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Challenges and Potential Solutions – Individualised Antibiotic Dosing at the Bedside for Critically Ill Patients: a structured review

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Summary

Infections in critically ill patients are associated with persistently poor clinical outcomes. These patients have severely altered and variable antibiotic pharmacokinetics and are infected by less susceptible pathogens. Antibiotic dosing that does not account for these features is likely to result in sub-optimal outcomes. In this paper, we review the patient- and pathogen-related challenges

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that contribute to inadequate antibiotic dosing and discuss how a process for individualised antibiotic therapy, that increases the accuracy of dosing, can be implemented to further optimise care for the critically ill patient. The process for optimised antibiotic dosing firstly requires determination of the physiological derangements in the patient that can alter antibiotic concentrations including altered fluid status, microvascular failure, serum albumin concentrations as well as altered renal and hepatic function. Secondly, knowledge of the susceptibility of the infecting pathogen should be determined through liaison with the microbiology laboratory. The patient and pathogen challenges can then be solved by combining susceptibility data with measured antibiotic concentration data (where possible) into a clinical dosing software. Such software uses pharmacokinetic-pharmacodynamic (PK/PD) models from critically ill patients to accurately predict the dosing requirements for the individual patient with the aim of optimising antibiotic exposure and maximising effectiveness.

Keywords

Antibacterial; Bayesian; Intensive Care Unit; pharmacodynamics; pharmacokinetics

Introduction

Patients in intensive care units (ICU) are markedly different from those in general ward environments and have significantly higher mortality rates. These patients are mostly critically ill and have a much higher level of sickness severity that is associated with profound pathophysiological changes and aggressive medical intervention[1, 2]. Indeed, the healthcare system is treating increasing numbers of critically ill patients and the clinical outcome for many patient sub-groups is not improving significantly[3]. In particular, critically ill patients with sepsis, septic shock and/or acute kidney injury are considered to be significant challenge to infectious diseases physicians, critical care physicians, nephrologists and clinical pharmacists and pharmacologists.

In sepsis and septic shock studies, interventions relating to optimisation of antibiotic therapy demonstrate the greatest improvements in clinical outcomes[4-9]. There is much evidence defining the impact of early and appropriate antibiotic administration on decreased mortality[6-8] but less information regarding the impact of appropriate dosage regimens on clinical outcome[10]. Although robust *in vitro* and animal *in vivo* data exist describing exposure-effect relationships of antibiotics and bacterial killing[11, 12], the impact of antibiotic exposure on mortality has not been defined as precisely. Nevertheless, some important studies, mostly observational or retrospective in nature, are available.

For aminoglycosides, a randomised controlled trial by Van Lent Evers demonstrated that a dedicated therapeutic drug monitoring (TDM) intervention in a general hospitalised patient cohort resulted in a significantly reduced patient hospital length of stay[13]. Quinolones[10, 14, 15], beta-lactams[10, 16-19], glycopeptides[20, 21] and linezolid[22] all have at least retrospective cohort analyses that demonstrate clinical cure and/or mortality advantages associated with achievement of target pharmacokinetic (PK)/pharmacodynamic (PD)

indices. The major challenge for clinicians remains how to ensure that dosing achieves these PK/PD targets in individual patients.

Guidance for effective antibiotic dosing in critically ill patients is usually not included in treatment guidelines. Clinically, use of the Product Information (or Package Insert) for the antibiotic is the mainstay for choosing antibiotic doses for critically ill patients. However, this information is based on dose-finding studies that are performed in non-critically ill patients and then extrapolated to critically ill patients. The presence of the severely altered PK means that many critically ill patients may be at risk for not achieving the PK/PD targets that are known to be associated with an improved likelihood of positive clinical outcomes[23, 24]. Even general dosing guidelines for ICU patients may not be a satisfactory solution because critically ill patients have significant PK variability. With increasing PK variability, the likelihood of accurately predicting a therapeutic dose in an individual patient decreases, potentially resulting in sub-optimal patient outcomes.

After many years of dosing antibiotics in critically ill patients using a ‘one dose fits all’ strategy, there is a strong rationale to move to an individualised dosing approach. This change in approach to dosing antibiotics is supported by the ubiquitous problem of reduced antibiotic development pipeline that requires better use of existing agents, for which antibiotic resistance is steadily emerging.

In this paper, we describe the challenges of altered PK caused by the pathophysiological changes that are commonly found in critically ill patients as well as the challenges of the reduced bacterial organism susceptibility frequently encountered in the ICU. Either PK or PD, or both, influence the PK/PD ratio and therefore, the magnitude of the PK/PD target. Therefore, we will consider solutions to the above challenges in the form of individualizing dosing strategies supported by different bedside dosing tools based on software packages that can improve the likelihood of effective dosing.

Search strategy and selection criteria

Data for this review were identified by searches of Pubmed (1966 to February 2014), EMBASE (1966 to July 2013) and the Cochrane Controlled Trial Register as well as references from relevant articles. Search terms related to antibiotic pharmacokinetics and pharmacodynamics in critically ill patients and dosing software were included. Numerous articles were identified through searches of the extensive files of the authors. All relevant papers available in English were reviewed for inclusion.

Challenge 1: The effect of critical illness pathophysiology on pharmacokinetics

Dysfunction of one or multiple organ systems occurs in critical illness and may result in significantly different antibiotic concentrations from those observed in noncritically ill patients as shown in Figure 1. Without rational dose adjustment, these changes in drug concentrations can predispose to clinical failure, emergence of antimicrobial resistance or

even drug toxicity. Below we review the PK effects caused by dysfunction of the cardiovascular, renal, pulmonary and hepatic systems.

The cardiovascular system

Fluid shifts, 'third spacing' and fluid overload—Critically ill patients frequently demonstrate a systemic inflammatory response syndrome (SIRS) caused by either infectious or non-infectious pathology[25]. A major consequence of SIRS, particularly in patients with severe sepsis and septic shock, is the extreme fluid extravasation into the interstitial space from endothelial damage and capillary leakage. This phenomenon is commonly described as 'third spacing'[25]. In response to the resulting hypotension, clinicians administer large volumes of resuscitation fluids that may also distribute into interstitial fluid thereby significantly increasing interstitial volume. For hydrophilic antibiotics, these processes may lead to a large increase in volume of distribution (V_d)[26]. In contrast, lipophilic antibiotics (e.g. fluoroquinolones and macrolides) possess an inherently larger V_d and their V_d is often not significantly influenced by such fluid movements and/or administration[27].

The increase in V_d for hydrophilic antibiotics such as the aminoglycosides[28, 29], beta-lactams[26, 30], glycopeptides[31] and linezolid[32] have been extensively documented in critically ill patients. Increases in $V_d$that are up to 2-fold greater than the $V_d$observed in non-critically ill patients are common.

Hypoalbuminaemia and altered protein concentrations—Hypoalbuminaemia, defined as a serum albumin concentration < 25 g/L, is a common but frequently neglected condition in the ICU. The incidence is reportedly as high as 40-50%[33]. Ulldemolins et al. have extensively reviewed this phenomenon and concluded that the influence of hypoalbuminaemia on antibiotic PK in critically ill patients may be clinically important[34]. With decreasing albumin concentrations, an increase in the unbound fraction of protein bound drugs can occur[35]. The unbound fraction of such antibiotics is not only available for elimination, but also for distribution. The V_d for moderate to highly-protein bound antibiotics including ceftriaxone[36], flucloxacillin[37], ertapenem[38, 39] and daptomycin[40] are found to increase by up to 100% in critically ill patients with hypoalbuminaemia.

Evidently, fluid shiftsand altered protein binding, as commonly seen in mechanically ventilated patients, will both increase Vd. An increased Vd may reduce the peak concentration of drugs which may be problematic for antibiotics exhibit concentration-dependent effects (e.g. aminoglycosides). These drugs require a high unbound peak concentration (C_{max}) over MIC (C_{max}/MIC) and area-under the curve to MIC (AUC/MIC) ratio for maximal bacterial killing[41-43]. However, where the drug has high protein binding (e.g. daptomycin), hypoalbuminaemia will likely to lead to a high free fraction in the early part of the dosing interval which may result in higher unbound concentrations which may be advantageous. In contrast, for time-dependent beta-lactam antibiotics, changes in Vd and protein binding can lead to unbound concentrations later in the dosing interval are consistently lower than those observed in non-critically ill patients putting the patient at risk of treatment failure from subtherapeutic concentrations[35, 36].

Importantly, increasing sickness severity is associated with increased V_d meaning that the most critically ill patients are likely to have the most reduced antibiotic exposures if standard dosing is used, at least in the first days of treatment[29]. With recovery from infection, the V_d will return to 'normal' and as such, in longer courses of therapy, dose modifications throughout treatment are often required. For all antibiotic classes including concentration-dependent antibiotics, an increased $V_d$may delay the time to achievement of therapeutic concentrations.

Tissue perfusion and target site distributions of antibiotics—Effective antibiotic concentrations need to be achieved in the interstitial fluid of tissues as this is the site of most infections[44]. However, severe infections can cause vascular dysfunction including microvascular failure, which can impair the drug delivery into body tissues[45]. Data describing impaired tissue penetration exists for various antibiotics including cefpirome[46], fosfomycin[47] piperacillin[45, 48]and levofloxacin[49] with sub-therapeuticconcentrations in tissue common in the early phase of treatment, particularly in patients with septic shock being treated with vasopressors[45]. Therefore, at least for the antibioticclasses above, plasma concentrations maybe an imprecise surrogate for tissue concentrations.

The renal system

Many of the commonly used antibiotics in critically ill patients are subject to renal clearance and therefore alterations in renal function will affect concentrations of those antibiotics. While it is standard practice to reduce an antibiotic dose in the presence of renal dysfunction, acute kidney injury (AKI), or renal replacement therapy (RRT) to avoid toxicity in the critically ill patient, it is less well appreciated that glomerular filtration can be increased in some patients as a result of a phenomenon known as augmented renal clearance (ARC). ARC is a potential reason for 'under-dosing'. Thus some critically ill patients may actually require a more intensive regimen, which may be just as relevant as dosage reduction in the setting of renal impairment.

Augmented renal clearance (ARC)—ARC is driven by pathophysiological responses to infection as well as treatment interventions (e.g. fluid resuscitation and use of vasopressors) that are also associated with early increase in cardiac output and an associated enhanced blood flow to major organs[50]. For the kidney, this increased perfusion leads to increased drug delivery and therefore significantly increased glomerular filtration and clearance of renally cleared solutes including antibiotics (e.g. aminoglycosides, beta-lactams and glycopeptides)[1, 51, 52]. ARC is being increasingly observed in critically ill patients with normal serum creatinine concentration. ARC typically occurs in younger males with trauma, sepsis, burns, haematological malignancy or pancreatitis[53]. ARC is defined as a creatinine clearance (CrCL) ≥130 mL/min. Udy et al, demonstrated up to 82% of patients demonstrating ARC will not achieve therapeutic antibiotic concentrations with standard antibiotic doses[54].

Renal dysfunction—A decline in kidney perfusion including microcirculatory failure can occur leading to AKI and reduced clearance of renally-eliminated antibiotics. AKI is identified by elevated serum creatinine concentrations or drop in urine output[55] and when

present will require appropriate dose decreases to ensure therapeutic and non-toxic antibiotic exposures. Importantly, large dose decreases are not required in the presence of AKI for antibiotics with a wide therapeutic index and where clearance occurs by multiple routes and the proportion of non-renal clearance is moderate to high (e.g. ceftriaxone, flucloxacillin and ciprofloxacin have both hepatic and renal clearance pathways).

Renal replacement therapy—If severe AKI occurs, RRT may be prescribed for clearance of metabolic waste products and/or fluid removal. RRT may take the form of continuous renal replacement therapy (CRRT) or intermittent haemodialysis (IHD) or a hybrid form of both such as sustained low-efficiency dialysis (SLED). CRRT is by far the most common form of RRT in critically ill patients, although hybrid forms of RRT are increasingly common. The principles of antibiotic dosing during RRT and factors that need to be considered have been discussed in significant detail previously[56, 57]. In general, drugs with a high V_d (> 1 L/kg), lipophilic drugs, and/or drugs with high protein binding (>80%) are poorly eliminated by RRT[56].

Sepsis in the presence of RRT is associated with a 50% increased likelihood of mortality compared to RRT alone[58]. In part, this may be explained by the difficulties in antibiotic dosing in these patients. Because there is no standardised approach to delivering RRT, with the exception of IHD, antibiotic clearance can be highly variable across different RRT modalities and settings. Recent papers have highlighted the dosing challenges for vancomycin, ciprofloxacin and beta-lactams, where anywhere from 10-50% of critically ill patients did not achieve target antibiotic concentrations[59, 60]. Dosing of antibiotics during RRT should ideally be individualised to the patient and the RRT modality and settings prescribed.

The pulmonary system

Pneumonia, (especially complicating mechanical ventilation), is the most common infection in critically ill patients and is an important cause of morbidity and mortality in ICU patients[61]. Providing optimal antibiotic exposure for hospital acquired pneumonia in ventilated patients may be challenging especially when clinicians consider the various patient, pathology and drug factors that can each affect drug penetration to the site of infection[62]. Alveolar compartments such as epithelial lining fluid (ELF) are considered the closest measurable site where extracellular pathogens accumulate and thus, optimal antibiotic concentrations in this area may determine therapeutic success[62]. Following systemic drug administration, the antibiotic must cross the alveolar capillary barrier before reaching and exerting their activity within the ELF. The passage across this barrier may be influenced by physicochemical (e.g. lipophilicity) and PK (e.g. protein binding) characteristics of the antibiotic and as well as patient specific characteristics (e.g. inflammation and/or chronic lung disease). The degree of ELF penetration for an antibiotic is characterized by the ratio of ELF exposure to the corresponding plasma exposure.

In the context of antibiotic physicochemistry,the more lipophilic antibiotics (e.g. fluoroquinolones, macrolides and oxazolidinones) have demonstrate an ELF: plasma exposure ratio of ≥1[63, 64]. Such high ELF:plasma exposure ratios are not always observed

for hydrophilic antibiotics although ratios may be underestimated due to technical errors[63, 65, 66]. In general, while blood concentrations may appear "therapeutic", ELF concentrations may be insufficient for optimal antibiotic treatment, especially in case of reduced bacterial susceptibility.For this reason, some authors suggest higher doses should be used in patients with severe nosocomial pneumonia to optimize ELF concentrations, for hydrophilic drugs[67, 68]. Alternatively, use of different administration approaches such as extended or continuous infusion of beta-lactam antibiotics[63, 65], or administration via nebulisation[69], may be used to increase antibiotic concentrations in ELF.

The hepatic system

During severe sepsis and septic shock, hepatic dysfunction may also cause a decrease in drug metabolism and clearance[70, 71]. To date, few data are available to guide antibiotic dose adjustments in critically ill patients with liver dysfunction[72], regardless of critical illness.

Challenge 2: Increased incidence of reduced bacterial susceptibility

The minimum inhibitory concentration (MIC) of the antibiotic against the pathogen causing the infection is a critical consideration for antibiotic dosing. The MIC is a critical factor of the PK/PD relationship that defines the drug exposure necessary to ensure a patient achieves a predefined PK/PD target that is associated with maximal efficacy.

Infections in the ICU are often caused by pathogens with higher MICs compared with other clinical settings[73, 74]. For example, a comparison of carbapenem susceptibility against predominantly Gram negative isolates in Germany, doripenem, meropenem and imipenem demonstrated a MIC_{90}in critically ill patients that was 4-, 8- and 8-fold greater than in non-critically ill patients, respectively[75]. As MICs increase, thePK exposure that is required to achieve the PK/PD threshold must increase in a proportional manner.To numerically highlight the difference in PK exposure required for an antibiotic in the presence of an elevated MIC, we can consider one example where vancomycin is being administered for a healthcare associated pneumonia for which, a PK/PD target $AUC_{0\text{-}24}$/MIC of 400, may be used[76]. In this case, if the methicillin resistant *Staphylococcus aureus*(MRSA) pathogen has an MIC of 0.5 mg/L, then an $AUC_{0\text{-}24}$ of 200 mg.h/L is required, which would be achieved comfortably with a trough concentration exceeding 10 mg/L. However, if the MIC is 2 mg/L, then an $AUC_{0\text{-}24}$ of 800 mg.h/L is required, thus necessitating a target trough concentration > 20-25 mg/L which would dramatically increase the risk of drug-related toxicity. In the latter case, consideration of an alternative antibiotic or combination therapy may be required.

Using the above example as an indicator of the challenges of achieving optimal dosing in the presence of decreased antibiotic susceptibility, it is clear that quantitative knowledge of antibiotic susceptibility will help guide dosing needs in critically ill patients. With a continuing decrease in susceptibility to the commonly used antibiotics in critically ill patients, regular surveillance is required[77]. These surveillance programs should also report MICs from ICU and non-ICU wards means as separate reports because differences in antibiotic susceptibility are common[73, 74, 78, 79]. These issues highlight the importance of having numerical data on the MIC of the pathogen causing the infection. At present, most

laboratories routinely report susceptibility with the classification 'S, I and R' (Susceptible, Intermediate-Susceptible and Resistant) based on MIC breakpoints. While this approach is suitable for many clinical situations because it unambiguously delineates when an antibiotic should not be administered, it may not be suitable for a critically ill patient with altered PK and antibiotic susceptibility close to the breakpoint. In this case, the relevant PK/PD target may still not be achieved despite the organisms have an MIC classified as "S"[80]. Therefore, knowledge of MIC data of the pathogen in the individual patient is essential to accurately calculate the PK exposure that patient needs such that the PK/PD target can be achieved. The local practitioner aiming to apply the dosage individualization concepts outlined in this paper should make it a priority to engage their microbiology lab to ensure that methods to obtain MIC data are in place.

Another important issue for treatment of infections in the critically ill is that MIC breakpoints published by groups such as the European Committee on Antimicrobial Susceptibility and Testing (EUCAST; available at www.eucast.org) and the Clinical and Laboratory Standards Institute (CLSI; available at www.clsi.org) are frequently determined using antibiotic exposures from non-critically ill patients. It follows that if an individual patient has profoundly altered PK and is infected by a pathogen with an MIC at or near the breakpoint, then use of a standard fixed regimen may increase the probability of under dosing (potential reasons for this PK variability are discussed above).

Given such inherent challenges relating to pathophysiology, PK and decreased bacterial susceptibility, what can be done to increase the likelihood of positive treatment outcomes for critically ill patients?

Solution: Individualised antibiotic dosing

Optimal patient outcomes from treatment of infection are most likely to occur when PK/PD targets that are associated with maximal antibiotic activity are achieved. The advent of *in vitro* and *in vivo*mathematical PK/PD models over the recent 30 years has allowed accurate description of the PK/PD targets that are associated with maximal antibiotic effect. More recent clinical analyses have attempted to confirm the results of these studies and have, for the most part, described similar PK/PD targets to those observed in the pre-clinical studies[81]. Table 1 describes various PK/PD targets that have been described in pre-clinical and clinical studies which could be considered as therapeutic targets to optimise dosing in individual patients.

To increase the likelihood of achieving therapeutic targets for systemically administered antibiotics, there are two main approaches to adjusting standard regimens: 1) altered administration techniques such as once-daily dosing or prolonged infusion which is often based on published studies of the specific dosing regimen and/or 2) dose adjustment that is guided by therapeutic drug monitoring (TDM).

Altered administration techniques

There are numerous PK studies that apply dosing simulations to identify optimised regimens to achieve PK/PD targets for infections caused by organisms with higher MICs or in the

setting of altered PK. Such an approach to dosing is not an individualised approach per se when it is employed on a population level, but is a form of therapeutic adaptation designed to enhance improve antibiotic efficacy. PK/PD-based dosing has changed the way aminoglycosides are prescribed clinically from thrice to once daily dosing and has improved the safety and efficacy of these compounds[115]. As such, extended interval dosing for aminoglycosides is widely considered the standard of care[116].

Studies for beta-lactams are particularly numerous. Collectively, these studies suggest that prolongation of the duration of infusion (either for 40-50% of the dosing interval (i.e., 3-4 hours), or as a continuous infusion) achieves a greater likelihood of achieving PK/PD targets than standard bolus dosing in critically ill patients[68, 117-124]. Recent studies have sought to investigate the clinical value of use of these prolonged infusions with prospective randomised controlled trials suggesting a potential advantage of continuous infusions for critically ill patients with severe sepsis[125, 126]. While some meta-analyses of these studies have not been able to quantify definitive advantages for either intermittent or prolonged infusions of beta-lactams, these studies have often not been stratified for patients with altered PK or reduced susceptibility[126, 127]. For example, in one study, changing the approach to dosing beta-lactams at an ICU-wide level from intermittent to extended infusion was not found to be clinically advantageous – this was likely because of a high proportion of susceptible pathogens in that ICU. These low MICs meant that standard infusions had already obtained requisite PK/PD thresholds in the vast majority of patients[128]. A clinician must determine whether the patient and/or pathogen is at risk of failing a standard fixed regimen. Changing the approach to dosing for all patients may not be necessary and not confer any therapeutic advantage. This study from Arnold et al[128], adds support to the important findings from Lodise et al. of the clinical effectiveness of administering piperacillin/tazobactam as an extended infusion for *Pseudomonas aeruginosa* infections in patients with higher levels of sickness severity[129].

For vancomycin, a few studies have compared continuous infusion versus intermittent dosing and have largely demonstrated equivalence[130]. Only one study, by Rello et al, has shown potential clinical outcome advantages for continuous infusion[131]. The value of continuous infusion for vancomycin is likely related to more consistent achievement of PK/PD targets[31]. The influence on emergence of resistance has not been addressed in these studies.

In general, the above concepts can be implemented at the ICU level when MIC data are available to justify a change at the ICU level empirically.

Therapeutic Drug Monitoring

TDM (also described as therapeutic drug management) is traditionally used to minimise toxicities for drugs, but in critically ill patients, is being increasingly used to optimise dosing in the presence of severely deranged PK[10, 132]. TDM relies on direct measurement of serum antibiotic concentrations with timely feedback to the clinician who would then interpret that result in the context of a therapeutic range. The adequacy of the measured concentration can be interpreted by directly comparing a single concentration value to a therapeutic target, or by describing antibiotic exposure using non-linear regression or Bayesian techniques. Doses

can then be increased or decreased as predicted by the clinician or the dosing software (therapeutic drug management).

Notably, an understanding of the importance of the unbound concentration of the assayed drug in the blood sample is vital for accuracy when interpreting drug exposure because only free drug concentrations are microbiologically active. Knowledge of free concentrations is most important for highly bound antibiotics[133]. The concentration result from the assay should also be made available in a timely manner so that rapid dose adjustment can be made. Given the dynamic nature of PK in these patients, delays that are too long, can result in inappropriate dose adjustment. Importantly, for ideal TDM, the antibiotic MIC of the organism and TDM target should also be available (i.e., Challenge 2).

To date, various studies reporting TDM for antibiotics in critically ill patients have been reported including aminoglycosides[134], glycopeptides[135], beta-lactams[10, 19, 136], linezolid[137]and quinolones[10]. Unfortunately, few of these studies have sought to measure clinical outcome advantages of using TDM compared with not applying TDM and a rigorous prospective evaluation of the benefit of individualised therapy should be considered essential.

Dosing nomograms—Dosing nomograms for dose adjustment of antibiotics are in common usage across many clinical areas[138]. These nomograms function by comparing a measured concentration value for the prescribed antibiotic at the time point that the sample was taken with a graph that defines the therapeutic range of concentrations at that stated time point. The dose of antibiotic can then be increased or decreased as necessary to ensure the next measured concentration is in the therapeutic range. These nomograms are simple to apply even for those without an advanced understanding of PK/PD and remain popular, with nomograms for vancomycin and aminoglycosides most widely available[138-140] simply because these agents have toxicity thresholds (i.e., low therapeutic index), have drug assays available and are often targets for TDM by pharmacists and physicians. A limitation of many nomograms, however, is that they are rarely designed with PK/PD targets from critically-ill patients and rely on the clinician's experience to make appropriate dose adjustments[141].

Non-linear regression based dose adaptation—Application of non-linear regression analysis to a series of concentration values at different time points can be useful to calculate basic PK parameters such as area under the curve (AUC), clearance, elimination rate constant, maximum concentration in the dosing interval (C_{max}) and trough concentration (C_{min}). From a drug dosing perspective, the measured or calculated values for AUC, C_{max} and/or C_{min} can be compared against the PK/PD targets for the prescribed antibiotic and the dose empirically increased or decreased as needed.

Bayesian dose estimation and adaptation—Population PK models for antibiotics in critically ill patients have been developed for many antibiotics. Problematic to many of these models are that although there is increased PK variability in these patients, the sample size used for many of these studies remains small (~10-20 patients) and so not all of the PK variability for the population is likely to be captured by these models[142, 143]. Nevertheless,

applying these population models is likely to be more accurate than using a model derived from another patient group[144]. The process for how dose individualisation could occur in a critically ill patient is described in the section, The process of how dose individualisation could occur for a patient.

To ensure greatest accuracy of dose adaptation based on drug concentration data, use of a stochastic control approach can be applied to define the timing and number of drug concentrations that should be taken from the patient and then used in the dose prediction[145]. This approach is particularly useful for drugs with high PK variability[72]. With more antibiotic concentration data over different dosing intervals, the accuracy of dose prediction improves[72].

How are patient-specific PK parameters calculated?—In Bayesian dose adaptation, the dose of the drug is adjusted to ensure the individual patient's exposure meets PK/PD targets. Information about the specific patient, in the form of serum drug concentrations, and a population PK model, from the relevant population, are included. This population PK model contains a series of mathematical equations including parameter estimates and their distribution for clearance and V_d.

The process of how dose individualisation could occur for a patient—A critically ill patient would receive a first dose at the clinician's discretion, preferably using a strategy associated with an increased likelihood of achieving PK/PD targets, e.g. vancomycin loading dose[31] or extended infusion beta-lactam[68, 117-124]. During the first or a subsequent dosage interval, one or more blood sample/s could be taken to estimate the patient's individual PK parameters for the antibiotic. The samples would then be assayed in a timely manner (e.g., within 6 hours) and the dosing history, drug concentrations and necessary patient data (e.g., weight or creatinine clearance) would be provided to the chosen software package. Meanwhile, a pathogen MIC is derived for the antibiotic by the microbiology lab. The software package could then combine the patient's observed data plus the population PK model to estimate the Bayesian posterior PK parameter values for the individual. The appropriate dose that achieves the PK/PD targets required for a critically ill patient could then be calculated and used in next dosing interval.

What antibiotic dosing software is available?—Numerous programs exist which apply different approaches to calculating individualised antibiotic doses for patients. A summary of various programs has been provided in Table 2, with other programs also identified by Fuchs et al[146]. Importantly, not all programs contain all relevant antibiotics, although the developers of most programs state that additional PK models for antibiotics can be included in these programs on request or by the user. To ensure robust bedside antibiotic dosing is possible, many of these programs have, or are developing electronic medical record interfaces and smart phone applications which can be literally used at the patient's bedside.

What might a future scenario for antibiotic dosing in a critically ill patient look like?—Based on best available evidence, we would suggest that a robust process for dose

individualisation in a critically ill patient would be as below. Note that part of this process would require baseline data of local bacterial susceptibility in the clinician's ICU.

1. Diagnosis of infection and selection of antibiotic is made.
2. The patient's physiological characteristics would be determined such that data of relevant covariate descriptors of the prescribed drug are known (e.g. weight, sex, creatinine clearance, serum albumin concentration, fluid overload status, presence of extracorporeal circuits).
3. First dose estimated based on patient characteristics and local susceptibility data preferably using dosing decision support software.
4. Dose is administered to the patient in a timely manner after diagnosis
5. Blood samples are taken at pre-determined time points and are assayed within a timely period.
6. The clinician can then enter the concentration-time data from the blood samples and the patient covariate data into the software which is in a smartphone or computer terminal at the patient's bedside. The output from the software is a personalised dosing regimen for the patient that can achieve an evidence-based PK/PD target. When pathogen specific susceptibility data is available, this should be incorporated into the dose estimation process.

Conclusions

Critically ill patients have dramatically varied PK compared with non-critically ill patients and are more likely to be infected by less susceptible bacteria. Traditional antibiotic dosing strategies are unlikely to consistently achieve PK/PD targets associated with maximal antibiotic activity thereby putting the patient at risk of clinical failure, the development of resistance, or both. Optimization of antibiotic dosing in the ICU, therefore, requires an individualized approach for the patient that considers the MIC of the infecting pathogen and selects a dosing regimen that provides a high likelihood of obtaining the requisite PK/PD index predictive of success. The challenges are clearly here, but so too are the solutions. Pro-active therapeutic management for antibiotics other than vancomycin and aminoglycosides is possible, but needs to be escalated to the next level and made available to all hospitals. The ability to acquire individualized antibiotic concentrations, combined with access to available software programs as described here will increase dosing accuracy and the likelihood of achieving PK/PD targets in our patients.

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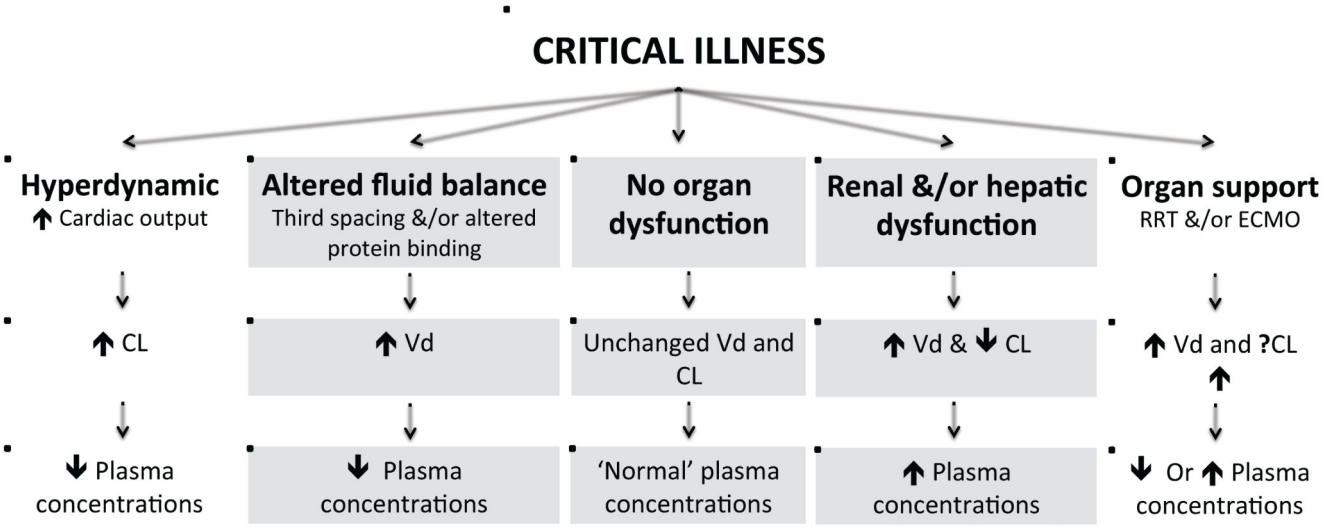

Figure 1.

The spectrum of critical illness-related altered pathophysiology and its effects on drug concentrations.

Legend: CL – clearance; Vd volume of distribution; RRT – renal replacement therapy; ECMO – extracorporeal membrane oxygenation

Table 1

Studies reporting PK/PD indices from pre-clinical and clinical evaluations

	Antibiotic classifications	Optimal PK/PD indices*					
		Pre-clinical studies			Clinical studies		
Concentration-dependent	**Aminoglycosides**	Maximal killing	AUC_{0-24}/MIC 80-100	43	Clinical Cure	C_{max}/MIC 8-10 AUC/MIC >70	82-86
		Resistance suppression	C_{max}/MIC 10-30	87	Microbiological Cure	-	
Time-dependent	**Carbapenems**	Maximal killing	40% $T_{>MIC}$	88	Clinical Cure	75% $T_{>MIC}$ C_{min}/MIC 5	89
		Resistance suppression	16 × MIC C_{min}/MIC >6.2	90 91	Microbiological Cure	54% $T_{>MIC}$	17
	Cephalosporins	Maximal killing	60-70% $T_{>MIC}$	11	Clinical Cure	100% $T_{>MIC}$	92
		Resistance suppression	-		Microbiological Cure	60-100% $T_{>MIC}$ 95% $T_{>4.3\times MIC}$	16 93
	Penicillins	Maximal killing	40-50% $T_{>MIC}$	11	Clinical Cure	-	
		Resistance suppression	40-50% $T_{>MIC}$	94	Microbiological Cure	40-50% $T_{>MIC}$	95
Concentration with time-dependence	**Fluoroquinolones**	Maximal killing	AUC_{0-24}/MIC >30-100	11, 96	Clinical Cure	AUC_{0-24}/MIC ≥125-250 C_{max}/MIC ≥8	15, 86, 96 86,97, 98
		Resistance suppression	AUC_{0-24}/MIC >160 AUC_{0-24}/MPC ≥22	99, 100 101	Microbiological Cure	AUC_{0-24}/MIC ≥34-125 C_{max}/MIC ≥8	14, 102 86
	Vancomycin	Maximal killing	AUC_{0-24}/MIC 86-460	103	Clinical Cure	AUC_{0-24}/MIC ≥400-450	20, 21
		Resistance suppression	AUC_{0-24}/MIC >200	104	Microbiological Cure	AUC_{0-24}/MIC ≥400	20
	Linezolid	Maximal killing	-		Clinical Cure	AUC_{0-24}/MIC ≥85 85% $T_{>MIC}$	22
		Resistance suppression	-		Microbiological Cure	AUC_{0-24}/MIC 80-120 85% $T_{>MIC}$	22
	Tigecycline	Maximal killing	50% $T_{>MIC}$	105	Clinical Cure	AUC_{0-24}/MIC >12.8-17.9 *f* AUC_{0-24}/MIC ≥0.9	106, 107 108
		Resistance suppression	-		Microbiological Cure	AUC_{0-24}/MIC 6.9-17.9	109, 110
	Daptomycin	Maximal killing	AUC_{0-24}/MIC 38-442	111, 112	Clinical Cure	-	
		Resistance suppression	AUC_{0-24}/MIC >200	104	Microbiological Cure	-	
	Colistin	Maximal killing	AUC_{0-24}/MIC 7-23	113, 114	Clinical Cure	-	

	Antibiotic classifications	Optimal PK/PD indices*					
		Pre-clinical studies			Clinical studies		
		Resistance suppression	-		Microbiological Cure	-	

*Where the index is reported as a range, the data included may have been derived from different infection models with different bacteria. Specific data about the contributing values can be found in the associated references.

**Data for the various indices has been reported in different studies according to total and free (unbound) drug. Where free concentrations have been reported, this is denoted using '*f*'

Legend: MIC – minimum inhibitory concentration; $AUC_{0\text{-}24}$/MIC – ratio of area under the concentration time curve from 0-24 hours to MIC; C_{max}/MIC – ratio of maximum concentration of antibiotic in a dosing interval to MIC; $T_{>MIC}$ – percentage of dosing interval that the antibiotic concentration is maintained above the MIC; $AUC_{0\text{-}24}$/MPC; ratio of the $AUC_{0\text{-}24}$ to mutant prevention concentration; C_{min} – minimum concentration of antibiotic in a dosing interval; *f* – free or fraction of drug not bound to plasma proteins

Table 2

Characteristics of various antibiotic dosing programs

	BestDose v1.0	**ID-ODS**	**MWPharm**	**DoseMe**	**TCI Works**	**First-dose**	**WinAUIC**	**CADDy Program v4.e**
PK Method	Bayesian non-parametric approach	Bayesian parametric approach	Bayesian parametric approach	Bayesian parametric approach	Bayesian parametric approach	Population PK parametric approach	Non-linear regression	Non-linear regression
Adaptive feedback?	Yes	Yes	Yes	Yes	Yes	No	No	No
Web, server or terminal based?	Terminal	Terminal and Server	Terminal and Server	Terminal and Server	Terminal and Server	Web	Terminal	Web or Server
Compatibility	Windows	Mac, Windows, Linux, Android, IOS	Windows	Mac, Windows, Linux, Android, IOS	Mac, Windows	Mac, Windows, Linux, Android, IOS	Windows	Mac, Windows, Linux, Android, IOS
Smart phone application?	No	Yes	No	Yes	No	Yes	No	No
Patient covariates in dose predictions?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Output from program?	Doses and PK parameter estimates	Dosing regimens, PK parameter estimates and PTAs	Doses and PK parameter estimates	Doses and PK parameter estimates	Doses and PK parameter estimates	Doses	PK parameter estimates	Doses
IT support available within 24 hours? *	Yes	Yes	No	Yes	Yes	No	No	Yes
Capacity for ICU and non-ICU dosing?	Yes	Yes	Yes	Yes	Yes	No	No	No
Further information	http://www.lapk.org	http://www.optimum-dosingstrategies.org	http://www.mediware.cz/index_en.html	www.doseme.com.au	www.tciworks.info	http://www.firstdose.org/	Contact the developers (Dr J Schentag)	www.jjpreisenberger.de
Cost	Current version is free.	Free	1250 euros per license	Dependent on requirements	Free	Free	Free	Free

* Response time often depends on the severity of the problem for the user (for non-urgent issues, responses may exceed 24 hours)

Legend – ID-ODS: Individually Designed Optimum Dosing Strategies; WinAUIC: Windows Antibiotic Utilisation Information and Consultation; PK: pharmacokinetic; RRT: renal replacement therapy; AUIC: area under the inhibitory curve; MIC: minimum inhibitory concentration; ICU: intensive care unit; IT: information technology; PTA: probability of target attainment