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Cefepime Extraction by Extracorporeal Life Support Circuits

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Abstract: Extracorporeal life support (ECLS) devices are lifesaving for critically ill patients with multi-organ dysfunction. Despite this, patients supported with ECLS are at high risk for ECLS-related complications, including nosocomial infections, and mortality rates are high in this patient population. The high mortality rates are suspected to be, in part, a result of significantly altered drug disposition by the ECLS circuit, resulting in suboptimal antimicrobial dosing. Cefepime is commonly used in critically ill patients with serious infections. Cefepime dosing is not routinely guided by therapeutic drug monitoring and treatment success is dependent upon the percentage of time of the dosing interval that the drug concentration remains above the minimum inhibitory concentration of the organism. This *ex vivo* study measured the extraction of cefepime by continuous renal replacement therapy (CRRT) and extracorporeal membrane oxygenation (ECMO) circuits. Cefepime was studied in four closed-loop CRRT circuit configurations and a single closed-loop ECMO circuit configuration. Circuits were primed with a physiologic human blood–plasma mixture and the drug was dosed to achieve therapeutic concentrations. Serial blood samples were collected over time and concentrations were quantified using validated assays. In *ex vivo* CRRT experiments, cefepime was rapidly cleared by dialysis, hemofiltration, and hemodiafiltration, with greater than 96% cefepime eliminated from the circuit by 2 hours. In the ECMO circuits, the mean recovery of cefepime was similar in both circuit and standard control. Mean (standard deviation) recovery of cefepime in the ECMO circuits ($n = 6$) was 39.2% (8.0) at 24 hours. Mean recovery in the standard control ($n = 3$) at 24 hours was 52.2% (1.5). Cefepime is rapidly cleared by dialysis, hemofiltration, and hemodiafiltration in the CRRT circuit but minimally adsorbed by either the CRRT or ECMO circuits. Dosing adjustments are needed for patients supported with CRRT. **Keywords**: cefepime, extracorporeal membrane oxygenation, renal replacement therapy, pharmacology, drug extraction. *J Extra Corpor Technol. 2022;54:212–22*

Continuous renal replacement therapy (CRRT) and extracorporeal membrane oxygenation (ECMO) are extracorporeal life support (ECLS) devices used in patients with refractory organ failure. Although these mechanical support devices can be lifesaving, mortality rates across the age spectrum are high (1–7). The high mortality is suspected to be due, in part, to alterations in drug pharmacokinetics (PK) by the ECLS circuit (8,9). The ECLS circuit affects drug PK via: 1) drug adsorption by components of the circuit; 2) increased volume of distribution due to exogenous fluids used to prime the circuit as well as inflammation and edema triggered by the circuit and underlying critical illness; and 3) direct drug clearance by the hemofilter (10,11).

Cefepime is a fourth-generation cephalosporin commonly used in critically ill patients when serious infections with resistant Gram-negative pathogens (e.g., *Pseudomonas aeruginosa*) are known or suspected to be involved. The bactericidal activity of cefepime is dependent upon the percentage of time of the dosing interval that the drug

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concentration remains above the minimum inhibitory concentration of the organism (12). However, excessive cefepime exposure has been associated with neurotoxicity (13). Cefepime dosing is not routinely guided by therapeutic drug monitoring, primarily due to the lack of widely available bioanalytical assays (14–17). This lack of therapeutic drug monitoring places patients at risk for treatment failure and toxicity, especially in patients on ECLS devices where drug disposition may be impacted.

Ex vivo experiments in which a drug is administered to an isolated circuit have been used to investigate the impact of CRRT (18–30) and ECMO (31–43) on drug disposition. As there is no patient connected to the circuit, any decrease in drug concentration is due to drug degradation or circuit extraction (adsorption or clearance). Adsorption by circuit components is more common with highly lipophilic and highly protein-bound drugs (38,44). In contrast, clearance by the hemofilter is more common with drugs that are hydrophilic and minimally protein bound (45). The extent of extraction also varies based on circuit materials and circuit flow/dialysis rates (46,47). Individual drug-circuit relationships are difficult to predict, however, and rapid technological advances in ECLS circuit design and equipment material over the past two decades have led to the development of newer, more refined, and more biocompatible materials that are constantly evolving, adding further variability to their impact on drug disposition.

This study used CRRT and ECMO *ex vivo* systems to determine the extent of cefepime removal by the CRRT and ECMO circuits, respectively. Cefepime is minimally protein bound, hydrophilic, and primarily renally cleared, leading to the hypothesis that it will be minimally adsorbed by the ECMO circuit but rapidly cleared by the CRRT circuit. Understanding the impact of ECLS devices on cefepime PK will help improve pharmacotherapy in patients supported with ECLS, ultimately improving the safety and efficacy of cefepime in this vulnerable population.

MATERIALS AND METHODS

CRRT Circuit Configurations

We designed four *ex vivo* CRRT circuit configurations (Figure 1, Table 1) based on previously described *ex vivo* models (18,19) to determine cefepime adsorption and transmembrane clearance. Adsorption experiments were performed to determine whether cefepime adsorbed to any CRRT components (i.e., hemofilter, tubing). Convection experiments using continuous venovenous hemofiltration (CVVH) circuit configurations were performed to determine cefepime's sieving coefficient via convection. Diffusion experiments using continuous venovenous hemodialysis (CVVHD) circuit configurations were performed to determine cefepime's saturation coefficient via diffusion. Finally, we performed hemodiafiltration experiments using continuous venovenous hemodiafiltration (CVVHDF) circuit configurations for two major reasons: 1) Convection and diffusion are independent processes and not necessarily additive, and 2) CVVHDF is the modality of choice for critically ill patients at our institutions. For all experiments, urea (Science-Company, Lakewood, CO) was added as a control solute as it is a stable molecule, freely filtered, and is not known to adsorb to CRRT systems (19). Each of the four experimental circuit configurations was replicated in triplicate and each experiment lasted 8 hours.

ECMO Circuit Configuration

Circuits were assembled to determine the extent of adsorption by circuit components and consisted of tubing, a pump, an oxygenator, and a cannula (Table 1, Figure 2). ECMO circuit experiments were replicated three times and each experiment lasted 24 hours.

CRRT Circuit Setup

The CRRT circuit was primed with ~500 mL of a human blood-crystalloid mixture created to simulate the in vivo environment (Table 2). The circuit was completed using a 500-mL EXACTAMIX (Baxter Healthcare, Deerfield, IL) bag as a reservoir. The blood reservoir was continuously stirred using an orbital shaker. Reservoir temperature was maintained at 37°C using a digitally controlled heating pad. Circuit pH was continuously monitored using an in-line blood gas monitoring tool (CDI® Blood Parameter Monitoring System 500, Terumo Cardiovascular, Ann Arbor, MI) that connected the return line (blue lumen) to the reservoir bag. Tris(hydroxymethyl)aminomethane (THAM®, Fisher Scientific, Pittsburgh, PA) was intermittently added to the system to maintain physiologic pH (7.2–7.5). Circuits were run using the following prescriptions: 1) Adsorption circuits: blood flow rate (Q_b) 100 mL/min, ultrafiltration (UF) rate 0 mL/h to maintain a constant volume in the extracorporeal system; 2) CVVH circuits: blood flow rate 80 mL/min, pre-blood pump (PBP) replacement fluid rate 600 mL/h, post-filter replacement fluid rate 200 mL/h, UF rate 0 mL/h, effluent dose 800 mL/h; 3) CVVHD circuits: blood flow rate 80 mL/min, dialysate rate (Q_d) 800 mL/h; 4) CVVHDF circuits: blood flow rate 80 mL/min, dialysate rate 400 mL/h, PBP replacement fluid rate 300 mL/h, post-filter replacement fluid rate 100 mL/h, UF rate was 0 mL/h, effluent dose 800 mL/h.

ECMO Circuit Setup

The ECMO circuit was primed with ~1 L of the human blood–crystalloid mixture (Table 2). The circuit was completed using a double-spiked intravenous (IV) bag as a reservoir, with operating volume maintained to prevent air entrainment into circuit. Temperature was

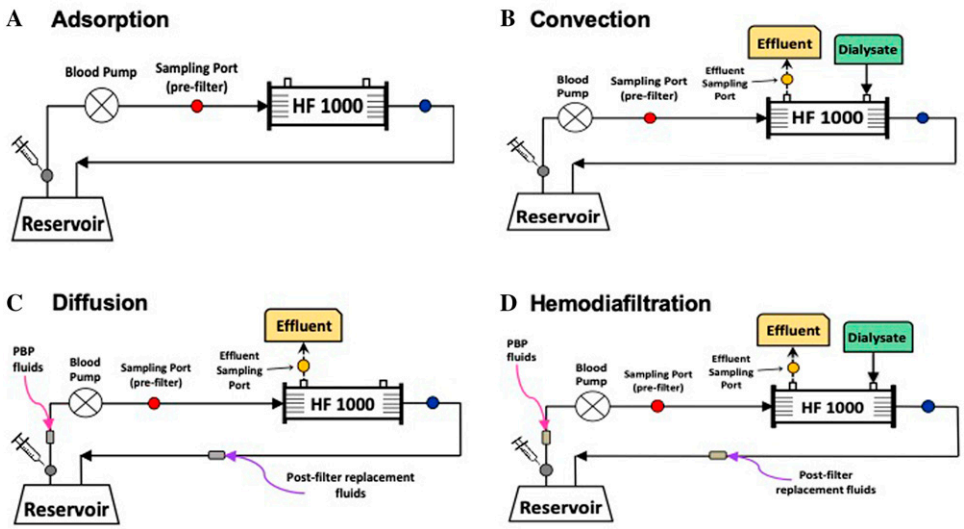

Figure 1. Continuous renal replacement therapy (CRRT) *ex vivo* circuit configurations: (A) This circuit configuration constituted a closed system. As a result, any decrease in drug concentration could only be due to adsorption to the CRRT circuit components or drug degradation. (B) A continuous venovenous hemofiltration (CVVH) circuit to determine clearance by hemofiltration. Pre- and post-filter replacement fluids were used to maintain a constant volume in the circuit. (C) A continuous venovenous hemodialysis (CVVHD) circuit to determine clearance by dialysis. Dialysate flows countercurrent to the blood and drains into a separate bag (effluent). (D) A continuous venovenous hemodiafiltration (CVVHDF) circuit to determine drug clearance by hemodiafiltration. Pre- and post-filter replacement fluids were used to maintain a constant volume in the circuit.

maintained at 37°C using an ECMO Water Heater (Cincinnati Sub-Zero, Cincinnati, OH) via the Quadrox-iD integrated heat exchanger. Physiologic pH (7.2–7.5) was maintained by adding additional sodium bicarbonate, THAM®, and/or carbon dioxide via the sweep gas. The reservoir return was directed into the IV bag via a 10 French arterial cannula (Medtronic, Minneapolis, MN). Flows were maintained at 1 L/min and were measured post-oxygenator using an HT110 bypass flow meter with H8XL flowsensor (Transonic, Davis, CA).

Controls

Three control samples were analyzed to determine the amount of natural drug degradation over time. The human blood-crystalloid mixture (Table 2) was added to polypropylene centrifuge tubes (229,426, CELLTREAT, Pepperell, MA). Blood was drawn from the primed ECMO circuit after 5 minutes of circulation but before cefepime administration, ensuring that the control sample medium was identical to the composition of the circuit medium. Control samples were maintained at 37°C for the duration of the experiment.

Table 1. ECLS circuit components.

Circuit Type	Component	Manufacturer	Model	Material
CRRT	System	Baxter	Prismaflex™	N/A
	Hemofilter	Baxter	HF1000, (1.1 m^2)	Polyarylethersulfone hollow fibers, plasticized polyvinyl chloride tubing
	TherMax Bag	Baxter	TherMax Blood Warmer Disposable, 27 mL	Polyurethane
	Reservoir	Baxter	EXACTAMIX EVA, 500 mL	Ethylene vinyl acetate
	System	Baxter	Prismaflex™	N/A
ECMO	Oxygenator	Maquet	Quadrox-iD Adult	Polymethylpentane hollow fibers with Softline* coating
	Pump	Maquet	Rotaflow RF-32 Centrifugal Pump	Polycarbonate with Bioline† coating
	Tubing	LivaNova	Smart Perfusion Pack, 3/8″ diameter	Polyvinyl chloride with Smart-X‡ coating
	Cannula	Medtronic	DLP™ One-Piece Pediatric Arterial Cannnula, 10 Fr	Polyvinyl chloride

CRRT, continuous renal replacement therapy; ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation.
*Softline coating: heparin free biopassive polymer; †Bioline coating: heparin + recombinant human albumin; ‡Smart-X coating: Tribloc Copolymer (Polycaprolactone-Polydimethylsiloxane-Polycaprolactone) integrated into plastic.

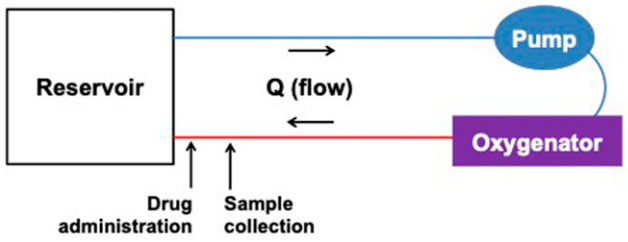

Figure 2. Extracorporeal membrane oxygenation (ECMO) *ex vivo* circuit configuration.

Observed cefepime degradation in the controls prompted additional post hoc experiments to assess the source of drug loss. In addition to the experiments in polypropylene centrifuge tubes above, three experimental conditions were studied: 1) Blood prime mixture in silanized glass to determine the extent of adsorption by the polypropylene; 2) Blood prime mixture in polypropylene centrifuge tubes protected from light to determine the impact of light on drug degradation; and 3) Crystalloid prime solution in polypropylene centrifuge tubes to determine the extent of drug metabolism in blood. The blood prime controls were filled with blood prime solution from the ECMO circuits (Table 2). The crystalloid prime controls were filled with the following crystalloid solution: Plasma-Lyte A (250 mL), heparin (1.75 U), sodium bicarbonate (3.5 mEq), calcium gluconate (1 g), and 25% albumin (6.25 g). All of the conditions were repeated in triplicate.

Drug

Cefepime was provided by our institutions' pharmacies. The drug was added to the *ex vivo* circuits to achieve peak plasma concentrations of 140–170 mg/L to match peak cefepime plasma concentrations typically observed in the clinical setting following recommended dosing guidelines (48–50). Cefepime was dosed in the control samples to achieve a comparable concentration to the CRRT and ECMO circuits.

Drug Administration and Sample Collection

After the CRRT circuit was primed with the blood mixture and connected to the reservoir, the blood recirculated through the CRRT circuit for 30–40 minutes to allow for uniform coating of the extracorporeal system. Cefepime was then administered via the PBP arterial sampling port located just downstream from the reservoir bag at time = 0. Sample collection times were 1, 5, 15, and 30 minutes, and 1, 2, 3, 4, 6, and 8 hours after cefepime administration. Cefepime and urea concentrations were determined from 1.5 mL blood samples obtained simultaneously from the pre-filter (red) sampling port, and 1.5 mL effluent samples from the post-filter (yellow) effluent sampling port of the circuit (Figure 1).

After the ECMO circuit was primed and connected to the reservoir, cefepime was introduced into the system at time = 0 via a three-way stopcock located just before the reservoir bag and downstream of the sampling port on the arterial limb of the circuit. Samples were collected at 1, 5, 15, and 30 minutes and 1, 2, 3, 4, 6, 10, and 24 hours after cefepime administration. Blood samples (1.5 mL) were collected via a second three-way stopcock located just upstream of the drug administration port on the arterial limb of the circuit (Figure 2).

Samples from both the CRRT and ECMO circuits were processed and stored as follows: 1) Effluent samples (if applicable) were directly transferred to cryovials (Fisher Scientific, Pittsburgh, PA); 2) Blood samples were immediately centrifuged at 3,000 *g*, 4°C for 10 minutes; 3) Separated plasma was transferred to cryovials; 4) All samples were frozen at −20°C for < 72 hours, then stored at −80°C until analysis.

Table 2. ECLS circuit prime solutions.

Component	Amount	
	CRRT	ECMO
Plasma-Lyte A*†	–	300–400 mL
PrismaSol® BGK 0/2.5*‡	50–100 mL	–
Human red blood cells (adenine saline added leukocytes reduced)	300 mL	400–500 mL
Thawed human plasma (frozen within 24 hours after phlebotomy)	125 mL	150 mL
Albumin 25%	6.25 g	12.5 g
Sodium bicarbonate 8.4%	7 mEq	7 mEq
Tris(hydroxymethyl)aminomethane§	1.5–2.0 g	2 g
Calcium gluconate 10%	–	650 mg
Calcium chloride 10%	180 mg	–
Heparin	350 units	500 units

ECLS, extracorporeal life support.
*Baxter Healthcare, Deerfield, IL; †mEq/L: Na^+ 140, K^+ 0, Cl^- 109, HCO_3^- 32, Ca^{2+} 2.5, Mg^{2+} 1.5, lactate 3; dextrose 100 mg/dL; 292 mOsmol/L; ‡mEq/L: Na^+ 140, K^+ 5, Cl^- 98, Mg^{2+} 3, acetate 27, gluconate 23, lactate 0, dextrose 0; 294 mOsmol/L; §THAM®, Fisher Scientific, Pittsburgh, PA.

Analysis

Drug concentrations were determined using assays developed and validated according to FDA guidance (51). CRRT plasma and effluent concentrations were measured in the laboratory of Douglas Fish (University of Colorado, Aurora CO) using high-performance liquid chromatography (HPLC) with ultraviolet (UV) detection according to previously published methods (52,53). The assay was validated in both plasma and effluent, with standard curves achieving coefficients of determination (r^2) of >.998 and coefficients of variation being <5.1% for concentrations across the range of the standard curves (1.0–250 mg/L) for both fluids. The lower limit of quantification (LLOQ) for cefepime in both plasma and effluent samples was 1.0 mg/L. Intraday and interday precision (%CV) for plasma cefepime samples ranged from 1.9% to 4.3% and 2.7% to 5.1%, respectively, across the range of the standard curve. Intraday and interday precision (%CV) for effluent samples ranged from .4% to 2.4% and .6% to 2.9%, respectively. For ECMO experiments, cefepime concentrations were measured at OpAns Laboratory (Durham, NC) using high-performance liquid chromatography-mass spectrometry (HPLC-MS/MS). The assay was validated with standard curves achieving coefficients of determination (r^2) of >.997 and coefficients of variation being <4.6% for concentrations across the range of the standard curves (.1–100 mg/L). The LLOQ for cefepime was .1 mg/L. The intraday precision ranged from 2.4% to 2.5% and the interday precision ranged from 3.0% to 4.6%.

Drug recovery in circuits and controls was calculated at each sample time using the following equation:

$$Recovery(\%) = \frac{C_t}{C_i} \times 100$$

where C_t is the concentration at time t and C_i is the initial concentration measured at time = 1 minute for the control and CRRT samples. In the ECMO circuits, there was an initial delay in drug mixing. Therefore, the maximum concentration of the first four time points was used as C_i. Data are reported as the mean and 95% confidence interval. Using paired plasma and effluent samples from six time points (t = 15 minutes through t = 4 hours), sieving and saturation coefficients as well as transmembrane clearances were calculated for the CVVH, CVVHD, and CVVHDF experiments using the following equations:

$$1)\ S_c = \frac{C_{uf}}{C_p},\ 2)\ S_a = \frac{C_d}{C_p},\ 3)\ CL_{CVVH} = Q_{uf} \times S_c,$$

$$4)\ CL_{CVVHD} = Q_d \times S_a,\ 5)\ S_{a(HDF)} = \frac{C_{eff}}{C_p},$$

$$6)\ CL_{CVVHDF} = Q_{eff} \times S_{a(HDF)}$$

where S_c is the sieving coefficient, C_{uf} is the ultrafiltrate concentration, C_P is the plasma concentration, S_a is the saturation coefficient, C_d is dialysate concentration, and C_{eff} is the effluent concentration. Q_{uf}, Q_d, and Q_{eff} are the rates of UF, dialysis, and effluent, respectively. Q_{eff} is the ultrafiltrate plus the dialysate flow rates ($Q_{uf}+Q_d$). CL_{CVVH}, CL_{CVVHD}, and CL_{CVVHDF} represent the transmembrane clearances for the CVVH and CVVHD, and CVVHDF experiments, respectively. $S_{a(HDF)}$ is the saturation coefficient for hemodiafiltration, calculated for the CVVHDF experiments. Data are reported as the mean (standard deviation [SD]).

Statistics

A two-sample t test was used to compare the mean recovery of ECMO and CRRT circuit replicates to the mean recovery in the standard control. We compared all four control conditions using a one-way analysis of variance (ANOVA) with Bartlett's test to confirm equal variance and Bonferroni correction for multiple comparisons.

RESULTS

CRRT Circuits

Cefepime was rapidly cleared by both diffusion (i.e., dialysis) and convection (i.e., hemofiltration) in *ex vivo* CRRT circuits with greater than 96% cefepime extraction by 2 hours (Figure 3). By 30 minutes, mean recovery in the standard control was significantly greater than mean recovery in the CVVH (n = 3; p = .0003), CVVHD (n = 3; p = <.0001), and CVVHDF (n = 3; p = <.0001) circuits. The mean (SD) recovery of cefepime in the adsorption circuits (n = 3) was not statistically different compared to the recovery in the standard control (p = .68 at 30 minutes and p = .29 at 6 hours). Table 3 summarizes the mean (SD) S_a, S_c, and CL values of cefepime for each *ex vivo* CRRT modality. Appendix Table 1 lists raw cefepime concentration data by CRRT circuit type.

ECMO Circuits

Due to circuit failures, a total of six ECMO circuit replicates were ultimately performed. The mean recovery of cefepime was similar in both circuit and standard control. Mean (SD) recovery of cefepime in the ECMO circuits (n = 6) was 82.9% (8.4) at 4 hours and 39.2% (8.0) at 24 hours. Mean recovery in the standard control (n = 3) at 4 hours was 88.8% (.9) and 52.2% (1.5) at 24 hours. Mean recovery in the standard control was not significantly different compared to recovery in the ECMO circuit at 4 hours (p = .28) but was significantly different compared to recovery in the ECMO circuit at 24 hours (p = .03) (Figures 4 and 5). See Appendix Table 3 for cefepime concentration data from control experiments. Cefepime concentration data for ECMO *ex vivo* experiments are shown in Appendix Table 2.

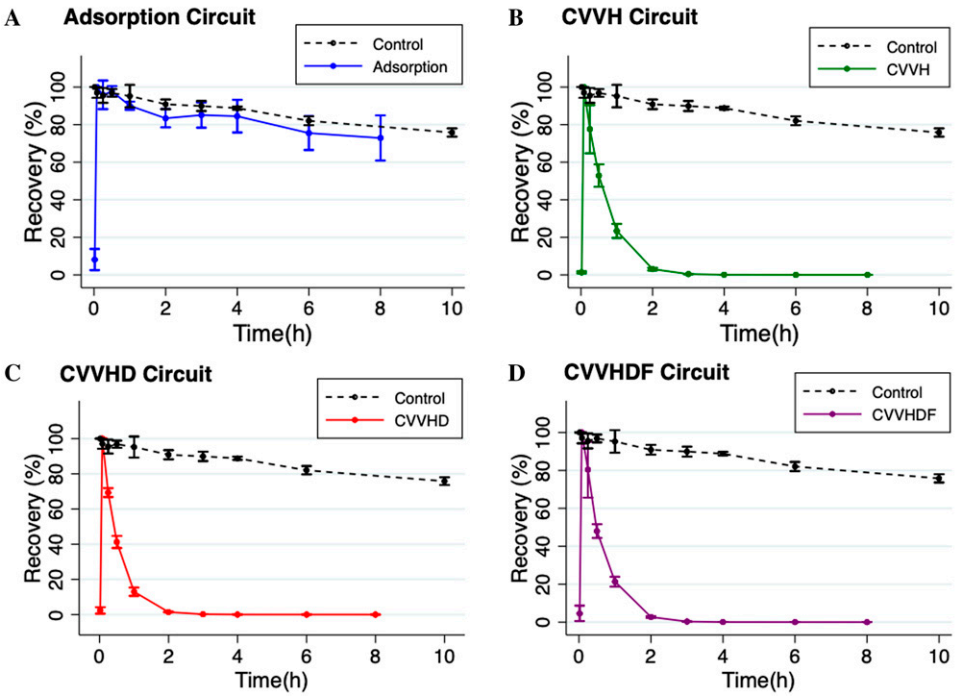

Figure 3. Cefepime recovery by *ex vivo* continuous renal replacement therapy (CRRT) circuit configuration, depicted as %-drug recovered over 8 hours for each circuit configuration. Values are mean; error bars indicate 95% confidence interval.

Control Experiments

Drug loss was more pronounced in the crystalloid prime samples compared with the other control conditions. At 24 hours, the standard control, light control, and silanized glass control, had mean recoveries of 52.2%, 50.7% (1.3), and 57.6% (1.8), respectively. The crystalloid prime control saw much lower mean recovery at .61% (.04). Significant differences were present (difference, adjusted p value) between the crystalloid prime control and the standard control (51.6%, $p = <.0001$), light control (50.1%, $p = <.0001$), and silanized glass control (57.0%, $p = <.0001$) at 24 hours. Significant differences were also present between the silanized glass control and the standard control (−5.39%, $p = .007$) and light control (6.9%, $p = .001$).

Table 3. *Ex vivo* saturation (S_a) and sieving (S_c) coefficients, and transmembrane clearance (CL_{TM}, mL/min) of cefepime in a human blood-crystalloid solution for each CRRT modality using a polyarylethersulfone (HF-1000) membrane.

CRRT Modality	S_a or S_c Coefficients	CL_{TM} (mL/min)
CVVH	1.20 (.08)†	15.96 (1.06)
CVVHD	1.29 (.09)*	17.23 (1.24)
CVVHDF	1.17 (.07)*	15.63 (.94)

All values are presented as mean (SD) and were calculated using sample times from 15 minutes to 4 hours. *S_a = saturation coefficient. †S_c = sieving coefficient. CRRT, continuous renal replacement therapy; CVVH = continuous venovenous hemofiltration; CVVHD = continuous venovenous hemodialysis; CVVHDF = continuous venovenous hemodiafiltration.

DISCUSSION

This study demonstrates the degree of cefepime extraction by the *ex vivo* ECMO and CRRT circuits. Although drug loss was observed in the adsorption experiments, the minimal difference between the adsorption circuits and the controls suggests that adsorption played a nominal role in either of the ECLS circuits. In CRRT, cefepime was rapidly cleared by both diffusion (i.e., dialysis) during CVVHD (mean S_a of 1.29) and convection (i.e., hemofiltration) during CVVH (mean Sc of 1.20), indicating that the drug passes freely through the HF-1000 hemofilter membrane. Our findings are similar to prior *ex vivo* CRRT studies of cefepime using different hemofilter membranes (54) and are consistent with our hypothesis that the physiochemical properties of cefepime would lead to minimal circuit-drug adsorption but rapid clearance by hemodiafiltration.

In this study, CVVHD provided the highest clearance of cefepime compared to CVVH and CVVHDF. This is not unexpected given small solute clearance (e.g., cefepime) is highest with diffusion and lowest with convection, whereas large solute clearance is highest with convection and lowest with diffusion (55). In addition, high rates of hemofiltration (or convection, as can be seen in CVVH and CVVHDF) typically require replacement fluid to prevent clotting and preserve the hemofilter's half-life. The replacement fluid acts as a pre-dilutional fluid which also

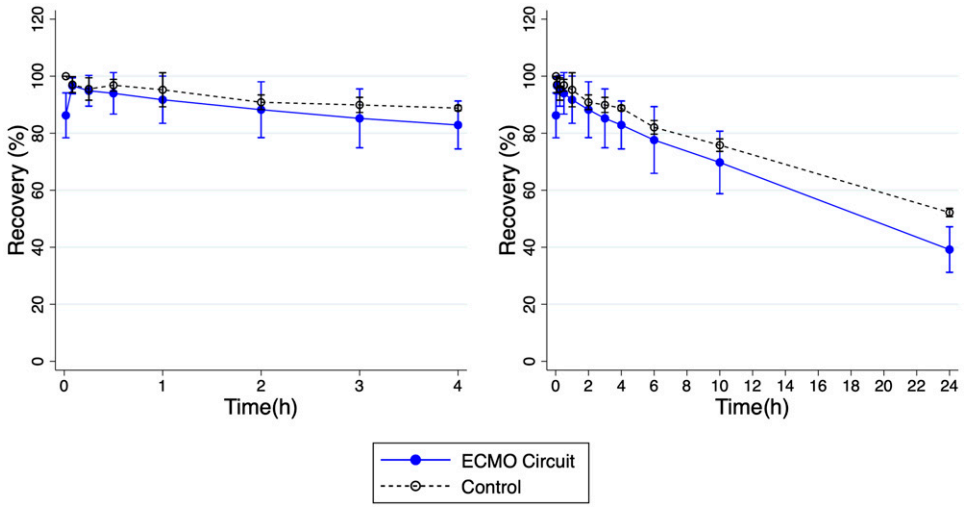

Figure 4. Cefepime recovery from *ex vivo* extracorporeal membrane oxygenation (ECMO) circuit depicted as %-drug recovered over 24 hours. Left panel shows recovery over the first 4 hours and right panel shows recovery over 24 hours. Values are mean; error bars indicate 95% confidence interval.

decreases the clearance of small molecular weight solutes. Although a few clinical and in vitro studies have described the PK of cefepime during CRRT (52,54,56–60), this is the first study evaluating the extracorporeal removal of cefepime by CVVH, CVVHD, and CVVHDF under operational settings for the HF-1000 filter. These results provide important insights into circuit-cefepime interactions that can affect bedside dosing recommendations.

While we observed minimal interaction between cefepime and the ECMO circuit, it is worth noting that there was significant adsorption present at 24 hours. Although statistically significant, this degree of adsorption is unlikely to be clinically significant given that: 1) There was little to no adsorption by the ECMO circuit at the other experimental time points, and 2) There was only a small quantitative difference in recovery between the standard control and experimental samples at 24 hours.

Our control experiments demonstrated a decline in cefepime recovery over time in all of the experimental conditions. Cefepime is known to undergo non-enzymatic degradation in plasma in vitro with accelerated degradation rates at temperatures >4°C (61). We surmised that because our experiments were performed at 37°C, the decline in cefepime concentrations over time was likely the result of this temperature-dependent degradation. Interestingly, there was more precipitous and significant cefepime degradation in the crystalloid prime controls relative to the other control conditions. Mehta et al. also

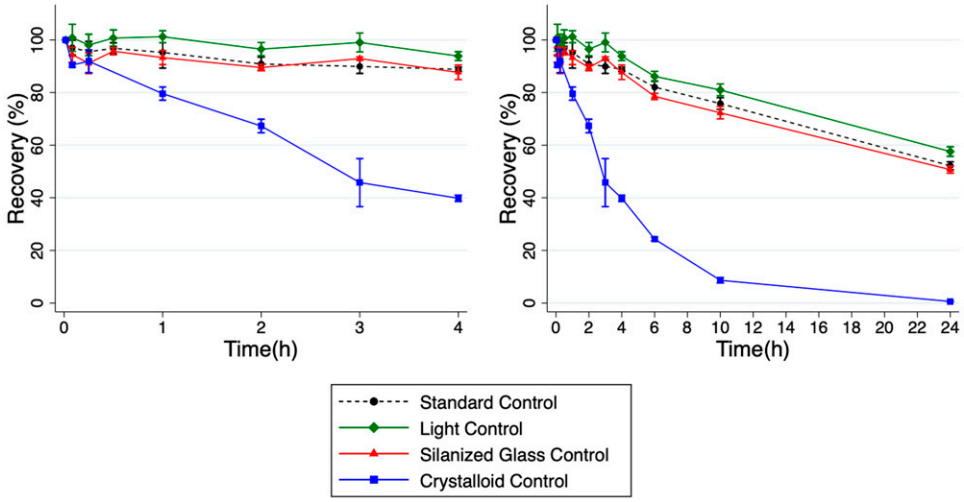

Figure 5. Cefepime recovery under four experimental control conditions depicted as %-drug recovered over 24 hours. Left panel shows recovery over the first 4 hours and right panel shows recovery over 24 hours. Values are mean; error bars indicate 95% confidence interval.

observed higher adsorption in crystalloid primed circuits relative to blood-primed circuited for a number of common drugs (42). It can thus be assumed that some component of the blood prime is offering protection against cefepime degradation. The exact mechanism of protection, however, is unclear.

Our study is not without limitations. Due to a miscalculation in dose-conversion (i.e., targeting a goal peak concentration of mg/dL rather than mg/L), cefepime concentrations were 10-fold higher in the *ex vivo* CRRT experiments. Although this could theoretically result in saturation of the circuit and artificially decrease apparent adsorption, we do not believe this occurred based on the fact that adsorption was comparable between CRRT circuits with the higher concentrations and ECMO circuits with a physiologic concentration. Second, due to constraints with the CRRT *ex vivo* system, CRRT experiments were conducted for a shorter duration than ECMO experiments (8 hours vs. 24 hours). We do not believe the shorter CRRT experiment duration significantly impacted our results because 1) The presence or absence of substantial adsorption should be observed within the first few hours after dosing (25,62–64), and 2) Cefepime was fully cleared within two hours of dosing. Additionally, we only evaluated one type of hemofilter membrane (i.e., HF-1000) in the *ex vivo* CRRT experiments, and it is well known that the degree of drug extraction can vary substantially based on the type (i.e., composition) of hemofilter (24,25,55). Finally, we used very similar flows (i.e., Q_b and Q_{uf}) for all experiments. This most likely did not impact our results given the rapidity and extent to which cefepime was removed from the CRRT system.

CONCLUSION

Cefepime is rapidly cleared by dialysis, hemofiltration, and hemodiafiltration in the CRRT circuit but minimally adsorbed by either the CRRT or ECMO circuits. Dosing adjustments are needed for patients supported with CRRT. Optimal dosing regimens can be predicted by incorporating *ex vivo* ECLS data into physiological-based PK models.

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Appendix Table 1. CRRT cefepime concentrations (mg/L).

	Adsorption Circuit – Blood			Adsorption Circuit - Effluent		
Time	Run 1	Run 2	Run 3	Run 1	Run 2	Run 3
1 minutes	153.47	147.29	27.97	-	-	-
5 minutes	1239.2	1421.42	1630.36	-	-	-
15 minutes	1250.06	1415.95	1420.55	-	-	-
30 minutes	1245.77	1387.38	1549.65	-	-	-
1 hours	1116.04	1310.99	1433.2	-	-	-
2 hours	1096.06	1179.91	1284.22	-	-	-
3 hours	1011.54	1319.9	1318.12	-	-	-
4 hours	947.57	1331.76	1358.76	-	-	-
6 hours	828.63	1207.05	1219.49	-	-	-
8 hours	757.12	1210.25	1180.78	-	-	-
	CVVH Circuit - Blood			CVVH Circuit - Effluent		
Time	Run 1	Run 2	Run 3	Run 1	Run 2	Run 3
1 minutes	6.15	17.6	14.3	958.85	1316.37	1915.03
5 minutes	803.29	1047.66	868.99	1256.3	1382.21	1319.75
15 minutes	618.16	682.18	788.55	1077.09	1030.77	914.02
30 minutes	467.21	485.9	469.8	670.89	670.14	737.56
1 hours	182.96	209.88	239.03	234.22	238.97	302.5
2 hours	21.29	28.78	34.04	28.65	30.58	22.05
3 hours	3.06	4.2	5.05	3.5	4.6	5.01
4 hours	.64	.76	.95	.48	.85	.89
6 hours	.19	.23	.29	0	.72	.24
8 hours	.19	.2	.2	0	.85	0
	CVVHD Circuit - Blood			CVVHD Circuit - Effluent		
Time	Run 1	Run 2	Run 3	Run 1	Run 2	Run 3
1 minutes	59.26	16.15	14.6	733.51	558.46	905.38
5 minutes	1315.53	1329.55	1012.87	1158.99	2450.07	1291.2
15 minutes	873.8	945.24	713.22	1064.31	1250.14	1114.5
30 minutes	594.55	522.37	397.69	640.44	805.61	445.04
1 hours	161.63	146.88	158.83	230.25	220.59	193.02
2 hours	16.77	18.2	16.99	26.13	26.87	18.87
3 hours	2.55	2.56	2.22	2.12	3.36	2.37
4 hours	.52	.59	.42	.43	.51	.9
6 hours	.16	.28	.41	.45	.41	.31
8 hours	.17	.25	.29	.11	.11	.21
	CVVHDF Circuit - Blood			CVVHDF Circuit – Effluent		
Time	Run 1	Run 2	Run 3	Run 1	Run 2	Run 3
1 minutes	17.95	94.45	24.19	1341.68	1263.93	4323.47
5 minutes	875.2	1015.27	997.15	1319.28	1330.65	1333.22
15 minutes	845.93	690.16	762.91	1195.69	1160.53	1142.33
30 minutes	455.74	459.11	464.73	725.43	767.75	697.37
1 hours	208.03	220.31	185.79	268.5	216.07	255.46
2 hours	25.89	30.39	22.05	25.37	29.59	24.26
3 hours	3.19	3.85	2.48	2.26	3.79	2.69
4 hours	.56	.6	.37	.31	.41	.38
6 hours	.32	.12	.11	.1	0	.12
8 hours	.3	.11	.1	0	0	0

Appendix Table 2. ECMO cefepime concentrations (mg/L).

Time	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6
1 minutes	196.95034	111.08942	168.76169	262.70758	103.34327	93.99746
5 minutes	221.12605	132.40337	174.75852	206.9969	107.72754	112.60044
15 minutes	229.14542	136.65941	163.75908	178.61292	113.00717	110.55926
30 minutes	228.80454	139.92037	152.94846	172.18674	105.61809	120.51624
1 hours	216.22497	139.72196	152.81494	159.79767	106.19672	117.70585
2 hours	205.78023	136.5953	146.25552	146.93519	103.44411	115.5767
3 hours	208.4848	123.59014	145.51425	141.60737	286.61903	114.57281
4 hours	196.645	122.03676	136.45963	141.43888	97.38119	110.59217
6 hours	182.37148	117.32404	115.85707	131.23024	87.40895	114.77545
10 hours	156.82844	95.73425	111.10991	113.99033	85.54847	105.28467
24 hours	90.78882	42.03206	75.00834	60.11575	51.49357	57.85821

Appendix Table 3. Cefepime control concentrations (mg/L).

	Standard Control			Silanized Glass Control		
Time	Run 1	Run 2	Run 3	Run 1	Run 2	Run 3
1 minutes	192.86238	205.55319	212.05363	191.89105	172.15995	168.65082
5 minutes	191.40225	201.45249	199.13072	195.62468	181.33379	160.55144
15 minutes	192.93888	192.25701	197.17461	179.15311	173.01319	169.34122
30 minutes	189.24266	201.2972	200.28896	186.8495	174.44978	174.52997
1 hours	196.50095	192.23312	191.51791	189.56502	174.78698	174.31031
2 hours	170.63481	192.3734	191.95817	179.85811	167.04442	166.56287
3 hours	178.29631	185.31742	184.84808	182.20511	173.178	171.39609
4 hours	173.21323	182.0862	186.75904	177.23313	164.69179	157.85155
6 hours	162.63344	169.18322	168.69401	161.07302	150.02695	147.35349
10 hours	151.06032	153.67052	157.68122	150.4807	141.04283	139.32183
24 hours	103.25456	107.75019	107.39349	106.90541	102.10431	97.3979

	Light Protected Control			Crystalloid Prime Control		
Time	Run 1	Run 2	Run 3	Run 1	Run 2	Run 3
1 minutes	196.97845	188.54589	192.27326	101.34747	99.26823	96.59257
5 minutes	190.15917	179.94511	175.32738	92.18619	88.83282	87.88802
15 minutes	182.46991	177.55372	166.75782	95.15595	94.2512	83.94168
30 minutes	191.79255	179.25861	182.11011	940.29744*	962.45564*	838.87809*
1 hours	188.44459	176.87172	173.7968	78.29515	81.61207	76.59731
2 hours	175.92757	171.28249	169.96549	65.6745	66.58957	67.59806
3 hours	184.56155	174.45904	177.90815	48.4884	53.33587	34.59568
4 hours	175.6372	168.4602	162.4127	41.47848	39.80336	37.19439
6 hours	153.77383	150.7026	149.35987	23.86695	24.3284	24.0626
10 hours	143.86192	140.01071	133.98007	9.3895	9.15086	7.26393
24 hours	101.11173	97.37865	94.60944	.58595	.58243	.63483

*Dropped from final analysis.