OBSERVATIONAL STUDY

OPEN

A New Dosing Frontier: Retrospective Assessment of Effluent Flow Rates and Residual Renal Function Among Critically Ill Patients Receiving Continuous Renal Replacement Therapy

Damini Lakshmipathy[1]

Xiaoyi Ye, MD[2]

Joseph L. Kuti, PharmD, FIDP, FCCP[1]

David P. Nicolau, PharmD, FCCP, FIDSA[1,3]

Tomefa E. Asempa, PharmD[1]

OBJECTIVES: In 2020, cefiderocol became the first Food and Drug Administration-approved medication with continuous renal replacement therapy (CRRT) dosing recommendations based on effluent flow rates (Q_E). We aimed to evaluate the magnitude and frequency of factors that may influence these recommendations, that is, Q_E intrapatient variability and residual renal function.

DESIGN: Retrospective observational cohort study.

SETTING: ICUs within Hartford Hospital (890-bed, acute-care hospital) in Connecticut from 2017 to 2023.

PATIENTS: Adult ICU patients receiving CRRT for greater than 72 hours.

MEASUREMENTS AND MAIN RESULTS: CRRT settings including Q_E and urine output (UOP) were extracted from the time of CRRT initiation (0 hr) and trends were assessed. To assess the impact on antibiotic dosing, cefiderocol doses were assigned to 0 hour, 24 hours, 48 hours, and 72 hours Q_E values per product label, and the proportion of antibiotic dose changes required as a result of changes in inpatient's Q_E was evaluated. Among the 380 ICU patients receiving CRRT for greater than 72 hours, the median (interquartile range) 0 hour Q_E was 2.96 (2.35–3.29) L/hr. Approximately 9 Q_E values were documented per patient per 24-hour window. Q_E changes of greater than 0.75 L/hr were observed in 21.6% of patients over the first 24 hours and in 7.9% (24–48 hr) and 5.8% (48–72 hr) of patients. Approximately 40% of patients had UOP greater than 500 mL at 24 hours post-CRRT initiation. Due to Q_E changes within 24 hours of CRRT initiation, a potential cefiderocol dose adjustment would have been warranted in 38% of patients (increase of 21.3%; decrease of 16.6%). Q_E changes were less common after 24 hours, warranting cefiderocol dose adjustments in less than 15% of patients.

CONCLUSIONS: Results highlight the temporal and variable dynamics of Q_E and prevalence of residual renal function. Data also demonstrate a risk of antibiotic under-dosing in the first 24 hours of CRRT initiation due to increases in Q_E. For antibiotics with Q_E-based dosing recommendations, empiric dose escalation may be warranted in the first 24 hours of CRRT initiation.

KEYWORDS: acute kidney injury; cefiderocol; continuous renal replacement therapy; dialysis; effluent flow rates; residual renal function

Continuous renal replacement therapy (CRRT) remains the mainstay of renal replacement therapy used in critically ill patients with acute kidney injury (AKI) (1). In a multinational prospective study (AKI-Epidemiology trial), 57% of the patients in the ICU had AKI, and 13.5%

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KEY POINTS

Question: What is the magnitude and frequency of effluent flow rate (Q_E) changes and residual renal function among critically ill patients receiving continuous renal replacement therapy (CRRT) and how does it impact antibiotic dosing?

Findings: In this retrospective study (n = 380), Q_E was more variable in the first 24 hours of CRRT initiation relative to 48 and 72 hours post-initiation. Approximately 40% of patients had urine output greater than 500 mL at 24 hours post-CRRT initiation.

Meaning: Results demonstrate the temporal and variable dynamics of Q_E as well as the high prevalence of patients with residual renal function may result in subtherapeutic drug exposures.

required renal replacement therapy, of which the majority (75%) were CRRT (2). CRRT modalities such as continuous venovenous hemofiltration (CVVHF) and continuous venovenous hemodialysis (CVVHD) allow for acid–base, electrolyte, and volume management with a goal of achieving hemodynamic stability in patients with AKI; however, mortality rates remain high at 50–70% (3–6). The optimal dosing of medications in patients receiving CRRT remains an area of active research and growing data have shown that CRRT modalities and settings (e.g., modes, blood flow rate, effluent flow rate [Q_E], filter material, and size) may impair the achievement of therapeutic exposures of drugs, particularly renally eliminated drugs (7–11).

The two main determinants of CRRT clearance (CL_{CRRT}; units: L/hr) are sieving (SC) or saturation (SA) coefficients and Q_E (L/hr) and can be estimated by the equation $CL_{CRRT} = Q_E \times SC$ or SA. For small solutes such as urea and drugs with low molecular weight, the entire protein-unbound (free) fraction is assumed to freely cross the filter membrane and thus clearance is considered equivalent to total effluent volume (5, 12–14). The Kidney Disease Improving Global Outcome Clinical Practice Guideline recommends an effluent dose of 20–25 mL/kg/hr in patients with AKI; however, higher doses are administered clinically to accommodate interruptions in CRRT and a decline in filter efficacy (1, 12). Frequent adjustments of the effluent dose are also made in response to the patient's hourly hemodynamic and clinical requirements. As such, understanding the relationship between Q_E and potential antibiotic exposure in these critically ill patients is paramount to improving therapeutic outcomes.

Little guidance exists for antibiotic dosing in patients receiving CRRT despite over 40 years of CRRT in medicine (1). To that end, efforts were made in the development phase of cefiderocol to integrate pharmacokinetic data from the phase 3 clinical trial with in vitro modeling, resulting in Q_E-based dosing recommendations that were incorporated in the packaging label (15, 16). This made cefiderocol the first and only antimicrobial agent with Food and Drug Administration (FDA)-approved dosing recommendations for CRRT. The recommended dosing regimen of cefiderocol among patients receiving CRRT is 1.5 g q 12 hours, 2 g q 12 hours, 1.5 g q 8 hours, and 2 g q 8 hours based on Q_E of less than or equal to 2 L/hr, 2.1–3 L/hr, 3.1–4 L/hr, and greater than or equal to 4.1 L/hr, respectively. The FDA product label also indicates that the recommended dosing regimen may need to be tailored based on residual kidney function and the patient's clinical status (13, 16). These recommendations suggest that cefiderocol dosing could vary often based on their Q_E, changes to those rates, and the return of renal function.

This current study therefore aims to quantify the variability in Q_E, present data on urine output (UOP) in critically ill patients receiving CRRT, and highlight opportunities to further optimize therapy for Q_E-dosed antibiotics.

MATERIALS AND METHODS

The study was approved by the Hartford Hospital institutional review board and deemed exempt via a waiver (HHC-2023-0083) as all patient care was delivered per standard of care and involved no collection of protected health information.

Study Design and Population

This was a retrospective evaluation of all ICU patients who received CRRT at an 890-bed, acute-care community teaching hospital in Hartford, CT between January 2017 and January 2023. The CRRT modality of choice at this institution is continuous venovenous hemodiafiltration (CVVHDF) and is managed by the nephrologists. Only the first CRRT session

per patient during the study years was included for analysis. Exclusion criteria included patients younger than 18 years, pregnant women, and patients who received CRRT for less than 72 hours. Demographic, clinical, and CRRT flowsheet data (CRRT settings, dialysis status, patient weight, UOP) were retrieved from the electronic health record. CRRT settings included blood flow rate, dialysate flow rate, and Q_E while the dialysis status included the time of CRRT initiation, discontinuation, or pauses due to filter changes, vascular access issues, or patient off the floor. Of note, ICU nurses record data into the CRRT flowsheet every 2–4 hours as standard of care.

Impact on Effluent-Based Antibiotic Dosing Strategies

The primary objective was to describe Q_E (L/hr) changes among this critically ill population. The largest absolute change (highest Q_E minus lowest Q_E) per 24-hour period was extracted to reflect the largest swing in flow rate within a day. Q_E can be calculated by multiplying the effluent dose (mL/kg/hr) by the patient's weight (kg) or considered to be equivalent to the ultrafiltrate flow rate for CVVHF, dialysis flow rate for CVVHD, or ultrafiltrate flow rate plus dialysis flow rate for CVVHDF (12, 16).

For clinical relevance, we determined the extent to which changes in Q_E would impact the dose selection of cefiderocol, the only antibiotic currently with FDA-approved Q_E-based dosing recommendations. To achieve that, all documented Q_E within the first 72 hours were obtained from each patient's flowsheet. Per FDA product labeling, the recommended CRRT dosing regimen of cefiderocol is 1.5 g q 12 hours, 2 g q 12 hours, 1.5 g q 8 hours, and 2 g q 8 hours based on Q_E of less than or equal to 2 L/hr, 2.1–3 L/hr, 3.1–4 L/hr, and greater than or equal to 4.1 L/hr, respectively. The recommended cefiderocol dose associated with Q_E at CRRT initiation (0 hr), 24, 48, and 72 hours were sequentially compared for each patient to assess if a dose adjustment (decrease or increase) would have been necessary per the FDA product label recommendations. The Q_E-based recommendations at these time points (0, 24, 48, 72 hr) were chosen to serve as "daily" actionable data points on which a pharmacist or prescriber would potentially adjust the antibiotic dose for each patient.

Residual renal function in patients receiving dialysis is the residual ability of the kidneys to produce urine and excrete waste products. To quantify residual renal function, each patient's UOP in 24-hour increments was calculated over the 72-hour study window and categorized as nonoliguria (UOP > 500 mL), oliguria (UOP > 100–500 mL), and anuria (UOP ≤ 100 mL) (17, 18).

Statistical Analysis

Descriptive statistics were used to describe patients and CRRT characteristics. Nominal data were presented as percentages and continuous data were presented as median (25–75% IQR).

RESULTS

Demographics and CRRT Characteristics

A total of 380 patients met the inclusion criteria. Patient demographics and CRRT characteristics are presented in **Table 1**. Median age was 61 years (51–69 yr) and the majority were male patients (64%). Almost all patients were ventilated (92%) and received at least one inotrope or vasopressor (99.5%). Approximately half of the patients evaluated (51.3%) died during hospitalization.

The median duration of CRRT was 158 hours and within the first 72 hours of CRRT, 94% of patients had an interruption in CRRT, totaling a cumulative 3 hours and 47 minutes. The most common reason for interruption was the need to change the filter due to clotting.

Trends in Effluent Flow Rates and Renal Residual Function

Each patient had a median (interquartile range [IQR]) of 21 (19–37) recorded Q_E over the first 72 hours, and the median starting Q_E upon CRRT initiation was 3 L/hr (Table 1). Q_E were dynamic over the 72 hours, but particularly in the first 24 hours, with a median (IQR) change of 0.36 (0.20–0.66) L/hr, whereas smaller changes were observed between 24 and 48 hours (0.24 L/hr; IQR: 0.15–0.38) and 48–72 hours (0.22 L/hr; IQR: 0.14–0.35). Within the first 24 hours, 82 patients (21.6%) had Q_E changes of greater than 0.75 L/hr, which decreased to 7.9% (24–48 hr) and

TABLE 1.
Demographics and Continuous Renal Replacement Therapy Characteristics of the Study Population

Characteristics	Population (*n* = 380)
Description	
Age, median (IQR), yr	61 (51–69)
Female sex, *n* (%)	138 (36.3)
Race, *n* (%)	
African American	52 (13.7)
White	247 (65)
Other	75 (19.7)
Unknown	6 (1.6)
Body weight, median (IQR), kg	89 (75–108)
Comorbidities, *n* (%)	
Cancer	40 (10.5)
Cerebrovascular disease	34 (8.9)
Chronic kidney disease	183 (48.2)
Chronic obstructive pulmonary disease	57 (15)
Congestive heart failure	119 (31.3)
Diabetes mellitus	115 (30.3)
Liver disease	52 (13.7)
Myocardial infarction	45 (11.8)
Peripheral vascular disease	66 (17.4)
Antibiotic administered during ICU stay, *n* (%)	202 (53.2)
Ventilatory support during ICU stay, *n* (%)	350 (92.1)
Vasopressor/Inotrope support during ICU stay, *n* (%)	378 (99.5)
Mortality, *n* (%)	195 (51.3)
CRRT characteristics	
Duration of CRRT, median (IQR), hr	158 (104 - 252)
Cumulative pause in CRRT[a], median (IQR), hr	3.78 (1.5–6.75)
Starting effluent dose, median (IQR), mL/kg/hr	32 (27-38)
Starting effluent flow rate, median (IQR), L/hr	2.96 (2.35-3.29)
Starting effluent flow rate, *n* (%)	
≤2 L/hr	30 (7.9)
2.1–3 L/hr	175 (46)
3.1–4 L/hr	153 (40.3)
≥4.1 L/hr	22 (5.8)
Maximum change in effluent flow rate[a], median (IQR), L/hr	
0–24 hr	0.36 (0.20–0.66)
> 24–48 hr	0.24 (0.15–0.38)
> 48–72 hr	0.22 (0.14–0.35)

CRRT = continuous renal replacement therapy, IQR = interquartile range.
[a]Within the first 72 hr of CRRT.

5.8% (> 48–72 hr) of patients (**Fig. 1**). Approximately 40% of patients were nonoliguric (> 500 mL) at 24 hours post-CRRT initiation (**Table 2**).

Impact on Effluent-Based Antibiotic Dosing Strategies

Tables 3–5 list the number of patients within Q_E ranges and their associated cefiderocol dose. The change in Q_E at 24 hours relative to their starting rate at 0 hours would be substantial enough to warrant a cefiderocol dose change in 38% of patients (dose increase in 21.3%; dose decrease in 16.6%). The most impacted group within the first 24 hours were patients (n = 30) with a starting Q_E of less than or equal to 2 L/hr. Indeed, 21 (70%) of these patients had new Q_E of greater than or equal to 2.1 L/hr at 24 hours which would have warranted a cefiderocol dose escalation (Table 3). Relative to the changes observed in the first 24 hours, Q_E between 24 and 48 hours and 48–72 hours were steadier but would have warranted cefiderocol dose adjustments in 14.8% and 11.3% of patients, respectively (Tables 4 and 5).

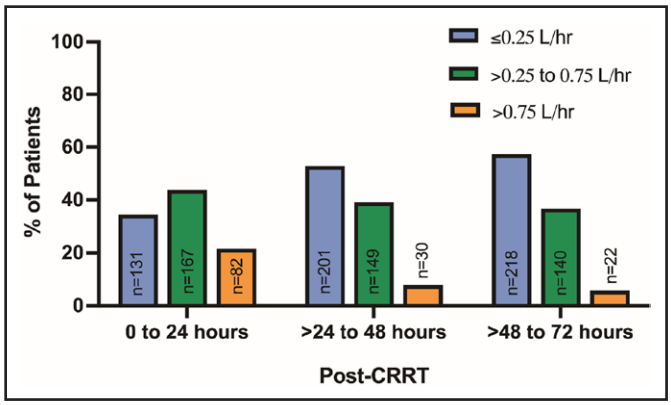

Figure 1. Percentage of patients with effluent flow rate changes of ≤ 0.25, > 0.25–0.75, > 0.75 L/hr within the first 72 hours post-continuous renal replacement therapy (CRRT) initiation.

TABLE 2.
Urine Output Over 72 Hours and Percentage of Patients With a Range of Residual Renal Functions

Urine Output	Post-Continuous Renal Replacement Therapy Initiation		
	0–24 Hr	> 24–48 Hr	> 48–72 Hr
Nonoliguria[a], *n* (%)	154 (40.5%)	108 (28.4%)	110 (28.9%)
Oliguria[b], *n* (%)	125 (32.9%)	141 (37.1%)	120 (31.6%)
Anuria[c], *n* (%)	101 (26.6%)	131 (34.5%)	150 (39.5%)

[a]> 500 mL.
[b]> 100–500 mL.
[c]≤ 100 mL.

DISCUSSION

In this study, Q_E were observed to be variable within the first 24 hours of CRRT initiation and held relatively steady afterward. A large proportion of patients also produced urine over the initial 24 hours, potentially contributing to clearance of renally eliminated drugs. With the growing interest in Q_E-based dosing recommendations (11, 13, 14), the baseline data presented in this study can sensitize pharmacists and clinicians on the dynamics, that is, temporal and variable nature of this CRRT setting, and highlight challenges to consider when applying as a dosing guide to all dialyzable drugs including β-lactams.

Drug clearance by the kidneys can remain an elimination pathway that may be under-appreciated in patients receiving CRRT, and results in lower-than-expected drug exposures. In a pragmatic multicenter pharmacokinetic study among critically ill patients receiving CRRT, higher total renal clearance (sum of the total effluent rate and patient's intrinsic glomerular filtration rate) was associated with lower trough concentrations and antibiotic concentrations failed to meet therapeutic targets (7). In another multicenter pharmacokinetic (PK) study (n = 30), Ulldemolins et al (18) assessed the effect of residual renal function (estimated by UOP) on meropenem dosing requirements. Fourteen patients (46.7%) were anuric (< 100 mL/24 hr), 36.7% of patients were oliguric (100–500 mL/24 hr), and 16.6% of patients had UOP greater than 500 mL/24 hr. Population PK model analysis identified residual diuresis to be a modifier of total meropenem clearance. The investigators recognized that to attain a pharmacodynamic target of 100% free time above the MIC (fT>MIC), dose adjustments would be necessary in patients with UOPs greater than 500 mL/day (18). In two recent cefiderocol case reports, simulation of residual renal function estimates within PK analysis showed that the addition of residual renal function, on top of the prescribed effluent

TABLE 3.

Percentage of Cefiderocol Dose Adjustments Warranted at 24 Hours Based on Changes in Effluent Flow Rate Relative to Effluent Flow Rate at Continuous Renal Replacement Therapy Initiation (0 hr)

		24 Hr Post-Continuous Renal Replacement Therapy Initiation		
Q_E Range at 0 hr (Cefiderocol Dose)	No. of Patients	No. of Patients Remaining Within 0 Hr Q_E Range (ie, Cefiderocol Dose Maintained)	No. of Patients at a Higher Q_E Range Relative to 0 Hr (ie, Cefiderocol Dose Increase Warranted)	No. of Patients at a Lower Q_E Range Relative to 0 Hr (ie, Cefiderocol Dose Decrease Warranted)
≤ 2 L/hr (1.5 g q 12 hr)	30	9 (30%)	21 (70%)	NA
2.1–3 L/hr (2 g q 12 hr)	175	115 (66%)	49 (28%)	11 (6%)
3.1–4 L/hr (1.5 g q 8 hr)	153	98 (64%)	11 (7%)	44 (29%)
≥ 4.1 L/hr (2 g q 8 hr)	22	14 (64%)	NA	8 (36%)
Total	380	236 (62.1%)	81 (21.3%)	63 (16.6)

NA = not applicable, Q_E = effluent flow rate.

TABLE 4.

Percentage of Cefiderocol Dose Adjustments Warranted at 48 Hours Based on Changes in Effluent Flow Rate Relative to 24 Hours Effluent Flow Rate

		48 Hr Post-Continuous Renal Replacement Therapy Initiation		
Q_E Range at 24 Hr (Cefiderocol Dose)	No. of Patients	No. of Patients Remaining Within 24 Hr Q_E Range (i.e., Cefiderocol Dose Maintained)	No. of Patients at a Higher Q_E Range Relative to 24 Hr (i.e., Cefiderocol Dose Increase Warranted)	No. of Patients at a Lower Q_E Range Relative to 24 Hr (i.e., Cefiderocol Dose Decrease Warranted)
≤ 2 L/hr (1.5 g q 12 hr)	22	18 (82%)	4 (18%)	NA
2.1–3 L/hr (2 g q 12 hr)	176	155 (88%)	15 (9%)	6 (3%)
3.1–4 L/hr (1.5 g q 8 hr)	152	126 (83%)	6 (4%)	20 (13%)
≥ 4.1 L/hr (2 g q 8 hr)	30	25 (83%)	NA	5 (17%)
Total	380	324 (85.3%)	25 (6.6%)	31 (8.2%)

NA = not applicable, Q_E = effluent flow rate.

rates, would result in reduced *f*T>MIC thresholds and suboptimal pharmacodynamic exposures (19, 20).

The early administration of appropriate antibiotic doses in patients with serious infections is critical given the knowledge that each hour of inappropriate therapy results in an increased risk of death (21–24). Given the safety profile of β-lactam antibiotics including cefiderocol, and the potential risk of suboptimal concentrations when Q_E increase, the observations herein suggest it is reasonable to empirically escalate the dose from the Q_E-based dosing recommendation to the next higher dose or use a more frequent dosing interval over the first 24 hours of CRRT initiation. After the 24-hour window, or upon observation of steady flow rates, the product label dosing recommendations could then be used as guidance to maintain steady-state exposure.

TABLE 5.

Percentage of Cefiderocol Dose Adjustments Warranted at 72 Hours Based on Changes in Effluent Flow Rate Relative to 48 Hours Effluent Flow Rate

		72 Hr Post-Continuous Renal Replacement Therapy Initiation		
Q_E Range at 48 Hr (Cefiderocol Dose)	No. of Patients	No. of Patients Remaining Within 48 Hr Q_E Range (i.e., Cefiderocol Dose Maintained)	No. of Patients at a Higher Q_E Range Relative to 48 Hr (i.e., Cefiderocol Dose Increase Warranted)	No. of Patients at a Lower Q_E Range Relative to 48 Hr (i.e., Cefiderocol Dose Decrease Warranted)
≤ 2 L/hr (1.5 g q 12 hr)	24	19 (79%)	5 (21%)	NA
2.1–3 L/hr (2 g q 12 hr)	179	159 (89%)	11 (6%)	9 (5%)
3.1–4 L/hr (1.5 g q 8 hr)	146	132 (90%)	3 (2%)	11 (8%)
≥ 4.1 L/hr (2 g q 8 hr)	31	27 (87%)	NA	4 (13%)
Total	380	337 (88.7%)	19 (5%)	24 (6.3%)

NA = not applicable, Q_E = effluent flow rate.

The alternative approach, that is, constant trending of Q_E during the first 24 hours by the pharmacist or clinician before each dose prescription may not be feasible given clinical workloads.

This pragmatic dose escalation approach within the first 24 hours of CRRT initiation is similar to other dose optimization strategies geared toward the critically ill population (25–28). One noteworthy study was by Crass et al (26) regarding renal dosing of patients with AKI but not requiring dialysis. The authors hypothesized that the unnecessary dose reduction in the setting of acute on chronic renal impairment may have led to the reduced clinical response in patients with baseline creatinine clearance of 30–50 mL/min in the clinical trials of ceftolozane/tazobactam, ceftazidime/avibactam, and telavancin that resulted in precautionary statements in their FDA labels. Using a clinical database, they showed that renal impairment in AKI resolves within 48 hours, thus the dose reductions that occur in that time should be deferred until 48 hours after initiation of therapy and then reassessed. Their study results as well as ours, highlight the disconnect between real-world clinical practice and regimented clinical trials that fail to capture the dynamism of the physiologic (e.g., renal function, weight) or mechanistic variables (CRRT settings) that can influence antibiotic dosing.

In addition to multicenter studies to corroborate our findings, the inclusion of blood sampling on the day of CRRT initiation will improve the utility of future population pharmacokinetic datasets. As a retrospective study, we were limited to using urine volume as a surrogate for residual renal function so future investigations assessing residual renal function through urine and serum creatinine measurements are needed.

CONCLUSIONS

There is growing interest in Q_E-based dosing for antibiotics. In this retrospective study, Q_E changes were more frequent and of larger magnitude in the first 24 hours than in the subsequent 24- to 48-hour or 48- to 72-hour windows. A high residual renal function was also observed in the first 24 hours. These data suggest that antibiotic dose selection may require frequent modification over the initial 24 hours due to changes in effluent rates and residual renal function. Considering the risk of mortality associated with subtherapeutic antibiotic exposures, dose escalation may be warranted in the first 24 hours of CRRT initiation, with resumption of Q_E-based dosing recommendations afterward or upon observation of steady Q_E.

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1 *Center for Anti-Infective Research and Development, Hartford Hospital, Hartford, CT.*

2 *Division of Nephrology, Hartford Hospital, Hartford, CT.*

3 *Division of Infectious Diseases, Hartford Hospital, Hartford, CT.*

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For information regarding this article, E-mail: tomefa.asempa@hhchealth.org

REFERENCES

1. Kellum JA, Lameire N, Aspelin P, et al: Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group: KDIGO clinical practice guideline for acute kidney injury. *Kidney Inter Suppl* 2012; 2:1–138
2. Hoste EA, Bagshaw SM, Bellomo R, et al: Epidemiology of acute kidney injury in critically ill patients: The multinational AKI-EPI study. *Intensive Care Med* 2015; 41:1411–1423
3. Karkar A, Ronco C, Ronco C: Prescription of CRRT: A pathway to optimize therapy. *Ann Intensive Care* 2020; 10:32
4. Uchino S, Kellum JA, Bellomo R, et al; Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators: Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators. Acute renal failure in critically ill patients: A multinational, multicenter study. *JAMA* 2005; 294:813–818
5. Tandukar S, Palevsky PM: Continuous renal replacement therapy: Who, when, why, and how. *Chest* 2019; 155:626–638
6. Rewa OG, Ortiz-Soriano V, Lambert J, et al: Epidemiology and outcomes of AKI treated with continuous kidney replacement therapy: The multicenter CRRTnet study. *Kidney Med* 2023; 5:100641
7. Roberts JA, Joynt GM, Lee A, et al; SMARRT Study Collaborators and the ANZICS Clinical Trials Group: SMARRT Study Collaborators and the ANZICS Clinical Trials Group: 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. *Clin Infect Dis* 2021; 72:1369–1378
8. Choi G, Gomersall CD, Tian Q, et al: Principles of antibacterial dosing in continuous renal replacement therapy. *Crit Care Med* 2009; 37:2268–2282
9. Hoff BM, Maker JH, Dager WE, et al: Antibiotic dosing for critically ill adult patients receiving intermittent hemodialysis, prolonged intermittent renal replacement therapy, and continuous renal replacement therapy: An update. *Ann Pharmacother* 2020; 54:43–55
10. Gillespie EL, Kuti JL, Nicolau DP: Pharmacodynamics of antimicrobials: Treatment optimisation. *Expert Opin Drug Metab Toxicol* 2005; 1:351–361
11. Jamal JA, Udy AA, Lipman J, et al: The impact of variation in renal replacement therapy settings on piperacillin, meropenem, and vancomycin drug clearance in the critically ill: An analysis of published literature and dosing regimens*. *Crit Care Med* 2014; 42:1640–1650
12. Vásquez Jiménez E, Anumudu SJ, Neyra JA: Dose of continuous renal replacement therapy in critically ill patients: A bona fide quality indicator. *Nephron* 2021; 145:91–98
13. Wei X, Naseer S, Weinstein EA, et al: Cefiderocol dosing for patients receiving continuous renal replacement therapy. *Clin Pharmacol Ther* 2022; 112:1004–1007
14. Wong WT, Choi G, Gomersall CD, et al: To increase or decrease dosage of antimicrobials in septic patients during continuous renal replacement therapy: The eternal doubt. *Curr Opin Pharmacol* 2015; 24:68–78
15. Wenzler E, Butler D, Tan X, et al: Pharmacokinetics, pharmacodynamics, and dose optimization of cefiderocol during continuous renal replacement therapy. *Clin Pharmacokinet* 2022; 61:539–552
16. Fetroja: Highlights of prescribing information. Osaka, Japan, Shionogi & Co., Ltd., 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213973s000lbl.pdf. Accessed November 9, 2023
17. Shafi T, Jaar BG, Plantinga LC, et al: Association of residual urine output with mortality, quality of life, and inflammation in incident hemodialysis patients: The Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) Study. *Am J Kidney Dis* 2010; 56:348–358
18. Ulldemolins M, Soy D, Llaurado-Serra M, et al: Meropenem population pharmacokinetics in critically ill patients with septic shock and continuous renal replacement therapy: Influence of residual diuresis on dose requirements. *Antimicrob Agents Chemother* 2015; 59:5520–5528
19. Kobic E, Gill CM, Mochon AB, et al: Cefiderocol pharmacokinetics in a patient receiving continuous venovenous hemodiafiltration. *Open Forum Infect Dis* 2021; 8:ofab252
20. Fratoni AJ, Kuti JL, Nicolau DP: Optimised cefiderocol exposures in a successfully treated critically ill patient with polymicrobial Stenotrophomonas maltophilia bacteraemia and pneumonia receiving continuous venovenous haemodiafiltration. *Int J Antimicrob Agents* 2021; 58:106395
21. Kumar A, Roberts D, Wood KE, et al: Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006; 34:1589–1596
22. Paul M, Shani V, Muchtar E, et al: Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis. *Antimicrob Agents Chemother* 2010; 54:4851–4863
23. Morata L, Cobos-Trigueros N, Martínez JA, et al: Influence of multidrug resistance and appropriate empirical therapy

on the 30-day mortality rate of Pseudomonas aeruginosa bacteremia. *Antimicrob Agents Chemother* 2012; 56:4833–4837

24. Lee CC, Lee CH, Hong MY, et al: Timing of appropriate empirical antimicrobial administration and outcome of adults with community-onset bacteremia. *Crit Care* 2017; 21:119
25. Kuti JL, Nicolau DP: Optimal cefepime and meropenem dosing for ventilator-associated pneumonia patients with reduced renal function: an update to our clinical pathway. *J Crit Care* 2010; 25:155–156
26. Crass RL, Rodvold KA, Mueller BA, et al: Renal dosing of antibiotics: Are we jumping the gun? *Clin Infect Dis* 2019; 68:1596–1602
27. Phe K, Heil EL, Tam VH: Optimizing pharmacokinetics-pharmacodynamics of antimicrobial management in patients with sepsis: A review. *J Infect Dis* 2020; 222(Suppl 2):S132–S141
28. Barreto EF, Chang J, Bjergum MW, et al: BLOOM Study Group: Adequacy of cefepime concentrations in the early phase of critical illness: A case for precision pharmacotherapy. *Pharmacotherapy* 2023; 43:1112–1120