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REVIEW

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# Clinical implications of antibiotic pharmacokinetic principles in the critically ill

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**Abstract** Successful antibiotic therapy in the critically ill requires sufficient drug concentrations at the site of infection that kill or suppress bacterial growth. The relationship between antibiotic exposure and achieving the above effects is referred to as pharmacokinetics/pharmacodynamics (PK/PD). The associated indices therefore provide logical targets for optimal antibiotic therapy. While dosing regimens to achieve such targets have largely been established from studies in animals and non-critically ill patients, they are often poorly validated in the ICU. Endothelial dysfunction, capillary leak, altered major organ blood flow, deranged plasma protein concentrations, extremes of body habitus, the application of extracorporeal support modalities, and a higher prevalence of intermediate susceptibility, independently, and in combination, significantly confound successful antibiotic treatment in this setting. As such, the prescription of standard doses are likely to result in sub-therapeutic concentrations, which in turn may promote treatment failure or the selection of resistant pathogens. This review article considers these issues in detail, summarizing the key changes in antibiotic PK/PD in the critically ill, and suggesting alternative dosing strategies that may improve antibiotic therapy in these challenging patients.

**Keywords** Antibiotics · Pharmacokinetics · Dosing · Critical illness

## Introduction

The management of infection in the intensive care unit (ICU) represents an ongoing challenge for critical care clinicians. The critically ill represent a unique population, either presenting with infection complicated by systemic inflammation (sepsis) or being predisposed to such complications by virtue of the underlying disease process. Multitrauma, hematological malignancy, and acute kidney injury (AKI) are relevant examples, where organ function is already significantly disturbed, while subsequent infection is common.

Successful therapy relies on early recognition of infection and the timely application of antibiotics against the contributing pathogen. Modest evidence supports this as an effective intervention that will improve outcomes [1]. However, mortality rates in this setting remain high, while antibiotic resistance is becoming more prevalent, suggesting further improvements are urgently needed. Optimization of antibiotic dosing, such that predefined pharmacokinetic/pharmacodynamic (PK/PD) targets for maximal bacterial killing are achieved, has been proposed as one such approach [2]. This premise is based on the growing body of literature demonstrating grossly

altered antibiotic pharmacokinetics (PK) in the critically ill [3].

Utilizing contemporary data, the aims of this review are therefore to (1) illustrate how critically ill patients differ from the non-critically ill in terms of their antibiotic dosing requirements, (2) examine the role of alternative dosing strategies in critical illness, and (3) provide clinicians with practical prescribing advice, which attempts to improve antibiotic exposure and patient outcomes in this setting.

## Antibiotic PK/PD in critical illness: volume of distribution, clearance, protein binding, and microbial susceptibility

Critical illness is characterized by marked homeostatic disturbance, altered end-organ function, variable pre-existing comorbidity, and anthropometric irregularity. Such changes will significantly distort the normal antibiotic PK profile, resulting in drug exposure that is markedly different from the 'healthy volunteer.' Complicating this is the increasing prevalence of microbial isolates with decreased susceptibility, mandating the application of higher antibiotic concentrations for successful bacterial killing. Figure 1 graphically summarizes some of the key issues that frequently complicate effective antibiotic administration in this setting.

### Volume of distribution ($V_d$)

Key physicochemical properties including molecular weight, degree of ionization, protein binding, and lipid solubility will greatly influence antibiotic distribution. Lipophilic agents (such as fluoroquinolones) typically have a large $V_d$ with greater tissue and intracellular penetration. Alternatively, hydrophilic antibiotics will primarily distribute into the extracellular space. As such, an increased $V_d$ has been demonstrated with aminoglycosides [4], beta-lactams [5], daptomycin [6], and glycopeptides [7] in the critically ill. This likely reflects significant capillary leak coupled with aggressive fluid loading [8], which expands the interstitial space. Higher acute physiology and chronic health evaluation (APACHE) II scores have also been correlated with a larger $V_d$ for aminoglycosides [9] and vancomycin [10]. These data suggest an important interaction between illness severity and antibiotic PK, which is infrequently considered in most contemporary dosing regimens.

Obesity represents an increasing challenge for accurate drug dosing in the critically ill. Of note, recent data suggested an association between obesity and antibiotic

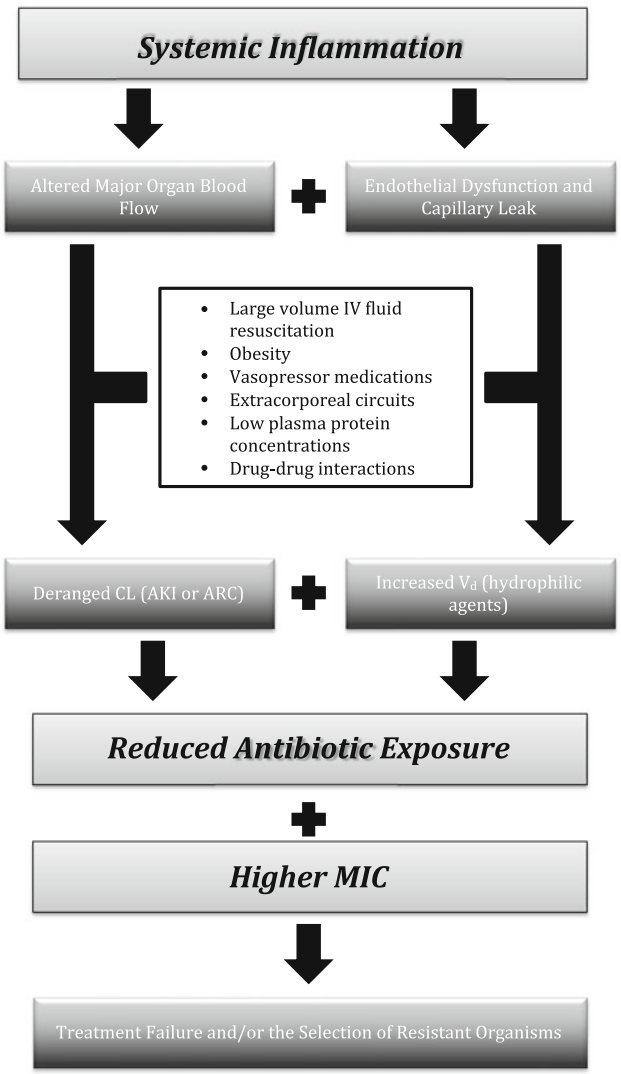


**Fig. 1** Altered physiology in the critically ill and the impact on antibiotic PK/PD. *ARC* augmented renal clearance, *AKI* acute kidney injury, *CL* clearance, *IV* intravenous, *MIC* minimum inhibitory concentration, $V_d$ volume of distribution

treatment failure in a large community-based cohort study [11]. In addition, separate reports have documented subtherapeutic concentrations of linezolid [12] and cefoxitin [13] in this setting, potentially contributing to adverse clinical outcomes. As current data are relatively sparse, few absolute recommendations can be made, although useful guidelines are provided elsewhere [14].

Recent data concerning doripenem in critically ill patients ≥100 kg with nosocomial pneumonia indicate that extended infusions (over 4-h) provide improved target attainment with susceptible bacteria [15]. Similar data have been reported with piperacillin/tazobactam in obese patients [16], where higher doses and extended infusions were required to achieve adequate drug exposure. As

such, at extremes of body habitus, higher empirical beta-lactam dosing should be regularly considered.

*Practical Tip: Aminoglycoside dosing should be calculated on the basis of adjusted body weight (ABW), daptomycin, and beta-lactam adjustments should utilize lean body weight (LBW) and vancomycin dosing should be based on total body weight (TBW).*

## Clearance (CL)

Many commonly prescribed antibiotics are primarily cleared from the body by renal elimination, including beta-lactams [17], aminoglycosides [18], and vancomycin [19].

### *Acute kidney injury and continuous renal replacement therapy*

The application of extracorporeal support for acute kidney injury (AKI), in the form of intermittent or continuous renal replacement therapy (CRRT), significantly confounds antibiotic dosing. In this circumstance, factors such as drug molecular weight, protein binding and hydrophilicity, mode of renal replacement therapy, filter porosity, blood flow rate, and total effluent rate will all influence extracorporeal drug handling [20]. Varying clinical characteristics, timing of CRRT, filter lifespan, and circuit changes make accurate PK/PD modeling problematic [21]. As such, antibiotic dosing is generally empiric, producing significant intra- and inter-patient variability in drug concentrations, which are often suboptimal [22]. How this impacts clinical outcomes remains uncertain, although AKI frequently complicates sepsis [23] and remains an independent predictor of poor outcomes [24].

As an illustration, studies investigating piperacillin dosing in the setting of CRRT are summarized in Table 1. These demonstrate inconsistent recommendations, primarily related to the heterogeneity in CRRT prescription and clinical characteristics. Emerging data suggest that the intensity of CRRT [25] and the degree of residual renal function [26] are crucial factors in accurately determining antibiotic requirements. A loading dose of 35 mg/kg vancomycin followed by 14 mg/kg/day continuous infusion has recently been recommended during CRRT [25], although very high concentrations were noted initially, suggesting that 20 mg/kg may be a more appropriate loading dose [21]. Other recommendations include cefepime 2 g 12 hourly [27], daptomycin 8 mg/kg 48 hourly [28, 29], and use of non-AKI doses with both polymyxin B [30] and colistin [31]. In contrast, higher doses (400 mg 12 hourly) of fluconazole are needed because of the absence of renal tubular reabsorption [32].

*Practical Tip: Antibiotic pharmacokinetics during CRRT is highly variable, and dosing regimens relevant to institutional practice should be established locally. Current data suggests that beta-lactam dosing should be similar to that employed in patients without renal failure in the first 48hrs of treatment [34].*

### *Augmented renal clearance*

Augmented renal clearance (ARC) refers to the enhanced renal elimination of circulating solute (such as waste products and drugs) [41]. This is based in part on PK studies demonstrating elevated renal clearances of beta-lactams [5, 17, 42], aminoglycosides [18], and glycopeptides [43], in varying subsets of critically ill patients.

A clinically useful measure of this phenomenon is a timed urinary creatinine clearance ($CL_{CR}$). Use of this surrogate is reinforced by its significance as a PK covariate for renally eliminated agents [41] and the observed association between elevated measures ($\geq$130 ml/min/1.73 $m^2$) and suboptimal antibiotic concentrations [44–46]. Numerous 'at-risk' populations have been reported, including multitrauma [47], traumatic brain injury [48], meningitis [49], postoperative patients [50], burn injury [51], ventilator-associated pneumonia [52], and pregnancy [53]. Overall, the prevalence of ARC varies considerably (30–85 % of study participants), although this is heavily influenced by case mix and definitions.

Younger age and lower illness severity scores have been repeatedly identified in patients manifesting ARC [47, 54–56]. As such, the interaction between physiological reserve (most marked in younger patients) and systemic inflammation appears to be a key driver. This was further substantiated in a recent report by Shimamoto et al. [57] in which an increasing number of SIRS criteria were strongly associated with higher drug clearance and lower plasma concentrations in non-ventilated critically ill patients receiving standard doses of vancomycin. The relevance of this finding to future dosing schedules is uncertain.

While outcome data are limited, a recent prospective, single-center observational study has demonstrated an association between ARC and therapeutic failure in critically ill patients receiving anti-infective therapy [56]. The implications for future clinical study of new or emerging antibiotics are therefore significant [2]. As an illustration, interim data analyses revealed greater

**Table 1** Clinical studies investigating piperacillin pharmacokinetics during continuous renal replacement therapy

| Reference | Mode(s) | Settings | Dose employed | Recommendation |
|---|---|---|---|---|
| Asin-Prieto et al. [26] | CVVHF | BFR, 140–230 ml/min<br>UFR, 1–2.15 l/h | 4 g 4–8 hourly | Dosing dependent on residual renal function and target MIC |
| Bauer et al. [33] | CVVHD | DR, 25 ml/kg/h | 2–3 g<br>6–12 hourly | ≥9 g/day |
| | CVVHDF | TER, 35 ml/kg/h (1:1 UFR + DR) | | |
| Seyler et al. [34] | CVVHDF or CVVHF | BFR, 150 ± 24 ml/min<br>UFR, 22 ± 12 ml/kg/h<br>DR, 23 ± 9 ml/kg/h | 4 g 6 hourly | At least 4 g 6 hourly for first 48 h of therapy |
| Joos et al. [35] | CVVHF | BFR, 100 ml/min<br>UFR, 13.2 ± 4.6 ml/min | 1–4 g<br>4–12 hourly | |
| van der Werf et al. [36] | CVVHF | UFR, 25.9 ± 9.8 ml/min | 4 g 8 hourly | Dose piperacillin alone intermittently |
| Capellier et al. [37] | CVVHF | BFR, 150 ml/min<br>UFR, 646 ± 49 ml/h | 4 g 8 hourly | 4 g 12 hourly |
| Valtonen et al. [38] | CVVHF | BFR, 100 ml/min<br>UFR, 0.8 l/h | 4 g | 4 g 8 hourly |
| | CVVHDF | BFR, 100 ml/min<br>UFR, 0.8 l/h<br>DR, 2 l/h | | |
| Mueller et al. [39] | CVVHD | BFR, 150 ml/min<br>DR, 1.5 l/h<br>UFR, 80–200 ml/h | 2–4 g<br>8–24 hourly | 4 g 12 hourly or 2 g 8 hourly |
| Arzuaga et al. [40] | CVVHF | BFR, 150–220 ml/min<br>UFR, 27.1 ± 7.8 ml/min | 4 g 6–8 hourly | Dosing dependent on residual renal function |

*BFR* blood flow rate, *CVVHD* continuous veno-venous haemodialysis, *CVVHDF* continuous veno-venous haemodiafiltration, *CVVHF* continuous veno-venous haemofiltration, *DR* dialysis rate, *MIC* minimum inhibitory concentration, *TER* total effluent rate, *UFR* ultrafiltration rate

mortality and lower clinical cure in patients with ventilator-associated pneumonia treated with a fixed course of doripenem compared with imipenem/cilastatin [58]. These findings were most marked in the subgroup with an estimated $CL_{CR} \geq 150$ ml/min. Of note, separate PK/PD modeling has suggested that significantly higher daily doripenem doses (up to 2 g 8 hourly) might have been required for adequate drug exposure in these patients [15].

The role of mathematical estimates in identifying ARC remains controversial. Plasma creatinine-based equations, such as the Cockcroft-Gault [59], modification of diet in renal disease (MDRD) [60] and chronic kidney disease epidemiology collaboration (CKD-EPI) [61], were primarily designed for use in an ambulatory or ward-based setting. They fail to consider the unique setting of critical illness, such that comparisons with measured $CL_{CR}$ values have revealed limited accuracy [62–64], particularly in patients manifesting ARC [65, 66]. As such, a urinary $CL_{CR}$ appears to be the most pragmatic, repeatable measure of renal function available to accurately guide dose selection [67].

*Practical Tip: A measured CLCR ≥ 130ml/min/1.73m2 has been associated with sub-therapeutic beta-lactam concentrations in critically ill patients receiving standard doses [46], and should prompt the clinician to consider alternative dosing. Eight-hour urinary collections appear to provide the best balance between feasibility and accuracy [68].*

## Protein binding

The free (unbound) fraction of drug ($f_u$) is that responsible for pharmacological efficacy and toxicity, in addition to being the fraction readily available for clearance via elimination pathways [69]. Measurement of the free drug concentration will therefore provide more useful PK/PD data, although this is not widely available. Using established PK principles, an increase in $f_u$ will result in a larger $V_d$, as has been noted with beta-lactams, aminoglycosides and glycopeptides [70]. Similar changes are appreciable for drug CL, where increasing $f_u$ prompts more rapid renal drug elimination [43].

Hypoalbuminaemia represents a common finding in the critically ill [71], with the PK of ceftriaxone [5], flucloxacillin [72], teicoplanin [43], daptomycin [6], and ertapenem [73] all markedly altered in this setting. While specific correction rules for dosing are currently lacking, albumin concentrations were often <25 g/l in these studies, providing a useful starting point to consider higher empirical dosing. Additional PK/PD analyses are required, although it is likely that higher total daily doses, more frequent administration, or use of extended or

continuous infusions may be required to achieve optimal drug exposure.

*Practical Tip: Hypoalbuminaemia (Alb < 25 g/l) is only likely to influence antibiotic PK when the agent is highly protein bound (>90%), and predominantly renally eliminated [69]. Examples include flucloxacillin, ertapenem, ceftriaxone and teicoplanin*

### Microbial susceptibility

Changes in bacterial susceptibility represents a growing concern for medical practice globally. Knowledge of the likely MIC of the infecting pathogen is crucial to accurately guide dose selection, as this denotes the denominator in the PK/PD relationship. Not surprisingly, dosing simulations suggest that with higher MIC values, conventional strategies are unlikely to achieve the required antibiotic exposure [15]. While local institutional data are preferred, where these are not available, a 'worst-case scenario' approach to dosing should be employed. In this respect, less susceptible pathogens are frequently isolated in the critical care unit [74], while wide variations in susceptibility patterns have been observed internationally [75].

The role of alternative dosing strategies in the setting of less susceptible bacteria remains untested in a prospective fashion. In a retrospective cohort analysis, improved outcomes with *P. aeruginosa* infection were observed with the use of extended infusions of beta-lactams [76]. Higher colistin doses have also been demonstrated to independently predict microbiological success in patients with multidrug-resistant gram-negative infection [77]. Of concern, current ciprofloxacin dosing regimes may promote the development of bacterial resistance, particularly with *P. aeruginosa* and *A. baumannii* infection [78].

*Practical Tip: The European Committee on Antimicrobial Susceptibility and Testing (available at* http://www.eucast.org*) provides useful epidemiological susceptibility data for dose optimization, in the absence of local laboratory antibiograms.*

These considerations make it clear that a 'one dose fits all' approach to antibiotic therapy, although logistically attractive, is grossly flawed in the ICU. This stems from drug development programs, in which dosing schedules (largely established from in vivo animal models) are assessed for clinical tolerability and efficacy in non-critically ill cohorts. Dosing regimens are then simply extrapolated into varying subpopulations, which in the critically ill may result in suboptimal outcomes [79]. Over the last decade, a number of alternative dosing strategies have been proposed in order to improve antibiotic exposure in this setting. These are summarized in Table 2.

**Table 2** Potential dosing solutions for altered antibiotic PK/PD in critical illness

| PK consideration | Dosing solution |
|---|---|
| Larger $V_d$ | Appropriately weight-adjusted loading doses |
| AKI requiring CRRT | Individualized patient dosing based on physicochemical properties, intensity of CRRT, and native renal function |
| | TDM |
| ARC | Increased total daily dose |
| | More frequent dosing (shorter dosing interval) |
| | Continuous/extended infusions |
| | TDM |
| Altered $f_u$ | Larger loading doses |
| | Increased frequency of dosing |
| | Continuous/extended infusions |
| | TDM (of unbound concentrations) |
| Reduced bacterial susceptibility | Increased total daily dose |
| | Continuous or extended infusions |
| | Application of PK/PD models |
| | TDM (early in the antibiotic course) |

*AKI* acute kidney injury, *ARC* augmented renal clearance, *CRRT* continuous renal replacement therapy, $f_u$ unbound (free) drug fraction, *PK/PD* pharmacokinetic/pharmacodynamics, *PK* pharmacokinetics, *TDM* therapeutic drug monitoring

## Future dosing strategies: methods to improve antibiotic exposure

Much of the data supporting newer approaches to antibiotic dosing in critical illness are based on PK/PD end points, reinforcing the need for ongoing well-designed large-scale clinical investigation. Dose selection should always consider the unique PK/PD characteristics of the chosen agent, the patients' physiology and underlying comorbidity, and the likely pathogen. Table 3 provides examples of some common empirical antibiotic doses employed in our ICU in patients without AKI. These are based on existing data or our institutional experience with therapeutic drug monitoring (TDM) of many different antibiotics in critical illness [80].

### Loading doses

Loading doses (LD) are primarily employed to ensure therapeutic concentrations are achieved rapidly, promoting fast, efficient bacterial killing. Mathematically, this is expressed as the product of the desired plasma concentration and the apparent $V_d$. After bolus IV administration, plasma antibiotic concentrations fall rapidly, primarily as a consequence of drug distribution (Fig. 2a). As such, in the setting of a larger than anticipated $V_d$, standard doses are likely to result in suboptimal drug exposure.

**Table 3** Intravenous antibiotic doses in critically ill patients without acute kidney injury

| Class of antibiotic | Initial empirical dose ('normal' renal function) |
|---|---|
| Aminoglycosides | Gentamicin 7 mg/kg ABW 24 hourly [4] |
| | Amikacin 30 mg/kg ABW 24 hourly [81] |
| | Dose adjusted by TDM [82] |
| Beta-lactams[a] [80] | Flucloxacillin 2 g 4 hourly |
| | Amoxycillin 2 g 4–6 hourly |
| | Ceftriaxone 1 g 12 hourly (2 g 12 hourly for CNS infection) |
| | Cefepime 2 g 8 hourly |
| | Ceftazidime 2 g 6–8 hourly |
| | Imipenem 0.5–1.0 g 6–8 hourly |
| | Piperacillin/tazobactam 4.5 g 4–6 hourly |
| | Ticarcillin/clavulanate 3.1 g 4–6 hourly |
| | Meropenem 1 g 6–8 hourly (2 g 6–8 hourly for CNS infection [83]) |
| | Ertapenem 1 g 12 hourly |
| Glycopeptides | Vancomycin 35 mg/kg TBW loading dose followed by 30 mg/kg/day continuous infusion [84] |
| | Dose adjusted by TDM |
| | Teicoplanin 12 mg/kg 12 hourly × 3 doses, followed by 6–12 mg/kg 24 hourly [85] |
| | Dose adjusted by TDM |
| Fluoroquinolones | Ciprofloxacin 400 mg 8 hourly [86] |
| | Levofloxacin 750–1,000 mg 24 hourly [87] |
| | Moxifloxacin 400 mg 24 hourly [88] |
| Miscellaneous | Linezolid 600 mg 12 hourly [89] |
| | Daptomycin 8–12 mg/kg 24 hourly |
| | Lincosamides 600–900 mg 8 hourly |
| | Tigecycline 100 mg loading dose, followed by 50 mg 12 hourly (or 200 mg followed by 100 mg 12 hourly when borderline susceptibility is suspected) [90] |
| | Colistin—dosing according to Garonzik et al. [91] |

*ABW* adjusted body weight, *TBW* total body weight, *TDM* therapeutic drug monitoring

[a] Administering beta-lactams by extended or continuous infusions should be considered where possible to optimize pharmacokinetics/pharmacodynamics

In early studies of aminoglycosides, high $C_{max}$:MIC ratios were strongly associated with therapeutic success in a graded fashion [92]. In patients without renal dysfunction, adequately weight-adjusted doses (7 mg/kg ABW gentamicin or equivalent) are therefore mandatory to ensure adequate PK/PD exposure is achieved [93]. Taccone and colleagues [94] recently reinforced the importance of this strategy, demonstrating that doses ≥25 mg/kg amikacin were required to ensure therapeutic concentrations against *P. aeruginosa*. This was largely due to the >60 % increase in $V_d$ when compared to healthy volunteers.

The importance of employing loading doses in critically ill patients receiving vancomycin has also recently been noted [95]. Specifically, doses of 30–35 mg/kg TBW have been recommended to rapidly achieve therapeutic concentrations [84]. Convenience doses are unlikely to be adequate [96], with recent data confirming the benefit of establishing local dosing protocols [97, 98]. Loading doses are also recommended for teicoplanin (12 mg/kg 12 hourly for 3 doses), with higher doses advocated in septic patients [85]. Insufficient beta-lactam concentrations, in association with a larger $V_d$, have also been demonstrated in the critically ill [99], although arguably more attention has focused on the role of continuous infusion with these agents.

In a small single-center study, Mohamed and colleagues examined the use of 480 mg colistin methanesulfonate as an LD in ten critically ill patients infected with multidrug-resistant gram-negative bacteria [100]. Modeling predictions of bacterial growth (utilizing a wild-type *P. aeruginosa* strain) demonstrated that this approach significantly reduces the time to bacterial eradication compared to maintenance therapy alone. Of note, no significant nephrotoxicity was reported [100]. Similar data have emerged with tigecycline, where higher loading doses have been associated with improved clinical cure in patients with hospital-acquired pneumonia, without additional safety concerns [90]. Loading doses have also been recommended with polymixin B therapy [101].

*Practical Tip: Clinicians should consider use of higher initial doses of aminoglycosides [94], beta-lactams [99], glycopeptides [84], tigecycline [90] and colistin [100] in septic, critically ill patients. Subsequent dosing can then be modified on the basis of drug eliminating organ function.*

## Continuous and extended infusions

Maintaining sufficient drug concentrations (>MIC) throughout the dosing interval represents a logical approach when prescribing time-dependent antibiotics, such as beta-lactams (ideally $fT_{>MIC} > 100$ % [102]). Options include more frequent administration, or use of continuous or extended infusions (Fig. 2c, d). For intermittent administration, the dosing interval will be determined by drug clearance, which is often heavily influenced by renal function. Adequate loading doses should still be employed with continuous infusions in order to prevent prolonged exposure to sub-therapeutic concentrations (Fig. 2b). In this respect, numerous small studies have demonstrated a distinct PK advantage to continuous infusions [42, 103, 104], although a clear clinical benefit remains to be fully established.

*Practical Tip: Continuous infusions should be commenced post loading dose at a point no further than halfway through the usual dosing interval. For convenience, we recommend starting the infusion at the conclusion of administration of the loading dose.*

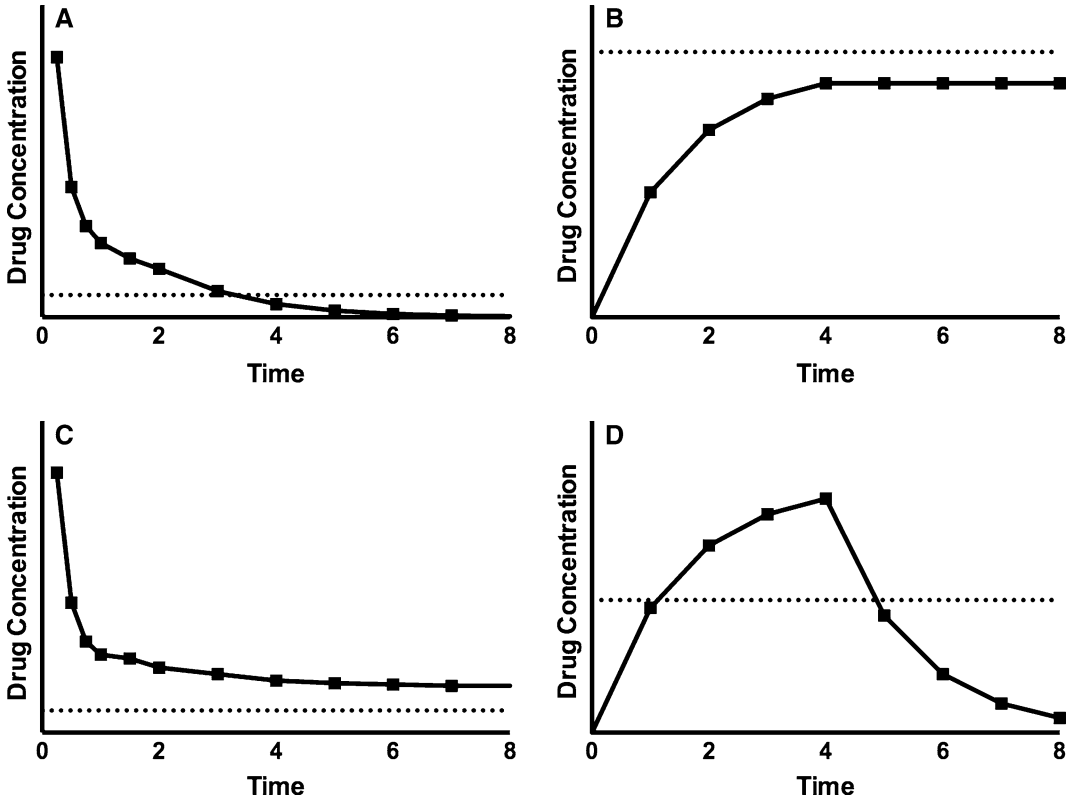


**Fig. 2** Drug concentration-time profiles for varying dosing strategies with time-dependent antibiotics. Hypothetical drug concentration versus time data following a single bolus dose (**a**), continuous infusion without a bolus dose (**b**), bolus dose followed immediately by a continuous infusion (**c**), and an extended infusion over 4 h (**d**). The *dotted line* represents the MIC of the infecting pathogen

Lodise and colleagues examined the role of extended infusions of piperacillin-tazobactam in a retrospective cohort of critically ill patients with *P. aeruginosa* infection. Extended infusions were associated with a significant improvement in 14-day survival in those patients with higher illness severity [76]. Similar retrospective analyses have been performed in patients with ventilator-associated pneumonia due to gram-negative bacilli, with continuous infusions of meropenem [105], ceftazidime [106], and piperacillin-tazobactam [107] all associated with improved rates of clinical cure, particularly with more difficult to treat organisms. In a small prospective study, Roberts et al. [108] reported a clinical advantage to continuous infusion of ceftriaxone when patients received 4 or more days of therapy.

However, a systematic review and meta-analysis performed in 2009 reported no significant clinical advantage to continuous infusion of beta-lactams in hospitalized patients [109]. More recently, Falagas and colleagues repeated this analysis, focusing on piperacillin/tazobactam and carbepenems. Overall, lower mortality was demonstrated with extended or continuous infusions, although only 3 of 14 included studies were randomized controlled trials [110]. Contrasting findings were recently reported from a single-center before and after study in which extended infusions of beta-lactams appeared to offer no advantage over intermittent dosing [111]. Concurrently, a multicenter double-blind randomized controlled trial of continuous infusion of beta-lactams reported improved $fT_{>MIC}$ and clinical cure in critically ill patients with severe sepsis, although no significant difference was noted in ICU-free days or survival to hospital discharge [112].

Vancomycin represents the other most studied agent, although data are currently conflicting on the clinical efficacy of continuous infusions. Specifically, Rello et al. [113] in a retrospective matched cohort analysis described the clinical superiority of vancomycin infusions in patients with MRSA ventilator-associated pneumonia, although a large, prospective multicenter study failed to demonstrate any significant microbiological or clinical benefit to continuous dosing [114]. A recent systematic review and meta-analysis has demonstrated comparable results, although a lower risk of nephrotoxicity in patients receiving continuous infusion [115].

Use of continuous or extended infusions of antibiotics in patients manifesting ARC represents an attractive approach, although to date there are no prospective data comparing dosing regimens in this setting. However, a recent observational study by Carlier et al. [116] suggests that despite the use of such strategies, elevated $CL_{CR}$ remains strongly

associated with suboptimal beta-lactam drug exposure. This in combination with the inferior clinical outcomes demonstrated in patients manifesting ARC [56] indicates that higher daily doses are also likely to be required. This is supported by dosing simulations reported for vancomycin [84], doripenem [15], meropenem [117], cefepime [118], and piperacillin-tazobactam [119], in which adjustments in total dose in addition to use of extended or continuous infusions are recommended.

### Therapeutic drug monitoring

TDM is commonplace in the prescription of aminoglycosides and glycopeptides, although outside of these classes, it is infrequently available. However, the growing body of literature supporting PK/PD optimization suggests that TDM is likely to be beneficial for a number of agents, most notably beta-lactams [120]. Recent data have confirmed the utility of measuring beta-lactam concentrations [121, 122], with dose adjustment required in approximately three-quarters of patients [80]. Limited uncontrolled evidence supports improved clinical outcomes with beta-lactam TDM [123], although large-scale clinical investigation is still lacking. If accurate, point-of-care devices can be developed to allow real-time dose adjustment, beta-lactam TDM will hopefully transition into wider clinical practice. Logical recipients would include those with significantly deranged PK (such as ARC or CRRT) or where an intermediate pathogen has been isolated.

### PK/PD modeling

For empirical dosing, or in the absence of TDM, improved antibiotic dosing strategies are urgently needed to optimize clinical outcomes in the critically ill. Integration of physiological, pharmacokinetic, and susceptibility data in robust PK/PD models derived from critically ill cohorts should yield dosing recommendations that have a greater likelihood of achieving optimal drug exposure [124]. While few outcome data are available, Dalfino and colleagues recently validated a previously published PK/PD model of colistin administration in the critically ill [125]. Higher rates of clinical cure without significant renal toxicity were demonstrated [126]. In the future, large controlled clinical trials should be planned to validate such dosing strategies for a variety of antibiotics in the ICU.

## Conclusions

Critically ill patients manifest physiology that is unlikely to be encountered in an ambulatory or ward-based environment. The application of ‘standard’ antibiotic doses is therefore grossly flawed. Strategies to achieve improved drug exposure, including adequate loading doses, extended/continuous infusions, and TDM, are supported by increasing PK/PD data, although prospective clinical trials are still needed. Optimal dosing should be determined prior to such investigation to avoid scenarios where drug development is prematurely curtailed. There is also significant impetus to re-examine existing dosing schedules in order to ensure ongoing therapeutic efficacy in an environment where few new antibiotics are entering clinical practice.

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