Closing the Loop—A Colistin Clinical Study to Confirm Dosing Recommendations From PK/PD Modeling

Jason A. Roberts1,2,3 and Jeffrey Lipman1,2
1Burns, Trauma and Critical Care Research Centre, The University of Queensland; 2Department of Intensive Care and 3Pharmacy Department, Royal Brisbane and Women’s Hospital, Brisbane, Australia

(See the Major Article by Dalfino et al, on pages 1720–6.)

INTRODUCTION

Inadequate antibiotic therapy is a critical determinant of survival in infected critically ill patients [1]. Mortality rates can be very high, even when appropriate antibiotic therapy and source control are present [2]. Improving patient outcomes can be even more difficult when infections are mediated by multidrug-resistant organisms (MROs) such as Acinetobacter baumannii, Pseudomonas aeruginosa, and Klebsiella pneumoniae. Indeed, MROs are likely to have a high capacity to develop resistance to even salvage therapies. With antibiotic resistance escalating globally and the dearth of antibiotics emerging with novel mechanisms of action, the reality of untreatable infections is becoming apparent. It follows that for these “bad bugs,” there are currently no (new) drugs [3].

THERAPEUTIC OPTIONS FOR TREATMENT OF MROs

For infections caused by MROs, clinicians have 3 main treatment options:

1. Use the standard antibiotics with increased doses that result in a higher pharmacokinetic (PK) exposure, so PK/pharmacodynamics (PK/PD) targets are still achieved;
2. Use nonstandard antibiotics for which resistance has not yet occurred; or
3. Use combination therapy with antibiotics from options 1 and/or 2.

Prescription of standard antibiotics is sometimes not possible because the level of bacterial resistance defined by the minimum inhibitory concentration (MIC) is so high that the desired PK/PD targets cannot be achieved without risking severe toxicity from extreme doses. Using non-standard antibiotics can be fraught with danger, as little data exist for these antibiotics or they have a narrow therapeutic index and therapeutic failure and toxicities are unacceptably common. The lack of robust dosing data for these antibiotics is not necessarily ameliorated by the use of combination therapy either.

COLISTIN

Prescribing colistin based on the microbiological and PK data that are decades old is likely to risk the same toxicities, as well as potentially therapeutic failure. Indeed, no data were available, until recently, to guide colistin treatment of MRO infections in critically ill patients. Knowledge of colistin PK in critically ill patients is essential as dosing based on data from noncritically ill patients would be suboptimal [4]. Dosing for critically ill patients based on PK data from noncritically ill patients has resulted in worse clinical outcomes for patients with the pathophysiology common to critical illness—augmented renal clearance. Two separate
phase 3 trials involving ceftobiprole and doripenem reinforce the importance of PK data from the population in which a drug is used [5, 6].

Colistin is a polymyxin antibiotic that was first used in the 1960s but subsequently lost appeal because of associated nephro- and neurotoxicities [7]. Colistin is parenterally administered as colistin methanesulfonate (CMS), which is then hydrolyzed to colistin’s 2 components, colistin A (polymyxin E1) and colistin B (polymyxin E2). Colistin is a hydrophilic molecule for which little PK information exists, and only data published in the last 10 years can be considered robust because of an inability of the older microbiological methods to discern between CMS and colistin [7].

**COLISTIN PHARMACOKINETICS**

Colistin and CMS have mixed routes of elimination (renal and nonrenal), a half-life that varies between different patient populations, and a volume of distribution that increases with critical illness [8, 9]. Knowledge of these data is vital for procuring optimal treatment of MROs. Although many renally cleared antibiotics undergo augmented renal clearance resulting in increased drug clearance [10, 11], the clearance of colistin actually seems to decrease in the presence of critical illness. For instance, the half-life of colistin in cystic fibrosis patients (4 hours) is much shorter than in critically ill patients (14 hours) [12]. Although CMS is predominantly renally eliminated, the hydrolyzed colistin undergoes extensive renal tubular reabsorption after which it is cleared by nonrenal mechanisms [13]; therefore, improvements in renal function are expected to affect clearance of CMS but not necessarily colistin. It follows that the prolonged half-life is caused by the increased volume of distribution common to critically ill patients [14]. These PKs support the use of a larger dose given less frequently for critically ill patients.

**COLISTIN PHARMACODYNAMICS**

Colistin has concentration-dependent bacterial killing activity with rapidly bactericidal activity and a significant post-antibiotic effect against gram-negative organisms [15]. Pharmacodynamically, the unbound area under the concentration time curve (f AUC)/MIC ratio is the parameter best associated with its efficacy [16]. In lung infection models, 3-log killing was possible with an f AUC:MIC ratio between approximately 50 and 65, although higher exposures are required in thigh infection models, which suggest that different dosing may be required for different sites of infection [17]. Achieving this ratio in patients requires dosing guided by PK/PD modeling.

**THE ROLE OF PK/PD MODELING IN COLISTIN DOSING**

With robust PK and PD data and associated PK/PD modeling, appropriate dosing regimens can be designed for validation in clinical settings. Recent papers by Plachouras et al [8] and Garonzik et al [9] provide excellent population PK descriptions of colistin PK in critically ill patients. These papers have independently suggested higher than standard dosing be used to decrease the time to achievement of therapeutic concentrations. Plachouras et al [8] recommended a loading dose of 9 or 12 million units (MU) followed by a dose of 4.5 MU twice daily. Garonzik et al [9] provided a more detailed loading dose and maintenance dose nomogram based on patient weight and renal function, as well as data on how to dose in the presence of intermittent hemodialysis and continuous renal replacement therapy. The similar findings mean that the respective papers complement each other. However, clinical validation of dosing generated from PK/PD modeling needs to be performed. This has now been completed.

**CLOSING THE LOOP—VALIDATING PK/PD DOSING STRATEGIES IN CLINICAL SETTINGS**

In the current issue of *Clinical Infectious Diseases*, the modeling work of Plachouras et al [8] has been validated in a critical care setting by Dalfino et al [18] in the treatment of MROs. The authors found a high clinical cure rate (82.1%) of predominantly bloodstream infections and ventilator-associated pneumonias in their cohort of 28 patients. The rate of nephrotoxicity was only 17.8%, and this subsided within 10 days after cessation of treatment. Furthermore, accepting the relatively small number of patients and despite concerns of resistance with monotherapy, no resistance to colistin was observed in any of the patients. Some limitations were present in this study, including the low observed MICs, the absence of PK data to confirm that the modeled concentrations were actually being achieved in these patients, and the lack of a control group. However, this study is valuable as it demonstrates the translation of a robust PK/PD dosing guideline into a clinical setting, resulting in noticeable benefits.

**CONCLUSION**

Increasing numbers of high-quality studies proposing dosing regimens designed by robust PK/PD modeling are becoming available. Rationally, these studies link the PK from a patient population with the PD of the antibiotic. However, few papers confirm that the revised doses lead to improved patient outcomes. The recent study by Dalfino et al [18], which sought to validate the colistin doses proposed by Plachouras et al [8], originally derived and modeled from a cohort of critically ill individuals, showed highly acceptable
clinical outcomes and tolerability in their critically ill patients. Although there was not a comparator group in this study, the results do validate the dosing proposed by Plachouras et al [8] as effective against serious infections by MROs. In the present climate of increasing frequency of infections by MROs in patients like the critically ill, for which product information dosing guidelines are not available, more clinical validation studies should be encouraged as a means to improve outcomes for these most difficult-to-treat patients. The higher dosing than originally thought for the old drug colistin has produced surprisingly good outcomes. We compliment Dalfino et al [18] for prospectively validating a predictive modeling algorithm.

Note

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References