Journal of Intensive Medicine 4 (2024) 287–298

Contents lists available at ScienceDirect

Journal of Intensive Medicine

journal homepage: www.elsevier.com/locate/jointm

Review

Understanding antimicrobial pharmacokinetics in critically ill patients to optimize antimicrobial therapy: A narrative review

Claire Roger[1,2,*]

[1] Department of Anesthesiology and Intensive Care, Pain and Emergency Medicine, Nîmes-Caremeau University Hospital, Nîmes, France
[2] UR UM 103 IMAGINE (Initial Management and prévention of orGan failures IN critically ill patiEnts), Faculty of Medicine, Montpellier University, Montpellier, France

ARTICLE INFO

Managing Editor: Jingling Bao/Zhiyu Wang

Keywords:
Pharmacokinetics/pharmacodynamics
ICU
Antibiotics
Dose optimization
TDM

ABSTRACT

Effective treatment of sepsis not only demands prompt administration of appropriate antimicrobials but also requires precise dosing to enhance the likelihood of patient survival. Adequate dosing refers to the administration of doses that yield therapeutic drug concentrations at the infection site. This ensures a favorable clinical and microbiological response while avoiding antibiotic-related toxicity. Therapeutic drug monitoring (TDM) is the recommended approach for attaining these goals. However, TDM is not universally available in all intensive care units (ICUs) and for all antimicrobial agents. In the absence of TDM, healthcare practitioners need to rely on several factors to make informed dosing decisions. These include the patient's clinical condition, causative pathogen, impact of organ dysfunction (requiring extracorporeal therapies), and physicochemical properties of the antimicrobials. In this context, the pharmacokinetics of antimicrobials vary considerably between different critically ill patients and within the same patient over the course of ICU stay. This variability underscores the need for individualized dosing. This review aimed to describe the main pathophysiological changes observed in critically ill patients and their impact on antimicrobial drug dosing decisions. It also aimed to provide essential practical recommendations that may aid clinicians in optimizing antimicrobial therapy among critically ill patients.

Introduction

The treatment of critically ill patients poses unique challenges to healthcare providers, particularly during the management of infections. In this context, antibiotics play a pivotal role in combating infections and improving patient outcomes. However, the pharmacokinetics (PK) and pharmacodynamics (PD) of antibiotics in these patients differ significantly from those in the general population. Understanding these pathophysiological alterations are crucial to the optimization of antibiotic therapy. Factors such as altered organ function, changes in tissue perfusion, and variations in fluid balance can significantly affect drug absorption, distribution, metabolism, and elimination. Traditional dosing regimens may therefore achieve inadequate therapeutic drug concentrations in critically ill patients. In addition, the pathophysiological condition in these patients may affect the PD of antibiotics. The achievement of optimal bactericidal effect and minimization of antibiotic resistance requires a thorough understanding of the mechanisms via which the drug interacts with the pathogen. This involves several considerations including the mechanism of action of the antibiotic, minimal inhibitory concentration (MIC) of the infecting organism, and duration of exposure.

This narrative review provides a comprehensive overview of the pathophysiological alterations occurring in critically ill patients, the main factors that influence antibiotic PK and PD in this population, challenges in dosing optimization, and strategies that healthcare providers may employ to ensure effective antibiotic therapy.

Pathophysiological Alterations in Intensive Care Unit (ICU) Patients

Drug PK may be significantly affected in the presence of pathophysiological changes that occur during critical illness. In conjunction with the strategies used for the early management of critical illness (such as administration of fluids and vasopressors), the development of systemic inflammatory response syn-

* Corresponding author: Claire Roger, Department of Anesthesiology and Intensive Care, Pain and Emergency Medicine, Nîmes-Caremeau University Hospital, Place du Professeur Robert Debré, 30029 Nîmes cedex 9, France.
E-mail address: claire.roger@chu-nimes.fr (C. Roger)

https://doi.org/10.1016/j.jointm.2023.12.007
Received 28 October 2023; Received in revised form 26 December 2023; Accepted 27 December 2023
Available online 29 February 2024

drome (in the setting of major surgery, trauma, burns, or sepsis) significantly affects the two major PK parameters related to drug dosing, namely, the volume of distribution (Vd) and drug clearance (CL).[1–3]

Changes in Vd

The development of increased vascular permeability and edema during sepsis may result in substantial transfer of fluids from the intravascular compartment to the interstitial space; this increases the Vd of antimicrobial drugs. Notably, the initial management of critical illnesses, which often involves the administration of fluids, inotropes, and vasopressors, exacerbates this phenomenon. Hydrophilic drugs (particularly β-lactams, aminoglycosides, and vancomycin) which have a low Vd are more susceptible to the impact of these pathophysiological changes. Factors such as the presence of pleural effusion, ascites, and surgical drains may further expand the Vd of these drugs.

Hypoalbuminemia is commonly found in critically ill patients, and baseline serum albumin concentrations fall below 25 g/L in over 40% of ICU patients.[4] This may lead to alterations in drug-albumin binding, particularly for drugs that are highly bound to plasma proteins and are commonly used in the ICU setting; these include ceftriaxone, cefazolin, ertapenem, echinocandins, and teicoplanin. These drugs demonstrate considerably high plasma protein binding, with levels of up to 95%. Hypoalbuminemia may therefore lead to an increase in the fraction of unbound drug in the blood; this fraction is freely distributed into tissues, further extending the Vd of these drugs. Increases in the Vd are likely to decrease the maximum plasma/serum drug concentration (Cmax) and total drug concentrations over time. This may lead to potential underdosing and provide sub-therapeutic concentrations. An increase in the dose may be necessary during the initial phase of treatment, and adjustments need to be made based on unbound drug levels.[5,6]

Changes in drug CL

Worsening of organ function with progression of the illness may lead to multiple organ dysfunction syndrome. In this context, impaired perfusion of the peripheral organs (such as the gastrointestinal tract and kidney) may hinder drug absorption and elimination. In addition, a reduction in hepatic blood flow may lead to a decrease in drug metabolism; this is particularly relevant to drugs that undergo significant hepatic metabolism and have a high extraction ratio. Chronic liver failure may further impact hepatic drug metabolism, and result in decreased drug dosing; in this context, the dosing of echinocandins is reduced in severe cirrhosis.[7]

Altered drug CL is a key determinant of maintenance dose (MD) adjustments in critically ill patients. Enhanced renal elimination, also known as augmented renal clearance (ARC), is an important phenomenon observed in critically ill patients, and may significantly affect drug PK.[8] In clinical practice, a measured urinary creatinine clearance (CrCl) value of $\geq$130 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ is most commonly used as the cut-off value for defining ARC. Hyperdynamic states resulting from fluid resuscitation and vasopressor administration may lead to increased blood flow in major organs such as the kidney, and thereby increase renal elimination. The concept of renal function reserve has also been used to explain the underlying mechanism for ARC. This concept refers to the ability of the kidneys to increase the glomerular filtration rate via nephron recruitment, increased renal blood flow, and hyperfiltration; it is seen in certain conditions such as systemic inflammatory response syndrome, trauma, burns, and pregnancy. In populations with neurological disorders, brain–kidney crosstalk has been hypothesized to be an underlying mechanism. Notably, autonomic dysregulation may result in variable alterations in both renal and cerebral perfusion, and the mutual crosstalk may enhance the overall regulation of perfusion in both organs.[9] Risk factors for the development of ARC include young age, sepsis, trauma, surgery or neurosurgery, febrile neutropenia, and burn injuries.[10] Hydrophilic drugs that are primarily cleared via the kidney may exhibit substantial changes in CL in the presence of ARC. In their study on a cohort of critically ill patients, Udy et al.[11] demonstrated a strong association between augmented creatinine CL and β-lactam underexposure. Several observational studies have also reported similar results in cases of traumatic brain injury and sepsis.[12–14]

In this context, a retrospective single-center study on critically ill patients (who were treated for hospital-acquired or ventilator-associated pneumonia [VAP]) found high-dose β-lactam regimens to be associated with improved outcomes (lower rate of therapeutic failure and recurrences) without an increase in adverse events.[15] Notably, dosing recommendations for ARC have been recently added to the package insert of new antibiotic drugs.

The methods used to assess the glomerular filtration rate warrant particular consideration. The Cockroft-Gault, Chronic Kidney Disease Epidemiology Collaboration, and Modification of Diet in Renal disease equations have been shown to underestimate renal function in critically ill patients. It is therefore essential to evaluate the measured CrCl on a daily basis to better identify ARC in patients receiving hydrophilic antibiotics (e.g., β-lactams, vancomycin, or aminoglycosides).[16–18] In this context, a recent study found that most patients who developed ARC in the cohort presented with an episode within the first week of admission; in addition, the condition developed within 3 days in half of the cases.[19] The duration of ARC varied widely, with a median and maximum time frame of 5 days and more than 1 month, respectively.[19]

Notably, altered renal elimination may also lead to varying degrees of renal impairment.

More than 50% of patients hospitalized in ICUs suffer from acute kidney injury and 20%–25% of affected individuals require renal replacement therapy (RRT) during the first week.[20] In this context, antimicrobial drug dosing is considerably more complex in patients with renal impairment. The administration of extracorporeal therapies such as RRT further adds to complexities in interpreting or predicting antimicrobial PK.[21,22] In this setting, changes to the PK depend on specific characteristics of the extracorporeal circuit, such as membrane permeability, intensity of therapy, and physicochemical properties of the drug itself (including the molecular size, degree of ionization, extent of protein binding, and hydro- or lipophilicity).[21] Residual renal function, which also contributes to drug excretion, may be an additional confounder during the calculation of optimal drug dosing in this setting.[23] As antibiotic concentrations vary widely within and between critically ill patients who receive

RRT, the selection of optimal empirical antimicrobial regimens is a complex clinical challenge in such cases. In this context, a large prospective, observational, multinational PK study demonstrated considerable variability (4–8-fold) in antibiotic dosing regimens and RRT prescriptions.[24] Median trough concentrations for meropenem and piperacillin were found to be mostly above (i.e., 12.1 mg/L and 78.6 mg/L, respectively) the recommended targets for drug efficacy (i.e., 2 mg/L and 16 mg/L, respectively). Overall, 4%–5% of cases demonstrated insufficient drug levels and 25%–35% of treated patients had excess concentrations (and were therefore at risk of potential toxicity). In a previous study on patients receiving RRT, those who were administered unadjusted regimens (similar to those used in patients with normal renal function) of broad-spectrum β-lactams showed excess levels of the drug.[25] Notably, renal impairment has been identified to be a risk factor for neurotoxicity in patients receiving unadjusted dosing regimens.[26] Alternative antimicrobials with low renal or continuous RRT-related CL should be considered where possible to limit the risk of inappropriate antimicrobial drug dosing in such settings.

Changes in drug absorption

Altered drug absorption has been previously reported in critically ill patients.[27] However, there are no clear recommendations for the management of those alterations. Critical illnesses may affect the gastrointestinal tract and lead to a decrease in intestinal peristalsis, mucosal impairment, and altered drug metabolism.[28] Enteric drug absorption and availability are difficult to predict, mainly due to fluctuations in gastric pH, loss of enteric architecture, and decreased enzymatic activity. In addition, the delay in gastric emptying extends the time needed to achieve maximum concentrations of the antibiotic. The impact of these pathophysiological alterations is illustrated by the significant decrease in the absorption of antibiotics such as ciprofloxacin in ICU patients.[29]

Changes in tissue penetration

The transport of antibiotics to tissues and subsequent distribution within tissues and cells depends on various factors including the characteristics of the drug itself, patient characteristics (e.g., obesity), disease severity, and target tissues.

Notably, different antimicrobial drugs demonstrate altered tissue penetration in critically ill patients.[30–33] As reported in the literature, the extent of these alterations varies widely among different tissues and organs.[34] In the presence of sepsis, the microcirculatory blood flow may be significantly impaired due to endothelial dysfunction and the presence of microthrombi, which decrease tissue perfusion. These alterations may lead to suboptimal antibiotic exposure at the site of infection and thereby to potential therapeutic failure, emergence of resistance, and higher morbidity.[30] Suboptimal tissue concentrations may even be found in patients with adequate plasma concentrations, as the antibiotic concentrations in plasma do not accurately reflect those in infected tissue.[31] Interestingly, clinical scoring systems such as the tissue penetration prediction score have been proposed for predicting tissue penetration of antimicrobials.[35] The main factors found to correlate with tissue penetration include oxygen saturation, serum lactate levels, and the dose per time unit of norepinephrine.[35] Although the tissue/plasma penetration ratio of antimicrobials may be an important factor for the selection of the most suitable treatment, there is currently no conclusive evidence to support the use of clinical scores for adjusting antibiotic dosing regimens. In addition, the limited availability of data pertaining to tissue penetration precludes their use in guiding antimicrobial dosing.

Changes due to extracorporeal therapies

Extracorporeal membrane oxygenation (ECMO) is an advanced life support system that is used in patients with life-threatening respiratory or cardiac failure. It provides cardiopulmonary support and can serve as a bridge to recovery, lung or heart transplantation, or the implantation of long-term ventricular assist devices. Studies have evaluated PK determinants during ECMO, and particularly the impact of the ECMO circuit on drug distribution and elimination.[36] The ECMO circuit consists of a blood pump, oxygenator, heat exchanger, and tubing; it can sequester drugs, alter apparent Vd, and affect drug CL. The degree of drug sequestration depends on physicochemical properties (lipophilicity and protein binding) and circuit factors (membrane surface area, type of tubing, oxygenator used, and priming solution), and newer technologies offer reduced risks.[37,38] Changes in apparent Vd are influenced by critical illness-related factors; the addition of an ECMO circuit leads to drug sequestration and hemodilution from the priming solution. Hemodilution is expected to have less impact on drugs with a large apparent Vd (e.g., quinolones) than on those with low Vd (e.g., β-lactams and aminoglycosides). Drug CL is generally decreased during ECMO due to reduced renal and hepatic perfusion. Estimating PK parameters during combined ECMO and RRT is therefore considerably challenging. In this context, almost half of the patients who receive ECMO require RRT; the presence of two extracorporeal circuits further adds to the complexity of drug PK.[39] An integrated approach involving mechanistic *ex vivo* experiments, animal models, and clinical studies has been employed to guide drug dosing optimization in patients receiving ECMO.[39–45]

Applying PK/PD Approaches to Optimize Antimicrobial Therapy

PK/PD targets for critically ill patients

PK/PD targets can be expressed as the Cmax/MIC, %T > MIC, or area under the curve (AUC)/MIC, depending on whether the antibiotic exhibits dose-, time-, or AUC-dependent killing. The optimal PK/PD target for guiding β-lactam dosing remains unclear. In critically ill patients, 100% of time where the free concentration is above the MIC (100% fT > MIC) is often suggested as a therapeutic target for β-lactams.[46,47] More aggressive β-lactam targets (i.e., 4–5 × MIC) have also been considered to minimize the occurrence of microbiological failure and/or resistance.[48,49] In their study, Tam et al.[50] found that a Cmin/MIC ratio of 1.7 was more commonly associated with the emergence of resistant clones than a ratio of 6 during the treatment of *Pseudomonas aeruginosa*. In a recent Italian study, a steady-state concentration/MIC ratio of ≤5 was identified as

an independent predictor of microbiological failure in critically ill patients with Gram-negative bacillary infections.[51] Consistent findings were observed in clinical trials that specifically addressed infections with a high risk of clinical or microbiological failure, such as hospital-acquired pneumonia (VAP) caused by *P. aeruginosa* and *Klebsiella pneumoniae*. These trials demonstrated improved clinical outcomes with Cmin/MIC ratio targets of >4–5.[51–53] Notably, the use of a higher target ratio is based on the considerations of tissue diffusion and technical uncertainties pertaining to MIC and β-lactam concentration measurements.[54] However, only observational studies have demonstrated higher PK/PD targets to offer improved microbiological and clinical remission without any notable impact on mortality.[51,53]

Actual MICs are considered to define the therapeutic range in documented infections. The turnaround time remains the main issue with the use of MICs. Alternatives need to be considered in the early phases of infection, when the MIC of the causative pathogen is unclear. The epidemiological cut-off (ECOFF) value, based on local ecology and the "worst-case scenario MIC" is the most common alternative used in this context. The "worst-case scenario MIC" refers to the highest MIC of susceptible pathogens that can be covered by the considered antibiotic. However, such approaches underestimate the probability of target attainment compared to actual MICs.[55,56] Notably, even the standardized method accepts standard deviations of 1–2 dilutions on a 2-logarithmic series; this leads to some degree of variability in PK/PD target attainment. On comparing these alternatives, Smekal et al.[57] found that the ECOFF MIC is the most suitable alternative. Rapid diagnostic and rapid antimicrobial susceptibility testing may help reduce turnaround times in the future, and potentially aid better tailoring of antimicrobial therapy.

Increased loading doses

As any delay in initiating adequate antibiotic therapy worsens the prognosis of septic patients, adequate drug concentrations need to be achieved in the early phases of sepsis management. However, empirical standard dosing regimens lead to subtherapeutic concentrations of different classes of antibiotics.[58–60] As the Vd of antibiotics is often increased, higher loading doses are needed for hydrophilic antimicrobials (e.g., β-lactams, vancomycin, aminoglycosides, and colistin) to achieve similar and adequate therapeutic concentrations.[61–63] New optimal β-lactam loading doses have been suggested (8 g in 3 h for piperacillin, 4 g in 3 h for ceftazidime and cefepime, and 2 g in 0.5 h for meropenem) based on population PK analysis and Monte Carlo simulations (which have gained popularity for the optimization of antibiotic dosing regimens).[61] Similarly, higher than recommended loading doses have been proposed for vancomycin, aminoglycosides, and colistin; this approach has been supported by findings from clinical validation studies, which have shown improvements in PK/PD target attainment for all three of these antibiotics.[64–67] Notably, the loading dose should not be altered in patients with renal impairment or those receiving RRT. The development of dosing nomograms may help clinicians better tailor the initial dosing of certain antibiotics (such as aminoglycosides) based on total body weight and renal CL.[68]

Optimal mode of administration of antibiotics

Continuous infusion mode

Beta-lactam antibiotics have traditionally been administered via intermittent infusions. However, an increasing body of research suggests that continuous infusions may be more effective in specific clinical situations. Studies that evaluated the continuous administration of β-lactam antibiotics have demonstrated improved outcomes including a higher rate of PK/PD target achievement, higher clinical remission rates, and superior microbiological eradication.[69,70] However, three previous meta-analyses that included randomized controlled trials (RCTs) did not demonstrate continuous β-lactam antibiotic infusions to be superior to intermittent administration in terms of survival; in this context, it is worth noting that studies performed to date have been small and underpowered, even when pooled.[71–73] A more recent meta-analysis of individual patient data from multicenter RCTs that compared continuous and intermittent infusions of β-lactam antibiotics found the hospital mortality (censored at day 30) to be lower in the continuous infusion than in the intermittent infusion group (19.6% *vs*. 26.3%; relative risk=0.74; 95% confidence interval [CI]: 0.56 to 1.00, P=0.045).[74] The most recent RCT that compared outcomes between continuous and intermittent infusions of meropenem in a cohort of 607 critically ill patients found no significant difference in terms of all-cause mortality and the emergence of pandrug- or extensively drug-resistant bacteria at day 28.[75] The results of the BLING III trial, which compared outcomes between continuous and intermittent infusions of β-lactam antibiotics in 7000 patients, are pending and will provide further information regarding the impact of mode of administration on clinical outcomes.[76] The benefits of continuous infusions have also been investigated for non-β-lactam antibiotics. In this context, observational studies have shown that continuous infusions of linezolid achieved the PK/PD targets (AUC_{24}/MIC >80 and %T > MIC >85%) in patients with ARC, those who were obese, and those with elevated MICs (2–4 mg/L).[77] Continuous infusion of linezolid was also found to be associated with improved alveolar diffusion and better clinical outcomes, in terms of clinical improvement and mortality.[78,79] However, RCTs comparing both modes of administration are lacking.

Inhaled antibiotics

Inhaled antibiotics have emerged as a potential means of treating pulmonary infections while limiting the emergence of multidrug-resistant (MDR) strains. High doses of inhaled antibiotics need to reach the infected lung parenchyma to optimize outcomes. Mesh nebulizers and specific ventilator settings that require short-acting sedation should therefore be preferred to optimize lung deposition and prevent patient-ventilator asynchrony.[80] The clinical benefit of inhaled antibiotics has been evaluated in a pairwise/network meta-analysis that included eight observational studies and RCTs, each.[81] Patients treated with inhaled antibiotics demonstrated significantly higher rates of clinical recovery (risk ratio: 1.21, 95% CI: 1.09 to 1.34; P=0.001) and microbiological eradication (risk ratio: 1.42, 95% CI: 1.22 to 1.650; P <0.0001), with no difference in terms of mortality or risk of nephrotoxicity. Two recent RCTs, namely, the INHALE and VAPORISE trials, assessed the efficacy of inhaled antibiotics (aminoglycosides and fosfomycin)

as adjunctive therapy; they failed to demonstrate any benefit of the inhaled route over standard-of-care intravenous administration in the treatment of Gram-negative bacteria (GNB) related VAP.[82,83] These trials mainly assessed the use of inhaled antibiotics as adjunctive and not substitutive therapy. However, no non-inferiority RCTs have compared inhaled polymyxins to new intravenous cephalosporins/β-lactamase inhibitor antibiotics in patients with VAP caused by MDR GNB.

Another strategy relies on the use of inhaled antibiotics to prevent, rather than to treat, VAP. In this context, a recently published RCT assessed the benefit of a 3-day course of inhaled amikacin therapy (20 mg/kg ideal body weight) in preventing VAP in mechanically ventilated patients; the study demonstrated a significant reduction in the development of the first episode of VAP (15% in the amikacin group *vs.* 22% in the placebo group, P=0.004).[84]

Therapeutic drug monitoring (TDM) and dosing software

Between-patient variability in drug response represents a critical challenge in clinical practice, and considerably complicates the identification of patients who are most likely to obtain benefits and experience adverse effects. Different doses may need to be tested before the best "fit" is determined for a particular patient. However, this approach is time-consuming and may occasionally frustrate healthcare professionals. Various strategies have emerged over the past few decades to address these challenges. Dosing nomograms and TDM had initially been introduced as pioneering solutions for optimizing drug dosages. The concept of model-informed precision dosing (MIPD) is a recently developed innovative approach.

Three narrative reviews and one systematic review and meta-analysis have recently evaluated the compelling subject of TDM for β-lactam antibiotics in critically ill patients.[85–88] Two of these reviews focused on the effect of TDM on clinical outcomes, with particular emphasis on mortality rates and the emergence of antimicrobial resistance.[87,88] Notably, neither of these comprehensive reviews found a significant association between the use of TDM for β-lactam antibiotics and either mortality or the development of antimicrobial resistance. It is worth noting, however, that certain risks of bias, categorized as critical to serious in severity, may have influenced the findings. This bias was predominantly related to non-adherence to TDM recommendations, deviation from intended intervention, and confounding. Additionally, prospective RCTs were lacking in both these reviews and the studies primarily focused on special populations (septic patients with normal renal function, those with burns, and neutropenic patients).[89] Notably, patients receiving RRT and those exhibiting ARC were not included in these investigations; however, both these factors have considerable association with inappropriate β-lactam exposure.

In the most recent RCT, Hagel et al.[90] included a substantial sCle (n=249) from multiple centers. The study focused solely on the use of piperacillin for empirical therapy, and the PK/PD target was based on the MIC of *P. aeruginosa*. The primary outcome, namely, the difference in mean sequential organ failure assessment scores with and without TDM, did not demonstrate significance (P=0.39).[90] Although TDM lowered the mortality rate by 4.2%, and offered a higher rate of microbiological and clinical remission, these differences were not statistically significant. TDM offered better achievement of target concentrations, thereby resulting in less underdosing. However, the optimal target (without overdosing) was achieved in less than 50% of patients within the first 5 days, with the nadir occurring on the first day.[90] The authors of the study attributed the lack of mortality benefit to the high PK/PD target (particularly on the first day), which was based on a relatively high MIC of piperacillin (16 mg/L) for *P. aeruginosa*. However, as most identified bacteria had lower MIC values, failure to achieve the target did not lead to poor outcomes. Few studies have compared the setting of an *a priori* PK/PD target (based on a worst-case scenario with high MIC, mainly for empirical therapy) to *a posteriori* MIC, as determined after bacterial identification. In their study, Leon et al.[91] demonstrated an increase in PK/PD target attainment in critically ill patients with intra-abdominal infections, both before (33%) and after bacterial documentation (71%). This highlights the critical role of MIC selection in defining the PK/PD target for therapy.[92] A notable distinction between clinical studies and daily practice is the delay in obtaining TDM results, which are typically accessible within a few hours after sample collection in clinical studies. However, a recent survey on TDM practices in real-world healthcare settings has demonstrated the delay in response time to be a significant barrier, and has identified it to be the primary obstacle to the effective implementation of TDM.[93] The survey also identified the interpretation of TDM results to be a second major challenge, especially in non-expert centers. Two factors need to be prioritized to reduce discrepancies between clinical study findings and everyday clinical practice; these include the reduction of turnaround time for TDM results and the improvement of support for result interpretation.

Monitoring the side effects of antibiotics

A growing body of evidence highlights the potential for significant toxicity with β-lactam antibiotics, particularly in specific populations such as those in the ICU.[94] TDM is deemed to be essential for mitigating the risk of excessive β-lactam exposure, which leads to toxicities. Given that the thresholds for dose-dependent β-lactam toxicity are generally on the higher side, this approach allows for the initial use of higher empirical dosing regimens, which can then be revised based on TDM. Recent studies have demonstrated the pivotal role of TDM in minimizing non-β-lactam antimicrobial-related toxicity.[95] In a retrospective study that included 93 patients, higher-than-licensed doses based on TDM did not result in excessive drug toxicity for either meropenem or piperacillin-tazobactam; this was observed despite the administration of more than 40% higher mean daily doses in the high-dose groups.[96] Nevertheless, the absence of well-established toxicity thresholds for β-lactams represents a major challenge to the implementation of TDM-based dosing adjustments for limiting toxicity. Efforts to define toxicodynamic targets are therefore urgently needed. In this context, some studies have focused on the relationship between β-lactam concentrations and neurotoxicity in the intensive care setting. For instance, a study found cefepime trough concentrations of above 22 mg/L (when administered via intermittent infusions) or steady-state concentrations of above 35 mg/L (with continuous infusion) to be associated with neurotoxicity in 50% of patients.[97,98] Similar risks have been reported for trough concentrations exceeding 64 mg/L for meropenem, 125 mg/L

for flucloxacillin, and 360 mg/L for piperacillin (when not used with tazobactam).[99] In addition, a steady-state plasma concentration of piperacillin exceeding 157 mg/L (when administered in combination with tazobactam) has been found to be predictive of neurological disorders in ICU patients with a specificity of 97% and a sensitivity of 52%.[100] Notably, a study found that in cases where the minimum free concentration normalized to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoint for *P. aeruginosa* (i.e., fCmin/MIC *P. aeruginosa* ratio) exceeded a value of 8, approximately half of ICU patients treated with piperacillin/tazobactam and two-thirds of those treated with meropenem demonstrated a significant deterioration in neurological status.[101] In this context, an ongoing prospective clinical trial, namely, the OPTIMAL TDM study (NCT03790631), aims to establish toxicity thresholds for cefepime, imipenem, meropenem, piperacillin, flucloxacillin, amoxicillin, and ceftazidime. However, the potential impact of TDM-guided dosing adjustments on the prevention of β-lactam toxicity and improvement of clinical outcomes remains to be determined.

New and Old Antibiotics in Critically Ill Patients

Repositioning old antibiotics

There has been renewed interest in old antibiotics to address the increase in bacterial resistance to commonly used antibacterial drugs (Table 1). As some old antibiotics show in vitro activity against MDR bacteria, these drugs may represent an alternative approach to treating these infections. However, clinical indications and dosing recommendations described in the product information have not been revised and may not be appropriate for critically ill patients.[102]

Colistin

Different formulations and conventions are currently used to describe doses of polymyxins (international unit or mg of colistin base activity) worldwide; this leads to some uncertainties regarding their optimal use in the clinic. Unlike polymyxin B, colistin is administered intravenously, as the inactive prodrug colistin methanesulfonate sodium (CMS) is transformed into various derivatives before being converted to colistin. The time to achieve therapeutic plasma colistin concentrations is longer compared to that of polymyxin B. Studies have found high inter- and intra-individual variations in colistin PK, which result in highly variable plasma concentrations following administration of the same dosing regimen.[66,103–105]

International consensus guidelines have therefore provided therapeutic recommendations to guide the optimal clinical use of polymyxins.[106] A recent systematic review that included population PK studies and prospective clinical trials on colistin has also highlighted the need for individualized dosing regimens and TDM for critically ill patients, based on the narrow therapeutic index of the drug and wide inter-individual

Table 1
PK and dosing of repurposed antimicrobial agents.

Antimicrobial agents	Spectrum of activity	Dosing regimens in ICU	Factors affecting PK	Protein binding	PK/PD targets	TDM recommended
Colistin[106,107]	Enterobacterales MDR/XDR *Pseudomonas aeruginosa* MDR/XDR *Acinetobacter baumannii*	LD: 9 MUI* MD: 4.5 MUI/12 h	• Renal function • RRT -CVVHD-related CL: 41% for CMS, 28% for colistin CVVHD: LD 9 MUI, MD 3 MUI/8 h -CVVHDF: 50%	40%	$AUC24h_{ss}$/MIC=50 mg/h/L ⇔Css=2 mg/L (total drug) EUCAST susceptible breakpoint: ≤2 mg/L for EB, PA, AB CLSI breakpoint: *S* ≤2, *R* >4 mg/L ECOFF: 2 mg/L (EB, AB), 4 mg/L (PA)	Yes
Fosfomycin (combination therapy)[115,117–120]	MDR/XDR *Pseudomonas aeruginosa* MDR/XDR *Acinetobacter baumannii* ESBL-E NDM KPC	LD: 8 g MD: CI 16–24 g/24 h Alternative: 8 g/8 h over 1–4 h	• Renal function • RRT -CVVHD: 28.7% reduction in AUC 4 g/6 h if CrCl >90 mL/min 5 g/8 h if CrCl >50 mL/min 4 g/8 h in anuric patients -PIRRT: 5 g/8 h	Negligible	AUC_{0-24}/MIC ≥21.5 for CRE $fAUC_{0-24}$/MIC ≥40.8 for MDR PA EUCAST breakpoint: 32 mg/L, CLSI breakpoint: 64 mg/L ECOFF: 128 mg/L (KP), 256 mg/L (PA), 512 mg/L (AB)	Yes
Temocillin[122,125]	Enterobacterales: ESBL-E AmpC KPC	LD: 2 g MD: CI 6 g/24 h	• Renal function • RRT -IHD: IHD-related CL ~55% 1.5–3 g based on interdialytic period	~80%	EUCAST breakpoints: *S* ≤0.001 mg/L, *R* >16 mg/L ECOFF: 16 mg/L (*E. coli*), 8 mg/L (KP) for UTI	Yes for infections outside the urinary tract

* 1 million IU corresponds to ~33 mg CBA, and to ~80 mg of the chemical CMS.

AB: *Acinetobacter baumannii*; AmpC: AmpC cephalosporinase; AUC: Area under the curve; CI: Confidence interval; CL: Clearance; CLSI: Clinical & Laboratory Standards Institute; CMS: Colistin methanesulfonate sodium; CrCl: Creatinine clearance; Css: Steady-state concentration; CVVHD: Continuous veno venous hemodialysis; CVVHDF: Continuous veno venous hemodiafiltration; *E. coli*: *Escherichia coli*; EB: Enterobacterales; ECOFF: Epidemiological cut-off; ESBL-E: Extended-Spectrum BetaLactamases; EUCAST: European Committee on Antimicrobial Susceptibility Testing; ICU: Intensive care unit; IHD: Intermittent hemodialysis; KP: *Klebsiella pneumoniae*; KPC: *Klebsiella pneumoniae* carbapenemase-producing Enterobacterales; LD: Loading dose; MD: Maintenance dose; MDR: Multidrug-resistant; MIC: Minimal inhibitory concentration; NDM: New Delhi Metallo BetaLactamases; PA: *Pseudomonas aeruginosa*; PD: Pharmacodynamics; PIRRT: Prolonged intermittent renal replacement therapy; PK: Pharmacokinetics; RRT: Renal replacement therapy; TDM: Therapeutic Drug Monitoring; UTI: Urinary tract infection; XDR: Extensively drug-resistant.

variability.[107] A CMS loading dose of 9 MIU (300 mg colistin base activity over 0.5–1 h has been recommended, followed by the administration of the first MD 12–24 h later. The international consensus guidelines have suggested adjustments to the MD based on renal function and TDM.[106] Notably, the conversion of the CMS fraction into colistin increases by 33%, 50%, and 67% for CrCl values of 120 mL/min, 50 mL/min, and 25 mL/min, respectively; this results in higher colistin concentrations among patients with impaired renal function. TDM is not widely available for colistin, as precautions need to be taken to ensure that sample collection, handling, and analysis are conducted appropriately to minimize *ex vivo* conversion of CMS to colistin. Preliminary data of TDM for CMS and colistin in critically ill patients show poor correlation between CMS and colistin concentrations; they also indicate a risk of both under and overdosing during the administration of guideline-based dosing regimens.[108] The use of colistin without TDM may be unsafe in critically ill patients (especially in those infected with pathogens that exhibit high MICs and having normal renal function).

Fosfomycin

The repurposing of fosfomycin combinations (based on its activity against MDR Enterobacterales and non-fermenting GNB) represents an important strategy for addressing the threat of antimicrobial resistance.[109–111] Fosfomycin is a hydrophilic drug which demonstrates low protein binding, low molecular weight, and extensive penetration into various tissues. Different intravenous formulations are available, and fosfomycin disodium is used in several countries other than the United States. However, several population PK studies have shown considerable intra- and inter-individual variability; the findings suggest that critically ill patients are exposed to inappropriate plasma concentrations when standard dosing is applied.[112–114] Experimental and in vitro studies on MDR pathogens have defined the 24-h area under the plasma drug concentration–time curve over the MIC ($AUC_{0–24}$/MIC) to be the best PK/PD index for fosfomycin.[115,116] Based on findings from Monte Carlo simulations, new dosing regimens involving prolonged and continuous infusions have been suggested to achieve optimal exposure in critically ill patients with carbapenem-resistant *Enterobacteriaceae* and carbapenem-resistant *P. aeruginosa* infections and those undergoing RRT.[113,114,117–120] The use of prolonged infusion may also decrease the risk of fosfomycin-related severe hypokalemia.[121]

Temocillin

Temocillin, a 6-a-methoxy derivative of ticarcillin, is an old antibiotic that is licensed in different European countries (including the United Kingdom, Belgium, Luxembourg, and France) for infections of the urinary tract, bloodstream, and lower respiratory tract. Its use has been limited by issues related to clinical breakpoints and optimal therapeutic regimens. The EUCAST has recently defined clinical breakpoints exclusively for urinary tract infections (UTI) ($S \leq 0.001$, $R > 16$ mg/L); other sites of infection have been excluded from its recommendations due to the lack of clinical and PK data.

Despite these limitations, a renew of interest due to its restricted spectrum to Enterobacterales including bacterial activity against ESBL, AmpC, and KPC-producing Enterobacterales has emerged in the last years.

Available PK data in critically ill patients show high inter-individual variability and efficacy with a 6-g daily continuous infusion (after a 2 g loading dose) across various sites of infection.[122–124] A population PK analysis of temocillin (in plasma and epithelial lining fluid) from patients with severe pneumonia has shown a lung penetration ratio of 0.73; it also demonstrated higher target attainment with continuous infusions of temocillin. However, on administering the 6-g daily regimen, the breakpoints in plasma and epithelial lining fluid were found to be 2 mg/L for intermittent infusions and 4 mg/L for continuous infusions; these values are well below the breakpoint of 8 mg/L, which has been established for systemic infections.[123] In intra-abdominal infections, population PK analysis demonstrated a risk of underdosing in patients with ascites and preserved renal function.[124] Higher (continuous infusions of 8 g/day) dosing may be necessary to achieve PK/PD targets in this population; however, robust clinical data are needed for these cases.[124] Adjusted drug dosing is also required for critically ill patients who are receiving RRT.[125] Temocillin needs to be administered with caution for severe infections in sites other than the urinary tract. In addition, MIC determination and TDM should be considered to ensure optimal temocillin exposure in critically ill patients.

New antibiotics

New antimicrobial drugs have been developed over the past decade to address the threat of antimicrobial resistance. These mostly include combinations of a β-lactam and a β-lactamase inhibitor.

The preservation of such an armamentarium requires in-depth knowledge of the microbiological spectrum of activity, PK/PD properties, and clinical study results for each drug. Several recently published reviews have addressed these issues.[126–130] The characteristics of new antimicrobials that are used in critically ill patients are summarized in Table 2.[131–136]

Future Perspectives and Conclusion

Due to the considerable and frequently unpredictable variability in PK among critically ill patients, it is essential to adopt a personalized approach for antimicrobial dosing in this population. Although TDM is of value for making precise dose adjustments based on individual patient requirements, it is not universally available for most antimicrobial agents.[93] In addition, TDM does not provide guidance for initial empirical drug dosing, which has been demonstrated to have a significant impact on crucial outcomes (such as mortality in cases of septic shock). Clinicians therefore need to predict drug distribution patterns and the likelihood of achieving adequate drug concentrations at the infection site; this creates a particular challenge in the clinic. Clinical prediction is based on the complex interplay between patient physiological characteristics, underlying diseases, physicochemical properties of the drug, and the influence of any extracorporeal treatments used (Figure 1).

Several approaches are being investigated for better tailoring of antimicrobial drug doses in critically ill patients. At the early phase of sepsis, the rapid determination of the causative pathogen susceptibility profile and MIC, through rapid diagnostic tools is emerging and can quickly inform clinicians on the

Table 2
PK and dosing considerations of new antibiotics.

Antimicrobial agents	Spectrum of activity							Dosing regimens in ICU	Factors affecting PK	Protein binding	PK/PD targets
	ESBL	AmpC	KPC	OXA-48	NDM	XDR/MDR PA	XDR/MDR AB				
Ceftolozane tazobactam[131]	√	√	✗	✗	✗	√	✗	Pneumonia: 3 g/8 h Other sites: 1.5 g/8 h	• Renal function -ARC: 1.5 g LD, MD: 4.5 g/24 h CI -CrCl >50: 1.5–3 g/8 h -CrCl 30–50: 0.75–1.5 g/8 h -CrCl 15–29: 0.375–0.75 g/8 h -CrCl <15: LD 0.375–0.75 g, MD: 0.15–0.30 g/8 h • RRT IHD: LD 0.375–0.75 g, MD: 0.15–0.30 g/8 h CRRT: 0.5–1 g/8 h	21%/30%	30% fT > MIC 20% fT > CT of 1 mg/L
Ceftazidime avibactam[130]	√	√	√	√	✗	√	✗	2.5 g/8 h	• Renal function -ARC: NA -CrCl >50: 2.5 g/8 h -CrCl 31–50: 1.25 g/8 h -CrCl 16–30: 0.9375 g/12 h -CrCl 6–15: 0.9375 g/24 h • RRT IHD: 0.9375 g/48 h CRRT: 1.25 g/8 h	<10%/5%–8%	50% fT > MIC 50% fT > CT of 1 mg/L
Cefiderocol[132,133]	√	√	√	√	√	√	√	2 g/8 h over 2 h	• Renal function -ARC: 2 g/6 h -CrCl 60–120: 2 g/8 h -CrCl 30–59: 1.5 g/8 h -CrCl 15–29: 1 g/8 h -CrCl <15: 0.75 g/12 h • RRT -IHD: 0.75 g/12 h -CVVH: dosing adjusted to effluent rate 1 L/h: 1.5 g/12 h 2 L/h: 2 g/12 h 3 L/h: 1.5 g/8 h ≥4 L/h: 2 g/8 h	40%–60%	75% fT > MIC
Aztreonam avibactam[134]	√	√	√	√	√	√	✗	LD: 0.5 g/0.167 g MD: 1.5 g/0.5 g/6 h	NA	56%/8%	60% fT > MIC 50% fT > CT
Imipenem relebactam[126,135]	√	√	√	✗	✗	√	✗	1.25 g/6 h	• Renal function -CrCl 90–150: 1.25 g/6 h -CrCl 60–89: 1 g/6 h -CrCl 30–59: 0.75 g/6 h -CrCl 15–29: 0.5 g/6 h • RRT -IHD: 0.5 g/6 h -CRRT: NA	20%/22%	40% fT > MIC fAUC/MIC=7.5
Meropenem vaborbactam[130,136]	√	√	√	✗	✗	✗	✗	4 g/8 h over 3 h	• Renal function -CrCl >40: 4 g/8 h -CrCl 20–39: 2 g/8 h -CrCl 10–19: 2 g/12 h -CrCl <10: 1 g/12 h • RRT -CVVHD: 2 g/8 h	2%/33%	45% fT > MIC fAUC/MIC ≥18–24

AB: *Acinetobacter baumannii*; AmpC: AmpC cephalosporinase; ARC: Augmented renal clearance; AUC: Area under the curve; CI: Confidence interval; CrCl: Creatinine clearance; CT: Threshold of concentration; CVVH: Continuous venovenous hemofiltration; CVVHD: Continuous veno venous hemodialysis; ESBL-E: Extended-Spectrum BetaLactamases; ICU: Intensive care unit; IHD: Intermittent hemodialysis; KPC: *Klebsiella pneumoniae* carbapenemase-producing Enterobacterales; LD: Loading dose; MD: Maintenance dose; MDR: Multidrug-resistant; MIC: Minimal inhibitory concentration; NA: Not available. NDM: New Delhi Metallo BetaLactamases; OXA-48: OXA-48 carbapenemase; PA: *Pseudomonas aeruginosa*; PD: Pharmacodynamics; PK: Pharmacokinetics; RRT: Renal replacement therapy; XDR: Extensively drug-resistant.

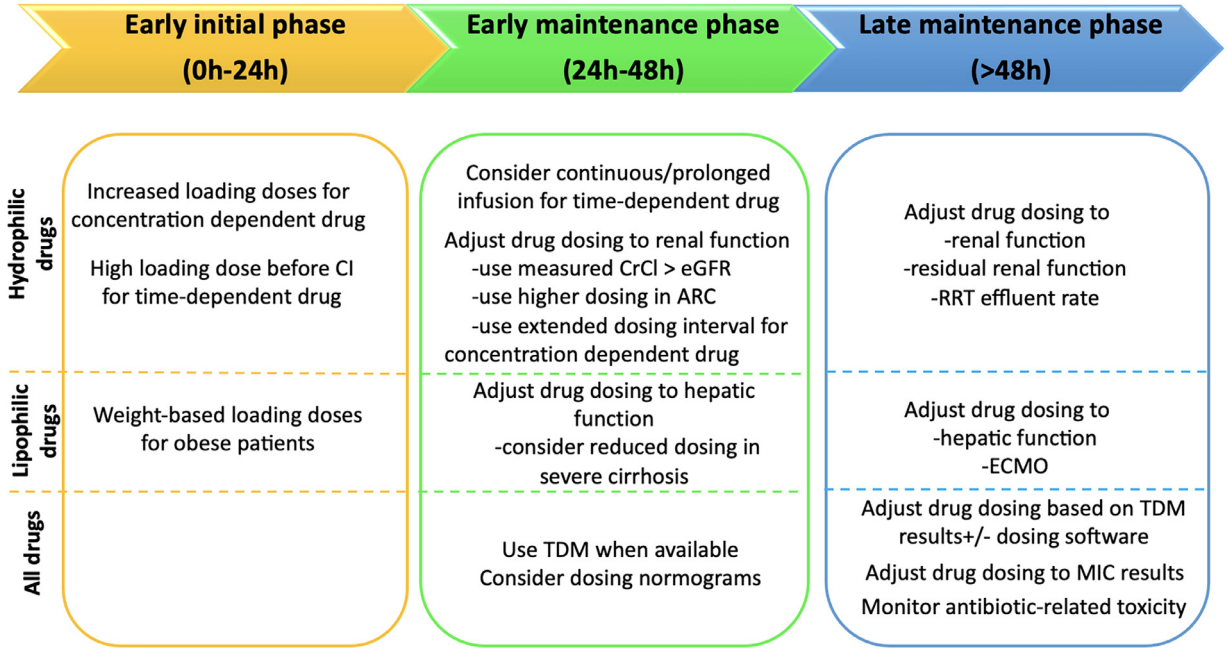

Figure 1. Drug dosing optimization across the antimicrobial course.
ARC: Augmented renal clearance; Cl: Clearance; CrCl: Creatinine clearance; ECMO: Extracorporeal membrane oxygenation; eGFR: Estimated glomerular filtration rate; MIC: Minimal inhibitory concentration; RRT: Renal replacement therapy; TDM: Therapeutic drug monitoring.

need for higher dosing regimens in case of resistant strains. In addition, MIPD has recently emerged as an approach for optimizing antimicrobial dosing in critically ill patients. It aims to improve therapeutic outcomes by achieving an optimal balance between efficacy and toxicity in the individual patient. The approach involves the application of mathematical and statistical algorithms that simultaneously integrate patient covariates (i.e., *a priori* prediction) and individual drug concentration measurements (i.e., *a posteriori* prediction or Bayesian forecasting). Although the use of these models is often perceived as sophisticated and complicated, they may be integrated into clinical practice via software tools. In addition to supporting clinical decision-making (regarding therapeutic individualization), they may improve bedside implementation. Preliminary studies have shown that the implementation of MIPD for vancomycin dose adaptation has helped reduce the incidence of vancomycin-associated nephrotoxicity; it was also found to be a cost-effective approach for preventing nephrotoxicity in patients with renal impairment.[95,137,138] In conclusion, well-designed prospective clinical trials are needed to determine the benefits of precision dosing for β-lactams.

Author Contributions

Claire Roger: Writing – original draft, Supervision, Methodology, Data curation, Conceptualization.

Acknowledgements

None.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics Statement

Not applicable.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

References

[1] Roberts JA, Taccone FS, Lipman J. Understanding PK/PD. Intensive Care Med 2016;42(11):1797–800. doi:10.1007/s00134-015-4032-6.
[2] Veiga RP, Paiva JA. Pharmacokinetics-pharmacodynamics issues relevant for the clinical use of beta-lactam antibiotics in critically ill patients. Crit Care 2018;22(1):233. doi:10.1186/s13054-018-2155-1.
[3] Jamal JA, Roger C, Roberts JA. Understanding the impact of pathophysiological alterations during critical illness on drug pharmacokinetics. Anaesth Crit Care Pain Med 2018;37(6):515–17. doi:10.1016/j.accpm.2018.10.006.
[4] Finfer S, Bellomo R, McEvoy S, Lo SK, Myburgh J, et al., SAFE Study Investigators Effect of baseline serum albumin concentration on outcome of resuscitation with albumin or saline in patients in intensive care units: analysis of data from the saline versus albumin fluid evaluation (SAFE) study. BMJ 2006;333(7577):1044. doi:10.1136/bmj.38985.398704.7C.
[5] Ulldemolins M, Roberts JA, Rello J, Paterson DL, Lipman J. The effects of hypoalbuminaemia on optimizing antibacterial dosing in critically ill patients. Clin Pharmacokinet 2011;50(2):99–110. doi:10.2165/11539220-000000000-00000.
[6] Bukkems LH, Roger C, Hodiamont CJ, Lefrant JY, Juffermans NP, Roberts JA, et al. Predictive performance of a gentamicin population pharmacokinetic model in two western populations of critically ill patients. Int J Antimicrob Agents 2018;52(2):218–25. doi:10.1016/j.ijantimicag.2018.04.016.
[7] Ewoldt TM, Abdulla A, Hunfeld N, Li L, Smeets TJL, Gommers D, et al. The impact of sepsis on hepatic drug metabolism in critically ill patients: a narrative review. Expert Opin Drug Metab Toxicol 2022;18(6):413–21. doi:10.1080/17425255.2022.2106215.

[8] Udy AA, Roberts JA, Lipman J. Implications of augmented renal clearance in critically ill patients. Nat Rev Nephrol 2011;7(9):539–43. doi:10.1038/nrneph.2011.92.
[9] Silva CM, Baptista JP, Santos I, Martins P. Recommended antibiotic dosage regimens in critically ill patients with augmented renal clearance: a systematic review. Int J Antimicrob Agents 2022;59(5):106569. doi:10.1016/j.ijantimicag.2022.106569.
[10] Khalid F, Yang GL, McGuire JL, Robson MJ, Foreman B, Ngwenya LB, et al. Autonomic dysfunction following traumatic brain injury: translational insights. Neurosurg Focus 2019;47(5):E8. doi:10.3171/2019.8.FOCUS19517.
[11] Udy AA, Varghese JM, Altukroni M, Briscoe S, McWhinney BC, Ungerer JP, 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(1):30–9. doi:10.1378/chest.11-1671.
[12] Carrie C, Bentejac M, Cottenceau V, Masson F, Petit L, Cochard JF, et al. Association between augmented renal clearance and clinical failure of antibiotic treatment in brain-injured patients with ventilator-acquired pneumonia: a preliminary study. Anaesth Crit Care Pain Med 2018;37(1):35–41. doi:10.1016/j.accpm.2017.06.006.
[13] Carrié C, Petit L, d'Houdain N, Sauvage N, Cottenceau V, Lafitte M, et al. Association between augmented renal clearance, antibiotic exposure and clinical outcome in critically ill septic patients receiving high doses of beta-lactams administered by continuous infusion: a prospective observational study. Int J Antimicrob Agents 2018;51(3):443–9. doi:10.1016/j.ijantimicag.2017.11.013.
[14] Jacobs A, Taccone FS, Roberts JA, Jacobs F, Cotton F, Wolff F, et al. Beta-lactam dosage regimens in septic patients with augmented renal clearance. Antimicrob Agents Chemother 2018;62(9):e02517–34. doi:10.1128/AAC.02534-17.
[15] Carrie C, Chadefaux G, Sauvage N, de Courson H, Petit L, Nouette-Gaulain K, et al. Increased beta-lactams dosing regimens improve clinical outcome in critically ill patients with augmented renal clearance treated for a first episode of hospital or ventilator-acquired pneumonia: a before and after study. Crit Care 2019;23(1):379. doi:10.1186/s13054-019-2621-4.
[16] Baptista JP, Neves M, Rodrigues L, Teixeira L, Pinho J, Pimentel J. Accuracy of the estimation of glomerular filtration rate within a population of critically ill patients. J Nephrol 2014;27(4):403–10. doi:10.1007/s40620-013-0036-x.
[17] Baptista JP, Udy AA, Sousa E, Pimentel J, Wang L, Roberts JA, et al. A comparison of estimates of glomerular filtration in critically ill patients with augmented renal clearance. Crit Care 2011;15(3):R139. doi:10.1186/cc10262.
[18] Gijsen M, Wilmer A, Meyfroidt G, Wauters J, Spriet I. Can augmented renal clearance be detected using estimators of glomerular filtration rate? Crit Care 2020;24(1):359. doi:10.1186/s13054-020-03057-4.
[19] Mikami R, Hayakawa M, Imai S, Sugawara M, Takekuma Y. Onset timing and duration of augmented renal clearance in a mixed intensive care unit. J Intensive Care 2023;11(1):13. doi:10.1186/s40560-023-00660-9.
[20] Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med 2015;41(8):1411–23. doi:10.1007/s00134-015-3934-7.
[21] Fiore M, Peluso L, Taccone FS, Hites M. The impact of continuous renal replacement therapy on antibiotic pharmacokinetics in critically ill patients. Expert Opin Drug Metab Toxicol 2021;17(5):543–54. doi:10.1080/17425255.2021.1902985.
[22] Kanji S, Roger C, Taccone FS, Muller L. Practical considerations for individualizing drug dosing in critically ill adults receiving renal replacement therapy. Pharmacotherapy 2023;43(11):1194–205. doi:10.1002/phar.2858.
[23] Lowenstein J, Grantham JJ. Residual renal function: a paradigm shift. Kidney Int 2017;91(3):561–5. doi:10.1016/j.kint.2016.09.052.
[24] Roberts JA, Joynt GM, Lee A, Choi G, Bellomo R, Kanji S, et al. The effect of renal replacement therapy and antibiotic dose on antibiotic concentrations in critically ill patients: data from the multinational sampling antibiotics in renal replacement therapy study. Clin Infect Dis 2021;72(8):1369–78. doi:10.1093/cid/ciaa224.
[25] Beumier M, Casu GS, Hites M, Seyler L, Cotton F, Vincent JL, et al. Beta-lactam antibiotic concentrations during continuous renal replacement therapy. Crit Care 2014;18(3):R105. doi:10.1186/cc13886.
[26] Fugate JE, Kalimullah EA, Hocker SE, Clark SL, Wijdicks EF, Rabinstein AA. Cefepime neurotoxicity in the intensive care unit: a cause of severe, underappreciated encephalopathy. Crit Care 2013;17(6):R264. doi:10.1186/cc13094.
[27] Roberts DJ, Hall RI. Drug absorption, distribution, metabolism and excretion considerations in critically ill adults. Expert Opin Drug Metab Toxicol 2013;9(9):1067–84. doi:10.1517/17425255.2013.799137.
[28] Mouly S, Meune C, Bergmann JF. Mini-series: I. Basic science. Uncertainty and inaccuracy of predicting CYP-mediated in vivo drug interactions in the ICU from in vitro models: focus on CYP3A4. Intensive Care Med 2009;35(3):417–29. doi:10.1007/s00134-008-1384-1.
[29] Mimoz O, Binter V, Jacolot A, Edouard A, Tod M, Petitjean O, et al. Pharmacokinetics and absolute bioavailability of ciprofloxacin administered through a nasogastric tube with continuous enteral feeding to critically ill patients. Intensive Care Med 1998;24(10):1047–51. doi:10.1007/s001340050714.
[30] Joukhadar C, Frossard M, Mayer BX, Brunner M, Klein N, Siostrzonek P, et al. Impaired target site penetration of beta-lactams may account for therapeutic failure in patients with septic shock. Crit Care Med 2001;29(2):385–91. doi:10.1097/00003246-200102000-00030.
[31] Sinnollareddy MG, Roberts MS, Lipman J, Lassig-Smith M, Starr T, Robertson T, et al. In vivo microdialysis to determine subcutaneous interstitial fluid penetration and pharmacokinetics of fluconazole in intensive care unit patients with sepsis. Antimicrob Agents Chemother 2016;60(2):827–32. doi:10.1128/AAC.02461-15.
[32] Mouton JW, Theuretzbacher U, Craig WA, Tulkens PM, Derendorf H, Cars O. Tissue concentrations: do we ever learn? J Antimicrob Chemother 2008;61(2):235–7. doi:10.1093/jac/dkm476.
[33] Tegeder I, Schmidtko A, Brautigam L, Kirschbaum A, Geisslinger G, Lotsch J. Tissue distribution of imipenem in critically ill patients. Clin Pharmacol Ther 2002;71(5):325–33. doi:10.1067/mcp.2002.122526.
[34] Viaggi B, Cangialosi A, Langer M, Olivieri C, Gori A, Corona A, et al. Tissue penetration of antimicrobials in intensive care unit patients: a systematic review-part II. Antibiotics (Basel) 2022;11(9):1193. doi:10.3390/antibiotics11091193.
[35] Zeitlinger BS, Zeitlinger M, Leitner I, Muller M, Joukhadar C. Clinical scoring system for the prediction of target site penetration of antimicrobials in patients with sepsis. Clin Pharmacokinet 2007;46(1):75–83. doi:10.2165/00003088-200746010-00004.
[36] Wildschut ED, Ahsman MJ, Allegaert K, Mathot RA, Tibboel D. Determinants of drug absorption in different ECMO circuits. Intensive Care Med 2010;36(12):2109–16. doi:10.1007/s00134-010-2041-z.
[37] Park J, Shin DA, Lee S, Cho YJ, Jheon S, Lee JC, et al. Investigation of key circuit constituents affecting drug sequestration during extracorporeal membrane oxygenation treatment. ASAIO J 2017;63(3):293–8. doi:10.1097/MAT.0000000000000489.
[38] Shekar K, Roberts JA, McDonald CI, Ghassabian S, Anstey C, Wallis SC, et al. Protein-bound drugs are prone to sequestration in the extracorporeal membrane oxygenation circuit: results from an ex vivo study. Crit Care 2015;19(1):164. doi:10.1186/s13054-015-0891-z.
[39] Roberts JA, Bellomo R, Cotta MO, Koch BCP, Lyster H, Ostermann M, et al. Machines that help machines to help patients: optimising antimicrobial dosing in patients receiving extracorporeal membrane oxygenation and renal replacement therapy using dosing software. Intensive Care Med 2022;48(10):1338–51. doi:10.1007/s00134-022-06847-2.
[40] Shekar K, Roberts JA, Barnett AG, Diab S, Wallis SC, Fung YL, et al. Can physicochemical properties of antimicrobials be used to predict their pharmacokinetics during extracorporeal membrane oxygenation? Illustrative data from ovine models. Crit Care 2015;19:437. doi:10.1186/s13054-015-1151-y.
[41] Cheng V, Abdul-Aziz MH, Burrows F, Buscher H, Cho YJ, Corley A, et al. Population pharmacokinetics of vancomycin in critically ill adult patients receiving extracorporeal membrane oxygenation (an ASAP ECMO study). Antimicrob Agents Chemother 2022;66(1):e0137721. doi:10.1128/AAC.01377-21.
[42] Cheng V, Abdul-Aziz MH, Burrows F, Buscher H, Cho YJ, Corley A, et al. Population pharmacokinetics and dosing simulations of ceftriaxone in critically ill patients receiving extracorporeal membrane oxygenation (an ASAP ECMO study). Clin Pharmacokinet 2022;61(6):847–56. doi:10.1007/s40262-021-01106-x.
[43] Cheng V, Abdul-Aziz MH, Burrows F, Buscher H, Cho YJ, Corley A, et al. Population pharmacokinetics of piperacillin and tazobactam in critically ill patients receiving extracorporeal membrane oxygenation: an ASAP ECMO study. Antimicrob Agents Chemother 2021;65(11):e0143821. doi:10.1128/AAC.01438-21.
[44] Donadello K, Antonucci E, Cristallini S, Roberts JA, Beumier M, Scolletta S, et al. beta-Lactam pharmacokinetics during extracorporeal membrane oxygenation therapy: a case-control study. Int J Antimicrob Agents 2015;45(3):278–82. doi:10.1016/j.ijantimicag.2014.11.005.
[45] Shekar K, Roberts JA, Smith MT, Fung YL, Fraser JF. The ECMO PK project: an incremental research approach to advance understanding of the pharmacokinetic alterations and improve patient outcomes during extracorporeal membrane oxygenation. BMC Anesthesiol 2013;13:7. doi:10.1186/1471-2253-13-7.
[46] Roberts JA, Paul SK, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, 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(8):1072–83. doi:10.1093/cid/ciu027.
[47] Abdul-Aziz MH, Alffenaar JC, Bassetti M, Bracht H, Dimopoulos G, Marriott D, et al. Antimicrobial therapeutic drug monitoring in critically ill adult patients: a position paper. Intensive Care Med 2020;46(6):1127–53. doi:10.1007/s00134-020-06050-1.
[48] Abdul-Aziz MH, Brady K, Cotta MO, Roberts JA. Therapeutic drug monitoring of antibiotics: defining the therapeutic range. Ther Drug Monit 2022;44(1):19–31. doi:10.1097/FTD.0000000000000940.
[49] Wong G, Taccone F, Villois P, Scheetz MH, Rhodes NJ, Briscoe S, et al. beta-Lactam pharmacodynamics in Gram-negative bloodstream infections in the critically ill. J Antimicrob Chemother 2020;75(2):429–33. doi:10.1093/jac/dkz437.
[50] Tam VH, Schilling AN, Neshat S, Poole K, Melnick DA, Coyle EA. Optimization of meropenem minimum concentration/MIC ratio to suppress in vitro resistance of *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 2005;49(12):4920–7. doi:10.1128/AAC.49.12.4920-4927.2005.
[51] Gatti M, Cojutti PG, Pascale R, Tonetti T, Laici C, Dell'Olio A, et al. Assessment of a PK/PD target of continuous infusion beta-lactams useful for preventing microbiological failure and/or resistance development in critically ill patients affected by documented Gram-negative infections. Antibiotics 2021;10(11):1311. doi:10.3390/antibiotics10111311.
[52] Li C, Du X, Kuti JL, Nicolau DP. Clinical pharmacodynamics of meropenem in patients with lower respiratory tract infections. Antimicrob Agents Chemother 2007;51(5):1725–30. doi:10.1128/AAC.00294-06.
[53] Pajot O, Burdet C, Couffignal C, Massias L, Armand-Lefevre L, Foucrier A, et al. Impact of imipenem and amikacin pharmacokinetic/pharmacodynamic parameters on microbiological outcome of Gram-negative bacilli ventilator-associated pneumonia. J Antimicrob Chemother 2015;70(5):1487–94. doi:10.1093/jac/dku569.
[54] Guilhaumou R, Benaboud S, Bennis Y, Dahyot-Fizelier C, Dailly E, Gandia P, et al. Optimization of the treatment with beta-lactam antibiotics in critically ill patients-guidelines from the French Society of Pharmacology and Therapeutics (Societe Francaise de Pharmacologie et Therapeutique-SFPT) and the French Society of Anaesthesia and intensive care medicine (Societe Francaise d'Anesthesie et Reanimation-SFAR). Crit Care 2019;23(1):104. doi:10.1186/s13054-019-2378-9.

[55] Woksepp H, Hällgren A, Borgström S, Kullberg F, Wimmerstedt A, Oscarsson A, et al. High target attainment for beta-lactam antibiotics in intensive care unit patients when actual minimum inhibitory concentrations are applied. Eur J Clin Microbiol Infect Dis 2017;36(3):553–63. doi:10.1007/s10096-016-2832-4.

[56] Novy E, Martiniere H, Roger C. The current status and future perspectives of beta-lactam therapeutic drug monitoring in critically ill patients. Antibiotics 2023;12(4):681. doi:10.3390/antibiotics12040681.

[57] Smekal AK, Furebring M, Lipcsey M, Giske CG. Swedish multicentre study of target attainments with beta-lactams in the ICU: which MIC parameter should be used? J Antimicrob Chemother 2023;78(12):2895–901. doi:10.1093/jac/dkad327.

[58] Roger C, Nucci B, Molinari N, Bastide S, Saissi G, Pradel G, et al. Standard dosing of amikacin and gentamicin in critically ill patients results in variable and subtherapeutic concentrations. Int J Antimicrob Agents 2015;46(1):21–7. doi:10.1016/j.ijantimicag.2015.02.009.

[59] Taccone FS, Laterre PF, Spapen H, Dugernier T, Delattre I, Layeux B, et al. Revisiting the loading dose of amikacin for patients with severe sepsis and septic shock. Crit Care 2010;14(2):R53. doi:10.1186/cc8945.

[60] Delattre IK, Taccone FS, Jacobs F, Hites M, Dugernier T, Spapen H, et al. Optimizing beta-lactams treatment in critically-ill patients using pharmacokinetics/pharmacodynamics targets: are first conventional doses effective? Expert Rev Anti Infect Ther 2017;15(7):677–88. doi:10.1080/14787210.2017.1338139.

[61] Delattre IK, Hites M, Laterre PF, Dugernier T, Spapen H, Wallemacq PE, et al. What is the optimal loading dose of broad-spectrum beta-lactam antibiotics in septic patients? Results from pharmacokinetic simulation modelling. Int J Antimicrob Agents 2020;56(4):106113. doi:10.1016/j.ijantimicag.2020.106113.

[62] Roger C, Nucci B, Louart B, Friggeri A, Knani H, Evrard A, et al. Impact of 30mg/kg amikacin and 8mg/kg gentamicin on serum concentrations in critically ill patients with severe sepsis. J Antimicrob Chemother 2015;71(1):208–12. doi:10.1093/jac/dkv291.

[63] Goncalves-Pereira J, Povoa P. Antibiotics in critically ill patients: a systematic review of the pharmacokinetics of beta-lactams. Crit Care 2011;15(5):R206. doi:10.1186/cc10441.

[64] Plachouras D, Karvanen M, Friberg LE, Papadomichelakis E, Antoniadou A, Tsangaris I, et al. Population pharmacokinetic analysis of colistin methanesulfonate and colistin after intravenous administration in critically ill patients with infections caused by Gram-negative bacteria. Antimicrob Agents Chemother 2009;53(8):3430–6. doi:10.1128/AAC.01361-08.

[65] Roberts JA, Taccone FS, Udy AA, Vincent JL, Jacobs F, Lipman J. Vancomycin dosing in critically ill patients: robust methods for improved continuous-infusion regimens. Antimicrob Agents Chemother 2011;55(6):2704–9. doi:10.1128/AAC.01708-10.

[66] Karaiskos I, Friberg LE, Pontikis K, Ioannidis K, Tsagkari V, Galani L, et al. Colistin population pharmacokinetics after application of a loading dose of 9 MU colistin methanesulfonate in critically ill patients. Antimicrob Agents Chemother 2015;59(12):7240–8. doi:10.1128/AAC.00554-15.

[67] Cristallini S, Hites M, Kabtouri H, Roberts JA, Beumier M, Cotton F, et al. New regimen for continuous infusion of vancomycin in critically ill patients. Antimicrob Agents Chemother 2016;60(8):4750–6. doi:10.1128/AAC.00330-16.

[68] Coste A, Bellouard R, Deslandes G, Jalin L, Roger C, Ansart S, et al. Development of a predictive dosing nomogram to achieve PK/PD targets of amikacin initial dose in critically ill patients: a non-parametric approach. Antibiotics 2023;12(1):123. doi:10.3390/antibiotics12010123.

[69] Dulhunty JM, Roberts JA, Davis JS, Webb SA, Bellomo R, Gomersall C, et al. Continuous infusion of beta-lactam antibiotics in severe sepsis: a multicenter double-blind, randomized controlled trial. Clin Infect Dis 2013;56(2):236–44. doi:10.1093/cid/cis856.

[70] Chytra I, Stepan M, Benes J, Pelnar P, Zidkova A, Bergerova T, et al. Clinical and microbiological efficacy of continuous versus intermittent application of meropenem in critically ill patients: a randomized open-label controlled trial. Crit Care 2012;16(3):R113. doi:10.1186/cc11405.

[71] Roberts JA, Webb S, Paterson D, Ho KM, Lipman J. A systematic review on clinical benefits of continuous administration of beta-lactam antibiotics. Crit Care Med 2009;37(6):2071–8. doi:10.1097/CCM.0b013e3181a0054d.

[72] Kasiakou SK, Sermaides GJ, Michalopoulos A, Soteriades ES, Falagas ME. Continuous versus intermittent intravenous administration of antibiotics: a meta-analysis of randomised controlled trials. Lancet Infect Dis 2005;5(9):581–9. doi:10.1016/S1473-3099(05)70218-8.

[73] Shiu J, Wang E, Tejani AM, Wasdell M. Continuous versus intermittent infusions of antibiotics for the treatment of severe acute infections. Cochrane Database Syst Rev 2013;2013(3):CD008481. doi:10.1002/14651858.CD008481.pub2.

[74] Roberts JA, Abdul-Aziz MH, Davis JS, Dulhunty JM, Cotta MO, Myburgh J, et al. Continuous versus intermittent beta-lactam infusion in severe sepsis. A meta-analysis of individual patient data from randomized trials. Am J Respir Crit Care Med 2016;194(6):681–91. doi:10.1164/rccm.201601-0024OC.

[75] Monti G, Redaelli MB, Zangrillo A. Continuous vs intermittent meropenem administration in critically ill patients with sepsis: the mercy randomized clinical trial. JAMA 2023;330(2):141–51. doi:10.1001/jama.2023.17736.

[76] Lipman J, Brett SJ, De Waele JJ, Cotta MO, Davis JS, Finfer S, et al. A protocol for a phase 3 multicentre randomised controlled trial of continuous versus intermittent β-lactam antibiotic infusion in critically ill patients with sepsis: BLING III. Crit Care Resusc 2019;21(1):63–8 PMID: 30857514.

[77] Barrasa H, Soraluce A, Uson E, Sainz J, Martin A, Sanchez-Izquierdo JA, et al. Impact of augmented renal clearance on the pharmacokinetics of linezolid: advantages of continuous infusion from a pharmacokinetic/pharmacodynamic perspective. Int J Infect Dis 2020;93:329–38. doi:10.1016/j.ijid.2020.02.044.

[78] Boselli E, Breilh D, Caillault-Sergent A, Djabarouti S, Guillaume C, Xuereb F, et al. Alveolar diffusion and pharmacokinetics of linezolid administered in continuous infusion to critically ill patients with ventilator-associated pneumonia. J Antimicrob Chemother 2012;67(5):1207–10. doi:10.1093/jac/dks022.

[79] Hui LA, Bodolea C, Vlase L, Hiriscau EI, Popa A. Linezolid administration to critically ill patients: intermittent or continuous infusion? A systematic literature search and review. Antibiotics 2022;11(4):436. doi:10.3390/antibiotics11040436.

[80] Rello J, Bougle A, Rouby JJ. Aerosolised antibiotics in critical care. Intensive Care Med 2023;49(7):848–52. doi:10.1007/s00134-023-07036-5.

[81] Xu F, He LL, Che LQ, Li W, Ying SM, Chen ZH, et al. Aerosolized antibiotics for ventilator-associated pneumonia: a pairwise and Bayesian network meta-analysis. Crit Care 2018;22(1):301. doi:10.1186/s13054-018-2106-x.

[82] Niederman MS, Alder J, Bassetti M, Boateng F, Cao B, Corkery K, et al. Inhaled amikacin adjunctive to intravenous standard-of-care antibiotics in mechanically ventilated patients with Gram-negative pneumonia (INHALE): a double-blind, randomised, placebo-controlled, phase 3, superiority trial. Lancet Infect Dis 2020;20(3):330–40. doi:10.1016/S1473-3099(19)30574-2.

[83] Stokker J, Karami M, Hoek R, Gommers D, van der Eerden M. Effect of adjunctive tobramycin inhalation versus placebo on early clinical response in the treatment of ventilator-associated pneumonia: the VAPORISE randomized-controlled trial. Intensive Care Med 2020;46(3):546–8. doi:10.1007/s00134-019-05914-5.

[84] Ehrmann S, Barbier F, Demiselle J, Quenot JP, Herbrecht JE, Roux D, et al. Inhaled amikacin to prevent ventilator-associated pneumonia. N Engl J Med 2023;389(22):2052–62. doi:10.1056/NEJMoa2310307.

[85] Pereira JG, Fernandes J, Duarte AR, Fernandes SM. Beta-lactam dosing in critical patients: a narrative review of optimal efficacy and the prevention of resistance and toxicity. Antibiotics 2022;11(12):1839. doi:10.3390/antibiotics11121839.

[86] Dilworth TJ, Schulz LT, Micek ST, Kollef MH, Rose WE. Beta-lactam therapeutic drug monitoring in critically ill patients: weighing the challenges and opportunities to assess clinical value. Crit Care Explor 2022;4(7):e0726. doi:10.1097/CCE.0000000000000726.

[87] Luxton T, King N, Walti C, Jeuken L, Sandoe J. A systematic review of the effect of therapeutic drug monitoring on patient health outcomes during treatment with penicillins. J Antimicrob Chemother 2022;77(6):1532–41. doi:10.1093/jac/dkac101.

[88] Pai Mangalore R, Ashok A, Lee SJ, Romero L, Peel TN, Udy AA, et al. Beta-lactam antibiotic therapeutic drug monitoring in critically ill patients: a systematic review and meta-analysis. Clin Infect Dis 2022;75(10):1848–60. doi:10.1093/cid/ciac506.

[89] Sime FB, Roberts MS, Tiong IS, Gardner JH, Lehman S, Peake SL, et al. Can therapeutic drug monitoring optimize exposure to piperacillin in febrile neutropenic patients with haematological malignancies? A randomized controlled trial. J Antimicrob Chemother 2015;70(8):2369–75. doi:10.1093/jac/dkv123.

[90] Hagel S, Bach F, Brenner T, Bracht H, Brinkmann A, Annecke T, et al. Effect of therapeutic drug monitoring-based dose optimization of piperacillin/tazobactam on sepsis-related organ dysfunction in patients with sepsis: a randomized controlled trial. Intensive Care Med 2022;48(3):311–21. doi:10.1007/s00134-021-06609-6.

[91] Leon L, Guerci P, Pape E, Thilly N, Luc A, Germain A, et al. Serum and peritoneal exudate concentrations after high doses of beta-lactams in critically ill patients with severe intra-abdominal infections: an observational prospective study. J Antimicrob Chemother 2020;75(1):156–61. doi:10.1093/jac/dkz407.

[92] Magreault S, Jaureguy F, Carbonnelle E, Zahar JR. When and how to use MIC in clinical practice? Antibiotics 2022;11(12):1748. doi:10.3390/antibiotics11121748.

[93] Tritscher P, Delannoy M, Agrinier N, Charmillon A, Degand N, Dellamonica J, et al. Assessment of current practice for beta-lactam therapeutic drug monitoring in French ICUs in 2021: a nationwide cross-sectional survey. J Antimicrob Chemother 2022;77(10):2650–7. doi:10.1093/jac/dkac291.

[94] Roger C, Louart B. Beta-lactams toxicity in the intensive care unit: an underestimated collateral damage? Microorganisms 2021;9(7):1505. doi:10.3390/microorganisms9071505.

[95] Neely MN, Kato L, Youn G, Kraler L, Bayard D, van Guilder M, et al. Prospective trial on the use of trough concentration versus area under the curve to determine therapeutic vancomycin dosing. Antimicrob Agents Chemother 2018;62(2):e02017–42. doi:10.1128/AAC.02042-17.

[96] McDonald C, Cotta MO, Little PJ, McWhinney B, Ungerer JP, Lipman J, et al. Is high-dose beta-lactam therapy associated with excessive drug toxicity in critically ill patients? Minerva Anestesiol 2016;82(9):957–65 PMID: 27054905.

[97] Lamoth F, Buclin T, Pascual A, Vora S, Bolay S, Decosterd LA, et al. High cefepime plasma concentrations and neurological toxicity in febrile neutropenic patients with mild impairment of renal function. Antimicrob Agents Chemother 2010;54(10):4360–7. doi:10.1128/AAC.01595-08.

[98] Huwyler T, Lenggenhager L, Abbas M, Ing Lorenzini K, Hughes S, Huttner B, et al. Cefepime plasma concentrations and clinical toxicity: a retrospective cohort study. Clin Microbiol Infect 2017;23(7):454–9. doi:10.1016/j.cmi.2017.01.005.

[99] Imani S, Buscher H, Marriott D, Gentili S, Sandaradura I. Too much of a good thing: a retrospective study of beta-lactam concentration-toxicity relationships. J Antimicrob Chemother 2017;72(10):2891–7. doi:10.1093/jac/dkx209.

[100] Quinton MC, Bodeau S, Kontar L, Zerbib Y, Maizel J, Slama M, et al. Neurotoxic concentration of piperacillin during continuous infusion in critically ill patients. Antimicrob Agents Chemother 2017;61(9):e00617–54. doi:10.1128/AAC.00654-17.

[101] Beumier M, Casu GS, Hites M, Wolff F, Cotton F, Vincent JL, et al. Elevated beta-lactam concentrations associated with neurological deterioration in ICU septic patients. Minerva Anestesiol 2015;81(5):497–506 PMID: 25220556.

[102] Muller AE, Theuretzbacher U, Mouton JW. Use of old antibiotics now and in the future from a pharmacokinetic/pharmacodynamic perspective. Clin Microbiol Infect 2015;21(10):881–5. doi:10.1016/j.cmi.2015.06.007.

[103] Kristoffersson AN, Rognås V, Brill MJE, Dishon-Benattar Y, Durante-Mangoni E, Daitch V, et al. Population pharmacokinetics of colistin and the relation to survival in critically ill patients infected with colistin susceptible and carbapenem-resistant bacteria. Clin Microbiol Infect 2020;26(12):1644–50. doi:10.1016/j.cmi.2020.03.016.
[104] Ram K, Sheikh S, Bhati RK, Tripathi CD, Suri JC, Meshram GG. Steady-state pharmacokinetic and pharmacodynamic profiling of colistin in critically ill patients with multi-drug-resistant Gram-negative bacterial infections, along with differences in clinical, microbiological and safety outcome. Basic Clin Pharmacol Toxicol 2021;128(1):128–40. doi:10.1111/bcpt.13482.
[105] Moni M, Sudhir AS, Dipu TS, Mohamed Z, Prabhu BP, Edathadathil F, et al. Clinical efficacy and pharmacokinetics of colistimethate sodium and colistin in critically ill patients in an Indian hospital with high endemic rates of multidrug-resistant Gram-negative bacterial infections: a prospective observational study. Int J Infect Dis 2020;100:497–506. doi:10.1016/j.ijid.2020.08.010.
[106] Tsuji BT, Pogue JM, Zavascki AP, Paul M, Daikos GL, Forrest A, et al. International consensus guidelines for the optimal use of the polymyxins: endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP). Pharmacotherapy 2019;39(1):10–39. doi:10.1002/phar.2209.
[107] Zabidi MS, Abu Bakar R, Musa N, Mustafa S, Wan Yusuf WN. Population pharmacokinetics of colistin methanesulfonate sodium and colistin in critically ill patients: a systematic review. Pharmaceuticals 2021;14(9):903. doi:10.3390/ph14090903.
[108] Ehrentraut SF, Muenster S, Kreyer S, Theuerkauf NU, Bode C, Steinhagen F, et al. Extensive therapeutic drug monitoring of colistin in critically ill patients reveals undetected risks. Microorganisms 2020;8(3):415. doi:10.3390/microorganisms8030415.
[109] Assimakopoulos SF, Karamouzos V, Eleftheriotis G, Lagadinou M, Bartzavali C, Kolonitsiou F, et al. Efficacy of fosfomycin-containing regimens for treatment of bacteremia due to pan-drug resistant *Acinetobacter baumannii* in critically ill patients: a case series study. Pathogens 2023;12(2):286. doi:10.3390/pathogens12020286.
[110] Russo A, Bassetti M, Bellelli V, Bianchi L, Marincola Cattaneo F, Mazzocchetti S, et al. Efficacy of a fosfomycin-containing regimen for treatment of severe pneumonia caused by multidrug-resistant *Acinetobacter baumannii*: a prospective, observational study. Infect Dis Ther 2021;10(1):187–200. doi:10.1007/s40121-020-00357-8.
[111] Gatti M, Viaggi B, Rossolini GM, Pea F, Viale P. An evidence-based multidisciplinary approach focused on creating algorithms for targeted therapy of infection-related ventilator-associated complications (IVACs) caused by *Pseudomonas aeruginosa* and *Acinetobacter baumannii* in critically ill adult patients. Antibiotics 2021;11(1):33. doi:10.3390/antibiotics11010033.
[112] Parker SL, Frantzeskaki F, Wallis SC, Diakaki C, Giamarellou H, Koulenti D, et al. Population pharmacokinetics of fosfomycin in critically ill patients. Antimicrob Agents Chemother 2015;59(10):6471–6. doi:10.1128/AAC.01321-15.
[113] Leelawattanachai P, Wattanavijitkul T, Paiboonvong T, Plongla R, Chatsuwan T, Usayaporn S, et al. Evaluation of intravenous fosfomycin disodium dosing regimens in critically ill patients for treatment of carbapenem-resistant Enterobacterales infections using Monte Carlo simulation. Antibiotics 2020;9(9):615. doi:10.3390/antibiotics9090615.
[114] Asuphon O, Montakantikul P, Houngsaitong J, Kiratisin P, Sonthisombat P. Optimizing intravenous fosfomycin dosing in combination with carbapenems for treatment of *Pseudomonas aeruginosa* infections in critically ill patients based on pharmacokinetic/pharmacodynamic (PK/PD) simulation. Int J Infect Dis 2016;50:23–9. doi:10.1016/j.ijid.2016.06.017.
[115] Albur MS, Noel A, Bowker K, MacGowan A. The combination of colistin and fosfomycin is synergistic against NDM-1-producing *Enterobacteriaceae* in in vitro pharmacokinetic/pharmacodynamic model experiments. Int J Antimicrob Agents 2015;46(5):560–7. doi:10.1016/j.ijantimicag.2015.07.019.
[116] Lepak AJ, Zhao M, VanScoy B, Taylor DS, Ellis-Grosse E, Ambrose PG, et al. In vivo pharmacokinetics and pharmacodynamics of ZTI-01 (fosfomycin for injection) in the neutropenic murine thigh infection model against *Escherichia coli, Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 2017;61(6):e00417–76. doi:10.1128/AAC.00476-17.
[117] Gatti M, Giannella M, Rinaldi M, Gaibani P, Viale P, Pea F. Pharmacokinetic/pharmacodynamic analysis of continuous-infusion fosfomycin in combination with extended-infusion cefiderocol or continuous-infusion ceftazidime-avibactam in a case series of difficult-to-treat resistant *Pseudomonas aeruginosa* bloodstream infections and/or hospital-acquired pneumonia. Antibiotics 2022;11(12):1739. doi:10.3390/antibiotics11121739.
[118] Albiero J, Mazucheli J, Barros J, Szczerepa M, Nishiyama SAB, Carrara-Marroni FE, et al. Pharmacodynamic attainment of the synergism of meropenem and fosfomycin combination against *Pseudomonas aeruginosa* producing metallo-beta-lactamase. Antimicrob Agents Chemother 2019;63(6):e00119–26. doi:10.1128/AAC.00126-19.
[119] Huppe T, Gotz KM, Meiser A, de Faria Fernandes A, Maurer F, Groesdonk HV, et al. Population pharmacokinetic modeling of multiple-dose intravenous fosfomycin in critically ill patients during continuous venovenous hemodialysis. Sci Rep 2023;13(1):18132. doi:10.1038/s41598-023-45084-5.
[120] Gerecke LKV, Schmidt JJ, Hafer C, Eden G, Bode-Boger SM, Martens-Lobenhoffer J, et al. Fosfomycin single- and multiple-dose pharmacokinetics in patients undergoing prolonged intermittent renal replacement therapy. J Antimicrob Chemother 2021;77(1):169–73. doi:10.1093/jac/dkab357.
[121] Florent A, Chichmanian RM, Cua E, Pulcini C. Adverse events associated with intravenous fosfomycin. Int J Antimicrob Agents 2011;37(1):82–3. doi:10.1016/j.ijantimicag.2010.09.002.
[122] Laterre PF, Wittebole X, Van de Velde S, Muller AE, Mouton JW, Carryn S, et al. Temocillin (6g daily) in critically ill patients: continuous infusion versus three times daily administration. J Antimicrob Chemother 2015;70(3):891–8. doi:10.1093/jac/dku465.
[123] Layios N, Visee C, Mistretta V, Denooz R, Maes N, Descy J, et al. Modelled target attainment after temocillin treatment in severe pneumonia: systemic and epithelial lining fluid pharmacokinetics of continuous versus intermittent infusions. Antimicrob Agents Chemother 2022;66(3):e0205221. doi:10.1128/aac.02052-21.
[124] Ngougni Pokem P, Wittebole X, Collienne C, Rodriguez-Villalobos H, Tulkens PM, Elens L, et al. Population pharmacokinetics of temocillin administered by continuous infusion in patients with septic shock associated with intra-abdominal infection and ascitic fluid effusion. Antibiotics 2022;11(7):898. doi:10.3390/antibiotics11070898.
[125] Miranda Bastos AC, Vandecasteele SJ, Spinewine A, Tulkens PM, Van Bambeke F. Temocillin dosing in haemodialysis patients based on population pharmacokinetics of total and unbound concentrations and Monte Carlo simulations. J Antimicrob Chemother 2018;73(6):1630–8. doi:10.1093/jac/dky078.
[126] Principe L, Lupia T, Andriani L, Campanile F, Carcione D, Corcione S, et al. Microbiological, clinical, and PK/PD features of the new anti-Gram-negative antibiotics: beta-lactam/beta-lactamase inhibitors in combination and cefiderocol-an all-inclusive guide for clinicians. Pharmaceuticals 2022;15(4):463. doi:10.3390/ph15040463.
[127] Kanj SS, Bassetti M, Kiratisin P, Rodrigues C, Villegas MV, Yu Y, et al. Clinical data from studies involving novel antibiotics to treat multidrug-resistant Gram-negative bacterial infections. Int J Antimicrob Agents 2022;60(3):106633. doi:10.1016/j.ijantimicag.2022.106633.
[128] Bakdach D, Elajez R, Bakdach AR, Awaisu A, De Pascale G, Ait Hssain A. Pharmacokinetics, pharmacodynamics, and dosing considerations of novel beta-lactams and beta-lactam/beta-lactamase inhibitors in critically ill adult patients: focus on obesity, augmented renal clearance, renal replacement therapies, and extracorporeal membrane oxygenation. J Clin Med 2022;11(23):6898. doi:10.3390/jcm11236898.
[129] Gatti M, Pea F. Pharmacokinetic/pharmacodynamic target attainment in critically ill renal patients on antimicrobial usage: focus on novel beta-lactams and beta lactams/beta-lactamase inhibitors. Expert Rev Clin Pharmacol 2021;14(5):583–99. doi:10.1080/17512433.2021.1901574.
[130] Gorham J, Taccone FS, Hites M. Drug regimens of novel antibiotics in critically ill patients with varying renal functions: a rapid review. Antibiotics (Basel) 2022;11(5):546. doi:10.3390/antibiotics11050546.
[131] Xiao AJ, Caro L, Popejoy MW, Huntington JA, Kullar R. PK/PD target attainment with ceftolozane/tazobactam using Monte Carlo simulation in patients with various degrees of renal function, including augmented renal clearance and end-stage renal disease. Infect Dis Ther 2017;6(1):137–48. doi:10.1007/s40121-016-0143-9.
[132] Wenzler E, Butler D, Tan X, Katsube T, Wajima T. Pharmacokinetics, pharmacodynamics, and dose optimization of cefiderocol during continuous renal replacement therapy. Clin Pharmacokinet 2022;61(4):539–52. doi:10.1007/s40262-021-01086-y.
[133] Katsube T, Wajima T, Ishibashi T, Arjona Ferreira JC, Echols R. Pharmacokinetic/pharmacodynamic modeling and simulation of cefiderocol, a parenteral siderophore cephalosporin, for dose adjustment based on renal function. Antimicrob Agents Chemother 2017;61(1):e01316–81. doi:10.1128/AAC.01381-16.
[134] Cornely OA, Cisneros JM, Torre-Cisneros J, Rodríguez-Hernández MJ, Tallón-Aguilar L, Calbo E, et al. Pharmacokinetics and safety of aztreonam/avibactam for the treatment of complicated intra-abdominal infections in hospitalized adults: results from the REJUVENATE study. J Antimicrob Chemother 2020;75(3):618–27. doi:10.1093/jac/dkz497.
[135] Fratoni AJ, Mah JW, Nicolau DP, Kuti JL. Imipenem/cilastatin/relebactam pharmacokinetics in critically ill patients with augmented renal clearance. J Antimicrob Chemother 2022;77(11):2992–9. doi:10.1093/jac/dkac261.
[136] Kufel WD, Eranki AP, Paolino KM, Call A, Miller CD, Mogle BT. In vivo pharmacokinetic analysis of meropenem/vaborbactam during continuous venovenous haemodialysis. J Antimicrob Chemother 2019;74(7):2117–18. doi:10.1093/jac/dkz103.
[137] Zhang Y, Wang T, Zhang D, You H, Dong Y, Liu Y, et al. Therapeutic drug monitoring coupled with Bayesian forecasting could prevent vancomycin-associated nephrotoxicity in renal insufficiency patients: a prospective study and pharmacoeconomic analysis. Ther Drug Monit 2020;42(4):600–9. doi:10.1097/FTD.0000000000000750.
[138] Vali L, Jenkins DR, Vaja R, Mulla H. Personalised dosing of vancomycin: a prospective and retrospective comparative quasi-experimental study. Br J Clin Pharmacol 2021;87(2):506–15. doi:10.1111/bcp.14411.