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Major Article

Pharmacokinetic/pharmacodynamic target attainment of intravenous β-lactam regimens against Gram-negative bacteria isolated in a Brazilian teaching hospital

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ABSTRACT

Introduction: Monte Carlo simulations have been used for selecting optimal antibiotic regimens for treatment of bacterial infections. The aim of this study was to assess the pharmacokinetic and pharmacodynamic target attainment of intravenous β-lactam regimens commonly used to treat bloodstream infections (BSIs) caused by Gram-negative rod-shaped organisms in a Brazilian teaching hospital. **Methods**: In total, 5,000 patients were included in the Monte Carlo simulations of distinct antimicrobial regimens to estimate the likelihood of achieving free drug concentrations above the minimum inhibitory concentration (MIC; *f*T > MIC) for the requisite periods to clear distinct target organisms. Microbiological data were obtained from blood culture isolates harvested in our hospital from 2008 to 2010. **Results:** In total, 614 bacterial isolates, including *Escherichia coli*, *Enterobacter* spp., *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*, were analyzed. Piperacillin/tazobactam failed to achieve a cumulative fraction of response (CFR) > 90% for any of the isolates. While standard dosing (short infusion) of β-lactams achieved target attainment for BSIs caused by *E. coli* and *Enterobacter* spp., pharmacodynamic target attainment against *K. pneumoniae* isolates was only achieved with ceftazidime and meropenem (prolonged infusion). Lastly, only prolonged infusion of high-dose meropenem approached an ideal CFR against *P. aeruginosa*; however, no antimicrobial regimen achieved an ideal CFR against *A. baumannii.* **Conclusions:** These data reinforce the use of prolonged infusions of high-dose β-lactam antimicrobials as a reasonable strategy for the treatment of BSIs caused by multidrug resistant Gram-negative bacteria in Brazil.

Keywords: Monte Carlo simulation. Pharmacodynamics. Gram-negative bacteria. Bloodstream infections.

INTRODUCTION

Owing to the continued emergence of antimicrobial-resistant bacterial strains, achieving therapeutic success with the antimicrobials that are currently available has become a major challenge. This is particularly true for infections caused by Gram-negative bacterial species, for which few agents are effective or are in an advanced stage of development[1,2].

Gram-negative bacteria are highly effective in acquiring and expressing genes that encode resistance to antimicrobials, making it difficult to treat the infections that they cause[3]. Moreover, these resistant organisms are often responsible for nosocomial infections, including pneumonia and urinary tract and bloodstream infections (BSIs), leading to increased morbidity and mortality, along with longer hospitalizations[1,2,3]. Indeed, data from the United States (US) National Healthcare Safety Network show that Gram-negative bacteria are responsible for more than 30% of hospital-acquired infections, and are the predominant causes of ventilator-associated pneumonia (47%) and urinary tract infections (45%) in the US. Similar data were reported in several other countries[4].

Notably, the prevalence of infections due to Gram-negative bacilli is higher in Latin American than in North American medical centers. Additionally, in recent years, decreased antimicrobial susceptibility among Gram-negative species has been observed in Latin American countries, particularly among *Pseudomonas aeruginosa* and *Acinetobacter baumannii* strains isolated in Brazil[5].

Given the scarcity of new antibiotics, pharmacokinetic and pharmacodynamic (PK/PD) concepts have been utilized to optimize the *in vivo* exposure of these problematic Gram-negative bacteria to antimicrobial compounds. For example, the administration of different infusions of β-lactam antibiotics comprises a viable alternative for eliminating these organisms. Indeed, infusion is the optimal way to maintain antibiotic serum levels above the minimum inhibitor concentration (MIC) for the target organism, and thereby

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enhance the efficacy of treatments[6,7]. The drawbacks to this type of system, however, include the reduced stability of the drug and the need for an intravenous line to maintain the treatment[6]. Despite these drawbacks, extended infusion has been shown to comprise a valid alternative for obtaining meaningful results[8,9]. In this context, Monte Carlo simulation (MCS) has been used as a tool for aiding in the selection of optimal antibiotic therapies. Through MCS, it is possible to determine dosing regimens that best match the desired therapeutic targets against bacteria of interest[10,11].

The aim of this study was to assess the PK/PD target attainment of intravenous β-lactam regimens commonly used to treat BSIs caused by Gram-negative rod-shaped organisms.

METHODS

Antimicrobial regimens

The following intravenous antimicrobial regimens were evaluated in this simulation: 0.5h [1.0g every 6h (q6h), and 2.0g q8h and q12h] and 3h (1.0g q6h and q8h, and 2.0g q8h) infusions of cefepime; 0.5h (1.0 and 2.0g q8h) and 3h (1.0 and 2.0g q8h) infusions of ceftazidime; 0.5h (0.5g q6h and q8h, and 1.0g q8h) and 3h (0.5g q6h and q8h, and 1.0g q8h) infusions of imipenem/cilastatin; 0.5h (1.0g q8h and 2.0g q8h) and 3h (0.5g q6h and q8h, and 1.0 and 2.0g q8h) infusions of meropenem; and 0.5h (4.5g q6h and q8h) and 3h (4.5g q6h), as well as 24h continuous infusion (9.0g, 13.5g, and 18.0g q24h), of piperacillin/tazobactam.

Pharmacokinetic model

Steady-state exposures were determined for each antibiotic regimen using serum pharmacokinetic parameters obtained from recently published population pharmacokinetic studies of infected and/or critically ill adult patients[1,12]. Briefly, the PK parameters included body clearance (CL), volume of distribution (Vd), and fraction of unbound (free) drug (f). The methodology used to simulate steady-state antibacterial exposures in a population of adult patients with normal renal function (i.e., ≥50mL/min) has been previously described[13].

Monte Carlo simulation

A 5,000-patient MCS (Crystal Ball 2000; Decisioneering, Inc., Denver, CO, USA) was conducted to estimate the % *f*T > MIC ratio for each antibiotic regimen/bacterial population combination, as well as the probability of a simulated patient achieving the pharmacodynamic target [referred to as the probability of target attainment (PTA)]. Probability of target attainment was calculated over a range of doubling MICs between 0.5 and 128mg/L. During each interaction, CL (in liters), Vd, *f*, and MIC values were substituted into the appropriate equations based on the probability distributions, thereby resulting in 5,000 different estimates of pharmacodynamic exposure for each antibiotic regimen tested against each bacterial species.

Values for % *f*T > MIC and AUC/MIC were plotted on frequency curves for further analysis. Pharmacodynamic targets were defined as *f*T > MIC for ≥40%, ≥50%, and ≥60% of the dosing interval for carbapenems, piperacillin/tazobactam, and cephalosporins, respectively[14,15].

PTAs were then used to calculate the cumulative fraction of response (CFR) for each antibiotic regimen against each bacterial population. CFRs were calculated as the summation of *PTAi*Fi*, with the subscript *i* indicating the MIC category, ranked from the lowest to the highest MIC value for a population of microorganisms, *PTAi* denoting the PTA of each MIC category for that drug regimen, and *F* denoting the fraction of the population of microorganisms at each MIC category. Regimens that achieved a CFR of at least 90% against a bacterial population were considered optimum.

Microbiological analyses

Microbiological data used in the pharmacodynamic model were obtained from the microbiology laboratory database of *Hospital São Paulo*, a 750-bed university-affiliated tertiary hospital belonging to the Federal University of São Paulo (São Paulo, Brazil).

The data aggregated in the present study were generated from bacterial isolates obtained from blood cultures harvested from hospitalized patients between 2008 and 2010. Identification and antimicrobial susceptibility testing of bacterial species were conducted either by conventional biochemical methodologies or by using the automated BD Phoenix system (Becton Dickinson, Franklin Lakes, NJ, USA). Antimicrobial susceptibility testing was interpreted according to the 2012 Clinical Laboratory Standards Institute (CLSI) guidelines.

RESULTS

The 614 bacterial isolates analyzed in this study included 194 *A. baumannii*, 192 *Klebsiella pneumoniae*, 89 *P. aeruginosa*, and 70 *Escherichia coli* strains, as well as 69 strains of *Enterobacter* spp. The MICs necessary to inhibit 50% and 90% (MIC_{50} and MIC_{90} susceptibility rates) of the growth of each isolate are listed in **Table 1** and **Table 2**. Of the antibiotics tested, piperacillin/tazobactam exhibited the lowest susceptibility rates against *E. coli*, *K. pneumoniae*, *A. baumannii*, and *P. aeruginosa*; however, this compound was also associated with the highest susceptibility rates against *Enterobacter* spp. Notably, none of the antimicrobials exhibited susceptibility rates against *P. aeruginosa* greater than 60%, while the susceptibility rates for each of the antibiotics tested against *A. baumannii* was greater than 27%.

The PTA for each dosing regimen of cefepime, ceftazidime, imipenem/cilastatin, meropenem, and piperacillin/tazobactam are depicted in **Figure 1A** and **Figure 1E**, respectively.

The CFRs for the various simulated antimicrobial dosing regimens are summarized in **Table 3**. Piperacillin/tazobactam failed to achieve a CFR > 90% for any of the isolates examined, regardless of the MIC and dosing regimens tested. Meanwhile, the highest CFRs for cefepime and piperacillin/tazobactam were obtained in *E. coli*. Indeed, nearly optimal results were obtained with the 2.0g q8h (3h infusion) and 4.5g q6h

TABLE 1 - Percent susceptibility and minimum inhibitory concentration distributions for various antimicrobials simulated against *Enterobacteriaceae* (*Escherichia coli*, *Enterobacter* spp., and *Klebsiella pneumoniae*) isolated in a Brazilian hospital between 2008 and 2010.

Species/antimicrobial	MIC (µg/mL)		Percentage	Percentage of isolates susceptible at MIC (µg/mL)								
	50%	90%	(%S)	0.5	1	2	4	8	16	32	64	128
Escherichia coli (n = 70)												
cefepime	≤1	≥32	82.9	0.0	78.6	0	2.9	1.4	1.4	15.7	0.0	0.0
ceftazidime	≤0.5	≥4	98.5	73.5	5.9	2.9	16.2	0.0	0.0	1.5	0.0	0.0
imipenem/cilastatin	≤1	≥1	94.4	0.0	94.4	1.4	1.4	1.4	1.4	0.0	0.0	0.0
meropenem	≤1	≥1	98.4	0.0	98.4	0.0	0.0	0.0	1.6	0.0	0.0	0.0
piperacillin/tazobactam	≤2	≥128	82.1	0.0	0.0	58.2	16.4	6.0	1.5	0.0	1.5	16.4
Enterobacter spp. (n = 69)												
cefepime	≤32	≥32	44.2	0.0	42.3	0.0	1.9	0.0	3.9	51.9	0.0	0.0
ceftazidime	≤4	≥16	89.7	44.1	2.9	1.5	41.2	0.0	2.9	7.4	0.0	0.0
imipenem/cilastatin	≤1	≥1	90.0	0.0	90.0	2.9	4.3	1.4	1.4	0.0	0.0	0.0
meropenem	≤1	≥1	98.0	0.0	98.0	0.0	2.0	0.0	0.0	0.0	0.0	0.0
piperacillin/tazobactam	≤1	1	100.0	0.0	90.0	2.9	4.3	1.4	1.4	0.0	0.0	0.0
Klebsiella pneumoniae (n = 192)												
cefepime	≤32	≥32	44.8	0.0	34.9	1.0	4.7	4.2	4.2	51.0	0.0	0.0
ceftazidime	≤4	≥32	84.3	15.2	4.0	3.5	61.6	1.0	3.5	8.6	2.5	0.0
imipenem/cilastatin	≤1	≥16	63.0	0.0	63.0	2.0	1.5	11.0	22.5	0.0	0.0	0.0
meropenem	≤1	≥16	61.8	0.0	61.8	1.6	2.7	7.1	26.8	0.0	0.0	0.0
piperacillin/tazobactam	≤128	>128	18.5	0.0	0.0	4.2	10.6	3.2	0.5	2.6	2.1	76.1

%S: percent susceptibility; **MIC:** minimum inhibitory concentration.

TABLE 2 - Percent susceptibility and minimum inhibitory concentration distributions for various antimicrobials simulated against nonfermenting Gram-negative bacilli (*Acinetobacter baumannii* and *Pseudomonas aeruginosa*) isolated in a Brazilian hospital between 2008 and 2010.

Species/antimicrobial	MIC (µg/mL)		Percentage	Percentage of isolates susceptible at MIC (µg/mL)								
	50%	90%	(%S)	0.5	1	2	4	8	16	32	64	128
Acinetobacter baumannii (n = 194)												
cefepime	≤32	≥32	17.5	0.0	4.6	4.1	3.1	5.7	6.2	76.3	0.0	0.0
ceftazidime	≤32	≤64	26.5	0.0	0.0	1.6	21.2	3.7	1.6	58.2	13.8	0.0
imipenem/cilastatin	≤16	≥16	16.5	0.0	15.5	1.0	0.5	0.5	82.5	0.0	0.0	0.0
meropenem	≤16	≥16	17.3	0.0	16.2	1.1	0.0	0.0	82.7	0.0	0.0	0.0
piperacillin/tazobactam	≤128	≥128	5.1	0.0	0.0	0.6	0.6	2.8	1.1	1.1	5.1	88.7
Pseudomonas aeruginosa (n = 89)												
cefepime	≤16	≥32	46.1	0.0	0.0	12.4	19.1	14.6	15.7	38.2	0.0	0.0
ceftazidime	≤8	≥32	56.0	0.0	6.1	26.8	14.6	8.5	9.8	26.8	7.3	0.0
imipenem/cilastatin	≤8	≥16	47.2	0.0	22.5	24.7	1.1	2.3	49.4	0.0	0.0	0.0
meropenem	≤4	≥16	49.4	0.0	44.9	4.5	6.7	6.7	37.1	0.0	0.0	0.0
piperacillin/tazobactam	≤32	≥128	42.2	0.0	0.0	0.0	8.5	28.9	4.8	10.8	6.0	41.0

%S: percent susceptibility; **MIC:** minimum inhibitory concentration.

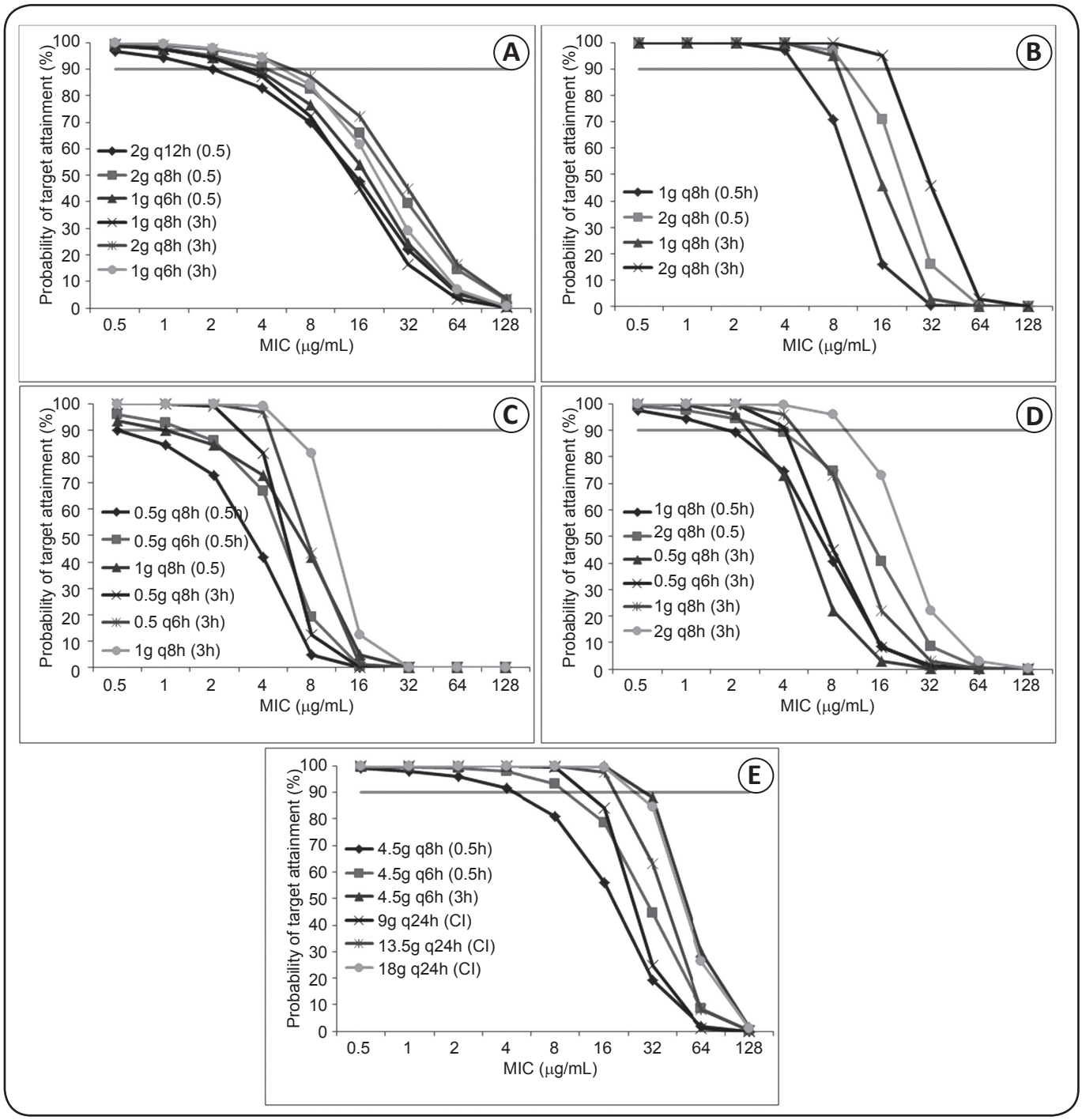

FIGURE 1 - PTA for antimicrobial regimens achieving 60% *f*T > MIC for cefepime (A) and ceftazidime (B), 40% *f*T > MIC for imipenem/cilastatin (C) and meropenem (D), and 50% *f*T > MIC for piperacillin/tazobactam (E) with various dosing regimens simulated for MICs up to128μg/mL. PTA: Probability of Target Attainment; **fT:** free time; **MIC:** Minimum Inhibitory Concentration.

TABLE 3 - Comparison of the CFR for antimicrobial regimens tested against *Escherichia coli*, *Enterobacter* spp., *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *and Pseudomonas aeruginosa*.

Antimicrobial regimens	Cumulative fraction of response (%)				
	E. coli	*Enterobacter* spp.	*K. pneumoniae*	*A. baumannii*	*P. aeruginosa*
Cefepime					
2.0g q12h (0.5h)	81.5	54.6	53.7	34.2	53.0
2.0g q8h (0.5h)	87.7	66.2	65.7	50.2	66.6
1.0g q6h (0.5h)	84.9	57.7	57.1	37.5	57.6
1.0g q8h (3h)	83.5	53.3	52.5	30.7	52.3
2.0g q8h (3h)	89.9	69.8	69.6	55.3	71.4
1.0g q6h (3h)	87.4	61.4	61.1	42.4	63.2
Ceftazidime					
1.0g q8h (0.5h)	98.1	89.0	83.9	25.3	54.9
2.0g q8h (0.5h)	98.7	92.9	89.2	36.9	67.1
1.0g q8h (3h)	98.6	91.2	87.1	28.6	60.9
2.0g q8h (3h)	99.2	95.9	92.7	55.0	77.9
Imipenem/cilastatin					
0.5g q8h (0.5h)	81.5	80.1	55.9	14.1	37.6
0.5g q6h (0.5h)	90.2	89.3	63.5	16.1	43.6
1.0g q8h (0.5h)	87.9	87.4	65.3	19.4	45.3
0.5g q8h (3h)	97.0	96.5	67.5	17.0	48.2
0.5g q6h (3h)	97.8	97.7	71.5	18.2	49.8
1.0g q8h (3h)	98.5	98.5	78.2	27.6	56.2
Meropenem					
1.0g q8h (0.5h)	93.1	94.1	67.0	23.4	57.4
2.0g q8h (0.5h)	96.7	97.4	80.5	50.5	74.2
0.5g q8h (3h)	98.1	99.1	67.4	19.6	56.6
0.5g q6h (3h)	98.6	99.8	71.3	24.2	61.7
1.0g q8h (3h)	98.8	99.9	77.1	35.4	68.9
2.0g q8h (3h)	99.6	99.9	92.5	77.6	89.7
Piperacillin/tazobactam					
4.5g q8h (0.5h)	76.7	46.2	17.2	4.3	36.0
4.5g q6h (0.5h)	80.8	53.3	19.5	5.7	44.4
4.5g q6h (3h)	82.7	62.6	22.5	8.8	54.0
9.0g q24h (CI)	81.8	51.5	19.1	5.2	44.0
13.5g q24h (CI)	82.2	57.1	20.4	6.2	49.4
18.0g q24h (CI)	82.6	61.7	22.1	8.2	53.3

CFR: cumulative fraction of response; ***E.:*** *Escherichia;* ***K.:*** *Klebsiella;* ***A.:*** *Acinetobacter;* ***P.:*** *Pseudomonas;* **CI:** continuous infusion.

(3h infusion) treatments, respectively. Ideal CFRs were achieved for *Enterobacteriaceae* with ceftazidime, imipenem/cilastatin, and meropenem, and ceftazidime achieved better CFRs against *Enterobacteriaceae* and nonfermenters than did cefepime. Additionally, prolonged infusion of high-dose meropenem achieved the highest CFRs for *E. coli, Enterobacter* spp., and *K. pneumoniae*, and approached an ideal CFR for *P. aeruginosa* (89.7%). Conversely, no antimicrobial regimen achieved an ideal CFR against *A. baumannii.* Overall, of the carbapenems, meropenem yielded better results than imipenem for all isolates tested.

DISCUSSION

Nosocomial infections caused by Gram-negative bacteria are notoriously difficult to treat owing to their limited antimicrobial susceptibility and the frequent emergence of resistant mutants during therapy[16]. In the hospital setting, β-lactam antibiotics are commonly used to treat these infections and are the most commonly prescribed antimicrobial class for treatment of Gram-negative bacterial infections[17].

Studies have shown that the PK/PD parameter that best predicts the efficacy of β-lactam antibiotics is the length of time for which the free drug remains above the MIC for the infecting microorganism ($fT > MIC$) between dosing intervals. Thus, adjusting the dosage and infusion time can influence the effectiveness of these antimicrobials[18] [19].

Indeed, in this study, we observed that higher doses and prolonged infusions resulted in greater CFRs for all of the β-lactams tested. Specifically, prolonged infusion of high-dose meropenem achieved the target CFR for *E. coli, Enterobacter spp*, and *K. pneumoniae* (>90%). Furthermore, a 3-h infusion of 2g meropenem approached the target CFR for *P. aeruginosa* (89.7%). Likewise, regimens comprising prolonged infusion of high-dose ceftazidime also reached the CFR for *E. coli, Enterobacter spp*, and *K. pneumoniae*, but not for *P. aeruginosa* or *A. baumannii*. Lastly, regardless of the dosage used, prolonged infusion of imipenem-cilastatin achieved the pharmacodynamic target for *E. coli* and *Enterobacteriaceae* only, while no cefepime or piperacillin-tazobactam regimen achieved the CFR for any of the organisms tested. Similar results have been reported in previous studies[1] [11] [15].

Koomanachai et al.[1] simulated optimized standard dosing of antimicrobials used in US hospitals for treatment of *E. coli*, *K. pneumoniae*, *A. baumannii*, and *P. aeruginosa* infections by using MIC data from a surveillance program[1]. These authors demonstrated that prolonged infusion of high-dose β-lactams was associated with increased exposure and enhanced pharmacodynamic results against *Enterobacteriaceae* and Gram-negative nonfermenters. While the CFR results obtained by this group were superior to those observed in the present study, these findings were likely because the percentage of β-lactam susceptibility was significantly lower in the current study. Furthermore, in an MCS using standard and optimized doses of β-lactam agents against Gram-negative bacteria isolated in 2009 in Canada, Keel et al. found that ideal CFRs were obtained against species from the *Enterobacteriaceae* family (*Enterobacter cloacae*, *E. coli*, and *K. pneumoniae*) by using standard dosing. Conversely, standard dosing yielded suboptimal CFRs against *P. aeruginosa* and *Acinetobacter* spp., suggesting that treatment of these organisms requires high-dose antimicrobial therapies[11]. In our study, only prolonged infusion (2g q8h for 3h each) of high-dose meropenem achieved the ideal PK/PD target for treating *P. aeruginosa*. The significant impact of increased dosing and prolonged infusions on the effectiveness of carbapenems against *P. aeruginosa* has been reported in previous studies[1] [11] [20].

It is noteworthy that *P. aeruginosa* is an important cause of BSI in humans, and is associated with high mortality rates, ranging from 18-61%[21]. Therefore, we emphasize the importance of empirical use of aggressive β-lactam doses for patients with risk factors for infection by *P. aeruginosa* or other multidrug-resistant bacteria.

None of the antimicrobial drug regimens tested yielded an ideal CFR against *A. baumannii*, which is consistent with the observed mechanisms of resistance of this organism, whereby the presence of several β-lactamases typically results in increases in the MIC values of each antimicrobial beyond what is clinically attainable with safe dosing regimens. As demonstrated in **Table 1**, the MIC_{50} values of each of the β-lactams tested for *A. baumannii* were several dilutions higher than those for other microorganisms. Indeed, the therapeutic options for multidrug-resistant *A. baumannii* are currently limited, and infections by these organisms typically result in poor clinical outcomes. Therefore, drug combination therapy has been suggested for treatment of such infections[20]. In a recent study, Housman et al. conducted an *in vitro* pharmacodynamics human-simulated exposures of ampicillin/sulbactam, doripenem, and tigecycline alone and combination against multidrug-resistant *A. baumannii*[22]. Their results demonstrate that therapeutic regimens comprised of combinations of aggressive doses of antimicrobials provide enhanced activity against *A. baumannii*. Specifically, the authors concluded that when polymyxins are not an option, aggressive doses of ampicillin/sulbactam combined with doripenem or tigecycline may be suitable for treating infections caused by sulbactam-susceptible *A. baumannii*.

Notably, in this study, antimicrobial therapies achieved lower CFRs than those achieved with the same drug regimens in North America for the majority of the strains examined[1] [11]. It is also noteworthy that the percentage of antimicrobial susceptibility directly influences the ability of the agent to reach the target (CRF > 90%), and resistance rates in our study were high. Our results are consistent with those reported in previous surveillance studies comparing antimicrobial resistance rates in developing countries (ex. Brazil vs. the US), including the resistance rates of *P. aeruginosa* to imipenem (47.2% vs. 23.0%, respectively), of *K. pneumoniae* to ceftazidime (76.3% vs. 27.1%, respectively), and of *E. coli* to ceftazidime (66.7% vs. 8.1%, respectively)[23].

Interestingly, ceftazidime reached greater CFRs than cefepime against *Enterobacteriaceae* in our study. These findings were likely due to the reduced usage of ceftazidime in our hospital in recent years. This factor might also explain the increased rates of susceptibility to ceftazidime among Gram-negative rod-shaped organisms observed in our facility. However, another possible explanation is that there is a higher prevalence of cefotaximase (CTX-M)-producing *Enterobacteriaceae* strains in Brazil than in other countries[24].

The present study aimed at providing assessment data that might influence pharmacodynamic clinical guidelines for the selection of appropriate empirical antibiotic therapies for bacteremia. To the best of our knowledge, only two other studies have attempted to utilize PK/PD analyses to determine optimal dosing regimens for treatment of nosocomial infections caused by Gram-negative bacteria in Brazil[25] [26]. In addition to the use of such MCS data, however, it is still important to consider the individual MIC values for the infecting bacteria to enable the selection of an adequate treatment.

There are several limitations to this study. First, while previous studies have shown differences in the susceptibility rates of organisms isolated from ICU and non-ICU infections, we were unable to separate the infections based on the location of origin in these hospitals. Second, it was not possible to

determine the MICs for each isolate by the broth microdilution method. Instead, we employed an automated MIC approach, which might have underestimated or overestimated the susceptibility rates. Third, while our results were obtained from a large university-affiliated hospital, they cannot be extrapolated to other hospitals.

In summary, the results of our study reinforce that prolonged infusion of high-dose β-lactam antimicrobials comprises the most effective treatment of BSIs caused by pathogens of the family *Enterobacteriaceae* and by nonfermenting rod-shaped bacteria.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

1. Koomanachai P, Bulik CC, Kuti JL, Nicolau DP. Pharmacodynamic modeling of intravenous antibiotics against Gram-Negative Bacteria Collected in the United States. Clin Therapeutics 2010; 32:766-779.
2. Gales AC, Azevedo HD, Cereda RF, Girardello R, Xavier DE. Antimicrobial activity of doripenem against Gram-negative pathogens: results from INVITA-A-DORI Brazilian Study. Braz J Infect Dis. 2011; 15:513-520.
3. Peleg AY, Hooper DC. Hospital-Acquired Infections Due to Gram-Negative Bacteria. N Engl J Med 2010; 362:1804-1813.
4. Evans HL, Lefrak SN, Lyman J, Smith RL, Chong TW, McElearney ST, et al. Cost of Gram-negative resistance. Crit Care Med 2007; 35:89-99.
5. Gales AC, Castanheira M, Jones RN, Sader HS. Antimicrobial resistance among Gram-negative bacilli isolated from Latin America: results from SENTRY Antimicrobial Surveillance Program (Latin America, 2008-2010). Diagn Microbiol Infect Dis 2012; 73:354-360.
6. Crandon JL, Nicolau DP. Pharmacodynamic approach to optimizing β-lactam therapy. Crit Care Clin 2011; 27:77-93.
7. DeRyke CA, Lee SY, Kuti JL, Nicolau DP. Optimising dosing strategies of antibacterials utilising pharmacodynamic principles – Impact on the development of resistance. Drugs 2006; 66:1-14.
8. Lodise TP, Lomaestro B, Drusano GL. Piperacillin-tazobactam for Pseudomonas aeruginosa infection: clinical implications of an extended-infusion dosing strategy. Clin Infect Dis 2007; 44:357-363.
9. Bauer KA, West JE, O'Brien JM, Goff DA. Extended infusion cefepime reduces mortality in patients with *Pseudomonas aeruginosa* infections. Antimicrob Agents Chemother 2013; 57:2907-2911.
10. Kim A, Kuti JL, Nicolau DP. Probability of pharmacodynamic target attainment with standard and prolonged-infusion antibiotic regimens for empiric therapy in adults with Hospital-Acquired Pneumonia. Clin Therapeutics 2009; 31:2765-2778.
11. Keel RA, Zhanel G, Zelenitsky S, Nicolau DP. Pharmacodynamic profiling of antimicrobials against Gram-negative respiratory isolates from Canadian hospitals. Can J Infect Dis Med 2011; 22:132-136.
12. Nicasio AM, Ariano RE, Zelenitsky SA, Kim A, Crandon JL, Kuti JL, et al. Population pharmacokinetics of high-dose, prolongedinfusion cefepime in adult critically ill patients with ventilator-associated pneumonia. Antimicrob Agents Chemother 2009; 53:1476-1481.
13. DeRyke CA, Kuti JL, Nicolau DP. Pharmacodynamic target attainment of six beta-lactams and two fluoroquinolones against *Pseudomonas aeruginosa, Acinetobacter baumannii, Escherichiacoli*, and *Klebsiella species* collected from United States intensive care units in 2004. Pharmacoth 2007; 27:333-342.
14. Drusano GL. Antimicrobial pharmacodynamics: Critical interactions of 'bug and drug'. Nat Rev Microbiol 2004; 2:289-300.
15. Roberts JA, Roberts MS, Robertson TA, Dalley AJ, Lipman J. Piperacillin penetration into tissue of critically ill patients with sepsis–Bolus versus continuous administration? Crit Care Med 2009; 37:926-933.
16. Peña C, Suarez C, Gozalo M, Murillas J, Almirante B, Pomar V, et al. Prospective Multicenter Study of the Impact of Carbapenem Resistance on Mortality in *Pseudomonas aeruginosa* Bloodstream Infections. Antimicrob Agents Chemother 2011; 56:1265-1272.
17. Suarez C, Gudiol F. Antibioticos betalactamicos. Enferm Infecc Microbiol Clin 2009; 27:116-129.
18. Nicolau DP. Pharmacodynamic optimization of b-lactams in the patient care setting. Crit Care 2008; 12 (supl IV):2.
19. Roberts JA, Paratz J, Paratz E, Krueger WA, Lipman J. Continuous infusion of beta-lactam antibiotics in severe infections: a review of its role. Int J Antimicrob Agents 2007; 30:11-18.
20. Villegas MV, Briceno DF, Ruiz SJ, Furtado GH, Nicolau DP. Assessing the pharmacodynamic profile of intravenous antibiotics against prevalent Gram-negative organisms collected in Colombia. Braz J Infect Dis 2011; 15:413-419.
21. Parkins MD, Gregson DB, Pitout JD, Laupland KB. Population-based study of the epidemiology and the risk factors for *Pseudomonas aeruginosa* bloodstream infection. Infection 2010; 38:25-32.
22. Housman ST, Hagihara M, Nicolau DP, Kuti JL. *In vitro* pharmacodynamics of human-simulated exposures of ampicillin/sulbactam, doripenem and tigecycline alone and in combinations against multidrug-resistant *Acinetobacter baumanii*. J Antimicrob Chemother 2013; 68:2296-2304.
23. Rosenthal VD, Bijie H, Maki DG, Mehta Y, Apisarnthanarak A, Medeiros E, et al. International Nosocomial Infection Control Consortium (INICC) report, data summar y of 36 countries, for 2004-2009. Am J Infect Control 2011; 40:396-407.
24. Chagas TP, Alves RM, Vallim DC, Seki LM, Campos LC, Asensi MD. Diversity of genotypes in CTX-M-producing *Klebsiella pneumoniae* isolated in different hospitals in Brazil. Braz J Infect Dis 2011; 15:420-425.
25. Kiffer CRV, Mendes C, Kuti JL, Nicolau DP. Pharmacodynamic comparisons of antimicrobials against nosocomial isolates of *Escherichia coli, Klebsiella pneumoniae, Acinetobacter baumannii* and *Pseudomonas aeruginosa* from the MYSTIC surveillance program: the OPTAMA Program, South America 2002. Diagn Microbiol Infect Dis 2004; 49:109-116.
26. Kiffer CRV, Kuti JL, Mendes CMF, Oplustil CP, Amarante JB, Biancalana ML, et al. A pharmacodynamic strategy to optimize empirical antibiotic therapy for Gram-negative bactéria in a Brazilian Intensive Care Unit. Braz J Infect Dis 2007; 11: 183-185.