



Pharmacokinetic and Pharmacodynamic Considerations of Antibiotics of Last Resort in Treating Gram-Negative Infections in Adult Critically Ill Patients

Mojdeh S. Heavner¹ · Kimberly C. Claeys¹ · Anne M. Masich¹ · Jeffrey P. Gonzales¹

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Abstract

Purpose of Review We provide an overview of antimicrobials that are considered last resort for the treatment of resistant gram-negative infections in adult critically ill patients. The role in therapy, pharmacodynamic (PD) goals, and pharmacokinetic (PK) changes in critical illness for aminoglycosides, polymyxins, tigecycline, fosfomycin, and fluoroquinolones are summarized.

Recent Findings Altered PK in septic patients in the intensive care unit (ICU) is observed with many of our agents of last resort. Based on the available literature, dosage adjustments may be required to optimize PK parameters and meet PD targets for most effective bacterial killing. Data is limited, studies are conducted in heterogeneous patient populations, and conclusions are frequently conflicting. Strategic dosing regimens such as high-dose extended interval dosing of aminoglycosides or loading doses with colistin and polymyxin B are examples of ways to optimize antibiotic PK in critically ill patients. Benefits of these strategies must be balanced with risks of increased toxicity.

Summary Patients with resistant gram-negative infections may present with septic shock in the ICU. Sepsis can significantly alter the PK of antibiotics and require dosage adjustments to attain optimal drug levels. An understanding of PK and PD properties of these agents of last resort will help to maximize therapeutic efficacy while minimizing toxic effects.

Keywords Aminoglycosides · Polymyxins · Tigecycline · Fosfomycin · Fluoroquinolones · ICU

Introduction

We are currently faced with a dilemma of increasing prevalence of drug resistance to our current antibiotic armamentarium [1]. Several new agents have recently been developed to combat multidrug resistant gram-negative organisms [2–5]. While these agents may overcome existing mechanisms of resistance, they target older mechanisms of action. It will take several years before

novel antibiotics are approved and even longer before we have pharmacokinetic (PK) and pharmacodynamic (PD) data in complex critically ill populations. Thus, the growth of our antibiotic armamentarium remains stagnant. In the setting of limited options to combat increasingly resistant gram-negative infections, we must identify ways to optimize available antibiotic options. This can be achieved through an understanding of PK and PD properties of available antimicrobials to maximize therapeutic efficacy while minimizing toxic effects.

Patients with resistant gram-negative infections may present with septic shock in the intensive care unit (ICU). Sepsis can significantly alter the PK of antibiotics and require dosage adjustments to attain optimal drug levels. For example, volume of distribution (V_d) is significantly increased for hydrophilic drugs, so a greater dose is needed to achieve optimal drug concentrations at the site of infection. In comparison, lipophilic antibiotics are characterized by a large V_d because of extensive diffusion through anatomic barriers and tissues.

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✉ Kimberly C. Claeys
kclaeys@rx.umaryland.edu

¹ Department of Pharmacy Practice and Science, University of Maryland School of Pharmacy, Baltimore, Maryland, USA

Physiologic changes in critical illness are less likely to alter the V_d and thus C_{max} of lipophilic agents [6]. Drug clearance (CL) through the kidneys can be increased, as in the setting of augmented renal clearance (ARC) [7], or decreased, as with acute kidney injury (AKI) [8]. Additionally, serum albumin levels decrease in critical illness, which leads to decreased protein binding and increased free levels for highly protein bound antibiotics. This impacts other PK parameters such as metabolism and elimination [9]. Patients in the ICU frequently require organ support in the form of renal replacement therapy (RRT) through intermittent hemodialysis (iHD) or continuous renal replacement therapy (CRRT), or cardiac and pulmonary support through extracorporeal membrane oxygenation (ECMO). Drugs that are cleared through iHD or CRRT include those with small molecular weight, low protein binding, and hydrophilic in nature [10]. Conversely, drugs that are likely to be removed or bind to the ECMO circuit include those that are highly protein bound and lipophilic in nature [11].

The purpose of this report is to provide an overview of antimicrobials that are considered last resort for the treatment of resistant gram-negative infections in adult critically ill patients. We review the role in therapy, PD goals, and PK changes in critical illness for aminoglycosides, polymyxins, tigecycline, fosfomycin, and fluoroquinolones.

Aminoglycosides

Role in Therapy

Recent Surviving Sepsis Campaign (SSC) international guidelines for management of sepsis and septic shock suggest aminoglycosides as an adjunct to extended spectrum β -lactam antibiotics for patients with severe infections associated with respiratory failure and septic shock [12]. Gentamicin, tobramycin, and amikacin are the most frequently prescribed aminoglycosides [13].

Pharmacokinetics and Pharmacodynamics

Aminoglycosides are small molecules with high hydrophilicity and poor plasma binding. As with other hydrophilic drugs, aminoglycosides undergo changes in V_d in patients with sepsis, due to alterations in microvascular permeability and abnormalities of extracellular body water. Early gentamicin V_d in sepsis is estimated at 0.43 L/kg compared to 0.29 L/kg by the seventh day of therapy when sepsis resolves [14]. Therapeutic drug monitoring (TDM) is required to avoid inappropriate dosing. Creatinine clearance (CrCL) is the most useful predictor of aminoglycoside CL [15]. Critically ill patients with AKI will have decreased aminoglycoside CL, whereas patients with ARC will have increased CL [16].

The pharmacodynamic goal for aminoglycosides is summarized in Table 1 [17–20]. Aminoglycosides also exhibit a post-antibiotic effect that suppresses regrowth of microorganisms even when drug concentrations fall below the minimum inhibitory concentration (MIC). Undetectable levels for too prolonged a period of time may permit regrowth of the organism and lead to clinical failures [21, 22].

Dosing Strategies

The 2016 SSC guidelines suggest extended interval dosing (EID) with 5–7 mg/kg/day of gentamicin or equivalent regimen with another agent to maximize efficacy and minimize nephrotoxicity. The guidelines recommend this dosing strategy for all patients given comparable efficacy and decreased toxicity compared with multiple daily dosing strategies, except patients with severe renal dysfunction who would not be expected to clear the drug for several days [12]. European aminoglycoside guidelines recommend gentamicin or tobramycin 3–8 mg/kg/day and amikacin 15–30 mg/kg/day based on severity of infection and patient factors for ≤ 5 days to minimize toxicity. They suggest a target C_{max} and trough (C_{min}) of 30–40 mg/L and < 0.5 mg/L for gentamicin/tobramycin and 60–80 mg/L and < 2.5 mg/L for amikacin, respectively. Higher doses are recommended at the onset of treatment, when risk of increased V_d is greatest [23]. Of note, a significant reduction in risk of nephrotoxicity has been observed by limiting treatment to ≤ 9 days [24].

Several studies have demonstrated suboptimal aminoglycoside C_{max} in the early phase of therapy in critically ill patients when following dosing guidelines [25–27]. In a study that reported 24% attainment of C_{max} goal for amikacin (> 60 mg/L) and 4% attainment of goal for gentamicin (> 30 mg/L), the authors suggested higher dosing in critically ill patients (30 mg/kg amikacin and 8 mg/kg gentamicin) [28]. A follow-up study using the higher recommendations and adjusted body weights for dosing reported 77% attainment of target amikacin C_{max} and 6% target attainment for gentamicin [29]. One ICU-based study aimed for lower amikacin C_{max} (> 45 mg/L) and showed clinical success (clinical response 94%, bacteriologic response 86%) and no nephrotoxicity. The authors speculated that therapeutic effect was observed because of synergy between aminoglycosides and β -lactam antibiotics [30]. Further work is needed to determine an optimal dosing strategy to maximize effectiveness with aminoglycosides for gram-negative infections in critically ill patients.

Special Considerations

Patients with AKI requiring iHD may have more rapid CL of aminoglycosides compared to patients with chronic kidney disease requiring iHD [31]. Aminoglycoside CL through iHD is approximately 50%. A lower CL is expected if iHD

Table 1 Pharmacodynamic goals for antibiotics of last resort for gram-negative infections

Antibiotic	Target	Mechanism	Comments
Aminoglycosides [17–20]	C_{\max} / MIC	Concentration-dependent	Optimal ratio ≥ 8 –10/1
Polymyxins [38]	AUC/MIC	Concentration- and time-dependent	
Tigecycline [60–63]	AUC/MIC	Concentration- and time-dependent	
Fosfomycin [75]	%T > MIC	Time-dependent	Optimal ratio ≥ 2 :1
Fluoroquinolones [98, 99]	AUC/MIC	Concentration- and time-dependent	Optimal ratio ≥ 125 :1

duration is < 2 h, blood flow is < 200 mL/min, ultrafiltration is only done with no hemodialysis, a less permeable dialyzer is used, or if the patient is fluid overloaded [31–33]. Redistribution in tissue and plasma occurs immediately after iHD which results in rebound plasma concentrations by about 20% [31].

Amikacin 10 mg/kg has been suggested for dosing in CRRT [34]. Taccone et al. studied 25 mg/kg amikacin in 13 septic patients on continuous veno-venous hemodiafiltration (CVVHDF) and found that 69% of patients reached target C_{\max} (> 64 mg/L), but only 23% met the goal C_{\min} (< 5 mg/L). The investigators calculated that a median of 34 h was needed to reach target C_{\min} . While 25 mg/kg would need to be dosed less frequently to avoid accumulation, 10 mg/kg would have led to significant under dosing based on peak goals [35].

Aminoglycoside CL during ECMO was studied using amikacin 25 mg/kg based on total body weight. No significant difference was found in C_{\max} (71.7 mg/L ECMO patients, 68.4 mg/L non-ECMO patients). The proportion of C_{\max} within goal (60–80 mg/L) was also not significantly different (50% for ECMO patients, 60% for non-ECMO patients) [36•].

Practical Recommendations

Based on the available evidence, we recommend amikacin 30 mg/kg and tobramycin or gentamicin 8 mg/kg. For amikacin, we suggest targeting a goal peak of 60–80 mg/L and redosing when C_{\min} is < 2.5 mg/L. For gentamicin and tobramycin, we suggest a goal peak of 30–40 mg/L and redosing when C_{\min} is < 0.5 mg/L. Aminoglycoside therapy should be discontinued once cultures and sensitivities allow. If it is clinically necessary to continue aminoglycoside therapy beyond an empiric course, we suggest a duration of therapy \leq 9 days. Aminoglycoside peak goals should be optimized once the microorganism sensitivity data is available to achieve 8 to $10 \times \geq$ MIC. In patients on RRT, it may be reasonable to consider extended interval dosing to achieve goal peaks with doses administered less frequently given expected slower CL. Based on currently available literature on PK in ECMO, no adjustments are recommended.

Polymyxins

Role in Therapy

Polymyxin antibiotics are hydrophilic antibiotics that were first used clinically in the late 1950s then fell out of favor due to nephrotoxicity. Polymyxin use has recently increased in the treatment of resistant gram-negative organisms [37, 38]. Currently, there are two systemically available polymyxin products, colistin and polymyxin B. Colistin is administered as a pro-drug, colistimethate sodium (also called colistin methanesulfonate), which is hydrolyzed in vivo to colistin (polymyxin E1 and polymyxin E2). Polymyxin B is administered as the active drug.

Pharmacokinetics and Pharmacodynamics

Since colistin and polymyxin B are older antimicrobials, there is a paucity of PK data in ICU patients. In healthy individuals, colistimethate sodium and colistin pharmacokinetic parameters are as follows: CL 148 and 48.7 mL/min; and V_d 14 and 12.4 L, respectively [37]. Colistimethate sodium is excreted unchanged (70%) by the kidney, whereas renal excretion of colistin is minimal [37]. Polymyxin B C_{\max} in critically ill patients has been reported as 2.38–13.9 mg/L, V_d 0.14–0.33 L/kg, and CL 0.46–0.504 mL/min/kg. Urinary recovery of unchanged polymyxin B was < 1 to 4.04% of administered dose, thus renal CL of polymyxin B is low [39, 40]. Studies suggest the lack of renal excretion limits the need for dose adjustment in renal insufficiency.

Inhaled polymyxin therapy has been used in critically ill patients with hospital- or ventilator-acquired pneumonia. Due to poor penetration into the lung tissue, using an inhaled therapy may achieve high lung concentrations. One study showed that inhaled colistin 80 mg every 8 h for 7 days resulted in epithelial lung concentrations higher than the MIC for all isolated organisms. However, epithelial lung concentrations at 4 h post-dose were lower than the MIC breakpoint for *Pseudomonas aeruginosa* (< 4 mcg/mL), indicating that 80 mg every 8 h may be sub-optimal for more resistant gram-negative infections [41]. Another study administered colistin 60 mg inhaled once, followed by 60 mg intravenously (IV) every 8 h. After

inhalational delivery, the epithelial lung fluid concentrations were higher than systemic concentrations (9.53–1137 mg/L versus 0.15–0.73 mg/L) [42].

The pharmacodynamic goal for polymyxins is summarized in Table 1 [38].

Dosing Strategies

In a cohort of critically ill patients, Garonzik and colleagues described population PK of colistimethate sodium V_d of 15.9 L and a CL of 115.7 mL/min, compared to colistin V_d of 164.8 L and a CL of 207.1 mL/min. They recommended a 9 million unit loading dose, with subsequent maintenance doses based on the degree of renal impairment and/or mode of hemodialysis [43]. Another pharmacokinetic model of colistimethate described a V_d of 18.2 L and a CL of 110.1 mL/min and colistin V_d and CL was 25.7 L and 94.3 mL/min, respectively [44]. A recent study evaluated the PK of colistin 2 million units every 8 h (dosing interval adjusted for renal dysfunction) in critically ill patients with gram-negative infections. Wide interpatient variability was observed at steady state: C_{max} 5.4 mcg/mL (1.8–21.8), half-life ($t_{1/2}$) 3.3 (1.2–5.4) hours, CL 1.1 (0.7–1.9) mL/kg/min, and an AUC/MIC of 26.3 (0.9–64.9) and 3.8 (2.3–10.9), for *Acinetobacter spp.* and *Pseudomonas spp.*, respectively. The authors concluded that the recommended dose may be inadequate to achieve optimal concentrations, especially when treating *Pseudomonas spp.* with higher MIC [45]. Population PK after a 9 million unit loading dose of colistimethate followed by 4.5 million units every 12 h in critically ill patients showed colistimethate V_d 1.42 L and CL 5.84 L/h and colistin V_d 80.4 L and CL 4.99 L/h. In the 12 patients with a CrCL > 80 mL/min, four patients failed to achieve plasma concentrations of > 2 mg/L at steady state despite receiving a loading dose. Depending on the organism MIC, adequate plasma concentrations may not be attained. Renal toxicity was reported at 20%, similar to the frequency seen in previous studies [46•]. One group evaluated the efficacy and safety of colistin protocol of 5 mg/kg of load, with a maintenance of 7.5 mg/kg/day based on actual body weight (adjusted body weight if patients were obese), adjusted based on renal function, and found no benefit in providing loading doses in terms of clinical outcomes, and no difference in nephrotoxicity [47]. Historically, renal injury from both colistin and polymyxin B has been reported to be 15–25%, depending on the definition of nephrotoxicity [38]. However, a study that compared the incidence of renal failure prospectively between the two drugs found a 4.27-fold higher rate in the colistimethate sodium group compared to the polymyxin B group, 38.3% versus 12.7%, ($p < 0.001$). In the colistimethate sodium group, loading doses were associated with a higher risk of renal failure (77.3 versus 23.7%, $p < 0.001$). Patients that received a loading dose had significantly lower creatinine

at admission, were older, and had a higher Charlson comorbidity index [48].

Special Considerations

Based on PK modeling from a recent study of eight critically ill patients with AKI on iHD, colistimethate sodium doses should be 1.5 million units every 12 h on non-iHD days. Hemodialysis should be administered at the end of the interval, if possible, and a supplemental dose of 1.5 million units should be given after iHD [49].

In critically ill patients receiving CVVHDF, colistimethate sodium dosing of 160 mg every 8 h may be inadequate for the treatment of resistant gram-negative infections [50•].

Sandri and colleagues evaluated the PK of polymyxin B in 2 ICU patients receiving continuous veno-venous hemodialysis (CVVHD). C_{max} was reported as 8.62 and 4.38 mg/L, total CL was 2.17 and 6.66 L/h (0.264 and 0.374 L/h from CVVHD CL), and V_d was 0.5 and 0.34 L/kg. Based on this small report, polymyxin B doses may not need to be adjusted in patients receiving CVVHD.

Practical Recommendations

Given the current evidence, we recommend loading doses of both colistin and polymyxin B to achieve adequate concentrations. Colistin CL and thus the dosing interval is based on the degree of renal dysfunction and RRT, whereas polymyxin B does not need adjustment in patients with renal dysfunction. In those patients, we recommend polymyxin B dosed on total body weight. Inhaled therapy with colistin is appropriate when treating patients with pneumonia and will optimize the concentrations of the drug in the epithelial lining fluid.

Tigecycline

Role in Therapy

Tigecycline is a lipophilic antibiotic commonly used in combination for the treatment of resistant gram-negative infections, such as those caused by *Acinetobacter spp.* Studies in variable disease states and combinations of therapies have varying conclusions [51–55]. Recently, a meta-analysis focusing on tigecycline in infections caused by multidrug-resistant *Acinetobacter baumannii* showed no differences in all-cause mortality (OR = 0.87, 95% CI 0.50–1.52; $p = 0.63$) [56]. In a subgroup analysis of studies comparing tigecycline-based combination regimens to colistin-based regimens, mortality was significantly higher in those treated with tigecycline (OR = 1.57, 95% CI 1.04–2.35; $p = 0.03$). In a meta-analysis of tigecycline for the treatment of carbapenem-resistant *Enterobacteriaceae spp.*, which included a total of 26 studies,

overall mortality was reported to be similar between tigecycline and comparator agents (OR = 0.96, 95% CI 0.75–1.22, $p = 0.73$) [57]. Mortality was significantly lower, however, in those patients that received tigecycline in combination as opposed to monotherapy (OR = 1.83, 95% CI 1.07–3.12, $p = 0.18$). Data regarding the use of tigecycline in combination for multidrug-resistant organisms continues to be conflicting, though use of tigecycline in combination is preferred to tigecycline alone [53, 58, 59].

Pharmacokinetics and Pharmacodynamics

Tigecycline is highly protein bound (80%) and has a large V_d (7 L/kg). It is primarily eliminated through biliary excretion. Recently, Xie et al. completed a population PK analysis of tigecycline in 10 critically ill patients with predominately pulmonary infections ($n = 6$). Using a two-compartment model, mean V_d was determined to be 72.49 L and CL was 7.50 L/h, with increasing body mass index associated with increased CL. Loading doses of at least 400 mg and maintenance doses of 200 mg every 12 h were needed to achieve a target of at least 17.9 AUC_{0–24}/MIC at an MIC breakpoint of 2 mg/L [60].

The pharmacodynamic goal for tigecycline is summarized in Table 1 [60, 61, 62, 63].

Dosing Strategies

The association between tigecycline and increased risk of all-cause mortality has not been completely elucidated and could be secondary to progression of disease due to suboptimal dosing [64]. A potential avenue to circumvent these issues is to increase the dose of tigecycline, since PK analyses have demonstrated that higher doses allow for linear increases in antibacterial activity [65]. Ramirez et al. completed a randomized phase II trial in hospital- and ventilator-acquired pneumonia where patients were randomized 1:1:1 tigecycline 150 mg IV load then 75 mg every 12 h; tigecycline 200 mg load then 100 mg every 12 h; or imipenem/cilastatin 1 g every 8 h [66]. Clinical response was higher in the 100-mg (85%) than the 75-mg regimen (69.6%) and imipenem/cilastatin regimen (75%) ($p < 0.05$). Difference in adverse events or mortality between 200 and 100 mg tigecycline regimens were not significant.

A 2016 meta-analysis of patients with hospital-acquired pneumonia demonstrated that higher doses of tigecycline were shown to be more effective than standard recommended dosing [67]. The authors aggregated results of four trials (1234 patients) that compared tigecycline to other standard of care agents. Among patients treated with high-dose tigecycline, clinical cure was higher, RR = 1.48 (95% CI 1.07–2.04), but there was no difference in mortality (RR = 0.65, 95% CI 0.42–1.00). Patients in the high-dose tigecycline group experienced greater incidence of adverse events (RR = 1.5, 95% CI 1.04–

2.15). A systematic review examining both the efficacy and safety of high-dose tigecycline was completed by Falagas et al. in 2014 [68]. A total of eight studies were included: the previously mentioned prospective randomized trial, two prospective observational cohort studies, two retrospective observational cohort studies, and three case reports, totally 263 patients. The majority of high-dose tigecycline cases were treated with 100 mg every 12 h, and concomitant antibiotics were frequently employed. Infection types were variable and 58% were critically ill. Mortality in the high-dose tigecycline group ranged from 8.3 to 26.0% versus 8.0 to 61.0% in patients that received standard dosing. Higher doses of tigecycline were associated with more adverse drug events, including increased diarrhea, and nausea and vomiting [69]. The risk of adverse events versus potential benefit of higher doses of tigecycline is an area of clinical debate. These higher dosing regimens may be reserved for last line therapy where no other options are available, given the limited evidence for use. What data is available, however, does provide a framework for future clinical use.

Practical Recommendations

Tigecycline remains used in clinical practice secondary to its broad spectrum of activity, including many multidrug-resistant gram-negative organisms. This is in spite of a black box warning associating tigecycline use with increased all-cause mortality [70]. To help decrease the risk of clinical failure, investigators have studied tigecycline use in doses higher than that recommended by the package insert (100 mg every 12 h) as well as in combination therapy with numerous other antibiotic therapies. We recommend to limit use to combination therapy and consider higher doses, especially for infections such as lower respiratory tract infections where tigecycline has suboptimal PK.

Fosfomycin

Role in Therapy

Fosfomycin was originally available as fosfomycin calcium for oral use and fosfomycin disodium for IV use [71]. Fosfomycin tromethamine is a hydrophilic salt with improved bioavailability compared to fosfomycin calcium. While the IV formulation is not currently available in the USA, it is frequently used for systemic infections in other countries [72].

Pharmacokinetics and Pharmacodynamics

Bioavailability of fosfomycin calcium is 12%, since it is inactivated by hydrolysis in the acidic gastric environment, compared to 40% for fosfomycin tromethamine [73, 74].

Fosfomycin is a hydrophilic drug with a small molecular weight (138 Da), negligible protein binding (10%), and a V_d of 0.2–0.4 L/kg [75, 76]. In critically ill patients, V_d can be increased by up to 50% and C_{max} decreased significantly [77]. Fosfomycin is mostly excreted unchanged via kidneys [75], and dose adjustments are needed for $CrCL < 50$ mL/min [78]. A population PK study of fosfomycin in mechanically ventilated ICU patients with septic shock and respiratory failure showed that CL in this population compared to healthy patients was substantially lower (2.06 L/h compared to 7.2 L/h). The mean V_d of 48.8 L was also higher than that observed in healthy patients (22.0 L) [79•].

The pharmacodynamic goal for fosfomycin is summarized in Table 1 [77]. Fosfomycin in combination with other agents targeted at resistant gram-negative organisms has demonstrated synergistic effects [80], and to ameliorate nephrotoxicity from aminoglycosides, glycopeptides, and amphotericin B in animal models [81–83].

Dosing Strategies

Limited data is available on alternate dosing strategies in ICU patients in order to optimize PK/PD. A Monte Carlo simulation of fosfomycin IV in combination with carbapenems for the treatment of *Pseudomonas aeruginosa* in critically ill patients showed that doses as high as 24 g as a prolonged infusion (8 h) may be necessary to achieve target PK/PD goals [84].

Special Considerations

Given the small molecular weight, minimal protein binding, and lower V_d of fosfomycin as discussed earlier, we would expect that drug levels would be significantly affected by dialysis. In one report, iHD was shown to decrease fosfomycin levels by 61–68%, at a rate of 75–116 mL/min [85].

Fosfomycin 8 g IV over 30 min in the setting of continuous veno-venous hemofiltration (CVVH) resulted in C_{max} and C_{min} were similar to serum levels in ICU patients not on RRT and even healthy volunteers [86–88]. However, a longer mean $t_{1/2}$ [88], and higher plasma AUC values were noted [89]. C_{min} exceeded 64 mg/L throughout the entire dosing interval on a regimen of 8 g fosfomycin IV every 12 h during CVVH [86].

Practical Recommendations

Based on the available evidence, fosfomycin IV is a reasonable option in combination therapy for severe systemic infections with resistant organisms [90•]. We recommend a loading dose of fosfomycin in critically ill patients, higher maintenance doses in the first 24–48 h, followed by frequent but lower doses based on estimated of $CrCL$ using urinary creatinine collection. Fosfomycin tromethamine could be considered an option for systemic infections but would require dosing based on

expected bioavailability of 40% and amount of fosfomycin in the formulation (fosfomycin tromethamine contains 53% active drug versus 76% active fosfomycin in the IV) [77].

Fluoroquinolones

Role in Therapy

Due to their broad-spectrum activity, fluoroquinolone antibiotics have historically been a popular choice for empiric treatment of infections, especially respiratory and urinary tract infections. However, the overuse of fluoroquinolones and other broad spectrum antibiotics has led to increasing gram-negative resistance, namely with *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Escherichia coli*, and *Acinetobacter* spp. [91, 92]. Although controversial, some clinicians have used fluoroquinolones in combination with a β -lactam antibiotic in the treatment critically ill patients who may be at risk for resistant gram-negative infections. This practice may provide a broader spectrum of activity and add possible synergistic effects [92].

Pharmacokinetics and Pharmacodynamics

Known PK/PD changes in critically ill patients have raised concerns of altered fluoroquinolone PK, potentially leading to inadequate dosing in this population [93•, 94]. Since the fluoroquinolones are lipophilic antibiotics, critical illness should have little impact on the V_d of the class; however, changes in elimination can likely occur in this population, and dose adjustments should be based on the patient's renal function [93•, 94•, 95•, 96•]. Many of these studies are limited by a small sample size, exclusion of RRT, and inclusion of less critically ill patients.

Szalek et al. evaluated ciprofloxacin PK in 20 critically ill patients after a 400-mg IV dose. In this population, ciprofloxacin V_d was 214.8 L and a CL of 39.7 L/h. The C_{max} was 4.74 (0.58–7.9) and AUC/MIC was 15.36 (4.8–108.95). In this population, targeted pharmacodynamics for $C_{max} (> 10)$ and AUC/MIC (> 125) were only found in 33% of patients. Authors suggested the use of loading doses may be beneficial to help achieve targeted endpoints [97].

An observational PK study by Roberts et al. compared the population PK of levofloxacin in critically ill and non-critically ill patients [93•]. Monte Carlo simulations were performed to determine optimal dosing regimens for these patients. Patients received either IV levofloxacin 500 or 750 mg every 24 h. There was no significant difference in the CL between critically ill and non-critically ill patients. Overall, this study found no significant effect of critical illness on levofloxacin PK. Based on the Monte Carlo simulations, only $CrCL$ influenced levofloxacin CL as patients with higher

CrCL had lower probability of target attainment (PTA). In general, PTA was suboptimal in this population, even with every 12 h dosing simulations.

The pharmacodynamic goals of fluoroquinolones are summarized in Table 1 [98, 99].

Dosing Strategies

To our knowledge, no recent studies have evaluated alternative dosing strategies for fluoroquinolones in critically ill patients. Based on the limited PK/PD data, fluoroquinolone therapy could potentially be optimized by utilizing loading doses and larger doses for organisms with a higher MIC [97]. However, this practice needs to be verified in clinical studies.

Special Considerations

A prospective observational study of ciprofloxacin PK in patients receiving CVVH found that only one patient out of 14 attained target peak concentration ($C_{max} \geq 10$ mcg/mL) and 57% attained an AUC/MIC > 100 [100]. Roger et al. described the effects of varying modes of RRT, specifically CVVH and CVVHDF, on ciprofloxacin PK [101]. Mean ciprofloxacin CL was 11.8 and 10.3 L/h for CVVH and CVVHDF, respectively. Monte Carlo simulations demonstrated that patients with increased total body weight on CRRT had a lower PTA and by increasing the dose or frequency results in increased PTA. These studies suggest that higher doses of ciprofloxacin (400 mg every 8 h) or TDM should be utilized for patients receiving CRRT. However, studies in patients receiving higher doses or TDM are lacking.

Practical Recommendations

While certain patient populations and infections may necessitate fluoroquinolone therapy (e.g., severe penicillin allergy), in general, the use of fluoroquinolones as empiric therapy in critically ill patients has fallen out of favor due to a rise in fluoroquinolone resistance and the increased risk of adverse events. In addition to QTc prolongation and tendon rupture, fluoroquinolones have recently been associated with the emergence of the fluoroquinolone-resistant *Clostridium difficile* and an increased risk of invasive *Candida* infection [92, 102]. However, if treatment with fluoroquinolones is considered, local antibiograms should be consulted to guide therapy. Loading doses may be considered in critically ill patients, and the patients' renal function should dictate dosing frequency.

Conclusions

Increasing resistance among gram-negative bacteria has led to the use of antibiotics of last resort in critically ill patients,

including aminoglycosides, polymyxins, tigecycline, fosfomycin, and fluoroquinolones. Critical illness alters drug PK and makes antibiotics particularly susceptible to suboptimal target attainment. Strategies to optimize use of these drugs in ICU patients include alternative dosing regimens to overcome changes in PK/PD and combination therapy to take advantage of underlying synergy. More studies are needed in the critically ill to evaluate optimal dosing in this population to ultimately improve clinical outcomes.

Compliance with Ethical Standards

Conflict of Interest Anne M. Masich, Mojdeh S. Heavner, Jeffrey P. Gonzales, and Kimberly C. Claeyes declare they have no conflicts of interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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