Pharmacokinetics, Pharmacodynamics, and Dosing Considerations of Novel β-Lactams and β-Lactam/β-Lactamase Inhibitors in Critically Ill Adult Patients: Focus on Obesity, Augmented Renal Clearance, Renal Replacement Therapies, and Extracorporeal Membrane Oxygenation

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Abstract: Objective: Dose optimization of novel β-lactam antibiotics (NBLA) has become necessary given the increased prevalence of multidrug-resistant infections in intensive care units coupled with the limited number of available treatment options. Unfortunately, recommended dose regimens of NBLA based on PK/PD indices are not well-defined for critically ill patients presenting with special situations (i.e., obesity, extracorporeal membrane oxygenation (ECMO), augmented renal clearance (ARC), and renal replacement therapies (RRT)). This review aimed to discuss and summarize the available literature on the PK/PD attained indices of NBLA among critically ill patients with special circumstances. Data Sources: PubMed, MEDLINE, Scopus, Google Scholar, and Embase databases were searched for studies published between January 2011 and May 2022. Study selection and data extraction: Articles relevant to NBLA (i.e., ceftolozane/tazobactam, ceftazidime/avibactam, cefiderocol, ceftobiprole, imipenem/relebactam, and meropenem/vaborbactam) were selected. The MeSH terms of “obesity”, “augmented renal clearance”, “renal replacement therapy”, and “extracorporeal membrane oxygenation”, “pharmacokinetic”, “pharmacodynamic” “critically ill”, and “intensive care” were used for identification of articles. The search was limited to adult humans’ studies that were published in English. A narrative synthesis of included studies was then conducted accordingly. Data synthesis: Available evidence surrounding the use of NBLA among critically ill patients presenting with special situations was limited by the small sample size of the included studies coupled with high heterogeneity. The PK/PD target attainments of NBLA were reported to be minimally affected by obesity and/or ECMO, whereas the effect of renal functionality (in the form of either ARC or RRT) was more substantial. Conclusion: Critically ill patients presenting with special circumstances might be at risk of altered NBLA pharmacokinetics, particularly in the settings of ARC and RRT. More robust, well-designed trials are still required to define effective dose regimens able to attain therapeutic PK/PD indices of NBLA when utilized in those special scenarios, and thus aid in improving the patients’ outcomes.

Keywords: novel beta-lactam antibiotics; critical care; augmented renal clearance; extracorporeal membrane oxygenation; renal replacement; obesity; pharmacokinetics; pharmacodynamics
1. Background

The incidence of deaths owing to sepsis/septic shock in noncardiac patients admitted to intensive care units (ICUs) continues to increase, despite advances in management and personalized treatments. Despite advances in management and personalized treatments, mortality rate of infected patients was found to be more than double of that noninfected patients admitted to intensive care units (ICUs) [1,2]. Sepsis-causing multi-drug-resistant (MDR) pathogens, including *Pseudomonasaeruginosa* (PsA), *Enterobacterspecies*, *methicillin-resistant Staphylococcus aureus*, and *Enterococcus faecium*, have become a remarkable burden, especially for severely ill patients [3,4]. Effective therapy for these patients relies not only on early diagnosis and timely antimicrobial administration, but also on dose-regimen optimization to achieve optimal pharmacokinetic (PK)/pharmacodynamic (PD) targets associated with maximal efficacy.

The interest in the use of novel β-lactam antibiotics (NBLA), which include both novel β-lactam and novel β-lactam/β-lactamase inhibitors (BLBLI) (namely ceftolozane/tazobactam (C/T), ceftazidime/avibactam (CAZ/AVI), cefiderocol, ceftobiprole, imipenem/relebactam (IMI/REL), and meropenem/vaborbactam (MEV)) as alternatives against MDR pathogens among critically ill patients has recently increased. Recommended dosing regimens of antimicrobials are often based on PK studies in healthy volunteers. However, critically ill patients are known to present with various physiological/pathological changes that result in substantial alterations of achieved drug concentrations, along with other key PK parameters [5,6]. Moreover, extracorporeal support (including renal replacement therapies (RRT) and extracorporeal membrane oxygenation (ECMO)) may sometimes be required, further contributing to PK-related variabilities [7–9]. Previous researchers utilizing the recommended package insert doses of conventional β-lactams in such heterogeneous populations revealed the risk of both under-/over-exposures depending on the underlying pathology and clinical condition [10–12]. Despite growing use in critically ill patients, limited evidence exists describing such variabilities for NBLA. Recently, the adequacy of the current monograph-recommended dosing of three different NBLA in ICU patients was investigated using Monte Carlo simulation [13]. While standard dosing resulted in adequate attainment of a PD index of 40–60% of free drug concentration above MIC (%fT > MIC) for CAZ/AVI, C/T, and MEV, such dosing did not attain more aggressive targets (i.e., 100%fT > 1–4 × MIC). Although some reviews had recently described altered PK/PD for various NBLA during critical illness [14,15], sub-populations that warrant special considerations including obesity, augmented renal clearance (ARC), RRT modalities, and ECMO were commonly excluded or not comprehensively addressed [14–18]. Hence, this narrative review seeks to [1] summarize the evidence for the effects of common ICU circumstances (including ECMO, ARC, RRT, and obesity) on the PK of NBLA, and [2] evaluate whether the utilized dosing regimens were adequate in achieving the required PK/PD indices.

2. Methods

PubMed, MEDLINE, Scopus, Google Scholar, and Embase databases were searched for studies published between January 2011 and May 2022 (to focus on NBLA approved during the last decade). Searched keywords included C/T, CAZ/AVI, cefiderocol, ceftobiprole, IMI/REL, and MEV. The following terms were used in combination with the keywords listed above: “obesity”, “augmented renal clearance”, “renal replacement therapy”, “extracorporeal membrane oxygenation”, “pharmacokinetic”, “pharmacodynamic”, “critically ill”, and “intensive care”. The search was limited to adult humans and articles published in English. Two authors (A. B. and R. E.) independently performed the systematic search. Disagreements were resolved by referring to a third author (D. B.). The inclusion of articles in this review was guided by the Population, Intervention, Comparator, Outcome (PICO) framework outlined in detail in Table 1. No additional analyses of the risk of bias were performed since the intention was purely descriptive narration.
Table 1. Eligibility criteria for the included studies.

| Population | 1. Critically ill adult patients (ICU admissions)  
|            | 2. Having any of the special scenarios (i.e., obesity, augmented renal clearance (ARC), extracorporeal interventions for life support (i.e., ECMO, prolonged intermittent renal replacement therapy (PIRRT), or continuous renal replacement therapy (CRRT)) |
| Intervention | Receiving novel β-lactam antibiotics of interest (including Ceftolozane/Tazobactam, Ceftazidime/Avibactam, Cefiderocol, Cefotibiprole, Imipenem/Relebactam and Meropenem/Vaborbactam) with reported dose being used |
| Comparator | None |
| Outcomes | 1. Reported PK profile of different novel β-lactam antibiotics under different scenarios studied  
|            | 2. Reported PK/PD target attained with different doses used +/- clinical outcomes associated with use of drug therapy under studied circumstances |
| Study design | PK studies (including phase 1 trials), population pharmacokinetic analyses (PopPK), PD studies, case-reports/case series, or clinical trials if PK/PD characteristics were reported |

3. Results

The initial search yielded 637 articles. After removing duplicates and applying limitations stated above, 64 full-text articles were obtained. Of these, 27 fulfilled the PICO outlined in Table 1 and thus were included in this review. A detailed overview of the selection process is illustrated in Figure 1.

3.1. Altered PK and Associated PD Targets

Physiologic alterations encountered in critically ill populations have been implicated in influencing drugs’ PK, specifically the two primary PK parameters: volume of distribution (Vd) and clearance (CL).

Endothelial dysfunction, capillary leakage, and fluid resuscitation, along with other factors result in increased Vd of hydrophilic antimicrobials. Clearance, on the other hand, is often determined by the properties of the drugs, with hydrophilic antimicrobials being principally cleared through the renal pathway. Both extremes of renal clearance (i.e., ARC/renal failure) are encountered in ICU and can thus have profound effects on the elimination of hydrophilic renally-eliminated antimicrobials. Hypoalbuminemia, as an acute-phase reactant, is commonly seen in critically ill patients and can potentially further impact the PK of antimicrobials, especially the highly protein-bounded. The increased free/unbound concentrations results in increased Vd and can be coupled with decreased overall exposure of the renally-cleared antimicrobials, as more unbound fraction is gaining access to the nephrons for elimination [19–22]. A detailed description of different sources of PK variabilities encountered during critical-illness is beyond the scope of this paper, and readers are referred to the literature for further details [23–25].

Given their physicochemical and PK properties, namely hydrophilicity and renal CL, NBLA are therefore considered susceptible to exposure discrepancies when used among critically ill patients [26–28].

Pharmacodynamically, like conventional β-lactams, the %fT > MIC has been described as the optimal PK/PD index associated with the efficacy of NBLA. However, the optimal percentage to target is still controversial [29]. Preclinical studies of conventional β-lactams suggested that approximately 1–2 log_{10} reductions of colony-forming units (CFU) can be achieved with <100%fT > MIC, depending on the used antimicrobial (i.e., 40%, 50–60%, and 50–70%fT > MIC for carbapenems, penicillins, and cephalosporins respectively) [30]. Although these animal/in-vitro derived targets were replicated in human studies, promising
outcomes were not always consistent and some suggested higher than 40–70% fT > MIC might sometimes be required for favorable outcomes, especially among severely sick patients [30,31]. For instance, the Defining Antibiotic Levels in ICU (DALI) trial described significant exposure variabilities of conventional β-lactams when used in ICU patients, with one-fifth of the included cohort failing to achieve the most conservative PD index of 50% fT > MIC. On the contrary, higher odds of favorable clinical outcomes were seen amongst patients achieving 50% fT > MIC and 100% fT > MIC targets (OR 1.02, 1.56 respectively; p < 0.03) [32]. Likewise, McKinnon et al., compared the PD of ceftazidime and cefepime and observed significantly higher rates of bacteriological eradication and clinical cure among patients achieving 100% fT > MIC as opposed to <100% fT > MIC [33]. Similar conclusion was recently reported with meropenem and piperacillin-tazobactam, with faster infection resolution being observed among patients attaining 100% fT > MIC [34].

![Flowchart](image)

Figure 1. Flow diagram of the study selection. * Three abstracts/posters were indentified through searching and were included in the review since pertinent data regarding PK/PD and target attainments in critically-ill patients were available.

Although the utilization of conventional PD thresholds (i.e., 40–60% fT > MIC) could be argued for NB LA, especially when considering the concentrations of BLIs, for the most part, BLIs by their own are inactive against invading pathogens [30]. The PD targets of such inhibitors (i.e., threshold of concentration (Cf) for avibactam/tazobactam and 24 h...
area under the free concentration–time curve (fAUC_{24}/MIC) for vaborbactam/relebactam) reflect the required concentrations to restore β-lactam activity, thus leaving PD targets of β-lactam backbone consistent with the PD targets described above for the severely sick population [29,35].

More aggressive indices (i.e., 100%fT > 4–8 × MIC) were recently advocated among critically ill patients (especially empirically upon initiation when the pathogen/MIC are still unknown) to improve the likelihood of favorable outcomes and prevent resistance development, a detrimental consequence frequently encountered in the ICU population [34,36–42]. However, given the limited available data, coupled with safety concerns of increased adverse outcomes/toxicities associated with such higher trough concentrations, this target might be more appropriately tailored to individualized situations only [34,36,39,43–45].

Hence, in this review, we stated the PK/PD indices that were targeted by the authors of each included study, and then compared the adequacy of the used regimen in attaining the aggressive target of 100%fT > MIC.

The leaflet-derived PK parameters along with conventional murine/in vitro-derived PD targets of NBLA included in this review are summarized in Supplementary Materials (Table S1) for reference. Table 2 summarizes the included studies in this review, along with their utilized dosage regimens and attained PD indices.

3.2. Obesity

Antimicrobial dosing for critically ill obese patients is challenging. Different pathophysiologic alterations seen in obesity can result in additive effects of altered PK including increased cardiac output, lean/fat masses, kidney size, and renal blood flow [39,46]. For hydrophilic antimicrobials, increased lean mass, coupled with increased renal CL translate to more PK variations. Different PK studies of conventional β-lactams confirmed altered PK in obese/morbidly-obese patients compared to non-obese population [44,47,48]. However, whether the effect of altered PK is significant enough to warrant dosage adjustment is still debatable [48,49].

Cojutti and colleagues [50] described the effect of obesity on PK/PD of ceftobiprole when used as an add-on to daptomycin against methicillin-resistant *Staphylococcus epidermidis* bacteremia in a morbidly obese critically ill patient (BMI 51.2 kg/m²). The utilization of standard dosing (0.5 g Q8h) as extended infusion (E.I) over 4 h (vs. recommended 2 h) resulted in 100%fT > MIC <2 mg/L attainment. However, more frequent administrations (Q6h) coupled with E.I were required to attain a more aggressive index (100%fT > 3 × MIC) and resulted in a favorable clinical outcome. Unfortunately, only maximum and minimum concentrations (C_{max}, C_{min} respectively) were reported in this case report, and thus the effects of obesity on other PK parameters could not be determined. Similarly, C/T use at the manufacturer’s recommended regimen resulted in an adequate exposure (100%fT > MIC) when used to treat ventilator-associated pneumonia in a morbidly obese patient, with higher targets (100%fT > 4 × MIC) being achieved using the continuous infusion (C.I) technique [51]. In both cases, the dose required to attain the conventional PD index (i.e., 30–50% and 40%fT > MIC for ceftobiprole and C/T respectively) was not investigated. No studies were found describing the effect of obesity on PK of CAZ/AVI, cefiderocol, IMI/REL, and MEV in critically ill patients.

In summary, limited data exist to guide dosing of NBLA in critically ill morbidly/obese patients, and interpretation of antimicrobial exposure is thus difficult, given the variabilities that exist in such populations. More research is still required, and therapeutic drug monitoring (TDM) might be warranted to guide therapy across such groups.

3.3. Extra-Corporeal Membrane Oxygenation (ECMO)

ECMO has been believed to have various effects on PK of antimicrobials, including altered protein binding, increased Vd (secondary to fluid boluses, transfusion requirements, drug sequestration into ECMO circuits, etc.) and altered CL, with lipophilic highly protein-bound drugs being mostly affected [7,52]. These observations were mainly extrapolated.
from old neonatal PK studies [53]. Nevertheless, despite the hydrophilicity and limited protein-binding of NBLA, the additive effects of critical-illness and ECMO might correlate with altered PK, and hence result in exposure variabilities.

The effects of ECMO on NBLA’s PK/PD were documented in four case reports/series: two with C/T [54,55] and two for cefiderocol [56,57].

Arena et al. utilized C/T in treating persistent PsA pneumonia in a patient requiring venoarterial ECMO (VA-ECMO) [54]. The standard dosage (3 g Q8h) was considered sufficient for both the conventional target and the aggressive target of 100%FT > MIC. Notably, the authors observed lower C_{max} and C_{min} during the last 2 days of therapy and attributed it to increased Vd (positive fluid balance) and/or enhanced renal CL.

In the other case, C/T was used as a part of chemoprophylaxis in a cystic fibrosis patient requiring ECMO post-lung transplantation [55]. RRT via continuous venovenous hemodiafiltration (CVVHDF) was also required for this patient, owing to acute kidney injury (AKI). When administered as an unadjusted regimen (i.e., regular manufacturer dosing irrespective of AKI/RRT modality), 100%FT > 4 × MIC was attained for ceftolozane. It was concluded that ECMO did not require dosing modifications; rather, given the incidence of AKI, reduced dosing might have been adequate.

Comparable with C/T, minimal effects on the PK of cefiderocol among two ECMO case-series [56,57] with adequate concentrations (i.e., 100%ft > MIC) were achieved using the regular manufacturer’s regimen.

In summary, based on the available human data, ECMO seemed to have minimal effects on NBLA. However, given the scarcity of reports, the use of CVVHDF in one patient, and keeping in mind that most reports were utilizing VA-ECMO [which might result in different physiological effects as opposed to venovenous ECMO (VV-ECMO)], more data are still required to confirm the observation. Additionally, no studies were found reporting the effect of ECMO on the PK of CAZ/AVI, ceftobiprole, IMI/REL, or MEV.

### 3.4. Augmented Renal Clearance (ARC)

ARC is a phenomenon frequently encountered across the ICU population secondary to fluid resuscitation, coupled with enhanced cardiac output, leading to amplified renal perfusion. ARC (defined as creatinine clearance (CrCL) > 130 mL/min/1.73 m²) has been linked to lower plasma drug concentrations of renally cleared antimicrobials and worse clinical outcomes [58–60]. Given the hydrophilicity and predominant renal clearance of NBLA, ARC may increase the risk of therapeutic failure and/or drug resistance. A total of six studies were retrieved describing the effects of ARC on PK of C/T [61,62], CAZ/AVI [26], IMI/REL [63] and ceftobiprole [50,64].

Sime et al. analyzed the PK of C/T using data from 12 ICU patients receiving either 1.5 g or 3 g Q8h regimens and performed Monte Carlo simulations to predict optimal regimens for critically ill patients with preserved kidney functionality, including those with ARC [61]. When utilized empirically (i.e., aiming for 40%FT > MIC_{≤4 mg/L} to cover PsA), a 1.5 g-regimen was found inadequate among the ARC cohort, and a 3 g regimen was required. Nevertheless, when a more aggressive index was targeted (i.e., 100%FT > MIC_{≤4 mg/L}), the 3 g intermittent regimen was not satisfactory, and 1.5 g loading over 30 min followed by 4.5 g C.I (over 24 h) was suggested instead. In contrast, directed therapy against MIC_{<4 mg/L} was adequately achieved with 1.5 g and 3 g intermittent regimens when aiming for 40% and 100%FT > MIC_{≤4 mg/L} respectively. Remarkably, the suggested empiric regimens were selected, aiming for 100%FT > 4 × MIC_{≤16 mg/L}, which is not routinely targeted in clinical practice nor representative given the sensitivity breakpoint of ceftolozane (≤4, 2 mg/L for PsA and Enterobacterales, respectively [65]).

In early 2021, the results of a phase I PK study of C/T among critically ill patients with confirmed ARC (using the 8 h urine collection method) were published [62]. The mean Vd was 1.5-fold higher in critically ill patients with ARC with a resultant lower C_{max} than that of retrospective healthy cohorts. A single dose of 3 g was considered sufficient to achieve 40%FT > MIC_{≤4 mg/L}, and almost half of the patients were able to attain 100%FT >
MIC \leq 4 \text{ mg/L} \) for ceftolozane with the same dose. It is noteworthy that, this was a single-dose PK assessment and thus might not reflect effects of accumulation/repeated administrations.

The PK of ceftobiprole use in ARC was investigated in a multicenter, open-label, and non-randomized trial [64]. The systemic CL of ceftobiprole in patients with CrCL > 150 mL/min was two-fold higher than that in patients with normal/slightly decreased CrCL. As part of the study protocol, patients received 1 g Q8h as E.I over 4 h (as opposed to 0.5 g over 2 h, according to the manufacturer’s dosing). This resulted in attaining 100%fT > MIC \leq 4 \text{ mg/L}. When extrapolated to the manufacturer’s recommended dosing of 0.5 g, only E.I over 4 h allowed the attainment of 100%fT > MIC [66]. Likewise, administration of 0.5 g by Cojutti et al. [50] was sufficient to attain 100%fT > MIC \leq 2 \text{ mg/L} when E.I over 4 h was utilized.

Serum levels of CAZ/AVI following administration of the recommended dose (2.5 g Q8h over 2 h) were used in a phase 4 study to simulate effects of CrCL on CAZ/AVI’s PK among critically ill patients [26]. Despite a two-fold increase in Vd of CAZ compared to healthy volunteers, the probability of target attainment(PTA) was successfully increased in patients with ARC when aiming for 50%fT > MIC \leq 16 \text{ mg/L} of CAZ. Higher targets (i.e., 100%fT > MIC \leq 16 \text{ mg/L}) were not investigated, and thus the adequacy of CAZ/AVI regular dosing among ARC patients when aiming for aggressive targets is yet to be defined.

The effects of ARC on IMI/REL’s PK were recently presented by Fratoni and colleagues [63]. Compared to healthy volunteers, the researchers observed an increased CL of IMI/REL. However, regular dosing (1.25 g over 30 min) was found adequate in providing IMI exposures > 40%fT > MIC (range: 40–90%). It is worth noting that this was a single-dose PK study, thus repeated administrations’ effects were not investigated, nor was an aggressive target (100%fT > MIC) achieved by any of the included cohorts.

Cefiderocol is the only NBLA that has a manufacturer recommendation for ARC. Such a recommendation was initially based on simulations using healthy volunteers’ concentrations, as opposed to critically ill patients [67,68]. However, using plasma concentrations of patients with ARC including patients from APEKS-NP (with 70% of the cefiderocol group being in ICU at time of randomization) and CREDIBLE-CR (with more than 50% of the cefiderocol group being in ICU at time of randomization), Kawaguchi and colleagues reported that adequacy of such a regimen (i.e., 2g Q6h each administered as E.I over 3 h), with its ability to attain 100%fT > MIC for MIC \leq 4 \text{ mg/L} [69–71]. Similarly, although MEVs’ PKs were not described for an ARC setting, extrapolation from meropenem use among ICU patients with ARC might be considered. Different reports have highlighted reduced meropenem concentrations in such settings, coupled with required regimens’ modifications to attain a PD target [60,72–74]. Moreover, keeping in mind the predominant renal CL of vaborbactam, studies are therefore required to characterize ARC effects on MEV in terms of not only altered PK/required dosage adjustments, but also retained efficacy.

In summary, ARC appeared to result in a disturbed PK of NBLA. Modified dosing regimens (including higher dosing, extended/or C.I) coupled with TDM might be warranted, especially when aggressive targets (i.e., 100%fT > MIC or higher) are required.

### 3.5. Renal Replacement Therapy

AKI is commonly encountered in ICU patients, resulting in the accumulation of renally cleared drugs, including NBLA, and can result in potential toxicities. Nevertheless, many of these patients require extracorporeal renal support (i.e., RRT) in form of either prolonged intermittent renal replacement therapy (PIRRT) or continuous renal replacement therapy (CRRT), based on the clinical scenario [75]. The differences in the used modalities (e.g., effluent flow rate, filter type, renal replacement method, etc.), patient’s residual kidney functionality, and the disturbed PK owing to critical illness may render the dosing of NBLA in such settings challenging [14,15].
3.5.1. Prolonged Intermittent Renal Replacement Therapy (PIRRT)

A case report described effects of PIRRT on C/T’s PK when used in a critically ill patient with MDR PsA (MIC: 4 mg/L) [76]. The patient received a loading dose of 0.75 g C/T (over 1.5 h), followed by 0.15 g Q8 h and 0.75 g Q12 h on non-PIRRT and PIRRT days respectively. Even though higher amounts of ceftolozane and tazobactam were removed during PIRRT than non-PIRRT days (>20× difference in overall CL), the administration of the aforementioned regimen during and immediately after PIRRT replenished the lost amount, and maintained concentrations above MIC for the entire therapy duration (both 40%, 100% T > MIC for ceftolozane).

The effects of PIRRT on CAZ/AVI, ceftobiprole, cefiderocol, IMI/REL, and MEV when used among ICU patients were not reported.

In summary, little data exist regarding the effects of PIRRT on the PK of NBLA. Until more data are available, therapies might better be guided by TDM to ensure adequacy.

3.5.2. Continuous Renal Replacement Therapy (CRRT)

Gatti and Pea have recently described the effects of various CRRT modalities on PK of NBLA [14]. Relevant studies provided in reviews by Gatti and Pea [14,15], along with several other studies, are highlighted in Table 2. In summary, NBLA’s PK is influenced by CRRT type (continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and CVVHDF), flow rates, and dilutional fluids. The PK is further affected by residual kidney functionality, which can impact its ability to attain the desired PD index. The results from different reported studies (highlighted in Table 2) suggest that higher doses and/or longer infusions might be necessary in cases of residual kidney function (as compared to anuric states), or when higher PK/PD indices are targeted, especially with highly-resistant pathogens. For a more detailed discussion on the effects of CRRT, readers are advised to refer to Gatti and Pea’s review [14,15].

Based on the limited available evidence, Table 3 briefly provides our suggested initial regimens of different NBLA based on PK/PD targets (i.e., in-vitro derived vs. 100% T > MIC targets) when used among critically ill patients with special scenarios. However, given that most of the reported data were based on case reports/series, those recommendations might be considered as initial dosing regimens. TDM might still be warranted especially among unstudied scenarios or when other PK/PD indices are targeted (e.g., 100% T > 4–8 × MIC).
| Reference | Study Design | Source of Infection | Pathogen/MIC (mg/L) | PK/PD Target Assayed by Investigations | Dose Administered | Patient/Critically Ill (ml/min)/Urine Output (ml/day) | Standard Scenario | PK/PD Target Achieved with Given Regimen | Clinical Outcome |
|-----------|-------------|---------------------|---------------------|--------------------------------------|------------------|-------------------------------------------------|-----------------|------------------------------------------|-----------------|
| Kato et al. [7] | Case Report (1) | VAP | P. aeruginosa; MIC: 8 | 100% T (over 1 h) > MIC | 3 g Q8h (over 1 h) | >20 mL/min | CVVHDF | 100% T = MIC | Clinical cure |
| Bremme et al. [70] | Case Report (1) | VAP | P. aeruginosa; MIC: 8 | 100% T (over 1 h) > MIC | 3 g Q8h (over 1 h) | >15 mL/min | CVVHDF | 100% T = MIC | Clinical cure |
| Aguilera et al. [61] | Case Report (1) | VAP | P. aeruginosa; MIC: 8 | 100% T (over 1 h) > MIC | 3 g Q8h (over 1 h) | <10 mL/min | CVVHDF | 100% T = MIC | Clinical failure |
| Martin et al. [61] | Case Report (1) | VAP | P. aeruginosa; MIC: 8 | 100% T (over 1 h) > MIC | 3 g Q8h (over 1 h) | <10 mL/min | CVVHDF | 100% T = MIC | Clinical failure |
| Sime et al. [62] | PK population Study (6) | CRBSI, VAP | P. aeruginosa; MIC: 4 | 100% T (over 1 h) > MIC | 3 g Q8h (over 1 h) | >30 mL/min | CVVHDF | 100% T = MIC | Clinical outcome |
| Sime et al. [63] | PK population Study (12) | CRBSI, VAP | P. aeruginosa; MIC: 4 | 100% T (over 1 h) > MIC | 3 g Q8h (over 1 h) | >30 mL/min | CVVHDF | 100% T = MIC | Clinical outcome |
| Necker et al. [64] | Phase I, prospective study (11) | CRBSI, VAP | P. aeruginosa; MIC: 4 | 100% T (over 1 h) > MIC | 3 g Q8h (over 1 h) | >30 mL/min | CVVHDF | 100% T = MIC | Clinical outcome |
| Andreu et al. [54] | Case Report (1) | CRBSI, VAP | P. aeruginosa; MIC: 4 | 100% T (over 1 h) > MIC | 3 g Q8h (over 1 h) | >30 mL/min | CVVHDF | 100% T = MIC | Clinical outcome |
| Aguilera et al. [61] | Case Report (1) | CRBSI, VAP | P. aeruginosa; MIC: 4 | 100% T (over 1 h) > MIC | 3 g Q8h (over 1 h) | >30 mL/min | CVVHDF | 100% T = MIC | Clinical outcome |

**Table 2.** Novel β-lactam antibiotics utilized dosing regimens and PK/PD target attained of the included studies.
### Table 2. Cont.

| Reference | Study Design (n of Patients) | Source of Infection | Pathogen (MIC mg/L) | PK/PD Target Aimed by Investigation | Dose Administered (mg/mL/min/Urinary Output) (mL/day) | Patient/Comorbidities Clarified | PK/PD Target Achieved with Given Regimen | Clinical Outcome |
|-----------|-----------------------------|---------------------|---------------------|-------------------------------------|-----------------------------------------------|-------------------------------|----------------------------------------|-----------------|
| Mertens et al. [80] | PI (n = 5) | Pneumonia | P. aeruginosa | CEA: 50% fT > MIC A. baumannii 75% fT > MIC | 2.5 g QID (over 2 h) | Mean 201 mL/min (range: 47–100 mL/min) | 2 patients had ARC simulations done for fT > 4 MIC 120–150 mL/min | 50% fT > MIC > 16 mg/L (based on Monte Carlo simulations) (100% fT > MIC was not investigated) | NA |
| Seidler et al. [81] | PI (n = 10) | Pneumonia | P. aeruginosa | CEA: 50% fT > MIC A. baumannii | 1.0 g QID (over 2 h) | 100% fT > 2 mg/L | CVVHDF 80% fT > 2 mg/L | Clinical cure | Death |
| Soukup et al. [82] | PI (n = 10) | Pneumonia | P. aeruginosa | CEA: 50% fT > MIC A. baumannii | 2.5 g QID (over 2 h) | <30 mL/day | CVVHDF 100% fT > 2 mg/L | Clinical cure | NA |
| Kline et al. [83] | Case report (1) | Pneumonia | A. baumannii | CAE: 50% fT > MIC A. baumannii | 1.5 g every 12 h | 30 mL/day | CVVHDF 100% fT > 2 mg/L | Clinical cure | Death |
| Soukup et al. [84] | PI (n = 10) | Pneumonia | A. baumannii | CAE: 50% fT > MIC A. baumannii | 1.0 g QID (over 2 h) | 100% fT > 2 mg/L | CVVHDF 80% fT > 2 mg/L | Clinical cure | NA |
| Kline et al. [85] | Case report (1) | Pneumonia | A. baumannii | CAE: 50% fT > MIC A. baumannii | 1.5 g QID (over 2 h) | 30 mL/day | CVVHDF 100% fT > 2 mg/L | Clinical cure | Death |
| Kline et al. [86] | Case report (1) | Pneumonia | P. aeruginosa | MIC: 4 | 1 g QID (over 2 h) | 0 mL/day | CVVHDF 90% fT > MIC | Clinical cure | Death |
| Kline et al. [87] | Case report (1) | Pneumonia | P. aeruginosa | MIC: 4 | 1 g QID (over 2 h) | 0 mL/day | CVVHDF 90% fT > MIC | Clinical cure | Death |
| Kline et al. [88] | Case report (1) | Pneumonia | P. aeruginosa | MIC: 4 | 1 g QID (over 2 h) | 0 mL/day | CVVHDF 90% fT > MIC | Clinical cure | Death |
| Kline et al. [90] | Case report (1) | Pneumonia | P. aeruginosa | MIC: 4 | 1 g QID (over 2 h) | 0 mL/day | CVVHDF 90% fT > MIC | Clinical cure | Death |
| Kline et al. [91] | Case report (1) | Pneumonia | P. aeruginosa | MIC: 4 | 1 g QID (over 2 h) | 0 mL/day | CVVHDF 90% fT > MIC | Clinical cure | Death |
| Kline et al. [92] | Case report (1) | Pneumonia | P. aeruginosa | MIC: 4 | 1 g QID (over 2 h) | 0 mL/day | CVVHDF 90% fT > MIC | Clinical cure | Death |
| Kline et al. [93] | Case report (1) | Pneumonia | P. aeruginosa | MIC: 4 | 1 g QID (over 2 h) | 0 mL/day | CVVHDF 90% fT > MIC | Clinical cure | Death |
| Kline et al. [94] | Case report (1) | Pneumonia | P. aeruginosa | MIC: 4 | 1 g QID (over 2 h) | 0 mL/day | CVVHDF 90% fT > MIC | Clinical cure | Death |
| Kline et al. [95] | Case report (1) | Pneumonia | P. aeruginosa | MIC: 4 | 1 g QID (over 2 h) | 0 mL/day | CVVHDF 90% fT > MIC | Clinical cure | Death |
| Kline et al. [96] | Case report (1) | Pneumonia | P. aeruginosa | MIC: 4 | 1 g QID (over 2 h) | 0 mL/day | CVVHDF 90% fT > MIC | Clinical cure | Death |
| Kline et al. [97] | Case report (1) | Pneumonia | P. aeruginosa | MIC: 4 | 1 g QID (over 2 h) | 0 mL/day | CVVHDF 90% fT > MIC | Clinical cure | Death |
| Kline et al. [98] | Case report (1) | Pneumonia | P. aeruginosa | MIC: 4 | 1 g QID (over 2 h) | 0 mL/day | CVVHDF 90% fT > MIC | Clinical cure | Death |
| Kline et al. [99] | Case report (1) | Pneumonia | P. aeruginosa | MIC: 4 | 1 g QID (over 2 h) | 0 mL/day | CVVHDF 90% fT > MIC | Clinical cure | Death |
| Kline et al. [100] | Case report (1) | Pneumonia | P. aeruginosa | MIC: 4 | 1 g QID (over 2 h) | 0 mL/day | CVVHDF 90% fT > MIC | Clinical cure | Death |
| Kline et al. [101] | Case report (1) | Pneumonia | P. aeruginosa | MIC: 4 | 1 g QID (over 2 h) | 0 mL/day | CVVHDF 90% fT > MIC | Clinical cure | Death |
| Kline et al. [102] | Case report (1) | Pneumonia | P. aeruginosa | MIC: 4 | 1 g QID (over 2 h) | 0 mL/day | CVVHDF 90% fT > MIC | Clinical cure | Death |
| Kline et al. [103] | Case report (1) | Pneumonia | P. aeruginosa | MIC: 4 | 1 g QID (over 2 h) | 0 mL/day | CVVHDF 90% fT > MIC | Clinical cure | Death |
| Kline et al. [104] | Case report (1) | Pneumonia | P. aeruginosa | MIC: 4 | 1 g QID (over 2 h) | 0 mL/day | CVVHDF 90% fT > MIC | Clinical cure | Death |
| Kline et al. [105] | Case report (1) | Pneumonia | P. aeruginosa | MIC: 4 | 1 g QID (over 2 h) | 0 mL/day | CVVHDF 90% fT > MIC | Clinical cure | Death |
| Kline et al. [106] | Case report (1) | Pneumonia | P. aeruginosa | MIC: 4 | 1 g QID (over 2 h) | 0 mL/day | CVVHDF 90% fT > MIC | Clinical cure | Death |
| Kline et al. [107] | Case report (1) | Pneumonia | P. aeruginosa | MIC: 4 | 1 g QID (over 2 h) | 0 mL/day | CVVHDF 90% fT > MIC | Clinical cure | Death |
| Kline et al. [108] | Case report (1) | Pneumonia | P. aeruginosa | MIC: 4 | 1 g QID (over 2 h) | 0 mL/day | CVVHDF 90% fT > MIC | Clinical cure | Death |
| Kline et al. [109] | Case report (1) | Pneumonia | P. aeruginosa | MIC: 4 | 1 g QID (over 2 h) | 0 mL/day | CVVHDF 90% fT > MIC | Clinical cure | Death |
| Kline et al. [110] | Case report (1) | Pneumonia | P. aeruginosa | MIC: 4 | 1 g QID (over 2 h) | 0 mL/day | CVVHDF 90% fT > MIC | Clinical cure | Death |
| Kline et al. [111] | Case report (1) | Pneumonia | P. aeruginosa | MIC: 4 | 1 g QID (over 2 h) | 0 mL/day | CVVHDF 90% fT > MIC | Clinical cure | Death |
| Kline et al. [112] | Case report (1) | Pneumonia | P. aeruginosa | MIC: 4 | 1 g QID (over 2 h) | 0 mL/day | CVVHDF 90% fT > MIC | Clinical cure | Death |
| Kline et al. [113] | Case report (1) | Pneumonia | P. aeruginosa | MIC: 4 | 1 g QID (over 2 h) | 0 mL/day | CVVHDF 90% fT > MIC | Clinical cure | Death |
| Kline et al. [114] | Case report (1) | Pneumonia | P. aeruginosa | MIC: 4 | 1 g QID (over 2 h) | 0 mL/day | CVVHDF 90% fT > MIC | Clinical cure | Death |
| Kline et al. [115] | Case report (1) | Pneumonia | P. aeruginosa | MIC: 4 | 1 g QID (over 2 h) | 0 mL/day | CVVHDF 90% fT > MIC | Clinical cure | Death |
| Kline et al. [116] | Case report (1) | Pneumonia | P. aeruginosa | MIC: 4 | 1 g QID (over 2 h) | 0 mL/day | CVVHDF 90% fT > MIC | Clinical cure | Death |
| Kline et al. [117] | Case report (1) | Pneumonia | P. aeruginosa | MIC: 4 | 1 g QID (over 2 h) | 0 mL/day | CVVHDF 90% fT > MIC | Clinical cure | Death |
| Reference | Study Design (No of Patients) | Source of Infection | Pathogen/ MIC (mg/L) | PK/PD Target Aimed by Investigators | Dose Administered | Patient(s) Creatinine Clearance (mL/min)/Urine Output (mL/Day) | Clinical Outcome |
|-----------|-------------------------------|---------------------|---------------------|-------------------------------------|-------------------|---------------------------------------------------------------|-----------------|
| Torres et al. [64,66] | Open-label, non-RCT (31) | MRSE | 2 | $\text{MIC} \times 1–4$ (i.e., $100\% \text{fT} > 1–4 \times \text{MIC}$) | $0.5 \text{g Q8h (over 4 h)}$ | - CrCL > 120 mL/min: 100% \text{fT} > MIC ≤ 2 mg/L | Clinical cure |
| Cojutti et al. [50] | Case report (1) | MRSA | 2 | $\text{MIC} \times 1–4$ (i.e., $100\% \text{fT} > 1–4 \times \text{MIC}$) | $0.5 \text{g Q6h (over 4 h)}$ | BMI 51.2 kg/m² | Clinical cure * |
| Cojutti et al. [89] | Case report (1) | Methicillin-resistant Staphylococcus aureus (MRSA) | 2 | $\text{MIC} \times 1–4$ (i.e., $100\% \text{fT} > 1–4 \times \text{MIC}$) | $0.25 \text{g Q12h (over 2 h)}$ | | Clinical failure |
| Fratoni et al. [63] | Prospective PK analysis (5) | XDR K. pneumoniae | 2 | $\text{MIC} \times 1–4$ (i.e., $100\% \text{fT} > 1–4 \times \text{MIC}$) | $1.25 \text{g once (over 30 min)}$ | > 130 mL/min | |
| Kufel et al. [90] | Case report (1) | XDR K. pneumoniae | 2 | $\text{MIC} \times 1–4$ (i.e., $100\% \text{fT} > 1–4 \times \text{MIC}$) | $2 \text{g Q8h (over 3 h)}$ | 0 mL/day | |

MIC: minimum inhibitory concentration, ARC: augmented renal clearance, RRT: renal replacement therapy, ECMO: extracorporeal membrane oxygenation, BSI: bloodstream infection, CNS: central nervous system, VAP: ventilator-associated pneumonia, cIAI: complicated intra-abdominal infection, CRBSI: catheter-related bloodstream infection, CVVH: continuous veno-venous hemofiltration, CCVHD: continuous venovenous hemodialysis, CVVHDF: continuous venovenous hemodiafiltration, PIRRT: prolonged intermittent renal replacement therapy, BMI: body mass index, VA-ECMO: venoarterial extracorporeal membrane oxygenation, NR: not reported, NA: not applicable, MARS: molecular adsorbent-recirculating-system, CI: continuous infusion, LD: loading dose, CF: cystic fibrosis, XDR: extensively drug-resistant, ESBL: Extended Spectrum B-Lactamase, Pt: patient, AUC: area under the concentration time curve, $\% \text{fT} > \text{MIC}$: percentage of free drug concentration above MIC, Cmin: minimal concentration, PK/PD: pharmacokinetic/pharmacodynamic, CrCL: creatinine clearance, Qxh: every x hours, IMI/REL: imipenem/relebactam, CAZ/AVI: ceftazidime/avibactam. * Patient death was considered non-infection related. Although ARC is commonly defined as >130 mL/min/1.73 m², different studies used different cut-offs ranging from >120 to >160 mL/min/1.73 m². Thus, this study was referenced as ARC for the sake of completeness.
Table 3. Suggested initial dosing of novel β-lactam antibiotics based on aimed PK/PD targets among critically ill patients with special scenarios.

| Novel β-Lactam Antibiotic | Standard Dose (Normal Kidney Function) | Aimed PK/PD Target (in-Vitro/Murine vs. 100%/T > MIC) | ARC | RRT | ECMO | Obesity |
|---------------------------|----------------------------------------|--------------------------------------------------|-----|-----|------|--------|
| **Ceftolozane/Tazobactam** | 1.5–3 g Q8h (over 1–3 h) | T: 20%/T > 1 mg/L | CVVHD: 3 g LD (over 0.5 h) for MIC ≤ 4 mg/L | CVVHD/CVVHDF | CVVHDF | CVVHDF/CVVHDF |
|                           | | 1.5 g LD (over 0.5 h) + 0.5 g CVVHDF (over 0.5 h) for MIC ≤ 4 mg/L | CVVHDF | CVVHDF | CVVHDF | CVVHDF |
| **Ceftazidime/Avibactam**  | 2.5 g Q8h (over 2 h) | CAZ: 50%/T > 1 mg/L | CVVHDF: 2.5 g Q8h (over 2 h) for MIC ≤ 16 mg/L | CVVHDF | CVVHDF | CVVHDF |
|                           | | AVI: 50%/T > 1 mg/L | CVVHDF | CVVHDF | CVVHDF | CVVHDF |
| **Cefiderocol**           | 2 g Q8h (over 3 h) | 75%/T > 1 mg/L | CVVHDF: 2 g Q8h (over 3 h) for MIC ≤ 2 mg/L | CVVHDF | CVVHDF | CVVHDF |
|                           | | All doses infused over 3 h | NA | NA | NA | NA |
|                           | | Effluent flow rate ≤ 2 L/h → 1.5 g Q12h | NA | NA | NA | NA |
|                           | | Effluent flow rate 2.1–3 L/h → 2 g Q12h | NA | NA | NA | NA |
|                           | | Effluent flow rate 3.1–4 L/h → 1.5 g Q8h | NA | NA | NA | NA |
|                           | | Effluent flow rate ≥ 4.1 L/h → 2 g Q12h | NA | NA | NA | NA |
| **Cefotiboprole**         | 0.5 g Q8h (over 2 h) | 25–40%/T > 1 mg/L | CVVHDF: 0.25 g Q12h (over 2 h) for MIC ≤ 2 mg/L | CVVHDF | CVVHDF | CVVHDF |
|                           | | 0.5 g Q8h (increase infusion rate to over 4 h) for MIC ≤ 4 mg/L | CVVHDF | CVVHDF | CVVHDF | CVVHDF |
| **Imipenem/Relebactam**   | 1.25–2 g Q8h (over 2 h) | ME: 45%/MIC < 7 mg/L | CVVHDF: 0.25 g Q12h (over 2 h) for MIC ≤ 2 mg/L | CVVHDF | CVVHDF | CVVHDF |
|                           | | 0.25 g Q12h (over 2 h) for MIC ≤ 2 mg/L | CVVHDF | CVVHDF | CVVHDF | CVVHDF |
| **Meropenem/Vaborbactam** | 2–4 g Q8h (over 3 h) | 45%/MIC < 18–24 mg/L | CVVHDF: 0.25 g Q12h (over 2 h) for MIC ≤ 2 mg/L | CVVHDF | CVVHDF | CVVHDF |
|                           | | 0.25 g Q12h (over 2 h) for MIC ≤ 2 mg/L | CVVHDF | CVVHDF | CVVHDF | CVVHDF |

**IMI/REL**: imipenem/relebactam, **CAZ/AVI**: ceftazidime/avibactam, **C/T**: ceftolozane/tazobactam, **MEV**: meropenem/vaborbactam, **LD**: loading dose, **MIC**: minimum inhibitory concentration, **ARC**: augmented renal clearance, **MIC**: minimum inhibitory concentration, **RRT**: renal replacement therapy, **ECMO**: extracorporeal membrane oxygenation, **CVVH**: continuous veno-venous hemofiltration, **CVVHD**: continuous venovenous hemodialysis, **CVVHDF**: continuous venovenous hemodiafiltration, **PIRRT**: prolonged intermittent renal replacement therapy, **NR**: not reported as a specific target of the included studies, **NA**: not available/no studies found, **C.I.**: continuous infusion. ‡ Dosing adaptation from 100%/T > MIC target can be considered. However, the effects of higher exposures or the need of decreased dosing requirements have not be studied/reported for this conventional PK/PD index among critically ill patients presenting with this special scenario.
4. Discussion

This review highlights the scarcity of evidence regarding optimal dose-regimens for NBLA in some of the special scenarios encountered among ICU patients. Variations within the studied settings and PK/PD-used targets across the included studies limited the overall generalizability of the findings. This is in line with earlier assessments that highlighted the lack of adequate information when conventional β-lactams were utilized among similar special scenarios [21,44]. Given the altered physiology/pathology of critically ill patients, standard dose regimens may be insufficient for NBLA and may increase the risk of therapeutic failure and/or resistance development. Such conclusion can be inferred from the pool of evidence pertaining to conventional β-lactams, where different antimicrobials were reported to be associated with altered PK when utilized among critically ill patients, and had suboptimal exposures when utilized at the usual manufacturer recommended dosing. Readers are encouraged to refer to the previous published literature for more in-depth information [17,25,91,92].

Although the “one size fits all” approach has been well-described to be inappropriate across such critically ill population, more studies are still required to properly adopt patient-centered treatment approaches [95]. The importance of achieving PK/PD targets in critically ill patients has recently been emphasized, considering the increasing microbial resistance, limited treatment alternatives, and severity of illnesses [94]. Various factors should be considered when administering such NBLA among critically ill patients with special circumstances, including critical-illness-related PK alterations, the physicochemical properties of the NBLA, the site of infection/MIC of invading pathogen, and the type/modality of extracorporeal support required [14,15]. However, caution should still be practiced when considering these factors. For instance, hydrophilic drugs with limited protein binding were previously reported to be minimally subjected to ECMO-mediated variations [52,95]. Thus, one would extrapolate such minimal effects of ECMO to NBLA’s PK given their similar physiochemical properties and support such extrapolation by the reported studies highlighted in the Section 3 above. However, recent ex-vivo ECMO models have shown substantial removal of various NBLAs (e.g., C/T [96] and MEV [97]. Despite the limitations of such ex-vivo models in terms of correlation with clinical settings (i.e., single dosing administrations, no effects of human metabolism/clearance, different oxygenators used, effects of different primed fluids, etc.), they reveal commonly encountered variations seen in practice, and thus highlight the need for more clinical research to clarify such heterogeneity.

Similarly, the effect of obesity on the PK of different antimicrobials has been a topic of debate. Despite being associated with alterations in different physiological parameters, including increased cardiac output and renal blood flow [44,47,48], different studies questioned the clinical significance in terms of required dosage adjustments. For instance, in a population PK study conducted by Alobaid and colleagues [48], obesity was associated with an altered central volume of the distribution of meropenem, yet such alteration did not translate into an altered probability of attaining PD targets. Rather, in their analysis, CrCl was found to be the significant covariate affecting PTA. Similar conclusions were drawn for other conventional β-lactams, too [49,98]. This might be in line with what we found in our review. Among the two reports of morbid obesity included in this review, both patients had altered renal functionalities (ARC in the case of ceftobiprole [50], and anuric requiring CVVHDF in the case of C/T [51]). In both cases, modifications targeted toward the altered renal functionality resulted in adequate exposures of the studied NBLA, without the requirement of further adjustments targeted towards BMI.

Renal functionality has been well documented to derive major changes in the altered PK of different antimicrobials, including β-lactams. ARC has been suggested to be associated with subtherapeutic plasma concentrations of conventional β-lactams, along with increased rates of therapeutic failure when utilized at the standard dosing regimens [59,60,99,100]. Such studies have proposed increased dosing requirements and/or modified dosing administrations (i.e., prolonged infusions) to ensure attaining therapeutic targets. Comparing the results of conventional β-lactams’ modified dosing requirements
in the setting of ARC to the studies of NBLA included in this review provide similar conclusions. Based on the limited available evidence from the included studies, modified administrations seemed to be required to achieve required PTA of different NBLAs. On the other extreme, Gatti and Pea [14,15] suggested four main factors to be considered when designing an appropriate regimen in the setting of CRRT. These included PK features/physiochemical properties of the utilized NBLA, RRT modality/setting/filter type, infection site/associated MIC of the pathogen, and critical illness related altered PK. Similar concepts are still applicable to the setting of PIRRT.

Considering the aforementioned variabilities associated with the four included special scenarios, TDM-based dosing coupled with modified dosing administrations (i.e., increased dosing and/or prolonged infusions) might still be warranted. Although a recent review questioned the role of comprehensive β-lactam TDM among critically ill patients, authors acknowledged the role of targeted TDM among special scenarios (including ARC, RRT, ECMO and obesity), where the benefits of preventing over or underexposure would be expected [101]. Nevertheless, keeping in mind that TDM is still not widely available across many centers worldwide, and until more robust data are available, one might consider utilizing actual creatinine clearance (e.g., using 12 h urine collection) to design an initial dosing regimen, especially in the settings of obesity and ECMO, where CrCL seemed to be the main determinant of PTA of NBLAs based on the available evidence included in this review.

Limitations

The findings of this review should be interpreted with caution. Although this is not a systematic review, we sought to include most of the relevant studies reported. Furthermore, most of the retrieved studies included small patient populations and were of low quality (i.e., case reports/series). Finally, remarkable heterogeneity was detected in the targeted %\(f\)T > MIC across different reports/studies (highlighted in Table 2). Therefore, extrapolating conclusions should be thoughtfully considered when different PK/PD indices are clinically targeted.

5. Conclusions

Alterations in PK are often encountered in critically ill adult patients, and can result in suboptimal %\(f\)T > MIC attainments and potential therapeutic failures. This can be further complicated by many of the commonly encountered circumstances during critical illness, including obesity, ECMO, and extreme renal functionalities (ARC/RRT). The available literature, although confined, highlights the limitations of current dosing strategies in such settings. Different studies and reports have suggested modified dosing approaches (such as increased dosing and/or prolonged infusions) to optimize NBLA dosing across ICU-encountered scenarios, yet evidence has been limited by small sample sizes and the low quality of the studies. More robust, well-designed, studies are still required to determine the optimal dosing strategies of NBLA for such patient populations, and thus aid in improving clinical outcomes. Until more robust data are available, the use of TDM two guide therapy in such specialized scenarios might still be warranted.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11236898/s1, Table S1: Pharmacokinetics and murine/in vitro-derived Pharmacodynamic targets of novel β-lactams.

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Abbreviations

AKI  acute kidney injury
ARC  augmented renal clearance
AUC  area under the concentration time curve
BLBLI β-lactam/β-lactamase inhibitors
BLI  β-lactamase inhibitors
BMI  body mass index
CAZ/AVI ceftazidime/avibactam
CFR  cumulative fraction of response
CFU  colony-forming units
C.I  continuous infusion
CL  clearance
Cmax  maximum concentration
Cmin  minimal concentration
CrCL  creatinine clearance
CRRT  continuous renal replacement therapy
CT  threshold of concentration
C/T  ceftolozane/tazobactam
CVVH  continuous venovenous hemofiltration
CVVHD  continuous venovenous hemodialysis
CVVHDF  continuous venovenous hemodiafiltration
ECMO  extracorporeal membrane oxygenation
E.I  extended infusion
g  gram
h  hour
ICUs  intensive care units
IMI/REL imipenem/relebactam
LD  loading dose
MDR  multidrug-resistant
MEV  meropenem/vaborbactam
MIC  minimum inhibitory concentration
MRSE  methicillin-resistant S. epidermidis
PICO  population, intervention, comparator, outcome
PIRRT  prolonged intermittent renal replacement therapy
PK/PD  pharmacokinetic/pharmacodynamic
PsA  Pseudomonas aeruginosa
PTA  probability of target attainment
Qxh  every x hours
RRT  renal replacement therapy
TDM  therapeutic drug monitoring
VA-ECMO  venoarterial ECMO
Vd  volume of distribution
VV-ECMO  venovenous ECMO
%fT > MIC  percentage of free drug concentration above MIC

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