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Critical Need for Clarity in Polymyxin B Dosing

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We read with interest the report by Thamlikitkul et al. describing polymyxin B exposures in 19 adult patients with and without renal insufficiency (1). No significant difference was observed in the dose-normalized 24-h area under the concentration-time curve (AUC_{24}) at steady state between those with normal renal function, defined as an estimated creatinine clearance (CL_{CR}) of ≥80 ml/min ($n = 5$; mean CL_{CR}, 90.0 ± 12.5 ml/min; mean AUC_{24}, 28.6 ± 7.0 mg · h/liter) and those with renal insufficiency ($n = 14$; mean CL_{CR}, 40.8 ± 21.8 ml/min; mean AUC_{24}, 29.7 ± 11.2 mg · h/liter; $P = 0.80$). A sensitivity analysis using lower CL_{CR} threshold values of <60 and <40 ml/min yielded similar results.

This study adds to mounting evidence that polymyxin B undergoes negligible renal excretion; thus, dose adjustment based solely on a patient's renal function may not be prudent (2, 3). Unfortunately, such observations conflict with current polymyxin B labeling, which instructs physicians to decrease doses in the setting of "renal impairment" (4). Administering less than the suggested 1.5 to 2.5 mg/kg of actual body weight daily may, in fact, be detrimental, increasing the risk of death as a consequence of insufficient drug exposure (5). However, the potential for nephrotoxicity and interpatient variability must also be considered when selecting polymyxin B dosing regimens (6). This raises two important questions: (i) what steps are necessary to provide clarity in polymyxin B dosing that will simultaneously achieve adequate pharmacodynamic (PD) response and minimize toxicodynamic (TD) events?; and (ii) how can we best apply information gained from the present (1) and previous (2, 3) studies to optimize polymyxin B dosing regimens?

The first question may be answered by considering the overall paucity of polymyxin B clinical pharmacokinetic (PK) studies; with the inclusion of Thamlikitkul et al. 's cohort, the literature is composed of 65 patients' data (1–3, 7–10). While such reports conclude that polymyxin B doses should not be modified because of differences in renal function (1–3, 7–9), larger, prospective studies are necessary to confirm their findings. Such efforts are under way; a multicenter clinical study will enroll 250 critically ill patients treated with intravenous polymyxin B, assessing the drug's PK, PD, and TD characteristics, expanding the evidence base nearly 4-fold (NCT02682355). The solution to the second question lies in the ability to harness the predictive power of combining population PK models with adaptive feedback control to derive patient-specific PK information (11, 12). Leveraging population PK parameter estimates, their degree of interpatient variability, and measured drug concentrations, a Bayesian estimator indi-

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vidualizes the presenting patient's dosing regimen so as to achieve a desired drug exposure. The aforementioned clinical study will make use of these concepts to develop optimal polymyxin B dosing regimens in a critically ill population that remains particularly vulnerable to the consequences of both over- and underexposure.

The rise in multidrug-resistant Gram-negative infections and the absence of novel antibiotics have resulted in increased utilization of polymyxin B. Consistent with previous reports (2, 3, 7–9), the paper by Thamlikitkul et al. (1). provides further evidence of the dissonance between contemporary PK studies of polymyxin B and the product label. PK, PD, and TD analyses combined with dose optimization techniques are urgently needed to establish the first scientifically based dosing recommendations for polymyxin B.

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