Pharmacokinetic/pharmacodynamic considerations for the optimization of antimicrobial delivery in the critically ill

Danny Tsai [a,b,c], *Jeffrey Lipman* [a,d], *and Jason A. Roberts* [a,d,e,f]

Purpose of review
Antimicrobials are very commonly used drugs in the intensive care setting. Extensive research has been conducted in recent years to describe their pharmacokinetics/pharmacodynamics in order to maximize the pharmacological benefit and patient outcome. Translating these new findings into clinical practice is encouraged.

Recent findings
This article will discuss mechanistic data on factors causing changes in antimicrobial pharmacokinetics in critically ill patients, such as the phenomena of augmented renal clearance as well as the effects of hypoalbuminemia, renal replacement therapy, and extracorporeal membrane oxygenation. Failure to achieve clinical cure has been correlated with pharmacokinetics/pharmacodynamics target nonattainment, and a recent meta-analysis suggests an association between dosing strategies aimed at optimizing antimicrobial pharmacokinetics/pharmacodynamics with improvement in clinical cure and survival. Novel dosing strategies including therapeutic drug monitoring are also now being tested to address challenges in the optimization of antimicrobial pharmacokinetics/pharmacodynamics.

Summary
Optimization of antimicrobial dosing in accordance with pharmacokinetics/pharmacodynamics targets can improve survival and clinical cure. Dosing regimens for critically ill patients should aim for pharmacokinetics/pharmacodynamics target attainment by utilizing altered dosing strategies including adaptive feedback using therapeutic drug monitoring.

Keywords
antibacterial, antimicrobial, critically ill, pharmacodynamics, pharmacokinetics

INTRODUCTION

Despite the advancement in the management of critically ill patients over the past few decades, severe sepsis and septic shock still remain responsible for persisting high mortality rates for patients in the ICU. The cornerstone of infection treatment is initiation of early antimicrobial therapy and source control of the infection, both of which have a high likelihood of improving clinical cure and survival rates [1,2]. There is increasing evidence that optimization of antimicrobial dosing regimens can lead to further patient outcome benefits. The aim of these dosing regimens is to maximize pathogen killing through application of pharmacokinetic/pharmacodynamic principles that account for the significant changes in pharmacokinetic and pathogen susceptibility that are common to the critically ill patient. This review will explore the recent evidence on dose optimization of antimicrobials in critically ill patients, as well as provide dosing recommendations based on these data.

[a]Burns, Trauma and Critical Care Research Centre, School of Medicine, The University of Queensland, Brisbane, Queensland, [b]Department of Intensive Care Medicine, [c]Pharmacy Department, Alice Springs Hospital, Alice Springs, Northern Territory, [d]Department of Intensive Care Medicine, [e]Pharmacy Department, The Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia and [f]Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, United Kingdom

Correspondence to Professor Jeffrey Lipman, Burns, Trauma and Critical Care Research Centre, The University of Queensland, Level 3, Ned Hanlon Building, Royal Brisbane and Women's Hospital, Herston, Brisbane, QLD 4029, Australia. Tel: +61 7 3646 8152; fax: +61 7 3646 3542; e-mail: j.lipman@uq.edu.au

KEY POINTS

- A recent meta-analysis shows improvement in survival and clinical cure rates for prolonged infusion administration of β-lactams when compared with intermittent boluses.

- Hypoalbuminemia significantly influences free drug concentration of highly protein bound drugs.

- There is high prevalence of augmented renal clearance in critically ill patients, which can significantly alter the pharmacokinetics of renally cleared antimicrobials such as β-lactams and glycopeptides.

- Therapeutic drug monitoring improves pharmacokinetics/pharmacodynamics target attainment for antimicrobials.

MAIN TEXT

Critically ill patients experience drastic derangements in their physiological parameters, subsequently impacting on the pharmacokinetics of antimicrobials. Unfortunately, treatment success for these drugs is heavily dependent on the drug concentration achieved at the site of infection, and thus extensive research has been committed to further our understanding of the physiological processes that cause pharmacokinetic changes, as well as, investigating treatment strategies that can address and overcome the aforementioned obstacles.

PHARMACOKINETICS/ PHARMACODYNAMICS OF ANTIMICROBIALS

In the context of pharmacokinetics/pharmacodynamics, antimicrobials can be categorized by either their physicochemical properties (Fig. 1) or pathogenic kill characteristics (Fig. 2 and Table 1). Understanding these characteristics can aid us in formulating an optimal antimicrobial treatment regimen for an individual patient.

Time-dependent – pathogenic kill is dependent on the time the free drug concentration (f) remains above the minimum inhibitory concentration (MIC) during the dosing interval ($f\mathrm{T}_{>\mathrm{MIC}}$).
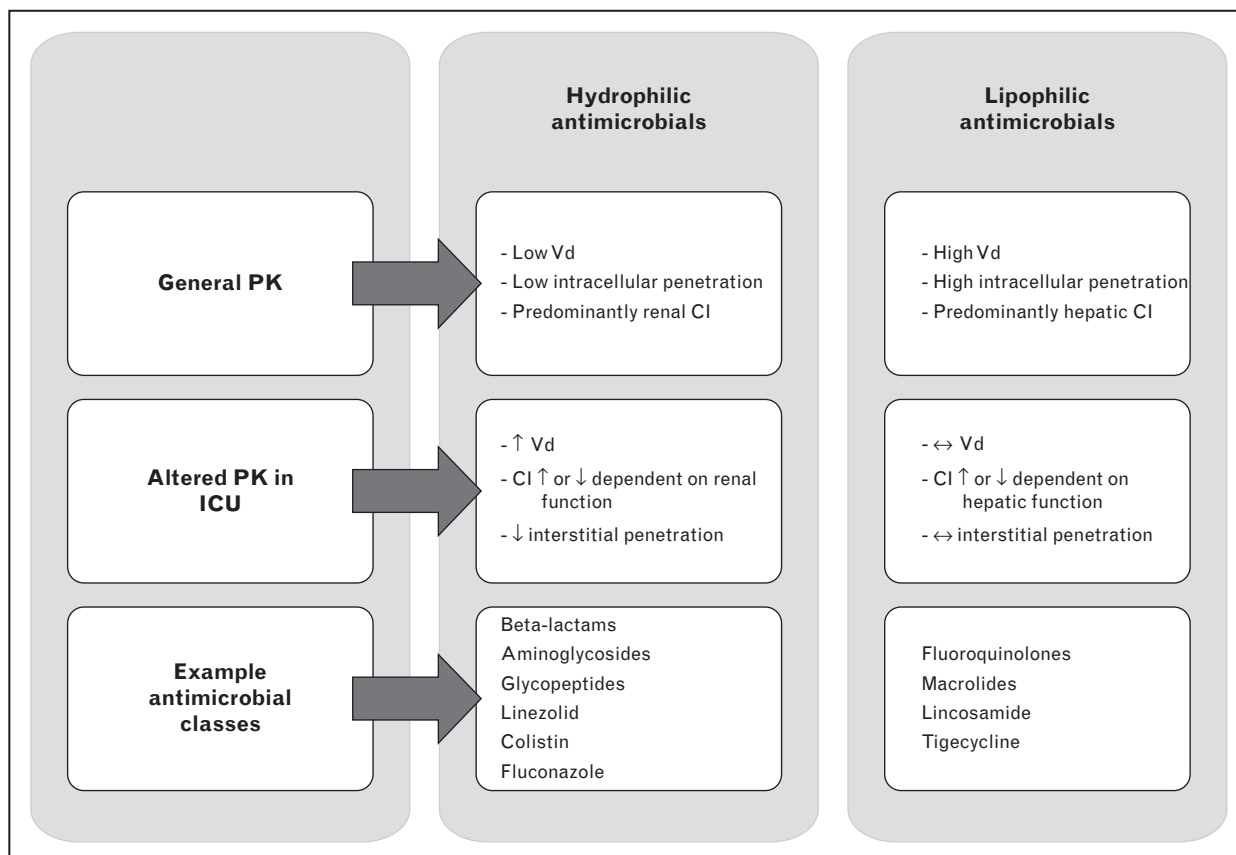

FIGURE 1. Physicochemical properties of antimicrobials, pharmacokinetics of general patients, pharmacokinetics in the critically ill and sample antimicrobials.
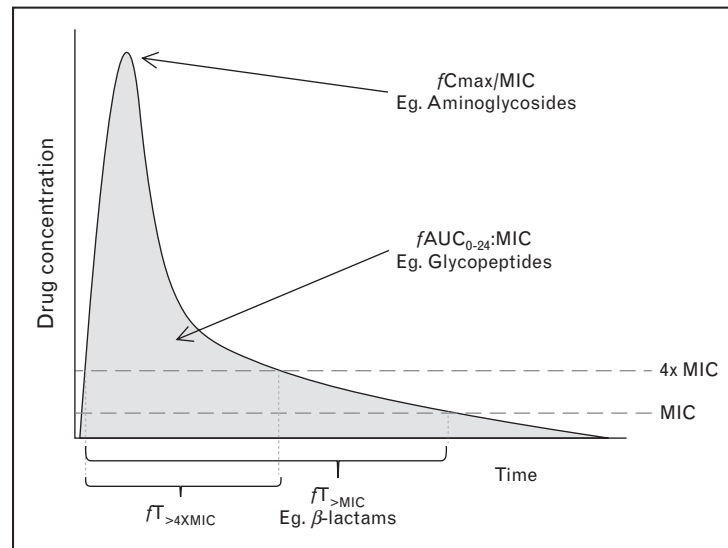
FIGURE 2. Pharmacokinetic/pharmacodynamics of antimicrobials.

Concentration-dependent – pathogenic kill is dependent on the ratio of the maximum-free drug concentration (fCmax) to the MIC of the pathogen (fCmax/MIC).

Concentration-dependent with time-dependence – pathogenic kill is dependent on the free drug exposure within 24 h relative to the MIC of the pathogen, and is represented by area under the concentration-time curve (fAUC$_{0-24}$:MIC).

FACTORS IMPACTING PHARMACOKINETICS/ PHARMACODYNAMICS OF ANTIMICROBIALS AND THEIR CLINICAL CONSEQUENCES

Numerous factors alter the pharmacokinetic of antimicrobials in the critically ill by changing either or both of the two main pharmacokinetic parameters – volume of distribution and clearance.

Table 1. Pharmacokinetics/pharmacodynamics of antimicrobials, optimal pharmacodynamics of antimicrobials, sample antimicrobials, and pathogenic kill targets

Pathogenic kill characteristics	Time-dependent	Concentration-dependent	Concentration-dependent with time-dependence
Optimal PD parameter	fT$_{>MIC}$	fCmax/MIC	fAUC$_{0-24}$:MIC
Antimicrobials	β-lactams	Aminoglycosides	Fluoroquinolones
	Lincosamide	Metronidazole	Aminoglycosides
	Erythromycin	Fluoroquinolones	Azithromycin
	Clarithromycin	Daptomycin	Glycopeptides
	Linezolid	Echinocandins	Tigecycline
	Flucytosine	Polyenes	Linezolid
			Echinocandins
			Triazoles
Pathogenic kill target	>40% fT$_{>MIC}$ for carbapenems >50% fT$_{>MIC}$ for penicillin >70% fT$_{>MIC}$ for cephalosporins (Maximal pathogenic kill activity seen at 4–5xMIC for some agents)	fCmax$_{>8-10xMIC}$ (Maximal pathogenic kill activity is often seen when fCmax$_{>8-10xMIC}$)	Each antimicrobial is individualized (Dose is the main determinant of achieving maximal pharmacological efficacy.)

PD, pharmacodynamics; fT$_{>MIC}$, time of the free drug concentration remains above the minimum inhibitory concentration during the dosing interval; fCmax/MIC, ratio of the maximum free drug concentration to the minimum inhibitory concentration; fAUC$_{0-24}$:MIC, free drug exposure within 24 h relative to the minimum inhibitory concentration; fCmax$_{>8-10xMIC}$, maximum free drug concentration is greater than 8–10x the minimum inhibitory concentration.

VOLUME OF DISTRIBUTION AND CLEARANCE IN THE CRITICALLY ILL

Volume of distribution significantly increases in critically ill patients mainly due to volume expansion from rigorous fluid resuscitation and the presence of systemic inflammatory response syndrome (SIRS), whereby the phenomenon of third spacing precipitates from capillary leakage. In this circumstance, hydrophilic antimicrobials will be diluted and the pharmacokinetic significantly altered. On the contrary, pharmacokinetic of lipophilic drugs are relatively unaffected due to more extensive intracellular and adipose tissue penetration [3]. The extent of volume expansion is described by changes in disease severity, with increasing Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment scores associated with increased volume of distribution for hydrophilic antimicrobials [4]. Volume of distribution is also affected by hypoalbuminemia, which may have profound effects on highly albumin bound antimicrobials [5,6], such as ceftriaxone, cefazolin, flucloxacillin, ertapenem, teicoplanin, and daptomycin, with protein binding percentage, approximating, 90, 80, 93, 90, 90, and 92%, respectively. In this scenario, a transient increase in free drug concentration will be observed, followed by an increase in volume of distribution and drug clearance. Furthermore, high variability of protein binding and free drug concentration is reported in the critically ill even for lower binding antimicrobials such as linezolid and vancomycin (31 and 55%, respectively) [7,8]. Obesity is also a major contributing factor to subtherapeutic dosing [9–11].

A decline in clearance is usually caused by end-organ dysfunction (renal and/or hepatic) [12]. Renal impairment significantly alters the pharmacokinetic of renally clear antimicrobials, in particular those with higher hydrophilicity and most of the commonly used antimicrobials in the ICU fall into this category. On the contrary, reduction for dose or dosing frequency for hepatically cleared antimicrobials is only recommended in the presence of liver decompensation [13]. Nonetheless, should altered renal function coexist, revision of dosing regimens based on the clearance mechanisms of the prescribed antimicrobial is especially necessary [12,13].

A recent multicenter observational study found that 65% of critically ill patients without a history of renal impairment will experience augmented renal clearance (ARC, defined as 'enhanced renal elimination of circulating solute' [14]), and factors correlate with its prevalence include male sex, younger age, multiple-trauma, and ventilation [15■]. Furthermore, many studies have demonstrated higher antimicrobial clearance in presence of burns, SIRS, multiple trauma, severe medical illnesses, use of inotropes, and an increase in cardiac output, which increases the risk of subtherapeutic drug concentration, and thus, treatment failure [10,16–19]. Udy *et al.* [20] have found high creatinine clearance (CrCl) in the critically ill the greatest predictor of pharmacokinetic/pharmacodynamic target nonattainment for β-lactams.

Renal replacement therapy (RRT) also increases antimicrobial clearance (especially β-lactams and other small molecule, hydrophilic, and low protein bound antimicrobials) relative to patients with renal dysfunction. The extent of this extracorporeal clearance varies with different settings of the RRT, RRT dose, and hemofilters used. A recent meta-analysis by Jamal *et al.* [21■] has found effluent flow rate the strongest predictor of the extent of drug removal by RRT, which includes vancomycin ($r_s = 0.90$; $P = 0.08$), meropenem ($r_s = 0.43$; $P = 0.12$), and piperacillin ($r_s = 0.77$; $P = 0.10$). The large multicenter SaMpling Antibiotics in Renal Replacement Therapy study is under progress, which examines antimicrobial dosing and pharmacokinetics in patients on RRT (Australian New Zealand Clinical Trials Registry ACTRN12613000241730). Its result hopes to provide further information to guide antimicrobial dosing in patients receiving any form of RRT.

Studies investigating antimicrobial pharmacokinetics for patients on extracorporeal membrane oxygenation (ECMO) have been mostly performed on pediatric patients and animals. Although these data show large variability between studies, higher volume of distribution, and lower clearance were generally observed in the ECMO arms. Notwithstanding these findings, small pharmacokinetic studies have found no significant pharmacokinetic differences for vancomycin, piperacillin/tazobactam, and meropenem in adult cohorts [22,23]. Currently, a multinational study investigating the effect of ECMO on conventional antimicrobial regimens is being conducted [24].

EVIDENCE OF FAILURE OF PHARMACOKINETIC/ PHARMACODYNAMIC TARGET ATTAINMENT AND ITS CLINICAL RELEVANCE

Changes in clearance and/or volume of distribution can lead to a significant decrease in the plasma drug concentration leading to nonattainment of pharmacokinetic/pharmacodynamic targets, and thus a higher treatment failure rate [25–27]. Recent studies have correlated ARC with failure of

pharmacokinetic/pharmacodynamic target attainment for a number of β-lactams, subsequently requiring dose escalation [28,29]. The Defining Antibiotic Levels in Intensive care unit patients (DALI) study, a multinational, observational study involving 68 hospitals, assessed β-lactam pharmacokinetic/pharmacodynamic target attainment in a large cohort of critically ill patients and found that 16% of the 361 enrolled patients failed to achieve $50\%fT_{>MIC}$ with conventional therapy, and were 32% less likely to achieve a positive clinical outcome [30■■].

PHARMACOKINETIC/PHARMACODYNAMIC TARGET ATTAINMENT OF ANTIMICROBIAL CLASSES

Despite confirmation of a relationship between unsuccessful pharmacokinetic/pharmacodynamic target attainment and treatment failure, the association of pharmacokinetic/pharmacodynamic target attainment and treatment success is still a subject of ongoing debate.

β-LACTAM

β-Lactams are the commonest and most extensively studied antibacterials in ICU. Maximized $fT_{>MIC}$ can be achieved by extending the infusion time, although a number of previous studies and meta-analyses failed to show superior clinical outcome. Many of the studies used lower doses in the prolonged infusion (includes extended and continuous infusion) arm and had small sample sizes. It has been shown that $T_{>MIC}$ for a thrice daily meropenem regimen is similar between 1 g infused over 30 min and 0.5 g over 3 h [31]. Similar results are found between a regimen of thrice daily imipenem 1 g infused over 30 min compared with a four times daily regimen of 0.5 g over 3 h [32], and thus a superior outcome would not be anticipated. Nonetheless, a number of recently published larger single-center studies have shown superior clinical outcome with prolonged infusion [33–36]. A meta-analysis by Teo et al. [37■■] has also demonstrated improvement in clinical cure with a significant reduction in mortality (relative risk = 0.66, 95% confidence interval 0.53–0.83) based on a total of 19 studies encompassing 1620 hospitalized patients. This important finding based on the most recent and robust data challenges some of the previously conducted systematic reviews [38,39]. Furthermore, Beta-Lactam Infusion Group study, the largest international multicenter randomized controlled trial studying the correlation between prolonged infusion and clinical outcome for β-lactams will report its results soon [40], to provide further clarification on this intervention.

GLYCOPEPTIDES

Recent studies suggest that vancomycin-induced nephrotoxicity is reduced via administration by continuous infusion (Tafelski et al. 26 versus 35%; Hanrahan et al. intermittent infusion with higher risk of nephrotoxicity odds ratio = 8.204, $P \leq 0.001$) [41,42]. Continuous infusion is also associated with earlier pharmacokinetic/pharmacodynamic target attainment and a lower incidence of subtherapeutic concentrations [42]. However, the low area under the drug concentration-time curve (AUC) achieved in the first 24 h of administration is an independent-risk factor for treatment failure for methacillin-resistant Staphylococcus aureus (MRSA) bacteremia (adjusted odds ratio = 4.39, 95%, confidence interval 1.26–15.35 by E test), and as such a loading dose is recommended prior to initiation of continuous infusion [27].

Teicoplanin is slightly different. In a retrospective pharmacokinetic study, Matsumoto et al. recommended three loading doses of 11–15 mg/kg 12 h apart for teicoplanin with a target trough concentration (Cmin) of 15–30 mg/l [43]. The 11 and 15 mg/kg regimens each achieved a respective Cmin of 17.5 and 27.8 mg/l after three loading doses. Due to teicoplanin's prolonged terminal half-life ($T_{1/2}$) of 90–157 h, therapeutic drug monitoring (TDM) is still recommended thereafter. Furthermore, teicoplanin's high protein binding complicates its pharmacokinetics/pharmacodynamics because of the increased free drug concentrations that have been described in hypoalbuminemia [6]. Studying the teicoplanin dataset of the DALI-study, Roberts et al. [6] have found albumin bound percentages varying between 71 and 97% and free drug Cmin between 0.1 and 4.5 mg/l (target 1.5–3 mg/l), and the free drug concentration inversely increases in proportion to the severity of hypoalbuminemia.

AMINOGLYCOSIDES

Two studies investigating the pharmacokinetics of 25 mg/kg dosing regimen of amikacin in critically ill patients have found 25–33% of participants failed to achieve the defined pharmacokinetic/pharmacodynamic target, which was a Cmax greater than 60–64 mg/l [4,44]. The 25 mg/kg dosing regimen was calculated according to total body weight (TBW). Neither study had an upper limit to the Cmax, nor was toxicity assessed. In the de Montmollin et al. [44] study, pharmacokinetic/pharmacodynamic

target nonattainment is correlated with positive 24-h fluid balance and BMI lower than 25 kg/m^2. This highlights the importance of using adjusted body weight (ABW) or lean body weight (LBW) especially in patients with lower BMI.

ECHINOCANDINS

The antifungal dataset from the DALI-study [45] revealed a significantly lower AUC$_{0-24}$ for a 100 mg daily regimen of anidulafungin when compared with the study by Liu *et al.* (55 versus 93 mg.h/l) [46]. Plasma sampling was obtained for Liu *et al.*'s study after 3–7 days (included a 200 mg loading dose) with the DALI-study having sampling on various days of therapy. Anidulafungin has a mean T$_{1/2}$ of 26.5 h, hence the AUC$_{0-24}$ may differ significantly on different dosing days before steady state is reached. Patients recruited from the Liu *et al.*'s study were older and had lesser weight than the DALI study (mean age and weight 51 versus 60 years, 82 versus 65 kg, respectively), and only patients with an APACHE II score of less than 25 were recruited, whereas the median score for DALI is 18 (range 15–32).

The DALI-study also found a mean AUC$_{0-24}$ of 52 mg.h/l for a 70 mg loading dose of caspofungin compared with 89 mg.h/l reported by Muilwijk *et al.* [47] on day 3 after a loading dose of 70 mg followed by 50 mg daily regimen [45]. For both Muilwijk *et al.* [47] and Liu *et al.*'s [46] studies, the pharmacokinetic findings are comparable to general patients, and therefore further studies are warranted to guide dosing regimens in the critically ill.

TRIAZOLES

The DALI-study found that of the 15 ICU patients receiving fluconazole regimens (mean daily dose 4.9 mg/kg), 33% did not reach the pharmacokinetic/pharmacodynamic index of AUC$_{0-24}$/MIC greater than 100 for an MIC of 2 mg/l (breakpoint for most *Candida species*) [45]. Fluconazole was observed to be given commonly as a standard 400 mg daily dose and hence have produced significantly varied pharmacokinetic in the DALI study. Weight-based dosing may need to be considered.

Hypoalbuminemia is also correlated to an increase in free drug concentration for voriconazole, and this relationship is more pronounced in the presence of hyperbilirubinemia [48]. Voriconazole is, approximately, 56% protein bound and is subject to saturable hepatic metabolism, monitoring of free drug concentration may prove to be a useful intervention in later studies.

APPLICATION OF PHARMACOKINETICS/ PHARMACODYNAMICS IN CLINICAL SETTING

Both subtherapeutic and toxic drug concentrations may eventuate in unwanted outcomes. Unfortunately, the unpredictability of pharmacokinetics in this patient group complicates pharmacodynamic target attainment, leading to the predicament wherein a consistent dosing regimen does not produce consistent concentrations [49,50■]. Various strategies can be implemented to address these challenges.

DOSE INDIVIDUALIZATION WITHOUT THERAPEUTIC DRUG MONITORING AVAILABILITY

Many ICUs do not have immediate access to a pathology service with drug assay capability for antimicrobials other than vancomycin and gentamicin, although there are an increasing number of such centers [51].

Loading dose

Timely administration of appropriate antimicrobial is imperative to ensure early achievement of therapeutic concentration [52]. This is commonly referred to as the bucket theory, in which the bucket needs to be filled (antimicrobial distribution) before water leak (clearance) needs to be considered, and hence the presence of end-organ dysfunction should not discourage the administration of a loading dose (Fig. 3). Usually, a single conventional dose is sufficient, exceptions are glycopeptides in which the change in volume of distribution can be quite high relative to standard doses. A loading dose up to twice the conventional dose (vancomycin) or multiple loading doses (teicoplanin) may be needed.

Maintenance dose

Accurate estimation of glomerular filtration rate (GFR) is imperative for renally cleared antimicrobials. CrCl calculated from 8 to 12 h urine collection remains the gold standard for clinical practice. Wherein this is not achievable in a timely manner, estimated GFR (eGFR) calculated from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula has been shown to be superior to the Modified Diet in Renal Diseases and eGFR of the Cockroft Gault CrCl in the critically ill, albeit the CKD-EPI eGFR has a tendency to underestimate the likely value in the presence of ARC [18,53]. TBW can generally be used for weight-based dosing for patients with average body weight, with LBW or
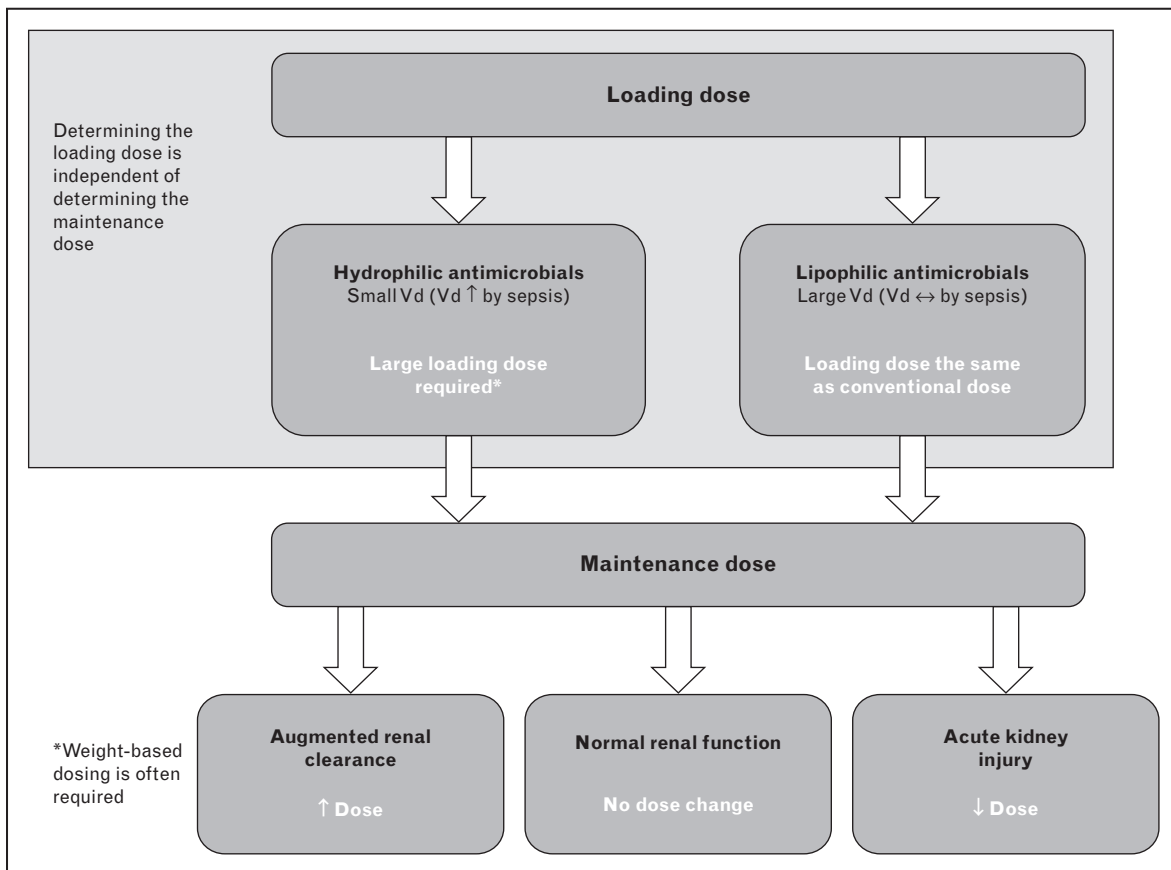
FIGURE 3. A proposed process for optimizing the dose for a renally cleared antimicrobial in a critically ill patient.

ABW recommended in either extremes of body weight (exception is vancomycin in which TBW should be used).

Administration

The administration method of an antimicrobial should be in accordance with its pathogenic kill characteristic, maximizing the chance of pharmacokinetic/pharmacodynamic target attainment.

Time-dependent antimicrobials – maximizing $fT_{>MIC}$ is the aim of dosing, especially when the suspected pathogen is likely to have a high MIC such as *Pseudomonas aeruginosa* [34]. This can be achieved by extending the infusion time to at least 3 h.

Concentration-dependent antimicrobials – achieving a high Cmax is the aim of dosing and is mainly achieved by choosing an adequate dose.

Concentration-dependent with time-dependence antimicrobials – administration method is individualized for each antimicrobial.

Regimen reassessment

Signs of antimicrobial toxicity should be monitored. Antimicrobial doses should be adjusted in accordance with the MIC of the pathogen cultured. ARC, third spacing and other inflammatory-related complications are likely to subside as the patient clinically improves [50■], and hence review of antimicrobial regimen is advised daily.

THERAPEUTIC DRUG MONITORING

Various methods of TDM show improvement in pharmacokinetic/pharmacodynamic target attainment (although their clinical relevance still needs to be ascertained), for example, one pharmacokinetic study suggests a 100% attainment of $100\%fT_{>MIC}$ if daily TDM is performed for two studied β-lactams [50■].

Time-dependent antimicrobials – after administration of a loading dose, subsequent maintenance doses should be guided by the pharmacokinetic/pharmacodynamic indices in concert with the MIC. Attaining a target of $100\%fT_{>MIC}$ is generally encouraged, wherein the Cmin can guide subsequent doses. For continuous infusions, a random concentration of at least 4× MIC is suggested. Drug assays usually describe the total drug concentration, but only the unbound concentration is of clinical value (calculated by multiplying the total

concentration by 1 less than the binding fraction). For deep tissue infection, the concentration ratio between serum and target site should also be addressed as serum concentrations may in fact not be sufficiently representative [54].

Concentration-dependent antimicrobials – achieving a Cmax (obtained 30 min after end of infusion) greater than $8-10 \times$ MIC of suspected pathogen is the aim of therapy unless if in toxicity. For example, Cmax greater than 64 mg/l is aimed for MIC of 8 mg/l. Doses can be adjusted in proportion to the change in concentration needed.

Concentration-dependent with time-dependence antimicrobials – TDM for each antimicrobial (e.g., ciprofloxacin, linezolid, and colistin) is different and individualized.

CONCLUSION

Optimization of antimicrobial dosing in accordance with pharmacokinetic/pharmacodynamic indices can improve survival and clinical cure rates for critically ill patients. Hence, dosing regimens should aim to maximize pharmacokinetic/pharmacodynamic target attainment by utilizing techniques such as TDM. Further studies may be needed to assess the clinical relevance of target site-free drug concentration, antimicrobial pharmacokinetics/pharmacodynamics in patients on ECMO and RRT.

Conflicts of interest
There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING
Papers of particular interest, published within the annual period of review, have been highlighted as:
- ■ of special interest
- ■■ of outstanding interest

1. Dellinger RP, Levy MM, Rhodes A, *et al.* Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013; 41:580–637.
2. Kumar A, Roberts D, Wood KE, *et al.* Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006; 34:1589–1596.
3. Kontou P, Manika K, Chatzika K, *et al.* Pharmacokinetics of moxifloxacin and high-dose levofloxacin in severe lower respiratory tract infections. Int J Antimicrob Agents 2013; 42:262–267.
4. Mahmoudi L, Mohammadpour AH, Ahmadi A, *et al.* Influence of sepsis on higher daily dose of amikacin pharmacokinetics in critically ill patients. Eur Rev Med Pharmacol Sci 2013; 17:285–291.
5. Wong G, Briscoe S, Adnan S, *et al.* Protein binding of beta-lactam antibiotics in critically ill patients: can we successfully predict unbound concentrations? Antimicrob Agents Chemother 2013; 57:6165–6170.
6. Roberts JA, Stove V, De Waele JJ, *et al.* Variability in protein binding of teicoplanin and achievement of therapeutic drug monitoring targets in critically ill patients: lessons from the DALI Study. Int J Antimicrob Agents 2014; 43:423–430.
7. Yagi T, Naito T, Doi M, *et al.* Plasma exposure of free linezolid and its ratio to minimum inhibitory concentration varies in critically ill patients. Int J Antimicrob Agents 2013; 42:329–334.
8. Kees MG, Wicha SG, Seefeld A, *et al.* Unbound fraction of vancomycin in intensive care unit patients. J Clin Pharmacol 2014; 54:318–323.
9. Velissaris D, Karamouzos V, Marangos M, *et al.* Pharmacokinetic changes and dosing modification of aminoglycosides in critically ill obese patients: a literature review. J Clin Med Res 2014; 6:227–233.
10. Roberts JA, Lipman J. Optimal doripenem dosing simulations in critically ill nosocomial pneumonia patients with obesity, augmented renal clearance, and decreased bacterial susceptibility. Crit Care Med 2013; 41:489–495.
11. Al-Dorzi HM, Al Harbi SA, Arabi YM. Antibiotic therapy of pneumonia in the obese patient: dosing and delivery. Curr Opin Infect Dis 2014; 27:165–173.
12. Blot SI, Pea F, Lipman J. The effect of pathophysiology on pharmacokinetics in the critically ill patient: concepts appraised by the example of antimicrobial agents. Adv Drug Deliv Rev 2014; 77C:3–11.
13. Halilovic J, Heintz BH. Antibiotic dosing in cirrhosis. Am J Health Syst Pharm 2014; 71:1621–1634.
14. Udy AA, Putt MT, Shanmugathasan S, *et al.* Augmented renal clearance in the Intensive Care Unit: an illustrative case series. Int J Antimicrob Agents 2010; 35:606–608.
15. Udy AA, Baptista JP, Lim NL, *et al.* Augmented renal clearance in the ICU:
■ results of a multicenter observational study of renal function in critically ill patients with normal plasma creatinine concentrations. Crit Care Med 2014; 42:520–527.
First multicenter observational study investigating the prevalence of augmented renal clearance in the ICU. This study also explores different factors which correlate with its prevalence.
16. Shimamoto Y, Fukuda T, Tanaka K, *et al.* Systemic inflammatory response syndrome criteria and vancomycin dose requirement in patients with sepsis. Intensive Care Med 2013; 39:1247–1252.
17. Lee J, Han S, Jeon S, *et al.* Population pharmacokinetic analysis of colistin in burn patients. Antimicrob Agents Chemother 2013; 57:2141–2146.
18. Conil JM, Georges B, Breden A, *et al.* Estimation of glomerular filtration rate to adjust vancomycin dosage in critically ill patients: superiority of the Chronic Kidney Disease Epidemiology Collaboration equation? Anaesth Intensive Care 2014; 42:178–184.
19. Binder L, Schworer H, Hoppe S, *et al.* Pharmacokinetics of meropenem in critically ill patients with severe infections. Ther Drug Monit 2013; 35:63–70.
20. Udy AA, Varghese JM, Altukroni M, *et al.* Subtherapeutic initial beta-lactam concentrations in select critically ill patients: association between augmented renal clearance and low trough drug concentrations. Chest 2012; 142:30–39.
21. Jamal JA, Udy AA, Lipman J, Roberts JA. The impact of variation in renal
■ replacement therapy settings on piperacillin, meropenem, and vancomycin drug clearance in the critically ill: an analysis of published literature and dosing regimens. Crit Care Med 2014; 42:1640–1650.
A systematic review examining the extracorporeal clearance of β-lactam for critically ill patients on continuous renal replacement therapy and describing the factors altering this drug clearance.
22. Donadello K, Roberts JA, Cristallini S, *et al.* Vancomycin population pharmacokinetics during extracorporeal membrane oxygenation therapy: a matched cohort study. Crit Care 2014; 18:632.
23. Donadello K, Antonucci E, Cristallini S, *et al.* beta-Lactam pharmacokinetics during extracorporeal membrane oxygenation therapy: a case-control study. Int J Antimicrob Agents 2015; 45:278–282.
24. Shekar K, Roberts JA, Welch S, *et al.* ASAP ECMO: Antibiotic, Sedative and Analgesic Pharmacokinetics during Extracorporeal Membrane Oxygenation: a multicentre study to optimise drug therapy during ECMO. BMC Anesthesiol 2012; 12:29.
25. De Waele JJ, Lipman J, Akova M, *et al.* Risk factors for target nonattainment during empirical treatment with beta-lactam antibiotics in critically ill patients. Intensive Care Med 2014; 40:1340–1351.
26. Carlier M, Noe M, Roberts JA, *et al.* Population pharmacokinetics and dosing simulations of cefuroxime in critically ill patients: nonstandard dosing approaches are required to achieve therapeutic exposures. J Antimicrob Chemother 2014; 69:2797–2803.
27. Jung Y, Song KH, Cho J, *et al.* Area under the concentration-time curve to minimum inhibitory concentration ratio as a predictor of vancomycin treatment outcome in methicillin-resistant Staphylococcus aureus bacteraemia. Int J Antimicrob Agents 2014; 43:179–183.

28. Carlier M, Carrette S, Roberts JA, et al. Meropenem and piperacillin/tazobactam prescribing in critically ill patients: does augmented renal clearance affect pharmacokinetic/pharmacodynamic target attainment when extended infusions are used? Crit Care 2013; 17:R84.

29. Roberts JA, Udy AA, Jarrett P, et al. Plasma and target-site subcutaneous tissue population pharmacokinetics and dosing simulations of cefazolin in posttrauma critically ill patients. J Antimicrob Chemother 2015; 70:1495–1502.

30. Roberts JA, Paul SK, Akova M, et al. DALI: defining antibiotic levels in intensive
■■ care unit patients: are current beta-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis 2014; 58:1072–1083.
First multicenter observational pharmacokinetic study that looked at the pharmacodynamic target attainment of antimicrobial administration in different ICU centers. This study also examined the clinical cure rates of different subgroups.

31. Langan KM, Jacob J, Li J, et al. Pharmacokinetics of short versus extended infusion meropenem dosing in critically ill patients: a pilot study. Crit Care Resusc 2014; 16:190–196.

32. Lips M, Siller M, Strojil J, et al. Pharmacokinetics of imipenem in critically ill patients during empirical treatment of nosocomial pneumonia: a comparison of 0.5-h and 3-h infusions. Int J Antimicrob Agents 2014; 44:358–362.

33. Lu Y, Yan Z, Wang DH, et al. Treatment study of hospital acquired pneumonia by optimizing dosing regimen of piperacillin/tazobactam: prolonged vs. regular infusion. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2013; 25:479–483.

34. Bauer KA, West JE, O'Brien JM, Goff DA. Extended-infusion cefepime reduces mortality in patients with Pseudomonas aeruginosa infections. Antimicrob Agents Chemother 2013; 57:2907–2912.

35. MacVane SH, Kuti JL, Nicolau DP. Clinical pharmacodynamics of antipseudomonal cephalosporins in patients with ventilator-associated pneumonia. Antimicrob Agents Chemother 2014; 58:1359–1364.

36. Hsaiky L, Murray KP, Kokoska L, et al. Standard versus prolonged doripenem infusion for treatment of gram-negative infections. Ann Pharmacother 2013; 47 (7–8):999–1006.

37. Teo J, Liew Y, Lee W, Kwa AL. Prolonged infusion versus intermittent boluses
■■ of beta-lactam antibiotics for treatment of acute infections: a meta-analysis. Int J Antimicrob Agents 2014; 43:403–411.
Recent meta-analysis that studies the correlation between prolonged infusion and clinical cure.

38. Roberts JA, Webb S, Paterson D, et al. A systematic review on clinical benefits of continuous administration of beta-lactam antibiotics. Crit Care Med 2009; 37:2071–2078.

39. Kasiakou SK, Sermaides GJ, Michalopoulos A, et al. Continuous versus intermittent intravenous administration of antibiotics: a meta-analysis of randomised controlled trials. Lancet Infect Dis 2005; 5:581–589.

40. Dulhunty JM, Roberts JA, Davis JS, et al. A protocol for a multicentre randomised controlled trial of continuous beta-lactam infusion compared with intermittent beta-lactam dosing in critically ill patients with severe sepsis: the BLING II study. Crit Care Resusc 2013; 15:179–185.

41. Hanrahan TP, Harlow G, Hutchinson J, et al. Vancomycin-associated nephrotoxicity in the critically ill: a retrospective multivariate regression analysis. Crit Care Med 2014; 42:2527–2536.

42. Tafelski S, Nachtigall I, Troeger U, et al. Observational clinical study on the effects of different dosing regimens on vancomycin target levels in critically ill patients: continuous versus intermittent application. J Infect Public Health 2015; 8:355–363.

43. Matsumoto K, Kanazawa N, Watanabe E, et al. Development of initial loading procedure for teicoplanin in critically ill patients with severe infections. Biol Pharm Bull 2013; 36:1024–1026.

44. de Montmollin E, Bouadma L, Gault N, et al. Predictors of insufficient amikacin peak concentration in critically ill patients receiving a 25 mg/kg total body weight regimen. Intensive Care Med 2014; 40:998–1005.

45. Sinnollareddy MG, Roberts JA, Lipman J, et al. Pharmacokinetic variability and exposures of fluconazole, anidulafungin, and caspofungin in intensive care unit patients: Data from multinational Defining Antibiotic Levels in Intensive care unit (DALI) patients Study. Crit Care 2015; 19:33.

46. Liu P, Ruhnke M, Meersseman W, et al. Pharmacokinetics of anidulafungin in critically ill patients with candidemia/invasive candidiasis. Antimicrob Agents Chemother 2013; 57:1672–1676.

47. Muilwijk EW, Schouten JA, van Leeuwen HJ, et al. Pharmacokinetics of caspofungin in ICU patients. J Antimicrob Chemother 2014; 69:3294–3299.

48. Vanstraelen K, Wauters J, Vercammen I, et al. Impact of hypoalbuminemia on voriconazole pharmacokinetics in critically ill adult patients. Antimicrob Agents Chemother 2014; 58:6782–6789.

49. Goncalves-Pereira J, Silva NE, Mateus A, et al. Assessment of pharmacokinetic changes of meropenem during therapy in septic critically ill patients. BMC Pharmacol Toxicol 2014; 15:21.

50. De Waele JJ, Carrette S, Carlier M, et al. Therapeutic drug monitoring-based
■ dose optimisation of piperacillin and meropenem: a randomised controlled trial. Intensive Care Med 2014; 40:380–387.
A randomized controlled trial that assessed the pharmacokinetic/pharmacodynamic target attainment rate for piperacillin and meropenem therapies comparing a group receiving therapeutic drug monitoring and those on normal conventional therapies.

51. Wong G, Brinkman A, Benefield RJ, et al. An international, multicentre survey of beta-lactam antibiotic therapeutic drug monitoring practice in intensive care units. J Antimicrob Chemother 2014; 69:1416–1423.

52. De Waele JJ, Danneels I, Depuydt P, et al. Factors associated with inadequate early vancomycin levels in critically ill patients treated with continuous infusion. Int J Antimicrob Agents 2013; 41:434–438.

53. Udy AA, Jarrett P, Stuart J, et al. Determining the mechanisms underlying augmented renal drug clearance in the critically ill: use of exogenous marker compounds. Crit Care 2014; 18:657.

54. Hayashi Y, Lipman J, Udy AA, et al. beta-Lactam therapeutic drug monitoring in the critically ill: optimising drug exposure in patients with fluctuating renal function and hypoalbuminaemia. Int J Antimicrob Agents 2013; 41:162–166.