Pharmacokinetic/pharmacodynamic target attainment in critically ill renal patients on antimicrobial usage: focus on novel beta-lactams and beta lactams/beta-lactamase inhibitors

Pharmacokinetic/pharmacodynamic target attainment in critically ill renal patients on antimicrobial usage: focus on novel beta-lactams and beta lactams/beta-lactamase inhibitors

Milo Gatti[1,2], **Federico Pea**[1,2]

[1] Department of Medical and Surgical Sciences, Alma Mater Studiorum, University of Bologna, Bologna, Italy

[2] SSD Clinical Pharmacology, University Hospital IRCCS Policlinico Sant'Orsola, Bologna, Italy

Corresponding author: Prof. Federico Pea, Department of Medical and Surgical Sciences, Alma Mater Studiorum, University of Bologna, Bologna, Italy; SSD Clinical Pharmacology, University Hospital IRCCS Policlinico Sant'Orsola, Bologna, Italy; Via Massarenti 9, 40138 Bologna, Italy

e-mail: federico.pea@unibo.it

Abstract

Introduction: Several novel beta-lactams (BLs) and/or beta lactams/beta-lactamase inhibitors (BL/BLIs) have been recently developed for the management of multidrug-resistant bacterial infections. Data concerning dose optimization in critically ill patients with altered renal function are scanty.

Areas covered: This article provides a critical reappraisal of pharmacokinetic and clinical issues emerged with novel BLs and/or BL/BLIs in renal critically ill patients. Clinical and pharmacokinetic studies published in English until December 2020 were searched on PubMed-MEDLINE database.

Expert opinion: Several issues emerged with the use of novel BLs and/or BL/BLIs in critically ill renal patients. Suboptimal clinical response rate with ceftazidime-avibactam and ceftolozane-tazobactam was reported in phase II-III trials in patients with moderate kidney injury; data on patients undergoing renal replacement therapy are limited to some case reports; dose adjustment in augmented renal clearance is provided only for cefiderocol. Implementation of altered dosing strategies (prolonged infusion and/or higher dosage) coupled with adaptive real-time therapeutic drug monitoring could represent the most effective approach in warranting optimal pharmacokinetic/pharmacodynamic targets with novel BLs and/or BL/BLIs in challenging scenarios, thus minimizing the risk of clinical failure and/or of resistance selection.

Keywords: acute kidney injury; antimicrobial resistance; augmented renal clearance; cefiderocol; ceftazidime-avibactam; ceftolozane-tazobactam; continuous renal replacement therapy; imipenem-relebactam; meropenem-vaborbactam; PK/PD optimization

Highlights

- Altered renal function ranging from augmented renal clearance (ARC) to transient or persistent acute kidney injury (AKI) eventually requiring continuous renal replacement therapy (CRRT), may affect elimination of novel BLs and/or BL/BLIs in renal critically ill patients.
- Suboptimal clinical response rate in patients with moderate AKI was reported in phase II-III clinical trials with ceftazidime-avibactam and ceftolozane-tazobactam, and data concerning dose optimization of novel beta-lactams in renal critically ill patients are scanty.
- Renal dose adjustment of novel BLs and/or BL/BLIs should be deferred in patients with transient AKI until 48 hours after starting therapy.
- Altered dosing strategies of novel BLs and/or BL/BLIs (prolonged infusion and/or higher dosage) should be implemented in patients with ARC or undergoing high intensity CRRT.
- Adaptive real-time therapeutic drug monitoring focused at achieving the aggressive PK/PD target of 100% $fT_{> 4\text{-}8 \times MIC}$ may be helpful in maximizing effectiveness of novel BLs and/or BL/BLIs in challenging scenarios and in preventing resistance emergence.

1. Introduction

Sepsis is the most common cause of death in critically ill patients [1-2]. The emergence of multidrug-resistant (MDR) pathogens, poorly responsive to existing antimicrobials, coupled with the unpredictable pharmacokinetic alterations arising from complex pathophysiological mechanisms, makes the treatment of septic patients increasingly challenging [3-4]. Optimization of antibiotic use plays a key role in this setting, considering that early and appropriate antimicrobial treatment showed to reduce mortality [5-6]. Appropriate antimicrobial dosing is required to maximize microbial killing, minimize the development of multidrug antimicrobial resistance, and avoid concentration-related adverse drug reactions [7].

Changes in antimicrobial volume of distribution (V_D) and clearance (CL) are observed often in critically ill patients, leading to significant variation in both plasma and tissue antibiotic concentrations, depending on the degree of ~~drug hydro/lipophilicity~~ physicochemical features and renal elimination (**Figure 1**) [7-10]. Notably, wide fluctuations in renal function, ranging from augmented renal clearance (ARC) to severe acute kidney injury (AKI) eventually requiring continuous or intermittent renal replacement therapy (RRT), may affect antibiotic exposure in septic patients [11].

Beta-lactams (BLs) are extremely susceptible to wide variations in drug exposure in critically ill patients due to their physicochemical/pharmacokinetic (PK) features (namely hydrophilicity, low V_D, and predominant renal CL) [7]. These peculiar properties make BLs prone to significant extracorporeal removal performed by the different modalities of RRT [12]. This may often cause subtherapeutic concentrations ~~with risk increase in~~ that could lead to negative clinical outcome [13]. ~~Beta-lactams~~ BLs exhibit time-dependent pharmacodynamics (PD), and efficacy is related to the percentage of the dosing interval that the unbound concentration is maintained above the minimum inhibitory concentration (MIC) of the targeted pathogen ($\%fT_{> MIC}$). The minimum $fT_{> MIC}$ value required for bactericidal activity ranges between 40 and 70%, but emerging clinical data suggest that more aggressive PK/PD target (up to $100\%fT_{> 4\text{-}5 \times MIC}$) may lead to better outcome in critically ill patients [13-15]. Noteworthy, no specific dosing regimens of ~~beta-lactams~~ BLs are usually implemented for the critically ill patients, despite that this patient population may often exhibit pathophysiological conditions significantly altering drug PK. Consistently, the use of conventional dosing

regimens may lead to failure in achieving even the most conservative PK/PD target in both RRT and non-RRT settings [16-17].

In the last five years, several novel ~~beta-lactams (~~BLs~~)~~ and/or beta-lactams/beta-lactamase inhibitors (BL/BLIs) have been approved (namely ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, imipenem-relebactam, and cefiderocol), and others are under development in phase I-III clinical trials (aztreonam-avibactam, cefepime-enmetazobactam, cefepime-taniborbactam, cefepime-tazobactam, sulbactam-durlobactam, ceftazidime-zidebactam, meropenem-nacubactam) [18-21]. These agents show promising activity against different MDR pathogens, including carbapenemase-producing *Enterobacteriaceae* (CPE) and extensively drug-resistant (XDR) *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, or *Stenotrophomonas maltophilia* (**Table 1**) [18-21]. Notably, all novel BL and/or BL/BLIs share the typical PK features of ~~bets-lactams~~ BLs, namely hydrophilicity, low plasma protein binding, limited V_D, and predominant renal clearance (**Table 1**). Consistently, dose adjustments are required in presence of altered renal function [18, 21]. Specific PK and PD features of novel BLs and BL/BLIs in patients showed alteration in renal function are showed in **Table 2** [22-36].

Dosing optimization of novel BL and/or BL/BLIs in renal critically ill patients represents an unmet clinical need considering the paucity of available data [21]. This concerns especially the settings of extreme renal variation, like ARC or RRT, and/or of rapidly changing situations, like transient AKI. The aim of this review is to highlight PK/PD target attainment and clinical issues emerged with novel BL and/or BL/BLIs providing a critical reappraisal focused at dosing optimization in ~~renal~~ critically ill patients exhibiting challenging variations in renal function, including requirement for RRT and occurrence of ARC.

2. Search strategy

A literature search was conducted on PubMed-MEDLINE (until December 2020) to retrieve PK studies (including population PK studies), clinical trials, and real-world experiences concerning the use and dosing adjustments of novel BL and/or BL/BLIs in special renal ~~patients~~ populations (namely patients affected by AKI, requiring RRT, or exhibiting ARC). The following terms were search in combination:

"ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, imipenem-relebactam, cefiderocol, aztreonam-avibactam, cefepime-enmetazobactam, cefepime-taniborbactam, cefepime-tazobactam, sulbactam-durlobactam, ceftazidime-zidebactam, meropenem-nacubactam, acute kidney injury, renal replacement therapy, continuous renal replacement therapy, prolonged intermittent renal replacement therapy, continuous venovenous hemofiltration, continuous venovenous haemodialysis, continuous venovenous hemodiafiltration, augmented renal clearance, pharmacokinetic, pharmacokinetic/pharmacodynamic, prolonged infusion, continuous infusion, extended infusion, therapeutic drug monitoring". Only articles published in English in the last five years were included.

3. Pharmacokinetic features of novel BL and/or BL/BLIs in patients affected by renal function fluctuations: from pivotal trials to real-world evidence

Novel BL and/or BL/BLIs exhibit time-dependent antimicrobial effect, and efficacy is closely associated with the $\%fT_{> MIC}$ of the targeted or suspected pathogen [7]. Both approved [22-24, 26, 37-38] and developing novel BL and/or BL/BLIs [39-41] showed a linear relationship between estimated glomerular filtration rate and total plasma CL, with drug CL reduction proportional to decreasing renal function. Consistently, dose adjustments are usually required in renal patients.

Alternative dosing strategies, namely multiple daily dosing coupled with prolonged infusion (extended- or continuous- infusion), may represent the best approach to maximize the time-dependent antimicrobial activity of beta-lactams, especially among renal critically ill patients [7, 42-43]. In this regard it is worth noting that, according to the available data retrieved from pivotal trials and/or from the summary of product characteristics (**Table 3**), clinicians may face several concerns when adjusting the dosage of novel BL and/or BL/BLIs in renal patients. These issues may be summarized into four main areas: a) use of prolonged infusion; b) maintenance of more refracted daily dosing in renal dysfunction; c) use in renal critically ill patients; d) PK/PD targets for efficacy and/or for resistance prevention.

a) Use of prolonged infusion. Prolonged infusion was shown to improve the effectiveness of ~~beta-lactams~~ BLs on patient outcome in terms of mortality, clinical cure rate, and length of intensive care unit

(ICU) or hospital stay [44-47]. Among the novel BL and/or BL/BLIs, only meropenem-vaborbactam and cefiderocol (extended infusion in 3 hours), and ceftazidime-avibactam (extended infusion in 2 hours) were developed taking care of this rationale, with the intent of maximizing the achievement of optimal PK/PD target. Conversely, both ceftolozane-tazobactam (infusion in 1 hour) and imipenem-relebactam (infusion in 30 minutes) were developed according to a conventional dosing scheme of intermittent infusion. Notably, no recommendation for the need of a specific starting loading dose by intermittent infusion (over 30 min to 1 h) was provided for those novel BL and/or BL/BLIs administered by extended infusion. This could cause some delay in achieving therapeutically effective concentrations in critically ill patients, especially when specific pathophysiological conditions may increase the V_D of hydrophilic agents [48], although data for novel BLs are lacking.

Notably, the stability in aqueous solution of the different BLs represents a critical issue for the implementation of prolonged infusion, potentially responsible for early antibiotic degradation and consequent lack of efficacy. While for ceftazidime and ceftolozane a continuous infusion for 24 hours may be performed, stability of meropenem was limited to a maximum of 8 hours according to ambient temperature, thus requiring reconstitution at most after 6-8 hours [49-51]. Imipenem showed 10% degradation after only 3.5 hours, thus being suitable only for extended infusion [52].

b) Maintenance of more refracted daily dosing in renal dysfunction. Dosing adjustments in patients with AKI should be carried out according to the antibiotic pharmacodynamics in order to guarantee the maximal achievement of the targets. The most appropriate strategy for preserving the maximal PK/PD target attainment of $fT_{>MIC}$ for novel BL and/or BL/BLIs should be to decrease the amount of each single dose while maintaining unmodified the dosing interval [8-9]. This criterion for AKI patients was extensively applied with both cefiderocol and imipenem-relebactam in almost all classes of renal dysfunction (up to a CLCr of 15-29 mL/min), and with ceftolozane-tazobactam in all classes of renal dysfunction (up to CLCr < 15 mL/min) including end-stage renal disease (ESRD) with intermittent haemodialysis (IHD) (Table 2). Conversely, this strategy was less rigorously implemented with meropenem/vaborbactam (up to a CLCr of 20-39 mL/min), and with ceftazidime-avibactam (up to a CLCr of 31-50 mL/min) (**Table 3**).

c) Use in renal critically ill patients. Critically ill patients are a special population that could benefit from the use of novel BL and/or BL/BLIs more intensely and strongly than others, given the high prevalence of MDR infections occurring in the ICU settings [11, 53]. This patient population is often characterized by extreme variations in renal function (i.e., IHD, ARC and/or by the requirement of continuous renal replacement therapy [CRRT]), and data on appropriate dosage adjustments under these circumstances are strongly needed. Whereas all of the novel BL and/or BL/BLIs have defined dosing schedules for patients undergoing IHD, those for patients undergoing CRRT are completely lacking. Only for cefiderocol dosage for patients requiring CRRT were proposed, although these were predicted on the basis of the reported CL_{CRRT} of cefepime, according to the similar PK features shared with cefiderocol in terms of molecular weights and protein binding [54]. In regard to ARC patients, a specific intensified dosing schedule was developed only for cefiderocol (2 g every 6 h over 3h when CLCr ≥ 120 mL/min). A warning about the risk of inadequate exposure when CLCr is ≥ 150 mL/min is reported in the label of imipenem-relebactam, whereas no specific recommendation was provided for the remaining novel BL and/or BL/BLIs.

d) PK/PD targets for efficacy and/or for resistance prevention. According to preclinical models, the percentage of $fT_{> MIC}$ required for ensuring bactericidal efficacy with ~~beta-lactams~~ BLs may range from ~~30~~ 40 to 70% [55]. Consistently, the PK/PD targets investigated during phase II and phase III pivotal clinical trials of the novel BL and/or BL/BLIs were of this magnitude. Data coming from real-world clinical experience suggests that more aggressive PK/PD targets up to $100\%fT_{> 4\text{-}5 \times MIC}$ may improve clinical outcome in critically ill patients and may also be helpful in preventing bacterial regrowth and emergence of resistant pathogens [13-16, 56-57]. Unfortunately, these more aggressive PK/PD targets were not tested with the novel BL and/or BL/BLIs up to date. Addressing this issue in the near future may help in preserving for longer the clinical effectiveness of these new agents in the therapeutic armamentarium.

Overall, based on the aforementioned issues, a sort of Dr. Jekyll-Mr. Hyde conundrum rises between data retrieved in pivotal trials and real-life needs in daily clinical practice for renal critically ill patients treated with the novel BL and/or BL/BLIs. Expert opinions could be helpful for dose optimization in some clinical scenarios.

3.1 Acute kidney injury (~~ARC~~ AKI)

~~Beta-lactam~~ BL dose optimization in patients with sepsis-related AKI represents a great challenge. The labelled dosages for renal patients are usually based on the findings of phase I trials performed in subjects with stable chronic kidney impairment. Unfortunately, it is unlikely that these dosages may fit in patients with sepsis-related AKI [58]. Patients with severe acute infections may show dynamic changes in renal function, as the initial AKI associated with severe infections is often transient. A prompt recovery of renal function frequently occurs within the first 48 hours thanks to resuscitation therapy and other supportive treatment. Additionally, significant alterations of V_D may occur in AKI patients, and this may affect the exposure profile of hydrophilic antibiotics, like ~~beta-lactams~~ BLs (**Figure 2**) [59-60]. Consistently, starting treatment with a dosage of ~~beta-lactam~~ BL adjusted for renal dysfunction could cause underexposure during the first 48 hours in patients with transient AKI. This may lead to treatment failure and poor clinical outcome, considering that this timeframe is life-threatening especially in critically ill patients with septic shock [58, 60].

Crass *et al.* [58] retrospectively investigated the incidence of AKI among patients admitted in hospital because of different types of bacterial infections (complicated urinary tract infections, complicated intraabdominal infections, bacterial pneumonia, and skin and soft tissue infections). Among 18,650 admissions, the overall rate of AKI at admission was 17.5% (3,256/18,650). Notably, AKI was transient in 57.2% of patients (1,862/3,256), who recovered to almost normal renal function within the first 48 hours. Additionally, approximately 50% of patients with moderate renal impairment on admission had an improvement of renal function up to CLCr > 50 mL/min within 48 hours. The conclusion was that starting treatment with reduced doses of ~~beta-lactams~~ BLs in patients with transient AKI may increase the risk of underexposure and clinical failure. Deferred renal dose reduction of wide therapeutic index ~~beta-lactam~~ BL antibiotics could improve outcomes of infectious diseases in patients with AKI on admission.

This concern emerged in several phase III trials investigating novel BL and/or BL/BLIs, since suboptimal clinical response rate was reported in patients with moderate AKI receiving adjusted dosing regimens based on phase I studies (**Table 4**) [58-59, 61-66].

An imbalance in response rate for ceftazidime-avibactam was observed in the phase III trials RECLAIM 1 and 2 among patients with moderate renal impairment [62]. Patients with moderate AKI (CLCr

31-50 mL/min) receiving 1.25 g q12h of ceftazidime-avibactam (a proportional dose reduction of 66% compared to normal renal function) showed a significant lower response rate (45.2% vs. 74.3%; p = 0.016) compared to those randomized to meropenem 1g q12h (proportional dose reduction of 33%). Furthermore, subjects with moderate renal impairment treated with 1g q12h meropenem showed a trend toward lower response rate compared to patients with normal kidney function receiving 1g q8h (74.3% vs. 86.1%; p = 0.06). This highlights once more the relevance that dosage adjustments based on decrease in the amount of each single dose rather than on extension of the dosing interval may have in preserving optimal PK/PD target of time-dependent antibiotics ($fT_{>MIC}$) in presence of renal impairment (i.e., 500 mg q6h is better than 1 g q12h) [8-9]. Notably, 67.2% of patients with moderate AKI at baseline who were randomized to ceftazidime-avibactam, subsequently improved renal function (CLCr> 50 mL/min) within 48-72 hours. These findings led to increase the recommended dose of ceftazidime-avibactam in moderate renal impairment from 1.25 g q12h up to 1.25 g q8h in the final product label [59, 61].

An imbalance in the response rate was noted also in the phase III ASPECT trials with ceftolozane-tazobactam among patients with renal impairment. Interestingly, the imbalance was against ceftolozane-tazobactam in the ASPECT-cIAI trial [63], and in favour in the subsequent ASPECT-NP trial [64]. Specifically, in the ASPECT-cIAI study [63], patients with moderate AKI (CLCr 30-50 mL/min) receiving 750 mg q8h ceftolozane-tazobactam (a proportional dose reduction of 50% compared to normal renal function) showed a trend toward lower clinical cure rate (47.8% vs. 69.2%; p = 0.21) compared to those randomized to meropenem 1g q12h (proportional dose reduction of 33%). Furthermore, also in this trial patients with moderate renal impairment treated with meropenem at 1g q12h showed a lower response rate compared to patients with normal kidney function receiving 1g q8h (69.2% vs. 87.9%; p = 0.047). On the other hand, in the ASPECT-NP study [64], an imbalance in 28-day all-cause mortality rate was reported among patients with severe renal impairment (CLCr 15-30 mL/min). Hospital- or ventilator-acquired pneumonia (HAP/VAP) patients with severe AKI receiving 750 mg q8h ceftolozane-tazobactam (a proportional dose reduction of 75% compared to normal renal function) showed a trend toward lower mortality rate (35.3% vs. 61.9%; p = 0.10) compared to those randomized to meropenem 500mg q12h (proportional dose reduction of 66%). This difference, although not reaching statistical significance due to the small size of the analysed sub-groups, stresses once more that decreasing the amount of each single dose

and maintaining the refraction of administrations is the best approach for ensuring optimal achievement of the PK/PD target and favourable clinical outcome with beta-lactams in renal patients [8-9]. Notably, mortality rate was more than doubled in both groups compared to patients with normal renal function.

Similar results were retrieved with cefiderocol in the APEKS-NP trial [65] and with meropenem-vaborbactam in the TANGO II trial [66]. In the APEKS-NP study [65], a ~~trend toward~~ lower mortality rate was reported in patients with moderate renal impairment treated with cefiderocol 1.5g q8h (infusion in 3-hours) compared to those receiving meropenem 2g q12h (7.0% vs. 19.0%; p = 0.26), although not significant according to low sample size. In the TANGO II study [66], a higher clinical cure rate was found in subjects with moderate AKI receiving meropenem-vaborbactam 1g/1g q8h (infusion in 3-hours) compared to patients randomized to best available therapy (28.6% vs. 0.0%; p = 0.49), including carbapenems at dosage recommended in the summary of product characteristics (i.e., administration q12h). However, it is important to underline that AKI itself represents a risk factor for increased mortality in critically ill patients affected by HAP/VAP.

A recent systematic review assessed the overall quality of evidence of achieving adequate drug exposure in renal patients when administering renally cleared antibiotics (including the ~~beta-lactams~~ BLs) at the adjusted doses recommended for renal function [67]. The conclusion drawn by the authors are consistent with the aforementioned findings as it was highlighted that there is no good evidence that these reduced dosages may ensure in renal patients exposure comparable to those achievable with the full dosages in patients with normal renal function [67].

Overall, these findings support the idea that in patients with sepsis-related AKI dose reduction of novel BL – BL/BLIs may often be inappropriate and unnecessary at the beginning of treatment, since AKI is transient in the majority of cases and may resolve within the first 48 hours. Deferral of renal dosage adjustment should be applied only after 48 hours to patients with persistent AKI. This approach may be effective and at the same time safe, considering the wide therapeutic index and the low toxicity of these antibiotics [58-59]. Refraction of daily dosing should be pursued as much as possible even in patients with persistent AKI. Adjustments based on reduction of the amount of each single dose rather than on extension of the dosing interval would better preserve optimal achievement of the PK/PD target. Prolonged infusion

may play a fundamental role in improving outcome in AKI patients as well, as reported in the clinical trials of cefiderocol and meropenem-vaborbactam.

3.2 Renal replacement therapy (RRT)

CRRT and/or prolonged intermittent RRT (PIRRT) are common practices in critically ill patients with sepsis-related severe AKI, as approximately 70% of patients may undergo RRT [68]. Appropriate dosing of novel BL and/or BL/BLIs may be highly challenging in septic shock patients undergoing CRRT because the extracorporeal circuit may significantly alter drug exposure. Physicochemical and PK features of ~~beta-lactams~~ BLs (namely low molecular weight, hydrophilicity, limited V_D, and low protein binding) make these drugs prone to CRRT removal [12]. Variations in RRT conditions and settings, namely modality of solute removal, type of filter composition, pre- vs. post-dilution mode, blood flow rate and effluent flow rate may *per se* affect antimicrobial PK, including novel BLs and/or BL/BLIs [69-70]. Residual renal function and/or progressive recovery of renal function may furtherly increase the elimination of renally cleared antimicrobials in patients receiving RRT [69, 71].

Unfortunately, for most of the novel BL – BL/BLIs dosing recommendations during RRT are currently lacking, and this might affect efficacy [21, 72]. Noteworthy, some real-world studies with both ceftazidime-avibactam and ceftolozane-tazobactam found CRRT as an independent predictor of clinical failure and development of resistance [73-74]. Higher emergence of resistance to ceftazidime-avibactam was reported by Shields *et* al. in patients requiring CRRT (OR 26.67; 95% CI 2.24-317.1) [73]. This could be theoretically related to antibiotic underexposure and failure in achieving an optimal PK/PD target.

Available PK data of novel BL and/or BL/BLIs during CRRT (**Table 5**) are currently limited to a population PK study carried out with ceftolozane-tazobactam among 6 patients undergoing ~~CVVHDF~~ continuous venovenous hemodiafiltration [27], and to single case reports concerning ceftolozane-tazobactam [75-79], ceftazidime-avibactam [28, 80] and meropenem-vaborbactam [29]. Those during PIRRT concerns only one case with ceftolozane-tazobactam [81]. Notably, the population PK study of ceftolozane-tazobactam performed by Sime *et al.* [27] showed that optimal cumulative fraction of response of the PD

target of 100% $fT_{>MIC}$ could be achieved only by implementing altered dosing strategies based on higher dosage (3 g q8h) or on continuous infusion (4.5 g or 9 g) after a loading dose of 1.5-3 g.

It is worth noting that the use of higher CRRT intensity (usually with a prescribed dose ≥ 35mL/kg/h) is growing in daily clinical practice [82-83]. This may raise additional concerns about which could be the best dosing schedule, especially in presence of deep-seated infections and/or of ~~borderline~~ non-susceptible isolates.

A direct association between effluent flow rate and antimicrobial CL was demonstrated both for some of the old BLs ~~beta-lactams~~, like piperacillin-tazobactam and meropenem [84], and of the novel ones, like ceftolozane-tazobactam [72] and meropenem-vaborbactam [85-86]. Ceftazidime-avibactam, imipenem-relebactam, and cefiderocol exhibit physicochemical and PK properties quite similar to those of the aforementioned agents. Consistently, it may be expected that also for these agents altered dosing strategies, based on higher dose and/or on prolonged infusion, could be needed for optimizing drug exposure during higher CRRT intensity.

3.3 Augmented renal clearance (ARC)

Augmented renal clearance (ARC) is a pathophysiological condition defined as the occurrence of a measured CLCr ≥ 130 mL/min/1.73 m^2 in males and ≥ 120 in females coupled with a normal serum creatinine value (0.6-1.4 mg/dL) [87-88]. Prevalence of ARC was shown to vary greatly among different patient populations having normal serum creatinine values. It was of 16.4% among febrile neutropenic patients, 39.5-56% among those with sepsis, 65% among burn patients, 85% among trauma patients, up to 100% among those with subarachnoid haemorrhage [87-88].

This phenomenon is quite worryingly when using ~~beta-lactams~~ BLs since, by enhancing drug CL, ARC may cause underexposure leading to poor clinical outcome [88]. Additionally, the potential development of antibiotic resistance related to drug underexposure cannot be overlooked. Studies investigating the impact of ARC on beta-lactam elimination reported consistent findings concerning drug underexposure, but evidence in terms of therapeutic failure and poor outcomes is conflicting and debated [89-93].

Altered dosing strategies based on more refracted dosing regimens coupled with prolonged infusion may represent a valuable approach for achieving optimal PK/PD target with ~~beta-lactams~~ BLs in ARC patients [88]. Among novel BL and/or BL/BLIs, cefiderocol is the only agent having these criteria applied during drug development. A more refracted dosage of 2g q6h (instead of q8h in patients with normal renal function) administered by extended infusion over 3 hours is currently recommended in the product fact sheet for ARC patients. This approach was based on Monte Carlo simulations carried out during phase III clinical trials showing that this enhanced dosage might allow a > 90% probability of target attainment of the PK/PD target of 100% $fT_{>MIC}$ in ARC patients with cUTIs, bloodstream infections, or HAP/VAP [22].

Unfortunately, none of the other novel BL and/or BL/BLIs applied such a strategy during drug development for identifying a specific dosing recommendation in ARC patients. Some useful data came from real-world after commercial licensing. A recent population PK study carried out with ceftolozane-tazobactam showed that among ARC patients having a CLCr of 140-180 mL/min a higher dosage of 9 g by continuous infusion (after a 3 g loading dose) is needed for ensuring a probability of target attainment ≥ 85% against *Pseudomonas aeruginosa* with an MIC up to the clinical breakpoint of 4 mg/L [94]. Additionally, prolonged infusion of ceftolozane-tazobactam (3 g every 8 h 4-hour infusion) was associated with improved probability of target attainment compared to intermittent infusion for resistant *Pseudomonas aeruginosa* (showing MIC ranging from 4 to 32 mg/L) in patients with a CLCr of 121-180 mL/min [95-96]. Nicolau *et al*. recently evaluated 11 critically ill patients showing ARC (median CLCr 214 mL/min) and receiving a single dose of 3 g ceftolozane-tazobactam in intermittent infusion [97]. A mean estimated ceftolozane fT>MIC at 4 µg/mL and tazobactam fT>threshold = 1 µg/mL respectively of 86.4% and 54.9% was found.

In regard to ceftazidime-avibactam, a subgroup analysis of patient populations included in the REPROVE trial showed that in ARC patients the standard dosage of 2.5g q8h over 2h ensured > 95% probability of target attainment of a more conservative target of 50% $fT_{>MIC}$ [31, 61]. It should be mentioned that a 35% decrease in drug exposure was observed compared to patients with normal renal (mean AUC) [31, 61]. Real-time experience is currently limited to a PK/PD analysis of ceftazidime-avibactam in two ARC critically ill patients in whom treatment with the standard dose of 2.5g q8h over 2h allowed to achieve the conservative target of 50% $fT_{>MIC}$ against pathogens with an MIC up to 16 mg/L [98].

4. PK/PD optimization of novel beta-lactams in renal critically ill patients: preventing resistance emergence and role of therapeutic drug monitoring (TDM)

The achievement of an adequate PK/PD target of novel BL and/or BL/BLIs in critically ill patients represents a debated issue. Only conservative thresholds (40-70% $fT_{>MIC}$) were considered during pivotal phase II and III clinical trials. However, several experiences in critically ill patients reported better clinical outcome with the achievement of higher PK/PD target [13-15]. In the DALI study [16], Roberts *et al*. found in critical septic patients a higher rate of positive clinical outcome with ~~beta-lactams~~ BLs when achieving a more aggressive PK/PD target of 100% $fT_{>MIC}$ compared to 50% $fT_{>MIC}$ (OR 1.56 vs. 1.02; $p < 0.03$). However, positive clinical outcome was defined as the completion of treatment course without change or addition of antibiotic therapy, while mortality or clinical cure rate were not investigated. Furthermore, only in 34.2% of cases a pathogen MIC was available.

Notably, antibiotic exposure showed a close relationship not only with clinical outcome, but also with the suppression of resistance emergence [57]. Global dissemination of antimicrobial resistance represents a worryingly health concern [99], and implementation of strategies aimed at minimizing the development of resistance to novel agents represents a compelling need.

Antibiotic dose optimization is a valid approach to overcome the emergence of resistance [57, 100]. A recent systematic review [39] of preclinical and clinical evidences ~~using~~ found that resistance emergence to beta-lactams may be prevented when trough levels are at least 4-fold higher than the MIC (C_{min}/MIC > 4). Consistently, antibiotic dosing regimens required to suppress the emergence of resistance should be focused at achieving PK/PD target of 100% $fT_{>4\text{-}8 \times MIC}$ [100].

Unfortunately, the remarkable prevalence of ~~borderline~~ non-susceptible isolates with high MIC in critical care setting [53], the inaccuracy in MIC determination with automated test [101], and the concomitant existence of PK alterations (i.e., ARC, higher CRRT intensity) may render the achievement of aggressive PK/PD target unpredictable in renal critically ill patients, even when the best altered dosing strategies (namely higher dose and prolonged infusion) have been implemented [100, 102].

Adaptative daily therapeutic drug monitoring (TDM) may represent a helpful tool in addressing these issues. Routine TDM of ~~beta-lactams~~ BLs is recommended in critically ill patients nowadays [14]. Adaptive TDM strategy was associated with an increased attainment of PK/PD target for ~~beta-lactams~~ BLs in different types of renal populations, including patients undergoing CRRT or having ARC [103-106]. The impact of adaptive TDM of ~~beta-lactams~~ BLs on clinical outcome remains to be established [107-108].

In regard to novel BL and/or BL/BLIs, real-world experiences of TDM approach are scanty. In a retrospective analysis of seven patients affected by deep-seated MDR *Pseudomonas aeruginosa* infections, a loading dose of 3 g of ceftolozane-tazobactam followed by a maintenance dose of 6g by continuous infusion warranted optimal 100% $fT_{>4xMIC}$ against all of the clinical isolates with an MIC ranging between 0.19 and 1.5 mg/L [109].

Some authors suggested that TDM-guided dosing of novel BL and/or BL/BLIs may be a safe and effective tool for achieving aggressive PK/PD target early (ideally within the first 24 hours), especially in patients with altered renal function, thus minimizing the risks of both poor clinical outcome and development of resistance [43]. Additionally, although BLs commonly exhibit a wide therapeutic index, high exposure could be associated with the occurrence of neurotoxicity or nephrotoxicity (mainly with meropenem, piperacillin, or cefepime) [14]. In this setting, TDM-guided dosing of novel BL and/or BL/BLIs may be also useful for minimizing the occurrence of toxicity. Although no specific toxicity thresholds have been established for both traditional and novel BLs, the avoidance of BL plasma concentrations above 8-10 times the MIC was suggested [14, 100].

Despite the importance of an adaptive daily TDM approach in critically ill patients is remarkable, many barriers to extensive use of TDM for BLs still exist [110-111]. A timely turnaround time of BL analytical assays represents a critical issue in ICU setting, where physiopathological conditions of patients could change rapidly and results of BL concentrations should be available in real-time. Furthermore, the development of accurate and sensitive assays characterized by rigorous validation should be pursued, particularly for novel BLs, to ensure accurate and consistent results. Additionally, while many laboratories prefer to develop their "home-made" methods, a robust and validate method shared among a large number of laboratories may be desirable [110-111]. Finally, for agents exhibiting a remarkable protein binding,

measurement of unbound concentrations should be performed. Currently, TDM is mostly available for traditional BLs (e.g., piperacillin, meropenem), although the implementation of real-time TDM also for novel BLs and/or BL/BLIs is strongly expected.

5. Conclusion

Unnecessary dose reduction in patients with sepsis-related transient AKI, lack of dedicated dosing regimens for patients undergoing RRT or showing ARC, and dose selection based on conservative but not on more aggressive PK/PD targets could render the use of novel BL and/or BL/BLIs suboptimal in critically ill renal patients. Implementation of altered dosing strategies based on multiple daily dosing and prolonged infusion coupled with real-time TDM-guided PK/PD optimization proved high efficacy in maximizing exposure with traditional ~~beta-lactams~~ BLs. Accordingly, we believe that a similar approach should be pursued for the novel BL and/or BL/BLIs as well, especially in challenging scenarios.

6. Expert opinion

In the last decade, several novel BL and/or BL/BLIs have been developed to overcome the widespread increase in antimicrobial resistance. The prevalence of infections caused by pathogens multi-drug resistant to traditional antibiotics, namely CPE, XDR *Pseudomonas aeruginosa* and *Acinetobacter baumannii* is worryingly high in the ICU setting. Consistently, the use of these agents is expected to progressively increase among critically ill patients in the next years. Dose optimization of novel BL and/or BL/BLIs is of paramount importance among critically ill patients, and should be focused not only at maximizing clinical efficacy, but also at preventing the emergence of bacterial resistance against these last-resort agents.

The high PK variability and the paucity of specific data make dose optimization of these novel agents extremely challenging in critically ill patients. Likewise traditional ~~beta-lactams~~ BLs, novel BL and/or BL/BLIs are extremely affected by the pathophysiological alterations commonly observed in critically ill patients. In regard to critically ill renal patients, three different challenging clinical scenarios have to be faced by the ICU physicians: AKI, RRT and ARC (**Figure 3**).

In AKI, renal dose adjustment of novel BL and/or BL/BLIs should be deferred until 48 hours from starting therapy. At that time, dose reduction should be applied only if AKI persisted. Extended or continuous infusion may be helpful in maximizing the achievement of the PK/PD target.

In CRRT, it is fundamental distinguishing between the type of replacement therapy (CVVH vs. CVVHDF), and to take care of flow intensity and of the pre- or post-dilution mode. Additionally, residual renal function might further increase drug removal. No dose reduction of novel BL and/or BL/BLIs (showing a Sieving coefficient > 0.8) should be performed in patients requiring high intensity CRRT (ultrafiltration flow rate > 2.5-3 L/h). Prolonged infusion coupled with higher doses could be necessary for patients showing residual significant diuresis or isolates with ~~borderline~~ non-susceptible MIC.

In regard to ARC, measurement of CLCr should be performed on a regular basis in patient populations at high-risk for ARC (e.g., febrile neutropenia, sepsis, burns, polytrauma, subarachnoid haemorrhage) showing normal serum creatinine values. Timely implementation of higher dosage and/or prolonged infusion is strongly suggested for the novel BL and/or BL/BLIs, as already scheduled for cefiderocol.

In all of the aforementioned scenarios, we believe that implementation of adaptive real-time TDM of the novel BL and/or BL/BLIs focused at attaining the very aggressive PK/PD target of 100% $fT_{> 4\text{-}8 \times MIC}$ would be the most powerful strategy in maximizing the effectiveness of and in preventing the development of resistance against these last-resort agents.

Although some stakeholders could still be reluctant to this project due to costs and conflicting evidence concerning impact on clinical outcome, it should not be overlooked that the concept of personalized medicine is gaining more and more relevance in daily clinical practice. Nowadays, real -time TDM- based optimization of antimicrobial therapy in critically ill patients should be considered a fundamental piece of the antimicrobial stewardship program. In this regard, a multidisciplinary taskforce involving the intensive care physician, the infectious disease consultant, the clinical microbiologist and the clinical pharmacologist or clinical pharmacist should work side by side with the intent of reducing as much as possible the sepsis-related mortality rate.

Funding

This paper was not funded.

Declaration of interests

FP participated in speaker bureau for Angelini, Basilea Pharmaceutica, Gilead, Hikma, Merck Sharp & Dohme,

Nordic Pharma, Pfzer and Sanof Aventis, and in advisory board for Angelini, Basilea Pharmaceutica, Correvio,

Gilead, Hikma, Merck Sharp & Dohme, Nordic Pharma, Novartis, Pfzer, Shionogi and Thermo-Fisher.

References

Paper of special note have been highlighted as:

* = of interest, ** = of considerable interest

1. Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med. 2013 Aug 29;369(9):840-51.

2. Kaukonen KM, Bailey M, Suzuki S, et al. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. JAMA. 2014 Apr 2;311(13):1308-16.

3. Sime FB, Roberts MS, Roberts JA. Optimization of dosing regimens and dosing in special populations. Clin Microbiol Infect. 2015 Oct;21(10):886-93.

4. Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. Crit Care Med. 2009 Mar;37(3):840-51.

5. Kumar A, Ellis P, Arabi Y, et al; Cooperative Antimicrobial Therapy of Septic Shock Database Research Group. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. Chest. 2009 Nov;136(5):1237-48.

6. Ulldemolins M, Nuvials X, Palomar M, et al. Appropriateness is critical. Crit Care Clin. 2011 Jan;27(1):35-51.

7. Blot SI, Pea F, Lipman J. The effect of pathophysiology on pharmacokinetics in the critically ill patient--concepts appraised by the example of antimicrobial agents. Adv Drug Deliv Rev. 2014 Nov 20;77:3-11.

8. Ulldemolins M, Roberts JA, Lipman J, et al. Antibiotic dosing in multiple organ dysfunction syndrome. Chest. 2011 May;139(5):1210-1220.

9. Pea F, Viale P. Bench-to-bedside review: Appropriate antibiotic therapy in severe sepsis and septic shock--does the dose matter? Crit Care. 2009;13(3):214. * an interesting review concerning pharmacokinetic alterations found in critically ill patients, and their impact on antimicrobial exposure and dose adjustment

10. Roberts JA, Joynt GM, Choi GY, et al. How to optimise antimicrobial prescriptions in the Intensive Care Unit: principles of individualised dosing using pharmacokinetics and pharmacodynamics. Int J Antimicrob Agents. 2012 Mar;39(3):187-92.

11. Roberts JA, Abdul-Aziz MH, Lipman J, et al; International Society of Anti-Infective Pharmacology and the Pharmacokinetics and Pharmacodynamics Study Group of the European Society of Clinical Microbiology and Infectious Diseases. Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis. 2014 Jun;14(6):498-509.

12. Pistolesi V, Morabito S, Di Mario F, et al. A Guide to Understanding Antimicrobial Drug Dosing in Critically Ill Patients on Renal Replacement Therapy. Antimicrob Agents Chemother. 2019 Jul 25;63(8):e00583-19. * An interesting guide focused on antimicrobial use in renal replacement therapy.

13. Abdul-Aziz MH, Lipman J, Roberts JA. Identifying "at-risk" patients for sub-optimal beta-lactam exposure in critically ill patients with severe infections. Crit Care. 2017 Nov 21;21(1):283.

14. Abdul-Aziz MH, Alffenaar JC, Bassetti M, et al; Infection Section of European Society of Intensive Care Medicine (ESICM); 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); Infections in the ICU and Sepsis Working Group of International Society of Antimicrobial Chemotherapy (ISAC). Antimicrobial therapeutic drug monitoring in critically ill adult patients: a Position Paper. Intensive Care Med. 2020 Jun;46(6):1127-53. ** a practical guide for the use of therapeutic drug monitoring in critically ill patients

15. Abdul-Aziz MH, Lipman J, Mouton JW, et al. Applying pharmacokinetic/pharmacodynamic principles in critically ill patients: optimizing efficacy and reducing resistance development. Semin Respir Crit Care Med. 2015 Feb;36(1):136-53.

16. Roberts JA, Paul SK, Akova M, et al; DALI Study. DALI: defining antibiotic levels in intensive care unit patients: are current β-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis.

2014 Apr;58(8):1072-83. ** An important prospective multinational pharmacokinetic study reporting a significant correlation between inadequate beta-lactam exposure and poor outcomes in critically ill patients.

17. 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:ciaa224. doi: 10.1093/cid/ciaa224. Online ahead of print.

18. Yahav D, Giske CG, Grāmatniece A, et al. New β-Lactam-β-Lactamase Inhibitor Combinations. Clin Microbiol Rev. 2020 Nov 11;34(1):e00115-20. doi: 10.1128/CMR.00115-20. Print 2020 Dec 16. * An interesting review concerning pharmacological features of novel beta-lactams.

19. Tamma PD, Hsu AJ. Defining the Role of Novel β-Lactam Agents That Target Carbapenem-Resistant Gram-Negative Organisms. J Pediatric Infect Dis Soc. 2019 Jul 1;8(3):251-60.

20. Noval M, Banoub M, Claeys KC, et al. The Battle Is on: New Beta-Lactams for the Treatment of Multidrug-Resistant Gram-Negative Organisms. Curr Infect Dis Rep. 2020 Jan 13;22(1):1.

21. Giannella M, Bartoletti M, Gatti M, et al. Advances in the therapy of bacterial bloodstream infections. Clin Microbiol Infect. 2020 Feb;26(2):158-67.

22. Kawaguchi N, Katsube T, Echols R, et al. Population Pharmacokinetic Analysis of Cefiderocol, a Parenteral Siderophore Cephalosporin, in Healthy Subjects, Subjects with Various Degrees of Renal Function, and Patients with Complicated Urinary Tract Infection or Acute Uncomplicated Pyelonephritis. Antimicrob Agents Chemother. 2018 Jan 25;62(2):e01391-17.

23. Merdjan H, Tarral A, Das S, et al. Phase 1 Study Assessing the Pharmacokinetic Profile and Safety of Avibactam in Patients With Renal Impairment. J Clin Pharmacol. 2017 Feb;57(2):211-8.

24. Wooley M, Miller B, Krishna G, et al. Impact of renal function on the pharmacokinetics and safety of ceftolozane-tazobactam. Antimicrob Agents Chemother. 2014;58(4):2249-55.

25. Bhagunde P, Colon-Gonzalez F, Liu Y, et al. Impact of renal impairment and human organic anion transporter inhibition on pharmacokinetics, safety and tolerability of relebactam combined with imipenem and cilastatin. Br J Clin Pharmacol. 2020 May;86(5):944-57.

26. Rubino CM, Bhavnani SM, Loutit JS, et al. Single-Dose Pharmacokinetics and Safety of Meropenem-Vaborbactam in Subjects with Chronic Renal Impairment. Antimicrob Agents Chemother. 2018 Feb 23;62(3):e02103-17.

27. 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. 2019 Dec 20;64(1):e01655-19.

28. Wenzler E, Bunnell KL, Bleasdale SC, et al. Pharmacokinetics and Dialytic Clearance of Ceftazidime-Avibactam in a Critically Ill Patient on Continuous Venovenous Hemofiltration. Antimicrob Agents Chemother. 2017 Jun 27;61(7).

29. Kufel WD, Eranki AP, Paolino KM, et al. In vivo pharmacokinetic analysis of meropenem/vaborbactam during continuous venovenous haemodialysis. J Antimicrob Chemother. 2019 Jul 1;74(7):2117-8.

30. Katsube T, Wajima T, Ishibashi T et al. Pharmacokinetic/Pharmacodynamic Modeling and Simulation of Cefiderocol, a Parenteral Siderophore Cephalosporin, for Dose Adjustment Based on Renal Function. Antimicrob Agents Chemother. 2016 Dec 27;61(1):e01381-16.

31. Das S, Li J, Riccobene T, et al. Dose Selection and Validation for Ceftazidime-Avibactam in Adults with Complicated Intra-abdominal Infections, Complicated Urinary Tract Infections, and Nosocomial Pneumonia. Antimicrob Agents Chemother. 2019 Mar 27;63(4):e02187-18.

32. Xiao AJ, Caro L, Popejoy MW et al. PK/PD Target Attainment With Ceftolozane/Tazobactam Using Monte Carlo Simulation in Patients With Various Degrees of Renal Function, Including Augmented Renal Clearance and End-Stage Renal Disease. Infect Dis Ther. 2017 Mar;6(1):137-48.

33. Nichols WW, Newell P, Critchley IA et al. Avibactam Pharmacokinetic/Pharmacodynamic Targets. Antimicrob Agents Chemother. 2018 May 25;62(6):e02446-17.

34. Xiao AJ, Miller BW, Huntington JA et al. Ceftolozane/tazobactam pharmacokinetic/pharmacodynamic-derived dose justification for phase 3 studies in patients with nosocomial pneumonia. J Clin Pharmacol. 2016 Jan;56(1):56-66.

35. Bhagunde P, Patel P, Lala M, et al. Population Pharmacokinetic Analysis for Imipenem-Relebactam in Healthy Volunteers and Patients With Bacterial Infections. CPT Pharmacometrics Syst Pharmacol. 2019 Oct;8(10):748-58.

36. Griffith DC, Sabet M, Tarazi Z, et al. Pharmacokinetics/Pharmacodynamics of Vaborbactam, a Novel Beta-Lactamase Inhibitor, in Combination with Meropenem. Antimicrob Agents Chemother. 2018 Dec 21;63(1):e01659-18.

37. Zhanel GG, Lawrence CK, Adam H, et al. Imipenem-Relebactam and Meropenem-Vaborbactam: Two Novel Carbapenem-beta-Lactamase Inhibitor Combinations. Drugs. 2018 Jan;78(1):65-98.

38. Smith JR, Rybak JM, Claeys KC. Imipenem-Cilastatin-Relebactam: A Novel β-Lactam-β-Lactamase Inhibitor Combination for the Treatment of Multidrug-Resistant Gram-Negative Infections. Pharmacotherapy. 2020 Apr;40(4):343-56.

39. Preston RA, Mamikonyan G, Mastim M, et al. Single-Center Investigation of the Pharmacokinetics of WCK 4282 (Cefepime-Tazobactam Combination) in Renal Impairment. Antimicrob Agents Chemother. 2019 Sep 23;63(10):e00873-19.

40. O'Donnell J, Preston RA, Mamikonyan G, et al. Pharmacokinetics, Safety, and Tolerability of Intravenous Durlobactam and Sulbactam in Subjects with Renal Impairment and Healthy Matched Control Subjects. Antimicrob Agents Chemother. 2019 Aug 23;63(9):e00794-19.

41. Preston RA, Mamikonyan G, DeGraff S, et al. Single-Center Evaluation of the Pharmacokinetics of WCK 5222 (Cefepime-Zidebactam Combination) in Subjects with Renal Impairment. Antimicrob Agents Chemother. 2018 Dec 21;63(1):e01484-18.

42. Parker SL, Sime FB, Roberts JA. Optimizing dosing of antibiotics in critically ill patients. Curr Opin Infect Dis. 2015 Dec;28(6):497-504.

43. Abdul-Aziz MH, Portunato F, Roberts JA. Prolonged infusion of beta-lactam antibiotics for Gram-negative infections: rationale and evidence base. Curr Opin Infect Dis. 2020 Dec;33(6):501-10. * an interesting review concerning the application in different settings of prolonged infusion of beta-lactams.

44. Vardakas KZ, Voulgaris GL, Maliaros A, et al. Prolonged versus short-term intravenous infusion of antipseudomonal beta-lactams for patients with sepsis: a systematic review and meta-analysis of randomised trials. Lancet Infect Dis. 2018 Jan;18(1):108-20. * An important systematic review showing decrease in mortality rate with the use of prolonged infusion of beta-lactams.

45. Rhodes NJ, Liu J, O'Donnell JN, et al. Prolonged Infusion Piperacillin-Tazobactam Decreases Mortality and Improves Outcomes in Severely Ill Patients: Results of a Systematic Review and Meta-Analysis. Crit Care Med. 2018 Feb;46(2):236-43.

46. Roberts JA, Abdul-Aziz MH, Davis JS, et al. Continuous versus Intermittent β-Lactam Infusion in Severe Sepsis. A Meta-analysis of Individual Patient Data from Randomized Trials. Am J Respir Crit Care Med. 2016 Sep 15;194(6):681-91.

47. Bartoletti M, Giannella M, Lewis RE, et al; ESGBIS/BICHROME study group. Extended Infusion of β-Lactams for Bloodstream Infection in Patients With Liver Cirrhosis: An Observational Multicenter Study. Clin Infect Dis. 2019 Oct 30;69(10):1731-9. * The first study reporting benefits of prolonged beta-lactam infusion in critically ill patients with liver cirrhosis.

48. De Waele JJ, Lipman J, Carlier M, et al. Subtleties in practical application of prolonged infusion of beta-lactam antibiotics. Int J Antimicrob Agents. 2015 May;45(5):461-3.

49. Raby E, Naicker S, Sime FB, et al. Ceftolozane-tazobactam in an elastomeric infusion device for ambulatory care: an in vitro stability study. Eur J Hosp Pharm. 2020 Mar;27(e1):e84-6.

50. Servais H, Tulkens PM. Stability and compatibility of ceftazidime administered by continuous infusion to intensive care patients. Antimicrob Agents Chemother. 2001 Sep;45(9):2643-7.

51. Franceschi L, Cojutti P, Baraldo M, et al. Stability of generic meropenem solutions for administration by continuous infusion at normal and elevated temperatures. Ther Drug Monit. 2014 Oct;36(5):674-6.

52. Viaene E, Chanteux H, Servais H, et al. Comparative stability studies of antipseudomonal beta-lactams for potential administration through portable elastomeric pumps (home therapy for cystic fibrosis patients) and motor-operated syringes (intensive care units). Antimicrob Agents Chemother. 2002 Aug;46(8):2327-32.

53. Valenza G, Seifert H, Decker-Burgard S, et al; COMPACT Germany Study Group. Comparative Activity of Carbapenem Testing (COMPACT) study in Germany. Int J Antimicrob Agents. 2012 Mar;39(3):255-8.

54. Katsube T, Echols R, Wajima T. Pharmacokinetic and Pharmacodynamic Profiles of Cefiderocol, a Novel Siderophore Cephalosporin. Clin Infect Dis. 2019 Nov 13;69(Suppl 7):S552-8.

55. Drusano GL. Antimicrobial pharmacodynamics: critical interactions of 'bug and drug'. Nat Rev Microbiol. 2004 Apr;2(4):289-300.

56. 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):429-33.

57. Sumi CD, Heffernan AJ, Lipman J, et al. What Antibiotic Exposures Are Required to Suppress the Emergence of Resistance for Gram-Negative Bacteria? A Systematic Review. Clin Pharmacokinet. 2019 Nov;58(11):1407-443. ** An interesting systematic review concerning the association between PK/PD targets and suppression of antimicrobial resistance.

58. 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. ** An important study reporting the prompt resolution of sepsis-related AKI in the first 48 hours after initiation of antibiotic therapy, associated with poor clinical outcome when unnecessary dose reduction is performed.

59. Bidell MR, Lodise TP. Suboptimal Clinical Response Rates with Newer Antibiotics Among Patients with Moderate Renal Impairment: Review of the Literature and Potential Pharmacokinetic and Pharmacodynamic Considerations for Observed Findings. Pharmacotherapy. 2018 Dec;38(12):1205-15. ** An interesting review describing pharmacokinetic and pharmacodynamic issues associated with renal dose adjustments of ceftolozane-tazobactam and ceftazidime-avibactam performed in pivotal trials.

60. 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):1589-96.

61. Li J, Lovern M, Riccobene T, et al. Considerations in the Selection of Renal Dosage Adjustments for Patients with Serious Infections and Lessons Learned from the Development of Ceftazidime-Avibactam. Antimicrob Agents Chemother. 2020 Mar 24;64(4):e02105-19.

62. Mazuski JE, Gasink LB, Armstrong J, et al. Efficacy and Safety of Ceftazidime-Avibactam Plus Metronidazole Versus Meropenem in the Treatment of Complicated Intra-abdominal Infection: Results From a Randomized, Controlled, Double-Blind, Phase 3 Program. Clin Infect Dis. 2016 Jun 1;62(11):1380-9.

63. Solomkin J, Hershberger E, Miller B, et al. Ceftolozane/Tazobactam Plus Metronidazole for Complicated Intra-abdominal Infections in an Era of Multidrug Resistance: Results From a Randomized, Double-Blind, Phase 3 Trial (ASPECT-cIAI). Clin Infect Dis. 2015 May 15;60(10):1462-71.

64. Kollef MH, Nováček M, Kivistik Ü, et al. Ceftolozane-tazobactam versus meropenem for treatment of nosocomial pneumonia (ASPECT-NP): a randomised, controlled, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis. 2019 Dec;19(12):1299-1311.

65. Wunderink RG, Matsunaga Y, Ariyasu M, et al. Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of Gram-negative nosocomial pneumonia (APEKS-NP): a randomised, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis. 2020 Oct 12:S1473-3099(20)30731-3. doi: 10.1016/S1473-3099(20)30731-3. Online ahead of print.

66. Wunderink RG, Giamarellos-Bourboulis EJ, Rahav G, et al. Effect and Safety of Meropenem-Vaborbactam versus Best-Available Therapy in Patients with Carbapenem-Resistant Enterobacteriaceae Infections: The TANGO II Randomized Clinical Trial. Infect Dis Ther. 2018 Dec;7(4):439-55.

67. de Vroom SL, van Daalen FV, Zieck SE, et al. Does dose reduction of renally cleared antibiotics in patients with impaired renal function lead to adequate drug exposure? A systematic review. Clin Microbiol Infect. 2020 Dec 5:S1198-743X(20)30728-X. doi: 10.1016/j.cmi.2020.11.032. Online ahead of print.

68. Uchino S, Kellum JA, Bellomo R, et al; Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA. 2005 Aug 17;294(7):813-8.

69. 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.

70. Li L, Li X, Xia Y, et al. Recommendation of Antimicrobial Dosing Optimization During Continuous Renal Replacement Therapy. Front Pharmacol. 2020 May 29;11:786.

71. Wong WT, Choi G, Gomersall CD, et al. To increase or decrease dosage of antimicrobials in septic patients during continuous renal replacement therapy: the eternal doubt. Curr Opin Pharmacol. 2015 Oct;24:68-78.

72. Gatti M, Giannella M, Raschi E, et al. Ceftolozane/tazobactam exposure in critically ill patients undergoing continuous renal replacement therapy: a PK/PD approach to tailor dosing. J Antimicrob Chemother. 2021 Jan 1;76(1):199-205.

73. Shields RK, Nguyen MH, Chen L, et al. Pneumonia and Renal Replacement Therapy Are Risk Factors for Ceftazidime-Avibactam Treatment Failures and Resistance among Patients with Carbapenem-Resistant Enterobacteriaceae Infections. Antimicrob Agents Chemother. 2018 Apr 26;62(5):e02497-17. * An important study identifying renal replacement therapy as independent factor for resistance emergence with ceftazidime-avibactam.

74. Bassetti M, Castaldo N, Cattelan A, et al; CEFTABUSE Study Group. Ceftolozane/tazobactam for the treatment of serious Pseudomonas aeruginosa infections: a multicentre nationwide clinical experience. Int J Antimicrob Agents. 2019 Apr;53(4):408-15.

75. Kuti JL, Ghazi IM, Quintiliani R Jr et al. Treatment of multidrug-resistant Pseudomonas aeruginosa with ceftolozane/tazobactam in a critically ill patient receiving continuous venovenous haemodiafiltration. Int J Antimicrob Agents 2016; 48: 342-3.

76. Bremmer DN, Nicolau DP, Burcham P et al. Ceftolozane/Tazobactam Pharmacokinetics in a Critically Ill Adult Receiving Continuous Renal Replacement Therapy. Pharmacotherapy 2016; 36: e30-3.

77. Oliver WD, Heil EL, Gonzales JP et al. Ceftolozane-Tazobactam Pharmacokinetics in a Critically Ill Patient on Continuous Venovenous Hemofiltration. Antimicrob Agents Chemother 2015; 60: 1899-901.

78. Aguilar G, Ferriols R, Martínez-Castro S et al. Optimizing ceftolozane-tazobactam dosage in critically ill patients during continuous venovenous hemodiafiltration. Crit Care 2019; 23: 145.

79. Carbonell N, Aguilar G, Ferriols R et al. Ceftolozane Pharmacokinetics in a Septic Critically Ill Patient under Different Extracorporeal Replacement Therapies. Antimicrob Agents Chemother 2019; 64; pii: e01782-19.

80. 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 Dec;39(12):1216-22.

81. Rawlins M, Cheng V, Raby E, et al. Pharmacokinetics of Ceftolozane-Tazobactam during Prolonged Intermittent Renal Replacement Therapy. Chemotherapy. 2018;63(4):203-6.

82. Fayad AI, Buamscha DG, Ciapponi A. Intensity of continuous renal replacement therapy for acute kidney injury. Cochrane Database Syst Rev. 2016 Oct 4;10(10):CD010613.

83. RENAL Replacement Therapy Study Investigators, Bellomo R, Cass A, Cole L, et al. Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med. 2009 Oct 22;361(17):1627-38.

84. 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):1640-50.

85. Wenzler E, Scoble PJ. An Appraisal of the Pharmacokinetic and Pharmacodynamic Properties of Meropenem-Vaborbactam. Infect Dis Ther. 2020;9:769–84.

86. Sime FB, Pandey S, Karamujic N, et al. Ex Vivo Characterization of Effects of Renal Replacement Therapy Modalities and Settings on Pharmacokinetics of Meropenem and Vaborbactam. Antimicrob Agents Chemother. 2018 Sep 24;62(10):e01306-18.

87. Hobbs AL, Shea KM, Roberts KM, et al. Implications of Augmented Renal Clearance on Drug Dosing in Critically Ill Patients: A Focus on Antibiotics. Pharmacotherapy. 2015 Nov;35(11):1063-75.

88. Cook AM, Hatton-Kolpek J. Augmented Renal Clearance. Pharmacotherapy. 2019 Mar;39(3):346-54. ** An interesting review describing the phenomenon of augmented renal clearance and its implications on dose adjustment.

89. 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.

90. Udy AA, Dulhunty JM, Roberts JA, et al; BLING-II Investigators; ANZICS Clinical Trials Group. Association between augmented renal clearance and clinical outcomes in patients receiving β-lactam antibiotic therapy by continuous or intermittent infusion: a nested cohort study of the BLING-II randomised, placebo-controlled, clinical trial. Int J Antimicrob Agents. 2017 May;49(5):624-30.

91. Huttner A, Von Dach E, Renzoni A, et al. Augmented renal clearance, low β-lactam concentrations and clinical outcomes in the critically ill: an observational prospective cohort study. Int J Antimicrob Agents. 2015 Apr;45(4):385-92.

92. Wu CC, Tai CH, Liao WY, et al. Augmented renal clearance is associated with inadequate antibiotic pharmacokinetic/pharmacodynamic target in Asian ICU population: a prospective observational study. Infect Drug Resist. 2019 Aug 16;12:2531-41.

93. Udy AA, Varghese JM, Altukroni M, et al. Subtherapeutic initial β-lactam concentrations in select critically ill patients: association between augmented renal clearance and low trough drug concentrations. Chest. 2012 Jul;142(1):30-9.

94. 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 Sep 23;63(10):e01265-19 doi: 10.1128/AAC.01265-19.

95. Thabit AK, Hobbs ALV, Guzman OE, et al. The Pharmacodynamics of Prolonged Infusion β-Lactams for the Treatment of Pseudomonas aeruginosa Infections: A Systematic Review. Clin Ther. 2019 Nov;41(11):2397-2415.e8.

96. Natesan S, Pai MP, Lodise TP. Determination of alternative ceftolozane/tazobactam dosing regimens for patients with infections due to Pseudomonas aeruginosa with MIC values between 4 and 32 mg/L. J Antimicrob Chemother. 2017 Oct 1;72(10):2813-6.

97. Nicolau DP, De Waele J, Kuti JL, et al. Pharmacokinetics and Pharmacodynamics of Ceftolozane/Tazobactam in Critically Ill Patients With Augmented Renal Clearance. Int J Antimicrob Agents. 2021 Feb 7:106299.

98. Stein GE, Smith CL, Scharmen A, et al. Pharmacokinetic and Pharmacodynamic Analysis of Ceftazidime/Avibactam in Critically Ill Patients. Surg Infect (Larchmt). 2019 Jan;20(1):55-61.

99. Marston HD, Dixon DM, Knisely JM, et al. Antimicrobial Resistance. JAMA. 2016 Sep 20;316(11):1193-1204.

100. Guilhaumou R, Benaboud S, Bennis Y, et al. Optimization of the treatment with beta-lactam antibiotics in critically ill patients-guidelines from the French Society of Pharmacology and Therapeutics (Société Française de Pharmacologie et Thérapeutique-SFPT) and the French Society of Anaesthesia and

Intensive Care Medicine (Société Française d'Anesthésie et Réanimation-SFAR). Crit Care. 2019 Mar 29;23(1):104. ** An important guideline for the optimization of beta-lactams in critically ill patients, including a specific section on TDM and consequent dose adjustments.

101. Mouton JW, Muller AE, Canton R, et al. MIC-based dose adjustment: facts and fables. J Antimicrob Chemother. 2018 Mar 1;73(3):564-8. * An interesting review concerning the implications of MIC determination on PK/PD target.

102. Abdul-Aziz MH, Sulaiman H, Mat-Nor MB, et al. Beta-Lactam Infusion in Severe Sepsis (BLISS): a prospective, two-centre, open-labelled randomised controlled trial of continuous versus intermittent beta-lactam infusion in critically ill patients with severe sepsis. Intensive Care Med. 2016 Oct;42(10):1535-45.

103. Sime FB, Roberts MS, Tiong IS, et al. Can therapeutic drug monitoring optimize exposure to piperacillin in febrile neutropenic patients with haematological malignancies? A randomized controlled trial. J Antimicrob Chemother. 2015 Aug;70(8):2369-75.

104. 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):380-7. * An interesting study reporting a significant greater achievement of beta-lactam PK/PD targets with the use of a TDM-based approach.

105. Economou CJP, Wong G, McWhinney B, et al. Impact of β-lactam antibiotic therapeutic drug monitoring on dose adjustments in critically ill patients undergoing continuous renal replacement therapy. Int J Antimicrob Agents. 2017 May;49(5):589-94.

106. Richter DC, Frey O, Röhr A, et al. Therapeutic drug monitoring-guided continuous infusion of piperacillin/tazobactam significantly improves pharmacokinetic target attainment in critically ill patients: a retrospective analysis of four years of clinical experience. Infection. 2019 Dec;47(6):1001-11.

107. Wong G, Sime FB, Lipman J, et al. How do we use therapeutic drug monitoring to improve outcomes from severe infections in critically ill patients? BMC Infect Dis. 2014 Nov 28;14:288.

108. Sime FB, Roberts MS, Peake SL, et al. Does Beta-lactam Pharmacokinetic Variability in Critically Ill Patients Justify Therapeutic Drug Monitoring? A Systematic Review. Ann Intensive Care. 2012 Jul 28;2(1):35.

109. Sheffield M, Nelson D, O'Neal M, et al. Use of continuous-infusion ceftolozane/tazobactam for resistant Gram-negative bacterial infections: a retrospective analysis and brief review of the literature. Int J Antimicrob Agents. 2020 Nov;56(5):106158.

110. Jager NG, van Hest RM, Lipman J, et al. Therapeutic drug monitoring of anti-infective agents in critically ill patients. Expert Rev Clin Pharmacol. 2016 Jul;9(7):961-79.

111. Williams P, Cotta MO, Roberts JA. Pharmacokinetics/Pharmacodynamics of β-Lactams and Therapeutic Drug Monitoring: From Theory to Practical Issues in the Intensive Care Unit. Semin Respir Crit Care Med. 2019 Aug;40(4):476-87.

Table 1 – Pharmacokinetic properties and spectrum of activity of novel beta-lactams (BL) and/or beta-lactams/beta-lactamase inhibitors (BL/BLIs). Green box: established *in vitro*/*in vivo* activity; red box: no proved or limited *in vitro*/*in vivo* activity.

BL or BL/BLI	Approval	Pharmacokinetic properties					Spectrum of activity (beta-lactamase classes and non-fermentative Gram-negative pathogens)						
		V_D (L)	$t_{1/2}$ (h)	% protein bound	Renal CL	$AUC_{ELF/plasma}$	Class A (KPC)	Class B (IMP/VIM/NDM)	Class C (AmpC)	Class D (OXA)	PA MDR/XDR	AB MDR/XDR	SM
Cefiderocol	FDA/EMA	18	2-3	40-60	90-98%	0.10-0.24							
Ceftazidime-Avibactam	FDA/EMA	17.0/22.2	2.7	7-10	72-87%	0.26-0.35							
Ceftolozane-Tazobactam	FDA/EMA	13.5/18.2	3.1	16-30	62-84%	0.50-0.62							
Imipenem-Relebactam	FDA/EMA	24.3/19.0	1.2	20-22	52-92%	0.54-0.55							
Meropenem-Vaborbactam	FDA/EMA	20.2/18.6	2.3	2-33	74%	0.63-0.79							
Aztreonam-Avibactam	Ongoing phase III	20/26	1.8-2.3	10-56	70-87%	NA							
Cefepime-Enmetazobactam	Ongoing phase III	NA	NA	NA	NA	0.53-0.61							
Cefepime-Taniborbactam	Ongoing phase III	NA	NA	NA	NA	NA							
Cefepime-Tazobactam	Only India Ongoing phase III	24	2.7	NA	90%	NA							
Sulbactam-Durlobactam	Ongoing phase III	17/21	1.5-2.8	90	>50%	NA							
Ceftazidime-Zidebactam	Completed phase I	15/18	1.8	15-20	>80%	0.31-0.55							
Meropenem-Nacubactam	Completed phase I	17/22	1.8-2.4	2	82-87%	NA							

AB: *Acinetobacter baumannii*; AUC: area under concentration-time curve; CL: clearance; ELF: epithelial lining fluid; KPC: Klebsiella pneumoniae carbapenemase; MDR: multi-drug resistant; NA: not available; NDM: New-Delhi metallo-b-lactamase; OXA: oxacillinase; PA: *Pseudomonas aeruginosa*; SM: *Stenotrophomonas maltophilia*; $t_{1/2}$: half-life; V_D: volume of distribution; VIM: Verona integron-encoded metallo-b-lactamase; XDR: extensively drug-resistant.

Table 2 – Pharmacokinetic properties in special renal populations and PD thresholds of novel beta-lactams (BL) and/or beta-lactams/beta-lactamase inhibitors (BL/BLIs).

BL or BL/BLI	**Pharmacokinetic properties – IHD** [22-26]				**Pharmacokinetic properties – CRRT** [27-29]				**Pharmacokinetic properties – ARC** [30-32]				**PD thresholds** [33-36]
	V_D (L)	**$t_{1/2}$ (h)**	**AUC (mg*h/L)**	**CL (L/h)**	**V_D (L)**	**$t_{1/2}$ (h)**	**AUC (mg*h/L)**	**CL (L/h)**	**V_D (L)**	**$t_{1/2}$ (h)**	**AUC (mg*h/L)**	**CL (L/h)**	
Cefiderocol	26.6±33.5	9.5±32.8	318.1±20.3	3.1±20.3	NA	NA	NA	NA	NA	NA	1278 (1037-1560)	NA	75% $fT_{>MIC}$
Ceftazidime-Avibactam													
Ceftazidime	NA	NA	NA	NA	27.2	6.1	347.9	2.9	NA	NA	542±108.1	NA	50% $fT_{>MIC}$
Avibactam	24.3±39.0	22.8±55.2	130.6±55.4	0.8±82.4	30.8	6.8	85.7	2.9	NA	NA	96±115.9	NA	50% $fT>C_T$ of 1 mg/L
Ceftolozane-Tazobactam													
Ceftolozane	54.6 (38.8-79.9)	43.2 (32.8-56.9)	574 (287-1024)	0.9 (0.5-1.7)	73.4±39.0	14.5	284.1	3.5±0.6	30.8±10.8	2.5±0.9	236±118	10.4±4.5	30% $fT_{>MIC}$
Tazobactam	27.4 (15.4-56.7)	5.0 (1.9-8.5)	40.3 (23.3-58.6)	6.2 (4.3-10.7)	77.2±32.3	8.8	82.0	6.1±0.8	54.8±20.1	1.5±0.4	35.5±18.5	35.3±16.5	20% $fT>C_T$ of 1 mg/L
Imipenem-Relebactam													
Imipenem	63.3 (47.3-84.6)	3.2±47.8	71.2 (54.2-93.6)	11.7 (8.9-15.2)	NA	NA	NA	NA	NA	NA	NA	NA	40% $fT_{>MIC}$
Relebactam	55.7 (44.5-69.7)	10.5±100.6	78.0 (50.3-121)	4.6 (3.0-7.1)	NA	NA	NA	NA	NA	NA	NA	NA	fAUC/MIC=7.5
Meropenem-Vaborbactam													
Meropenem	30.0±7.2	9.3±1.9	280.0±58.7	3.7±0.8	49.81	6.4	182.42	5.48	NA	NA	NA	NA	45% $fT_{>MIC}$
Vaborbactam	59.1±16.8	55.2±33.6	533±124	1.2±0.8	86	16.8	290.65	3.44	NA	NA	NA	NA	fAUC/MIC≥18-24

AUC: area under concentration-time curve; CL: clearance; C_T: critical threshold concentration; MIC: minimum inhibitory concentration; NA: not available; $t_{1/2}$: half-life; V_D: volume of distribution

Table 3 – Dosing adjustments of novel BL and/or BL/BLIs in renal patients retrieved from summary of product characteristics and pivotal trials.

BL and/or BL/BLIs	PK/PD target adopted in pivotal trials	Dosing adjustments in patients with various classes of renal function (CLCr in mL/min)	Preservation of more refracted dosing regimens in renal impairment	Scheduled prolonged infusion	Scheduled dose adjustment for IHD	Scheduled dose adjustment for CRRT	Scheduled dose adjustment for ARC
Cefiderocol	75% $fT_{>MIC}$	CLCr ≥ 120: 2 g every 6 h CLCr 60-120: 2 g every 8 h CLCr 30-59: 1.5 g every 8 h CLCr 15-29: 1 g every 8 h CLCr< 15/IHD: 0.75 g every 12 h	✓ Maintained frequency of administration every 8 h except for severe AKI/IHD	✓ Extended infusion in 3 h	✓	✓ 1 g every 12 h (CVVH) 1.5 g every 12 h (CVVHD/CVVDHF)**	✓ 2 g every 6 h
Ceftazidime-Avibactam	50% $fT_{>MIC}$	CLCr> 50: 2.5 g every 8 h CLCr 31-50: 1.25 g every 8 h CLCr 16-30: 0.9375 g every 12 h CLCr 6-15: 0.9375g every 24 h CLCr ≤ 5/IHD: 0.9375 g every 48 h	✗	✓ Extended infusion in 2 h	✓	✗	✗
Ceftolozane-Tazobactam	30% $fT_{>MIC}$	CLCr> 50: 3.0*/1.5 g every 8 h CLCr 30-50: 1.5*/0.75g every 8 h CLCr 15-29: 0.75*/0.375 g every 8 h CLCr< 15/IHD: LD 1.5*/0.75g → MD 0.30*/0.15 g every 8 h	✓ Maintained frequency of administration every 8 h	✗ Intermittent infusion in 1 h	✓	✗	✗
Imipenem-Relebactam	40% $fT_{>MIC}$	CLCr 90-150: 1.25 g every 6 h CLCr 60-89: 1 g every 6 h CLCr 30-59: 750 mg every 6 h CLCr 15-29: 500 mg every 6 h IHD: 500 mg every 6 h CLCr< 15 and not IHD: should not be administered	✓ Maintained frequency of administration every 6 h	✗ Intermittent infusion in 0.5 h	✓	✗	✓ Scheduled dose may be inadequate for CLCr≥ 150 (consider higher dosage)
Meropenem-Vaborbactam	45% $fT_{>MIC}$	CLCr≥ 40: 4 g every 8 h CLCr 20-39: 2 g every 8 h CLCr 10-19: 2 g every 12 h CLCr< 10: 1 g every 12 h	✓ Maintained frequency of administration every 8 h except for severe AKI/IHD	✓ Extended infusion in 3 h	✓	✗	✗

* The doubled dose is indicated for nosocomial pneumonia including ventilator-associated pneumonia

** Dosing schedule are predicted on the basis of the reported CLCRRT of cefepime, according to the similar PK features shared with cefiderocol in terms of molecular weights and protein binding

ARC: augmented renal clearance; CVVH: continuous venovenous haemofiltration; CVVHD: continuous venovenous haemodialysis; CVVHDF: continuous venovenous haemodiafiltration; CRRT:

continuous renal replacement therapy; IHD: intermittent haemodialysis LD: loading dose; MD: maintenance dose; PK/PD: pharmacokinetic/pharmacodynamic.

Table 4 – Pivotal clinical trials of novel BL and/or BL/BLIs showing imbalance in different outcomes between study arms in subgroup analysis investigating degree of acute kidney injury. In bold significant differences between intervention and comparator group.

Novel beta-lactam / Study	Study arms	Outcome	All renal function categories (No. outcome / No. subjects)		Normal renal function (CLCr > 50 mL/min) (No. outcome / No. subjects)		Impaired renal function* (CLCr < 50 mL/min) (No. outcome / No. subjects)	
			Intervention	Comparator	Intervention	Comparator	Intervention	Comparator
Ceftazidime-Avibactam RECLAIM 1-2 (cIAI) [62]	CAZ-AVI 2.5 g q8h (CLCr>50 mL/min) 1.25 g q12h (CLCr 31-50 mL/min) Meropenem 1 g q8h (CLCr>50 mL/min) 1 g q12h (CLCr 31-50 mL/min)	Clinical cure: mMITT Clinical cure: MITT Clinical cure: CE	337/413 (81.6%) 429/520 (82.5%) 376/410 (91.7%)	349/410 (85.1%) 444/523 (84.9%) 385/416 (92.5%)	322/379(85.0%) 407/476 (85.5%) 356/383 (93.0%)	321/373 (86.1%) 410/478 (85.8%) 362/390 (92.8%)	**14/31 (45.2%)** **20/41 (48.8%)** 18/25 (72.0%)	**26/35 (74.3%)** **32/43 (74.4%)** 22/25 (88.0%)
Ceftolozane-Tazobactam ASPECT-cIAI [63]	CEFT-TZB 1.5 g q8h (CLCr>50 mL/min) 750 mg q8h (CLCr 31-50 mL/min) Meropenem 1 g q8h (CLCr>50 mL/min) 1 g q12h (CLCr 31-50 mL/min)	Clinical cure: MITT Clinical cure: CE	323/389 (83.0%) 259/275 (94.2%)	364/417 (87.3%) 304/321 (94.7%)	312/366 (85.2%) 251/264 (95.1%)	355/404 (87.9%) 299/314 (95.2%)	11/23 (47.8%) 8/11 (72.7%)	9/13 (69.2%) 5/7 (71.4%)
Ceftolozane-Tazobactam ASPECT-NP [64]	CEFT-TZB 3 g q8h (CLCr>50 mL/min) 1.5 g q8h (CLCr 30-50 mL/min) 750 mg q8h (CLCr 15-29 mL/min) Meropenem 1 g q8h (CLCr>50 mL/min) 1 g q12h (CLCr 26-50 mL/min) 500 mg q12h (CLCr 15-25 mL/min)	28-day mortality: ITT Clinical cure: ITT	87/362 (24.0%) 197/362 (54.4%)	92/364 (25.3%) 194/364 (53.3%)	40/227 (17.6%) 132/227 (58.1%)	45/236 (19.1%) 138/236 (58.5%)	6/17 (35.3%) 7/17 (41.2%)	13/21 (61.9%) 10/21 (47.6%)
Cefiderocol APEKS-NP [65]	Cefiderocol 2 g q8h (CLCr>50 mL/min) 1.5 g q8h (CLCr 31-50 mL/min) Meropenem 2 g q8h (CLCr>50 mL/min) 2 g q12h (CLCr 31-50 mL/min)	14-day mortality: MITT	18/145 (12.4%)	17/146 (11.6%)	4/33 (12.0%)	3/35 (9.0%)	2/27 (7.0%)	6/31 (19.0%)
Meropenem-Vaborbactam TANGO II [66]	Meropenem-Vaborbactam 2 g/2 g q8h (CLCr≥ 50 mL/min) 1 g/1 g q8h (CLCr 30-49 mL/min) 1 g/1 g q12h (CLCr 20-29 mL/min) BAT (mono/combination therapy with polymyxins, carbapenems, aminoglycosides, tigecycline; or CAZ-AVI alone) Dose reduction according to SPC	Clinical cure: MITT	21/32 (65.6%)	5/15 (33.3%)	17/24 (70.8%)	4/9 (44.4%)	2/7 (28.6%)	0/4 (0.0%)

* Moderate impairment (CLCr 31-50 mL/min) for RECLAIM 1-2, ASPECT-cIAI, APEKS-NP; Severe impairment (CLCr≤ 30 mL/min) for ASPECT-NP; CLCr≤ 50 mL/min for TANGO II

BAT: best available therapy; CAZ-AVI: ceftazidime-avibactam; CEFT-TZB: ceftolozane-tazobactam; CE: clinically evaluable; cIAI: complicated intra-abdominal infection; MITT: modified intention-to-treat;

mMITT: microbiologically modified intention-to-treat; NP: nosocomial pneumonia; SPC: summary of product characteristics

Table 5 – Pharmacokinetic features of novel BL and/or BL/BLIs in patients requiring continuous or prolonged intermittent renal replacement therapy

Beta-lactam/ study reference	Study design	No. of patients	Dose	Pathogen	RRT type	RRT settings	Sieving coefficient	CL_{CRRT}/ Total CL ratio	Achieved PK/PD target
Continuous renal replacement therapy (CRRT)									
Ceftolozane-Tazobactam Sime *et al.* [27]	PK population study	6	1.5 g q8h (1-h infusion)	Bacteraemia: 4 patients Pneumonia: 3 patients *Pseudomonas aeruginosa*: 2 patients *Serratia marcescens*: 2 patients *Stenotrophomonas maltophilia*: 2 patients	CVVHDF	Qd: 1250 ± 273.9 mL/h* Quf: 1277.8 ± 743.2 mL/h* Qb: 150±44.7 mL/h* ST100: 3 patients ST150: 3 patients	0.94 ± 0.24 (ceftolozane) 1.08 ± 0.30 (tazobactam)	81.7% (ceftolozane) 47.7% (tazobactam)	1.5 g q8h, 3 g q8h, 3 g LD + 9 g CI, 1.5 g LD + 4.5 g CI were suggested to achieve optimal CFR for 100% $fT_{>MIC}$
Ceftolozane-Tazobactam Kuti *et al.* [75]	Case report	1	3g q8h (1-h infusion)	*Pseudomonas aeruginosa* VAP	CVVHDF	Qd: 1000 mL/h Quf: 200 mL/h Qb: 150 mL/h AN-69 high-flux M100	NC	NC	100% $fT_{>MIC}$ for MIC up to 32 mg/L and 100% $fT_{>4xMIC}$ for MIC up to 8 mg/L
Ceftolozane-Tazobactam Bremmer *et al.* [76]	Case report	1	3g q8h (1-h infusion)	*Pseudomonas aeruginosa* bacteraemic osteomyelitis	CVVHDF	Qd: 1000 mL/h Quf: 750 mL/h Qb: 200 mL/h AN-69 high-flux M100	NC	82.8% (ceftolozane) 36.3% (tazobactam)	100% $fT_{>MIC}$ for MIC up to 32 mg/L and 100% $fT_{>4xMIC}$ for MIC up to 16 mg/L
Ceftolozane-Tazobactam Olivier *et al.* [77]	Case report	1	1.5g q8h (EI 4h)	*Pseudomonas aeruginosa* osteomyelitis	CVVH	Quf: 2000 mL/h Qb: 250 mL/h AN-69 high-flux M150	NC	NC	100% $fT_{>MIC}$ for MIC up to 32 mg/L and 100% $fT_{>4xMIC}$ for MIC up to 4 mg/L
Ceftolozane-Tazobactam Aguilar *et al.* [78]	Case report	1	3g q8h (1-h infusion)	*Pseudomonas aeruginosa* VAP	CVVHD	Qd: 2000 mL/h Quf: 1000 mL/h Qb: 100 mL/h Polysulphone membrane	NC	NC	100% $fT_{>MIC}$ for MIC up to 16 mg/L and 100% $fT_{>4xMIC}$ for MIC up to 4 mg/L
Ceftolozane-Tazobactam Carbonell *et al.* [79]	Case report	1	3g q8h (3-h infusion)	*Pseudomonas aeruginosa* catheter-related bacteraemia	CVVHDF	Qd: 1600 mL/h Quf: 500 mL/h Qb: 180 mL/h AN-69 high-flux M150	NC	NC	100% $fT_{>MIC}$ for MIC up to 32 mg/L and 100% $fT_{>4xMIC}$ for MIC up to 8 mg/L
Ceftazidime-Avibactam Wenzler *et al.* [28]	Case report	1	1.25 g q8h (2-h infusion)	*Pseudomonas aeruginosa* bacteraemia (MIC 6 mg/L)	CVVH	Quf: 2000 mL/h Qb: 200 mL/h 1.6 m^2 Polyethersulfone membrane filter	0.96 (ceftazidime) 0.93 (avibactam)	57.1% (ceftazidime) 54.3% (avibactam)	100% $fT_{>4 \times mic}$
Ceftazidime-Avibactam Soukup *et al.* [80]	Case report	1	2.5 g q8h (2-h infusion)	*Pseudomonas aeruginosa* pneumonia (MIC 8 mg/L)	CVVHDF	Qd: 1500 mL/h Quf: 1000 mL/h Qb: 250 mL/h	NC	NC	100% $fT_{>4 \times mic}$

						M100 filter			
Meropenem-Vaborbactam Kufel *et al*. [29]	Case report	1	1 g/1 g q8h (3-h infusion)	Carbapenem- resistant *Klebsiella pneumoniae* joint infection (MIC 0.094/8 mg/L)	CVVHD	Qd: 3000 mL/h Qb: 250 mL/h 1.6 m^2 Polyethersulfone membrane filter	NC	NC	100% $fT_{>MIC}$
Prolonged intermittent renal replacement therapy (PIRRT)									
Ceftolozane-Tazobactam Rawlins *et al*. [81]	Case report	1	LD 750 mg MD 150 mg q8h (non-PIRRT days) + 2 doses of 750 mg during PIRRT	*Pseudomonas aeruginosa* osteomyelitis (MIC 4 mg/L)	PIRRT	Qd: 200 mL/h Quf: 250 mL/h Qb: 200 mL/h 1.4 m^2 membrane filter 7.5 hours duration	NC	96.6% (ceftolozane) 91.2% (tazobactam)	100% $fT_{>MIC}$

* data expressed as mean ± standard deviation

CFR: cumulative fraction response; CI: continuous infusion; CVVH: continuous venovenous haemofiltration; CVVHD: continuous venovenous haemodialysis; CVVHDF: continuous venovenous haemodiafiltration; EI: extended infusion; LD: loading dose; NC: not calculated; PIRRT: prolonged intermittent renal replacement therapy; Qb: blood flow rate; Quf: ultrafiltrate rate; Qd: dialysate rate; VAP: ventilator-associated pneumonia

Figure legends

Figure 1 – Relationship between volume of distribution, renal clearance, and supposed plasma exposure to beta-lactam antimicrobial according to scheduled dosing. Red box: antibiotic concentrations could be too high, and dose reduction could be suggested. Green box: adequate antibiotic concentrations, with no need for dose adjustment. Yellow box: antibiotic concentrations could be low, and higher dose could be required. Orange box: antibiotic concentrations could be very low and altered dosing strategies are strongly advised. NSTI: necrotizing soft tissue infection; IHD: intermittent haemodialysis; AKI: acute kidney injury; CRRT: continuous renal replacement therapy; ARC: augmented renal clearance.

Figure 2 – Relationship between severity of sepsis-related acute kidney injury and antimicrobial exposure in the first 72 hours after initiation of therapy. In most cases, the prompt resolution of renal impairment leads to inadequate antibiotic exposure if renal dose adjustment is performed. If a large increase of V_D exists, low antibiotic concentrations could be achieved at an earlier stage. AKI: acute kidney injury; V_D: volume of distribution.

Figure 3 – A proposal of algorithm for the management of critically ill patients requiring novel beta-lactams in challenging scenarios concerning variations in renal function. * In case of persistent AKI, renal dose adjustment without variations of the intervals would be recommend. AKI: acute kidney injury; ARC: augmented renal clearance; CRRT: continuous renal replacement therapy; MIC: minimum inhibitory concentration; PD: pharmacodynamic; PK: pharmacokinetic; TDM: therapeutic drug monitoring.

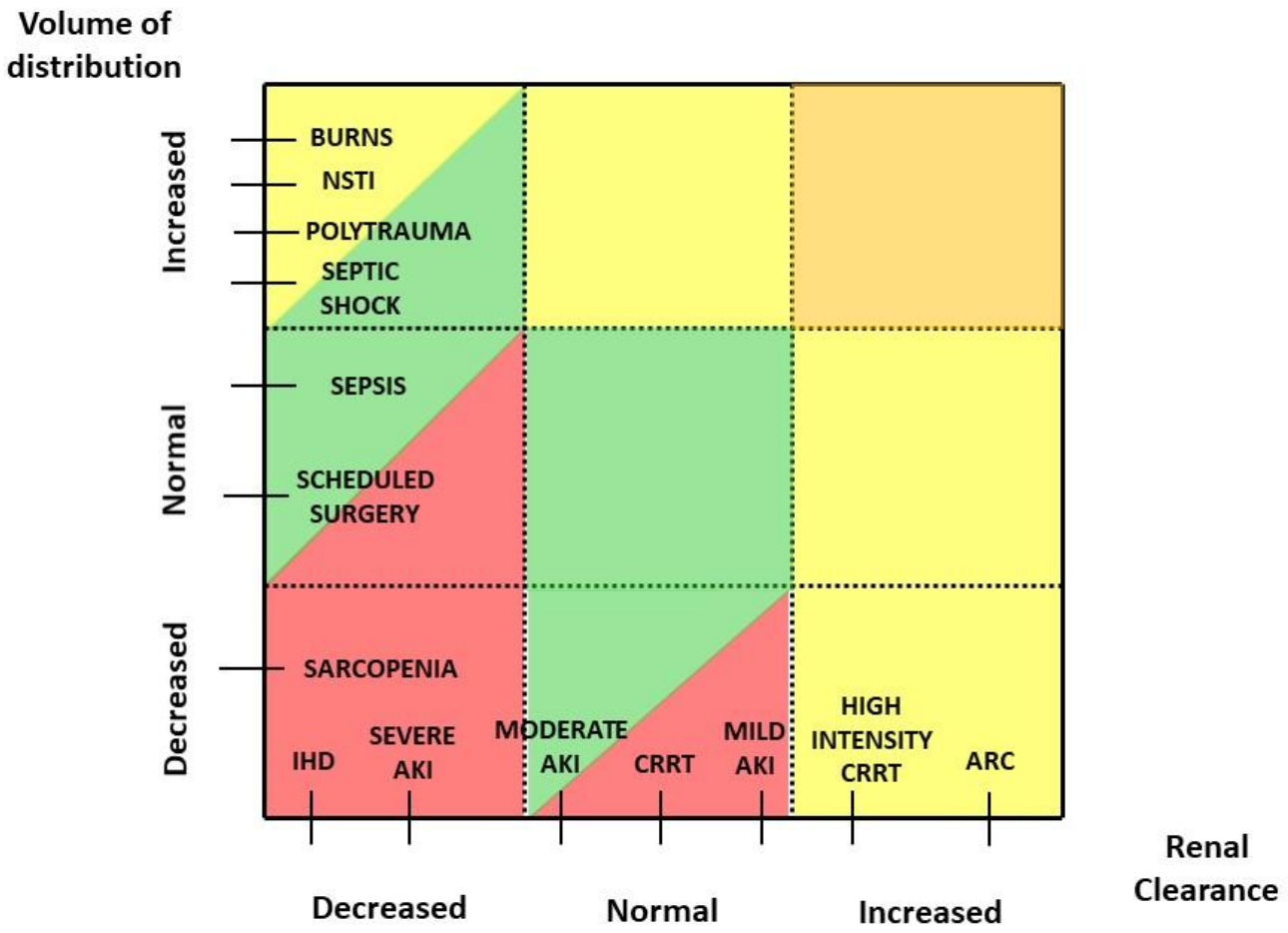
Volume of distribution
Increased
Normal
Decreased
BURNS
NSTI
POLYTRAUMA
SEPTIC SHOCK
SEPSIS
SCHEDULED SURGERY
SARCOPENIA
IHD
SEVERE AKI
MODERATE AKI
CRRT
MILD AKI
HIGH INTENSITY CRRT
ARC
Decreased
Normal
Increased
Renal Clearance

Fig.1

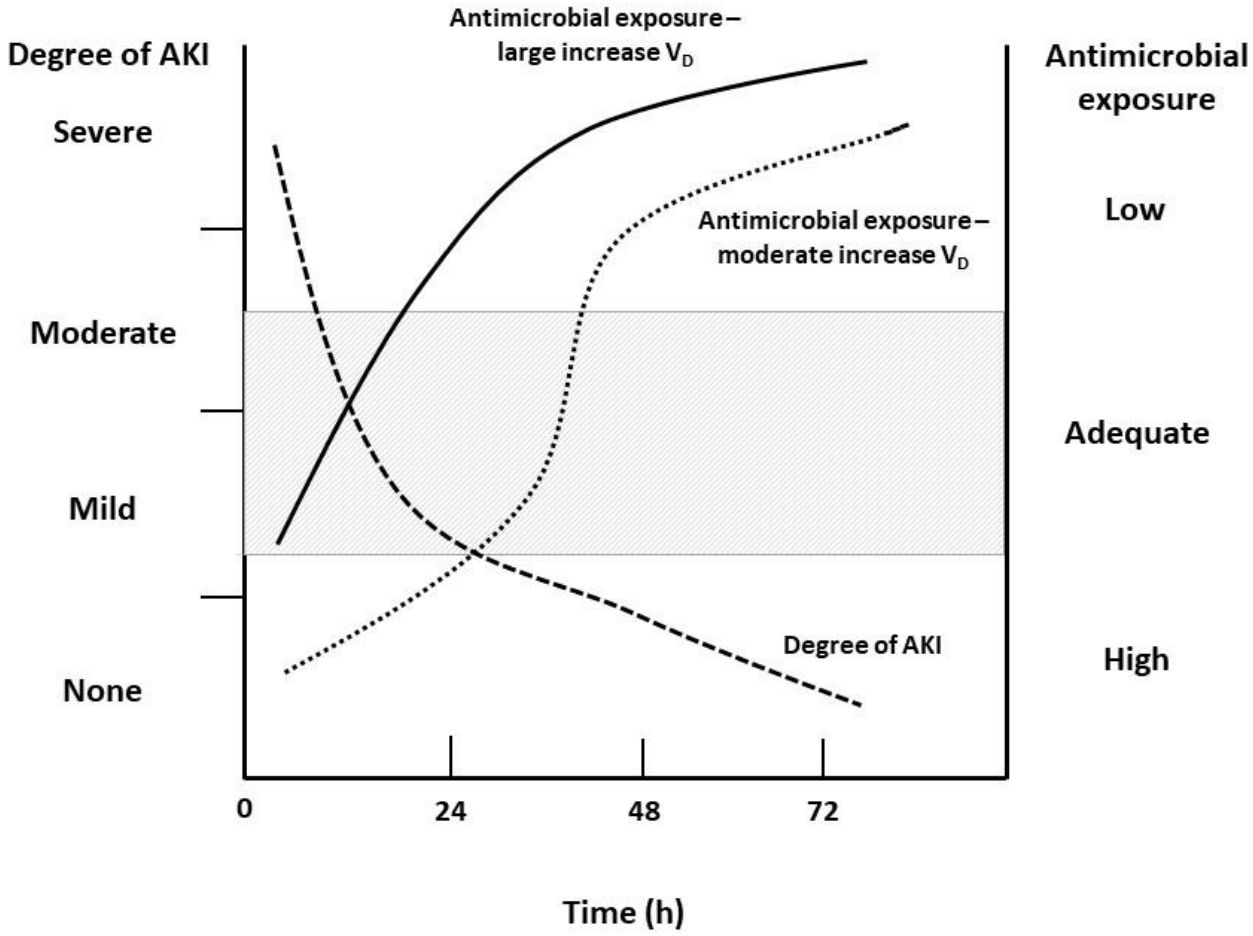
Degree of AKI
Severe
Moderate
Mild
None
Antimicrobial exposure – large increase V_D
Antimicrobial exposure – moderate increase V_D
Degree of AKI
Antimicrobial exposure
Low
Adequate
High
0
24
48
72
Time (h)

Fig.2

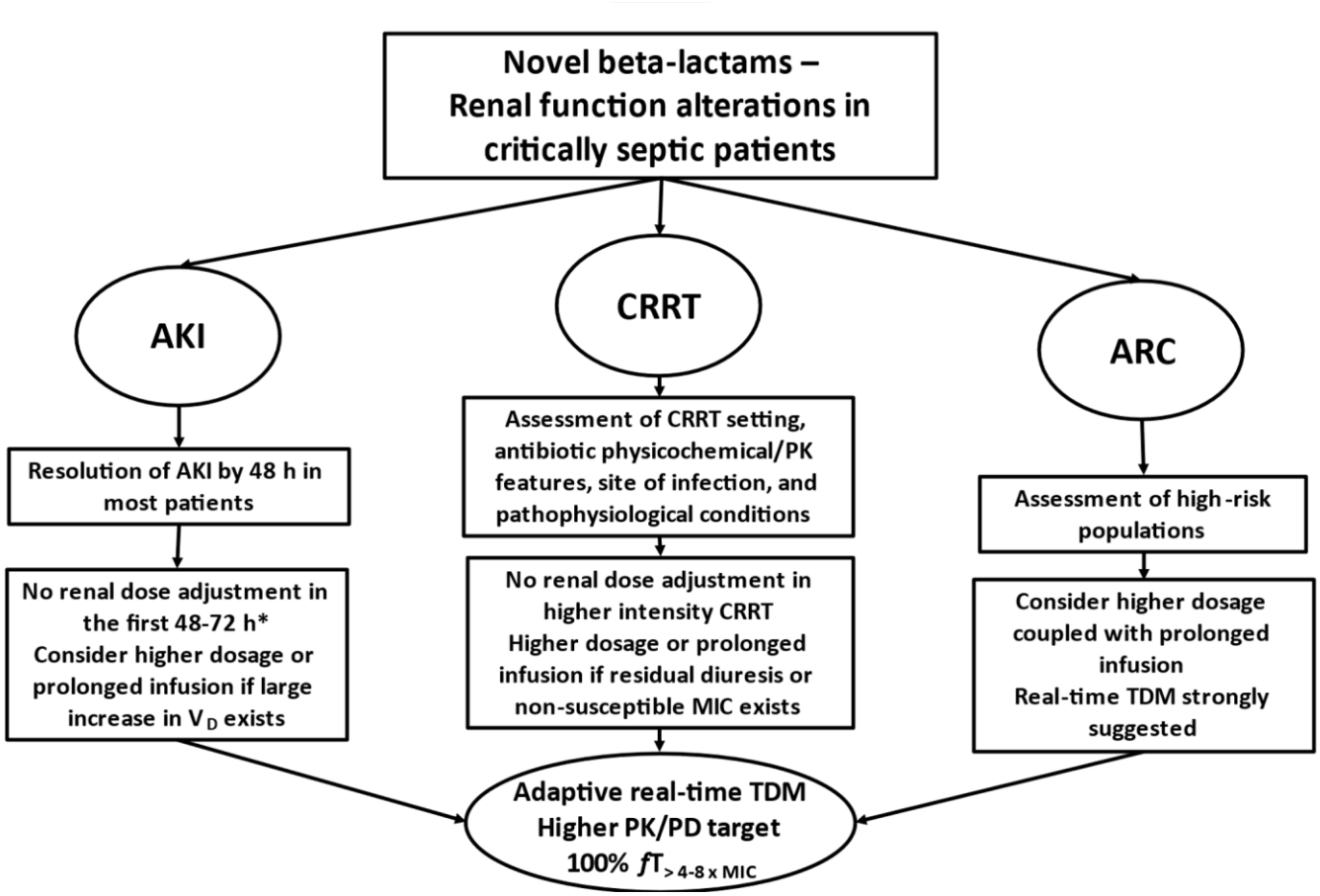
Novel beta-lactams –
Renal function alterations in
critically septic patients
AKI
CRRT
ARC
Resolution of AKI by 48 h in most patients
Assessment of CRRT setting, antibiotic physicochemical/PK features, site of infection, and pathophysiological conditions
Assessment of high-risk populations
No renal dose adjustment in the first 48-72 h*
Consider higher dosage or prolonged infusion if large increase in V_D exists
No renal dose adjustment in higher intensity CRRT
Higher dosage or prolonged infusion if residual diuresis or non-susceptible MIC exists
Consider higher dosage coupled with prolonged infusion
Real-time TDM strongly suggested
Adaptive real-time TDM
Higher PK/PD target
100% $fT_{>4\text{-}8 \times MIC}$

Fig.3