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Are there any ways around the exposure-limiting nephrotoxicity of the polymyxins?

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ABSTRACT

The polymyxins (colistin and polymyxin B) have emerged over the past 20 years as essential antibacterial agents that often are the only remaining active class against troublesome multidrug-resistant Gram-negative bacilli such as carbapenem-resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and Enterobacteriaceae. The utility of this class is limited by its dose-dependent nephrotoxicity, which can occur in more than one-half of patients receiving therapy with either agent. Strategies are urgently needed to optimise the use of this class of agents to ensure optimal activity while minimising the treatment-limiting nephrotoxicity. This review will focus on risk factors for polymyxin-associated nephrotoxicity, potential strategies for limiting this exposure-dependent toxicity and, finally, unknowns and future research directions pertinent to this topic.

1. Introduction and history of polymyxin-associated nephrotoxicity

The polymyxin class of antibiotics was discovered midway through the 20th century; however, preliminary studies of the antibiotics in this class revealed that the majority of agents were too toxic to the mammalian kidney to be used safely in humans [1,2]. Exceptions to this finding were polymyxin B (PMB) and polymyxin E (colistin), and over the next two decades these 'safe' polymyxins were brought to market to combat *Pseudomonas* spp. and other Gram-negative infections. At the time that these agents became commercially available, the strict pre-approval requirements of the US Food and Drug Administration (FDA) had not yet been implemented, resulting in the availability of agents that lacked sufficient data regarding optimal use. Early clinical studies of the commercially available polymyxins reported no evidence of nephrotoxicity with either agent when administered intramuscularly at doses of 2.5 mg/kg/day [3]. However, as the polymyxins became incorporated into clinical practice it was quickly discovered that, contrary to initial observations, these agents were capable of causing high rates of renal dysfunction, especially when administered at higher doses [4,5]. For this reason, PMB and colistin were ultimately shelved in favour of new, safer agents and what little research was being done on the polymyxins subsequently ceased.

At the end of the 20th century a renewed interest in the polymyxins occurred secondary to increasing rates of multidrug-resistant (MDR) infections with limited treatment options [6]. Colistin was used preferentially over PMB in most patients for a number of reasons. Most significantly, there was a belief perpetuated in historic literature that colistin was considerably less nephrotoxic than PMB. Although widely believed as truth, it has now become apparent that this was based solely on expert opinion, as no head-to-head trials had been performed at the time [7]. Second, reports describing the successes associated with intravenous (i.v.) and inhaled colistin in patients with cystic fibrosis who were colonised or infected with MDR organisms occasionally appeared in the literature in the late 20th century often enough to keep colistin more relevant than PMB [8–10]. Lastly, of the two polymyxin agents, colistin was, and still is, the only parenterally available polymyxin agent in Europe. Much of the present-day literature regarding polymyxins originates from Greece, Italy and Israel, countries with some of the highest MDR infection rates worldwide [11]. The lack of polymyxin choice in Europe caused an unintentional publication bias lending greater literature support towards usage of colistin. Despite the reasons listed above, PMB has emerged as the polymyxin of choice in various locations throughout the USA and South America, allowing continued research to be done with both agents. As clinicians face increasing rates of polymyxin resistance, it is imperative that the dose–efficacy relationship of these agents be understood

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in order to minimise the development of resistance and maximise bacterial killing all the while remaining cognisant of the limits imposed on these outcomes by dose-dependent nephrotoxicity. This review will focus on risk factors for polymyxin-associated nephrotoxicity, potential strategies for limiting this exposure-dependent toxicity and, finally, unknowns and future research directions pertinent to this topic.

2. Risk factors for polymyxin-associated nephrotoxicity

It is now known that the risk of developing polymyxin-associated nephrotoxicity is not negligible but is highly variable and strongly dependent on patient- and dose-specific risk factors. Several studies both of colistin and PMB have reported increased age as an independent risk factor for developing acute kidney injury (AKI). Rigatto et al. noted a significant age difference in patients receiving PMB who developed AKI and those who did not (66.7 ± 15.3 years vs. 61.7 ± 17.9 years, respectively; $P = 0.03$) [12]. Similarly, Balkan et al. reported that patients aged >60 years had a significantly higher risk of AKI while on colistin therapy [13]. Interestingly, a third study also reported age to be a significant predictor of colistin-associated nephrotoxicity, albeit in a younger cohort of patients (median age of 56 ± 10.1 years and 47 ± 15.7 years in the nephrotoxicity and non-toxicity groups, respectively; $P = 0.04$) [14]. Based on this information, the exact age beyond which toxicity is more likely to occur remains unknown and, in actuality, there might be a continually increasing risk over the full spectrum of age. However, age as a potential risk factor requires further investigation as multiple studies have shown no association between age and AKI and it is possible that older patients might be at higher risk for AKI owing to an increase in frequency of co-morbid conditions [15,16].

Higher weight and/or body mass index (BMI) is an additional risk factor that appears to increase the risk for developing AKI with either polymyxin agent. Interestingly, however, this is not solely due to increased daily doses [13,14,16]. Gauthier et al. observed a significant difference in mean BMI between patients who experienced nephrotoxicity and those who did not (33.5 kg/m^2 vs. 30.4 kg/m^2, respectively; $P = 0.015$) despite higher BMI patients receiving a lower daily dose (in mg/kg) of colistin (1.81 mg/kg vs. 2.19 mg/kg; $P = 0.02$). In addition, a BMI of ≥31.5 kg/m^2 was an independent predictor of colistin-associated nephrotoxicity in this analysis [14]. Similarly, Riggato et al. reported that higher patient weight was a predictor for AKI and renal failure in patients treated with PMB regardless of the total daily dose of PMB received [12]. The reason for the association between weight and AKI remains unclear.

Another important potential risk factor is the receipt of concomitant nephrotoxic medications. Various studies have demonstrated significant increases in nephrotoxicity rates when polymyxins are administered concurrently with vancomycin, i.v. contrast media, loop diuretics, angiotensin-converting enzyme inhibitors, rifampicin and/or non-steroidal anti-inflammatory drugs [12,17–19]. This is worth noting for clinicians given the preference for polymyxin-based combination therapy and the fact that in many instances the only other antibiotic class to which a MDR organism remains susceptible is the aminoglycosides. Limited evidence has suggested that patients receiving aminoglycosides are not at increased risk for the development of nephrotoxicity while on polymyxin therapy [15–17,19,20]. However, it is important to note that data supporting an increased risk with co-administration of a polymyxin and a particular nephrotoxin are inconsistent. AKI appears to be more likely in patients receiving any concomitant nephrotoxic agent (such as an aminoglycoside) in addition to a polymyxin, rather than any single agent in particular. Therefore, the risk of causing additional nephrotoxicity by adding an aminoglycoside must be weighed against providing potentially suboptimal therapy. Other independent risk factors of polymyxin-associated nephrotoxicity include general markers of poor health status such as diabetes mellitus, hypoalbuminaemia and intensive care unit admission [17,18].

In addition to patient-specific risk factors, two polymyxin exposure-specific risk factors have been shown to increase the risk of polymyxin nephrotoxicity, namely dose administered and serum concentration. Nephrotoxicity due to polymyxin agents is a dose-dependent phenomenon and this has been observed in multiple studies. In 2011, a retrospective cohort study of 126 patients reported that the mean daily colistin dose [measured as mg/kg of ideal body weight (IBW)] in patients who developed nephrotoxicity was 5.3 mg/kg/day compared with only 3.95 mg/kg/day in patients who did not experience nephrotoxicity ($P < 0.001$) [17]. In addition, colistin doses ≥5 mg/kg/day were noted to be an independent risk factor for the development of nephrotoxicity [odds ratio (OR) = 23.41, 95% confidence interval (CI) 5.30–103.55]. Interestingly, a study by Dubrovskaya et al. reported that a higher daily PMB dose based on actual body weight (ABW), but not IBW, was a significant independent risk factor for nephrotoxicity ($P = 0.022$). Of note, however, mean daily doses, weight-based or otherwise, among patients who did and did not develop nephrotoxicity were not discussed [19].

Rather than examine the effect of weight-based doses, Tuon et al. reported rates of nephrotoxicity based on the total daily polymyxin dose administered [20]. The daily polymyxin dose cut-offs selected for analysis were >270 mg colistin base activity (CBA) or ≥200 mg PMB. Daily doses above these thresholds were an independent risk factor for development of nephrotoxicity ($P = 0.04$). In addition, Rigatto et al. analysed risk factors for PMB-associated nephrotoxicity in 410 patients and concluded that daily PMB doses of ≥150 mg were predictive of AKI ($P = 0.001$); however, they also observed that there was no additional increase in rates of nephrotoxicity when daily doses >200 mg were administered [12]. On the other hand, Elias et al. did find an association between PMB doses ≥200 mg and AKI. Although there are discordances regarding the exact dose threshold values for the polymyxins to increase the risk of AKI, a consistent dose-dependent toxicity has been reported [21].

Based on the fact that higher polymyxin dose appears to correlate with an increase in risk for nephrotoxicity, it seems logical that higher serum polymyxin concentrations also pose an increased risk for AKI. To date, there are no data looking at the relationship between PMB concentrations and toxicity, however there are limited data with colistin.

Sorli et al. reported on the association between serum trough colistin values and the development of AKI. The authors obtained steady-state colistin trough levels (C_{min}) from 102 patients receiving the drug for ≥4 days [22]. The authors found a significant difference in C_{min} on Day 3 between those patients who did not and those who did experience nephrotoxicity on Day 7 [C_{min}, 0.78 (0.11–3.2) mg/L vs. 3.11 (0.45–5.99) mg/L; $P < 0.0001$] and at the end of therapy [C_{min}, 0.7 (0.11–5.7) mg/L vs. 1.18 (0.16–5.99) mg/L; $P < 0.0001$]. Colistin C_{min} was found to be an independent risk factor for nephrotoxicity at both time points, with concentrations of 3.33 mg/L and 2.42 mg/L being the predictive serum concentration breakpoints for nephrotoxicity on Day 7 and at end of therapy, respectively [22]. This C_{min} value associated with AKI at the end of therapy is very similar to the average steady-state concentration seen in the largest pharmacokinetic study to date on colistin in critically ill patients, suggesting that commonly utilised doses will put patients at increased risk for AKI [23].

These findings are strengthened by a recent abstract by Forrest et al. [24]. The data presented in this abstract were the finalised data set from the aforementioned pharmacokinetic study in critically ill patients. In this analysis, an association was seen between serum colistin concentration and severity of AKI [24]. Patients from the study were divided into two groups based on baseline creatinine clearance (CL_{Cr}), i.e. those with $CL_{Cr} \geq 80$ mL/min and those with $CL_{Cr} < 80$ mL/min. In the group with higher baseline CL_{Cr}, a median