Acute renal failure (ARF) often develops in the setting of other organ dysfunction in critically ill patients. ARF has a significant impact on patient morbidity and mortality [1–5]. Current management of ARF includes optimization of hemodynamic and volume status, avoidance of further renal insults, optimization of nutrition, and institution of renal replacement therapy (RRT). Indications for RRT include oligoanuria, decreased creatinine clearance, severe acidemia, hyperkalemia, and other metabolic and electrolyte disorders linked to kidney failure. It is recognized that morbidity and mortality are strictly correlated to hemodialysis (HD) dose in patients who have end-stage renal disease (ESRD) [6–9], and current practice guidelines recommend a minimum standard treatment dose [10]. Nevertheless, the Hemodyalysis study, examining the effect of intermittent hemodialysis (IHD) dose, failed to confirm the intuition that “more dialysis is better” [11]. Optimal strategies to improve patient morbidity and mortality in ARF have not been examined in such a clinical trial. However, some authors have suggested recently that improved survival of critically ill ARF patients could be correlated to delivered therapy dose [12–18]. This article focuses on RRT dose measurement and prescription in the intensive care setting as well as the current scientific evidence concerning RRT dose and outcome.

**Dose measurements in acute renal replacement therapy**

The treatment dose of RRT can be defined by various aspects such as efficiency, intensity, frequency, and clinical efficacy. Efficiency of RRT can be
represented by clearance (K). Technically, K depends on blood flow rate, dialysate flow rate, ultrafiltration rate, reference molecules, and hemodialyzer type and size. K can be normally used to compare the treatment dose within each modality. Between different modalities, however, K is typically higher in IHD than continuous renal replacement therapy (CRRT) and sustained low efficiency dialysis, even though IHD does not remove the solutes better than the others. This is not surprising, because K represents only the amount of treatment per unit of time. Therefore, K cannot be employed to compare various modalities differing in treatment duration. Finally, K represents an instantaneous measurement, and it correlates with the amount of solute removal at the time point of the measurement. Although K might remain stable over time, if blood levels of the reference molecule will change, removal rate will also change. Intensity of RRT can be described by the product of clearance × time (Kt). Because the time is accounted, Kt is more effective than K in the comparison of various RRT modalities. Frequency is an essential factor to further describe treatment dose in different modalities. Thus weekly clearance, intensity × frequency (Kt × treatment d/wk), is superior to Kt because it offers the comparison of different modalities in the more extensive view. Clinical efficacy of RRT represents the effective clinical outcome resulting from the implication of a given treatment. It can be described by a fractional clearance (Kt/V) where V is the volume of distribution of the marker molecule. Kt/V is an established maker of adequacy correlating with survival in chronic hemodialysis patients [19]. Hence, Kt/V is widely applied clinically in patients with ESRD, but its application in patients with ARF requiring emergent dialysis has not been rigorously validated.

The search for specific toxins to be cleared, furthermore, has not been successful despite years of research, and urea and creatinine are generally used as “marker” solutes to measure renal replacement clearance for renal failure. Although available evidence does not allow direct correlation of the degree of uremia with outcome, in the absence of a specific solute, clearances of urea and creatinine are used in chronic renal disease to guide treatment dose, and a single-pool Kt/V_{UREA} of at least 1.2 is currently recommended [10].

Kt/V application on treatment dose in the acute setting is theoretically intriguing, but many concerns have been raised by its practical use. Problems intrinsic to ARF can hinder the accuracy of dose measurement; these include the lack of a steady state, uncertainty about urea volume of distribution (V_{UREA}), high protein catabolic rate, labile fluid volumes, and eventual residual renal function. Furthermore, delivery of a prescribed dose can be limited by technical problems such as access recirculation, poor blood flows with temporary venous catheters, clotting, and mechanical inaccuracies; clinical issues such as hypotension and vasopressor requirements can be responsible for solute disequilibrium within tissues and organs.

Time-averaged blood urea nitrogen (TAC_{UREA}) is the area under the sawtooth curve produced by intermittent dialysis sessions. TAC_{UREA} is a function of dialysis dose, but it is also associated with urea generation rate (G) and protein intake with nutrition. As such, it is not a good indicator of RRT dose.
CRRT allows for the expression of dose measurement in simplified forms. For pure postdilution hemofiltration, the ultrafiltration rate can be used to measure clearance [18]. For other modalities, dialysate and ultrafiltrate flow are required to measure clearance [20–23]. Different techniques alter different parameters, and no consensus exists as to which technique should be used in clinical practice. Emerging evidence suggests the importance of using equivalent renal clearance [24,25]. If G and TACUREA are known, using the same principle as computing creatinine clearance, equivalent renal clearance can be calculated by the ratio of the two. A modification of this equation was described by Gotch as standardized Kt/V (stdKt/V), and it is calculated as the ratio of G and mean weekly urea pretreatment concentrations normalized for VUREA [26]. These formulas would allow comparing dose measurement of disparate therapies and different frequencies of RRT, but G, mean weekly urea pretreatment concentration, and TACUREA calculations are less immediate than K, t, and VUREA, which seem easier to achieve without formal modeling.

The differences between prescribed and delivered dose in patients with ARF undergoing IHD were analyzed by Evanson and co-workers [27]. The authors found that a high patient weight, male sex, and low blood flow were limiting factors affecting RRT administration and that approximately 70% of dialysis delivered a Kt/V of less than 1.2. This year, during the Third International Course on Critical Care Nephrology in Vicenza, Italy, we conducted a survey on aspects of ARF, including treatment prescription, among about 550 participants (equally distributed between nephrologists and intensivists) from about 500 different centers worldwide (unpublished data). Surprisingly, we realized that approximately 75% of responders do not apply any measure of RRT dose, and 60% do not even prescribe a dose for ARF patients.

These observations highlight the fact that RRT prescriptions for ARF patients in the intensive care unit should be standardized and monitored closely to ensure adequate delivery of prescribed dose.

**Dose prescriptions in acute renal replacement therapy and impact on outcome**

Based on evidence from ESRD, a minimum Kt/V of 1.2 thrice weekly should be delivered to patients with ARF [10]. However, higher doses of dialysis may be beneficial in critically ill patients with ARF. Specifically, Brause and co-workers [28] using Kt/V as the evaluation method for continuous veno-venous hemofiltration (CVVH) dose, found that higher values (0.8 versus 0.53) were correlated with improved uremia control and acid–base balance. The small groups they studied did not achieve a difference in outcome. Paganini and colleagues [13,14] retrospectively evaluated 844 patients with ARF requiring CRRT or IHD over a 7-year period and 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 inter-
Fig. 1. Critically ill patients requiring RRT 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. (Modified from Paganini EP, Kanagasudaram NS, Larive B, et al. Prescription of adequate renal placement in critically ill patients. Blood Purif 2001;19: 238–44.)

Fig. 2. The S. Bortolo Hospital Study: an intensity of CVVH of 35mL/kg/h was associated with improved survival when compared with 20 mL/kg/h in 450 critically ill patients with ARF. Improvement was not significant if compared with further increase of dose to 45 mL/kg/h. (Data 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: 26–30.)
mediate degrees of illness (Fig. 1). A mean Kt/V greater than 1.0 or TACUREA less than 45 mg/dL was associated with increased survival. Daily IHD compared with every-other-day delivery also seemed to be associated with improved patient outcome in a recent trial [29]. Although this study was flawed in some aspects (recruitment, power, dosing level comparisons), it prospectively established a potential dialysis dose/patient outcome relationship. In the first randomized controlled trial on CRRT dose, an intensity of CVVH of 35 mL/kg/h was associated with improved survival when compared with 20 mL/kg/h in 450 critically ill patients who had ARF 27 (Fig. 2) [18]. Setting a Kt/V threshold that could guide clinicians toward adequate treatment, the target of 35 mL/kg/h should be possibly met. In a 70-kg patient treated for 24 hours a day, this value would approach a Kt/V of 1.4. In spite of uncertainty on V calculation, as described by Himmelfarb and colleagues [30], such a prescription would still provide an effective daily delivery of 1.2, even in the presence of an underestimation of VUREA by 20%.

**Impact of renal replacement therapy modality on dose and outcome**

It must be underscored that clearance-based techniques quantifying RRT dose may not be comparable to assess the effectiveness of different modalities. For example, peritoneal dialysis, traditionally providing less urea clearance per week than HD, has comparable patient outcomes. To confirm this intuition, it has been shown that when equivalent renal clearance is used to compare highly intermittent and continuous therapies, it does not appear to be equivalent in terms of outcome [31]. The reason for this difference may be that urea is less compartmentalized than other low–molecular weight solutes, and equivalent amounts of urea removal where one therapy is intermittent rather than continuous do not represent equivalent therapies.

From another point of view, when the critical parameter is the 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 impossible to reach even through intensive IHD regimens [32]. Moreover, daily hemofiltration, high-flux HD, and continuous ambulatory peritoneal dialysis provided equivalent weekly clearances of small solutes, but daily hemofiltration was more efficient in clearing middle and large molecules [33]. In a recent trial that compared hemofiltration and peritoneal dialysis in infection-associated ARF in Vietnam, Phu and colleagues described that urea clearance was similar in the two groups, while creatinine clearance in the group that received CVVH was almost double [34,35].

In addition to the benefits specifically pertaining to the kinetics of solute removal, increased RRT frequency results in decreased ultrafiltration requirements per treatment. The avoidance of hypotensive episodes related to rapid ultrafiltration rates may also indirectly improve solute removal by decreasing the risk of therapy interruptions. However, despite the development of new
dialyzer membrane materials, sophisticated dialysis machinery, varying and tailored dialysate composition, and the continuous methodology of dialysis delivery, a relationship between dialysis intensity and patient outcome has not been fully established.

Recently, the Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock [36] have disclosed that in ARF, in the presence of hemodynamic stability, CVVH and IHD are considered equivalent. Continuous hemofiltration would offer easier management of fluid balance in hemodynamically unstable patients. This statement is supported by two references. The first recalls a trial that randomized 166 critically ill patients with ARF to CRRT versus IHD [37]. The authors found that CRRT population, despite randomization, had significantly greater severity of illness scores, and that, despite better control of clearance and fluid balance, had increased mortality. The trial is not substantially useful to ultimately define the superiority of continuous modalities over intermittent ones. The second paper cited by the guidelines, a meta-analysis of 13 studies conducted by Kellum and colleagues [38], concluded that, after stratification of 1400 patients according to disease severity, when similar patients were compared, CRRT was associated with a significant decrease in death risk ratio. The authors confirmed that a large carefully controlled randomized clinical trial should be undertaken.

In the debate between continuous and intermittent RRT, a hybrid technique has been used recently, and different schedules have been described: slow low-efficiency extended dialysis [39], prolonged intermittent daily RRT [40], extended daily dialysis (EDD) [41], or simply extended dialysis [42]. Theoretically speaking, the purpose of such therapy would be the optimization of the advantages offered by either CRRT or IHD, including efficient solute removal with minimum solute disequilibrium, reduced ultrafiltration rate with hemodynamic stability, increased delivery to prescribed ratio, less anticoagulant administration. Initial trials comparing hybrid therapies to CRRT have shown satisfying results in terms of dose delivery and hemodynamic stability [39,41,42].

**Adequacy of therapy beyond renal dose**

“Ad equum” is a latin expression that means “equal to.” In critically ill patients, ARF is frequently part of multiple organ failure or sepsis and septic shock, and despite technical improvements in RRT delivery, patients are still dying of ARF independently of other comorbidities [43], being evident that absence of kidney functions presents a specific and independent risk factor for poor prognosis (Fig. 3). Hence, beyond “adequate renal” RRT dose, there may be a role for “adequate septic” RRT dose, intended as a hypothetical therapy that closely mimics the features of the native kidney [44]. The Surviving Sepsis Campaign Guidelines alert that there is no current evidence to support the use of CVVH for the treatment of sepsis independent of renal replacement needs, and no conclusive evidence has shown that hemofiltration is able to affect circulating
levels of inflammatory mediators [36]. Nonetheless, it has recently been hypothesized that the peak concentration of either the pro- or anti-inflammatory mediators in plasma are responsible for the malignity of sepsis; this is known as “the peak concentration hypothesis” [45]. These mediators normally exist in a state of immune homeostasis, the excess of one over the other being responsible for the complex septic syndrome. This is the rationale for a nonselective extracorporeal elimination of these cytokine peaks that give the possibility to restore immune homeostasis (Fig. 4). In a randomized clinical trial comparing CVVH versus no CVVH in early sepsis, however, it has been demonstrated that 2 L/h of postdilution hemofiltration did not reduce cytokine concentrations and organ dysfunction. Higher rates of RRT (high volume hemofiltration) or alternative techniques must be investigated to better understand the role for extracorporeal depuration in sepsis [46].

Fig. 3. Mortality for ARF has not changed over the years, but the case mix did: 30 years ago, most patients with ARF would die, whereas now they mainly die in the intensive care unit because of kidney and multiple organ failure.

![Fig. 3: ARF Mortality Chart](image-url)

![Fig. 4: Excess Mediator Removal](image-url)

Fig. 4. Unselective high efficiency extracorporeal therapies might remove excess pro- and anti-inflammatory mediators diminishing the amplified inflammatory response and the immunoparalysis induced by cell hyporesponsiveness.
Summary

As concluded by the Acute Dialysis Quality Initiative in 2001 [47,48], delivered clearance should be monitored daily 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 best achieved by adequately powered, observational multicentered 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.

In the absence of currently determined optimal RRT dose, it can only be recommended that the prescription should exceed that calculated to be “adequate.” In fact, intrinsic limits of every measurement technique, metabolic and clinic characteristic of critically ill patients and objective technical difficulties to deliver prescribed dose are all factors contributing to a significant underestimation of “adequate” dose. Finally, a higher intensity of treatment and convective clearance might help to optimize clearance of ARF toxins.

References


