Application of Continuous Renal Replacement Therapy: What Should We Consider Based on Existing Evidence?

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Key Words

Acute kidney injury · Continuous renal replacement therapy · Indication · Prescriptions

Abstract

Background: Continuous renal replacement therapy (CRRT) is performed mainly in patients with acute kidney injury, severe sepsis, or septic shock. Evidence has emerged about the indications for and therapeutic conditions of CRRT. In this review, we focus on the evidence for CRRT to date. **Summary:** CRRT employs diffusion, convection and adsorption to remove solutes from plasma. Indications can be divided into renal and non-renal indications. Concrete renal indications have not yet been determined, except for life-threatening absolute indications. Modality selection is a point of debate. Intermittent renal replacement therapy is reportedly equivalent to CRRT in terms of overall survival. However, the selection of modality must consider individual circumstances. The optimal dosage of CRRT has proven to be lower than that previously recommended, and the dosage is almost the same as the one employed in the 'real-world' setting. Patients treated by CRRT often have bleeding complications. In this situation, regional citrate anticoagulation can be used, but nafamostat is widely used in Japan. The right jugular vein is the most preferred vascular access site because it has the lowest likelihood of catheter malfunction. As for the complications of CRRT, hypophosphatemia and nutrient loss should be managed properly. When CRRT is no longer necessary, we

should consider the appropriate timing of discontinuation.

Key Messages: Even though CRRT is an established technique, several points remain under debate. Individualization of therapy should be considered in light of the changes in patient characteristics.

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Overview of Continuous Renal Replacement Therapy

Renal replacement therapy (RRT) is the method for replacing failing renal function. Continuous renal replacement therapy (CRRT) is a pivotal treatment strategy for renal failure in the intensive care setting [1]. In addition to the removal of waste products, other molecules such as cytokines are also the target of removal in CRRT, especially in septic patients.

The modalities of CRRT include continuous (veno-venous) hemofiltration (CVVH or CHF), continuous (veno-venous) hemodialysis (CVVHD or CHD), and continuous (veno-venous) hemodiafiltration (CVVHDF or CHDF) [1] (fig. 1). CHD uses diffusion, CHF uses convection, and CHDF uses both. Differences in concentration and transmembrane pressure are the driving force of diffusion and convection, respectively. Substances with a larger molecular weight can be removed through filtration, whereas they can hardly be removed by diffusion. Adsorption is also the mechanism of solute removal of CRRT. It uses physicochemical interaction between the

Fig. 1. Diagrams of the modalities of continuous renal replacement therapy. The circuits of each modality are outlined (**a–c**). **a** Continuous hemodialysis (CHD). **b** Continuous hemofiltration (CHF) with post-dilution. **c** Continuous hemodiafiltration (CHDF). **d** Scheme of the flow of fluids and their significance.

Larger solutes are eliminated by ultrafiltration only, while smaller solutes are eliminated by either ultrafiltration or dialysis. To simplify this figure, the flows of blood and dialysate are in the same direction, but in actual practice, their flows are in the opposite directions.

membrane material and target substances. Polymethyl methacrylate [2, 3] and polyacrylonitrile (specifically AN69™) [4] are two major materials used in adsorption during CRRT.

Indications of Renal Replacement Therapy

Renal Indications

Although several groups of indications for RRT for acute kidney injury (AKI) have been proposed, definitive indications have not been determined except for life-

threatening conditions such as hyperkalemia, severe congestion, profound acidosis, and uremic conditions [5, 6]. A proposal describes the indications from the perspective of absolute or relative indications [6] (table 1). The Kidney Disease Improving Global Outcomes (KDIGO) guideline for AKI also describes the indications for RRT, including renal support [7].

Timing of Initiation of Renal Replacement Therapy

Several observational studies demonstrated that, before the era of AKI, patients who started RRT at urea levels of 70–150 mg/dl had better survival than those who

Table 1. Renal indications for renal replacement therapy in acute kidney injury

Indication	Characteristics	Absolute/Relative
Metabolic abnormality	BUN >76 mg/dl (27 mmol/l)	Relative
	BUN >100 mg/dl (35.7 mmol/l)	Absolute
	Hyperkalemia >6 mEq/l	Relative
	Hyperkalemia >6 mEq/l with ECG abnormalities	Absolute
	Dysnatremia	Relative
	Hypermagnesemia >8 mEq/l (4 mmol/l)	Relative
	Hypermagnesemia >8 mEq/l (4 mmol/l) with anuria and absent deep tendon reflexes	Absolute
Acidosis	pH >7.15	Relative
	pH <7.15	Absolute
	Lactic acidosis related to metformin use	Absolute
Anuria/oliguria	RIFLE class R	Relative
	RIFLE class I	Relative
	RIFLE class F	Relative
Fluid overload	Diuretic sensitive	Relative
	Diuretic resistant	Absolute

From Gibney et al. [6]. The proposed indications for renal replacement therapy are categorized as either absolute (life-threatening) or relative indications. BUN = Blood urea nitrogen.

started at 150–200 mg/dl [8]. In the era of AKI, the definitive timing of initiation based on urea concentration remains controversial. A large prospective cohort study involving 1,238 patients with AKI from 23 countries investigated the relationship between urea levels at initiation or timing and mortality. However, the results were inconsistent in the definitions of timing [9]. Several meta-analyses investigated the influence of timing of RRT initiation on mortality [10–12], and while some of them demonstrated that an ‘early start’ lead to better survival [11, 12], the concrete definitions of ‘early start’ were diverse and definitive conclusions have not been drawn. Therefore, a urea level at 100 mg/dl seems to be a clinically relevant indication for RRT initiation, as some articles and guidelines have proposed [5, 6].

Selection of Modality: Intermittent, Continuous, or Other?

Intermittent conventional hemodialysis and CRRT are the major options for RRT in AKI patients. Table 2 shows the characteristics of each modality. CRRT can perform volume reduction continuously with minimal effects on hemodynamics compared with intermittent RRT (IRRT) [13, 14] and it attains volume control more easily [15]. Solute rebound does not occur during the course of CRRT. Thus, peaks in solute levels are seen in

IRRT but not in CRRT [16–18]. A study reported that brain edema on computed tomography was evident after IRRT, while no edema was observed after CRRT because of equilibrated removal of solutes [19]. Thus, CRRT might be more favorable for patients who are prone to elevation of intracranial pressure. CRRT, however, requires larger doses of anticoagulant and is a labor-intensive procedure. In conditions such as hyperkalemia where higher clearance is required, IRRT is more favorable than CRRT because of the limited hourly clearance of CRRT.

Many clinical trials have compared the prognoses of patients who underwent IRRT or CRRT. To date, however, conclusive evidence of survival benefits has not been shown in randomized controlled trials (RCTs) [15, 20–22] or meta-analyses [13, 23]. Hemodynamic stability was observed in one meta-analysis [13]. From the clinical point of view, patients with unstable hemodynamics or oxygenation who require a large amount of fluid removal might benefit from CRRT. Patients who require removal of larger solutes such as cytokines or myoglobin are also the target group for CRRT.

Extended Daily Dialysis: The Third Modality

Extended daily dialysis (EDD) is another modality of choice. This modality utilizes the same machine as IRRT. However, the blood and dialysate flow rates are reduced

Table 2. Comparison of intermittent and continuous renal replacement therapy

	Advantages	Disadvantages
Continuous renal replacement therapy (CRRT)	Slow fluid removal Minimum effects on hemodynamics Large amount of fluid can be eliminated Removal of larger solutes (myoglobin, cytokines) No rebound in plasma concentration	Continuous anticoagulation Increases risks of bleeding Higher costs and labor-intensive Lower clearance Requires longer time until attainment of target concentration range Continuous therapy: patients are required to stay in bed
Intermittent renal replacement therapy (IRRT)	Limited doses of anticoagulation Limited risks of bleeding Same technique as maintenance hemodialysis Lower costs and less labor intensive Higher clearance Rapid control of life-threatening hyperkalemia Off-time of renal replacement is intended to enhance the physical activity of the patient	Intermittent therapy Larger fluid removal rate Prone to hemodynamics disturbance Rebound of concentrations during the course; fluctuation of levels of solutes is inevitable Limited clearance of larger solutes

and treatment time is prolonged [24]. Patients treated by EDD attained volume control that was comparable with CRRT, although those treated by EDD experienced lower blood pressure because of the higher rate of fluid reduction [25]. Solute removal is equivalent between EDD and CRRT [26–28]. A smaller amount of anticoagulation was required in EDD than in CRRT [27]. A meta-analysis comparing the two modalities demonstrated similar survival [29].

Non-Renal Indications

CRRT potentially removes larger solutes such as cytokines by means of convection or adsorption. The AN69 membrane was shown to adsorb cytokines [4, 30], including high mobility group box 1 [30]. The group at Chiba University has extensively demonstrated that the polymethyl methacrylate membrane reduces the levels of plasma cytokines by adsorption and improves clinical outcomes in conditions with hypercytokinemia [2, 3].

Removal of cytokines by the CRRT hemofilter has been demonstrated [31–33]. On the other hand, the effects of CRRT on the plasma level of cytokines are controversial; some studies demonstrated their reduction [34, 35], while others did not [32, 36]. It is hypothesized that the peak concentrations of cytokines are crucial in organ injury and it is beneficial to cap their levels by CRRT (peak concentration hypothesis) [37].

Prescription of Continuous Renal Replacement Therapy

Dose of Continuous Renal Replacement Therapy

Solute removal in CRRT is achieved by diffusion, convection, and adsorption. The efficacy of diffusion or convection can be modified by adjusting the dialysate flow rate and ultrafiltration rate, respectively. Clearance of small solutes by diffusion is determined by the dialysate flow rate, and it is almost equal to the flow rate in usual conditions [38]. On the other hand, the clearance of small molecules by convection is equal to the ultrafiltration rate [38]. Thus, the clearance attained by CHDF is theoretically equal to the sum of dialysate flow rate and ultrafiltration rate, that is, the effluent flow rate. Clinical trials have therefore utilized the effluent flow rate in their assessments. However, there are concerns that the effluent volume is not necessarily equal to actual clearance [39, 40]. Moreover, the length of time of discontinuation of therapy is considerable, mainly due to clotting of the circuit. Such ‘down time’ is also an issue that reduces the actual dose of CRRT [39].

Evidence on Continuous Renal Replacement Therapy Doses

In 2000, Ronco et al. [41] published epoch-making evidence that higher effluent volume, as much as 35 or 45 ml/kg/h, was associated with better survival among patients with acute renal failure. This was bolstered by sub-

sequent studies demonstrating that similar [42] or even higher [43] doses of CRRT were associated with better prognosis in such patients. However, registry data from 23 countries demonstrated that the median effluent flow rate was 20.4 ml/kg/h [44]. Data from 34 intensive care units in Australia and New Zealand demonstrated similar results, with typical urea clearance of 24.3 ml/kg/h [45]. Discrepancies between evidence and 'real-world' practice have become evident. Thereafter, several observational studies [46] and RCTs [47] found that intense CRRT (>35 ml/kg/h [46] or 72 liters/day [47]) does not necessarily result in better prognoses. RCTs were conducted to compare the doses of CRRT in terms of patient survival [48–50]. One compared 20 and 35 ml/kg/h in 200 critically ill patients [48]. The VA/NIH Acute Renal Failure Trial compared 20 and 35 ml/kg/h in 1,124 AKI patients with at least one non-renal organ failure or sepsis [49]. The most recent study is RENAL Replacement Therapy Study that compared 25 and 40 ml/kg/h in 1,508 patients [50]. All of the trials demonstrated that the 'lower' doses and the 'higher' doses were equivalent in terms of patient survival. Therefore, the disparity between evidence and 'real-world' practice was resolved.

In Japan, the maximum volume of supplementary fluid that can be used per day is determined by the government healthcare reimbursement system, which is as low as 15–20 liters/day (the volume differs depending on prefecture). Data from questionnaire surveys revealed a median effluent volume of 16 ml/kg/h in Japan. However, survival was better than that predicted from acute physiology and chronic health evaluation II (APACHE II) score [51].

Anticoagulation

Blood purification therapy usually requires anti-coagulation. Unfractionated heparin is widely used for this purpose, and is also used in CRRT [44]. However, anti-coagulation potentially causes bleeding complications. Regional citrate anticoagulation (RCA) is used for bleeding diathesis or heparin-induced thrombocytopenia. RCA reportedly showed non-inferiority [52, 53] or even favorable results [54] compared with heparin in terms of filter life. Moreover, clinical studies [52–54] consistently indicated that RCA was associated with a lower incidence of bleeding complications. Therefore, the KDIGO guideline recommends RCA as the first-line anti-coagulant in patients with bleeding complications [7].

Hirudin, a low molecular weight heparin (LMWH), and nafamostat are other anti-coagulants that are being investigated or used for CRRT. Hirudin is a recombinant

peptide that is degraded in the kidneys and reportedly has a markedly prolonged half-life in patients with renal failure [55]. Therefore, this agent has a very limited indication and does not seem appropriate for CRRT anticoagulation. One trial compared LMWH with unfractionated heparin in CRRT and found comparable results, but the cost of the LMWH is higher than that of unfractionated heparin [56].

Nafamostat is a synthetic serine protease inhibitor commonly used in Japan and Korea. The drug inhibits the activity of a range of coagulation factors and acts as an anti-coagulant [57]. Its half-life is short (alpha phase 1.1 min and beta phase 23.1 min based on manufacturer data) and it is eliminated by dialysis because of its small molecular weight (539.6). Therefore, this anticoagulant is not expected to exacerbate bleeding. Evidence from both observational [58] and interventional [59, 60] studies have demonstrated its utility in CRRT.

Vascular Access

Placement of vascular access is another crucial step in blood purification therapy. Non-cuffed temporary catheter is usually preferred for vascular access. Options exist with regard to the insertion site and length of catheters. One study of 736 patients compared insertion sites in terms of catheter malfunction and the dosage of RRT. Compared with femoral veins, the right jugular vein was associated with a lower incidence of malfunction while the left jugular vein was associated with a higher incidence [61]. Another study demonstrated that the femoral vein was significantly associated with infectious complications, especially in heavier (>90 kg) patients [62]. Therefore, the KDIGO guideline recommends the following order of preference of insertion site: the right jugular vein, femoral vein, left jugular vein, and subclavian vein, with preference for the dominant side for preparation of future permanent vascular access for maintenance dialysis [7].

Adverse Events and Adjunctive Therapies

Electrolyte Disorders

Hypophosphatemia is one of the major complications of CRRT. Post-hoc analysis of the RENAL study demonstrated that 32.1% of patients had hypophosphatemia <0.6 mmol/l. The incidence was highest 2–3 days after initiation of CRRT and the overall incidence was 58 episodes per 1,000 patient-days for the lower dose, while it was 112 episodes per 1,000 patient-days for the higher dose. Multivariate analysis also demonstrated that the higher dose was significantly associated with hypophos-

phatemia [63]. Therefore, phosphate supplementation might be warranted for those who continue CRRT for >3 days; monitoring of phosphate should be performed at least daily.

Nutrition

The target of RRT is small, water-soluble molecules. Therefore, many nutrients including both macronutrients and micronutrients are removed during RRT. One of the most clinically important issues is the removal of amino acids including glutamine. ESPEN guidelines or other articles recommend larger amounts of protein intake (>1.5 g/kg/day [64], 1.5–1.8 g/kg/day [65, 66], or even 1.5–2.0 g/kg/day [67]). Micronutrients are also removed through CRRT treatments. One article recommended supplementation of thiamin (100 mg/day), vitamin C (250 mg/day), and selenium (100 µg/day) [65].

Discontinuation of Continuous Renal Replacement Therapy

Discontinuation or transition to maintenance intermittent hemodialysis should be considered at an appropriate time because of the nature of CRRT. When condi-

tions that require continuous treatment no longer exist, the transition to IRRT must be considered. On the other hand, sufficient urinary output and a spontaneous fall in creatinine without a change in the prescription of RRT are signs that prompt us to consider discontinuing RRT. Urinary volume >400 ml/day without diuretics or >2,300 ml/day with diuretics have been demonstrated to be good indicators for the discontinuation of CRRT [68].

Conclusion

CRRT is widely used for AKI patients, especially in the intensive care unit. CRRT has become an established technique but uncertainty remains about when to start RRT in AKI patients. Moreover, the characteristics of AKI patients are changing in terms of age and comorbidities, and we should therefore further investigate CRRT in these patients.

Conflicts of Interest

The author declares no conflicts of interest or financial support in relation to this article.

References

- 1 Tolwani A: Continuous renal-replacement therapy for acute kidney injury. *N Engl J Med* 2012;367:2505–2514.
- 2 Abe R, Oda S, Shinozaki K, Hirasawa H: Continuous hemodiafiltration using a polymethyl methacrylate membrane hemofilter for severe acute pancreatitis. *Contrib Nephrol* 2010;166:54–63.
- 3 Matsuda K, Moriguchi T, Oda S, Hirasawa H: Efficacy of continuous hemodiafiltration with a cytokine-adsorbing hemofilter in the treatment of acute respiratory distress syndrome. *Contrib Nephrol* 2010;166:83–92.
- 4 De Vriese AS, Colardyn FA, Philippé JJ, Vanholder RC, De Sutter JH, Lameire NH: Cytokine removal during continuous hemofiltration in septic patients. *J Am Soc Nephrol* 1999;10:846–853.
- 5 Bagshaw SM, Cruz DN, Gibney RT, Ronco C: A proposed algorithm for initiation of renal replacement therapy in adult critically ill patients. *Crit Care* 2009;13:317.
- 6 Gibney N, Hoste E, Burdmann EA, Bunchman T, Kher V, Viswanathan R, Mehta RL, Ronco C: Timing of initiation and discontinuation of renal replacement therapy in AKI: unanswered key questions. *Clin J Am Soc Nephrol* 2008;3:876–880.
- 7 Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group: KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int Suppl* 2: 1–138.
- 8 Palevsky PM: Clinical review: timing and dose of continuous renal replacement therapy in acute kidney injury. *Crit Care* 2007;11:232.
- 9 Bagshaw SM, Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Oudemans-van Straaten HM, Ronco C, Kellum JA: Timing of renal replacement therapy and clinical outcomes in critically ill patients with severe acute kidney injury. *J Crit Care* 2009;24:129–140.
- 10 Seabra VF, Balk EM, Liangos O, Sosa MA, Cendoroglo M, Jaber BL: Timing of renal replacement therapy initiation in acute renal failure: a meta-analysis. *Am J Kidney Dis* 2008;52:272–284.
- 11 Karvellas CJ, Farhat MR, Sajjad I, Mogensen SS, Leung AA, Wald R, Bagshaw SM: A comparison of early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury: a systematic review and meta-analysis. *Crit Care* 2011;15: R72.
- 12 Wang X, Jie Yuan W: Timing of initiation of renal replacement therapy in acute kidney injury: a systematic review and meta-analysis. *Ren Fail* 2012;34:396–402.
- 13 Rabindranath K, Adams J, Macleod AM, Muirhead N: Intermittent versus continuous renal replacement therapy for acute renal failure in adults. *Cochrane Database Syst Rev* 2007;CD003773.
- 14 John S, Griesbach D, Baumgärtel M, Weihprecht H, Schmieder RE, Geiger H: Effects of continuous haemofiltration vs intermittent haemodialysis on systemic haemodynamics and splanchnic regional perfusion in septic shock patients: a prospective, randomized clinical trial. *Nephrol Dial Transplant* 2001; 16:320–327.
- 15 Augustine JJ, Sandy D, Seifert TH, Paganini EP: A randomized controlled trial comparing intermittent with continuous dialysis in patients with ARF. *Am J Kidney Dis* 2004;44: 1000–1007.
- 16 Bellomo R, Farmer M, Wright C, Parkin G, Boyce N: Treatment of sepsis-associated severe acute renal failure with continuous hemodiafiltration: clinical experience and comparison with conventional dialysis. *Blood Purif* 1995;13:246–254.

- 17 Clark WR, Mueller BA, Alaka KJ, Macias WL. A comparison of metabolic control by continuous and intermittent therapies in acute renal failure. *J Am Soc Nephrol* 1994;4:1413–1420.
- 18 Bellomo R, Farmer M, Bhonagiri S, Porceddu S, Ariens M, M'Pisi D, Ronco C: Changing acute renal failure treatment from intermittent hemodialysis to continuous hemofiltration: impact on azotemic control. *Int J Artif Organs* 1999;22:145–150.
- 19 Ronco C, Bellomo R, Brendolan A, Pinna V, La Greca G: Brain density changes during renal replacement in critically ill patients with acute renal failure. Continuous hemofiltration versus intermittent hemodialysis. *J Nephrol* 1999;12:173–178.
- 20 Uehlinger DE, Jakob SM, Ferrari P, Eichelberger M, Huynh-Do U, Marti HP, Mohaupt MG, Vogt B, Rothen HU, Regli B, Takala J, Frey FJ: Comparison of continuous and intermittent renal replacement therapy for acute renal failure. *Nephrol Dial Transplant* 2005;20:1630–1637.
- 21 Vinsonneau C, Camus C, Combes A, Costa de Beauregard MA, Klouche K, Boulain T, Pallot JL, Chiche JD, Taupin P, Landais P, Dhainaut JF: Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre randomised trial. *Lancet* 2006;368:379–385.
- 22 Lins RL, Elseviers MM, Van der Niepen P, Hoste E, Malbrain ML, Damas P, Devriendt J: Intermittent versus continuous renal replacement therapy for acute kidney injury patients admitted to the intensive care unit: results of a randomized clinical trial. *Nephrol Dial Transplant* 2009;24:512–518.
- 23 Bagshaw SM, Berthiaume LR, Delaney A, Bellomo R: Continuous versus intermittent renal replacement therapy for critically ill patients with acute kidney injury: a meta-analysis. *Crit Care Med* 2008;36:610–617.
- 24 Marshall MR, Golper TA, Shaver MJ, Alam MG, Chatoth DK: Sustained low-efficiency dialysis for critically ill patients requiring renal replacement therapy. *Kidney Int* 2001;60:777–785.
- 25 Baldwin I, Bellomo R, Naka T, Koch B, Fealy N: A pilot randomized controlled comparison of extended daily dialysis with filtration and continuous veno-venous hemofiltration: fluid removal and hemodynamics. *Int J Artif Organs* 2007;30:1083–1089.
- 26 Marshall MR, Ma T, Galler D, Rankin AP, Williams AB: Sustained low-efficiency daily dialysis (SLEDD-f) for critically ill patients requiring renal replacement therapy: towards an adequate therapy. *Nephrol Dial Transplant* 2004;19:877–884.
- 27 Kumar VA, Yeun JY, Depner TA, Don BR: Extended daily dialysis vs. continuous hemodialysis for ICU patients with acute renal failure: a two-year single center report. *Int J Artif Organs* 2004;27:371–379.
- 28 Baldwin I, Naka T, Koch B, Fealy N, Bellomo R: A pilot randomised controlled comparison of continuous veno-venous haemofiltration and extended daily dialysis with filtration: effect on small solutes and acid-base balance. *Intensive Care Med* 2007;33:830–835.
- 29 Zhang L, Yang J, Eastwood GM, Zhu G, Tanaka A, Bellomo R: Extended daily dialysis versus continuous renal replacement therapy for acute kidney injury: a meta-analysis. *Am J Kidney Dis* 2015;66:322–330.
- 30 Yumoto M, Nishida O, Moriyama K, Shimomura Y, Nakamura T, Kuriyama N, Hara Y, Yamada S: In vitro evaluation of high mobility group box 1 protein removal with various membranes for continuous hemofiltration. *Ther Apher Dial* 2011;15:385–393.
- 31 Bellomo R, Tipping P, Boyce N: Continuous veno-venous hemofiltration with dialysis removes cytokines from the circulation of septic patients. *Crit Care Med* 1993;21:522–526.
- 32 Heering P, Morgera S, Schmitz FJ, Schmitz G, Willers R, Schultheiss HP, Strauer BE, Grabensee B: Cytokine removal and cardiovascular hemodynamics in septic patients with continuous venovenous hemofiltration. *Intensive Care Med* 1997;23:288–296.
- 33 Kellum JA, Johnson JP, Kramer D, Palevsky P, Brady JJ, Pinsky MR: Diffusive vs. convective therapy: effects on mediators of inflammation in patient with severe systemic inflammatory response syndrome. *Crit Care Med* 1998;26:1995–2000.
- 34 Peng Y, Yuan Z, Li H: Removal of inflammatory cytokines and endotoxin by veno-venous continuous renal replacement therapy for burned patients with sepsis. *Burns* 2005;31:623–628.
- 35 Peng Z, Pai P, Hong-Bao L, Rong L, Han-Min W, Chen H: The impacts of continuous venovenous hemofiltration on plasma cytokines and monocyte human leukocyte antigen-DR expression in septic patients. *Cytokine* 2010;50:186–191.
- 36 Cole L, Bellomo R, Hart G, Journois D, Davenport P, Tipping P, Ronco C: A phase II randomized, controlled trial of continuous hemofiltration in sepsis. *Crit Care Med* 2002;30:100–106.
- 37 Ronco C, Tetta C, Mariano F, Wratten ML, Bonello M, Bordoni V, Cardona X, Inguaggiato P, Pilotto L, d'Intini V, Bellomo R: Interpreting the mechanisms of continuous renal replacement therapy in sepsis: the peak concentration hypothesis. *Artif Organs* 2003;27:792–801.
- 38 Brunet S, Leblanc M, Geadah D, Parent D, Courteau S, Cardinal J: Diffusive and convective solute clearances during continuous renal replacement therapy at various dialysate and ultrafiltration flow rates. *Am J Kidney Dis* 1999;34:486–492.
- 39 Claure-Del Granado R, Macedo E, Chertow GM, Soroko S, Himmelfarb J, Ikizler TA, Paganini EP, Mehta RL: Effluent volume in continuous renal replacement therapy overestimates the delivered dose of dialysis. *Clin J Am Soc Nephrol* 2011;6:467–475.
- 40 Lyndon WD, Wille KM, Tolwani AJ: Solute clearance in CRRT: prescribed dose versus actual delivered dose. *Nephrol Dial Transplant* 2012;27:952–956.
- 41 Ronco C, Bellomo R, Homel P, Brendolan A, Dan M, Piccinni P, La Greca G: Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. *Lancet* 2000;356:26–30.
- 42 Saudan P, Niederberger M, De Seigneux S, Romand J, Pugin J, Perneger T, Martin PY: Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure. *Kidney Int* 2006;70:1312–1317.
- 43 Ratanarat R, Brendolan A, Piccinni P, Dan M, Salvatori G, Ricci Z, Ronco C: Pulse high-volume haemofiltration for treatment of severe sepsis: effects on hemodynamics and survival. *Crit Care* 2005;9:R294–R302.
- 44 Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Oudemans-van Straaten H, Ronco C, Kellum JA: Continuous renal replacement therapy: a worldwide practice survey. The beginning and ending supportive therapy for the kidney (B.E.S.T. kidney) investigators. *Intensive Care Med* 2007;33:1563–1570.
- 45 RENAL Study Investigators: Renal replacement therapy for acute kidney injury in Australian and New Zealand intensive care units: a practice survey. *Crit Care Resusc* 2008;10:225–230.
- 46 Vesconi S, Cruz DN, Fumagalli R, Kindgen-Milles D, Monti G, Marinho A, Mariano F, Formica M, Marchesi M, René R, Livigni S, Ronco C: Delivered dose of renal replacement therapy and mortality in critically ill patients with acute kidney injury. *Crit Care* 2009;13:R57.
- 47 Bouman CS, Oudemans-Van Straaten HM, Tijssen JG, Zandstra DF, Kesecioglu J: Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: a prospective, randomized trial. *Crit Care Med* 2002;30:2205–2211.
- 48 Tolwani AJ, Campbell RC, Stofan BS, Lai KR, Oster RA, Wille KM: Standard versus high-dose CVVHDF for ICU-related acute renal failure. *J Am Soc Nephrol* 2008;19:1233–1238.
- 49 VA/NIH Acute Renal Failure Trial Network, Palevsky PM, Zhang JH, O'Connor TZ, Chertow GM, Crowley ST, Choudhury D, Finkel K, Kellum JA, Paganini E, Schein RM, Smith MW, Swanson KM, Thompson BT, Vijayan A, Watnick S, Star RA, Peduzzi P: Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med* 2008;359:7–20.
- 50 Renal Replacement Therapy Study Investigators, Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lo S, McArthur C, McGuinness S, Myburgh J, Norton R, Scheinkestel C, Su S: Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med* 2009;361:1627–1638.

- 51 Fujii T, Namba Y, Fujitani S, Sasaki J, Narihara K, Shibagaki Y, Uchino S, Taira Y: Low-dose continuous renal replacement therapy for acute kidney injury. *Int J Artif Organs* 2012;35:525–530.
- 52 Betjes MG, van Oosterom D, van Agteren M, van de Wetering J: Regional citrate versus heparin anticoagulation during venovenous hemofiltration in patients at low risk for bleeding: similar hemofilter survival but significantly less bleeding. *J Nephrol* 2007;20:602–608.
- 53 Brophy PD, Somers MJ, Baum MA, Symons JM, McAfee N, Fortenberry JD, Rogers K, Barnett J, Blowey D, Baker C, Bunchman TE, Goldstein SL: Multi-centre evaluation of anticoagulation in patients receiving continuous renal replacement therapy (CRRT). *Nephrol Dial Transplant* 2005;20:1416–1421.
- 54 Kutsogiannis DJ, Gibney RT, Stollery D, Gao J: Regional citrate versus systemic heparin anticoagulation for continuous renal replacement in critically ill patients. *Kidney Int* 2005;67:2361–2367.
- 55 Nowak G, Bucha E, Gööck T, Thieler H, Markwardt F: Pharmacology of r-hirudin in renal impairment. *Thromb Res* 1992;66:707–715.
- 56 Reeves JH, Cumming AR, Gallagher L, O'Brien JL, Santamaria JD: A controlled trial of low-molecular-weight heparin (dalteparin) versus unfractionated heparin as anticoagulant during continuous venovenous hemodialysis with filtration. *Crit Care Med* 1999;27:2224–2228.
- 57 Nakae H, Tajimi K: Pharmacokinetics of nafamostat mesilate during continuous hemodiafiltration with a polyacrylonitrile membrane. *Ther Apher Dial* 2003;7:483–485.
- 58 Maruyama Y, Yoshida H, Uchino S, Yokoyama K, Yamamoto H, Takinami M, Hosoya T: Nafamostat mesilate as an anticoagulant during continuous veno-venous hemodialysis: a three-year retrospective cohort study. *Int J Artif Organs* 2011;34:571–576.
- 59 Baek NN, Jang HR, Huh W, Kim YG, Kim DJ, Oh HY, Lee JE: The role of nafamostat mesilate in continuous renal replacement therapy among patients at high risk of bleeding. *Ren Fail* 2012;34:279–285.
- 60 Lee YK, Lee HW, Choi KH, Kim BS: Ability of nafamostat mesilate to prolong filter patency during continuous renal replacement therapy in patients at high risk of bleeding: a randomized controlled study. *PLoS One* 2014;9:e108737.
- 61 Parienti JJ, Mégarbane B, Fischer MO, Lautrette A, Gazui N, Marin N, Hanouz JL, Ramackers M, Daubin C, Mira JP, Charbonneau P, du Cheyron D: Catheter dysfunction and dialysis performance according to vascular access among 736 critically ill adults requiring renal replacement therapy: a randomized controlled study. *Crit Care Med* 2010;38:1118–1125.
- 62 Chua HR, Schneider AG, Sherry NL, Lotfy N, Chan MJ, Galtieri J, Wong GR, Lipcsey M, Matte Cde A, Collins A, Garcia-Alvarez M, Bellomo R: Initial and extended use of femoral versus nonfemoral double-lumen vascular catheters and catheter-related infection during continuous renal replacement therapy. *Am J Kidney Dis* 2014;64:909–917.
- 63 Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Kim I, Lee J, Lo S, McArthur C, McGuinness S, Norton R, Myburgh J, Scheinkestel C: The relationship between hypophosphataemia and outcomes during low-intensity and high-intensity continuous renal replacement therapy. *Crit Care Resusc* 2014;16:34–41.
- 64 Cano NJ, Aparicio M, Brunori G, Carrero JJ, Cianciaruso B, Fiaccadori E, Lindholm B, Teplan V, Fouque D, Guarnieri G: ESPEN Guidelines on Parenteral Nutrition: adult renal failure. *Clin Nutr* 2009;28:401–414.
- 65 Wiesen P, Van Overmeire L, Delanaye P, Dubois B, Preiser JC: Nutrition disorders during acute renal failure and renal replacement therapy. *JPEN J Parenter Enteral Nutr* 2011;35:217–222.
- 66 Honoré PM, De Waele E, Jacobs R, Mattens S, Rose T, Joannes-Boyau O, De Regt J, Verfaille L, Van Gorp V, Boer W, Collin V, Spapen HD: Nutritional and metabolic alterations during continuous renal replacement therapy. *Blood Purif* 2013;35:279–284.
- 67 Bellomo R, Ronco C: How to feed patients with renal dysfunction. *Curr Opin Crit Care* 2000;6:239–246.
- 68 Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Straaten HO, Ronco C, Kellum JA: Discontinuation of continuous renal replacement therapy: a post hoc analysis of a prospective multicenter observational study. *Crit Care Med* 2009;37:2576–2582.