Closing the loop - a colistin clinical study to confirm
dosing recommendations from PK/PD modeling

Jason A. Roberts (1,2,3), *Jeffrey Lipman (1,2)

(1) Burns, Trauma and Critical Care Research Centre, The University of Queensland, Brisbane, Australia
(2) Department of Intensive Care, Royal Brisbane and Women’s Hospital, Brisbane, Australia
(3) Pharmacy Department, Royal Brisbane and Women’s Hospital, Brisbane, Australia

*Address for correspondence:
Prof Jeffrey Lipman, Dept of Intensive Care Medicine, Level 3 Ned Hanlon Building, Royal Brisbane and Women’s Hospital, Butterfield St, Brisbane, Queensland, Australia 4029; Phone +617 3636 1852; Facsimile +617 3636 3542
j.lipman@uq.edu.au
Introduction

Inadequate antibiotic therapy is a critical determinant of survival in infected critically ill [1]. Mortality rates can be very high, even when appropriate antibiotic therapy and source control are present [2]. Improving patient outcomes can be even harder when infections are mediated by multi-drug 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 three 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 **non-standard 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 exists for these antibiotics or they have a narrow therapeutic index and
therapeutic failure and toxicities are unacceptably common. The dearth of robust
dosing data for these antibiotics is not necessarily ameliorated by the use of
combination therapy either.

PK investigations of non-standard antibiotics have rarely been performed in each of
the patient populations likely to manifest unique PK, but are vital. Supplementing PK
data with PK/PD modelling to design optimised dosing strategies should be strongly
considered, even essential. Subsequent validation of model-based dosing in a clinical
setting, preferably in a randomised controlled trial, is then necessary to confirm the
clinical outcomes and acceptable toxicity of the new approach. An antibiotic
previously discarded because of toxicities but that has been re-invented over the last
decade is colistin.

**Colistin**

Prescribing colistin based on the microbiological and PK data that is decades old, is
likely to risk the same toxicities as well as potentially therapeutic failure. Indeed no
data was 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 non-critically ill patients would be sub-optimal [4]. Dosing
for critically ill patients based on PK data from non-critically 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 two 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 micro-biological methods to discern between CMS and colistin [7].

**Colistin Pharmacokinetics**

Colistin and CMS have mixed routes of elimination (renal and non-renal), a half-life that varies between different patient populations and a volume of distribution that increases with critical illness [8, 9]. Knowledge of this 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 hrs, is much shorter than in critically ill patients, 14 hrs [12]. Although CMS is predominantly renally eliminated, the hydrolysed colistin undergoes extensive renal tubular reabsorption after which it is cleared by non-renal mechanisms [13] and therefore, improvements in renal function are expected to affect clearance of CMS but not necessarily colistin. It follows then that the prolonged half-life is caused by the increased volume of distribution common to critically ill patients [14]. These PK supports 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 postantibiotic effect against Gram negative organisms [15]. Pharmacodynamically, the unbound area under the concentration-time curve (fAUC)/MIC ratio is the parameter best associated with its efficacy [16]. In lung infection models, 3-log killing was possible with an fAUC:MIC ratio between ~50 and 65, although higher exposures are required in thigh infection models suggesting 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 and Garonzik et al provide excellent population PK descriptions of colistin PK in critically ill patients [8, 9]. These papers have independently suggested higher than standard dosing be used to decrease the time to achievement of therapeutic concentrations. Plachouras et al recommended a loading dose of 9 or 12 million units (MU) followed by a dose of 4.5 MU 12-hourly [8]. Garonzik et al 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 [9]. The similar findings mean that the respective papers compliment 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 edition of *Clinical Infectious Diseases*, the modeling work of Plachouras et al [8] has been validated in a critical care setting by Dalfino et al in the treatment of MROs [18]. 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 for 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, 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 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.

Notes

Disclosures Both authors have no related conflicts of interest to the material presented in this article.
References


14. Markou N, Markantonis SL, Dimitrakis E, et al. Colistin serum concentrations after intravenous administration in critically ill patients with serious multidrug-


