

Pharmacokinetic Assessment in Patients Receiving Continuous RRT: Perspectives from the Kidney Health Initiative

Thomas D. Nolin, George R. Aronoff, William H. Fissell, Lokesh Jain, Rajnikanth Madabushi, Kellie Reynolds, Lei Zhang, Shiew Mei Huang, Rajnish Mehrotra, Michael F. Flessner, John K. Leypoldt, Jennifer W. Witcher, Issam Zineh, Patrick Archdeacon, Prabir Roy-Chaudhury, and Stuart L. Goldstein

Abstract

The effect of AKI and modern continuous RRT (CRRT) methods on drug disposition (pharmacokinetics) and response has been poorly studied. Pharmaceutical manufacturers have little incentive to perform pharmacokinetic studies in patients undergoing CRRT because such studies are neither recommended in existing US Food and Drug Administration (FDA) guidance documents nor required for new drug approval. Action is urgently needed to address the knowledge deficit. The Kidney Health Initiative has assembled a work group composed of clinicians and scientists representing academia, the FDA, and the pharmaceutical and dialysis industries with expertise related to pharmacokinetics, AKI, and/or CRRT. The work group critically evaluated key considerations in the assessment of pharmacokinetics and drug dosing in CRRT, practical constraints related to conducting pharmacokinetic studies in critically ill patients, and the generalizability of observations made in the context of specific CRRT prescriptions and specific patient populations in order to identify efficient study designs capable of addressing the knowledge deficit without impeding drug development. Considerations for the standardized assessment of pharmacokinetics and development of corresponding drug dosing recommendations in critically ill patients with AKI receiving CRRT are proposed.

Clin J Am Soc Nephrol 10: 159–164, 2015. doi: 10.2215/CJN.05630614

Due to the number of contributing authors, the affiliations are provided in the Supplemental Material.

Correspondence: Dr. Thomas D. Nolin, Department of Pharmacy and Therapeutics, University of Pittsburgh School of Pharmacy, 808 Salk Hall, 3501 Terrace Street, Pittsburgh, PA 15261. Email: nolin@pitt.edu

Introduction

Few clinical data exist on the effect of AKI and modern continuous RRT (CRRT) methods on drug disposition (pharmacokinetics) and response. The incidence of dialysis-requiring AKI has risen sharply in recent years, averaging a 10% increase per year from 2000 to 2009 in the United States (1). Pharmacokinetic data are necessary for the development of individualized drug dosing recommendations, particularly in critically ill patients with impaired organ function receiving extracorporeal treatment, yet pharmacokinetic studies have been conducted during CRRT for <20% of currently marketed drugs (2). Consequently, drug clearance and dosing data derived from patients with ESRD undergoing intermittent hemodialysis are often extrapolated to patients with AKI receiving CRRT, potentially leading to under- or overdosing of important drugs. Pharmaceutical manufacturers have little incentive to perform these studies because the studies are neither recommended in existing US Food and Drug Administration (FDA) guidance documents nor required for new drug approval. Most existing data were generated *via* small, single-center investigator-initiated studies, which are infrequently and inconsistently performed (3,4). Moreover, practical institutional experience with specific drugs and CRRT modalities, while valuable, is often not published or disseminated. Collectively, the increasing use of CRRT, the varied CRRT modalities,

and reliance on a large number of potentially life-saving medications in patients undergoing CRRT necessitate action to address the knowledge deficit. Appropriately designed pharmacokinetic studies could optimize dosing recommendations for new and currently approved drugs likely to be used in critically ill patients who often exhibit altered pharmacokinetics in the setting of AKI and CRRT.

The Kidney Health Initiative assembled a work group of members composed of clinicians and scientists representing academia, FDA, and pharmaceutical and dialysis industries with expertise related to pharmacokinetics, AKI, and/or CRRT (5). The work group critically evaluated key considerations in pharmacokinetic assessment and drug dosing in CRRT, practical constraints related to conducting pharmacokinetic studies in critically ill patients, the generalizability of observations made in the context of specific CRRT prescriptions and specific patient populations, in order to identify efficient study designs capable of addressing the knowledge deficit without impeding drug development. We propose standardized assessment of pharmacokinetics and development of corresponding drug dosing recommendations in critically ill patients with AKI receiving CRRT.

Prioritization of Drugs to Be Studied

Almost any combination of diagnoses requiring pharmacotherapy may coexist in a critically ill patient

receiving CRRT. The vast majority of drugs are dosed using either a one-size-fits-all approach made possible by a drug's wide therapeutic index (*i.e.*, many antibiotics), titration to effect (*i.e.*, antihypertensives), or using therapeutic drug monitoring, as with calcineurin inhibitors. Generally speaking, drugs that are dosed by titration to effect or therapeutic drug monitoring may be a lower priority for studying in patients receiving CRRT. Drug attributes that decrease the likely need for studying pharmacokinetics during CRRT are listed in Table 1. Drugs that do not exhibit these attributes and that are likely to be used in the critical care setting should be considered for inclusion in a CRRT pharmacokinetic study.

The physiochemical and pharmacokinetic properties of a drug determine whether dosage adjustment is required in patients with impaired kidney function (6). These properties may also be used to predict whether pharmacokinetics will be altered in the setting of AKI and CRRT. Molecular weight of a drug strongly influences renal clearance (CL_R) and extracorporeal clearance (CL_{EC}). In general, molecular weight is inversely related to CL_{EC} . The degree of plasma protein binding of a drug influences its renal and CL_{EC} because the drug-protein complex is too large to be filtered. In addition, plasma protein binding prevents movement or distribution of drug out of the intravascular space to extravascular sites, so drugs with high protein binding are often associated with modest volumes of distribution (V_D) (*i.e.*, <1 L/kg). Generally speaking, drugs with a large V_D (>1 L/kg) or high plasma protein binding ($>80\%$) exhibit low CL_{EC} (7). The larger the V_D , the greater the fraction of drug that is located in extravascular sites and thus not exposed to the extracorporeal circuit. CL_R or CL_{EC} of a drug can exert a clinically significant impact on the amount in the body only if clearance by these routes is similar to, or greater than, other endogenous nonrenal clearance (CL_{NR}) pathways.

It is extremely important to properly dose-adjust narrow therapeutic index drugs that are likely cleared by dialysis modalities, and for which therapeutic drug monitoring is not standard. Dose adjustment may also be important for some drugs with wider therapeutic indices; underdosing with azole antifungals and glycopeptide or β -lactam antibiotics, for instance, may contribute to treatment failures and the emergence of drug-resistant pathogens (8). Table 2 lists some candidate classes of drugs in which pharmacokinetic assessment in the setting of CRRT was identified by Kidney Health Initiative work group members to be a high priority.

Patient Populations

CRRT can be used in adults with a variety of conditions and with AKI. However, given the overall equivalency of

Table 1. Drug attributes that decrease the likely need for studying pharmacokinetics during continuous RRT

Attribute
Dosing guided by immediate titration to effect
Large molecular weight
Large volume of distribution
Highly protein bound
Extensively cleared <i>via</i> nonrenal pathways
Therapeutic drug monitoring is a standard practice

Table 2. Examples of drug classes in which pharmacokinetic testing and dosing guidance for continuous RRT are likely to be clinically useful

Drug Class	
Antibiotics	Antipsychotics
Anticoagulants	Antivirals
Anticonvulsants	Immunosuppressants
Antifungals	Muscle relaxants
Antineoplastic agents	Sedatives

outcomes in dialysis-dependent patients with AKI treated with intermittent hemodialysis or with CRRT, the latter is used primarily in patients with hemodynamic instability requiring vasoactive support, severe volume overload, marginal BPs at risk for dysrhythmias with rapid volume removal during intermittent hemodialysis, severe catabolism or septic disorders (9–11). Hence, pharmacokinetic studies in hemodynamically unstable individuals with AKI undergoing CRRT may provide the most relevant data to inform clinical practice. Studies could also be conducted while performing CRRT in hemodynamically stable patients with AKI; however, the V_D of many drugs may differ considerably from individuals who are most likely to be treated clinically with CRRT. Fluid resuscitation typically required by hemodynamically unstable patients often results in large increases in the extravascular volume or marked changes in protein binding, both of which affect drug distribution and can impact drug response (12). While pharmacokinetic studies could be carried out by performing CRRT in hemodynamically stable individuals with ESRD (13), dramatic differences in pathophysiologic processes, including nonrenal clearance of drugs, and blood and effluent flow rates will likely lead to considerably different dosing requirements in unstable critically ill patients (with or without ESRD) versus stable ESRD patients.

In addition to adults, CRRT has been provided to patients representing the entire age and size range encountered by pediatricians (14,15). Smaller patients with AKI demonstrate higher mortality rates than larger children and represent an especially vulnerable cohort (16). It is important to note that the most commonly used CRRT devices are currently cleared by the FDA only for the indications of continuous solute and/or fluid removal in patients with AKI or fluid overload. Accordingly, we recommend that CRRT pharmacokinetic studies be conducted in the setting of AKI or fluid overload, even though CRRT has been used to remove exogenous and endogenous toxins (*e.g.*, hyperammonemia) in patients without AKI or fluid overload (15,17,18).

Irrespective of patient population, the relevant patient characteristics to be considered when designing such studies include patient age, height, weight, residual kidney function, hepatic function, serum albumin concentration, AKI etiology, nutritional status, and comorbid conditions (4).

Study Design Considerations

Two fundamentally important factors considered were feasibility of study conduct and generalizability of the study findings to any CRRT modality. It may be possible to provide

generalizable dosing recommendations, based on the premise that CRRT modalities are prescribed on the basis of total effluent flow rate (11), consistent with the recommendations of the 2012 Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline for AKI (9). Because effluent flow rate (Q_E) is easily quantified and is the most important parameter in determining drug removal (7), it may prove ideal to incorporate into drug dosing recommendations. Derivation of dosing recommendations would begin by characterizing the relationship between pharmacokinetic parameters and total Q_E during CRRT in a standardized fashion. One possible approach might be use of a fixed blood flow rate with one or two commonly prescribed effluent flow rates. The dialysate and replacement flow rates could be varied as needed to generate the target Q_E . If multiple effluent flow rates are assessed, a simple parallel study design in which separate groups of participants are enrolled (with each group receiving the test treatment under only one effluent flow rate) may be more feasible than a crossover study (*i.e.*, patient clinical status may not be amenable to multiple effluent flow rates and the required washout period in a crossover study). Unlike a “dedicated” renal impairment study, a CRRT study may not require active enrollment of a matched healthy control group (19). CRRT studies will probably enroll heterogeneous patients exhibiting a variety of demographic characteristics, comorbidities, and organ dysfunction, which may contribute to greater variability in pharmacokinetics. This variability may require a larger sample size to achieve adequate statistical power and precision for key pharmacokinetic attributes.

Study Duration

Pharmacokinetic assessment could be carried out in a single-dose study over at least a standard dosing interval of the test treatment. Alternatively, a multiple-dose study characterizing the pharmacokinetics to steady state (or of a sufficient duration to adequately determine the intra- and intersubject variability) would provide more granular information (*e.g.*, change in conditions of the critically ill patient and the CRRT procedure, and corresponding variability in CRRT clearance).

Flow Rates

Adult Patients. In CRRT, the primary determinant of small solute clearance is the Q_E , which is the sum of dialysis fluid, replacement fluid (pre- and post-filter), and net ultrafiltration (*i.e.*, net fluid removal) rates (11). Moreover, Q_E exerts an important effect on pharmacokinetics (20,21), predicts extracorporeal clearance of antimicrobial agents (22), and inversely influences achievement of therapeutic drug concentrations *in vivo* (23). Typical CRRT prescriptions specify the target dialysate flow rate (Q_D) and/or the fluid replacement rate (Q_R) parameters along with the net ultrafiltration rate, while Q_E is a calculated parameter. The blood flow rate (Q_B) varies little over time. Although it may affect solute clearance in convective modalities (continuous venovenous hemofiltration) due to dilution effects related to infusing replacement fluids prefilter, Q_B is a relatively minor determinant of effective solute clearance compared with Q_E in diffusive modalities (continuous venovenous hemodiafiltration) and continuous venovenous hemodiafiltration). Therefore, to streamline and enhance the feasibility of carrying out these

studies, investigators could use a fixed Q_B , representative of that typically used in the clinical setting (*e.g.*, $Q_B=200$ ml/min) during pharmacokinetic assessments. In addition, we suggest assessing one effluent flow rate per period or per patient (depending on the study design), representative of contemporary clinical practice. For example, two well studied and commonly used targets of 25 ml/kg per hour or 35 ml/kg per hour (24,25) are practical effluent flow rates that could be incorporated into a CRRT study. While KDIGO recommends delivering an effluent volume of 20–25 ml/kg per hour for CRRT in AKI (9), this will usually require higher prescription of effluent volume due to access malfunction, machine downtime, and other factors. Thus, the ranges that occur in clinical practice to achieve 20–25 ml/kg per hour are encompassed in our recommendation. The Q_D and Q_R may be varied as clinically indicated to maintain the target Q_E . Replacement fluid may be infused pre- or postfilter according to institutional experience and preference. However, there may be differences in drug clearance with use of pre- versus postfilter replacement at the same effluent and blood flow rates (26,27), so we encourage a consistent approach throughout the duration of pharmacokinetic sampling with individual participants at each institution. Standard replacement fluid and dialysate solutions may also be used according to institutional preference. In the event that any additional fluid removal in excess of the Q_E is prescribed, then the total ultrafiltration rate is also important to know. Certainly, one may consider alternative CRRT prescriptions for study. However, the interpretation of any study design will be simplified by holding constant all settings and parameters for the duration of pharmacokinetic sampling.

Pediatric Patients. As in adults, use of a fixed Q_B in pediatric patients may facilitate standardized assessment of pharmacokinetics. One or two blood flow rates that vary by patient weight according to typical clinical practice may be considered. Use of one Q_E per patient in a parallel design may be feasible as described above. Effluent flow rates for consideration that are representative of current clinical practice include 2000 ml/1.73 m² per hour and 3000 ml/1.73 m² per hour (28). The Q_D and Q_R may be varied as clinically indicated to maintain the target Q_E , and replacement fluid may be infused pre- or postfilter according to institutional experience and preference. Standard replacement fluid and dialysate solutions may be used.

Hemofilter

Investigators could use any standard contemporary hemofilter according to institutional experience and preference. The filter brand, manufacturer, membrane composition, surface area, and clearance characteristics, such as molecular weight cutoff, should be reported. If more than one type of hemofilter is used in a study, the relationship between Q_E and drug clearance may differ among hemofilters; such relationships may be explored during the study and accounted for in the analysis of pharmacokinetic parameters. Finally, because clearance may decrease as filter life increases, the hour or day of filter life should be considered in the pharmacokinetic model.

Drug Dose

CRRT pharmacokinetic studies may evaluate standard starting doses of the drug under investigation, unless

adjusted doses have been previously shown to be required (*i.e.*, in the setting of impaired kidney function, obesity, or substantial volume expansion), in which case an appropriate adjusted dose should be considered. Alternatively, the initial dosing could be based on *in silico* estimates of CL_{EC} , as demonstrated previously (29).

Sampling/Measurement

Blood and effluent samples are needed to calculate CL_{EC} during CRRT (7). The A-V pair and the recovery methods are potential approaches to determine CL_{EC} (30). Serial plasma samples for drug and metabolite (if applicable) concentrations should be collected over at least a standard dosing interval after dosing. An interim analysis early in the study would allow appropriate adjustment of the pharmacokinetic sampling schedule, if necessary, to optimally estimate the parameters. This approach could potentially minimize the burden of unnecessarily prolonged sampling if clearance is high with the CRRT. Other sampling considerations include determination of total volume of effluent in a planned time window, as well as collection of serial effluent samples at the corresponding time points for collection of plasma samples (31). Ideally, protein binding, total and free drug concentrations and corresponding clearance parameters are characterized in CRRT studies (4,7,32). The minimum data required for pharmacokinetic analysis, including all necessary details for the above measurements, such as exact sampling time points, timing of changes in procedure or altered conditions (*e.g.*, Q_B , Q_E) should be carefully considered as previously described (4,7).

Data Analysis and Development of Dosing Recommendations

The primary intent of the data analysis is to characterize the pharmacokinetics in patients undergoing CRRT and determine the need for dosage adjustment. On the basis of the information collected in these studies, a population pharmacokinetic modeling approach may be considered for derivation of dosing recommendations; simulations may be useful in deriving recommendations for CRRT conditions not tested in the study (33). Important aspects of data analysis might include the following:

- Estimation of pharmacokinetic parameters, including variability
- Comparison of pharmacokinetic parameters to those of typical patients with normal kidney function (literature or sponsor data) or the appropriate reference population
- Quantification of the impact of changes in the prescribed Q_E on the pharmacokinetic parameters of interest, and interpolation for flow rates not evaluated in this study
- Assessment of whether dosage adjustment is warranted in CRRT recipients
- If dosage adjustment is warranted, derivation of specific dosing recommendations for the studied conditions

Estimation of Pharmacokinetic Parameters

Standard noncompartmental modeling may be used to calculate key pharmacokinetic parameters. In addition, CL_{EC} should be calculated as appropriate based on the specific modality used (6,7). CL_{EC} may then be compared

with total clearance (CL_{TOT}) to determine the contribution of CRRT to CL_{TOT} , where $CL_{TOT}=CL_{EC}+CL_R+CL_{NR}$ (6). Historically, if CL_{EC} exceeds 25%–30% of CL_{TOT} , then the contribution of CRRT to CL_{TOT} is considered clinically significant, and dosage adjustment is often warranted (6,34). Investigators may also consider calculating the fraction of the administered dose that is recovered in the effluent in order to assess the need to administer supplemental drug doses to CRRT patients. Finally, determination of the contribution of adsorption to CL_{EC} may be important for select drugs and hemofilters (6,35).

While standard noncompartmental modeling may be used to calculate key pharmacokinetic parameters, the time course for drug concentrations in the plasma, effluent, and urine (when available) can also be subjected to compartmental modeling using a population-based approach (36–38). Based on the model that best describes the data, covariate relationships can be evaluated to describe the effect of covariates such as treatment and patient variables (*e.g.*, Q_E , body weight) on the pharmacokinetic model parameters (such as clearance and V_D). These equations can help simulate the plasma concentration–time profiles and prediction of dosing requirements for effluent flow rates that may have not been tested in the current study. Moreover, physiologically-based pharmacokinetic modeling and simulation may be informative in evaluating the effect of intrinsic (*e.g.*, organ function, age, albumin) and extrinsic (*e.g.*, effluent flow rate) factors on systemic drug exposure (39). This approach has been used for assessing the effect of kidney disease on the pharmacokinetics of non–renally eliminated drugs (40). There is limited experience with model-based simulation in the CRRT context; however, this may prove important if it can be routinely shown to predict pharmacokinetics in heterogeneous complex patients, such as critically ill patients exhibiting a variety of demographic characteristics, comorbidities, and organ function (33).

Derivation of Dosing Recommendations

Pharmacokinetic parameters in CRRT recipients could be compared with those of a reference population (*i.e.*, healthy persons or critically ill patients without AKI) for which a dose recommendation exists to determine whether dosing adjustment is needed to achieve similar exposure in CRRT recipients. For example, the total clearance and elimination half-life can be compared with that observed in control participants to assess the need for adjusting the dosing frequency. Typically the dose, dosing interval, or both are adjusted to produce a range of plasma concentrations of drug or active metabolites that is similar to that observed in control participants who require the standard dose of the drug.

Provision of Dose Recommendations (Labeling)

The information generated from CRRT studies could be included in prescribing information to provide dosing recommendations for the studied conditions and may be valuable in extrapolating dosing recommendations to other modalities, assuming effluent flow rate is known. Any documents, including product labeling, that include dosing recommendations for patients undergoing CRRT may benefit

from inclusion of a brief summary of the studies that provide the data to support the recommendations. Summary information could include relevant patient characteristics (e.g., age range, underlying illnesses), details of CRRT conditions evaluated (e.g., modality, flow rates), drug dosage regimen, and pharmacokinetic parameter estimates. If dosing instructions are provided for methods of CRRT that were not studied, the document could describe the method of dosing extrapolation.

Other Regulatory Considerations

Pharmacokinetic studies of investigational and marketed drugs conducted with the intent to inform proper dosing should be performed under the auspices of an Investigational New Drug application (IND) for both adult and pediatric study populations. In addition, because of current FDA restrictions on use of CRRT devices in patients below certain weight thresholds, the division within the Center for Drug Evaluation and Research responsible for reviewing the IND should consult the Center for Devices and Radiologic Health for additional perspectives for relevant study populations. Studies not conducted under an IND that involve CRRT devices in populations below the weight threshold would require an Investigational Device Exemption.

Acknowledgments

The support and assistance of Kidney Health Initiative (KHI) Program Director Melissa West were instrumental to the success of this project and are gratefully acknowledged. We also thank William R. Clark, from Gambro (a subsidiary of Baxter International) for his critical review of the manuscript.

This work was supported by the KHI, a public-private partnership between the American Society of Nephrology, the US Food and Drug Administration, and over 60 kidney member organizations and companies to enhance patient safety and foster innovation in kidney disease. KHI funds were used to defray costs incurred during the conduct of the project, including travel and support staff. However, no honorarium or other financial support was provided to KHI work group members. The pharmacokinetics work group, which includes the authors of this paper, had final review authority and takes responsibility for the content. KHI makes every effort to avoid actual, potential, or perceived conflicts of interest that may arise as a result of industry relationships or personal interests among the members of the writing committee and work group. More information on KHI, the pharmacokinetics work group, or the conflict of interest policy can be found at www.kidneyhealthinitiative.org.

The views expressed are those of the authors and do not necessarily reflect official policy of the US Food and Drug Administration.

Disclosures

R.M. has received grant support and/or honoraria from Baxter Healthcare Corporation and DaVita. J.K.L. is an employee of Baxter Healthcare Corporation with ownership interests. J.W.W. is an employee and a minor stock owner of Eli Lilly and Co.

References

- Hsu RK, McCulloch CE, Dudley RA, Lo LJ, Hsu CY: Temporal changes in incidence of dialysis-requiring AKI. *J Am Soc Nephrol* 24: 37–42, 2013
- Mueller BA, Smoyer WE: Challenges in developing evidence-based drug dosing guidelines for adults and children receiving renal replacement therapy. *Clin Pharmacol Ther* 86: 479–482, 2009
- Vaara S, Pettila V, Kaukonen KM: Quality of pharmacokinetic studies in critically ill patients receiving continuous renal replacement therapy. *Acta Anaesthesiol Scand* 56: 147–157, 2012
- Li AM, Gomersall CD, Choi G, Tian Q, Joynt GM, Lipman J: A systematic review of antibiotic dosing regimens for septic patients receiving continuous renal replacement therapy: do current studies supply sufficient data? *J Antimicrob Chemother* 64: 929–937, 2009
- Archdeacon P, Shaffer RN, Winkelmayer WC, Falk RJ, Roy-Chaudhury P: Fostering innovation, advancing patient safety: The kidney health initiative. *Clin J Am Soc Nephrol* 8: 1609–1617, 2013
- Schetz M: Drug dosing in continuous renal replacement therapy: General rules. *Curr Opin Crit Care* 13: 645–651, 2007
- Choi G, Gomersall CD, Tian Q, Joynt GM, Freebairn R, Lipman J: Principles of antibacterial dosing in continuous renal replacement therapy. *Crit Care Med* 37: 2268–2282, 2009
- Blot S, Lipman J, Roberts DM, Roberts JA: The influence of acute kidney injury on antimicrobial dosing in critically ill patients: Are dose reductions always necessary? *Diagn Microbiol Infect Dis* 79: 77–84, 2014
- Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group: KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl* 2: 1–138, 2012
- Rabindranath K, Adams J, Macleod AM, Muirhead N: Intermittent versus continuous renal replacement therapy for acute renal failure in adults. *Cochrane Database Syst Rev* (3): CD003773, 2007
- Tolwani A: Continuous renal-replacement therapy for acute kidney injury. *N Engl J Med* 367: 2505–2514, 2012
- Boucher BA, Wood GC, Swanson JM: Pharmacokinetic changes in critical illness. *Crit Care Clin* 22: 255–271, vi, 2006
- Cirillo J, Vaccaro N, Balis D, Redman R, Matzke GR: Influence of continuous venovenous hemofiltration and continuous venovenous hemodiafiltration on the disposition of doripenem. *Antimicrob Agents Chemother* 55: 1187–1193, 2011
- Symons JM, Brophy PD, Gregory MJ, McAfee N, Somers MJ, Bunchman TE, Goldstein SL: Continuous renal replacement therapy in children up to 10 kg. *Am J Kidney Dis* 41: 984–989, 2003
- Symons JM, Chua AN, Somers MJ, Baum MA, Bunchman TE, Benfield MR, Brophy PD, Blowey D, Fortenberry JD, Chand D, Flores FX, Hackbarth R, Alexander SR, Mahan J, McBryde KD, Goldstein SL: Demographic characteristics of pediatric continuous renal replacement therapy: A report of the prospective pediatric continuous renal replacement therapy registry. *Clin J Am Soc Nephrol* 2: 732–738, 2007
- Askenazi DJ, Goldstein SL, Koralkar R, Fortenberry J, Baum M, Hackbarth R, Blowey D, Bunchman TE, Brophy PD, Symons J, Chua A, Flores F, Somers MJ: Continuous renal replacement therapy for children ≤ 10 kg: A report from the prospective pediatric continuous renal replacement therapy registry. *J Pediatr* 162: 587–592, e3, 2013
- Fleming GM, Walters S, Goldstein SL, Alexander SR, Baum MA, Blowey DL, Bunchman TE, Chua AN, Fletcher SA, Flores FX, Fortenberry JD, Hackbarth R, McBryde K, Somers MJ, Symons JM, Brophy PD; Prospective Pediatric Continuous Renal Replacement Therapy Registry Group: Nonrenal indications for continuous renal replacement therapy: A report from the Prospective Pediatric Continuous Renal Replacement Therapy Registry Group. *Pediatr Crit Care Med* 13: e299–e304, 2012
- Spinale JM, Laskin BL, Sondheimer N, Swartz SJ, Goldstein SL: High-dose continuous renal replacement therapy for neonatal hyperammonemia. *Pediatr Nephrol* 28: 983–986, 2013
- U.S. Food and Drug Administration: Guidance for industry: Pharmacokinetics in patients with impaired renal function—study design, data analysis, and impact on dosing and labeling. Draft guidance, March 2010. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory-Information/Guidances/UCM204959.pdf>. Accessed June 2, 2014
- Valtonen M, Tiula E, Takkunen O, Backman JT, Neuvonen PJ: Elimination of the piperacillin/tazobactam combination during continuous venovenous haemofiltration and haemodiafiltration in patients with acute renal failure. *J Antimicrob Chemother* 48: 881–885, 2001

21. Valtonen M, Tiula E, Backman JT, Neuvonen PJ: Elimination of meropenem during continuous veno-venous haemofiltration and haemodiafiltration in patients with acute renal failure. *J Antimicrob Chemother* 45: 701–704, 2000
22. Jamal JA, Udy AA, Lipman J, Roberts JA: 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* 42: 1640–1650, 2014
23. Frazee EN, Kuper PJ, Schramm GE, Larson SL, Kashani KB, Osmon DR, Leung N: Effect of continuous venovenous hemofiltration dose on achievement of adequate vancomycin trough concentrations. *Antimicrob Agents Chemother* 56: 6181–6185, 2012
24. Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lo S, McArthur C, McGuinness S, Myburgh J, Norton R, Scheinkestel C, Su S; RENAL Replacement Therapy Study Investigators: Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med* 361: 1627–1638, 2009
25. Palevsky PM, Zhang JH, O'Connor TZ, Chertow GM, Crowley ST, Choudhury D, Finkel K, Kellum JA, Paganini E, Schein RM, Smith MW, Swanson KM, Thompson BT, Vijayan A, Watnick S, Star RA, Peduzzi P; VA/NIH Acute Renal Failure Trial Network: Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med* 359: 7–20, 2008
26. Susla GM: The impact of continuous renal replacement therapy on drug therapy. *Clin Pharmacol Ther* 86: 562–565, 2009
27. Gashti CN, Rodby RA, Huang Z, Gao D, Zhang W: Effects of high blood flow and high pre-dilution replacement fluid rates on small solute clearances in hemofiltration. *Blood Purif* 32: 266–270, 2011
28. Bunchman TE, Brophy PD, Goldstein SL: Technical considerations for renal replacement therapy in children. *Semin Nephrol* 28: 488–492, 2008
29. U.S. Food and Drug Administration: Emergency use authorization of peramivir IV fact sheet for health care providers. Available at: <http://www.fda.gov/downloads/drugs/drugsafety/post-market-drugsafety-information-for-patients-and-providers/ucm187811.pdf>. Accessed June 2, 2014
30. Lavergne V, Nolin TD, Hoffman RS, Roberts D, Gosselin S, Goldfarb DS, Kielstein JT, Mactier R, Maclaren R, Mowry JB, Bunchman TE, Juurlink D, Megarbane B, Anseuw K, Winchester JF, Dargan PI, Liu KD, Hoegberg LC, Li Y, Calello DP, Burdmann EA, Yates C, Laliberté M, Decker BS, Mello-Da-Silva CA, Lavonas E, Ghannoum M: The EXTRIP (EXtracorporeal TReatments In Poisoning) workgroup: Guideline methodology. *Clin Toxicol (Phila)* 50: 403–413, 2012
31. Connor MJ Jr, Salem C, Bauer SR, Hofmann CL, Groszek J, Butler R, Rehm SJ, Fissell WH: Therapeutic drug monitoring of piperacillin-tazobactam using spent dialysate effluent in patients receiving continuous venovenous hemodialysis. *Antimicrob Agents Chemother* 55: 557–560, 2011
32. Tortorici MA, Cutler D, Zhang L, Pfister M: Design, conduct, analysis, and interpretation of clinical studies in patients with impaired kidney function. *J Clin Pharmacol* 52[Suppl]: 109S–118S, 2012
33. Zhang L, Boulton DW, Pfister M: A pharmacometric approach to quantify the impact of chronic kidney disease and hemodialysis on systemic drug exposure: application to saxagliptin. *J Clin Pharmacol* 52[Suppl]: 126S–133S, 2012
34. Levy G: Pharmacokinetics in renal disease. *Am J Med* 62: 461–465, 1977
35. Markou N, Fouteri M, Markantonis SL, Zidianakis B, Hroni D, Boutzouka E, Baltopoulos G: Colistin pharmacokinetics in intensive care unit patients on continuous venovenous haemodiafiltration: an observational study. *J Antimicrob Chemother* 67: 2459–2462, 2012
36. Isla A, Rodríguez-Gascón A, Trocóniz IF, Bueno L, Solinís MA, Maynar J, Sánchez-Izquierdo JA, Pedraz JL: Population pharmacokinetics of meropenem in critically ill patients undergoing continuous renal replacement therapy. *Clin Pharmacokinet* 47: 173–180, 2008
37. Liesenfeld KH, Staab A, Härtter S, Formella S, Clemens A, Lehr T: Pharmacometric characterization of dabigatran hemodialysis. *Clin Pharmacokinet* 52: 453–462, 2013
38. Yamamoto T, Yasuno N, Katada S, Hisaka A, Hanafusa N, Noiri E, Yahagi N, Fujita T, Suzuki H: Proposal of a pharmacokinetically optimized dosage regimen of antibiotics in patients receiving continuous hemodiafiltration. *Antimicrob Agents Chemother* 55: 5804–5812, 2011
39. Zhao P, Zhang L, Grillo JA, Liu Q, Bullock JM, Moon YJ, Song P, Brar SS, Madabushi R, Wu TC, Booth BP, Rahman NA, Reynolds KS, Gil Berglund E, Lesko LJ, Huang SM: Applications of physiologically based pharmacokinetic (PBPK) modeling and simulation during regulatory review. *Clin Pharmacol Ther* 89: 259–267, 2011
40. Zhao P, Vieira ML, Grillo JA, Song P, Wu TC, Zheng JH, Arya V, Berglund EG, Atkinson AJ Jr, Sugiyama Y, Pang KS, Reynolds KS, Abernethy DR, Zhang L, Lesko LJ, Huang SM: Evaluation of exposure change of nonrenally eliminated drugs in patients with chronic kidney disease using physiologically based pharmacokinetic modeling and simulation. *J Clin Pharmacol* 52[Suppl]: 91S–108S, 2012

Published online ahead of print. Publication date available at www.cjasn.org.

This article contains supplemental material online at <http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.05630614/-/DCSupplemental>.