Introduction

For CRRT to be truly continuous, the integrity of the extracorporeal circuit must be maintained. The passage of blood through the extracorporeal circuit results in the activation of platelets, coagulation cascade proteins, complement and inflammatory white blood cells, resulting in platelet microthrombi formation, with subsequent platelet and fibrin deposition on the surface of the dialyzer membrane. Typically this occurs first in the outer fibers, due to the reduced flow within the fiber bundle.

The majority of patients with ARF in the ICU require anticoagulation for successful CRRT, as these patients typically have evidence of underlying platelet activation and thrombin generation coupled with reduced levels of the natural anticoagulants. The effectiveness of anticoagulation is important in determining dialyzer efficacy in terms of both solute and water removal, circuit longevity and optimum patient management. If anticoagulation is insufficient, filtration performance deteriorates and the dialyzer may eventually clot, contributing to blood loss. Excessive anticoagulation, on the other hand, may result in bleeding complications, which have been reported to occur in 5-26% of treatments. Anticoagulation is thus one of the most important components of CRRT. Vascular access, in terms of the choice of the type of arterial and venous catheters, and the site of insertion can significantly influence blood flow rates and contribute to CRRT circuit life and performance. Several options now exist for access and anticoagulation and can be selected based on individual patient requirements, local availability of the various anticoagulants and catheters, and unit expertise.

Vascular Access

Should arterial access still be used for CRRT?

Continuous arterio-venous (AV) therapies require an arterial access for system inflow in combination with venous access for blood return. Options for arterial access include arteriovenous (Scribner) shunts and large bore arterial catheters. The use of large bore arterial catheters in the femoral position is generally preferred due to its large flow capacity and low risk of infection.
preferable to the use of shunts as they generally provide better blood flow, especially in the setting of
hypotension\(^1\)\(^-\)\(^2\) (level III). Compared to venovenous access, the use of arterial access is associated with a
significantly increased incidence of vascular injury, especially in the elderly, including hemorrhage, arterial
thrombosis, pseudoaneurysm formation, traumatic fistulas and infection. Serious complication rates in
excess of 10% of patients have been reported with prolonged arterial access for continuous AV therapies\(^3\)\(^-\)\(^4\)
(Level III). The use of soft silicone arterial catheters has been associated with a decreased incidence of
complications compared to more rigid teflon or polyurethane catheters.\(^5\)

**Summary:** There is currently no consensus on vascular access, although the majority of recently published
reports suggest that most centers are now moving to a single dual lumen venous catheter. Given the greater
risk of access complications and the lesser efficiency of solute clearance associated with AV therapies,
pump-assisted veno-venous therapies are the preferred modality (see also workgroup 5).

**Recommendations for clinical practice:** AV therapies should be reserved for situations in which pump-
assisted venovenous therapy is not available (Grade D). When AV therapies are utilized, the use of short,
large-bore silicon catheters is preferable, with close monitoring of cannulation sites for evidence of
vascular injury (Grade E). AV shunts are not recommended, as the commercial production of catheter tips
has been discontinued (Grade D). **Recommendations for future research:** To compare thermal heat loss
during AV and veno-venous therapies, and to assess the effect of spontaneous arterial and pumped venous
vascular access on platelet activation in settings where AV circuits are still needed.

**Can A-V fistulae and A-V grafts in ESRF patients be used for CRRT?**

Grafts and fistulae in ESRF patients have not been reported as vascular access sites for CRRT. Whereas
grafts and A-V fistulae could be used for SLED and other forms of intermittent treatment in the ICU, most
centers have not used these pre-formed accesses for CRRT due to concern that if needles were inserted in
the same position for many consecutive days, this could lead to possible permanent vessel or graft wall
damage. If these accesses are used, the question arises as to whether plastic needles should be used in
preference to steel, and also as to the size of the needle (as flow is not as great an issue for CRRT compared
to intermittent hemodialysis). **Recommendations for clinical practice:** Currently, A-V fistulae and grafts are
not recommended for use in CRRT (Grade E).

**Recommendations for future research:** To compare the safety and efficacy of small bore steel and plastic
needles for long term access for CRRT (or “mid-term” access for EDD/SLED) in patients with fashioned
A-VF and A-V Grafts.

**What is the optimum site of central venous access for CRRT in adults and children?**

Venous access sites include the subclavian, internal jugular and femoral veins. The optimal site in any
given patient will be determined by the risks of thrombosis\(^6\)\(^-\)\(^15\) and infection,\(^6\)\(^-\)\(^15\) ease of placement and
adequacy of function.
**Thrombosis:** Many clinicians avoid subclavian access because of the risk of late stenosis, which is as high as 50% with subclavians compared to 0% for internal jugular (IJ) access. However, the clinical significance of late stenosis in this population is. Overall complications appear to be lower with internal jugular (10%) vs. subclavian veins (19.6%).

**Infection risk and site of venous catheter:** Most clinicians do not consider catheter location to be a determinant of risk of infection, although femoral vein catheters have been reported to have increased risk of infection compared to IJ and subclavian central venous catheters. The published literature is conflicting. One study of polyurethane, duel-lumen catheters (Vascath®) found no difference in the risk of infection between femoral, IJ and subclavian sites (level II). Conversely, a level III study using non-tunneled long-term catheters (Qunton® permacaths), and semi-occlusive dressing found the risk of infection increased with duration of catheterisation. Compared with subclavian (no femoral lines were used) this risk was increased by IJ location, hazard ratio 3.97 (also increased with diabetes). Finally, a recent study by Oliver (218 patients) found an increased for femoral catheters compared to the IJ location.

**Adequacy:** In general recirculation is greatest with shorter catheters. It is recommended that when femoral catheters are used, the tip should be located in the inferior vena cava. However, there is generally better catheter performance when tips are located in the right atrium, or atrial/caval junction. Kelber et al reported recirculation rates of 4%, 5%, and 10% for IJ, subclavian, and 24cm femoral catheters, respectively (level III). There is some evidence that right IJ placement provides the least recirculation, compared to left IJ and subclavian access. However the effect of catheter design, two single lumen, vs. dual lumen (OO vs. OD, DD, coaxial vs. parallel) has not been formally assessed in ARF, although studies from regular hemodialysis patients have shown increased recirculation rates when there is minimal separation between the catheter tips.

**Recommendations for clinical practice:** Due to the risk of thrombosis and late stenosis, if possible, subclavian veins should be avoided for CRRT access in adults (Grade C). Femoral vein thrombosis is a significant problem in neonates and young children and thus these vessels should be avoided if possible (Grade D). Based on available evidence, no recommendation can be made regarding the risk of infection with various sites of catheter placement. Recirculation is likely to be significant for blood flow rates in excess of 200 ml/min, but will vary depending upon catheter design and location with IJ locations generally being superior (Grade C).

**Recommendations for future research:** 1. Additional prospective studies are required to determine the risks of vascular thrombosis and infection with vascular access for CRRT in adults and children. 2. Assess the effects of different catheter designs, insertion site, catheter tip location and anticoagulation on catheter performance and recirculation rates in ARF patients.

**How and by whom should temporary venous access be obtained?**

Ultrasound guidance has been reported in level II and III studies to reduce the failure and complication rates of central venous catheter insertion. Similarly, infection rates and placement failure rates are less when catheters are placed by specialized/experience vascular access teams. Although there is a lack of controlled data about the type of catheter and trauma and complications at insertion, traumatic insertion is a
risk for subsequent catheter related infection (Grade E) **Recommendations for clinical practice:** Central venous catheters should be inserted using stringent sterile precautions. The use of ultrasound guidance and specialized access teams is encouraged (Grade C). **Recommendations for future research:** To collect prospective data on central venous catheter insertion technique, and subsequent complications, such as thrombus formation and infection rates.

**Do the physical or chemical properties of the catheter influence infection rates?**

Important characteristics of dialysis catheters, which may influence infection rates, include the catheter material, and antimicrobial coating or impregnation. Laboratory data show that hydrophobic Staphylococci have increased adherence to polyvinyl chloride, silicone, polyethylene compared to tetrafluoroethylene and polyurethane. Clinical studies have borne out this laboratory data, showing reduced bacterial colonization with polyurethane catheters (level III). Clinical studies of silver coated dialysis access catheters have not shown any reduction in infection rates, and some catheters have had to be removed to silver allergy. To date, there have been no trials of antibiotic coated catheters for dialysis access. However, other types antibiotic coated catheters have been used in the ICU setting with reported reductions in catheter related bacteremia.

**Recommendations for clinical practice:** Polyurethane catheters are preferable for CRRT access (Grade D). Silver coating is currently not effective and antibiotic coating/impregnation has not been studied for this indication. Vascular access sites should be managed in accord with previously published recommendations. **Recommendations for future research:** Further study is required to assess the benefits or lack of benefit of (1) tunneling catheters, (2) topical antimicrobials to the exit site, (3) the use of antibiotic and or antiseptic packs in patients treated with EDD/SLED, where there is continual connection and disconnection of the CRRT circuit, and (4) antibiotic coated venous dialysis catheters.

**Anticoagulation**

**Is anticoagulation necessary for successful CRRT?**

Some patients with ARF in the ICU have a significant coagulopathy, and are “auto-anticoagulated”, and therefore do not require additional anticoagulation. Martin et al reported a positive correlation between peripheral platelet count and anticoagulation requirement. In addition several centers have reported that CRRT circuit longevity was similar for both anticoagulant free and those anticoagulated with heparin. This may be due to circuit design, in terms of predilutional fluid replacement, to reduce hematocrit, and spontaneous rather than pumped circuits. It may also be due to patient selection, in that patients with worse coagulation are selected for treatment without anticoagulation. Similarly pumped hemofiltration circuits were reported not to last as long as CVVHD, due to increased hematocrit within the dialyzer/hemofilter. Most clotting of circuits takes place within the dialyzer/hemofilter, as this is the largest contact surface area in the extracorporeal circuit. Platelet and inflammatory cell activation and fibrin deposition on the membrane surface depends upon the polymer composition and smoothness of the membrane surface,
geometrical design and flow characteristics within the dialyzer, and the surface area available for contact
activation. Clotting may also occur at other sites within the extracorporeal circuit, including the venous
air detector and the vascular access catheter.

Recommendations for clinical practice: In patients who are auto-anticoagulated, or are at high risk of
bleeding, consensus exists that CRRT can be carried out successfully without any anticoagulation, although
circuit life may be less than 24 hours (Grade D). Recommendations for future research: To determine the
effect of different vascular access devices, and blood flow on filter performance and longevity in the
presence or absence of anticoagulation. Determine the impact of underlying patient characteristics, circuit
and filter design, and operational characteristics on circuit life and filter performance with modern pumped
systems.

What determines the choice of anticoagulant for CRRT?

Most ICUs have chosen one form of anticoagulation or another for CRRT based on the patient population
served and local expertise. Standard unfractionated heparin remains the most commonly used anticoagulant
for CRRT, based on experienced gained in intermittent hemodialysis. Heparin, although widely used, may
not necessarily be the most effective extracorporeal anticoagulant, as most patients with ARF in the ICU
have reduced antithrombin III concentrations, and will therefore be somewhat resistant to heparin.

Although initial studies reported the beneficial effect of replacing antithrombin III, this has not been borne
out in subsequent controlled trials. Continuous exposure to heparin may result in the development of
severe thrombocytopenia due to the development of heparin-IgG4 complexes, which bind and activate
platelets, causing filter/dialyzer clotting and potentially both arterial and venous thrombosis. The current
commercially available tests for HIT are relatively insensitive, so a negative test does not exclude HIT, as a
series of antibodies can be generated. Although the synthetic heparinoids can be used to replace heparin
or low molecular weight heparin, as the anticoagulant, there is still a risk of cross reactivity. Under these
circumstances recombinant hirudin, a direct thrombin inhibitor can be used. Hirudin dosing depends upon
the type of hemofilter/dialyzer membrane, as unlike the family of heparins, it can be cleared by high
efficiency and highflux altered cellulosic membranes. Approximately 40% of patients treated with hirudin
will develop so-called “hirudin antibodies”, these antibodies reduce plasma clearance, so extending the
biological half life. Recently the FDA has also approved the use of argatroban, a synthetic arginine
derivative for the treatment of patients with heparin induced thrombocytopenia. Unlike heparin, which can
be reversed with protamine, the direct thrombin inhibitors, hirudin and argatroban, require the
administration of fresh frozen plasma to reverse bleeding due to overdosage.

Heparin is a systemic anticoagulant and is associated with increased risk of hemorrhage. Therefore some
centers have developed expertise in the use of other agents, which may act as regional or systemic
anticoagulants. Whereas the effect of heparin can be assessed at the bedside, using a whole blood clotting
time, most anticoagulants require monitoring by the hematology laboratory. Others such as the low
molecular weight heparins require specialized assays, and therefore cannot be readily monitored, and there
are no simple tests to assess the effects of the vasodilatory prostanoids. Regional citrate anticoagulation has been successfully utilized for CRRT techniques (CAVHD, CVVH and CVVHDF) for both adult and pediatric patients.\textsuperscript{47-48} Filter patency and circuit life reported with these techniques is generally in excess of those reported with circuits using heparin or no anticoagulation. Anticoagulation with citrate requires the use of a specialized replacement/dialysate solution, and variations of the technique have been reported.\textsuperscript{49-50} Although citrate is commercially available, as trisodium citrate and acid citrate dextrose, dialysate and replacement solutions are not currently commercially available, and this requires the services of a pharmacy department with the capacity to produce sterile fluid. In addition citrate should be cautiously used with bioartificial devices, such as those containing hepatocytes or renal tubular epithelial cells, as too high a citrate concentration and hypocalemia may be toxic to the cell cultures. \textbf{Recommendations for clinical practice:} The choice of anticoagulant for CRRT should be determined by patient characteristics, local expertise, nursing comfort, ease of monitoring (bed side vs. specialized lab tests) and pharmacy issues (including preparing specialized replacement solutions) (Grade E). Systemic anticoagulation with heparin (standard unfractionated, low molecular weight, or synthetic heparinoids), or direct thrombin inhibitors (hirudin and argatroban) should probably be avoided in patients at high risk of bleeding (Grade E). There is no consensus currently on which anticoagulant should be the first choice for all CRRT patients.

\textbf{Recommendations for future research:} 1. Development of standard criteria to evaluate the efficacy of anticoagulation on CRRT circuits, in terms of filter performance and filter clotting. 2. Evaluation of the effects of different anticoagulation regimes and their interaction with different membrane designs, operational characteristics and pumped systems on filter performance and circuit longevity. 3. Comparison of systemic and regional anticoagulants for different CRRT techniques (i.e. hemofiltration compared to hemodialysis and haemodiafiltration). 4. Assess the effect of activated protein C and other recombinant proteins administered to critically ill ICU patients, which may impact on the coagulation system.

\textbf{How should anticoagulation be monitored for effectiveness and safety?}

Monitoring should include evaluation of anticoagulant effect, filter efficacy and circuit life, and complications. For unfractionated heparin, anticoagulant effect is most often monitored by periodic measurement of post-filter ACT or systemic APTT.\textsuperscript{51} As low molecular weight heparins and synthetic heparinoids mainly act at the tenase level, these should be regularly monitored by factor Xa activity. Although these assays may not be readily available, monitoring is advisable as the half-life of low molecular weight heparins and heparinoids is significantly increased in renal failure, and accumulation increases the risk of overtanticoagulation and hemorrhage.\textsuperscript{52} Although the effect of hirudin and argatroban can be measured using the APTT, some centers additionally monitor the effect of hirudin by the ecorin clotting time and direct measurement of the plasma concentration.\textsuperscript{53} Prostacyclin and other vasodilatory prostanoids do not have any reliable bedside or laboratory test to quantitate the anticoagulant effect. Regional anticoagulation with citrate can be monitored using the post-filter ACT and ionized calcium, and the systemic calcium concentration.\textsuperscript{49} Specific targets for post-filter and systemic values of ACT and
ionized and total calcium are described to achieve filter patency of the CRRT circuit without increasing the risk of complications.47

Since the objective of any anticoagulant is to prolong filter patency, early recognition of filter dysfunction is an important consideration. Currently there is little consensus regarding the evaluation of filter dysfunction. In clinical practice most centers use CRRT circuit life as a measure of the effectiveness of anticoagulation. Filter patency can be assessed by trends in the hourly ultrafiltration rate in both spontaneous arteriovenous and pumped veno-venous circuits when the ultrafiltrate is not mechanically controlled. However, this method cannot be readily used when a mechanical pump controls the ultrafiltrate rate. In which case monitoring of transmembrane pressure is recommended to detect membrane fouling. Membrane fouling due to fiber clotting is reduced most by citrate and to a lesser extent by prostacyclin54-55 (level II). However, direct measurements of mean pre and post filter pressures have not been shown to be predictive of filter clotting58 (level IV).

Anticoagulants differ in their propensity for complications. Bleeding is the most important complication and careful observation for occult bleeding should be performed. Systemic heparinization, the most widely used anticoagulation in CRRT, has reported bleeding rates between 10 and 50%34-56 (level III), and heparin-induced thrombocytopenia (HIT) in 5-10%, depending on the source of the heparin51 (level IV). Prospective randomized controlled trials have not shown a reduction in complication rates using LMWH or prostanoids57-58 (level II). Other studies have reported reduced bleeding with prostacyclin and no bleeding with regional citrate anticoagulation50,55 (Level IV). Prostanoids vary in their effects on hemodynamic parameters.54-55 Metabolic complications have been reported with citrate and include hypocalcemia, hypernatremia, and metabolic alkalosis.59 Direct toxicity with citrate is not reported, however citrate can accumulate leading to an anion gap in patients with impaired capacity to metabolize citrate, e.g. fulminant hepatic failure.51 Regional anticoagulation using protamine to reverse the effect of heparin has been used, but protamine can accumulate in ARF during CRRT due to the difference in half-life when compared to heparin. In addition post-mortem evidence has revealed that heparin-protamine complexes may not be adequately degraded and can accumulate in body tissues during CRRT. Although protamine may have some effect in reversing anticoagulation with low molecular weight heparins and synthetic heparinoids, fresh frozen plasma remains the definitive treatment.60 Similar fresh frozen plasma should be given in cases of bleeding due to excessive anticoagulation with the thrombin inhibitors, hirudin and argatroban.61

Recommendations for clinical practice: Safety monitoring is recommended with anticoagulation (Grade E). During heparin anticoagulation, measurement of activated clotting times (ACT) and systemic APTT should be regularly performed to minimize complications. Additionally, routine measurement of platelets should be made to monitor for HIT. During citrate anticoagulation, frequent measurements of post-filter and serum ionized calcium should be done to appropriately titrate the dose of citrate and calcium replacement solutions (Grade E). Less-frequent monitoring of systemic acid-base balance is also advisable in patients at high risk for citrate accumulation. Without additional safety data, regional anticoagulation
using heparin-protamine cannot be recommended given the risk of protamine accumulation in patients with ARF. Low molecular weight heparins and synthetic heparinoids require regular monitoring of anti-factor Xa activity (Grade E). Hirudin and argatroban can be monitored with APTT, but in addition it is recommended that for hirudin either plasma drug levels or ecarin clotting time is also measured due to the risk of hirudin accumulation in ARF 61 (Grade E). If patients develop HIT, then heparin and low molecular weight heparin anticoagulation must be withdrawn. In cases complicated by venous and or arterial thrombosis, then hirudin or argatroban are preferred 41 (Grade E). The synthetic heparinoids, danaparoid can be used, but there is a small risk of cross-reactivity with the HIT antibody, so prior to usage this should be tested.62 In cases of HIT without any systemic effects, then regional anticoagulation with citrate can be used.51 There is no consensus on whether or how to monitor for filter performance during CRRT.

Recommendations for future research: To compare the incidence and nature of the adverse effects of the currently used anticoagulants in different patient populations. To evaluate the sensitivity of the commercially available assays for HIT

References


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