Dose of Dialysis in Acute Renal Failure

Zaccaria Ricci,* Rinaldo Bellomo,† and Claudio Ronco‡

*Department of Anesthesiology and Intensive Care, University of Rome “La Sapienza,” Rome, Italy; †Department of Intensive Care, Austin Hospital, Melbourne, Australia; and ‡Department of Nephrology, Dialysis and Transplantation, San Bortolo Hospital, Vicenza, Italy


One to 25% of critically ill patients who are admitted to intensive care unit (ICU) develop acute renal failure (ARF), depending on the definition used (1). ARF has a significant impact on morbidity and represents an independent risk factor for mortality. The mortality rate for severe ARF exceeded 50% over the past three decades (2–6). The wide range of incidence in the literature depends on the lack of a reliable definition of the syndrome. On the basis of the most recent RIFLE classification (an acronym indicating Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and ESRD) (7), ARF can be stratified for severity, and different outcomes depend on the degree of severity as assessed by the extent of GFR loss. Current management depends on the level of severity and includes optimization of hemodynamics and fluid status, avoidance of further renal insults, optimization of nutrition, and, when appropriate, the application of renal replacement therapy (RRT).

Indications for RRT generally are clear for patients with the most severe of conditions (e.g., anuria with severe hyperkalemia in the setting of septic shock), whereas they can be a matter of controversy and require individualized assessment in less severe situations (e.g., polyuric ARF in a patient who has previous chronic renal dysfunction and is otherwise well 2 d after cardiac surgery). Optimal strategies to improve patient outcome in ARF may include optimization of delivered RRT dose (8–15). This review focuses on RRT dose and its measurement and prescription in the ICU and on the current evidence concerning the relationship between RRT dose and outcome.

What Is RRT Dose, and How Is It Measured?

The conventional view of RRT dose is that it is a measure of the quantity of blood purification achieved by means of extracorporeal techniques. As this broad concept is too difficult to measure and quantify, the operative view of RRT dose is that it is a measure of the quantity of a representative marker solute that is removed from a patient. This marker solute is taken to be reasonably representative of similar solutes, which require removal for blood purification to be considered adequate. This premise has several major flaws: the marker solute cannot and does not represent all of the solutes that accumulate in renal failure. Its kinetics and volume of distribution are also different from such solutes. Finally, its removal during RRT is not representative of the removal of other solutes. This is true for both end-stage renal failure and acute renal failure. However, a significant body of data in the end-stage renal failure literature (16–21) suggests that, despite all of the above major limitations, single solute marker assessment of dose of dialysis seems to have a clinically meaningful relationship with patient outcome and, therefore, clinical utility. Nevertheless, the HEMO study, examining the effect of intermittent hemodialysis (IHD) doses, failed to confirm the intuition that “more dialysis (than recommended by current guidelines) is better” (21). Thus, if this premise that seems useful in end-stage renal failure is accepted to be potentially useful in ARF for operative purposes, then the amount (measure) of delivered dose of RRT can be described by various terms: efficiency, intensity, frequency, and clinical efficacy. Each is discussed below.

Efficiency of RRT is represented by the concept of clearance (K), i.e., the volume of blood cleared of a given solute over a given time. K does not reflect the overall solute removal rate (mass transfer) but rather its value 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 (blood flow rate, dialysate flow rate, ultrafiltration rate, hemodialyzer type, and size). K can be normally used to compare the treatment dose during each dialysis session, but it cannot be used as an absolute dose measure to compare treatments with different time schedules. For example, K is typically higher in IHD than in continuous renal replacement therapy (CRRT) and 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, the 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 in comparing various RRT. A further step in assessing dose must include frequency of the Kt application over a particular period (e.g., 1 wk). This additional dimension is given by the product of intensity × fre-
quency (Kt × treatment days/wk = Kt d/w). Kt d/w is superior to Kt because it offers information beyond a single treatment: patients with ARF typically require more than one treatment. This concept of Kt d/w offers the possibility to compare disparate treatment schedules (intermittent, alternate day, daily, continuous). However, it does not take into account the size of the pool of solute that needs to be cleared. This requires the dimension of efficacy.

Efficacy of RRT represents the effective solute removal outcome that results from the administration of a given treatment to a given patient. It can be described by a 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 maker of adequacy of dialysis for small solute correlating with medium term (several years) survival in chronic hemodialysis patients (21). Urea is typically used as a marker molecule in end-stage kidney disease to guide treatment dose, and a single-pool Kt/V of at least 1.2 is currently recommended. However, Kt/V application to patients with ARF has not been validated rigorously. In fact, although the application of Kt/V to the assessment of dose in ARF is theoretically intriguing, many concerns have been raised because problems that are intrinsic to ARF can hinder accuracy and meaning of such dose measurement. These include the lack of a metabolic steady state, uncertainty about the VUREA, a high protein catabolic rate, labile fluid volumes, and possible residual renal function, which changes dynamically during the course of treatment. Furthermore, delivery of prescribed dose in ARF can be limited by technical problems such as access recirculation, poor blood flows with temporary venous catheters, membrane clotting, and machine malfunction. Furthermore, clinical issues such as hypotension and vasopressor requirements can be responsible for solute disequilibrium within tissues and organs.

These aspects are particularly evident during IHD, less so during SLEDD, and even less so during CRRT. This difference is the result of patients’ urea levels approaching a real steady state, after some days of CRRT. Access recirculation is also an issue of lesser impact during low efficiency continuous techniques. Finally, because the therapy is applied continuously, the effect of compartmentalization of solutes is minimized, and, from a theoretical point of view, single-pool kinetics can be applied (spKt/V) with a reasonable chance of approximating true solute behavior. To study the use of spKt/VUREA as a feasible method for the measurement of CRRT dose and to standardize disparate prescriptions, we recently tested a software called “Adequacy Calculator for ARF” (22). This is a simple Microsoft Excel-based program (23) that calculates urea clearance and estimates fractional clearance and Kt/VUREA for all RRT modalities. The calculator works on the assumption that urea sieving coefficient is 1 for convective therapies and that complete saturation of spent dialysate occurs during continuous dialysis. We found that, in a pilot evaluation of a small cohort of patients, the value of clearance predicted by the calculator correlated significantly to the value obtained from direct blood and dialysate determination during the first 24 treatment hours, irrespective of the renal replacement modality used (Figure 1). It must be acknowledged, nonetheless, that the final spKt/VUREA value was approximated considering VUREA as a function of total body weight (TBW) (see below).

Other dose measurement methods have been used in patients with end-stage renal failure but have not been investigated sufficiently in the setting of ARF. The time-averaged blood urea concentration (TACUREA) is the area under the saw tooth curve produced by intermittent dialysis sessions. TACUREA is a function of dialysis dose, but it also is of the urea generation rate (G) from protein intake. As such, it is not a good indicator of RRT dose per se. Emerging evidence from patients with end-stage renal failure suggests the importance of using equivalent renal clearance (EKRC). If G and TACUREA are known, then EKRC can be calculated as the ratio of total urea removal (equal to G at steady state) and TACUREA. A modification of this equation was described by Gotch and colleagues (24–26) as standardized Kt/V (stdKt/V), and it is calculated as the ratio of G and mean weekly urea pretreatment concentrations (MPC) normalized for VUREA. These formulas would allow comparisons among the dose measurement of disparate therapies and different frequencies of RRT. However, G, MPC, and TACUREA calculations are less immediate than K, t, and VUREA, which seem easier to be achieved without formal modeling. Furthermore, G likely is extremely variable from day to day in patients with ARF.

Finally, in patients who might receive only three or four sessions of IHD, the concept of MPC, which would require a parametric distribution of values, is simply statistically incorrect. VUREA is also dynamic and not as easily estimated using anthropometric calculations.

To evaluate VUREA in patients with ARF, Himmelfarb et al. (27) undertook a systematic study in a cohort of 28 patients with ARF. They found that VUREA estimated by double-pool Kt/V and by equilibrated Kt/V was statistically significantly higher than VUREA determined by single-pool Kt/V (67.9 ± 19.2 or 61.2 ± 13.6 versus 55.3 ± 12.9 L; difference of 16 and 11%, respectively). Furthermore, determination of TBW by different

Figure 1. Bland-Altman analysis illustrates correlation between urea clearance obtained by the two methods: Urea clearance calculated with the described software (KCALC) and urea clearance obtained by direct measure on prefiltre blood and effluent samples (KDEL). The average KCALC–KDEL value for each treatment is presented on the x axis; the difference between both methods is shown on the y axis. Parallel lines indicate 95% limit of agreement. Difference between KCALC and KDEL tends to increase for mean KCALC–KDEL values >60 ml/min. Adapted from (21).
approaches to anthropometric measurements (Watson, 42.5 ± 7.0 L; Hume-Weyer, 43.6 ± 7.1 L; Chertow, 46.8 ± 8.1 L) yielded significantly lower measures compared with TBW determined by physiologic formulas and by bioimpedance (51.1 ± 11.6 and 51.1 ± 13.3 L, respectively). Finally and more important, all measures of $V_{\text{UREA}}$ by blood-based kinetics exceeded TBW measurements by any method (7 to 50% difference). These investigators inevitably concluded that estimates of TBW cannot be used as a surrogate for $V_{\text{UREA}}$ in patients with ARF.

These observations highlight the gross inadequacies of applying end-stage renal failure paradigms to patients with ARF. They also indicate that, unlike in the field of chronic hemodialysis, only major changes in the application of dose (e.g., changing from second daily to daily dialysis while prescribing the same Kt/V) can be reasonably believed truly to deliver a “different” dose in the setting of ARF. More subtle adjustments such as prescribing a calculated Kt/V of 1 versus 1.2 can easily be criticized as being within the calculation error around each prescription and not necessarily representing a reliable change in dose delivery.

**Critique of the Traditional Concept of Dose**

The major shortcoming of the traditional solute marker–based approach to dialysis dose in ARF lies well beyond any methodologic critique of single-solute kinetics-based thinking similar to that offered in the preceding paragraphs. In patients with ARF, 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/need to be affected by the “dose” of RRT are many more than the simple control of small solutes as represented by urea. They include acid-base control, toxicity control, potassium control, magnesium control, calcium and phosphate control, intravascular volume control, extravascular volume control, temperature control, and the 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 h) than for Kt/V to be any particular value at all. Dose of RRT is about prophylactic volume control.

In a patient who has right ventricular failure, ARF, and acute respiratory distress syndrome (ARDS) 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 h/d. The Kt/V (or any other solutocentric 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 who has fulminant liver failure, ARF, sepsis, and cerebral edema, who is awaiting urgent liver transplantation, and whose cerebral edema, who is worsening because of fever, RRT dose is all about lowering the temperature without any tonicity shifts that might increase intracranial pressure.

Finally, in a patient with pulmonary edema after an ischemic ventricular septal defect that required emergency surgery, ARF, ischemic hepatitis, and the need for inotropic and intraaortic balloon counterpulsation support, RRT dose is all about removing 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 ARF, because it is likely that patients die more often from incorrect “dose” delivery of this kind than 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 ARF should include all dimensions of such dose, not one dimension picked because of a similarity with end-stage renal failure: 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.

**Prescribed Dose of Solute Removal: How Much?**

Despite all of the uncertainty surrounding its meaning and the gross shortcomings related to its accuracy in patients with ARF, the idea that there might be an optimal dose of solute removal continues to have a powerful hold in the literature. This is likely due to evidence from ESRD, for which a minimum Kt/V of 1.2 thrice weekly is indicated as standard (21). However, the benefits of greater Kt/V accrue over years of therapy. In ARF, 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.

Nonetheless, the hypothesis that higher doses of dialysis may be beneficial in critically ill patients with ARF must be considered by analogy and investigated. Several reports exist in the literature dealing with this issue.

Brause et al. (28), using continuous venovenous hemofiltration (CVVH), found that higher Kt/V values (0.8 versus 0.53) were correlated with improved uremic control and acid-base balance. This would be expected. No clinically important outcome was affected. Investigators from the Cleveland Clinic (9,10) retrospectively evaluated 844 patients who had ARF and required CRRT or IHD over a 7-yr period. They found that when patients were stratified for disease severity, dialysis dose did not affect outcome in patients with very high or very low scores but did correlate with survival in patients with intermediate degrees of illness. A mean Kt/V >1.0 or $\text{TAC}_{\text{UREA}} <45$ mg/dl was associated with increased survival. This study, of course, was retrospective with a clear post hoc selection bias. The validity of these observations remains highly questionable.

Daily IHD compared with alternate-day dialysis also seemed to be associated with improved outcome in a recent trial (29). Daily hemodialysis resulted in significantly improved survival...
calculation of VUREA, CVVH at 35 ml/kg per h would still of 1.4 also applied daily. Despite uncertainty regarding the compared with 20 ml/kg per h in 425 critically ill patients with ml/kg per h was associated with improved survival when

dertaken to assess the effect of dose of IHD on outcome.

In a randomized, controlled trial of CRRT dose, continuous venous postdilution hemofiltration (CVVH) at 35 or 45 ml/kg per h was associated with improved survival when compared with 20 ml/kg per h in 425 critically ill patients with ARF (14). Applying the Kt/V dose assessment method to CVVH at a dose of 35 ml/kg per h in a 70-kg patient who is treated for 24 h, a treatment day would be equivalent to a Kt/V of 1.4 also applied daily. Despite uncertainty regarding the calculation of VUREA CVVH at 35 ml/kg per h would still provide an effective daily delivery of 1.2, even in the presence of an underestimation of VUREA by 20%.

Many technical and/or clinical problems, however, can make it difficult, in routine practice, to apply such strict protocol 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 is the observation that this study was conducted over 6 yr in a single center, that uremic control was not reported, that the study was unblinded and therefore potentially subject to a Hawthorne effect, that the incidence of sepsis was low compared with the typical populations reported to develop ARF in the world (31), and that its final outcome was not the accepted 28- or 90-d mortality typically used in ICU trials. Thus, the external validity of this study remains untested.

Another prospective, randomized trial conducted by Bouman et al. (32) assigned patients to three intensity groups: Early high-volume hemofiltration (72 to 96 L/24 h), early low-volume hemofiltration (24 to 36 L/24 h), and late low-volume hemofiltration (24 to 36 L/24 h). These investigators found no difference in terms of renal recovery or 28-d 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 the incidence of sepsis low compared with the typical populations reported to develop ARF in the world.

All of these studies must be seen, however, in the light of an absolute lack of any previous attempt to adjust ARF treatment dose to specific target levels. During the third International

![Figure 2. Participants’ view about dialysis efficiency targets (K) for urea during the third International Course on Critical Care Nephrology held in Vicenza, Italy.](image)
Are New Studies Needed?

The practice of CRRT seems not to have changed in recent years. Despite a strong rationale and positive findings of some prospective trials, the practice of a higher intensity CRRT has not been widely adopted into routine ICU practice. A survey of several units in the Australian and New Zealand Intensive Care Society Clinical Trials Group (Bellomo R., unpublished data) found that very few units had adopted the intensive CRRT regimen proposed by Ronco et al. (14). Data from such Australian units showed that the vast majority prescribe a standard CRRT intensity of 2 L/h of effluent to all patients irrespective of weight. If we consider that the median body weight for Australian patients is approximately 80 kg, we can assume that the median prescribed CRRT dose in Australia is approximately 25 ml/kg per h. Finally, in the study conducted by Ronco et al. (14), the technique of CRRT was CVVH with postdilution, whereas current practice in Australia includes a variety of techniques in addition to CVVH, such as CVVHD and CVVHDF. Thus, current practice in CRRT even within a single country is extremely varied. A recent study (31) also showed marked variability worldwide.

Because current practice for RRT in ICU remain poorly defined, the DOse RESponse Multicenter International collaboration (DO-RE-MI) (35) is currently seeking to address the issue of how practice patterns are currently chosen and performed. DO-RE-MI is an observational, multicenter study conducted in ICU. The primary aim is to study the delivered dose of dialysis, which then will be compared with ICU mortality, 28-d mortality, hospital mortality, ICU length of stay, and number of days of mechanical ventilation. It is hoped that this international collaboration will provide a clearer picture of how RRT is chosen, prescribed, and delivered and how such delivery may affect outcome.

In November 2003, the Acute Renal Failure Trial Network initiated a multicenter, prospective, randomized, parallel-group trial (ATN Study) of an intensive-dose strategy versus a conventional-dose strategy of RRT for the treatment of ARF caused by acute tubular necrosis in critically ill patients. The planned total enrollment is 1164 patients at 27 institutions during 3 yr to achieve a power of 0.90 to detect a reduction in mortality from 55 to 45% on the basis of RRT dose (36). Patients will be randomized to one of two dosing strategies for RRT; in both strategies, hemodynamically stable patients receive IHD, whereas unstable patients receive either CRRT or SLED. In the low-dose arm, patients receive IHD and SLED on a 3×/wk schedule or CVVHDf with an effluent flow rate of 20 ml/kg per h; in the high-dose arm, patients receive IHD and SLED on a 6×/wk schedule or CVVHDF with an effluent flow rate of 35 ml/kg per h. This design is intended to deliver data on both a comparison between intermittent therapy and CRRT and one between “low” and “high” dose of RRT, irrespective of treatment modality.

The Australian and New Zealand Intensive Care Group has also recently been funded to conduct a multicenter, randomized, controlled trial of CRRT dose in critically ill patients with ARF. The study will randomize 1500 patients in 35 Australian and New Zealand ICU to receive either postdilution CVVHDF at 25 or at 40 ml/kg per h of effluent. In Australia, RRT prescription occurs in closed ICU under Intensivist control in almost 100% of cases and is almost exclusively in the form of CRRT (37,38). Patients will be included in the study if the following criteria are fulfilled: the clinician believes that the patient requires RRT for ARF; the patient fulfills one of the following clinical criteria for initiating RRT: oliguria (urine output <100 ml/6 h) unresponsive to fluid resuscitation measures, hyperkalemia ([K⁺] > 6.5 mmol/L), severe acidemia (pH < 7.20) in the setting of ARF, urea concentration >25 mmol/L secondary to ARF, clinically significant organ edema in the setting of ARF, creatinine >300 µmol/L secondary to ARF, and the treating clinician anticipates treating the patient with CRRT for at least 72 h.

The treatment effect observed in the previous dose of CRRT study was a reduction in mortality from 59 to 42% (29% relative risk reduction and 17% absolute risk reduction). This study will assume a conservative 90-d mortality rate of 60% in the control group. This study will also assume a conservative estimate for the reduction in mortality in patients of only half that reported by Ronco et al. (i.e., an absolute reduction of 8.5%). On the basis of these figures, this study is projected to have 90% power of detecting an 8.5% absolute reduction from a 90-d mortality of 60 to 51.5% (α < 0.05). Thus, given these two large studies that are either under way or about to start, it is likely that, in the near future, two large, randomized, controlled trials that assess the impact of RRT dose in ARF will be available to better inform clinical practice.

Dose Delivery: Continuously or Intermittently?

Clearance-based dose quantification methods may not be adequate to compare effectiveness. For example, peritoneal dialysis (PD), traditionally providing less urea clearance per week than IHD, has comparable patient outcomes. Even when EKRC is used to compare intermittent and continuous therapies, it does not seem to be equivalent in terms of outcome (39). The reason for this difference may be that urea is less compartmentalized than other solutes and equivalent amounts of urea removal where one therapy is intermittent rather than continuous do not represent equivalent therapies for a broader range of solutes. Again, when the critical parameter is metabolic control, an acceptable mean blood urea nitrogen level of 60 mg/dl, easily obtainable in a 100-kg patient with a 2-L/h CVVH, in a computer-based simulation, has been shown to be very difficult to reach even by intensive IHD regimens (40). In addition to the benefits that pertain specifically to the kinetics of solute removal, increased RRT frequency results in decreased ultrafiltration requirements per treatment. The avoidance of volume swings related to rapid ultrafiltration rates may also represent another dimension of dose for which comparability is difficult.

However, despite the development of new membranes, sophisticated dialysis machinery, tailored dialysate composition, and continuous dialysis therapies, a relationship between delivery of RRT continuously instead of intermittently has not been fully established. Most recently, the Surviving Sepsis Campaign guidelines for management of severe sepsis and
septic shock (41) concluded that, on the basis of actual scientific evidence, during ARF, CVVH and IHD should be considered equivalent. The largest comparative trial so far conducted randomly assigned 166 critically ill patients with ARF to either CRRT or IHD (42). The authors found that the CRRT population, despite randomization, had significantly greater severity of illness scores. Furthermore, despite better control of azotemia and a greater likelihood of achieving the desired fluid balance, CRRT had increased mortality. A more recent smaller trial by the Cleveland Clinic group (43) also failed to find a difference in outcome between one therapy and another. A meta-analysis of 13 studies conducted by Kellum et al. (44), which concluded that, after stratification of 1400 patients according to disease severity, when similar patients were compared, CRRT was associated with a significant decrease in the risk for death. The authors confirmed that a large, carefully controlled, randomized clinical trial should be undertaken (44).

However, another meta-analysis (45) found no difference between the two techniques. Thus, it remains uncertain whether the choice of RRT modality (intermittent or continuous) actually matters to patient outcome. One major problem with all of these comparisons remains that for the purpose of randomized, controlled trials, relatively fixed approaches must be chosen. So, for example, patients may be randomly assigned to an IHD at a calculated Kt/V of 1.2 versus CRRT at an effluent flow rate of 35 ml/kg per h. If one approach was found superior, then the immediate question would be whether the difference was dependent on the nature of the therapy (intermittent or continuous) or the “dose” of solute removal.

If IHD were found to be inferior, then the protagonists of IHD then simply would say that it all would be just a matter of increasing the time or the frequency and hence the overall weekly dose of IHD and the outcome difference would disappear. Similarly, if CRRT were found to be inferior, then the protagonists of continuous therapy simply would say that it all was a matter of prescribing the right CRRT dose, and, if effluent flow rates were increased to 45 ml/kg per h, the difference in outcome again would disappear. Thus, the dispute simply might be insoluble. Given this kind of impasse, people then might consider compromise solutions. One such solution might be represented by hybrid techniques such as SLEDD.

### Hybrid Techniques

Hybrid techniques have been given a variety of names, such as SLEDD, prolonged intermittent daily RRT, extended daily dialysis, or simply extended dialysis (46–49), depending on variations in schedule and type of solute removal (convective or diffusive). Theoretically speaking, the purpose of such therapy would be the optimization of the advantages offered by either CRRT and IHD, including efficient solute removal with minimum solute disequilibrium, reduced ultrafiltration rate with hemodynamic stability, optimized delivered-to-prescribed ratio, low anticoagulant needs, diminished cost of therapy delivery, efficiency of resource use, and improved patient mobility.

Initial case series have shown the feasibility and high clearances that potentially are associated with such approaches (47,48). A single short-term, single-center trial comparing hybrid therapies with CRRT has shown satisfying results in terms of dose delivery and hemodynamic stability (49).

The arrival of technology that can be used in the ICU by ICU nurses to deliver SLEDD with convective components offers further options from a therapeutically point of view. One can now easily use technology in ICU to generate ultrapure replacement fluid and administer it like in CRRT but at lower cost, in greater amounts, and for shorter periods of time or combine such hemofiltration with diffusion or use pure diffusion at any chosen clearance for a period of time that can encompass a given nursing shift, the 9 to 5 maximum staff availability period or the nighttime period. Thus, like in a computerized drop-down menu, the choices now are almost limitless: should it be 3 or 4 h of IHD with standard settings? Or should it be CRRT at 35 ml/kg per h effluent flow rate? Or should it be SLEDD at blood and dialysate flow rates of 150 ml/min for 8 h during the day? Or should we apply SLEDD for 12 h overnight? Or should we add a convective component to SLEDD and make it SLEDD? Or should we combine CRRT for the first 2 or 3 d when the patient is in the hyperacute phase, with SLEDD thereafter as recovery takes place?

Indeed, from the point of view of the intensivist, the modes of RRT are beginning to resemble the modes of mechanical ventilation, with ventilator settings seamlessly being changed to fit into the therapeutic goals and patient needs and phases of illness. Just like stereotyped approaches to ventilation are anachronistic and inappropriately try to fit the patient into a fixed therapy rather than tailoring the therapy to the patient, so should RRT be adjusted to fulfill the needs of the individual and his or her illness. Just like the concept of showing that one mode of ventilation is better than another seems a lost cause, the same might happen with RRT.

### Is There Adequacy Beyond Adequacy?

“Ad equatum” is a Latin expression that means “equal to.” Can we make RRT equal to the metabolic challenge that we might face in different patients? ARF in the critically ill patient is frequently part of multiple organ failure (MOF) and sepsis, and patients, independent from other comorbidities and despite technical improvements in RRT delivery, are still dying of ARF (50): it is evident that absence of kidney function accounts for some specific and independent risk factor for poor prognosis of unknown magnitude. Hence, beyond “adequate” RRT dose for ARF, there may be a role for an “adequate” RRT dose for ARF with sepsis, intended as a hypothetical therapy that would closely mimic the features of the native kidney in this setting and perhaps enhance them (51). It is logical to hypothesize that the blood purification dose needed in patients with uncomplicated ARF would be very different from that needed in patients with ARF in the setting of septic MOF. It was hypothesized further recently that the peak concentration of either the pro- and anti-inflammatory mediators in plasma might be responsible for some of the ill effects of sepsis (52). These mediators normally exist in a state of immune homeostasis, whereas the excess of one over the other might be responsible for the...
complex septic syndrome. This might be the rationale for a nonselective extracorporeal elimination of these cytokine peaks to restore immune homeostasis. Higher rates of blood purification by RRT or alternative techniques must be investigated to understand better the role for extracorporeal de
puration in sepsis (53). These notions challenge the concept that there would be an adequate dose level in an absolute sense, which applies to all patients with ARF. We recognize nonetheless that the journey of the concept of dose has barely started in this field, and before we can even consider such fine adjustments, much more investigational work needs to be done.

**Conclusion**

As concluded by the Acute Dialysis Quality Initiative work-
group in 2001 (www.adqi.net) (54,55), delivered clearance
should be monitored during all renal supportive therapies. No recommendations can be made for specific dialysis dosing for patients with specific diseases at this time. A minimum dose of RRT needs to be established for ARF. This may be achieved best by adequately powered, observational, multicenter, prospective studies of delivered dose and outcome in patients with varied comorbidity followed by severity-stratified, prospective, randomized trials of varying delivered dose and modality versus outcome. Well-powered prospective studies of outcome comparing intermittent and continuous therapy with similar dose and technique are also needed. Such studies now are either under way or about to start.

In the absence of currently determined optimal RRT dose, it can only be recommended that the prescription should exceed that calculated to be “adequate” because of the known gap between prescribed and delivered dose. In fact, the intrinsic limits of every measurement technique, metabolic and clinical characteristic of critically ill patients, and objective technical difficulties to deliver prescribed dose all are factors that contribute to a significant underestimation of “adequate” dose. Finally, a higher intensity of treatment and convective clearance might help to optimize the clearance of ARF toxins in specific situations such as severe sepsis and MOF.

Beyond such observations, a solute-based approach to the concept of dose seems too “monodimensional,” although operationally relatively simple and, by analogy with end-stage renal failure, potentially linked to outcome. In critically ill patients with ARF, other dimensions of adequacy of RRT or RRT dose remain unexplored but likely also important. Future studies should focus on other aspects of dose (e.g., volume control, acid-base control, tonicity control) and assess their potential link with outcome.

Finally, a stereotyped approach to choice of therapy or choice of dose may be inappropriate beyond ensuring that at least a minimum dose is delivered to all. As the spectrum of RRT has expanded from PD and IHD alone approximately 25 yr ago to the full spectrum of therapy from standard IHD to daytime SLEDD to nocturnal SLEDD to pulse high-volume hemofiltration to high-volume CRRT, physicians ultimately may choose to take a much more flexible approach to RRT and RRT dose. In this setting, dynamic clinical judgments and knowledge of the technology that is available and frequent multidisciplinary setting of physiologic and clinical goals would dictate therapeutic choices that are adapted to the patient and his or her illness rather than the other way around. Future trials then would have to assess whether such goal-directed RRT is superior to fixed approaches to RRT dosing. Such questions are already being tested in the study of resuscitation septic shock and likely soon will have an impact on the field of RRT.

**References**


4. DuBose T, Warnock DG, Mehta RL, Bonventre JV, Ham


