Should We Accept Colistin-Induced Nephrotoxicity To Ensure Attainment of a Therapeutic Steady State in Those with Good Renal Function?

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We applaud Lodise and colleagues for their recent publication addressing the pathophysiology of colistin-induced nephrotoxicity and the potential protective effect of minocycline, a broad-spectrum tetracycline antibiotic (1). Our recent experience of colistin in the treatment of multidrug-resistant (MDR) *Pseudomonas aeruginosa* has been troubled by rapid development of nephrotoxicity on one hand and the inability to attain adequate plasma colistin concentrations due to high creatinine clearance (CL_{CR}) on the other.

Faced with the rapid global dissemination of MDR Gram-negative pathogens, colistin is increasingly being called upon as a last-resort treatment option (2). Subsequently, there has been an emergence of pharmacokinetic/pharmacodynamic (PK/PD) and toxodynamic studies clarifying the treatment strategies required to achieve adequate concentrations in plasma, while avoiding undue toxicity (3, 4). An average plasma steady-state concentration ($C_{ss,avg}$) of colistin of 2 mg/liter is desirable when starting intravenous therapy; however, administration is as colistin methanesulfonate, a predominantly renally excreted inactive prodrug (5–7). The pharmacokinetic data published by Nation et al. confirm that patients with a CL_{CR} in excess of 80 ml/min have a very low probability of achieving a $C_{ss,avg}$ of 2 mg/liter and are therefore at risk of failing treatment (5). It is clear, thanks to the work of Falagas and colleagues, that getting the dose of colistin right has a positive impact on 30-day mortality (8). To attempt to attain a $C_{ss,avg}$ of >2 mg/liter when the CL_{CR} is >80 ml/min would require doses of colistin associated with nephrotoxicity (4, 9).

This raises an interesting dilemma; in the desperate setting of requiring systemic treatment with colistin and a CL_{CR} of >80 ml/min, should we use these extremely high doses to achieve the target $C_{ss,avg}$ but also tolerate an element of therapeutic nephrotoxicity, with a view to reaching a dose/toxicity balancing act? In our experience, when treating a patient with a CL_{CR} of 150 ml/min, achieving a $C_{ss,avg}$ was not possible until an element of renal dysfunction was tolerated. This approach has been thrown into dispute by the recent work of Benattar and colleagues, who found no association between high-dose colistin and improved 28-day mortality but a strong association with high doses and nephrotoxicity, although that study was limited by a lack of measurement of CL_{CR} and colistin $C_{ss,avg}$ (10).

While the work of Lodise and colleagues suggests that minocycline may ameliorate colistin-induced nephrotoxicity, they do not comment on how this impacts colistin's PK/PD profile (1). We must be cognizant of the fact that preventing nephrotoxicity may unduly prevent attainment of the target $C_{ss,avg}$, especially in those with a CL_{CR} of >80 mg/liter, although we still need to prospectively clarify the association of colistin dose

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and clinical outcomes (4, 10). Further research clarifying the impact of minocycline on colistin's PK/PD dynamics, the correct colistin dosing regimen in patients with good renal function, and the potential for minocycline in those with coexistent renal dysfunction is encouraged.

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