The future of continuous renal replacement therapy

Emily See MBBS[1,2,3], Claudio Ronco MD[4,5,6], Rinaldo Bellomo MBBS[1,3,7]

Affiliations

1. Department of Intensive Care, Austin Hospital, Heidelberg, Melbourne, Victoria Australia
2. Department of Nephrology, The Royal Melbourne Hospital, Parkville, Melbourne, Victoria, Australia
3. Centre for Integrated Critical Care, School of Medicine, University of Melbourne, Parkville, Melbourne, Victoria, Australia
4. Chair of Nephrology, Department of Medicine, University of Padova, Padova, Italy
5. International Renal Research Institute of Vicenza (IRRIV), Vicenza Italy
6. Department of Nephrology, San Bortolo Hospital, Vicenza, Italy
7. Department of Intensive Care, The Royal Melbourne Hospital, Parkville, Melbourne, Victoria, Australia

Corresponding author:

Prof. Rinaldo Bellomo

Department of Intensive Care

Austin Hospital

Heidelberg, Victoria 3084

Australia

Tel: +61-3-9496 5992

Fax: +61-3-9496 3932

rinaldo.bellomo@austin.org.au

Abstract: 205

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/SDI.12961

Word count: 3390

Figures/tables: 3/1

Keywords: continuous renal replacement therapy; hemodiafiltration; hemodialysis; hemofiltration; prescription; information technology.

DR. EMILY SEE (Orcid ID : 0000-0003-4436-4319)

Article type : Special Issue Article

The future of continuous renal replacement therapy

Abstract

Over the last 40 years, acute renal replacement therapy (RRT) in the intensive care units (ICUs) of high-income countries has transitioned from the predominant use of intermittent haemodialysis (and the much less common use of peritoneal dialysis) to the almost exclusive use of continuous renal replacement therapy (CRRT). Accordingly, CRRT has become one of the most common forms of vital organ support delivered to critically ill patients. A series of clinical and technical advances has enabled the transformation of basic CRRT machines into highly sophisticated and customised devices. Recent work has focused on using evidence from clinical trials to enhance the application of CRRT with regard to timing of initiation, choice of modality, dose, and anticoagulation. However, many questions remain unanswered. Uncertainty surrounding volume control and the utility of strategies to minimise circulatory stress are key areas for future development. Advances in membrane technology, combination with other extracorporeal therapies, and personalisation of CRRT delivery may provide additional benefit to certain subgroups. Development of quality metrics and use of data analytics to audit and benchmark could provide important insight into practice, while biofeedback and automated CRRT prescription could increase safety. In this review, we summarise the evolution of CRRT and highlight several future areas for development.

Introduction

The increasing availability of mechanical ventilation and vasoactive drugs in the 1970s meant that a growing number of patients in the intensive care unit (ICU) survived long enough to develop 'acute renal failure' and require renal replacement therapy (RRT). Although established in the chronic setting, the application of intermittent haemodialysis and peritoneal dialysis to critically ill patients was associated with substantial morbidity and mortality. Peritoneal dialysis could not achieve adequate solute control in patients who were highly catabolic and the high glucose content of dialysate solutions caused hyperglycaemia and increased the risk of peritonitis.[1] Vasopressor-dependent patients were unable to tolerate rapid removal of fluid and osmotically active solutes with intermittent haemodialysis.[2] Severe cardiovascular instability was a common complication of this therapy and mortality rates were as high as 70%.[3]

The need to develop an alternative dialytic technique for critically ill patients who could not tolerate conventional therapies led to the inception of continuous renal replacement therapy (CRRT). In contrast to other forms of RRT, CRRT was able to deliver solute clearance, volume removal, thermal control, and acid-base regulation without compromising haemodynamic stability. It also proved successful at controlling plasma tonicity and removing non-uraemic water-soluble toxins, which had been found to accumulate in specific conditions (e.g. ammonia in severe acute liver failure and creatine kinase in rhabdomyolysis). Accordingly, CRRT came to represent the dominant form of RRT in the ICU of high-income and many middle-income countries and one of the most common forms of vital organ support provided to critically ill patients.

Since its inception, CRRT has undergone significant transformation. Machines have become increasingly sophisticated, double lumen catheters permit venovenous therapy, dual-port filters allow the addition of diffusion to convection, and membranes are more biocompatible and efficient. Randomised controlled trials have informed CRRT prescription. Still, the therapy has far to go and to understand the future, one has to understand the past. In this article, we will summarise the evolution of CRRT and highlight key areas for future development.

The evolution of CRRT

Introduction of continuous renal replacement therapy

The earliest form of CRRT was continuous arteriovenous haemofiltration (CAVH). First performed in 1977, this technique involved cannulation of the femoral artery and vein to create an arteriovenous circuit.[4,5] Arterial pressure drove blood through a haemofilter and provided sufficient transmembrane pressure to generate an ultrafiltrate. Ultrafiltration was controlled manually by altering the height of the effluent bag with respect to the haemofilter. An electrolyte solution similar to plasma water replaced the ultrafiltrate. The rate of ultrafiltration was proportional to the solute clearance, while the difference between the rates of ultrafiltration and replacement fluid administration reflected the fluid balance. Having been safely performed in adults for several years, CAVH was trialled in critically ill paediatric and neonatal cohorts from the mid-1980s.[6]

Addition of diffusion to convection

Although well tolerated, CAVH provided limited solute clearance, which was often insufficient for hypercatabolic patients.[7] The addition of diffusive solute clearance to CAVH was made possible by the introduction of dual-ported haemofilters that permitted countercurrent dialysate flow. Originally designed for intermittent haemodialysis, the use of these haemofilters more than doubled solute clearance because dialysate flow rates could be titrated up to 1.5 to 2L per hour.[8] First available in 1983, techniques combining diffusion and convection greatly increased in popularity throughout the late 1980s and early 1990s. This created an opportunity for the commercial production of dedicated dialysis fluids (for use as dialysate and replacement fluid), which were initially buffered by lactate and subsequently bicarbonate.

Transition to venovenous modes

Arteriovenous therapies presented several limitations. Cannulation of the femoral artery increased the risk of limb ischaemia. Periods of hypotension led to haemofilter clotting due to poor blood flow. Regular monitoring and adjustment of the height of the effluent bag were required to control ultrafiltration according to variations in arterial blood pressure and

progressive membrane fouling. The addition of peristaltic pumps to CRRT machines and the adoption of double-lumen vascular catheters made venovenous techniques possible.[9] By the mid-1980s, continuous venovenous haemofiltration (CVVH), continuous venovenous haemodialysis (CVVHD), and continuous venovenous haemodiafiltration (CVVHDF) replaced CAVH.[10] CRRT machines progressively became more sophisticated and soon provided automated control of ultrafiltration and dialysate delivery with sufficient precision to achieve therapeutic goals.

First to fourth generation CRRT machines

Although the first generation of CRRT machines closely resembled those used for intermittent haemodialysis, the second generation of CRRT machines (e.g. the Prisma machine) represented the first dedicated CRRT-specific platform. Integration of the many components of the extracorporeal circuit (i.e. blood pump, ultrafiltrate pump, reinfusion pump, and anticoagulation management) into a single system led to improved safety and performance.[11] Third generation CRRT machines (e.g. the Prismaflex, Multifiltrate, Aquarius) were capable of delivering higher volumes of convection and more complex therapies. They also offered improved software capability, with user-friendly interfaces that enhanced the timely communication of critical information from the machine to the clinician. Disposable kits with preassembled filter and line sets allowed rapid and automated priming. Paediatric-specific CRRT machines have also been released (e.g. CARPEDIEM).[12] Most recently, fourth generation CRRT machines (e.g. the Prismax, ACUsmart, OMNI) have become available. These machines offer increased automation, more accurate delivery of the prescribed CRRT dose, and improved precision of fluid balance to increase the safety and reliability of treatments.

Themes of modern CRRT

Timing of CRRT initiation and cessation

With the availability of sophisticated, dedicated machines and devices for CRRT, the focus of recent work has shifted to optimising the prescription of CRRT. Several large clinical trials have evaluated whether the timing of CRRT initiation influences outcome. Although

preliminary studies suggested that early initiation of CRRT may be associated with improved clinical outcomes, subsequent randomised controlled trials have failed to demonstrate a consistent benefit.[13,14] Accordingly, decisions surrounding the initiation of CRRT are largely driven by clinical judgement and the presence and severity of metabolic and volume status derangements. For patients in whom CRRT has been initiated, evidence to guide cessation of therapy is less clear. Observational studies have identified that higher urine output, higher creatinine clearance, and lower serum creatinine predict successful CRRT cessation.[15,16] However, large trials in this area have not been performed. Uncertainty surrounding the optimal timing of CRRT discontinuation is reflected in the consensus recommendation that CRRT should be discontinued when kidney function has recovered sufficiently to reduce the demand-capacity imbalance to acceptable levels.[17]

Choice of CRRT modality

The capability of modern machines to perform multiple forms of CRRT (i.e. CVVH, CVVHD, CVVHDF) prompted investigation into whether the choice of CRRT modality contributes to patient outcome. Theoretically, diffusive therapies are capable of delivering a higher dialysis dose without increasing the filtration fraction, while convective therapies offer superior middle- and large-molecule clearance. Current evidence does not support the superiority of one modality over another, although study populations have been heterogeneous.[18] Until further evidence is available, it is recommended that the choice of CRRT modality be made based on local expertise and resources.

Prescribed CRRT dose

The dose of CRRT has been the subject of several large randomised controlled trials. These trials failed to demonstrate a survival benefit with high dose CRRT (>35 to 40 mL/kg/h) compared to standard dose CRRT (20 to 25 mL/kg/h).[19,20] However, subsequent work has highlighted that specific patient subgroups (e.g. patients with hyperammonaemia) may benefit from a higher dose.[21] Moreover, the non-specific removal of a broad range of inflammatory mediators was considered potentially beneficial in patients with sepsis. This observation was the rationale for testing high-volume ultrafiltration (>50 mL/kg/h) in combination with coupled plasma filtration-adsorption (CFPA) as an immunomodulatory

treatment in sepsis.[22,23] Although it was hypothesised that removal of inflammatory mediators could reconstitute immune homeostasis, this has, so far, not been confirmed by randomised controlled trials.[24]

Anticoagulation

Significant progress in the modern era of CRRT has also been made with respect to anticoagulation to maintain circuit patency. Regional and systemic anticoagulation regimens are currently available, with regional citrate anticoagulation and unfractionated heparin being the most commonly prescribed. A meta-analysis of randomised controlled trials found that regional citrate anticoagulation reduced the risk of circuit loss, filter failure, bleeding and heparin-induced thrombocytopaenia compared to heparin.[25] As such, this approach is preferred in many countries and newer CRRT machines have integrated software to automate and modulate citrate delivery.[26]

The future of CRRT

The future of CRRT will involve a number of technical changes, technological innovations, scientific and trial-based insights, and electronic medical records/informatics-based advances in monitoring, which will aim to address aspects of CRRT that remain suboptimal and to identify problem areas that require performance improvement (Table 1).

Volume control

Achieving optimal control of volume status is of paramount importance in CRRT. Volume status is a key determinant of haemodynamic stability, organ function (including the kidney), and patient outcome (Figure 1). Data from several large studies have demonstrated that positive fluid balance in patients receiving CRRT is associated with worse survival at 60 days.[27–29] On the other hand, data from the RENAL study showed that a negative daily fluid balance was associated with improved clinical outcomes, including a decreased risk of death at 90 days, an increased number of RRT-free days, and reduced intensive care and hospital length of stay.[30] Despite its clear importance, randomised controlled trials comparing volume

control strategies have not yet been performed, but will be a key area of research focus in the next decade.

Assessment of volume status

In light of the apparent contribution of volume control to patient outcome, robust methods to objectively estimate total and compartmental fluid status are needed. Clinical techniques (e.g. body weight, fluid balance, oedema) have poor sensitivity. More advanced approaches, such as bioelectrical impedance analysis and lung ultrasound, are impractical in critically ill patients. Relative blood volume monitors have been used to assess intravascular volume status in patients receiving intermittent haemodialysis for some time. These devices consist of a clear plastic blood chamber, which is inserted between the arterial blood line and the haemofilter, and a sensor clip. The sensor clip is applied over the blood chamber and contains a light-emitting diode and a photodetector. Multiple wavelengths of visible and infrared light are directed through the blood chamber. From this, haematocrit concentration, haemoglobin concentration, and oxygen saturation are continuously estimated, and relative blood volume is reported. The two most widely used devices are the Crit-Line (Fresenius) and the Hemoscan (Gambro). The Crit-Line is a standalone device that can be incorporated into any CRRT circuit (Figure 2).

In intermittent haemodialysis, relative blood volume monitors appear to be moderately successful at reducing intradialytic hypotension and symptoms.[31,32] However, they have not been shown to improve hard clinical outcomes. Very few studies have been performed to test the impact of relative blood volume monitoring in critically ill patients. One study of 25 critically ill patients receiving intermittent haemodialysis found that relative blood volume monitoring was not useful for predicting hypotension.[33] Two subsequent studies in CRRT have provided insightful descriptive information in small numbers of patients.[34,35] Randomised controlled trials evaluating tools to assess total and compartmental volume status will no doubt be another future area of CRRT research.

Net ultrafiltration

Like volume overload, rapid volume removal through CRRT may also be associated with heightened risk. An increasing number of studies from the intermittent haemodialysis literature have supported the association between high ultrafiltration rate, intravascular volume contraction and hypoperfusion of the heart, brain, kidneys, and gastrointestinal tract (Figure 1).[36–39] Emerging evidence supports similar significance of net ultrafiltration (NUF) intensity in critically ill patients receiving CRRT.[40] A NUF rate that is too low may precipitate or prolong fluid overload, while a NUF rate that is too high may aggravate intravascular volume control. A recent secondary analysis of the RENAL study found that NUF rates less than 1.01 mL/kg/h or greater than 1.75 mL/kg/h carried a greater risk of death at 90 days (44.9% and 48.6%) compared with NUF rates of between 1.01 and 1.75 mL/kg/h.[41] Prospective studies comparing NUF rates are now warranted.

Hypothermia management

Newer machines include warming devices that are associated with a lower risk of hypothermia when compared to historical controls.[42] Future machines will fully integrate blood warming technology and permit a high degree of accuracy in temperature management, reducing the need for external patient warming.

Extracorporeal carbon dioxide removal

Outside of volume management, interest in extracorporeal carbon dioxide removal ($ECCO_2R$) also continues to mount. $ECCO_2R$ has been studied in patients with acute respiratory failure. The aim of $ECCO_2R$ is to allow ultra-protective lung ventilation in order to reduce ventilator-induced lung injury by decreasing tidal volume, plateau pressure, and driving pressure.[43–45] Whether $ECCO_2R$ is efficacious at avoiding intubation in patients with severe hypercapnic respiratory failure is under active investigation.[46] $ECCO_2R$ coupled with CRRT could be beneficial in patients with hypercapnic respiratory acidosis and acute kidney injury (AKI) requiring CRRT. Placement of the oxygenator before or after the hemofilter does not appear to influence outcome.[47] Currently, $ECCO_2R$ can be performed with or without CRRT as standalone therapies. In the future, integration of both technologies into a single platform with multiple modular components may be possible.

Connection with other blood purification devices

Like $ECCO_2R$, CRRT offers the capability to combine kidney support with other extracorporeal therapies. Extracorporeal membrane oxygenation (ECMO) has been successfully combined with CRRT in several studies. In this setting, CRRT delivery can either be integrated (i.e. using an in-line haemofilter or fully integrated device) or provided in parallel.[48] The coupling of CRRT with ECMO will no doubt prove to be another important area of research because the best technical approach to combine these therapies is unknown.[49]

CRRT can also be delivered concurrently with therapeutic plasma exchange (TPE). TPE is a blood purification technique designed to remove large molecular weight toxins by centrifuge or membrane.[50] Membranes used in TPE have significantly larger pores than those used in CRRT, allowing convective transport of macromolecules, including pathogenic antibodies and lipoproteins. The availability of compatible systems for delivering CRRT and TPE has increased the potential for combining therapies, which may be particularly useful in critically ill patients who require urgent TPE but in whom RRT cannot be interrupted (e.g. immune-mediated AKI, thrombotic thrombocytopenic purpura).[51] Combining modalities allows continuous delivery of both therapies and use of a single vascular access.

There is increasing interest in utilising CRRT as a platform for other forms of organ support. Extracorporeal systems designed to remove cytokines (as an adjunct to sepsis therapy) may also provide patient benefit.[52] To ensure the safety of such multiorgan support systems, in-depth knowledge of intra-circuit pressure changes, risks of air entrapment and haemolysis, and implications for ultrafiltration and solute clearance are essential.

Adsorptive devices

The possibilities that CRRT offers to remove non-uraemic pro-inflammatory solutes (e.g. cytokines) will lead to continued exploration into the role of extracorporeal blood purification in patients with sepsis. Along with high volume haemofiltration, there is increasing interest in developing new membranes using sorbent technology for adsorption of endotoxin and/or cytokines. One of the most widely used endotoxin removal therapies is the Toraymyxin

membrane. Composed of polystyrene fibres coated in polymyxin-B, its endotoxin-absorptive properties are well established.[53,54] However, its impact on mortality remains inconclusive.[55] Cytosorb is a hemoperfusion cartridge filled with polymer beads that can absorb pro-and anti-inflammatory mediators (but not endotoxins).[56] Despite case series reporting encouraging results on haemodynamic parameters, a recent randomised trial failed to demonstrate a reduction in IL-6 levels.[57]

The oXiris haemofilter was developed to enhance the adsorptive properties of the previously well-studied AN69 surface treated membrane (copolymer combining acrylonitrile and sodium methallylsulfonate). It offers combined cytokine and endotoxin removal properties and is preheparinised, which confers an antithrombogenic property.[58,59] The oXiris membrane has 4 key benefits: renal support, cytokine removal, endotoxin removal, and local anticoagulant treatment. New sorbent membranes present potential for the future treatment of sepsis. Despite compelling pre-clinical data, suitably powered randomised controlled trials with appropriate patient phenotyping have not yet been conducted.

Ammonia removal

CRRT may also be efficacious in the treatment and/or prevention of hyperammonaemia in patients with life-threatening liver failure. Hyperammonaemia is a serious complication of acute liver failure (or inborn errors of metabolism in paediatric patients) that can lead to cerebral oedema, brain herniation and death. Previous studies investigating the utility of novel systems, including Molecular Adsorbent Recirculating System (MARS), Single-Pass Albumin Dialysis system (SPAD), and Fractionated Plasma Separation and Adsorption system (Prometheus^{TM}), as a bridge to transplantation were disappointing. Although these systems appear to reduce hepatic encephalopathy, their impact on survival is controversial.[60,61]

Successful experiments with high-volume haemofiltration in this population have proved to be hypothesis generating. Contemporary work is actively investigating the role of CRRT in reducing serum ammonia concentration. Because ammonia is a small, water-soluble molecule that is not significantly protein bound, it is cleared in a similar manner to urea. Recently,

delivery of CRRT (using CVVHDF or CVVH) with a median effluent rate of 43 mL/kg/h was shown to be associated with reduced serum ammonia concentration in patients with acute liver failure.[21] The effect on ammonia concentration was directly proportional to the cumulative CRRT dose delivered. Another study suggested that high volume CRRT is associated with superior 21-day transplant-free survival.[62] Given the morbidity and mortality associated with hyperammonaemia, the optimal timing, mode, intensity and duration of CRRT warrants further investigation and the value of high-dose CRRT requires confirmation in randomised controlled trials. The ability of CRRT to remove substantial quantities of ammonia from the blood of such patients is likely to be further explored in coming years.[63]

Precision CRRT

Individualising CRRT prescription was highlighted as an area of future development by the members of the Acute Dialysis Quality Initiative.[64] The term 'precision CRRT' describes the application of technology and evidence-based medicine on an individual basis rather than to a heterogeneous population. As part of precision CRRT, treatment must be dynamic and adapt to the constantly changing clinical status of the individual patient.[65] Regular assessment and reassessment of the patient, prescribed and delivered dialysis dose, solute control indicators, circuit and filter pressure trends, vascular access function, fluid and haemodynamic management, and anticoagulation are all important. This information should be used to generate a personalised CRRT prescription according to patient needs, desired physiological targets, and on the basis of therapy actually delivered.

Quality metrics

Lack of standardised quality metrics for CRRT may be one of the major factors limiting improvements in outcome. Investigators are actively assessing which aspects of CRRT prescription should be targets for quality metric development. Potential metrics of interest include prescribed and delivered CRRT dose, duration of therapy downtime, circuit life, small solute clearance, catheter infection, and mortality. Some groups have proposed that information on the quality, safety, and efficiency of CRRT be presented in the format of a quality metric 'dashboard'.[66] Such metrics could be regularly reported, audited, and benchmarked to ensure the highest standard of CRRT care. In the future, consensus initiatives

will likely establish and recommend the implementation of a core set of reportable quality metrics for CRRT to ensure standardisation of care.

Data analytics

Advances in information technology should be used to improve the safety and quality CRRT practice. In intermittent haemodialysis, automated feedback technology is available through transmission of machine-level data in real-time to online clouds or data warehouses. However, technical limitations of CRRT machines currently require machine data to be manually collected, exported and analysed. This hinders the further development and implementation of dynamic CRRT, which relies on the availability of real-time data as part of a biofeedback system. If the requisite technology was available, automated biofeedback loop-guided changes to CRRT prescriptions could be an important component of dynamic CRRT (Figure 2). Both treatment-level data from the CRRT machine and patient-level data from the electronic medical record could be integrated into automated biofeedback loops.[67]

The utility of longitudinal CRRT data for research and quality assurance purposes also warrants further investigation. These data could be used to facilitate the design and implementation of pragmatic trials by increasing their feasibility and cost effectiveness.[68] Cloud-based connectivity could help clinicians generate virtual registries for the analysis of individual or centre-level treatment data. This could allow comparison of centre performance and identification of outliers. Data collected and stored in electronic medical records could be rapidly evaluated and managed to alert clinicians of any dangerous trends as early as possible.

Conclusion

CRRT has rapidly evolved over the last forty years. It has greatly benefited from important technological advances in CRRT machines and devices, which have allowed delivery of increasingly complex CRRT modalities. As the predominant form of RRT in the ICU, CRRT will undoubtedly continue to undergo significant transformation over the coming decades. Unanswered questions regarding the best way to assess and control volume status in patients

receiving CRRT require urgent attention and will likely be addressed by future trials. The use of CRRT to remove non-uraemic solutes (e.g. ammonia, endotoxin, cytokines) and the combination of CRRT with other forms of organ support (e.g. $ECCO_2R$ and ECMO) are other areas of active exploration, which will continue in the years to come. Prescription of CRRT should be individualised and dynamic and sophisticated Big Data-based technologies will emerge to facilitate this. Standardised quality metrics will likely be defined to allow audit and benchmarking of CRRT safety and efficacy between centres. Information technology will likely be harnessed to explore the possibility of using Wi-Fi transmitted real-time CRRT data for biofeedback-guided prescription, large database registries, and pragmatic trials. Modifications to CRRT machines and technologies will increasingly consider affordability and sustainability. This is especially true for low and lower-middle income countries where reimbursement policies are variable and infrastructure to reduce the environment footprint associated with extracorporeal therapies are often unavailable. Miniaturized technologies, including wearable devices, will aid in addressing these problems. CRRT is here to stay and will continue to improve and deliver better outcomes to critically ill patients.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

References

1. Vaamonde CA, Michael UF, Metzger RA, Carroll KE. Complications of acute peritoneal dialysis. J Chronic Dis. 1975;28(11–12):637–59.
2. Kjellstrand CM, Evans RL, Petersen RJ, Shideman JR, von Hartitzsch B, Buselmeier TJ. The “unphysiology” of dialysis: a major cause of dialysis side effects? Kidney Int Suppl. 1975;(2):30–4.
3. Routh GS, Briggs JD, Mone JG, Ledingham IM. Survial from acute renal failure with and without multiple organ dysfunction. Postgrad Med J. 1980;56(654):244–7.
4. Kramer P, Schrader J, Bohnsack W, Grieben G, Gröne HJ, Scheler F. Continuous arteriovenous haemofiltration. A new kidney replacement therapy. Proc Eur Dial Transpl Assoc. 1981;18:743–9.

5. Ronco C, Brendolan A, Bragantini L, et al. Continuous Arterio-Venous Haemofiltration. In: Contributions to nephrology. 1985. p. 70–88.

6. Ronco C, Brendolan A, Bragantini L, et al. Treatment of acute renal failure in newborns by continuous arterio–venous hemofiltration. Kidney Int. 1986;29(4):908–15.

7. Lauer A, Saccaggi A, Ronco C, Belledonne M, Glabman S, Bosch JP. Continuous arteriovenous hemofiltration in the critically ill patient. Clinical use and operational characteristics. Ann Intern Med. 1983;99(4):445–60.

8. Geronemus R, Schneider N. Continuous arteriovenous hemodialysis: a new modality for treatment of acute renal failure. Trans Am Soc Artif Intern Organs. 1984;30:610–3.

9. Baldwin IC, Elderkin TD. Continuous hemofiltration: nursing perspectives in critical care. New horizons. 1995;3(4):738–47.

10. Macias WL, Mueller BA, Scarim SK, Robinson M, Rudy DW. Continuous Venovenous Hemofiltration: An Alternative to Continuous Arteriovenous Hemofiltration and Hemodiafiltration in Acute Renal Failure. Am J Kidney Dis. 1991;18(4):451–8.

11. Ricci Z, Bonello M, Salvatori G, et al. Continuous Renal Replacement Technology: From Adaptive Technology and Early Dedicated Machines towards Flexible Multipurpose Machine Platforms. Blood Purif. 2004;22(3):269–76.

12. Ronco C, Garzotto F, Brendolan A, et al. Continuous renal replacement therapy in neonates and small infants: development and first-in-human use of a miniaturised machine (CARPEDIEM). Lancet. 2014;383(9931):1807–13.

13. Bagshaw SM, Wald R, Adhikari NKJ, et al. Timing of Initiation of Renal-Replacement Therapy in Acute Kidney Injury. N Engl J Med. 2020;383(3):240–51.

14. Gaudry S, Hajage D, Schortgen F, et al. Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit. N Engl J Med. 2016;375(2):122–33.

15. Stads S, Kant KM, de Jong MFC, et al. Predictors of short-term successful discontinuation of continuous renal replacement therapy: results from a prospective multicentre study. BMC Nephrol. 2019;20(1):129.

16. Zarbock A, Kellum JA, Schmidt C, et al. Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury: The ELAIN Randomized Clinical Trial. JAMA. 2016;315(20):2190–9.

17. Ostermann M, Joannidis M, Pani A, et al. Patient Selection and Timing of Continuous Renal Replacement Therapy. Blood Purif. 2016;42(3):224–37.

18. Friedrich JO, Wald R, Bagshaw SM, Burns KEA, Adhikari NKJ. Hemofiltration compared to hemodialysis for acute kidney injury: systematic review and meta-analysis. Crit Care. 2012;16(4):R146.

19. Bellomo R, Cass A, Cole L, et al. Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med. 2009;361:1627–38.

20. Palevsky PM, Zhang JH, O'Connor TZ, et al. Intensity of Renal Support in Critically Ill Patients with Acute Kidney Injury. N Engl J Med. 2008;359(1):7–20.

21. Warrillow S, Fisher C, Bellomo R. Correction and Control of Hyperammonemia in Acute Liver Failure. Crit Care Med. 2020;48(2):218–24.

22. Ronco C, Brendolan A, D'Intini V, Ricci Z, Wratten M Lou, Bellomo R. Coupled Plasma Filtration Adsorption: Rationale, Technical Development and Early Clinical Experience. Blood Purif. 2003;21(6):409–16.

23. Reiter K, Bellomo R, Ronco C, Kellum JA. Pro/con clinical debate: is high-volume hemofiltration beneficial in the treatment of septic shock? Crit Care. 2002;6(1):18–21.

24. Borthwick EMJ, Hill CJ, Rabindranath KS, Maxwell AP, McAuley DF, Blackwood B. High-volume haemofiltration for sepsis in adults. Cochrane Database Syst Rev. 2017;1:CD008075.

25. Bai M, Zhou M, He L, et al. Citrate versus heparin anticoagulation for continuous renal replacement therapy: an updated meta-analysis of RCTs. Intensive Care Med. 2015;41(12):2098–110.

26. Szamosfalvi B, Frinak S, Yee J. Sensors and Hybrid Therapies: A New Approach with Automated Citrate Anticoagulation. Blood Purif. 2012;34(2):80–7.

27. Grams ME, Estrella MM, Coresh J, Brower RG, Liu KD. Fluid Balance, Diuretic Use, and Mortality in Acute Kidney Injury. Clin J Am Soc Nephrol. 2011;6(5):966–73.

28. Bouchard J, Soroko SB, Chertow GM, et al. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. Kidney Int. 2009;76(4):422–7.

29. Payen D, de Pont A-CJM, Sakr Y, Spies C, Reinhart K, Vincent J-L. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. Crit Care. 2008;12(3):R74.

30. Bellomo R, Cass A, Cole L, et al. An observational study fluid balance and patient outcomes in the randomized evaluation of normal vs. augmented level of replacement therapy trial. Crit Care Med. 2012;40(6):1753–60.

31. Steuer RR, Leypoldt JK, Cheung AK, Senekjian HO, Conis JM. Reducing symptoms during hemodialysis by continuously monitoring the hematocrit. Am J Kidney Dis. 1996;27(4):525–32.

32. Santoro A, Mancini E, Paolini F, Cavicchioli G, Bosetto A, Zucchelli P. Blood Volume Regulation During Hemodialysis. Am J Kidney Dis. 1998;32(5):739–48.

33. Tonelli M, Astephen P, Andreou P, Beed S, Lundrigan P, Jindal K. Blood volume monitoring in intermittent hemodialysis for acute renal failure. Kidney Int. 2002;62(3):1075–80.

34. Ronco C, Brendolan A, Bellomo R. Online monitoring in continuous renal replacement therapies. Kidney Int. 1999;56:S8–14.

35. Kron S, Leimbach T, Wenkel R, Thieme U, Kern H, Kron J. Relative Blood Volume Monitoring during Renal Replacement Therapy in Critically Ill Patients with Septic Shock: A Preliminary Report. Blood Purif. 2015;40(2):133–8.

36. Buchanan C, Mohammed A, Cox E, et al. Intradialytic cardiac magnetic resonance imaging to assess cardiovascular responses in a short-term trial of hemodiafiltration and hemodialysis. J Am Soc Nephrol. 2017;28(4):1269–77.

37. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced cardiac injury: Determinants and associated outcomes. Clin J Am Soc Nephrol. 2009;4(5):914–20.

38. Findlay MD, Dawson J, Dickie DA, et al. Investigating the relationship between cerebral blood flow and cognitive function in hemodialysis patients. J Am Soc

Nephrol. 2019;30(1):147–58.

39. Marants R, Qirjazi E, Grant CJ, Lee T-Y, McIntyre CW. Renal perfusion during hemodialysis: intradialytic blood flow decline and effects of dialysate cooling. J Am Soc Nephrol. 2019;30(6):1086–95.

40. Naorungroj T, Neto AS, Zwakman-Hessels L, et al. Mediators of the Impact of Hourly Net Ultrafiltration Rate on Mortality in Critically Ill Patients Receiving Continuous Renal Replacement Therapy. Crit Care Med. 2020;48(10):e934–42.

41. Murugan R, Kerti SJ, Chang C-CH, et al. Association of Net Ultrafiltration Rate With Mortality Among Critically Ill Adults With Acute Kidney Injury Receiving Continuous Venovenous Hemodiafiltration. JAMA Netw Open. 2019;2(6):e195418.

42. Bell M, Ronco C, Hansson F, Broman M. Hypothermia during CRRT, a comparative analysis. Acta Anaesthesiol Scand. 2020;64(8):1162–6.

43. Combes A, Pesenti A, Ranieri VM. Fifty Years of Research in ARDS. Is Extracorporeal Circulation the Future of Acute Respiratory Distress Syndrome Management? Am J Respir Crit Care Med. 2017;195(9):1161–70.

44. Terragni PP, Del Sorbo L, Mascia L, et al. Tidal Volume Lower than 6 ml/kg Enhances Lung Protection. Anesthesiology. 2009;111(4):826–35.

45. Combes A, Fanelli V, Pham T, Ranieri VM. Feasibility and safety of extracorporeal CO2 removal to enhance protective ventilation in acute respiratory distress syndrome: the SUPERNOVA study. Intensive Care Med. 2019;45(5):592–600.

46. Cove ME, MacLaren G, Federspiel WJ, Kellum JA. Bench to bedside review: Extracorporeal carbon dioxide removal, past present and future. Crit Care. 2012;16(5):232.

47. Allardet-Servent J, Castanier M, Signouret T, Soundaravelou R, Lepidi A, Seghboyan J-M. Safety and Efficacy of Combined Extracorporeal CO2 Removal and Renal Replacement Therapy in Patients With Acute Respiratory Distress Syndrome and Acute Kidney Injury. Crit Care Med. 2015;43(12):2570–81.

48. Ostermann M, Connor M, Kashani K. Continuous renal replacement therapy during extracorporeal membrane oxygenation. Curr Opin Crit Care. 2018;24(6):493–503.

49. Lee C-C, Chen S-W, Cheng Y-L, et al. The impact of CRRT modality in patients with AKI receiving ECMO: A nationwide registry study in Taiwan. J Crit Care. 2020;57:102–7.

50. Kes P, Janssens ME, Bašić-Jukić N, Kljak M. A randomized crossover study comparing membrane and centrifugal therapeutic plasma exchange procedures. Transfusion. 2016;56(12):3065–72.

51. Ahmed S, Kaplan A. Therapeutic Plasma Exchange Using Membrane Plasma Separation. Clin J Am Soc Nephrol. 2020;15(9):1364–70.

52. Schmidt M, Hodgson C, Combes A. Extracorporeal gas exchange for acute respiratory failure in adult patients: a systematic review. Crit Care. 2015;19(1):99.

53. Ronco C. The place of early haemoperfusion with polymyxin B fibre column in the treatment of sepsis. Crit Care. 2005;9(6):631–3.

54. Cruz DN, De Cal M, Piccinni P, Ronco C. Polymyxin-B hemoperfusion and endotoxin removal: Lessons from a review of the literature. In: Contributions to Nephrology. 2010. p. 77–82.

55. Payen D. Haemoperfusion with polymyxin B membrane: Recent results for an old debate! Anaesth Crit Care Pain Med. 2019;38(1):3–4.

56. Gruda MC, Ruggeberg K-G, O'Sullivan P, et al. Broad adsorption of sepsis-related PAMP and DAMP molecules, mycotoxins, and cytokines from whole blood using CytoSorb® sorbent porous polymer beads. Eller K, editor. PLoS One. 2018;13(1):e0191676.

57. Schädler D, Pausch C, Heise D, et al. The effect of a novel extracorporeal cytokine hemoadsorption device on IL-6 elimination in septic patients: A randomized controlled trial. Eller K, editor. PLoS One. 2017;12(10):e0187015.

58. Shiga H, Hirasawa H, Nishida O, et al. Continuous Hemodiafiltration with a Cytokine-Adsorbing Hemofilter in Patients with Septic Shock: A Preliminary Report. Blood Purif. 2014;38(3–4):211–8.

59. Kobashi S, Maruhashi T, Nakamura T, Hatabayashi E, Kon A. The 28-day survival rates of two cytokine-adsorbing hemofilters for continuous renal replacement therapy: a single-center retrospective comparative study. Acute Med Surg. 2019;6(1):60–7.

60. Shen Y, Wang X-L, Wang B, et al. Survival Benefits With Artificial Liver Support System for Acute-on-Chronic Liver Failure. Medicine (Baltimore). 2016;95(3):e2506.

61. Bañares R, Nevens F, Larsen FS, et al. Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure: The RELIEF trial. Hepatology. 2013;57(3):1153–62.

62. Cardoso FS, Gottfried M, Tujios S, Olson JC, Karvellas CJ. Continuous renal replacement therapy is associated with reduced serum ammonia levels and mortality in acute liver failure. Hepatology. 2018;67(2):711–20.

63. Warrillow S, Tibballs H, Bailey M, et al. Characteristics, management and outcomes of patients with acute liver failure admitted to Australasian intensive care units. Crit care Resusc. 2019;21(3):188–99.

64. Kellum JA, Ronco C. The 17th Acute Disease Quality Initiative International Consensus Conference: Introducing Precision Renal Replacement Therapy. Blood Purif. 2016;42(3):221–3.

65. Bagshaw SM, Chakravarthi MR, Ricci Z, et al. Precision Continuous Renal Replacement Therapy and Solute Control. Blood Purif. 2016;42(3):238–47.

66. Mottes TA, Goldstein SL, Basu RK. Process based quality improvement using a continuous renal replacement therapy dashboard. BMC Nephrol. 2019;20(1):17.

67. Kashani K, Herasevich V. Utilities of Electronic Medical Records to Improve Quality of Care for Acute Kidney Injury: Past, Present, Future. Nephron. 2015;131(2):92–6.

68. Clark WR, Villa G, Neri M, Ronco C. Advances in Machine Technology. In: Contributions to Nephrology. 2018. p. 80–9.

Table 1. Future areas for development in CRRT

Theme	Problem	Area for future development	Timeline
Volume control	Paucity of evidence to inform optimal CRRT	Prospective comparison of outcomes with varying (restrictive vs standard vs	3 years

	volume strategy	liberal) CRRT volume strategies	
Assessment of volume status	Lack of objective methods to assess fluid status in patients receiving CRRT	Investigation into the impact of available fluid status assessment tools (e.g. relative blood volume monitoring) on outcomes	5 years
Net ultrafiltration	Poor understanding of optimal targets of prescribed NUF	Audit local net ultrafiltration practice Retrospective examination of the association between NUF rate and outcomes Prospective examination of the effect of targeted NUF rate on outcomes	3 years
$ECCO_2R$	Uncertain association with key clinical outcomes	Exploration of the efficacy of $ECCO_2R$ in reducing intubation and mortality	5 years
Other blood purification devices	The best technical approach to combine therapies is unknown	Comparison of the safety and efficacy of available approaches to combine CRRT with other devices	10 years
Adsorptive devices	Unclear impact on mortality	Assessment of the impact of cytokine and endotoxin adsorptive devices on mortality through randomized controlled trials Investigation into patient phenotypes most likely to benefit from adsorption	10 years
Ammonia removal	Impact of extracorporeal ammonia removal has only tested in small retrospective studies	Randomized controlled trials exploring whether high-dose CRRT improves serum ammonia, development of encephalopathy, and survival compared to standard dose CRRT	10 years

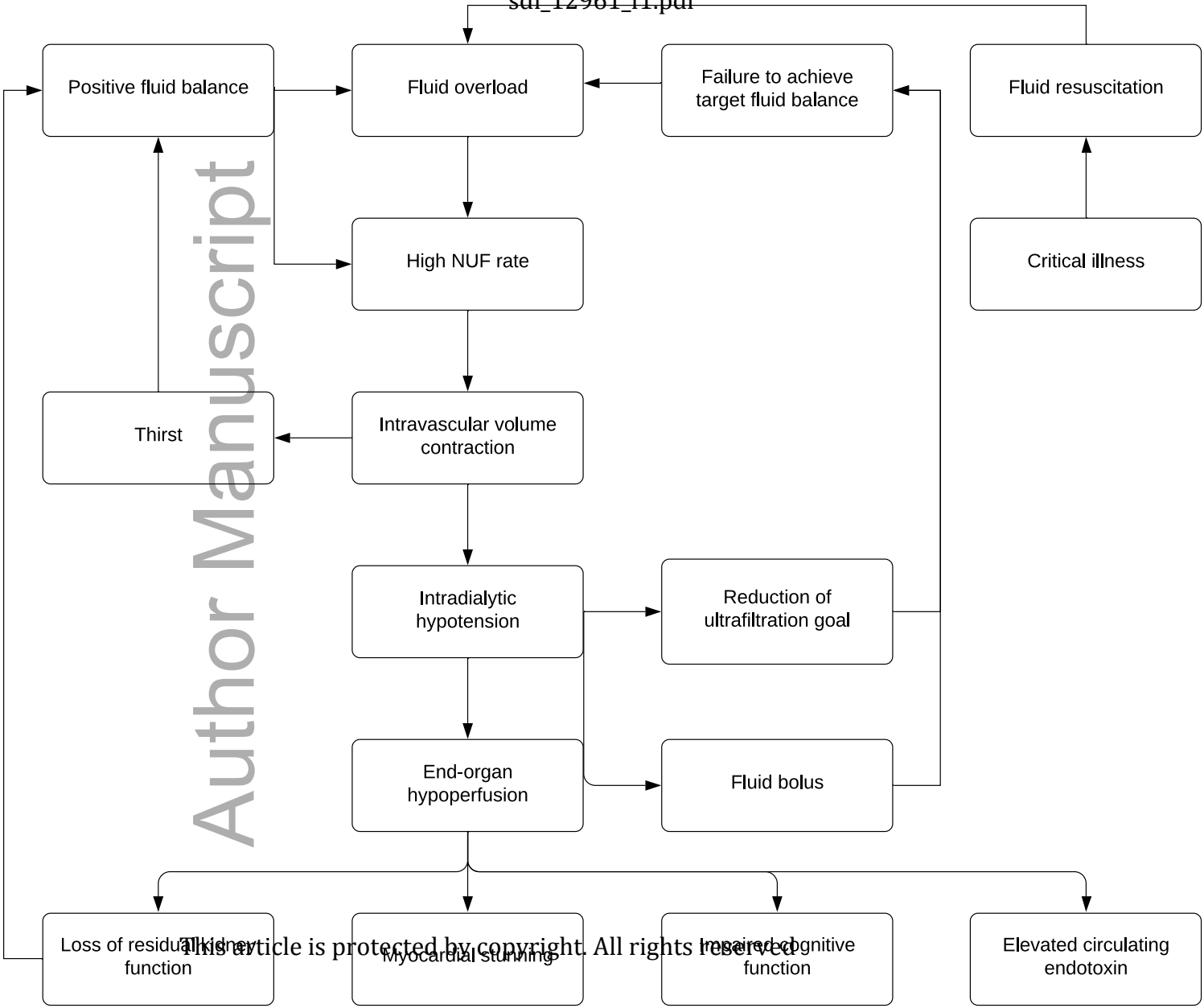
Precision CRRT	"One size fits all" approach to CRRT prescription	Evaluation of the impact of personalized CRRT prescription according to patient characteristics (e.g. hypercatabolic, septic, comorbid) on outcome	15 years
Quality metrics	Metrics to assess the quality and safety of CRRT provision have not been standardized	Reach consensus on developing a core set of quality metrics to be reported, audited and benchmarked. Involvement of consumers in prioritizing metrics could be considered.	5 years
Data analytics	Poor integration and utilization of routinely collected data to enhance and automate CRRT using biofeedback	Collaboration between clinicians, data scientists, and machine technicians to maximize available technology and assess whether biofeedback can improve CRRT quality	15 years

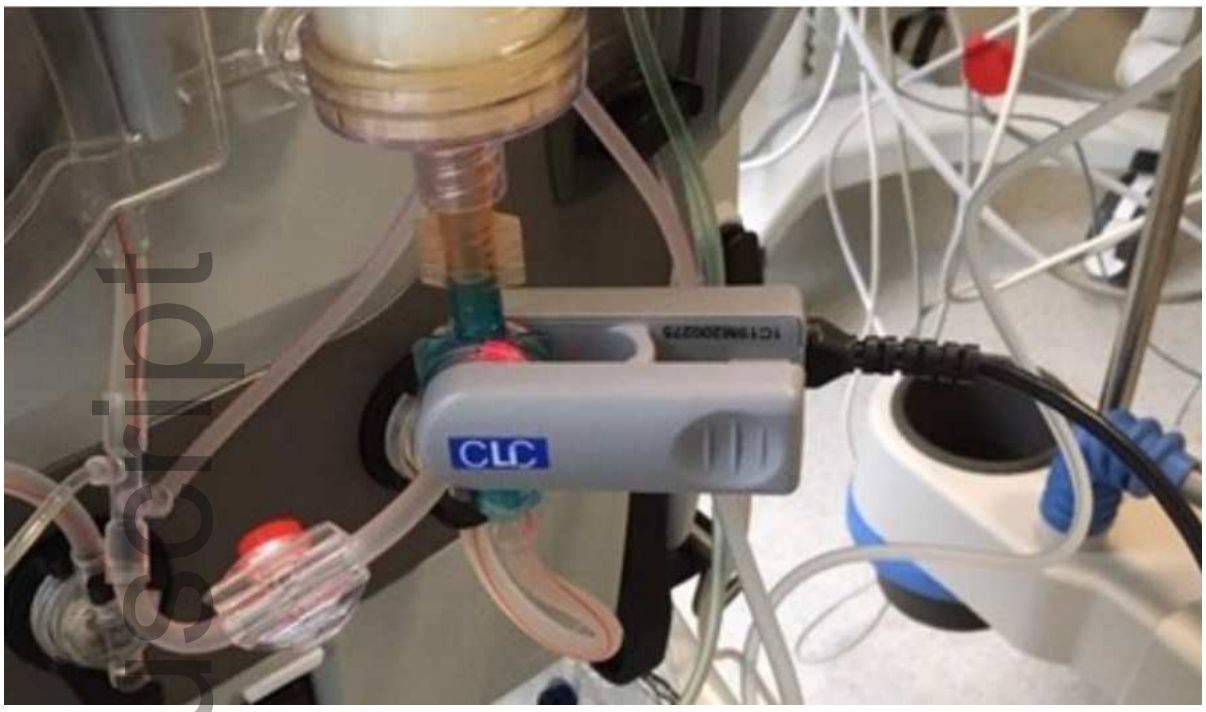
Figure Legends

Figure 1. Complex interplay of factors contributing to and resulting from suboptimal volume control in critically ill patients

Figure 2. Relative blood volume monitoring in CRRT using the Crit-Line device

Figure 3. Schematic representation of the integration and storage of data from the electronic medical record, laboratory and CRRT machine for use in biofeedback-guided dynamic CRRT prescription.





sdi_12961_f2.png

sdi_12961_f3.pdf