Current Infectious Disease Reports (2018) 20: 9
https://doi.org/10.1007/s11908-018-0613-1

HEALTHCARE ASSOCIATED INFECTIONS (G BEARMAN AND D MORGAN, SECTION EDITORS)

Pharmacokinetic/Pharmacodynamic Considerations of Beta-Lactam Antibiotics in Adult Critically Ill Patients

Anne M. Masich[1] · Mojdeh S. Heavner[1] · Jeffrey P. Gonzales[1] · Kimberly C. Claeys[1]

Published online: 4 April 2018

Abstract

Purpose of Review Beta-lactam antibiotics are commonly prescribed in critically ill patients for a variety of infectious conditions. Our understanding of how critical illness alters beta-lactam pharmacokinetics/pharmacodynamics (PK/PD) is rapidly evolving.

Recent Findings There is a growing body of literature in adult patients demonstrating that physiological alterations occurring in critically ill patients may limit our ability to optimally dose beta-lactam antibiotics to reach these PK/PD targets. These alterations include changes in volume of distribution and renal clearance with multiple, often overlapping causative pathways, including hypoalbuminemia, renal replacement therapy, and extracorporeal membrane oxygenation. Strategies to overcome these PK alterations include extended infusions and therapeutic drug monitoring. Combined data has demonstrated a possible survival benefit associated with extending beta-lactam infusions in critically ill adult patients.

Summary This review highlights research on physiological derangements affecting beta-lactam concentrations and strategies to optimize beta-lactam PK/PD in critically ill adults.

Keywords Beta-lactams · Critically ill · Pharmacokinetics · Pharmacodynamics · Renal replacement therapy · Extracorporeal membrane oxygenation

Introduction

Beta-lactam antibiotics (penicillins, cephalosporins, and carbapenems) are routinely used to treat serious infections in critically ill patients managed in the intensive care unit (ICU). All beta-lactams exhibit time-dependent bactericidal activity, which is determined by the free drug concentration time above the minimum inhibitory concentration (MIC) for the causative organism (%*f*T > MIC). The exact target that results in optimal bacterial killing and best clinical outcomes varies depending on the beta-lactam, but the generally agreed upon pharmacodynamic (PD) goals for target attainment include 50%*f*T > MIC for piperacillin-tazobactam, 60%*f*T > MIC for cephalosporins, and 40%*f*T > MIC for carbapenems [1, 2]. In addition to %*f*T > MIC, maximal bacterial killing occurs when the free antibiotic concentration is consistently four to five times above the MIC, though correlation to improved clinical outcomes is inconsistent. Beta-lactam antibiotics are hydrophilic molecules and most beta-lactams are eliminated primarily through the kidneys, making their pharmacokinetics (PK) highly susceptible to alterations seen in critical illness. This review will focus on the PK alterations of beta-lactam antibiotics in critically ill adult patients, including specialized patient populations, and dosing strategies to optimize probability of PK/PD target attainment and clinical outcomes.

Review of Physiological Changes in Critically Ill Patients

In critically ill patients, volume of distribution (Vd) is significantly larger compared to non-critically ill patients due to aggressive fluid resuscitation and capillary leakage [3–6]. Hydrophilic beta-lactam concentrations are greatly influenced by the increase in Vd, which may lead to lower concentrations at the site of infection. In addition to volume changes, critically ill patients may also develop hypoalbuminemia (< 3.5 g/dL)

This article is part of the Topical Collection on *Healthcare Associated Infections*

✉ Kimberly C. Claeys
kclaeys@rx.umaryland.edu

[1] Department of Pharmacy Practice and Science, University of Maryland School of Pharmacy, Baltimore, Maryland, USA

secondary to severe systemic inflammatory response, which can lead to increased free plasma concentrations [7, 8]. Although only a portion of beta-lactam agents are highly protein bound (i.e., ceftriaxone), alterations of protein binding can significantly alter free concentrations of these agents. Additionally, increases in Vd and increased clearance (Cl) are seen with hypoalbuminemia, further adding to the alterations discussed above [7, 9, 10]. Critically ill patients can also develop organ dysfunction, such as renal or hepatic impairment, or improved organ function in the case of augmented renal clearance [5, 11].

Beta-Lactam PK/PD Considerations in Special Patient Populations

Augmented Renal Clearance

In the presence of increased cardiac output and fluid resuscitation in critically ill patients, there is increased perfusion to the kidneys resulting in potentially increased clearance of drugs such as beta-lactams. This phenomenon is referred to as augmented renal clearance, defined as creatinine clearance (CrCl) ≥ 130 mL/min/1.73m^2. In this setting, drug clearance is increased, resulting in potential sub-therapeutic drug concentrations [11, 13•, 14]. There is evidence supporting the presence of augmented renal clearance in critically ill patient populations leading to worse clinical outcomes [14]. A prospective, observational study found that overall, 65.1% (38.4–54.4%) of patients exhibited augmented renal clearance on at least one occasion during their first 7 days in the ICU [15•]. Patients with augmented renal clearance were young, male, had lower sequential organ failure assessment (SOFA) scores, and mechanically ventilated.

A single-center observation study from Udy et al. explored the impact of augmented renal clearance on PK/PD target attainment with intermittent dosing of piperacillin-tazobactam [13•]. Using nonlinear mixed-effect modeling, the study found that only 34% of patients achieved 100%*f*T > MIC using an MIC breakpoint of 16 mg/L. Patients who failed to achieve 100%*f*T > MIC had significantly higher drug clearance ($r = 0.58$, $p < 0.01$), but no significant difference in Vd. Only 28.5% of patients exhibiting augmented renal clearance had a cumulative fraction of response at 100%*f*T > MIC.

Carlier et al. conducted a prospective observational study of critically ill patients in either medical or surgical ICUs receiving meropenem 1 g every 8 h or piperacillin/tazobactam 4.5 g every 6 h [16]. Drug levels were obtained from 61 patients; 48% did not achieve the PK/PD target of 100%*f*T > MIC. The authors noted that among these patients, 76% demonstrated augmented renal clearance with median (IQR) CrCl of 165 (138–208) mL/min. Through multivariable logistic regression analysis, augmented renal clearance was independently associated with failure to achieve the desired PK/PD target of 100%*f*T > MIC. A PK/PD target of 50%*f*T > MIC was also investigated. Among patients with CrCl > 130 mL/min, 37% did not achieve this target. Augmented renal clearance was again independently associated with inability to reach target based on multivariable logistic regression. Augmented renal clearance, and its effects on beta-lactam PK/PD, is still a relatively novel concept and future studies are needed to assess the outcomes of patients when receiving beta-lactam antibiotics.

Continuous Renal Replacement Therapy,

Renal impairment results in decreased elimination of beta-lactam antibiotics, leading to drug accumulation and potential toxicity. Up to 25% of ICU patients develop acute kidney injury, of which 70% necessitating continuous renal replacement therapy (CRRT) to remove excess volume and solutes [17, 18]. Solute removal is achieved through hemofiltration, hemodialysis, or a combination [19]. In hemodialysis, solute is removed through diffusion across a concentration dependent gradient. Drugs with small molecular weight, low protein binding, and small volume of distribution are easily removed. During hemofiltration, hydrostatic pressure pulls solutes and water across a semi-permeable membrane. Larger drug molecules are removed compared to hemodialysis. In general, continuous veno-venous hemodiafiltration (CVVHDF) removes the most solute, followed by continuous veno-venous hemodialysis (CVVHD), and continuous veno-venous hemofiltration (CVVH) removing the least amount of solute. It is thus imperative that clinicians are aware of the various renal replacement methods employed in their ICUs [20, 21].

Beta-lactam dosing in CRRT can be challenging, as the use of extracorporeal circuits and different modalities may alter PK in an additive manner to the already altered PK of critical illness [22, 23]. Alterations in beta-lactam PK are dependent on the mode and settings of CRRT, filter type, and fluid replacement [19]. Flow intensity (effluent flow rate) has been shown to have the most significant impact on beta-lactam PK, specifically clearance [24•]. While PK parameters of the more frequently used beta-lactams have been previously described, there is limited applicable data guiding dosing in CRRT to achieve PK/PD targets that optimize outcomes in ICU setting.

Jamal et al. evaluated the effect of CRRT modalities, predominately CVVH and CVVHDF, on the clearance of commonly used antimicrobial agents, including meropenem and piperacillin-tazobactam from 30 studies [24•]. The analysis of different PK studies showed that CRRT intensity (determined by effluent flow rate) increased extracorporeal drug elimination, while blood flow rate did not correlate with drug clearance overall. These correlations were observed independent of the CRRT modality. For both meropenem and piperacillin-

tazobactam, various dosing strategies used by the different studies achieved 89 and 83% of the PK/PD targets, respectively.

An additional review by Jamel et al. described dosing strategies that could be applied in patients receiving CRRT to improve targeted drug concentrations [19]. Ceftazidime and cefepime when dosed 4 to 8 g/day and 2 to 6 g/day, respectively, consistently resulted in a minimum concentration (C_{min}) above MIC breakpoint of 8 mg/L. Doses of 8 to 16 g/day of piperacillin-tazobactam exceed a MIC breakpoint of 16 mg/L for various CRRT settings. Meropenem dosed 2–3 g/day resulted in C_{min} above 2 mg/L. Higher doses of these drugs would be necessary for organisms that are more resistant; however, this may lead to adverse effects. To avoid toxicity and to improve PK/PD target attainment, alternative dosing strategies could be considered, such as increasing infusion time or therapeutic drug monitoring.

More recent prospective, randomized controlled studies have evaluated PK/PD target attainment of meropenem and piperacillin-tazobactam continuous infusion (CI) versus intermittent bolus dosing in critically ill patients receiving CVVH [25]. Intermittent bolus dosing of meropenem (loading dose 2 g followed by 1 g every 8 h) resulted in 100%$fT > 4 \times$ MIC at a MIC breakpoint of 2 mg/L, however CI dosing (loading dose of 1 g followed by CI) resulted in 100%$fT > 10 \times$ MIC. Eighty-eight percent of patients receiving piperacillin-tazobactam CI (2.25 g loading dose followed by CI) achieved 100%$fT > 4 \times$ MIC at a MIC breakpoint of 16 mg/L. Only 62.5% of the intermittent bolus dosing patients (4.5 g loading dose followed by 2.25 g every 6 h) achieved 50%$fT > 4 \times$ MIC. While emerging studies are beginning to compare PK/PD between different CRRT modalities, an evaluation of patient clinical outcomes are still needed to determine the best dosing strategies for critically ill patients requiring CRRT [23].

Obesity

Limited data exist to guide antibiotic dosing in obese and morbidly obese patients, even less so for obese critically ill patients [26]. Alobaid et al. provide a detailed examination of the effects of obesity and critical illness on antimicrobial pharmacokinetics that is beyond the scope of this review [27].

Hites et al. performed a case-control study of therapeutic target attainment in adult obese versus non-obese critically ill patients receiving beta-lactam antibiotics [28]. Drug concentration for beta-lactams were obtained as part of routine care in the participating ICU. Obese patients (BMI $\geq$ 30 kg/m^2) receiving cefepime, piperacillin-tazobactam, or meropenem were matched to non-obese patients (BMI $\leq$ 25 kg/m^2) according to the following covariates: antibiotic received, renal function (i.e. CRRT), SOFA score, sex, and age. A total of 49 obese patients were matched to 59 non-obese patients. Adequate therapeutic levels were obtained in 25% (cefepime), 47% (piperacillin-tazobactam), and 49% (meropenem) of patients. Obese patients receiving meropenem not on CRRT were significantly more likely to not achieve PK/PD target of %$fT > 4 \times$ MIC compared to non-obese patients (0% vs 35%, $p = 0.02$). No differences in target attainment were seen in patients receiving cefepime or piperacillin-tazobactam. In a subsequent publication, the authors sought to evaluate target attainment in obese, non-critically ill patients [29]. Among 56 obese patients (median BMI = 36 kg/m^2), augmented renal clearance was determined to be the predominant cause of low serum beta-lactam levels. These findings cannot be definitely extrapolated to obese patients in the ICU, but highlight the difficulty of determining the independent influence of obesity on beta-lactam PK as multiple overlapping alterations are likely.

Alobaid et al. retrospectively reviewed 1400 patients from multiple ICUs across the world in order to compare PK/PD targets among non-obese versus obese critically ill patients [30]. The PK/PD targets of interest were 100%$fT >$ MIC and 100%$fT > 4 \times$ MIC. Patients were dosed with either intermittent or continuous infusions of meropenem ($n = 481$) or piperacillin-tazobactam ($n = 919$) according to local prescribing practices. Piperacillin had lower median (IQR) trough concentrations among obese versus non-obese patients (29.4 (17.0–58.0) vs 42.0 (21.5–73.5) mg/L, $p = 0.001$). This was not the case for patients treated with meropenem (10.3 (4.8–16.0) vs 11.0 (4.3–18.5) mg/L, $p = 0.296$). A significantly lower proportion of obese patients targets of 100%$fT > 4 \times$ MIC for piperacillin (20.7 vs 30.9%, $p = 0.002$); otherwise, there were no significant differences among obese and non-obese achieving target attainment. Overall, attainment of 100%$fT > 4 \times$ MIC was low (< 65%) regardless of obese versus non-obese, or meropenem versus piperacillin.

A one-compartment population PK model evaluated the probability of target attainment (PTA) of 50%$fT >$ MIC with MIC breakpoint of 16 mg/L using in nine surgical ICU patients with BMI > 40 kg/m^2 [31]. Using Monte Carlo simulations, researchers found 100% PTA using a piperacillin-tazobactam dose of 4.5 g every 6 h intermittently infused. Extended infusion regimens did not confer additional advantage and the authors contribute this finding to the long piperacillin half-life among studied patients. In a recent prospective population PK model of piperacillin-tazobactam of critically ill non-obese, obese, and morbidly obese patients, Monte Carlo simulations were also performed to determine optimal dosing regimens [32•]. Thirty-seven patients (non-obese $n =$ 13, obese $n = 12$, morbidly obese $n = 12$) were enrolled and received piperacillin-tazobactam 4 g every 6 h, with the exception of two patients who received every 12 h dosing frequency. Piperacillin Vd and Cl demonstrated high intra-group variability, especially among morbidly obese patients. PTA for piperacillin 4 g every 6 h varied by clearance, with PTAs for

non-obese, obese, and morbidly obese being similar only when Cl was impaired. Overall, increasing BMI was associated with increased Vd. Extended and continuous infusions were able to achieve target attainment in all populations up to an MIC of 8 mg/L.

Although Vd is increased for most antibiotics, including beta-lactams, clearance is altered through both augmented renal clearance and higher incidence of renal impairment. Summarizing data for beta-lactam exposure in morbidly obese patients, especially those that are critically ill, is difficult due to the variability within this patient population. There is a lack of PK/PD data in this population and more research is needed.

Extracorporeal Membrane Oxygenation

Due to multi-organ dysfunction, patients may also need additional oxygenation and circulatory support. Extracorporeal membrane oxygenation (ECMO) is a form of life support meant to bypass the cardiopulmonary system in order to aid in oxygenation, ventilation, and cardiac output [33]. ECMO is used in the ICU to support patients in pulmonary and/or cardiac failure and works by providing a mechanical circulatory system, externally oxygenated, and returned to the body, through either veno-venous (VV) or veno-atrial (VA) configuration depending on whether the goal is respiratory or circulatory support, respectively [34, 35•]. ECMO can lead to either increased or decreased antibiotic clearance, increased volume of distribution, alterations in drug protein binding, and potential sequestration in ECMO circuits. Evidence regarding how ECMO alters and influences patients' PK variables is ongoing.

As previously mentioned, ECMO is a form of mechanical life support meant to bypass the pulmonary and/or cardiac systems. There are several PK alterations caused by ECMO that need to be considered when administering beta-lactam antibiotics. Although data in adults is scarce, in general, studies of PK alterations in patients receiving ECMO have demonstrated potential increases in Vd and potential drug sequestration, which may necessitate larger doses of beta-lactams to combat infection [36–38].

There is conflicting evidence surrounding PK alterations with meropenem when patients are on ECMO. In vitro models have reported alterations related to drug sequestration, increased Vd, and increased Cl [39, 40]. Shekar et al. completed a matched cohort study and population PK analysis of adults patients receiving either VV ECMO ($n = 6$) or VA ECMO ($n = 5$) with or without CRRT [41]. Using a two-compartment model, the investigators performed Monte Carlo simulations in order to describe the effect of ECMO on PK parameters, including Cl, Vd, and doses of meropenem needed to achieve therapeutic target attainment (trough concentrations of 2 mg/L for susceptible and 8 mg/L for non-susceptible organism). Meropenem clearance was significantly decreased (7.9 ± 5.9 vs 11.7 ± 6.5 L/h, $p = 0.18$), while the Vd was increased (0.45 ± 0.17 vs 0.41 ± 0.13 L/kg, $p = 0.21$) in patients on ECMO. Dosing of 1 g every 8 h was determined to likely achieve target attainment in susceptible organisms.

A 2015 case control study of patients on beta-lactam antibiotics with and without ECMO failed to find significant differences in PK parameters [42•]. Adult ICU patients receiving ECMO were matched 1:1 with adult ICU patients not receiving ECMO based on the following covariates: beta-lactam antibiotic, renal function, total body weight, SOFA score, and age. Forty-one drug levels from 26 ECMO patients were matched to 41 from non-ECMO patients (meropenem = 27, piperacillin-tazobactam = 14). Overall, the investigators concluded that there was a low achievement of target attainment ($50\%fT > 4–8 \times MIC$ for piperacillin-tazobactam and $40\%fT > 4–8 \times MIC$, meropenem) in both the ECMO (68%) and non-ECMO (71%) groups and there were no significant differences in beta-lactam PK. There were no significant differences between ECMO versus non-ECMO patients in Vd [0.38 (0.27–0.68) vs 0.46 (0.33–0.79) L/kg, $p = 0.37$] or Cl [132 (66–200) vs 141 (93–197) mL/min, $p = 0.52$]. More evidence is needed to determine if ECMO exhibits an independent effect on meropenem PK or if the differences seen are the result of an accumulation of underlying physiological alterations related to critical illness.

Unlike most other beta-lactam antibiotics, ceftriaxone is highly protein bound, upwards of 95%, which allows for significant alterations in PK different from other beta-lactams [9]. An ex vivo study compared ceftriaxone administered through four ECMO circuits compared to polypropylene control jars [43]. Mean 24-h drug recovery varied significantly with 80% ceftriaxone recovery from ECMO circuits versus 102% from control jars ($p = 0.01$). The authors concluded that protein binding influenced drug sequestration more than stability or lipophilicity. A 2017 ex vivo model, however, did not find similar results [44]. In this comparative study, plasma concentrations for several beta-lactams, including ceftriaxone, were collected for up to 48 h after administration through five ECMO circuits and compared to glass or polyvinyl chloride tubing controls. Concentrations remained similar; with 104% mean drug recovery from circuits versus 94 and 95% from control glass and tubing, respectively. The authors note that the conflicting results may be secondary to differences in study design, such as use of fresh human whole blood with or without albumin.

As evidence increases demonstrating ECMOs potential contributions to decreasing patient mortality in the ICU, there is an increasing need to understand the physiological effects of ECMO. The Analgesic, Sedative and Antibiotic Pharmacokinetics during Extracorporeal Membrane Oxygenation (ASAP ECMO) trial is ongoing and will greatly improve our understanding of ECMOs influence on beta-lactam PK [45].

Approaches to Optimizing Beta-Lactam Therapy in Critically Ill Adults

Due to the physiological derangements detailed above, current standard dosing of beta-lactam agents may fail to achieve PK/PD target attainment in critically ill patients. There are two types of interventions commonly employed to help overcome these physiological derangements and optimize beta-lactam PK/PD through extending the $\%fT > MIC$. These interventions include modifying the administration of beta-lactam by extending the duration of the infusion and/or monitoring beta-lactam serum levels and adjusting dosage (infusion duration or frequency of administration) based on these levels.

Extended or Continuous Beta-Lactam Infusion

Beta-lactam PK-PD studies have shown that time free drug concentration over the MIC is significantly reduced in critically ill patients, which may lead to poorer outcomes and increased antimicrobial resistance [46–48]. To optimize bacterial killing and improve clinical outcomes, studies have supported the use of extended infusion (EI) or CI of beta-lactams, especially for organisms with higher MICs [49•, 50–52]. However, many of these studies are not without limitations, including small sample sizes, heterogeneous patient populations, and suboptimal study designs.

Lodise et al. conducted a retrospective cohort study using Monte Carlo simulations to determine if EI of piperacillin-tazobactam (3.375 g every 8 h infused over 4 h) results in superior clinical outcomes in *Pseudomonas aeruginosa* infection compared to intermittent bolus dosing (3.375 g every 4 or 6 h) [50]. Patients with an APACHE II scores of ≥ 17 receiving EI piperacillin-tazobactam had significantly decreased mortality and length of stay (LOS) compared to patients receiving intermittent bolus dosing [(14-day mortality 12.2 vs 31.6%; $p = 0.04$) (LOS 21 (3–98) vs 38 (6–131); $p = 0.02$)]. However, there was no significant difference in mortality or LOS in patients with an APACHE II score of < 17.

The Beta-lactam Infusion Group (BLING) trials were prospective, randomized trials to determine the difference between CI and intermittent dosing of adult patients across ICUs [53•, 54•]. In the larger BLING II, authors found there was no significant difference in median ICU-free days [18 [2–12, 13•, 14, 15•, 16–23, 24•] vs 20 [3–12, 13•, 14, 15•, 16–23, 24•]; $p = 0.38$], 90-day survival [156 (74.3%) vs 158 (72.5%); $p = 0.67$] or clinical cure [111 (52.4) vs 109 (49.5%); $p = 0.56$]. Several limitations of this study include inclusion of potentially noninfectious patients, inclusion of non-susceptible pathogens, and participants receiving CRRT. The Beta-lactam Infusion in Severe Sepsis (BLISS) study was a prospective, randomized clinical trial to determine if CI beta-lactams were associated with improved clinical outcomes compared to intermittent dosing in critically ill patients not on CRRT [55]. Clinical cure at 14 days after antibiotic cessation and median ventilator-free days were significantly increased in the CI group [clinical cure 39 (56%) vs. 24 (34%), $p = 0.011$; ventilator-free days 22 (IQR 0–24) vs 14 (IQR 0–24), $p = 0.043$]. Additionally more patients receiving CI achieved PK/PD targets of $50\%fT > MIC$ and $100\%fT > MIC$ compared to patients receiving intermittent dosing [$50\%fT > MIC$ 55 (97%) vs 37 (70%), $p < 0.001$; $100\%fT > MIC$ 55 (97%) vs 36 (68%, $p < 0.00$ [1]]. There was no significant difference in 14-day and 30-day mortality; however, the study was not powered to determine effect on survival. A meta-analysis using data from the BLISS and BLING trials found that hospital mortality was significantly lower (risk ratio (RR) = 0.74; 95% CI, 0.56–1.00; $p = 0.045$) and clinical cure was significantly higher (RR = 1.20; 95% CI, 1.03–1.40; $p = 0.021$) with CI [56•]. There was no difference between the groups in ICU-free days at day 28 (RR = 0; 95% CI, 23 to 3; $p = 0.90$) or ICU mortality (RR = 0.82; 95% CI, 0.58–1.16; $p = 0.26$). A separate meta-analysis of CI versus intermittent infusion beta-lactams found similar results with respect to patient survival and clinical cure [57•].

Evidence of PK/PD target attainment in patients with augmented renal clearance receiving EI dosing regimens is conflicting. Currently, data is lacking in augmented renal clearance patients receiving CI dosing regimens. A doripenem PK/PD modeling study using Monte Carlo dose simulations in obese patients and increased CrCl demonstrated that EI regimens increased the likelihood of achieving PK/PD targets [58]. Seventy to 80% of patients with CrCl of ≥ 100 mL/min achieved target attainment of $40\%fT > MIC$ at an MIC breakpoint of 4 mg/L when doripenem was infused over 1 h; however, when doripenem was infused over 4 h, > 90% of patients achieved target attainment. Another study assessing EI meropenem or piperacillin-tazobactam in patients without renal dysfunction found that the majority of patients manifesting augmented renal clearance failed to achieve PK/PD target attainment at $100\%fT > MIC$ (76%) and at $50\%fT > MIC$ (37%) [52].

Based on the available studies, patients who are critically ill may benefit from either EI or CI dosing regimens, especially if the MIC of the causative organism is elevated. While several studies favor the use of EI or CI of beta-lactams in critically ill patients, more robust data are needed to determine the effect on mortality and PK/PD targets for optimizing clinical benefit.

Therapeutic Drug Monitoring

Therapeutic drug monitoring (TDM) involves the direct measurement of antibiotic concentrations in the blood to allow clinicians to tailor dosing to the individual patient. This concept has been incorporated into standard practice for vancomycin and aminoglycosides, largely secondary to their narrow therapeutic windows and need for avoidance of adverse drug events

[59]. Use of TDM for monitoring and adjusting beta-lactam agents is primarily targeted toward optimizing PK/PD with the overall goal of improving efficacy. Currently, TDM is performed inconsistently across different countries and is still in its infancy with very few ICUs implementing TDM to guide beta-lactam therapy clinically [60].

The majority of literature supporting TDM with beta-lactams are small case-series in various patient populations, for example, burn patients, those on CRRT, and those with augmented renal clearance [8, 61]. In a 2010 proof-in-concept study from Roberts et al., TDM was performed twice weekly in eligible patients receiving any beta-lactam while in the ICU. Doses were adjusted (increased frequency, use of extended or continuous infusion) if levels failed to achieve the goal of 100%*f*T > 4–5MIC. Among 236 patients, doses were increased in 50.4% and doses were decreased in 23.7% of patients. A total of 51 patients had a follow-up TDM levels 2 to 5 days after first level and adjustment; among those patients, 43.1% subsequently met PK/PD targets. The authors highlighted the inadequacies of traditional beta-lactam dosing and provided compelling initial evidence for use of TDM in clinical practice. In 2017, Economou et al. evaluated the utility of TMD in patients undergoing CRRT and among 76 patients studied, 35% of beta-lactam dosing regimens were adjusted. The majority of those changes (24%) were decreases to the beta-lactam dose [62]. As detailed in a recent TDM practice survey, PK/PD targets for beta-lactam exposure to optimize clinical outcomes are unknown, and institutions using TDM have different target goals [63•].

In 2014, Roberts et al. performed a multicenter point prevalence study of over 60 ICUs across multiple countries with the goal of associating PK targets with clinical outcomes in critically ill patients [46]. Among the 361 evaluable patients, 78.9% achieved 50%*f*T > MIC, 60.4% achieved 100%*f*T > MIC, and 35% achieved 100%*f*T > 4 × MIC. A total of 248 patients were treated for an infection, and 58.1% of these patients experienced positive clinical outcomes, defined as completion of treatment course without antibiotic escalation. Through multivariable regression analysis, 100%*f*T > MIC was associated with a 1.56 (95% CI 1.15–2.13) times increased odds of positive clinical outcome. The authors also highlighted that extending infusions of beta-lactams may not always succeed in optimizing beta-lactam PK/PD, demonstrating the complementary nature of these interventions. As is the case for most large-scale practice changes, clinical benefit will likely need to be demonstrated through a large, randomized control trial.

Conclusions

Critically ill adult patients have altered PK which may decrease beta-lactam target attainment of %*f*T > MIC, leading to potential suboptimal outcomes. Additional patient factors, including obesity, augmented renal clearance, CRRT, and ECMO further alter beta-lactam PK and complicate ability to obtained desired PK/PD targets. Further confounding our ability to optimize beta-lactam therapy in critically ill adults is the heterogeneity of study designs, PK/PD targets, and desired patient outcomes. To optimize beta-lactam dosing in these patients, individual patient and organism factors should be taken into consideration. Increasing infusion time (either EI or CI) and/or TDM of beta-lactam antibiotics should be considered in patients who are obese, exhibit augmented renal clearance, or require CRRT, especially when organisms with elevated MICs are isolated. Future studies evaluating patient outcomes, including mortality, are necessary to definitively determine the effectiveness of dosing strategies discussed in these populations.

Compliance with Ethical Standards

Conflict of Interest Anne M. Masich, Mojdeh S. Heavner, Jeffrey P. Gonzales, and Kimberly C. Claeys declare they have no conflicts of interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- Of importance

1. Ambrose PG, Bhavnani SM, Rubino CM, Louie A, Gumbo T, Forrest A, et al. Pharmacokinetics-pharmacodynamics of antimicrobial therapy: it's not just for mice anymore. Clin Infect Dis. 2007;44(1):79–86.
2. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis. 1998;26(1):1–10. quiz 11-2
3. Tsai D, Lipman J, Roberts JA. Pharmacokinetic/pharmacodynamic considerations for the optimization of antimicrobial delivery in the critically ill. Curr Opin Crit Care. 2015;21(5):412–20.
4. Pea F, Viale P. Bench-to-bedside review: appropriate antibiotic therapy in severe sepsis and septic shock—does the dose matter? Crit Care. 2009;13(3):214.
5. 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;77:3–11.
6. Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. Crit Care Med. 2009;37(3):840–51. quiz 859
7. 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.
8. Hayashi Y, Lipman J, Udy AA, Ng M, McWhinney B, Ungerer J, 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(2):162–6.
9. Schleibinger M, Steinbach CL, Topper C, Kratzer A, Liebchen U, Kees F, et al. Protein binding characteristics and pharmacokinetics of ceftriaxone in intensive care unit patients. Br J Clin Pharmacol. 2015;80(3):525–33.
10. Roberts JA, Pea F, Lipman J. The clinical relevance of plasma protein binding changes. Clin Pharmacokinet. 2013;52(1):1–8.
11. Claus BO, Hoste EA, Colpaert K, Robays H, Decruyenaere J, De Waele JJ. Augmented renal clearance is a common finding with worse clinical outcome in critically ill patients receiving antimicrobial therapy. J Crit Care. 2013;28(5):695–700.
12. 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.
13.• Udy AA, Lipman J, Jarrett P, Klein K, Wallis SC, Patel K, et al. Are standard doses of piperacillin sufficient for critically ill patients with augmented creatinine clearance? Crit Care. 2015;19:28. 015-0750-y. **PK/PD study of adultl patients receiving piperacillin-tazobactam demonstrating mean clearance was 1.5 fold increased in critically ill adults compared to healthy volunteers**.
14. 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.
15.• Udy AA, Baptista JP, Lim NL, Joynt GM, Jarrett P, Wockner L, 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(3):520–7. **Prospective observational study of over 900 adult patients in the ICU. Based on eight-hour creatinine clearances, more than half of patients experienced augmented renal clearance**.
16. Carlier M, Carrette S, Roberts JA, Stove V, Verstraete A, Hoste E, 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(3):R84.
17. Hoste EA, Lameire NH, Vanholder RC, Benoit DD, Decruyenaere JM, Colardyn FA. Acute renal failure in patients with sepsis in a surgical ICU: predictive factors, incidence, comorbidity, and outcome. J Am Soc Nephrol. 2003;14(4):1022–30.
18. de Mendonca A, Vincent JL, Suter PM, Moreno R, Dearden NM, Antonelli M, et al. Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score. Intensive Care Med. 2000;26(7):915–21.
19. Jamal JA, Mueller BA, Choi GY, Lipman J, Roberts JA. How can we ensure effective antibiotic dosing in critically ill patients receiving different types of renal replacement therapy? Diagn Microbiol Infect Dis. 2015;82(1):92–103.
20. Roberts JA, Choi GY, Joynt GM, Paul SK, Deans R, Peake S, et al. SaMpling Antibiotics in Renal Replacement Therapy (SMARRT): an observational pharmacokinetic study in critically ill patients. BMC Infect Dis. 2016;16:103. –016–1421-6
21. Heintz BH, Matzke GR, Dager WE. Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. Pharmacotherapy. 2009 May;29(5):562–77.
22. Ulldemolins M, Vaquer S, Llaurado-Serra M, Pontes C, Calvo G, Soy D, et al. Beta-lactam dosing in critically ill patients with septic shock and continuous renal replacement therapy. Crit Care. 2014;18(3):227.
23. Roger C, Cotta MO, Muller L, Wallis SC, Lipman J, Lefrant JY, et al. Impact of renal replacement modalities on the clearance of piperacillin-tazobactam administered via continuous infusion in critically ill patients. Int J Antimicrob Agents. 2017;50(2):227–31.
24.• 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(7):1640–50. **Analysis of PK data from 30 studies to determine the effects of renal replacement modalities on clearance of beta-lactam antibiotics**.
25. Asin-Prieto E, Rodriguez-Gascon A, Troconiz IF, Soraluce A, Maynar J, Sanchez-Izquierdo JA, et al. Population pharmacokinetics of piperacillin and tazobactam in critically ill patients undergoing continuous renal replacement therapy: application to pharmacokinetic/pharmacodynamic analysis. J Antimicrob Chemother. 2014;69(1):180–9.
26. Meng L, Mui E, Holubar MK, Deresinski SC. Comprehensive guidance for antibiotic dosing in obese adults. Pharmacotherapy. 2017;37:1415–31.
27. Alobaid AS, Hites M, Lipman J, Taccone FS, Roberts JA. Effect of obesity on the pharmacokinetics of antimicrobials in critically ill patients: a structured review. Int J Antimicrob Agents. 2016;47(4): 259–68.
28. Hites M, Taccone FS, Wolff F, Cotton F, Beumier M, De Backer D, et al. Case-control study of drug monitoring of beta-lactams in obese critically ill patients. Antimicrob Agents Chemother. 2013 Feb;57(2):708–15.
29. Hites M, Taccone FS, Wolff F, Maillart E, Beumier M, Surin R, et al. Broad-spectrum beta-lactams in obese non-critically ill patients. Nutr Diabetes. 2014;4:e119.
30. Alobaid AS, Brinkmann A, Frey OR, Roehr AC, Luque S, Grau S, et al. What is the effect of obesity on piperacillin and meropenem trough concentrations in critically ill patients? J Antimicrob Chemother. 2016;71(3):696–702.
31. Sturm AW, Allen N, Rafferty KD, Fish DN, Toschlog E, Newell M, et al. Pharmacokinetic analysis of piperacillin administered with tazobactam in critically ill, morbidly obese surgical patients. Pharmacotherapy. 2014;34(1):28–35.
32.• Jung B, Mahul M, Breilh D, Legeron R, Signe J, Jean-Pierre H, et al. Repeated piperacillin-tazobactam plasma concentration measurements in severely obese versus nonobese critically ill septic patients and the risk of under- and overdosing. Crit Care Med. 2017;45(5):e470–8. **Prospective PK/PD study demonstrating under-dosing of piperacillin in obese compared to non-obese patients when causative pathogens have high MICs**.
33. Mosier JM, Kelsey M, Raz Y, Gunnerson KJ, Meyer R, Hypes CD, et al. Extracorporeal membrane oxygenation (ECMO) for critically ill adults in the emergency department: history, current applications, and future directions. Crit Care. 2015;19:431. –015–1155-7
34. Abrams D, Brodie D. Extracorporeal membrane oxygenation for adult respiratory failure: 2017 update. Chest. 2017;152(3):639–49.
35.• Dzierba AL, Abrams D, Brodie D. Medicating patients during extracorporeal membrane oxygenation: the evidence is building. Crit Care. 2017;21(1):66. –017-1644-y. **Comprehensive review of PK/PD alterations during ECMO**.
36. Sherwin J, Heath T, Watt K. Pharmacokinetics and dosing of anti-infective drugs in patients on extracorporeal membrane oxygenation: a review of the current literature. Clin Ther. 2016;38(9):1976–94.
37. Mousavi S, Levcovich B, Mojtahedzadeh M. A systematic review on pharmacokinetic changes in critically ill patients: role of extracorporeal membrane oxygenation. Daru. 2011;19(5):312–21.
38. Shekar K, Fraser JF, Smith MT, Roberts JA. Pharmacokinetic changes in patients receiving extracorporeal membrane oxygenation. J Crit Care. 2012;27(6):741.e9–18.
39. Shekar K, Roberts JA, Mcdonald CI, Fisquet S, Barnett AG, Mullany DV, et al. Sequestration of drugs in the circuit may lead

to therapeutic failure during extracorporeal membrane oxygenation. Crit Care. 2012;16(5):R194.
40. Shekar K, Roberts JA, Ghassabian S, Mullany DV, Wallis SC, Smith MT, et al. Altered antibiotic pharmacokinetics during extracorporeal membrane oxygenation: cause for concern? J Antimicrob Chemother. 2013;68(3):726–7.
41. Shekar K, Fraser JF, Taccone FS, Welch S, Wallis SC, Mullany DV, et al. The combined effects of extracorporeal membrane oxygenation and renal replacement therapy on meropenem pharmacokinetics: a matched cohort study. Crit Care. 2014;18(6):565. -014-0565-2
42.• 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. **Case-control study of 41 ECMO versus 41 matched non-ECMO patients receiving meropenem or piperacillin-tazobactam that did not demonstrate significant difference in PK**.
43. 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;19:164. –015-0891-z
44. Leven C, Fillatre P, Petitcollin A, Verdier MC, Laurent J, Nesseler N, et al. Ex vivo model to decipher the impact of extracorporeal membrane oxygenation on beta-lactam degradation kinetics. Ther Drug Monit. 2017;39(2):180–4.
45. Shekar K, Roberts JA, Welch S, Buscher H, Rudham S, Burrows F, et al. ASAP ECMO: Antibiotic, Sedative and Analgesic Pharmacokinetics during Extracorporeal Membrane Oxygenation: a multi-centre study to optimise drug therapy during ECMO. BMC Anesthesiol. 2012;12:29. 2253–12-29
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.
47. Carlier M, Noe M, Roberts JA, Stove V, Verstraete AG, Lipman J, et al. Population pharmacokinetics and dosing simulations of cefuroxime in critically ill patients: non-standard dosing approaches are required to achieve therapeutic exposures. J Antimicrob Chemother. 2014;69(10):2797–803.
48. Abdul-Aziz MH, Lipman J, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, et al. Is prolonged infusion of piperacillin/tazobactam and meropenem in critically ill patients associated with improved pharmacokinetic/pharmacodynamic and patient outcomes? An observation from the Defining Antibiotic Levels in Intensive care unit patients (DALI) cohort. J Antimicrob Chemother. 2016;71(1):196–207.
49.• 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. **Prospective, randomized comparative study showed significantly increased microbiological success rate, but no significant difference in clinical cure of meropenem continuous infusion**.
50. Lodise TP, Jr LB, Drusano GL. Piperacillin-tazobactam for Pseudomonas aeruginosa infection: clinical implications of an extended-infusion dosing strategy. Clin Infect Dis. 2007;44(3):357–63.
51. Rhodes NJ, MacVane SH, Kuti JL, Scheetz MH. Impact of loading doses on the time to adequate predicted beta-lactam concentrations in prolonged and continuous infusion dosing schemes. Clin Infect Dis. 2014;59(6):905–7.
52. Fan SY, Shum HP, Cheng WY, Chan YH, Leung SM, Yan WW. Clinical outcomes of extended versus intermittent infusion of piperacillin/tazobactam in critically ill patients: a prospective clinical trial. Pharmacotherapy. 2017;37(1):109–19.
53.• Dulhunty JM, Roberts JA, Davis JS, Webb SA, Bellomo R, Gomersall C, et al. A multicenter randomized trial of continuous versus intermittent beta-lactam infusion in severe sepsis. Am J Respir Crit Care Med. 2015;192(11):1298–305. **Randomized, controlled trial of 432 critically ill patients with severe sepsis showed no difference in outcomes between continuous and intermittent infusion of piperacillin-tazobactam, ticarcillin-clavulanate, or meropenem**.
54.• 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. **Prospective, double-blind, randomized controlled trial demonstrated beta-lactam antibiotics achieved higher plasma concentrations with continuous infusion compared to intermittent infusion**.
55. Abdul-Aziz MH, Sulaiman H, Mat-Nor MB, Rai V, Wong KK, Hasan MS, et al. Beta-Lactam Infusion in Severe Sepsis (BLISS): a prospective, two-centre, open-labelled randomised controlled trial of continuous versus intermittent beta-lactam infusion in critically ill patients with severe sepsis. Intensive Care Med. 2016;42(10):1535–45.
56.• Roberts JA, Abdul-Aziz MH, Davis JS, Dulhunty JM, Cotta MO, Myburgh J, et al. Continuous versus intermittent beta-lactam infusion in severe Ssepsis. A meta-analysis of individual patient data from randomized trials. Am J Respir Crit Care Med. 2016;194(6):681–91. **Meta-analysis of 3 randomized controlled trials resulted in significantly lower hospital mortality in patients with severe sepsis who received continuous infusion beta-lactam antibiotics**.
57.• 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(5):403–11. **A systematic review and meta-analysis of 29 studies demonstrated that prolonged infusion of anti-pseudomonal beta-lactam antibiotics were associated with significantly lower mortality**.
58. 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(2):489–95.
59. Jager NG, van Hest RM, Lipman J, Taccone FS, Roberts JA. Therapeutic drug monitoring of anti-infective agents in critically ill patients. Expert Rev Clin Pharmacol. 2016;9(7):961–79.
60. Wong G, Brinkman A, Benefield RJ, Carlier M, De Waele JJ, El Helali N, et al. An international, multicentre survey of beta-lactam antibiotic therapeutic drug monitoring practice in intensive care units. J Antimicrob Chemother. 2014;69(5):1416–23.
61. Pea F, Cojutti P, Sbrojavacca R, Cadeo B, Cristini F, Bulfoni A, et al. TDM-guided therapy with daptomycin and meropenem in a morbidly obese, critically ill patient. Ann Pharmacother. 2011;45(7–8):e37.
62. Economou CJP, Wong G, McWhinney B, Ungerer JPJ, Lipman J, Roberts JA. Impact of beta-lactam antibiotic therapeutic drug monitoring on dose adjustments in critically ill patients undergoing continuous renal replacement therapy. Int J Antimicrob Agents. 2017;49(5):589–94.
63.• Charmillon A, Novy E, Agrinier N, Leone M, Kimmoun A, Levy B, et al. The ANTIBIOPERF study: a nationwide cross-sectional survey about practices for beta-lactam administration and therapeutic drug monitoring among critically ill patients in France. Clin Microbiol Infect. 2016;22(7):625–31. **Cross-sectional survey of French hospitals found that most infectious disease and intensive care specialist are in favor of optimizing administration of beta-lactams through extended infusions or therapeutic drug monitoring (TDM), however that lack of guidelines and limited TDM availability were barriers to implementing such strategies**.