Role of citrate and other methods of anticoagulation in patients with severe liver failure requiring continuous renal replacement therapy

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Abstract
Anticoagulation is required during continuous renal replacement therapy to prevent filter clotting and optimize filter performance. However, anticoagulation may also be associated with serious bleeding complications. Patients with liver failure often suffer from underlying coagulopathy and are especially prone to anticoagulation complications. The aim of this review is to present the unique features of patients with hepatic injury in terms of anticoagulation disorders and to analyze data on safety and efficacy of the different anticoagulation methods for liver failure patients undergoing continuous renal replacement therapy.

Keywords: anticoagulation; citrate; continuous renal replacement therapy; liver failure

Introduction
During continuous renal replacement therapy (CRRT), anticoagulation is required to preserve filter performance, avoid filter clotting and prevent blood loss due to circuit clotting. As anticoagulation is optimized, the risk of haemorrhage is also heightened [1]. No optimal strategy has been established to prevent filter clotting while minimizing related adverse events. Some populations at risk for acute kidney injury (AKI) are especially prone to anticoagulation complications. Liver failure patients often present with AKI and bleeding thus presenting therapeutic challenges for CRRT anticoagulation. The aim of this review is to present the unique features of patients with hepatic injury in terms of anticoagulation disorders and to analyze data on safety and efficacy of the different anticoagulation methods for liver failure patients undergoing CRRT.

Unique coagulation characteristics of liver failure patients
Liver failure patients are prone to bleeding complications, variceal haemorrhage occurring in one-third of all cirrhotic patients [2]. Although thrombotic events are less well characterized, portal vein thrombosis can be diagnosed in up to 20% of cirrhotic patients [3]. Hence, patients with liver failure have concurrent bleeding and thrombotic diatheses, the resulting clinical state usually being determined by the predominant mechanism involved [4]. A thrombotic event can occur at one site, for example the dialysis filter, even if a systemic bleeding tendency is present [4].

Bleeding diathesis
In chronic liver disease, bleeding tendency has commonly been attributed to decreased production and dysfunction of platelets, reduced synthesis of clotting factors and vitamin K deficiency [4,5]. Quantitative and qualitative abnormalities of fibrinogen have also been documented [3,5]. In acute and fulminant hepatic failure (FHF), there is respectively a partially reversible deficit in vitamin K and reduced platelet aggregation, although adhesion to glass beads is increased [5]. Disseminated intravascular coagulation (DIC) can contribute to bleeding in cirrhosis and FHF [5–7]. Several characteristics contributing to enhance risk of bleeding are often present in patients with liver failure. These include advanced age, poor general condition, recent bleeding and variceal haemorrhage, hepatic dysfunction itself, sepsis, coagulopathy and low platelets [5,8]. In patients undergoing CRRT, other risk factors include heparin dose [8] and dialysis-induced platelet damage and loss [9].

Thrombotic tendency
Mechanisms underlying hypercoagulability in these patients are less clearly defined. In acute and chronic diseases, elevated levels of factor VIII and von Willebrand factor, DIC, and reduced synthesis of the natural anticoagulants (protein C, S and antithrombin III) have been suggested as contributing factors [4,5]. Abnormal platelet adhesion and decreased levels of plasminogen commonly
occur in chronic liver failure, while hypofibrinolysis is usually present in acute liver failure. Patients with cholestatic liver disease may be more prone to thrombosis, but this has not been adequately assessed [5]. There are limited data on diagnostic tests able to predict hypercoagulability. In one study, only a low albumin level was shown to be predictor of venous thrombotic events [10]. Low antithrombin levels have also been associated with filter clotting but are rarely measured [11,12].

Methods of anticoagulation

Although there is increasing use of renal replacement therapy (RRT) in a liver failure population, no study has primarily looked at the frequency of thrombosis of extracorporeal circuits in these patients [4]. Recent review articles and one case report suggest a significant incidence of circuit and filter clotting without the use of anticoagulation [4,8,13]. The different methods of anticoagulation in this population are reviewed and summarized in Table 1.

No anticoagulation, saline flushes and pre-dilution

No anticoagulation. CRRT without anticoagulation is performed in patients judged to be at high risk for bleeding. Bellomo and colleagues have defined this population with the following criteria: platelet count <60 x 10^9/l, activated partial thromboplastin time (aPTT) >60 s, INR >2, DIC and spontaneous bleeding [14].

In patients without liver failure undergoing CRRT, one trial compared no anticoagulation to low-dose heparin or regional heparin–protamine. Filter life was not statistically different between the groups [14]. Another similar study including 48 patients assessed the efficacy of no anticoagulation versus regional anticoagulation with heparin–protamine (1000 IU/h + protamine 10 mg/h) versus low-dose heparin (5 IU/kg/h) on bleeding complications and filter survival. No bleeding complications and no significant difference in filter life were observed, although patients without anticoagulation showed a trend towards thrombocytopenia and higher INR [15].

A prospective cohort study of 24 patients at high risk of bleeding reported that the mean circuit life was significantly higher in patients without anticoagulation compared to controls with low-dose pre-filter heparin infusion (5–10 IU/kg/h) (32 h versus 19.5 h; P = 0.017) [16]. Interestingly, the former group had statistically higher INR and lower platelet counts. However, the largest retrospective study available reported that filter life was similar with no anticoagulation or different doses of heparin, including doses superior to 700 IU/h [17]. Platelet count seemed to correlate with clot formation. Thus, in patients without liver failure, CRRT without anticoagulation seems mostly appropriate for severely thrombocytopenic patients [17].

There are scant data on dialysis without anticoagulation in liver failure. A retrospective study of 66 patients including 26 transplants showed that no anticoagulation is the predominant method used, being prescribed in 58% and 73% of transplanted and non-transplanted patients, respectively [18]. Unfortunately, no data on filter survival or bleeding complications were presented. A retrospective study of 11 liver transplanted patients undergoing CRRT without anticoagulation did not include information related to filter life [19].

Saline flushes and pre-dilution. Saline flushes can be infused every 30–60 min in the circuit in an attempt to decrease filter clotting. This method is simple and relatively safe but has not been studied extensively. Pre-dilution has been postulated to decrease filter clotting by reducing blood viscosity with the infusion of substitution fluid before the filter [20]. In patients without liver failure, two studies have evaluated the effect of pre-dilution on filter life during CRRT. Both studies have demonstrated a significant increase in filter life with pre-dilution compared to post-dilution [21,22].

In one randomized study of 34 patients, including 21 patients with pre-existing liver disease, saline flushing every 30 min compared to every hour did not prevent filter clotting [23]. Hence, very limited data are available on the efficacy of saline flushes and pre-dilution in patients with liver failure.

Citrate

Regional citrate anticoagulation (RCA) has been advocated to be the preferred method of anticoagulation in patients at risk of bleeding [12,24]. However, it is more hazardous in patients with liver failure and important precautions must be taken before its use is considered safe in this population. We will briefly review the mechanisms, advantages and potential complications of RCA, and its use in patients with liver impairment.

Method of anticoagulation, advantages and complications.

Several different protocols and modalities (haemofiltration and/or haemodialysis) can be used for citrate anticoagulation [12,25,26]. More commonly, 4% tri-sodium citrate (TSC) is used and is delivered pre-filter. Less frequently, citrate can be administered in the dialysate. Citrate exerts its anticoagulation effect by chelating ionized calcium, an essential component in the clotting cascade. The target post-filter ionized calcium concentration is usually <0.4 mmol/l [27,28]. Citrate–calcium complexes are normally partly removed by the filter, and the remaining are metabolized in bicarbonate by the liver [29]. The chelated calcium is then liberated and returned to the total calcium body pool [30]. There is risk of hypocalcaemia and hypomagnesaemia due to the binding of citrate to ionized calcium and magnesium and possibly due to freely filtered calcium and magnesium citrate complexes [24,31,32]. Calcium losses are usually proportional to the effluent dose [33]. Additional calcium is infused into the systemic circulation to compensate for the loss of calcium through the filter [28]. Most protocols use either calcium-free or calcium-reduced dialysate or replacement fluid and thus enhance calcium losses [27,33,34]. Moreover, since citrate provides a sodium load, the dialysate and/or the substitution fluid need to be hypotonic to avoid hypernatraemia. Due to citrate metabolism into bicarbonate, metabolic alkalosis can also occur. To avoid metabolic disorders, many centres use customized solutions with...
Table 1. Summary of anticoagulation methods in liver failure

| Method                       | Advantages                                                                 | Disadvantages                                                                 | Comments                                                                 |
|------------------------------|-----------------------------------------------------------------------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| No anticoagulation           | No risk                                                                     | Limited efficacy in preventing filter clotting                               | Close monitoring of citrate accumulation with total to ionized calcium ratio; monitor serum and ionized calcium 2 h after a modification of calcium or citrate administration and every 4 h if stable |
| Pre-dilution Saline flushes  | No risk                                                                     | Decrease solute clearance                                                     |                                                                          |
| Citrate                      | No systemic anticoagulation                                                 | Risk of citrate accumulation with hypocalcaemia and metabolic acidosis       |                                                                          |
| Unfractionated heparin       | Anticoagulation effect easily monitored with aPTT; complete reversal with protamine | Limited data on its safety in liver failure                                  | Use only if needed by another indication and target aPTT 1–1.4 × baseline if possible; monitor aPTT every 6 h; close monitoring of bleeding |
| Heparin–protamine            |                                                                             | Limited data on safety and efficacy                                          |                                                                          |
| Low-molecular-weight heparin  |                                                                             | Increased risk of bleeding in AKI; incomplete reversal with protamine; no data in AKI and liver failure | Should be avoided until further data available; if used, close monitoring with anti-Xa is recommended (target 0.25–0.35 IU/ml and monitor daily) |
| Prostacyclin                 |                                                                             | Limited data on efficacy and safety                                          |                                                                          |
| Nafamostat mesilate          |                                                                             | Limited data on efficacy and safety                                          |                                                                          |

Reduced sodium and buffer content [26]. These complications are more frequent at the beginning of a new citrate anticoagulation program due to a lack of training [34].

In patients without liver failure, three randomized trials have compared citrate to unfractionated heparin (UFH), including a total of 98 patients and 270 filters [12,35,36]. In two of these studies, citrate increased filter life [12,35] and reduced the number of blood transfusions [35,36]. Citrate also decreased bleeding complications in patients both at high [12] and low risk of bleeding [36]. Non-randomized studies have reported prolonged filter life with citrate compared to UFH [27,37]. When compared to nadroparin in a cohort of patients at high risk for bleeding, citrate also significantly reduced the incidence of bleeding complications during CRRT (14.8% versus 25%; \( P = 0.04 \)). However, there was no difference in the number of transfusions and the nadroparin group had a longer filter run time (31.5 h versus 22.5 h, \( P = 0.0001 \)) [38]. The authors did not mention the targeted post-filter calcium values. Higher values could shorten filter lifetime. One observational study compared citrate to prostacyclin-heparin and showed superior filter survival, reduced risk of hypotension, more stable platelet count and lower cost with citrate [39].

Possible adverse events of citrate in liver failure. In liver failure, the two major complications related to RCA are hypocalcaemia and metabolic acidosis [8,25,30,31,40,41]. Hypocalcaemia occurs due to the reduced liver function that leads to the accumulation of citrate–calcium complexes. Consequently, there is a reduction in ionized calcium and a possible rise in total calcium levels [28,30]. In liver failure, an associated decrease in muscle perfusion can also contribute to impaired citrate metabolism. The increase in total calcium and decrease in ionized calcium (total to ionized calcium ratio) are directly proportional to the concentration of citrate in systemic blood [30]. Hence, total to ionized calcium ratio values > 2.5 are suggestive of citrate accumulation. However, in two different studies, a ratio > 2.5 could only identify 17.6% (3/17) and 75% (3/4) of patients with citrate concentrations > 1.5 mmol/l [28,42]. In the former study, calcium supplementation was remarkably high and could have contributed to normalize ionized calcium [42].

Impairment in citrate metabolism can also lead to high anion gap metabolic acidosis. Acidosis is explained by the incapacity of the liver to metabolize citrate into 3 moles of bicarbonate, and the anion gap is caused by the accumulation of citrate. As expected, metabolic acidosis mainly occurs when citrate is the principal buffer and is lessened when bicarbonate is included in the dialysate and/or the replacement fluid solution. Patients with acute liver failure may also suffer from significant respiratory alkalosis due to hyperventilation, and this may need to be considered when using citrate.

Once excess citrate is metabolized, potential complications include hypercalcaemia and hypermagnesaemia, due to the release of these electrolytes from their complexes with citrate [28,43]. Therefore, calcium and magnesium should be monitored for a few days after citrate metabolism is returned to normal [28].

Management of citrate in liver failure. Until recently, most caregivers considered citrate to be contraindicated
citrate anticoagulation: risk factors, suggested monitoring and strategies for the prevention and treatment of citrate accumulation

| Risk factors for citrate accumulation | Suggested monitoring |
|--------------------------------------|---------------------|
| Severity of liver failure            | pH, bicarbonate and anion gap |
| Hypocalcaemia                        | Total and ionized calcium |
| Citrate-containing blood products (blood transfusions, fresh frozen plasma) | Total to ionized calcium ratio (abnormal >2.5) |
| Prevention and treatment strategies  | Decrease citrate administration |
|                                      | Decrease blood flow rate |
|                                      | Target higher post-filter calcium value |
|                                      | Avoid citrate-containing blood products |
| In occurrence or worsening of complica- | Increase convective dialysis dose |
| tions associated with impaired citrate metabolism, several strategies may be implemented (Table 2). First, the amount of citrate administered can be decreased [20,27,42]. For example, the infusion of 4% TSC can be started at 90 ml/h instead of 180 ml/h [27]. Other protocols target higher post-filter ionized calcium values, such as 0.38–0.45 mmol/l [48]. However, some centres have experienced increased filter clotting with this strategy [30]. Although the following recommendation has not been formerly validated, reducing the blood flow rate to 100 ml/min can also theoretically decrease the amount of citrate required without compromising clearance. In addition, citrate-containing blood products should be avoided. |
| To prevent the occurrence or worsening of complications associated with impaired citrate metabolism, severe strategies may be implemented (Table 2). First, the amount of citrate administered can be decreased [20,27,42]. For example, the infusion of 4% TSC can be started at 90 ml/h instead of 180 ml/h [27]. Other protocols target higher post-filter ionized calcium values, such as 0.38–0.45 mmol/l [48]. However, some centres have experienced increased filter clotting with this strategy [30]. Although the following recommendation has not been formerly validated, reducing the blood flow rate to 100 ml/min can also theoretically decrease the amount of citrate required without compromising clearance. In addition, citrate-containing blood products should be avoided. |
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| A second strategy to prevent the occurrence or worsening of complications associated with impaired citrate metabolism is to increase citrate clearance through increased convective or diffusive dialysis dose [29]. One publication reported a diffusive citrate clearance ranging from 28 to 54 ml/min with dialysate flow rates of 2000 and 4000 ml/h, respectively [29]. The sieving coefficient for citrate was 0.87 ± 0.06, and the total citrate clearance was almost equal to the sum of diffusive and convective clearances [29]. In this study, haemodiafiltration could remove 35–50% of the citrate–calcium chelate. |
| At some point, when citrate cannot be sufficiently metabolized into bicarbonate because of severe liver impairment, the only available strategy to prevent and treat metabolic acidosis is to administer bicarbonate [8,25,41]. The sodium content of the dialysate and replacement fluids needs to be adjusted when sodium bicarbonate is added to prevent a total sodium delivery higher than the normal concentration range. When commercial solutions are used, the sodium content cannot be easily customized. However, the use of pharmacy-made solutions can avoid this pitfall. Ultimately, if acidosis remains a problem despite adequate treatment, alternatives to citrate should be considered. |
| Similarly, when citrate–calcium complexes cannot be sufficiently metabolized to normalize ionized calcium, calcium supplementation should be provided by increasing calcium infusion and if necessary, by intravenous bolus [40]. When hypocalcaemia and acidosis are present concomitantly in a patient, it is recommended to correct hypocalcaemia before acidemia, because rapid administration of bicarbonate may enhance calcium deficit. In addition, hypomagnesaemia [28] should also be corrected. |

**Unfractionated heparin**

Despite bleeding complications reported in 10–50% of patients [8], UFH remains the most commonly used method of anticoagulation in acute RRT [49]. Heparin is easily monitored with aPTT. However, during UFH administration, partial anticoagulation can occur with normal aPTT values [24]. This finding is particularly important for liver failure patients for whom a normal aPTT should not be automatically considered as a low risk of bleeding. In one study,

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**Table 2.** Citrate anticoagulation: risk factors, suggested monitoring and strategies for the prevention and treatment of citrate accumulation

| Risk factors for citrate accumulation | Suggested monitoring |
|--------------------------------------|---------------------|
| Severity of liver failure            | pH, bicarbonate and anion gap |
| Hypocalcaemia                        | Total and ionized calcium |
| Citrate-containing blood products (blood transfusions, fresh frozen plasma) | Total to ionized calcium ratio (abnormal >2.5) |
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maintaining aPTT between 35 and 45 s seemed to be the best compromise between bleeding and clotting [1]. However, variation in aPTT results occurs due to the different reagents used in practice [50]. Therefore, a target aPTT 1–1.4 times normal has been suggested to minimize the risk of bleeding [24]. The use of activated clotting times cannot be recommended due to their inaccuracy in critically ill patients [51].

There are limited data regarding the safety of heparin in patients with liver failure. Liver failure itself is not a formal contraindication to UFH. Common reported contraindications are platelet count <20–60 × 10^9/l, heparin-induced thrombocytopenia (HIT), acute bleeding, gastro-intestinal or intracranial haemorrhage (<3 months), significant trauma (<3 days), first 24 h post-surgery, coagulopathy (aPTT > 65–80 s, INR >2.5–3.0) or other conditions judged at high risk of bleeding [12,18,36,52,53]. Due to the perceived risk of bleeding, there is a restricted use of heparin in liver failure patients undergoing RRT. A retrospective study of 66 patients with liver failure has shown a rate of utilization of only 12% for transplanted and 20% for non-transplanted patients [18]. No data on filter survival or bleeding complications were available. In 24 patients with FHF treated with intermittent dialysis, Langley and colleagues used heparin with a target ACT of 200–250 s, and nine minor and three major bleeding complications occurred [9].

In summary, no large studies have assessed the safety of UFH during acute RRT in patients with liver failure. Since these patients are at high risk of bleeding, careful evaluation must be made before starting UFH and close monitoring of bleeding complications should be assessed.

Heparin–protamine. The continuous infusion of heparin pre-filter and protamine post-filter allows regional anticoagulation, since protamine will counteract the systemic effect of UFH. These medications can be initiated at a 1:100 ratio (protamine 1 mg:heparin 100 IU), and the circuit aPTT and the systemic aPTT should be 1.5–2 times baseline and in the normal range, respectively [54].

In general populations undergoing CRRT, when heparin–protamine was compared to no anticoagulation and low-dose heparin (500 IU/h), heparin–protamine did not offer any significant benefit on filter survival [14,15]. The side effects of protamine include hypotension, pulmonary hypertension, haemorrhage and allergic reactions [22]. Moreover, this method is time and resource consuming [13]. A recent evidence-based review did not recommend its use due to better alternatives [24], whereas another supported its use in patients at high risk of bleeding who do not have acceptable filter life without anticoagulation [20].

There is only one study on the use of heparin–protamine in liver failure patients, all of them being liver transplant recipients [55]. Heparin–protamine was compared to low-dose heparin (5–10 IU/kg/h) in 27 patients, and no difference in circuit life and no pathologic bleeding were observed. Adverse events related to protamine were not reported [55].

Hence, there are very limited data related to the use of heparin–protamine in liver failure and formal recommendations cannot be made. There is a possible influence of liver on the clearance of heparin–protamine from plasma, and therefore, careful monitoring is advised if these medications are used.

Low-molecular-weight heparin
In critically ill patients with AKI, low-molecular-weight heparins (LMWH) have major drawbacks: an increased half-life and risk of bleeding and an incomplete reversal of their anticoagulation effect by protamine [50]. Therefore, the American College of Chest Physicians support the use of UFH rather than LMWH in severe AKI [50]. If LMWH are used, anti-Xa should be closely monitored [24,50].

In patients without liver failure, two randomized studies comparing LMWH and UFH in CRRT have appeared in full paper [56,57]. The first study included 46 patients and did not show any difference between filter life and incidence of haemorrhages between dalteparin and UFH. Thirty-seven patients completed the second study. Similar numbers of bleeding and a superior filter lifetime were reported with the use of enoxaparin adjusted to the anti-Xa level at 0.25–0.3 IU/ml (30.6 h versus 21.7 h; \( P = 0.017 \)). One cohort study including 55 patients found that nadroparin significantly increased filter life (31.5 h versus 22.5 h; \( P = 0.0001 \)) and risk of bleeding complications compared to citrate (25% versus 14.8%; \( P = 0.04 \)), even though patients at high risk for haemorrhage received citrate [38].

Hence, there are no data available on the safety and efficacy of LMWH in patients with liver failure undergoing CRRT. Due to their prolonged half-life and incomplete reversal with protamine, we do not recommend the use of LMWH in patients with severe liver failure undergoing CRRT.

Minimal systemic anticoagulation
Prostacyclin. Prostacyclin is an arachidonic metabolite that inhibits interaction between platelets and artificial membranes [8,20]. Prostacyclin use has been limited by hypotension, possible bleeding, difficulty in dose adjustment and absence of antagonist [8,14,17,58]. The haemodynamic complications can be reduced by priming the circuit with human albumin solutions and increasing vasoconstrictors prior to starting the perfusion.

More importantly, in patients with fulminant liver failure, the direct (intravenous) administration of prostacyclin has been shown to increase intracranial pressure and reduce cerebral perfusion, being hazardous in this population at risk for cerebral oedema [59,60]. However, the same authors have reported that infusion of prostacyclin pre-filter is safe [61]. Prostacyclin has been reported to be associated with a significant longer filter life (60 h versus 8 h; \( P < 0.01 \)) and a reduction in bleeding complications compared to heparin (3 versus 8 major haemorrhages) [61].

Nafamostat mesilate. Nafamostat is a synthetic serine protease inhibitor mainly used in Japan in patients at high risk of bleeding [8,20,62,63]. There are limited data on its use in patients with liver failure undergoing CRRT [64].
levels more slowly, and argatroban should be stopped sev-

Table 3. Summary of anticoagulation methods in HIT and liver failure

| Method      | Advantages                                      | Disadvantages                                      | Recommended dosage                                      | Comments                                      |
|-------------|-------------------------------------------------|-----------------------------------------------------|----------------------------------------------------------|------------------------------------------------|
| Argatroban  | Data available in kidney and liver failure      | Prolonged half-life; no antagonist                   | Start at 0.5 µg/kg/min [78]; adjust for aPTT 1.5-(3×)  | Increasing safety in liver failure and AKI; close |
|             |                                                 |                                                     | baseline and monitor 4–5 h after a dose change           | monitoring for bleeding                       |
| Hirudin     | May be reversed by recombinant factor VII and/or haemofiltration with high-flux polysulfone membrane | No data in liver and kidney failure; risk of antibodies preventing removal; monitoring with aPTT unreliable | Start at 0.005 mg/kg/h; adjust for aPTT 1.5-(2×) baseline [78] or ecarin clotting time (ECT) assay 50–100 s or hirudin 0.6–1.4 mg/l (both two not widely available), monitor ECT every 2 h × 2 and every 4 h [76] | Close monitoring for bleeding if used; should probably be avoided in patients with liver and renal failure |
| Bivalirudin | Preliminary data suggest good safety             | Not yet approved for HIT                             | Start at 0.03–0.04 mg/kg/h; adjust for aPTT 2 × baseline and monitor aPTT frequently (usually every 6 h) [81,82]; careful anticoagulant monitoring if antilepirudin antibodies because they may influence pharmacokinetics [82] | May be promising; no specific antidote; haemodialysis, haemofiltration and plasmapheresis may reduce levels [82] |
| Danaparoid  | Prolonged half-life; no antagonist               |                                                     | Bolus 750 IU and start infusion at 1–2 IU/kg/h; adjusted for anti-Xa 0.2–<0.35 IU/ml and monitor daily | Close monitoring for bleeding; could be used as a possible alternative to argatroban |

Anticoagulation agents for HIT

HIT type 2 is a potential life-threatening condition caused by antibodies against the platelet factor 4-heparin complex [65] and must be considered when platelet count decreases by 50% or <100 × 10^9/l. HIT causes paradoxal hypercoagulability and requires immediate cessation of all forms of heparins [65]. Systemic anticoagulation with selected molecules should be provided if not contraindicated to avoid thromboses. In most cases, the prescribed anticoagulant is argatroban, hirudin or danaparoid. Table 3 summarizes the various agents that may be used for HIT.

Argatroban. Argatroban is a direct thrombin inhibitor mainly metabolized by the liver available in North America and Europe [66]. This drug significantly prolongs INR. A retrospective study of 82 patients, including 43 with both liver and kidney dysfunctions, showed that this medication may be used safely and effectively with adequate dosing and monitoring [66]. In this study, hepatic dysfunction was defined as bilirubin >25.5 µmol/l, aspartate aminotransferase >100 IU/l and/or alanine aminotransferase >100 IU/l. However, all four major bleeding occurred in patients with both liver and kidney injury. Another retrospective study showed three major bleeding episodes in 14 patients with renal and liver failures requiring RRT, but dose adjustments were not correctly performed [67]. No bleeding occurred in the 16 patients without liver failure.

For patients with hepatic impairment, it is recommended to start argatroban with a reduced dosage [66]. CRRT procedures do not significantly modify argatroban clearance [68]. Patients with liver failure should reach steady-state levels more slowly, and argatroban should be stopped several hours to days before a procedure requiring temporary reversal of anticoagulation [66,69]. Monitoring for bleeding complications should be emphasized and targeting the lower range of therapeutic aPTT values must be considered [69,70]. Activated factor VII has been reported to reverse its anticoagulation effect [71].

Hirudin. Hirudin is also a direct thrombin inhibitor. The commercially available drug, lepirudin, has an increased half-life in severe renal failure (50 h), and the risk of haemorrhage is related to creatinine levels [72]. In addition, antibodies preventing lepirudin removal in RRT occur in up to 60% of patients [65]. Monitoring with aPTT is difficult due to the absence of linear relationship between aPTT and hirudin concentrations [65]. As an alternative, monitoring with ecarin clotting time assay or hirudin concentrations should be emphasized and targeting the lower range of therapeutic aPTT values must be considered [69,70]. Activated factor VII has been reported to reverse its anticoagulation effect [71].

Bivalirudin. Bivalirudin is a direct thrombin inhibitor that has a prolonged half-life (3.5 h) in patients on dialysis [78]. A retrospective study has shown its successful use in patients with hepatic impairment on CRRT [79].
Role of citrate and other methods of anticoagulation

Danaparoid. Danaparoid is a heparinoid that has a prolonged half-life in renal failure (36–48 h versus 25 h) and no antagonist [24]. Only one retrospective study of 13 patients has assessed its use in CRRT [80]. Major bleeding was observed in 46.2% of patients even if anti-Xa levels were in the prophylactic or low therapeutic range. No data are available for patients with liver impairment.

Summary and recommendations

Patients with both renal and hepatic impairments present unique coagulation characteristics that complicate the choice of anticoagulation therapies for CRRT. In addition, there are limited data regarding the safety and efficacy of different methods of anticoagulation in these patients.

In liver failure patients, to minimize bleeding and other complications, we suggest (1) to use pre-dilution rather than post-dilution CRRT; (2) to attempt CRRT without anticoagulation as a first step and (3) to use RCA as a second step for repeated filter coagulation in centres with previous experience with citrate anticoagulation. Centres without experience with RCA should avoid using citrate in patients with liver failure. Strict monitoring of acid base status and total to ionized calcium ratio is required to rapidly detect citrate accumulation and its related complications. There is no definite cut-off level of total to ionized calcium ratio that should prompt discontinuation of citrate anticoagulation, although a ratio >2.5 is typically reported to be associated with citrate accumulation. Citrate serum levels can also be measured directly (when available) when the risk of accumulation is believed to be very high. Citrate accumulation can be prevented by lowering the amount of citrate administered and enhancing its clearance. In the setting of hypocalcaemia, calcium delivery should be optimized. If citrate-induced metabolic acidosis occurs, the amount of bicarbonate administered should be optimized in the dialysate and the replacement fluid. Serum sodium should be closely monitored if an increase in sodium delivery (through the use of sodium bicarbonate) occurs concomitantly. The use of citrate should be reassessed if any or little improvement in the acid base status is not quickly noticed.

UFH may be used when required by other conditions, such as Budd-Chiari syndrome, and when clinical risk of bleeding is felt to be low to moderate. In our opinion, the use of LMWH should be avoided in this population due to its prolonged half-life and incomplete reversal by transitory use of protamine. In patients with HIT and combined liver and renal failure, there is no optimal anticoagulation method. We tend to use argatroban as a first choice due its shorter half-life, availability and increasing clinical experience in liver failure. Danaparoid can be used as an alternative. Prospective studies are needed to assess the required level of anticoagulation during RRT and to determine the optimal method of anticoagulation in this population.

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References

1. van de Wetering J, Westendorp RG, Van Der Hoeven JG et al. Heparin use in continuous renal replacement procedures: the struggle between filter coagulation and patient hemorrhage. J Am Soc Nephrol 1996; 7: 145–150
2. Grace ND. Prevention of initial variceal hemorrhage. Gastroenterol Clin North Am 1992; 21: 149–161
3. Violi F. How to concile bleeding and thrombotic tendency in liver cirrhosis? J Thromb Haemost 2006; 4: 2065–2066
4. Northup PG, Sundaram V, Fallon et al. Hypercoagulation and thromboophilia in liver disease. J Thromb Haemost 2008; 6: 2–9
5. Senzolo M, Burra P, Cholongitas E et al. New insights into the coagulopathy of liver disease and liver transplantation. World J Gastroenterol 2006; 12: 7725–7736
6. Bakker CM, Knaut EA, Stibbe J et al. Disseminated intravascular coagulation in liver cirrhosis. J Hepatol 1992; 15: 330–335
7. Langley PG, Forbes A, Hughes RD et al. Thrombin-antithrombin iii complex in fulminant hepatic failure: evidence for disseminated intravascular coagulation and relationship to outcome. Eur J Clin Invest 1990; 20: 627–631
8. Abramson S, Niles JL. Anticoagulation in continuous renal replacement therapy. Curr Opin Nephrol Hypertens 1999; 8: 701–707
9. Langley PG, Keays R, Hughes RD et al. Antithrombin iii supplementation reduces heparin requirement and platelet loss during hemodialysis of patients with fulminant hepatic failure. Hepatology 1991; 14: 251–256
10. Northup PG, McMahon MM, Ruhl AP et al. Coagulopathy does not fully protect hospitalized cirrhosis patients from peripheral venous thromboembolism. Am J Gastroenterol 2006; 101: 1524–1528; quiz 1680
11. Bastien O, French P, Paulus S et al. Antithrombin iii deficiency during continuous venovenous hemodialysis. Contrib Nephrol 1995; 116: 154–158
12. Kutsogiannis DJ, Gibney RT, Stollery D et al. Regional citrate versus systemic heparin anticoagulation for continuous renal replacement in critically ill patients. Kidney Int 2005; 67: 2361–2367
13. Tobe SW, Aujla P, Walele AA et al. A novel regional citrate anticoagulation protocol for CRRT using only commercially available solutions. J Crit Care 2003; 18: 121–129
14. Bellomo R, Teede H, Boyce N. Anticoagulant regimens in acute continuous hemodiafiltration: a comparative study. Intensive Care Med 1993; 19: 329–332
15. Uchino S, Fealy N, Baldwin I et al. Continuous venovenous hemofiltration without anticoagulation. ASAIO J 2004; 50: 76–80
16. Tan HK, Baldwin I, Bellomo R. Continuous veno-venous hemofiltration without anticoagulation in high-risk patients. Intensive Care Med 2000; 26: 1652–1657
17. Martin PY, Chevron JC, Suter P et al. Anticoagulation in patients treated by continuous venovenous hemofiltration: a retrospective study. Am J Kidney Dis 1994; 24: 806–812
18. Naka T, Wan L, Bellomo R et al. Kidney failure associated with liver transplantation or liver failure: the impact of continuous veno-venous hemofiltration. Int J Artif Organs 2004; 27: 949–955
19. Fiore G, Donadio PP, Gianferrari P et al. CVVH in postoperative care of liver transplantation. Minerva Anestesiol 1998; 64: 83–87
20. Amanzadeh J, Reilly RF, Jr. Anticoagulation and continuous renal replacement therapy. Semin Dial 2006; 19: 311–316
21. Uchino S, Fealy N, Baldwin I et al. Pre-dilution vs. post-dilution during continuous veno-venous hemofiltration: impact on filter life and azotemic control. Nephron Clin Pract 2003; 94: e94–e98
22. Van Der Voort PH, Gerritsen RT, Kuiper MA et al. Filter run time in CVVH: pre- versus post-dilution and nadroparin versus regional heparin-protein anticoagulation. Blood Purif 2005; 23: 175–180
23. Ramesh Prasad GV, Palevsky PM, Burr R et al. Factors affecting system clotting in continuous renal replacement therapy: results of a randomized, controlled trial. Clin Nephrol 2000; 53: 55–60
24. Oudemans-van Straaten HM, Wester JP, de Pont AC et al. Anticoagulation strategies in continuous renal replacement therapy: can the choice be evidence based? Intensive Care Med 2006; 32: 188–202
25. Palsson R, Niles JL. Regional citrate anticoagulation in continuous venovenous hemofiltration in critically ill patients with a high risk of bleeding. *Kidney Int* 1999; 55: 1991–1997

26. Mehta RL, McDonald BR, Aguilar M et al. Regional citrate anticoagulation for continuous arteriovenous hemodialysis in critically ill patients. *Kidney Int* 1990; 38: 976–981

27. Bagshaw SM, Laupland KB, Boteju PJ et al. Is regional citrate superior to systemic heparin anticoagulation for continuous renal replacement therapy? A prospective observational study in an adult regional critical care system. *J Crit Care* 2005; 20: 155–161

28. Hetzel GR, Taskaya G, Sucker C et al. Citrate plasma levels in patients under regional anticoagulation in continuous venovenous hemofiltration. *Am J Kidney Dis* 2006; 48: 806–811

29. Swartz R, Pasko D, O’Toole J et al. Improving the delivery of continuous renal replacement therapy using regional citrate anticoagulation. *Clin Nephrol* 2004; 61: 134–143

30. Meier-Kriesche HU, Gitomer J, Finkel K et al. Increased total to ionized calcium ratio during continuous venovenous hemodialysis with regional citrate anticoagulation. *Crit Care Med* 2001; 29: 748–752

31. Scott VL, De Wolf AM, Kang Y et al. Ionized hypomagnesemia in patients undergoing orthotopic liver transplantation: a complication of citrate intoxication. *Liver Transpl Surg* 1996; 2: 343–347

32. Diaz J, Acosta F, Parrilla P et al. Serum ionized magnesium monitoring during orthotopic liver transplantation. *Transplantation* 1996; 61: 835–837

33. Morgera S, Haase M, Ruckert M et al. Regional citrate anticoagulation in continuous hemodialysis—acid-base and electrolyte balance at an increased dose of dialysis. *Nephron Clin Pract* 2005; 101: c211–c219

34. Gabutti L, Marone C, Colucci G et al. Citrate anticoagulation in continuous venovenous hemofiltration: a metabolic challenge. *Intensive Care Med* 2002; 28: 1419–1425

35. Monchi M, Berghmans D, Ledoux D et al. Citrate vs. Heparin for anticoagulation in continuous venovenous hemofiltration: a prospective randomized study. *Intensive Care Med* 2004; 30: 260–265

36. Betjes MG, van Oosterom D, van Agteren M et al. Regional citrate versus heparin anticoagulation during venovenous hemofiltration in patients at low risk for bleeding: similar hemofilter survival but significantly less bleeding. *J Nephrol* 2007; 20: 602–608

37. Morgera S, Scholle C, Voss G et al. Metabolic complications during regional citrate anticoagulation in continuous venovenous hemodialysis: single-center experience. *Nephron Clin Pract* 2004; 97: c131–c136

38. Van Der Voort PH, Postma SR, Kingma WP et al. Safety of citrate based hemofiltration in critically ill patients at high risk for bleeding: a comparison with nadroparin. *Int J Artif Organs* 2006; 29: 559–563

39. Balik M, Waldauf P, Plasil P et al. Prostacyclin versus citrate in continuous haemodiafiltration: an observational study in patients with high risk of bleeding. *Blood Purif* 2005; 23: 325–329

40. Meier-Kriesche HU, Gitomer J, Finkel K et al. Unexpected severe hypocalcemia during continuous venovenous hemodialysis with regional citrate anticoagulation. *Am J Kidney Dis* 1999; 33: e8

41. Apnser R, Druml W. More on anticoagulation for continuous hemofiltration. *N Engl J Med* 1998; 338: 131–132

42. Kramer L, Bauer E, Soukhardt C et al. Citrate pharmacokinetics and metabolism in cirrhotic and noncirrhotic critically ill patients. *Crit Care Med* 2003; 31: 2450–2455

43. Kirschbaum B, Galishoff M, Reines HD. Lactic acidosis treated with continuous hemodiafiltration and regional citrate anticoagulation. *Crit Care Med* 1992; 20: 349–353

44. Palsson R, Laliberte KA, Niles JL. Choice of replacement solution and anticoagulant in continuous venovenous hemofiltration. *Clin Nephrol* 2006; 65: 34–42

45. Gong D, Ji D, Xu B et al. Regional citrate anticoagulation in critically ill patients during continuous blood purification. *Clin Med J (Engl)* 2003; 116: 360–363

46. Mehta RL, McDonald BR, Ward DM. Regional citrate anticoagulation for continuous arteriovenous hemodialysis. An update after 12 months. *Crit Care Med* 1991; 93: 210–214

47. Sanghvi SR, Becker B, Brunson A et al. Efficacy and safety of regional citrate anticoagulation in high flow CVVH (abstract). *Blood Purif* 2006; 24: 262

48. Sutaria S, Hoffert G, Fitzpatrick J et al. Regional citrate anticoagulation for CVVHDF in patients with liver failure (abstract). *Blood Purif* 2005; 23: 166

49. Uchino S, Bellomo R, Morimatsu H et al. Continuous renal replacement therapies: a worldwide practice survey: the beginning and ending supportive therapy for the kidney (B.E.S.T. Kidney) investigators. *Intensive Care Med* 2007; 33: 1563–1570

50. Hirsh J, Raschke R. Heparin and low-molecular-weight heparin: the seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest* 2004; 126: 1885–2035

51. De Waele JJ, Van Cauwenberghhe S, Hoste E et al. The use of the activated clotting time for monitoring heparin therapy in critically ill patients. *Intensive Care Med* 2003; 29: 325–328

52. Leslie GD, Jacobs IG, Clarke GM. Proximally delivered dilute heparin does not improve circuit life in continuous venovenous haemodiafiltration. *Intensive Care Med* 1996; 22: 1261–1264

53. Vargas Hein O, von Heymann C, Lippis M et al. Hirudin versus heparin for anticoagulation in continuous renal replacement therapy. *Intensive Care Med* 2001; 27: 673–679

54. Morabito S, Guzzo I, Solazzo A et al. Continuous renal replacement therapies: anticoagulation in the critically ill at high risk of bleeding. *J Nephrol* 2003; 16: 566–571

55. Biancofiore G, Esposito M, Bindi L et al. Regional filter heparinization for continuous veno-venous hemofiltration in liver transplant recipients. *Minerva Anestesiol* 2003; 69: 527–534 (in English) and 534–538 (in Italian)

56. Reeves JH, Cumming AR, Gallagher L et al. A controlled trial of low-molecular-weight heparin (dalteparin) versus unfractionated heparin as anticoagulant during continuous venovenous hemodialysis with filtration. *Crit Care Med* 1999; 27: 2224–2228

57. Joannidis M, Kountchev J, Rauchenzauner M et al. Enoxaparin vs. unfractionated heparin for anticoagulation during continuous venovenous hemofiltration: a randomized controlled crossover study. *Intensive Care Med* 2007; 33: 1571–1579

58. Langenbecker SA, Felfernig M, Werba A et al. Anticoagulation with prostacyclin and heparin during continuous venovenous hemofiltration. *Crit Care Med* 1994; 22: 1774–1781

59. Davenport A, Will EJ, Davison AM. The effect of prostacyclin on intracranial pressure in patients with acute hepatic and renal failure. *Clin Nephrol* 1991; 35: 151–157

60. Davenport A, Will EJ, Davison AM. Adverse effects on cerebral perfusion of prostacyclin administered directly into patients with fulminant hepatic failure and acute renal failure. *Nephron* 1991; 59: 449–454

61. Davenport A, Will EJ, Davison AM. Comparison of the use of standard heparin and prostacyclin anticoagulation in spontaneous and pump-driven extracorporeal circuits in patients with combined acute renal and hepatic failure. *Nephron* 1994; 66: 431–437

62. Matsuo T, Kario K, Nakao K et al. Anticoagulation with nafamostat mesilate, a synthetic protease inhibitor, in hemodialysis patients with a bleeding risk. *Haemostasis* 1993; 23: 135–141

63. Inagaki O, Nishian Y, Iwaki R et al. Adsorption of nafamostat mesilate by hemodialysis membranes. *Artif Organs* 1992; 16: 553–558

64. Hu ZJ, Iwama H, Suzuki R et al. Time course of activated coagulation time at various sites during continuous haemodiafiltration using nafamostat mesilate. *Intensive Care Med* 1999; 25: 524–527

65. Davenport A. Anticoagulation options for patients with heparin-induced thrombocytopenia requiring renal support in the intensive care unit. *Crit Care Nephrol* 2007; 156: 259–266

66. Levine RL, Hursting MJ, McCollum D. Argatroban therapy in heparin-induced thrombocytopenia with hepatic dysfunction. *Chest* 2006; 129: 1167–1175

67. Reddy BV, Grossman EJ, Treviso SA et al. Argatroban anticoagulation in patients with heparin-induced thrombocytopenia requiring renal replacement therapy. *Ann Pharmacother* 2005; 39: 1601–1605
68. Tang IY, Cox DS, Patel K et al. Argatroban and renal replacement therapy in patients with heparin-induced thrombocytopenia. Ann Pharmacother 2005; 39: 231–236
69. Dager WE, White RH. Argatroban for heparin-induced thrombocytopenia in hepato-renal failure and CVVHD. Ann Pharmacother 2003; 37: 1232–1236
70. Williamson DR, Boulanger I, Tardif M et al. Argatroban dosing in intensive care patients with acute renal failure and liver dysfunction. Pharmacotherapy 2004; 24: 409–414
71. Young G, Yonekawa KE, Nakagawa PA et al. Recombinant activated factor vii effectively reverses the anticoagulant effects of heparin, enoxaparin, fondaparinux, argatroban, and bivalirudin ex vivo as measured using thromboelastography. Blood Coagul Fibrinolysis 2007; 18: 547–553
72. Keeling D, Davidson S, Watson H. The management of heparin-induced thrombocytopenia. Br J Haematol 2006; 133: 259–269
73. Kern H, Ziemer S, Kox WJ. Bleeding after intermittent or continuous r-hirudin during CVVH. Intensive Care Med 1999; 25: 1311–1314
74. Hein OV, von Heymann C, Morgera S et al. Protracted bleeding after hirudin anticoagulation for cardiac surgery in a patient with HIT II and chronic renal failure. Artif Organs 2005; 29: 507–510
75. Frank RD, Farber H, Lanzmich R et al. In vitro studies on hirudin elimination by haemofiltration: comparison of three high-flux membranes. Nephrol Dial Transplant 2002; 17: 1957–1963
76. Hein OV, von Heymann C, Diehl T et al. Intermittent hirudin versus continuous heparin for anticoagulation in continuous renal replacement therapy. Ren Fail 2004; 26: 297–303
77. Saner F, Hertl M, Broelsch CE. Anticoagulation with hirudin for continuous veno-venous hemodialysis in liver transplantation. Acta Anaesthesiol Scand 2001; 45: 914–918
78. Selleng K, Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia in intensive care patients. Crit Care Med 2007; 35: 1165–1176
79. Kiser TH, Fish DN. Evaluation of bivalirudin treatment for heparin-induced thrombocytopenia in critically ill patients with hepatic and/or renal dysfunction. Pharmacotherapy 2006; 26: 452–460
80. Lindhoff-Last E, Betz C, Bauersachs R. Use of a low-molecular-weight heparinoid (danaparoid sodium) for continuous renal replacement therapy in intensive care patients. Clin Appl Thromb Hemost 2001; 7: 300–304
81. Dang CH, Durkalski VL, Nappi JM. Evaluation of treatment with direct thrombin inhibitors in patients with heparin-induced thrombocytopenia. Pharmacotherapy 2006; 26: 461–468
82. Warkentin TE, Greinacher A, Koster A. Bivalirudin. Thromb Haemost 2008; 99: 830–839

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