



REVIEW

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Pharmacokinetics and pharmacodynamics of beta-lactam antibiotics in critically ill patients

Farmacocinética y farmacodinámica de los antibióticos betalactámicos en pacientes críticos

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Abstract

Optimal antibiotic therapy for critically ill patients can be complicated by the altered physiology associated with critical illness. Antibiotic pharmacokinetics and exposures can be altered driven by the underlying critical illness and medical interventions that critically ill patients receive in the intensive care unit. Furthermore, pathogens that are usually isolated in the intensive care unit are commonly less susceptible and "resistant" to common antibiotics. Indeed, antibiotic dosing that does not consider these unique differences will likely fail leading to poor clinical outcomes and the emergence of antibiotic resistance in the intensive care unit. The aims of this narrative review were to describe the pharmacokinetics of beta-lactam antibiotics in critically ill patients, to highlight pharmacokinetic/pharmacodynamic targets for both non-critically ill and critically ill patients, and to discuss important strategies that can be undertaken to optimize beta-lactam antibiotic dosing for critically ill patients in the intensive care unit.

Resumen

La terapia antibiótica óptima en los pacientes en estado crítico puede complicarse por la alteración de la fisiología asociada a esta etapa de la enfermedad. La farmacocinética y la exposición a los antibióticos pueden verse alteradas por la enfermedad crítica subyacente y las intervenciones médicas que reciben estos pacientes en la unidad de cuidados intensivos. Además, las cepas que suelen encontrarse en la unidad de cuidados intensivos suelen ser menos susceptibles y "resistentes" a los antibióticos más habituales. De hecho, una dosificación de antibióticos que no tenga en cuenta estas diferencias únicas, probablemente fracasará y dará lugar a resultados clínicos deficientes y a la aparición de resistencia a los antibióticos en la unidad de cuidados intensivos. Los objetivos de esta revisión son describir la farmacocinética de los antibióticos betalactámicos en pacientes críticos, destacar los objetivos farmacocinéticos/farmacodinámicos para los pacientes y exponer algunas estrategias importantes que pueden optimizar la dosificación de los antibióticos betalactámicos en pacientes críticos en la unidad de cuidados intensivos.

KEYWORDS

Antibiotics; Beta-lactams, Critically ill patient;
Clinical pharmacokinetics.

PALABRAS CLAVE

Antibióticos; Beta-lactámicos; Paciente crítico;
Farmacocinética clínica.



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Overview

Sepsis is defined as a life-threatening organ dysfunction due to dysregulated physiological response following infection¹. In a large audit involving 10,069 critically ill patients managed in intensive care units (ICU) worldwide, 13.6% to 39.3% of ICU patients were diagnosed with sepsis². Mortality rates due to sepsis may range between 15% to 20%^{3,5}, with in-hospital mortality rates reported as high as 50.9% in Germany and 58.6% in Italy when septic shock is present^{6,7}. The Surviving Sepsis Campaign International Guidelines for the Management of Sepsis and Septic Shock recommends aggressive resuscitation, source identification and source control, optimization of glycemic control, as well as timely administration of empiric antibiotic therapy during the early hours of sepsis⁸. Timely and optimal antibiotic therapy (including both spectrum of antibiotic activity and therapeutic concentration) is an important intervention for critically ill patients with sepsis or septic shock. In a recent study by Seymour *et al.*⁹, the odds for in-hospital mortality increased by 1.04 for every hour that an appropriate antibiotic is delayed in such a patient population. However, optimal antibiotic therapy, which includes prompt delivery of antibiotics in sufficient concentrations, can be influenced and complicated by the altered physiology in critically ill patients. Antibiotic pharmacokinetic (PK) disposition, namely absorption, distribution, metabolism, and elimination can be altered in such patients, driven by the underlying critical illness and medical interventions (i.e., mechanical and pharmacological) that the patient receives. Additionally, pathogens that are usually isolated in the ICU are commonly less susceptible and "resistant" to common antibiotics¹⁰. Antibiotic dosing that does not consider these unique differences will likely fail leading to poor clinical outcomes and the emergence of antibiotic resistance in the ICU.

The aims of this narrative review were to describe the PK of beta-lactam antibiotics in critically ill patients, to highlight pharmacokinetic/pharmacodynamic (PK/PD) targets for both non-critically ill and critically ill patients, and to discuss important strategies that can be undertaken to optimize beta-lactam antibiotic dosing for critically ill patients in the ICU.

Pharmacokinetic changes

Absorption

The amount of drug absorbed from the site of administration (e.g., enteral, subcutaneous, and intramuscular) to the systemic circulation is influenced by physicochemical properties of beta-lactam antibiotics (e.g., solubility and molecular size), as well as the properties of the organ/tissue through which the beta-lactam antibiotics are absorbed¹¹. In sepsis and septic shock, reduced gut motility, diminished regional blood flow, and delayed gastric emptying have been suggested to reduce drug absorption¹². Intravenous (IV) administration of antibiotics is preferred to account for impaired drug absorption in critically ill patients in the ICU.

Distribution

Abnormal fluid balance following aggressive fluid resuscitation and capillary leak syndrome can result in the "third spacing" phenomenon and cumulative fluid accumulation¹³. This can lead to an increase in the volume of distribution, especially for hydrophilic antibiotics, including beta-lactam antibiotics, glycopeptides, aminoglycosides, linezolid, and lipopeptides¹⁴⁻¹⁸. The impact is more pronounced for hydrophilic antibiotics compared to lipophilic antibiotics, as the latter already has a larger volume of distribution compared to the former¹⁷. A systematic review of clinical studies that evaluated the PK of beta-lactam antibiotics in critically ill patients reported that large volume of distribution differences were commonly observed and most studies reported a 2-fold variation in this PK parameter when compared with the non-critically ill population¹⁹. This phenomenon is likely to decrease concentrations of beta-lactam antibiotics, particularly in the earlier phase of the disease. Therefore, higher initial loading doses should be applied in critically ill patients with sepsis or septic shock to compensate for the enlarged volume of distribution. Numerous studies have shown that higher initial loading doses of beta-lactam antibiotics and other antibiotics (e.g., amikacin, colistin, gentamicin, teicoplanin, and vancomycin) are required to rapidly attain effective concentrations in patients with sepsis or septic shock²⁰⁻²⁵.

Hypoalbuminemia (serum albumin < 25 g/L) is also common in critically ill patients, and this can lead to increased antibiotic distribution and clearance especially for moderately to highly-protein bound beta-lactam antibiotics (e.g., flucloxacillin, ceftriaxone, and ertapenem)²⁶⁻²⁹. The volume of distribution for highly-protein bound beta-lactam antibiotics, such as ceftriaxone and flucloxacillin, are found to be increased (as much as 90%) in critically ill patients with hypoalbuminemia. However, tissue concentrations remain low due to the "third spacing" phenomenon and cumulative fluid accumulation associated with this patient population. Furthermore, as these beta-lactam antibiotics are also cleared renally, the increase in the free fraction of drugs will also result in rapid drug clearance. The altered volume of distribution and clearance for beta-lactam antibiotics may lead to low antibiotic concentrations particularly at the end of the dosing interval. Maintenance doses for these antibiotics should be increased to compensate for this phenomenon and this is particularly relevant for time-dependent antibiotics.

Several medical interventions in the ICU, such as aggressive fluid resuscitation³⁰, mechanical ventilation³¹, extracorporeal circuits³², the presence of post-surgical drains³³, and total parenteral nutrition³⁴, have also been reported to be associated with enlarged volume of distribution and consequently decreased concentrations of hydrophilic antimicrobials.

Clearance

Enhanced renal clearance of antibiotics due to elevated glomerular filtration and tubular secretion/reabsorption has been increasingly described in critically ill patients, leading to subtherapeutic concentrations of antibiotics and treatment failure³⁵. This phenomenon is known as augmented renal clearance (ARC), which is defined as glomerular filtration rate (GFR) of above 130 mL/min/1.73 m² (preferably based on urinary creatinine clearance)³⁶. The phenomenon is likely observed in polytrauma, postoperative and head trauma patients, as well as younger patients, especially in those with lower disease severity^{37,38}. Augmented renal clearance has been strongly associated with suboptimal beta-lactam antibiotic^{39,40} and vancomycin⁴¹⁻⁴³ exposures, which may partly explain the poor clinical outcomes associated with critically ill patients receiving these antibiotics. Therefore, for these antibiotics, which display time-dependent properties and predominantly cleared by the kidneys, applying altered dosing strategies, such as extended or continuous infusion, may likely maintain effective drug concentrations for a longer duration in critically ill patients with ARC.

On the other hand, reduced antibiotic metabolism and clearance might occur following organ hypoperfusion leading to renal and/or hepatic dysfunction. As the disease progresses in a critically ill patient, myocardial depression may occur leading to decreased organ perfusion and microcirculatory failure. These could cause end-organ damage or in extreme cases, multi-organ dysfunction syndrome³². This syndrome often includes renal and/or hepatic dysfunction that consequently results in decreased antibiotic clearance. Renal dysfunction or acute kidney injury (AKI) leads to reduced GFR and clearance of renally eliminated antibiotics. Nonetheless, dose reduction of antibiotics is not straight forward in patients with AKI, as the decision should consider patient's residual kidney function and fluid status, use of renal replacement therapy (RRT), and the antibiotic PK/PD target⁴⁴. Beta-lactam antibiotic dosing requirements for critically ill patients are highly dynamic, and regular dosing reviews and modifications are likely required to prevent both suboptimal dosing and development of adverse events.

Mechanical intervention

Mechanical intervention for organ support has been shown to alter antibiotic PK⁴⁵⁻⁴⁹. Mechanical ventilation can alter antibiotic PK by increasing the intrathoracic pressure, leading to a decreased venous return to the heart⁵⁰. This can lead to an increase in the antibiotic volume of distribution, as well as reduced clearance due to decreased GFR^{47,51,52}. In a study performed by Medellín-Garibay *et al.*, mechanical ventilation was shown to reduce the clearance of vancomycin by 20%⁴⁶. The decrease in drug clearance was linked to hemodynamic changes in mechanically ventilated patients, which reduced the renal blood flow leading to a reduction in the glomerular function and urine output⁵³. Renal replacement therapy may alter the PK of beta-lactam antibiotics by augmenting antibiotic clearance and volume of distribution⁵⁴. This is dependent on a few factors including

dialysate flow rate, mode of dialysis, type of dialysis membrane, dialysis duration, as well as antibiotic physicochemical properties, and the degree of protein binding⁵⁵. Patients with AKI receive various forms of RRT, but continuous renal replacement therapy (CRRT) remains the common mode of RRT for critically ill patients in the ICU^{56,57}. CRRT is commonly not applied in a uniform way and therefore, antibiotic clearance may greatly vary and be lower than what has been initially prescribed^{48,57}. No conclusive dosing recommendations can be made currently for critically ill patients receiving CRRT but as a general rule, antibiotics with a high volume of distribution (1 L/kg or greater) and/or that are highly protein bound (80% or greater) are generally poorly eliminated by CRRT⁵⁸. Current data suggest that a significant proportion of CRRT patients are at an increased risk for either antibiotic underexposure or overexposure⁴⁸.

Another form of mechanical intervention in the ICU is extracorporeal membrane oxygenation (ECMO). It is an artificial and temporary respiratory and/or cardiac support that is carried out extracorporeally (i.e., cardio-pulmonary bypass) in patients with cardiorespiratory failure refractory to conventional medical therapies⁵⁹. Its use has increased steadily, especially during the current COVID-19 pandemic, whereby the World Health Organization (WHO) recommends its use in COVID-19 patients with profound hypoxemia (with or without hypercapnia) not amenable to the lung-protective ventilation⁶⁰. Earlier neonatal and paediatric data suggest that ECMO has the potential to alter the PK of many important antibiotics including beta-lactam antibiotics⁶¹. ECMO extracorporeal circuits consisting of conduit tubing provide an additional "compartment" through which beta-lactam antibiotics can distribute⁶². The circuit tubes, as well as the oxygenator membrane, introduce additional surface areas that the beta-lactam antibiotics can adhere and sequester onto. This is particularly problematic to antibiotics that are lipophilic⁶³, highly-protein bound (e.g., ceftriaxone⁶⁴), or chemically unstable (e.g., meropenem⁶⁵). The priming of the ECMO circuit can also dilute and sequester the drug further⁶⁶. All the above are theorized to lead to an increase in the beta-lactams volume of distribution and possibly treatment failure due to subtherapeutic concentrations⁶⁵. In addition, ECMO patients have lower drug clearance when compared to patients not undergoing ECMO⁶⁷. However, based on current clinical evidence: (1) modern ECMO circuits have minimal impact on the PK of most antibiotics, including beta-lactam antibiotics; (2) PK changes in patients receiving ECMO are more reflective of critical illness rather than ECMO therapy itself; and (3) apart from lipophilic and highly-protein bound antibiotics, the impact of ECMO on the PK and dosing requirements is likely to be minimal^{68,73}.

In conclusion, profound alteration of beta-lactam antibiotic PK is common in critically ill patients, especially in those receiving mechanical organ support. Nonetheless, contemporary antibiotic dosing is largely based on dose-finding studies which mostly included healthy participants and patients who are not critically ill. Such a dosing approach has been increasingly shown to increase risks of suboptimal beta-lactam antibiotic exposure in a large proportion of critically ill patients^{74,75}.

Beta-lactam antibiotic pharmacodynamics

Antibiotics can be broadly categorized into three pharmacokinetics/pharmacodynamics (PK/PD) groups based on their modes of bacterial killing⁷⁶: concentration-dependent, time-dependent, and both concentration- and time-dependent agents. For concentration-dependent antibiotics, a direct relationship exists between antibiotic concentration and efficacy where increasing concentrations enhance bacterial killing. For these antibiotics (e.g., aminoglycosides and fluoroquinolones), the maximum concentration (C_{max}) relative to the minimum inhibitory concentration (C_{max}/MIC) best describes their activity. For time-dependent antibiotics (e.g., beta-lactam antibiotics), prolonging the duration of exposure enhances bacterial killing and it is the percentage of the dosing interval that the free drug concentrations remain above the MIC ($\%fT_{>MIC}$) that drives their efficacy. For antibiotics that display both concentration- and time-dependent killing characteristics, the ratio of area under the concentration-time curve (AUC) to MIC (AUC/MIC) best describes their activity. For antibiotics, achieving these PK/PD indices may decrease the likelihood of microbiological and clinical response.

The PK/PD index associated with optimal beta-lactam antibiotic activity is the $\%fT_{>MIC}$ (40 – 70%)⁷⁷. Beta-lactam antibiotics demonstrate superior bacterial killing the longer that drug concentrations remain above the

MIC of a pathogen. Clinical data from critically ill patients suggest that these patients may benefit from longer (e.g., 100% $fT_{>MIC}$) and higher (e.g., 2 – 5 × MIC) beta-lactam exposures than those previously described in *in vitro* and *in vivo* animal model studies⁷⁷.

Beta-lactam antibiotic optimization in critically ill patients

Pharmacokinetic changes of beta-lactam antibiotics in critically ill patients

Poor beta-lactam antibiotic PK/PD target attainment in critically ill patients has been illustrated in two recently published multicentre clinical studies^{48,74}. In a large point prevalence PK study of beta-lactam antibiotics (i.e., the DALL study) involving 384 patients, up to 500-fold variations were seen in the unbound concentrations of the studied beta-lactam antibiotics⁷⁴. Of these, 248 (64.5%) patients were treated for infection and 40 (16.0%) of them did not achieve the predefined PK/PD target (50% $fT_{>MIC}$) and they were 32.0% less likely to have a positive clinical outcome. Similarly, poor target attainment was seen in the SMARRT study, a large prospective, multinational PK study, involving 381 patients on RRT receiving either meropenem, piperacillin-tazobactam or vancomycin⁴⁸. Up to 55% of the concentrations failed to achieve the low target trough concentrations, with higher failure rates (up to 72.0%) seen with the high target trough concentrations. The trough concentrations were inversely associated with the estimated total renal clearance of the prescribed RRT and residual renal clearance. In addition, highly variable trough concentrations (up to 8-fold) were seen in this study.

Strategies to improve PK/PD target attainment

Altered dosing strategy via prolonged infusion

Numerous studies have shown better PK/PD target attainment with prolonged (PI) or continuous infusion (CI) of beta-lactam antibiotic compared to intermittent bolus (IB) dosing^{78,79}. The altered dosing strategy increases the percentage of time that free beta-lactams concentrations remains above the target MIC for a given dosing interval, allowing enhanced bacterial killing⁸⁰. Roberts *et al.*, demonstrated median steady-state concentrations of 16.6 mg/L with CI of piperacillin when compared to median C_{min} concentrations of 4.9 mg/L following IB dosing, despite a lower total CI daily dose (25% lower than the IB regimens)⁷⁹. Noteworthy, systemic review and meta-analyses comparing between CI/PI and IB dosing of beta-lactam antibiotics in terms of survival benefit have shown mixed results⁸¹⁻⁸⁷. However, when the studies are limited to patients with severe sepsis who received equivalent doses of antibiotics in both arms (IB vs. PI/CI), lower in-hospital mortality was shown in patients receiving CI of beta-lactam antibiotics⁸¹.

Prior to the rollout of CI or PI dosing of beta-lactam antibiotics in the ICU, physicians should consider the following: 1) the use of loading dose; 2) antibiotic stability; 3) residual volume or dead space; 4) compatibility with other drugs; 5) drug accumulation in patients with renal dysfunction; and 6) target population and knowledge of susceptibility data for antibiotics aimed for PI program. Application of loading dose would shorten the time to therapeutic exposure^{88,89}. A loading dose is a short-term dose given as an intermittent bolus (30-60 minutes) followed by the total recommended daily dose given as PI or CI⁹⁰. Infusion duration, beta-lactam antibiotic concentrations (with lower final concentrations post reconstitution being more stable compared to higher concentrations), types of diluents, and container used for reconstitution can affect the beta-lactam stability, and therefore, these need to be considered prior to the beta-lactam antibiotic CI/PI dosing rollout in the ICU. Of the beta-lactam antibiotics that have been studied for PI, both meropenem and imipenem show the shortest duration of stability (4 to 9 hours after reconstitution with water for injection)^{91,92}. Other beta-lactam antibiotics including amoxycillin, benzylpenicillin, and ceftazidime have also been reported to be stable less than 24 hours⁹³⁻⁹⁵. Therefore, multiple infusions need to be given over 24 hours when these agents are used. Next, residual volume following beta-lactams infusion can reduce the total amount of beta-lactams given to patients.

Bolla *et al.*, showed that more than 10% of antimicrobial would be lost for 26 of 39 studied antibiotics if the residual volume is not infused back to patients at the end of the infusion⁹⁶. Noteworthy, rapid flushing of the intravenous (IV) line to deliver this “infusion line dead space” to patients is contra to the principle of PI as the residual volume will be delivered in a bolus form rather than prolonged infusion⁹⁷. Therefore, the residual volume should instead be infused at an appropriate rate with clear administration instructions given to the nurses. Another strategy that can be used to overcome this is by giving higher doses to compensate for the loss from the residual volume⁹⁸. To the best of our knowledge, there is yet a published PK study assessing the effectiveness of these strategies in improving beta-lactam antibiotic exposures in patients with the infusion line dead space. Another consideration is the beta-lactam antibiotics compatibility with other IV drugs when the beta-lactams cannot be given through a dedicated line. The issue can be handled through three possible ways: 1) co-administration of a drug/drugs that is proven to be compatible with the beta-lactam antibiotics; 2) the placement of additional IV line; and 3) shortening the infusion time of the beta-lactams (i.e., less than 24 hours) with the adjustment of medication administration time to allow the incompatible drug(s) to be administered at different occasions⁹⁹.

TDM-based strategy

Dose personalization for beta-lactam antibiotics guided by therapeutic drug monitoring (TDM) is still under investigation as beta-lactam antibiotics have a wide therapeutic range with a favorable safety profile, unlike aminoglycosides and vancomycin. However, given the high PK variability seen with beta-lactam antibiotics in critically ill patients¹⁰, TDM might be useful in optimizing drug exposure as the variability might lead to subtherapeutic or supratherapeutic concentrations. It might also be useful in a certain group of critically ill patients, such as those who are obese, immunocompromised, infected by resistant bacterial strains, and in those receiving RRT or having augmented renal clearance¹⁰⁰⁻¹⁰³. These patients are at high risk of underdosing. Nonetheless, there are only two published randomized controlled trials (RCT) on beta-lactam antibiotics TDM, with both using PK/PD target attainment rather than clinical endpoints (e.g., survival benefit) as their outcome measures^{104,105}. Currently, there are two ongoing randomized controlled trials (RCTs) investigating this question: does beta-lactam antibiotics TDM improve clinical outcomes^{106,107}?

Several observational studies on beta-lactam antibiotics TDM have been published (Table 1)¹⁰⁸⁻¹¹². In these studies, samples for TDM were performed

at steady-state prior to the next dosing (i.e., trough or C_{min} concentration), except in one study, whereby mid-dose and trough samplings were performed in patients receiving IB dosing of beta-lactams (in the same study, the sampling was performed at steady state in the CI arm)¹⁰⁸. Variable PK/PD targets were used, with dosing adjustments performed in patients who did not achieve the predefined targets. For example, Wong *et al.*, increased the dosing frequency of the beta-lactams by 25% to 50% or changed the infusion strategy from IB to PI/CI dosing when the beta-lactams concentrations were below the PK/PD target (i.e., $100\%fT_{>MIC}$)¹⁰⁸. Conversely, the dose was either decreased by 50% or the frequency was reduced by 25% to 50% of the same daily dose when the PK/PD exposures were higher than $100\%fT_{>MIC}$. The rates of PK/PD target attainment for $100\%fT_{>MIC}$ and $100\%fT_{>4 \times MIC}$ were 66.9% and 36.6%, respectively for the seven studied beta-lactam antibiotics. Collectively, these studies showed that a significant number of critically ill patients did not achieve the desired PK/PD targets for patient benefits. Poor target attainment, even with alternative dosing strategy (e.g., PI dosing)¹⁰⁸ in some studies, underlines the difficulty of getting the dose right in critically ill patients. Therefore, applying aggressive initial dosing regimen (e.g., high-dose regimens via CI or PI during the initial empiric therapy) coupled with TDM may currently be the best strategy to optimize of beta-lactam antibiotic exposures in critically ill patients.

Conclusion

Appropriate beta-lactam antibiotic dosing remains a challenge in critically ill patients, who are at a high risk of mortality due to sepsis and septic shock. These patients are usually managed in the ICU, where infections by resistant pathogens, especially Gram-negative microorganisms are common. This makes the attainment of PK/PD target in this group even more difficult. Therefore, alternative dosing strategies for beta-lactam antibiotics should be considered for these patients, which may include the use of PI or CI dosing. Personalized dosing guided by TDM can also improve PK/PD target attainment within an individual patient, and data from ongoing RCTs are needed to support a global practice of performing TDM for beta-lactam antibiotics in critically ill patients.

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Conflict of interest

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Table 1. Observational TDM studies of beta lactams

No	Paper (year) Antibiotics	PK/PD target	Population	Intervention Control	Outcome measures
1	Therapeutic drug monitoring of beta-lactams in critically ill patients (2012) ¹⁰⁴ Penicillin, ampicillin, dicloxacillin, flucloxacillin, piperacillin, cephalothin, cefazolin, ceftriaxone, ceftazidime, cefepime, ertapenem and meropenem	Trough-based at steady state Primary $100\%fT_{>4-5 \times MIC}$	Critically ill adults	Dose adjustment when the concentrations were not within target No control arm	Positive <ul style="list-style-type: none"> Completion of the treatment course without change Addition of antibiotic therapy or commencement of additional antibiotics within 48 h of discontinuation of the antibiotic therapy De-escalation of therapy to a narrower-spectrum agent Negative <ul style="list-style-type: none"> Patient death Escalation of therapy Cessation of antibiotic owing to an adverse drug reaction

Table 1 (cont.). Observational TDM studies of beta lactams

No	Paper (year) Antibiotics	PK/PD target	Population	Intervention Control	Outcome measures
2	Therapeutic Drug Monitoring of Beta-Lactam Antibiotics in Burns Patients—A One-Year Prospective Study (2012) ¹⁰³ Flucloxacillin, dicloxacillin, penicillin, ampicillin, piperacillin, ceftriaxone and meropenem	Trough-based at steady state Primary $100\%fT_{>MIC}$ Secondary $100\%fT_{>4 \times MIC}$	Patients who were admitted into the burn unit	Dose adjustment when the concentrations were not within target No control arm	Positive <ul style="list-style-type: none"> • Completion treatment course without change or addition of antibiotic therapy • Commencement of additional antibiotics within 48 hours of discontinuation of antibiotic therapy Negative <ul style="list-style-type: none"> • Any change in the antibiotic therapy • Addition of another antibiotic to manage the infection • Development of a super infection (i.e., infection caused by an organism not susceptible at any stage to the original antibiotic)
3	Impact of the introduction of real-time therapeutic drug monitoring on empirical doses of carbapenems in critically ill burn patients (2015) ¹⁰² Imipenem and meropenem	Trough-based at steady state For empiric therapy: $C_{min} > MIC_{90}$ The MIC ₉₀ was based on the bacteria isolated in their burn unit For targeted therapy: $C_{min} > MIC$ The target MIC was fixed at > 1 mg/L when no organism was isolated, except when sepsis or septic shock was present, whereby the target was > 2 mg/L then	Patients who were admitted into the burn ICU	Dose adjustment was made based on the TDM results to meet the predefined targets stratified by the infection severity Methodology section does not discuss on the control arm. However, the TDM was requested at the discretion of physicians. Therefore, some of the patients did not undergo beta-lactams TDM. In the results, patients who underwent TDM was compared to those who did not undergo the monitoring	Not defined in the methodology section
4	Impact of β -lactam antibiotic therapeutic drug monitoring on dose adjustments in critically ill patients undergoing continuous renal replacement therapy (2017) ¹⁰¹ Benzylpenicillin, ampicillin, flucloxacillin, piperacillin/tazobactam, ceftriaxone and meropenem	Trough-based at steady state $100\%fT_{>MIC}$ The dose was reduced when the $C_{min} > 10 \times MIC$	Adults (≥ 18 years old) undergoing CRRT and TDM for the beta-lactams that they received	Dose adjustment was made based on the TDM results No control arm	Not defined in the methodology section

Table 1 (cont.). Observational TDM studies of beta lactams

No	Paper (year) Antibiotics	PK/PD target	Population	Intervention Control	Outcome measures
5	Therapeutic drug monitoring of β -lactam antibiotics in the critically ill: direct measurement of unbound drug concentrations to achieve appropriate drug exposures (2018) ¹⁰⁰ Ampicillin, benzylpenicillin, dicloxacillin, flucloxacillin, piperacillin, cephalothin, cefazolin, ceftriaxone, meropenem andertapenem	Sampling was done at steady state For IB, two samplings were performed: at mid-point and immediately prior to the next dose within a single dosing interval For CI, samplings were taken after at least four half-lives $100\% fT >_{MIC}$ The dose was reduced when the $C_{min} > 10X MIC$	Adults (≥ 18 years old) admitted into ICU	Dose adjustment was made based on the TDM results No control arm	Positive Resolution or improvement of the infection as assessed by independent clinicians Negative Any outcome other than above

CI: continuous infusion; IB: intermittent bolus; ICU: intensive care unit.

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