Continuous renal replacement therapy: individualization of the prescription

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Purpose of review
Continuous renal replacement therapy (CRRT) is now the mainstay of renal organ support in the critically ill. As our understanding of CRRT delivery and its impact on patient outcomes improves there is a focus on researching the potential benefits of tailored, patient-specific treatments to meet dynamic needs.

Recent findings
The most up-to-date studies investigating aspects of CRRT prescription that can be individualized: CRRT dose, timing, fluid management, membrane selection, anticoagulation and vascular access are reviewed. The use of different doses of CRRT lack conventional high-quality evidence and importantly studies reveal variation in assessment of dose delivery. Research reveals conflicting evidence for clinicians in distinguishing which patients will benefit from 'watchful waiting' vs. early initiation of CRRT. Both dynamic CRRT dosing and precision fluid management using CRRT are difficult to investigate and currently only observational data supports individualization of prescriptions. Similarly, individualization of membrane choice is largely experimental.

Summary
Clinicians have limited evidence to individualize the prescription of CRRT. To develop this, we need to understand the requirements for renal support for individual patients, such as electrolyte imbalance, fluid overload or clearance of systemic inflammatory mediators to allow us to target these abnormalities in appropriately designed randomized trials.

Keywords
acute kidney injury, continuous renal replacement therapy, critical care

INTRODUCTION

Worldwide, continuous renal replacement therapy (CRRT) forms the cornerstone of supportive care for critically ill patients with severe acute kidney injury (AKI) [1]. Historically, the evidence informing the prescription and delivery of CRRT has been derived from studies in which aspects of CRRT delivery have been investigated under the underlying assumption that the 'optimum' prescription of CRRT will be the same in all patients at all points during an individual's need for renal replacement therapy. Thus, while clinical studies do provide valuable information to guide baseline standards of CRRT delivery uncertainty remains in how best to adapt and personalize CRRT delivery to individual patient's needs. For instance, 10 years ago two landmark trials [2,3] established an effective dose for CRRT in critically ill patients with AKI, however there remains an ongoing need to investigate a more individualized therapy to meet the requirements of specific clinical scenarios including AKI subtypes [4]. To this end the 17th Acute Disease Quality Initiative Consensus Conference meeting in Asiago, Italy (10–13 June 2016) 'Precision Continuous Renal Replacement Therapy' outlined an extensive research agenda to enhance, deliver and monitor a dynamic CRRT prescription tailored to meet the individual solute and fluid requirements of patients [5–7]. With these recommendations in mind, we assess the most recent evidence that might support precision CRRT through individualization of its prescription and delivery (Table 1).

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KEY POINTS

- Good evidence to guide individualization of CRRT is currently lacking as such there remains much variability in CRRT delivery.
- The use of different doses of CRRT lack conventional high-quality evidence and there is conflicting evidence for clinicians in distinguishing which patients will benefit from 'watchful waiting' vs. early initiation of CRRT.
- Both dynamic CRRT dosing and precision fluid management using CRRT are difficult to investigate and currently only observational data supports individualization of prescriptions.

INDIVIDUALIZATION OF DOSE

Dose of CRRT is commonly calculated as the ultrafiltrate in continuous veno-venous hemofiltration, delivered dialysate volume in continuous veno-venous haemodialysis (with slow dialysate flow rates much less than the blood flow rate) and a combination of both for continuous veno-venous hemodiafiltration. The resulting volume often expressed as effluent flow rate in millilitres per hour or millilitres per kilogram of body weight per hour (ml/kg/h) is a reasonable surrogate for clearance of small molecules such as urea. Based on results of various studies, the Kidney Disease: Improving Global Outcomes (KDIGO) AKI guidelines [8] recommends a target dose of 20–25 ml/kg/h, but also allows for dynamic adjustment of dosing to meet the needs of acute illness. Although there is no evidence to demonstrate dynamic dosing of CRRT improves short or long-term outcomes, individualized management is inherently difficult to research. Even in the randomized studies establishing dose-recommendations important patient groups were excluded such as those with extremes of weight or advanced chronic kidney disease (CKD) and variation from protocol occurred in cases in which metabolic abnormalities were persistent on the original prescription. Importantly current dose-recommendations don't cover commonly practiced adjustment of CRRT dose in the context of severe acute metabolic abnormalities or recovery and clinical stability. Furthermore, while dose-recommendations for CRRT prescription may be wildly adopted delivery of treatment to these targets is often poorly assessed as highlighted by a recent systematic review evaluating quality measures for CRRT which reported that many aspects of CRRT therapy such as solute removal were inconsistently evaluated with no clear benchmark for CRRT delivery assessment [9▪].

To this end the need for additional markers of solute clearance and consequently efficacy of delivered CRRT has been emphasized by expert consensus groups [7]. One suggestion has been to refining dose-assessment based on effluent flow rate to a CRRT-specific, standardized Kt/V (Clearance of Urea over Time Indexed to Urea Distribution Volume) [10▪], however while more theoretically sound it is unclear if the additional complexity is clinically useful at the bedside. Overall our ability to tailor

Table 1. The continuous renal replacement therapy prescription domains and areas for individualization

Prescription domains	Parameter	Potential situations for individualization	Potential pitfalls of prescription
Dose	Effluent flow rate	Solute load Acidosis Electrolyte disturbances	Antibiotic removal Disequilibrium Micronutrient losses Alkalosis
Timing	Criteria for commencing therapy	Postoperative AKI Fluid overload	Inappropriate therapy Nonrecovery of renal function
Ultrafiltration	Fluid removal rate	Fluid overload	Hemodynamic instability and organ injury
Replace/dialysis fluid	Fluid electrolyte composition	Electrolyte abnormalities	Inappropriate rates of correction Clinical errors
Membrane	Adsorption properties	Sepsis and systemic inflammation	Removal of beneficial exogenous and endogenous substances (antibiotics, albumin, etc)
Anticoagulation	Anticoagulant choice	Bleeding diathesis, mitochondrial dysfunction, liver dysfunction	Bleeding, circuit loss, citrate accumulation, heparin-induced thrombocytopenia
Vascular access	Anatomical site	Poor filter lifespan difficult vascular anatomy	Short and long-term complications of line insertion

AKI, acute kidney injury.

CRRT dose is limited if we cannot guarantee achieving standardized doses when prescribed. In the DO-RE-MI prospective observational study [11] significant variability of delivered dose of CRRT was seen between patients during the course of treatments within individuals. In several studies the delivered CRRT dose has been shown to be 20–30% below that prescribed with unintended circuit loss and attendant filter downtime the principal cause [11–13]. Improvements in CRRT technology to assist clinicians in the accurate delivery of target dose and improve dose-assessments are becoming available such as downtime dose compensation but their effectiveness remains to be investigated [6].

The concept of tailoring CRRT intensity to the demands of illness has been further explored by analysing the effect of dosing on specific categories of critically ill patients. Several studies have failed to show any benefit of higher doses of CRRT in patients with sepsis [14,15] similar outcomes in meta-analysis of CRRT dosing studies were not influenced by the percentage of patients with sepsis or septic shock suggesting overall conclusions on intensity of CRRT pertain to a sepsis subgroup [16]. Similarly, patients with liver failure represent a group with potential to benefit from higher intensity CRRT, with data associating the reduction in ammonia with improved clinical outcomes [17], yet a post-hoc analysis of the liver dysfunction subgroup of the the Randomized Evaluation of Normal vs. Augmented Level Replacement Therapy study did not show that an increased intensity reduced mortality [18]. In addition, patients with liver dysfunction prescribed with a higher dose often failed to achieve the prescribed dose and experienced a higher rate of hypophosphatemia. A small, prospective study investigating higher dose continuous veno-venous haemofiltration (CVVH) in burns patients showed no difference in mortality compared with a normal dose except in the subgroup of patients with the severest burns [19]. Similarly in rhabdomyolysis, in which biological plausibility exists for higher intensity CRRT to remove myoglobin there are no sufficiently powered randomised controlled trials (RCTs) to provide evidence of efficacy. Thus, there continues to be a lack of support for higher intensity CRRT based only on distinct patient groups. On the one hand this may suggest that a one size fits all approach to CRRT intensity is the correct one, however on the other it is possible that individual patient factors may be more important than overarching clinical categories, that may vary greatly in clinical context and severity.

Importantly, while the benefits of higher dose CRRT are not clear the presumption that it may benefit some patients must be tempered against the possibility of harm with greater intensity of treatment. A recent collaborative, individual patient data meta-analysis [20▪], demonstrated a longer time to cessation of renal replacement therapy in patients receiving a higher intensity regime. The study included both CRRT and intermittent modalities, but subgroup analysis showed consistent findings between groups and therefore emphasizes the lack of evidence and potential for harm of more intensive CRRT regimes. Furthermore, the association of higher doses of CRRT with electrolyte disturbances has become increasingly recognized as has the impact of CRRT on other important factors such as antibiotics and micronutrients [21,22]. Thus, individualization of the CRRT prescription has to be accompanied with individualization of other therapies. Concern has been raised regarding significant under dosing of antibiotics, often one of the essential treatments offered to critically ill patients [23] and the increases in chance of resistance and treatment failure eventually leading to an increasing number of antibiotics being used. Studies of the pharmacodynamic and pharmacokinetic characteristics of antibiotics in critically ill patients on CRRT are lacking with a move towards therapeutic drug monitoring (TDM) as the ideal assessment measure [24]. A recent study assessing the use of TDM to guide β-lactam therapy reported 35% of patients required dose adjustment [25], while the impact on outcomes remains to be studied in patients receiving CRRT. The availability and practicalities of TDM limit its widespread use for all antibiotics and although modelling based on pharmacodynamic principles of common antibiotics has provided some reassurance regarding predicted therapeutic levels across the range of KDIGO recommended CRRT dosing (20–35 ml/kg/h) [26], the changing and complex fluid dynamics of critically ill patients is a major limitation to such methods [22].

The clearance and requirement of micronutrients including trace elements and vitamins for patients receiving CRRT has been the subject of recent investigations. Kamel *et al.* [27] reported 80% of patients in a retrospective study to have a below-normal level of at least one micronutrient. Little guidance exists as to the best practice for the prescription of vitamins for patients receiving CRRT. Similarly, research is developing into the impact of CRRT on calorie intake and the metabolic demands of critically ill patients with a citrate-dextrose regional anticoagulation and dextrose-containing replacement fluid in a CVVH circuit shown to significantly contribute to calorie intake [28]. Future work is needed to assess the impact of nutritional changes in CRRT on patient centred outcomes.

INDIVIDUALIZATION OF TIMING

Two recent RCTs [29,30] in two populations of critically ill patients failed to provide consensus on when to initiate RRT and could not support data from observational trials that suggested early initiation may be better. As we await the completion of a large multicentre RCT, Standard vs. Accelerated Initiation of RRT in Acute Kidney Injury, NCT02568722 further commentary and analysis from both ELAIN (Effect of Early vs. Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury) and AKIKI (Artificial Kidney Initiation in Kidney Injury) has recently been released. Although the ELAIN study only analysed CRRT, AKIKI also included multiple forms of RRT including intermittent and extended duration hemodialysis, further complicating its application to CRRT delivery. A post-hoc analysis of the AKIKI trial adult respiratory distress syndrome (ARDS) and septic shock cohorts supported the original trial results showing no benefit of starting early RRT in these important subgroups that might be expected to most benefit [31▪]. In addition, a further, smaller post-hoc analysis of AKIKI supported a hypothesis that early RRT in patients with underlying CKD might be harmful [32]. Conversely a post hoc analysis from the ELAIN study which extended follow-up to 1 year after the study enrolment found less major adverse kidney events (a composite outcome for persistent renal dysfunction, dialysis dependence and mortality) at 1 year [33▪]. Important differences between these studies in case-mix and the presence of RRT indications such as fluid overload suggest that the differential results could be explained by patient-specific factors. This raises the possibility that earlier RRT may be beneficial in some circumstances (postoperative AKI with fluid overload), but harmful in others (patients with advanced CKD). Distinguishing which patient will benefit from 'watchful waiting' and which could benefit from early initiation of CRRT remains a difficult challenge for critical care clinicians. Irrespective of the actual guidelines, variable and inconsistent clinical practice may itself contribute to poorer outcomes and use of algorithms to decide on when to initiate CRRT may be of potential benefit merely by ensuring consistency of practice [34▪].

In comparison with commencement of RRT, there are few studies to provide evidence for decisions on when to stop CRRT. The role of restoration of spontaneous urine output as a predictor of successful discontinuation of RRT is well described, while more recent research has suggested roles for urinary and serum biomarkers, including serum cystatin C [35], in a prospective study of patients receiving CRRT, however none of these results have been reproduced.

INDIVIDUALIZATION OF FLUID MANAGEMENT

The ADQI-17 consensus statement suggests precision fluid management in CRRT should incorporate effects on the patient's fluid balance, circuit integrity and plasma composition [5]. This dynamic process should be tailored to the demands of the patient and requires a balance between net fluid removal to enable treatments such as antibiotics and net fluid intake to achieve haemodynamic targets. The association of fluid accumulation with mortality is well reported [36–38] and is particularly strong in the context of AKI. A recent retrospective study supported deresuscitation of patients with iatrogenic fluid overload and showed reduced mortality when a minimal fluid balance was targeted at day 3 using diuretics and/or RRT [39▪]. Focused studies on the specific role of CRRT on fluid removal in such patients are not currently available and a recent pilot study testing a fluid removal strategy including use of CRRT in critical illness suggests it will be challenging to acquire this data, as inclusion rates were very low [40▪]. Haemodynamic instability at or near the initiation of CRRT has been associated with poorer outcomes and may limit fluid removal. A recent systematic review of RRT associated haemodynamic instability identified only two CRRT trials examining interventions for hypotension related to CRRT, and found no evidence to recommend specific approaches to treatment [41]. Given the lack of evidence the ideal timing of fluid removal, ideal target fluid balance and methods of achieving a precision fluid balance have been identified as key future research questions [5].

Although there are many different types of CRRT replacement fluid available with a range of different electrolyte compositions and buffers, there is little evidence available to help guide a clinician's selection of fluid replacement in patients while is often manufacture and protocol rather than patient-specific. Severe electrolyte abnormalities, particularly those of serum sodium, are a situation in which tailoring of CRRT prescription and solutions is strongly indicated to prevent over rapid correction of abnormalities, however specific protocols remain based on expert advice and experience from small case series [42,43] with little prospect of conventionally defined high-quality evidence becoming available to guide clinicians in this important area.

INDIVIDUALIZATION OF MEMBRANE

Modifications to the membranes used in CRRT offer the potential to enhance removal of a range of potentially harmful compounds such as the inflammatory mediators present in patients with septic AKI [44]. A recent in-vitro study [45▪] investigating the varying adsorption properties of advanced devices including oXiris membrane, highlights their potential for removing endotoxin and other inflammatory mediators to modulate the immune response in patients with sepsis, however large prospective randomized clinical trails have not yet been performed. Alternatively, instead of adsorption, high cut-off filters allow the removal of a wider range of higher molecular weight mediators due to their increased pore sizes [46]. However, a RCT investigating the treatment of critically ill patients with high cut-off membranes revealed no reduction in vasopressor support or mortality [47▪]. These data support the current view point that strategies individualizing the membrane use in CRRT remain experimental.

INDIVIDUALIZATION OF ANTICOAGULATION

Regional citrate anticoagulation is now recommended as mode of anticoagulation of choice for CRRT [8], based on studies which demonstrate improved filter life, less systemic bleeding and thus a better delivery of treatment [48]. However, this recommendation remains to be supported by evidence from large multicentre studies and the completion of Investigating Different Anticoagulants for Renal Replacement Therapy trial (NCT02669589) will provide further information on filter life-span and stronger data regarding any influence on survival. In 2017, two studies highlighted the role of hyperlactemia in predicting citrate intolerance (failure of systemic citrate metabolism), suggesting that changes in serum lactate can help guide clinician's individualization of mode of anticoagulation as reflected in many contemporary citrate RCT protocols [49,50]. The importance of anticoagulation to maintain circuit integrity was supported further by a recent RCT which showed the effect of lowering the filtration fraction via increasing the blood pump speed offered no improvement in circuit life, suggesting anticoagulation instead was the predominant factor [51].

INDIVIDUALIZATION OF ACCESS

Dialysis catheter placement, including anatomical site and catheter tip position, can have effects on the life-span of the CRRT circuit. A post-hoc analysis of the Acute Renal Failure Trial Network Study exploring the patterns of catheter insertion and associated impact on CRRT delivery highlighted the impact of patient characteristics such as high BMI, presence of coagulopathy and diagnosis of peripheral vascular disease on catheter placement [52]. In addition, the analysis suggested that placement in the subclavian vein resulted in lower flow rates and increased frequency of clotting. In an extensive review of nonanticoagulant factors associated with filter life in CRRT [53], jugular and femoral sites resulted in better filter longevity than subclavian catheters. The authors also reported no significant differences in filter lifespan when using different catheter types. Thus, individualizing access to enhance CRRT delivery, is another important aspect of a personalized RRT prescription.

CONCLUSION

Failure to develop high-quality evidence to support either more intensive or earlier use of CRRT for AKI in mixed critically ill populations has encouraged very standardized protocols for prescription and delivery of CRRT during critical illness. However, in clinical practice, use and delivery of CRRT has been shown to be very variable. In the absence of strong positive evidence some clinicians individualize CRRT prescription on the basis of clinical intuition while others adopt a *laissez-faire* approach to CRRT delivery. In fact, many common clinical scenarios fall outside the scope of the available evidence base. Potential therefore exists for prescriptions specific to the requirements of individual patients and their illnesses, but this probably does not extend to broad definitions such as septic-AKI which is actually very heterogenous. However, good evidence to guide individualization of therapy is currently lacking. To develop this, we need to understand the key requirement for renal support in an individual, such as electrolyte imbalance or fluid overload, and to target these abnormalities in appropriately designed randomized trials. Finally, as delivery of any individualized prescription is highly dependent on filter lifespan and performance, individualization of operational aspects of CRRT such as catheter position and anticoagulation, is a key adjunct to reliably deliver an individualized prescription.

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