Renal Replacement Therapy

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Imipenem dosing recommendations for patients undergoing continuous renal replacement therapy: systematic review and Monte Carlo simulations

Dhakrit Rungkitwattanakul[1], Taniya Charoensareerat[2], Pathakorn Kerdnimith[2], Nutsinee Kosumwisaisakul[2], Piyakamol Teeranaew[2], Apinya Boonpeng[3], Sutthiporn Pattharachayakul[4], Nattachai Srisawat[5,6,7,8,9,10] and Weerachai Chaijamorn[2*]

Abstract

Background: The appropriate dosing of imipenem for critically ill AKI patients undergoing CRRT remains scarce.

Purpose: This study aimed to (1) gather the available published pharmacokinetic studies conducted in septic patients receiving continuous renal replacement therapy (CRRT) and (2) to define the optimal imipenem dosing regimens in these populations via Monte Carlo simulations.

Methods: The databases of PubMed, Embase, and ScienceDirect were searched from inception to May 2020. We used the Medical Subject Headings of "Imipenem," "CRRT," and "pharmacokinetics" or related terms or synonym to identify the studies for systematic reviews. A one-compartment pharmacokinetic model was conducted to predict imipenem levels for the initial 48 h of therapy. The pharmacodynamic target was 40% of free drug level above 4 times of the MIC (40% fT > 4 MIC). The dose that achieved at least 90% of the probability of target attainment was defined as an optimal dose.

Results: Eleven articles were identified and included for our systematic review. The necessary pharmacokinetic parameters such as the volume of distribution and the CRRT clearance were mentioned in 100 and 90.9%, respectively. None of the current studies reported the complete necessary parameters. A regimen of 750 mg q 6 h was the optimal dose for the predilution-CVVH and CVVHD modality with two effluent rates (25 and 35 mL/kg/h) for the pharmacodynamic target of 40% fT > 4MIC.

Conclusions: None of the current studies showed the complete necessary pharmacokinetic parameters for drug dosing. Pharmacodynamic target significantly contributed to imipenem dosing regimens in these patients. Different effluent rates and types of CRRT had minimal impact on dosing regimens. Clinical validation of the recommendation is necessary.

Keywords: Imipenem, Drug dosing, AKI, CRRT, Critically ill patients

Introduction

In the critical care setting, both acute kidney injury (AKI) and critically ill are common complicating factors to therapeutic management. Anuric AKI patients may need therapeutic renal support by continuous renal

*Correspondence: weerachai.cha@siam.edu
[2] Faculty of Pharmacy, Siam University, Bangkok, Thailand
Full list of author information is available at the end of the article

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replacement therapies (CRRT), which can further complicate drug dosing regimens. Imipenem is one of the carbapenem antibiotics possessing a broad spectrum of activity against many Gram-positive, Gram-negative aerobic, and anaerobic bacteria. In patients without history of renal impairment, the clearance of imipenem is 165–207 ml/min [1]. The volume of distribution (Vd) of imipenem in adults averages 0.23–0.35 L/kg [2]. Due to its properties, imipenem is susceptible to be removed from CRRT treatments. In adult patients without renal impairment, the dosing recommendation of imipenem is 500–1,000 mg given intravenous (IV) every 6–8 h (h), with the maximum daily dose of 4 g [3]. Though its use is often limited by the availability of other carbapenems, imipenem is still recommended as one of the first-line treatments by several society practice guidelines for the management of serious infections due to resistant pathogens [4–6]. Imipenem is often implicated with neurological side effects. However, recent reports showed that the risk of adverse effects remains low (< 0.2%) as long as the dose is appropriate [7]. Most patients who developed neurological toxicities had predisposing risk factors to increase brain permeability to imipenem [8]. Therefore, appropriate dosing to achieve therapeutic effect and to avoid adverse event is very important. Seyler et al. reported that in infected patients receiving CRRT, the recommended doses of several beta-lactams are inadequate to achieve pharmacodynamic targets [9]. However, the data reflecting dose recommendation for imipenem in patients undergoing CRRT are scarce.

Previous studies reported that free drug concentration for which exceeds the MIC for 40% of the dosing interval is essential for clinical success in using anti-infective therapy [10]. In our study, we aim to define the optimal dosing by utilizing Monte Carlo simulation to predict serum drug concentration based on available dosing regimens for patients undergoing CRRT. The optimal dose is referred to the regimen that is able to achieve probability of target attainment of > 90%.

Several factors must be considered before selecting the imipenem dose for patients receiving CRRT. Both CRRT modality and intensity play major roles in drug clearance in CRRT [11]. An effluent flow rate of 25 ml/kg/h is nowadays considered the most commonly used for critically ill patients with AKI [12]. However, in some cases, a high intensity (35 ml/kg/h) flow rate can also be used. Chaijamorn et al. reported higher antibiotic clearance in AKI patients receiving high intensity continuous venovenous hemofiltration (CVVH) [13]. Therefore, studies recommending dosage regimens should provide important operational treatment characteristics for the clinicians to determine the similarities or differences in order to provide the accurate recommendation for the individual patient.

Thus, both antibiotic-related pharmacokinetics and CRRT-related operational characteristics are essential to make dosing recommendations. This systematic review is aimed to evaluate the sufficient data reporting in pharmacokinetic studies conducted in AKI patients receiving CRRT and to define the optimal imipenem dosing recommendation by Monte Carlo Simulation based on pharmacokinetic parameters derived from published studies.

Methods

Search strategies

The following databases were used to search for original research articles from November 1998 to May 2020: PubMed, Embase, and Science direct. We used the Medical Subject Headings (MeSH) of "Imipenem," "continuous renal replacement therapy," "pharmacokinetics," "continuous venovenous hemofiltration," "continuous venovenous hemodiafiltration," "continuous venovenous hemodialysis." We also manually searched the reference lists of the retrieved studies to identify additional studies for systematic reviews. The search was limited to human study and the English language.

Study selection

The articles were included if they were the traditional pharmacokinetics study of imipenem and conducted in the patient who received the continuous renal replacement therapy. The following criteria were excluded: (1) population pharmacokinetics, (2) intermittent hemodialysis (IHD) or sustained low-efficiency dialysis (SLED) pharmacokinetics studies, (3) concomitant use of Extracorporeal Membrane Oxygenation (ECMO) with CRRT, (4) non-English language article or review articles.

Data extraction

Two authors (TC and PK) independently extracted data using a data extraction form following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline. Disagreements between the independent researchers were resolved by discussions with a third independent researcher (WC).

Main outcomes measurement

Studies included in this review were assessed for sufficient data reporting in the septic patients receiving CRRT using the ideal dataset required from the previous study [14]. This dataset includes (1) Drug data: antibiotic assayed, specific pharmacodynamic target and dose recommendation, (2) Patient demographics: age, weight, the severity of illness, number of the patients in the study, residual renal function, and hepatic function, (3) Basic

pharmacokinetics: volume of distribution (Vd), total clearance, CRRT clearance, non-CRRT clearance (CL_{NR}), and protein binding or serum albumin, and (4) specific CRRT clearance parameters depended on CRRT mode:

- pre-dilution CVVH: sieving coefficient (SC), ultrafiltration rate (Qf), blood flow rate (Qb), hematocrit (Hct), and predilution replacement flow rate (Qpre)
- post-dilution CVVH: sieving coefficient (SC) and ultrafiltration rate (Qf)
- CVVHD: saturation coefficient (SA) and dialysis flow rate (Qd)
- CVVHDF: SC or Sd, ultrafiltration rate (Qf) and dialysis flow rate (Qd) or effluent flow rate (Qf + Qd)

The quality assessments were performed independently by two investigators (DR and TC). The percentage of each variable was calculated to describe the completion of data provided.

Monte Carlo simulations and pharmacodynamic target

The one-compartmental pharmacokinetic models of the first 48-h imipenem concentration for AKI receiving CRRT were developed based on the previous literature [15]. The necessary pharmacokinetic parameters from 11 studies of imipenem conducted in anuric or oliguric patients receiving CRRT were selected and included in the models [2, 16–25]. Blood flow rate of 200 mL/min and hematocrit 30% were used in our pharmacokinetic model. The infusion time of the drug was 0.5-h. The correlation (r^2) between body weight and Vd or CL_{NR} was input to the model to generate a population specific virtual patient. SA was obtained from a study included 35 patients receiving CVVHD. Due to its similar principle, we decided to incorporate the SA obtained from two hemodialysis studies, for a total of 54 patients to improve the generalizability. Free fraction of imipenem in plasma was also obtained and incorporated into the model [3].

Based on Kidney Disease: Improving Global Outcomes (KDIGO) recommendation, ultrafiltration, or dialysate flow rates of 25 mL/kg/h were used in the pre-hemofilter dilution CVVH and CVVHD models, respectively [12]. High CRRT intensity, the ultrafiltration, or dialysate flow rates of 35 mL/kg/h, which were represented to the common effluent flow rate in clinical practice, were also used in this simulation [26].

The drug concentration–time profile of 5000 virtual patients was created by Monte Carlo simulation (Oracle Crystal Ball Classroom) [11, 27]. In this study, the pharmacodynamic targets of 40%, 100% of unbound fraction of drug level above the MIC (40% fT > MIC, 100% fT > MIC), and 40% of unbound fraction of drug level above 4 times of the MIC (40% fT > 4 MIC) were studied. The MIC breakpoint of 2 mg/L based on Clinical and Laboratory Standards Institute (CLSI) was chosen for susceptible *Pseudomonas aeruginosa* [28]. The proportion of patients that attain the pharmacodynamic (PD) target was calculated as the probability of target attainment (PTA). The optimal dosage regimens were considered when the lowest dose was able to achieve the PTA at least 90%.

To calculate drug concentration profile, the equations used in the model were the following:

$$CL_{HD}(L/h) = SA^{*}Qd$$
$$CL_{HF}(L/h) = SC^{*}Q_{uf}^{*}[Q_{plasma}/Q_{plasma} + Q_{replacement}]$$
$$Vd = Vd(L/kg)\,^{*}Wt(kg)$$
$$k_e = (CL_{NR} + CL_{HD})/Vd$$
$$k_e = (CL_{NR} + CL_{HF})/Vd$$

where CL_{HF} is the transmembrane clearance in hemofiltration; SC is sieving coefficient; Q_{uf} is the ultrafiltrate flow rate; Q_{plasma} is the plasma flow rate ($Q_{plasma} = Q_{blood}{}^{*}(1—\text{hematocrit})$; hematocrit is 30%); $Q_{replacement}$ is the replacement fluid flow rate ($Q_{replacement} = Q_{uf}$); CL_{HD} is the transmembrane clearance in hemodialysis; SA is the saturation coefficient; Q_d is the dialysate flow rate; Vd is the volume of distribution; Wt (kg) is the body weight; k_e is the elimination rate constant.

Results

The study selection chart is shown in Fig. 1. The literature search yielded 148 studies related to our search terms. Duplicated and irrelevant studies were eliminated via screening from two independent pharmacists. As a result, 16 articles were eligible for full-text assessment. Only 11 studies met the inclusion criteria and included in the assessment for completion of the pharmacokinetic parameters (Table 1). All studies are based on prospective data and included patients undergoing CRRT. The studies included were published from 1989 to 2019.

Main outcome assessment

Notably, none of the included studies reported completion of necessary pharmacokinetic parameters.

Drug data

All studies reported drug assay. Most studies reported dose recommendations; however, only 22% reported prespecified pharmacodynamic target. None of the studies reported the free fraction of imipenem in the plasma (Fig. 2a).

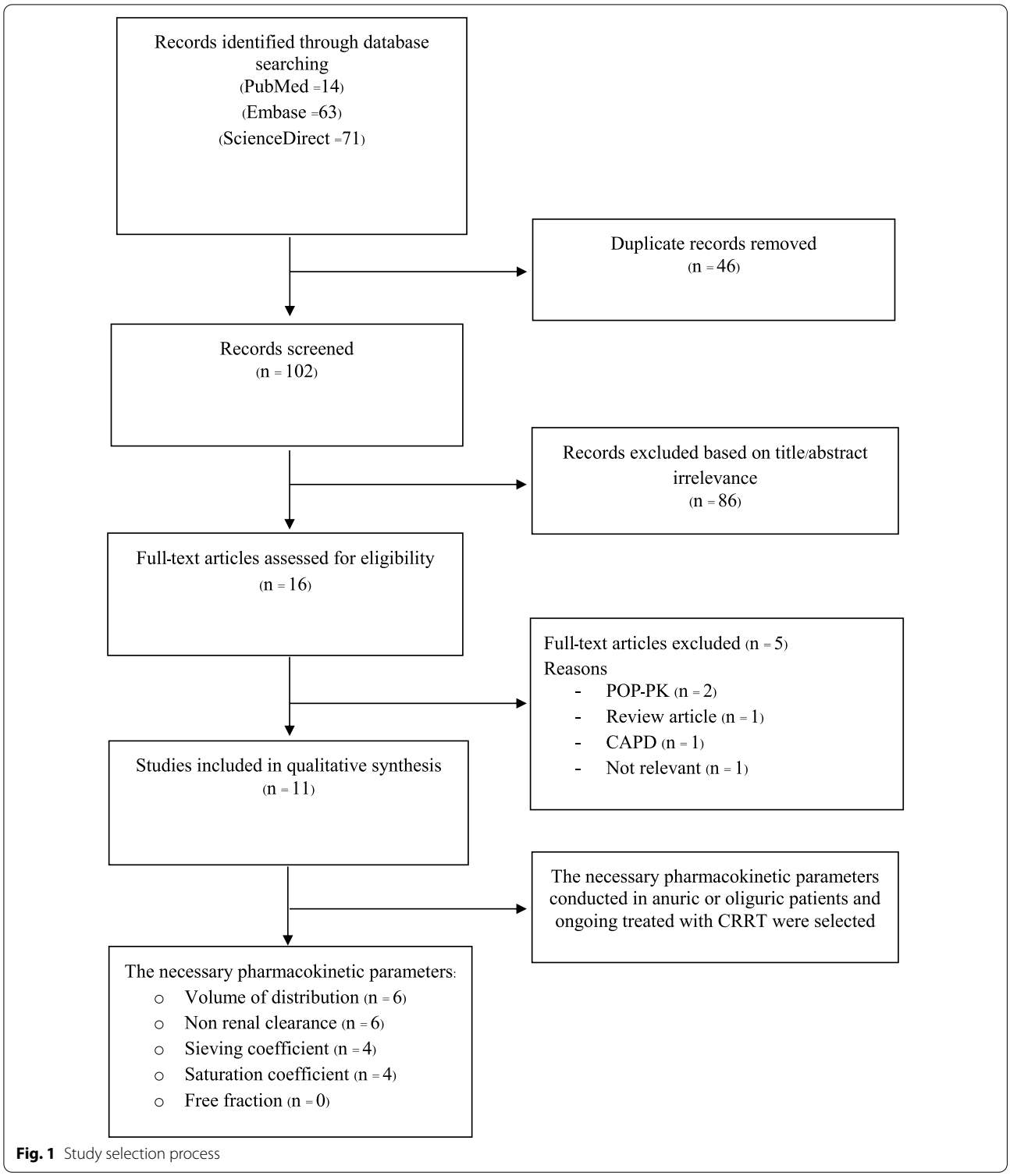

Fig. 1 Study selection process

Patient demographics

Most studies reported age and sample size of the studied population. About 80% of studies described residual renal function. Less than 10% reported hepatic function (Fig. 2b).

Table 1 Key characteristics of published pharmacokinetics studies of imipenem in critically ill patients undergoing CRRT [2, 9–18]

References	CRRT mode	SC or SA	Vd (L/kg)	CL_{NR} (ml/min)	CL_{CRRT} (ml/min)	Pre-specified PD target	Dose recommendation
Keller et al. [20]	CAVH	1.16	0.29	108.5 ± 29.6	7.0 ± 3.4	NS	NS
Przechera et al. [16]	CAVH	1.13 ± 0.12	0.47 ± 0.16	–	6.49	NS	NS
Vos et al. [18]	CAVH CAVHD	SC: 1.05 ± 0.19	–	–	9 ± 3 (CVVH) 16 ± 7 (Qd 1 L/h) 30 ± 7 (Qd 3 L/h)	NS	NS
Mueller et al. [2]	CVVH	0.8	0.33 ± 0.09	95 ± 13.8	13.3	NS	NS
Hashimoto et al. [24]	CVVHD	–	0.38 ± 0.13	70.62 ± 14.6	18.74 ± 1.2	NS	NS
Fish et al. [23]	CVVH CVVHDF	1.21 ± 0.11 (CVVH), 1.28 ± 0.17 (CVVHDF)	0.36 ± 0.1 (CVVH), 0.37 ± 0.13 (CVVHDF)	109 ± 24 (CVVH), 120 ± 32 (CVVHDF)	36 ± 13 (CVVH), 57 ± 28 (CVVHDF)	Yes	Yes
Afshartous et al. [21]	CVVHD	–	0.32	–	32.4 ± 9.8*	Yes	NS
Boucher et al. [22]	CVVH	1.01 ± 0.12	0.39 ± 0.27	191.5	54.5	No	NS
Wen et al. [19]	CVVHDF CVVH	–	0.37 ± 0.19 (CVVHDF) 1.11 (CVVH)	–	1.9 mL/min/kg (CVVHDF) 2.8 mL/min/kg (CVVH)	Yes	NS
Breilh et al. [26]	CVVH	0.52–0.80	0.33	236.59	32.62	Yes	NS

NS, data not stated

*Carbapenem CRRT clearance

Basic pharmacokinetic parameters

The pharmacokinetic parameters of interest were Vd, and clearance where all studies reported Vd, and 90% reported total and CRRT clearances. Only 27% mentioned protein binding or serum albumin levels (Fig. 2c).

Specific CRRT clearance parameters

Across 10 selected studies, five of them studied patients undergoing CVVH, where most of them were treated with either polysulfone or AN-69 hemofilters. CVVHD and CVVHDF were utilized in 3 and 2 studies, respectively. Dilution methods were reported in 75% of the studies. Pre-dilution mode was mentioned at 62.5% of both CVVH and CVVHDF modalities. Blood flow rate and hematocrit, the parameters for calculating the correction factor in pre-dilution CVVH, were revealed and accounted for 83.3% and 16.6%, respectively. Of note, 72% of the studies reported SC or SA (Fig. 2d).

The optimal dosage regimens of imipenem

The PTAs of imipenem dosing regimens for *Pseudomonas aeruginosa* infections with MIC ≤ 2 mg/L in pre-dilution CVVH and CVVHD modalities with 25 and 35 mL/kg/h effluent rates are shown in Tables 2 and 3. A regimen of 500 mg every 8 h is the optimal dose to achieve pharmacodynamic targets of 40% fT > MIC for both CVVH and CVVHD at the effluent rate of 25 and 35 mL/kg/h. However, with more aggressive target of 40% fT > 4MIC, regardless of the effluent flow rates or modality, the optimal dose is 750 mg every 6 h. For a target of 100% fT > MIC, the optimal regimens for CVVH include 2500 mg every 8 h and 2000 mg every 6 h for the effluent flow rates of 25 and 35 ml/min/kg, respectively. All necessary variables for dosing the drug including pharmacokinetic parameters, CRRT setting, and patient characteristics are described in Table 4. The recommendations of imipenem dosing regimens for treating *Pseudomonas aeruginosa* infections with various pharmacodynamic targets in critically ill patients undergoing CRRT from the simulations are summarized in Table 5. Figure 3 demonstrates the PTA results of meropenem dosing regimens at different MICs in pre-dilution CVVH with 25 mL/kg/h effluent rates for treatment of *Pseudomonas aeruginosa* infection in virtual patients for the first 48 h.

Discussions

In our study, we conducted a systematic review of pharmacokinetic studies of imipenem in critically ill patients receiving CRRT. Our review indicated that the current

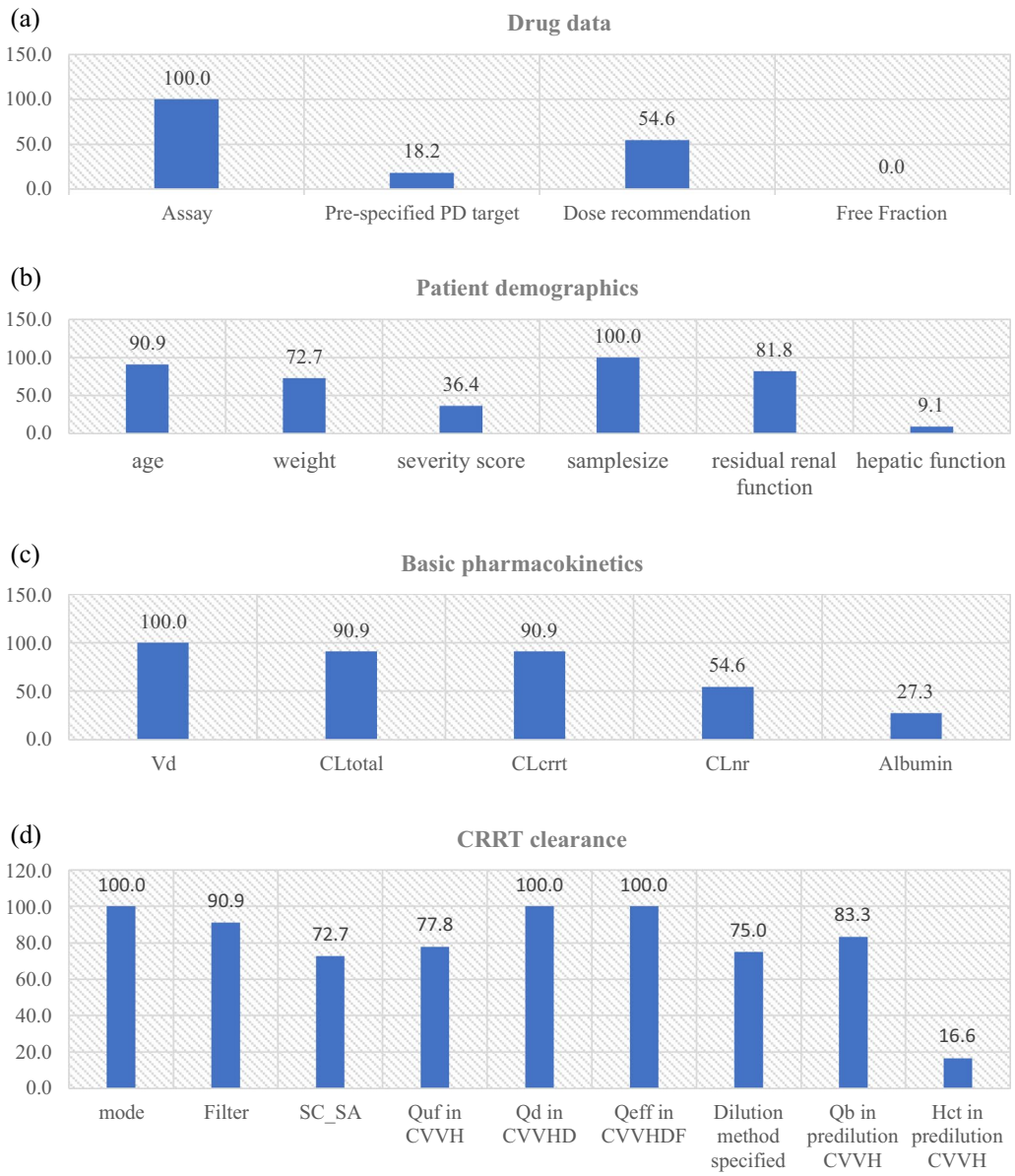

Fig. 2 Data on characteristics obtained from literature analysis

literature does not provide sufficient information for drug dosing in patients with CRRT. CRRT operational characteristics and pharmacokinetic parameters as well as the pharmacodynamic target should be considered to design dosage regimen in this population.

Effect of CRRT modality and drug clearance

The studies evaluated for this review were mostly done as continuous treatments (> 24 h). However, the variability in treatment modalities and operational characteristics (blood, dialysate, effluent flow rates, pre- vs post-dilution, etc.) were significant. With all the variability, overall key pharmacokinetic parameters are comparable across all modalities (Vd: 0.29–0.47 L/kg for CAVH, 0.33–0.39 L/kg for CVVH, and 0.32–0.38 L/kg for CVVHDF) (Table 1) [2, 16–26].

Imipenem is a moderately hydrophilic drug with Vd of 0.23–0.35 L/kg [2] and low protein binding (~ 20%) [3]. Because of these characteristics, it can be removed efficiently by CRRT with consequent need for a careful dosage adjustment [29]. Theoretically, diffusive technique is considered to be a better modality for solute

Table 2 PTA of all recommended imipenem dosing regimens for *Pseudomonas aeruginosa* infections in pre-dilution CVVH modality with 25 and 35 mL/kg/h effluent rates

Dosage regimens	Probability of target attainment over 48 h, MIC of 2 mg/L					
	Effluent rates 25 mL/kg/h			Effluent rates 35 mL/kg/h		
	40% fT > MIC	40% fT > 4MIC	100% fT > MIC	40% fT > MIC	40% fT > 4MIC	100% fT > MIC
500 mg q 8 h*	0.9994	0.1708	0.0290	0.9998	0.1076	0.0172
750 mg q 12 h*	0.9850	0.1044	0.0142	0.9752	0.0598	0.0062
500 mg q 6 h*	1	0.5594	0.1288	1	0.4654	0.1074
1000 mg LD 500 mg q 8 h*	1	0.3090	0.2288	0.9996	0.2280	0.1706
1000 mg LD 500 mg q 6 h	1	0.6942	0.5554	1	0.6088	0.4992
750 mg q 6 h	1	0.9396	0.4388	1	0.9208	0.4122
1000 mg q 8 h	1	0.9280	0.4702	1	0.8878	0.4174
2000 mg LD 1000 mg q 8 h	1	0.9700	0.7122	1	0.9560	0.6818
2000 mg q 12 h	0.9996	0.9426	0.4750	0.9984	0.9082	0.3946
2500 mg q 8 h	1	1	0.9108	1	0.9996	0.8938
2000 mg q 6 h	1	1	0.9558	1	1	0.9536
3000 mg q 8 h	1	1	0.9430	1	1	0.9204
16,000 mg q 12 h	1	0.9998	0.9002	1	0.9996	0.8772
22,000 mg q 12 h	1	1	0.9334	1	1	0.9010

PTA probability of target attainment, *CVVH* continuous venovenous hemofiltration, *LD* loading dose

*Literature based regimens

Table 3 PTA of all recommended imipenem dosing regimens for *Pseudomonas aeruginosa* infections in CVVHD modality with 25 and 35 mL/kg/h effluent rates

Dosage regimens	Probability of target attainment over 48 h, MIC of 2 mg/L					
	Effluent rates 25 mL/kg/h			Effluent rates 35 mL/kg/h		
	40% fT > MIC	40% fT > 4MIC	100% fT > MIC	40% fT > MIC	40% fT > 4MIC	100% fT > MIC
500 mg q 8 h*	1	0.1970	0.0408	0.9992	0.1318	0.0196
750 mg q 12 h*	0.9864	0.1340	0.0238	0.9734	0.0674	0.0096
500 mg q 6 h*	1	0.5812	0.1484	0.9998	0.4710	0.1182
1000 mg LD 500 mg q 8 h*	1	0.3434	0.2676	0.9994	0.2490	0.1910
1000 mg LD 500 mg q 6 h*	1	0.7230	0.5804	1	0.6152	0.4968
750 mg q 6 h	1	0.9388	0.4668	1	0.9052	0.4234
1000 mg q 8 h	1	0.9214	0.4926	1	0.8700	0.4112
2000 mg q 12 h	0.9988	0.9408	0.4906	0.9976	0.9000	0.4010
1500 mg q 8 h	1	0.9966	0.7700	1	0.9948	0.7128
1500 mg q 6 h	1	1	0.9016	1	0.9992	0.8826
2000 mg LD then 1500 mg q 6 h	1	1	0.9500	1	0.9996	0.9402
2500 mg q 8 h	1	0.9998	0.9254	1	1	0.8872
3000 mg LD then 2500 mg q 8 h	1	0.9998	0.9322	1	1	0.9138
16,000 mg q 12 h	1	0.9998	0.9036	1	0.9998	0.8862
22,000 mg q 12 h	1	0.9998	0.9330	1	0.9998	0.9058

PTA probability of target attainment, *CVVHD* continuous venovenous hemodialysis, *LD* loading dose

*Literature based regimens

Table 4 Virtual patient characteristics and key pharmacokinetic parameters from simulation

Parameters	Simulation-based values (mean ± SD (range limits))
Weight (kg)	86.6 ± 29.2 (40− ∞), N = 100
V_d (L/kg)	0.34 ± 0.11 (0.15–0.63), N = 33
CL_{NR} (mL/min)	103.82 ± 28.95 (52.51–168.0), N = 31
Residual renal clearance (mL/min)	0
SC	1.05 ± 0.17 (0.8–1.34), N = 32
SA	0.77 ± 0.33 (0.37–1.52), N = 54
Qb (mL/min)	200
Hct (%)	30
Qf or Qd (mL/kg/h)	25 and 35
Free fraction	0.8 ± 0.16
Pharmacodynamic target	40% fT > MIC 40% fT > 4MIC 100% fT > MIC

SD standard deviation, *kg* kilogram, *N* number of patients, *L* liter, *mL* milliliter, *min* minute, *SC* seiving coefficient, *SD* saturation coefficient, *Qb* blood flow rate, *Hct* hematocrit, *Qf* ultrafiltration rate, *Qd* dialysate flow rate, *fT/MIC* free drug level above 4 times of the minimum inhibitory concentration

Table 5 Recommendations of imipenem dosing regimens for treating *Pseudomonas aeruginosa* infections with various PD target in critically ill patients undergoing CRRT

PD target	Effluent rates (mL/kg/h)	CVVH (pre-hemofilter dilution)	CVVHD
40% fT > MIC	25 mL/kg/h	500 mg q 8 h or 750 mg q 12 h	500 mg q 8 h
	35 mL/kg/h		750 mg q 12 h
40% fT > 4MIC	25 mL/kg/h	750 mg q 6 h	750 mg q 6 h
	35 mL/kg/h		
100% fT > MIC	25 mL/kg/h	2500 mg q 8 h	1500 mg q 6 h
	35 mL/kg/h	2000 mg q 6 h	2000 mg LD then 1500 mg q 6 h

CVVH continuous venovenous hemofiltration, *CVVHD* continuous venovenous hemodialysis, *LD* loading dose

clearance, than of the convection technique. Thus, one can assume that the clearance of imipenem in CVVHDF should be greater than CVVH. However, several pharmacokinetic studies published over the past years have shown the opposite. Giles et al. reported meropenem clearance (similar PK characteristics to imipenem, Vd 0.35 L/kg, MW 383 Da [30]) between CVVH and CVVHDF with the comparable intensity to be 3.9 L/h and 4.7 L/h, respectively [31]. Similar results were reported in simulation studies which they suggested that modality had a minimal impact on drug clearance and drug dosing recommendation [32, 33]. In our review, Fish reported CL_{CVVHDF} was 57 ± 28 ml/min, while the CL_{CVVH} was only 36 ± 13 ml/min. Though it seemed that CVVHDF yielded a higher imipenem clearance, the replacement fluid rate from CVVHDF was 35.5 mL/min, while it was only 18.8 mL/min for CVVH, suggesting that imipenem clearance between CRRT modalities cannot be determined solely based on the mode, rather the replacement fluid rate should also be considered. Vos et al. reported imipenem clearance to be 16 ± 7 (Qd 1 L/h) and 30 ± 7 (Qd 3 L/h) in patients receiving CAVHD [18]. Similar findings were also reported in simulation studies in which rates of replacement fluid impact the drug concentration and pharmacodynamic target attainment [32, 33]. In our review, all studies reported CRRT modality; however, only 77% reported effluent flow rate for CVVH. This discrepancy can explain why the clearance and ultimately dosing recommendations from each study were different.

Effect of pharmacokinetic parameters

The pharmacokinetic changes of hydrophilic drug in critically ill patients such as increased Vd due to volume overload and decreased protein binding due to catabolic state can drastically lower drug concentration [34]. Based on our review, the imipenem volume of distribution from critically ill AKI patients approximated 0.29 to 1.1 L/kg. This value is slightly higher than reported in normal population (0.2–0.3 L/kg). As $Cl = k_e \times Vd$, the variation in Vd would affect drug clearance and the probability of pharmacodynamic target attainment.

As most patients in the reviewed studies were anuric, non-renal clearance was regarded as all clearance that was not due to the effect of hemofilter. In the studies that specifically examined non-renal clearance, some was calculated as the difference between total body clearance and clearance due to hemofilter ($CL_{NR} = CL_{TOT} - CL_{CRRT}$). Based on this equation, the non-renal equation is comprised of hepatic clearance and the remaining clearance that came from urine production. Therefore, examining residual renal function in each study is important to determine the dosing recommendation from the pharmacokinetic studies. However, only 80% of the studies reviewed elaborated the residual renal function. In our review, non-renal clearance averages 103.82 mL/min. Mueller et al. described the significant of non-renal clearance for imipenem by comparing AKI and CKD patients receiving CVVH and found that non-renal clearance in critically ill AKI patients was greater than CKD (95 vs 51 mL/min, respectively), resulting in the higher dose recommended in the AKI group [2]. This shows the significant of examining non-renal clearance in clinical studies. Unfortunately, only 50% reported CL_{NR} in the studies reviewed.

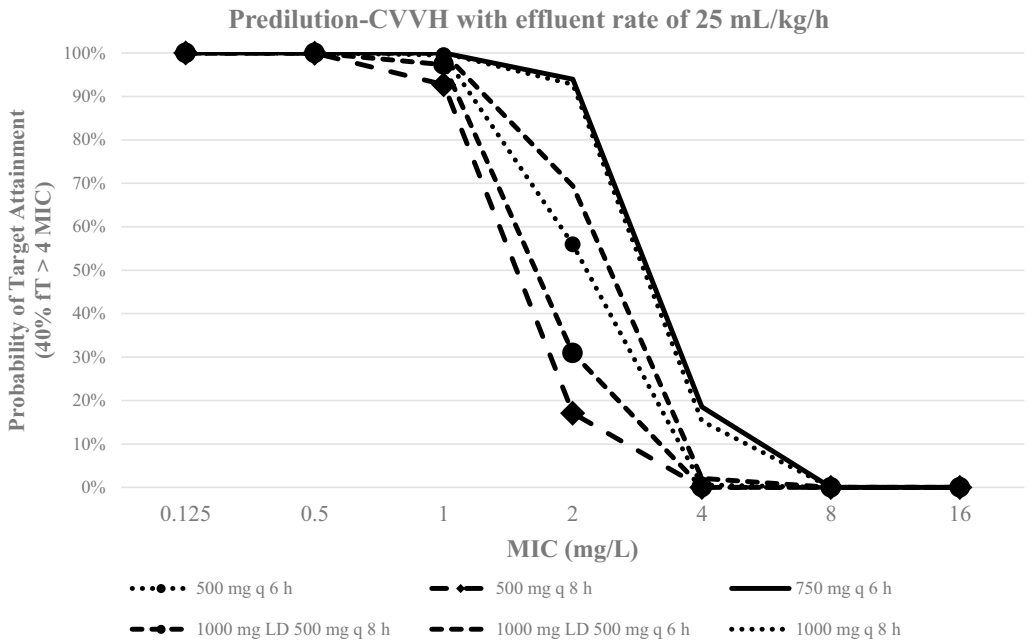

Fig. 3 PTA results of imipenem dosing regimens at different MICs in pre-dilution CVVH with 25 mL/kg/h effluent rates for treatment of *Pseudomonas aeruginosa* infection in virtual patients for the first 48 h

Additionally, volume overload in ICU patients has been shown to be associated with hypoalbuminemia and could increase free drug concentrations that would be removed by CRRT, the liver, and the kidney [34]. Given these reasons described, the loading dose concept is crucial to attain the PTA target in these situations. Therefore, knowing the serum albumin for the patients studied could be beneficial in determining drug dosing. However, less than 30% reported serum albumin in our review.

Effect of pharmacodynamic parameters

In this systematic review, wide variability of dosing recommendation was observed. Doses ranging from 500 mg every 24 h to 1,000 mg every 24 h was suggested. The variety of dosing recommendations can be explained by the difference in pharmacodynamic targets. In an animal study, the bacteriostatic effect was demonstrated when fT > MIC greater than 20%. When the fT > MIC greater than 40%, the bactericidal effect can be observed [35]. Nonetheless, Tam et al. suggested that achieving higher target as fourfold MIC was associated with maximum bactericidal activity of β-lactams [36]. Fish et al. recommended imipenem dosing regimen of 500 mg every 6 h for the PD target of 50–80% fT > MIC (MIC of ≤ 4 mcg/ml in patients undergoing CVVH and CVVHDF [23]. While Afshartous et al. aimed for more aggressive target of 40% fT > 4MIC, the dose of 500 mg every 6–8 h failed to achieve the target and was not recommended [21]. This showed the significance of including pharmacodynamic target in the study as the impact on dosing recommendation is immense. Unfortunately, only 18% of the studies reviewed reported the pharmacodynamic target to support their dosing recommendation.

Effect of patient demographic

The demographic of the studied patients should be mentioned for the generalizability of the study. Extracellular volume overload may increase the apparent volume of distribution of highly water-soluble drugs; thus, usual doses may result in low plasma levels in volume overloaded patients and may require a loading dose or higher maintenance dose. Non-renal clearance as mentioned above also contributes significantly to total drug clearance and therefore should be described. Further, residual renal function of the patients studied will impact the clearance and ultimately dosing recommendation. Li et al. suggested that with the same pharmacodynamic target, patients with oliguria were less likely to achieve pharmacodynamic target attainment [15]. Thus, to be able to apply the results to the specific patients, these patient demographics must be demonstrated. In our review, about 80% reported residual renal function with only 30% reported disease severity.

The optimal dosage regimens of imipenem

Our simulation suggested that imipenem dosing regimen of 750 mg every 6 h is able to achieve a PD target of 40% fT > 4MIC (MIC of 2 mg/L), regardless of effluent rates and modalities. The aggressive pharmacodynamic target was chosen in our simulation, particularly for the treatment of severe infection which are common in critically ill patients. Our dosing recommendations are higher than the previous study by Fish et al., which they recommended at lower PD target of 40% fT > MIC (MIC of 2 mg/L). Both Fish et al. and our simulations showed also that the effect of different CRRT modality was minimal. Conversely, Wen et al. recommended that the doses of 500 mg every 6 h and 1 g every 8 h could not achieve the therapeutic target of 40% fT > 4MIC (MIC of 16 mg/L) and may cause therapeutic failure. The difference in dosing recommendation can be explained by the different in PD targets and several patients in Wen's study had significant residual renal function, both of which resulted in the higher dosing requirement. When applying more aggressive target of 100% fT > MIC, our simulations showed the regimen of 2,500 mg every 8 h is recommended for CVVH at the effluent rate of 25 mL/kg/h. Though this dose is able to meet PD target, it is exceeding the maximum dosing recommendation for normal renal function (4 g/day). Despite the negligible neurological side effect of imipenem vs other carbapenems [7], imipenem has been associated with several reports of causing seizures and central nervous system toxicity in circumstance that the therapeutic drug level is elevated and in patients with predisposing factors [8]. Therefore, the safety for the aforementioned doses cannot be guaranteed. Applying this high dose in clinical practice cannot be recommended.

Limitation

The clinicians using the results from our simulation should be aware that we did not account for residual renal function to our dosing recommendation. The articles were included if they were published in English. Lastly, our recommendations should be utilized for the patients who share similar clinical characteristics. Clinical validation of our recommendations is suggested.

Conclusions

None of the current published studies reported both necessary pharmacokinetic parameters and operational characteristics of CRRT. CRRT dose and modality have minimal impact on drug dosing requirement to achieve PD target. On the other hand, we found that the aggressiveness of PD target is the key contributor for imipenem dosing regimens. Our study suggests that a regimen of 750 mg every 6 h is the optimal dose to achieve pharmacodynamic targets of 40% fT > 4MIC for both CVVH and CVVHD at the effluent rate of 25 and 35 mL/kg/h. Further exploring clinical outcomes and validation are recommended.

Abbreviations

AKI: Acute kidney injury; APACHE: Acute Physiology and Chronic Health Evaluation; CL_{NR}: Non-renal clearance; CRRT: Continuous renal replacement therapy; CVVH: Continuous venovenous hemofiltration; CVVHD: Continuous venovenous hemodialysis; ECMO: Extracorporeal Membrane Oxygenation; fT > MIC: The cumulative percentage of a 48 h period with 1 times MIC; fT > 4MIC: The cumulative percentage of a 48 h period with 4 times MIC; g: Gram; g/mol: Gram/mol; h: Hour; Hct: Hematocrit; IHD: Intermittent hemodialysis; KDIGO: Kidney Disease: Improving Global Outcomes; kg: Kilogram; L: Liter; LD: Loading dose; MeSH: Medical Subject Headings; mg: Milligram; MIC: Minimum inhibitory concentration; mL: Milliliter; N: Number; POP-PK: Population pharmacokinetics study; PTA: Probability of target attainment; Q: Every; Qb: Blood flow rate; Qd: Dialysate flow rate; Qrep: Replacement flow rate; Qf: Ultrafiltrate rate; r^2: Population-specific correlation; SA: Saturation coefficient; SC: Sieving coefficient; SD: Standard deviation; SLED: Sustained low-efficiency dialysis; SOFA: The Sequential Organ Failure Assessment; Vd: Volume of distribution.

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Authors' contributions

TC and WC equally contributed to the conception and design of the research; TC, WC, PK, NK, PT, AP, and SP equally contributed to the acquisition, analysis, and interpretation of the data; TC, DR, and WC drafted the manuscript. All authors critically revised the manuscript, read, and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethic approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

All authors declare that they have no competing interests.

Author details

[1]Department of Clinical and Administrative Pharmacy Sciences, Howard University College of Pharmacy, Washington, DC, USA. [2]Faculty of Pharmacy, Siam University, Bangkok, Thailand. [3]Division of Pharmacy Practice, Department of Pharmaceutical Care, School of Pharmaceutical Sciences, University of Phayao, Phayao, Thailand. [4]Department of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Songkhla, Thailand. [5]Division of Nephrology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital, Bangkok, Thailand. [6]Excellence Center for Critical Care Nephrology, King Chulalongkorn Memorial Hospital, Bangkok, Thailand. [7]Critical Care Nephrology Research Unit, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. [8]Academic of Science, Royal Society of Thailand, Bangkok, Thailand. [9]Tropical Medicine Cluster, Chulalongkorn University, Bangkok, Thailand. [10]Department of Critical

Care Medicine, Center for Critical Care Nephrology, The CRISMA Center, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA.

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