Adequate Dialysis in the ICU - A Multidimensional Aspect

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Prescription and delivery of an adequate treatment is a fundamental issue in a critically ill patient but especially when he or she requires continuous renal replacement therapy. This short review will detail basic concepts related to the dialytic dose and current evidence available on this topic. The paper further expands the concept of adequacy leading to other important dimensions of treatment adequacy.

Efficiency, Intensity, Efficacy

Acute kidney injury (AKI) is frequently observed in critically ill patients, and approximately 6% of the ICU population receives renal replacement therapy (Uchino et al. 2005). Continuous renal replacement therapies (CRRT) represent an extracorporeal dialysis modality particularly suitable for haemodynamically unstable patients who require fluid and solute control (Davenport et al. 1993; Uchino et al. 2001; Swartz et al. 1999). This feature is one of the reasons why many physicians prefer CRRT in intensive care patients rather than intermittent haemodialysis (Uchino et al. 2007). Several factors may affect the efficacy and safety of these procedures (Uchino et al. 2007), and particular attention is usually paid to treatment adequacy, which may allow reproduction, as close as possible, of the function of the native kidney. In this context, CRRT technique and treatment parameters (flows and clearances) are often protocoled, and the adequacy has been generally identified with the concept of dose (quantity of a marker molecule removed over time or as a fraction of the blood flow).

Dialytic dose may be represented in many ways: efficiency (or clearance) of the treatment is the amount of blood cleared by the system over a given period of time (Ricci et al. 2006). The concept of clearance needs to be referred to a particular solute, and it does not represent an actual mass removal, but rather its value normalised for the solute serum (or plasma) concentration. Moreover, considering that CRRT is usually performed over several days or weeks, it is essential to provide information about the total time during which the treatment clearance is maintained. The intensity of treatment is thus expressed as the product of the clearance (instantaneous) and the effective time of treatment (Ricci et al. 2006). Prescribed and effective treatment time may differ significantly. If one calculates the downtime (the amount of time in which the treatment is interrupted), significant difference can be found between the prescribed and the actually delivered doses. Finally, considering the pool of solute (related to volume of distribution) that needs to be cleared, it is possible to express the efficacy of the treatment as the ratio between Intensity (in litres) and the volume of distribution of the marker solute (in litres) (Ricci et al. 2006). The result is a dimensionless number defined as Kt/V (Clearance x time / volume of distribution).

In chronic kidney disease (CKD) patients treated with haemodialysis, efficiency, intensity and efficacy are routinely measured because they correlate with long term outcome (Ronco et al. 1996). In AKI patients treated with CRRT in the ICU, these variables may be grossly estimated considering the effluent flow rate set in the CRRT machine (Uchino et al. 2007) (or directly measured) and then by indexing it over the patient body weight (i.e. if a 60kg patient is treated with 1200 ml/h of isovolaemic postdilution haemofiltration, the treatment dose may be indicated as 20 ml/kg/h). As for every simplification, with this method a relatively broad level of error should be accepted, especially when continuous pre-dilution haemofiltration or continuous haemodialysis are delivered. Furthermore, the estimation does not take into consideration the progressive fall of membrane performance during the length of the session (especially after the first 24 hours). Nevertheless, the ease of this calculation may be very useful in real clinical life (Ricci et al. 2005).

How to Pick the Dose

Several efforts have been made in the literature to define the most adequate dose: the idea is that CRRT delivery may imply a dose-dependent range, where the treatment efficiency correlates with outcomes, and a dose-independent range, in which further improvements will not result in more benefits for these patients. Consequently, during the last decade, several attempts have been made to confirm the first dose proposal (35 ml/kg/h) that showed a direct correlation between CRRT efficiency and patients' outcome (Ronco et al. 2000). However, the RENAL (RENAL Replacement Therapy Study Investigators et al. 2009) and the ATN (VA/NIH Acute Renal Failure Trial Network et al. 2008) studies seemed to definitely confute this evidence. These two large multicentre, randomised controlled trials did not show an improved outcome with a "more intensive dose" (40 and 35 ml/kg/hr respectively) compared to a "less intensive dose" (25 and 20 ml/kg/hr respectively) (Ricci and Ronco 2011). Based on these findings, the current KDIGO guidelines recommend delivering an effluent volume of 20–25 ml/kg/hr for CRRT in patients with AKI (Kidney Disease: Improving Global Outcomes 2012).

In addition, by comparing two multicentre CRRT databases, Uchino et al. found that treating patients with AKI with low-dose CRRT was not associated with worse shortterm outcome compared to patients treated with what is currently considered the standard dose (Uchino et al. 2013). In particular, comparing patients from The Beginning and Ending Supportive Therapy (BEST) study (Uchino et al. 2005) and from the Japanese Society for Physicians and Trainees in Intensive Care (JSEPTIC) Clinical Trial Group (Kawarazaki et al. 2013), the author observed no differences between groups of patients treated with doses of 14.3 ml/kg/hr and 20.4 ml/kg/hr.

Finally, considering that high-dose CRRT could lead to electrolyte disorders, removal of nutrients and drugs (e.g. antibiotics) and high costs (Rimmele and Kellum 2011), but at the same time low-dose may expose patients to undertreatment thus worsening outcome, seeking the range of adequate treatment dose is a crucial issue. Nowadays, it is considered as clinically acceptable an actually delivered dose (without downtime) between 20 and 35 ml/kg/hr (Uchino et al. 2013). In particular a dialytic dose under 20 ml/kg/hr and over 35ml/kg/hr may be definitely identified as the dose-dependent range. On the other hand, the doses between these two limits can be considered as practicedependent, and variables such as timing, patient characteristics, comorbidities or concomitant supportive pharmacological therapies may have a significant role for patients' outcome.

How to Customise the Dose

The innovations in diagnosis, classification and prevention of AKI and the development of fourth generation CRRT machines, specifically designed for critically ill patients with particular attention to safety features and accuracy, have modified the idea that dialysis in these patients is indicated only after the development of anuria. The redefinition of AKI treatment, different than mere renal replacement therapy, allows modulation of the timing, indication and prescription for personalised renal support therapy. In this context, it could be speculated that conventional protocoled treatments (that in most cases might be seen as "rescue therapies") are substituted by proactive therapy, which can be modulated according to the different phases of patient clinical condition observed during the ICU stay (Ricci et al. 2011).

In these terms, dose, filter membrane characteristics, anticoagulation and fluid solution should be utilised to tailor the treatment to patients' specific needs.

One of the key issues of the modern concept of renal support therapy is the clinical target: deriving from nephrology considerations, urea is the main solute, which has been referred as the biomarker indicating how efficiently solutes are removed. However, urea is not the only solute accumulated during kidney injury and its kinetics of removal and its volume of distribution differ from the other uraemic toxins (Ricci et al. 2006). Moreover, considering urea as a target solute may lack clinical usefulness. Unlike patients with chronic kidney disease (CKD), uraemic symptoms are rarely observed in the ICU, and usually do not affect clinical decisionmaking regarding CRRT in these patients (Ricci and Ronco 2012). Other target solutes, different from urea, should be considered in ICU patients. In particular, CRRT should be directed at specific targets during specific clinical conditions (e.g. myoglobin in a patient with compartment syndrome, interleukins during septic episodes, novel biomarkers in case of early AKI, fluid balance in case of fluid overload). This concept would also redefine the concept of adequacy itself, including not only the amount of dialysis to provide but also the exact circuits, filters, machines and timing.

Fluid overload probably deserves a dedicated paragraph: it is currently considered one of the most important indications for CRRT in the ICU. Although not easy to assess and currently not included in any standardised definition, the fluid removal (net ultrafiltration) obtainable during CRRT can be personalised to patient clinical condition and should be carefully targeted. For example, in a post hoc analysis of the RENAL trial the authors showed that duration of mechanical ventilation, length of stay and survival was significantly improved if negative fluid balance was reached before 48 hours after CRRT start (RENAL Replacement Therapy Study Investigators et al. 2012). Much effort will have to be paid in the near future in the field of monitoring fluid administration, fluid loading and fluid downloading.

Furthermore, although operatively simple and, by analogy with CKD patients, potentially related to hard outcomes, a target-based approach might be too simplistic and "monodimensional". Dimensions of adequacy other than dose, e.g. body fluid composition modification, electrolyte, acid-base or tonicity control, should be evaluated in critically ill patients (Ricci et al. 2006) (see Figure 1).

Anticoagulation (and filter patency) is another fundamental issue strictly related to dialysis delivery and to the personalised prescription of an adequate CRRT treatment. Systemic and regional anticoagulation, as well as heparin grafting membranes, are potentially able to reduce the filter clotting and consequently the membrane fouling. Analysing data from the PICARD study, Claure-del Granado et al. Evaluated the association of anticoagulation strategy used on solute clearance efficacy and circuit longevity (Claure-del Granado et al. 2014). In particular the authors showed that, if compared to heparin or no anticoagulation, the use of regional citrate for anticoagulation in CRRT significantly prolonged filter life and increased its efficacy in term of delivered dose (Claure-del Granado et al. 2014). Despite the most recent guidelines suggesting use of regional citrate anticoagulation in patients without contraindications (Kidney Disease: Improving Global Outcomes 2012), systemic unfractioned heparin remains the most used anticoagulation during CRRT. The anticoagulation choice could also be referred to the therapeutic target to be obtained for that specific patient, and depends on his or her clinical condition, vascular access, kind of membrane and target solutes, which have to be removed. In a prospective study on septic patients, De Vriese et al. clearly demonstrated that membrane dysfunction affected cytokine clearance during CRRT treatment (De Vriese et al. 1999). Unfortunately, this predictable mechanism is not simply quantifiable in clinical practice. When the membrane fouling occurs and clearance of urea (a 60-dalton non protein-bound molecule) falls by 20%, the clearance of larger solutes may have already been impaired in the CRRT circuit life span (Pasko et al. 2011). In this context, if middle molecular weight molecules are the solute target to be removed, accurate anticoagulation should be performed also to ensure that an adequate sieving coefficient for these molecules is maintained for a long period of time.

Attention has to be paid to the dialysate and replacement solutions used during CRRT. An adequate control of electrolyte and acid-base disturbances is usually obtained through a personalised choice of modality of depuration and fluid solutions utilised. The specific ion composition

in the dialysate or in the replacement solutions allows, for example, a more accurate control of hyperkalaemia or phosphate reintegration during CRRT. In particular, hypophosphataemia has been reported in up to 80% of cases when standard CRRT solutions are used (Demirjian et al. 2011; VA/NIH Acute Renal Failure Trial Network et al. 2008; RENAL Replacement Therapy Study Investigators et al.2009). The adoption of phosphate-containing CRRT solutions could be helpful to reduce the incidence of RRT-related phosphate depletion, and to minimise the requirement of parenteral supplementation (Broman et al. 2011).

Figure 1. Several Patient Characteristic Have to be Evaluated (in this figure dimensionless graphic representation is offered) in order to personalize the CRRT in the ICU and the treatment characteristics consequently modelled to be adequate for the actual patient necessities
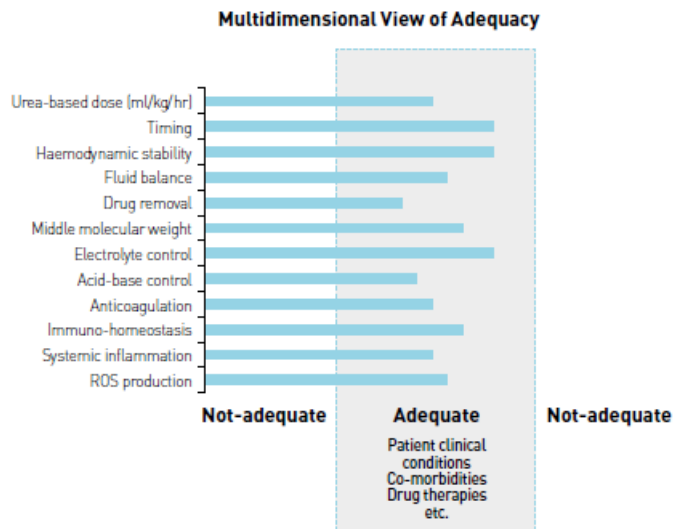
The different buffers and their balance mass evaluation may allow restoration of acid-base homeostasis in critically ill patients when the underlying cause is going to be resolved. In these patients, acidosis is usually due to increased unmeasured anions and hyperlactataemia: CRRT is able to correct these conditions affecting the patient's strong ion gap, phosphate and chloride concentrations and, in particular in persistent hypoalbuminaemic patients, may further lead to metabolic alkalosis (Naka and Bellomo 2004). The nature and extent of acid–base changes are related to the treatment intensity and to the 'buffer' content of the replacement fluid/ dialysate, with different effects depending on whether lactate, acetate or bicarbonate is used (Naka and Bellomo 2004). Moreover, during regional anticoagulation performed with citrate, the amount of citrate returning to the patient and metabolised by the liver and the skeletal muscle in the Krebs cycle results in bicarbonate production providing buffer supply to the patient. The amount of citrate administered to the patient has to be evaluated for the buffers mass balance (Morabito et al. 2013).

In conclusion, a specific treatment that could be defined "adequate" for all patients in all conditions does not exist but, like mechanical ventilation, CRRT should be continuously tailored to patients' characteristics and their actual clinical needs. Dialytic prescription is a recipe where different ingredients have to be adequately balanced from patient to patient and it is not to be seen as an index derived from the rigid application of simplified recommendations.

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