Nephrotoxicity of Colistin: New Insight into an Old Antibiotic

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(See the brief report by Hartzell et al. on pages 1724–8)

We commend Hartzell et al. [1] for their study on the nephrotoxicity associated with intravenous administration of colistimethate sodium (hereafter, referred to as "colistin"). Despite its retrospective nature, the study has special merit because it addresses an important clinical issue.

Colistin (also known as polymyxin E) was developed ∼60 years ago but was rarely used in clinical practice (except for patients with cystic fibrosis) during the period 1980–2000 because of concerns related to reported high rates of nephrotoxicity. However, it was recently reintroduced in clinical practice in many parts of the world, primarily as a consequence of necessity. Specifically, it was revived because of the challenges faced by physicians caring for patients with infections due to lactose-nonfermenting, gram-negative bacilli, mainly *Pseudomonas aeruginosa* and *Acinetobacter baumannii* [2].

There is certainly a disparity in the reported rates of nephrotoxicity associated with intravenous administration of colistin between old and recent studies. Indeed, in a systematic review of the relevant literature, the reported rate of nephrotoxicity was higher in older studies than in studies published after 1995 [3]. This may be partly caused by the lack of common criteria to define renal function impairment. However, the variance in definitions alone cannot account for the important differences in reported nephrotoxicity associated with colistin. Fewer chemical impurities of colistin, better intensive care unit monitoring (especially of the patient’s hydration status), and avoidance of coadministration of other nephrotoxic drugs may be the main causes of the differences [3]. A growing body of evidence from studies originating from hospitals in several countries has shown that colistin is effective and acceptably safe [4]. Although most of the revival of polymyxin use is associated with colistin, satisfactory figures of effectiveness and safety have also been reported for the other polymyxin antibiotic available for intravenous use, polymyxin B [5].

The assessment of nephrotoxicity associated with a medication is not an easy task. Ideally, a control group receiving another antibiotic or placebo is needed for better insight in studies that address issues of adverse events. We believe that the lack of randomized, controlled trials of intravenous colistin hampers the evaluation of its effectiveness and safety. However, the fact that intravenous colistin is administered mainly to patients with infection due to polymyxin-only-susceptible bacteria makes the performance of relevant randomized, controlled trials unlikely at this time. This is because it may be unethical not to prescribe colistin for a patient with an infection for which the drug is the only available therapeutic option.

Thus, one currently has to rely on the available data from studies other than randomized, controlled trials. It is noteworthy that the effectiveness and nephrotoxicity of colistin and a carbapenem were not different in 2 relevant comparative studies performed in Spain and Tunisia [6, 7]. In addition, in a study from a hospital in Texas, nephrotoxicity was not different in patients with cancer receiving treatment with colistin, compared with those receiving treatment with other antibiotics (a quinolone or a β-lactam antibiotic with or without aminoglycosides) [8]. It must be kept in mind that, in these studies, the level of antimicrobial resistance varied between the compared groups (carbapenem-resistant infections among patients who received colistin and carbapenem-susceptible infections among patients who received other antibiotics). Specifically, a higher level of antimicrobial resistance was present among patients with polymyxin-only-susceptible infections. One could ar-

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gure that this higher level of resistance could be associated with a biological cost (fitness to survive) of resistant bacteria that may have had an impact on the outcome. However, this is not verified by data from clinical practice; for example, in patients with inappropriately treated A. baumannii infection, a considerable mortality directly attributable to infection is observed [9].

The effect of sepsis, per se, on renal function should not be disregarded [10]. Sepsis may potentiate the effects of colistin and other drugs on the kidney. In addition, the evaluation of nephrotoxicity may be confounded further by the use of other potentially nephrotoxic agents. Although the study by Hartzell et al. [1] did not find any statistically significant differences in the use of other potentially nephrotoxic drugs between patients who developed nephrotoxicity and patients who did not, it would be better to avoid such therapeutic combinations. In fact, the study had limited statistical power to find such differences. Aminoglycosides and colistin share a common adverse-event profile, with potential nephrotoxicity, neuromuscular blockade, and paresthesias. The potential problems due to the concomitant use of other nephrotoxic agents, especially intravenous radiocontrast agents and nonsteroidal anti-inflammatory drugs, should also be taken into consideration.

It cannot be emphasized enough that the dosage and frequency of administration of colistin should be adjusted for serum creatinine levels and that renal function should be monitored when colistin is prescribed [11, 12]. This dose adjustment may permit the completion of life-saving therapy in patients with renal impairment. The observation in the study by Hartzell et al. [1] that the total cumulative dose (not the daily dose) of colistin was associated with nephrotoxicity leads to the suggestion that shortening the duration of treatment of various infections, including ventilator-associated pneumonia, could help decrease the rate of occurrence of nephrotoxicity [13].

The RIFLE criteria (risk, injury, failure, loss, and end-stage kidney disease) used for assessment of nephrotoxicity are welcome not only in studies of colistin but also in studies of other medications with potential nephrotoxicity [1, 14]. It is traditional teaching that the serum creatinine level increases above the upper normal limit only when a substantial impairment of nephrons is present—that is, normal serum creatinine levels do not exclude nephrotoxicity. Therefore, measurement of serum creatinine levels will not help in the detection of early renal toxicity. The proportional increase in serum creatinine levels over baseline is a commonly neglected factor in everyday practice, and the reminder from Hartzell et al. is valuable. However, proportional increases in serum creatinine levels (or decreases in the glomerular filtration rate) may not always be a specific index for nephrotoxicity; thus, both the proportional change and the absolute serum creatinine levels have to be taken into consideration.

The clinical significance of a potential proportional increase in serum creatinine levels has to be assessed for each patient. For example, for a patient with bacteremia caused by polymyxin-only-susceptible A. baumannii, the decision to withdraw colistin treatment, even in the presence of some degree of nephrotoxicity, is of paramount importance. Therefore, the withdrawal of colistin treatment on the basis of risk (as defined by RIFLE criteria) alone is probably not always justified, given the severity of the infections that warrant its use. In cases of renal toxicity, physicians should modify the colistin dose or frequency of administration (or both) or resort to another therapeutic agent (tigecycline may be a useful antibiotic for treatment of a subset of A. baumannii infections [15]), provided that the need for continuation of antimicrobial therapy remains.

One may wonder, why prescribe a medication with a 10%–20% potential for nephrotoxicity? As explained above, colistin is prescribed either because bacteria are susceptible only to it or because of the failure or intolerance of other therapeutic options. Thus, it represents the last antibiotic frontier to treat infections with almost no other therapeutic alternative [16]. The attributable mortality associated with A. baumannii infection should not be underestimated [9]. From this point of view, the mortality observed in patients who received colistin for treatment of severe infections in the study by Hartzell et al. [1] was actually lower than what one would expect, given the Acute Physiology and Chronic Health Evaluation II scores. Thus, the risk for nephrotoxicity of colistin has to be weighed against its beneficial effect on survival.

In conclusion, fortunately, the evidence from the evolving recent literature shows that, despite the occurrence of mild renal dysfunction in a proportion of patients who received intravenous colistin, the need for renal replacement therapy and permanent kidney damage are rare events (neither occurred in the study by Hartzell et al. [1]). Moreover, none of the patients in the study by Hartzell and colleagues who had nephrotoxicity during colistin treatment had signs of kidney injury or failure at 3 months after treatment [1]. We believe that periodic assessment of serum creatinine levels, modification of the colistin dose according to renal function, avoidance of coadministration of other nephrotoxic agents (if possible), shortening the duration of antimicrobial treatment, and attention to overall patient care, including hydration status, will minimize the potential for nephrotoxic effects of this valuable old antibiotic.

Acknowledgments

References


