Increased Intensity of Renal Replacement Therapy to Reduce Mortality in Patients with Acute Kidney Injury

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6.1 General Principles

Because initial studies showed a direct relationship between the intensity of renal replacement therapy (RRT) and survival, both for intermittent and continuous techniques [1–3], great attention has been paid to identify the optimal "dose" of RRT in the last 10 years.

Dose of RRT may be represented by the *efficiency* of the treatment, which can in turn be expressed as clearance (K) that is the amount of blood cleared of toxins and waste products by the extracorporeal circuit during a given period of time [4]. The concept of clearance needs to be referred to a particular solute. Urea is widely adopted as uremic toxin marker in clinical practice, and its clearance is most commonly used to quantify RRT efficiency and, accordingly, dose. Given that RRT is usually performed over several days or weeks, it is important to provide information about the total time during which the treatment clearance is delivered. The *intensity* of treatment (Fig. 6.1) is thus expressed as the product of clearance and the effective time (t) of treatment (Kt) [4]. Including the downtime (i.e., the amount of time in which the treatment is interrupted), a significant difference could be found between the prescribed and the actually delivered doses. Finally, considering the entire pool of solutes that needs to be cleared, the *efficacy* of treatment (Fig. 6.1) can be

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G. Landoni et al. (eds.), *Reducing Mortality in Acute Kidney Injury*,
DOI 10.1007/978-3-319-33429-5_6

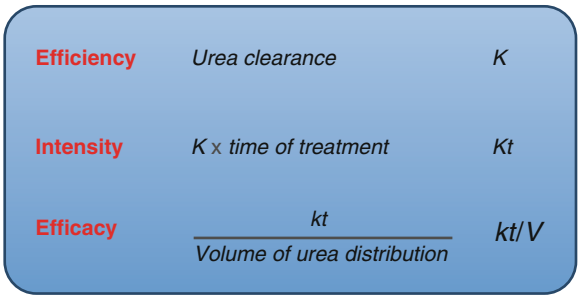

Fig. 6.1 Defining dose of renal replacement therapy (see text)

expressed as the ratio between the intensity and the volume of distribution (V) of the marker solute (*Kt*/*V*) [4]. Considering all these concepts during the prescription phase of RRT, it has seemed reasonable, since the birth of critical care nephrology [5], that an adequate treatment should have to be delivered to critically ill patients. In a few words, the idea was to provide "intense" blood purification, generally proportional to the severity of critical illness. However, back in the late 1980s, RRT machines used in the intensive care units (ICUs) were mostly adapted from the chronic hemodialysis ward, or in any case lacked several of current automatisms which are routinely applied to third- and fourth-generation RRT machines, and were probably unsuited for providing accurate and targeted treatments to critically ill patients with acute kidney injury (AKI) [6]. At that time, accordingly, RRT was certainly mostly underdosed. In this chapter, the available literature is analyzed with the aim to identify the current "optimal" dose of RRT in ICU patients with AKI, as well as to clarify whether and to what extent an increased treatment dose/intensity might provide a survival benefit in these patients.

6.2 Main Evidence

Several efforts have been made in the literature in order to define the most adequate RRT dose in AKI: the underlying idea is that RRT delivery may imply a dose-dependent range, where treatment efficiency correlates with outcomes, and a dose-independent range in which further dose increases will not result in additional benefits for the patients. Accordingly, during the last decade, the dose that was first shown to be associated to better patient outcome ($\geq$35 mL kg^{-1} h^{-1}) has been considered a milestone of critical care nephrology [1]. In particular, in 2000 Ronco et al. [1] randomized 425 ICU patients with acute renal failure (ARF) to receive continuous venovenous hemofiltration (CVVH) at 20, 35, or 45 mL kg^{-1} h^{-1} and found a significantly higher mortality in the 20 mL kg^{-1} h^{-1} group, as compared with the other two groups (which had similar survival rates). This study also suggested that post-dilution hemofiltration at higher does (45 mL kg^{-1} h^{-1}) may be indicated in specific conditions such as sepsis. The hypothesis that an increased intensity of RRT may improve survival was apparently confirmed also in patients receiving intermittent hemodialysis (IHD). In 2002, in fact, Schiffl et al. [2] randomized 160 ARF

patients to either daily or conventional (i.e., on alternate days) IHD and showed a significant reduction in mortality in the daily dialysis group (28 % vs. 46 %, $p = 0.01$). Interestingly, a few years later, Saudan et al. [3] evaluated the effect of additional RRT dose, delivered by adding a continuous diffusive technique to a purely convective treatment, in 206 ICU patients with ARF: again, patients receiving continuous venovenous hemodiafiltration (CVVHDF) showed a significant improvement in 90-day survival as compared with patients receiving CVVH (59 % vs. 34 %, $p = 0.0005$).

More recently, however, two large multicenter randomized clinical trials examined the issue of the optimal RRT dose in ICU patients with AKI and the effect of increased intensity of RRT on mortality: the Randomized Evaluation of Normal versus Augmented Level of RRT (RENAL) study [7] and the Veterans Affairs/National institutes of Health Acute Renal Failure Trial Network (ATN) study [8].

In the RENAL trial [7], 1,508 patients were randomized to receive post-dilution CVVHDF with an effluent flow of either 25 or 40 mL kg^{-1} h^{-1}. The ATN study [8] included 1,124 patients who were randomly assigned to either 20 mL kg^{-1} h^{-1} CVVHDF or thrice-weekly IHD. Both studies failed to demonstrate that higher RRT doses were associated with better outcomes, except for a septic subgroup of the RENAL study with a reduced mortality when a higher dose was applied (odds ratio [OR] 0.84, 95 % confidence interval [CI] 0.62–1.12). However, under-dialysis should be always avoided in critically ill patients with AKI, and great attention should be paid in order to minimize the discrepancy between the prescribed and the actually delivered dose.

In light of this major issue, RRT downtime (defined as the overall time of RRT "standstill" over 24 h) was specifically explored in the "DOse REsponse Multicenter International collaborative initiative" (DO-RE-MI) [9]. Membrane clotting, vascular access issues (inducing physicians to modify the setting), and prescription errors (due to lack of knowledge) were the main contributors to continuous RRT (CRRT) stop. Therefore, if a "minimal" dose of 20–25 mL kg^{-1} h^{-1} (according to RENAL and ATN studies) should be prescribed, physicians should be advised to overprescribe the dose of at least 25 % (targeting 30–35 mL kg^{-1} h^{-1}), in order to limit the downtime effect.

Two important post hoc analyses of the RENAL trial were performed [10, 11]. The first suggested that fluid balance, rather than RRT dose, may actually affect patients' outcomes (see Chap. 19) [10]. In fact, the authors found that mean daily fluid balance among survivors was −234 mL/day compared with +560 mL/day among non-survivors ($p < 0.0001$) and that a negative fluid balance was independently associated with favorable outcomes, including survival, RRT days, mechanical ventilation days, and both ICU and hospital length of stay. The second post hoc analysis examined acid-base balance and vasopressor utilization in the subgroup of patients with metabolic acidosis [11]. This study showed that the high-intensity group had a greater increase in mean arterial pressure from baseline to 24 h (7 ± 3 vs. 0 ± 3 mmHg, $p < 0.01$) and a greater decrease in norepinephrine dose (from 12.5 to 3.5 vs. 5 to 2.5 μg/min, $p < 0.05$). Despite a similar improvement in acid-base balance was observed in both groups, strong ion gap seemed to be better corrected by

high-dose RRT. Although the authors acknowledged that a mechanistic analysis of the physiological effects induced by high-intensity RRT cannot be provided, they suggested that a more efficient removal of biologic mediators which are responsible for hypotension or vasodilation might be the potential mechanism of the observed hemodynamic improvement. Indeed, the changes in strong ion gap may indicate the removal of some of these mediators [11].

Finally, Uchino et al. [12] analyzed data from two multicenter investigations, the Beginning and Ending Supportive Therapy (BEST) study [13] and the Japanese Society for physician and trainees Intensive Care (JSEPTIC) trial [14], including 1,006 patients from 54 ICUs around the world and 343 patients from 12 Japanese ICUs, respectively. They found that AKI patients receiving low-dose CRRT (14.3 mL kg^{-1} h^{-1}) had not a worse short-term outcome as compared with patients receiving CRRT at doses closer to those currently considered as standard (20.4 mL kg^{-1} h^{-1}).

6.3 Pathophysiological Principles

One of the key issues of the modern concept of RRT is the clinical target: deriving from nephrology considerations, urea is the main solute that has been referred as the biomarker indicating how efficiently solutes are removed. However, urea is not the only solute which accumulates due to kidney injury and its kinetic of removal and volume of distribution differ by the other uremic toxins [15]. Considering urea as a target solute could result particularly useless in ICU patients. In fact, unlike patients with chronic kidney disease (CKD), uremic symptoms are rarely observed in the ICU, and they usually do not affect the clinical decision about CRRT in these patients. Other target solutes rather than urea should be considered in ICU patients. In particular, CRRT should be addressed to specific targets in specific clinical conditions (e.g., myoglobin in patients with compartment syndrome, interleukins during sepsis, novel biomarkers in case of early AKI, fluid balance in case of fluid overload). This concept would also redefine the concept of adequacy itself, which should probably include not only the amount of RRT to provide but also the exact circuits, filters, machines, and timing to be applied.

6.4 Therapeutic Use

A specific treatment that can be defined as "adequate" for all ICU patients in all conditions does not exist but, like mechanical ventilation, CRRT should be continuously tailored on patients' characteristics and their actual clinical needs.

Advantages and disadvantages of the different RRT modalities are summarized in Table 6.1 (see also Chap. 4).

Although three studies suggested a survival advantage with higher effluent dose [1], more frequent (daily) IHD [2], and the adjunct of continuous dialysis to CVVH [3], respectively, subsequent studies failed to confirm these findings.

Table 6.1 Advantages and disadvantages of different renal replacement therapy (RRT) modalities

RRT modality	Advantages	Disadvantages
Intermittent (IHD)	Rapid removal of toxins and circulating solutes Reduced downtime for diagnostic and therapeutic procedures Reduced exposure to anticoagulation Lower cost than CRRT	Rapid fluid removal and frequent hypotension Dialysis disequilibrium and risk of cerebral edema Technically complex
Prolonged (SLEDD)	Slower volume and solute removal than IHD Faster solutes clearance than CRRT Reduced downtime than CRRT Reduced exposure to anticoagulation than CRRT	Faster volume and solute removal than CRRT (increased risk for hypotension and disequilibrium syndrome in prone patients) Technically complex
Continuous (CRRT)	Continuous removal of toxins and solutes (avoid concentration rebound) Hemodynamic tolerability Easy control of fluid balance Avoid disequilibrium syndrome User-friendly machines	Slower solutes clearance than IHD Need for prolonged anticoagulation Reduced possibility of patient's mobilization Hypothermia Increased costs than IHD

IHD intermittent hemodialysis, *SLEDD* sustained low-efficiency daily dialysis, *CRRT* continuous RRT

Accordingly, an increase in RRT intensity in order to reduce mortality cannot be recommended [16].

Currently, a CRRT dose prescription below 20 mL kg^{-1} h^{-1} and over 35 mL kg^{-1} h^{-1} may be definitely identified as the dose-dependent range [17] (Fig. 6.2). In fact, reducing RRT intensity below 20 mL kg^{-1} h^{-1} is likely to negatively affect outcomes due to under-dialysis, while increasing it above 35 mL kg^{-1} h^{-1} might lead to electrolyte disorders and removal of nutrients and drugs, also potentially reducing survival. Conversely, prescriptions between 20 and 35 mL kg^{-1} h^{-1} can be considered as practice dependent: within this range, variables such as timing, patients' characteristics, comorbidities, or concomitant supportive pharmacological therapies may have a significant role in affecting patients' outcome and should trigger a careful prescription and a close monitoring of dose delivery.

Nowadays, a delivered dose (without downtime) between 20 and 25 mL kg^{-1} h^{-1} may be considered as clinically acceptable [17]. From a practical standpoint, considering that average downtime reduces delivered dose by 10–20%, it might be recommended to prescribe 25–35 mL kg^{-1} h^{-1} in order to achieve an actual dose of at least 20–25 mL kg^{-1} h^{-1}. A dose prescription above 35 mL kg^{-1} h^{-1}, which is also associated to increased costs [18], is currently not recommended in any clinical condition.

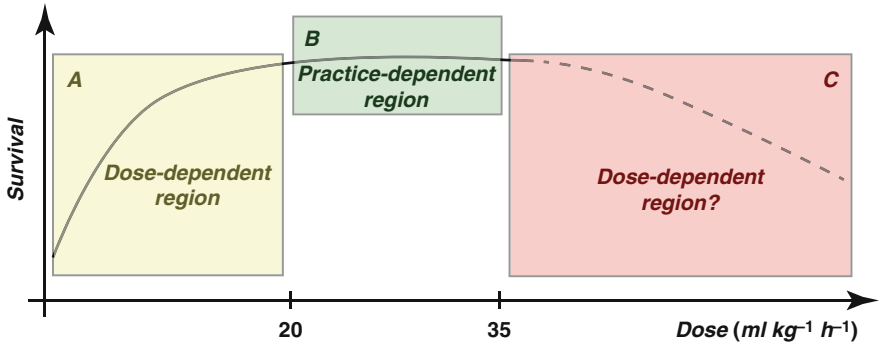

Fig. 6.2 Relationship between delivered dose and patient's survival. Below 20 mL kg^{-1} h^{-1} (panel **a**), the higher the dose the higher patients' survival (dose-dependent region). Above this limit, further increase in dose prescription (up to 35 mL kg^{-1} h^{-1}) may not influence patients' survival (panel **b**). In this range, other variables (e.g., time of treatment, optimization of blood perfusion, drug adjustments) may influence the outcome (practice-dependent region). With further increase of prescribed dose (over 35 mL kg^{-1} h^{-1}), electrolyte disorders and removal of nutrients and drugs (e.g., antibiotics) may occur, potentially reducing survival (panel **c**)

Clinical Summary

Strategy	Side effects	Dose	Notes
Increased intensity of renal replacement therapy	Possible electrolyte disorders and removal of nutrients and drugs (e.g., antibiotics) with effluent dose >35 mL kg^{-1} h^{-1} Increased costs	Increased intensity intended as: Increased effluent dose (≥35 mL kg^{-1} h^{-1}) Daily (rather than alternate-day) dialysis	None recommended in order to reduce mortality A targeted approach depending on the clinical condition may be rather advisable

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