CHAPTER 146

Quantification of Acute Renal Replacement Therapy

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OBJECTIVES

This chapter will:

1. Provide a clinical context for acute renal replacement therapy (RRT) dosing.
2. Discuss the role and limitations of urea kinetic modeling for the quantification of dose.
3. Discuss the concepts and demonstrate the use of practical tools for the quantification of dose that are specific to either intermittent or continuous RRT.
4. Discuss the concept and demonstrate the use of equivalent renal urea clearance as a unified expression of dose for all acute RRT modalities.

In critically ill patients treated with acute renal replacement therapy (ARRT), the fraction of mortality that is attributable to acute kidney injury (AKI) is an estimated 25% to 50%.[1] The prevailing view among opinion leaders is that adequate replacement of failing renal function will minimize this attributable risk and optimize patient outcomes. This chapter presents and clinically contextualizes tools for dose quantification of ARRT.

Uremic toxicity in critically ill patients with AKI is uncommon, insofar as it is not in the familiar form seen in end-stage renal disease (ESRD). Deaths in this setting occur in the context of nonspecific physiologic derangement, such as nonresolving infection, hemorrhage, or nonresolving shock despite optimal care. These conditions therefore may constitute an acute uremic syndrome specific to AKI. It follows that mediators and markers of this acute uremic injury also may be unique. There is promising research evaluating dose-response relationships for various ARRT modalities in terms of their capacity for immunomodulation.[2] In time, it is possible (and even probable) that data from such studies may change fundamentally practice patterns, although definitive studies are lacking at present. Dose-response relationships have been defined only in terms of solute clearance, using either empiric means or urea kinetic modeling (UKM).

Studies of ARRT dose have used different expressions for solute clearance for different modalities. These expressions can be unified on a small-solute therapy map, although there is not as much experience in assessing larger-solute clearance. Because of these difficulties, true dose equivalence across the full range of purported uremic toxins has not been established for intermittent hemodialysis (IHD) compared with continuous renal replacement therapy (CRRT), or among continuous venovenous hemofiltration (CVVH), hemodialysis (CVVHD), and hemodiafiltration (CVVHDF).

CLINICAL DOSING TARGETS FOR ACUTE INTERMITTENT HEMODIALYSIS

A number of studies have suggested a relationship between small-solute control or clearance and patient outcomes during acute IHD. In the 1950s and 1960s, it was demonstrated conclusively during the Korean and Vietnam wars that IHD saved lives,[3,4] although subsequent underpowered and clinically outdated studies arising from that experience fell short of proving the case for "early" IHD (initiated when the blood urea nitrogen [BUN] level was <100 to 150 mg/

dL) or for "intensive" IHD (maintaining BUN <60 mg/dL and serum creatinine <5 mg/dL).[5]

Since then, three multicenter randomized controlled trials (RCTs) evaluated the effect of IHD dose in AKI patients.[6–8] compared daily with alternate-day IHD in 146 ICU patients with AKI. The daily arm received an average single-pool fractional clearance (spKt/V) of 0.92 on 6.2 occasions per week (i.e., a weekly Kt/V of 5.8). The alternate-day arm received an average spKt/V of 0.94 on 3.2 occasions per week, with a weekly Kt/V of 3.0.[6] However, it has been observed that in this study the randomization was inadequate, and the dose in the control group was very low.[9] Moreover, the low overall mortality in the study (34%) suggests that the results may not generalize.[9] Furthermore, as noted by Palevsky,[10] the higher rates of altered mental status, gastrointestinal bleeding, and sepsis in the alternate day arm potentially could be due to the low dialysis dose per treatment.

The Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network (ARFTN) study[7] compared intensive to less-intensive RRT in 1124 ICU patients with AKI. Within each randomization arm patients were switched between IHD and CRRT or slow-efficiency extended hemodialysis (SLED), based on their hemodynamic status. Intermittent treatments were prescribed at a Kt/V of 1.4, with a delivered Kt/V averaging 1.3, and were performed three (less-intensive arm) or six (more-intensive arm) times per week. Consequently, the weekly Kt/V was approximately 6.5 in the intensive and 3.9 in the less-intensive arm. Mortality at 60 days was similar in both groups (53.6% and 51.5%) as was the percentage of patients recovering kidney function (15.4% and 18.4%).

The Hannover Dialysis Outcome Study[8] randomized 148 ICU patients with AKI to two different doses of SLED: a standard-dialysis arm dosed to maintain plasma urea levels between 120 and 150 mg/dL (20–25 mmol/L), or an intensified dialysis arm dosed to maintain plasma urea levels less than 90 mg/dL (<15 mmol/L). No significant differences in either survival at day 28 (39% vs. 44%) or recovery of kidney function (63% vs. 60% of survivors) were found.

There are no data supporting a relationship between larger-solute clearance and outcomes for acute IHD. Intermittent hemodiafiltration (IHDF) and high-flux IHD for critically ill AKI patients have demonstrated no clinical or laboratory advantage over low-flux IHD. This likely is due to the low clearances of larger solutes afforded by these modalities. Whereas low-flux IHD clears approximately 3 mL/min of β_2-microglobulin from blood water during the course of treatment, high-flux IHD clears only about 35 mL/min, and even IHDF clears only 50 to 150 mL/min, depending on the substitution fluid rate.[11] Given the short duration over which these modalities are applied, a meaningful clinical effect seems unlikely. The effect of IHD on solute control is therefore, for the most part, restricted to small solutes.

In summary, data suggest that the dose of IHD in AKI requires a weekly Kt/Vurea of 3.9[9]. There are no published data relating clearance of larger solutes to outcome for acute IHD.

CLINICAL DOSING TARGETS FOR CONTINUOUS RENAL REPLACEMENT THERAPY

The first study to link solute clearance to outcomes for CRRT was performed over 25 years ago. However, it is only recently that clinical dosing targets have been refined. In a prospective, RCT from Ronco et al., mortality was lowest for patients receiving postdilution CVVH with an ultrafiltration rate (UFR) of 35 mL/kg/hr or greater (indexed to patient premorbid weight), provided it was applied more than 85% of the time.[12] The external validity of this study is perhaps questionable because the participants were relatively small (average weight, 68 kg) and had a low incidence of sepsis (12%). A subsequent trial failed to confirm these findings, but it was underpowered and also was performed in patients who had undergone cardiosurgical procedures, for whom factors other than solute control were likely to be relatively more important as determinants of outcomes.[13]

It is uncertain from the study of Ronco et al. whether the superior survival with higher UFR was related to clearance of small or larger solutes. Small-solute clearance would be equal to the UFR, but clearance of larger solutes was not reported. This issue was addressed in a later study from Saudan et al., which showed that the addition of approximately 18 mL/kg/hr of diffusive clearance using CVVHD to a basal amount of approximately 24 mL/kg/hr of convective clearance using CVVH resulted in superior patient survival.[14] This finding demonstrated that at least some of the benefit of a higher dose of CRRT in Ronco's study was the result of increased small solute clearance.

Even higher doses of CRRT may benefit those with septic shock and a high predicted mortality risk. In Ronco's study, there was a trend to lower mortality for septic patients receiving a UFR of 45 mL/kg/hr or greater. These findings were supported by observational data from Honore et al., who found that the dose of high-volume CVVH was greater (average UFR, 132.5 mL/kg/hr) in those patients whose hemodynamic parameters improved during treatment than in those whose parameters did not improve (average UFR, 107.5 mL/kg/hr).[15]

In contrast with the results of these earlier single-center studies, two large multicenter trials have found that a much lower dose of CRRT could suffice.[7,16] The first trial, the ARFTN study, compared standard-intensity predilution CVVHDF with a prescribed effluent flow of 20 mL/kg/hr to high-intensity CVVHDF at 35 mL/kg/hr.[7] No differences in outcomes between the two study arms were found.[7] Importantly, more than 95% of the prescribed dose of CRRT was delivered in the less-intensive group.[7]

The second trial, the RENAL study, compared the effects of postdilution CVVHDF at dosages of 25 and 40 mL/kg/hr on 28- and 90-day mortality rates in 1464 AKI patients.[16] The delivered dose was 88% and 84% of prescribed dose in the low- and high-dose groups, respectively. As in the ARFTN study, there was no difference in mortality between the two groups.

On these bases, it has been concluded that there are no benefits of increasing CRRT dosage in AKI patients above effluent flows of 20 to 25 mL/kg/hr.[9] In clinical practice, to achieve a dosage of 20 to 25 mL/kg/hr, a greater dosage, in the range of 25 to 30 mL/kg/hr, should be prescribed. Moreover, based at least on a small single-center RCT, it is possible that a higher dose could be beneficial in some patients with septic shock.[17]

There are no published data relating specifically to larger-solute clearance to outcomes during CRRT.

CALCULATION OF FRACTIONAL CLEARANCE FOR INTERMITTENT HEMODIALYSIS

To calculate Kt/V, UKM must be applied. UKM is based on the mass balance principle that "urea accumulation equals

urea input minus urea output." Practically, this principle is embodied in a model that estimates urea concentration based on three patient-dependent parameters—urea distribution volume (V), urea generation rate (G), and renal urea clearance (Kr)—and three treatment-dependent parameters—dialyzer urea clearance (K_D), session length (T), and treatment schedule. A differential equation can be developed from this model, whose solution provides the general equations for UKM that are presented later.

Urea kinetics can be assessed through either blood measurements or direct dialysate quantification. The former option is logistically more feasible, although the role of partial dialysate collection or online urea and ionic dialysate monitors warrants further study in this setting. For the moment however, the standard approach is to use blood measurements. The blood urea nitrogen (BUN) and available estimates of UKM parameters are entered into the general equations for UKM. These equations are solved iteratively to impute UKM parameters that are not provided to the model (usually G and V) from those that are (usually K_D). This allows the calculation of Kt/V.

Studies of urea kinetics show four major differences between the critically ill AKI population and the ESRD population.[18] First, critically ill patients often have markedly increased values for G, attributable to a more catabolic state. Second, they often have markedly increased V at 65% to 70% of their body weight, compared with ESRD patients at 55% to 60% of body weight. Some of this increase is attributable to Na^+ and H_2O loading (and concurrent loss of lean body mass) in critical illness, although most of the increase is attributable to the dissociation of V from its usual anatomic correlate of total body water (TBW): V is between 10% and 30% higher than TBW in critically ill AKI patients.[15,19] This discrepancy is not just a by-product of UKM but a literal one demonstrable with the use of radiolabeled (^{13C}) urea and deuterium oxide.[20] This discrepancy is not satisfactorily explained by intercompartmental urea dysequilibrium (i.e., delayed entrance of urea into the blood from body pools that have high resistance to solute transfer resulting from a low ratio of tissue perfusion to water, such as muscle or skin), which is, in fact, surprisingly similar to that seen in patients with ESRD.[18]

Third, critically ill patients often have values for K_D that are lower than expected and specifically lower than those calculated by usual means (e.g., Michael's formula).[21] Venovenous angioaccess leads to high recirculation rates, especially in short femoral catheters, where it can approach 25%, and this is exacerbated by the frequent need for line reversal in 25% to 50% of treatments. Fiber-bundle clotting also reduces K_D, especially in the absence of anticoagulation.

Finally, critical illness is associated with marked variation in all of these UKM parameters over time.[18] The assumption of urea steady state underlies many of the UKM calculations in the maintenance IHD population and affords convenience (e.g., model fitting using two BUN points rather than three). However, urea steady state cannot be assumed for critically ill AKI patients or for the modeling of IHD dose in this setting.

Calculations using UKM equations provide a critical and extremely important benefit when dealing with the uncertainties and sources for error mentioned previously, in that they allow for the mathematic phenomenon, whereby erroneous UKM parameters are offset. In this manner, any error in the calculation of, for instance, K_D leads to proportional overestimates (or underestimates) of V and G and little or no error in the final value of Kt/V or normalized protein catabolic rate (nPCR). Such offsetting of error does not occur if UKM techniques are not used. Occasionally, we see Kt/V directly calculated from values of K_D and V that have been measured by other means (e.g., K_D from Michael's equation, V from bioimpedance analysis). We do not recommend this. As shown previously, values for K_D and V are unpredictable in critically ill AKI patients, and any error in their assessment will result in a proportional error in Kt/V during direct substitution. We therefore recommend that such measurements be used as input UKM parameters.

The most common UKM equations for formal iterative calculation of Kt/V are those derived from the variable-volume single-pool (VVSP) model developed by Sargent and Gotch.[22] Alternatively, simplified (noniterative) calculation of Kt/V is possible using equations such as those of Daugirdas and Garred (Box 146.1 and Table 146.1).[23,24] Formal UKM calculation is preferable for accuracy, although some data suggest that the simplified equations may provide reasonable estimates of dose.[25] All of these approaches calculate spKt/V. To obtain the equilibrated Kt/V (eKt/V), the Daugirdas rate equation ($eKt/V = [spKt/V - 0.47] \times [K/V] + 0.02$) has been shown to be as accurate as complicated double-pool variable-volume modeling in this setting.[23,26] The eKt/V undoubtedly provides a more realistic reflection of acute IHD dose; however, spKt/V defines dosing targets from the literature and should be used preferentially in clinical practice.

In summary, spKt/V can be calculated most accurately using formal three-point UKM, or less accurately by simplified formulas. The eKt/V can be calculated using the Daugirdas rate equation but is correspondingly harder to relate to clinical dosing targets. Kt/V by itself is an inadequate assessment of IHD dose; concurrent consideration of the frequency of treatments is essential.

CALCULATION OF INDEXED SOLUTE CLEARANCE FOR CONTINUOUS RENAL REPLACEMENT THERAPY

To calculate CRRT dose, one considers the effluent (dialysate and/or filtrate) flow rate of the particular CRRT and the saturation of the effluent with the solute in question. After indexing of solute clearance to body weight, the units of CRRT dose are therefore milligrams per kilogram per hour. Unlike IHD and its variants, effect of CRRT on solute control applies to small and larger solutes. For the moment however, we will consider small-solute clearance only.

Theoretically, the effluent during CRRT should be saturated completely with small solutes. During CVVHD, dialysate flow rates are sufficiently low for complete equilibration of small solutes between dialysate and blood water by diffusion across the membrane. During CVVH, solutes are dragged across the membrane in association with ultrafiltered water, unless they are above a certain weight, at which point sieving occurs. For small solutes, the sieving coefficient (proportionality constant between the rate of solute movement and fluid movement across the membrane) approximates 1. The ultrafiltrate therefore will have the same concentration of small solutes as the blood water, and the CRRT dose will equal the effluent flow rate (Box 146.2).[18]

Practically however there are common situations in which complete saturation of effluent does not occur. The first of these occurs when the filter is performing poorly. Filters typically develop progressive fiber-bundle clotting over time, and they also may develop concentration polarization, a condition in which protein fouling of the membrane leads

BOX 146.1

Useful Equations for Calculating Single-Pool Kt/V (spKt/V) During Intermittent Hemodialysis (IHD)

Formal Iterative Urea Kinetic Modeling (UKM) Equations Derived From the Variable-Volume, Single-Pool (VVSP) Model by Sargent and Gotch

$$V = \frac{(BW_{PRE} - BW_{POST})}{\left[\frac{BUN_{PRE} \times (K_D - (BW_{PRE} - BW_{POST})/T + K_R) - G}{BUN_{POST} \times (K_D - (BW_{PRE} - BW_{POST})/T + K_R) - G}\right]^{\frac{((BW_{PRE} - BW_{POST})/T)}{(K_D - (BW_{PRE} - BW_{POST})/T + K_R)}}}$$

$$G = ((BW_{\Phi} - BW_{POST})/\Phi + K_R) \times \left[\frac{BUN_{\Phi} \times \left[\frac{V + (BW_{\Phi} - BW_{POST})}{V}\right]^{\frac{(BW_{\Phi} - BW_{POST})/\Phi + K_R}{(BW_{\Phi} - BW_{POST})/\Phi}} - BUN_{POST}}{\left[\frac{V + (BW_{\Phi} - BW_{POST})}{V}\right]^{\frac{(BW_{\Phi} - BW_{POST})/\Phi + K_R}{(BW_{\Phi} - BW_{POST})/\Phi}} - 1}\right]$$

BUN refers to blood urea nitrogen (mg/mL). *T*, Φ, and *BW* refer to intradialytic time (min), interdialytic time (min), and body weight (g), respectively, and the subscripts of $_{PRE,\ POST,}$ and $_{\Phi}$ refer, respectively, to predialysis values, immediate postdialysis values, and values measured before the following dialysis. K_D and K_R refer, respectively, to effective intradialytic patient urea clearance (which can be estimated by in vivo hemodialyzer urea clearance) and residual renal urea clearance (mL/min). K_D is provided to the equations, which are then solved for stable values of urea distribution volume (*V*) and generation rate (*G*), with *V* used in the final calculation of the fractional clearance (*Kt/V*). (See Table 146.1.)

Simplified UKM Equations of Daugirdas and Garred

$$Kt/V = -\ln(R - 0.008 \times T) + (4 - 3.5 \times R) \times UF/W = \frac{-\ln(R) + 3 \times UF/W}{1 - 0.01786 \times T}$$

R refers to the ratio of postdialysis to predialysis BUN. *T*, *UF*, and *W* refer to intradialytic time (hr), ultrafiltrate volume (L), and postdialysis weight (kg), respectively.

BOX 146.2

Useful Equations for Calculating Small Solute Clearance (*K*) During Continuous Renal Replacement Therapy

Continuous Venovenous Hemofiltration (CVVH), Hemodialysis (CVVHD), and Hemodiafiltration (CVVHDF), Respectively, Assuming Complete Saturation of Effluent

$$K = UFR = QD = UFR + QD$$

where UFR is the ultrafiltration rate and .QD is the dialysate flow rate.

Predilution CVVH and CVVHDF, Respectively, Assuming Complete Saturation of Effluent Other Than for the Predilution Modality

$$K = UFR \times [QB_{H_2O}/QB_{H_2O} + UFR] = (UFR + QD) \times [QB_{H_2O}/(QB_{H_2O} + UFR)]$$

where QB_{H2O} is the blood water flow rate, equal to the product of blood flow rate and (1 –hematocrit). The influence of plasma water fraction and red cell water fraction can be ignored with acceptable error at the bedside.

CVVH, CVVHD, CVVHDF, Respectively, Using the Ratio of Effluent Urea Nitrogen (EUN) to Blood Urea Nitrogen (BUN)

$$K = UFR \times \frac{EUN}{BUN} = QD \times \frac{EUN}{BUN} = (UFR + QD) \times \frac{EUN}{BUN}$$

UFR (mL/kg/hr) Needed in Predilution CVVH to Provide 35 mL/kg/hr of Small Solute Clearance, Assuming Complete Saturation of Effluent Other Than for the Predilution Modality

$$UFR = \frac{QB_{H_2O} \times 35 \times (BW/60)}{(QB_{H_2O} - 35 \times (BW/60))} \times 60/BW$$

where BW is body weight. For example, for an 80-kg person, QB is 267 mL/min and hematocrit is 0.25; therefore QBH_2O is 200 mL/min at the blood pump. The UFR required to achieve a small solute clearance of 35 mL/kg/hr is 45.65 mL/kg/hr.

UFR (mL/hr/kg) and QD (mL/hr/kg) Needed in Predilution CVVHDF to Provide a Combination of Small Solute Clearance by Filtration ($K_{CONV\text{-}TARG}$) and Dialysis ($K_{DIFF\text{-}TARG}$), Assuming Complete Saturation of Effluent Other Than for the Predilution Modality

$$UFR = \frac{QB_{H_2O} \times K_{CONV-TARG} \times (BW/60)}{(QB_{H_2O} \times K_{CONV-TARG} \times (BW/60))} \times BW/60; \quad \text{UFR is then substituted in}$$

$$QD = k_{DIFF-TARG} \times \frac{QB_{H_2O} + UFR \times (BW/60)}{QB_{H_2O}}$$

For example, for an 80-kg person when a total small solute clearance of 35 mL/kg/hr is desirable through a combination of $K_{CONV\text{-}TARG}$ equal to 20 mL/kg/hr plus $K_{DIFF\text{-}TARG}$ equal to 15 mL/kg/hr, assuming again that QB H_2O is 200 mL/min, the UFR required to achieve this $K_{CONV\text{-}TARG}$ is 23.1 mL/kg/hr, and the QD to achieve this $K_{DIFF\text{-}TARG}$ is 17.3 mL/kg/hr.

TABLE 146.1

Formal Iterative Urea Kinetic Modeling (UKM) for the Calculation of Single-Pool Kt/V (spKt/V) Using Microsoft Excel (Microsoft Corporation, Seattle, WA)

WORKED EXAMPLE	SYMBOLS	CYCLE 1
Clinical Data (Units)		
Predialysis body weight (g)	BW_{pre}	90000
Postdialysis body weight (g)	BW_{post}	89000
Next predialysis body weight (g)	BW_{Φ}	91000
Predialysis blood urea nitrogen (BUN) (mg/mL)	BUN_{PRE}	0.952
Postdialysis BUN (mg/mL)	BUN_{POST}	0.392
Next predialysis BUN (mg/mL)	BUN_{Φ}	0.756
Residual renal urea clearance (mL/min)	K_R	0
Intradialytic patient urea clearance (mL/min)	K_D	190.1
Treatment duration (min)	T	240
Interdialytic duration (min)	Φ	1440
Equations		
Seeded G	$G^{\#}$	12.10
$BW_{PRE} - BW_{POST}$	wl	1000
$BW_{\Phi} - BW_{POST}$	wg	2000
wl/T	dwl	4.17
wg/Φ	dwg	1.39
BUN_{PRE}* (K_D – dwl + K_R)	Z1	177.01
BUN_{POST}* (K_D – dwl + K_R)	Z2	72.89
(K_R + dwg)/dwg	Z3	1.00
dwl/(K_D – dwl + K_R)	Z4	0.02
$[(Z1 - G^{\#})/(Z2 - G^{\#})]^{Z4}$	Z5	1.02
wl/(Z5 – 1)	V	44212.12
$((V + wg)/V)^{Z3}$	Z6	1.05
(K_R + dwg)*(BUN_{Φ}*Z6 – BUN_{POST})/(Z6 – 1)	G	12.23
$(G - G^{\#})/G^{\#}*100$	Convergence of G and $G^{\#}$	1.00
$(G + G^{\#})/2$	Suggested New $G^{\#}$	12.16
Kd*T/V	Kt/V	1.03
Practice Tips		
Step 1. Create a spreadsheet with the equations entered as shown.		
Step 2. Enter clinical data, including an estimated value for K_D, and an arbitrary seeding value for $G^{\#}$ between 10 and 20.		
Step 3 (Manual). Manually input new values for G by overwriting the "$G^{\#}$" cell with values suggested in the "Suggested New $G^{\#}$" cell. Usually four to five iterations will be needed to bring the value in the "convergence" cell to 1 (i.e., to bring modeling accuracy to within 1%).		
Step 3 (Automated). Use the Microsoft Excel Solver add-in function, specifying the "convergence" cell as the target cell to equal 1 (i.e., modeling accuracy to within 1%) and the "$G^{\#}$" cell as that which Solver is to change.		

to diffusive transport of especially larger solutes back into the blood from a concentrated layer immediately adjacent to the membrane. In both of these situations, the concentration of all solutes is lower in effluent than in blood water.

The second situation is during predilution, a modality that involves infusion of substitution fluid before the filter in the extracorporeal circuit. The concentration of all solutes again is lower in effluent than in blood water. Predilution reduces clearance of small solutes by approximately 15% for low-dose prescriptions (UFR < 2 L/hr) and by about 40% for high-dose prescriptions (UFR > 4.5 L/hr).[27,28] The impact of the predilution modality on small-solute clearance can be estimated by a number of formulas (see Box 146.2).

The final situation in which complete saturation of effluent does not occur is when the blood flow rate (Qb) is very low or the dialysate flow rate (Qd) is very high. In this case, the mismatch of flow results in incomplete equilibration of small solutes between dialysate and blood water. This also can occur if the dialyzer is large in relation to Qb and Qd as a result of incomplete fiber-bundle penetration.

Because of these uncertainties, opinion leaders recommend regular monitoring of the ratio between effluent urea nitrogen (EUN) and BUN (the EUN/BUN ratio) (see Box 146.2).[29,30] In addition to providing a measure of small solute clearance, it also provides a measure of filter performance: A decrease of 20% has been suggested as a threshold for action and replacement of the extracorporeal circuit. The measurement of simultaneous effluent and blood concentrations is also the only way to determine the clearance of larger solutes, which have a sieving coefficient of less than 1 and therefore saturate the effluent to a lower degree than the blood water.

In summary, small-solute clearance during CRRT can be estimated empirically as the effluent flow rate, although the practitioner should be alert to situations in which complete saturation of the effluent cannot be assumed. We recommend regular measurement of the EUN/BUN ratio for more accurate quantification of CRRT dose and quality assurance of therapy delivery. To further refine the assessment of CRRT dose, we recently have suggested that it could be expressed in terms of time averaged dialyzer urea clearance (TAKd).[31,32] This allows accounting for the "downtime," that is, the time period between the end of one session and the start of the next one, a frequent well-known phenomenon that affects the dialysis dose delivery.[33,34] In short, we suggested considering the entire time period (ETP) between the start of the first dialysis session and the end of the last one,[31,32] so including also all nondialysis times. The contribution of each individual session can be expressed by the KT product, that is, the delivered Kd times the session length, so that the total cleared volume (TCV) over ETP can be computed by summing up all KT products. This allows computing the time averaged Kd, as follows: TAKd = TCV/ETP. For comparison purposes, the latter could be expressed either in units of mL/kg/hr, to be compared with the effluent dose, or in units of mL/min/35 L, to be compared with the continuous clearance (see below).

UNIFIED EXPRESSIONS OF DOSE FOR ACUTE RENAL REPLACEMENT THERAPY

The ideal expression for ARRT dose should be numerically comparable across all modalities and treatment schedules. The expression also should be simple to calculate without sacrificing accuracy. This does not mean necessarily that the mathematics must be simple, because the most complex of calculations are made easily on modern computers. Instead, this means that the UKM input parameters should be simple and, in particular, readily available to the practitioner. An expression of ARRT dose, no matter how elegant, is clinically unworkable if the input variables are wholly unknown to the practitioner. Furthermore, the ideal expression of dose should be intuitively meaningful, guiding the practitioner in optimizing the process of solute removal.

As described previously, CRRT dose is expressed as mL/kg/hr. This unit is attractive because it is numerically

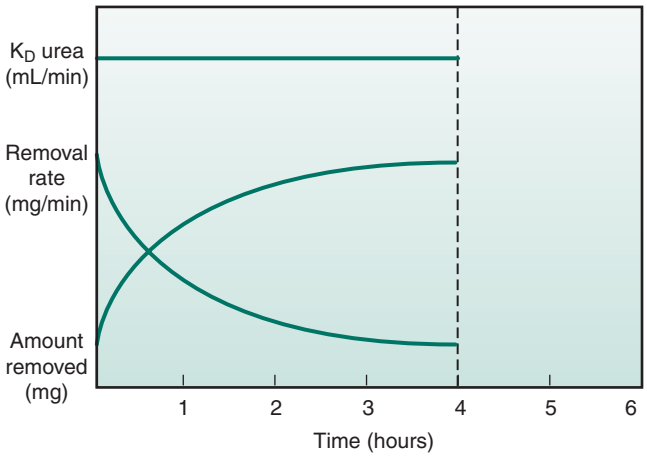

FIGURE 146.1 A representation of solute transport during single-pass intermittent hemodialysis. The curves demonstrate the relationship between the clearance rate of urea (K_D) and urea removal with time.

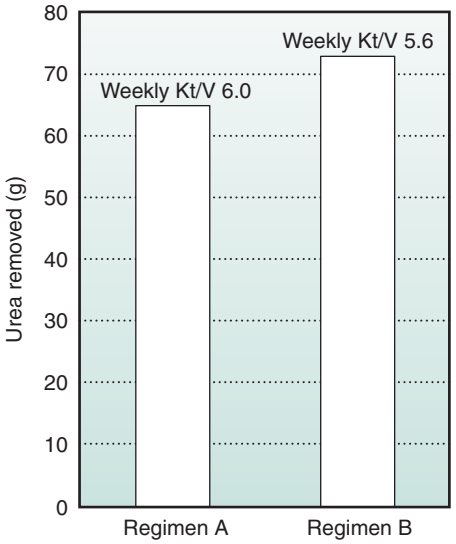

FIGURE 146.2 A comparison of urea nitrogen removed per week during two dialysis regimens, where residual renal function is absent, normalized protein catabolic rate (nPCR) is 0.8 g/kg/day, and starting blood urea nitrogen (BUN) concentration for the week is 93 mg/dL. In regimen A, three hemodialysis (HD) treatments are given per week, with a duration of treatment of 240 minutes, a volume (V) of 40 L, and a clearance rate (K_D) of 333 mL/min. In regimen B, seven HD treatments are given per week, with a duration of 120 minutes, V of 40 L, and K_D of 267 mL/min.

comparable with glomerular filtration rate (GFR) and has clear meaning to the practitioner. Moreover, one of the major controversies in ARRT is the timing of therapy initiation in relation to residual renal function, and future studies are likely to use GFR as at least one criterion for therapy initiation. Such studies may result in a single clinical target for solute clearance to optimize patient outcomes, which could be met by any combination of residual renal function and ARRT. Occasionally, we see attempts to express CRRT dose as a daily Kt/V. We do not recommend this. The calculations require potentially unreasonable assumptions about V, and they result in an expression for dose that is generally less meaningful than mL/kg/hr.

As also described earlier, IHD dose is expressed as Kt/V. There are difficulties with the use of unit of dose in critically ill AKI patients. The main issue is that there is dissociation between Kt/V and solute mass removal over the course of an IHD treatment: Clearance stays the same, but the mass removal rate goes down as solute concentrations decrease in the body (Fig. 146.1). This dissociation does not affect comparisons of Kt/V within a given dosing schedule (e.g., daily, three times a week). It does mean however that cumulative Kt/V does not change proportionally with cumulative solute mass removal for IHD regimens that vary in terms of frequency. It is therefore invalid to quantify cumulative IHD over a given time period by simple addition of Kt/V. It is also invalid to compare the sum of Kt/V per week, for instance, unless the number of treatments within the period of observation is the same. As an example, Fig. 146.2 illustrates the increased removal of urea, despite a lower cumulative weekly Kt/V, that occurs as a result of more frequent treatments.

The most reasonable approach to a unified expression for ARRT dose is to model small-solute clearance using UKM. The dose of all ARRT modalities can be expressed in this manner, at least in terms of small-solute clearance. We do acknowledge that uremic toxicity in the setting of AKI is far from well characterized, but we believe that the evidence associating clearance of larger solutes with outcomes is too preliminary to be incorporated into dosing paradigms at the present time.

There are several competing UKM equations that provide unified expressions of dose across different modalities. Gotch derived the "standard Kt/V" (stdKt/V)[35] and Keshaviah and Star derived the "solute removal index" (SRI) in the 1990s.[36] Both expressions are based on the peak urea concentration hypothesis; kinetically equivalent therapy prescriptions are those that produce the same urea mass removal rate at the same predialysis BUN. There are two difficulties with this paradigm in critically ill AKI patients. First, BUN concentrations can be very asymmetric and variable as a result of urea non–steady-state or irregular IHD schedules, and arbitrary definitions of peak BUN concentration are likely to have less validity. Second, the peak urea concentration hypothesis is legitimized in the ESRD setting by the clinical equivalence of IHD and continuous ambulatory peritoneal dialysis (CAPD) and the coincidence that adequate doses of IHD and CAPD are characterized by numerically equal values for stdKt/V and SRI. However, these arguments cannot be extrapolated to critically ill AKI patients. A comparison of IHD and CAPD by Phu et al. showed disparate clinical outcomes, despite adequate doses of dialysis by ESRD standards and therefore similar values for stdKt/V and SRI.[37] This finding undermines the validity of the peak urea concentration hypothesis in this setting, as well as the use of stdKt/V and SRI as unified expressions of dose.

In our opinion, the most suitable expression of ARRT dose is the equivalent renal urea clearance (EKR), which has the unit of milliliters per minute.[38] When applied to intermittent ARRT, EKR expresses dose as the continuous urea clearance that will result in the same TAC_{BUN} for a given amount of urea mass removal over the period of observation. When applied to CRRT, EKR is simply the time-averaged continuous urea clearance over the period of observation. EKR is modeled using time-averaged as opposed to peak urea concentration, which is easier to define and likely to be more valid for critically ill AKI patients. EKR is corrected in a manner analogous to GFR to account for different body sizes (EKRc). The correction factor is still based on the archetypal 70-kg male, and his ideal V of 40,000 mL (rather than body surface area) is used as the correction factor ($EKRc = EKR/V \times 40{,}000$). This correction

is critical because it allows for the previously mentioned mathematical phenomenon that offsets error in the input UKM variables so that there is little or no error in the final value of EKRc. Such offsetting of error does not occur if EKR is corrected to actual body weight or body surface area, which are parameters that are bound less tightly to the kinetic parameter V.

EKRc also has been used in research settings to determine kinetic equivalence between ARRTs for the clearance of larger solutes.[39] There are fewer studies validating this approach, and a workable tool that may be applied in the clinical setting has not yet been presented. Our preliminary work suggests that the methodology described in the next section could be developed into a unified expression of β_2-microglobulin clearance as well, although the tool is still under development.

PRACTICAL QUANTIFICATION OF ACUTE RENAL REPLACEMENT DOSE USING CORRECTED EQUIVALENT RENAL UREA CLEARANCE

Approximate EKRc values can be calculated for acute IHD from the Kt/V per treatment and the treatments per week, using nomograms based on either single-pool or double-pool modeling (Fig. 146.3).[38,40] However, these nomograms are based on the traditional formula for calculating for EKR (G/TAC_{BUN}). This formula is valid only during the urea steady state, because it underestimates when the TAC_{BUN} is falling and overestimates when it is rising. The urea non–steady state can render error as high as 30% to 40%.[11]

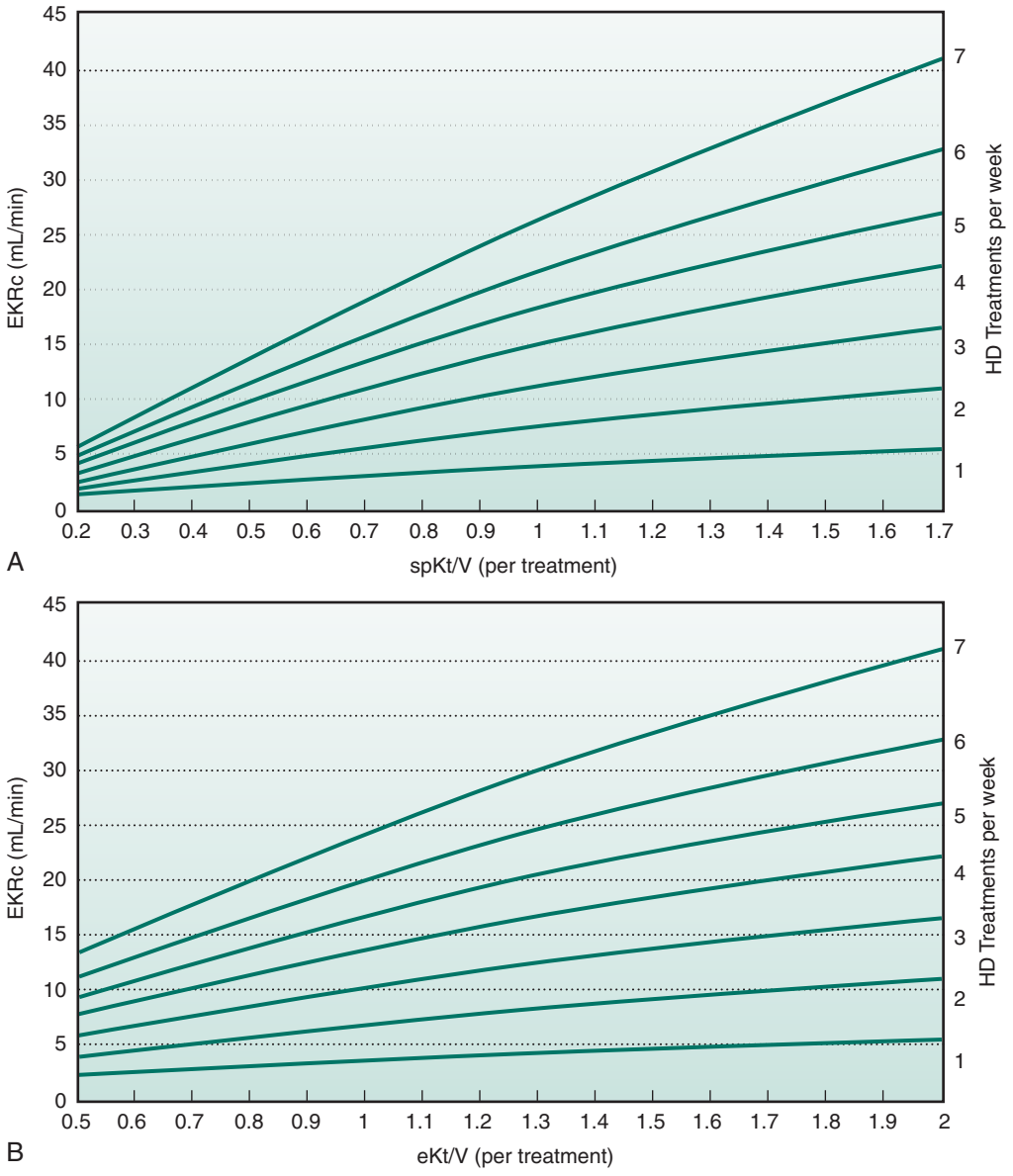

FIGURE 146.3 A, Relationship between corrected equivalent renal urea clearance (EKRc) and single-pool fractional clearance (spKt/V) per treatment for a frequency of one to seven treatments per week. B, Relation between EKRc and equilibrated Kt/V (eKt/V) per treatment for a frequency of one to seven treatments per week.

More accurate values can be calculated by discarding the assumption that the urea mass removal rate for solute J (Jm) is equal to the urea generation rate (G) and modeling instead using the core equation EKRj = Jm/TAC_{BUN}. We previously have presented simple algebraic formulas that derive the necessary input data for the calculation of EKRj and corrected EKRj (EKRjc) from BUN time-concentration profiles over the weekly interval (Table 146.2).[41] These formulas can be used in any commercial spreadsheet program, with input of sequential pre-IHD and post-IHD BUN and paired estimations of pre-IHD and post-IHD V. These estimations of V need not be exact, because the accuracy of the calculated value for EKRjc by this method is not compromised until the estimation error of V is greater than 25% to 50% in either direction. Our practice is to estimate V by using a value of 0.65 times body weight. The calculated value

TABLE 146.2

Calculation of Corrected Equivalent Urea Clearance by Convection (EKRJc) Over Consecutive Cycles (Dialysis and Following Interdialytic Period) of Intermittent Hemodialysis (IHD) Using Microsoft Excel*

WORKED EXAMPLE	SYMBOLS	CYCLE 1	CYCLE 2	CYCLE 3	CYCLE 4 … *N*
Clinical Data (Units)					
Predialysis urea distribution volume (mL)	$V_{PRE(n)}$	43440	42640	44190	45090
Postdialysis urea distribution volume (mL)	$V_{POST(n)}$	42700	42000	44100	44000
Next predialysis urea distribution volume (mL)	$V_{\Phi(n)}$	42640	44190	45090	46590
Predialysis blood urea nitrogen (BUN) (mg/mL)	$BUN_{PRE(n)}$	1.43	1.04	0.77	0.68
(Equilibrated) postdialysis BUN (mg/mL)	$BUN_{POST(n)}$	0.93	0.66	0.39	0.36
Next predialysis BUN (mg/mL)	$BUN_{\Phi(n)}$	1.04	0.77	0.68	0.66
Residual renal urea clearance (mL/min)	K_R	3.2	2.8	3	2.6
Treatment duration (min)	$T_{(n)}$	120	180	240	240
Interdialytic duration (min)	$\Phi_{(n)}$	1380	3000	3720	2880
Equations					
$TT = T + \Phi$	TT	1500	3180	3960	3120
Sum TT	ΣTT	1500	4680	8640	11760
$G = (V_\Phi * BUN_\Phi - V_{POST} * BUN_{POST})/\Phi + K_R * (BUN_{POST} + BUN_\Phi)/2$	G	6.51	4.10	5.22	6.50
$nPCR = (9.35 * G + 0.294 * V_{POST}/1000)/(V_{POST}/580)$	$nPCR$	1.00	0.70	0.81	0.97
$A_{CY} = G * TT$	A_{CY}	9766	13051	20687	20289
Sum $A_{CY} = \Sigma A_{CY}$	ΣA_{CY}	9766	22817	43503	63792
$AUC_D = T * (BUN_{PRE} - BUN_{POST})/\ln(BUN_{PRE}/BUN_{POST})$	AUC_D	139	150	134	121
$AUC_I = \Phi * (BUN_{POST} + BUN_\Phi)/2$	AUC_I	1359	2145	1990	1469
$AUC_T = AUC_D + AUC_I$	AUC_T	1499	2295	2124	1590
Sum $AUC_T = \Sigma AUC_T$	$\Sigma AUCT$	1499	3794	5918	7508
$V_\Phi * BUN_\Phi - V_{PRE} * BUN_{PRE}$	$\Delta\ VC$	– 17774	– 10319	– 3365	88
Sum $\Delta VC = \Sigma\Delta\ VC$	$\Sigma\Delta\ VC$	– 17774	– 28093	– 31458	– 31370
$M_{CY} = A_{CY} - \Delta VC$	M_{CY}	27539	23370	24052	20201
Sum $M_{CY} = \Sigma M_{CY}$	ΣM_{CY}	27539	50910	74961	95162
$EKRj = \Sigma M_{CY}/\Sigma AUC_T$	$EKRj$	18.4	13.4	12.7	12.7
$V_{POST} * TT$	$V_{POST} * TT$	6.41E+07	1.34E+08	1.75E+08	1.37E+08
Sum $V_{POST} * TT = \Sigma V_{POST} * TT$	$\Sigma V_{POST(M)} * TT$	6.41E+07	1.98E+08	3.72E+08	5.10E+08
VPOST(M) = $\Sigma V_{POST} * TT/\Sigma TT$	$V_{POST(M)}$	42700	42224	43084	43327
EKRjc = EKRj*40000/$V_{POST(M)}$	EKRjc	17.1	12.7	11.8	11.7
$K_RC^{\#} = K_R * 40000/V_{POST(M)}$	$K_RC^{\#}$	3.0	2.7	2.8	2.4
$K_RC^{\#} * TT$	$K_RC^{\#} * TT$	4496.5	8434.9	11029.6	7489.1
Sum $K_RC^{\#} * TT = \Sigma K_RC^{\#} * TT$	$\Sigma K_RC^{\#} * TT$	4496.5	12931.4	23961.0	31450.1
$K_RC = \Sigma K_RC^{\#} * TT/\Sigma TT$	K_RC	3.0	2.8	2.8	2.7
dEKRjc = EKRjc – K_RC	dEKRjc	14.2	9.9	9.0	9.0

Practice Tips

Step 1. Create a spreadsheet with the equations entered as shown.

Step 2. Enter data for input variables including an estimated value for volume of distribution (V*)*. Because any error is offset in the subsequent calculations, this estimation does not need to be exact and can be estimated as 0.65 × body weight. Postdialysis BUN can be entered as immediate postdialysis values (BUN_{POST}) or as equilibrated values ($BUN_{POST(EQ)}$) according to the equation from Tattersall:

$$BUN_{POST(EQ)} = BUN_{PRE} \times (BUN_{POST}/BUN_{PRE})^{T/T+35}$$

Columns in the spreadsheet should be replicated for every cycle of IHD over a weekly interval.

*Microsoft Corporation, Seattle, WA.

for EKRjc using this spreadsheet method is not compromised by the urea non–steady state or by variations in G. In addition, EKRjc can be calculated in a manner that accounts for compartment effects by adjusting the post-IHD BUN for urea dysequilibrium using the formula from Tattersall.[42]

For CRRT, the approximate EKRjc values can be calculated from small-solute clearance. The only difference between EKRjc (mL/min) and CRRT dose (mL/kg/hr) is that the former is corrected to a V of 40 L and the latter is indexed to body weight. To calculate EKRjc (mL/min), one can assume V to be 0.65 × body weight and divide the indexed small-solute clearance by 0.975.[11]

More accurate values for EKRjc for CRRT can be calculated in a similar manner as for IHD, but using a different set of algebraic formulas from those used for IHD, based on a differently modeled BUN time-concentration profile over the weekly interval.[41]

EKRc is not simply time-averaged hemodialyzer urea clearance. By way of an example, EKRc would not triple if hemodialyzer clearance were to be tripled for a given IHD regimen. EKRc is a true mass balance parameter that accounts for the inefficiency of intermittent therapies.

In summary, in our opinion EKRjc is the best expression to unify dose of ARRT between different modalities and schedules. We believe that acute IHD dose should be expressed preferentially as EKRjc, to provide an expression that accounts for the frequency of treatments and allows some comparison with CRRT in terms of small solute clearance. Furthermore, we believe that CRRT dose can be expressed legitimately as EKRjc, which certainly can be used in the research setting to quantify dose across a range of solutes and clarify the relative impact of small versus larger solute clearance on patient outcomes.

To allow an easier comparison between EKRc, which has units of mL/min/40L, and the glomerular filtration rate (GFR), which has units of mL/min/1.73 m^2, we recently have suggested correcting EKRc for a volume (V) of 35 L, in the place of 40 L.[43] In fact, since the V to Body Surface Area (BSA) ratio is about 20, a patient with BSA = 1.73 m^2 will have a V of 1.73 m^2 × 20 = about 35 L.[44] As a consequence of such a reduction in the reference V, the new EKRc values are lessened by about 13%, in fact 35/40 = 0.125. For chronic patient in maintenance HD, the adequate EKRc level corresponding to an equilibrated Kt/V of 1.2 on thrice-weekly schedule can be approximated to about 12 mL/min/35 L.

CONCLUSION

The prescription and quantification of ARRT according to dosing standards is an increasingly popular and widespread practice pattern and will become ubiquitous in the future if various studies that are currently underway provide definitive results proving a causal relationship between ARRT dose and clinical outcomes.

We have presented an overview of methods to calculate small-solute clearance during ARRT that are comparable between modalities and schedules. This does not mean that we believe large-solute clearance to be unimportant, merely that small-solute clearance is currently the best correlate of outcomes for patients treated with ARRT. We believe that there are as yet insufficient data to support the inclusion of large-solute clearance in clinical dosing targets for ARRT.

Two major uncertainties arise when using solute clearance to define ARRT dose. First, it is unknown whether solute control (i.e., levels of uremic toxins or markers) is more important than solute clearance. Second, it is increasingly apparent that mass transfer across membranes may play a relatively minor role in the removal of certain potential uremic toxins, such as proinflammatory cytokines. Their sieving coefficient is frequently much less than 1, and their removal has been shown to be due to an adsorptive mechanism resulting in up to a 10-fold higher removal of such mediators in comparison with mass transfer alone.[45] Adsorption is critically dependent on membrane composition and structure, and it may become necessary to stratify or adjust expressions for ARRT dose for membrane type, if studies in the future show adsorption to be clinically important.

Key Points

1. In critically ill patients with acute renal injury treated with acute renal replacement therapy (ARRT), the relationship between solute clearance and clinical outcomes is best defined for small solutes, although there are preliminary data supporting a similar relationship for larger solutes.
2. The "best" expression for ARRT dose is determined by whatever expression has been correlated with clinical outcomes in the literature: that is, single-pool fractional clearance (spKt/V) for intermittent hemodialysis and ultrafiltration rate for continuous renal replacement therapy (CRRT).
3. Urea kinetics are different in critically ill patients with AKI; and spKt/V is most accurately calculated using formal iterative three-point urea kinetic modeling, and less accurately using simplified formulas.
4. The ultrafiltration rate is known directly in post-dilution conventional CRRT. In other situations, it can be estimated by a variety of formulas depending on the exact modality or, alternatively, by the ratio of the urea concentration in the effluent to that in the blood (EUN/BUN ratio).
5. The corrected equivalent renal urea clearance (EKRjc) is the most accurate unified expression for ARRT dose, and it is easy to calculate using commercial spreadsheet programs.

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A complete reference list can be found online at ExpertConsult.com.

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