Regional citrate anticoagulation for renal replacement therapies in patients with acute kidney injury: a position statement of the Work Group “Renal Replacement Therapies in Critically Ill Patients” of the Italian Society of Nephrology

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Abstract Patients with acute kidney injury (AKI) on renal replacement therapy (RRT) are at increased risk for bleeding but usually require anticoagulation of the extracorporeal circuit, a key prerequisite for delivery of an adequate RRT dose. To this end, many anti-hemostatic strategies have been proposed, unfractionated heparin—with all of its significant drawbacks and complications—being the most common method used so far. In this clinical context, regional citrate anticoagulation (RCA) could represent the most promising strategy, and it has been endorsed by recent guidelines on AKI. The aim of this position statement is to critically review the current

evidence on RCA for the extracorporeal circuit of RRT in patients with AKI, in order to provide suggestions for its application in clinical practice. To this purpose, the most relevant clinical studies and recent guidelines on AKI with special regard to anti-hemostatic strategies for RRT circuit maintenance have been reviewed and commented. Experts from the Working Group “Renal Replacement Therapies in Critically Ill Patients” of the Italian Society of Nephrology have prepared this position paper, which discusses the basic principles, advantages and drawbacks of RCA based on the available safety and efficacy data. Advice is given on how to use and monitor RCA in the different RRT modalities, in order to avoid complications while maximizing the delivery of the prescribed RRT dose.

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Introduction

Continuous renal replacement therapies (CRRT), along with prolonged intermittent renal replacement therapies (PIRRT), such as sustained low-efficiency dialysis (SLED), are the most widely used techniques for the treatment of critically ill patients with acute kidney injury (AKI) requiring renal replacement therapy (RRT) [1–5]. In this clinical context, the choice of the anti-hemostatic strategy for the extracorporeal circuit of RRT is critical but still remains a matter of debate [6]. Indeed, it is well recognized that AKI is a high bleeding risk condition, and that clinically important bleeding significantly increases mortality risk in this clinical setting [7]. Although the incidence of hemorrhagic complications in patients with AKI on RRT is extremely variable across different studies [8–10], the

occurrence of major bleeding is not uncommon and cannot be neglected, especially when systemic anticoagulation with heparin is adopted [11, 12]. Hence, alternatives to standard heparinization, such as RRT without anticoagulation [13, 14], minimal systemic anticoagulation [12], antiplatelet agents such as the synthetic analogues of prostacyclin [15], supplementation of antithrombin-III [16, 17] and regional anticoagulation strategies [18–21] have been evaluated in the past to minimize the occurrence of hemorrhagic complications. On the other hand, it is well known that premature clotting of the RRT circuit due to inadequate anticoagulation may increase blood loss, downtime, nursing workload and costs [12]. Moreover, aside from vascular access malfunction/recirculation, circuit clotting still remains the main cause of discrepancy between prescribed and delivered dose in RRT [11, 12]. In this regard, the anticoagulation strategy used in the multicenter randomized Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network (ATN) study, aimed at limiting the use of systemic heparinization in favor of no anticoagulation, was able to achieve a full delivery of the prescribed CRRT dose in less than 70 % of patients undergoing continuous veno-venous hemodiafiltration (CVVHDF) [22]. Recently, also the 2012 KDIGO Clinical Practice Guidelines for AKI have underscored that the actual delivered dose of RRT in AKI patients is frequently lower than the prescribed one, indicating early filter clotting as a major hindrance to adequate RRT dose delivery [6]. Therefore, a higher prescribed dose combined with the reduction of RRT interruptions has been suggested to achieve the recommended dose targets (i.e. delivered Kt/V of 3.9 per week for intermittent or prolonged RRT, and delivered effluent volume of 20–25 ml/kg/h for CRRT) [6]. Among potential alternatives to standard heparin use, the 2012 KDIGO Clinical Practice Guidelines for AKI suggested regional citrate anticoagulation (RCA) as the first choice anticoagulation modality in AKI patients undergoing CRRT, regardless of the patient's bleeding risk and coagulation status [6]. This suggestion has been endorsed by the Canadian Society of Nephrology [23], while other recently published guidelines on AKI [24, 25] did not provide specific indications on RCA in critically ill patients with AKI on RRT (Table 1).

Several clinical studies support the superiority of RCA over standard heparin in terms of both prolonged circuit lifespan [26–31] and reduced incidence of hemorrhagic complications and transfusional needs [26–30, 32, 33]. Moreover, these findings have for the most part been confirmed by two recent meta-analyses pooling almost 500 patients from the 6 most relevant randomized clinical trials comparing RCA with heparin anticoagulation [34, 35].

Despite the positive reports about safety and efficacy of RCA, its clinical use has not gained widespread diffusion.

In a recent survey on intensive care unit (ICU) practice in north-west Italy, unfractionated heparin was the anticoagulant of choice in the vast majority of RRT sessions (5,296 out of 7,842 sessions). Interestingly, in patients at high risk of bleeding, RCA was performed in only 18 % of the cases, whereas RRT without heparin or low heparin doses with saline flushes (77.6 %) were the most commonly adopted anticoagulation strategies [36]. However, it has been previously reported that the use of intermittent saline flushes does not appear to be a valid option to reduce filter clotting risk during low-dose heparin hemodialysis [37].

RCA has not been very popular so far for several reasons [1, 21, 22, 38]: complexity of the early clinical RCA protocols, concerns about the potential risk of metabolic complications, need for customized solutions to prevent sodium and/or buffer overload, and lack of commercially available solutions dedicated for RCA-CRRT use [39]. However, most of these issues have been progressively solved by the most recent advances in RCA, leading to simplification of citrate-based protocols and increasing availability of RCA solutions specific for CRRT [21, 40]. Finally, the use of latest generation monitors for CRRT with integrated infusion systems and specific software provides a near-automated RCA with user-friendly and safe citrate delivery [41, 42]. This modern approach to RCA should allow both to reduce the risk of errors and to more easily tailor RCA settings according to clinical needs of the patients, thus facilitating a wider diffusion of this highly effective anticoagulation method in the coming years [43].

This position statement provides a critical overview of the use of RCA for the extracorporeal circuit of RRT in patients with AKI, in order to make suggestions about its application in clinical practice. Experts from the Working Group “Renal Replacement Therapies in Critically Ill Patients” of the Italian Society of Nephrology prepared this position paper in order to facilitate a better understanding of the basic principles of RCA, and to discuss the main advantages and potential drawbacks of citrate in the clinical setting of AKI in the ICU. Advice is given on how to use and monitor RCA in the different modalities of RRT, in order to avoid complications while maximizing the delivery of the prescribed RRT dose.

Basic principles of RCA

Biochemical aspects and mechanisms of action

Citrate ($\text{C}_6\text{H}_5\text{O}_7^{3-}$; MW 189) is the anion of citric acid ($\text{C}_6\text{H}_8\text{O}_7$; MW 192), and is more commonly available for RCA in the form of trisodium citrate salt ($\text{Na}_3\text{C}_6\text{H}_5\text{O}_7$; MW 258). Citrate accumulates in the mitochondria, where it is metabolized as an intermediate of the Krebs cycle. Red

Table 1 Summary of the recommendations and suggestions from recent Guidelines/Commentaries on RCA use for RRT in patients with AKI

Guidelines or commentaries	General indications to anticoagulation for RRT in AKI	Patients at high bleeding risk	Contraindications to RCA	Anti-hemostatic strategy for patients with contraindications to citrate, or in patients with severe liver dysfunction and/or shock
KDIGO Guidelines for AKI (Kidney Int Supplements 2012; 2:1–138)	5.3.1: In a patient with AKI requiring RRT, base the decision to use anticoagulation for RRT on assessment of the patient's potential risks and benefits from anticoagulation. (<i>Not Graded</i>) 5.3.1.1: We recommend using anticoagulation during RRT in AKI if a patient does not have an increased bleeding risk or impaired coagulation and is not already receiving systemic anticoagulation. (<i>1B</i>) 5.3.2: For patients without an increased bleeding risk or impaired coagulation and not already receiving effective systemic anticoagulation, we suggest the following: RRT, we recommend using either unfractionated or low-molecular-weight heparin, rather than other anticoagulants. (<i>1C</i>) 5.3.2.2: For anticoagulation in CRRT, we suggest using RCA rather than heparin in patients who do not have contraindications for citrate. (<i>2B</i>)	5.3.3: For patients with increased bleeding risk who are not receiving anticoagulation, we suggest the following for anticoagulation during RRT: 5.3.3.1: We suggest using RCA, rather than no anticoagulation, during CRRT in a patient without contraindications for citrate. (<i>2C</i>) 5.3.3.2: We suggest avoiding regional heparinization during CRRT in a patient with increased risk of bleeding. (<i>2C</i>)	A major contraindication for the use of citrate anticoagulation is severely impaired liver function or shock with muscle hypoperfusion, both representing a risk of citrate accumulation	5.3.2.3: For anticoagulation during CRRT in patients who have contraindications for citrate, we suggest using either unfractionated or low-molecular-weight heparin, rather than other anticoagulants. (<i>2C</i>)
KDOQI US Commentary on the 2012 KDIGO Guidelines for AKI (Am J Kidney Dis 2013; 61:649–672)	With regard to the use of anticoagulation for CRRT, the Work Group believed that there is no consensus on which anticoagulant should be first choice for CRRT. Rather, the choice of anticoagulant for CRRT should be determined by patient characteristics, local expertise, nursing comfort, ease of monitoring, and pharmacy issues. Monitoring should include evaluation of anticoagulant effect, filter efficacy, and circuit life and complications. Although RCA is gaining wide acceptance with the development of simpler and safer protocols, citrate is not approved by the US Food and Drug Administration (FDA) as an anticoagulant for CRRT. As a result, the commercially available citrate solutions in the US are used for blood banking and are hypertonic, increasing the risk of metabolic complications. Because citrate is not universally available in the US, it cannot be recommended over heparin. Along the same lines, citrate cannot be recommended over no anticoagulation during CRRT at present	No indication	No indication	No indication

Table 1 continued

Guidelines or commentaries	General indications to anticoagulation for RRT in AKI	Patients at high bleeding risk	Contraindications to RCA	Anti-hemostatic strategy for patients with contraindications to citrate, or in patients with severe liver dysfunction and/or shock
Canadian Society of Nephrology (CNS) Work Group Commentary on the 2012 KDIGO Guidelines for AKI (Am J Kidney Dis 2013; 61:673–685)	The CSN Work Group acknowledges that the lower risk of bleeding with RCA represents a clinically relevant advantage in favor of this anticoagulation strategy	No indication	The KDIGO guideline cites “severely impaired liver function or shock with muscle hypoperfusion” as “major” contraindications for the use of regional citrate anticoagulation. The Work Group agrees that RCA should be used cautiously in these settings, but we do not believe that these represent absolute contraindications	The CSN work group believes that the use of RCA may still be considered in the setting of shock
ERBP position statement on the 2012 KDIGO Guidelines for AKI (Nephrol Dial Transplant 2013; 28:2940–2945)	No indication	No indication	No indication	No indication
AKI acute kidney injury, KDIGO Kidney Disease Improving Global Outcomes, KDOQI Kidney Disease Outcomes Quality Initiative, RCA regional citrate anticoagulation, RRT renal replacement therapies, US United States				

blood cells are not freely permeable to citrate, which is distributed only in the plasma volume [44].

In the clinical setting citrate can be measured in plasma and ultrafiltrate with conventional enzymatic methods or by high performance liquid chromatography (HPLC) methods [44, 45]. Citrate levels in healthy subjects are <0.1 mmol/l. Citrate is able to form stable complexes with divalent cations such as calcium and magnesium. On this basis, citrate acts as anticoagulant agent for the extracorporeal circuit by chelating ionized calcium [20, 46], the key cofactor of many steps of the clotting cascade [47]. Depending on the different protocols, citrate concentrations in the extracorporeal circuit during RCA are 3–5 mmol/l, with ionized calcium levels in the 0.1–0.4 mmol/l range. When citratemia is 6 mmol/l or more, ionized calcium is 0.1 mmol/l or less and blood coagulation is totally inhibited [48].

Citrate has, in addition, anti-hemostatic and anti-inflammatory effects due to reduced activation of white blood cells and platelets [49–54], and protective effects against endothelial cell inflammation and oxidative stress [55, 56].

Citrate pharmacokinetics

As a general rule, during RCA citrate is infused upstream in the extracorporeal circuit at an infusion rate strictly related to blood flow and target circuit citrate values. Since RRT fluids are usually calcium-free, calcium-containing solutions (calcium chloride or calcium gluconate) should be infused at the end of the extracorporeal circuit in the blood returning to the patient, or directly to the patient through a central venous line, in order to replace calcium losses in the effluent fluid. As filter membranes are freely permeable to citrate, 30–70 % of calcium–citrate complexes are lost in the effluent fluid (ultrafiltrate and/or dialysate), these losses being directly proportional to the effluent volume [44].

Citrate entering the patient’s blood pool through the venous line of the circuit is rapidly metabolized in the Krebs cycle as citric acid; thus, since three hydrogen ions for each citrate molecule are consumed in this metabolic process, three bicarbonate molecules will be produced. Citrate is metabolized mainly in the liver and to a lesser extent in the kidney and skeletal muscle. Total body clearance of citrate is similar in critically ill patients with AKI and in healthy volunteers (648.0 ± 347.0 vs. 686.6 ± 353.6 ml/min; $p = 0.62$) [45], but is reduced in cirrhotic patients (340 ± 185 vs. 710 ± 397 ml/min in cirrhotic and control patients, respectively; $p = 0.002$), in parallel to prolonged half-life (69 ± 33 vs. 36 ± 18 min in cirrhotic patients and control patients, respectively; $p = 0.001$) [57].

Citrate also represents a source of energy in the form of carbohydrate-like calories (0.59 kcal/mmol) [20, 58]. With the most commonly used citrate protocols, the net citrate load to the patient is about 11–20 mmol/h, roughly corresponding to 150–280 kcal/day derived from citrate metabolism [21, 59]. However, in the case of CRRT with high blood flow rate (150–180 ml/min) and high target citrate values in the circuit (4–5 mmol/l), a total bioenergetic gain from RCA of up to 1,000 kcal/day has been reported when a citrate solution containing glucose, such as ACD-A (anticoagulant-citrate-dextrose solution A, 2.5 % dextrose) is coupled with lactate-buffered CRRT solutions [58].

RCA monitoring and complications of citrate anticoagulation

Several metabolic alterations have been described in the course of RCA, including: (1) hypo- or hyper-calcemia related to inadequate calcium replacement; (2) hyponatremia, more often seen in the past when citrate solutions hypertonic in sodium were used in the older RCA protocols; (3) metabolic alkalosis due to excessive citrate loads; (4) metabolic acidosis related to inadequate buffer supply due to inappropriate RCA parameter-setting or inadequate matching of the solutions adopted (imbalance between citrate/bicarbonate delivered to the patient and citrate/bicarbonate removed with the effluent); (5) citrate accumulation, mainly characterized by worsening metabolic acidosis and ionized hypocalcemia, respectively due to the impaired bicarbonate production from citrate and to the lack of calcium release from calcium–citrate complexes [21].

Citrate accumulation is more frequently reported in clinical conditions at higher risk for inadequate citrate metabolism, such as severe liver failure/liver transplant and septic or cardiogenic shock with organ tissue hypoperfusion [21]. In patients with suspected accumulation of citrate, direct measurement of plasma citrate concentration is the gold standard for quantitative assessment of systemic citrate levels [28, 44]. However, since the measurement of citrate levels is not widely available in daily practice, surrogate criteria for early detection of inadequate citrate metabolism have been proposed (Table 2) [60–62]. By applying these criteria, RCA can be safely performed without clinically relevant electrolyte and acid–base alterations due to citrate accumulation [33, 41, 63]. In particular, also in patient populations at higher risk of inadequate citrate metabolism, normal levels of citrate [28] and no metabolic derangements have been demonstrated [64–66], especially when strategies aimed at preventing citrate accumulation are applied. In this regard, citrate kinetics studies have shown that lowering of blood flow in the

extracorporeal circulation (with consequently reduced citrate infusion rate), as well as the optimization of citrate diffusive clearance (throughout an increased dialysate flow rate), are able to reduce the citrate load to the patient [28, 67]. Although early citrate protocols, adopting a citrate dose of up to 4–6 mmol/l, were characterized by a longer filter survival, it should be underlined that a higher than usual target for ionized calcium (<0.5 mmol/l) in the RRT circuit, obtained by achieving lower citrate concentration targets in the circuit (2.5–3 mmol/l), is still able to ensure an adequate filter life [68], and represents a valid strategy in patients at higher risk of citrate accumulation. Specific clinical settings, such as severe rhabdomyolysis, can potentially complicate the management of RCA [21]. Indeed, although hypocalcemia is a common complication in the early phase of rhabdomyolysis, full correction of calcium levels is not recommended because of potentially harmful effects of excessive calcium supplementation (e.g. tissue calcium deposition and episodes of late hypercalcemia). Thus, a lower than usual systemic ionized calcium level (0.9–1 mmol/l) should be considered a reasonable target while performing RCA-CRRT in this clinical scenario [21].

Citrate use in CRRT

Several RCA protocols have been developed using commercially available or hospital pharmacy-made citrate solutions, not always specifically intended for RRT use. Along with the off-label use of anticoagulant-citrate-dextrose formulations (i.e. ACD-A), specific citrate solutions for CRRT are now available in many countries, and are increasingly adopted in the more recently developed RCA protocols. RCA solutions may be classified on the basis of their citrate concentration as high- and low-citrate concentration solutions and are respectively characterized by hypertonicity and isotonicity in sodium [21]. Provided that correct matching of citrate and CRRT solutions (dialysate/replacement fluids) is ensured, RCA protocols can be designed in convective and/or diffusive modalities.

RCA in convective CRRT

RCA can be performed in convective CRRT modalities with either high- or low-citrate concentration solutions [26–30, 33, 68–77]. In CVVH with high-concentration citrate solutions, a separate pre-filter citrate infusion is usually combined with a replacement fluid, which can be optionally delivered in post-dilution only [26, 33] or pre-post dilution modality [73]. In both cases, a lower sodium and lower bicarbonate replacement fluid is required to prevent acid–base and/or electrolyte derangements related

Table 2 Monitoring for early detection of citrate accumulation during RCA

Parameter	Monitoring intensity	Aim and significance
Systemic ionized calcium	Baseline Within 1 h from the start of the treatment and then at least every 4–6 h	To early detect systemic ionized hypocalcemia due to the lack of calcium release from calcium–citrate complexes because of impaired citrate metabolism (after excluding inappropriate calcium replacement)
Systemic total calcium (<i>simultaneously to systemic ionized calcium</i>)	Every 12–24 h or more frequently if citrate accumulation is suspected	To calculate the calcium ratio (total to ionized systemic calcium) as an indirect index of citrate accumulation (≥ 2.5) In the presence of impaired citrate metabolism, a progressively higher calcium infusion rate is required to maintain the systemic ionized calcium concentration within the intended target; the consequent disproportionate rise in total systemic calcium concentration leads to an increase of total-to-ionized calcium ratio
Acid–base parameters (pH, bicarbonate)	Baseline Within 1 h from the start of the treatment and then at least every 4–6 h	To early detect worsening metabolic acidosis due to impaired bicarbonate production related to inadequate citrate metabolism
Serum magnesium	At least every 24 h	To evaluate the need and the amount of magnesium supplementation
Serum sodium	Once daily	To exclude hypernatremia or hyponatremia (rarely observed with a correct matching of RCA solutions) and to prevent sudden increase of serum sodium in chronic liver disease patients with hyponatremia.
Citratemia	Not routinely used for clinical purposes	If available, direct measurement of plasma citrate concentration represents the gold standard to confirm citrate accumulation
Serum lactate	Baseline with subsequent checks scheduled according to clinical needs	To identify patients at higher risk for citrate accumulation (basal values ≥ 3.4 mmol/l or upward trend of lactatemia)

to buffer and/or sodium overload (metabolic alkalosis, hypernatremia) [26, 33, 73].

Regarding low-concentration citrate solutions, also known as “citrate-buffered” replacement solutions, simplified protocols have been proposed for RCA in pre-dilution only CVVH [29, 72, 75, 76]. In this case, the citrate-buffered solution acts both as regional anticoagulant and convective dialysis dose [29, 72, 75, 76]. This option may have the drawback of a CRRT dose strictly related to citrate dose, with a potentially higher risk of citrate accumulation if a high dialysis dose is required [76]. By combining the pre-dilution citrate-buffered solution with a post-dilution replacement fluid, RCA can be performed in pre-post dilution CVVH allowing to separately modulate citrate load and CRRT dose [30]. The “physiological” sodium content and the low citrate concentration of isotonic solutions also avoid the need for customized replacement fluids (lower sodium, lower bicarbonate) specifically formulated for RCA, thus simplifying CRRT handling. In this regard, the adoption of conventional calcium-containing CRRT replacement fluids represents a further simplification that reduces the need for calcium infusion, as well as the risk of errors when calcium-free solutions are handled [30, 70]. It has been reported that this strategy is still compatible with an adequate filter lifespan without increasing the risk of venous drip chamber clotting [30, 70].

By using low-concentration [68, 74] as well as high-concentration citrate solutions [27, 71], RCA-CVVHDF protocols can be designed by adding a standard or customized dialysate with the advantage that they operate at lower filtration fractions.

Finally, commercially available calcium and phosphate containing CRRT solutions have been recently proposed for RCA in CVVH and in CVVHDF, both in adult and pediatric patients. These solutions can be used either as post-dilution replacement fluid and/or as dialysate in combination with a low-concentration citrate solution [41, 68–70]. This approach significantly reduces the incidence of CRRT-induced hypophosphatemia, minimizing the need for intravenous phosphate supplementation [68, 70].

RCA in diffusive CRRT

At variance with convective modalities, RCA can be performed in continuous veno-venous hemodialysis (CVVHD) only with the use of hypertonic citrate solutions. Indeed, the high citrate concentration of these solutions allows the achievement of target citrate values in the circuit by adopting relatively low infusion rates; thus, hypertonic citrate solutions act only as an anticoagulant without contributing to the total RRT dose [21].

Although the use of calcium-containing dialysate has also been reported [65, 78], in RCA-CVVHD protocols the

citrate solution is typically combined with a customized calcium-free dialysis fluid [41, 79] to avoid excessive blood recalcification inside the filter. In addition, pharmacy-made or commercially available dialysis fluids are commonly characterized by lower sodium and lower bicarbonate concentrations to prevent hyponatremia and metabolic alkalosis [21]. In particular, lower bicarbonate dialysate allows to obtain a negative mass balance of bicarbonate, thus compensating the buffer overload due to the bicarbonate production ensuing from the net citrate load to the patient. The use of a hypertonic trisodium citrate solution (4 %, citrate 136 mmol/l), combined with a customized lower bicarbonate dialysate (20 mmol/l), has been successfully reported in CVVHD [41]. Optimal acid–base control was achieved in most of the patients by adapting the dialysate flow rate or by parallel modifications of blood flow and citrate flow rates. Dialysate flow rate was increased in the case of metabolic alkalosis, to enhance diffusive citrate clearance, while in the case of metabolic acidosis, unrelated to inadequate citrate metabolism, a parallel increase of blood flow and citrate flow rates was able to increase buffer supply. This approach, when guided by strict protocols, is characterized by a high flexibility in RCA-CRRT buffer balance, but the potential drawback is metabolic acidosis if a high CRRT dose is required [41, 79]. Indeed, the increase of lower bicarbonate dialysate flow rate, aimed at achieving a higher dialysis dose, is invariably associated to a proportional increase of diffusive removal of citrate and, within certain limits, also of bicarbonate [41, 79].

In summary, safe and efficacious RCA protocols can be implemented in all CRRT modalities (CVVH, CVVHD, CVVHDF). Since diffusive and convective transport of citrate is comparable, citrate loss during RCA-CRRT is closely related to total effluent flow rate [44]. Thus, during convective RCA protocols, similarly to the diffusive ones, modulation of citrate load can be achieved through modifications of CRRT dose, along with other strategies such as interventions on blood flow rate and citrate dose. In this regard, an appropriate setting and subsequent adjustments of the main CRRT parameters are critical to perform a safe RCA and to modulate buffer supply according to clinical needs, avoiding acid–base and metabolic derangements.

Regardless of the CRRT modality used, the introduction of latest generation CRRT monitors, equipped with integrated infusion systems and specifically developed software that allow near-automated RCA [41, 42], represents a perspective of simplification that can significantly improve the safety of citrate anticoagulation protocols. These systems are able to keep the citrate dose stable even when the blood flow rate changes, and to roughly estimate calcium balance during RCA-CRRT (Fig. 1), reducing the nurse workload related to the need for additional interventions on

operational parameters [41, 42]. In particular, in the more recently introduced technologically advanced CRRT systems, citrate and calcium infusion pumps are fully integrated and linked to blood and effluent pumps. This approach avoids incorrect infusion in the case of modifications of the CRRT parameter setting or in the case of temporary interruption of the treatment [41].

Key messages

- ✓ RCA protocols can be implemented in convective (CVVH) or mixed (CVVHDF) CRRT modalities with both high- and low-concentration citrate solutions; while in pure diffusive CRRT modality (CVVHD) RCA can be performed only with the use of hypertonic citrate solutions
- ✓ The use of calcium- and phosphate-containing replacement solutions can be implemented in convective or mixed RCA protocols as a part of the CRRT dose, reducing calcium infusion need and minimizing the incidence of CRRT-induced hypophosphatemia.
- ✓ The use of calcium-containing replacement solutions (CVVH/CVVHDF) does not appear to increase the risk of venous drip chamber clotting during RCA.

RCA in prolonged intermittent RRT (PIRRT)

PIRRT methods are increasingly used in ICU patients with AKI [4, 5, 22, 36, 76–81]. They are known under different acronyms, such as SLED, extended daily dialysis (EDD), or extended daily hemofiltration/hemodiafiltration if a convective component is added. A duration of 8–12 h represents the key feature of PIRRT, which combine the main advantages of conventional intermittent forms of RRT (e.g. standard dialysis monitor use, online produced dialysate, flexible scheduling, and lower costs) with those of CRRT (e.g. hemodynamic tolerance, excellent metabolic control, and gentle osmotic fluctuation and fluid removal capacity) [15, 80, 82–85].

Despite shorter treatment duration as compared to CRRT, even with PIRRT anticoagulation of the extracorporeal circuit is usually required, but the optimal anticoagulation strategy remains to be defined [11, 12]. Among the different options proposed for the maintenance of the extracorporeal circuit in PIRRT, saline flushes without any anti-hemostatic agent, unfractionated heparin, and prostacyclin have been reported [15, 84–88]. Although no extracorporeal circuit clotting has been observed with unfractionated heparin in SLED [84], other series reported clotting in 17–26 % of treatments [85–88]; clotting rates were 10 % with epoprostenol, a synthetic analogue of the

Regional Citrate Anticoagulation in RRT: general principles

Fig. 1 General principles of regional citrate anticoagulation in renal replacement therapies Target citratemia and target circuit ionized calcium may vary according to the different RCA protocols. The risk of citrate accumulation can be reduced by applying strategies aimed at maintaining a low citrate load for the patient: **a** low blood flow rate; **b** low target citratemia, associated with a higher target ionized

calcium in the circuit; **c** modulation of RRT dose, aimed at increasing the diffusive/convective removal of citrate. CVVH, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemodialysis; CVVHDF, continuous veno-venous hemodiafiltration; Qb, blood flow rate; RCA, regional citrate anticoagulation; RRT, renal replacement therapies

antiaggregant and vasodilatory prostacyclin PGI₂ [15], and 29–46 % without any anticoagulation [85–88]. As in the case of CRRT, citrate has been also introduced as anticoagulant for PIRRT. In an observational study on diffusive PIRRT (117 SLED in 30 patients) circuit clotting never occurred with an average treatment duration of 6.7–7.3 h [89]; however, only 19 patients had AKI and only a few were critically ill patients. The protocol required zero calcium dialysis fluid and calcium supplementation [89]. More recently, a new RCA protocol for SLED has been proposed [90], based on the use of the ACD-A solution and standard dialysis equipment, with the patient's blood recalcification obtained by calcium back-transport from calcium-containing dialysis fluid (1.25 mmol/l). Interruptions of PIRRT due to impending/irreversible clotting were recorded in 19/807 sessions (2.4 %) in 116 critically ill patients; blood restitution was complete in 98 % of the cases. Major bleeding was observed in 6 patients (5.2 % or 0.4 episodes/100 person-days on PIRRT), with hemorrhagic complication rates similar to or even lower than that reported in previous studies [8, 9, 34, 35, 91–94]. No citrate accumulation was observed, even in patients with liver

dysfunction [90]. Intravenous calcium for systemic hypocalcemia (ionized calcium levels <0.90 mmol/l) was needed in 28 sessions (3.4 %); however, in 8 of these 28 sessions, low ionized calcium was already present before starting PIRRT. Systemic coagulation of patients remained unchanged, even in patients with liver failure, and metabolic/fluid control was easily achieved; citrate load is, in fact, limited in the case of a highly efficient diffusive modality such as SLED, since in this case about 2/3 of the citrate administered is removed by the treatment itself [90]. Moreover, since the usual duration of PIRRT is 8–12 h, a time window with no citrate administration is available for citrate metabolism, further reducing the risk of accumulation.

In conclusion, although the ideal anticoagulant for PIRRT remains to be found, and the available findings are exclusively from observational data, the use of citrate in the context of a mainly diffusive prolonged intermittent modality, such as SLED, could represent an easy method to maintain the extracorporeal circuit. On this basis citrate could become the preferred anticoagulant for PIRRT.

Key messages

- ✓ Although PIRRT can be performed without any anticoagulant agent in high bleeding risk patients, increased rates of circuit interruptions have been reported; thus, alternative methods of anticoagulation are usually required to ensure circuit patency for the full PIRRT session.
- ✓ Commercially available citrate solutions, at least in observational studies, seem to allow safe and effective RCA for PIRRT, requiring limited laboratory monitoring and without the need for systemic calcium infusion in most patients. Patient's blood recalcification can be easily obtained by calcium back-transport from calcium-containing dialysis fluid.
- ✓ The risk and incidence of metabolic complications (citrate accumulation, metabolic alkalosis) is low with PIRRT, since most of the citrate infused in the circuit is removed by the treatment itself.

RCA in coupled plasma filtration adsorption (CPFA)

Coupled plasma filtration adsorption (CPFA) is a modular system composed of a plasmafilter, a hydrophobic resin cartridge and an in-series hemofilter [67, 95]. It has been proposed for non-selective removal of circulating soluble inflammatory mediators in critically ill patients with septic shock with or without AKI [67, 95]. In the CPFA system, the plasmafiltrate deriving from plasma separation passes through the resin cartridge for the removal of the excess of pro- and anti-inflammatory mediators by non-specific adsorption [95]. After the adsorption process, plasma is returned to the blood for additional purification through a conventional hemodialyzer/hemofilter [95]. In CPFA, citrate has been successfully used for the first time in 13 critically ill AKI patients with septic shock at high risk of bleeding or with active bleeding [67]. The number of lost cartridges, due to clotting or fibrin fragment formation in the plasma circuit, was significantly lower with citrate, when compared with heparin. Citrate levels in the plasma taken before and after the cartridge were comparable, suggesting that citrate is not retained by the hydrophobic resin [67]. A remarkable stability of blood ionized calcium and acid–base parameters was observed during the whole length of the RCA-CPFA session. The availability of citrate protocols for CPFA [67, 96] and the introduction of newer generation machines could facilitate a safe implementation of RCA in this setting, thus allowing to meet the prescribed target of plasma volume treated per day, which has been shown to be reached in a low proportion of CPFA

sessions when standard heparin anticoagulation was used [97].

Key messages

- ✓ RCA is a feasible and effective alternative to heparin anticoagulation during CPFA, which can reduce CPFA session interruptions due to circuit clotting, thus allowing to achieve higher targets of plasma volume treated per day.
- ✓ The availability of citrate protocols for CPFA and the introduction of newer generation machines could facilitate a safe implementation of RCA also in this setting.

RCA in extracorporeal liver support (ELS)

Due to the high hemorrhagic risk, and the frequent hypercoagulability status of patients with liver failure, regional anticoagulation of the extracorporeal circuit may represent an ideal option, since it may reduce at the same time hemorrhagic complications and circuit clotting rate [98].

The use of RCA in patients with liver dysfunction is often considered hazardous, due to deranged liver metabolism and the increased risk of accumulation. The most likely adverse effects of citrate use in this clinical setting are acute alterations of acid–base equilibrium and electrolyte status, ionized hypocalcemia and worsening metabolic acidosis being the most clinically significant [33].

However, many of the potential risks related to the use of citrate in these patients have been overcome, thanks to the recent evolution in dialysis machine engineering technology. The new software generation is in fact able to adapt citrate infusion to blood flow changes, thus limiting the risk of an inappropriate citrate/blood flow ratio. Moreover, with the CRRT monitors citrate dose can be modified at any time during treatment, in the event of a documented or suspected citrate overload. Last, the modulation of convective and/or diffusive CRRT dose may prevent the development of citrate accumulation, due to the substantial removal of citrate with the effluent fluid [21].

Recent data on RCA in patients with liver failure undergoing CRRT [99] have provided important information that can be also extrapolated to ELS treatments. In spite of substantial increases of citrate levels, metabolic consequences were less significant than expected: a trend towards metabolic alkalosis was found instead of acidosis, and no significant electrolyte disturbances (including hypocalcemia) were observed. Blood citrate levels were related to the calcium ratio; prothrombin activity $\leq 26\%$

and lactate level ≥ 3.4 mmol/l proved to be acceptable predictors of citrate accumulation [99].

Most of these issues can be deemed as valid in the case of ELS treatments usually adopted as a “bridge” to liver transplantation or liver recovery, such as the Molecular Adsorbent Recirculating System (MARS) and Prometheus [100, 101]. Both are able to remove lipo- and hydrophilic substances (bilirubin, biliary salts, ammonia and other toxic solutes) by using different adsorbers, dedicated membranes, and dialysis filters removing hydrophilic substances [102, 103]. Both ELS modalities can be performed with citrate anticoagulation, even though the experience is scanty [64, 66, 104].

Prometheus treatment is carried out with a dedicated machine equipped with a built-in citrate/calcium algorithm. The citrate dose (3–4 mmol/l of blood) is automatically re-calculated from the ionized calcium content in the patient’s venous blood. Few studies are available, due to the recent introduction of the machine. In a randomized controlled trial on 145 patients comparing Prometheus to standard medical therapy [104], 60 % of the treatments were performed with low-dose citrate anticoagulation (3.33 mmol/l of blood). Anticoagulation was effective in 84 % of the sessions, and no difference in bleeding rate was observed between patients treated with Prometheus and patients receiving standard medical therapy. However, the study was not aimed to evaluate specifically the metabolic derangements possibly due to citrate accumulation. The same holds true for another study evaluating safety and efficacy of fractionated plasma separation and adsorption with RCA in patients with liver failure [105].

The feasibility and safety of RCA during liver support using MARS, as well as its effects on electrolyte and acid–base status, have been evaluated in a prospective observational study conducted in 20 critically-ill patients with liver failure [64]. Under close monitoring, no clinically significant electrolytes or acid–base disorders were observed, suggesting that RCA is a safe and feasible method to maintain adequate circuit lifespan without increasing the risk of hemorrhagic complications [64]. More recently, a randomized cross-over trial with the MARS system in 10 patients with liver failure compared RCA with an anticoagulation-free protocol [66]. The use of citrate appeared safe, and no significant citrate-related side-effects were reported: calcium levels and acid–base status remained in a physiological range in all the patients [66].

In conclusion, RCA may be performed safely even in ELS treatments. Protocols with frequent checks of blood gas analysis with the determination of ionized calcium and acid–base status, as well as of total calcium, are needed (Table 2). The evaluation of the basal levels of both lactate

and prothrombin activity could be potentially introduced in the routine clinical practice as surrogate indexes (respectively ≥ 3.4 mmol/l and ≤ 26 %) to identify patients more prone to citrate overload, and for whom a greater attention to electrolyte/acid base control should be paid [21, 99]. Patients with acute and hyper-acute liver failure are likely to be more at risk than those with decompensated cirrhosis.

Key messages

- ✓ RCA may be performed safely even in patients undergoing extracorporeal liver support (ELS) for severe liver failure.
- ✓ Considering that ELS treatments are mainly performed in clinical settings with relative contraindication to citrate use, a closer than usual monitoring of ionized calcium, acid–base status and total calcium is mandatory throughout the treatment, particularly in the first hours, in order to ensure a timely detection of early signs of inadequate citrate metabolism.

Costs of RCA

Comparative data on the cost-effectiveness ratio of different anticoagulation methods for RRT in AKI are still lacking [23]. RCA could be more costly than heparin-based anticoagulation because of the higher cost of citrate solutions and the need for more intensive monitoring of metabolic parameters [88]. On the other hand, the savings related to both the lower incidence of bleeding complications and the lower frequency of circuit replacement could shift the balance toward RCA [106]. Finally, in the cost-benefit evaluation of RCA, indirect costs should be taken into account, such as platelet and red cell transfusions, as well as the need for antithrombin-III supplementation [30].

Final suggestions

- The Working Group acknowledges that RCA could offer significant clinical advantages over the other anti-hemostatic strategies for RRT in patients with AKI. Compared to the current gold standard (anticoagulation with unfractionated heparin), RCA significantly prolongs circuit life in all of the different RRT modalities, facilitating a full delivery of the prescribed dose; at the same time bleeding risk and transfusion needs are reduced.
- Regardless of clinical setting, the Working Group suggests to perform RCA using the lowest citrate dose compatible with an adequate circuit life. In this regard, recently published RCA protocols have shown that they

can ensure prolonged filter life by maintaining target citrate concentrations in the circuit around 3 mmol/l.

- The Working Group acknowledges that no absolute contraindication to RCA exists. However, RCA should be applied with particular caution in clinical settings characterized by severe or worsening lactic acidosis likely due to liver hypoperfusion and severe intracellular hypoxia (e.g. septic or cardiogenic shock), or by severe liver failure/liver transplant.
- The Working Group suggests that closer than usual monitoring of RCA, along with strategies aimed at reducing citrate load (low blood flow rate, low citrate dose with higher target circuit ionized calcium, higher citrate removal through an increase of CRRT dose, switch to PIRRT to maximize diffusive citrate clearance and to create a window for citrate metabolism), may allow RCA to be performed safely also in clinical settings with relative contraindication to citrate use.
- The Working Group suggests that in patients with severe liver failure basal levels of both lactate (≥ 3.4 mmol/l) and prothrombin activity (≤ 26 %) may help identify patients at higher risk of citrate accumulation. Given that direct measurement of citrate levels is not widely available in daily practice, the calcium ratio can be used as an effective surrogate index of citrate accumulation, values ≥ 2.5 being indicative of possible citrate overload. However, where available, plasma citrate measurement should be used to confirm citrate accumulation. In the case of metabolic derangement, possibly related to citrate accumulation, RCA should be at least temporarily suspended, and RRT should be performed without anticoagulation or, if not contraindicated, with low-dose unfractionated or low molecular weight heparin.
- The Working Group firmly believes that in order to achieve good clinical practice, strict RCA protocols and adequate staff education are required before starting an RCA program. The protocol should include: (1) detailed composition of citrate and RRT solutions; (2) detailed infusion rates of citrate and calcium supplementation according to initial RRT operational setting and basal patient parameters; (3) indications about the need to modify citrate infusion rate according to any variation of blood flow rate if near-automated CRRT systems are not available; (4) intensive metabolic monitoring; and (5) detailed algorithms about variation of citrate, calcium and RRT parameters according to clinical needs.

Conflict of interest None.

References

1. Uchino S, Bellomo R, Morimatsu H et al (2007) 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* 33:1563–1570
2. Morabito S, Pistolesi V, Cibelli L, Pierucci A (2009) Continuous renal replacement therapies (CRRT) will remain the most widely adopted dialysis modality in the critically ill. *G Ital Nefrol* 26:13–21
3. Prowle JR, Bellomo R (2010) Continuous renal replacement therapy: recent advances and future research. *Nat Rev Nephrol* 6:521–529
4. Fliser D, Kielstein JT (2006) Technology insight: treatment of renal failure in the intensive care unit with extended dialysis. *Nat Clin Pract Nephrol* 2:32–39
5. Marshall MR, Creamer JM, Foster M et al (2011) Mortality rate comparison after switching from continuous to prolonged intermittent renal replacement for acute kidney injury in three intensive care units from different countries. *Nephrol Dial Transplant* 26:2169–2175
6. Kidney Disease Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group (2012) KDIGO Clinical Practice Guideline for Acute Kidney Injury 2012. *Kidney Int* 2 Suppl:1–138
7. Fiaccadori E, Maggiore U, Clima B, Melfa L, Rotelli C, Borghetti A (2001) Incidence, risk factors, and prognosis of gastrointestinal hemorrhage complicating acute renal failure. *Kidney Int* 59:1510–1519
8. Ward DM, Mehta RL (1993) Extracorporeal management of acute renal failure patients at high risk of bleeding. *Kidney Int* 43:S237–S244
9. Brophy PD, Somers MJ, Baum MA et al (2005) Multicentre evaluation of anti-coagulation in patients receiving continuous renal replacement therapy (CRRT). *Nephrol Dial Transplant* 20:1416–1421
10. Tolwani AJ, Wille KM (2009) Anticoagulation for continuous renal replacement therapy. *Semin Dial* 22:141–145
11. Oudemans-van Straaten HM, Wester JP, de Pont AC, Schetz MR (2006) Anticoagulation strategies in continuous renal replacement therapy: can the choice be evidence based? *Intensive Care Med* 32:188–202
12. Joannidis M, Oudemans-van Straaten HM (2007) Clinical review: patency of the circuit in continuous renal replacement therapy. *Crit Care* 11:218
13. Tan HK, Baldwin I, Bellomo R (2000) Continuous veno-venous hemofiltration without anticoagulation in high-risk patients. *Intensive Care Med* 26:1652–1657
14. Uchino S, Fealy N, Baldwin I, Morimatsu H, Bellomo R (2004) Continuous venovenous hemofiltration without anticoagulation. *ASAIO J* 50:76–80
15. Fiaccadori E, Maggiore U, Parenti E et al (2007) Sustained low-efficiency dialysis (SLED) with prostacyclin in critically ill patients with acute renal failure. *Nephrol Dial Transplant* 22:529–537
16. Joannes-Boyau O, Laffargue M, Honore P et al (2005) Short filter life span during hemofiltration in sepsis: antithrombin (AT) supplementation should be a good way to sort out this problem. *Blood Purif* 23:149–174
17. du Cheyron D, Bouchet B, Bruel C, Daubin C, Ramakers M, Charbonneau P (2006) Antithrombin supplementation for anticoagulation during continuous hemofiltration in critically ill patients with septic shock: a case-control study. *Crit Care* 10:R45

18. Mariano F, Tetta C, Ronco C, Triolo G (2006) Is there a real alternative anticoagulant to heparin in continuous treatments? *Expert Rev Med Devices* 3:5–8
19. Morabito S, Guzzo I, Solazzo A, Muzi L, Luciani R, Pierucci A (2003) Continuous renal replacement therapies: anticoagulation in the critically ill at high risk of bleeding. *J Nephrol* 16:566–571
20. Oudemans-van Straaten HM, Ostermann M (2012) Bench-to-bedside review: citrate for continuous renal replacement therapy, from science to practice. *Crit Care* 16:249
21. Morabito S, Pistolesi V, Tritapepe L, Fiaccadori E (2014) Regional citrate anticoagulation for RRTs in critically ill patients with AKI. *Clin J Am Soc Nephrol*. doi:10.2215/CJN.01280214
22. VA/NIH Acute Renal Failure Trial Network, Palevsky PM, Zhang JH, O'Connor TZ et al (2008) Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med* 359:7–20
23. James M, Bouchard J, Ho J et al (2013) Canadian Society of Nephrology commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. *Am J Kidney Dis* 61:673–685
24. Palevsky PM, Liu KD, Brophy PD et al (2013) KDOQI US commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. *Am J Kidney Dis* 61:649–672
25. Jörres A, John S, Lewington A et al (2013) Ad-hoc working group of ERBP. A European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines on acute kidney injury: part 2: renal replacement therapy. *Nephrol Dial Transplant* 28:2940–2945
26. Monchi M, Berghmans D, Ledoux D, Canivet JL, Dubois B, Damas P (2004) Citrate vs. heparin for anticoagulation in continuous venovenous hemofiltration: a prospective randomized study. *Intensive Care Med* 30:260–265
27. Kutsogiannis DJ, Gibney RT, Stollery D, Gao J (2005) Regional citrate versus systemic heparin anticoagulation for continuous renal replacement in critically ill patients. *Kidney Int* 67:2361–2367
28. Mariano F, Tedeschi L, Morselli M, Stella M, Triolo G (2010) Normal citratemia and metabolic tolerance of citrate anticoagulation for hemodiafiltration in severe septic shock burn patients. *Intensive Care Med* 36:1735–1743
29. Hetzel GR, Schmitz M, Wissing H et al (2011) Regional citrate versus systemic heparin for anticoagulation in critically ill patients on continuous venovenous haemofiltration: a prospective randomized multicentre trial. *Nephrol Dial Transplant* 26:232–239
30. Morabito S, Pistolesi V, Tritapepe L et al (2012) Regional citrate anticoagulation in cardiac surgery patients at high risk of bleeding: a continuous veno-venous hemofiltration protocol with a low concentration citrate solution. *Crit Care* 16:R111
31. Schilder L, Nurmohamed S, Bosch FH et al (2014) Citrate anticoagulation versus systemic heparinisation in continuous venovenous hemofiltration in critically ill patients with acute kidney injury: a multi-center randomized clinical trial. *Crit Care* 18:472
32. Betjes MG, van Oosterom D, van Agteren M, van de Wetering J (2007) Regional citrate versus heparin anticoagulation during venovenous hemofiltration in patients at low risk for bleeding: similar hemofilter survival but significantly less bleeding. *J Nephrol* 20:602–608
33. Oudemans-van Straaten HM, Bosman RJ, Koopmans M et al (2009) Citrate anticoagulation for continuous venovenous hemofiltration. *Crit Care Med* 37:545–552
34. Zhang Z, Hongying N (2012) Efficacy and safety of regional citrate anticoagulation in critically ill patients undergoing continuous renal replacement therapy. *Intensive Care Med* 38:20–28
35. Wu MY, Hsu YH, Bai CH, Lin YF, Wu CH, Tam KW (2012) Regional citrate versus heparin anticoagulation for continuous renal replacement therapy: a meta-analysis of randomized controlled trials. *Am J Kidney Dis* 59:810–818
36. Mariano F, Pozzato M, Canepari G et al (2011) Piedmont and Aosta Valley Section of Italian Society of Nephrology. Renal replacement therapy in intensive care units: a survey of nephrological practice in northwest Italy. *J Nephrol* 24:165–176
37. Sagedal S, Hartmann A, Osnes K et al (2006) Intermittent saline flushes during haemodialysis do not alleviate coagulation and clot formation in stable patients receiving reduced doses of dalteparin. *Nephrol Dial Transplant* 21:444–449
38. RENAL Replacement Therapy Study Investigators, Bellomo R, Cass A, Cole L et al (2009) Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med* 361:1627–1638
39. Szamosfalvi B, Frinak S, Yee J (2010) Automated regional citrate anticoagulation: technological barriers and possible solutions. *Blood Purif* 29:204–209
40. Morabito S, Pistolesi V, Pierucci A (2012) Regional citrate anticoagulation: towards a first-choice treatment. *G Ital Nefrol* 29:14–19
41. Morgera S, Schneider M, Slowinski T et al (2009) A safe citrate anticoagulation protocol with variable treatment efficacy and excellent control of the acid-base status. *Crit Care Med* 37:2018–2024
42. Liet JM, Allain-Launay E, Gaillard-Leroux B et al (2014) Regional citrate anticoagulation for pediatric CRRT using integrated citrate software and physiological sodium concentration solutions. *Pediatr Nephrol* 29:1625–1631
43. Mariano F (2012) Citrate: a different mental approach to extracorporeal circuit anticoagulation. *G Ital Nefrol* 29:27–32
44. Mariano F, Morselli M, Bergamo D et al (2011) Blood and ultrafiltrate dosage of citrate as a useful and routine tool during continuous venovenous haemodiafiltration in septic shock patients. *Nephrol Dial Transplant* 26:3882–3888
45. Zheng Y, Xu Z, Zhu Q et al (2013) Citrate pharmacokinetics in critically ill patients with acute kidney injury. *PLoSOne* 8:e65992
46. Davenport A, Tolwani A (2009) Citrate anticoagulation for continuous renal replacement therapy (CRRT) in patients with acute kidney injury admitted to the intensive care unit. *NDT Plus* 2:439–447
47. Abramson S, Niles JL (1999) Anticoagulation in continuous renal replacement therapy. *Curr Opin Nephrol Hypertens* 8:701–707
48. Mariano F, Bergamo D, Gangemi EN, Hollo' Z, Stella M, Triolo G (2011) Citrate anticoagulation for continuous renal replacement therapy in critically ill patients: success and limits. *Int J Nephrol* 2011:748320
49. Böhler J, Schollmeyer P, Dressel B, Dobos G, Hörl WH (1996) Reduction of granulocyte activation during hemodialysis with regional citrate anticoagulation: dissociation of complement activation and neutropenia from neutrophil degranulation. *J Am Soc Nephrol* 7:234–241
50. Bos JC, Grooteman MP, van Houte AJ, Schoorl M, van Limbeek J, Nubé MJ (1997) Low polymorphonuclear cell degranulation during citrate anticoagulation: a comparison between citrate and heparin dialysis. *Nephrol Dial Transplant* 2:1387–1393
51. Dhondt A, Vanholder R, Tielemans C et al (2000) Effect of regional citrate anticoagulation on leukopenia, complement activation, and expression of leukocyte surface molecules during hemodialysis with unmodified cellulose membranes. *Nephron* 85:334–342

52. Gabutti L, Ferrari N, Mombelli G, Keller F, Marone C (2004) The favorable effect of regional citrate anticoagulation on interleukin-1 β release is dissociated from both coagulation and complement activation. *J Nephrol* 17:819–825
53. Gritters M, Grooteman MP, Schoorl M et al (2006) Citrate anticoagulation abolishes degranulation of polymorphonuclear cells and platelets and reduces oxidative stress during haemodialysis. *Nephrol Dial Transplant* 21:153–159
54. Schilder L, Nurmohamed SA, ter Wee PM et al (2014) Citrate confers less filter-induced complement activation and neutrophil degranulation than heparin when used for anticoagulation during continuous venovenous haemofiltration in critically ill patients. *BMC Nephrol* 15:19
55. Bryland A, Wieslander A, Carlsson O, Hellmark T, Godaly G (2012) Citrate treatment reduces endothelial death and inflammation under hyperglycaemic conditions. *Diab Vasc Dis Res* 9:42–51
56. Iacobazzi V, Infantino V (2014) Citrate - new functions for an old metabolite. *Biol Chem* 395:387–399
57. Kramer L, Bauer E, Joukhadar C et al (2003) Citrate pharmacokinetics and metabolism in cirrhotic and noncirrhotic critically ill patients. *Crit Care Med* 31:2450–2455
58. Balik M, Zakharchenko M, Leden P et al (2013) Bioenergetic gain of citrate anticoagulated continuous hemodiafiltration—a comparison between 2 citrate modalities and unfractionated heparin. *J Crit Care* 28:87–95
59. Mariano F (2013) Focusing on the basic principles of dialysis to optimize regional citrate anticoagulation. *J Crit Care* 28:99–100
60. Meier-Kriesche HU, Gitomer J, Finkel K, DuBose T (2001) Increased total to ionized calcium ratio during continuous venovenous hemodialysis with regional citrate anticoagulation. *Crit Care Med* 29:748–752
61. Hetzel GR, Taskaya G, Sucker C et al (2006) Citrate plasma levels in patients under regional anticoagulation in continuous venovenous hemofiltration. *Am J Kidney Dis* 48:806–811
62. Bakker AJ, Boerma EC, Keidel H, Kingma P, van der Voort PH (2006) Detection of citrate overdose in critically ill patients on citrate-anticoagulated venovenous haemofiltration: use of ionised and total/ionised calcium. *Clin Chem Lab Med* 44:962–966
63. Balogun RA, Turgut F, Caldwell S, Abdel-Rahman EM (2012) Regional citrate anticoagulation in critically ill patients with liver and kidney failure. *J Nephrol* 25:113–119
64. Faybik P, Hetz H, Mitterer G et al (2011) Regional citrate anticoagulation in patients with liver failure supported by a molecular adsorbent recirculating system. *Crit Care Med* 39:273–279
65. Saner FH, Treckmann JW, Geis A et al (2012) Efficacy and safety of regional citrate anticoagulation in liver transplant patients requiring post-operative renal replacement therapy. *Nephrol Dial Transplant* 27:1651–1657
66. Meijers B, Laleman W, Vermeersch P, Nevens F, Wilmer A, Evenepoel P (2012) A prospective randomized open-label crossover trial of regional citrate anticoagulation vs. anticoagulation free liver dialysis by the Molecular Adsorbents Recirculating System. *Crit Care* 16:R20
67. Mariano F, Tetta C, Stella M, Biolino P, Miletto A, Triolo G (2004) Regional citrate anticoagulation in critically ill patients treated with plasma filtration and adsorption. *Blood Purif* 22:313–319
68. Morabito S, Pistolesi V, Tritapepe L et al (2013) Continuous venovenous hemodiafiltration with a low citrate dose regional anticoagulation protocol and a phosphate-containing solution: effects on acid-base status and phosphate supplementation needs. *BMC Nephrol* 14:232
69. Morabito S, Pistolesi V, Tritapepe L et al (2013) Regional citrate anticoagulation in CVVH: a new protocol combining citrate solution with a phosphate-containing replacement fluid. *Hemodial Int* 17:313–320
70. Morabito S, Pistolesi V, Tritapepe L et al (2013) Continuous veno-venous hemofiltration using a phosphate-containing replacement fluid in the setting of regional citrate anticoagulation. *Int J Artif Organs* 36:845–852
71. Gupta M, Wadhwa NK, Bukovsky R (2004) Regional citrate anticoagulation for continuous venovenous hemodiafiltration using calcium-containing dialysate. *Am J Kidney Dis* 43:67–73
72. Shum HP, Chan KC, Yan WW (2012) Regional citrate anticoagulation in predilution continuous venovenous hemofiltration using prismocitrate 10/2 solution. *Ther Apher Dial* 16:81–86
73. Cubattoli L, Teruzzi M, Cormio M, Lampati L, Pesenti A (2007) Citrate anticoagulation during CVVH in high risk bleeding patients. *Int J Artif Organs* 30:244–252
74. Tolwani AJ, Prendergast MB, Speer RR, Stofan BS, Wille KM (2006) A practical citrate anticoagulation continuous venovenous hemodiafiltration protocol for metabolic control and high solute clearance. *Clin J Am Soc Nephrol* 1:79–87
75. Nurmohamed SA, Vervloet MG, Girbes AR, ter Wee PM, Groeneveld AB (2007) Continuous venovenous hemofiltration with or without predilution regional citrate anticoagulation: a prospective study. *Blood Purif* 25:316–323
76. Nurmohamed SA, Jallah BP, Vervloet MG, Yldirim G, ter Wee PM, Groeneveld AB (2013) Continuous venovenous haemofiltration with citrate-buffered replacement solution is safe and efficacious in patients with a bleeding tendency: a prospective observational study. *BMC Nephrol* 14:89
77. Khadzhyunov D, Slowinski T, Lieker I, Neumayer HH, Peters H (2014) Evaluation of acid-base control, electrolyte balance, and filter patency of a Prismaflex-based regional citrate anticoagulation protocol for pre-dilution continuous veno-venous hemodiafiltration. *Clin Nephrol* 81:320–330
78. Mitchell A, Daul AE, Beiderlinden M et al (2003) A new system for regional citrate anticoagulation in continuous venovenous hemodialysis (CVVHD). *Clin Nephrol* 59:106–114
79. Kalb R, Kram R, Morgera S, Slowinski T, Kindgen-Milles D (2013) Regional citrate anticoagulation for high volume continuous venovenous hemodialysis in surgical patients with high bleeding risk. *Ther Apher Dial* 17:202–212
80. Marshall MR, Golper TA (2011) Low-efficiency acute renal replacement therapy: role in acute kidney injury. *Semin Dial* 24:142–148
81. Schwenger V, Weigand MA, Hoffmann O et al (2012) Sustained low efficiency dialysis using a single-pass batch system in acute kidney injury—a randomized interventional trial: the RENAL Replacement Therapy Study in Intensive Care Unit PatiEnts. *Crit Care* 16:R140
82. Fieghen HE, Friedrich JO, Burns KE et al (2010) The hemodynamic tolerability and feasibility of sustained low efficiency dialysis in the management of critically ill patients with acute kidney injury. *BMC Nephrol* 11:32
83. Kron J, Kron S, Wenkel R et al (2012) Extended daily on-line high-volume haemodiafiltration in septic multiple organ failure: a well-tolerated and feasible procedure. *Nephrol Dial Transplant* 27:146–152
84. Kielstein JT, Kretschmer U, Ernst T et al (2004) Efficacy and cardiovascular tolerability of extended dialysis in critically ill patients: a randomized controlled study. *Am J Kidney Dis* 43:342–349
85. Marshall MR, Golper TA, Shaver MJ, Alam MG, Chatoth DK (2001) Sustained low-efficiency dialysis for critically ill patients requiring renal replacement therapy. *Kidney Int* 60:777–785
86. Kumar VA, Craig M, Depner TA, Yeun JY (2000) Extended daily dialysis: a new approach to renal replacement for acute renal failure in the intensive care unit. *Am J Kidney Dis* 36:294–300

87. Marshall MR, Ma T, Galler D, Rankin AP, Williams AB (2004) Sustained low-efficiency daily diafiltration (SLEDD-f) for critically ill patients requiring renal replacement therapy: towards an adequate therapy. *Nephrol Dial Transplant* 19:877–884
88. Berbece AN, Richardson RM (2006) Sustained low-efficiency dialysis in the ICU: cost, anticoagulation, and solute removal. *Kidney Int* 70:963–968
89. Clark JA, Schulman G, Golper TA (2008) Safety and efficacy of regional citrate anticoagulation during 8-hour sustained low-efficiency dialysis. *Clin J Am Soc Nephrol* 3:736–742
90. Fiaccadori E, Regolisti G, Cademartiri C et al (2013) Efficacy and safety of a citrate-based protocol for sustained low-efficiency dialysis in AKI using standard dialysis equipment. *Clin J Am Soc Nephrol* 8:1670–1678
91. Fiaccadori E, Lombardi M, Leonardi S, Rotelli CF, Tortorella G, Borghetti A (1999) Prevalence and clinical outcome associated with preexisting malnutrition in acute renal failure: a prospective cohort study. *J Am Soc Nephrol* 10:581–593
92. Ronco C, Bellomo R, Homel P et al (2000) Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. *Lancet* 356:26–30
93. Schiff H, Lang SM, Fischer R (2002) Daily hemodialysis and the outcome of acute renal failure. *N Engl J Med* 346:305–310
94. Bouman CS, Oudemans-Van Straaten HM, Tjissen JG, Zandstra DF, Kesecioglu J (2002) 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* 30:2205–2211
95. Ronco C, Brendolan A, d'Intini V, Ricci Z, Wratten ML, Bellomo R (2003) Coupled plasma filtration adsorption: rationale, technical development and early clinical experience. *Blood Purif* 21:409–416
96. Pozzato M, Ferrari F, Cecere P et al (2012) A new citrate anticoagulation protocol in extracorporeal treatment for septic shock patients with coupled plasma filtration adsorption (CPFA). *Nephrol Dial Transplant* 27(suppl 2):ii348–ii377
97. Livigni S, Bertolini G, Rossi C et al (2014) Efficacy of coupled plasma filtration adsorption (CPFA) in patients with septic shock: a multicenter randomised controlled clinical trial. *BMJ Open* 4:e003536
98. Tripodi A, Mannucci PM (2011) The coagulopathy of the chronic liver disease. *N Engl J Med* 365:147–156
99. Schulteß C, Saugel B, Philip V et al (2012) Continuous veno-venous hemodialysis with regional citrate anticoagulation in patients with liver failure: a prospective observational study. *Crit Care* 16:R162
100. Stange J, Hassanein TI, Mehta R, Mitzner SR, Bartlett RH (2002) The molecular adsorbents recycling system as a liver support system based on albumin dialysis: a summary of pre-clinical investigations, prospective, randomized, controlled clinical trial, and clinical experience from 19 centers. *Artif Organs* 26:103–110
101. Rifai K, Ernst T, Kretschmer U et al (2003) Prometheus-a new extracorporeal system for the treatment of liver failure. *J Hepatol* 39:984–990
102. Santoro A, Mancini E (2004) The kidney in hepatorenal syndrome (I Part). *Int J Artif Organs* 27:95–103
103. Santoro A, Faenza S, Mancini E et al (2006) Prometheus system: a technological support in liver failure. *Transpl Proc* 38:1079–1082
104. Kribben A, Gerken G, Haag S, Herget-Rosenthal S et al (2012) HELIOS Study Group. Effects of fractionated plasma separation and adsorption on survival in patients with acute-on-chronic liver failure. *Gastroenterology* 142:782–789
105. Herget-Rosenthal S, Lison C, Treichel U et al (2003) Citrate anticoagulated modified fractionated plasmaseparation and adsorption: first clinical efficacy and safety data in liver failure. *J Am Soc Nephrol* 14:779A
106. Park JS, Kim GH, Kang CM, Lee CH (2011) Regional anticoagulation with citrate is superior to systemic anticoagulation with heparin in critically ill patients undergoing continuous veno-venous hemodiafiltration. *Korean J Intern Med* 26:68–75