


## REVIEW ARTICLE

# Pharmacokinetics of piperacillin and tazobactam in critically ill patients treated with continuous kidney replacement therapy: A mini-review and population pharmacokinetic analysis

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## Abstract

**What is known and objective:** Timely and appropriate dosing of antibiotics is essential for the treatment of bacterial sepsis. Critically ill patients treated with continuous kidney replacement therapy (CKRT) often have physiologic derangements that affect pharmacokinetics (PK) of antibiotics and dosing may be challenging. We sought to aggregate previously published piperacillin and tazobactam (pip-tazo) pharmacokinetic data in critically ill patients undergoing CKRT to better understand pharmacokinetics of pip-tazo in this population and better inform dosing.

**Methods:** The National Library of Medicine Database was searched for original research containing piperacillin or tazobactam clearance (CL) or volume of distribution (V) estimates in patients treated with CKRT. The search yielded 77 articles, of which 26 reported suitable estimates of CL or V. Of the 26 articles, 10 for piperacillin and 8 for tazobactam had complete information suitable for population pharmacokinetic modelling. Also included in the analysis was piperacillin and tazobactam PK data from 4 critically ill patients treated with CKRT in the Military Health System, 2 with burn and 2 without burn.

**Results and Discussion:** Median and range of literature reported PK parameters for piperacillin (CL 2.76 L/hr, 1.4–7.92 L/hr, V 31.2 L, 16.77–42.27 L) and tazobactam (CL 2.34 L/hr, 0.72–5.2 L/hr, V 36.6 L, 26.2–58.87 L) were highly consistent with population estimates (piperacillin CL 2.7 L/hr, 95%CI 1.99–3.41 L/hr, V 25.83–29.59 L, tazobactam CL 2.49 L/hr, 95%CI 1.55–3.44, V 30.62–37.54). The proportion of patients meeting pre-defined pharmacodynamic (PD) targets (median 88.7, range 71%–100%) was high despite significant mortality (median 44%, range 35%–60%). High mortality was predicted by baseline severity of illness (median APACHE II score 23, range 21–33.25). Choice of lenient or strict PD targets (ie 100% $f_T > MIC$

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or 100% $f_T > 4 \times \text{MIC}$ ) had the largest impact on probability of target attainment (PTA), whereas presence or intensity of CKRT had minimal impact on PTA.

**What is new and conclusion:** Pip-tazo overexposure may be associated with increased mortality, although this is confounded by baseline severity of illness. Achieving adequate pip-tazo exposure is essential; however, risk of harm from overexposure should be considered when choosing a PD target and dose. If lenient PD targets are desired, doses of 2250–3375 mg every 6 h are reasonable for most patients receiving CKRT. However, if a strict PD target is desired, continuous infusion (at least 9000–13500 mg per day) may be required. However, some critically ill CKRT populations may need higher or lower doses and dosing strategies should be tailored to individuals based on all available clinical data including the specific critical care setting.

#### KEYWORDS

continuous kidney replacement therapy, critical illness, pharmacokinetics, piperacillin, tazobactam

## 1 | WHAT IS KNOWN AND OBJECTIVE

Sepsis remains a leading cause of mortality throughout the world.<sup>1</sup> In addition to supportive care, appropriate antibiotic therapy is essential to the successful treatment of bacterial sepsis.<sup>2</sup> However, critical illness is associated with physiologic derangements that may significantly affect the volume of distribution (V) or clearance (CL) of antibiotics. Physiologic derangements commonly encountered in critically ill patients that are known to alter V or CL include increased capillary permeability, hypoalbuminemia, augmented renal clearance (ARC), acute kidney injury (AKI) and acid-base disorders.<sup>3–6</sup> Furthermore, continuous kidney replacement therapy (CKRT) is commonly prescribed in critically ill patients with AKI and may contribute to the extracorporeal clearance of antibiotics.<sup>7</sup> Piperacillin and tazobactam (pip-tazo) is a broad-spectrum  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combination that has anti-pseudomonal activity and is one of the most commonly used antibiotics to treat a wide range of bacterial infections in critical care settings. Of interest, the ideal pharmacodynamic target for pip-tazo is not well defined, and aggressive pip-tazo regimens commonly prescribed to critically ill patients placed on CKRT may be associated with significant adverse effects.<sup>8,9</sup> Therefore, we sought to aggregate previously published pip-tazo pharmacokinetic data in critically ill patients undergoing CKRT to better understand pharmacokinetics of pip-tazo in this population, better inform dosing and explore the relationship of pharmacokinetics to pharmacodynamic targets and mortality.

## 2 | METHODS

### 2.1 | Literature review and data synthesis

The National Library of Medicine Database was searched with the following terms “pharmacokinetics of piperacillin OR tazobactam AND (continuous renal replacement therapy OR continuous

venovenous hemofiltration OR continuous venovenous hemodialysis OR continuous venovenous hemodiafiltration)” on 26OCT2021. There were 77 results, of which 26 met the broad inclusion criteria of containing raw pharmacokinetic data, aggregated pharmacokinetic data or estimates of pharmacokinetic parameters in patients treated with CKRT for piperacillin or tazobactam. A summary of all included studies can be found in [Tables 1,2](#) and [3](#). Of note, 6 included studies contained tazobactam PK from case reports or small population PK studies in patients receiving ceftolozane/tazobactam. These studies are summarized in [Table 3](#). Of the 26 studies included overall, a subset of 10 studies for piperacillin and 8 studies for tazobactam contained complete data (ie complete dose information, number of patients contributing to PK curve, CKRT dose etc.) to digitize and compile PK curves appropriate for aggregated population PK modelling. The complete digitized dataset can be visualized in [Figure 1](#).

### 2.2 | Military health system data

The protocol and associated documents, to include informed consent forms, were reviewed and approved by the IRB at the United States Army Medical Research and Development Command (MRDC; Fort Detrick, MD). De-identified patient data were obtained from an IRB-approved protocol at the US Army Institute of Surgical Research (USAISR), US Army Burn Center and Brooke Army Medical Center (BAMC) Surgical Trauma Intensive Care Unit (STICU). There was a total of 4 patients, 2 with no burn injury and 2 with burn injury and all received continuous veno-venous hemofiltration (CVVH). One patient received 2250 mg every 6 h, and the other 3 patients received 3375 every 6 h. All doses were infused over 30 min. For each patient, pre-filter plasma, post-filter plasma and effluent samples were collected at steady state. There was a total of 14 post-dose piperacillin time-concentration observations with patients

TABLE 1 Summary of Mean or Median Demographics of Piperacillin/Tazobactam CKRT PK Studies

Study	Number of Patients	Age (y)	Weight (kg)	Creatinine (mg/dL) <sup>a</sup>	CrCl (mL/min) <sup>a</sup>	Albumin (mg/dL)	APACHE II	Mortality (%)	Dose <sup>b</sup>	PKPD Target Achieved (%) <sup>c</sup>
Current Study	4	74	88.63	1.27	77.34	2.45			2.25–4.5 G q6 h	
Arzuaga et al <sup>35</sup>	14	56.6	75.6		40.91	2.2	22		4.5 G q6 h	
Asin-Prieto et al <sup>29</sup>	16	57	74		43	2.15	22		4.5 G q 4–8 h	
Awissi et al <sup>36</sup>	20	63	86		15.1	2.6	23	35	4.5 G q8 h	90
Bauer et al <sup>19</sup>	42	56.8	95.1					50	2.25–3.375 q 6–12 h	77 <sup>d</sup>
Beumier et al <sup>37</sup>	20							60	4.5 G q 6 h	80
Bue et al <sup>30</sup>	10	70.5	79	1.84	41	2.65			4.5 G q 8 h	
Capellier et al <sup>38</sup>	10	70	72						4.5 G q 8 h	
Jamal et al <sup>39</sup>	16	54.5	71.5				33.25		10 G/day as CI or 2.25 G q 6 h	62.5 or 87.5 <sup>e</sup>
Joos et al <sup>40</sup>	8								1–4 G q 4–12 h	
Kohama et al <sup>41</sup>	10	71.83	60.3	3.39	18.03	2.93			2.25 G q 8 h	
Mueller et al <sup>42</sup>	8	66	67	4.11	8				2.25–4.5 G q 8–24 h	89.9 <sup>f</sup>
Richter et al <sup>18</sup>	71									
Roberts et al <sup>43</sup>	10		77					42		
Roger et al <sup>44</sup>	18	70	77	2.72	28	2.51		42	12 G/day as CI	100
Seyler et al <sup>45</sup>	21								4.5 G q6 h	71
Shotwell et al <sup>34</sup>	68							46	2.25–3.375 G q 6–12 h	
Ulldemolins et al <sup>46</sup>	19	70	80	1.2	65	2.11	21		2.25–4.5 G q6–8 h	
Valtonen et al <sup>47</sup>	6	54	90						4.5 G q12 h	
van der Werf et al <sup>48</sup>	9	56.4	86.55				30.11		4.5 G q8 h	
Varghese et al <sup>49</sup>	10	54	83			2.5	33		4.5 G q8 h	100
Median (Range)	14 (4–71)	63 (54–74)	78 (60.3–95.1)	2.28 (1.2–4.11)	40.91 (8–77.34)	2.5 (2.11–2.93)	23 (21–33.25)	44 (35–60)	4.5 G q8 h	88.7 (71–100)

<sup>a</sup>Creatinine is filtered by CKRT and studies did not consistently report whether sCr and CrCl estimates were obtained prior or during CKRT therapy.

<sup>b</sup>CI = continuous infusion. Most commonly piperacillin-tazobactam was infused over 30 minutes.

<sup>c</sup>PKPD targets were most commonly 50%–100% FT >1–4X MIC =16 mg/L

<sup>d</sup>Stricter target of 50% FT >4X MIC, however 100% of patients met more liberal target of 50% FT >MIC.

<sup>e</sup>Patients received continuous infusion to target 100% FT >4X MIC. Intermittent bolus patients had PTA 62.5% to target 50% FT >4X MIC. Dose 9 g piperacillin/day.

<sup>f</sup>This estimate includes patients not on CKRT. The study did not provide a subgroup PTA analysis for the CKRT population, but mentioned serum concentrations were on average higher in the CKRT population compared to the no-CKRT population.

TABLE 2 Summary of Literature Reported Pharmacokinetic Parameters for Piperacillin and Tazobactam

Study	Piperacillin						Tazobactam					
	Body Clearance (L/h)	CKRT (L/h) <sup>a</sup>	Volume of Distribution (L) <sup>b</sup>	Percent Unbound (%)	Sieving Coefficient	Body Clearance (L/h)	CKRT (L/h) <sup>a</sup>	Volume of Distribution (L) <sup>b</sup>	Percent Unbound (%)	Sieving Coefficient		
Current Study	2.36	1.62	32.4	55.92	0.69	0.72	1.44	28.96	93.11	0.68		
Arzuaga et al <sup>35</sup>	7.92	0.56	31.61		0.34	5.2	0.98	34.65		0.78		
Asin-Prieto et al <sup>29</sup>	6.34	0.64	42.27	78	0.37	4.95	1.02	58.87	66	0.76		
Awissi et al <sup>36</sup>	1.83	2.3		94.4	0.809							
Bauer et al <sup>19</sup>	3.87	1.66	34.5	71		2.9	1.54	38.1	85.4			
Beumier et al <sup>37</sup>	1.4	1.75	18.35									
Bue et al <sup>30</sup>	3.3	2.156	16.77									
Capellier et al <sup>38</sup>	2.6	0.52	22.59									
Jamal et al <sup>39</sup>	2.15	0.86										
Joos et al <sup>40</sup>	2.76	0.6		84								
Kohama et al <sup>41</sup>	1.57	0.71	21.9			1.57	0.56	26.2		0.64		
Mueller et al <sup>42</sup>	1.5	1.32			0.84	0.75	1.02					
Richter et al <sup>18</sup>	2.87 <sup>c</sup>	1.43 <sup>c</sup>										
Roberts et al <sup>43</sup>	2.01	1.53	18.7			4.05	2.73	49.3				
Roger et al <sup>44</sup>	3.3	2.8										
Seyler et al <sup>45</sup>	3.75	1.08	30.8			0.96	1.8	36.6				
Shotwell et al <sup>34</sup>	2.55	1.8	33									
Ulldemolins et al <sup>46</sup>	4.29	1.82	32.3									
Valtonen et al <sup>47</sup>	3.88	0.93				2.17	0.93					
van der Werf et al <sup>48</sup>	1.43	1.09	25.88			3.35	1.09	46.56				
Varghese et al <sup>49</sup>	3.45	1.65	34.86		0.67	2.34	1.46	26.56		0.59		
Median (Range)	2.76 (1.4–7.92)	1.43 (0.52–2.8)	31.2 (16.77–42.27)	78 (55.92–94)	0.68 (0.34–0.84)	2.34 (0.72–5.2)	1.09 (0.56–2.73)	36.6 (26.2–58.87)	85.4 (66–93.11)	0.68 (0.59–0.78)		

<sup>a</sup>When CKRT clearance was not reported, CKRT clearance was assumed to be 0.7 × (Reported Dose of CKRT).

<sup>b</sup>When two-compartment models were reported, this is the sum of the peripheral and central volume of distribution estimates.

<sup>c</sup>The total piperacillin CL in this study was reported as 4.3 L/h. No CKRT CL was reported, so the median value across all studies was imputed.

TABLE 3 Summary of Demographics and Tazobactam Pharmacokinetics from Ceftolozane/Tazobactam Pharmacokinetic Studies

Study <sup>a</sup>	Number of Patients	Age (y)	Weight (kg)	Creatinine (mg/dL) <sup>b</sup>	CrCl (mL/min) <sup>b</sup>	Albumin (mg/dL)	APACHE II	Body Clearance (L/h)	CKRT Clearance (L/h) <sup>b</sup>	Volume of Distribution (L) <sup>c</sup>	Percent Unbound (%)	Sieving Coefficient
Aguilar et al <sup>50</sup>	1	68						5	1.4	108.9		
Bremner et al <sup>51</sup>	1	47	82					4.78	2.72	91.99		
Kuti et al <sup>52</sup>	1	75	66					4.2	0.7	19.2		
Mahmoud et al <sup>53</sup>	1	37	187					2.33	4.27			
Oliver et al <sup>54</sup>	1	61	78.8					0	1.4	52.41		
Sime et al <sup>31</sup>	6	61.5	72.5	1.72	46	2.85	25.2	3.25	2.973	105.33	90	1.08

Note: Patients in Sime et al and Olivier et al received 1.5 G ceftolozane-tazobactam every hours and patients from the other studies received 3 G ceftolozane-tazobactam every 8 h.

<sup>a</sup>All studies except Sime et al are case reports.

<sup>b</sup>Creatinine is filtered by CKRT and studies did not consistently report whether sCr and CrCl estimates were obtained prior or during CKRT therapy.

<sup>c</sup>When two-compartment models were reported, this is the sum of the peripheral and central volume of distribution estimates.

contributing a median of 4 observations (range 2–4). Only 3 patients had tazobactam time-concentration observations with a total of 10 post-dose observations (median 4 observations per patient, range 2–4). These data can be visualized in Figure S1. Methods for determination of piperacillin and tazobactam plasma concentrations are described in the [Supplementary Materials](#).

### 2.3 | Population pharmacokinetic modelling and simulations

Population pharmacokinetic modelling and simulations were performed in Pumas (version 1.1).<sup>10</sup> The first-order conditional estimation method with interaction (FOCEI) was used to estimate population parameters. Data preparation, exploratory analysis and graphs were performed in either Pumas or R (version 3.6.1). The CL due to CVVH ( $CL_{CKRT}$ ) for individual patients from the MHS dataset was calculated as the product of the delivered ultrafiltrate flow rate ( $Q_f$ ), the sieving coefficient ( $S_c$ ) and correction factor for pre-filter fluid administration (CF) as follows:

$$CL_{CKRT} = Q_f \times S_c \times CF \quad (1)$$

where

$$S_c = \frac{C_{effluent}}{(C_{pre} + C_{post})/2} \quad (2)$$

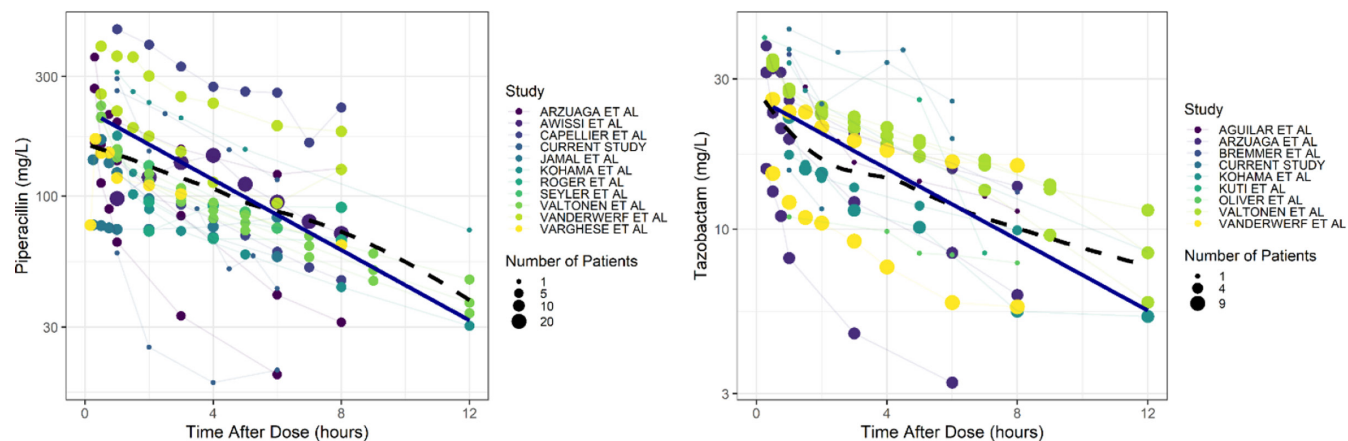
and

$$CF = \frac{Q_b}{Q_b + Q_{rep}} \quad (3)$$

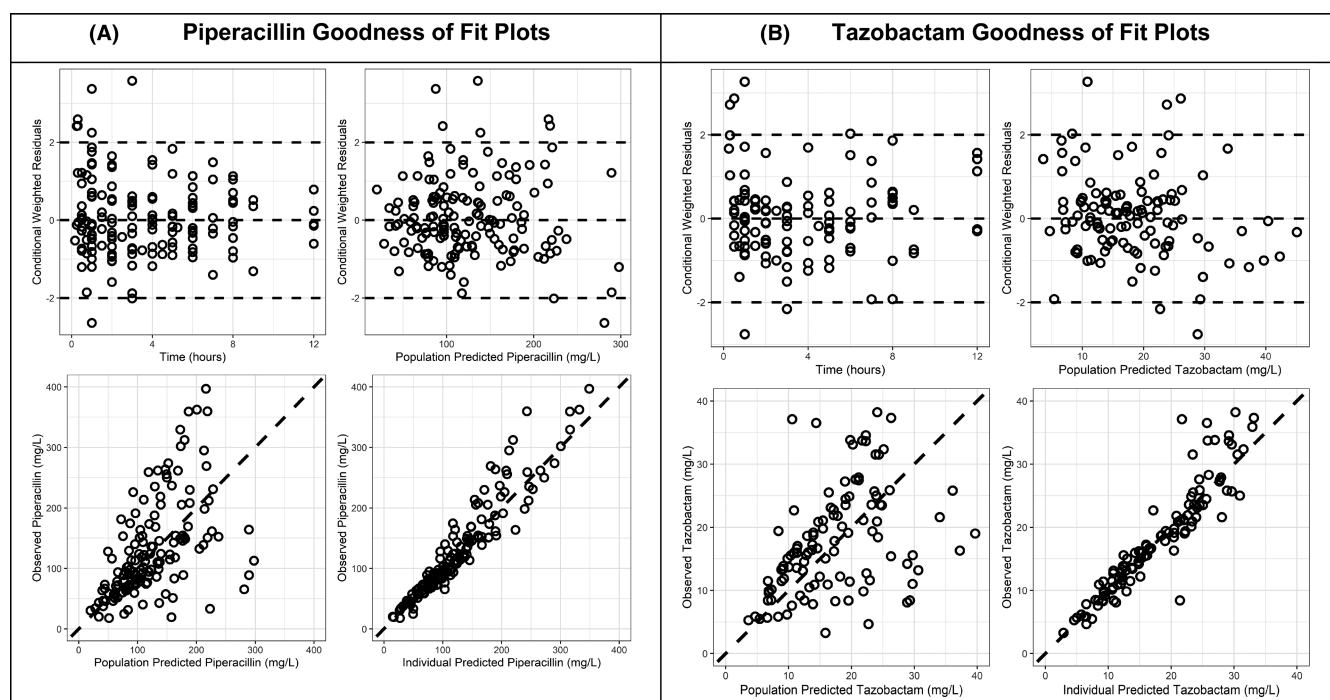
Where  $C_{pre}$ ,  $C_{post}$ ,  $C_{effluent}$ , denote the observed pre-filter, post-filter and effluent concentrations,  $Q_b$  denotes the blood flow rate and  $Q_{rep}$  denotes the rate of pre-filter replacement fluid.<sup>7,11</sup> For data from other studies, the  $CL_{CKRT}$  was extracted from the individual study. If a study did not report  $CL_{CKRT}$ , as both piperacillin and tazobactam fraction unbound and  $S_c$  are approximately 0.7,  $CL_{CKRT}$  was assumed to be 70% of the reported total CKRT dose.<sup>12</sup>

### 2.4 | Pharmacokinetic parameter estimates for MHS Data

The MHS data did not contain sufficient samples in the distribution phase for two-compartment modelling and were not adequate for NCA given significant missing time-concentration data. Therefore, a one-compartment model using FOCEI was utilized to obtain CL and V estimates of piperacillin and tazobactam from the MHS data. The sample size was insufficient to make meaningful inference of covariate effects on CL and V from the MHS dataset; therefore, no covariate analysis was performed. Estimates are provided in [Table 2](#).



**FIGURE 1** Plot of aggregated time-concentration data for piperacillin (left) and tazobactam (right). Blue solid lines represent mean simulations for 4000 mg or 500 mg every 8 hours for piperacillin and tazobactam, respectively (median doses). Black dotted represent locally estimated scatterplot smoothing (LOESS) trend lines weighted by number of patients



**FIGURE 2** Goodness-of-fit plots

## 2.5 | Pharmacokinetic modelling on aggregated data

The aggregated dataset is visualized in [Figure 1](#) and a modified version of this dataset is available in the [Supplementary Material](#) (MHS data are not available to be shared). Exploratory plots ([Figure 1](#)) demonstrated that 1- or 2-compartment models may adequately describe the piperacillin or tazobactam aggregate datasets. As prior probability of target attainment (PTA) analysis demonstrated little difference in results when using 1 or 2 compartment models, and a 1-compartment model is simpler and easier to interpret, we only explored 1-compartment models to describe the aggregate data. For simplicity, each arm in individual studies was considered as its

own trial and between study variability (BSV) is to be interpreted as the variability of mean parameters across all arms of the literature reported PK studies. BSV was modelled using an exponential error model under the assumption that pharmacokinetic parameters are distributed log normally. Parameters generally took the form

$$\theta_i = tv\theta \times e^{\eta_i} \quad (4)$$

where  $\theta_i$  is the post hoc estimated parameter value for study  $i$ ,  $tv\theta$  is the population mean parameter and  $\eta_i \sim (0, \omega^2)$  is the between study random effects for study  $i$ . A proportional error model was used and was scaled by  $\frac{1}{\sqrt{N}}$ , where  $N$  is the number of patients in each arm of the respective PK study. Aggregate data and individual data were modelled together.

## 2.6 | Covariate testing

Covariates were initially evaluated by plotting mean or median demographics from the studies against reported values for CL and V (Supplemental Figure 2). Covariates evaluated for CL were total body weight (WT) and creatinine clearance (CrCl), and covariates evaluated for V were WT and albumin. CrCl was generally extracted from studies. If the CrCl was not reported, CrCl was calculated based off of mean or median demographics with the Cockcroft-Gault (C-G) equation.<sup>13</sup> All covariates were continuous and modelled as

$$\theta_i = tv\theta \times \left( \frac{COV}{COV_{median}} \right)^{\theta_{cov}} \quad (5)$$

Covariate modelling was performed with a forward addition process. A decrease of at least 3.84 units ( $\alpha = 0.05$ ,  $df = 1$ ) in the objective function value (OFV) was considered statistically significant. When covariates were missing, means of all studies were imputed.

## 2.7 | Final model qualification

Final model qualification included examination of standard goodness-of-fit plots, precision of parameter estimates and plausibility of parameter estimates as compared to reported literature.

## 2.8 | Monte carlo simulations

Commonly reported PKPD targets for piperacillin were free piperacillin concentrations 1–4 times above the minimum inhibitory concentrations (MIC) greater than 50%–100% of the time at steady state within the dosing interval ( $ft > 1-4 \times MIC_{50\%-100\%}$ ). The European Committee on Antimicrobial Susceptibility Testing (EUCAST)<sup>14</sup> and Clinical and Laboratory Standards Institute (CLSI)<sup>15</sup> breakpoints for piperacillin to pseudomonas are 16 mg/L. Free piperacillin concentrations were assumed to be 70%<sup>12</sup> of the total piperacillin concentration. To understand the impact of CKRT intensity on dosing requirements, 2000 mg q6 h and continuous infusions of 8000 mg q12 h were simulated with increasing levels of theoretical  $CL_{CKRT}$ . The total per cent of patients achieving various PKPD targets were calculated and plotted, with 1000 time-concentration profiles simulated in each group. PTA simulations were performed only for piperacillin as the tazobactam PK is very similar to piperacillin PK and tazobactam PKPD targets are not as well established.

## 3 | RESULTS AND DISCUSSION

### 3.1 | Patient demographics

Demographics of the individual patients from the MHS are summarized in Table S1. Mean demographics reported in the literature for piperacillin/tazobactam studies are summarized in Table 1.

Demographics were inconsistently reported in ceftolozane/tazobactam and are described separately in Table 3. MHS patient demographics were generally comparable to other critically ill populations receiving CKRT as reported in the literature (Table 1). However, the mean CrCl in the MHS was markedly higher than the median of all studies (77.34 vs. 40.91 mL/min). When interpreting the CrCl, it is important to note that CKRT clears creatinine from the body and not all studies reported clearly whether CrCl measurements were prior or after initiation of CKRT. CrCl estimates from the MHS data were obtained while patients were on CKRT.

Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were reported in 8 of 26 studies (31%). APACHE II scores (median 23, range 21–33.25) were comparable across the populations when reported and corresponded appropriately to high mortality rates (median 44%, range 35%–60%,  $N$  reported = 6, 23% of studies). Reported per cent of patients achieving PKPD targets were disproportionately high (median 87.5%, range 62.5%–100%,  $N$  reported = 8, 31% of studies) as compared to mortality rates. Of note, Bauer et al reported 77% of patients meeting a target of  $ft > 4 \times MIC_{50\%}$ , but when using a more liberal target of  $ft > MIC_{50\%}$ , 100% of patients met the PKPD goal.

### 3.2 | Summary of literature reported pharmacokinetics

Tables 2 and 3 summarize the literature reported PK of both piperacillin and tazobactam in patients with CKRT. Median piperacillin inherent body CL and V were 2.76 L/hr (range 1.4–7.92 L/hr) and 31.2 L (range 16.77–42.27 L), respectively. The median piperacillin  $CL_{CKRT}$  was 1.43 L/hr (range 0.52–2.8 L). The median piperacillin  $S_c$  and fraction piperacillin unbound were 0.68 (0.34–0.84) and 78% (range, 55.92%–94%), respectively, which are appropriately correlated.

Median tazobactam inherent body CL and V from piperacillin/tazobactam studies were 2.34 L/hr (range 0.72–5.2 L/hr) and 36.6 L (26.2–58.87 L), respectively. The tazobactam CLs reported from ceftolozane/tazobactam studies were similar; however, the V in those studies was markedly higher (median 91.99 L, range 19.2–108.9 L). The median tazobactam  $CL_{CKRT}$  from piperacillin/tazobactam studies was 1.09 L/hr (range 0.56–2.73 L/hr), which was similar to those reported in ceftolozane/tazobactam studies. The median tazobactam  $S_c$  and fraction tazobactam unbound reported in piperacillin/tazobactam studies were 0.68 (0.59–0.78) and 85.4% (range, 66%–93.11%), respectively. These estimates are similar to those of piperacillin and are appropriately correlated. Ceftolozane/tazobactam studies did not consistently report tazobactam fraction unbound or tazobactam  $S_c$ .

Exploratory covariate plots (Figure S2) demonstrate that CrCl is likely a covariate to piperacillin and tazobactam CL. This finding is physiologically consistent with the known high proportion of renal clearance of both piperacillin and tazobactam.<sup>12</sup> However, of note, CrCl estimates were limited in this study due to the presence of CKRT. To highlight, the MHS patients had the highest reported

mean CrCl (77.34 mL/min), but the lowest reported tazobactam CL (0.72 L/hr). In regard to volume of distribution, weight appeared to correlate with piperacillin V, but the relationship was not as clear for tazobactam (Figure S2). Serum albumin was negatively related to both piperacillin and tazobactam V. This finding is physiologically consistent where decreased albumin may lead to less protein binding or could be a surrogate marker for capillary permeability.<sup>16,17</sup>

### 3.3 | Final population pharmacokinetic models from aggregate data

Final model estimates and associated metrics are summarized in Table 4a and 4b. The model building process is summarized in Table S1a and b (Supplementary Material). Goodness-of-fit plots (Figure 2) demonstrate that both the piperacillin and tazobactam models were adequately described by a 1-compartment model. Figure 1 demonstrates that the model predicted mean time-concentration profiles are similar to a naïve weighted moving averages for both piperacillin and tazobactam. The final model estimates of piperacillin (CL =2.7 L/hr, V =25.83 L) and tazobactam (CL =2.49 L/hr, 30.62 L) are plausible, and very similar to the median literature reported estimates for piperacillin (CL =2.76 L/hr, V =31.2 L) and tazobactam (CL =2.34 L/hr, V =36.6 L), respectively.

### 3.4 | Probability of target attainment

Figure 3a and 3b summarizes PTA for 8000 mg piperacillin daily either as an intermittent infusion 2000 mg q6 h or as a continuous infusion over 24 h, respectively. An intermittent infusion of 2000 mg q6 h would be adequate to achieve a PKPD target of  $fT > MIC_{50\%}$  up to an MIC of 16 mg/L. However, for stricter targets,  $fT > MIC_{99\%}$  or  $fT > 4 \times MIC_{99\%}$  either increased doses or continuous infusion would be required to reliably achieve a target MIC of 16 mg/L. Of note, the choice of lenient or strict PKPD target had a much greater impact on PTA than  $CL_{CKRT}$ . For any given PKPD target,  $CL_{CKRT}$  had little impact on ability to achieve the goal MIC of 16 mg/L. The only exception was if defining the PKPD target as  $fT > MIC_{99\%}$ , where presence of CKRT was associated with PTA <90%. Nevertheless, even in this case, when  $CL_{CKRT} \leq 2$ , PTA remained high over 75%.

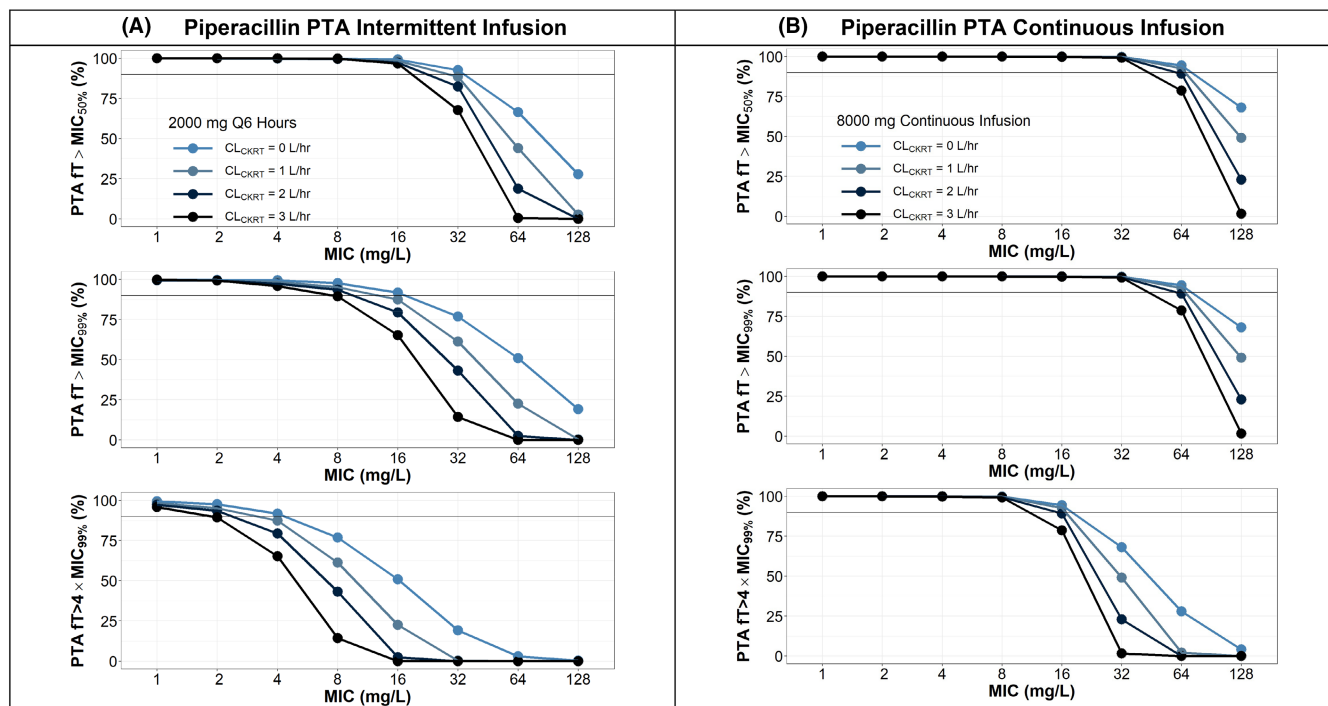
## 4 | DISCUSSION

Here, we present a review and synthesis of the majority of piperacillin and tazobactam PK CKRT literature. Given PK data in critically ill burn patients receiving CKRT are significantly lacking in the literature, particularly unique to our dataset is the addition of 2 critically ill burn patients treated with CVVH from the MHS (Table S1). Further,

TABLE 4 Pharmacokinetic Parameters For (A) Final Piperacillin Model and (B) Final Tazobactam Model

(A)		
<b>Fixed Effects</b>		
Parameter	FOCEI Estimate (%RSE)	FOCEI 95% CI
CL (L/hr)	2.7 (13.48)	1.99–3.41
$V_c$ (L)	25.83 (7.43)	22.07–29.59
<b>Random Effects</b>		
$\omega^2$ CL	0.38 (32.58)	0.14–0.63
$\omega^2 V_c$	0.067 (31.01)	0.026–0.11
$\eta$ -shrinkage CL: 2.4%, $\eta$ -shrinkage $V_c$ : 26.8%, Pearson's correlation coefficients: $\eta$ - $V_c$ & $\eta$ -CL: 0.6		
<b>Residual Unexplained Variability</b>		
Proportional Error	0.42 (8.47)	0.35–0.49
$\epsilon$ -shrinkage: 10.83% condition number: 11666, total observations: 152, 2-log-likelihood: 1446.62		
(B)		
<b>Fixed Effects</b>		
Parameter	FOCEI Estimate (%RSE)	FOCEI 95% CI
CL (L/hr)	2.49 (19.43)	1.55–3.44
$V_c$ (L)	30.62 (11.53)	23.7–37.54
<b>Random Effects</b>		
$\omega^2$ CL	0.61 (55.91)	0–1.28
$\omega^2 V_c$	0.12 (30.47)	0.05–0.2
$\eta$ -shrinkage CL: 1.09%, $\eta$ -shrinkage $V_c$ : 19.76%, Pearson's correlation coefficients: $\eta$ - $V_c$ & $\eta$ -CL: 0.58		
<b>Residual Unexplained Variability</b>		
Proportional Error	0.3 (12.4)	0.23–0.37
$\epsilon$ -shrinkage: 12.26% condition number: 14874, total observations: 112, 2-log-likelihood: 638.37		





**FIGURE 3** Probability of target attainment assuming total daily dose of 8000 mg piperacillin given as either an intermittent infusion (left) or continuous infusion (right) at steady state. Each simulation group included 1000 virtual patients

our review provides robust estimates and confidence intervals of the typical values of CL and V for both piperacillin and tazobactam, validating current trends and recommendations in piperacillin/tazobactam dosing for critically ill patients treated with CKRT.

Surprisingly, despite CKRT commonly reported as a potential cause for inability to achieve appropriate antibiotic levels, we found that a substantially high proportion of patients met their PKPD targets (median 87.5%, range 62.5%–100%). This is further supported by Richter et al<sup>18</sup> who noted patients with CKRT had a 43% increase in piperacillin concentrations compared to patients with no CKRT in a retrospective cohort study. Furthermore, the choice of lenient or strict PKPD target had a large impact on target attainment. In contrast, CKRT intensity had minimal impact on achieving PKPD targets. This is supported by our PTA analysis (Figure 3a and 3b) and observed clinically by Bauer et al<sup>19</sup> where 100% of study patients met a pre-defined lenient target and only 77% of study patients met the pre-defined strict target.

Despite patients with CKRT generally achieving piperacillin PKPD targets at very high rates, mortality was high. Estimates of mortality from this review (median mortality 44%, range 35%–60%) are highly consistent with literature reported mortality in patients receiving CKRT from a wide range of critically ill patient populations.<sup>20–22</sup> Interestingly, the median APACHE II score of 23 observed in this review predicts a 46% mortality rate,<sup>23,24</sup> which is highly consistent with the median observed mortality of 44%.

Rapidly achieving adequate antibiotic concentrations is essential to the successful treatment of sepsis. In fact, delays of antibiotics are associated with increased mortality.<sup>25</sup> However, the optimal antibiotic PKPD target and relationship to mortality is less clear. For example, Scharf et al<sup>26</sup> found that achieving 100%

fT > MIC was associated with more rapid infection resolution in the critically ill; however, no additional benefit was observed by achieving a stricter target of 100% fT > 4XMIC. Further, Richter et al<sup>18</sup> found the lowest mortality rates among patients achieving PKPD targets but the highest mortality rates in patients that significantly exceeded PKPD targets. In Richter et al, patients exceeding PKPD targets commonly had severely impaired renal function, so although mortality is more likely attributed to underlying severity of illness, piperacillin overexposure cannot be ruled out as a contributing cause. In contrast, Dhaese et al<sup>27</sup> found higher mortality rates among patients achieving PKPD targets compared to patients that did not achieve PKPD targets. However, this may be explained that in Dhaese et al, patients achieving PKPD targets had a baseline higher severity of illness and significantly impaired renal function (APACHE 25.1, CrCl 68.6 mL/min) compared to patients that did not achieve PKPD targets (APACHE 22.2, CrCl 124.4 mL/min). These findings suggest that although PKPD target attainment is essential, the optimal PKPD target is not yet defined and factors such as baseline severity of illness may play a significant role in predicting the success or failure of piperacillin therapy as achieving a pre-defined PKPD target.

With balancing the importance of achieving PKPD targets and the possibility of increased mortality associated with exceedingly high piperacillin concentrations, we suggest the following dosing approach for patients receiving CKRT. A pre-defined PKPD target should be chosen based on all the available clinical data and the experiences of the clinicians in their specific clinical setting. If a lenient PKPD target is chosen (ie 100% fT > MIC) then a total daily dose of 9000 mg piperacillin/tazobactam either as an intermittent infusion or continuous infusion

would be adequate for most patients. However, if a strict PKPD target is chosen (ie  $100\%fT > 4 \times MIC$ ), then only a continuous infusions dosing strategy would adequately achieve such a target. In such a case, to target a pathogen with theoretical MIC of 8 mg/L, continuous infusions of 9000 mg piperacillin/tazobactam per day would be adequate. However, to target a pathogen with theoretical MIC of 16 mg/L, depending on the critical care setting, continuous infusions of 13500–16000 mg piperacillin/tazobactam per day may be required.

Although continuous (or prolonged) infusions of beta-lactams provide advantages over intermittent infusion such as improved rates of PKPD target attainment and clinical cure rates, the overall effect on mortality is unclear.<sup>28</sup> Further, there may be some disadvantages to continuous infusion such as the constant use of an intravenous line. Therefore, although generally the benefits of a continuous infusion outweigh those of intermittent infusions, the choice should be individualized to the needs of the patient with consideration of the resources available in a particular critical care setting.

The main limitations of our model are possible model misspecification and lack of covariates to explain significant between study variability. Both piperacillin and tazobactam are likely to be best explained by 2-compartment models, and in some circumstances, a non-linear clearance model.<sup>29–33</sup> Nevertheless, the distribution phases of piperacillin and tazobactam are very rapid and our diagnostic plots demonstrate that a 1-compartment model was adequate and regardless of analysis technique with high consistency among CL estimates across the literature (Table 2). Furthermore, our PTA analyses were similar to Bue et al<sup>30</sup> and Cojutti et al<sup>32</sup> despite differences in the structural model. This is supported by Shotwell et al<sup>34</sup> who found piperacillin PTA performed with 1- or 2-compartment modelling provided essentially equivalent results. Therefore, we selected a 1-compartment structural model as it was the simplest model that adequately described the data.

There was a particularly large BSV observed for piperacillin (62%CV) and tazobactam (78%CV). In contrast to individual studies, Asin-Prieto et al<sup>29</sup> estimated 44%CV and 25%CV for piperacillin CL and tazobactam CL, respectively, Bue et al<sup>30</sup> estimated a 10.9%CV for piperacillin CL and Sime et al<sup>31</sup> estimated 26.6%CV for tazobactam CL. The high BSV may be explained by the synthesis of data across many, diverse critical care populations. We suspect that this variability could be partially explained by the inclusion of CrCl as a covariate on piperacillin and tazobactam CL. However, CKRT clears creatinine and reporting of timing of CrCl estimates (ie before or during CKRT) was inconsistent throughout the literature. These confounding factors explain why CrCl, a known covariate for piperacillin CL and tazobactam CL, was not observed to be a statistically significant covariate in this study.

## 5 | WHAT IS NEW AND CONCLUSION

Achieving PKPD targets is essential in the critical care setting; however, patients with significant overexposure to piperacillin and tazobactam may have higher mortality risk. This mortality risk is likely related to baseline severity of illness; however, antibiotic overexposure cannot be

ruled out as a contributing factor. The definition of PKPD target rather than the utilization or intensity of CKRT had the largest impact on PTA. For lenient PD targets, standard doses of 2250–3375 mg every 6 hours would be appropriate for most CKRT patients. However, for strict PD targets continuous infusion of at least 9000–13500 mg per day may be required. Some patients will require higher or lower doses and final dose selection should be based on all available clinical data, an individual patient's risk factors and specific critical care setting.

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## CONFLICT OF INTEREST

The authors have no conflicts of interest to report. Material has been reviewed by the Walter Reed Army Institute of Research, the Uniformed Services University of the Health Sciences and the United States Institute of Surgical Research. There is no objection to its presentation and/or publication. The opinions and assertions expressed in this article are those of the authors and do not reflect the official policy or position of the U.S. Army Medical Department, Department of the Army, DoD, or the U.S. Government.

## PATIENT CONSENT STATEMENT

Informed consent was obtained when applicable.

## PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

No material was used from other sources that require permission to reproduce.

## DATA AVAILABILITY STATEMENT

Military datasets are not available. However, a large subset of data that was previously publicly available and now better formatted for analysis is shared in [supplementary material](#).

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#### SUPPORTING INFORMATION

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