renal function [5]. The administration of a loading dose was suggested for patients with all degrees of renal function.

In this cost-effective analysis, the authors used probabilities from a retrospective analysis of patients treated at their institution rather than those from previously published clinical trials. Their rationale for this approach was not clearly explained. While their approach may provide a better reflection of the outcomes expected in the patient population studied, the methods used to compare the effectiveness of the two doses had several limitations. First is the lack of a power analysis to determine the sample size necessary to perform such a comparison and thus there remains a high possibility of a type 2 error in the findings reported. Second is related to the patients included in the study. Eligible patients were those who received colistin for "documented nosocomial pneumonia", but the authors do not describe how nosocomial pneumonia was diagnosed. Furthermore, the specific criteria for inclusion was not clearly defined. Did the investigators rely solely on a medical note stating that the patients had nosocomial pneumonia (which is generally the case for retrospective studies)? Given that patients in both

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groups had a prolonged hospital stay (average over 100 days) and the absence of clear criteria for defining nosocomial pneumonia, there is a possibility that at least some of the patients were colonized rather than truly infected, which is the population we seek to better understand.

In addition, the study consisted of critically-ill patients as well as those treated on the medical wards, suggesting that the groups evaluated were heterogenous in their underlying characteristics and expected outcomes. Furthermore, the primary end point to evaluate the effectiveness was clinical cure, which was defined as "resolution of signs and symptoms of infection including absence of fever for a minimum of 72 h and a white blood cell count below 12,000 cells/mm^3." This definition excluded microbiologic data and is therefore subjective. Finally, there were several factors that may have impacted the outcomes which were not mentioned in the study. While the authors reported the concomitant nephrotoxic antibiotics that patients received, they did not report if any patients had colistin combined with other therapies, such as carbapenems, which may impact the clinical outcomes. Furthermore, the time to initiation of antibiotics, the minimum inhibitory concentration (MIC) for the pathogens identified, and receipt of mechanical ventilation should have been reported since those are confounding variables that may impact the clinical cure.

In conclusion, we believe that the results of the study by Cara et al. should be interpreted with caution. While there may be cases where "low-dose" colistin may be effective, such as in the non-critically ill patients or for treating pathogens with low MIC, we do not yet have strong data to support such conclusions. Dosing colistin remains a challenge and while it is important to use the least nephrotoxic dose and the most cost-effective therapy, we must ensure that we are providing doses that can achieve the therapeutic levels to be able to successfully treat patients.

Conflicts of interest None.

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