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Monte Carlo simulations: maximizing antibiotic pharmacokinetic data to optimize clinical practice for critically ill patients

Jason A. Roberts^{1–3}, Carl M. J. Kirkpatrick⁴ and Jeffrey Lipman^{1,2*}

¹Burns, Trauma and Critical Care Research Centre, The University of Queensland, Brisbane, Australia; ²Department of Intensive Care, Royal Brisbane and Women's Hospital, Brisbane, Australia; ³Pharmacy Department, Royal Brisbane and Women's Hospital, Brisbane, Australia; ⁴School of Pharmacy, The University of Queensland, Brisbane, Australia

*Corresponding author. Department of Intensive Care Medicine, Level 3 Ned Hanlon Building, Royal Brisbane and Women's Hospital, Butterfield St, Brisbane, Queensland, Australia 4029. Tel: +617-3636-1852; Fax: +617-3636-3542; E-mail: j.lipman@uq.edu.au

Infections in critically ill patients continue to result in unacceptably high morbidity and mortality. Although few data exist for correlating antibiotic exposure with outcome, antibiotic dosing is likely to be highly important for maximizing resolution of infection in many patients. The practical and financial difficulties of performing pharmacokinetic (PK) studies in critically ill patients mean that analyses to maximize data such as Monte Carlo simulation (MCS) are highly valuable. MCS uses computer software to perform virtual clinical trials. The building blocks for MCS are: firstly, a robust population PK model from the patient population of interest; secondly, descriptors of the effect of covariates that influence the PK parameters; thirdly, description of the susceptibility of bacteria to the antibiotic and finally a PK/pharmacodynamic (PD) target associated with antibiotic efficacy. Probability of target attainment (PTA) outputs can then be generated that describe the proportion of patients that will achieve a pre-specified PD target for an MIC distribution. Such analyses can then inform dosing requirements, which can be used to have a high likelihood of achieving PK/PD targets for organisms with different MICs. In this issue of *JAC*, Zelenitsky *et al.* provide a very useful example of MCS for interpreting the optimal methods for dosing meropenem, piperacillin/tazobactam, cefepime and ceftobiprole in critically ill patients.

Keywords: pharmacodynamics, dosing, population pharmacokinetics, susceptibility, minimum inhibitory concentration

Introduction

Infections in the critically ill continue to result in unacceptable morbidity and mortality with an in-hospital mortality rate of 37.5% for patients with severe sepsis.¹ Furthermore, in the presence of acute kidney injury necessitating renal replacement therapies, mortality rates escalate to almost 50%.² A significant body of data supports the proposition that early and appropriate antibiotic therapy is the most effective intervention to reduce this burden.^{3,4} To date, few studies have described the importance of antibiotic dose or exposure to clinical outcome.^{5–8} However, there are many *in vitro* and animal *in vivo* studies available to demonstrate the importance of antibiotic exposure in killing bacteria^{9,10} and minimizing the development of antibiotic resistance.¹¹ It follows that improving antibiotic dosing practices may serve to minimize morbidity and mortality.

Antibiotic dosing is best performed with an understanding of pharmacokinetics (PK: the drug concentrations resulting from a specific dose) and pharmacodynamics (PD: the ability of a certain antibiotic concentration to kill or inhibit growth of a bacteria). Complicating antibiotic dosing in critically ill patients are the disease-driven physiological changes to critically ill patients, which can alter antibiotic PK and will therefore alter the

effectiveness of the antibiotic. It follows that many antibiotic dosing regimens that have been developed in non-critically ill patients are likely to be inappropriate in the critically ill population.¹²

On a daily basis, clinicians are confronted with the challenge of developing antibiotic dosing regimens for critically ill patients that meet the PK/PD targets likely to achieve maximal bacterial killing and increase the opportunity for resolution of infection. The spectrum of pathology that can influence PK is immense,¹² whilst the throughput of patients able to be included in studies is disproportionately limited. Therefore, the use of data maximization strategies, such as Monte Carlo simulation (MCS), should be considered a highly valuable technique to guide clinical practice where robust descriptive PK data exist.

What is MCS?

MCS is essentially the use of computer software via simulation platforms to 'expand' the sample size of a study to provide predictions of the likely result of different therapeutic approaches such as altered drug dose or frequency on the probable outcome of treatment, or more correctly the achievement of

therapeutic targets. The term ‘Monte Carlo’ was introduced by Ulam and Von Neumann during the Second World War in their development of the atomic bomb, and was a reference to the gaming city in Monaco.¹³ As stated by Bonate in his review on MCS, the PK model is a principal requirement of MCS and is built on data that ‘look back in time’ whereas the simulations build on these models and ‘look forward in time’.¹³ MCS allows researchers and clinicians to ask the many ‘what if?’ questions about different dosing regimens and targets in virtual clinical trials without the capital and human cost of conducting the many possible clinical trials in patient populations. From this information, a single definitive multicentre trial could be developed and executed.

In the context of antibiotic dosing, the principal requirements to perform MCS are: (i) a well-evaluated and robust PK model with defined distribution and covariance of PK parameters; (ii) a covariate model that provides information about how the PK parameters change with respect to observable physiological signs, symptoms and patient demographics (e.g. how drug clearance changes with measured, but altered renal function); and (iii) a PD model with a defined interrelationship between PK and PD. Therefore, to perform MCS to guide antibiotic dosing for critically ill patients, the minimum data requirements are the inputs, as described in Figure 1.

As depicted in Figure 1 using the structural PK model and covariate model A (developed in a population PK analysis of patient data), the MCS generates a set of PK parameter values, e.g. clearance and volume of distribution, by random sampling of values within the predefined PK parameter distribution in B for each simulated patient. From these PK parameters a full antibiotic concentration–time profile is generated for each simulated

patient, which can then be evaluated against susceptibility data, D, in light of antibiotic PD in C. The likelihood of achieving the predefined therapeutic target E, or clinical outcome, is calculated for the entire simulated population. More complex simulations that may predict the effect of altered dosing strategies on the development of antibiotic resistance, disease progression and drug toxicity are also possible although not illustrated here.

The value of MCS

Intensive Care is a relatively recent specialty, with a still developing understanding of altered physiology and associated pharmacology.^{12,14} In this critical care environment, application of MCS can be valuable for maximizing knowledge of an antibiotic in the absence of large-scale studies. In critically ill patients where PK data can be difficult to obtain, once the PK of an antibiotic has been described, these data can be used to predict otherwise unknown concentration–time profiles of different doses. This is on the proviso that the initial population PK model is adequately and correctly identified and that the covariates identified for the simulation platform are biologically plausible. Therefore, instead of performing multiple studies in the same population at different doses, significant time and money can be saved by generating the same data using an MCS approach. Ideally, a model that incorporates a large dataset with very broad PK variability, then simulations and therefore dosing recommendations, will be highly valuable for more patients and be of greater use to clinicians. Further to this, the outputs of simulations (e.g. recommended doses for bacteria with different MICs) are generally easier to understand than complex PK equations generated as part of the PK

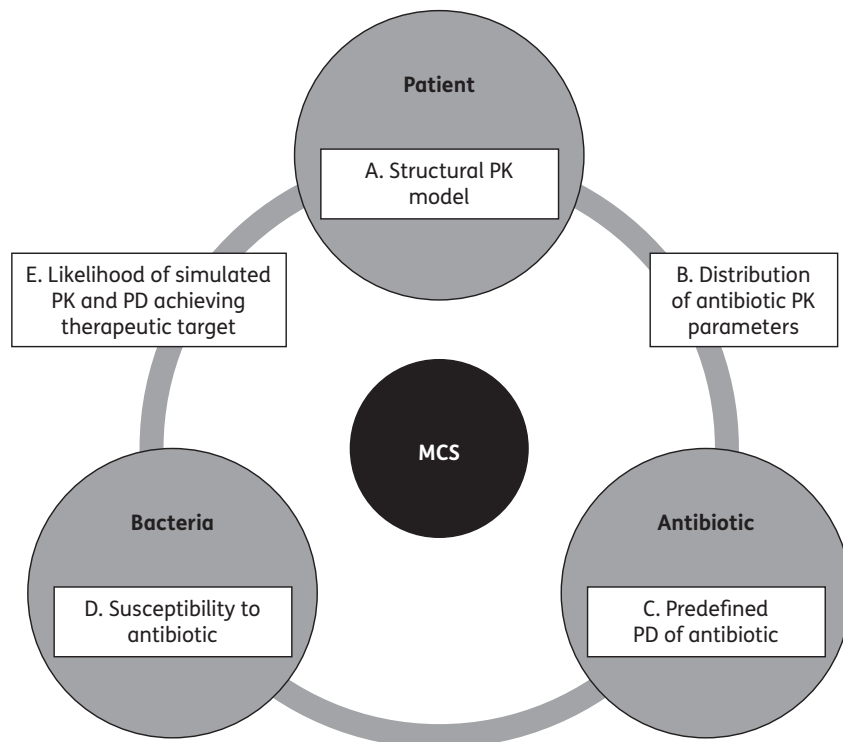


Figure 1. Interrelationship between factors necessary for MCSs.

modelling process.¹³ However, the methodology of the MCS process must be interpreted carefully, because certain decisions by the modelling and simulation researcher may reduce the generalizability of final results.

Potential confounding factors to MCS

Like any mathematical construct, errant input (or merely poor assumptions) from any of the components into an MCS will result in potentially invalid simulations. Therefore, attention to the appropriateness and robustness of the principal requirements described in Figure 1 is vitally important.

For example, a study with a small sample size may not have enough patients to describe all the likely PK variability in a patient population and therefore have a suboptimal distribution and covariance of PK parameters.¹⁵ Such an example could be possible with a population PK model based on 10 patients, which would be unlikely to describe all of the PK variability likely to be encountered in the critically ill.¹⁶ Of course, the ideal study would recruit a larger sample that includes patient examples of all the possible PK changes and provides a 'true' distribution of PK parameters. Unfortunately, recruitment of large numbers of critically ill patients is problematic due to the acuity of illness, the smaller number of patients in a critical care unit, the higher turnover of patients compared with a ward situation, as well as the difficulty of obtaining consent from a legally authorized representative in a timely manner. Anyone who has performed PK studies in critically ill patients soon realizes the untimely hours of most prescribed dosage regimens.

Therefore, in the absence of other data, MCSs based on small patient cohorts are instructive of the ramifications of altered

dosing approaches for achieving PK/PD targets in the critically ill. Such MCSs could not be considered as definitive analyses.

Another example of a technique used in some studies where there may be insufficient PK data in critically ill patients, is to mix PK data from non-critically ill patients with PD data from critically ill patients.¹⁷ The utility of such an MCS would be to demonstrate the effect of PD that is specific to a critical care environment on achieving the chosen therapeutic target, but the downside of this is possible incorrect assumptions of similarity of effect. For instance, MCSs could be performed using PK data from patients with serious infections who would not be defined as critically ill and bacterial susceptibility data from a critically ill environment, which are usually less susceptible organisms. These MCSs would show that the increased MICs for these pathogens will reduce the likelihood of standard dosing regimens achieving PK/PD targets. However, it would not be wholly relevant to critically ill patients by not accounting for the profound pathophysiology likely to cause altered PK that make such standard doses even less successful in achieving therapeutic targets.¹²

Another potential confounding factor is the use of published MIC data. Susceptibility patterns of bacteria to antibiotics can vary over time, between countries, between hospitals and between critical care and ward environments. It follows that data selected for inclusion as part of a randomly sampled MIC distribution may not always be representative of the reality at a particular point in time. For this reason, use of the probability of target attainment (PTA: the probability that the simulated subjects can attain the predefined PK/PD target such as 40% $f_{T > MIC}$) for a given range of MICs is useful for allowing the reader to interpret the effect of different dosing strategies on achievement of PK/PD targets for pathogens of different

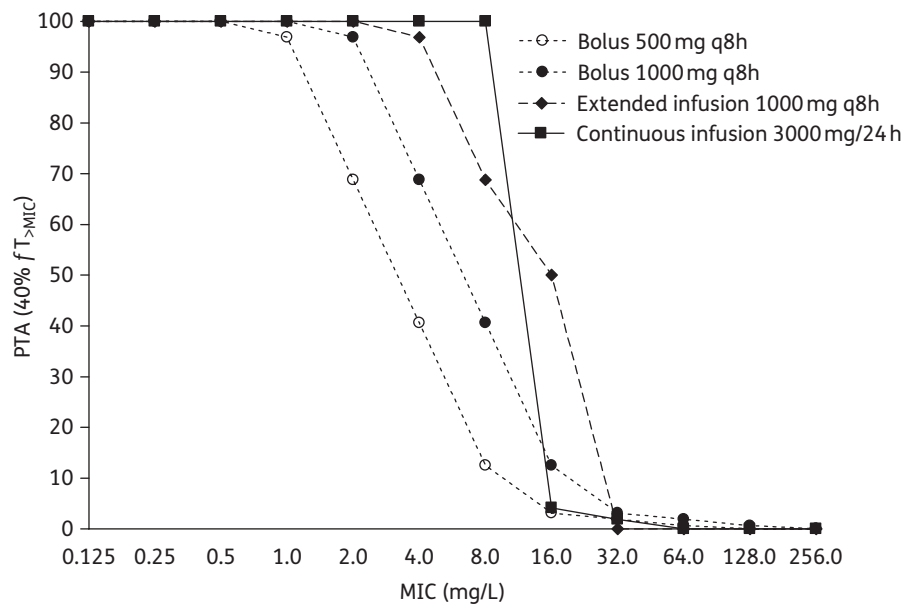


Figure 2. An example of differential PTAs for a range of MICs. This figure describes the ability of different dosing strategies of meropenem (bolus administration over 3 min; extended infusion 4 h) to achieve a chosen PK/PD target (40% $f_{T > MIC}$) in critically ill patients for an MIC distribution. Adapted from Roberts *et al.*¹² In this example all dosing regimens have a 100% probability of achieving 40% $f_{T > MIC}$ against organisms for which the MIC is ≤ 0.25 mg/L. However, if the MIC for an organism is 8 mg/L, only extended infusion and continuous infusion strategies should be prescribed as only they achieve the PK/PD target to an acceptable level (>90%). Therefore, use of this type of PTA data can inform the optimal method of dosing of an antibiotic given a known or presumed MIC. q8h, every 8 h.

susceptibilities. An example is described in Figure 2 with the capability of different meropenem doses and infusion times to achieve a predefined PK/PD target against different MIC values.¹² Therefore, the reader can choose the options for a dosing strategy to achieve a PK/PD target for a pathogen for which the MIC is 0.25 mg/L compared with the strategies available for a pathogen for which the MIC is 8 mg/L.

The final confounder to MCS that readers must be aware of is when modelling is based on total drug concentration, as opposed to the pharmacologically active free drug concentration. Such MCS will give falsely high PTAs from simulated dosing strategies, the implications of which may be major, for highly protein-bound antibiotics.

In the present issue of *JAC*, Zelenitsky *et al.*¹⁸ provide a very useful paper that utilizes MCS to maximize interpretation of population PK models for meropenem, piperacillin/tazobactam, ceftipime and ceftobiprole achieving different PD targets. In this context, they can compare the likelihood of a different dose or infusion duration achieving a preferred target (e.g. 50%, 75% or 100% time for which the free concentration is maintained above the MIC; $fT_{>MIC}$). The authors concluded that using standard doses, ceftobiprole achieved the highest PTAs with standard doses of piperacillin/tazobactam being least successful. However, as for most papers, important limitations need noting.

Firstly, as declared by the authors, some of the PK models selected for MCS include PK data from critically ill and non-critically ill patients. Although the results should not be considered optimal, they provide a degree of guidance for a drug where these data are currently lacking and therefore are useful for informing clinical practice.

The second limitation of this paper is the recognized problem of using a formula-derived approach^{19,20} for calculating creatinine clearance.¹⁴ The absence of adequate validation of any of the available formulas in critically ill patients precludes their use in PK interpretation.²¹ A timed urinary creatinine clearance should be preferred for minimizing likely errors that may result from a formula-guided approach.²²

Thirdly, although the authors simulate unbound concentrations, they used a fixed value for the fraction unbound, which is likely to be errant in critically ill patients where a range of alterations in protein binding may occur between patients.^{23–25} Despite the low protein binding of the studied antibiotics, simulation from a function that describes the likely distribution of protein binding values in this population would be likely to provide more accurate results.

In spite of these limitations, this paper provides excellent guidance to clinicians about doses and infusion duration that should be used to treat critically ill patients in their units. To this end, it supports the further application of MCS to antibiotic dosing for critically ill patients.

Conclusions

In conclusion, MCS provides a favourable method to maximize data analysis where robust descriptive PK models exist. Many confounders to obtaining clinically relevant results are possible and the reader should be aware of errors that can be made. With this in mind, the paper by Zelenitsky *et al.*¹⁸ provides a highly relevant example of the application of MCS in critically ill patients, as well as its capability to inform clinical decision-making.

Transparency declarations

None to declare.

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