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Optimal treatment of Imipenem and meropenem against bloodstream infections caused by the *Citrobacter spp*

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Abstract

Objectives This work was to investigate the optimal treatments of imipenem (IPM) and meropenem (MEM) against bloodstream infections (BSIs) caused by *Citrobacter spp*.

Methods A total of 230 nonduplicate BSIs *Citrobacter spp*. were collected from 2014 to 2020 in three hospitals in Zhejiang Province in China. The minimum inhibitory concentrations (MICs) of 17 antibiotics were determined. Monte Carlo simulation (MCS) was used to investigate the cumulative fraction of response (CFR) of 8 regimens of IPM and 10 regimens of MEM.

Results *C. freundii* (Cfr) was the predominant epidemic isolate (83.9%, 193/230). The resistance rates to IPM and MEM showed an increasing trend from 2015 to 2019. Fosfomycin showed excellent activity from 2014 to 2020. The probability of target attainment of IPM and MEM by prolonged 3 h infusion therapy (PIT) was higher than that by traditional 0.5 h (h) infusion therapy (TIT) during the same administration dosage. The CFR of all IPM regimes was above 90%, while MEM with 500 mg q8h was lower than 90%, especially for Cfr.

Conclusions Cfr is the most common BSIs. *Citrobacter spp*. PIT is more adequate to provide activity against BSIs *Citrobacter spp*., especially for IPM.

Keywords *Citrobacter spp*, Imipenem, Meropenem, Monte carlo simulation, Optimization of treatment

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Introduction

Citrobacter spp., including 16 subspecies, are commonly found in environmental and industrial settings [1]. In recent years, healthcare-associated infections caused by *Citrobacter spp*., especially for carbapenem resistant isolates, are gaining significant concern in clinic [2–4]. Among *Citrobacter spp*. members, *C. freundii* was the predominant epidemic isolate [1, 5]. Current studies demonstrated the carriage of *Citrobacter spp*. was a mortality risk factor for the elderly and immunocompromised patients with bacteremia [6–7]. Therefore, early diagnosis and treatment are the key for recovery of *Citrobacter spp*. infections.

C. freundii is one of the most common *Enterobacterales* with moderate to high risk for clinically significant AmpC production, whereas *C. koseri* does not often harbors a chromosomal *ampC* [8–9]. A meta-analysis showed ill-appearing patients with bloodstream infections caused by *Citrobacter spp*. were more likely to receive carbapenems therapy [10]. However, research on optimization of carbapenems against *Citrobacter spp*. is limited. Monte Carlo simulation (MCS) could effectively integrate pharmacokinetic and pharmacodynamic aspects of antibiotics[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(2):227 – 31. https://doi.org/10.1093/jac/dkq449] [Yu W, Ji J, Xiao T, Ying C, Fang J, Shen P, Xiao Y. Determining optimal dosing regimen of oral administration of dicloxacillin using Monte Carlo simulation. Drug Des Devel Ther. 2017,11:1951–1956. https://doi.org/10.2147/DDDT.S139632]. Therefore, the aim of this study was to explore rea sonable dosage regimens of IPM and MEM against BSIs *Citrobacter spp*. using MCS.

Materials and methods

Bacterial isolates

A total of non-duplicate 230 BSIs *Citrobacter spp*. isolates were collected from 2014 to 2020 in three hospitals (Zhejiang Provincial People's Hospital, Hangzhou Normal University Affiliated Hospital and The First Affiliated Hospital, Zhejiang University School of Medicine) in China.

The minimum inhibitory concentrations (MICs) of 17 antibiotics, including piperacillin-tazobactam, cefoperazone-sulbactam, ceftazidime, ceftriaxone, cefepime, moxalactam, ciprofloxacin, levofloxacin, imipenem, meropenem, trimethoprim-sulfamethoxazol, amikacin, gentamicin, fosfomycin, aztreonam, tigecycline and polymyxin were determined as previous study [11].

Pharmacokinetics (PK) parameters and pharmacokinetics/pharmacodynamics target (PK/PD)

The equations of the time of free plasma concentration above the minimum inhibitory concentration (MIC) (%fT > MIC) were calculated as a previous study [12]. The main PK parameters, including volume of distribution, clearance rate, and free drug fraction, referred to published PK studies of IPM and MEM [13–15]. The PK/PD indexes of %fT > MIC > 40% was used as the target [16]. The administrations included traditional 0.5 h (h) infusion therapy (TIT) and prolonged 3 h infusion therapy (PIT).

Monte carlo simulation (MCS)

A total of 8 regimens of IPM and 10 regimens of MEM were investigated (Supplementary Table 1). The MICs of IPM and MEM were used from 0.015 mg/L to 32 mg/L. A 10,000-subject MCS was performed to calculate the probability of target attainment (PTA) and cumulative fraction of response (CFR) of each dosing regimen against BSIs *Citrobacter spp*. using Crystal Ball software (version 11.1.2.4; Oracle). Plasma clearance rate and volume of distribution were assumed to follow log-normal distribution.

Results

Distribution of BSIs caused by *Citrobacter spp*

There were 141 patients (61.4%) were male. Mean age of patients was 60 ± 12. Among 230 BSIs *Citrobacter spp*. isolates, there were 193 *C. freundii* (Cfr), 26 *C. diversus* (Cdi), 8 *C. braakii* (Cbk), 2 *C. amalonaticus* (Cml) and 1 *C. youngae* (Cyo). The separation rates of Cfr exceeding 20% in 2019 and 2020 (Supplemental Fig. 1).

Antimicrobial susceptibility

The antimicrobial susceptibility results of IPM, MEM and others 15 antibiotics were listed in Table 1 and Supplementary Table 2. Resistance rates to ceftazidime and ceftriaxone were higher than cefepime. The resistance rates to IPM and MEM showed an increasing trend from 2015 to 2019, especially for Cfr (Supplementary Table 3). Aminoglycosides showed better activity than fluoroquinolones against *Citrobacter spp*. Except for 2015, tigecycline retained higher susceptibility rate than polymyxin B. Fosfomycin displayed excellent activity with a susceptibility rate of above 82% from 2014 to 2020.

MCS of IPM and MEM

The PTA of IPM and MEM by PIT was higher than that by TIT during the same administration dosage (Fig. 1). PTA of IPM with 1 g every 6 h (q6h) reached ≥ 90% against isolates with MICs ≤ 4 mg/L. Among PIT administrations, PTA of IPM with 1 g prolonged 3 h infusion q6h yielded > 90% against isolates with MIC ≤ 8 mg/L.

Table 1 MICs of IPM and MEM against BSIs *Citrobacter spp*

Antibiotics	2014 (*N* = 16)			2015(*N* = 18)			2016 (*N* = 35)			2017(*N* = 17)			2018(*N* = 25)			2019(*N* = 65)			2020(*N* = 54)		
	MIC_{90} (mg/L)	S (%)	*R* (%)	MIC_{90} (mg/L)	S (%)	*R* (%)	MIC_{90} (mg/L)	S (%)	*R* (%)	MIC_{90} (mg/L)	S (%)	*R* (%)	MIC_{90} (mg/L)	S (%)	*R* (%)	MIC_{90} (mg/L)	S (%)	*R* (%)	MIC_{90} (mg/L)	S (%)	*R* (%)
Imipenem	0.5	100.0	0.0	1	94.4	5.6	4	88.6	11.4	0.5	94.1	5.9	4	88.0	12.0	4	80.0	13.8	0.25	96.3	1.9
Meropenem	0.06	93.8	0.0	2	88.9	5.6	1	88.6	11.4	0.03	94.1	5.9	2	88.0	12.0	8	81.5	18.5	0.06	94.4	3.7

PTA of MEM with 1 g q6h and 2 g q8h every 8 h (q8h) against the isolates with the MIC ≤ 4 mg/l achieved above 95%. Similarly, except PIT (2 g q8h 3 h infusion), other simulated regimens did not obtain PTA > 95% for MEM against *Citrobacter spp.* All IPM regimes displayed the CFR > 90% (Table 1). However, the CFR of MEM with 500 mg q8h was lower than 90%, especially for Cfr (Supplementary Table 4).

Discussion

Citrobacter spp., especially for carbapenemase-producing strains, are cause of utmost concern to health care services globally due to their ability to resist therapy [4]. In the present study, Cfr is most common species among BSIs caused by *Citrobacter spp.*. An increase in the carbapenem resistant *Citrobacter spp.* isolates was observed from 2015 to 2019. Fortunately, PIT had the potential to optimize efficacy of IPM and MEM against BSIs *Citrobacter spp.*.

Recently, the increase of infections caused by *Citrobacter spp.* is of significant public health concern [1, 5, 17]. Inside *Citrobacter spp.*, Cfr is now the most prevalent specie in humans [18]. Similarly, our results showed the separation rates of Cfr exceeding 20% from 2019 in BSIs. Notably, previous studies and our results found carbapenem resistant *Citrobacter spp.* has yearly increased in worldwide, posing a public health challenge [1, 3]. Recent evidence regarding the molecular epidemiology showed carbapenem resistant *Citrobacter spp.* carried various plasmid-borne resistance genes, including KPCs, NDMs, and OXA-48-like carbapenemases [1, 4]. In addition, co-production of two or three carbapenemases were also identified in *Citrobacter spp*. isolates [1, 19–21]. However, the global carbapenem resistant *Citrobacter spp.* population varied geographical distribution, requiring continued monitoring.

Among *Citrobacter spp.*, Cfr showed moderate to high risk for clinically significant AmpC production [8]. Emergence of resistance occurred in the treatment with third-generation cephalosporins against murine infections and clinical infections caused by *Citrobacter spp.* [8, 22–23]. Therefore, carbapenems remain an important therapeutic choice for *Citrobacter spp.* infections. Previous studies demonstrated that prolonged infusions for carbapenems have the potential to optimize clinical outcomes [15, 24]. In addition, more resistant strains require higher doses of carbapenems [24]. In the present study, PIT of IPM and MEM showed higher PTA than that TIT during the same administration dosage. High-dose of IPM by PTA led to a sufficiently high %fT > MIC for *Citrobacter spp.*. However, CFR of MEM was not significantly different between TIT and PIT at 2 g every 8 h and 1 g every 6 h. A randomized, single-blind clinical trial also demonstrated that MEM did not provide a significantly higher clinical success rate

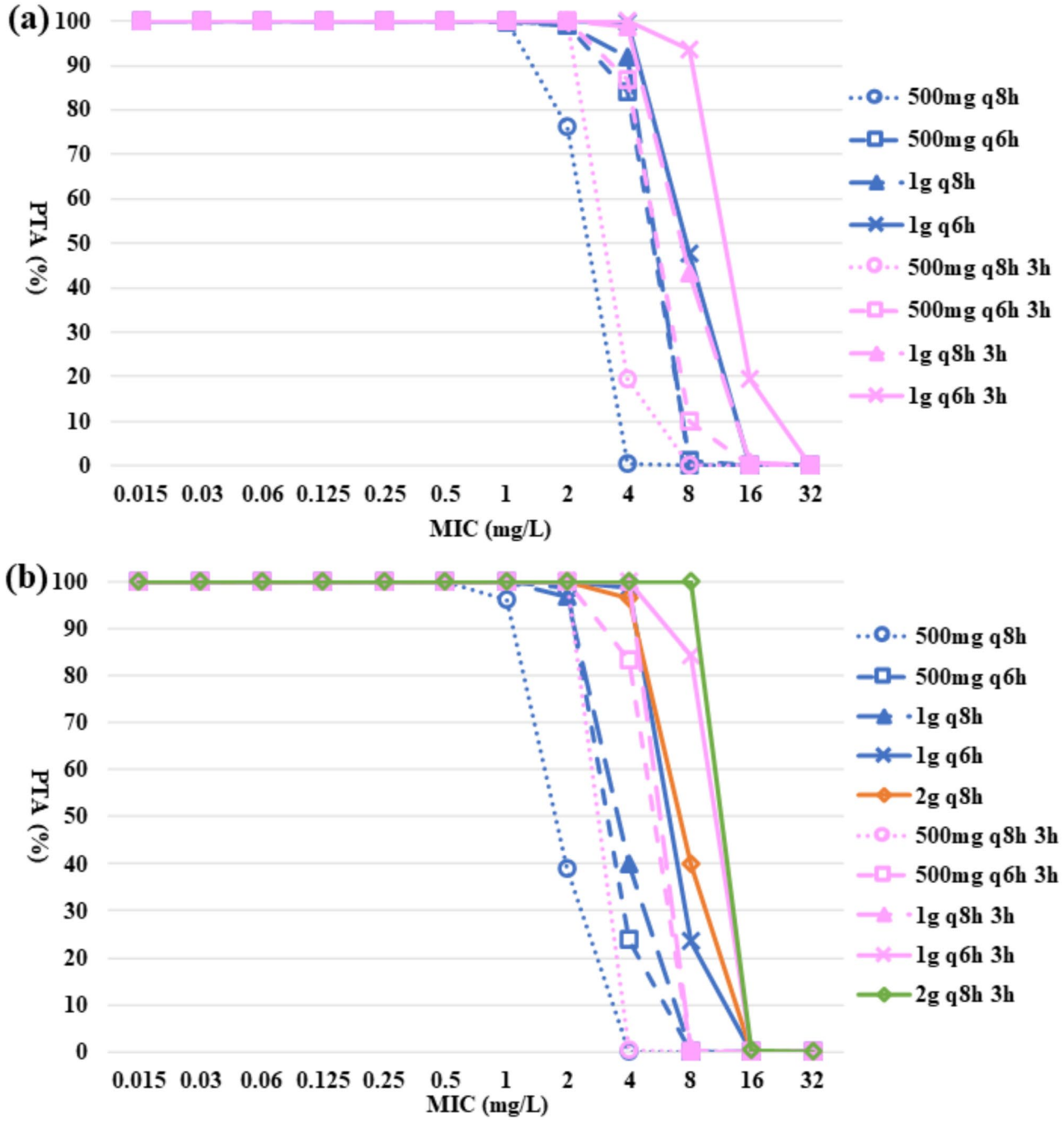

Fig. 1 PTA-MIC curves of IPM and MEM at different simulated regimens. PTA, probability of target attainment; MIC, minimum inhibitory concentration; q8h, every 8 h; q6h, every 6 h. (**a**) IPM; (**b**) MEM

in comparison with the standard dose [25]. It is of note that high Charlson comorbidity index and Pitt bacteremia score were significant risk factors for BSIs *Citrobacter spp* [7]. Thus, randomized clinical trials for different severity of BSIs are urgently needed to evaluate the clinical effectiveness of a high-dose of carbapenems by PIT.

This study has several limitations. Firstly, few isolates in one region may not be fully representative of the population of *Citrobacter spp.*. Secondly, the resistant gene did not identify due to limited number of carbapenem resistant *Citrobacter spp.*. Additionally, the in vitro study is lack of comprehensive evaluation for the interactions between *Citrobacter spp.*, carbapenems, and host. Finally, the patient-related information, such as underlying disease and severity did not collect. Therefore, more

comprehensive researches for BSIs caused by *Citrobacter spp.* are needed in the future.

Conclusions

Cfr is the predominant species among BSIs caused by *Citrobacter spp.*. Treatment with prolonged infusions of carbapenems, especially for IPM, seems to be more potential to optimize clinical outcomes for BSIs *Citrobacter spp.*

Abbreviations

IPM	Imipenem
MEM	Meropenem
BSIs	Bloodstream infections
MICs	Minimum inhibitory concentrations
MCS	Monte carlo simulation
PTA	Probability of target attainment
CFR	Cumulative fraction of response
PIT	Prolonged 3 h infusion therapy
TIT	Traditional 0.5 h (h) infusion therapy
PK	Pharmacokinetics
PK/PD	Pharmacokinetics/pharmacodynamics target
Cfr	*C. freundii*
Cdi	*C. diversus*
Cbk	*C. braakii*
Cml	*C. amalonaticus*
Cyo	*C. youngae*

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-10760-6.

Supplementary Material 1: **Supplemental Fig. . 1**: Distribution of BSIs caused by the ***Citrobacter spp.***. Cfr, ***C. freundii***; Cdi, ***C. diversus***; Cbk, ***C. braakii***; Cml, ***C. amalonaticus***; Cyo, ***C. youngae***

Supplementary Material 2

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Not applicable.

Author contributions

The work presented here was carried out in collaboration between all authors. Wei Yu and Yunqing Qiu developed the concept and designed the study. Lushun Jiang, Jiajie Zhang, Jiaheng Fang, Kanghui Zhang carried out the literatures research. Jiajie Zhang, Kanghui Zhang, Junpeng Yue, Kaixuan Dong and Jiaying Shen co-worked on associated antimicrobial susceptibility test. Monte Carlo simulation carried out by Lushun Jiang, Jiajie Zhang and Jiaheng Fang. The manuscript was written by Lushun Jiang and Jiaheng Fang, and corrected by Yunqing Qiu and Wei Yu. All authors discussed the results and implications and commented on the manuscript at all stages.

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Data availability

All data generated or analysed during this study are included in this published article and supplementary information files.

Declarations

Ethics approval and consent to participate

We declare no ethical competing interest. This study was conducted following the Declaration of Helsinki and obtained approval from the clinical research ethics committee of The First Affiliated Hospital, Zhejiang University School of Medicine [No. 2018 – 752]. The need for consent to participate was deemed unnecessary according to the clinical research ethics committee of The First Affiliated Hospital, Zhejiang University School of Medicine.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

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