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MAJOR ARTICLE

The Effect of Renal Replacement Therapy and Antibiotic Dose on Antibiotic Concentrations in Critically Ill Patients: Data From the Multinational Sampling Antibiotics in Renal Replacement Therapy Study

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Background. The optimal dosing of antibiotics in critically ill patients receiving renal replacement therapy (RRT) remains unclear. In this study, we describe the variability in RRT techniques and antibiotic dosing in critically ill patients receiving RRT and relate observed trough antibiotic concentrations to optimal targets.

Methods. We performed a prospective, observational, multinational, pharmacokinetic study in 29 intensive care units from 14 countries. We collected demographic, clinical, and RRT data. We measured trough antibiotic concentrations of meropenem, piperacillin-tazobactam, and vancomycin and related them to high- and low-target trough concentrations.

Results. We studied 381 patients and obtained 508 trough antibiotic concentrations. There was wide variability (4–8-fold) in antibiotic dosing regimens, RRT prescription, and estimated endogenous renal function. The overall median estimated total renal

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clearance (eTRCL) was 50 mL/minute (interquartile range [IQR], 35–65) and higher eTRCL was associated with lower trough concentrations for all antibiotics ($P < .05$). The median (IQR) trough concentration for meropenem was 12.1 mg/L (7.9–18.8), piperacillin was 78.6 mg/L (49.5–127.3), tazobactam was 9.5 mg/L (6.3–14.2), and vancomycin was 14.3 mg/L (11.6–21.8). Trough concentrations failed to meet optimal higher limits in 26%, 36%, and 72% and optimal lower limits in 4%, 4%, and 55% of patients for meropenem, piperacillin, and vancomycin, respectively.

Conclusions. In critically ill patients treated with RRT, antibiotic dosing regimens, RRT prescription, and eTRCL varied markedly and resulted in highly variable antibiotic concentrations that failed to meet therapeutic targets in many patients.

Keywords. pharmacokinetic; continuous renal replacement therapy; extended daily dialysis; beta-lactam; renal clearance.

Acute kidney injury (AKI) is a common complication of critical illness, and patients treated with renal replacement therapy (RRT) have high hospital mortality rates [1, 2]. Sepsis-related AKI is associated with increased severity of illness, greater need for mechanical ventilation and vasoactive therapy [3], a longer duration of hospitalization, and a 50% higher risk of death [4].

To maximize patient survival, early recognition of sepsis and the timely and optimal administration of antibiotics are vital [5]. Therapeutic antibiotic concentrations should be attained rapidly and maintained diligently in order to maximize bacterial killing [6–8] and minimize toxicity [9–11]. However, recent evidence demonstrates that major changes in antibiotic pharmacokinetics in critically ill patients, particularly those with sepsis [12–14], significantly affect blood concentrations. This makes optimal prescription of antibiotics problematic, especially if renal function changes dynamically and/or RRT is applied.

Currently used RRT modalities include conventional intermittent hemodialysis (IHD), continuous renal replacement therapy (CRRT), and prolonged intermittent RRT (PIRRT), such as extended daily dialysis-filtration [15–17]. Based on international surveys, CRRT remains the preferred technique in Europe, Asia, and Australasia, while IHD is more commonly prescribed in North America [18–20]. In addition to significant heterogeneity in the choice of RRT mode, the intensity of RRT also varies widely, as does the use of predilution or postdilution fluid replacement, with wide variations in effluent rates, and thus small solute clearance achieved [20]. These characteristics make optimal prescription of antibiotics difficult.

The Sampling Antibiotics in Renal Replacement Therapy (SMARRT) Study was a multinational, prospective, observational pharmacokinetic study in critically ill patients receiving RRT [21] that aimed to develop evidence-based antibiotic regimens for patients receiving RRT. In this paper, we aim to describe the RRT practices and antibiotic dosage regimens from the SMARRT study and assess their relative associations with trough antibiotic concentrations. Secondarily, we sought to describe the relationship of observed trough antibiotic concentrations with predefined optimal concentrations. We hypothesized there would be major (>2-fold) variability in antibiotic dosing and RRT techniques and clearance with unpredictable effects on trough antibiotic concentrations.

METHODS

Study Design and Population

The detailed study protocol for the SMARRT study has been published previously [21]. The antibiotics studied in this analysis were meropenem, piperacillin-tazobactam, and vancomycin. The study was approved at the lead site by the Royal Brisbane and Woman's Hospital Human Ethics Research Committee (HREC/13/QRBW/1). All participating sites obtained individual research ethics approval.

We enrolled patients from 29 participating intensive care units (ICUs) according to predefined inclusion and exclusion criteria (Table 1). We conducted the study in centers with critically ill patients receiving continuous veno-venous hemofiltration (CVVH), continuous veno-venous hemodialysis (CVVHD), continuous veno-venous hemodiafiltration (CVVHDF), or PIRRT. The SMARRT study was powered to establish the confidence boundaries of individual pharmacokinetic parameters under different RRT modalities and settings. Due to slow recruitment, it was not possible to achieve the target enrollment and, as such, additional patient data were included from contemporary pharmacokinetic studies at participating sites that followed similar entry criteria and data collection methods (Supplementary Table 1).

The study antibiotic dose and administration was determined by the treating clinical team. The mode and dose of RRT were determined by local practice and recorded. Trough antibiotic blood samples were collected prefilter from designated ports within the RRT circuit during 1 dosing interval between days 1 and 3 and, where possible, also between days 4 and 6 after study antibiotic commencement.

We used measured serum and urine creatinine, as well as urine volume produced, during the antibiotic dosing interval to estimate creatinine clearance [21]. We collected effluent volume during the sampling interval and recorded effluent flow rate. We defined estimated total renal clearance (eTRCL) for all CRRT patients as the sum of the total effluent rate and patient's intrinsic glomerular filtration rate estimated by measuring urinary creatinine clearance [21].

We obtained demographic data, serum albumin concentration, cumulative fluid balance since ICU admission, and components of the Sequential Organ Function Assessment (SOFA) score [22] on the dosing interval day. We calculated a modified

Table 1. Inclusion and Exclusion Criteria

Inclusion criteria
• Age ≥18 y
• AKI requiring RRT (defined according to RIFLE,[a] AKIN,[b] or KDIGO[c] criteria)
• Expected to require RRT for at least 4 days with 2 sampling schedules
• Clinical indication for intravenous meropenem, piperacillin-tazobactam, imipenem-cilastatin, vancomycin, or linezolid
• Presence of intra-arterial line for blood sampling if RRT filter port sampling not possible
• Informed consent from patient or patient's authorized representative
Exclusion criteria
• Imminent death or patient not expected to survive for sampling schedules
• Major bleeding or blood hemoglobin concentration <70 g/L or platelets <20 × 10^9/L
• Regular dosing with any of the 5 study antibiotics for >36 h, within the 7 days prior to enrollment
• Unable to obtain informed consent

Abbreviations: AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; KDIGO, Kidney Disease Improving Global Outcomes; RIFLE, Risk, Injury, Failure, Loss, and End-stage renal disease; RRT, renal replacement therapy.

[a]Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P; Acute Dialysis Quality Initiative Workgroup. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004;8(4):R204–12.

[b]Mehta RL, Kellum JA, Shah SV, et al; Acute Kidney Injury Network. Report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11(2):R31.

[c]Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2012,2:1–138.

SOFA score by summation of respiratory, coagulation, liver, cardiovascular, and renal components. We omitted the neurological component as it is difficult to assess in sedated patients and because it has no plausible potential influence on antibiotic trough concentrations.

A clinical assessment of improvement, resolution, or failure of antibiotic therapy was made by the treating physician who was blinded to any antibiotic concentration data (Supplementary Table 2). Patient survival was followed up to 28 days post–study enrollment.

The methods for blood sampling and bioanalysis are provided in the Supplementary Materials.

Minimum Inhibitory Concentration Breakpoints and Adequacy of Concentration Definitions

Measured trough plasma concentrations were compared with published minimum inhibitory concentration (MIC) breakpoints for commonly encountered and difficult to treat bacteria in critically ill patients [23], as defined by the European Committee on Antimicrobial Susceptibility Testing (EUCAST; available at www.eucast.org).

Two target exposures were assessed. For B-lactams, the "lower" therapeutic target was defined as free B-lactam trough concentration above the MIC ($fT_{>MIC}$) [24], and the "higher" therapeutic target where maximal killing occurs, as a trough concentration 4 times higher than the MIC ($fT_{>4xMIC}$) [25]. Thus, the lower and higher target trough concentrations for *Pseudomonas aeruginosa* were 2 and 8 mg/L for meropenem and 16 and 64 mg/L for piperacillin-tazobactam. To measure the association of meropenem and/or piperacillin exposure on clinical cure and survival, concentrations between the low and high therapeutic target were used, similar to that used by Richter et al [26].

To measure the association of tazobactam exposure on clinical cure and survival, we used a threshold of 5 mg/L [27, 28].

For vancomycin, we defined a trough concentration of more than 15 mg/L as the lower target and more than 20 mg/L as the higher target [29], in accordance with guidelines on the management of severe methicillin-resistant *Staphylococcus aureus* [30]. To measure the association of vancomycin exposure on clinical cure and survival, we used the lower target (>15 mg/L) [29].

Potentially toxic trough concentrations were defined as far exceeding (>10 times) exposures reported in healthy volunteers, or likely to result in toxicity: piperacillin >150 mg/L, tazobactam >20 mg/L, meropenem >50 mg/L, and >25 mg/L for vancomycin [31–33].

Statistical Analysis

Descriptive statistics were performed for all variables. Discrete variables are expressed as counts (percentage) and continuous variables as means and SD or medians and interquartile range (IQR) as appropriate after assessing normality (Shapiro-Wilk's test). Generalized estimating equations (GEEs), with a Gaussian distribution, identity-link function, exchangeable correlation with robust standard errors were used to compare measured prefilter trough concentrations on first sampling between CRRT and PIRRT groups to account for center effects, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and modified total SOFA score at sampling. The GEE model was also used to examine the association between eTRCL and trough concentrations at first sampling for each type of antibiotic. The association between trough concentration and risk of mortality (hazard ratio [HR], 95% confidence interval [CI]) was assessed using a Cox proportional hazards model, adjusting for center effects, age, APACHE II score, and modified total SOFA score at sampling; when proportional hazards assumption was not met, we reported the relative risk (RR) and 95% CI from a GEE model. The level of significance was set at 2-sided $P < .05$.

RESULTS

We studied 381 patients who met the study inclusion criteria and no exclusion criteria (Figure 1) and contributed 508 antibiotic trough concentrations. Patients were enrolled directly into the study from December 2011 to March 2017 (n = 210) or from similar (but non-SMARRT funded) studies conducted between October 2008 and June 2016 (n = 174) (Supplementary Table 2).

Patients were enrolled from 29 sites in 14 countries (Supplementary Table 3). Demographic and baseline characteristics of the combined cohort are shown in Table 2. The type of bacteria by infection site and antibiotic are shown in Supplementary Table 4.

During sampling, 80 (21.1%) patients received CVVH, 56 (14.7%) CVVHD, 140 (36.8%) CVVHDF, and 104 (27.4%) PIRRT. One patient did not have sufficient data for classification. In patients receiving CRRT, the median (IQR) eTRCL was 50 (35–66) mL/minute.

The antibiotic dosing regimens showed a daily dose variation of 4-fold for vancomycin and more than 8-fold for meropenem and their corresponding median (IQR) measured trough concentrations (Table 3). Of a total of 536 occasions, 1 trough sample was analyzed. The observed trough concentrations for meropenem, piperacillin, tazobactam, and vancomycin demonstrated marked variability (Figure 2). The adjusted mean (95% CI) trough concentration by RRT mode is shown in Table 4. No significant associations were observed between the modified total SOFA score at time of sampling and trough concentration, or between serum albumin concentration on the day of sampling and trough concentration for any of the tested antibiotics, except for tazobactam and modified total SOFA score (P = .005). Higher eTRCL was associated with lower trough concentrations for all antibiotics (Supplementary Figure 1).

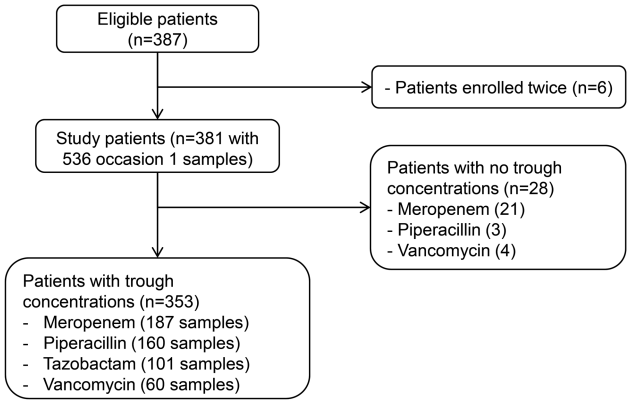

Figure 1. Patient flow diagram.

Meropenem

The trough concentration data in 187 patients receiving meropenem are shown in Figure 2 and by RRT mode (Table 4). There was an association between total daily dose normalized (TDD) by eTRCL (TDD/eTRCL index) and trough concentration (coefficient = 3.25; 95% CI, .44–6.06; P = .023) (Figure 3A). There were 180 patients (96.2%) with documented clinical outcomes associated and trough concentration data; resolution of infection, improvement, and failure occurred in 75 (41.7%), 55 (30.6%), and 50 (27.8%), respectively. Of the 208 patients given meropenem, 100 (48.4%) died at study follow-up. A meropenem trough concentration less than 1× MIC was associated with a higher risk of mortality (HR, 2.55; 95% CI, 1.33–4.90) (Table 5).

Piperacillin

The trough concentration data in 160 patients receiving piperacillin are shown in Figure 2 and by RRT mode (Table 4). There was a strong association between TDD/eTRCL and piperacillin trough concentration (coefficient = 9.06; 95% CI, 5.48–12.65; P < .001) (Figure 3B). There were 153 (95.6%) patients with documented clinical outcome and trough concentration data; resolution of infection, improvement, and failure occurred in 55 (35.9%), 36 (23.5%), and 62 (40.5%), respectively. Of the 163 patients given piperacillin, 92 (56.4%) had died at study follow-up. Piperacillin trough concentration was not associated with the risk of mortality (P = .317) (Table 5).

Table 2. Demographic and Clinical Characteristics of Study Patients

Characteristics	Values
Gender, males, n (%); females, n (%)	246 (64.6); 135 (35.4)
Age, y	63 (53–74)
Body weight, kg	80 (68–95)
BMI,[a] kg/m^2	27.3 (24.5–32.7)
Admission APACHE II score[b]	26 (21–31)
Total modified SOFA score at sampling[c]	11 (9–14)
Urinary creatinine clearance sampling, mL/min	0 (0–0)
Effluent flow rate at sampling,[d] mL/min	47 (34–58)
eTRCL,[d] mL/min	50 (35–65)
Serum albumin concentration,[e] g/L	24 (20–27)
Length of stay, d	
ICU[f]	13.5 (7.0–26.0)
Hospital[g]	27.0 (15.0–51.8)

Values are reported as median (interquartile range) unless otherwise indicated.

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; CRRT, continuous renal replacement therapy; eTRCL, estimated total renal clearance; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment Score.

[a]n = 354.

[b]n = 360.

[c]n = 288.

[d]n = 262 (only CRRT patients included).

[e]n = 310.

[f]n = 378.

[g]n = 376.

Tazobactam

The trough concentration data in 101 patients for whom tazobactam trough concentration data were available are shown in Figure 2 (not all patients receiving piperacillin had tazobactam concentrations quantified) and by RRT mode (Table 4). In 14 patients receiving PIRRT, adjusted mean (95% CI) tazobactam trough concentrations (4.7 mg/L; 1.2–8.1 mg/L) were lower than in the 87 patients receiving CRRT (11.4 mg/L; 10.3–12.6 mg/L; $P < .001$). There was a strong association between TDD/eTRCL and tazobactam trough concentration (coefficient = 8.03; 95% CI, 2.56–13.51; $P = .004$) (Figure 3C). There were 100 patients with documented clinical outcome and trough concentration data; resolution of infection, improvement, and failure occurred in 38 (38.0%), 26 (26.0%), and 36 (36.0%), respectively. Of the 101 patients given tazobactam, 52 (51.5%) had died at study follow-up. Tazobactam trough concentrations more than 5 mg/L were associated with a lower risk of mortality (RR, .74; 95% CI, .58–.94) (Table 5).

Vancomycin

The trough concentration data in 60 patients receiving vancomycin are shown in Figure 2 and by RRT mode (Table 4). In 32 patients receiving PIRRT, the adjusted mean (95% CI) vancomycin trough concentrations (14.9 mg/L; 13.8–16.1 mg/L) were lower than in 28 patients receiving CRRT (18.3 mg/L; 16.9–19.6; $P < .001$). There was a strong association between TDD/eTRCL and trough concentration (coefficient = 8.45; 95% CI, 2.56–14.35; $P = .005$) (Figure 3D). There were 53 patients with documented clinical outcome and trough concentration data; resolution of infection, improvement, and failure occurred in 17 (32.1%), 18 (34.0%) ,and 18 (34.0%), respectively. Of the 62 patients given vancomycin, 30 (48.4%) had died at study follow-up. Due to the small sample size, we are uncertain of the association between high vancomycin trough concentration and risk of mortality (Table 5).

Table 3. Dose Regimens Administered to Patients at First Sampling and Their Corresponding Median (IQR) Measured Trough Concentration

Antibiotic and Dose	Cases (%)	Median (IQR), mg/L
Meropenem		
500 mg every 6 h	2 (1.0)	8.1 (2.6–NR)
500 mg every 8 h	34 (16.3)	9.0 (4.1–22.7)
500 mg every 12 h	1 (0.5)	23.9 (23.9–23.9)
1000 mg every 6 h	16 (7.7)	16.0 (14.1–24.3)
1000 mg every 8 h	117 (56.3)	11.6 (7.6–17.4)
1000 mg every 12 h	17 (8.2)	11.1 (6.6–20.6)
2000 mg every 8 h	15 (7.2)	16.2 (10.6–23.6)
2000 mg every 12 h	1 (0.5)	12.5 (12.5–12.5)
2000 mg every 24 h	1 (0.5)	13.6 (13.6–13.6)
3000 mg every 8 h	2 (1.0)	7.5 (6.1–NR)
3000 mg every 24 h	1 (0.5)	8.2 (8.2–8.2)
4000 mg every 8 h	1 (0.5)	9.0 (9.0–9.0)
Piperacillin		
1000 mg every 8 h	1 (0.6)	NR
2000 mg every 6 h	3 (1.8)	49.0 (34.5–NR)
2000 mg every 8 h	10 (6.1)	81.6 (49.9–115.7)
3000 mg every 8 h	34 (20.9)	178.7 (59.4–396.3)
3600 mg every 8 h	1 (0.6)	57.6 (57.6–57.6)
4000 mg every 6 h	34 (20.9)	121.3 (75.5–153.1)
4000 mg every 8 h	70 (42.9)	64.3 (45.0–92.9)
4000 mg every 12 h	9 (5.5)	54.3 (40.2–105.1)
4000 mg every 24 h	1 (0.6)	108.8 (108.8–108.8)
Tazobactam		
250 mg every 8 h	3 (3.0)	7.8 (4.4–NR)
375 mg every 8 h	9 (8.9)	0.6 (0.4–1.4)
500 mg every 6 h	26 (25.7)	14.7 (9.5–20.9)
500 mg every 8 h	58 (57.4)	9.4 (6.6–13.2)
500 mg every 12 h	5 (5.0)	13.3 (7.6–16.5)
Vancomycin		
750 mg every 8 h	3 (4.8)	29.3 (27.3–NR)
960 mg every 24 h	1 (1.6)	24.0 (24.0–24.0)
1000 mg every 8 h	7 (11.3)	27.1 (19.5–27.8)
1000 mg every 12 h	14 (22.6)	16.0 (12.1–23.1)
1000 mg every 24 h	26 (41.9)	12.4 (10.9–14.4)
1250 mg every 24 h	1 (1.6)	13.5 (13.5–13.5)
1500 mg every 12 h	2 (3.2)	19.6 (15.7–NR)
1500 mg every 24 h	5 (8.1)	11.8 (10.3–22.3)
2000 mg every 12 h	1 (1.6)	13.6 (13.6–13.6)
2000 mg every 24 h	2 (3.2)	12.2 (8.2–NR)

Abbreviations: IQR, interquartile range; NR, not reported.

DISCUSSION

Key Findings

In this large, prospective, multinational study, we found highly variable modes and intensity of RRT prescription with up to an 8-fold variability in eTRCL. Similarly, antibiotic dosing regimens demonstrated up to 8-fold variability in daily dose. The above factors led to highly variable trough antibiotic concentrations with failure to achieve higher therapeutic target concentrations in a substantial number of patients (≥25%). Similarly, the lower therapeutic target was not delivered in up to 55% of patients receiving vancomycin, and excessive antibiotic concentrations occurred with moderate frequency. We also observed higher mortality rates for patients receiving B-lactam (meropenem or piperacillin) or vancomycin therapy when less than 1× MIC or very high concentrations were present. Finally, our estimate of total combined RRT and renal clearance, eTRCL, was generally inversely associated with trough antibiotic concentrations, while other potentially influential factors (SOFA score and serum albumin concentration) showed no associations with trough concentration.

Relationship to Previous Studies

Variability in RRT prescription was not unexpected [20]; however, the broad distribution of dosing regimens was marked and aligns with a previous smaller multicenter study [31]. Similarly, smaller studies have hypothesized that critically ill patients receiving RRT may inconsistently achieve therapeutic drug exposures. A single-center study reported that 35% of critically ill

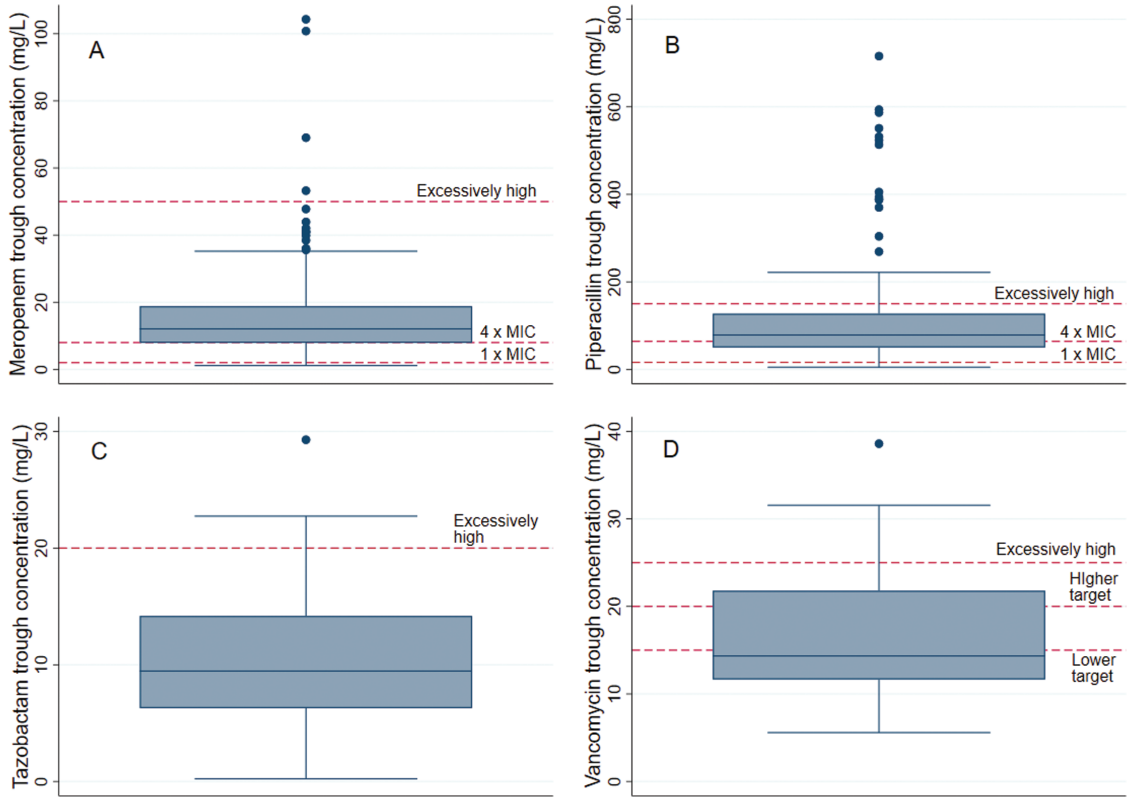

Figure 2. Observed trough concentrations by antibiotic. *A*, meropenem (n = 187); *B*, piperacillin (n = 160); *C*, tazobactam (n = 101); and *D*, vancomycin (n = 60). The whiskers of the box plot represent the 1.5× interquartile range. The magnitude of trough concentration variability (highest to lowest concentration) was as follows: meropenem, 8-fold; piperacillin, 5.3-fold; vancomycin, 4.1-fold; and tazobactam, 2.5-fold. Reference lines include MIC (1× MIC) and 4 times the MIC (4× MIC) for meropenem and piperacillin. Lower and higher target concentrations for vancomycin and excessively high concentration reference lines drawn for each antibiotic are defined in the Methods. Abbreviation: MIC, minimum inhibitory concentration.

patients receiving CRRT had B-lactam trough concentrations less than 1× MIC. For meropenem and piperacillin, the percentage of patients with concentrations below this lower target was 16% and 6%, respectively [31]. In the present study, we observed that 4% and 4% of meropenem and piperacillin patients, respectively, had trough concentrations less than 1× MIC.

In critically ill patients, an independent association between worsening neurological status and increasing concentration for B-lactam antibiotics has been reported (>8 mg/L for meropenem and 128 mg/L for piperacillin) [32]. In the present study, more than 50% and more than 25% of meropenem and piperacillin patients would meet this threshold. Our predefined thresholds for toxicity were met by only 2% of meropenem and 18% of piperacillin patients.

Vancomycin toxicity is well described [34], with trough concentrations of 20–35 mg/L and greater than 35 mg/L being

Table 4. Mean (95% Confidence Interval) Measured Trough Concentrations for Various Types of Renal Replacement Therapy by Antibiotic, Adjusted for Total Daily Antibiotic Dose (Meropenem, Piperacillin, Tazobactam) or Total Daily Antibiotic Dose/Body Weight (Vancomycin), APACHE II Score, Modified Total SOFA Score at Sampling, and Center Effects Using Generalized Estimating Equations

Antibiotic (n = 508)	Trough Concentration Targets	CVVH (n = 112; 22%)	CVVHD (n = 80; 16%)	CVVHDF (n = 187; 37%)	PIRRT (n = 129; 25%)	*P*
Meropenem (n = 187)	Low: 2 mg/L; high: 8 mg/L; toxic: >50 mg/L	17.3 (12.3–22.3) (n = 42; 22%)	15.9 (13.3–18.5) (n = 34; 18%)	14.5 (10.4–18.7) (n = 72; 39%)	14.0 (9.8–18.2) (n = 39; 21%)	.707
Piperacillin (n = 160)	Low: 16 mg/L; high: 64 mg/L; toxic: >150 mg/L	81.8 (50.8–112.7) (n = 31; 19%)	90.9 (44.6–137.2) (n = 20; 13%)	83.0 (57.6–108.3) (n = 65; 41%)	104.0 (31.4–176.6) (n = 44; 28%)	.934
Tazobactam (n = 101)	>5 mg/L; toxic: >20 mg/L	9.8 (7.6–12.0) (n = 22; 22%)	13.9 (9.4–18.4) (n = 20; 20%)	11.1 (9.8–12.4) (n = 45; 45%)	4.6 (1.5–7.6) (n = 14; 14%)	<.001
Vancomycin (n = 60)	Low: >15 mg/L; high: >20 mg/L; toxic: >25 mg/L	16.8 (15.0–18.5) (n = 17; 28%)	21.5 (18.3–24.6) (n = 6; 10%)	17.8 (12.1–23.5) (n = 5; 8%)	15.3 (14.1–16.6) (n = 32; 53%)	.002

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafitration; CVVHF, continuous venovenous hemofiltration; PIRRT, prolonged intermitted renal replacement therapy; SOFA, Sequential Organ Failure Assessment.

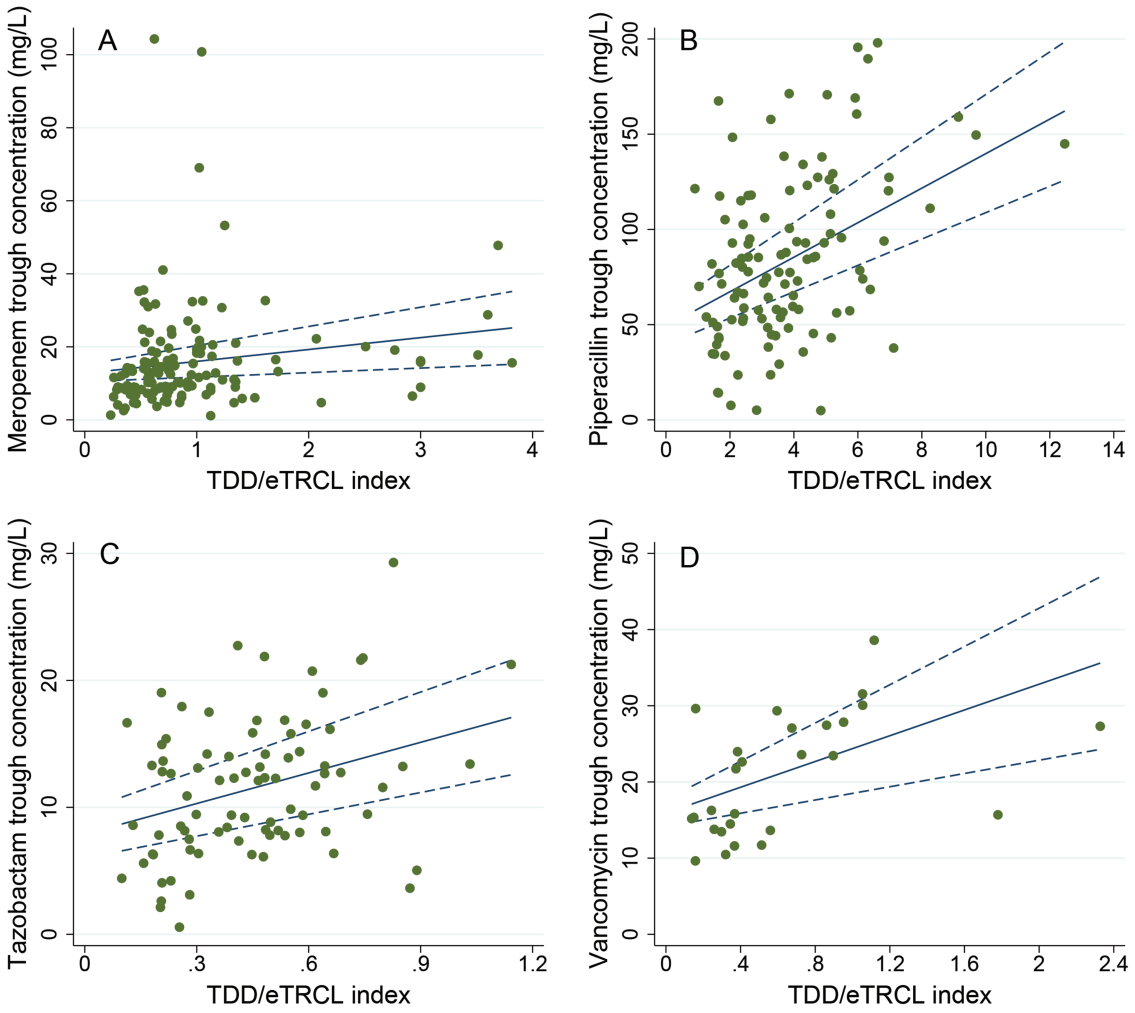

Figure 3. The relationship between the total daily dose (TDD) of antibiotic normalized by estimated total renal clearance (eTRCL index) and observed trough concentration in CRRT patients. *A*, meropenem (n = 139 from 16 centers; $P = .023$); *B*, piperacillin (n = 112 from 16 centers; $P < .001$); *C*, tazobactam (n = 83 from 14 centers; $P = .004$); and *D*, vancomycin (n = 27 from 8 centers; $P = .005$). TDD units are in milligrams per kilogram, and eTRCL is in milliliters per minute. The solid regression line and its 95% confidence interval (dashed lines) represent the association between TDD/eTRCL and trough concentration, adjusted for APACHE II score, modified total SOFA score at sampling, and center effects using generalized estimating equations. Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; CRRT, continuous renal replacement therapy; SOFA, Sequential Organ Function Assessment.

associated with a 23.6% and 81.8% incidence of nephrotoxicity, respectively [33]. The high proportion of trough concentrations in this study that fall within this concentration range for toxicity supports the need for increased dosing accuracy in this population. Although vancomycin is almost universally dosed with therapeutic drug monitoring (TDM), over half the patients failed to meet even the lower therapeutic concentration target (15 mg/L), highlighting the need for improved individualized dosing to meet target thresholds.

The range of trough concentrations observed was wide, confirming results of other studies [31]. Although tazobactam concentration targets have not been clinically defined, the in vitro studies' targets against Enterobacterales of more than 0.5 mg/L and B-lactamase–producing *Escherichia coli* of more than 2 mg/L were achieved in 97% and 91% of patients, respectively [27, 28].

Clearance of the antibiotics investigated was expected to be influenced by RRT mode and settings. Previous research has demonstrated that the clearance of meropenem, piperacillin, and tazobactam changes significantly with different RRT modalities and prescriptions [35, 36], and a recent meta-regression analysis demonstrated a visually consistent association between effluent flow rate during CRRT and antibiotic clearance for these antibiotics, although only piperacillin reached statistical significance [37]. Our findings support the hypotheses that increasing eTRCL is associated with decreased trough antibiotic concentrations. This relationship, adjusted for unit effects, exists despite high variability in dose selection and provides some evidence that attempts to individualize dosing are feasible. However, for clinical practice guidance, the correlation was not sufficiently strong, and other relevant factors affecting trough concentrations require exploration.

Table 5. Association Between Measured Trough Concentration and Risk of 28-Day Mortality (Unadjusted and Adjusted Hazard Ratio) by Antibiotics

Antibiotic	Mortality, n (%)	HR (95% CI)	*P*	Adjusted HR (95% CI)[a]	*P*
Meropenem (n = 187)					
2–8 mg/L	14 (34.1)	1.00		1.00	
<2 mg/L	4 (57.1)	2.02 (1.10–3.72)	.011	2.55 (1.33–4.90)	.012
>8 mg/L	71 (51.1)	1.55 (1.05–2.29)		1.39 (.89–2.15)	
Piperacillin (n = 160)					
16–64 mg/L	25 (49.0)	1.00		1.00	
<16 mg/L	3 (50.0)	1.06 (.38–2.99)	.605	1.41 (.77–2.58)[b]	.317
>64 mg/L	62 (60.2)	1.26 (.80–2.00)		1.19 (.92–1.53)[b]	
β-Lactam (n = 347)					
Meropenem or piperacillin 1× MIC–4× MIC	39 (42.4)	1.00		1.00	
Meropenem or piperacillin <1× MIC	7 (53.8)	1.41 (.73–2.76)	.212	1.54 (1.03–2.30)[b]	.053
Meropenem or piperacillin >4× MIC	133 (55.0)	1.33 (.95–1.87)		1.23 (.99–1.51)[b]	
Tazobactam (n = 101)					
≤5 mg/L	12 (63.2)	1.00		1.00	
>5 mg/L	40 (48.8)	0.66 (.39–1.13)	.127	0.74 (.58–.94)[b]	.014
Vancomycin (n = 60)					
≤15 mg/L	20 (60.6)	1.00		1.00	
>15 mg/L	9 (33.3)	0.44 (.14–1.43)	.175	0.45 (.14–1.51)	.197

P values are for overall group effect of trough concentrations.

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; HR, hazard ratio; MIC, minimum inhibitory concentration; SOFA, Sequential Organ Failure Assessment.

[a]Adjusted for center effects, age, APACHE II score, and total modified SOFA score at sampling.

[b]Values are relative risks and 95% confidence intervals from generalized estimating equation models as the proportional hazards assumption was not met in the Cox regression model.

Although not a primary objective of this study, we observed associations of patient survival with the achievement of either therapeutic B-lactam (either meropenem or piperacillin) or tazobactam exposure. Interestingly, high drug exposures were associated with a higher likelihood of death, presumably because a higher severity of illness means higher organ failure, which, in turn, leads to decreased elimination of antibiotics and hence higher trough concentrations. A similar effect has been reported previously [38, 39]. The interaction between therapeutic antibiotic exposure and clinical cure and/or survival has been described previously [40, 41], although not in this patient population. These data may be useful for guiding design of therapeutic targets for future dosing intervention studies in critically ill patients receiving RRT.

Implications

Our analysis demonstrates that current practice in RRT prescription and antibiotic dosing has great variability and often results in inadequate or potentially toxic trough concentrations in a substantial number of patients. Moreover, despite demonstrating statistical correlations between dose and eTRCL with trough concentrations, our findings imply that accurately predicting dosing requirements based on eTRCL is currently impossible. No RRT prescription or dosing regimen could reliably be considered to enable more consistent achievement of target exposures. Indeed, TDM should be applied, where available, to avoid harm from both, undertreatment and toxicity [42, 43].

Strengths and Weaknesses

This is the largest pharmacokinetic study in critically ill patients receiving RRT. In all patients, RRT prescriptions and antibiotic dosing regimens were determined by treating clinicians, providing a pragmatic view of the variability of international clinical practice. The comparison of funded and nonfunded datasets revealed minor differences, with the exception of vancomycin trough concentrations. The lower concentrations in the nonfunded cohort reflect the higher usage of PIRRT in this subgroup. Nevertheless, the overall dataset combining data from studies with substantially similar methodology greatly increased the available data from various modes and intensities of RRT and ensured achievement of optimal sample sizes for piperacillin and meropenem. Although the target sample size was not achieved, this study provides one of the largest vancomycin datasets available for this patient group. The estimation of eTRCL has limitations, particularly when predilution flow rates are high. Although optimal antibiotic concentration targets are not definitively known, the targets chosen are the most widely accepted [29, 44], and they provide a marker against which local antibiotic MIC values can be compared.

Conclusions

In a multicenter pragmatic pharmacokinetic study of antibiotic therapy during RRT in critically ill patients, we found considerable variation in RRT prescription and antibiotic dosing resulting in subtherapeutic or excessive antibiotic concentrations in many patients. We also found no close and consistent associations between trough antibiotic concentration and dosage choice, acute physiological disturbance, eTRCL, and markers of protein binding such as albumin concentration, demonstrating the difficulty in ensuring target antibiotic concentrations. These findings highlight the need to improve our understanding of

antibiotic pharmacokinetics in these patients and our ability to adjust antibiotic concentrations in response to real-time measurements.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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APPENDIX

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