Optimal Usage of Colistin: Are We Any Closer?

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(See the Major Article by Dalfino et al on pages 1771–7.)

Keywords. colistin; polymyxin; nephrotoxicity; pharmacokinetics/pharmacodynamics; ascorbic acid.

Despite being the mainstay of treatment for carbapenem-resistant gram-negative bacilli for more than a decade, optimal strategies for dosing and administration of colistin remain unclear. Colistin dosing regimens vary considerably throughout the world. In some instances, the total daily dose delivered varies 2-fold depending on geography. Compounding the issue is the fact that the majority of dosing strategies currently utilized were developed in the absence of accurate pharmacokinetic and pharmacodynamic data. Further complicating the issue of colistin dosing is the issue of nephrotoxicity, which often limits the dose and duration of therapy. Although many risk factors for acute kidney injury (AKI) with colistin have been identified, data supporting protective factors mitigating this dose-limiting side effect are lacking.

In 2011, Garonzik and colleagues published interim results from a pharmacokinetic study that described colistin exposures in critically ill patients and, for the first time, provided pharmacokinetically based dosing recommendations [1]. The authors demonstrated the need for a loading dose and developed a dosing equation for colistin. In this issue of Clinical Infectious Diseases, Dalfino and colleagues describe their experience using this dosing algorithm and its impact on the incidence of AKI [2].

After administering a loading dose, the authors utilized the maintenance dose algorithm to target a colistin steady-state concentration of 2.5 mg/L, in accordance with the recommendations from Garonzik et al [1]. As described in detail elsewhere [3, 4], this suggested target concentration is not a “magic bullet” for efficacy, but was selected by Garonzik et al by balancing efficacy and safety. Although this target concentration would only be associated with bactericidal activity for organisms at the lower end of the susceptibility range, the authors did not feel comfortable recommending higher targets given that the median colistin concentration in their study was 2.36 mg/L and the nephrotoxicity rate was 48% [1]. Additionally, given that doses in the Dalfino et al study were capped at 9 million units (270 mg of colistin base activity) for patients with creatinine clearances of 60–130 mL/minute or 12 million units in patients with clearances >130 mL/minute, patients with creatinine clearances >60 mL/minute likely did not attain the target concentration of 2.5 mg/L.

When the targeted concentrations are put into context with the minimum inhibitory concentration (MIC50) and MIC90 data from pathogens presented in this article (0.5/2 mg/L for Acinetobacter baumannii, 2/2 mg/L for Pseudomonas aeruginosa, and 1/1.5 mg/L for Klebsiella pneumoniae) the free area under the curve to MIC ratio exposures that patients in this study obtained would likely only be associated at best with a 1 log10 kill, and, in some cases, a bacteriostatic effect in a significant proportion of patients [5, 6]. The 44% toxicity rate reported, even in the setting of suboptimal pharmacodynamic exposures, underscores the difficulty in safely targeting “therapeutic concentrations” with colistin. Importantly, however, despite these potential exposure limitations, the authors reported a clinical success rate of 77%. Unfortunately, interpretation of this success rate is difficult due to a lack of information on how infections were defined, the incidence and impact of polymicrobial or additional infections and their treatment, a lack of actual patient serum concentration data, and the frequent use of combination therapy.

Although efficacy assessment is complex, this study provides the first analysis looking at a pharmacokinetically driven dosing regimen, with daily dose modifications based on renal function, on the incidence of AKI. Importantly, the authors...
showed that by using this type of approach and targeting a concentration of 2.5 mg/L, the incidence of AKI was high (44%).

A notable finding in this study was the lack of an association between colistin dose and AKI risk. The lack of association between increasing dose and AKI is primarily explained by the “dose-capping” utilized in this study. Patients with clearances between 60 and 130 mL/minute received 9 million units of colistimethate (CMS), despite the fact that these doses would not reach the targeted concentration of 2.5 mg/L in patients with clearances >60 mL/minute. For example, given a creatinine clearance of 100 mL/minute, the equation used by the authors would predict the need for a dose of 13.5 million units CMS to reach a target colistin steady-state concentration of 2.5 mg/L, and a dose of 9 million units would only be predicted to achieve a concentration of approximately 1.7 mg/L. Furthermore, even though patients with clearances >130 mL/minute were allowed doses up to 12 million units, a similar likelihood of suboptimal exposure holds true. For example, if a patient had a creatinine clearance of 150 mL/min and received a dose of 12 million units, the projected steady-state concentration would be just under 1.6 mg/L.

Furthermore, the capped dosing strategy also explains the association between baseline renal impairment and AKI risk as steady-state concentrations were likely higher in patients with baseline renal insufficiency even though they received lower doses. The median baseline creatinine clearance in patients developing AKI was 67 mL/minute (interquartile range [IQR], 36–78 mL/minute). Thus, dose-capping would have occurred only in a minority of patients who developed AKI and, when it did occur, would only have led to a modest decrease from “target doses.” In contrast, among patients who did not develop AKI, the median baseline creatinine clearance was 133 mL/minute (IQR, 82–182 mL/minute) and therefore dose-capping occurred in nearly all patients in this subgroup. The higher estimated concentrations seen in patients who developed AKI (2.5 mg/L) vs those who did not develop AKI (approximately 1.3–2.0 mg/L) are clinically relevant, as concentrations associated with occurrence and severity of colistin-associated AKI have ranged from 1.9 mg/L to 2.4 mg/L [7, 8]. Thus, patients with baseline renal insufficiency were more likely to have attained concentrations associated with AKI, despite lower doses. It is important to keep in mind that this explanation is based on theoretical concentrations, and actual concentrations in these patients are unknown. Given the high interpatient variability for colistin levels of up to 10-fold [1], definitive conclusions about concentrations and toxicity in this study cannot be made.

Undoubtedly though, the most encouraging finding in this study was that of intravenous ascorbic acid being highly protective against nephrotoxicity. AKI was seen in 13 of 43 (30%) of patients receiving ascorbic acid compared with 18 of 27 (67%) of those who did not (P < .05), and ascorbic acid remained protective for AKI in multivariate analysis (adjusted odds ratio, 0.27 [95% confidence interval, .13–.57]). This is an important finding as it marks the first protective therapeutic factor reported for colistin-associated nephrotoxicity. Mechanistically, this finding is plausible as evidence has suggested that in colistin-induced nephrotoxicity, oxidative stress initiates renal cell apoptosis. Animal models have demonstrated that ascorbic acid, by serving as a free radical scavenger/antioxidant, can decrease kidney tissue apoptosis and tubular damage [9].

Although this finding is encouraging and statistically significant, it is important to remember that this is a small, non-randomized study, and the differences in characteristics of patients who received ascorbic acid compared with those who did not are unknown. Additionally, a small, preliminary, randomized trial looking at the protective effect of intravenous ascorbic acid (4 g/day) on colistin-associated nephrotoxicity failed to show a benefit [10]. Furthermore, animal modeling has shown that concomitant ascorbic acid significantly altered the pharmacokinetics of colistin by increasing the volume of distribution, decreasing the clearance, and increasing the half-life [9]. Therefore, analyses on the impact of ascorbic acid on human pharmacokinetics of colistin are clearly warranted if concomitant use is to become more common. The contrasting clinical findings and pharmacokinetic unknowns underscore the need for well-controlled data in a larger sample size to better assess the potential benefit of ascorbic acid.

In summary, despite the small numbers in this trial, these data represent the first safety data with a rigorous, pharmacokinetic/pharmacodynamic-based, consistent dosing strategy with colistin with well-described renal dose-adjustment strategies. Importantly, the authors reported an AKI rate exceeding 40% when targeting a serum concentration of 2.5 mg/L, and toxicity was likely more prevalent in patients who approached this target. Interestingly, despite these decreased exposures and relatively high MICs in a good proportion of the study pathogens, the clinical success rate exceeded 75%. Unpredictable exposures of colistin in patients and the high frequency of combination regimens undoubtedly influenced the success rate and underscores the critical need for patient data equating in vivo exposures of colistin and efficacy, to minimize potential overexposure. Given the findings of this study, other toxicodynamic studies with colistin, and the absence of data suggesting that higher exposures improve outcomes, the upper end of a realistic target steady-state concentration of colistin appears to be approximately 2 mg/L, even though this target will likely be associated with, at best, modest bactericidal activity for pathogens with MICs at the upper end of the colistin susceptibility breakpoint. Although the evidence is currently contradictory regarding ascorbic acid’s protective effect on colistin-associated nephrotoxicity, given the independent
association between even small degrees of AKI and mortality and excess hospital costs [11], it is reasonable to give concomitant ascorbic acid to patients at high risk for colistin-associated nephrotoxicity. However, higher-quality evidence, as well as data assessing ascorbic acid’s impact on colistin pharmacokinetics in humans, are warranted before ascorbic acid administration becomes standard of care in patients receiving colistin.

Note

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

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References