CHAPTER 145

# The Concept of Renal Replacement Therapy Dose and Efficiency

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**OBJECTIVES**

This chapter will:

1. Describe the main dimensions of renal replacement therapy (RRT) dose: efficiency, intensity, and clinical efficacy.
2. Describe the most important studies addressing the impact of RRT dose on the survival of critically ill patients.
3. Describe some practical concepts guiding the clinician to RRT prescription.

The conventional view of renal replacement therapy (RRT) dose is that it is a measure of the quantity of blood purification achieved by means of extracorporeal techniques. However, this broad concept seems difficult to measure and quantify. The *operational* view of RRT dose is that it is a measure of the quantity of a representative marker solute that is removed from a patient by dialysis. This marker solute is considered to be reasonably representative of similar solutes that require removal for blood purification to be considered adequate. This premise has several major flaws. The marker solute cannot and does not represent all the solutes that accumulate in renal failure. Its kinetics and volume of distribution are also different from those of the solutes of interest. Finally, its removal during RRT is not representative of the removal of other solutes. This is true for end-stage renal disease (ESRD) and acute kidney injury (AKI).

However, a significant body of data in the ESRD literature[1–6] suggests that, despite these major limitations, single solute marker assessment of dialysis dose appears to have a clinically meaningful relationship to patient outcome and therefore to clinical utility. Nevertheless, the Hemodialysis (HEMO) Study, which examined the effect of intermittent hemodialysis (IHD) doses, enforced the concept that "less dialysis is worse" but failed to confirm the intuition that "more dialysis is better."[6] Therefore this premise seems useful in ESRD and is accepted to be potentially useful in AKI for operational purposes.

Therefore the amount (measure) of delivered dose of RRT can be described by various terms: efficiency, intensity, and clinical efficacy. Each of these is discussed in the following sections.

## EFFICIENCY, INTENSITY, EFFICACY: KT/V

*Efficiency* of RRT is represented by the concept of clearance (K)—the volume of blood cleared of a given solute over a given time. K does not reflect the overall solute removal rate (mass transfer); rather, its value is normalized by the serum concentration. Even when K remains stable over time, the removal rate will vary if the blood levels of the reference molecule change. K depends on solute molecular size, transport modality (diffusion or convection), and circuit operational characteristics such as blood flow rate (Qb), dialysate flow rate (Qd), ultrafiltration rate (Qf), and hemodialyzer type and size. K can be used to compare the treatment dose during each dialysis session, but it cannot be employed as an absolute dose measure to compare treatments with different time schedules. For example, K is typically higher in IHD than in continuous RRT (CRRT) or sustained low-efficiency daily dialysis (SLEDD). This is not surprising, because K represents only the instantaneous efficiency of the system. However, mass removal may be greater during SLEDD or CRRT. For this reason, information about the time span during which K is delivered is fundamental to describe the effective dose of dialysis.

*Intensity* of RRT can be defined by the product "clearance × time" (Kt). Kt is more useful than K for comparing different RRTs. A further step in assessing dose must include the frequency of the Kt application over a particular period (e.g., 1 week). This additional dimension is given by the product of intensity × frequency (Kt × treatment days/week, or Kt × d/w). Kt × d/w is superior to Kt because it offers information beyond a single treatment, and patients with AKI typically require more than one treatment. This concept of Kt × d/w offers the possibility of comparing disparate treatment schedules (e.g., intermittent, alternate-day, daily, continuous). However, it does not take into account the size of the pool of solute that must be cleared. This requires the dimension of efficacy.

*Efficacy* of RRT represents the effective solute removal outcome resulting from the administration of a given treatment to a given patient. It can be described by the fractional clearance of a given solute (Kt/V), where V is the volume of distribution of the marker molecule in the body. Kt/V is an established marker of adequacy of dialysis for small solutes correlating with medium-term (several years) survival in patients undergoing chronic hemodialysis.[6] Urea is used typically as a marker molecule in ESRD to guide treatment dose, and a $Kt/V_{UREA}$ of at least 1.2 currently is recommended.

As an example, we can consider the case of a 70-kg patient who is treated for 20 hr/day with a postfilter hemofiltration of 2.8 L/hr at a zero balance. His $K_{UREA}$ will be 47 mL/min (2.8 L/hr = 2800 mL/60 min), because we know that during postfilter hemofiltration the ultrafiltered plasma water will drag all urea across the membrane, making its clearance identical to the ultrafiltration flow. His treatment time (t) will be 1200 minutes (60 minutes for 20 hours). His urea volume of distribution will be approximately 42,000 mL (60% of 70 kg), roughly equal to total body water. Simplifying this patient's $Kt/V_{UREA}$, we will have $47 \times 1200/42000 = 1.34$.

However, $Kt/V_{UREA}$ application in patients with AKI has not been validated rigorously. In fact, although the application of Kt/V to the assessment of dose in AKI is theoretically intriguing, many concerns have been raised because problems intrinsic to AKI can hinder the accuracy and meaning of such dose measurement. These problems include lack of a metabolic steady state, uncertainty about the volume of distribution of urea ($V_{UREA}$), a high protein

catabolic rate, labile fluid volumes, and possible residual renal function, which changes dynamically during the course of treatment. To evaluate $V_{UREA}$ in patients with AKI, Himmelfarb et al.[7] undertook a systematic study in a cohort of 28 patients with AKI. They determined $V_{UREA}$ by various approaches to anthropometric measurements (Watson, 42.5 ± 7.0 L; Hume-Weyer, 43.6 ± 7.1 L; Chertow, 46.8 ± 8.1 L) and found that they yielded significantly lower measures than $V_{UREA}$ determined by physiologic formulas or by bioimpedance (51.1 ± 11.6 L and 51.1 ± 13.3 L, respectively). Finally, all measures of $V_{UREA}$ by blood-based kinetics exceeded measurements by any other method (7% to 50% difference). The investigators inevitably concluded that estimates of $V_{UREA}$ cannot be used reliably in patients with AKI.[7]

Furthermore, delivery of the prescribed dose in AKI can be limited by technical problems (e.g., access recirculation, poor blood flows with temporary venous catheters, membrane clotting, and machine malfunction) and by clinical issues (hypotension and vasopressor requirements that can be responsible for solute dysequilibrium within tissues and organs). These aspects are particularly evident during IHD, less so during SLEDD, and even less so during CRRT. This difference occurs because, after some days of CRRT, patients' urea levels approach a real steady state: Because the therapy is applied continuously, the effect of compartmentalization of solutes is minimized; from a theoretical point of view, purification of total body water can be considered uniform in all organs, and single-pool kinetics can be applied (spKt/V).

Despite all the uncertainty surrounding its meaning and the gross shortcomings related to its accuracy in patients with AKI, the idea that there may be an optimal dose of solute removal continues to have a powerful hold in the literature. This is likely due to evidence from ESRD, in which a minimum Kt/V of 1.2 thrice weekly is indicated as standard.[6] However, the benefits of greater Kt/V accrue over years of therapy, whereas in AKI any difference in dose would apply for days to weeks. The view that it would still be sufficient to alter clinical outcomes remains somewhat optimistic.

## HISTORY OF CLINICAL TRIALS ON CONTINUOUS RENAL REPLACEMENT THERAPY DOSE

The concept of prescription dose is a powerful tool to help clinicians at the bedside and to at least avoid undertreatment. Nevertheless, this aspect may be inadequately addressed and monitored by intensive care clinicians. During the third International Course on Critical Care Nephrology held in Vicenza, Italy, a survey on various aspects of AKI, including treatment prescription, was conducted among about 550 participants (equally distributed between nephrologists and intensivists) from about 500 different centers.[8] More than one third of responders declared that they did not prescribe any specific RRT dose for AKI patients, and 75% did not monitor RRT delivered dose. In fact, although a clear understanding of the adequate dose of RRT has not yet been achieved, it is also true that, as for antibiotic blood levels during severe infections, adequate prescription should be followed by adequate administration.

The first randomized controlled trial of CRRT dose showed that postdilution CVVH at 35 or 45 mL/kg/hr was associated with improved survival, compared with 20 mL/kg/hr, in 425 critically ill patients with AKI.[9] Applying Kt/V dose assessment methodology to CVVH at a dose of 35 mL/kg/hr in a 70-kg patient treated for 24 hours, a treatment day would be equivalent to a Kt/V of 1.4 also applied daily. Despite uncertainty regarding the calculation of $V_{UREA}$, CVVH at 35 mL/kg/hr would still provide an effective *daily* delivery of 1.2, even if $V_{UREA}$ were underestimated by 20%. However, many technical and/or clinical problems can make it difficult, in routine practice, to apply such strict protocols by pure postdilution hemofiltration. They include filter clotting; high filtration fraction in the presence of access dysfunction and fluctuations in blood flow; and circuit down-time during surgery, radiologic procedures, and filter changes. Equally important are the observations that this study was conducted over 6 years in a single center, that uremic control was not reported, that the incidence of sepsis was low compared with that in the typical populations reported to develop AKI in the world, and that its final outcome was not the accepted 28-day or 90-day mortality typically used in ICU trials. Therefore the external validity of this study remains untested.

Another prospective, randomized trial, conducted by Bouman et al.,[10] assigned patients to three intensity groups: early high-volume hemofiltration (72 to 96 L/24 hr), early low-volume hemofiltration (24 to 36 L/24 hr), and late low-volume hemofiltration (24 to 36 L/24 hr). No difference was found in terms of renal recovery or 28-day mortality. Unfortunately, prescribed doses were not standardized by weight, making the potential variability in RRT dose large. Furthermore, the number of patients was small, making the study insufficiently powered, and, again, the incidence of sepsis was low compared with that in the typical populations reported to develop AKI in the world. A recent randomized trial from a Swiss group[11] enrolled 371 patients with AKI, assigning 102 to CVVH and 104 to continuous venovenous hemodiafiltration (CVVHDF), and prescribed 25 mL/kg/hr ultrafiltration in the CVVH group and 24 mL/kg/hr in the CVVHDF group; patients receiving CVVHDF were prescribed an adjunctive mean dialysis dose of 18 mL/kg/hr. The CVVHDF patients had significantly higher mean urea and creatinine reduction ratios 48 hours after the initiation of continuous RRT than did the CVVH patients (50% vs. 40%, $p < .009$, and 46% vs. 38%, $p < .014$, respectively). Survival rates at 28 days and 90 days were higher with CVVHDF than with CVVH. Like previous trials, this study was underpowered; furthermore, it confounded the effects of dose and technique by adding dialysis to filtration.

Nevertheless, pooled results from all the studies described here indicate a very large effect on survival in favor of augmented dosing, with an odds ratio of 1.95.[12] Although these data may still not be definitive, the best evidence supports that 35 mL/kg/hr for CVVH, CVVHDF, or daily IHD should be the comparator of any further clinical trial.

Recently, two multicenter trials were devised, one in the United States and the other in Australia. These efforts ultimately became the Acute Renal Failure Trial Network (ATN) study[13] and the Randomised Evaluation of Normal versus Augmented Level of RRT (RENAL) study.[14] RENAL and the ATN study were designed to compare "normal" or "less-intensive" renal support with an "augmented" or "intensive" therapy: in particular, RENAL compared 25 mL/kg/hr CVVHDF with 40 mL/kg/hr, and the ATN study compared 20 mL/kg/hr CVVHDF or thrice-weekly intermittent dialysis with 35 mL/kg/hr CVVHDF or daily intermittent dialysis. Both studies showed no benefit in outcomes with increases in intensity of RRT dose: mortality ranged between 40% and 50% in all arms and, apparently, no secondary outcome (including duration of mechanical ventilation, length of hospital stay, recovery of renal function) was improved by augmented dialytic dose. Both trials were rigorous and greatly minimized the

discrepancy between prescribed dose and delivered dose. As shown by the DOse REsponse Multicentre International (DoReMi) Collaborative Initiative,[15] the difference between the prescribed dose and delivered dose of CRRT is affected by therapy downtime (the length of time that CRRT is not running during a 24-hour period), clotting of the circuit (the cause of the majority of unexpected treatment stops), and vascular access problems (which push clinicians to modify therapy settings and prescription errors). Therefore when doses of 20 to 25 mL/kg/hr are prescribed during CRRT in clinical practice, consistent with those in the RENAL and ATN studies, the possibility that the delivered dialysis dose may be considerably lower than the prescribed dose should be considered. Therefore clinicians may need to overprescribe RRT with a 25% safety margin, targeting 30 to 35 mL/kg/hr to achieve an "adequate" delivered dose.

After such milestone trials however, the Kidney Disease: Improving Global Outcome (KDIGO) clinical practice guidelines (CPGs) for AKI have recommended a default CRRT dose prescription (for urea clearance) of 20 to 25 mL/kg/hr effluent flow rate, regardless of the chosen modality or proportion of replacement fluid given pre- or postfilter.[16] Recent data have shown that CRRT dose lower than recommended by the KDIGO CPGs default dose can achieve adequate control of serum urea concentrations.[17] This study implies that providers can adjust or adapt the default CRRT dose based on the patient's clinical condition and need. Effluent flow rate can be increased or decreased in response to changes in clinical, physiologic, and/or metabolic status (dynamic prescription). Importantly, there are currently no data to support the concept that dynamic prescription improves surrogate or patient-centered outcomes. However, the rationale for dynamic prescription integrating audit and feedback from routine quality measures theoretically could better optimize solute control and quality of delivered CRRT.

These observations underline the recommendation that RRT prescriptions for AKI patients in the ICU should be monitored closely if one wishes to ensure adequate delivery of prescribed dose. The use of a software called Adequacy Calculator for AKI was tested recently. This is a Microsoft Excel-based program[18] that calculates urea clearance and estimates fractional clearance and $Kt/V_{UREA}$ for all RRT modalities. The software allowed to strictly monitor CRRT treatments during the study period, and an average 10.7% ($p < .05$) reduction of therapy delivery was found, compared with the prescribed dose.[19] This delivery reduction sometimes was due to calculator overestimation and more often to an operative treatment time that was shorter than prescribed (because CRRT is not administered during bag substitution, troubleshooting of alarms, and filter changes). In the CVVH dose trial,[9] only patients who achieved more than 85% of the prescribed dose were included: To obtain this goal, compensation for interruptions in treatment because of ICU procedures was made by increasing effluent flow rates in the subsequent hours. Furthermore, an adequate monitoring of delivered may allow the clinicians to reassess prescription (i.e., an a daily basis) to modify it based on changing critically ill patients clinical conditions.

## FROM BENCH TO BEDSIDE: THE CLINICAL MEANING OF DOSE

The initial hypothesis that "more dose is better" should be reinterpreted cautiously in the light of novel KDIGO recommendations.

The major shortcoming of the traditional solute marker–based approach to dialysis dose in AKI lies well beyond any methodologic critique of single-solute kinetics–based prescriptions. In patients with AKI, the majority of whom are in intensive care, a restrictive (solute-based only) concept of dialysis dose seems grossly inappropriate. In these patients, the therapeutic needs that can be or must be affected by the "dose" of RRT are more than the simple control of small solutes as represented by urea. They include control of acid-base, tonicity, potassium, magnesium, calcium, phosphate, intravascular volume, extravascular volume, and temperature and avoidance of unwanted side effects associated with the delivery of solute control.

In the critically ill patient, it is much more important (e.g., in the setting of coagulopathic bleeding after cardiac surgery) for 10 units of fresh-frozen plasma, 10 units of cryoprecipitate, and 10 units of platelets to be administered rapidly without inducing fluid overload (because 1 to 1.5 L of ultrafiltrate is removed in 1 hour) than for the Kt/V to be of any particular value at all. The dose of RRT is about prophylactic volume control. In a patient with right ventricular failure, AKI, and acute respiratory distress syndrome who is receiving lung-protective ventilation with permissive hypercapnia and who has acidemia, inducing a further life-threatening deterioration in pulmonary vascular resistance, the "dose" component of RRT that matters immediately is acid-base control and normalization of pH 24 hr/day. The Kt/V (or any other solute-centric concept of dose) is almost just a by-product of such dose delivery. In a young man with trauma, rhabdomyolysis, and rapidly rising serum potassium already at 7 mmol/L, dialysis dose, to begin with, is all about controlling kalemia. In a patient with fulminant liver failure, AKI, sepsis, and cerebral edema who is awaiting urgent liver transplantation and whose cerebral edema is worsening because of fever, RRT dose is all about lowering the temperature without any tonicity shifts that may increase intracranial pressure. Finally, in a patient with pulmonary edema after an ischemic ventricular septal defect requiring emergency surgery, AKI, ischemic hepatitis, and the need for inotropic and intraaortic balloon counterpulsation support, RRT dose is intended to remove fluid gently and safely so that the extravascular volume falls while the intravascular volume remains optimal. Solute removal is just a by-product of fluid control.

These aspects of dose must be considered explicitly when discussing the dose of RRT in AKI, because it is likely that patients die more often from incorrect "dose" delivery of this kind than from incorrect dose delivery of the Kt/V kind. Although each and every aspect of this broader understanding of dose is difficult to measure, clinically relevant assessment of dose in critically ill patients with AKI should include all dimensions of dosing, not just one dimension picked because of a similarity with ESRD: there is no evidence in the acute field that such solute control data are more relevant to clinical outcomes than volume control or acid-base control or tonicity control.

## FROM BENCH TO BEDSIDE: THE PRESCRIPTION

During RRT, clearance depends on circuit blood flow (Qb), ultrafiltration rate (Qf) or dialysate flow rate (Qd), the molecular weights of the solutes, and hemodialyzer type and size. Qb, as a variable in delivering RRT dose, is dependent primarily on vascular access and operational characteristics of machines used in the clinical setting. Qf

is strictly linked to Qb, during convective techniques, by filtration fraction. Filtration fraction does not limit Qd, but when the Qd/Qb ratio exceeds 0.3, it can be estimated that dialysate will not be completely saturated by blood-diffusing solutes. The search for specific toxins to be cleared has not been successful despite years of research, and urea and creatinine generally are used as reference solutes to measure renal replacement clearance for renal failure. Although the available evidence does not allow direct correlation of the degree of uremia with outcome in chronic renal disease, in the absence of a specific solute, clearances of urea and creatinine blood levels are used to guide treatment dose.

During ultrafiltration, the driving pressure jams solutes, such as urea and creatinine, against the membrane and into the pores, depending on the membrane sieving coefficient (SC) for that molecule. SC expresses a dimensionless value and is estimated by the ratio of the concentration of the solutes in the filtrate divided by that in the plasma water or blood. An SC of 1.0, as is the case for urea and creatinine, demonstrates complete permeability, and a value of 0 reflects complete rejection. Molecular size larger than approximately 12 kDa and filter porosity are the major determinants of SC.

The K during convection is measured by the product of Qf × SC. Therefore in contrast to diffusion, there is a linear relationship between K and Qf, the SC being the changing variable for different solutes. During diffusion, the linear relationship is lost when Qd exceeds about one third of the Qb. As a rough estimate, we can consider that, during continuous slow-efficiency treatments, the RRT dose is a direct expression of Qf–Qd, independently of which solute must be removed from the blood. Continuous treatment is suggested to deliver a urea clearance of at least 2 L/hr, with the clinical evidence that 20 to 25 mL/kg/hr may be the best prescription (i.e., about 1.4–1.8 L/hr in a 70-kg patient).[14] Other authors have suggested a prescription based on patient requirements, according to the urea generation rate and the catabolic state of the individual patient. However, it has been shown that, during continuous therapy, a clearance rate of less than 2 L/hr almost definitely is insufficient in an adult critically ill patient. For more exact estimations, simple computations have been shown to adequately estimate clearance.[19,20]

Tables 145.1 and 145.2 show an algorithm and an example that could be followed each time an RRT prescription is indicated.

## TABLE 145.1

**Algorithm for Prescription of Renal Replacement Therapy**

| CLINICAL VARIABLES | OPERATIONAL VARIABLES | SETTING |
|---|---|---|
| Fluid balance | Net ultrafiltration | Continuous management of negative balance (100–300 mL/hr) is preferred in hemodynamically unstable patients. Complete monitoring (arterial pressure, heart rate, ECG, arterial oxygen saturation) is recommended. |
| Adequacy and dose | Clearance/modality | Prescribe 1400–1700 mL/hr K (or 20–25 mL/kg/hr) for CRRT; consider first CVVHDF. If IHD is selected, a daily 4-hr prescription is recommended. Prescribe a Kt/V > 1.2. |
| Acid-base balance | Solution buffer | Bicarbonate-buffered solutions are preferable to lactate-buffered solutions in cases of lactic acidosis and/or hepatic failure. |
| Electrolyte balance | Dialysate/ replacement fluid | Consider solutions without $K^+$ in cases of severe hyperkalemia. Manage accurately $MgPO_4$. |
| Timing | Schedule | Early and intense RRT is suggested. |
| Protocol | Staff/machine | Well-trained staff routinely should use RRT monitors according to predefined institutional protocols. |

*CRRT,* Continuous renal replacement therapy; *CVVHDF,* continuous venovenous hemodiafiltration; *ECG,* electrocardiogram; *IHD,* intermittent hemodialysis.

## TABLE 145.2

**Schematic Example of a Possible Prescription for Continuous Treatment in a 70-kg Adult Patient**[a]

| TREATMENT MODALITY | ESTIMATED UREA CLEARANCE | NOTES | VALUE OF Q REQUIRED TO OBTAIN 35 mL/kg/hr | VALUE OF Q REQUIRED TO OBTAIN A Kt/V OF 1 |
|---|---|---|---|---|
| CVVH Postdilution | $K_{CALC}$ = Qrep | Always keep filtration fraction < 20% (Qb must be 5 × Qrep) | Qrep = 41 mL/min (2450 mL/hr) | Qrep = 29 mL/min (1750 mL/hr) |
| CVVH Predilution | $K_{CALC}$ = Quf/[1 + (Qrep/Qb)] | Filtration fraction computation changes (keep <20%) | For a Qb of 200 mL/min, Qrep = 53 mL/min (3200 mL/hr) | For a Qb of 200 mL/min, Qrep = 35 mL/min (2100 mL/hr) |
| CVVHD | $K_{CALC}$ = Qd | Keep Qb at least 3 × Qd | Qd = 41 mL/min (2450 mL/hr) | Qd = 29 mL/min (1750 mL/hr) |
| CVVHDF Postdilution (50% convective and diffusive clearance) | $K_{CALC}$ = Qrep + Qd | Consider all of the above notes | Qrep = 20 mL/min + Qd = 21 mL/min | Qrep = 14 mL/min replacement solution + Qd = 15 mL/min |

[a]Assuming a 70-kg patient ($V_{UREA}$ = 42 L) during an ideal session of 24 hours (t = 1440 minutes), with net ultrafiltration (patient fluid loss) considered to be zero in $K_{CALC}$ for simplicity. V = BW × 0.6. $Kt/V_{CALC} = K_{CALC} \times t$. A clearance rate of 35 mL/kg/hr roughly corresponds to a Kt/V of 1.4; a Kt/V of 1 approximately corresponds to 25 mL/kg/hr. Postdilution filtration fraction = Qrep/Qb × 100; Predilution filtration fraction = Qrep/(Qb + Qrep) × 100. *BW,* Body weight; *CVVH,* continuous venovenous hemofiltration; *CVVHD,* continuous venovenous hemodialysis; *CVVHDF,* continuous venovenous hemodiafiltration; $K_{CALC}$, estimated urea clearance (mL/min); $Kt/V_{CALC}$, estimated fractional clearance; *Qb,* blood flow rate; *Qd,* dialysate solution flow rate; *Qnet,* patient's net fluid loss; *Qrep,* replacement solution flow rate; *Quf,* ultrafiltration flow rate (Quf = Qrep + Qnet); *t,* prescribed treatment time (min); $V_{UREA}$, urea volume of distribution (mL).

## Key Points

1. The best evidence supports a continuous renal replacement therapy dose of at least 25 mL/kg/hr of effluent flow rate, for venovenous hemofiltration, hemodialysis, or hemodiafiltration.
2. A standard dose prescription and strict control of delivered dose is recommended to ensure adequate delivery of the prescribed dose.
3. Prescription and delivery should be reassessed frequently to meet the changing patients' needs.

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