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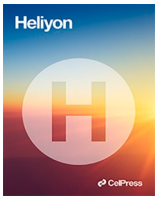

Research article

Application of Monte Carlo simulation to optimise the dosage regimen of meropenem in patients with augmented renal clearance for *Pseudomonas aeruginosa* infection

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ABSTRACT

Objective: To optimise the dosing regimen of meropenem for treating *Pseudomonas aeruginosa* (PA) infections in critically ill patients with augmented renal clearance (ARC) using pharmacokinetic/pharmacodynamic (PK/PD) principles and Monte Carlo simulation (MCS).
Methods: This research involves an MCS based on PK data from patients with ARC and a minimum inhibitory concentration (MIC) distribution of PA. This study simplifies the methods section, focusing on the critical aspects of simulation and target values for effective treatment.
Results: The study highlights key findings and emphasises that tailored dosing based on bacterial MIC values is essential for patients with ARC. It also notes that empirical treatment in patients with ARC should consider the MIC distribution, with 2 g every (q) 6 h administered to achieve the PK/PD target, while 3 g q 6 h is effective in inhibiting resistance.
Conclusion: Tailored dosing based on bacterial MIC values is crucial for patients with ARC. Prolonged infusion time alone does not enhance efficacy. Empirical treatment in patients with ARC should consider MIC distribution; a dosage of 2 g q 6 h achieves the PK/PD target, while 3 g q 6 h (≥12 g daily) inhibits resistance.

1. Introduction

Pseudomonas aeruginosa (PA) is an aerobic gram-negative bacillus and is one of the more common opportunistic pathogens in clinical practice. Due to heavy infections or invasive operations, carbapenem antibacterial drugs are widely used for critically ill patients, resulting in yearly increases in the clinical detection and drug resistance rates of PA. This makes clinical anti-infection treatment more difficult, and as meropenem-resistant strains continue to emerge, major concerns are arising regarding drug resistance [1].

Pseudomonas aeruginosa is a highly adaptable pathogen capable of causing a wide range of infections, particularly in immunocompromised individuals. The increasing prevalence of multidrug-resistant (MDR) PA strains has become a global health concern because they significantly limit treatment options and lead to poor clinical outcomes. The epidemiology of PA infections varies across

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different regions, with higher rates of MDR strains reported in certain countries. The virulence factors of PA, such as biofilm formation, quorum sensing and secretion systems, contribute to its pathogenicity and resistance to antimicrobial agents. Contemporary strategies to combat MDR PA include the development of novel antibiotics, combination therapy and the use of alternative approaches such as phage therapy and antimicrobial peptides [2].

Meropenem is a time-dependent antimicrobial drug, the efficacy of which depends on the proportion of time that the drug concentration (%*f*T) exceeds the minimum inhibitory concentration (MIC) (%*f*T > MIC). Meropenem has a half-life of approximately 1 h and is mainly excreted in urine as the prototype. In addition, its plasma clearance is related to creatinine clearance (CrCl) [3]. The glomerular filtration rate and renal clearance of patients with augmented renal clearance (ARC) increases, resulting in a decrease in meropenem drug concentration, thus affecting its efficacy and resistance [4].

With the increasing use of computers, computer simulation for drug clinical research has recently attracted attention. Monte Carlo simulation (MCS) [5] is a stochastic method that uses different statistical sampling techniques (e.g. random numbers, pseudo-random numbers) to provide approximate solutions to quantitative problems [6].

This study utilises the MCS method to optimise the meropenem dosing regimen for patients with ARC. We establish an MCS model based on pharmacokinetic/pharmacodynamic (PK/PD) analysis, input the MIC distribution data of PA strains isolated from our hospital, simulate the efficacy and resistance of different dosing regimens and evaluate the probability of achieving the %*f*T > MIC and %*f*T > 4MIC targets. The %*f*T > 4MIC target is a novel PK/PD target that reflects the resistance inhibition potential of meropenem, which has not been considered in previous studies. We also compare our simulation results with clinical validation and literature data as well as identify several factors and limitations that influence the treatment effect of meropenem.

2. Materials and methods

2.1. Study design

This study employed an MCS approach to optimise the meropenem dosing regimen for patients with ARC who were also infected with PA. The study utilised PK data from patients with ARC and the MIC distribution of PA isolates to establish an MCS model. The efficacy and resistance of different dosing regimens were simulated, and the probability of achieving the %*f*T > MIC and %*f*T > 4MIC targets was evaluated.

2.2. Designing optimised two-step administration therapy and traditional simple prolonged infusion therapy

Both optimised two-step administration therapy and traditional simple prolonged-infusion (TSPI) therapy were designed as alternative dosing strategies for meropenem administration. Optimised two-step administration therapy involves a loading dose followed by a maintenance dose to rapidly achieve and maintain the target concentration. Conversely, TSPI therapy involves administering the drug over an extended period to maintain the target concentration.

2.3. Target values for meropenem pharmacokinetic/pharmacodynamic effects

This study used higher %*f*T > MIC and %*f*T > 4MIC target values (i.e. %*f*T > MIC >70 % and %*f*T > 4MIC >70 %) to predict the effectiveness and resistance inhibition of meropenem. These target values were based on the efficacy and resistance criteria for carbapenems proposed in the literature [7–12] and were consistent with the American Clinical and Laboratory Standards Institute (CLSI) sensitivity classification criteria.

2.4. Pharmacokinetic model of meropenem pharmacokinetic/pharmacodynamic

Some studies have demonstrated that there is no statistical difference in the results of the *f*T > MIC formula based on one- or two-compartment models [13]. One study [14] demonstrated that the intravenous dripping and intravenous injection of meropenem based on the one-compartment model could not be used interchangeably, meaning the formula of *f*T > MIC should be consistent with the mode of administration. For patients with severe infections, the clinical common application of intravenous dripping for antimicrobial therapy [15] was applied; therefore, this study used the intravenous dripping formula for *f*T > MIC in a one-compartment model as follows [16]:

$$fT > MIC = T_{\text{inf}} - \ln\left(\frac{R_0/CL}{R_0/CL - MIC}\right) \times V_d \Big/ CL + \ln\left(\frac{R_0/CL - R_0/CL \times e^{-CL/V_d \times T_{\text{inf}}}}{MIC}\right) \times V_d \Big/ CL$$

Assuming a dosing interval of τ, according to the definition of %*f*T > MIC [14,17], %*f*T > MIC = *f*T > MIC ÷ τ × 100 %.

In the above formula, *f* is the proportion of free drug (1-protein binding rate), T_{inf} is the infusion time (h), *ln* is the natural logarithm, R_0 is the zero-level infusion rate (dose × *f* ÷ T_{inf} in mg × h^{-1}), the dose is the single dose administered (mg), *CL* is the drug clearance (L × h^{-1}), MIC is the minimum inhibitory concentration (μg × mL^{-1}), V_d is the apparent volume of distribution of the drug (L) and *e* is the natural constant.

2.5. Meropenem pharmacokinetic/pharmacodynamic parameters

2.5.1. Dosing regimen for meropenem

The dosing regimens for meropenem in this study were set to 1 g every (q) 8 h, 2 g q 8 h, 3 g q 8 h, 1 g q 6 h, 2 g q 6 h and 3 g q 6 h, based on the safe therapeutic dose range of meropenem recommended in the National Guidelines for Antimicrobial Therapy (2nd edition), the Sanford Guidelines for Antimicrobial Therapy (50th edition) and the ABX Guide to the Diagnosis and Treatment of Infectious Diseases (2nd edition), combined with higher dose regimens described in the literature. Therefore, the doses were 1,000, 2,000 and 3,000 mg, and the dosing intervals (τ) were 6 and 8 h. Some studies have indicated that the infusion time should be extended to 3 h in patients with severe infections. One study showed that patients with ARC should be titrated for 3–6 h to achieve %$fT > MIC$ >50 % and an effective therapeutic concentration [18]. However, a study by Carlier [19] concluded that prolonging the infusion time of meropenem alone did not improve the blood concentration in patients with ARC. Other literature makes different statements; therefore, this study combined the findings of several studies and took the value of the infusion time (T_{inf}) as 0.5–3 h.

2.5.2. Pharmacokinetic parameters of meropenem

Meropenem is primarily used for patients with severe infections, and therefore the CL and volume of distribution (V_d) of meropenem are more representative of patients with severe infections. Since the PK parameters reported in various studies also differed, the principal factor analysis affecting the PK/PD effect of meropenem performed by Yin Zhao [17] included several PK parameters reported in the literature to exclude differences in results; however, the results showed no significant differences in the cumulative fraction of response (CFR) obtained with different PK parameters for the same dosing regimen. Zhao's study confirmed that the main factors influencing the susceptibility to the CFR and the PK/PD effect differed between strains, and for PA, the main factor influencing the CFR of meropenem was the MIC (i.e. the drug susceptibility of the isolated strain) and was not strongly related to the individualised PK parameters [17]. In contrast, the participants in the current study were patients with ARC (CrCl $\geq$130 mL $\times$ min^{-1} $\times$ 1.73 m^{-2}) [8]; therefore, the PK parameters of patients with severe infection with ARC were selected for this study (i.e. a V_d of 25.35 $\pm$ 4.9 L $\times$ h^{-1} and a CL of 19.22 $\pm$ 4.1 L $\times$ h^{-1}) (Table 1).

2.5.3. Pharmacodynamic parameters of meropenem

The MIC distribution of the target strains was the PD parameter of meropenem. Gram-negative bacteria cultured from patient specimens (including blood, sterile body fluids, sputum, urine and wound exudate) received by the microbiology laboratory were selected for drug susceptibility testing. The meropenem MIC values were determined using the broth dilution method. Sensitivity, intermediary or resistance was determined according to the Executive Standards for Antimicrobial Drug Susceptibility Testing (2019) [25] developed by the CLSI. *Pseudomonas aeruginosa* (ATCC 27853) was used as a quality control strain. A retrospective analysis was performed on the MIC data between 2018 and 2022 for the last 5 years of isolation of PA against meropenem from different strains. The frequency of distribution of MIC values of meropenem to PA was calculated according to the discrete uniform distribution (Table 2).

2.6. Monte Carlo simulation

Oracle Crystal Ball (V11.1.2.4.850) software was used to perform an MCS of meropenem with different dosing regimens for the treatment of PA-induced infections. The authors calculated the effectiveness of the dosing regimen corresponding to each MIC value, the probability of target attainment (PTA) for the inhibition of drug-resistant mutations and the expected probability (i.e. the CFR) of each dosing regimen reaching the target threshold for the pathogen population, as shown in the following equation:

$$CFR = \sum_{i=1}^{n} PTAi \times Fi,$$

where PTAi is the probability of target attainment in determining MIC values and Fi is the relative probability of each MIC distribution

Table 1
Comparison of meropenem PK parameters in different studies.

Research Groups	Vd (L·h-1)	CL (L·h-1)	References
sepsis, septic shock patients	26.15 ± 3.86	9.44 ± 2.27	Niu Sha [20], 2013
critically ill patients	21.7 ± 5.7	9.3 ± 2.4	Ariano [21], 2005
elderly infected patients	28.97 ± 13.42	9.34 ± 5.94	Chen IH [22], 2020
Infected patients with creatinine clearance >50 mL min^{-1}·1.73 m^{-2}	25.35 ± 4.9	None	Novelli A [18], 2005
seriously ill patients	13.25 ± 4.59	14.61 ± 4.98	Kim A [23], 2009
ARC patients	25.35 ± 4.9	19.22 ± 4.1	Razzazzadeh S [24], 2022
Sepsis patients (Inclusion of six studies)	21.2 ± 4.7;	11.3 ± 4.0;	Yin Zhao [17], 2020
	26.6 ± 3.2;	9.4 ± 1.2;	
	34.4 ± 15.9;	11 ± 4.3;	
	19.7 ± 5.0;	7.3 ± 3.1;	
	16.0 ± 3.7;	8.5 ± 3.2;	
	23.8 ± 4.9	6.7 ± 4.2	

Note: PK: pharmacokinetic; ARC: augmented renal clearance.

Table 2
Frequency distribution of meropenem MIC on PA (%).

MIC(μg·mL^{-1})	≤0.25	0.5	1	2	4	8	≥16
Distribution frequency (%)	51.43	12.38	23.81	2.86	2.86	0.95	5.91

Note: PA: *Pseudomonas aeruginosa;*MIC: minimum inhibitory concentration.

in the population strain.

During the simulations, the dose τ and the MIC were set to obey custom distributions (dose = 1,000, 2,000 and 3,000 mg; τ = 6 and 8 h), MIC was set to obey discrete uniform distributions (frequency values at each value), the PK parameters (V_d and CL) were set to obey lognormal distributions (mean ± standard deviation) and *f* and T_{inf} were set to obey uniform distributions ($f \in [0.85, 0.98]$, $T_{inf} \in [0.5, 3]$), with a 95 % confidence interval and 5,000 simulations. All the above parameters were integrated into a %*f*T > MIC PK model, the simulation results were expressed as the PTA and CFR for a dosing regimen at a specific MIC value and the dosing regimen with a PTA or CFR >90 % was selected (Table 3).

2.7. Clinical validation

This was an observational PK/PD study. Medical records of patients infected with PA between 2018 and 2022 were randomly selected from the hospital medical record system, from which patients with concomitant ARC status and receiving meropenem treatment were screened, and the meropenem dosage and clinical efficacy were recorded and compared with the simulated results. The following databases were searched with the keywords 'meropenem', 'augmented renal clearance' and '*Pseudomonas aeruginosa*': China Knowledge Network (http://www.cqvip.com/), Wanfang Data, PubMed, Embase and the Cochrane Library. The dosage and anti-infective effects of meropenem for PA in patients with ARC were searched in the literature and compared with the simulation results. The technical roadmap of the study is illustrated in Fig. 1, which outlines the key steps involved in optimising the meropenem dosing regimen for patients with ARC infected with PA.

3. Results

3.1. Minimum inhibitory concentration distribution of Pseudomonas aeruginosa in the study hospital in the past 5 years

Between 2018 and 2022, the study hospital detected a wide range (0.25–16 μg × mL^{-1}) of MIC for meropenem against PA. Notably, the highest frequency PA strains exhibited an MIC of <0.25 μg × mL^{-1}. This distribution was similar when compared with global antimicrobial resistance data and international best resistance surveillance (as per https://atlas-surveillance.com/#/database/micdistribution) [26]. However, the global dataset indicated a higher proportion of PA strains with MIC ≥16 μg × mL^{-1}, signifying a more pronounced trend of resistance to meropenem globally (Fig. 2).

3.2. Probability of target attainment and cumulative fraction of response

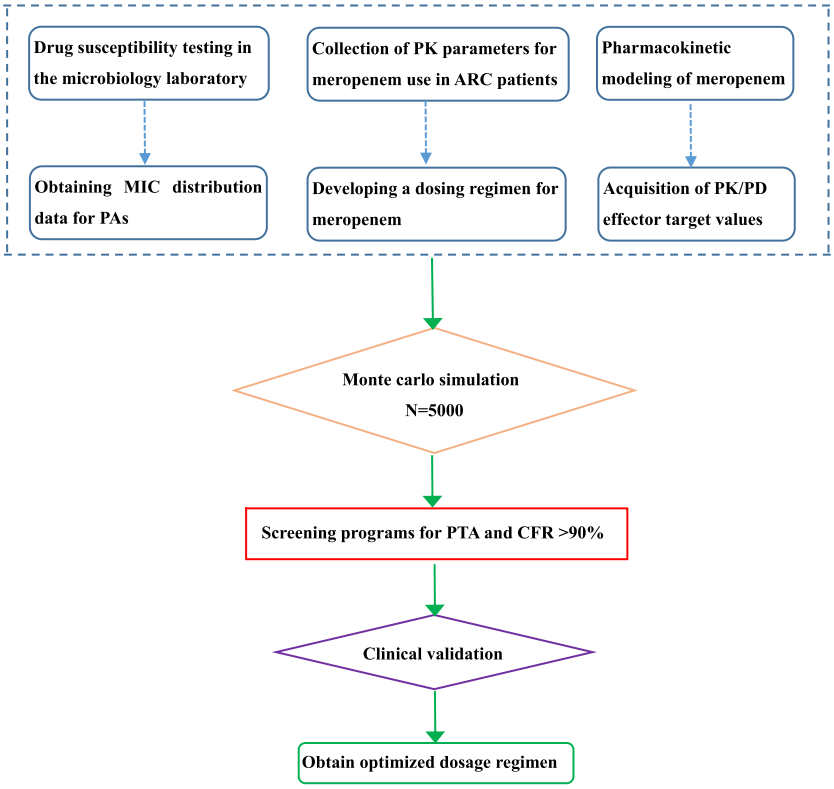
3.2.1. Probability of target attainment and cumulative fraction of response values of the effectiveness of different dosing regimens of meropenem on each minimum inhibitory concentration of Pseudomonas aeruginosa

Monte Carlo simulations (refer to Table 4) revealed that in patients with PA and concomitant ARC status, a PTA of >90 % was achievable across all meropenem dosing regimens when the MIC was at a level of 0.25 μg × mL^{-1}. For an MIC of 0.5 μg × mL^{-1}, increasing the dose of meropenem to 2 g q 8 h in patients with ARC resulted in a PTA of 90.38 %. At an MIC of 1 μg × mL^{-1}, administering meropenem at a dosage of 1 g q 6 h achieved a PTA of 92.36 %. For an MIC of 2 μg × mL^{-1}, it was necessary to elevate the dose to 2 g q 6 h, reaching a PTA of 91.66 %. For an MIC ≥4 μg × mL^{-1}, none of the dosing regimens could achieve a PTA above 90 %. The CFR for the 2 g q 6 h and 3 g q 6 h regimens exceeded 90 % when considering the population distribution of MIC, suggesting these regimens as primary considerations for empirical treatment of PA in patients with ARC (Fig. 3).

Table 3
Summary of PK/PD target values, dosage regimens and PK parameters for meropenem.

Effectiveness	%*f*T > MIC>70 %					
Inhibit drug resistance	%*f*T>4MIC>70 %					
Dosing regimen	1 g q 8 h	2 g q 8 h	3 g q 8 h	1 g q 6 h	2 g q 6 h	3 g q 6 h
Dose (mg)	1000	2000	3000	1000	2000	3000
T (h)	8	8	8	6	6	6
T_{inf} (h)	$T_{inf} \in [0.5, 3]$					
f	$f \in [0.85, 0.98]$					
V_d (L·h-1)	25.35 ± 4.9					
CL (L·h^{-1})	19.22 ± 4.1					

Note: PK/PD: pharmacokinetic/pharmacodynamic; MIC: minimum inhibitory concentration.



Note: PK, pharmacokinetic; ARC, augmented renal clearance; MIC, minimum inhibitory concentration; PA, Pseudomonas aeruginosa; PK/PD, pharmacokinetic/pharmacodynamic; PTA, probability of target attainment; CFR, cumulative fraction of response.

Figure 1. Technical roadmap of the study. Note: PK, pharmacokinetic; ARC, augmented renal clearance; MIC, minimum inhibitory concentration; PA, *Pseudomonas aeruginosa*; PK/PD, pharmacokinetic/pharmacodynamic; PTA, probability of target attainment; CFR, cumulative fraction of response.

3.2.2. Probability of target attainment and cumulative fraction of response values of inhibition of drug-resistant mutation by different minimum inhibitory concentrations of Pseudomonas aeruginosa by different dosing regimens of meropenem

Utilising %$fT > 4MIC$ >70 % as the target value for inhibiting resistance in PA, this study observed that administering meropenem at 1 g q 6 h to patients with ARC with an MIC of 0.25 μg × mL^{-1} resulted in a PTA of 92.06 %. At an MIC of 0.5 μg × mL^{-1}, the 2 g q 6 h dosing regimen achieved a PTA of 91.36 %. For an MIC ≥1 μg × mL^{-1}, all dosing regimens resulted in PTA values < 90 %, with the 3 g q 6 h regimen showing the highest relative PTA. When considering the population distribution of MIC, only the 3 g q 6 h regimen achieved the highest relative CFR of 85.36 % (Table 5).

Therefore, as is shown in Fig. 3, the dosing regimen should be set to 3 g q 6 h (i.e. a daily dose of >12 g) in the empirical treatment of the MIC population distribution of PA to safeguard the antimicrobial efficacy of meropenem application and suppression of resistance mutations in patients with ARC.

3.2.3. Major pharmacokinetic/pharmacodynamic factors affecting the cumulative fraction of response sensitivity

The assessment of various PK/PD parameters influencing CFR sensitivity for each meropenem regimen in treating PA is illustrated in Fig. 4. The most impactful factor on CFR was found to be the MIC, both for achieving PK/PD targets and inhibiting resistance mutations. This finding aligns with the existing literature [16], suggesting that the effectiveness of meropenem against PA primarily depends on the drug's sensitivity to the isolated strains. The study specifically focused on the ARC population, known for increased glomerular filtration rates, typically quantified as CrCl ≥130 mL × min^{-1} × 1.73 m^{-2} [8]. Therefore, it was logical to use population-specific PK parameters for patients with ARC in the MCSs. The second most influential factor was the dosing interval (τ), considering meropenem's time-dependent nature and short half-life of approximately 1 h. Given that the drug's plasma clearance is closely related to CrCl [3], faster clearance in patients with ARC implies that shorter dosing intervals could maintain relatively stable blood concentrations. The values of V_d, T_{inf} and the fraction of free drug (f) were found to have a minor impact on the CFR, indicating that merely prolonging the infusion time for intravenous meropenem in patients with ARC would not significantly enhance its PK/PD effect against PA.

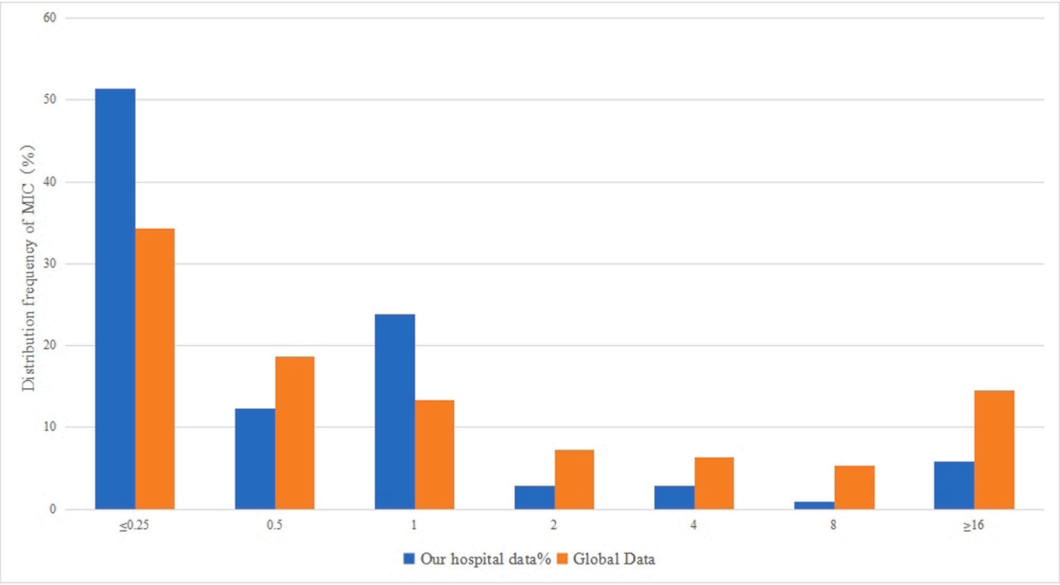


Fig. 2. Comparison of the frequency of MIC distribution of *Pseudomonas aeruginosa* (PA) isolates between the study hospital and the global database. The study hospital data shows a higher frequency of PA strains with MIC <0.25 μg × mL−1, while the global data indicates a larger proportion of strains with MIC ≥16 μg × mL−1, suggesting a more pronounced trend of meropenem resistance worldwide.

Table 4
PTA and CFR of the effectiveness of different dosing regimens of meropenem on PA.

No.	T (h)	Dose (mg)	PTA (in MIC, %)							CFR/%
			0.25	0.5	1	2	4	8	16	
1	8	1000	90.82 %	78.72 %	54.70 %	22.24 %	1.50 %	0.00 %	0.00 %	70.16 %
2	8	2000	96.68 %	90.38 %	77.82 %	52.90 %	21.40 %	1.64 %	0.00 %	81.58 %
3	8	3000	97.98 %	94.86 %	86.74 %	68.76 %	39.66 %	10.58 %	0.36 %	86.01 %
4	6	1000	99.36 %	98.02 %	92.36 %	72.08 %	25.74 %	0.34 %	0.00 %	88.03 %
5	6	2000	99.88 %	99.42 %	97.88 %	91.66 %	72.78 %	26.66 %	0.20 %	91.95 %
6	6	3000	99.92 %	99.72 %	99.10 %	96.50 %	86.34 %	57.28 %	9.74 %	93.68 %

Note: PTA: probability of target attainment; CFR: cumulative fraction of response; PA: *Pseudomonas aeruginosa;*MIC: minimum inhibitory concentration.

3.3. Clinical validation

For clinical validation, 300 medical records of patients with PA infections, including 39 records of patients with ARC treated with meropenem, were randomly selected from the medical record system for the period 2018–2022. In cases where the MIC was <1 μg × mL^{-1}, 19 out of 25 (76.0 %) records showed meropenem dosages aligning with the simulation results. For an MIC >1 μg × mL^{-1}, 10 out of 14 cases (71.4 %) were consistent with the simulated outcomes. The overall compliance rate with the simulation results was 74.3 %, indicating a substantial alignment between actual clinical medication use and the simulated findings. Eight articles related to the optimisation of meropenem dosing in patients with ARC were reviewed [18,19,22,23],[27–30]. These studies suggested that for population-distributed MICs, a daily dose increase to >8 g/day (2 g q 6 h) is required to achieve effective blood concentrations or clinical efficacy of meropenem. In one case, a daily dose of up to 16 g was needed [30]. The literature also indicated that using only the prescribed dose, even with an extended infusion time, did not result in increased blood concentrations in patients with ARC [19,23]. This finding aligns with our simulation results, which show that T_{inf} is not a major factor influencing the PK/PD of meropenem.

4. Discussion

Meropenem, recognised as a time-dependent antimicrobial drug, exerts its clinical efficacy primarily by maintaining its free blood concentration above the MIC of the targeted pathogen (denoted as $fT > MIC$) [31]. Research indicates that meropenem demonstrates effective antimicrobial action when $\%fT > MIC$ is >40 %. However, in cases of severe infections, where the risk of bacterial resistance is heightened, achieving $\%fT > MIC$ >70 % is deemed necessary for optimal efficacy.

Pseudomonas aeruginosa, a frequently encountered clinical pathogen, is responsible for severe infections such as hospital-acquired pneumonia, urinary tract infections and bloodstream infections [32]. This pathogen most commonly affects the respiratory tract,

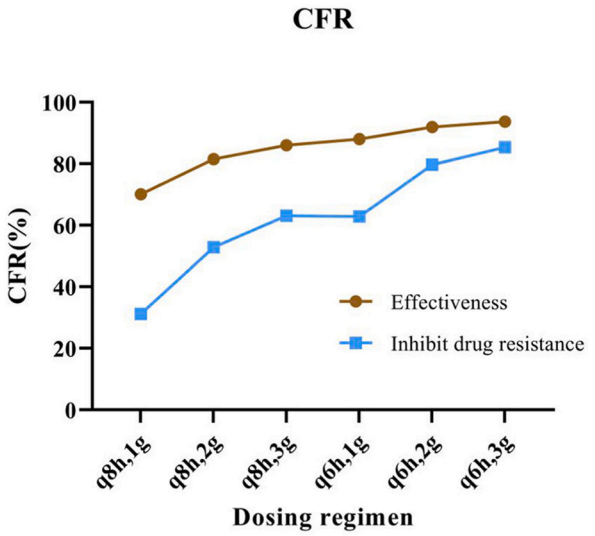


Fig. 3. Cumulative fraction of response (CFR) values for different meropenem dosing regimens in achieving the pharmacokinetic/pharmacodynamic (PK/PD) target (Effectiveness) and inhibiting drug-resistant mutations (Inhibit drug resistance). The results show that a dosage of 2 g every 6 h (q 6 h, 2 g) achieves the PK/PD target for effectiveness, while 3 g every 6 h (q 6 h, 3 g) is necessary to suppress resistance development.

Table 5
PTA and CFR of different dosing regimens of meropenem for PA inhibition of drug-resistant mutations.

No.	τ(h)	Dose (mg)	PTA (in MIC, %)							CFR/%
			0.25	0.5	1	2	4	8	16	
1	8	1000	54.40 %	22.16 %	1.96 %	0.00 %	0.00 %	0.00 %	0.00 %	31.19 %
2	8	2000	79.80 %	54.56 %	21.16 %	1.36 %	0.00 %	0.00 %	0.00 %	52.87 %
3	8	3000	87.16 %	69.42 %	39.52 %	10.20 %	0.20 %	0.00 %	0.00 %	63.13 %
4	6	1000	92.06 %	72.96 %	27.36 %	0.30 %	0.00 %	0.00 %	0.00 %	62.90 %
5	6	2000	97.90 %	91.36 %	72.46 %	26.66 %	0.42 %	0.00 %	0.00 %	79.69 %
6	6	3000	99.00 %	96.80 %	86.60 %	55.98 %	8.26 %	0.00 %	0.00 %	85.36 %

Note: PTA: probability of target attainment; CFR: cumulative fraction of response; PA: *Pseudomonas aeruginosa;*MIC: minimum inhibitory concentration.

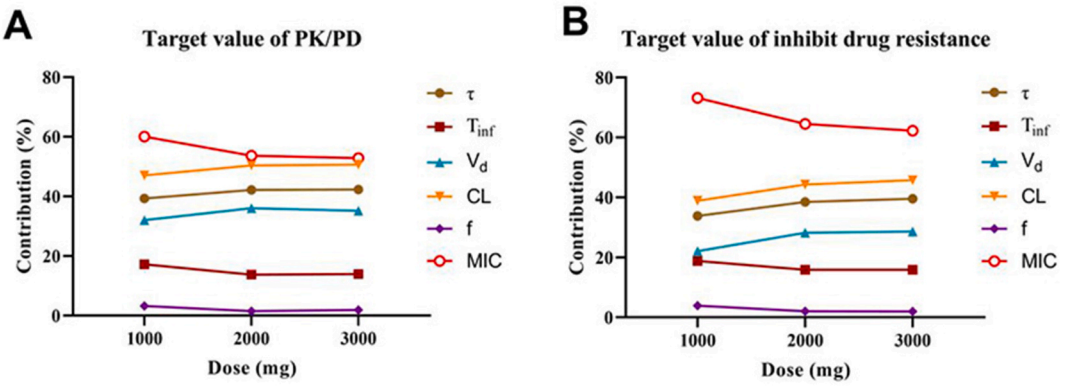


Fig. 4. Sensitivity analysis of various pharmacokinetic/pharmacodynamic parameters to the cumulative fraction of response (CFR) in meropenem regimens for treating *Pseudomonas aeruginosa* infections. (A) Target value of PK/PD effectiveness. (B) Target value of inhibiting drug resistance. The minimum inhibitory concentration (MIC) is identified as the most influential factor, followed by the dosing interval (τ), infusion time (Tinf), volume of distribution (Vd), clearance (CL), and fraction of free drug (*f*).

particularly in patients with severe conditions in respiratory units, intensive care units (ICUs) and neurosurgery departments [33]. The widespread usage of carbapenems has led to an annual increase in bacterial resistance, positioning carbapenem-resistant PA as one of the top three bacteria urgently requiring new antibiotic solutions [34]. Numerous studies have concluded that maintaining a

meropenem trough concentration to MIC ratio of >4 is essential to prevent resistance transmission [10–12]. Consequently, to effectively inhibit bacterial resistance, %ƒT > 4MIC >70 % is required.

Augmented renal clearance presents a high risk in critically ill patients, patients with systemic inflammatory response syndrome and those admitted to ICUs. Studies have shown a prevalence of ARC in approximately 20%–65 % of hospitalised patients [4]. Augmented renal clearance significantly influences the PK/PD of drugs, particularly those that undergo renal elimination, are time dependent and have a short half-life. In such drugs, ARC can lead to increased clearance rates, resulting in lower blood concentrations and, consequently, reduced therapeutic efficacy. In-vitro studies have demonstrated that the primary route of meropenem excretion is renal active transport. However, the mechanisms underlying the accelerated clearance of meropenem in patients with ARC remain not fully understood [30]. It is plausible that mechanisms other than renal excretion could influence the drug's efficacy, warranting further investigation.

Monte Carlo simulation is a numerical method underpinned by probabilistic statistical theory, utilised to analyse the impact of variables and assumptions in experimental designs and predict potential outcomes of various study protocols [35]. Given that MIC is a critical factor influencing the PK/PD of meropenem treatment in PA, it is important to consider both the variability in drug susceptibility across different PA strains and patient-specific drug disposition processes when determining dosing regimens for patients diagnosed with ARC. Therefore, implementing thousands of simulations is essential to enhance prediction accuracy and provide reliable guidance for clinical drug regimen formulation.

Recent studies have employed population PK modelling and target attainment analysis to evaluate empirical dosing regimens for meropenem in patients in the ICU [36]. These approaches have proven valuable in optimising dosing strategies and improving clinical outcomes. Similarly, population PK/PD modelling and MCSs have been used to determine the optimal dosing regimen of biapenem in patients with febrile neutropenia and haematological malignancies [37]. These studies highlight the importance of considering patient-specific factors and utilising advanced modelling techniques to personalise antimicrobial therapy.

The relationship between target time above MIC achievement rate of meropenem using MCS and in-hospital survival in patients with PA bacteraemia has also been investigated [38]. The findings suggested that achieving a higher target time above MIC is associated with improved clinical outcomes, emphasising the significance of optimising meropenem dosing based on individual patient characteristics and pathogen susceptibility.

Another study addressed the question of whether meropenem monotherapy is truly incompetent for meropenem-nonsusceptible bacterial strains using PK/PD modelling with MCS [39]. The results indicated that meropenem monotherapy can still be effective against meropenem-nonsusceptible strains, provided that appropriate dosing adjustments are made based on the MIC values and patient-specific PK parameters.

The results of the current study indicate that for the patients with ARC, the maximum permissible meropenem dose of 1 g q 8 h retains effective antibacterial activity against PA strains with MIC $\leq$0.25 μg × mL^{-1}. However, a dosing regimen of 1 g q 6 h is more efficacious in inhibiting bacterial resistance. For MIC values of 1 μg × mL^{-1}, the recommended dosing regimen is 1 g q 6 h. When the MIC reaches 2 μg × mL^{-1}, an increase in the meropenem dose to 2 g q 6 h is advised. For an MIC >4 μg × mL^{-1}, a regimen of 3 g q 6 h, equating to a daily dose exceeding 12 g, is necessary to achieve the desired clinical efficacy. In situations where the MIC $\geq$1 μg × mL^{-1}, a 3 g q 6 h dosing regimen is expected to inhibit bacterial resistance. In the absence of specific MIC values, empirical treatment with meropenem should cover strains with varying MIC distributions. According to this study, a 2 g q 6 h regimen achieves >90 % CFR across the entire bacterial population. Thus, for patients with ARC without definitive MIC results, the recommended meropenem dosing regimen is 2 g q 6 h to achieve the PK/PD target, ensuring the desired antibacterial effect on PA and inhibiting bacterial resistance.

Research by Kim et al. [23] employed MCS to assess the likelihood of achieving PD targets in the empirical treatment of adult patients with hospital-acquired pneumonia using standard and extended infusion antibiotic regimens. Their findings suggested that extending infusion time enhanced the PD profile of β-lactams. However, for meropenem dosages of 1 g q 8 h and 2 g q 8 h, an infusion duration of just 0.5 h was sufficient to attain a probability of more than 90 %. Yin et al. [17] observed that extending the infusion time of meropenem had a minimal impact on the overall therapeutic effect on various target species. Carlier et al. [19] explored whether extending the infusion time of meropenem in critically ill patients with ARC could meet PK/PD targets. A multivariate regression analysis indicated that an increase in CrCl was an independent predictor of failing to achieve PK/PD targets, and without an increase in dosage, even extending the infusion time up to 3 h resulted in ineffective anti-infective therapy. These studies are in line with the findings of the current study, suggesting that in the treatment of PA in patients with ARC with meropenem, better clinical efficacy can be achieved by adjusting the dosage according to different MIC values rather than simply prolonging the infusion time.

4.1. Strengths and limitations

This study has several strengths. First, it utilises MCS, a powerful tool for predicting the PTA and CFR for various meropenem dosing strategies in patients with ARC infected with PA. The simulation incorporates patient-specific PK parameters and the MIC distribution of the pathogen population, providing a more realistic representation of clinical scenarios. Second, the study considers both the effectiveness and resistance inhibition potential of meropenem by evaluating the %ƒT > MIC and %ƒT > 4MIC targets, respectively. This comprehensive approach ensures that the recommended dosing regimens not only achieve optimal clinical efficacy but also minimise the risk of bacterial resistance development.

However, this study also has some limitations. The simulation is based on a limited sample size of PK data from patients with ARC and the MIC distribution of PA isolates from a single hospital. Therefore, the generalisability of the findings to other patient populations and geographical regions may be limited. Additionally, the study does not account for potential variations in PK parameters

within the ARC population, which may impact the accuracy of the simulation results. The study also focuses solely on meropenem and does not consider the potential role of combination therapy or alternative antimicrobial agents in the treatment of PA infections.

Despite these limitations, this study provides valuable insights into the optimisation of meropenem dosing in patients with ARC and highlights the importance of considering patient-specific factors and pathogen susceptibility in the selection of antimicrobial therapy. Future research should aim to validate these findings in larger, multi-centre clinical trials and explore the potential benefits of personalised dosing strategies based on real-time monitoring of PK/PD parameters.

5. Conclusion

This study demonstrates the importance of tailoring meropenem dosing regimens based on individual patient characteristics, particularly in the context of ARC and the MIC values of the infecting pathogen. Monte Carlo simulation proves to be a valuable tool in predicting the PTA and CFR for various dosing strategies. The findings suggest that higher doses and shorter dosing intervals are necessary to achieve optimal clinical efficacy and inhibit bacterial resistance in patients with ARC infected with PA. Empirical treatment should consider the MIC distribution of the pathogen population; however, in the absence of definitive MIC results, a dosing regimen of 2 g q 6 h is recommended. Future research should focus on validating these findings in clinical settings and exploring alternative strategies to combat the increasing prevalence of MDR PA strains.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Weihai Municipal Hospital (No.2021067). Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Data availability statement

Data will be made available on request.

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CRediT authorship contribution statement

Jia Hou: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Min Zhang:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Formal analysis. **Shu-Qing Ma:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Formal analysis. **Ri-Nan Cong:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **Jin-Feng Li:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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