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Review

Clinical considerations for optimal use of the polymyxins: A focus on agent selection and dosing

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ABSTRACT

Polymyxins have remained the drug of choice for treatment due to carbapenem-resistant Gram-negative bacilli. Unfortunately, the utility of these agents has been limited by a lack of pharmacokinetic understanding, a high toxicity rate, and an extremely narrow therapeutic index. Significant advancements have been achieved in the understanding of the polymyxins over the past decade, and have led to the recognition of several differences between available intravenous formulations. The purpose of this review is to discuss the implications of these differences, assess comparative efficacy and safety of the polymyxins, and provide recommendations for polymyxin dosing and selection. **J.M. Pogue, Clin Microbiol Infect 2017;23:229**

Introduction

Colistin (polymyxin E) and polymyxin B became commercially available around the same time and one, or both, of these agents are available in many countries worldwide. A nearly identical chemical structure, save for one amino acid difference, is responsible for the myriad of similarities between these two agents, including mechanism of action and spectrum of activity [1]. In addition, this minor structural difference between polymyxins does not appear to impact the comparative efficacy or *in vitro* potency of either agent to a significant degree [2]. Importantly, however, while polymyxin B is available directly as its sulphate salt for intravenous administration, colistin is only commercially available for intravenous use in the form of its inactive pro-drug, colistin methanesulphonate (CMS), which must be hydrolysed *in vivo* to active colistin. This difference in formulation leads to significant pharmacokinetic differences *in vivo* [3].

These *in vivo* differences stem from the fact that CMS has a slower than desirable conversion rate to colistin and is an inefficient pro-drug, taking up to 7 h or more to achieve maximum serum concentrations of colistin after administration [3,4]. It is worth noting, however, that this is not a universal finding, and other analyses suggest a more rapid conversion [5]. This delayed conversion, on its own, would have significant therapeutic implications on time to optimal colistin concentrations, but it is compounded by the fact that, due to this slow conversion, the vast majority of CMS is renally eliminated before conversion in patients with normal renal function. This slow conversion has significant implications for both the ability to achieve therapeutic concentrations of active colistin in patients with good renal function as well as the toxicity profile, as discussed below. Conversely, as polymyxin B is administered as its active moiety it rapidly attains its peak concentration after infusion followed by distinct trough concentrations before the subsequent dose [6].

There are also renal dosing differences between the agents that are related to the characteristics of the pro-drug, CMS. Although CMS, colistin and polymyxin B are all filtered by the glomeruli, only CMS is significantly eliminated via the kidneys [3]. Hence,

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CMS doses must be adjusted for patients with decreased renal function to prevent overexposure to colistin, as decreased renal clearance of CMS will allow for more extensive *in vivo* conversion to active colistin. Colistin and polymyxin B undergo extensive reabsorption and are eliminated largely through poorly described non-renal mechanisms [5,7]. As a result, based on currently available evidence, no renal dosing adjustments are required for polymyxin B [6].

Therefore, although active colistin and polymyxin B are probably identical in their exposure–response relationships, important differences occur in patients with the commercially available polymyxin products (CMS and polymyxin B). However, the important question remains—do these differences impact the comparative efficacy or toxicity of these two polymyxin agents? The purpose of this review is to discuss the implications of these differences, assess comparative efficacy and safety of the polymyxins, and provide recommendations for polymyxin dosing and selection.

Comparative efficacy data: has one polymyxin performed better in patients?

Limited comparative clinical data exist and available information comes from studies primarily aimed at measuring rates of nephrotoxicity. This is important to note because these studies generally do not assess many important characteristics associated with efficacy end points including time to appropriate therapy, use of antimicrobial combinations, severity of illness, infection versus colonization, site of infection, type of organisms, polymyxin dose and MIC. Furthermore, these studies are underpowered to truly answer the question. Without adequate assessment of these variables, it is very difficult to critically compare the efficacy of these agents. To date, four studies have provided information regarding clinical outcomes [8–11], but only one of the four has evaluated mortality as the primary end point [8]. This study, performed by Oliveira et al., evaluated clinical outcomes among 41 patients treated with CMS and 41 treated with polymyxin B [8]. No significant differences were found between the CMS and polymyxin B populations for clinical success (39% versus 39%; p 0.48), hospital death (46% versus 54%; p 0.51), and 30-day mortality (56% versus 61%; p 0.66). Multivariate analyses of prognostic factors associated with mortality were performed and type of polymyxin was not associated with mortality.

Phe et al. evaluated in-hospital mortality rates among 121 patients receiving CMS and 104 receiving polymyxin B [9]. Overall, significantly higher rates of hospital mortality were observed among patients receiving polymyxin B (30.8% versus 8.3%; $p < 0.001$). However, when hospital mortality was evaluated in a matched subgroup that excluded patients with cystic fibrosis and patients who received suboptimal polymyxin doses there was no difference in mortality between CMS and polymyxin B (21.4% versus 21.4%; p 1.00). Hospital mortality was also assessed as a secondary outcome in a nephrotoxicity study performed by Tuon et al. [10]. Rates of hospital mortality were not significantly different among patients receiving CMS and polymyxin B at 45.8% and 50%, respectively (p 0.48). Similarly, Rigatto et al. assessed 30-day mortality as a secondary outcome among 81 patients receiving CMS and 410 receiving polymyxin B [11]. Overall, 30-day mortality occurred in 30.9% and 43.4% in the CMS and polymyxin B groups, respectively (p 0.083). A multivariate model adjusting for age, intensive care unit admission and Charlson co-morbidity score found no difference in mortality among patients receiving CMS or polymyxin B (hazard ratio (HR) 0.89; 95% CI 0.56–1.38). Based on the available data, there does not appear to be a significant difference in clinical efficacy between the two polymyxin agents. However, as previously mentioned, these data are insufficient to truly determine whether there is a difference in clinical efficacy of the two polymyxins.

Comparative nephrotoxicity: is one polymyxin safer than the other?

To date, five studies have assessed comparative nephrotoxicity in patients receiving CMS or polymyxin B. The first, published in 2009 by Oliveira et al., used a unique definition for nephrotoxicity of a two-fold increase in serum creatinine compared with baseline or an increase of 1 mg/dL if the initial creatinine was >1.4 mg/dL [8]. The authors found no significant difference in the rates of nephrotoxicity, which occurred in 26% and 27% of patients receiving CMS and polymyxin B, respectively (p 0.92).

In 2013, Akajagbor et al. compared rates of nephrotoxicity between 106 patients receiving CMS and 67 receiving polymyxin B [12]. Nephrotoxicity was measured according to the RIFLE criteria. Nephrotoxicity rates were significantly higher among patients receiving CMS compared with polymyxin B (60.4% versus 41.8%, respectively; p 0.02). In a multivariate analysis CMS use remained a significant predictor of nephrotoxicity (HR 2.27; 95% CI 1.35–3.82).

A third study performed by Tuon et al. examined nephrotoxicity rates according to Acute Kidney Injury Network criteria among 36 patients receiving CMS and 96 receiving polymyxin B [10]. There was no significant difference in acute kidney injury in the CMS group compared with those patients receiving polymyxin B (38.9% versus 20.8%, respectively; p 0.06). This lack of association remained true in a multivariate model where the adjusted HR for nephrotoxicity and CMS, as compared to polymyxin B, was 1.74 (95% CI 0.82–3.69).

It is important to recognize that a major shortcoming of the three previously mentioned analyses is that patients with renal dysfunction probably received dose-adjusted polymyxin B. As mentioned earlier, renal dose adjustments for polymyxin B are probably not warranted. Therefore, these unnecessary dose adjustments in patients with impaired baseline renal function would result in decreased polymyxin B exposure and, consequently, lower rates of nephrotoxicity. This limits the interpretation and applicability of these findings.

Two additional studies attempted to minimize this confounding effect of unnecessary polymyxin B dose reductions. The first study, performed by Phe et al. excluded patients with a baseline serum creatinine >1.5 mg/dL [9]. Nephrotoxicity was evaluated in 225 patients, 121 receiving CMS and 104 receiving polymyxin B, based on RIFLE criteria. Overall, nephrotoxicity occurred in 33.9% of patients who received CMS and 23.1% who received polymyxin B (p 0.08). A matched subgroup of 76 patients (38 pairs) was performed, with median administered doses of polymyxin agents noted to be 297.7 ± 99.3 mg/day of colistin base activity (CBA) and 125.9 ± 35.3 mg/day of polymyxin B. With these regimens, which more closely approximated optimal dosing, nephrotoxicity occurred significantly more often among those receiving CMS than polymyxin B (55.3% versus 21.1%; p 0.003).

Most recently, Rigatto et al. prospectively observed polymyxin nephrotoxicity rates in 81 patients receiving CMS and 410 patients receiving polymyxin B [11]. CMS and polymyxin B dosing were consistent with a more optimal dosing strategy based on currently accepted best practices (colistin median dose 300 mg CBA (interquartile range 253–300 mg), polymyxin B median dose 150 mg (interquartile range 140–187 mg)). Renal failure was significantly higher among patients receiving CMS (38.3%) compared with those receiving polymyxin B (12.7%; $p < 0.001$). Additionally, multivariate analysis identified receipt of CMS to be an independent risk factor for the development of renal failure.

Based on the literature, there appears to be a potential safety advantage for polymyxin B over CMS. There is some biological plausibility to this finding as well. Polymyxin uptake into the renal tubules appears to be a saturable process [13]. Therefore, rapid