CHAPTER 170

# Adequacy of Continuous Renal Replacement Therapy: Prescription and Delivery

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### OBJECTIVES

This chapter will:

1. Help the reader understand the concept of clearance and the manner in which it is applied to estimate dose of renal replacement therapy.
2. Describe the differences in the use of urea kinetic modeling (UKM) for end-stage renal disease and acute kidney injury.
3. Help the reader understand the important studies that have employed urea kinetic approaches to quantify the dose of continuous renal replacement therapy (CRRT).
4. Discuss the major studies that have assessed the relationship between CRRT dose and patient outcome.
5. Explain the rationale for applying a continuous-equivalent UKM.

Measurement of delivered dialysis therapy is performed routinely in the management of patients with end-stage renal disease (ESRD), and urea-based quantification tools validated in prospective clinical trials are available to clinicians.[1] On the other hand, the quantification of renal replacement delivery in acute kidney injury (AKI) is less established.[2–4] Although the advent of continuous renal replacement therapy (CRRT) involved a focus on its hemodynamic benefits relative to conventional hemodialysis (HD),[5,6] early kinetic studies employing adaptations of chronic dialysis approaches also demonstrated clear advantages for CRRT with respect to urea clearance and azotemia control.[7–9] Additional kinetic comparisons also have indicated CRRT has advantages over HD for the removal of solutes over a broad molecular weight range.[10–12] Although the greater solute clearance capabilities afforded by CRRT relative to intermittent therapies generally are recognized by clinicians, neither urea nor any other solute is employed specifically for CRRT dose assessments in clinical practice. Instead, the landmark trial performed by Ronco et al. has established effluent-based dosing as the standard of care for CRRT.[13,14] Nevertheless, this parameter does not provide an accurate estimation of actual solute clearance and has created confusion among many clinicians, especially those familiar with urea-based dose measurements in the chronic dialysis setting. To address this problem, we reappraise dose prescription and delivery for CRRT and propose an adaptation of a chronic dialysis parameter (standard Kt/V) as a benchmark to supplement effluent-based dosing. (In this expression, which represents a normalized dose of dialysis, K is urea clearance, t is treatment time, and V is urea volume of distribution.) Before this, the key differences in the application of renal replacement therapy (RRT) quantification to the ESRD and AKI populations are discussed, and a comprehensive review of the literature regarding the application of these methodologies to CRRT is provided.

## USE OF CLEARANCE TO QUANTIFY DOSE IN RENAL REPLACEMENT THERAPY

### Overview of Clearance

The concept of solute clearance, integral to therapy dose in chronic dialysis, is defined as the ratio of mass removal rate (N) to blood concentration ($C_B$)[15]:

$$K = N/C_B$$

(Equation 1)

When this equation is applied, a steady-state assumption typically is made, implying that net solute generation is balanced by net removal. For continuous depuration processes (e.g., endogenous kidney function), the indexing of mass removal rate to blood concentration allows for patients with widely varying kidney function to be compared with the same standard. Although not readily evident by inspection of Eq. 1, the relationship between solute removal and clearance is therapy specific. This issue has been evaluated critically by several investigators, including Clark and Henderson.[16] Assuming constant urea clearance, these investigators have demonstrated that although conventional HD's relatively high efficiency results in a high urea mass removal rate early in a treatment, this rate decreases substantially as the transmembrane concentration gradient for removal is dissipated as a result of falling blood concentrations (Fig. 170.1A). As such, cumulative solute removal begins to reach a plateau later in treatment, leading to a "self-defeating" situation for removal of small solutes eliminated efficiently.[17] Fig. 170.1B demonstrates the same relationship between urea mass removal rate and instantaneous clearance for a CRRT filter operated at steady state (i.e., constant clearance and urea generation rate with a constant blood urea nitrogen (BUN) as a result). In this case, mass removal rate also remains constant, leading to a linear increase in cumulative solute removal over time. This comparison demonstrates the powerful effect of long treatment duration in CRRT, even though instantaneous clearance rates are relatively low.

Unified clearance expressions have been proposed to quantify solute removal by ESRD therapies ranging from conventional (thrice-weekly) HD to continuous therapies. These approaches include equivalent renal clearance,[18] solute removal index,[19] and standard urea clearance.[20] In different ways, these methodologies attempt to incorporate intermittent effects on treatment efficiency and actual solute removal. As suggested above, the differences in solute removal rates early versus late during an intermittent treatment (despite constant clearance) do not allow direct comparison of Kt/V values derived, for example, from a 2-hour treatment and a 4-hour treatment. Likewise, direct comparison of the dose provided by intermittent and continuous therapies is not

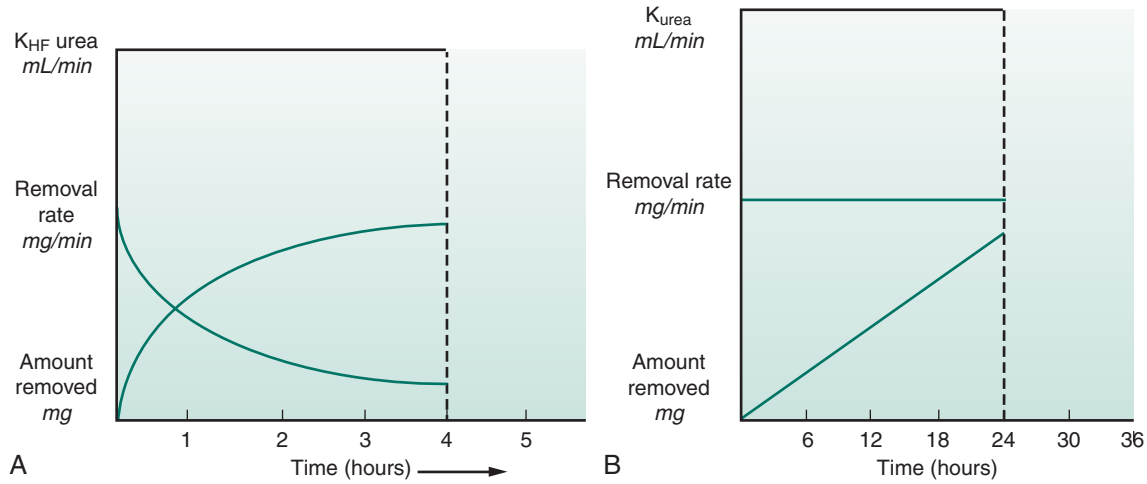


**FIGURE 170.1** Relationship between mass removal rate and clearance for a high-efficiency dialysis modality (intermittent hemofiltration: HF) used for end-stage renal disease (A) and continuous renal replacement therapy used for acute kidney injury (B). (Modified from Clark WR, Henderson LW: Renal vs continuous vs intermittent therapies for removal of uremic toxins. Kidney Int 2001;59 [Suppl. 78]:S298-S303.)

straightforward. Standard Kt/V is a "continuous-equivalent" methodology in which effective clearances provided by various intermittent schedules are referenced to a weekly continuous Kt/V provided by chronic peritoneal dialysis (PD).[20] In this approach, pretreatment (peak) and steady-state BUN values for intermittent therapies and PD, respectively, are incorporated. Although the original application of standard Kt/V was in chronic dialysis, it is also suited to CRRT, as discussed subsequently.

Finally, dialysis quantification parameters other than clearance are also important to consider. Although clearance is a representation of treatment efficiency at a specific time or over a relatively limited time period, *intensity* can be defined as the product of clearance and cumulative treatment time. This parameter can be employed to demonstrate that despite relatively low solute clearance rates, cumulative solute removal with CRRT is typically much greater in comparison to more efficient therapies delivered intermittently. Finally, *efficacy* measures the effective removal of a specific solute resulting from a given treatment in a given patient. Efficacy can be defined numerically as the ratio of intensity to volume of distribution for a specific solute—as such, urea Kt/V is an efficacy parameter. A recent consensus publication regarding nomenclature used for acute RRT therapies reinforces these concepts.[21]

## QUANTIFICATION OF RENAL REPLACEMENT THERAPY DOSE IN ACUTE KIDNEY INJURY VERSUS END-STAGE RENAL DISEASE: IMPORTANT DISTINCTIONS

A fundamental assumption of urea kinetic modeling (UKM) when applied to ESRD is the existence of a quasi-steady state. This assumption is clearly not applicable in critically ill AKI patients, whose clinical status changes on a daily or even hourly basis. As such, application of UKM to the AKI population must be done with caution for several reasons. First, in ESRD patients at steady state, dietary protein intake can be estimated from another UKM parameter, protein catabolic rate (PCR).[1] However, this relationship is clearly invalid in the non–steady-state condition of AKI. Nevertheless, PCR still provides an estimate of the degree of hypercatabolism and net negative nitrogen balance, both of which are characteristic of the critically ill AKI population.[22–24] Another fundamental component of UKM, urea distribution volume (V), frequently is deranged in the AKI population,[25,26] and assumptions for this population based on values typical for ESRD patients may dramatically underestimate the degree of volume expansion. In turn, removal of water-soluble compounds (e.g., urea) may be reduced substantially relative to expected values.[27]

**TABLE 170.1**

**Urea Kinetic Parameters for Critically Ill Acute Kidney Injury Patients Treated With Continuous Venovenous Hemofiltration**

| PARAMETER | MEAN±SD |
|---|---|
| Whole blood urea clearance (mL/min) | 15.2±0.9 |
| Steady-state serum urea nitrogen (mg/dL) | 79.0±17.0 |
| Urea generation rate (mg urea N/min) | 11.7±3.1 |
| Urea distribution volume (L/kg) | 0.55±0.11 |
| Normalized protein catabolic rate (mg/kg/d) | 1.82±0.95 |
| Net nitrogen deficit (g/d) | 8.1±4.5 |

Modified with permission from Clark WR, Murphy MH, Alaka KJ, Mueller BA, Pastan SO, Macias WL. Urea kinetics in continuous hemofiltration. *ASAIO J.* 1992;38:664–667.

## USE OF UREA KINETICS TO ESTIMATE CONTINUOUS RENAL REPLACEMENT THERAPY DOSE

The first formal assessment of urea kinetics for CRRT was performed by Clark et al. in a series of critically ill AKI patients treated with predilution CVVH.[23] Estimates of V along with urea generation rate, PCR, and nitrogen balance were provided (Table 170.1). In a separate report from the same group, normalized PCR was found to increase steadily during the course of CRRT from an initial mean value of

1.55±0.14 g/kg/d on day 1 to 1.95±0.15 g/dk/d on day 6.[8] The latter findings, corroborated by other investigators,[22–24] confirmed the pronounced hypercatabolism and nitrogen deficits characteristic of this population. These investigators extended their analysis by applying formal UKM to estimate delivered dose for the same group of CRRT patients in comparison with a separate group treated with conventional HD.[9] Although the mean delivered Kt/V per day was the same in both groups (0.59±0.23 vs. 0.59±0.20 in the CRRT and HD groups, respectively), the mean steady-state BUN in the CRRT group was significantly lower than the mean peak BUN in the HD group (79±17 vs. 101±12, respectively; $p < .05$).

Leblanc et al. also characterized CRRT efficacy with urea Kt/V as a dose parameter[7] in a series of 25 patients. Based on an assumed V of 55% of body weight, delivered Kt/V calculations were made for different continuous therapies and compared with that provided by conventional HD. Daily mean delivered Kt/V values for the CRRT modalities ranged from 0.88 to 2.03, depending on the specific combination of dialysate flow and ultrafiltration rates prescribed. For example, continuous venovenous hemodialysis (CVVHD) applied with a dialysate flow rate of 1 L/hr and mean ultrafiltration rate of 1.1 L/hr resulted in a mean delivered Kt/V of 1.14±0.25 per day or Kt/V of 8.0 per week. (Based on the mean values for the parameters provided, the corresponding effluent-based dose can be estimated to be approximately 26 mL/kg/hr.) On the other hand, delivered Kt/V per conventional HD treatment (urea clearance, 175 mL/min) was 1.07 on a mean basis. In reference to the specific CVVHD protocol described above, a simple summation of daily Kt/V values would suggest approximate equivalence between it and daily HD. However, as suggested previously, such a comparison does not account for the inherent inefficiency of intermittent therapies, so this comparison is not valid.

Other approaches developed originally for chronic dialysis also have been applied to the spectrum of renal replacement therapies used in AKI.[11,28] Claure et al. have reported CRRT dose parameters, including EKR and urea Kt/V, in a series of 52 patients.[28] They estimated both blood-side and effluent-side parameters on an instantaneous basis from simultaneous urea nitrogen concentration determinations, accounting for treatment downtime. Urea clearance estimated from EKR and effluent-side UKM correlated well with clearance estimated by the reference method of effluent collection (i.e., direct quantification).

## CONTINUOUS RENAL REPLACEMENT THERAPY DOSE AND OUTCOME STUDIES

Ronco et al. used normalized effluent rate as a novel dosing parameter to demonstrate survival in patients prescribed doses of 35 or 45 mL/kg/hr of postdilution continuous venovenous hemofiltration (CVVH) was significantly higher than in those prescribed a dose of 20 mL/kg/hr[13] (Fig. 170.2). The rationale for this dosing approach was the well-described direct relationship that exists between effluent rate and urea clearance in this modality as long as filter function is preserved. In other words, in the context of postdilution hemofiltration, there is a 1:1 relationship between doses based on effluent rate and urea clearance as long as filter function is preserved (i.e., filtration fraction and hemoconcentration are managed appropriately).

Subsequent to the Ronco et al. trial, several additional single-center randomized clinical trials assessed the relationship between effluent-based dose and outcome.[29–31] These trials, which employed a broad spectrum of CRRT modalities, produced inconsistent results. Furthermore, none incorporated detailed urea kinetic analyses. Among randomized CRRT dose/outcome studies, the ATN trial was the first conducted on a multicenter basis.[32] Between the two dose arms, a total of almost 6000 CRRT treatments were provided in the study, representing 56% of all renal replacement treatments. Because the CRRT doses of 35 mL/kg/hr and 20 mL/kg/hr were delivered with predilution continuous venovenous hemodiafiltration (CVVHDF) at a mean blood flow rate 140 to 150 mL/min, the urea clearance-based dose was approximately 29 mL/kg/hr and 17 mL/kg/hr, respectively, on a delivered basis. The average effluent volumes per day in the intensive and less intensive groups were approximately 50 L and 30 L, respectively, with dialysate (diffusion) and replacement fluid (convection) given in equal volumes. The primary end point, all-cause mortality 60 days after initiation of renal replacement therapy, did not differ between the intensive and less intensive groups. The design of the trial, in which RRT assignment was based on hemodynamic status, does not allow the effect of CRRT on outcome to be isolated because most patients were treated with more than modality.[33]

The design of the RENAL trial, the second multicenter AKI dose/outcome trial, differed substantially from that of ATN.[34] In RENAL, all patients initially were treated with CRRT, and only a small percentage had any exposure to HD while in the ICU. For all practical purposes, therefore, RENAL was exclusively a CRRT dose/outcome trial. The treatment modality was postdilution CVVHDF, prescribed at doses of 25 or 40 mL/kg/hr. Mean delivered effluent doses were reported to be 33.4 and 22 mL/kg/hr in the higher-intensity and lower-intensity groups, respectively. These values correspond to 84% and 88% delivery of the prescribed dose. Similar to ATN, no significant difference in all-cause mortality 90 days after initiation of CRRT was observed between the two dose groups.

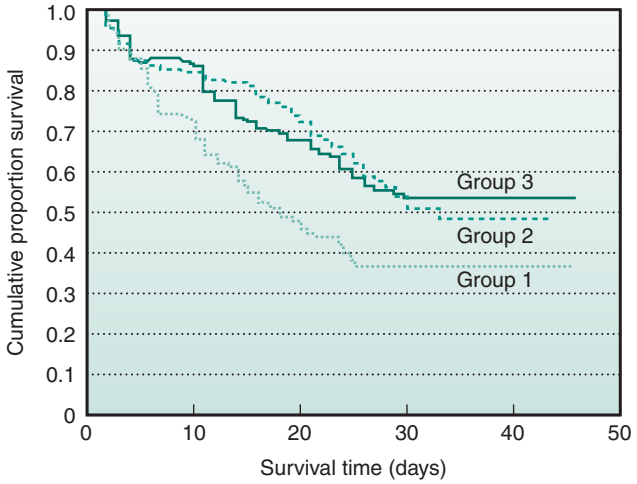


**FIGURE 170.2** Relationship between survival and effluent dose in acute kidney injury patients treated with postdilution continuous venovenous hemofiltration. (Reprinted with permission from Ronco C, Bellomo R, Homel P, et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. *Lancet.* 2000;356[9223]:26–30.)

## PRESCRIBED VERSUS DELIVERED CONTINUOUS RENAL REPLACEMENT THERAPY DOSE

Based on the series of randomized controlled trials (especially ATN and RENAL), the Kidney Disease: Improving Global Outcomes (KDIGO) AKI Clinical Practice Guideline recommends delivery of an effluent dose of 20 to 25 mL/kg/hr in CRRT.[14] However, this consensus statement includes a caveat that the prescribed dose should be higher than the delivered dose target in most instances. Indeed, available data suggest shortfalls in the delivery of the prescribed CRRT dose are common even in the setting of clinical trials and may be substantial in clinical practice. For the sake of clarity, the actual failure of the delivered effluent dose to match the prescribed effluent dose should be differentiated from dimiunitions in the effective dose (i.e., solute clearance). Predilution is primarily responsible for the latter, and some trials employing CRRT in this mode have made reference to this phenomenon. In the series of randomized CRRT dose/outcome trials, greater than 80% of the prescribed dose was delivered on average.[13,29–34] However, in some trials, interventions not typically made in general clinical practice occurred to preserve dose delivery. For example, when shortfalls in treatment delivery occurred on a particular day in the Ronco trial, compensatory dose increases could be made the following day.[13] Furthermore, filter changes occurred routinely every 24 hours according to institutional practice.

Other trials performed outside the relatively controlled environment of a randomized controlled trial have been less sanguine. In an early study, Venkataraman et al. retrospectively evaluated 115 CRRT patients treated during 1999 and 2000.[35] The mean treatment duration was only 16.1±3.5 (mean±SD) hours per day, leading to a mean effluent flow rate (averaged over 24 hours) of 1.4±0.3 L/hr. The mean prescribed and delivered CRRT doses were 24.5±6.7 and 16.6±5.4 mL/Kg/hr, respectively ($p < .000001$), equating to delivery of only 68% of the prescribed dose. Clotting of the extracorporeal circuit was the most common cause of downtime.

In the DO-RE-MI trial, approximately 80% of patients received only CRRT in the trial, and significant variability in delivered dose was observed among patients and even within the same patient on different days.[36] (In the CRRT group, data from 81 patients having at least one treatment interruption of 18 hours or more notably were not included in the analysis.) Intensive CRRT was defined by a prescribed dose of at least 35 mL/kg/hr, but only 22% of patients fell in this category. Although the median prescribed dose was 34.3 mL/kg/hr, the median delivered dose was approximately 20% less (27.1 mL/kg/hr), with circuit clotting contributing to 74% of downtime incidents.

Claure et al. performed a thorough analysis of prescribed versus delivered CRRT dose in 52 patients treated with predilution CVVHDF.[37] Despite the use of citrate anticoagulation in all patients, filter clotting was the single leading cause of therapy downtime, although causes unrelated to the extracorporeal circuit were more common overall. Delivered (urea-based) dose, estimated from standard CRRT clearance equations (accounting for predilution), was only 73% of the prescribed effluent dose. Thus treatment downtime and predilution combined to produce a 27% decline in the urea clearance actually delivered on average, relative to the theoretical clearance based only on the prescribed effluent volume.

## MODALITY CONSIDERATIONS FOR CONTINUOUS RENAL REPLACEMENT THERAPY DOSE

Although a 1:1 relationship exists between effluent rate and urea clearance when postdilution CVVH is performed properly, this is not necessarily the case for other CRRT modalities.[38] For predilution CVVH, Clark et al. evaluated the interrelationship between blood flow rate and replacement fluid rate in the achievement of urea clearances equivalent to 35 mL/kg/hr.[39] For this modality, predilution precludes the possibility of a 1:1 relationship between effluent rate and urea clearance, and therapy prescription should aim to achieve desired depuration with acceptable volumes of replacement fluid. At low blood flow rates (<150 mL/min), the relatively high replacement fluid rates required to provide effluent doses frequently desired in clinical practice (25 mL/kg/hr or more) result in a substantial reduction of blood urea concentration resulting from predilution. This dilution effect reduces urea clearance by the filter in a potential "vicious cycle," which can be interrupted only by an increase in blood flow rate. In most patients, a blood flow rate of at least 200 mL/min is needed for efficient operation of predilution CVVH. (The same is true for postdilution CVVH to avoid excessive hemoconcentration.) When traditional CRRT blood flow rates in the range of 125 to 150 mL/min are used, Troyanov et al. have demonstrated the decrease in solute clearances for predilution (relative to postdilution) CVVH can be as high as 30% to 40%.[40]

With consideration of other CRRT modalities, the prescription parameters most significantly influencing small solute clearance in CVVHD are filter surface area and dialysate flow rate.[41,42] For optimal functioning of CVVHD with respect to urea clearance, saturation of the effluent dialysate is necessary, implying equivalence between the incoming blood and effluent urea nitrogen concentrations. For effluent doses of 20 mL/kg/hr and beyond, filters having membrane surface areas of at least 1.0 $m^2$ are required to achieve this saturation. Finally, CVVHDF involves consideration of all of the above factors, especially when prescribed in the predilution mode.[43]

## RECONCILING EFFLUENT-BASED AND CLEARANCE-BASED DOSE

Effluent-based dosing is the foundation for prescription and delivery of CRRT because of the strength of the underlying evidence base. However, as emphasized in this review, substantial differences between effluent dose and actual solute clearance may exist under many CRRT operating conditions. Providing clinicians with an additional parameter that clarifies these differences is especially timely in light of the most recent consensus conference of the Acute Dialysis Quality Initiative (ADQI). The conference highlighted the need for adapting continuous therapies to conform to the era of personalized medicine, specifically calling for the application of "precision CRRT" in clinical practice.[44] In the opinion of the authors, supplementation of evidence-based effluent dosing with a CRRT-specific standard Kt/V is one step in this direction.

At the initiation of CRRT, a hypothetical patient of target weight 80 kg (W) can be used to define standard Kt/V

in relation to effluent-based dosing. The following assumptions apply:

1. Urea volume of distribution at CRRT initiation = 0.65 × W = 52 L (corresponding to 10% fluid accumulation at that point)
2. Average V during the course of CRRT = 48 L (assuming 100% correction of fluid overload)[45,46]
3. 24-hour operation of CRRT with delivered CRRT dose of 25 mL/kg/hr

Based on these values, standard (daily) Kt/V can be calculated, with the assumption that a 1:1 relationship between effluent volume and urea clearance exists over a 24-hour period.

$$\text{Kt/V} = (25\ \text{mL/kg/hr}) \times (80\ \text{kg}) \times (24\ \text{hrs}) \cdot (1\ \text{L}/1000\ \text{mL})/48\ \text{L} = 1.0$$

As discussed previously, the major factors causing divergence between the effluent-based dose and this daily Kt/V parameter are fluid overload, impaired filter performance, treatment downtime during the course of a particular day, and predilution. Estimates for urea distribution volume in AKI have varied significantly in previous trials and the above Kt/V calculation, developed for a typical CRRT population, attempts to bracket the range that has been reported in the literature. Based on a study using stable isotopes to estimate distribution volume, Ikizler et al. reported values substantially above those based on conventional total body water estimates.[26] For purposes of dosing RRT, they recommended a 20% increase in V relative to these conventional estimates; the 65% initial estimate in the above standard Kt/V calculation is very much in line with this recommendation.

Likewise, clinicians should be vigilant for potential signs of impaired filter performance, leading to reduced solute clearance. Effluent urea nitrogen concentrations that are less than expected and increasing circuit pressures suggest this possibility. Finally, in Fig. 170.3, estimates are provided for the degree to which delivered Kt/V may be reduced for varying levels of treatment downtime (in hours per day). These dosage adjustments are consistent with the concept of "dynamic CRRT," in which the treatment is adapted to the constantly changing clinical status of a critically ill AKI patient.[47] This concept also allows for the standard Kt/V target to be modified in a given patient, depending on the clinical course (e.g, a hypercatabolic, septic patient in need of higher dose to control azotemia).

Standard Kt/V was proposed first by Gotch to allow for comparisons of continuous and intermittent therapies in chronic dialysis; it incorporates two fundamental tenets.[20] First, despite having lower instantaneous clearance rates, continuous therapies in general provide more effective small solute removal than intermittent therapies (on a mL/min of clearance basis). Second, Kt/V values from individual treatments in an intermittent schedule cannot be added together simply for comparison with a therapy provided continuously during the same period. On the other hand, because of the continuous nature of CRRT, simple addition of daily Kt/V values can produce a representative weekly standard Kt/V. The current calculation of a standard daily Kt/V of 1.0, corresponding to a delivered CRRT dose of 25 mL/kg/hr, is aligned precisely with the original standard Kt/V description, which used another continuous therapy (PD) as the reference.[20] However, it is worthwhile emphasizing the recommended target for delivered *weekly* Kt/V in AKI patients treated with PD is only 3.5,[48] demonstrating the substantial difference in small solute removal capability between this modality and CRRT.

Although effluent-based and solute clearance-based dosing are important considerations in the overall adequacy of CRRT provided to a given patient, many other factors are important. Indeed, fluid management, electrolyte/acid-base control, nutrition, and drug dosing are but a few of the other challenges that require thoughtful consideration by the clinical team.[49] Only by addressing the entire spectrum of the patient's clinical needs can sustained improvements be achieved for this population.[50]

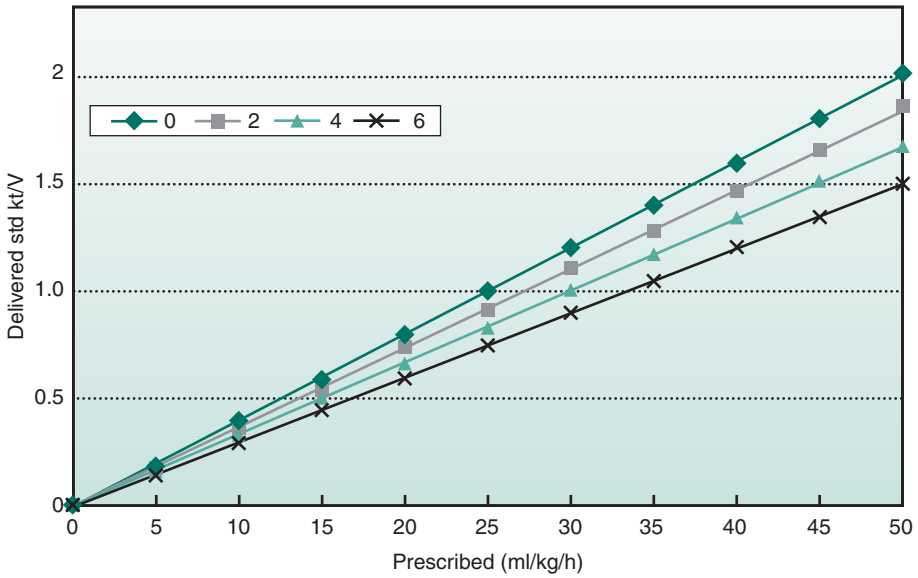


**FIGURE 170.3** Estimates for the decrement in delivered Kt/V resulting from treatment downtime during continuous renal replacement therapy. The influence of downtime ranging from 0 to 6 hours per day is shown. (Reprinted from Bagshaw SM, Chakravarthi MR, Ricci Z, et al. on behalf of the ADQI Consensus Group. Precision continuous renal replacement therapy: Solute control in continuous renal replacement therapy. *Blood Purif.* 2016;42[3]:238–247.)

## SUMMARY

A comprehensive review of RRT quantification in AKI has been presented, with a focus on urea kinetics. Previous work in applying UKM to AKI has provided a good foundation for the development of a unified parameter, the standard Kt/V, for use in conjunction with effluent-based dosing in CRRT. This parameter is certainly not designed to supplant effluent-based dosing but, instead, to complement it. Future advances in clinical practice and technology, such as incorporation of effluent urea nitrogen measurements either through clinical protocols[28] or CRRT machines equipped with online sensors,[51] can improve upon this approach. In the meantime, hopefully this new parameter can solidify clinicians' understanding of CRRT dosing and improve the care of critically ill AKI patients treated with this modality.

### Key Points

1. Extrapolation of end-stage renal disease–based dialysis quantification techniques to acute kidney injury (AKI) requires an understanding of the clinical differences between the two patient populations.
2. Based on level 1 evidence, effluent-based continuous renal replacement therapy (CRRT) dosing is accepted as the gold standard in AKI clinical practice.
3. However, the studies comprising the CRRT dose/outcome evidence base employed different modalities in which similar effluent doses potentially were associated with variable solute clearances.
4. Standard Kt/V is proposed as a way to help clinicians reconcile the discrepancy between effluent-based and clearance-based dosing of CRRT.

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

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