The Pharmacodynamics of Prolonged Infusion β-Lactams for the Treatment of *Pseudomonas aeruginosa* Infections: A Systematic Review

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ABSTRACT

Purpose: *Pseudomonas aeruginosa* is a commonly isolated nosocomial pathogen for which treatment options are often limited for multidrug-resistant isolates. In addition to newer available antimicrobial agents active against *P. aeruginosa*, strategies such as extended (eg, prolonged or continuous) infusion have been suggested to optimize the pharmacokinetic and pharmacodynamic profiles of β-lactams. Literature regarding clinical outcomes for extended infusion β-lactams has been controversial; however, this use seems most beneficial in patients with severe illness. Prolonged infusion of β-lactams (eg, 3- to 4-hour infusion) can enhance the pharmacodynamic target attainment via increasing the amount of time throughout the dosing interval to which the free drug concentration remains above the MIC (minimum inhibitory concentration) of the organism ($fT > MIC$). This systematic review summarizes current literature related to the probability of target attainment (PTA) of various antipseudomonal β-lactam regimens administered as prolonged infusions in an effort to provide guidance in selecting optimal dosing regimens and infusion times for the treatment of *P. aeruginosa* infections.

Methods: A literature search for all pertinent studies was performed by using the PubMed database (with no year limit) through March 31, 2019.

Findings: Thirty-nine studies were included. Although many standard antipseudomonal β-lactam intermittent infusion regimens can provide adequate PTA against most susceptible isolates, prolonged infusion may enhance percent $fT > MIC$ for organisms with higher MICs (eg, nonsusceptible) or patients with altered pharmacokinetic profiles (eg, obese, critically ill, those with febrile neutropenia).

Implications: Prolonged infusion β-lactam regimens can enhance PTA against nonsusceptible *P. aeruginosa* isolates and may provide a potential therapeutic option for multidrug-resistant infections. Before implementing prolonged infusion antipseudomonal β-lactams, institutions should consider the half-life of the antibiotic, local incidence of *P. aeruginosa* infections, antibiotic MIC distributions or MICs isolated from individual patients, individual patient characteristics that may alter pharmacokinetic variables, and PTA (eg, critically ill), as well as implementation challenges. (*Clin Ther*. 2019;41:2397–2415)

Keywords: Antipseudomonal, β-lactams, MIC, pharmacodynamics, prolonged infusion, *Pseudomonas aeruginosa*.

INTRODUCTION

Pseudomonas aeruginosa is the sixth most commonly reported nosocomial pathogen in the United States, with ~14% of isolates displaying multidrug resistance.[1] Treatment options for multidrug-resistant *P. aeruginosa* infections are often limited.

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Although newer therapies have come to market (eg, ceftazidime/avibactam, ceftolozane/tazobactam), nonsusceptibility has been reported. Additional strategies such as the use of combination therapy and pharmacodynamic (PD) dose optimization have been suggested for treatment of multidrug-resistant *P. aeruginosa* in the setting of limited treatment options.

Antibiotic dose optimization is a strategy recommended by the Centers for Disease Control and Prevention Core Elements of Hospital Antibiotic Stewardship Programs.[2] These core elements define dose optimization as "dose adjustments based on therapeutic drug monitoring, optimizing therapy for highly drug-resistant bacteria, achieving central nervous system penetration, extended-infusion administration of β-lactams, etc."

Extended infusions, including prolonged and continuous, often increase the bacterial exposure time, thereby increasing the amount of time in which the free drug concentration remains above the minimum inhibitory concentration ($fT > MIC$).[3] Prolonged infusion (PI) typically refers to extending the infusion time to 3−4 h compared with intermittent infusion of 0.5−1 h. Continuous infusion is the administration of the entire daily dose continuously over 24 h. Logistical challenges with continuous infusion therapy, such as requiring 24-hour room temperature stability and uninterrupted intravenous access, often make PI a more viable option when intermittent infusion of antipseudomonal β-lactams fails to achieve adequate $fT > MIC$.

The literature regarding clinical outcomes for PI β-lactams has been conflicting, with most meta-analyses combining results of PI and continuous infusion (ie, extended infusion) versus intermittent infusion. Several meta-analyses, which included observational and randomized controlled trials (RCTs), identified significant benefit in clinical outcomes and/or mortality when comparing extended versus intermittent infusion[4−8]; however, this was not consistently evident when only RCTs were evaluated.[4−6,9] Similar inconsistencies in clinical outcomes have been observed within individual studies comparing PI versus intermittent infusion (see the Supplemental Table in the online version at https://doi.org/10.1016/j.clinthera.2019.09.010). Assessment of the disparity in outcomes between these meta-analyses and individual trials suggests differences in study design, sample size, patient population, infection type, severity of illness, infecting pathogens, antibiotic doses, utilization of loading doses, and/or concomitant antibiotics used.

Severity of illness seems to be a crucial factor for observing clinical benefit with extended infusion β-lactams. The majority of studies, consisting of mostly severe infections (eg, nosocomial pneumonia, sepsis) and/or critically ill patients, found significant mortality benefit with extended infusion β-lactam administration.[6−8,10]

As discussed throughout this systematic review, one potential advantage of extended versus intermittent infusion β-lactams is to provide enhanced PD target attainment against nonsusceptible isolates; however, extended infusion is unlikely to provide additional benefit for infections due to highly susceptible organisms with lower MICs.[6] Thus, a difference in outcomes may not be observed when adequate PD target attainment is achieved with intermittent infusion. Further prospective RCTs are needed to definitively provide clarity on outcomes and identify specific subgroups of patients that may benefit most from the use of PI administration of β-lactams. Of note, the BLING (Beta-Lactam Infusion Group) III trial is an ongoing multicenter RCT comparing outcomes between continuous infusion and intermittent infusion piperacillin/tazobactam or meropenem in critically ill patients with sepsis; it will hopefully provide additional insight into the clinical benefit of extended infusions.[54] However, for the purposes of this systematic review, only studies assessing the PD variables of PI antipseudomonal β-lactams were included.

β-lactams are considered time dependent, which indicates that their antimicrobial activity is dependent on the percent $fT > MIC$.[3] The reported $fT > MIC$ PD target for bactericidal effect of β-lactams versus gram-negative organisms is 50%−60% for penicillins, 60%−70% for cephalosporins (40% for ceftolozane/tazobactam), and 40% for carbapenems.[3,11] Population pharmacokinetic (PK) modeling via Monte Carlo simulation is often used to assess the probability of target attainment (PTA) of various antimicrobial dosing regimens to determine optimal dosing strategies. A Monte Carlo simulation takes the serum drug concentrations from a small number of observed patients and calculates the PTA

of various dosing regimens for a range of MICs.[12] A goal PTA ≥90% is typically reported in PD studies (and is referenced as such throughout this review).[13] A PK/PD breakpoint is a dosage regimen–related and nonspecies-related MIC at which the PD target is likely to be attained (ie, achievement of goal PTA).[14] This systematic review highlights the PD variables of antipseudomonal β-lactam antibiotics administered as PI based on Monte Carlo simulations in an effort to provide guidance in selecting optimal dosing regimens and infusion times for the treatment of *P. aeruginosa*.

MATERIALS AND METHODS

A literature search for all pertinent studies was performed by using the PubMed database without a year limit through March 31, 2019. The following search terms were used: *pharmacokinetic, pharmacodynamic, β-lactams, piperacillin, piperacillin/tazobactam, cefepime, ceftazidime, ceftazidime/avibactam, ceftolozane/tazobactam, imipenem, doripenem,* and *meropenem*. The age, human, and English language filter were used to include studies on adults and English language only, respectively. The original search identified 446 articles. A total of 39 studies were included after excluding the articles including the following topics: those specifically assessing renal dysfunction (ie, creatinine clearance [CrCl] <50 mL/min), elderly, surgical prophylaxis, cystic fibrosis, Asian ethnicity, prolonged infusion times <3 h or >4 h or continuous infusion, studies that used PD targets other than those described within this systematic review, studies that did not include PD analyses, population PK modeling, or PTA.

Prolonged Versus Intermittent Infusion of Antipseudomonal β-lactams

Several studies have assessed the ability of PI versus intermittent infusion in achieving goal PTA for antipseudomonal β-lactams.[3,15–26] Table I provides a summary of various antipseudomonal β-lactam PD targets and the PK/PD breakpoint associated with the different dosing regimens in patients with normal renal function based on Monte Carlo simulation. Overall, the use of intermittent infusion dosing regimens for most antipseudomonal β-lactams provides near-optimal PTA at current Clinical Laboratory and Standards Institute (CLSI) susceptibility breakpoints for *P. aeruginosa*, except piperacillin/tazobactam. PI β-lactams may enhance PTA at higher, nonsusceptible MICs.

Prolonged Infusions (3–4 hours)

Penicillins

The PTA of PI piperacillin or piperacillin/tazobactam has been evaluated in 10 studies in hospitalized patients. Unlike intermittent infusions, PI dosing regimens of 3.375 and 4.5 g (or 4 g piperacillin) q8h infused over 4 h are more likely to achieve goal PTA up to an MIC of 16 mg/L, the current CLSI susceptibility breakpoint for *P. aeruginosa*.[3,15–18,20,26–28] Four of six studies assessing the PTA of the 3.375 g q8h PI (4 h) consistently found ≥90% PTA up to an MIC of 16 mg/L.[3,17,18,26] Thabit et al,[15] however, simulated PTAs based on a specific CrCl range (41–120 mL/min) and found lower PTA attained at an MIC of 16 mg/L (76.8%) yielding a PK/PD breakpoint of 8 mg/L. In addition, Patel et al[27] assessed optimal renal dosage adjustments for PI piperacillin/tazobactam 3.375 g q8h (4-hour infusion) in hospitalized patients and found that only patients with a CrCl ≤60 mL/min were able to achieve ≥90% PTA up to an MIC of 16 mg/L. However, patients with a CrCl of 80, 100, and 120 mL/min achieved optimal PTA only up to an MIC of 8 mg/L.

Increasing the PI dosing regimen to 4.5 g (or piperacillin 4 g) q8h with a 4-hour infusion enhanced the consistency within available studies in achieving the PD target up to an MIC of 16 mg/L.[15–17,20,26,29] Dosing regimens with 4-hour infusions of 4.5 g q6h or 6.75 g q8h were identified as potential strategies to enhance PTA at an MIC of 32 mg/L. Five studies evaluated a PI regimen of 4.5 g (or piperacillin 4 g) q6h with a 3- or 4-hour infusion and found optimized PTA at an MIC of 16 mg/L.[15,16,18–20] Three studies identified PTAs that were near or exceeded 90% at this dosing regimen up to an MIC of 32 mg/L.[16,19,20] Thabit et al[15] found lower PTA (67.2%) at an MIC of 32 mg/L; Eagye et al[18] did not assess PTA at this MIC.

Cephalosporins

The PTA of PI cefepime has been evaluated in 2 studies. Cheatham et al[30] found that a dosing regimen of 1 g and 2 g q8h infused over 4 h resulted in a PK/PD breakpoint of 8 mg/L and 16 mg/L, respectively. Eagye et al[18] identified that a cefepime

Table I. Pharmacokinetic-pharmacodynamic (PK/PD) breakpoints of intermittent and prolonged infusion regimens of antipseudomonal β-lactams.

β-Lactam Dosing Regimen	Pharmacodynamic Target	PK/PD Breakpoint (mg/L)	*Pseudomonas aeruginosa* CLSI Susceptibility Interpretation (mg/L)[28]		
			Susceptible	Intermediate	Resistant
Penicillin					
Piperacillin/tazobactam	50% *f*T > MIC		≤16/4	32/4—64/4	≥128/4
3.375 g q6h (0.5 h)[3,15—18]		8			
4.5 g q6h (0.5 h)[15—19]		8			
4.5 g q8h (0.5 h)[17,19]		4			
3.375 g q8h (4 h)[3,15,17,18,26]		8—16			
3.375 g q6h (4 h)[15]		16			
4.5 g q8h (4 h)[15—17,20,26,29]		16			
4.5 g q6h (3—4 h)[15,16,18—20]		16—32			
6.75 g q8h (4 h)[17,26]		32			
Cephalosporins					
Cefepime	60%—67% *f*T > MIC		≤8	16	≥32
1 g q12 h (0.5 h)[18]		1			
2 g q12 h (0.5 h)[3,18]		2			
2 g q8h (0.5 h)[3,18]		4—8			
1 g q8h (4 h)[30]		8			
2 g q8h (3 h)[18]		4 (87% PTA at 8)			
2 g q8h (4 h)[30]		16			
Ceftazidime[18]	60% *f*T > MIC		≤8	16	≥32
1 g q8h (0.5 h)		4			
2 g q8h (0.5 h)		8			
1 g 8 h (3 h)		8			
2 g 8 h (3 h)		16			
Ceftolozane/tazobactam[22,63]	40% *f*T > MIC		≤4/4	8/4	≥16/4
1.5 g q8h (1—4 h)		8—16			
3 g q8h (1—4 h)		16—32			
Carbapenems					
Doripenem[18,23]	40% *f*T > MIC		≤2	4	≥8
0.5 g q8h (1 h)		0.5—1			
1 g q8h (1 h)		1—2			
0.5 g q8h (4 h)		2—4			
1 g q8h (4 h)		4—8			
Imipenem[18]	40% *f*T > MIC		≤2	4	≥8
0.5 g q6h (0.5 h)		1			
1 g q8h (0.5 h)		1			
0.5 g q6h (3 h)		4			
1 g q8h (3 h)		4			

Table I. (*Continued*)

β-Lactam Dosing Regimen	Pharmacodynamic Target	PK/PD Breakpoint (mg/L)	*Pseudomonas aeruginosa* CLSI Susceptibility Interpretation (mg/L)[28]		
			Susceptible	Intermediate	Resistant
Meropenem	40% *f*T > MIC		≤2	4	≥8
0.5 g q6h (0.5 h)[3,18]		1–2			
1 g q8h (0.5 h)[3,18,24,25]		1–2			
2 g q8h (0.5 h)[18,24]		2–4			
0.5 g q8h (3 h)[3]		2			
0.5 g q6h (3 h)[18]		4			
1 g q8h (3 h)[3,18,24,25]		4			
2 g q8h (3 h)[18,24]		8			

CLSI = Clinical Laboratory Standard Institute; *f*T > MIC = time in which the free drug concentration remains above the MIC; PTA = probability of target attainment.

PI dosing regimen of 2 g q8h infused over 3 h resulted in near optimal PTA (87%) at an MIC of 8 mg/L. In addition, a ceftazidime PI dosing regimen of 1 g and 2 g q8h (3-hour infusion) was achieved at an MIC of 8 mg/L and 16 mg/L, respectively. Natesan et al,[22] however, found that ceftolozane/tazobactam 1.5 and 3 gram every 8 h dosing regimens with infusion times >1 h did not provide enhanced goal PTA achievement in patients with a CrCl of 50–120 mL/min.

Carbapenems

The PTA of PI doripenem has been evaluated in 2 studies. Administering doripenem 0.5 g or 1 g q8h over 4 h resulted in a PK/PD breakpoint of 2–4 mg/L and 4–8 mg/L, respectively.[18,23] Eagye et al[18] found near-optimal PTA of 85% at an MIC of 4 mg/L and 8 mg/L with doses of 0.5 g and 1 g. In addition, prolonging the infusion time of imipenem 0.5 g q6h by 3 h increased the PK/PD breakpoint to an MIC of 4 mg/L. However, increasing to a PI regimen of 1 g every 8 h resulted in only 81% PTA at an MIC of 8 mg/L. The PTA of PI meropenem has been evaluated in 4 studies. Meropenem dosing regimens of 0.5, 1, and 2 g q8h infused over 3 h resulted in PK/PD breakpoints of 2, 4, and 8 mg/L.[3,18,24,25]

Summary

Most standard intermittent infusion β-lactam dosing regimens for *P. aeruginosa* treatment achieve adequate PTA at current CLSI susceptibility interpretations except for piperacillin/tazobactam, which requires PI. PI provides enhanced PTA versus intermittent infusion in patients with normal renal function, particularly against organisms with higher, often nonsusceptible MICs. PK/PD breakpoints within the CLSI intermediate interpretation category were achieved for various 4-hour PI regimens of piperacillin/tazobactam (eg, 6.75 g q8h), cefepime (eg, 2 g q8h), and doripenem (eg, 1 g q8h) and 3-hour infusions of ceftazidime (eg, 2 g q8h), imipenem (eg, 0.5 g q6h or 1 g q8h), and meropenem (eg, 0.5 g q6h or 1 g q8h). Of these agents, only meropenem PI was consistently able to provide optimal PTA at a CLSI resistant interpretation (8 mg/L) with a dose of 2 g q8h (3-hour infusion). In addition, PI and intermittent infusion ceftolozane/tazobactam regimens were able to achieve PK/PD breakpoints within the CLSI intermediate and resistant interpretations using a *f*T > MIC target of 40%. However, patients with higher CrCl or altered PK profiles (eg, critically ill, obese, those with febrile neutropenia) may require alternative dosing strategies of these β-lactams.

Critically Ill and Augmented Renal Clearance

Physiologic changes that occur in critically ill patients with sepsis alter the PK and serum concentrations achieved with β-lactams. Shifts in fluid balance and serum albumin can increase V_d, and changes in renal and hepatic function alter drug clearance.[31] Augmented renal clearance (ARC [eg,

Table II. Pharmacokinetic/pharmacodynamic (PK/PD) breakpoints of intermittent and prolonged infusion regimens of antipseudomonal β-lactams in critically ill and augmented renal clearance patients.

β-Lactam Dosing Regimen (Infusion Time)	CrCl (mL/min)	PK/PD Breakpoint (mg/L)*
Piperacillin/tazobactam		
4 g q8h (0.5 h) without tazobactam	50†	8[36]
	150†	< 0.25[36]
4 g q6h (0.5 h) without tazobactam	50†	16[36]
	150†	1[36]
4.5 g q6h (0.5 h)	Median, 73 (range, 47–251)‡	8[33]
	120§	1[27]
3.375 g q8h (4 h)	120§	8[27]
4 g q8h (4 h) without tazobactam	50†	16[36]
	150†	8[36]
4.5 g q6h (3 h)	Median, 79 (range, 53–278)‡	16[33]
4 g q6h (4 h) without tazobactam	50†	32[36]
	150†	8[36]
4.5 g q6h (4 h)	Median, 132 (IQR, 99,188)‖	8 (PTA 86% at 16)[32]
Cefepime		
1 g q12 h (0.5 h)	50–120¶	1[34]
1 g q8h (0.5 h)	50–120¶	2[34]
2 g q12 h (0.5 h)	50–120¶	2[34]
2 g q8h (0.5 h)	50–120¶	4[34]
2 g q8h (3 h)	50–120¶	8[34]
	130†	4 (PTA 89% at 8)[37]
2 g q6h (3 h)	130†	8 (PTA 89% at 16)[37]
	150†	8[37]
Meropenem		
0.5 g q8h (0.5 h)	50**	4[36]
	71**	2 (PTA 86% a 4)[42]
	100**	2[42]
	150**	<0.5[41]
0.5 g q6h (0.5 h)	50–120††	1 (PTA >85% at 2)[38]
1 g q8h (0.5 h)	Median, 39.0 (range, 3–231.4)‡‡	4 (PTA near 90% at 8)[39]
	>30‖ + CVVH, 50–120††	2[38,40]
	50**	8[41]
	71**	4 (PTA 86% at 8)[42]
	100**	4[42]
	>100‡‡	2 (PTA 85% at 4)[39]
	150**	<0.5[41]
2 g q8h (0.5 h)	50–120††	4[38,40]
	50**	16[41]
	71**	8 (PTA 87% at 16)[42]
	100**	8[42]
	150**	0.5[41]

Table II. (*Continued*)

β-Lactam Dosing Regimen (Infusion Time)	CrCl (mL/min)	PK/PD Breakpoint (mg/L)*
0.5 g q8h (3 h)	50,** 71,** 100**	4[41]
	150**	2[41]
1 g q8h (3 h)	>30†† + CVVH	4[28]
	50,** Median, 39.0 (range, 3–231.4),‡‡ 71,** 100**	8[39,41,42]
	>100‡‡	4–8[39]
	150**	4[41]
2 g q8h (3 h)	>30†† + CVVH, 50–120,†† 150**	8[38,40,41]
	50,** 71,** 100**	16[41,42]
Doripenem		
0.5 g q8h (1 h)	100,§150§	2[35]
1 g q8h (1 h)	100,§150§	4[35]
2 g q8h (1 h)	100,§150§	8[35]
0.5 g q8h (4 h)	100§	4[35]
	150§	2[35]
1 g q8h (4 h)	100§	8[35]
	135,§ 150§	4[35,43]
2 g q8h (4 h)	100§	16[35]
	150§	8[35]

CrCl = creatinine clearance; CVVH = continuous venovenous hemofiltration; PTA = probability of target attainment.
* PK/PD breakpoint, the minimum inhibitory concentration to which the probability of target attainment is ≥ 90%.
† Measured CrCl.
‡ Calculation not specified.
§ eCrCl with Cockcroft-Gault equation.
‖ eGFR with Modification of Diet in Renal Disease Study (MDRD) equation.
¶ eCrCl with modified Cockcroft-Gault equation (weight not used).
** eCrCl with Cockcroft-Gault equation (actual body weight).
†† eCrCl with Cockcroft-Gault equation (ideal body weight unless >20% above actual, then adjusted body weight).
‡‡ eCrCl with Cockcroft-Gault equation (actual body weight unless body mass index >25 kg/m^3, then ideal body weight).

CrCl ≥120–130 mL/min]) has been reported in 30%–65% of intensive care unit (ICU) patients and can result in lack of goal PTA achievement with intermittent infusion of β-lactams.[14] PK/PD breakpoints derived from Monte Carlo simulations for various PI and intermittent infusion regimens in the critically ill and ARC are summarized in Table II. Due to the incidence of ARC in critically ill patients, studies evaluating ARC in non-ICU patients were included. Studies have shown that many β-lactam intermittent infusion regimens fail to achieve goal PTA in critically ill patients at current CLSI susceptibility breakpoints.[27,32–36] PI β-lactams is one potential strategy to enhance PTA in the critically ill.

Penicillins

Four studies evaluated piperacillin (with or without tazobactam) PI in critically ill patients. Alobaid et al[36] performed a population PK analysis and Monte Carlo simulation in 13 critically ill, nonobese (body mass index [BMI], 20 kg/m^2) patients and assessed various 4 g intermittent infusion and PI (4-hour) piperacillin dosing regimens based on renal function (measured CrCl of 30, 50, and 150 mL/min). PI regimens were typically associated with enhanced PTA in patients with a CrCl of 50 mL/min with a more dramatic increase at a CrCl of 150 mL/min. Patel et al[27] simulated PTAs from 105 hospitalized patients at various CrCls. At an estimated CrCl (eCrCl) of

120 mL/min, patients achieved ≥90% PTA up to an MIC of 1 mg/L and 8 mg/L dosing regimens of 4.5 g intermittent infusion q6h and 3.375 g PI q8h, respectively. Similarly, Akers et al[32] used PK data from 13 surgical or trauma ICU patients and found that the same maintenance dosing regimen achieved similar PTA in patients with a median eCrCl (eCrCl of 132 mL/min/1.73 m^2; interquartile range, 99–188 mL/min/1.73 m^2). Finally, Bao et al[33] evaluated PTA in 50 critically ill patients with hospital-acquired pneumonia and found that only the 4.5 g q6h 3-hour PI regimen achieved goal PTA up to an MIC of 16 mg/L.

Cephalosporins

Two studies evaluated cefepime in critically ill patients. Nicasio et al[34] used PK data from 32 critically ill patients with ventilator-associated pneumonia and a PD target of 50% *f*T > MIC. For patients with an eCrCl of 50–120 mL/min, goal PTA was achieved for various intermittent infusion regimens up to MICs of 1–4 mg/L, and 8 mg/L was attained for a 2 g q8h (3-hour infusion) regimen. Zasowski et al[37] evaluated the PK data from 36 hospitalized patients to assess different cefepime dosing strategies in patients with varying degrees of renal function, using measured clearance. With an eCrCl of 130 mL/min, 2 g q8h (3-hour infusion) achieved 89% PTA at an MIC of 8 mg/L. Administering treatment as PI q6h enhanced PTA at higher MICs and CrCls. Natesan and colleagues simulated various ceftolozane/tazobactam dosing regimens and infusion times with population PK data and various CrCls. Using a target of 40% *f*T > MIC, 4-hour infusions of 1.5 and 3 g every 8 h were associated with improved PTA vs. intermittent infusion for resistant isolates in patients with a mean CrCl of 150 (121–180) mL/min.[22]

Carbapenems

Five studies evaluated PI meropenem in critically ill patients. Crandon et al[38] modeled PK data from 21 ICU patients and found that 0.5 g q6h intermittent infusion only achieved goal PTA up to an MIC of 1 mg/L; however, this dosing regimen still achieved >85% PTA at an MIC of 2 mg/L. Intermittent infusions of 1 and 2 g q8h achieved >90% PTA up to MICs of 2 and 4 mg/L, respectively. Usman et al[39] modeled PK data from 178 elderly ICU patients (median age, 75 years; range, 65–94 years) with a median weight of 75 kg (range, 37–147 kg). The median eCrCl was 39 mL/min calculated with the Cockcroft-Gault equation using total body weight unless the BMI was >25 kg/m^2, in which case ideal body weight was used. Overall, 1 g q8h intermittent infusion achieved nearly 90% PTA up to an MIC of 8 mg/L; however, with an eCrCl >100 mL/min, goal PTA was only observed up to an MIC of 2 mg/L. Extending the infusion time to 3 h enhanced achievement of optimal PTA up to an MIC of 4–8 mg/L with an eCrCl >100 mL/min. Frippiat et al[40] simulated data from 55 critically ill patients with nosocomial pneumonia and an eCrCl >30 mL/min in addition to patients with continuous venovenous hemofiltration. Of note, 56.4% of patients had an eCrCl >60 mL/min, and 30.9% of patients were found to have a measured CrCl via 24-hour urine collection of >120 mL/min. An intermittent infusion of 1 g q8h was found to have high probability of achieving the PK/PD target for susceptible isolates, and 2 g q8h PI achieved goal PTA up to an MIC of 8 mg/L. Alobaid et al[41] used data from 6 critically ill patients to evaluate meropenem using measured CrCl. Modeled patients with an eCrCl of 50 mL/min achieved the goal PTA up to an MIC of 4 mg/L with an intermittent infusion regimen of 0.5 g q8h. However, when the eCrCl increased to 150 mL/min, a 3-hour PI regimen was required to achieve similar PTAs up to an MIC of 2 mg/L, and higher dosed PI regimens were necessary to achieve goal PTA for nonsusceptible isolates. Finally, Isla et al[42] performed simulations based on PK from 2 previous studies in critically ill patients. Intermittent infusion regimens of 0.5 g q8h achieved the goal PTA at an MIC of 2 mg/L at an eCrCl of 71 mL/min and 100 mL/min. PI regimens using 0.5, 1, and 2 g q8h achieved >90% PTA at MICs of 4–16 mg/L depending on dose and CrCl.

Two studies evaluated doripenem in the critically ill patient population. Roberts[35] evaluated various dosing regimens at an eCrCl of 100 and 150 mL/min and utilized PK data of a Phase III trial that included 31 critically ill patients with nosocomial pneumonia with a mean (SD) eCrCl 137 (71) mL/min. An intermittent infusion regimen of 0.5 g q8h achieved goal PTA up to an MIC of 2 mg/L at an eCrCL of 100 and 150 mL/min in patients with a simulated total body weight of 80 kg; however, PI with doses of 0.5–2 g

q8h was necessary to achieve similar PTAs at an MIC of 4−16 mg/L depending on eCrCl.[35] Finally, Rahbar et al[43] analyzed PK of 30 trauma patients with sepsis who had a mean eCrCl of 135 mL/min. A dosing regimen of 1 g q8h PI achieved goal PTA up to an MIC of 4 mg/L.

Summary

PK alterations in the critically ill, such as altered clearance and V_d, may result in lack of achievement of goal PTA with intermittent infusion β-lactams. Although most intermittent infusion dosing regimens of meropenem and doripenem are sufficient to treat *P. aeruginosa* infections due to susceptible organisms in critically ill patients, PI of piperacillin/tazobactam (eg, 4.5 g q8h, 4-hour infusion) and cefepime (2 g every 6−8 h, 3- to 4-hour infusion) should be considered to optimize PTA with an MIC at the respective CLSI susceptibility breakpoints. However, PI piperacillin/tazobactam regimens do not consistently achieve goal PTA at an MIC of 16 mg/L in the setting of ARC. Likewise, data are lacking regarding PTA for PIs with a CrCl >150 mL/min; therefore, optimal dosing in this setting is unclear, and PI may be suboptimal. PK/PD breakpoints within the CLSI nonsusceptible interpretation category were achieved for PI dosing regimens of 1−2 g q8h of meropenem and doripenem, depending on CrCl and MIC; however, this outcome was unlikely with PI piperacillin/tazobactam or cefepime. Ceftolozane/tazobactam 1.5 and 3 g every 8 h (4-hour infusion) may enhance PTA for resistant *P. aeruginosa* isolates in patients with CrCl > 120 mL/min.

Obesity

Literature regarding optimal β-lactam dosing regimens in obese (BMI >30 kg/m^2) and morbidly obese (BMI >40 kg/m^2) patients is limited. Challenges to antibiotic dosing in obesity are associated with altered PK variables such as V_d and drug clearance. V_d can be affected due to both increased adipose tissue and lean body mass; however, the percentage of lean body mass typically decreases as the percentage of total body weight increases. Glomerular filtration rate is often increased initially in obese patients; however, decreases occur over time in the elderly, patients with nephropathy, or patients with cardiovascular disease.[45] Multiple studies have investigated various PI regimens (with or without intermittent infusion) in obese patients via Monte Carlo simulation (Table III). BMI, total body weight, CrCl, and patient population (ie, ICU status) were included due to the variability of PTA identified with these factors.

Penicillins

Four PK/PD studies have been conducted to evaluate the PTA of piperacillin (with or without tazobactam) PI within obese and morbidly obese patients by using a PD target of 50% *f*T > MIC. Cheatham et al[21] performed a Monte Carlo simulation based on 14 hospitalized patients with a mean (SD) BMI of 52 (10.8) kg/m^2 who received piperacillin/tazobactam 4.5 g q8h or 6.75 g q8h administered as PI (4 h). PD exposures were modeled for various dosing regimens administered q8h with a 4-hour infusion (3.375 g, 4.5 g, 6.75 g, and 9 g). Investigators found that dosing regimens ≥4.5 g q8h achieved a PTA ≥90% at MICs ≤16 mg/L. At an MIC of 32 mg/L, a dosing regimen of 9 g q8h was required, and no regimen achieved goal PTA at an MIC of 64 mg/L. The authors concluded that higher dosing is needed in obese patients to achieve serum concentrations similar to nonobese patients and that these differences can likely be explained by higher V_d and faster drug clearance in obese patients (mean measured CrCl, 132 [61] mL/min). Chung et al[26] found comparable PTA results with a Monte Carlo simulation of PI piperacillin/tazobactam based on 16 obese patients with similar mean BMI (50 [11.5] kg/m^2) and measured CrCl (120 [66] mL/min).

Sturm et al[46] performed a PK analysis in 9 critically ill, morbidly obese surgical patients with lower mean measured CrCl (75 [37] mL/min) than the 2 previous studies. PTA was assessed for various intermittent infusion and PI regimens of 3.375 g and 4.5 g q6h and q8h. All modeled regimens achieved >90% PTA with an MIC of 16 mg/L; however, both intermittent infusion and PI (4 h) regimens of 4.5 g q6h and q8h achieved goal PTA at an MIC of 32 mg/L. Prolonging the infusion time had no impact on achievement of goal PTA. All patients exhibited increased steady-state V_d without increased CrCl, unlike that observed in previous studies. The authors concluded that the use of PI regimens seemed to confer no significant advantages in this subset of morbidly obese surgical patients with decreased renal function (mean eCrCl, 75 [37] mL/min), which contributed to a prolonged half-life (mean, 3.7 [1.2] hours) compared with the reported half-life

Table III. Pharmacokinetic/pharmacodynamic (PK/PD) breakpoints of intermittent and prolonged infusion regimens of antipseudomonal β-lactams in obese patients.

β-Lactam Dosing Regimen (infusion time)	BMI (kg/m^2)*	Total Body Weight (kg)*	CrCl (mL/min)*	Patient Population*	PK/PD Breakpoint (mg/L)†
Piperacillin/tazobactam					
3.375 g q8h (0.5 h)	57 (15.3)	164 (50)	75 (37)‡	Surgical ICU, APACHE II: median 22 (IQR 21,26)	16[46]
3.375 g q6h (0.5 h)	57 (15.3)	164 (50)	75 (37)‡	Surgical ICU, APACHE II: median 22 (IQR 21,26)	16[46]
4 g q8h (0.5 h) without tazobactam	30	90 (10)	50§	ICU, APACHE II: 21 (7)	8[36]
	30	90 (10)	150§	ICU, APACHE II: 21 (7)	0.25[36]
	40	143 (34)	50§	ICU, APACHE II: 21 (7)	16[36]
	40	143 (34)	150§	ICU, APACHE II: 21 (7)	0.5[36]
4.5 g q8h (0.5 h)	57 (15.3)	164 (50)	75 (37)‡	Surgical ICU, APACHE II: median 22 (IQR 21,26)	32[46]
4 g q6h (0.5 h) without tazobactam	30	90 (10)	50§	ICU, APACHE II: 21 (7)	16[36]
	30	90 (10)	150§	ICU, APACHE II: 21 (7)	2[36]
	40	143 (34)	50§	ICU, APACHE II: 21 (7)	16[36]
	40	143 (34)	150§	ICU, APACHE II: 21 (7)	4[36]
4.5 g q6h (0.5 h)	57 (15.3)	164 (50)	75 (37)‡	Surgical ICU, APACHE II: median 22 (IQR 21,26)	32[46]
4 g q8h (4 h) without tazobactam	30	90 (10)	50§	ICU, APACHE II: 21 (7)	16[36]
	30	90 (10)	150§	ICU, APACHE II: 21 (7)	8[36]
	40	143 (34)	50§	ICU, APACHE II: 21 (7)	16[36]
	40	143 (34)	150§	ICU, APACHE II: 21 (7)	8[36]
4.5 g q8h (4 h)	50 (11.5)	154 (34)	120 (66)§	43.8% ICU	16[26]
	52 (10.8)	161 (29)	132 (61)§	50% ICU	16[21]
	57 (15.3)	164 (50)	75 (37)‡	Surgical ICU, APACHE II: median 22 (IQR 21,26)	32[46]
3.375 g q8h (4 h)	50 (11.5)	154 (34)	120 (66)§	43.8% ICU	8[26]
	52 (10.8)	161 (29)	132 (61)§	50% ICU	8[21]
	57 (15.3)	164 (50)	75 (37)‡	Surgical ICU, APACHE II: median 22 (IQR 21,26)	16[46]
3.375 g q6h (4 h)	57 (15.3)	164 (50)	75 (37)‡	Surgical ICU, APACHE II: median 22 (IQR 21,26)	16[46]
4 g q6h (3 h) without tazobactam	30	90 (10)	50§	ICU, APACHE II: 21 (7)	32[36]

Table III. (*Continued*)

β-Lactam Dosing Regimen (infusion time)	BMI (kg/m^2)*	Total Body Weight (kg)*	CrCl (mL/min)*	Patient Population*	PK/PD Breakpoint (mg/L)†
	30	90 (10)	150§	ICU, APACHE II: 21 (7)	8[36]
	40	143 (34)	50§	ICU, APACHE II: 21 (7)	32[36]
	40	143 (34)	150§	ICU, APACHE II: 21 (7)	8[36]
4.5 g q6h (4 h)	57 (15.3)	164 (50)	75 (37)‡	Surgical ICU, APACHE II: median 22 (IQR 21,26)	32[46]
6.75 g q8h (4 h)	50 (11.5)	154 (34)	120 (66)§	43.8% ICU	16[26]
	52 (10.8)	161 (29)	132 (61)§	50% ICU	16[21]
9 g q8h (4 h)	52 (10.8)	161 (29)	132 (61)§	50% ICU	32[21]
Meropenem					
0.5 g q8h (0.5 h)	30	103 (6.8)	50‖	ICU, APACHE II: 15 (4.2)	4[41]
	30	103 (6.8)	150‖	ICU, APACHE II: 15 (4.2)	<0.5[41]
	34 (2.2)	96 (14)	57 (23)¶	78% ICU	2 (PTA near 90% at 4)[49]
	40	109 (23.3)	50‖	ICU, APACHE II: 20 (6.9)	4[41]
	40	109 (23.3)	150‖	ICU, APACHE II: 20 (6.9)	0.5[41]
	55 (8.6)	152 (31)	107 (44)‡	ICU	1[47]
	62 (14.7)	176 (58.3)	103 (33)‡	55% ICU	2[49]
	66 (17.5)	200 (67.9)	112 (27)‡	Non-ICU	4[48]
0.5 g q6h (0.5 h)	34 (2.2)	96 (14)	57 (23)¶	78% ICU	4[49]
	55 (8.6)	152 (31)	107 (44)‡	ICU	2[47]
	62 (14.7)	176 (58.3)	103 (33)‡	55% ICU	2 (PTA near 90% at 4)[49]
1 g q8h (0.5 h)	30	103 (6.8)	50‖	ICU, APACHE II: 15 (4.2)	8[41]
	30	103 (6.8)	150‖	ICU, APACHE II: 15 (4.2)	0.5[41]
	34 (2.2)	96 (14)	57 (23)¶	78% ICU	4 (PTA near 90% at 8)[49]
	40	109 (23.3)	50‖	ICU, APACHE II: 20 (6.9)	8[41]
	40	109 (23.3)	150‖	ICU, APACHE II: 20 (6.9)	1[41]
	55 (8.6)	152 (31)	107 (44)‡	ICU	2[47]
	62 (14.7)	176 (58.3)	103 (33)‡	55% ICU	4[49]
	66 (17.5)	200 (67.9)	112 (27)‡	Non-ICU	4 (PTA near 90% at 8)[48]
1 g q6h (0.5 h)	34 (2.2)	96 (14)	57 (23)¶	78% ICU	8[49]
	55 (8.6)	152 (31)	107 (44)‡	ICU	4[47]
	62 (14.7)	176 (58.3)	103 (33)‡	55% ICU	4 (PTA near 90% at 8)[49]
2 g q8h (0.5 h)	30	103 (6.8)	50‖	ICU, APACHE II: 15 (4.2)	16[41]
	30	103 (6.8)	150‖	ICU, APACHE II: 15 (4.2)	1[41]
	34 (2.2)	96 (14)	57 (23)¶	78% ICU	8 (PTA near 90% at 16)[49]

(*continued on next page*)

Table III. (*Continued*)

β-Lactam Dosing Regimen (infusion time)	BMI (kg/m^2)*	Total Body Weight (kg)*	CrCl (mL/min)*	Patient Population*	PK/PD Breakpoint (mg/L)†
	40	109 (23.3)	50‖	ICU, APACHE II: 20 (6.9)	16[41]
	40	109 (23.3)	150‖	ICU, APACHE II: 20 (6.9)	2[41]
	55 (8.6)	152 (31)	107 (44)‡	ICU	4[47]
	62 (14.7)	176 (58.3)	103 (33)‡	55% ICU	8[49]
0.5 g q8h (3 h)	30	103 (6.8)	50‖	ICU, APACHE II: 15 (4.2)	4[41]
	30	103 (6.8)	150‖	ICU, APACHE II: 15 (4.2)	2[41]
	34 (2.2)	96 (31)	57 (23)¶	78% ICU	4[49]
	40	109 (23.3)	50‖	ICU, APACHE II: 20 (6.9)	4[41]
	40	109 (23.3)	150‖	ICU, APACHE II: 20 (6.9)	2[41]
	55 (8.6)	152.3 (31)	107 (44)‡	ICU	2[47]
	62 (14.7)	176 (58.3)	103 (33)‡	55% ICU	4[49]
	66 (17.5)	200 (67.9)	112 (27)‡	Non-ICU	4[48]
0.5 g every q6 (3 h)	34 (2.2)	96 (14)	57 (23)¶	78% ICU	8[49]
	55 (8.6)	152 (31)	107 (44)‡	ICU	4[47]
	62 (14.7)	176 (58.3)	103 (33)‡	55% ICU	4[49]
1 g q8h (3 h)	30	103 (6.8)	50‖	ICU, APACHE II: 15 (4.2)	8[41]
	30	103 (6.8)	150‖	ICU, APACHE II: 15 (4.2)	4[41]
	34 (2.2)	96 (14)	57 (23)¶	78% ICU	8[49]
	40	109 (23.3)	50‖	ICU, APACHE II: 20 (6.9)	8[41]
	40	109 (23.3)	150‖	ICU, APACHE II: 20 (6.9)	4[41]
	55 (8.6)	152.3 (31)	107 (44)‡	ICU	4[47]
	62 (14.7)	176 (58.3)	103 (33)‡	55% ICU	4[49]
	66 (17.5)	200 (67.9)	112 (27)‡	Non-ICU	8[48]
1 g q6h (3 h)	34 (2.2)	96 (14)	57 (23)¶	78% ICU	16[49]
	55 (8.6)	152.3 (31)	107 (44)‡	ICU	8[47]
	62 (14.7)	176 (58.3)	103 (33)‡	55% ICU	8[49]
2 g q8h (3 h)	30	103 (6.8)	50‖	ICU, APACHE II: 15 (4.2)	16[41]
	30	103 (6.8)	150‖	ICU, APACHE II: 15 (4.2)	8[41]
	34 (2.2)	96 (14)	57 (23)¶	78% ICU	16[49]
	40	109 (23.3)	50‖	ICU, APACHE II: 20 (6.9)	16[41]
	40	109 (23.3)	150‖	ICU, APACHE II: 20 (6.9)	8[41]
	55 (8.6)	152 (31)	107 (44)‡	ICU	8[47]
	62 (14.7)	176 (58.3)	103 (33)‡	55% ICU	16[49]
Doripenem					
0.5 g q8h (1 h)	62 (22.3)	177 (49)	126 (42)‡	50% ICU	2[50]
	65 (27.5)	180 (61.1)	114 (40)‡	Non-ICU	2[48]
1 g q8h (1 h)	62 (22.3)	177 (49)	126 (42)‡	50% ICU	4[50]
	65 (27.5)	180 (61.1)	114 (40)‡	Non-ICU	4[48]
0.5 g q8h (4 h)	62 (22.3)	177 (49)	126 (42)‡	50% ICU	4[50]
	65 (27.5)	180 (61.1)	114 (40)‡	Non-ICU	4[48]

Table III. (*Continued*)

β-Lactam Dosing Regimen (infusion time)	BMI (kg/m^2)*	Total Body Weight (kg)*	CrCl (mL/min)*	Patient Population*	PK/PD Breakpoint (mg/L)†
1 g q8h (4 h)	62 (22.3)	177 (49)	126 (42)‡	50% ICU	8[50]
	65 (27.5)	180 (61.1)	114 (40)‡	Non-ICU	8[48]

APACHE II = Acute Physiology and Chronic Health Evaluation II; BMI = body mass index; CrCl = creatinine clearance; ICU = intensive care unit; IQR = interquartile range; PTA = probability of target attainment.
* Data represent mean (SD) unless otherwise indicated.
† PK/PD breakpoint, the MIC to which the probability of target attainment is ≥ 90%.
‡ eCrCl with Cockcroft-Gault equation (lean body weight).
§ Measured CrCl.
|| eCrCl with Cockcroft-Gault equation (toal body weight).
¶ eCrCl with Cockcroft-Gault equatin (ideal body weight).

observed in obese patients with normal or increased CrCl (mean, 2 [1] hours).[21,26]

Alobaid et al[36] performed population PK analysis and Monte Carlo simulation in 37 critically ill patients, including 13 nonobese, 12 obese, and 12 morbidly obese subjects. PTA was assessed for various 4 g intermittent infusion and PI piperacillin dosing regimens based on renal function (measured CrCl of 30, 50, and 150 mL/min) and BMI classes (20, 30, and 40 kg/m^2). Variable PTA was observed between BMIs of 30 and 40 kg/m^2 with intermittent infusion regimens; however, PI regimens provided more consistent PTAs regardless of BMI, particularly with a measured CrCl of 150 mL/min. Achievement of goal PTA occurred with a measured CrCl of 50 mL/min with both obesity classified BMIs (30 and 40 kg/m^2) at an MIC of 16 and 32 mg/L with PI regimens of 4 g q8h (4-hour infusion) and q6h (3-hour infusion), respectively. However, neither regimen obtained goal PTA at an MIC >8 mg/L with a CrCl of 150 m/min. Investigators concluded that BMI did not largely affect PTA in critically ill patients; however, increased CrCl was strongly associated with lower achievement of goal PTA.

Carbapenems

Four studies have performed Monte Carlo simulations for meropenem PI regimens in obese and morbidly obese ICU and/or non-ICU patients. Cheatham et al[47] used PK data from 9 morbidly obese ICU patients (mean BMI, 55 [8.6] kg/m^2) to assess PTA of meropenem intermittent infusion and PI dosing regimens (0.5 and 1 g q6h and q8h, 2 g q8h). Intermittent infusion regimens of 0.5 g q6h and 1 g q8h achieved adequate PTA up to an MIC of 2 mg/L. PI dosing regimens of 0.5 g q6h and 1 g q8h achieved goal PTA up to an MIC of 4 mg/L; 1 g q6h and 2 g q8h achieved PTA up to an MIC of 8 mg/L. The authors concluded that although V_d was increased in morbidly obese patients, standard dosing regimens achieved adequate PD exposures for susceptible pathogens, but higher doses and/or PIs are necessary to achieve the goal PTA with MICs of 4−8 mg/L.

Kays et al[48] modeled 0.5 and 1 g dosing regimens for meropenem as intermittent infusion and PI in 10 obese hospitalized patients (mean BMI, 66 ± 17.5 kg/m^2). Goal PTA was achieved up to an MIC of 4 mg/L for both intermittent infusion and PI regimens of 0.5 g q8h and 1 g q8h intermittent infusion. Prolonging the infusion time to 3 h for the 1 g q8h dosing regimen provided optimized PTA at an MIC of 8 mg/L.

Chung et al[49] also evaluated meropenem in hospitalized nonobese (n = 11), obese (n = 9), and morbidly obese (n = 20) patients. Intermittent infusion and PI dosing regimens included 0.5 g every 6, 8, and 12 h, 1 g every 6 and 8 h, and 2 g every 8 h. All regimens achieved adequate PD exposure for bacterial pathogens with an MIC ≤2 mg/L, regardless of infusion type or obesity classification. However, morbidly obese patients required either a PI regimen or 2 g q8h intermittent infusion for adequate exposure for an MIC of 8−16 mg/L. The authors concluded that meropenem PK variables are comparable among nonobese, obese,

and morbidly obese patients and that dosage adjustments based solely on weight are not indicated.

Alobaid et al[41] performed Monte Carlo simulation of data from 19 critically ill patients to determine the PTA for various meropenem intermittent infusion and PI regimens (0.5 g, 1 g, and 2 g q8h) at a variety of CrCls (30, 50, and 150 mL/min) and 3 BMI classes (nonobese, obese, and morbidly obese). The study investigators found that an increased CrCl was associated with lower PTA, whereas different BMIs did not greatly affect PK/PD target attainment. With a CrCl of 50 mL/min, intermittent infusions of 0.5 and 1 g q8h achieved goal PTA up to an MIC of 4 and 8 mg/L, respectively. A CrCl of 150 mL/min was associated with a lower achievement of goal PTA for all intermittent infusion dosing regimens. When PI was administered, PTA increased for all dosing regimens, but only the 2 g q8h regimen administered via PI was able to achieve the target PTA in all patient categories of obesity and CrCl up to an MIC of 8 mg/L. The authors suggest that higher doses or PI of meropenem should be applied for known or suspected pathogens with a higher MIC (eg, >4 mg/L) and/or for critically ill patients with high CrCl (eg, 150 mL/min) regardless of obesity category.

Two studies performed Monte Carlo simulations to assess PTAs of various doripenem PI regimens in obese patients. Kays et al[48] (10 patients) as well as Chung et al[50] (20 patients) found that intermittent infusions of 0.5 g and 1 g q8h achieved goal PTA up to an MIC of 2 and 4 mg/L, respectively. In addition, PI regimens of 0.5 and 1 g q8h achieved PK/PD breakpoints of 4 and 8 mg/L, respectively. The authors concluded that currently approved dosing regimens provide adequate PD attainment in obese patients; however, PI may be needed for higher MICs.

Summary

PK alterations that may occur in obesity, such as increased V_d and clearance, should be taken into consideration when selecting β-lactam regimens. PK/PD analysis of PI regimens for antipseudomonal β-lactams in obesity has been limited to piperacillin (with or without tazobactam), meropenem, and doripenem. In obese patients with normal renal function, intermittent infusion regimens seem to provide adequate PTA up to current susceptibility breakpoints for meropenem and doripenem; however, a piperacillin/tazobactam regimen of at least 4.5 g q8h (4-hour infusion) is required for consistent achievement of goal PTA up to the current CLSI *P. aeruginosa* susceptibility breakpoint. PI β-lactams, particularly at higher doses, should be considered for obese patients with increased CrCl (eg, ≥150 mL/min) or infected with nonsusceptible isolates depending on the MIC, obesity classification, and the patient's CrCl.

Febrile Neutropenia

Hematologic malignancies and febrile neutropenia may yield altered PK variables, including increased clearance and V_d.[51] Increased cardiac output can increase organ perfusion and renal elimination. V_d can be increased due to hypoalbuminemia, fluid resuscitation, or systemic inflammation resulting in additional fluid in the interstitial space. PI dosing strategies have been assessed via Monte Carlo simulation for piperacillin, cefepime, and doripenem in patients with febrile neutropenia.

Penicillins

Sime et al[51] evaluated piperacillin in 37 patients with hematologic malignancies and febrile neutropenia with a median eCrCl of 94 mL/min/1.73 m^3 (interquartile range, 71−132 mL/min/1.73 m^3). Investigators conducted a Monte Carlo simulation using trough concentrations drawn at presumed steady state (ie, 72 h). Neither intermittent infusion regimen of 4.5 g q6h or q8h was able to achieve >90% PTA up to the current CLSI susceptibility breakpoint (16 mg/L) in patients with an eCrCl ≥60 mL/min/1.73 m^3. A PI regimen of 4 g q8h (4-hour infusion) was able to achieve goal PTA up to an MIC of 16 mg/L only in patients with an eCrCl ≤80 mL/min/1.73 m^3. However, 4 g q6h (3-hour infusion) was required for an MIC of 16 mg/L in patients with a CrCl up to 100 mL/min/1.73 m^3. Of note, only a 16 g continuous infusion regimen (following a 4 g loading dose) was able to achieve goal PTA up to an MIC of 16 mg/L at CrCl up to 140 mL/min/1.73 m^3. The authors concluded that alternative dosing (eg, prolonged or continuous infusion) should be considered for patients with febrile neutropenia and a high MIC pathogen and/or ARC.

Cephalosporins

Rhodes et al[52] evaluated population PK variables of cefepime in 9 patients with febrile neutropenia and a mean eCrCl of 149 (35.5) mL/min. Intermittent

infusion regimens of 1 g q6h and 2 g q8h achieved ≥90% PTA at an MIC of 4 mg/L; 2 g q6h intermittent infusion, 2 g q8h PI (4 h), or 4 g continuous infusion was required to achieve the PK/PD target at the CLSI susceptibility breakpoint of 8 mg/L. Of note, a 6 or 8 g continuous infusion regimen were the only simulated regimens to achieve goal PTA up to an MIC of 16 mg/L. Rhodes et al stated that for MIC values near the current susceptibility breakpoint, more aggressive dosing may be considered in patients with preserved renal function after weighing the benefits versus risks of cefepime toxicity.

Carbapenems

Stein et al[53] evaluated PTA of doripenem using 12 patients with febrile neutropenia. The mean eCrCl was 144 mL/min (range, 73−178 mL/min). Intermittent infusion (1 h) of 0.5 g and 1 g q8h achieved ≥90% PTA at an MIC of 1 mg/L and 2 mg/L, respectively. The same dosing regimens of 0.5 g and 1 g administered as PI (4 h) achieved goal PTA at an MIC of 2 and 4 mg/L. Higher doses (eg, 1 g) and/or prolonged infusion regimens may therefore be required for treating febrile neutropenic patients with infections due to *P. aeruginosa*, depending on the MIC.

Summary

Increased clearance and/or V_d may occur in patients with hematologic malignancies and febrile neutropenia. Intermittent infusion of β-lactams may provide inadequate PTA at current CLSI breakpoints for *P. aeruginosa*. Based on CLSI *P. aeruginosa* susceptibility interpretations and available literature, the following dosing regimens may be considered: piperacillin 4 g q8h infused over 4 h (CrCl ≤80 mL/min), 4 g q6h infused over 3 h (CrCl 80−100 mL/min), and 16 g continuous infusion (CrCl >100−140 mL/min); cefepime 2 g q8h (4-hour infusion) or 4 g continuous infusion; and doripenem 1 g q8h (1-hour infusion) or 0.5 g q8h (4-hour infusion). Dosing regimens of cefepime 6 g continuous infusion and doripenem 1 g q8h (4-hour infusion) may be considered for isolates with intermediate susceptibility.

Implementation of Prolonged Infusion

Consideration of PI dosage regimens should depend on several factors, including the half-life of the β-lactam, incidence of multidrug-resistant pathogens, local MIC distributions, patient-specific microbiological data (eg, organism and MICs), renal function (eg, CrCl), and implementation challenges.

Extended infusion of antipseudomonal β-lactams may be considered when intermittent infusion regimens fail to achieve the PK/PD breakpoint, the antibiotic has a short half-life, and alternative therapeutic options are limited. In addition, this may be a cost-effective administration method versus standard intermittent infusion depending on the dosing regimen used (eg, piperacillin-tazobactam 4.5 g q8h PI vs q6h intermittent infusion). Except for piperacillin/tazobactam and cefepime in some patient populations, many intermittent infusion regimens of antipseudomonal β-lactams can achieve the PK/PD target up to the CLSI *P. aeruginosa* susceptibility interpretation; however, extended infusions may be considered for some nonsusceptible isolates or in the setting of febrile neutropenia and ARC when *P. aeruginosa* is the targeted pathogen. However, it should be noted that patients with ARC may not always achieve target PTA. In addition, improved clinical outcomes with extended infusions have primarily been reported with severe infections (eg, nosocomial pneumonia, sepsis) and/or critically ill patients; their necessity for the treatment of less severe infections (eg, urinary, skin and soft tissue) is therefore unknown.

Challenges associated with extended infusions include prolonged intravenous line access, which can limit patient mobility and increase the potential for medication errors (eg, incorrect duration of infusion, omission of loading doses in critically ill, drug incompatibilities). Before universal implementation of extended infusions, availability of intravenous pumps should be verified. Lastly, pharmaceutical stability must be assessed because some β-lactams have a relatively short stability at room temperature (ie, carbapenems).

PI is often the preferred extended infusion method in the inpatient setting because implementation challenges (eg, incompatibilities, limited mobility) are more frequent with continuous infusion. Continuous

infusions also require 24-hour stability and a dedicated central line. Advantages of continuous infusion over PI include a lower potential risk of accidental intermittent infusion, as many continuous infusions require large-volume infusion bags. In addition, continuous infusions may be preferred in the outpatient setting when there is limited access to home health for multiple daily infusions.

There are three ways by which facilities can implement PI dosing regimens: universal hospital-wide, unit or population specific, and patient isolate specific. Universal hospital-wide PI implementation should be considered for piperacillin/tazobactam based on the PK/PD breakpoint as well as the CLSI susceptibility interpretation for *P. aeruginosa* and Enterobacteriaceae (16 mg/L). Before universal implementation of PI for other β-lactams, local incidence of *P. aeruginosa* as well as MIC_{90} distributions should be assessed and compared with the PK/PD breakpoint achieved by various regimens (Table I) to select an optimal empiric dosing regimen. If MIC_{90}s are not readily available, the facility's antibiogram should be assessed for susceptibility of antipseudomonal β-lactams versus *P. aeruginosa*. Empiric PI should be considered for facilities with a high incidence of *P. aeruginosa* and <85%−90% susceptibility for antipseudomonal β-lactams. Likewise, PI should be considered in specific hospital units (eg, ICU, hematology-oncology) or patient populations (eg, pneumonia, ARC) with frequent isolation of *P. aeruginosa* when the hospital antibiogram or MIC_{90} indicates an MIC above the PK/PD breakpoint. These implementation strategies may not be needed or cost-effective in facilities with a low incidence of *P. aeruginosa* and/or high susceptibility of antipseudomonal β-lactams. Instead, facilities may opt to use a patient isolate−specific approach and initiate PIs upon identification of an isolate with an MIC above the PK/PD breakpoint.

When PIs are used, a loading dose should be considered in critically ill patients or patients with a high severity infection to ensure optimal initial concentrations.[6,44] Vardakas et al[6] performed a subgroup analysis of 13 extended infusion studies within a meta-analysis in critically ill patients and found significantly lower mortality with administration of an initial loading dose (risk ratio, 0.63; 95% CI, 0.47−0.84). Literature regarding optimal timing of maintenance dose initiation after the initial load is lacking; however, it seems reasonable to begin the first PI dose halfway through the standard dosing interval. In addition, assessing renal function to appropriately adjust maintenance PI regimens is imperative to prevent supratherapeutic concentrations and risk of adverse drug events.

CONCLUSIONS

Intermittent infusion of β-lactams is adequate for most susceptible *P. aeruginosa* infections based on current CLSI breakpoints; however, PI should be considered for piperacillin/tazobactam to achieve optimal PTA. Patients with infections due to elevated MICs or populations with altered PK variables (eg, critically ill, febrile neutropenia), particularly with higher CrCls, may also benefit from PI.

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REFERENCES

1. Nguyen L, Garcia J, Gruenberg K, MacDougall C. Multidrug-resistant *pseudomonas* infections: hard to treat, but hope on the horizon? *Curr Infect Dis Rep*. 2018;20:23.
2. Centers for Disease Control and Prevention. *Core Elements of Hospital Antibiotic Stewardship Programs*. Atlanta, GA: US Department of Health and Human Services, CDC; 2014.
3. Lodise TP, Lomaestro BM, Drusano GL, Pharmacists SoID. Application of antimicrobial pharmacodynamic concepts into clinical practice: focus on beta-lactam antibiotics: insights from the Society of Infectious Diseases Pharmacists. *Pharmacotherapy*. 2006;26:1320−1332.
4. Teo J, Liew Y, Lee W, Kwa AL. Prolonged infusion versus intermittent boluses of β-lactam antibiotics for treatment of acute infections: a meta-analysis. *Int J Antimicrob Agents*. 2014;43:403−411.

5. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. *Crit Care Med*. 2017;45:486–552.
6. Vardakas KZ, Voulgaris GL, Maliaros A, Samonis G, Falagas ME. Prolonged versus short-term intravenous infusion of antipseudomonal beta-lactams for patients with sepsis: a systematic review and meta-analysis of randomised trials. *Lancet Infect Dis*. 2018;18:108–120.
7. Falagas ME, Tansarli GS, Ikawa K, Vardakas KZ. Clinical outcomes with extended or continuous versus short-term intravenous infusion of carbapenems and piperacillin/tazobactam: a systematic review and meta-analysis. *Clin Infect Dis*. 2013;56:272–282.
8. Yu Z, Pang X, Wu X, Shan C, Jiang S. Clinical outcomes of prolonged infusion (extended infusion or continuous infusion) versus intermittent bolus of meropenem in severe infection: a meta-analysis. *PLoS One*. 2018;13, e0201667.
9. Tamma PD, Putcha N, Suh YD, Van Arendonk KJ, Rinke ML. Does prolonged β-lactam infusions improve clinical outcomes compared to intermittent infusions? A meta-analysis and systematic review of randomized, controlled trials. *BMC Infect Dis*. 2011;11:181.
10. Drusano GL, Lodise TP. Saving lives with optimal antimicrobial chemotherapy. *Clin Infect Dis*. 2013;56:245–247.
11. Grupper M, Kuti JL, Nicolau DP. Continuous and prolonged intravenous β-lactam dosing: implications for the clinical laboratory. *Clin Microbiol Rev*. 2016;29:759–772.
12. Roberts JA, Kirkpatrick CM, Lipman J. Monte Carlo simulations: maximizing antibiotic pharmacokinetic data to optimize clinical practice for critically ill patients. *J Antimicrob Chemother*. 2011;66:227–231.
13. Maglio D, Kuti JL, Nicolau DP. Simulation of antibiotic pharmacodynamic exposure for the empiric treatment of nosocomial bloodstream infections: a report from the OPTAMA program. *Clin Ther*. 2005;27:1032–1042.
14. Hobbs AL, Shea KM, Roberts KM, Daley MJ. Implications of augmented renal clearance on drug dosing in critically ill patients: a focus on antibiotics. *Pharmacotherapy*. 2015;35:1063–1075.
15. Thabit AK, Grupper M, Nicolau DP, Kuti JL. Simplifying piperacillin/tazobactam dosing: pharmacodynamics of utilizing only 4.5 or 3.375 g doses for patients with normal and impaired renal function. *J Pharm Pract*. 2017;30:593–599.
16. Kim A, Sutherland CA, Kuti JL, Nicolau DP. Optimal dosing of piperacillin-tazobactam for the treatment of *Pseudomonas aeruginosa* infections: prolonged or continuous infusion? *Pharmacotherapy*. 2007;27:1490–1497.
17. Shea KM, Cheatham SC, Smith DW, Wack MF, Sowinski KM, Kays MB. Comparative pharmacodynamics of intermittent and prolonged infusions of piperacillin/tazobactam using Monte Carlo simulations and steady-state pharmacokinetic data from hospitalized patients. *Ann Pharmacother*. 2009;43:1747–1754.
18. Eagye KJ, Banevicius MA, Nicolau DP. *Pseudomonas aeruginosa* is not just in the intensive care unit any more: implications for empirical therapy. *Crit Care Med*. 2012;40:1329–1332.
19. Furtado GH, Cardinal L, Macedo RS, et al. Pharmacokinetic/pharmacodynamic target attainment of intravenous beta-lactam regimens against Gram-negative bacteria isolated in a Brazilian teaching hospital. *Rev Soc Bras Med Trop*. 2015;48:539–545.
20. Andersen MG, Thorsted A, Storgaard M, Kristoffersson AN, Friberg LE, Obrink-Hansen K. Population pharmacokinetics of piperacillin in sepsis patients: should alternative dosing strategies be considered? *Antimicrob Agents Chemother*. 2018;62.
21. Cheatham SC, Fleming MR, Healy DP, et al. Steady-state pharmacokinetics and pharmacodynamics of piperacillin and tazobactam administered by prolonged infusion in obese patients. *Int J Antimicrob Agents*. 2013;41:52–56.
22. Natesan S, Pai MP, Lodise TP. Determination of alternative ceftolozane/tazobactam dosing regimens for patients with infections due to *Pseudomonas aeruginosa* with MIC values between 4 and 32 mg/L. *J Antimicrob Chemother*. 2017;72:2813–2816.
23. Bhavnani SM, Hammel JP, Cirincione BB, Wikler MA, Ambrose PG. Use of pharmacokinetic-pharmacodynamic target attainment analyses to support phase 2 and 3 dosing strategies for doripenem. *Antimicrob Agents Chemother*. 2005;49:3944–3947.
24. Santos Filho L, Eagye KJ, Kuti JL, Nicolau DP. Addressing resistance evolution in *Pseudomonas aeruginosa* using pharmacodynamic modelling: application to meropenem dosage and combination therapy. *Clin Microbiol Infect*. 2007;13:579–585.
25. Li C, Kuti JL, Nightingale CH, Nicolau DP. Population pharmacokinetic analysis and dosing regimen optimization of meropenem in adult patients. *J Clin Pharmacol*. 2006;46:1171–1178.
26. Chung EK, Cheatham SC, Fleming MR, Healy DP, Shea KM, Kays MB. Population pharmacokinetics and

pharmacodynamics of piperacillin and tazobactam administered by prolonged infusion in obese and nonobese patients. *J Clin Pharmacol*. 2015;55(8):899—908.
27. Patel N, Scheetz MH, Drusano GL, Lodise TP. Identification of optimal renal dosage adjustments for traditional and extended-infusion piperacillin-tazobactam dosing regimens in hospitalized patients. *Antimicrob Agents Chemother*. 2010;54:460—465.
28. Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing: Twenty-Eighth Informational Supplement [document M100-S29]*. Wayne, PA: National Committee for Clinical Laboratory Standards; 2019.
29. Shea KM, Cheatham SC, Wack MF, Smith DW, Sowinski KM, Kays MB. Steady-state pharmacokinetics and pharmacodynamics of piperacillin/tazobactam administered by prolonged infusion in hospitalised patients. *Int J Antimicrob Agents*. 2009;34:429—433.
30. Cheatham SC, Shea KM, Healy DP, et al. Steady-state pharmacokinetics and pharmacodynamics of cefepime administered by prolonged infusion in hospitalised patients. *Int J Antimicrob Agents*. 2011;37:46—50.
31. Roberts JA, Lipman J. Antibacterial dosing in intensive care: pharmacokinetics, degree of disease and pharmacodynamics of sepsis. *Clin Pharmacokinet*. 2006;45:755—773.
32. Akers KS, Niece KL, Chung KK, Cannon JW, Cota JM, Murray CK. Modified augmented renal clearance score predicts rapid piperacillin and tazobactam clearance in critically ill surgery and trauma patients. *J Trauma Acute Care Surg*. 2014;77(3 Suppl 2):S163—S170.
33. Bao H, Lv Y, Wang D, Xue J, Yan Z. Clinical outcomes of extended versus intermittent administration of piperacillin/tazobactam for the treatment of hospital-acquired pneumonia: a randomized controlled trial. *Eur J Clin Microbiol Infect Dis*. 2017;36:459—466.
34. Nicasio AM, Ariano RE, Zelenitsky SA, et al. Population pharmacokinetics of high-dose, prolonged-infusion cefepime in adult critically ill patients with ventilator-associated pneumonia. *Antimicrob Agents Chemother*. 2009;53:1476—1481.
35. Roberts JA, Lipman J. Optimal doripenem dosing simulations in critically ill nosocomial pneumonia patients with obesity, augmented renal clearance, and decreased bacterial susceptibility. *Crit Care Med*. 2013;41:489—495.
36. Alobaid AS, Wallis SC, Jarrett P, et al. Population pharmacokinetics of piperacillin in nonobese, obese, and morbidly obese critically ill patients. *Antimicrob Agents Chemother*. 2017;61.
37. Zasowski E, Bland CM, Tam VH, Lodise TP. Identification of optimal renal dosage adjustments for high-dose extended-infusion cefepime dosing regimens in hospitalized patients. *J Antimicrob Chemother*. 2015;70:877—881.
38. Crandon JL, Ariano RE, Zelenitsky SA, Nicasio AM, Kuti JL, Nicolau DP. Optimization of meropenem dosage in the critically ill population based on renal function. *Intensive Care Med*. 2011;37:632—638.
39. Usman M, Frey OR, Hempel G. Population pharmacokinetics of meropenem in elderly patients: dosing simulations based on renal function. *Eur J Clin Pharmacol*. 2017;73:333—342.
40. Frippiat F, Musuamba FT, Seidel L, et al. Modelled target attainment after meropenem infusion in patients with severe nosocomial pneumonia: the PROMESSE study. *J Antimicrob Chemother*. 2015;70:207—216.
41. Alobaid AS, Wallis SC, Jarrett P, et al. Effect of obesity on the population pharmacokinetics of meropenem in critically ill patients. *Antimicrob Agents Chemother*. 2016;60:4577—4584.
42. Isla A, Canut A, Arribas J, Asin-Prieto E, Rodriguez-Gascon A. Meropenem dosing requirements against Enterobacteriaceae in critically ill patients: influence of renal function, geographical area and presence of extended-spectrum beta-lactamases. *Eur J Clin Microbiol Infect Dis*. 2016;35:511—519.
43. Rahbar AJ, Lodise TP, Abraham P, et al. Pharmacokinetic and pharmacodynamic evaluation of doripenem in critically ill trauma patients with sepsis. *Surg Infections*. 2016;17:675—682.
44. Rhodes NJ, MacVane SH, Kuti JL, Scheetz MH. Impact of loading doses on the time to adequate predicted beta-lactam concentrations in prolonged and continuous infusion dosing schemes. *Clin Infect Dis*. 2014;59:905—907.
45. Meng L, Mui E, Holubar MK, Deresinski SC. Comprehensive guidance for antibiotic dosing in obese adults. *Pharmacotherapy*. 2017;37:1415—1431.
46. Sturm AW, Allen N, Rafferty KD, et al. Pharmacokinetic analysis of piperacillin administered with tazobactam in critically ill, morbidly obese surgical patients. *Pharmacotherapy*. 2014;34:28—35.
47. Cheatham SC, Fleming MR, Healy DP, et al. Steady-state pharmacokinetics and pharmacodynamics of meropenem in morbidly obese patients hospitalized in an intensive care unit. *J Clin Pharmacol*. 2014;54:324—330.
48. Kays MB, Fleming MR, Cheatham SC, Chung EK, Juenke JM. Comparative pharmacokinetics and pharmacodynamics of doripenem and meropenem in obese patients. *Ann Pharmacother*. 2014;48:178—186.
49. Chung EK, Cheatham SC, Fleming MR, Healy DP, Kays MB. Population pharmacokinetics and pharmacodynamics of meropenem in nonobese, obese, and morbidly

obese patients. *J Clin Pharmacol*. 2017;57:356–368.
50. Chung EK, Fleming MR, Cheatham SC, Kays MB. Population pharmacokinetics and pharmacodynamics of doripenem in obese, hospitalized patients. *Ann Pharmacother*. 2017;51:209–218.
51. Sime FB, Hahn U, Warner MS, et al. Using population pharmacokinetic modeling and Monte Carlo simulations to determine whether standard doses of piperacillin in piperacillin-tazobactam regimens are adequate for the management of febrile neutropenia. *Antimicrob Agents Chemother*. 2017;61.
52. Rhodes NJ, Grove ME, Kiel PJ, et al. Population pharmacokinetics of cefepime in febrile neutropenia: implications for dose-dependent susceptibility and contemporary dosing regimens. *Int J Antimicrob Agents*. 2017;50:482–486.
53. Stein GE, Kulhanek G, Smith CL, et al. Pharmacokinetics and Monte Carlo simulations of doripenem in patients with febrile neutropenia. *Ann Pharmacother*. 2012;46:1281–1286.
54. Lipman J, Brett SJ, De waele JJ. A protocol for a phase 3 multicentre randomised controlled trial of continuous versus intermittent β-lactam antibiotic infusion in critically ill patients with sepsis: BLING III. *Crit Care Resusc*. 2019;21(1):63–68.
55. Xiao AJ, Miller BW, Huntington JA, Nicolau DP. Ceftolozane/tazobactam pharmacokinetic/pharmacodynamic-derived dose justification for phase 3 studies in patients with nosocomial pneumonia. *J Clin Pharmacol*. 2016;56:56–66.

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APPENDIX

Table 1. Clinical outcomes of prolonged vs. intermittent infusion antipseudomonal β-lactams

Study	Study Design	Infection Type and Population	Antimicrobial Regimen	Outcomes
Piperacillin/tazobactam				
Lodise, et al[1]	■ Retrospective cohort study ■ (n = 194)	■ Mixed infections (103/194 respiratory tract) ■ ICU patients (126/194) ■ *Pseudomonas aeruginosa*	3.375 g q8h PI (4-hour infusion; n = 102) vs. 3.375 g q4-6 h II (0.5-hour infusion; n = 92)	■ Mortality rate at 14 days was lower in the PI group than in the II group (8.8% vs. 15.2%; $P = 0.17$) ■ Median length of stay after culture sample collection was lower in the PI group than in the II group (18 vs. 22.5 days; $P = 0.09$) ■ When APACHE II score was ≥17, significantly lower 14-day mortality rate was identified in the PI vs. II groups (12.2% vs. 31.6%; $P = 0.04$) ■ Significantly shorter median duration of hospital stay in the PI vs. II groups (21 vs. 38 days; $P = 0.02$)
Patel, et al[2]	■ Multicenter, retrospective, quasi-experimental study ■ (n = 129)	■ Mixed infections ■ ICU and non-ICU patients ■ Gram-negative bacteria (MIC ranged from <8 to 16 mg/L)	3.375 g q8h PI (4-hour infusion; n = 70) vs. 3.375 −4.5 g q6-8 h II (0.5-hour infusion; n = 59)	■ No difference in 30-day mortality rates (5.7% vs. 8.5%; $P > 0.05$) and median hospital length of stay (8 days in both groups; $P > 0.05$) between PI vs. II ■ Clinical outcomes did not differ when stratified by urinary vs. non-urinary source of infection ($P > 0.05$) ■ Hospital length of stay did not differ when stratified according to MIC ($P > 0.05$)
Yost, et al[3]	■ Multicenter retrospective chart review ■ (n = 359)	■ Mixed infections ■ ICU and non-ICU patients ■ Gram-positive and Gram-negative bacteria	3.375 g q8h PI (4-hour infusion; n = 186) vs. II of β-lactams of similar spectrum, including CAZ, FEP, IPM, MEM, DOR, and TZP (n = 173)	■ No difference in antibiotic duration ($P = 0.06$), hospital length of stay ($P = 0.21$), and ICU length of stay ($P = 0.14$) between PI vs. II ■ Significant decrease of in-hospital mortality with PI vs. II (9.7% vs. 17.9%; $P = 0.02$) ■ Multivariate analysis found PI was associated with: o Prolonged survival by 2.77 days ($P < 0.01$) ■ Reduced risk of mortality (OR, 0.43; $P = 0.05$)

Table 1. (*Continued*)

Study	Study Design	Infection Type and Population	Antimicrobial Regimen	Outcomes
Lee, et al[4]	■ Multicenter retrospective chart review ■ (n = 148)	■ Pneumonia and/or sepsis ■ ICU patients ■ Gram-negative bacteria	3.375 g q8h PI (4-hour infusion; n = 68) vs. 2.25−4.5 g q6-8 h II (0.5-hour infusion; n = 80)	■ Significantly lower 30-day mortality (19% vs. 38%; $P = 0.01$) and shorter median duration of mechanical ventilation (3 vs. 7 days; $P = 0.001$) with PI vs. II ■ No difference in median ICU length of stay (5 vs. 5 days; $P = 0.4$)
Cutro, et al[5]	■ Retrospective, quasi-experimental study ■ (n = 843)	■ Mixed infections ■ ICU and non-ICU patients ■ Gram-negative bacteria, including non-susceptible *P. aeruginosa*	3.375−4.5 g q8h PI (4-hour infusion; n = 662) vs. 4.5 g q6h II (0.5-hour infusion; n = 181)	■ In the total cohort, there was no difference in mortality rates (10.9% vs. 13.8%; $P = 0.28$), median hospital length of stay (14.9 vs. 15 days; $P = 0.17$), and clinical failure rates (18.4% vs. 19.9%; $P = 0.76$) between PI vs. II ■ In the ICU subgroup (n = 493 vs. 138), there was no difference in mortality rates (14.2% vs. 17.4%; $P = 0.35$), median hospital length of stay (17.1 days in both groups; $P = 0.47$), and clinical failure rates (22.1% vs. 23.9%; $P = 0.62$) between PI vs. II ■ Significantly shorter mean duration of therapy with PI vs. II (6 vs. 7 days; $P < 0.001$) ■ Significantly lower mortality rates in the subgroup of patients with structural lung disease with PI vs. II (10.7% vs. 23.4%; $P = 0.03$) ■ Significantly lower clinical failure rates in the subgroup of patients with urinary tract infections with PI vs. II (6.3% vs. 26.7%; $P = 0.006$)
Brunetti, et al[6]	■ Retrospective, quasi-experimental study ■ (n = 2150)	■ Mixed infections ■ ICU and non-ICU patients	3.375 g q8-12 h PI (4-hour infusion; n = 632) vs. 3.375−4.5 g q6-8 h II	■ No difference in 14-day mortality rates (OR = 1.2; 95%CI, 0.85−1.57; $P = 0.37$) and mean hospital length of stay (12.5 vs. 11.8 days; $P = 0.1$) between PI vs. II

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Table 1. (*Continued*)

Study	Study Design	Infection Type and Population	Antimicrobial Regimen	Outcomes
		■ Gram-positive and Gram-negative bacteria	(0.5-hour infusion; n = 1518)	■ Significantly lower total cost per treatment course with PI vs. II ($565.9 vs. $648.3; $P < 0.001$)
Fan, et al[7]	■ Prospective, open-label study ■ (n = 367)	■ Mixed infections ■ ICU patients ■ Gram-positive and Gram-negative bacteria, including non-susceptible isolates	4.5 g q8-12 h PI (4-hour infusion; n = 182) vs. 4.5 g q6-8 h II (0.5-hour infusion; n = 185)	■ No difference in 14-day mortality rates (11.5% vs. 15.7%; $P = 0.29$), in-hospital mortality rates (28.6% vs. 31.9%; $P = 0.5$), mean duration of mechanical ventilation (5 days in both groups; $P = 0.79$), median length of ICU stay (3 vs. 4 days; $P = 0.3$), and median length of hospital stay (20 vs. 21 days; $P = 0.4$) between PI vs. II ■ Significantly shorter time to defervescence with PI vs. II (4 vs. 6 days; $P = 0.01$) ■ Significantly lower mortality with PI in the subgroup of patients with respiratory tract infections (8.9% vs. 18.7%; $P = 0.02$) and APACHE II score of $\geq$29.5 (12.9% vs. 40.5%; $P = 0.01$)
Chan, et al[8]	■ Retrospective, quasi-experimental study ■ (n = 553)	■ Mixed infections ■ ICU patients ■ Gram-positive and Gram-negative bacteria	4.5 g over 0.5-hour q4h × 2 then 3.375 g q8h PI (4-hour infusion; n = 429) vs. 3.375−4.5 g q6-8 h II (0.5-hour infusion; n = 124)	■ No significant difference in mortality (OR = 1.2; 95%CI, 0.65 to 2.1) and mean ICU length of stay (8 vs. 6.4 days; $P > 0.05$) between PI vs. II ■ Significantly lower hospital length of stay with PI vs. II (20.4 vs. 26.3 days; $P < 0.05$)
Lyu, et al[9]	■ Prospective RCT ■ (n = 120)	■ HAP ■ Cancer patients ■ Gram-negative bacteria	4.5 g q6h PI (3-hour infusion; n = 60) vs. II (0.5-hour infusion; n = 60)	■ Significantly lower mortality with PI vs. II (1.7% vs. 8.3%; $P = 0.02$), particularly in patients with severe infections (3.1% vs. 14.3%; $P = 0.03$) ■ Significantly higher clinical cure (88.3% vs. 86.7%; $P = 0.04$) and microbiological eradication (98.3% vs. 75%; $P < 0.001$) with PI vs. II

Table 1. (*Continued*)

Study	Study Design	Infection Type and Population	Antimicrobial Regimen	Outcomes
Cefepime				
Bauer, et al[10]	■ Retrospective, quasi-experimental study ■ (n = 304)	■ Bacteremia or pneumonia ■ ICU and non-ICU patients ■ *P.* aeruginosa (MIC = 1−32 mg/L)	2 g q8h PI (4-hour infusion; n = 33) vs. II (0.5-hour infusion; n = 54)	■ Significantly lower mortality (3% vs. 20%; $P = 0.03$) and shorter mean ICU length of stay (8 vs. 18.5 days; $P = 0.04$) with PI vs. II ■ Trend towards a lower mean hospital costs with PI vs. II ($28,048 vs. $51,231; $P = 0.1$)
Wrenn, et al[11]	■ Prospective, randomized, observational study ■ (n = 63)	■ Febrile neutropenia ■ Cancer patients ■ Gram-negative bacteria	2 g q8h PI (3-hour infusion; n = 30) vs. II (0.5-hour infusion; n = 33)	■ No significant difference in time to defervescence ($P > 0.05$), clinical success (77% vs. 88%; $P = 0.33$), in-hospital mortality (17% vs. 9%; $P = 0.46$), and mean hospital length of stay (27 vs. 25 days; $P = 0.59$) between PI vs. II
Carbapenems				
Itabashi, et al[12]	■ Prospective, observational ■ (n = 42)	■ Severe pneumonia ■ Gram-positive and Gram-negative bacteria	MEM 0.5 g q12 h PI (4-hour infusion; n = 18) vs. II (0.5-1-hour infusion; n = 24)	■ Significantly lower mortality with PI vs. II (5.6% vs. 37.5%; $P < 0.05$) ■ No difference in the total duration of therapy and decrease in C-reactive protein in either group ($P > 0.05$)
Wang, et al[13]	■ Prospective RCT ■ (n = 30)	■ HAP ■ ICU patients ■ Multidrug-resistant *Acinetobacter baumannii*	MEM 0.5 g q6h PI (3-hour infusion; n = 15) vs. 1 g q8h II (1-hour infusion; n = 15)	■ No difference in clinical success at 5-days (93.3% vs. 86.7%; $P > 0.05$) or 7-days (100% in both groups; $P > 0.05$) with PI vs II. ■ No difference in the total duration of therapy with PI vs. II (4.8 vs. 5.3 days; $P > 0.05$) ■ Significantly lower cost of therapy with PI vs. II ($684.1 ± 36.3 vs. $1,038.8 ± 51.1; $P < 0.01$)
Esterly, et al[14]	■ Retrospective, quasi-experimental study ■ (n = 71)	■ Bacteremia ■ ICU patients ■ Gram-negative bacteria, IPM MIC $\leq$ 2 mg/L (82%) and $\geq$4 mg/L (18%)	IPM 1 g q6h or MEM 1−2 g q8h PI (3-hour infusion; n = 42) vs. II (0.5-hour infusion; n = 29)	■ No difference in mortality with PI vs. II (28.6% vs. 24.1%; $P > 0.05$)

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Table 1. (*Continued*)

Study	Study Design	Infection Type and Population	Antimicrobial Regimen	Outcomes
Ahmed, et al[15]	■ Retrospective cohort study ■ (n = 148)	■ Mixed infections ■ ICU patients ■ Gram-negative bacteria	MEM 1 g q8h PI (3-hour infusion; n = 52) vs. 0.5 g q6h II (0.5-hour infusion; n = 96)	■ Significantly lower ICU mortality (19% vs. 37%; $P = 0.03$) and higher clinical cure (83% vs. 46%; $P = 0.0005$) with PI vs. II ■ No significant difference in microbiological eradication (20% vs. 25%; $P = 0.74$), median time to defervescence (3 vs. 2 days; $P = 0.64$), and median time to white blood cells normalization (4 vs. 5 day; $P = 0.34$) between PI vs. II
Goff, et al[16]	■ Retrospective cohort study ■ (n = 116)	■ Bacteremia or pneumonia ■ ICU and non-ICU patients ■ *P. aeruginosa*	DOR 0.5 g q8h PI (4-hour infusion; n = 51) vs. IPM 0.5 g q6h II (0.5-hour infusion; n = 65)	■ No difference in mortality (24% vs. 32%; $P = 0.41$), median ICU length of stay (21 vs. 22 days; $P = 0.65$), median hospital length of stay (18 vs. 28; $P = 0.21$), median duration of antibiotic therapy (7 vs. 6 days; $P = 0.91$), median ventilator days (13 vs. 17 days; $P = 0.43$), and median total hospital costs ($75,983 vs. 104,979; $P = 0.25$)
Hsaiky, et al[17]	■ Retrospective, quasi-experimental study ■ (n = 200)	■ Mixed infections ■ ICU and non-ICU patients ■ Gram-negative bacteria, including ESBL-producing	DOR 0.5 g q8h PI (4-hour infusion; n = 94) vs. II (1-hour infusion; n = 106)	■ No difference in clinical success rates (72.3% vs. 66%; $P = 0.34$), inpatient mortality rates (12.8% vs. 12.3%; $P = 0.92$), median hospital length of stay (11 vs. 12 days; $P = 0.4$), and infection recurrence rates within 90 days after end of initial therapy (18.1% vs. 16%; $P = 0.7$) ■ No difference in outcomes was seen in the subgroup of critically ill patients ($P > 0.05$) except in clinical success rates (72.7% vs. 42.6%; $P = 0.02$)
β-lactam Combinations				
Nicasio, et al[18]	■ Prospective, observational study with historical controls	■ VAP ■ ICU patients ■ Gram-positive and Gram-negative	FEP 2 g q8h or MEM 2 g q8h administered as PI (3-hour infusion; n = 94) or II (0.5-hour infusion;	■ Significantly lower infection-related mortality rate with PI vs. II (8.5% v 21.6%; $P = 0.03$)

Table 1. (*Continued*)

Study	Study Design	Infection Type and Population	Antimicrobial Regimen	Outcomes
	■ (n = 168)	bacteria (only 9 patients had MICs at or above susceptibility breakpoint for *P. aeruginosa*)	n = 74), both in combination with tobramycin and vancomycin	■ Significantly shorter mean infection-related length of stay with PI vs. II (11.7 vs. 26.1 days; $P < 0.001$) ■ No difference in total hospital length of stay (37.9 ± 20.1 vs. 43.3 ± 23.6 days; $P = 0.1$) ■ Significantly fewer superinfection rates with PI vs. II (16% vs. 35.1%; $P = 0.007$) ■ Some patients with non-susceptible *P. aeruginosa* were successfully treated with PI regimens (8/9; 88.9%)
Dow, et al[19]	■ Retrospective, quasi-experimental study ■ (n = 121)	■ Mixed infections ■ ICU patients ■ Gram-negative bacteria	TZP 3.375 g q8h PI (4-hour infusion) or MEM 0.5 g q6h PI (3-hour infusion) (n = 67) vs. TZP 3.375 g q6h or MEM 0.5 g q6h II (0.5-hour infusion; n = 54)	■ PI was associated with a significant reduction in ventilator days vs. II (−7.2 days; 95% CI, −12.4 to −2.4), ICU length of stay (−4.5 days; 95% CI, −8.3 to −1.4), hospital length of stay (−8.5 days; 95% CI, −18.7 to −1.2) ■ No difference between the two groups in rates of in-hospital mortality (12.4% vs. 20.7%; OR, 0.54; 95% CI, 0.2 to 1.7)
Arnold, et al[20]	■ Retrospective, quasi-experimental study ■ (n = 503)	■ Blood or respiratory infections ■ ICU patients ■ Gram-negative bacteria (Enterobacteriaceae and *P. aeruginosa*; 88% susceptibility)	FEP 2 g q8h, MEM 1 g q8h, or TZP 4.5 g q6h PI (3-hour infusion; n = 261) vs. II (0.5-hour infusion; n = 242)	■ No difference was found for clinical success rates among the clinically evaluable population (51% vs. 56.6%; $P = 0.2$),14-day mortality rates (18% vs. 13.2%; $P = 0.1$), 30-day mortality rates (25.7% vs. 23.6%; $P = 0.6$), median hospital length of stay (15.6 vs. 17 days; $P = 0.3$), or median ICU length of stay (10.8 vs. 9.3 days; $P = 0.1$) between PI vs. II
Turner, et al[21]	■ Retrospective, quasi-experimental study ■ (n = 108)	■ Blood or respiratory infections ■ ICU patients ■ Gram-negative bacteria	CAZ or FEP PI (loading dose over 0.5-hour followed by 3-hour infusion; n = 44) vs. II (0.5-hour infusion; n = 64)	■ No difference in in-hospital mortality rates (13.6% vs. 23.4%; $P = 0.2$), clinical cure (47.7% vs. 42.2%; $P = 0.6$), mean hospital length of stay (27.3 vs. 22.6 days; $P = 0.2$) with PI vs. II ■ Longer mean ICU stay with PI vs. II (10.1 vs. 5.7 days; $P = 0.003$)

(*continued on next page*)

Table 1. (*Continued*)

Study	Study Design	Infection Type and Population	Antimicrobial Regimen	Outcomes
Ram, et al[22]	■ Prospective, open-label RCT ■ (n = 105)	■ Febrile neutropenia ■ Cancer patients ■ Gram-positive and Gram-negative bacteria	TZP 4.5 g q8h or CAZ 2 g q8h PI (4-hour infusion; n = 47) vs. II (0.5-hour infusion; n = 58)	■ Significantly higher clinical cure rates with PI vs. II (74.4% vs. 55.1%; $P = 0.04$) ■ No significant difference in the duration of fever, mortality, or hospital length of stay

APACHE II, Acute Physiology and Chronic Health Evaluation II; CAZ, ceftazidime; DOR, doripenem; ESBL, extended-spectrum β-lactamase; FEP, cefepime; HAP, hospital-acquired pneumonia; ICU, intensive care unit; IPM, imipenem; MEM, meropenem; MIC, minimum inhibitory concentration; MSSA, methicillin-susceptible *Staphylococcus aureus*; OR, odds ratio; PI, prolonged infusion; RCT, randomized controlled trial; SOFA, Sequential Organ Failure Assessment; II, traditional infusion; TZP, piperacillin/tazobactam VAP, ventilator-associated pneumonia.

REFERENCES

1. Lodise TP, Lomaestro B, Drusano GL. Piperacillin-tazobactam for *Pseudomonas aeruginosa* infection: clinical implications of an extended-infusion dosing strategy. *Clin Infect Dis.* 2007;44(3):357-363.
2. Patel GW, Patel N, Lat A, et al. Outcomes of extended infusion piperacillin/tazobactam for documented Gram-negative infections. *Diagn Microbiol Infect Dis.* 2009;64(2):236-240.
3. Yost RJ, Cappelletty DM, group RS. The Retrospective Cohort of Extended-Infusion Piperacillin-Tazobactam (RECEIPT) study: a multicenter study. *Pharmacotherapy.* 2011;31(8):767-775.
4. Lee GC, Liou H, Yee R, Quan CF, Neldner K. Outcomes of extended-infusion piperacillin-tazobactam: a retrospective analysis of critically ill patients. *Clin Ther.* 2012;34(12):2297-2300.
5. Cutro SR, Holzman R, Dubrovskaya Y, et al. Extended-Infusion versus standard-infusion piperacillin-tazobactam for sepsis syndromes at a tertiary medical center. *Antimicrob Agents Chemother.* 2014;58(8):4470-4475.
6. Brunetti L, Poustchi S, Cunningham D, et al. Clinical and Economic Impact of Empirical Extended-Infusion Piperacillin-Tazobactam in a Community Medical Center. *Ann Pharmacother.* 2015;49(7):754-760.
7. Fan SY, Shum HP, Cheng WY, Chan YH, Leung SM, Yan WW. Clinical Outcomes of Extended Versus Intermittent Infusion of Piperacillin/Tazobactam in Critically Ill Patients: A Prospective Clinical Trial. *Pharmacotherapy.* 2017;37(1):109-119.
8. Chan JD, Dellit TH, Lynch JB. Hospital Length of Stay Among Patients Receiving Intermittent Versus Prolonged Piperacillin/Tazobactam Infusion in the Intensive Care Units. *J Intensive Care Med.* 2018;33(2):134-141.
9. Lyu Y, Yang Y, Li X, et al. Selection of piperacillin/tazobactam infusion mode guided by SOFA score in cancer patients with hospital-acquired pneumonia: a randomized controlled study. *Therapeutics and clinical risk management.* 2018;14:31-37.
10. Bauer KA, West JE, O'Brien JM, Goff DA. Extended-infusion cefepime reduces mortality in patients with *Pseudomonas aeruginosa* infectionsExtended-infusion cefepime reduces mortality in patients with *Pseudomonas aeruginosa* infections. *Antimicrob Agents Chemother.* 2013;57(7):2907-2912.
11. Wrenn RH, Cluck D, Kennedy L, Ohl C, Williamson JC. Extended infusion compared to standard infusion cefepime as empiric treatment of febrile neutropenia. *Journal of oncology pharmacy practice : official publication of the International Society of Oncology Pharmacy Practitioners.* 2018;24(3):170-175.
12. Itabashi S. [Clinical efficacy of prolonged (4 hour) drip infusion of meropenem against severe pneumonia]. *Jpn J Antibiot.* 2007;60(3):161-170.
13. Wang D. Experience with extended-infusion meropenem in the management of ventilator-associated pneumonia due to multidrug-resistant *Acinetobacter baumannii*. *Int J Antimicrob Agents.* 2009;33(3):290-291.
14. Esterly JS, Wagner J, McLaughlin MM, Postelnick MJ, Qi C, Scheetz MH. Evaluation of clinical outcomes in patients with bloodstream infections due to Gram-negative bacteria according to carbapenem MIC stratification. *Antimicrob Agents Chemother.* 2012;56(9):4885-4890.
15. Ahmed N, Jen SP, Altshuler D, Papadopoulos J, Pham VP, Dubrovskaya Y. Evaluation of Meropenem Extended Versus Intermittent Infusion Dosing Protocol in Critically Ill Patients. *J Intensive Care Med.* 2018:885066618784264.
16. Goff D, Bauer K, West J. A cohort study comparing outcomes of extended-infusion doripenem to standard infusion imipenem forpatients with invasive *Pseudomonas aeruginosa* infections, abstract O298. 22nd European Congress of Clinical Microbiology and Infectious Diseases; 2012; London, UK.
17. Hsaiky L, Murray KP, Kokoska L, Desai N, Cha R. Standard versus prolonged doripenem infusion for treatment of gram-negative infections. *Ann Pharmacother.* 2013;47(7-8):999-1006.
18. Nicasio AM, Eagye KJ, Nicolau DP, et al. Pharmacodynamic-based clinical pathway for empiric antibiotic choice in patients with ventilator-associated pneumonia. *J Crit Care.* 2010;25(1):69-77.
19. Dow R, Rose W, Fox B, Thorpe J, Fish J. Retrospective study of prolonged versus intermittent infusion piperacillin-tazobactam and meropenem in intensive care unit patients at an academic medical center. *Infect Dis Clin Pract.* 2011;19:413-417.
20. Arnold HM, Hollands JM, Skrupky LP, et al. Prolonged infusion antibiotics for suspected gram-negative infections in the ICU: a before-after study. *Ann Pharmacother.* 2013;47(2):170-180.
21. Turner RB, Slain D, Petros K, Keller LA, Sarwari AR. Clinical outcomes following hospital-wide implementation of prolonged-infusion cefepime and ceftazidime. *Int J Antimicrob Agents.* 2015;46(1):129-130.
22. Ram R, Halavy Y, Amit O, et al. Extended vs Bolus Infusion of Broad-Spectrum beta-Lactams for Febrile Neutropenia: An Unblinded, Randomized Trial. *Clin Infect Dis.* 2018;67(8):1153-1160.