How to optimize antibiotic pharmacokinetic/pharmacodynamics for Gram-negative infections in critically ill patients

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Purpose of review
Optimized antibiotic dosing regimens improve survival rates in critically ill patients. However, dose optimization is challenging because of fluctuating antibiotic pharmacokinetics both between patients and within a single patient. This study reviews the pharmacokinetic changes that occur in critically ill patients, along with the pharmacodynamics and toxicodynamics of antibiotics commonly used for the treatment of Gram-negative bacterial infections to formulate a recommendation for antibiotic dosing at the bedside.

Recent findings
Recent studies highlight that critically ill patients do not achieve therapeutic antibiotic exposures with standard antibiotic dosing. Although dose increases are required, the method of administration, such as the use of β-lactam antibiotic continuous infusions and nebulized aminoglycoside administration, may improve efficacy and limit toxicity. In addition, the increased availability of therapeutic drug monitoring and antibiotic dosing software allow the formulation of individualized dosing regimens at the bedside.

Summary
When prescribing antibiotic doses, the clinician should consider antibiotic pharmacokinetic and pharmacodynamic principles. Before initiating high-dose antibiotic therapy, therapeutic drug monitoring may be considered to assist the clinician to optimize antibiotic treatment and minimize potential toxicity.

Keywords
antibiotics, dose optimization, pharmacodynamics, pharmacokinetic, sepsis, septic shock

INTRODUCTION

Many advances in the management of Gram-negative bacterial sepsis are related to enhanced recognition and prompt administration of an appropriate antibiotic [1,2]. The importance of an appropriate antibiotic dose cannot be understated. There is a clear association between antibiotic exposure and probability of treatment success, although robust prospective clinical evidence is lacking [3▪,4]. However, selecting the antibiotic dose that achieves the target exposure is challenging in critically ill patients [5]. Antibiotic doses recommended in the product information are often derived from studies in healthy volunteers. These dosing regimens are unlikely to achieve therapeutic antibiotic concentrations in critically ill patients in the ICU because of profound and variable physiological changes that occur in patients that may be infected with pathogens that are less susceptible to antibiotic therapy [6,7].

We will review the pharmacokinetics of commonly prescribed antibiotics used for the treatment of critically ill patients with Gram-negative bacterial infections and the antibiotic exposures (concentrations) required for both therapeutic efficacy and toxicity. These concepts will be integrated to provide methods to optimize antibiotic dosing.

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KEY POINTS

- Clinicians should consider using supranormal doses to ensure therapeutic exposures are achieved in critically ill patients.
- TDM will assist with dose selection and mitigate toxicity risks.
- Altered dosing strategies that consider the infection target site may improve therapeutic outcomes.

PHARMACOKINETIC/PHARMACODYNAMIC RATIOS AND THE MINIMUM INHIBITORY CONCENTRATION

Pharmacokinetic/pharmacodynamic (PK/PD) ratios relate the antibiotic concentration–time curve to the bacterial minimum inhibitory concentration (MIC) and are correlated with improved clinical outcomes or enhanced bacterial killing (Table 1) [19,38]. Given that antibiotic therapy cannot be guided by a clinical endpoint (measurable marker of effectiveness) in a timely manner, PK/PD ratios provide the clinician with an appropriate target to guide antibiotic dosing; however, the exact PK/PD target in plasma for a specific antibiotic varies with the pathogen and site of infection (Fig. 1) [3▪,4].

Aminoglycosides are an example of a concentration-dependent antibiotic whereby the bacterial killing and clinical efficacy are related to the ratio of the maximum concentration to the MIC (C_{max}/MIC) [6]. For time-dependent antibiotics, such as β-lactam antibiotics, bacterial killing is optimized when the unbound (or free) antibiotic concentration exceeds the MIC throughout the dosing interval ($fT_{>MIC}$) [3▪]. When bacterial killing and clinical outcomes are described by a mixed concentration and time-dependent effect, as with the fluoroquinolones, the relevant PK/PD ratio is the area under the antibiotic concentration–time curve, typically over a 24-h period, to the MIC (AUC_{0-24}/MIC) (Table 1, Fig. 1) [19].

At initial patient presentation, the causative pathogen and the associated MIC are generally unknown. Thus, we would recommend setting the target PK/PD ratio considering an MIC equal to the clinical breakpoint, which will have the greatest probability of ensuring a therapeutic exposure against pathogens for which the antibiotic is intended to be effective [39▪▪]. This approach allows the implementation of PK/PD targets in settings that do not provide a pathogen MIC. If an MIC less than the clinical breakpoint is identified, it is not advised to reduce the dose because of the variability in the MIC assay, particularly as the MIC may not represent resistant subpopulations, which may contribute to treatment failure in some patients [39▪▪,40]. Although knowledge of the specific MIC of a susceptible bacterial pathogen should not

Table 1. Pharmacokinetic/pharmacodynamic ratios associated with clinical efficacy and toxicity

	Type of PK/PD ratio and minimum target value for clinical efficacy			PK/PD toxicity threshold		
Antibiotic class	**PK/PD ratio**	**Target value**	**References**	**Toxicity**	**Threshold**	**References**
Aminoglycoside	C_{max}/MIC	>8	[8–10]	Nephrotoxicity	Gentamicin/tobramycin C_{min} >1 mg/l; Amikacin C_{min} >5 mg/l	[11–18]
	AUC/MIC	>70	[8–10]			
Penicillins	$fT_{>MIC}$	100% 1–4xMIC	[3▪,19–21]	Neurotoxicity	Piperacillin C_{min} >64–361 mg/l	[22–24]
				Nephrotoxicity	Piperacillin C_{min} >452 mg/l	[22]
Cephalosporins	$fT_{>MIC}$	100% 1–4xMIC	[3▪,21,25,26]	Neurotoxicity	Cefepime C_{min} ≥22 mg/L	[27]
Carbapenems	$fT_{>MIC}$	100% 1–4xMIC	[19,20,28]	Neurotoxicity	Meropenem C_{min}> 64 mg/l	[22]
				Nephrotoxicity	Meropenem C_{min} >44 mg/l	[22]
Fluoroquinolones	AUC/MIC	>125	[29–31]		N/A	
	C_{max}/MIC	>8	[10]			
Colistin	AUC/MIC	>50	[32][a]	Nephrotoxicity	C_{ss} ≥1.88 mg/l; C_{min} ≥2.42 mg/l	[33]
Polymyxin B	AUC/MIC	N/A	[34]	Nephrotoxicity	Daily dose ≥250 mg	[35]
Tigecycline	AUC/MIC	>4.5	[36,37]		N/A	

AUC, area-under the concentration–time curve over 24 h; C_{max}, maximum antibiotic concentration over the dosing interval; C_{min}, minimum antibiotic concentration over the dosing interval; C_{ss}, average steady-state antibiotic concentration; *f*, free drug concentration; MIC, minimum inhibitory concentration; N/A, data unavailable; PK/PD, pharmacokinetic/pharmacodynamic.
[a]Based on animal models of bactericidal activity.

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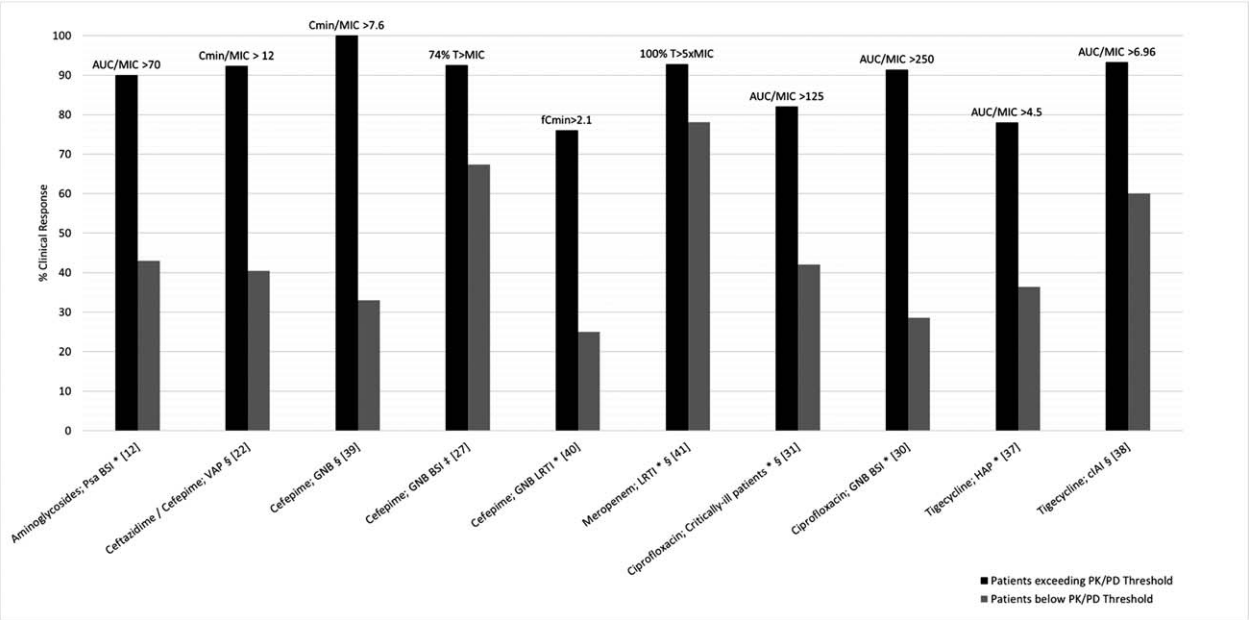

FIGURE 1. Clinical response rates relative to pharmacokinetic/pharmacodynamic targets. BSI, bloodstream infection; cIAI, complicated intra-abdominal infection; GNB, Gram-negative bacillary infection; HAP, hospital-acquired pneumonia; LRTI, lower respiratory tract infection; Psa, *Pseudomonas aeruginosa*; VAP, ventilator-associated pneumonia. *Clinical response determined by clinical cure. §Clinical response determined by microbiological cure. ‡Clinical response determined by survival rates.

change dosing, rapid identification and susceptibility determination are critical for timely antibiotic selection [41].

Pharmacokinetics in the critically ill

Prescribing a therapeutic antibiotic dose is challenging given the pharmacokinetic changes that occur in critically ill patients (Supplementary Figure 1, http://links.lww.com/COID/A26).

The volume of distribution relates the drug dose following a bolus intravenous injection to the peak plasma concentration. For hydrophilic antibiotics, the volume of distribution is often increased in critically ill patients, potentially necessitating loading doses [5]. The volume of distribution is also influenced by the degree of antibiotic protein binding. Hypoalbuminaemia occurs in 50% of patients, possibly affecting protein binding that results in an increased unbound antibiotic fraction that can change both the volume of distribution and clearance [42–44]. Additionally, extracorporeal membrane oxygenation may increase the antibiotic volume of distribution; however, current evidence suggests that dosing recommendations for extracorporeal membrane oxygenation are equivalent with other critically ill patients (Table 2) [70].

To facilitate determination of the maintenance dose, the clearance of the antibiotic should be considered. Renally cleared antibiotics may have a decreased clearance in the case of an acute kidney injury (AKI), or increased in approximately 50% of patients admitted to the ICU because of augmented renal clearance (ARC; creatinine clearance $\geq$130 ml/min/1.73 m^2) [71,72]. Patients with ARC are more likely to be younger (age $\leq$50 years), male, have a modified Sequential Organ Failure Assessment score $\leq$4 or less, and be admitted because of trauma [72]. Identifying patients with AKI and ARC is challenging. Renal function is mostly estimated using equations based on a serum creatinine concentration; however, in critically ill patients, these equations can overestimate the renal function by up to 80% in patients with AKI [73] and underestimate the renal function by up to 42% in patients with ARC [74,75]. If available, urine creatinine clearance may improve renal function estimates to guide antibiotic dosing [76]. Antibiotic dosing is also influenced by renal replacement therapy (RRT). RRT is complicated by the type, duration, dose, and filter used for RRT [77]. Given the complexity and variability in antibiotic dosing in patients receiving RRT, the reader is referred to the cited review that provides in-depth dosing guidance [78].

DOSE OPTIMIZATION AT THE BEDSIDE

Empiric dosing regimens should consider the pharmacokinetic changes in critically ill patients and the likely target site of the infection [79▪]. A suggested work flow is outlined in Fig. 2.

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Table 2. Suggested empiric dosing regimens for common antibiotics used for the treatment of critically ill patients with Gram-negative bacterial infections

Antibiotic	Current recommended dose	Minimum recommended dose in critically ill patients				References
		CLCr >130 ml/min/1.73 m^2	CLCr 60–130 ml/min/1.73 m^2	CLCr 40–60 ml/min/1.73 m^2	CLCr 20–40 ml/min/1.73 m^2	
Piperacillin/tazobactam	4/0.5 g q6h, 0.5 h infusion	LD 4/0.5 g, 0.5 h infusion; 24/3 g continuous infusion over 24 h	LD 4/0.5 g, 0.5 h infusion; 16/2 g continuous infusion over 24 h	LD 4/0.5 g, 0.5 h infusion; 12/1.5 g continuous infusion over 24 h	LD 4/0.5 g, 0.5 h infusion; 8/1 g continuous infusion over 24 h	[57▪▪,58,59]
Cefepime	2 g q12h, 0.5 h infusion	LD 2 g, 0.5 h infusion; 8 g continuous infusion over 24 h	LD 2 g, 0.5 h infusion; 6 g continuous infusion over 24 h	LD 2 g, 0.5 h infusion; 4 g continuous infusion over 24 h	LD 2 g, 0.5 h infusion; 2 g continuous infusion over 24 h	[48,49]
Ceftriaxone	1–2 g q24h	1–2 g q12h				[50–52]
Meropenem	1 g q8h, 0.5 h infusion	LD 2 g, 0.5 h infusion; 4 g continuous infusion over 24 h	LD 2 g, 0.5 h infusion; 3 g continuous infusion over 24 h	LD 2 g, 0.5 h infusion; 2 g continuous infusion over 24 h	LD 2 g, 0.5 h infusion; 1 g continuous infusion over 24 h	[53–55]
Gentamicin	5 mg/kg q24h	7 mg/kg q; dosing interval and subsequent doses dependent on TDM				
Tobramycin	5 mg/kg q24h	7 mg/kg q; dosing interval and subsequent doses dependent on TDM				[56,57]
Amikacin	15 mg/kg q24h	30 mg/kg q; dosing interval and subsequent doses dependent on TDM				
Colistin	31250–62500 IU CMS/kg in two to four divided doses daily	LD 9 MIU CMS; maintenance dose 5.45 MIU CMS q12h		LD 9 MIU CMS; 3.325 MIU CMS q12h	LD 9 MIU CMS; 2.2 MIU CMS q12h	[58,59]
Polymyxin B	0.75–1.25 mg/kg q12h	LD 2.5 mg/kg; 1.3–1.5 mg/kg q12h (max daily dose 250 mg)				[60]
Ciprofloxacin	400 mg q12h	600 mg q8h for up to 48 h followed by 400 mg q8h	400 mg q8h		400 mg q12h	[61–64]
Levofloxacin	500 mg q24h, 0.5–1 h infusion	1000 mg q24h or 500 mg q12h		750 mg q24h #	750 mg q24h #	[65,66]
Tigecycline	LD 100 mg; 50 mg q12h	LD 200 mg; 100 mg q12h				[67–69]

Recommended doses are likely to achieve the desired PK/PD target for most patients with a Gram-negative bacterial pathogen (*Enterobacterales* for tigecycline and ceftriaxone or *Pseudomonas aeruginosa* for other listed antibiotics) with an MIC at the clinical breakpoint.

CMS, colistin methanesulfonate; CLCr, creatinine clearance; IU, international units; LD, loading dose; MIU, million international units; TDM, therapeutic drug monitoring; q36h, administered every 36 h; q24 h, administered every 24 h; q12 h, administered every 12 h; q8 h, administered every 8 h; q6 h, administered every 6 h.

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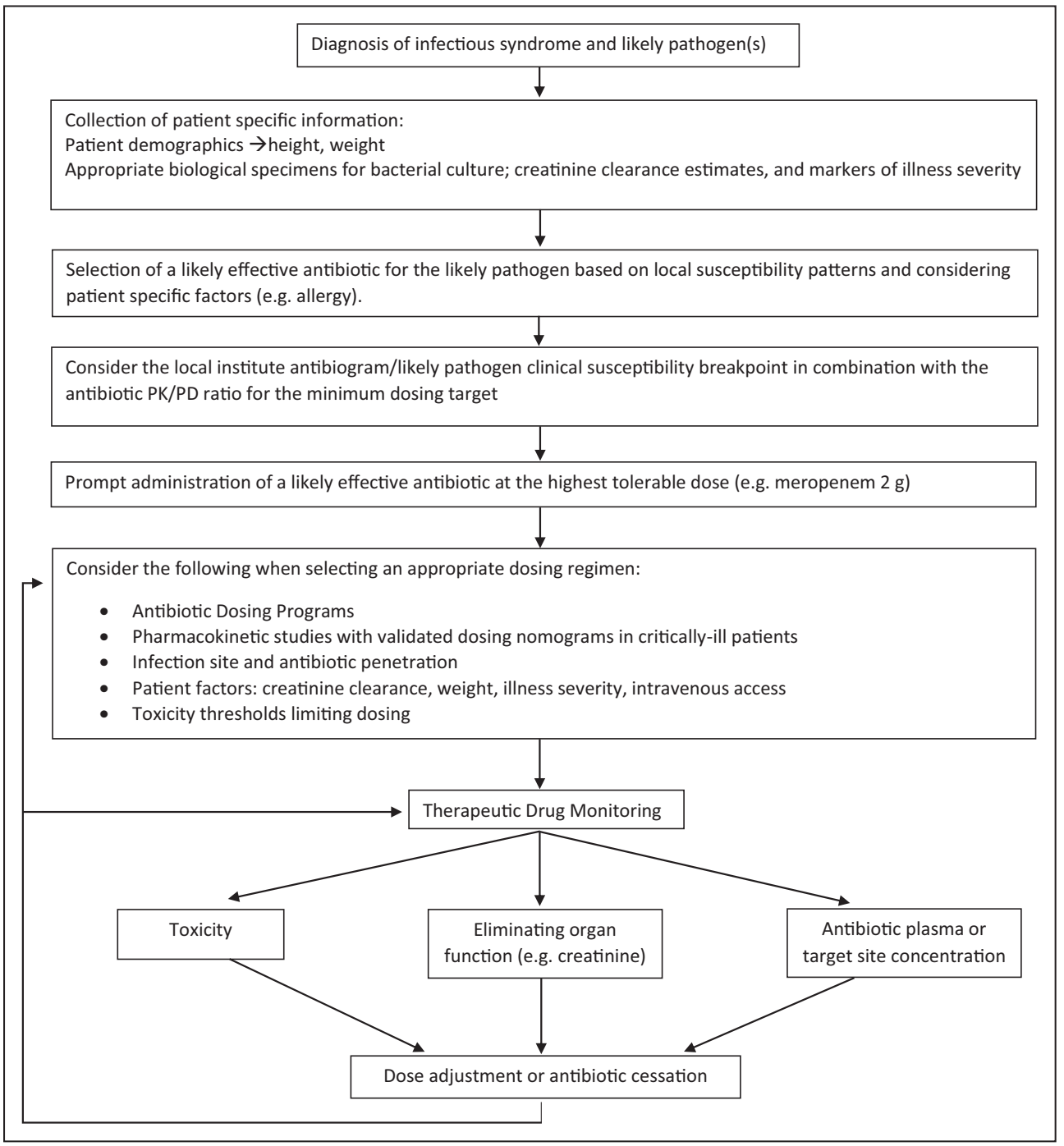

FIGURE 2. Suggested steps for dose optimization.

Aminoglycosides

Current regimens for empiric sepsis treatment are unlikely to achieve PK/PD targets for commonly encountered pathogens in many patients (Table 2) [57,80,81]. High-dose therapy (Table 2), potentially in combination with RRT, has been shown to improve the rate of PK/PD target attainment, although the safety of high-dose therapy is yet to be extensively studied [56,82–84]. Where high doses are used, further doses should be separated by 36–48 h with therapeutic drug monitoring (TDM) guiding future dose selection [57].

β-lactam antibiotics

The serum PK/PD target of 100% $fT_{>4xMIC}$ results in maximal killing against most Gram-negative bacterial pathogens; however, clinical studies have

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shown improved survival rates following exposures of 100% $fT_{>MIC}$ (Table 1). Achievement of the 100% $fT_{>1-4xMIC}$ target may be as low as 16% using conventional dosing regimens [85]. One potential strategy includes a loading dose to achieve therapeutic concentrations within 15 min of treatment initiation, followed by the commencement of a continuous infusion (Table 2) [86–88]. The total daily dose may be determined using previously published nomograms or antibiotic dosing software (see below) and should not be altered when a loading dose is administered [53,89,90]. This dosing approach has been associated with improved survival rates in clinical trials [91].

Importantly, the use of a continuous infusion with standard daily doses may not provide a therapeutic β-lactam antibiotic concentration in patients with ARC, and thus may require a higher than standard dose to avoid treatment failure [92]. Furthermore, clinicians must consider the practicalities of continuous β-lactam antibiotic infusions such as drug stability (meropenem is stable in 0.9% sodium chloride for only up to 8 h) and the 'dead space' in the infusion tubing to ensure that the full dose is administered [93].

Polymyxins

Colistin has complex pharmacokinetics, partly as it is administered as the prodrug colistin methanesulfonate. Given the delay in conversion of the inactive prodrug, colistin methanesulfonate, to colistin, a loading dose is required (Table 2) [58,94]. Maintenance doses are determined by creatinine clearance and may be administered every 12 h; however, the optimal dosing interval remains uncertain [58]. Given that the recommended maximum colistin dose of 4.5 million international units failed to achieve the target steady-state concentration in ≥60% of patients with a creatinine clearance at least 80 ml/min/1.73 m^2, current dosing strategies are unlikely to be maximally effective in patients with ARC [58]. However, the optimal polymyxin PK/PD target associated with improved clinical outcomes is yet to be confirmed, although preclinical infection model data are likely to be predictive [32]. Polymyxin B is an alternative to colistin with more predictable pharmacokinetics, although clinical and in-vitro PK/PD data are limited [60,95▪]. For critically ill patients, an optimal simulated dose of polymyxin B (1.5 mg/kg twice daily) based on the colistin PK/PD target (Table 1) exceeds current dosing recommendations [60]. High doses are likely necessary for optimal clinical outcomes given that a daily dose of less than 200 mg or less than 1.3 mg/kg have been associated with increased mortality [35,60,96]. Given the high rates of nephrotoxicity, further studies are required to elucidate the benefits and risks of high-dose polymyxin B [96].

Fluoroquinolones

Ciprofloxacin and levofloxacin may be considered for the management of Gram-negative bacillary infections. Most patients receiving ciprofloxacin 400 mg administered intravenously thrice daily are likely to achieve a therapeutic exposure against a susceptible pathogen (Table 1) [61–63,81]. However, up to 30% of patients may require at least 600 mg administered thrice daily [61,62,81]. In contrast, levofloxacin at currently studied doses of up to 1000 mg administered once-daily are unlikely to achieve therapeutic PK/PD ratios for many Gram-negative pathogens [65,81].

Tigecycline

Currently recommended tigecycline doses are likely to be insufficient for critically ill patients (Table 2), and may be a contributing factor to the increased mortality observed in patients with a bacteraemia receiving tigecycline compared with other active antibiotics [97]. Recent evidence suggests that a 200 mg loading dose followed by 100 mg twice daily are more likely to meet PK/PD targets and is supported by a six-fold increased clinical cure rate in critically ill patients, predominantly with ventilator-associated pneumonia [67–69].

THE IMPORTANCE OF THE INFECTION SITE AND ALTERNATIVE ROUTES OF ADMINISTRATION

It is often assumed that the antibiotic concentration in the plasma approximates that at the infection site; however, recent evidence suggests this assumption may be incorrect in certain infectious pathologies (Supplementary Table 1, http://links.lww.com/COID/A26) [98–128].

Lung

Hydrophilic antibiotics such as aminoglycosides, polymyxins, and most β-lactam antibiotics have impaired penetration into the epithelial lining fluid (ELF), the site of bacterial infection in pneumonia (Supplementary Table 1, http://links.lww.com/COID/A26). It is difficult to meet the optimal PK/PD targets associated with improved outcomes in the ELF of many patients [129–131]. Nebulized antibiotic administration is an alternative delivery method, which can achieve exposures up to 100-

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fold that possible with intravenous administration [132–136]. Small clinical trials have shown improved clinical cure rates with this approach, although recent phase III clinical trials of nebulized amikacin and the combination of amikacin and fosfomycin have not shown reduced mortality; however, this may in part be related to trial design [137▪,138,139▪]. In contrast, lipophilic antibiotics such as fluoroquinolones and tigecycline achieve high ELF concentrations with standard therapeutic dosing.

Interstitial fluid

Infection most commonly occurs within tissue interstitial fluid (ISF), and achieving therapeutic concentrations here is likely to be important for patient outcomes [140]. Microdialysis methods allow the determination of unbound antibiotic concentrations in the ISF [141,142]. This method has been used in clinical studies to demonstrate the increased ISF concentrations of meropenem and piperacillin/tazobactam when administered as a continuous infusion compared with intermittent bolus dosing [141,142].

Cerebrospinal fluid

Achieving therapeutic antibiotic exposures in the cerebrospinal fluid is limited by the blood–brain barrier and pharmacokinetic alterations in critical illness (Supplementary Table 1, http://links.lww.com/COID/A26) [143]. To overcome the reduced penetration, intraventricular administration of preservative-free antibiotics improves the achievement of target PK/PD ratios at the site of infection and has been successfully used for aminoglycosides and colistin [144,145]. Given the severity of nosocomial meningitis and difficulties in intraventricular antibiotic dosing, expert opinion should be sought [146].

THERAPEUTIC DRUG MONITORING AND ANTIBIOTIC TOXICITY

Although TDM has been traditionally used for monitoring toxicity, it may be implemented to increase the rate of attainment of therapeutic antibiotic concentrations. The advantages of such an approach have been demonstrated in a cohort study of patients with nosocomial pneumonia receiving dose optimization for aminoglycosides, fluoroquinolones, and β-lactam antibiotics [147]. In this nonrandomized study, clinical failure (18 vs. 32%; $P < 0.001$), mortality (10 vs. 24%; $P < 0.001$), and length of stay (12 vs. 15 days; $P < 0.008$) were significantly less for patients receiving antibiotic TDM ($n = 205$) compared with patients not receiving TDM ($n = 433$) [147].

TDM is widely available for aminoglycosides; however, there are variable monitoring practices [148]. We would recommend peak (1-h postinfusion cessation) and trough sampling, which may be combined with Bayesian dosing optimization or dose optimization based on the calculated AUC [149]. In addition to improving the C_{max}/MIC target attainment rate, TDM reduces nephrotoxicity risk, which is associated with prolonged therapy duration (>3 days) and elevated trough concentrations (Table 1) [11–18,150]. However, the risk of aminoglycoside-induced nephrotoxicity in patients with severe sepsis or septic shock receiving aminoglycosides dosed once daily for up to 3 days is similar to those not receiving aminoglycosides [151].

β-lactam antibiotic TDM is becoming increasingly common, particularly for piperacillin and meropenem [152]. Current protocols dose-adjust based on a trough concentration taken at steady state (between 24–48 h after treatment onset) [152]. Some clinical sites have incorporated β-lactam Bayesian dose adjustment; however, most sites perform a linear dose adjustment, or reduce the dosing interval to increase the exposure. This approach has been shown in a randomized controlled trial to improve the PK/PD target attainment rate for piperacillin and meropenem [153]. Dose-dependent β-lactam antibiotic neurotoxicity may limit dose escalation (Table 1) [22–24,154]. However, the threshold concentrations for dose-dependent toxicity are generally high, allowing the use of supranormal empiric dosing regimens that can then be refined with TDM (Table 2).

TDM for other drug classes is not currently widespread. Fluoroquinolones are subject to interpatient variability like β-lactam antibiotics [61,62]. Patients with extracorporeal circuits such as RRT or severe infections may benefit from peak and trough monitoring for AUC determination if this is available [147,155]. Fluoroquinolones have been associated with QT interval prolongation and subsequent Torsade de Pointes, the risk of which may be increased with drug interactions and cardiac disease, albeit there is no clear dose-response effect [156]. When high-dose fluoroquinolone therapy is employed, both the QT interval relative to the heart rate and electrolytes should be monitored accordingly [157,158].

Colistin is also a likely candidate for TDM, although complicated laboratory analytical methods limit its clinically feasibility [159]. Further supporting the potential utility of colistin, TDM is the association of colistin-induced nephrotoxicity in approximately 10% of patients with a steady-state concentration ~2 mg/l (Table 1) [33,160].

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ANTIBIOTIC DOSING SOFTWARE

Antibiotic dosing software, such as ID-ODS (Optimum Dosing Strategies, Bloomingdale, New Jersey, USA) [161] and DoseMe (DoseMe Pty Ltd, Houston, Texas, USA), can assist clinicians by providing a user-friendly interface to utilize previously published pharmacokinetic models for more accurate antibiotic dosing [38]. A clinician enters patient-specific data, including antibiotic concentrations, weight, and creatinine concentration, thus enabling the prediction of an individualized dosing regimen. Despite the potential issues outlined in Supplementary Table 2, http://links.lww.com/COID/A26, the use of pharmacokinetic models incorporated in readily available packages, combined with clinician experience, provides a significant advancement in personalized antibiotic dosing [162].

CONCLUSION

Antibiotic dosing in the critically ill patient is complex. Integrating knowledge about the patient's pharmacokinetics, the infecting bacterial pathogen MIC and site of infection, and antibiotic PK/PD can improve dosing practices in critically ill patients. Combining these principles with TDM can provide individualized dosing that optimizes the probability of achieving therapeutic exposures, whereas minimizing toxicity.

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Conflicts of interest

There are no conflicts of interest.

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- ■■ of outstanding interest

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