Colistin Dosing: Does the Fun Ever Start?

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(See the Major Article by Benattar et al on pages 1605–12.)

Keywords. colistin; colistimethate; polymyxin; acute kidney injury; PK/PD.

In this issue of Clinical Infectious Diseases, Benattar and colleagues present findings from a large cohort study comparing high-dose colistin, defined as a loading dose of 9 million international units (MIU) followed by a maintenance dose of 9 MIU/day, to all other regimens (median dose, 4 MIU/day [interquartile range, 3–6 MIU/day]). Recent pharmacokinetic (PK) data support this dosing strategy so as to target an average steady-state concentration above the minimum inhibitory concentration (MIC) for susceptible organisms [1]. In this large cohort, the authors were unable to find any clinical benefit with the high-dose regimen. Although these data become somewhat complicated by the fact that a significant proportion of patients assigned to the low-dose colistin group actually received high-dose maintenance regimens without loading doses, and significant differences in important baseline characteristics existed between the groups, the authors perform appropriate subgroup analyses to ensure these factors did not impact the findings. Perhaps the most convincing results are those in the propensity score–matched subgroup of patients (n = 111 with high-dose colistin and n = 178 with “other” regimens). In this well-matched subgroup, mortality rates were nearly identical between high- and low-dose colistin (36% and 34%, respectively), and these results did not change when the authors did not require that the loading dose be administered for a regimen to be considered “high dose” (ie, maintenance dosing of 9 MIU/day regardless of receipt of loading dose). These findings demonstrated no mortality benefit to high-dose colistin. Importantly, and unsurprisingly, higher nephrotoxicity rates were seen in patients receiving higher doses.

The findings from this study do not support the use of high-dose colistin. Of note, while regimens were considered to be high dose in this study based on recent changes to the European Medicines Agency package insert recommendations, these doses are still slightly lower than those listed in the United States package insert for patients with normal renal function. The US package insert recommends 5 mg/kg/day of colistin base activity (CBA), where 1 MIU = 30 mg CBA [2]. Thus, in a 70-kg patient, the US package insert recommends 350 mg CBA or 12.7 MIU/day. Therefore, by US standards, dosing was not actually “high dose” in this study.

Other literature on the topic of high- vs low-dose colistin has found conflicting results. The most commonly cited data supporting the use of higher doses of colistin are from Falagas and colleagues, where a stepwise decrease in 30-day mortality was observed in patients who received 3, 6, and 9 MIU/day of colistin [3]. However, this analysis did not account for renal dosing adjustments as the reason for lower doses; thus, patients who received lower doses due to renal insufficiency likely received similar daily exposures of colistin. In addition, in this same analysis, no association was reported between increasing colistin doses and rates of clinical cure.

So what, exactly, is the treating clinician to make of all of these data? Unfortunately, these conflicting findings are significantly complicated by heterogeneity in patient populations studied, target organism treated, use of combination therapies, actual colistin dosage used, renal dosing adjustments, site of infection, MICs of target organisms, severity of illness of the patient population, and delays in the time to effective therapy. Furthermore, the available literature differs in the endpoints studied, and there is significant controversy regarding what the most optimal clinical endpoint should be. While it might seem logical that an objective 30-day all-cause mortality endpoint is preferred, it could be argued that it is not the most relevant endpoint when looking at the efficacy of an antimicrobial regimen or dose in these types of patient populations. The primary goal of any antimicrobial regimen is to eradicate a patient’s infection. Given the complexity as well as the types and severity of comorbidities present in many patients with invasive infections due to extensively drug-resistant Acinetobacter baumannii, Pseudomonas aeruginosa, or carbapenem-resistant Enterobacteriaceae, 30-day all-cause mortality might not be related to infections.
caused by these pathogens. In fact, 2 separate analyses by Tri et al [4] and Gibson et al [5] both suggest that improvements in clinical and microbiological cure occur at earlier time points with higher colistin dosing regimens similar to those used in the Benattar et al study; however, they fail to correlate these improvements in clinical and microbiological outcomes with improvements in 28- to 30-day mortality. Therefore, infection cure might be a more relevant measure to assess the adequacy of an antimicrobial regimen.

It is also crucial to appreciate that to interpret the efficacy of colistin dosing, important PK and pharmacodynamic (PD) complexities must be considered as well. Recent PK/PD work in mouse models demonstrated that a ratio of the free area under the concentration-time curve to MIC (fAUC/MIC) target of approximately 7–17 was required for 1–2 log kill in a mouse thigh model for A. baumannii and P. aeruginosa, whereas much higher exposures were needed in a mouse lung model [6]. In fact, in the lung model, bacteriostasis was unable to be achieved with colistin for 2 of the 3 A. baumannii strains tested at the highest dose tolerated by the mice. Additionally, PK/PD targets have not yet been elucidated for Enterobacteriaceae. To put these targets into context, dosing regimens targeting average colistin concentrations of 2–2.5 mg/L would equate to an AUC of 48–60 mg x hour/L over 24 hours. When accounting for the 50%-60% protein binding of colistin [6, 7], free AUC exposures of approximately 19–30 mg x hour/L would be expected. Thus, even at the upper end of the susceptibility breakpoint of colistin (MIC = 2 mg/L), the targets for 1–2 log kill in the thigh model would be achieved (fAUC/MIC of approximately 10–15). Importantly, as described above, targets in the lung are unlikely to be achieved with any common dosing regimen, but even in the best-case scenarios, only at extremely low MICs.

While on the surface this suggests a good likelihood of target attainment with the high-dose regimen used in this analysis, it is important to understand that PK studies have demonstrated significant interpatient variability with regards to serum colistin levels achieved in patients. In these analyses, it has been shown that at a given dose and renal function, patient colistin levels can vary up to 10-fold [1]. Therefore, even if the dosing strategies used in this study were targeting average colistin concentrations of 2–2.5 mg/L, it is likely that patients had huge variations in actual exposures to the drug, therefore further complicating interpretation of the findings. In fact, Benattar and colleagues state in their discussion that, in their ongoing randomized controlled trial (RCT) using the same high dosing strategy, concentrations were commonly >3–4 mg/L. Therefore, it is also reasonable to conclude that many patients who received “lower” doses of colistin may still achieve target concentrations. This is particularly relevant in this study as MIC90 values in both treatment arms were relatively low (0.5 mg/L), and thus target concentrations, at least based on the thigh model, were likely attained in both groups.

Despite the negative findings of this study, given the limitations described above, it is still reasonable and appropriate to continue to utilize “high-dose” regimens of colistin (either 9 MIU/day or 5 mg/kg CBA/day). Given the known interpatient variability in colistin exposures, the limited PK/PD data available to colistin, varying MICs of target organisms, and known dose (and concentration)-dependent toxicity of colistin, evidence is urgently needed evaluating actual patient exposures (serum concentrations) with regard to microbiologic and clinical outcomes. Fortunately, there are currently 2 ongoing RCTs comparing colistin monotherapy to colistin combination therapy with meropenem, which should help to provide some clinical PK/PD guidance. The first trial, based in Europe, is utilizing high-dose colistin as defined in this study [8]. The second trial, based in the United States, is administering higher, weight-based doses according to the US package insert (5 mg/kg/day of CBA) [9]. Importantly, both of these trials are obtaining serum concentrations of colistin and will be attempting to relate PK exposures to both PD (clinical efficacy, microbiological eradication) and toxicodynamic (nephrotoxicity) outcomes. Hopefully, findings from these studies will lead to recommendations for clinically relevant target colistin concentrations and a potential opportunity for optimizing both future empiric dosing regimens and therapeutic drug monitoring strategies.

**Note**

**Potential conflicts of interest.** All authors: No potential conflicts of interest. All 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.

**References**