Dear Editor,

Nation and coworkers recently published algorithms for individualized colistin dosing to achieve optimal plasma drug concentration in critically ill patients with a wide range of renal function (RF) and those on renal replacement therapy (RRT) [1]. The updated dosing suggestions are greatly improved compared with previously published algorithms from the same authors based on interim analysis [2]. Indeed, the updated version is based on a large cohort of patient population and includes specific information on how to estimate the maintenance colistin dose also in patients receiving or not RRT or undergoing sustained low-efficiency dialysis. Authors attempted to balance potential antibacterial activity and nephrotoxicity targeting probability of attainment rates of >80% for colistin concentration ≥2 mg/L and <30% for colistin concentration ≥4 mg/L. When the developed algorithms were applied back to individual patients stratified to different degrees of RF, it was shown that more than 80% of patients with creatinine clearance (Cr-CI) <80 mL/min achieved colistin concentration ≥2 mg/L, whereas less than 30% achieved more than 4 mg/L. Authors concluded that the study generated clinician-friendly algorithms to be used in critically ill patients over a wide range of RF.

Some methodological drawbacks may partially challenge these conclusions. It shouldn’t be correct to validate the goodness of the proposed equations through a “back application” in the same population used to develop the models but in an independent cohort of patients. Actually, the risk might be to develop algorithms working very well in the development populations but largely failing in real life. As shown in Table 1, it seems that hyperfiltrating patients (Cr-CI ≥2300 mL/min) were included in the study, but no specific colistin dosing suggestions have been provided for this population. This may eventually explain why the proposed equations largely failed in patients with Cr-CI >80 mL/min, with less than 40% of subjects achieving colistin concentration ≥2 mg/L. Indeed, it is well known that augmented renal clearance is frequent in critically ill patients and can result in elevated renal elimination and subtherapeutic plasma antibiotic concentrations [3]. Similarly, looking at Table 1, patients enrolled in the study weighted up to 130 kg, rendering virtually impossible to verify if the equations can fit for obese patients too. Finally, the authors do not consider as an additional covariate the levels of serum albumin. Indeed, colistin has a protein binding of 40–75% and colistin A has a concentration dependent binding [4]. Therefore, it cannot be excluded that the application of the proposed equations for the prediction of colistin loading/maintenance dosing to hypoalbuminemic patients may result in higher than expected colistin clearance, suboptimal drug exposure and development of colistin resistance [5].

Note

Potential conflicts of interest. Both authors: No reported conflicts of interest. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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References


Reply to Corona and Cattaneo

To the Editor—We thank Corona and Cattaneo [1] for their comments on our recent article in which we described dosing guidance for intravenous colistin in critically ill patients [2].

Because of the very substantial interpatient variability in pharmacokinetics of formed colistin, even at a given creatinine clearance, it was most appropriate to use the data from the entire cohort to derive the dosing suggestions, instead of dividing our available cases into a “learning” and a “validation” data set. The patients included in the study were being cared for in 4 centers across 3 continents, and displayed characteristics typical of critically ill patients requiring intravenous colistin [2]. Our report included the largest number of patients in a single analysis. In relation to the influence of renal function, in another study only 4 of 12 patients with creatinine clearance >80 mL/minute and receiving...
300 mg colistin base activity (CBA) daily achieved an average steady-state plasma colistin concentration \(C_{\text{ss,avg}}\) of \(\geq 2\) mg/L [3]; this is in good agreement with \(<40\%\) attainment of this target that we reported in patients receiving 340–360 mg CBA daily [2]. Moreover, in regard to patients receiving continuous renal replacement therapy, an independent study has indicated the need to consider a daily dose similar to, or higher than, would be used in patients with normal renal function [4], as we proposed originally [5] and more recently [2]. However, we agree that it is important to formally prospectively validate the dosing suggestions.

We are perplexed by the comment of Corona and Cattaneo relating to patients with high creatinine clearance [1]. As can be seen from Figure 2 in our report [2], approximately 32% of patients had creatinine clearance >80 mL/minute and approximately 15.5% had creatinine clearance >130 mL/minute, the latter commonly used to define augmented renal clearance [6]. The regression equation in Figure 2B, with the intercept adjusted to allow the desired target attainment rates across various categories of renal function, led to the renally based dosing algorithm (equation 2, Table 2) [2]. This equation can be used to estimate the daily dose needed to achieve each 1 mg/L of plasma colistin \(C_{\text{ss,avg}}\) in patients with creatinine clearance up to 236 mL/minute. We explained the reason for excluding the data for the patient with creatinine clearance of 314 mL/minute [2]. In the “look-up” table (Table 3), we listed daily colistimethate doses for attainment of a plasma colistin \(C_{\text{ss,avg}}\) of 2 mg/L. This concentration was suggested because colistin has a very narrow therapeutic window and the minimum inhibitory concentration may not be known at the initiation of therapy [2]. For patients with creatinine clearance >80 mL/minute, a maximum (“capped”) daily dose of 340–360 mg CBA was suggested in the “look-up” table and text because there is very little information on the rate and impact of nephrotoxicity for higher doses; as discussed, this daily dose resulted in attainment of a target of 2 mg/L in <40% of patients [2]. However, clinicians may choose to balance potential benefit vs risk in individual patients and use equation 2 in Table 2 to calculate a daily dose to achieve any desired plasma colistin \(C_{\text{ss,avg}}\). We suggested consideration of the possible role of combination therapy and, where appropriate, other routes of administration (eg, nebulization), although the benefit of these modalities is not fully elucidated [2].

We reported that >30% of patients were overweight or obese [2, 7]. The population pharmacokinetic analysis revealed that neither body weight (actual or ideal) nor serum albumin was a covariate for the apparent clearance of colistin and hence the daily dose requirements of colistimethate; creatinine clearance was the only patient covariate identified [2]. Finally, we do not agree with the comment of Corona and Cattaneo regarding protein binding [1]. If there is no alteration in intrinsic clearance of unbound colistin, any decrease in plasma protein binding resulting from hypoalbuminemia or displacement interaction would lower the steady-state concentration of total (unbound plus bound) colistin in plasma but is not expected to change the steady-state concentration of the unbound drug [8], which is the active/toxic entity. Thus, a pure change in fraction bound, for an otherwise effective regimen, would not lead to suboptimal drug exposure or development of resistance.

Notes

Disclaimer. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Allergy and Infectious Diseases (NIAID) or the National Institutes of Health.

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