Section 5.1 DIALYSIS INTERVENTIONS FOR THE TREATMENT OF ACUTE KIDNEY INJURY: ANTICOAGULATION

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GUIDELINES

a. During AKI we recommend commencing RRT using anticoagulation unless the risk is considered unacceptable. (1B)

b. If a patient is receiving systemic anticoagulation, we suggest that this may be sufficient for RRT. (2B)

c. For anticoagulation in intermittent RRT, we recommend using either unfractionated or low-molecular weight heparin, rather than other anticoagulants. (1C).

d. For anticoagulation in CRRT, we recommend using either regional citrate anticoagulation, low dose unfractionated heparin, a protocol-based heparin dose targeting a systemic APTT or a weight-based dose of low molecular weight heparin. The choice should be based on patient characteristics and local practices and resources. (1B)

e. For CRRT in a patient with impaired coagulation or increased bleeding risk: it is reasonable to choose between no anticoagulation with attention to optimising circuit function and regional anticoagulation either with UFH and protamine or citrate. (2C)

f. In a patient with suspected heparin-induced thrombocytopenia (HIT), all heparin must be stopped. We recommend using direct thrombin inhibitors (such as argatroban) or Factor Xa inhibitors (such as danaparoid or fondaparinux) rather than other or no anticoagulation during RRT. (1A)

g. In a patient with HIT who does not have severe liver failure, we suggest using argatroban rather than other thrombin or Factor Xa inhibitors during RRT. (2C)

UNGRADED SUGGESTIONS FOR CLINICAL CARE

- We suggest that when a patient with AKI requires RRT, the decision to use anticoagulation for RRT is based on the risks and benefits of anticoagulation to the patient. (Ungraded)
- Excessive clotting should be managed with attention to both anti-coagulant and non-anticoagulant factors. [1] (Ungraded)

**IMPLEMENTATION AND AUDIT**

Individual units should consider an audit of rates of complications such as clotted extracorporeal circuits and bleeding from the use and or withholding of anticoagulation.

**BACKGROUND**

Coagulation management for renal replacement therapy (RRT) in patients with AKI requires careful consideration. Ideally anticoagulation is implemented to optimise filter and circuit functioning. Clotting issues can have significant effects on the treatment including reduction in clearance efficiency and serious blood consumption. Conversely anticoagulation can cause serious bleeding complications with significant morbidity and mortality. There is great heterogeneity in anticoagulation practice in RRT. Evidence based guidelines are critically important.

**SEARCH STRATEGY**

The search strategy was an update of that used by KDIGO (refer to Table 21 in the Appendix of the KDIGO guideline) (Kidney International Supplements 2 (2012); 2: 102-113). Additional key papers have been identified the authors that were published after the KHA-CARI update search.

**Databases searched:** Medline, Central, Cochrane database of systematic reviews

**Date of searches:** June 2012

**ADEQUACY OF KDIGO SEARCH STRATEGY**

The search strategy and evidence provided by KDIGO was comprehensive and included some important randomised controlled trials (RCTs). A number of systematic reviews and RCTs have subsequently been identified in the updated search by KHA-CARI and included in this update.

**APPLICABILITY IF KDIGO RECOMMENDATIONS AND SUGGESTIONS**

KDIGO guidelines generally reflect Australian and New Zealand clinical practice for anticoagulation in patients requiring RRT in AKI. However it recommends regional citrate anticoagulation as preferred for continuous
treatments. We would recommend the use of citrate in centres only with previous experience with its use, adequate laboratory support and appropriate protocols.

OVERVIEW OF THE EVIDENCE

The following provides an overview of the evidence as identified by the update searches conducted by KHA-CARI as part of the adaptation process.

a. During AKI we recommend commencing RRT using anticoagulation unless the risk in considered unacceptable. (1B)

b. If a patient is receiving systemic anticoagulation this may be sufficient for RRT. (2B)

c. For anticoagulation in intermittent RRT, we recommend using either unfractionated or low-molecular weight heparin, rather than other anticoagulants. (1C)

d. For anticoagulation in CRRT, we suggest using either regional citrate anticoagulation, low dose unfractionated heparin, a protocol based heparin dose targeting a systemic APTT or a weight based dose of low molecular weight heparin. The choice should be based on patient characteristics and local practices and resources. (1B)

Whilst unfractionated heparin (UFH) is still the most widely used anticoagulant for all forms of RRT, many centers, have switched to low-molecular-weight heparin (LMWH) for routine anticoagulation during IHD. Advantages and disadvantages of each type of heparin are summarized in Table 1.

Citrate anticoagulation (CA) is a safe and effective alternative to UFH or LWMH for CRRT in centers with appropriate protocols including the ability to provide urgent biochemical laboratory support. CA may have lower bleeding complications than either of the heparin approaches but there is insufficient published information on outcomes from routine clinical use to recommend citrate anticoagulation. A recent meta-analysis of the six available RCTs comparing citrate anticoagulation with some form of heparin showed no difference in circuit survival time, incidence of metabolic alkalosis, or heparin-induced thrombocytopenia (HIT) between the groups. Hypocalcaemia was increased in the citrate group, although no hypocalcaemia related serious adverse events were reported. Favourably, citrate treatment was associated with less bleeding [1]. The previous suggestion from a single center study that citrate anticoagulation in AKI may have a survival benefit has not been sustained in the larger multi-center study or the subsequent meta-analysis [2].

The availability of specialised replacement fluids and improved software on dialysis machines has made regional citrate anticoagulation less time consuming. However, as the safe use of regional citrate requires access to measurement and replacement of ionised calcium and bicarbonate 24 hours a
The randomised trials of CA generally excluded patients with acute liver failure, increased bleeding risk and HITs. Recently, some small case series describe safe use of citrate in these groups suggesting regional citrate may become a useful alternative in patients with impaired coagulation or increased bleeding risk [3, 4]. However there are currently no randomised studies to support a recommendation for the use of CA in this group of patients.

Other drugs (Prostacyclin [5], the direct thrombin inhibitors and Nafamostat (a serine protease inhibitor)), have been used successfully in case series, however as there are no RCTs directly comparing these agents with UFH or LMWH, there is no formal recommendation for their use. It may however be reasonable to consider use them as second line agents either alone or in combination with UFH.

Using any anticoagulation in AKI requires a precise approach to dosing, and appreciation of the variable pharmacokinetics and disordered coagulation that occurs during multi organ failure. The purpose of monitoring tests needs to be clearly understood. A test may be used to measure a target for anticoagulant dosing or it may be a safety measure to prevent overdosing. Assessment of circuit function is more important that reliance on an APTT. If circuit function is adequate, an APTT target is not required; the role of APTT testing is to avoid over anticoagulation. In this setting, excessive testing may contribute to overtreatment, with unnecessary dose adjustments and the risks of bleeding and increased cost. Conversely, if premature circuit clotting is a concern, the dose of UFH may be increased to target a particular APTT, using a well validated protocol. Factors effecting circuit flow should be evaluated with each episode of circuit failure to prevent unnecessary escalation of anticoagulation. When using heparins it is necessary to monitor platelet count at least daily.

There is no data to regard the use of UFH or LMWH for DVT prophylaxis as significant; this group may be considered in the “no systemic anticoagulation category”.

**e. For CRRT in a patient with impaired coagulation or increased bleeding risk: it is reasonable to choose between no anticoagulation with attention to optimising circuit function or regional anticoagulation either with UFH and protamine or citrate. (2C)**

Patients with AKI who require RRT may have associated coagulopathies creating both increased risk of bleeding and rates of clotting extracorporeal circuits. There are no high quality studies to provide a recommended approach in this situation. We suggest that in patients with impaired coagulation or significant bleeding risk, commence RRT without anticoagulation and give special attention to non-anticoagulant strategies to prolong filter survival. These strategies include well-functioning, high flow vascular access, the reduction of blood viscosity and haemo-concentration by saline flushes and pre-dilution, high blood flow rates, diffusive treatment, the
reduction of blood-air contact in the bubble trap, and assuring prompt reaction to alarms [6]. There are no accepted definitions of APTT, INR or platelet count that predict the ability to perform RRT without anticoagulation.

If the desired dose of RRT is unable to be delivered then regional anticoagulation should be commenced. UFH and protamine reversal post filter has been used in IHD and CRRT. The protamine dose must adequately reverse the heparin and take into account the possible anticoagulant effects of excess protamine. CA is also a regional approach to anticoagulation of the extra corporeal circuit. There are observational studies describing citrate anticoagulation in patients with impaired coagulation and or increased bleeding risk. Randomised trials comparing citrate with heparins have mostly excluded patients with increased bleeding risk. Therefore the choice between the two should be based on local experience.

Continued circuit clotting requires investigation for HITS, consumptive coagulopathy and an adjustment of the anticoagulation plan.

f. In a patient with suspected heparin-induced thrombocytopenia (HIT), all heparin must be stopped. We recommend using direct thrombin inhibitors (such as argatroban) or Factor Xa inhibitors (such as danaparoid or fondaparinux) rather than other or no anticoagulation during RRT. (1A)

g. In a patient with HIT who does not have severe liver failure, we suggest using argatroban rather than other thrombin or Factor Xa inhibitors during RRT. (2C)

Excessive clotting of the RRT circuit requires an evaluation of both dosing and delivery of existing anticoagulation, appropriate management of the RRT circuit and consideration of inherent or acquired coagulation disorders. Heparin resistance induced by anti-thrombin III deficiency in severe sepsis has been described as a cause early filter clotting [7] Immune-mediated HIT results from antibodies directed against platelet factor 4, and occurs in 1–3% of heparin-exposed patients.

When HIT is suspected, all heparins have to be stopped, including any “heparin lock” solutions for dialysis or other catheters. The likelihood of having HIT can be predicted using either the HEP score, or the 4T score - both use the degree of thrombocytopenia, the timing of onset of the fall in platelet count, the presence of thrombosis or acute systemic symptoms, and the presence of other etiologies of thrombocytopenia. Confirmation of the diagnosis and management of HIT should be in conjunction with a specialist hematologist.

Recent guidelines recommend the use of therapeutic doses of an alternative no heparin anticoagulant in patients with strong suspicion of HIT [8]. Options include the direct thrombin inhibitors (Lepirudin, Argatroban, or Bivalirudin), or the anti-thrombin-dependent Factor Xa inhibitors (Danaparoid or Fondaparinix). In the absence of liver failure, Argatroban seems a better
alternative because it is eliminated by the liver, has a short half-life, and can be monitored with APTT. In patients with liver failure or in those in whom bleeding occurs regional citrate anticoagulation has been used along with reduced doses of argatroban or other non-heparin anticoagulants.

However, there are no published reports on these practices. There are no RCTs trials showing which anticoagulant is best for HIT. The choice should take into account local availability and monitoring experience.

UNGRADED SUGGESTIONS

- We recommend when a patient with AKI requires RRT, the decision to use anticoagulation for RRT is based on the risks and benefits of anticoagulation to the patient. (Ungraded)

- Excessive clotting should be managed with attention to both anticoagulant and non-anticoagulant factors\(^1\). (Ungraded)

Anticoagulation is used during RRT to prevent clotting of the filter and the associated reduction in membrane permeability and circuit down time, which compromises the delivered dose of RRT. These benefits have to be weighed against the risk of bleeding, other adverse effects of the anticoagulant agent(s) and economic issues, such as workload and costs. The decision to commence anticoagulation for an individual patient should take into consideration the patients underlying risks from systemic anticoagulation including any specific risks associated with the cause of the AKI.
<table>
<thead>
<tr>
<th>Agent</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin (UFH) Low dose</td>
<td>Cheap, widely available, Antagonist available Short half life</td>
<td>Variable kinetics Heparin resistance in sepsis Needs laboratory testing Adverse effects of heparin</td>
</tr>
<tr>
<td>Heparin (UFH) Targeting an APTT</td>
<td>Cheap, widely available, Antagonist available Short half life</td>
<td>More testing to achieve target APTT</td>
</tr>
<tr>
<td>Low molecular weight heparin (LMWH)</td>
<td>Widely available Simple administration Less variable kinetics and weight based dosing may limit laboratory testing, Lower risk HITS</td>
<td>More expensive Accumulation risk in ARF May have increased risk of bleeding Some monitoring of anti X a required Incomplete reversal Longer half life</td>
</tr>
<tr>
<td>Regional citrate</td>
<td>Regional anticoagulation Short half life</td>
<td>Metabolic complications Acidosis /alkalosis calcium abnormalities Technically more complex Requires additional biochemistry at least initially</td>
</tr>
<tr>
<td>Agatroban</td>
<td>Hepatic metabolism to inactive metabolites Short half life Monitor APTT or ACT</td>
<td>No reversal Some hypotension</td>
</tr>
<tr>
<td>Prostacyclin</td>
<td>May be used in addition to UFH Has been used in HITS Reduced systemic anticoagulant effect</td>
<td>Expensive Potential for hypotension and raised ICP</td>
</tr>
<tr>
<td>Danaparoid</td>
<td>Suitable for use in HITS</td>
<td>May have availability issues Requires anti Xa monitoring Long half life No reversal</td>
</tr>
<tr>
<td>Nafamostat</td>
<td>Short half life Suitable for HITS</td>
<td>No hypotension compared with prostacyclin Expensive Not currently available in Australia Serious adverse effects</td>
</tr>
<tr>
<td>No anticoagulant</td>
<td>Cheap Minimal monitoring</td>
<td>Shorter circuit life May not meet dialysis requirement and risk blood loss if frequent circuit clot</td>
</tr>
</tbody>
</table>
Figure 1. Recommendations for Anticoagulation during RRT in AKI

During AKI, we recommend commencing RRT using anticoagulation unless the risk is considered unacceptable. (1B)

If a patient is receiving systemic anticoagulation, this may be sufficient for RRT. (2B)

For anticoagulation in intermittent RRT, we recommend using either unfractionated or low-molecular-weight heparin, rather than other anticoagulants. (1C)

For anticoagulation in CRRT, we suggest using either regional citrate anticoagulation, low-dose unfractionated heparin, a protocol based heparin dose targeting a systemic APPT or a weight-based dose of low molecular weight heparin. The choice should be based on patient characteristics and local practices and resources. (1B)

For CRRT in a patient with impaired coagulation or increased bleeding risk, it is reasonable to choose between no anticoagulation with attention to optimizing circuit function or regional anticoagulation either with UFH and protamine or citrate. (2C)

Excessive clotting should be managed with attention to both anticoagulant and non-anticoagulant factors. (Ungraded)

In a patient with suspected heparin-induced thrombocytopenia (HIT), all heparin must be stopped, and we recommend using direct thrombin inhibitors (such as argatroban) or Factor Xa inhibitors (such as danaparoid or fondaparinux) rather than other or no anticoagulation during RRT. (1A)

In a patient with HIT who does not have severe liver failure, we suggest using argatroban rather than other thrombin or Factor Xa inhibitors during RRT. (2C)

RRT requiring AKI

Systemic anti-coagulation

YES

Continue Add LMWH or Low-dose heparin if short filter life

IHD

CRRT

High bleeding risk

Usual bleeding risk

LMWH

Heparin targeting APPT.

Regional citrate

LMWH

Heparin targeting APPT.

Regional citrate

Complications

Filter Clotting

Review circuit management
Scale up anticoagulation
Target increased Appt
Add second line agent
Consider HITS ATIII def

HITS

Co-manage with haematology
Cease all heparin
Commence Argatroban

Bleeding complication

Scale down to no anticoagulation
Optimise access flow, filter blood flow, rate and haematocrit
If bleeding continues consider IHD
WHAT DO OTHER GUIDELINES SAY?

Kidney Disease Outcome Quality Initiative (2013):
No recommendations

UK Renal Association (2011):
No recommendations

Canadian Society of Nephrology (CSN) Commentary on KDIGO 2012 AKI clinical practice guidelines indicates that CSN views the recommendation to avoid regional citrate anticoagulation in the setting of shock as impractical. Thus CSN believes the use of citrate anticoagulation can still be considered in the setting of shock.

European Renal Best Practice Guidelines (2012):
No recommendations

SUGGESTIONS FOR FUTURE RESEARCH
Opportunities for more experience and use of regional citrate based anticoagulation.

CONFLICT OF INTEREST
B.B. Hickey has no financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by KHA-CARI.
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