Renal replacement therapy in critically ill patients

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Objective	To provide updated information (including on treatment) in relation to renal replacement therapy in critically ill patients.
Data sources and study selection	Literature search of Medline and PubMed till June 2008.
Data extraction	Original studies, literature review, and book chapters.
Data synthesis	The prevalence of acute renal failure in critically ill patients remains high and mortality is up to 60%. Both the practice of renal replacement therapy (continuous against intermittent, haemofiltration against haemodialysis) and patient outcomes vary widely between studies. To better understand this heterogeneous group of patients, a unified classification of acute renal failure proposed by the Acute Dialysis Quality Initiative allows better understanding of the epidemiology and outcome of this disease. Similar to patients with chronic renal failure, there exists a direct relationship between the dose of dialysis and survival; 35 mL/kg/h is the accepted norm. However, this traditional practice is being challenged by recent trials. Although the use of citrate as anticoagulant in renal replacement therapy can prolong circuit patency and decrease bleeding risk, its use is limited by the complex set up and metabolic problems.
Conclusions	The RIFLE classification allows an accurate description of the epidemiology and outcome of critically ill patients with acute renal failure. The well-accepted continuous renal replacement therapy dose of 35 mL/kg/h in critically ill patients needs further verification from ongoing clinical trials. The complex set-up and the use of citrate anticoagulant has limited the use of such dialysis, which can nevertheless be overcome with the support of pharmaceutical companies.

Introduction

In most developed countries, the prevalence of acute renal failure (ARF) in critically ill patients ranges from 1 to 25%.[1] Approximately 4% of this group receive renal replacement therapy (RRT) and the ensuing hospital mortality is up to 60%.[1] Patient outcome is difficult to interpret due to the heterogeneous nature of those who present with ARF in the Intensive Care Unit (ICU). Besides, there are different options for treating ARF, ranging from intermittent haemodialysis (IHD) to continuous veno-venous haemofiltration (CVVH), and the hybrid system of sustained low-efficiency dialysis. The dose and timing of treatment initiation, and the effect of down time due to clotting of the system all affect patient outcomes. In the following review, we discuss the so-called RIFLE classification of ARF, as well as the indications for RRT and the calculation of respective treatment doses. We also present the different arguments pertaining to the intensive RRT controversy. Lastly, we share local experience about using citrate anticoagulants in the ICU.

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The RIFLE classification of acute renal failure

In evaluating ARF clinically, meaningful conclusions can only be drawn when there is a common standard of reference. Accordingly in 2002, an expert panel from the Acute Dialysis Quality Initiative established a consensus definition called RIFLE (www.ADQI. net) [Fig 1].[2,3] The acronym RIFLE refers to three severity gradings (in ascending order of Risk, Injury and Failure) and two clinical outcomes (Loss and End-stage renal failure). The severity grading is based on the change from baseline of either urine output or serum creatinine, whichever is greater.

For the past 3 years, the RIFLE criteria have been widely published in different clinical

settings.[4-7] With these new criteria, the prevalence of acute kidney injury is 2-to-10 fold greater than previously reported, ranging from 15.4 to 78.3%.[6] RIFLE was also valuable in outcome prediction and correlated well with mortality.[6,7]

Indications for renal replacement therapy in the Intensive Care Unit

The Box[8,9] shows the renal and non-renal indications for initiating dialysis. The concept of 'prophylactic haemodialysis' was first introduced in 1960.[10] Patients with ARF usually died from sepsis, infection, and bleeding. Patients with ARF who received early dialysis tended to have better wound healing, fewer haemorrhages, improved nutritional support, and better survival.[10,11] Since then, blood urea has been used as one of the surrogate markers for the 'timing of intervention'; the threshold having decreased from 54 mmol/L in the 1960s to 33 mmol/L in 1970s.[12] In Conger's study of post-traumatic ARF,[13] five out of eight patients survived after receiving early dialysis at a mean blood urea of 18 mmol/L; while only two out of 10 survived when dialysis was initiated at a mean urea of 43 mmol/L.

Survival benefit was consistently demonstrated in patients suffering ARF after cardiac surgery.[14,15] One recent study addressed early versus late intensive initiation of continuous veno-venous haemodiafiltration (CVVHDF) in patients with less than 100 mL urine in the 8 consecutive hours after operation and a urine sodium level of more than 40 mmol/L.[15] Early versus late initiation (average lapse 0.88 vs 2.56 days) was associated with reduced ICU stay (8 vs 12 days), reduced ICU mortality (18 vs 48%), and reduced hospital mortality (24 vs 56%).

This observed benefit cannot be generalised to all critically ill patients. Bouman et al[16] prospectively evaluated 106 patients to assess the combined effect of early against late as well as low-volume haemofiltration (LVHF) against high-volume haemofiltration (HVHF). Patients were randomised into one of the three groups: early HVHF (72-96 L/day), early LVHF (24-36 L/day), and late LVHF (24-36 L/day). On average, the early group started haemofiltration 7 hours after inclusion with the mean starting urea of 17 mmol/L, compared to the late group starting 42 hours after inclusion with a mean urea of 37 mmol/L. There was no difference in 28-day mortality or renal recovery between the three groups.

Thus, the indications and timing of dialysis for ARF are still evolving and more studies are needed to address these issues.

Dose and dose calculation of renal replacement therapy

Dose required

In end-stage renal dysfunction, there is an inverse

危重患者的腎臟替代治療

目的　危重患者腎臟替代治療的資料更新。

資料來源　搜索至2008年6月於Medline及PubMed發表過的文獻。
與研究選取

資料選取　論著、文獻及書籍文章。

資料綜合　危重患者急性腎功能衰竭的現患率依然偏高，死亡率達60%。腎臟替代治療（連續性比間歇性、血液濾過比血液透析）及治療結果在不同的研究中有很大差異。急性腎衰透析生存質量指南（Acute Dialysis Quality Initiative）把急性腎功能衰竭作標準分類，有助透徹了解此病的流行病學及治療結果。與慢性腎衰竭相似，急性腎衰竭病人的存活率與透析劑量有直接關係；35 mL/kg/h為可接受劑量。可是，這傳統學說卻被近代研究質疑。雖然腎臟替代治療中使用枸櫞酸作抗凝劑可延長透析電路通暢時間及減少出血的危險，其複雜的組件及牽涉的代謝問題卻限制了它的使用。

結論　RIFLE的標準分類可準確界定危重患者急性腎功能衰竭病的流行病學及治療結果。須透過不斷的臨床研究，進一步檢測連續性腎臟替代治療在危重患者中一向被接受的劑量（35 mL/kg/h）。雖然這種透析法複雜的組件及枸櫞酸作抗凝劑都限制了它的使用，但透過藥廠，相信有助解決這些難題。
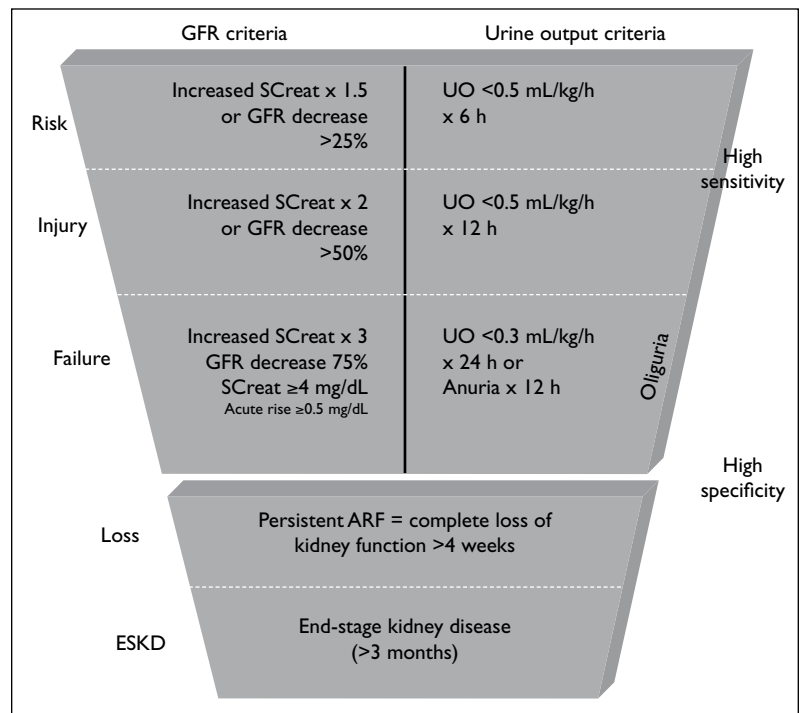
FIG 1. RIFLE, adapted from Bellomo et al (reproduced with permission)[3]

GFR denotes glomerular filtration rate, SCreat serum creatinine, UO urine output, and ARF acute renal failure

relationship between dialysis adequacy and morbidity/mortality.[17] The delivered single-pool (sp)

BOX. Renal and non-renal indications for initiating dialysis[8,9]

Renal indications for initiating dialysis
Fluid overload unresponsive to diuretic treatment
Hyperkalaemia (>6.5 mmol/L or rapidly rising level)
Azotaemia (urea >36 mmol/L)
Severe acidaemia (pH <7.1)
Oliguria (urine output <200 mL/12 hours) or anuria (urine output <50 mL/12 hours)
Uraemic complication like bleeding, pericarditis, or encephalopathy
Non-renal indications for initiating dialysis
Drug overdose with dialysable toxin
Patients requiring large amount of blood product but at risk of developing pulmonary oedema or acute respiratory distress syndrome
Sepsis and systemic inflammation
Cardiac failure
Hyperthermia with core temperature >39.5°C

Kt/v of 1.2 per dialysis (or urea reduction ratio [URR] of 65%) is the accepted minimal standard.

However, ARF patients represent an entirely different spectrum to those with end-stage renal dysfunction. Reporting in the *Lancet*, Ronco et al[18] randomised 425 ICU patients with ARF to receive three different doses of CVVH, namely 20, 35, and 45 mL/kg/h. At 15 days after discontinuation of treatment, survival in the 20 mL/kg/h group was significantly lower than that in the other two groups. Survival for 35 and 45 mL/kg/h did not differ; respective mortality rates in the three groups were 41, 57, and 58%. Since then, the 35 mL/kg/h has become the minimum recommended dose. To achieve this minimum standard, we need to calculate and monitor the dose of dialysis delivered to each patient.

Dose calculation

Formal Urea Kinetic Model

In the formal Urea Kinetic Model (UKM),[19] urea is chosen as a surrogate marker to reflect the clearance of small molecules. The efficacy of RRT is described as the fractional clearance of a given solute *Kt/V*, where *K* is the urea clearance obtained from the manufacturer in millilitre per minute, multiplied by the treatment duration *t* in minutes and divided by the volume of distribution of urea in the body *V* in millilitres. In the formal UKM, the calculation of the volume of distribution of urea is complicated and necessitates assistance of computer software, making it unpopular.

Kt/V natural logarithm formula

Due to the complexity of the formula to calculate *Kt/V* by the formal UKM, the Dialysis Outcome Quality Initiative (DOQI) Hemodialysis Adequacy Work Group has recommended the use of a natural log (ln)

formula with a *spKt/V* as the best alternative.[20] The latter does not take into account urea rebound.

$$spKt/V = -\ln(R - 0.008t) + (4 - 3.5R) \times UF/W$$

(*R*=post-dialysis urea/pre-dialysis urea; *t*=dialysis time in hours; *UF*=ultrafiltrate volume in litre; *W*=post-haemodialysis weight in kg)

Urea reduction ratio

Among these methods, the DOQI Hemodialysis Adequacy Working Group considered that measuring the delivered dose of dialysis (URR) was the simplest to execute.[21]

URR = (1 – [post-dialysis urea/pre-dialysis urea])

Ultrafiltration volume as surrogate of treatment dose

In CVVH, the clearance *Kc* is defined as the volume of blood from which a substance is completely removed.[22-25]

$$Kc = Q_{UF}S$$

(where Q_{UF}=ultrafiltration rate and *S*=sieving coefficient)

For solute with a sieving coefficient equal to 1 (like urea), clearance *Kc* is equal to Q_{UF}. This assumption holds true only when replacement is post-dilutional (after the filter). Similarly, in continuous veno-venous haemodialysis, the clearance is equal to the effluent which is the sum of dialysate inflow and ultrafiltration rate provided both the blood and dialysate compartments are in complete equilibrium. Therefore, at the prescribed effluent rate of 2 L/h in a 50-kg person, the dose of dialysis is 40 mL/kg/h. The Adequacy Calculator proposed by Pisitkun et al[24] also used a similar principle to generate a Microsoft Excel–based program to calculate the dose of RRT delivered.[24,25]

High-volume haemofiltration

Diffusion and convection are the two basic mechanisms, by which solute is removed during RRT. In diffusion, solute moves across a semi-permeable membrane driven by a concentration gradient. This is the predominant mechanism in IHD. Convection, a process in which haemofiltration predominates, is different; the solute moves across the semi-permeable membrane together with the solvent (solvent drag in response to the trans-membrane pressure). Therefore, the dialyser used for haemofiltration has a higher ultrafiltration coefficient to allow greater 'solvent drag'. Convection also implies the need for replacement fluid, which can be given before the dialyser (pre-dilution) or after (post-dilution). Soluble mediators and middle molecules like inflammatory mediators can be removed through convective methods.

TABLE 1. Summary of dosing and outcomes in studies using continuous renal replacement treatment (CRRT)[*]

Study	No. of patients	Randomisations	CRRT mode	Prescribed dose (mL/kg/h)	Delivered dose	Primary outcome	Results
Ronco et al,[18] 2000	425	3 Arms comparing 3 different doses (n=146 vs 139 vs 140)	Post-dilution CVVH: Q_B 120-240 mL/min	20 vs 35 vs 45	>85% Prescribed dose	Survival at 15 days	41%[†] vs 57% vs 58%
Bouman et al,[16] 2002	106	3 Arms comparing EHV vs ELV vs LLV (n=35 vs 35 vs 30)	Post-dilution CVVH: EHV—Q_B 200 mL/min, Q_R 72 L/day ELV—Q_B 100-150 mL/min, Q_R 24-36 L/day LLV—Q_B 150 mL/min, Q_R 24-36 L/day	48.2 vs 20.1 vs 19.7	Not mentioned	Survival at 28 days; renal recovery	74.3% vs 68.8% vs 75% (all except 1 in ELV)
Saudan et al,[30] 2006	206	2 Arms comparing 2 different doses (n=102 vs 104)	Pre-dilution: CVVH (low dose)—Q_B 100-125 mL/min, Q_R 1-2.5 L/h CVVHDF (high dose)—Q_B 100-125 mL/min, Q_R 1-2.5 L/h, Q_D 1-1.5 L/h	25 vs 44	Achieved 87% vs 83% of the delivered dose	28 Days survival; 90 days survival	39%[†] vs 59% \ 34%[†] vs 59%
ATN trial,[31] 2008	1124	2 Arms comparing intense vs less-intense therapy (n=563 vs 561)	CVVHDF: Intensive—Q_B 150 mL/min, Q_D 1410 mL/h, Q_R 1390 L/h Less intensive—Q_B 140 mL/min, Q_D 820 mL/h, Q_R 83 mL/h \ For both arms: Haemodynamically unstable— CVVH/SLED Haemodynamically stable—IHD	36.2 vs 21.5 (for IHD/SLED, 6x/wk vs 3x/wk with Kt/V of 1.2-1.4 per session)	35.8 vs 22.0	60 Days mortality	51.2% vs 48.0%
Tolwani et al,[32] 2008	200	2 Arms comparing 2 different doses (n=100 vs 100)	Pre-dilution CVVHDF: Standard dose—Q_B 100-150 mL/min, Q_D 1005 mL/h, Q_R 793 mL/h High dose—Q_B 100-150 mL/min, Q_D 1831 mL/h, Q_R 1406 mL/h	20 vs 35	17 vs 29	Survival to ICU discharge or 30 days	56% vs 49%

* CVVH denotes continuous veno-venous haemofiltration; CVVHDF continuous veno-venous haemodiafiltration; EHV early high volume; ELV early low volume; ICU intensive care unit; IHD intermittent haemodialysis; LLV late low volume; Q_B blood flow; Q_D dialysate flow; Q_R replacement rate; and SLED sustained low-efficiency dialysis
† Statistically significant

The *Lancet* trial suggested that convective clearance was important and that there was a beneficial effect of a higher dose in a subgroup of patients with sepsis and ARF.[18] The concept of 'septic dose' of haemofiltration gradually evolved and ultrafiltration beyond 3 L/h can be considered 'high volume treatment'.[26] Various parameters like the patient's haemodynamic state, inotrope usage, gaseous exchange, weaning, ICU stay and mortality were favourably affected by HVHF. However, most studies were either too small, had no controls, or used historical controls.[27,28]

Negative studies

Not all studies could demonstrate the benefit of convective clearance or HVHF. Bouman et al[16] could not show any survival benefit for early or late, as well as HVHF or LVHF. The French Hemodiaf study[29] did not show any difference in 60-day survival between IHD and CVVHDF (32% vs 33%). Similarly, Saudan et al[30] only showed survival benefit with higher doses (42 vs 25 mL/kg/h) but the treatment modality (CVVH vs CVVHDF) had no impact on survival.

The high percentage of cardiac surgical patients in the Bouman's study,[16] together with the 100% renal recovery rate among hospital survivors, make it atypical in comparison to most ICU settings. The other two studies had randomised the continuous renal replacement treatment (CRRT) group to a dose that was different from the recommended 35 mL/kg/h, which might partly account for their observed results.

The recently published ATN trial (Acute renal failure Trial Network[31]) in the United States did not show any survival benefit with intensive dialysis therapy. This study recruited 1164 critically ill patients with ARF to compare any mortality difference between the conventional dose of 20 mL/kg/h with the more intense dose of 35 mL/kg/h. Haemodynamically stable patients were randomised to IHD, while unstable patients received CVVHDF or sustained low-efficiency dialysis. The death rate was similar, 53.6% in the intensive therapy and 51.5% in the less-intense therapy groups. There was no difference in duration of RRT or recovery of renal function. A summary of various studies on dosing and outcome in CRRT is listed in Table 1.[16,18,30-32]

Future studies

Two large randomised trials are going to resolve some of these controversial dosing issues in RRT for patients with ARF:

TABLE 2. Contents of 4% trisodium citrate and anticoagulant-citrate-dextrose A (ACDA)[39]

	Sodium (mmol/L)	Citrate (mmol/L)	Bicarbonate (mmol/L)
4% Trisodium citrate	420	140	320
ACDA	224	113	203

1. Randomised Evaluation of Normal against Augmented Level of renal replacement therapy in the ICU[33] is being conducted by the Australian and New Zealand group. It sets out to compare post-dilutional CVVHDF at 25 against 40 mL/kg/h in patients with severe ARF in ICUs. The trial entails 1500 patients recruited over 2 years and aims at a 90% power to detect an 8.5% absolute reduction in 90-day mortality; that is from 60 to 51.5%.

2. IVOIRE (hIgh VOlume in Intensive caRE)[34] in Europe will study the use of standard volume (35 mL/kg/h) against HVHF (70 mL/kg/h) in ARF patients with septic shock. It aims to enrol 460 patients to detect a 15% absolute risk reduction in 30-day mortality.

Use of anticoagulation in continuous renal replacement therapy

In one international multicentre observational cohort,[35] RRT downtime ranged from 8 to 28% of total treatment time; clotting of the circuit was the major reason (74%) for treatment interruption. Therefore, it is important to maintain circuit patency to minimise the discrepancy between the prescribed and delivered dose.

Commonly used anticoagulants in CRRT include unfractionated heparin, low-molecular-weight heparin (LMWH), citrate, prostaglandin, and serine protease inhibitors such as nafamostat mesilate and aprotinin.[36,37] If the use of anticoagulation is contra-indicated, the alternative is to flush the system with saline and administer the replacement solution before it enters the filter. However, significant clotting is still encountered in up to 15 to 40% of patients.

According to the BEST Kidney study,[38] around one third of patients received CRRT without any anticoagulation. Among the various anticoagulants, use of unfractionated heparin ranks highest (43%), followed by sodium citrate (10%) and then nafamostat mesilate (6%).

Unfractionated heparin remains the standard anticoagulant with the benefit of wide clinical experience, low cost, ease of use, ability to monitor the level of anticoagulation, and availability of antidotes like protamine to reverse the anticoagulant effect if needed. Heparin acts by binding to and activating anti-thrombin III, which in turn inhibits factors IXa, Xa, and thrombin. The anticoagulant effect can be achieved by giving an initial heparin bolus of 10 to 20 U/kg, followed by a continuous infusion of 3 to 20 U/kg/h to achieve 1.5 to 2 times of the normal activated clotting time or activated partial prothrombin time. For patients at risk of bleeding, low dose or a 'tight' heparin regimen with a bolus of 5 to 10 U/kg, followed by infusions of 5 to 10 U/kg/h can be used.[37]

Low-molecular-weight heparin refers to heparin in the range of 3000 to 7000 daltons and its biological activity is quantified by the extent of factor Xa inhibition. Hence, dosing differs between different brands of LMWH and the dialyser used. With respect to unfractionated heparin, LMWH has the advantage of a longer half-life, greater bioavailability, dose-independent clearance, and less bleeding because of less impact on platelet function. However, the half-life of LMWH is prolonged in renal failure and a single injection at the start of dialysis usually suffices for up to 5 hours.[37] For example, enoxaprin 40 mg (4000-5000 anti-factor Xa units or 60-70 anti-factor Xa units/kg) can be given as a loading dose, followed by 10 to 40 mg every 6 hours if needed.[37]

By infusing citrate through a side-port where blood exits the patient (but before it enters into the dialyser), calcium is chelated in the extracorporeal circuit mediating an anticoagulant effect.[39-43] This citrate-calcium complex is partly removed by the dialyser. The remaining citrate enters the body and mixes with the central venous blood. As the central venous blood flow is much greater than the citrate infusion rate, the blood citrate concentration is diluted to such an extent that any systemic anticoagulant effect is minimal. Subsequently, all the residual effect of citrate is terminated by the liver, where it is metabolised through the tricarboxycyclic cycle into bicarbonate in a 1:3 ratio, which releases the chelated calcium. To prevent the filter clotting, a pre-filter citrate concentration of 3.5 to 4 mmol/L is needed to keep the ionised calcium concentration in the circuit below 0.25 mmol/L.[37,39]

Citrate is commonly formulated in 4% tri-sodium citrate or as anticoagulant-citrate-dextrose A (ACDA), and the difference between these formulations are shown in Table 2.[39] Although citrate is superior in terms of anticoagulant effect, the metabolic problems associated with it make it unpopular. These include hypernatraemia, metabolic alkalosis and the potential for hypocalcaemia (secondary to accumulation of citrate). Citrate toxicity should be suspected whenever ionised calcium is persistently low or the total-to-ionised calcium ratio is higher than 2.5.[40] Symptoms of hypocalcaemia include paraesthesia, nausea, cramps, tetany, hypotension, decrease in cardiac output, or a prolonged QT interval.[37]

In some observational studies, regional citrate anticoagulation has been associated with longer circuit survival and less bleeding.[44] Two

randomised controlled trials[45,46] comparing citrate with unfractionated heparin showed that citrate could prolong filter lifetime (70 vs 40 hours and 124 vs 38 hours) and decrease transfusion requirements. A larger trial recruiting 200 patients to compare citrate with nadroparin in post-dilutional CVVH is to be published; its preliminary results show citrate is both safe and superior.[47] A variety of homemade citrate regimens have been described, using it either as a separate infusion or mixed with a calcium-free pre-dilutional replacement solution.[48] Here, we present the regimen developed and used in our unit.

Local experience with citrate anticoagulant

Since 1995, citrate was the default anticoagulant for CRRT in our unit. Continuous RRT is performed by inserting a 12-Fr central venous catheter (Arrow-Howes Large-Bore Multi-lumen Arrow+gard Blue catheter; Arrow International Inc, PA, US) into either the femoral or jugular vein. Then CVVH or CVVHDF is performed based on the availability of our unit's CRRT machines, namely the AK10 (Gambro, Sweden) or the Prisma CFM (Hospal-Gambro, Sweden). Although there are slight differences in these two protocols, the blood flow and the ACDA infiltration rates are fixed at 120 mL/min and 240 mL/h, respectively.

AK10 with citrate continuous veno-venous haemofiltration

Continuous veno-venous haemofiltration (post-dilution) is performed with the AK10 machine and the high-flux Polysulfone APS650 dialyser (Asahi Kasei Medical Co Ltd, Chiyoda-ku, Tokyo, Japan) [Fig 2a]. The solution for replacement is customised and made by mixing two separate solutions. Solution A consists of 3 L saline with 16 mmol/L of potassium chloride added to give a final potassium concentration of 3 mmol/L, the amount added can vary according to the prevailing serum potassium level. Solution B consists of 2 L of water with 100 mL 8.4% sodium bicarbonate and 30 mL of 23.4% sodium chloride added to create a hypotonic solution. Because of the instability of bicarbonate solution, solution B needs to be mixed just before infusion. Both solutions A and B are guarded by two separate volumatic infusion pumps (Infusomat fmS; B. Braun, Melsungen, Germany), running at 990 and 750 mL/h, respectively. The final concentration of the solution before entering the dialyser consists of sodium 132 mmol/L, chloride 112 mmol/L, bicarbonate 20 mmol/L, and potassium 3 mmol/L. The ultrafiltration rate is the sum of the ACDA infusion rate, and the in-flow rate of solutions A and B amounting to 1980 mL/h. For an average of 50-to-60–kg Chinese subject, the dose is 40 to 33 mL/kg/h. To replace the lost of calcium through the dialyser, an undiluted 10% calcium chloride solution is run through the central line at a rate of 6 mL/h; the rate being titrated to maintain an
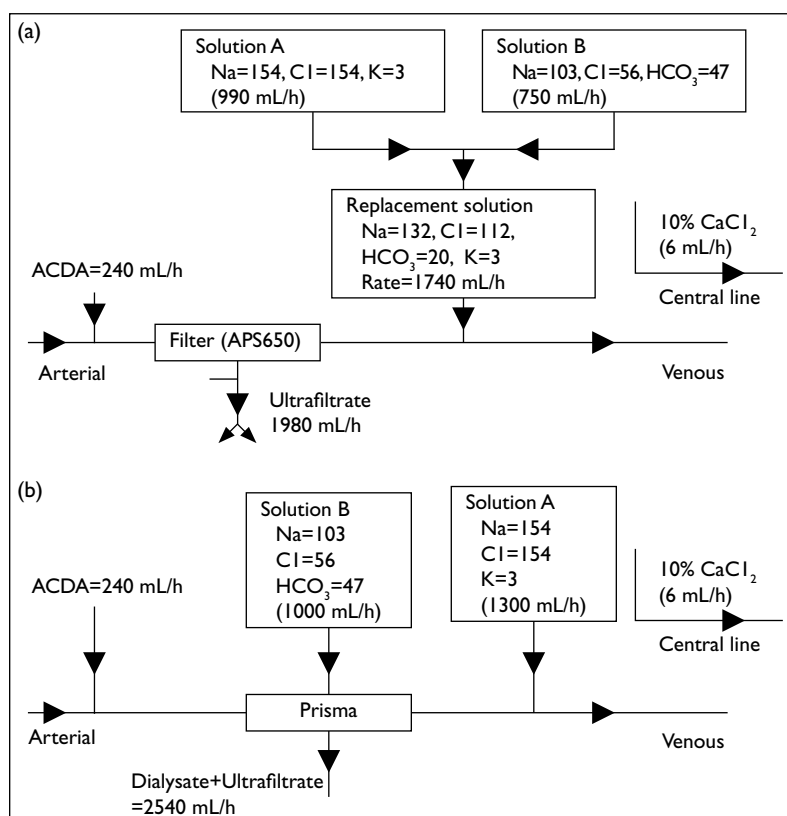

FIG 2. Circuit diagrams for (a) citrate continuous veno-venous haemofiltration (CVVH), and (b) citrate continuous veno-venous haemodiafiltration (CVVHDF) in Pamela Youde Nethersole Eastern Hospital

All electrolyte concentrations are in mmol/L. ACDA denotes anticoagulant-citrate-dextrose A

ionised calcium of 1.0 to 1.2 mmol/L.

Prisma with citrate continuous veno-venous haemodiafiltration

Slight modification of the AK10 protocol is required. Prisma has incorporated the fluid balance system with four different pumps for blood, dialysate, replacement and effluent flow, respectively (Fig 2b). As one pump can run only a single solution at a time, mixing of solutions A and B as in AK10 is not feasible. Therefore, solution B is re-directed to the dialysate compartment and solution A is used as the replacement. For which reason, CVVHDF is employed in this situation instead of CVVH. A disposable set consisting of a pre-connected multiflow 100 polyacrylonitrile, 0.9 m² AN69 filter (Hospal-Gambro) and fluid circuitry is used in the Prisma machine. The total effluent rate is increased to 2540 mL/h to partially compensate for the loss of the convective component.

Monitoring during citrate continuous renal replacement therapy

By fixing both the blood flow (at 120 mL/min) and citrate infusion rate (at 240 mL/h), a stable pre-filter

citrate level of 3.6 mmol/L[39,47] is achieved to ensure an optimal anticoagulant effect. A separate citrate infusion independent of the replacement solution can eliminate the need to monitor ionised calcium in the circuit, enabling flexibility to alter the rate of replacement fluid without affecting the anticoagulant effect. At steady state, a calcium infusion is used to replace calcium eliminated by the filter; 6 mL/h of 10% calcium chloride (4 mmol/L) usually suffices. The infusion rate varies from 5 to 7 mL/h. Any increase beyond 8 mL/h (5.4 mmol/L) to maintain ionised calcium input to higher than 0.8 mmol/h should suggest possible citrate accumulation.

Toxicity from accumulation of citrate manifests as a decrease in ionised calcium level. In those without a history of liver disease, blood is sampled for ionised calcium via the arterial line upon initiation of therapy and then every 12 hours. Total serum calcium is monitored daily or when an infusion exceeds 8 mL/h. A ratio of ionised-to-total calcium of more than 2.5 suggests citrate accumulation.[40,47] This, together with worsening of metabolic acidosis, are grounds for terminating citrate infusion. We also monitor electrolyte levels and arterial blood gas every 6 hours to begin with, and once the patient is stable decrease the sampling to every 8 to 12 hours.

Precautions and troubleshooting

Use of citrate is contra-indicated in severe liver disease (especially if there is cirrhosis, or the bilirubin exceeds 80 µmol/L), and in patients receiving massive blood transfusions. The use of customised replacement solutions with low concentrations of sodium (130 mmol/L) and bicarbonate (20 mmol/L) can counteract the hypernatraemia and metabolic alkalosis frequently affecting citrate users. The common electrolyte problems encountered are hypokalaemia and hypophosphataemia, and are corrected by exogenous replacement.

Implementation of the use of citrate anticoagulant in Intensive Care Unit

The successful use of citrate in our unit is partly related to the simplicity of the regimen, with minimal variations and need for titration. Without the help of a pharmacy department, customised replacement solutions require a backup team of skilled and dedicated nurses. Medication errors, lack of flexibility to adapt the regimen to different needs, and inaccuracy of fluid balance records when the AK10 machine is used, are some of the regimen limitations. For patients with severe metabolic acidosis (pH<6.9), it takes at least 36 to 48 hours to correct the disturbance fully. In which case, we use bicarbonate-based replacement solutions without anticoagulant to achieve a pH of >7.1 before reverting to citrate. Besides, any alteration of blood flow and citrate infusion demands careful titration of ionised calcium and more frequent monitoring of electrolytes and acid-base status.

Acknowledgements

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