Expert Opinion on Drug Metabolism & Toxicology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iemt20

# The impact of continuous renal replacement therapy on antibiotic pharmacokinetics in critically ill patients

Marco Fiore, Lorenzo Peluso, Fabio Silvio Taccone & Maya Hites

**To cite this article:** Marco Fiore, Lorenzo Peluso, Fabio Silvio Taccone & Maya Hites (2021): The impact of continuous renal replacement therapy on antibiotic pharmacokinetics in critically ill patients, Expert Opinion on Drug Metabolism & Toxicology, DOI: 10.1080/17425255.2021.1902985

**To link to this article:** https://doi.org/10.1080/17425255.2021.1902985

Published online: 28 Mar 2021.

EXPERT OPINION ON DRUG METABOLISM & TOXICOLOGY
https://doi.org/10.1080/17425255.2021.1902985

Taylor & Francis
Taylor & Francis Group

REVIEW



# The impact of continuous renal replacement therapy on antibiotic pharmacokinetics in critically ill patients

Marco Fiore[a], Lorenzo Peluso[a], Fabio Silvio Taccone[a] and Maya Hites[b]

[a]Department of Intensive Care, Hopital Erasme, Brussels, Belgium; [b]Department of Infectious Diseases, Hopital Erasme, Brussels, Belgium

**ABSTRACT**

**Introduction**: Mortality due to severe infections in critically ill patients undergoing continuous renal replacement therapy (CRRT) remains high. Nevertheless, rapid administration of adequate antibiotic therapy can improve survival. Delivering optimized antibiotic therapy can be a challenge, as standard drug regimens often result in insufficient or excessive serum concentrations due to significant changes in the volume of distribution and/or drug clearance in these patients. Insufficient drug concentrations can be responsible for therapeutic failure and death, while excessive concentrations can cause toxic adverse events.

**Areas covered**: We performed a narrative review of the impact of CRRT on the pharmacokinetics of the most frequently used antibiotics in critically ill patients. We have provided explanations for the changes in the PKs of antibiotics observed and suggestions to optimize dosage regimens in these patients.

**Expert opinion**: Despite considerable efforts to identify optimal antibiotic dosage regimens for critically ill patients receiving CRRT, adequate target achievement remains too low for hydrophilic antibiotics in many patients. Whenever possible, individualized therapy based on results from therapeutic drug monitoring must be given to avoid undertreatment or toxicity.

**ARTICLE HISTORY**
Received 23 July 2020
Accepted 10 March 2021

**KEYWORDS**
Aminoglycosides; antibiotics; acute kidney injury; beta-lactams; critically ill patients; renal replacement therapy; glycopeptides; lipopeptides; pharmacokinetics; sepsis

## 1. Introduction

Renal replacement therapy (RRT) is generally performed in case of kidney failure, including acute kidney injury (AKI) or end-stage chronic kidney disease (CKD). This technique has been plagued with a confusing array of nomenclature in the literature because it includes peritoneal dialysis (PD), intermittent hemodialysis (IHD), sustained low-efficiency dialysis (SLED), extended daily dialysis (EDD) and continuous renal replacement therapy (CRRT). Moreover, CRRT encompasses different modalities, such as slow continuous ultrafiltration (SCUF), continuous veno-venous hemofiltration (CVVH), continuous veno-venous hemodialysis (CVVHD) or a combination of convective and diffusive therapies, e.g. continuous veno-venous hemodiafiltration (CVVHDF) [1].

In patients with AKI, the different renal functions are altered: glomerular filtration, tubular secretion, and reabsorption [2]. The objective of RRT is therefore to substitute kidney function of glomerular filtration by removing fluid overload, reestablishing physiological acid-base equilibrium and eliminating endogenous or exogenous toxins. The patient populations that benefit from RRT can vary significantly, but it is only in the intensive care unit (ICU) that all modalities of RRT are used [3–5]. In this setting, RRT is used frequently in 25–65% of ICU patients developing AKI during their stay [2,6–8]. AKI is usually multifactorial, but most frequent causes are shock, drug toxicity, and/or sepsis [9], a life threatening organ dysfunction caused by a dysregulated response to infection [10].

Antibiotics are therefore one of the drugs often administered to these critically ill patients receiving RRT. Mortality rates due to infection remain very high in this patient population, but rapid, appropriate and adequate antibiotic therapy may improve outcome [11–13]. Appropriate therapy means that the antibiotic administered is active *in-vitro* against the pathogen(s) responsible for the infection, and adequate therapy means that the concentration of the antibiotic at the site of the infection will be sufficient to treat these same pathogen(s). However, giving appropriate and adequate antibiotic therapy to critically ill patients receiving RRT can be a real challenge because they are at greater risk of presenting infections due to resistant pathogens compared to patients hospitalized in the general ward [14,15], and standard drug regimens often do not provide adequate drug concentrations at the site of the infection [12,-,16–18]. Indeed, critically ill patients (not only septic patients) present unpredictable pharmacokinetics (PK), showing significant inter- and/or intra-individual variability [19–21]. The PK variations are due to significant changes in the volume of distribution (VD) and the total body clearance of drugs (CL) caused by the host's response to infectious or noninfectious pathological changes, but also by the treatments given to these patients. The VD of hydrophilic drugs can be increased due to altered fluid balance, increased capillary permeability, or hypoalbuminemia, while the CL can be either decreased due to organ failure (i.e. acute liver failure for lipophilic drugs, and acute renal failure for hydrophilic drugs), or increased due to augmented renal clearance in the case of hydrophilic drugs [22]. The PK of

**CONTACT** Fabio Silvio Taccone Fabio.Taccone@erasme.ulb.ac.be Department of Intensive Care, CUB - Erasme Hospital, Route De Lennik, 808, Brussels, 1070, Belgium

**Article highlights**

- Rapid, appropriate and adequate antibiotic therapy is necessary to increase survival in critically ill patients with severe bacterial infections on continuous renal replacement therapy (CRRT)
- There is significant inter and/or intra-individual antibiotic pharmacokinetic (PK) variability in critically ill patients on CRRT, due to unpredictable changes in volume of distribution and drug clearance, very heterogeneous CRRT prescription (i.e. modality, intensity and the use of pre- or post-dilution fluid replacement) and to variability in drug regimens.
- Many critically ill patients on CRRT fail to reach antibiotic therapeutic target concentrations, at least for less susceptible strains.
- Individualized antibiotic therapy, guided by therapeutic drug monitoring and minimal inhibitory concentration (MIC) determination, should be given, whenever possible, to all critically ill patients on CRRT to increase chances of attaining therapeutic concentrations and avoid potentially toxic levels.

This box summarizes key points contained in the article.

drugs can be further impacted by organ support, such as RRT (and the different modalities used), or extracorporeal membrane oxygenation (ECMO) or both [23].

The purpose of this article was therefore to perform a narrative review of the potential PK changes of different antibiotics in critically ill patients receiving CRRT, and to provide dose suggestions for these patients. We focused on CRRT to reduce variability in data analysis and drug regimen proposals; also, only the most frequently used antibiotics were discussed. We concluded this review with our opinion on how best to optimize antibiotic therapy in this patient population.

## 2. Pharmacokinetic/pharmacodynamic targets of antibiotics

When trying to optimize antibiotic therapy, it is important to know which are the targets of our therapy. The PK/Pharmacodynamics (PD) of an antibiotic is the relationship between its dose and effect. The dose of an antibiotic administered to a patient will result in different drug concentrations in different body fluids and tissues over time, otherwise defined as PKs. Antibiotic concentrations can be described by trough concentrations (i.e. the concentration measured just before administering the next dose of the antibiotic; Cmin), the maximal concentration after administration of a dose (Cmax), and the area under the concentration curve (AUC). The PD of an antibiotic is its *in-vivo* effect on killing or inhibiting bacterial growth at different concentrations. The pathogen's response to an antibiotic can be quantified by measuring the minimal antibiotic concentration (MIC) that inhibits bacterial growth under standard conditions. There are three different PK/PD indexes; antibiotics can be classified according to the PK/PD index that best describes their efficacy. Furthermore, specific PK/PD targets have been identified for most antibiotics to ensure optimal efficacy. The PK/PD indexes are as follows:

- The time that the free fraction of the antibiotic remains above the MIC of the pathogen (fT>MIC). These antibiotics are classified as time-dependent antibiotics because an increase in concentrations above fourfold the MIC of the pathogen will have little effect on efficacy;
- The ratio of the Cmax/MIC during one dosing interval. These antibiotics are classified as concentration-dependent;
- The ratio of the AUC of the free fraction of the antibiotic/MIC of the pathogen (fAUC/MIC). These antibiotics are classified as concentration-dependent antibiotics with time dependency [24].

As free drug concentration is not always measurable and protein link is neglectable for some drugs (i.e. ß-lactams, aminoglycosides), total drug concentration can also be used to quantify T> MIC, Cmax/MIC and AUC/MIC. Moreover, although these PK/PD indexes can help guide clinicians to aim to obtain optimal efficacy, this is only a very simplified way of trying to describe very complex clinical situations. These PK/PD indexes have never been validated in situations with profoundly different PKs such as prolonged half-life and considerably extended dose intervals. For example, continuous infusion of ß-lactam antibiotics is sometimes proposed to facilitate PD target attainment. However, data are emerging suggesting that PK/PD targets for ß-lactam antibiotics to obtain the same level of bacterial cell kill may differ in function of whether the antibiotic is administered in a continuous or intermittent fashion [25].

## 3. Pharmacokinetic drug changes during CRRT: a general overview

In order to perform CRRT, patients need to be connected to a dialysis machine with a permeable membrane via an extracorporeal circuit (with a pump). The different CRRT modalities use convection, diffusion or both to substitute the kidney's function of glomerular filtration. Convection is the movement of water from the blood compartment, across a semi-permeable membrane to the dialysis machine, caused by a transmembrane pressure gradient resulting from differences in oncotic and hydrostatic pressure. Diffusion depends on the osmotic pressure gradient between the plasma and the dialyzate compartments; molecules will follow the pressure gradient from high to low pressure. In contrast to IHD, which uses both convection and diffusion during 3 to 4 hours sessions, and intermittent prolonged dialysis, which is performed during 6 to 12 hours sessions using conventional hemodialysis machines (but with lower blood and dialyzate flows), CRRT is performed continuously (e.g. 24 hours per day), with the possibility of eliminating molecules by convection (CVVH), diffusion (CVVHD), or both (CVVHDF). The different CRRT modalities and/or intensities employed can theoretically alter the PK of antibiotics due to changes in drug distribution or clearance. The PKs of antibiotics can be further altered in function of the physicochemical properties of the drug, and inherent specific patient characteristics at the given time.

### 3.1. Drug distribution

Although the VD of hydrophilic antibiotics can be very significantly increased in critically ill patients on CRRT, the intensity

of the RRT will have no effect on the VD of an antibiotic, as shown in a multicenter study on the effect of continuous hemodiafiltration intensity on the PKs of ciprofloxacin, meropenem, piperacillin-tazobactam and vancomycin in 24 critically ill patients [26]. Furthermore, the VD of an antibiotic can vary in function of the fluid status of the patient and/or the quantity of fluids removed during the dialysis procedure [27].

Table 1. Estimated glomerular filtration provided by each continuous renal replacement therapy (CRRT) modality.

| Renal replacement therapy | Glomerular filtration (mL/min) |
|---|---|
| CVVH | 15–25 |
| CVVHD | 15–25 |
| CVVHDF | 30 à 40 |
| SLED | 10–50 |

Abbreviations: CVVH, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemodialysis; CVVHDF, continuous veno-venous hemodiafiltration; SLED, sustained-low efficiency dialysis

### 3.2. Drug clearance

Renal replacement therapy significantly alters the CL of renally excreted antibiotics. There are several factors that will influence the CL of the antibiotic when using CRRT: a) CRRT modality and intensity employed; b) the physicochemical properties of the molecule; c) patient's characteristics (Figure 1). Table 1 provides the estimated glomerular filtration rates obtained in function of each CRRT modality [28]. However, the intensity or « dose » of CRRT modalities can also vary. The « dose » of CRRT is the effluent flow rate (e.g., the outgoing flow rate), which is equal to the ultrafiltrate rate added to the dialyzate rate. Therefore, the greater the ultrafiltration rate (e.g. the quantity of water and solutes eliminated per unit of time), and/or the greater the dialyzate flow, the greater the CL of the antibiotic will be. To avoid significant variations in volume for the patient, fluids can be replaced either as pre- or post-dilution (e.g. before or after the dialyzate filter). When replaced as 'predilution,' the CL of antibiotics will be reduced because the plasma is diluted before being filtered (e.g. the concentration gradient is reduced). When fluids are replaced as 'post-dilution', drug CL is maximized. The membrane used for CRRT will also influence the CL of the antibiotic. As the size of the pores of the membrane increase, the size, and number of molecules that can be filtered can increase as well. The membranes used for intermittent hemodialysis usually have small pores, not allowing the elimination of molecules bigger than 500 Da. On the other hand, membranes used for CRRT have bigger pores (20,000–50,000 Da), and are quite permeable to water and molecules of 1000–12,000 Da. Furthermore, as the surface area of the membrane increases, so does the filtration capacity of the membrane [29]. The membranes made of « natural » or biocompatible substances (e.g. cuprophane) have small pores. These membranes can be responsible for adsorption of certain molecules, especially in the case of polyacrylonitrile. The membrane is saturable; therefore, adsorption of antibiotics is a function of the frequency that the membrane is changed. The effects on the PK of antibiotics seem to be negligible, with the exception of amikacin and levofloxacin: these drugs fix irreversibly to the membranes made of polyacrylonitrile [30,31].

### 3.3. The physicochemical properties of a drug

When considering the molecule, the characteristics that can influence its CL are drug size, its hydrophilic, or lipophilic

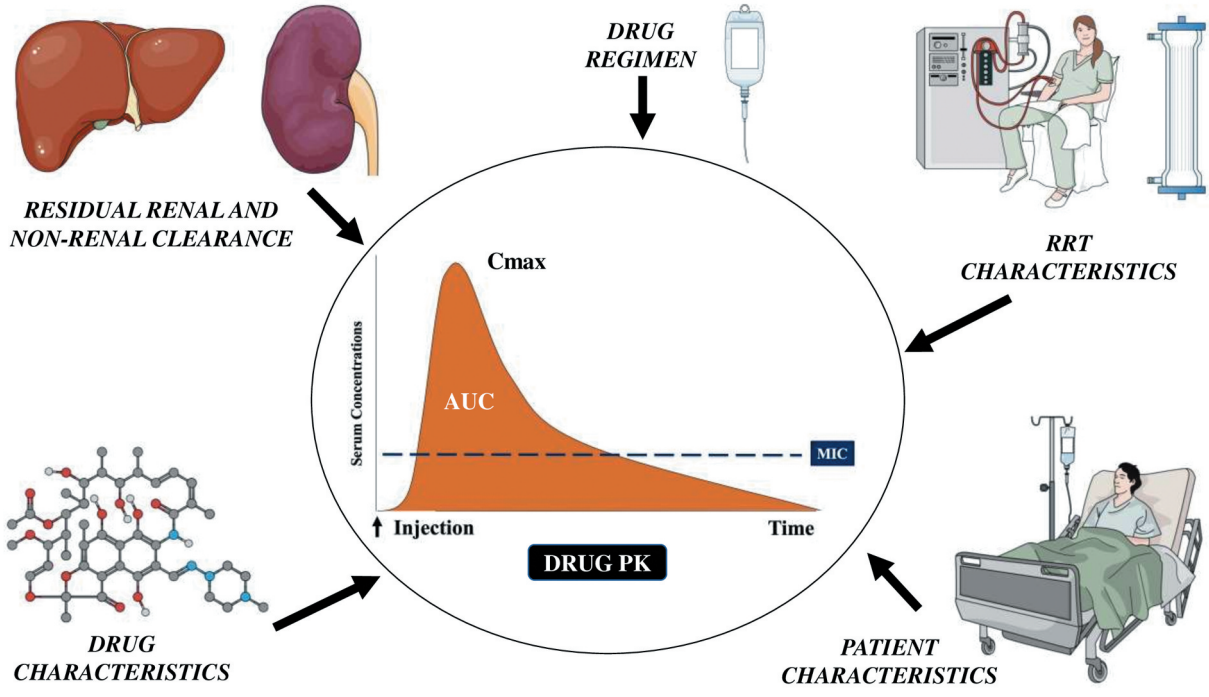


Figure 1. Impact of different factors on antibiotic pharmacokinetics during critical illness and continuous renal replacement therapy.

nature, the VD, the degree of protein-binding and its ionization. Most antibiotics are bigger than 500 Da; a molecule smaller than 500 Da will be eliminated easily both by convection and diffusion, but if larger than 15,000 Da, it can only be eliminated by convection. The CRRT modalities that use convection (e.g. CVVH) eliminate bigger molecules than those dependent only on diffusion (e.g. CVVHD). If a molecule has a large VD, as observed with lipophilic drugs, the concentration in the plasma will only be a small fraction of the concentration of the antibiotic in the whole body. Therefore, because the drug will be eliminated by filtration of the plasma, the CL of the antibiotic via the CRRT will be minimal. When an antibiotic is protein-bound, the molecule is significantly larger (>50,000 Da) than when it is free or unbound. It is the free fraction of the antibiotic that is eliminated by CRRT. Antibiotics can sometimes be ionized. If they are charged positively (e.g. aminoglycosides), their elimination across the filtration membrane will be reduced by anionic molecules, such as albumin. On the other hand, anionic antibiotics, like ceftazidime and cefotaxime, will be pushed across the filtration membrane: this is known as the Gibbs-Donnan effect [29]. The coefficient of Sieving is a coefficient that take into account all of these factors that influence the CL of a molecule in case of ultrafiltration. More specifically, this coefficient is the ratio of a specific solute concentration in the ultrafiltrate to the mean plasma concentration (in theory, void of proteins) in the filter. This coefficient is specific for each solute and for every membrane. A molecule with a coefficient close to « 1 » will be almost completely eliminated by CRRT, but a molecule with a coefficient of « 0 » will not traverse the filter [32].

### 3.4. The patient

The patient-related factors are as follows: albumin serum levels, non-renal clearance of the antibiotic and the residual diuresis. When patients have hypoalbuminemia, the renal clearance of highly protein-bound antibiotics is increased [33]. Furthermore, an increase in the hepatic and biliary metabolism of a drug (e.g. fluoroquinolones) can sometimes be observed in patients with renal insufficiency [2]. Finally, critically ill patients needing CRRT will have varying levels of residual diuresis (and so drug clearance) over time. In a prospective, multicentric PK study including 30 critically ill patients on meropenem, higher or extended dosage regimens were needed in patients with residual diuresis compared to anuric patients to attain PD targets [34]. The same observation was made in another study on linezolid [35]. Assessment of residual renal function is challenging, as glomerular filtration rate (GFR) and creatinine clearance estimation based on the Modified Diet in Renal Disease (MDRD), the Cockcroft-Gault, or the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equations are unreliable in this setting. Indeed, the MDRD and the CKD-EPI equations were developed in stable chronic kidney disease, and therefore are not appropriate for use in AKI. Serum creatinine has variable kinetics in critically ill patients, and when the kidney is injured, it may take at least 72 hours before a new steady state is established [36]. The performance of measured creatinine clearance and GFR estimations using the MDRD, CKD-EPI and Cockcroft-Gold were compared to a gold standard GFR measurement by chromium-ethylenediaminetetraacetic acid; measured creatinine clearance performed best despite its' poor precision to determine GFR. Therefore, measured creatinine clearance during short urine collection periods is currently the most reliable method for GFR measurement in critically ill patients [37].

## 4. Pharmacokinetic drug changes during CRRT: specific drug considerations

### 4.1. Aminoglycosides

Aminoglycosides are small, hydrophilic molecules generally used to treat severe infections due to Gram-negative bacilli, including *Pseudomonas aeruginosa* [38]. The PK characteristics of all aminoglycosides are very similar [39]; they are poorly protein-bound, they have a small VD (~0,25 L/kg), and they are eliminated essentially by the kidneys. Aminoglycosides are concentration-dependent antibiotics with a significant post-antibiotic effect. The PK/PD index that best describes their efficacy is the Cmax/MIC; the PD target is a Cmax/MIC of 8 to 12 [40–42], although this has been validated when these drugs were used as monotherapy, mainly to treat urinary tract infections, and dosing was three administrations per day.

In the case of CRRT, aminoglycosides have a lower Cmax due to increased VD, and they are eliminated efficiently, as the Sieving coefficient is approximately 0.8 (e.g. suggesting that aminoglycosides traverse the filtration membrane very easily) [43]. A strategy of an extended-interval high-dose regimen (e.g. for amikacin: 25 mg/kg every 48 hours; for gentamicin and tobramycin: 7–8 mg/kg every 48 hours) associated with therapeutic drug monitoring (TDM) [44] should be the preferred approach for aminoglycoside treatment in critically ill patients receiving CRRT with severe infections [43]. However, if a high dose (e.g. >35 mL/Kg.h) CRRT is administered, the interval between doses of aminoglycosides may be reduced to once daily [45]; this strategy is of particular interest for the management of multidrug resistant pathogens which remain susceptible to aminoglycosides (Table 2). In clinical practice, TDM should include the assessment of Cmax (e.g. 30–60 minutes after the onset of drug administration, as well as Cmin (e.g. before the next dose) [46,47]. To optimize efficacy, a Cmax/MIC ≥8–10 should be aimed for. To minimize risks of additional nephrotoxicity, a new dose of the aminoglycoside should be administered when the Cmin of amikacin is ≤2.5 mg/L and the Cmin of gentamicin or tobramycin is ≤0.5 mg/L [48]. Monitoring of Cmin is very useful to guide therapy because CL of aminoglycosides is very variable in critically ill patients undergoing CRRT (e.g. reported CL of amikacin in this population varies from 0.4 L/h to 7.10 L/h) [43,49].

### 4.2. ß-lactams

ß-lactams are the most widely used class of antibiotics in the world. They are hydrophilic, most often poorly protein-bound

**Table 2.** Drug regimens for main antibiotics administered in critically ill patients, with some proposed dosages according to the type of continuous renal replacement therapy.

| | | | | | | CRRT | | | |
|---|---|---|---|---|---|---|---|---|---|
| Class | Drug | Dosage (IV) | Renal Excretion (%) | Vd (L/Kg) | CL tot (L/h) | CVVH | CVVHD | CVVHDF | SLED |
| Aminoglycosides | Amikacin | 15 mg/Kg q24h | 100 | 0.22–0.5 | 4 | 25 mg/Kg LD > TDM | 25 mg/Kg LD > TDM | 25 mg/Kg LD > TDM | 25 mg/Kg LD > TDM |
| | Gentamicin | 7 mg/Kg q24h | 100 | 0.36 | 3.4 | 7 mg/Kg LD > TDM | 7 mg/Kg LD > TDM | 7 mg/Kg LD > TDM | 7 mg/Kg LD > TDM |
| ß-lactams | Penicillins Piperacillin/tazobactam | 4.5 g q6h | 63.8 | 0.24/0.40 | 11.9 | 4.5 g q8h | 4.5 g q8h | 4.5 g q6h | 4.5 g q8h |
| | Carbapenems Meropenem | 2 g q8h | 65 | 0.35 | 7.8 | 1 g q12h | 1 g q12h | 1 g q8h | 1 g q8 h |
| | Cephalosporins Cefepime | 2 g q8h | 85 | 0.3 | 7.3–8.1 | 2 g LD >2 g q24h | 2 g LD > 2 g q24h | 2 g q12 h | 2 g LD > 1 g q6h |
| Fluoroquinolones | Moxifloxacin | 400 mg q24h | 20 | 1.7–3.5 | 10.7–14.7 | 400 mg q24h | 400 mg q24h | 400 mg q24h | 400 mg q24h |
| | Levofloxacin | 750 mg-1 g q24h | 70 | 1.1–1.5 | 8.6–13.5 | 250 mg/24 h | 250–500 mg/24 h | 750 mg/24 h | 500 mg/24 h |
| | Ciprofloxacin | 400 mg q8h | 60 | 2.76 | 40.7 | 400 mg IV q12h | 400 mg IV q12h | 400 mg IV q12h | No Data |
| Glycopeptides | Teicoplanin | 12 mg/Kg q12h x 3 days + 12 mg/Kg q24h | 50 | 0.5–1.2 | 7.2^ | 12 mg/Kg q12h x 3 days LD + 12 mg/Kg q48 h | 400 mg/Kg q12h (1.2 g LD) > TDM | 400 mg/Kg LD > TDM | No Data |
| | Vancomycin | 15–20 mg/Kg q24h | 90 | 0.47–1.1 | 7.2^ | 25–30 mg/Kg + 500–750 mg q12h | 20–25 mg/Kg LD > TDM | 20–25 mg/Kg + 450 mg q12h | 20–25 mg/Kg LD > TDM |
| Polymyxines | Colistin | 9 MIU^ | 99 | 0.17 | 3 | 6.5 MIU q12h | 6.5 MIU q12h | 6.5 MIU q12h | 4 MIU q12h |
| Lipopeptides | Daptomycin | 4–6 mg/Kg q24h | 60 | 0.5–0.8 | 0.8 | 6 mg/Kg q48 h | 6 mg/kg q48 h | 8 mg/Kg q24h | 6 mg/Kg q24h |
| Oxazolidinones | Linezolid | 600 mg q6-8 h | 30 | 0.5–0.8 | 4.7–8.3 | 600–900 mg q8-12 h° | 600 mg q8-12 h | 600 mg q8-12 h | 600 mg q8-12 h |

CRRT, continuous renal replacement therapy; CVVH, continuous veno-venous hemofiltration CVVHD, continuous veno-venous hemodialysis; CVVHDF, continuous veno-venous hemodiafiltration; SLED, sustained low-efficiency dialysis; LD, loading dose; ^ adult male who weighs 70 kg; °patients with residual renal function; CL, clearance; Vd, steady-state volume of distribution; t1/2, terminal elimination half-life.

with some exceptions, such as flucloxacillin [50] and ceftriaxone [51], with a small VD and eliminated from the body principally by the kidneys. They are time-dependent antibiotics and therefore the PK/PD index that best describes their efficacy is the time the concentration of the unbound fraction of the antibiotic remains above the MIC of the infecting pathogen (fT> MIC). Although there is debate concerning the optimal PD target for ß-lactam antibiotics, two targets are regularly used in the literature in critically ill patients: fT>1x MIC and fT>4x MIC of the infecting pathogen during 100% of the dosing interval [52].

In the critically ill patient, the VD of many ß-lactam antibiotics is increased, resulting in insufficient serum concentrations in the early phases of sepsis and septic shock [53]. A loading dose of broad-spectrum ß-lactams (ceftazidime, cefepime, piperacillin-tazobactam, and meropenem) has been suggested to help rapidly attain adequate drug concentrations of the antibiotics at the site of the infection but awaits clinical validation studies. Usually, after a loading dose, drug regimens need to be adapted to the CL of the antibiotic. Nevertheless, because ß-lactam loading doses are not yet validated for routine clinical practice, standard drug regimens of ß-lactams should be administered during the first 48 hours of therapy in patients without chronic renal failure. Indeed, studies have shown that in patients with AKI receiving CRRT, drug concentrations are insufficient in these patients to provide adequate circulating levels when dosage regimens have been reduced immediately due to altered kidney function. By giving standard dosage regimens during the first 48 hours of treatment, the probability of PD target attainment early on in the infection is greater [54]. Furthermore, renal impairment is very dynamic in acutely infected patients. In a retrospective study on 18,500 patients with an acute urinary tract infection or bacterial pneumonia, 17.5% of the patient population presented an AKI on admission, but kidney injury was resolved in 57% of patients after 48 hours [55].

After these first 48 hours of antibiotic treatment, the dosage regimen needs to be adapted to the CL of the antibiotic. However, in the critically ill patient receiving CRRT, the CL of ß-lactam antibiotics with renal elimination is very variable [56]. Studies have shown that the CL of meropenem and piperacillin-tazobactam is influenced by the different CRRT modalities and prescriptions, the effluent flow rate during CRRT, and residual renal function [7,57,58]. As such, high dialyzate rate is associated with higher drug CL and higher risk of underdosing. Table 2 provides a summary of proposed drug regimens during CRRT.

The great variability in the CL of these antibiotics makes it very difficult to provide clear recommendations concerning optimal dosage regimens to be administered. The lack of international consensus in the optimal dosage regimens for meropenem and piperacillin-tazobactam has been clearly shown in a recent prospective, observational multinational, PK study in 29 ICUs from 14 countries that included 381 patients on RRT. Very variable dosage regimens of these drugs were administered all over the world. Unfortunately, no associations between trough concentrations and dosage choice, clinical gravity, residual renal function, and albumin

concentrations could be identified [13]. As a result, TDM of ß-lactam antibiotics must be performed whenever possible to help guide therapy, as insufficient serum concentrations and high drug exposures are associated with increased mortality [59,60].

ß-lactam antibiotic toxicity has been considered minimal in the past. However, with high PD targets for ß-lactam antibiotics in critically ill patients, it is becoming more apparent that high concentrations of ß-lactams can cause neurotoxicity (myoclonus, hallucinations, confusion, convulsions) and piperacillin/tazobactam can cause AKI as well, resulting in increased morbidity and mortality. Different thresholds for ß-lactam toxicity have been proposed, but there is currently no consensus on this matter [61–64]. Nevertheless, as clinicians strive to attain PD targets rapidly, they must be aware that they may also increase the risk of causing other undesirable adverse events.

New ß-lactam antibiotics are making their way to the clinic to provide therapeutic options to treat multi-drug resistant Gram-negative bacteria. These new antibiotics are combinations of either new ß-lactams with older ß-lactam inhibitors, or older ß-lactams associated with new ß-lactam inhibitors. The antibiotics that have already received FDA and EMA approval are ceftolozone-tazobactam, ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam and cefiderocol. Data concerning dosage regimens of these antibiotics in critically ill patients on CRRT is nevertheless scarce. There are currently only two case reports with PK data on ceftazidime-avibactam in critically ill patients with infections due to multidrug resistant *Pseudomonas aeruginosa* (MIC: 8 mg/L). In both cases, regimens of 2.5 g q8h and 1.25 g q8h attained the PD target of 100%fT>4xMIC [65,66].

In the case of ceftolozone-tazobactam, lower success rates were observed in patients with sepsis or those receiving CRRT than in non-septic patients, possibly due to lack of PD target attainment, in a multicentric (22 hospitals), retrospective study in Italy on 101 patients with serious and diverse infections due to *P. aeruginosa* (over 50% of strains were extensively resistant) [67]. Another population PK model-guided evaluation of dosing in six patients undergoing continuous veno-venous hemodiafiltration (CVVHDF) showed that CL of ceftolozane-tazobactam is decreased in this situation [68]. However, no dosage adjustments for patients receiving CRRT are currently recommended. There is currently no data on imipenem-relebactam, meropenem-varobactam, and cefiderocol in critically ill patients on CRRT.

### 4.3. Glycopeptides

Glycopeptides, such as teicoplanin and vancomycin, are active against Gram-positive pathogens, such as *Staphylococcus aureus, Enterococcus* spp. and *Staphylococcus epidermidis*.

Vancomycin is a large (1448 Da), hydrophilic molecule, with low protein-binding (varying from 10% to 50%) [69]. The antibiotic is concentration-dependent with time dependency; the PK/PD index that best describes its efficacy is the $AUC_{0\text{-}24}$/MIC. The widely accepted PD target is an $AUC_{0\text{-}24}$/MIC >400 [70,71]. To reach this PD target, target trough serum concentrations need to be above at least 10 to 15 mg/L when vancomycin is given intermittently, but between 20 and 25 mg/L when it is administered as a continuous infusion, for pathogens with a MIC ≤ 1 mg/L.

The VD of vancomycin is small, varying from 0.4 to 1.0 L/kg, and the CL varies from approximately 5.9 L/h to 7 L/h in non-critically ill patients with an apparent normal renal function [72,73]. This drug is eliminated essentially by the kidneys via glomerular filtration. In critically ill patients, the VD is significantly increased (ranging from 0.96 to 1.69 L/kg) [74,75], and the CL in patients undergoing CRRT is significantly decreased (varying from 2.0 to 2.5 L/h for an approximate intensity of 30 mL/minute) [74,76,77] when compared to non-critically ill patients.

Because of the increased VD and the decreased CL in patients on CRRT, a loading dose of 35 mg/kg over a 4 h period followed by 14 mg/kg/day given as a continuous infusion allows for rapid PD target attainment in the majority of patients. Patients can also receive intermittent dosage regimens of vancomycin, but PD targets are reached more rapidly, there is less variability in vancomycin serum concentrations, the treatment is less expensive, and there is less nephrotoxicity when continuous infusions are given instead of intermittent infusions [78,79]. Regardless of whether intermittent or continuous infusions of vancomycin are given, all patients receiving this antibiotic should benefit from TDM, followed by rapid dosage adjustments, as vancomycin CL is highly variable according to different CRRT doses.

Contrary to vancomycin, teicoplanin is strongly protein-bound (e.g.>90%), and it has a longer elimination half-life. However, teicoplanin also has similarities to vancomycin, as it is also a big hydrophilic, molecule (>1560 Da), and essentially eliminated renally [80]. The PD index that best describes teicoplanin's antibacterial effect is the AUC/MIC; a ratio of 610.4 is bactericidal for methicillin resistant *Staphylococcus aureus* (MRSA) causing a 2 $\log_{10}$ cell kill *in-vivo*. However, the antibacterial effect from even higher drug exposures caused emergence of drug resistance in a hollow-fiber infection model and a murine thigh infection model of MRSA. Higher teicoplanin exposure thresholds (e.g. AUC/MIC = 1500, corresponding to trough levels significantly greater than 25 mg/L) than those needed for bactericidal effect are therefore needed to suppress emergence of resistance in case of infection due to MRSA, but these thresholds are not attainable using current dosage regimens (e.g. 400 mg every 12 hours for 3 doses, followed by 400 mg once daily). This higher threshold is not even attainable with dosage regimens of 800 mg every 12 hours for 3 doses, followed by 400 mg every 12 hours [81]. Therefore, the clinician should consider administering another antibiotic if treating a serious infection due to MRSA in a critically ill patient. Finally, data concerning optimal dosage regimens in critically ill patients receiving RRT are scarce. A loading dose of 1200 mg followed by doses varying from 600 to 1800 mgs was required to achieve trough levels of 15–25 mg/L. Guidance with TDM is recommended due to considerable variability of drug PKs [82].

### 4.4. Fluoroquinolones

Fluoroquinolones are small lipophilic molecules with a big VD; the VD of fluoroquinolones is not significantly altered in critically ill patients. They are concentration-dependent antibiotics with time dependency; maximal bactericidal effect is obtained when the AUC/MIC >125 or the Cmax/MIC >10 for Gram-negative infections [83], and AUC/MIC >30 for Gram-positive infections [70]. To attain PK/PD targets, the recommended doses for critically ill patients are 400 mg TID for ciprofloxacin, 1 g QD for levofloxacin, and 400 mg QD for moxifloxacin.

The three antibiotics are metabolized in different ways. Moxifloxacin is strongly protein-bound and is metabolized by the liver; dosage regimens do not need to be adapted in case of renal insufficiency or in case of CRRT. On the other hand, ciprofloxacin is poorly protein-bound and is eliminated both by the kidney and the liver which is mediated by CYP1A2 and unspecific biliary secretion. In case of AKI, the daily dose needs to be reduced only slightly because the loss of renal function is compensated by an increase in intestinal secretion and by the hepatic cycle. However, if there is concomitant hepatic insufficiency, doses may need to be reduced further [70,83]. Indeed, in a population PK model based on serum concentrations from 15 critically ill patients with severe infections, clearance of total ciprofloxacin was related to total bilirubin, but not to measured creatinine clearance. The predicted risk of over-exposure was 20% in elderly female patients (>65 years-old-women) with total bilirubin of 4 mg/dL [84]. Furthermore, ciprofloxacin is poorly eliminated by CVVH, and doses may need to be reduced in this situation. Indeed, CL of ciprofloxacin in patients undergoing CRRT has been reported to vary from 0.34 to 1.70 mL/min/kg [85], compared to 7 to 8 mL/minute/kg in patients with a normal renal function [86,87]. Nevertheless, in a population PK study using PK data from 42 critically ill patients receiving ciprofloxacin, and 10 of whom were receiving CVVH, no significant covariate could be found to add to the structural two-compartment model. In other words, PK variability could not be explained by different degrees of renal function. Significant inter-individual variability of PK parameters was observed, emphasizing the need to guide therapy with TDM [88]. Finally, levofloxacin is poorly protein-bound, and eliminated renally. Despite that CRRT enhances elimination of levofloxacin, the median CL was 0.42 to 0.58 mL/min.Kg in patients undergoing CVVH [85], compared to 2 mL/min.Kg in patients with a normal renal function [89,90]. Therefore, doses of levofloxacin must also be reduced in case of CRRT [83,91].

### 4.5. Oxazolidones

Oxazolidinones are a class of synthetic antibiotics active against Gram-positive pathogens; they are particularly of interest to treat infections due to methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE). Oxazolidones exhibit their antibacterial effects by inhibiting protein synthesis. Today, two oxazolidones are available: linezolid and, more recently, tedizolid [92].

Linezolid is a lipophilic concentration-dependent with time-dependent antibiotic. The PK/PD target is an AUC/MIC between 80 and 120. Its oral formulation has a bioavailability of 100%. (100%). The drug is 30% protein bound with a large VD of 36–47 l. It is eliminated from the body by renal and hepatic mechanisms (approximately 30% and 65%, respectively) the CL varies from 4.7 to 8.3 L/h [92]. The standard dosage regimen is 600 mg q12h; however, higher doses (e.g. 600 mg q6-8 h) may be needed in critically ill patient, particularly when the infection is due to a pathogen with an MIC ≥ 2 mg/L [92]. Furthermore, although no dosage adjustment is recommended in patients with renal dysfunction or on hemodialysis [93], clinical failure has been reported in critically ill septic patients with AKI treated with CRRT. In these patients, particularly those with residual renal function, the standard dose is insufficient; 900 mg q8h provides a higher probability of treatment success without compromising safety [35]. Another option to be considered is the administration of linezolid as a continuous infusion, although no data are available on drug PKs during CRRT using this modality of administration.

Tedizolid has greater *in-vitro* activity against key gram-positive pathogens such as MRSA, and VRE, and a half-life almost twofolds longer than linezolid. The PK index that best describes its' efficacy is the AUC/MIC. The drug received FDA and EMA approval in 2014 and 2015, respectively, for acute bacterial skin and skin structure infections. The registered dose is 200 mg, once a day. *In-vitro* models do not support the need for dose adjustments when using CVVH or CVVHD, however clinical data is currently lacking [94].

### 4.6. Colistin

Colistin is an old antibiotic that was « revived » as a treatment option for infections due to multidrug resistant Gram-negative bacteria, despite that its therapeutic index is very narrow. Indeed, the target therapeutic concentration is >2 mg/L, but there is a significant risk of developing renal insufficiency already at a drug concentration of 2.5 mg/L [95]. Colistin is a concentration-dependent antibiotic; the PK/PD index that best describes its efficacy is the AUC/MIC. Colistin is 10–50% protein-bound in critically ill patients, and it results from the hydrolysis of a pro-drug that is administered as colistin methane-sulfate (CMS). The amount of colistin present in a vial is expressed in colistin-based activity (CBA) or in international units (IU): 33 mg of CBA is equal to 1 million IU (MIU) of CBA [96].

A loading dose of 9 MIU of colistin is recommended, followed by a first maintenance dose 12–24 hours later (depending on the recommended interval of the maintenance dose). Without the loading dose, studies have shown that colistin plasma concentrations increase slowly over time (hours to days) [97]. In the absence of renal insufficiency, the CMS is eliminated mostly by glomerular filtration, and then reabsorbed by the tubules. However, in case of renal insufficiency, the CL of CMS and colistin is decreased and the conversion of CMS to colistin is increased. Nevertheless, in case of RRT, CMS

and colistin are efficiently cleared and therefore supplementary doses of CMS are needed. RRT removes 10% of colistin/hour; because the duration of intermittent HD, SLED and CRRT is significantly different from each other, the supplementary doses needed to depend on the RRT modality used. Total daily maintenance doses for patients receiving CRRT are even greater than doses needed by patients with a normal renal function [97]. Because of the narrow therapeutic index, TDM should be performed, whenever possible [97].

### 4.7. Daptomycin

This is a concentration-dependent with time-dependent antibiotics active against Gram-positive pathogens. However, this antibiotic should not be used to treat infections due to *Enterococcus spp*. with MICs ≥4 mg/L because of poor clinical efficacy (even with doses of 10–12 mg/kg) [97]. The PK/PD index that best describes its clinical efficacy is the AUC/MIC.

Daptomycin has a very small VD of approximately 0.1 L/kg [98] due to high-protein binding (e.g. approximately 92%) [99]; approximately 60% of the drug is eliminated renally unchanged from the body and the half-life is long (e.g. 8–9 hours). The standard dosage regimen is 4–6 mg/kg/day in one administration per day. In critically ill patients, higher doses may be considered (i.e. 8–12 mg/kg), but the risk of toxicity (particularly muscular toxicity) will be increased. Toxicity can be monitored by measuring the blood CPK levels.

Although studies conducted in patients receiving hemodialysis reported low drug CL [100,101], in critically ill patients on CRRT with an infection due to *Staphylococcus aureus*, the combination of 6 mg/kg q24h daptomycin and a CRRT dose of 30–35 mL/h/kg provided the best balance between efficacy and safety [102]. The dosage regimen is the same as for patients with a normal renal function because the clearance of daptomycin in patients undergoing CRRT is similar to that observed in patients with a creatinine clearance ≥30 mL/minute: 0.53 L/h-0.94 L/h compared to 0.75 L/h [101].

## 5. Conclusions

CRRT is frequently employed in critically ill patients all over the world. Antibiotics are frequently prescribed to these same patients because they often present infections. Delivering optimized antibiotic dosage regimens to critically ill patients undergoing CRRT remains a challenge because these patients present severe altered PK of antibiotics, their infections are severe, and often due to resistant or difficult-to-treat pathogens. The VD of hydrophilic antibiotics is often significantly increased regardless of whether or not the patient needs CRRT. The CL of renally eliminated antibiotics is significantly affected by the modality of the CRRT employed, the intensity of the CRRT delivered, the physicochemical characteristics of the antibiotic itself (e.g. size, ionization, lipophilic or hydrophilic character), and patient characteristics such as residual renal function which can vary significantly from patient to patient.

We have reviewed the most frequently used antibiotics in the ICU setting and discussed the influence of CRRT on the PKs of these different antibiotics. Dosage regimens have also been proposed, but they are only offered as guidance to try to optimize antibiotic therapy.

## 6. Expert opinion

The recently published results of the Sampling Antibiotics in Renal Replacement Therapy (SMARRT) study, a prospective, observational, multinational, pragmatic PK study in 29 ICUs from 14 countries in 381 critically ill patients on RRT (CVVH, CVVHD, CVVHDF, or prolonged intermittent RRT), showed that patients failed to reach optimal target trough concentrations in 26%, 36%, and 72% of patients receiving meropenem, piperacillin-tazobactam and vancomycin, respectively [13]. Furthermore, potentially toxic concentrations of antibiotics were observed in 50%, and 25% of patients receiving piperacillin-tazobactam and meropenem [13]. These results are disappointing as they illustrate to what point delivering optimized hydrophilic antibiotic dosage regimens to critically ill patients undergoing CRRT remains a challenge, despite significant efforts over the last 15 to 20 years to get the doses right, and despite that ß-lactams and vancomycin are very frequently prescribed antibiotics in ICUs, worldwide. This study, the largest one on critically ill patients receiving RRT, concurs with other smaller studies showing that antibiotic dosing regimens, RRT prescriptions, and residual renal functions are very variable in the ICU setting [56,57,103]. Nevertheless, no specific RRT prescription or dosing regimen allowed to achieve more consistent target exposures. Furthermore, it was impossible to accurately predict dosing requirements despite statistical correlations between antibiotic dose and the estimated total renal clearance.

In light of these results, individualized therapy, guided by TDM is the only way forward in this setting. This individualized therapy may not be needed for all of the antibiotics covered in this review, but certainly for ß-lactams, aminoglycosides, glycopeptides, polymyxines, and linezolid. This is in line with the recent position paper on antimicrobial TDM in critically ill adult patients, on behalf of the Infection Section of European Society of Intensive Care Medicine (ESICM), the Pharmacokinetic/pharmacodynamic and Critically Ill Patient Study Groups of European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Group of International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT) and Infections in the ICU and Sepsis Working Group of International Society of Antimicrobial Chemotherapy (ISAC) [48].

TDM should be performed after giving a first dose of the antibiotic. In the ICU setting, there is substantial evidence to give a loading dose for hydrophilic antibiotics, to compensate for the often-increased VD. This loading dose is the same dose to be given to all critically ill patients, regardless of their renal function. Loading doses have already been proposed and clinical validation studies have confirmed the improvement in rapid PK/PD target attainment for vancomycin, colistin, and amikacin [104–106]. Loading doses for ß-lactam antibiotics has also been suggested, based on insufficient antibiotic concentrations in the very early stages of sepsis, but not yet validated [53].

TDM is based on the direct measurement of serum antibiotic concentrations at specific pre-determined relevant sampling time points, followed by feedback of accurate and timely results from bioanalytical assay methods for drug measurement to clinicians who then interpret the results in function of pre-defined therapeutic ranges. In the past, TDM has been used to minimize toxic effects of drugs, but it can also be used to optimize dosing in the critically ill patient with unpredictable PKs of antibiotics.

TDM-based dosing can be performed in several ways. The first way is for the clinician to compare results from TDM to the therapeutic target and adapt the dosage regimen. However, this method is the least accurate for dose adaptation. Dosing nomograms can also be used; they integrate PK/PD data with clinical parameters such as renal clearance. However, incorporating more than one covariate for dosing adjustments is not possible, and the PK sampling must be performed as pre-defined. Finally, dosing software can also be used with the application of population PK models. However, clinicians must remember that the precision of the dose prediction will depend on the quality of the PK model. Even when the PK model does describe a specific patient population, prediction performance can be variable. Therefore, clinical validation of the population models used in daily clinical practice should always be performed [107]. When considering optimizing dosage regimens in patients on CRRT, the validation should be performed in patients receiving the same modality of CRRT.

Despite efforts to optimize dosage regimens of frequently used antibiotics in critically ill patients undergoing RRT, many patients are still not within therapeutic ranges. Therefore, individualized therapy to increase therapeutic target attainment and to limit the risks of drug toxicity due to potentially excessive drug concentrations is essential. Studies should focus on demonstrating that TDM guided therapy will improve PK/PD target attainment and possibly improve survival in critically ill patients receiving CRRT. Indeed, only a few studies have tried to compare clinical outcomes of TDM-guided dosing of anti-infectious agents to those without TDM intervention [108–110]. In this light, well-designed and controlled studies focusing on individualized patient outcomes are being performed, aimed at trying to demonstrate the benefits of performing TDM as part of daily ICU practice. One study is exploring TDM-based dosed piperacillin/tazobactam to improve outcome in patients with sepsis (TARGET) in a multi-centric, randomized, controlled trial (German CTR: DRKS00011159) [111], and the other is exploring the effect of TDM of ß-lactams and fluoroquinolones on clinical outcome in critically ill patients (the DOLPHIN trial). (EudraCT: 2017–004677-14) [112].

Finally, a last but important issue to consider when individualizing antibiotic treatment is the choice of antibiotic when patients are on CRRT, and recuperation of the renal function is anticipated. Indeed, some antibiotics are more nephrotoxic than others: aminoglycosides, glycopeptides, and colistin are more nephrotoxic than ß-lactams, oxazolidones, and flouroquinolones. Therefore, as a clinician, it makes sense to treat patients who may recuperate their renal function with the least nephrotoxic agent. In this light, when faced with an infection due to a multi-resistant Gram-positive pathogen, oxazolidones, and daptomycin are to be preferred over glycopeptides. This has been shown in a retrospective, multicentric study assessing the impact of vancomycin compared to linezolid on renal function in 147 patients with renal failure not yet on RRT and admitted to ICUs. Renal function improved to a greater extent in patients receiving linezolid than vancomycin (percent increase in creatinine clearance: 95.96 vs. 55.06; $p = 0.05$) [113]. A meta-analysis on seven randomized, controlled trials published from 1990 to September 2015, based on moderate quality evidence, showed that treatment with vancomycin is associated with a higher risk of AKI, with a relative risk of 2.45 (95% confidence interval: 1,69 to 3,55). The majority of other comparators to vancomycin was linezolid [114]. When considering infections due to Gram-negative bacilli, ß-lactams and fluoroquinolones should be preferred to colistin [115] and aminoglycosides [116], because less nephrotoxic. However, when colistin and/or aminoglycosides are administered, it is often because a patient has a suspected or confirmed infection due to a resistant pathogen, or because the patient is in septic shock in the case of aminoglycosides.

## Funding

This paper was not funded.

## Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

## Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

## References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Fleming GM. Renal replacement therapy review: past, present and future. Organogenesis. 2011 Jan-Mar;7(1):2–12.
2. Kumar A, Singh NP. Antimicrobial dosing in critically ill patients with sepsis-induced acute kidney injury. Indian J Crit Care Med. 2015 Feb;19(2):99–108.
3. Legrand M, Darmon M, Joannidis M, et al. Management of renal replacement therapy in ICU patients: an international survey. Intensive Care Med. 2013 Jan;39(1):101–108. .
4. Villa G, Neri M, Bellomo R, et al. Nomenclature for renal replacement therapy and blood purification techniques in critically ill patients: practical applications. Crit Care. 2016 Oct 10;20(1):283.
5. Kitchlu A, Adhikari N, Burns KE, et al. Outcomes of sustained low efficiency dialysis versus continuous renal replacement therapy in critically ill adults with acute kidney injury: a cohort study. BMC Nephrol. 2015 Aug;4(16):127. .
6. Jamal JA, Mueller BA, Choi GY, et al. How can we ensure effective antibiotic dosing in critically ill patients receiving different types of renal replacement therapy? Diagn Microbiol Infect Dis. 2015 May;82(1):92–103. .
7. Jamal JA, Udy AA, Lipman J, et al. 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 Jul;42 (7):1640–1650.

•• **Clinical study reporting that effluent flow rates predict antibiotic clearance in critically ill patients**

8. O'Reilly P, Tolwani A. Renal replacement therapy III: IHD, CRRT, SLED. Crit Care Clin. 2005 Apr;21(2):367–378.
9. Deepa C, Muralidhar K. Renal replacement therapy in ICU. J Anaesthesiol Clin Pharmacol. 2012 Jul;28(3):386–396.
10. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016 Feb 23;315(8):801–810.
11. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006 Jun;34(6):1589–1596. .
12. Roberts JA, De Waele JJ, Dimopoulos G, et al. DALI: defining Antibiotic levels in intensive care unit patients: a multi-centre point of prevalence study to determine whether contemporary antibiotic dosing for critically ill patients is therapeutic. BMC Infect Dis. 2012 Jul ;6(12):152. .
13. Roberts JA, Joynt G, Lee A, et al. The effect of renal replacement therapy and antibiotic dose on antibiotic concentrations in critically ill patients: data from the multinational SMARRT Study. Clin Infect Dis. 2020 Mar 9; DOI:10.1093/cid/ciaa224.

•• **Very important prospective, observational, multi-national, pharmacokinetic study describing the variability in renal replacement therapy techniques and antibiotic dosing in critically ill patients.**

14. Sader HS, Farrell DJ, Flamm RK, et al. Antimicrobial susceptibility of Gram-negative organisms isolated from patients hospitalized in intensive care units in United States and European hospitals (2009-2011). Diagn Microbiol Infect Dis. 2014 Apr;78(4):443–448.
15. Feretzakis G, Loupelis E, Sakagianni A, et al. A 2-Year single-centre audit on Antibiotic Resistance of Pseudomonas aeruginosa, Acinetobacter baumannii and Klebsiella pneumoniae Strains from an Intensive Care Unit and Other Wards in a General Public Hospital in Greece. Antibiotics (Basel). 2019 May 15;8(2):2.
16. De Waele JJ, Carrette S, Carlier M, et al. Therapeutic drug monitoring-based dose optimisation of piperacillin and meropenem: a randomised controlled trial. Intensive Care Med. 2014 Mar;40(3):380–387. .
17. Claus BO, Hoste EA, Colpaert K, et al. Augmented renal clearance is a common finding with worse clinical outcome in critically ill patients receiving antimicrobial therapy. J Crit Care. 2013 Oct;28(5):695–700. .
18. Roberts JA, Norris R, Paterson DL, et al. Therapeutic drug monitoring of antimicrobials. Br J Clin Pharmacol. Jan;73(1):27–36. .
19. Jacobs A, Taccone FS, Roberts JA, et al. β-Lactam Dosage Regimens in Septic Patients with Augmented Renal Clearance. Antimicrob Agents Chemother. 2018 Sep;62(9). DOI:10.1128/AAC.02534-17

•• **Clinical study reporting the effects of augmented renal clearance on β-lactams concentrations in critically ill patients.**

20. Jung B, Mahul M, Breilh D, 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 May;45(5):e470–e478.
21. Carlier M, Carrette S, Stove V, et al. Does consistent piperacillin dosing result in consistent therapeutic concentrations in critically ill patients? A longitudinal study over an entire antibiotic course. Int J Antimicrob Agents. 2014 May;43(5):470–473.
22. Roberts JA, Abdul-Aziz MH, Lipman J, et al. Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis. 2014 Jun;14(6):498–509.
23. Hites M, Dell'Anna AM, Scolletta S, et al. The challenges of multiple organ dysfunction syndrome and extra-corporeal circuits for drug delivery in critically ill patients. Adv Drug Deliv Rev. 2014 Nov;20 (77):12–21. .
24. Drusano GL. Antimicrobial pharmacodynamics: critical interactions of 'bug and drug'. Nat Rev Microbiol. 2004 Apr;2(4):289–300.
25. Dhaese S, Heffernan A, Liu D, et al. Prolonged versus intermittent infusion of ß-lactam Antibiotics: a systematic review and meta-regression of bacterial killing in preclinical infections models. Clin Pharmacokinet. 2020 Oct;59(10):1237–1250.
26. Roberts DM, Liu X, Roberts JA, et al. A multicenter study on the effect of continuous hemodiafiltration intensity on antibiotic pharmacokinetics. Crit Care. 2015 Mar 13;19(1):84.

• **This study showed that in patients receiving CRRT, there was a great variability in antibiotic pharmacokinetics, which complicates an empiric approach to dosing**

27. Macedo E, Mehta RL. Continuous Dialysis Therapies: core Curriculum 2016. Am J Kidney Dis. 2016 Oct;68(4):645–657.
28. Ashley CM, Clare. Introduction to Renal Therapeutics. Ann Pharmacother 2008; p. 127–136.
29. Kuang D, Verbine A, Ronco C. Pharmacokinetics and antimicrobial dosing adjustment in critically ill patients during continuous renal replacement therapy. Clin Nephrol. 2007 May;67(5):267–284.
30. Tian Q, Gomersall CD, Ip M, et al. Adsorption of amikacin, a significant mechanism of elimination by hemofiltration. Antimicrob Agents Chemother. 2008 Mar;52(3):1009–1013.
31. Choi G, Gomersall CD, Lipman J, et al. The effect of adsorption, filter material and point of dilution on antibiotic elimination by haemofiltration an in vitro study of levofloxacin. Int J Antimicrob Agents. 2004 Nov;24(5):468–472.
32. Choi G, Gomersall CD, Tian Q, et al. Principles of antibacterial dosing in continuous renal replacement therapy. Crit Care Med. 2009 Jul;37(7):2268–2282.
33. Ulldemolins M, Roberts JA, Rello J, et al. The effects of hypoalbuminaemia on optimizing antibacterial dosing in critically ill patients. Clin Pharmacokinet. 2011 Feb;50(2):99–110.
34. Ulldemolins M, Soy D, Llaurado-Serra M, et al. Meropenem population pharmacokinetics in critically ill patients with septic shock and continuous renal replacement therapy: influence of residual diuresis on dose requirements. Antimicrob Agents Chemother. 2015 Sep;59(9):5520–5528.
35. Barrasa H, Soraluce A, Isla A, et al. Pharmacokinetics of linezolid in critically ill patients on continuous renal replacement therapy: influence of residual renal function on PK/PD target attainment. J Crit Care. 2019 Apr;50:69–76.
36. Endre ZH, Pickering JW. Acute kidney injury: cell cycle arrest biomarkers win race for AKI diagnosis. Nat Rev Nephrology. 2014 Dec;10(12):683–685.
37. Pickering JW, Frampton CM, Walker RJ, et al. Four hour creatinine clearance is better than plasma creatinine for monitoring renal function in critically ill patients. Crit Care. 2012;16(3):R107.
38. Agence française de sécurité sanitaire des produits de santé. Update on good use of injectable aminoglycosides, gentamycin, tobramycin, netilmycin, amikacin. Pharmacological properties, indications, dosage, and mode of administration, treatment monitoring. Med Mal Infect. 2012;42(7):301–308.
39. Bennett J, Dolin R, Blaser MJ. Principles and Practice of Infectious Diseases. 8th Edition (2014). Ed: Saunders.
40. Moore RD, Lietman PS, Smith CR. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. J Infect Dis. 1987 Jan;155(1):93–99.
41. Deziel-Evans LM, Murphy JE, Job ML. Correlation of pharmacokinetic indices with therapeutic outcome in patients receiving aminoglycosides. Clin Pharm. 1986 Apr;5(4):319–324.
42. Marsot A, Guilhaumou R, Riff C, et al. Amikacin in Critically Ill Patients: a Review of Population Pharmacokinetic Studies. Clin Pharmacokinet. 2017 Feb;56(2):127–138.
43. Roger C, Wallis SC, Muller L, et al. Influence of Renal Replacement Modalities on Amikacin Population Pharmacokinetics in Critically Ill Patients on Continuous Renal Replacement Therapy. Antimicrob Agents Chemother. 2016 Aug;60(8):4901–4909.

• **Interesting trial describing amikacin pharmacokinetics in critically ill patients receiving equal doses of continuous veno-venous hemofiltration or continuous veno-venous hemodiafiltration.**

44. Drusano GL, Louie A. Optimization of aminoglycoside therapy. Antimicrob Agents Chemother. 2011 Jun;55(6):2528–2531.
45. Brasseur A, Hites M, Roisin S, et al. A high-dose aminoglycoside regimen combined with renal replacement therapy for the treatment of MDR pathogens: a proof-of-concept study. J Antimicrob Chemother. 2016 May;71(5):1386–1394.
46. Bacopoulou F, Markantonis SL, Pavlou E, et al. A study of once-daily amikacin with low peak target concentrations in intensive care unit patients: pharmacokinetics and associated outcomes. J Crit Care. 2003 Jun;18(2):107–113.
47. Botha FJ, Van Der Bijl P, Seifart HI, et al. Fluctuation of the volume of distribution of amikacin and its effect on once-daily dosage and clearance in a seriously ill patient. Intensive Care Med. 1996 May;22 (5):443–446.
48. Abdul-Aziz MH, Alffenaar JC, Bassetti M, et al. Antimicrobial therapeutic drug monitoring in critically ill adult patients: a Position Paper. Intensive Care Med. 2020 Jun;46(6):1127–1153.

•• **Very Important multi-society position paper on the therapeutic drug monitoring of antibacterials, antifungals and antivirals in critically ill adult patients in the intensive care unit**

49. Taccone FS, De Backer D, Laterre PF, et al. Pharmacokinetics of a loading dose of amikacin in septic patients undergoing continuous renal replacement therapy. Int J Antimicrob Agents. 2011 Jun;37(6):531–535. .
50. Ulldemolins M, Roberts JA, Wallis SC, et al. Flucloxacillin dosing in critically ill patients with hypoalbuminaemia: special emphasis on unbound pharmacikinetics. JAC. 2010 Aug;65(8):1771–1778.
51. Schleibinger M, Steinbach CL, Töpper C, et al. Protein binding characteristics and pharmacokinetics of ceftriaxone in intensive care unit patients. Br J Clin Pharmacol. 2015 Mar;80(3):525–533.
52. Delattre IK, Taccone FS, Jacobs F, et al. Optimizing β-lactams treatment in critically-ill patients using pharmacokinetics/pharmacodynamics targets: are first conventional doses effective? Expert Rev Anti Infect Ther. 2017 Jul;15(7):677–688.
53. Taccone FS, Laterre PF, Dugernier T, et al. Insufficient beta-lactam concentrations in the early phase of severe sepsis and septic shock. Crit Care. 2010;14(4):R126.
54. Seyler L, Cotton F, Taccone FS, et al. Recommended β-lactam regimens are inadequate in septic patients treated with continuous renal replacement therapy. Crit Care. 2011;15(3):R137.
55. Crass RL, Rodvold KA, Mueller BA, et al. Renal Dosing of Antibiotics: are We Jumping the Gun? Clin Infect Dis. 2019 Apr 24;68(9):1596–1602.
56. Roberts DM, Roberts JA, Roberts MS, et al. Variability of antibiotic concentrations in critically ill patients receiving continuous renal replacement therapy: a multicentre pharmacokinetic study. Crit Care Med. 2012 May;40(5):1523–1528.
57. Valtonen M, Tiula E, Backman JT, et al. Elimination of meropenem during continuous veno-venous haemofiltration and haemodiafiltration in patients with acute renal failure. J Antimicrob Chemother. 2000 May;45(5):701–704. .
58. Valtonen M, Tiula E, Takkunen O, et al. Elimination of the piperacillin/tazobactam combination during continuous venovenous haemofiltration and haemodiafiltration in patients with acute renal failure. J Antimicrob Chemother. 2001 Dec;48(6):881–885.
59. Zelenitsky S, Rubinstein E, Ariano R, et al. Vancomycin pharmacodynamics and survival in patients with methicillin-resistant Staphylococcus aureus-associated septic shock. Int J Antimicrob Agents. 2013 Mar;41(3):255–260. .
60. Wong G, Taccone F, Villois P, et al. β-Lactam pharmacodynamics in Gram-negative bloodstream infections in the critically ill. J Antimicrob Chemother. 2020 Feb 1;75(2):429–433.
61. Quinton MC, Bodeau S, Kontar L, et al. Neurotoxic Concentration of Piperacillin during Continuous Infusion in Critically Ill Patients. Antimicrob Agents Chemother. 2017 Sep;61(9). doi:10.1128/AAC.00654-17.
62. Imani S, Buscher H, Marriott D, et al. Too much of a good thing: a retrospective study of β-lactam concentration-toxicity relationships. J Antimicrob Chemother. 2017 Oct 1;72(10):2891–2897.
63. Lau C, Marriott D, Gould M, et al. A retrospective study to determine the cefepime-induced neurotoxicity threshold in hospitalized patients. J Antimicrob Chemother. 2020 Mar 1;75(3):718–725.
64. Beumier M, Casu GS, Hites M, et al. Elevated β-lactam concentrations associated with neurological deterioration in ICU septic patients. Minerva Anestesiol. 2015 May;81(5):497–506.
65. Soukup P, Faust AC, Edpuganti V, et al. Steady-state Ceftazidime-Avibactam serum concentrations and dosing recommendations in a critically ill patient being treated for Pseudomonas aeruginosa Pneumonia and undergoing continuous venovenous hemodiafiltration. Pharmacotherapy. 2019;39(12):1216–1222.
66. Wenzler E, Bunnell KL, Bleasdale SC, et al. Pharmacokinetics and dialtic clearance of ceftazidime-avibactam in a critically ill patient on continuous venovenous hemofiltration. Antimicrob Agents Chemother. 2017;61(7):e00464–17.
67. Sime FB, Lassig-Smith M, Starr T, et al. Population Pharmacokinetics of Unbound Ceftolozane and Tazobactam in Critically Ill Patients without Renal Dysfunction. Antimicrob Agents Chemother. 2019;63(10): e01265–19.
68. Sime FB, Lassig-Smith M, Starr T, et al. A population Pharmacokinetic Model-Guided Evaluation of Ceftolozane-Tazobactam Dosing in Critically Ill Patients Undergoing Continuous Venovenous Hemodiafiltration. Antimicrob Agents Chemother. 2020;64(1):e01655–19.
69. Rybak MJ. The pharmacokinetic and pharmacodynamic properties of vancomycin. Clin Infect Dis. 2006 Jan 1;42(Suppl 1):S35–9.
70. Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. Crit Care Med. 2009 Mar;37(3):840–851. . quiz 859.
71. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm. 2009 Jan 1;66(1):82–98.
72. Rodvold KA, Blum RA, Fischer JH, et al. Vancomycin pharmacokinetics in patients with various degrees of renal function. Antimicrob Agents Chemother. 1988 Jun;32(6):848–852.
73. Golper TA, Noonan HM, Elzinga L, et al. Vancomycin pharmacokinetics, renal handling, and nonrenal clearances in normal human subjects. Clin Pharmacol Ther. 1988 May;43(5):565–570.
74. Van De Vijsel LM, Walker SA, Walker SE, et al. Initial vancomycin dosing recommendations for critically ill patients undergoing continuous venovenous hemodialysis. Can J Hosp Pharm. 2010 May;63 (3):196–206. .
75. Del Mar Fernández De Gatta GM, Revilla N, Calvo MV, et al. Pharmacokinetic/pharmacodynamic analysis of vancomycin in ICU patients. Intensive Care Med. 2007 Feb;33(2):279–285.
76. DelDot ME, Lipman J, Tett SE. Vancomycin pharmacokinetics in critically ill patients receiving continuous venovenous haemodiafiltration. Br J Clin Pharmacol. 2004 Sep;58(3):259–268.
77. Santré C, Leroy O, Simon M, et al. Pharmacokinetics of vancomycin during continuous hemodiafiltration. Intensive Care Med. 1993;19 (6):347–350.
78. James JK, Palmer SM, Levine DP, et al. Comparison of conventional dosing versus continuous-infusion vancomycin therapy for patients with suspected or documented gram-positive infections. Antimicrob Agents Chemother. 1996 Mar;40(3):696–700.
79. Wysocki M, Delatour F, Faurisson F, et al. Continuous versus intermittent infusion of vancomycin in severe Staphylococcal infections: prospective multicenter randomized study. Antimicrob Agents Chemother. 2001 Sep;45(9):2460–2467.
80. Yagasaki K, Gando S, Matsuda N, et al. PKs of teicoplanin in critically ill patients undergoing continuous hemodiafiltration. Intensive Care Med. 2003;29(11):2094–2095.
81. Ramos-Martin V, Johnson A, McEntee L, et al. Pharmacodynamics of teicoplanin against MRSA. JAC. 2017;72(12):3382–3389.
82. Bellman R, Falkensammer G, Seger C, et al. Teicoplanin pharmacokinetics in critically ill patients on continuous veno-venous hemofiltration. Int J Clin Pharmacol Ther. 2010;48(4):243–249.

83. Conil JM, Georges B, De Lussy A, et al. Ciprofloxacin use in critically ill patients: pharmacokinetic and pharmacodynamic approaches. Int J Antimicrob Agents. 2008 Dec;32(6):505–510.
84. Li X, Zoller M, Fuhr U, et al. Ciprofloxacin in critically ill subjects: considering hepatic function, age, and sex to choose the optimal dose. J Antimicrob Chemother. 2019;74(3):682–690.
85. Malone RS, Fish DN, Abraham E, et al. Pharmacokinetics of levofloxacin and ciprofloxacin during continuous renal replacement therapy in critically ill patients. Antimicrob Agents Chemother. 2001 Oct;45(10):2949–2954.
86. Drusano GL, Weir M, Forrest A, et al. Pharmacokinetics of intravenously administered ciprofloxacin in patients with various degrees of renal function. Antimicrob Agents Chemother. 1987 Jun;31(6):860–864.
87. Boelaert J, Valcke Y, Schurgers M, et al. The pharmacokinetics of ciprofloxacin in patients with impaired renal function. J Antimicrob Chemother. 1985 Jul;16(1):87–93.
88. Abdulla A, Rogouti O, Hunfeld NGM, et al. Population PKs and target attainment of ciprofloxacin in critically ill patients. European J Clin Pharmacology. 2020;76(7):957–967.
89. Chien SC, Rogge MC, Gisclon LG, et al. Pharmacokinetic profile of levofloxacin following once-daily 500-milligram oral or intravenous doses. Antimicrob Agents Chemother. 1997 Oct;41(10):2256–2260.
90. Fish DN, Chow AT. The clinical pharmacokinetics of levofloxacin. Clin Pharmacokinet. 1997 Feb;32(2):101–119.
91. Czock D, Hüsig-Linde C, Langhoff A, et al. Pharmacokinetics of moxifloxacin and levofloxacin in intensive care unit patients who have acute renal failure and undergo extended daily dialysis. Clin J Am Soc Nephrol. 2006 Nov;1(6):1263–1268.
92. Roger C, Roberts JA, Clinical Pharmacokinetics ML. Pharmacodynamics of Oxazolidinones. Clin Pharmacokinet. 2018 May;57(5):559–575.
93. Brier ME, Stalker DJ, Aronoff GR, et al. Pharmacokinetics of linezolid in subjects with renal dysfunction. Antimicrob Agents Chemother. 2003 Sep;47(9):2775–2780.
94. Lewis SJ, Switaj LA, Mueller BA. Tedizolid adsorption and transmembrane clearance during in vitro continuous renal replacement therapy. Blood Purif. 2015;40(1):66–71.
95. Sorli L, Luque S, Grau S, et al. Trough colistin plasma level is an independent risk factor for nephrotoxicity: a prospective observational cohort study. BMC Infect Dis. 2013;13(1):380.
96. Michalopoulos AS, Falagas ME. Colistin: recent data on pharmacodynamics properties and clinical efficacy in critically ill patients. Ann Intensive Care. 2011 Aug 2;1(1):30.
97. Tsuji BT, Pogue JM, Zavascki AP, 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 Jan;39(1):10–39.
98. Estes KS, Derendorf H. Comparison of the pharmacokinetic properties of vancomycin, linezolid, tigecyclin, and daptomycin. Eur J Med Res. 2010 Nov 30;15(12):533–543.
99. Dvorchik BH, Brazier D, DeBruin MF, et al. Daptomycin pharmacokinetics and safety following administration of escalating doses once daily to healthy subjects. Antimicrob Agents Chemother. 2003 Apr;47(4):1318–1323.
100. Chaves RL, Chakraborty A, Benziger D, et al. Clinical and pharmacokinetic considerations for the use of daptomycin in patients with Staphylococcus aureus bacteraemia and severe renal impairment. J Antimicrob Chemother. 2014 Jan;69(1):200–210.
101. Xu X, Khadzhynov D, Peters H, et al. Population pharmacokinetics of daptomycin in adult patients undergoing continuous renal replacement therapy. Br J Clin Pharmacol. 2017 Mar;83(3):498–509.
102. Xie F, Li S, Cheng Z. Population pharmacokinetics and dosing considerations of daptomycin in critically ill patients undergoing continuous renal replacement therapy. J Antimicrob Chemother. 2020 Jun 1;75(6):1559–1566.
103. Investigators RS. Renal replacement therapy for acute kidney injury in Australian and New Zealand intensive care units: a practice survey. Crit Care Resusc. 2008 Sep;10(3):225–230.
104. Taccone FS, Laterre PF, Spapen H, et al. Revisiting the loading dose of amikacin for patients with severe sepsis and septic shock. Crit Care. 2010;14(2):R53.
    - **Important prospective, multicenter study evaluating the adequate loading dose of amikacin for the treatment of life-threatening infections**
105. Karaiskos I, Friberg LE, Pontikis K, et al. Colistin Population Pharmacokinetics after Application of a Loading Dose of 9 MU Colistin Methanesulfonate in Critically Ill Patients. Antimicrob Agents Chemother. 2015 Dec;59(12):7240–7248.
106. Cristallini S, Hites M, Kabtouri H, et al. New Regimen for Continuous Infusion of Vancomycin in Critically Ill Patients. Antimicrob Agents Chemother. 2016 Aug;60(8):4750–4756.
107. Sime FB, Roberts MS, Roberts JA. Optimization of dosing regimens and dosing in special populations. Clin Microbiol Infect. 2015 Oct;21(10):886–893.
108. Van Lent-evers NA, Mathot RA, Geus WP, et al. Impact of goal-oriented and model-based clinical pharmacokinetic dosing of aminoglycosides on clinical outcome: a cost-effectiveness analysis. Ther Drug Monit. 1999;21(1):63–73.
109. Stickel F, Worni M, Pache I, et al. Optimizing ribavirin exposure by therapeutic drug monitoring improves treatment response in patients with chronic hepatitis C genotype 1. Am J Gastroenterol. 2013;108(7):1176–1178.
110. Park WB, Kim NH, Kim KH, et al. The effect of therapeutic drug monitoring on safety and efficacy of voriconazole in invasive fungal infections: a randomized controlled trial. Clin Infect Dis. 2012;55 (8):1080–1087.
111. Hagel S, Fiedler S, Hohn A, et al. Therapeutic drug monitoring-based optimisation of piperacillin/tazobactam to improve outcome in patients with sepsis (TARGET): a prospective, multi-centre, randomised controlled trial. Trials. 2019;20(1):330.
112. Abdulla A, Ewoldt TM, Hunfeld NGM, et al. The effect of therapeutic drug monitoring of beta-lactam and fluoroquinolones on clinical outcome in critically ill patients: the DOLPHIN trial protocol of a multi-centre randomised controlled trial. BMC Infect Dis. 2020 Jan;20 (1):57.
113. Rodriguez Colomo O, Alvrez Lerma F, Gonzalez Pérez MI, et al. Impact of administration of vancomycin or linezolid to critically ill patients with impaired function. Eur J Clin Microbiol Infect Dis. 2011 May;30(5):635–643.
114. Abhisekh SR, Haikal A, Hammoud KA, et al. Vancomycin and the Risk of AKI: a systematic review and meta-analysis. Clin J Am Soc Nephrol. 2016;11(12):2132–2140.
115. Ordooei JA, Shokouhi S, Sahraei Z. A review on colistin nephrotoxicity. Eur J Clin Pharmacol. 2015;71(7):801–810.
116. Wargo KA, Edwards JD. Aminoglycoside-induced nephrotoxicity. J Pharm Pract. 2014;27(6):573–577.