ASN COVID-19: Overcoming Challenges to the Provision of Acute Dialysis for COVID-19 Positive Patients

Welcome and Opening Statement

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Anticoagulation During Acute RRT in Patients with COVID-19: Heparin and Citrate

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CLOTTING AND RRT
Disclaimer / Outline

• We are not here to debate the guidelines
• We’ll discuss:
  • COVID-19 and Thrombosis
  • Heparin (unfractionated and LMWH)
  • Non-Citrate Based Alternatives to Heparin
• This guy is going to talk to you about Citrate in general and his program’s protocol/ experience.
• Other Clotting issues

Summary of Thrombotic Events in ICU Cohort Studies and in Kidney on Autopsy

• 25% - 69% of those in the ICU with Severe COVID pneumonia has Venous Thromboembolism (VTE)
  • Depends on if you actively screen vs. look when there is an indication.
  • VTE associated with mortality
  • 56% w/ prophylactic anticoag still developed VTE/ PE
• Post-mortem biopsy case series: 3 of 26 (12%) with focal or diffuse fibrin thrombi in kidney
  • Others showed proximal tubular injury, loss of brush border and inflammatory infiltrates.

Cui et al. J Thromb Haemost 2020
Hua Su et al – KI – 2020
AKI AND COVID

- AKI rates vary 0-29%
- Depend on definition
- Cohort
- Timing
- RRT needed in 0-10% of those infected
- Impacted by resources
- Modality
- Best Estimates are 10-20% of those in the ICU need RRT

5.3.1: In a patient with AKI requiring RRT, base the decision to use anticoagulation for RRT on assessment of the patient’s potential risks and benefits from anticoagulation (see Figure 17). (Not Graded)

5.3.1.1: We recommend using anticoagulation during RRT in AKI if a patient does not have an increased bleeding risk or impaired coagulation and is not already receiving systemic anticoagulation. (IB)
Per Guidelines: Citrate Preferred Over Heparin Regardless of Risk

5.3.2: For patients without an increased bleeding risk or impaired coagulation and not already receiving effective systemic anticoagulation, we suggest the following:
5.3.2.1: For anticoagulation in intermittent RRT, we recommend using either unfractionated or low-molecular-weight heparin, rather than other anticoagulants. (1C)
5.3.2.2: For anticoagulation in CRRT, we suggest using regional citrate anticoagulation rather than heparin in patients who do not have contraindications for citrate. (2B)
5.3.2.3: For anticoagulation during CRRT in patients who have contraindications for citrate, we suggest using either unfractionated or low-molecular-weight heparin, rather than other anticoagulants. (2C)

5.3.3: For patients with increased bleeding risk who are not receiving anticoagulation, we suggest the following for anticoagulation during RRT:
5.3.3.1: We suggest using regional citrate anticoagulation, rather than no anticoagulation, during CRRT in a patient without contraindications for citrate. (2C)
5.3.3.2: We suggest avoiding regional heparinization during CRRT in a patient with increased risk of bleeding. (2C)
Systemic Heparin gtt: Targeting Higher PTTs

- Likely managed by primary team
- Check baseline PTT prior to starting
- Loading dose 50-80 units/kg prior to gtt
- Then 18-20 units/kg/hr gtt
- Targeting PTT of 80-100 seconds roughly 2x normal
- Shorter than normal filter lives in our first 6 CRRT pts and implemented higher targets now our filter lives (mean 37.5 hrs; n = 25)
- But hyper-clotters remain and all heparin increases bleeding risk
Pre-filter Heparin for CRRT

- As with systemic need to check coagulation studies before starting
- Goal is to anticoagulated the circuit not the patient
- Can use post filter protamine if want to neutralize heparin
  - I rarely use this
- Can start with a bolus as with systemic heparin – consider lower dosing 2-5,000 units x1
- For COVID we have been starting at 10-15 units/kg/hr – with aggressive up titration (normally 5-10 units/kg/hr)
- Target a PTT just above the normal values (for us this is 40-45 secs)
  - Enough to show that heparin is leaving the circuit to the patient....

Modified from Tobon et al. CIASH 2006
Other Options: Low Molecular Weight Heparin e.g. Enoxaparin

- Half life 2.5-6 hours (longer in renal insufficiency / failure)
- Decent bioavailability
- Some clearance of LMWH with CRRT
- Not to be used in setting of thrombocytopenia or low fibrinogen (50-100 mg/dl)
- Normally dose to anti-Factor Xa levels of 0.25-0.35 Units/ml
  - Dosing can be variable but 0.35 units/ml ~ 65 seconds (PTT)
  - Historically levels don’t correspond with risk of bleeding (similar to PTT)
- Protamine can be used for some reversal

Slide Courtesy of Roger Rodby, Rush University @nephrodby @RUSH_Nephrology
5.3.4: In a patient with 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)

5.3.4.1: 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)

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**Argatroban Anticoagulation in Patients with Heparin-Induced Thrombocytopenia Requiring Renal Replacement Therapy**

Bharathi V Reddy, Eric J Grossman, Sharon A Trevino, Marcie J Hursting, and Patrick T Murray

- Direct Thrombin Inhibitor
- Usually given systemically – your hospital may already have a protocol
- Dosing differently in those with or without hepatic and renal dysfunction
- Consider dosing starting at
  - 0.5 mcg/kg/min in those with normal liver function
  - 0.2-0.25 ug/kg/min in those with liver dysfunction
- Target a PTT 2x the normal value (important to have a baseline)
Argatroban Dosing in Critically Ill / Liver Dysfunction

Table 3 – Argatroban dose adjustments for critically ill patients or those with hepatic dysfunction

<table>
<thead>
<tr>
<th>aPTT (sec)</th>
<th>Dose adjustment</th>
<th>Next aPTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>aPTT &lt; 1.5x baseline</td>
<td>Increase dose by 20%</td>
<td>6 hours after rate change</td>
</tr>
<tr>
<td>aPTT 1.5 to 2.5x baseline (goal)</td>
<td>No change</td>
<td>Every 6 hours x 24 hours, followed by every 24 hours</td>
</tr>
<tr>
<td>aPTT &gt; 2.5x baseline</td>
<td>Stop infusion for 4 hours (8 hours for critically ill patients), then restart at 50% of infusion rate</td>
<td>6 hours after rate change</td>
</tr>
</tbody>
</table>

Table 4 – Argatroban Therapeutic Range*

<table>
<thead>
<tr>
<th>Argatroban Concentration (mcg/ml)</th>
<th>Estimated PTT</th>
<th>Estimated Dose Adjustment</th>
<th>Next Argatroban Concentration (mcg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.4</td>
<td>&lt;62</td>
<td>Increase dose by 20%</td>
<td>6 hours after rate change</td>
</tr>
<tr>
<td>0.4-0.8</td>
<td>62-73</td>
<td>No change</td>
<td>Every 6 hours x 24 hours, followed by every 24 hours</td>
</tr>
<tr>
<td>&gt;0.8</td>
<td>&gt;73</td>
<td>Stop infusion for 4 hours (8 hours for critically ill patients), then restart at 50% of infusion rate</td>
<td>6 hours after rate change</td>
</tr>
</tbody>
</table>

*limited data exists for the adjustment of argatroban dosing based on serum concentration, above recommendations are extrapolated from the dosing information in table 3

Regional Citrate Anticoagulation

- Off-label in U.S.
- Efficacy (filter life) equal or greater than heparin in RCTs
- Better safety profile than heparin
  - No increased bleeding risk
  - Mild electrolyte (hypocalcemia) and metabolic (alkalosis) disturbances
- No universal protocol

2012 Meta-analysis, 6 RCTs (n=488)
Wu et al, AJKD 2012;59:810-8

Mean filter life:
+26.9h (-14.5-68.3)

RR bleeding:
0.34 (0.17-0.65)
Michigan RCA Protocol

- Weight based effluent dosing
  - 25-30 ml/kg/hr
- Fixed citrate (ACD-A) dosing
- Titration of CaCl and monitoring of iCa
- Solutions: 0 Ca, 0 glucose
- Maximum filter life 96hrs
- “Shock” protocol to maximize citrate clearance and reduce risk of citrate toxicity

![Diagram of crane and machinery]{.fig}

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**Step 1: CRRT Prescription (CVVHDF)**

<table>
<thead>
<tr>
<th>Settings</th>
<th>Blood Flow QB ml/min</th>
<th>ACD A Citrate Flow ml/hour</th>
<th>Dialysate Flow QD mL/hour</th>
<th>Post-Dilution Flow QRF mL/hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>61-70 kg</td>
<td>100</td>
<td>250</td>
<td>800</td>
<td>800</td>
</tr>
<tr>
<td>71-80 kg</td>
<td>100</td>
<td>250</td>
<td>950</td>
<td>950</td>
</tr>
<tr>
<td>81-90 kg</td>
<td>150</td>
<td>300*</td>
<td>1050</td>
<td>1050</td>
</tr>
<tr>
<td>91-110 kg</td>
<td>150</td>
<td>300*</td>
<td>1200</td>
<td>1200</td>
</tr>
<tr>
<td>111-120 kg</td>
<td>150</td>
<td>300*</td>
<td>1350</td>
<td>1350</td>
</tr>
</tbody>
</table>

**Step 2: CaCl Infusion Rate**

<table>
<thead>
<tr>
<th>Albumin</th>
<th>2.3-2.7 g/dL</th>
<th>2.8-3.2 g/dL</th>
<th>3.3-3.7 g/dL</th>
<th>3.8-4.2 g/dL</th>
<th>4.3-4.7 g/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effluent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=1400 mL/h</td>
<td>19</td>
<td>19</td>
<td>20</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>1401-1700 mL/h</td>
<td>23</td>
<td>23</td>
<td>24</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>1701-2000 mL/h</td>
<td>27</td>
<td>28</td>
<td>28</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>2001-2300 mL/h</td>
<td>31</td>
<td>32</td>
<td>32</td>
<td>33</td>
<td>34</td>
</tr>
<tr>
<td>2301-2600 mL/h</td>
<td>37</td>
<td>38</td>
<td>39</td>
<td>40</td>
<td>41</td>
</tr>
<tr>
<td>2601-2900 mL/h</td>
<td>41</td>
<td>42</td>
<td>43</td>
<td>44</td>
<td>45</td>
</tr>
<tr>
<td>2901-3200 mL/h</td>
<td>44</td>
<td>46</td>
<td>47</td>
<td>48</td>
<td>50</td>
</tr>
<tr>
<td>3201-3500 mL/h</td>
<td>48</td>
<td>50</td>
<td>51</td>
<td>53</td>
<td>54</td>
</tr>
<tr>
<td>3501-3800 mL/h</td>
<td>52</td>
<td>54</td>
<td>55</td>
<td>57</td>
<td>58</td>
</tr>
<tr>
<td>3801-4100 mL/h</td>
<td>56</td>
<td>57</td>
<td>59</td>
<td>61</td>
<td>63</td>
</tr>
<tr>
<td>4101-4400 mL/h</td>
<td>59</td>
<td>61</td>
<td>63</td>
<td>65</td>
<td>67</td>
</tr>
<tr>
<td>4401-4700 mL/h</td>
<td>63</td>
<td>65</td>
<td>67</td>
<td>69</td>
<td>71</td>
</tr>
</tbody>
</table>

**Step 3: Monitoring and adjustments**

- The patient’s ionized calcium level checked every 6 hours
- Increase Rate: +10%
- Reduce Rate: -10%

<table>
<thead>
<tr>
<th>Current Ca Infusion Rate</th>
<th>Increase Rate</th>
<th>Reduce Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>+20%; notify ICU and Nephro fellows</td>
<td>+10%</td>
<td>-20%; notify ICU and Nephro fellows</td>
</tr>
<tr>
<td>&lt;=0.95 mmol/L</td>
<td>+6 mL/h</td>
<td>-4 mL/h</td>
</tr>
<tr>
<td>0.95 - 1.04 mmol/L</td>
<td>+8 mL/h</td>
<td>-6 mL/h</td>
</tr>
<tr>
<td>1.05 - 1.25 mmol/L</td>
<td>+10 mL/h</td>
<td>-8 mL/h</td>
</tr>
<tr>
<td>1.26 - 1.4 mmol/L</td>
<td>+12 mL/h</td>
<td>-10 mL/h</td>
</tr>
<tr>
<td>&gt;1.4 mmol/L</td>
<td>+14 mL/h</td>
<td>-12 mL/h</td>
</tr>
</tbody>
</table>

*Calcium is 136mM CaCl solution (12.5g in 625mL 0.9% NS)*
Michigan CRRT Experience in COVID-19

- First 16 patients: 55±12yrs, 109±28kg, 75% DM
  - BL eGFR 65±28 (31% CKD), Cr at CRRT start 5.1±1.7
  - Ferritin 1158, CRP 23.2, D-dimer 9.3
  - 100% mechanically ventilated, PaO2/FIO2 142±74
- 80 CRRT pt-days: 35 different filter sets
  - 10 filters lasted <24hrs → 5 with documented catheter dysfunction
- Outcomes: 6 (37.5%) died, 8 remain hospitalized (6 on RRT), 2 discharged alive (without RRT)

Challenges With Citrate Anticoagulation

- Risk of error with multiple anticoagulation protocols
  - E.g. 2.5 vs 0 Ca++ solutions
- Potential CaCl shortages
- Increased monitoring (iCa)
- It takes a village: nephrologists, intensivists, trainees, dialysis and ICU nurses, pharmacy
  - Requires institutional and stakeholder commitment
  - Need momentum!
Not All Clotting in a COVID Pt is related to COVID

• CVVH / CVVHDF clotting will still correlate with higher filtration fractions – so CVVHD may be favorable.
  • Now is not the time to debate middle molecule clearance
• Who is placing the dialysis line? Do they have experience?
  • Poorly placed lines still malfunction
  • Wrong size line in wrong location can increase clotting
  • Lines collapsing – due to ventilator issues
• How is the machine being staffed?
  • Team’s familiarity with CRRT machine can impact filter life
  • Nursing / staffing ratios -ability to get to the machine quickly to troubleshoot
• All the other normal clotting issues
  • Platelet consumption, underlying thrombotic states (e.g. active cancer)

• Placing the machine outside of the room may help – but longer lines may be needed and these may increase clotting on their own.
• Have to balance risks and benefits of your machines / practice etc...
Managing RRT Resources in the Midst of a Pandemic

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The COVID Pandemic in New York

<table>
<thead>
<tr>
<th>Age group</th>
<th>Cases</th>
<th>Hospitalized</th>
<th>%</th>
<th>Deaths</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 17</td>
<td>3,555</td>
<td>273</td>
<td>8%</td>
<td>7</td>
<td>0%</td>
</tr>
<tr>
<td>18 – 44</td>
<td>58,042</td>
<td>5,695</td>
<td>10%</td>
<td>592</td>
<td>10%</td>
</tr>
<tr>
<td>45 – 64</td>
<td>58,143</td>
<td>14,156</td>
<td>24%</td>
<td>3,448</td>
<td>22%</td>
</tr>
<tr>
<td>65 – 74</td>
<td>19,749</td>
<td>9,240</td>
<td>47%</td>
<td>3,769</td>
<td>41%</td>
</tr>
<tr>
<td>≥ 75</td>
<td>17,909</td>
<td>11,212</td>
<td>63%</td>
<td>7,845</td>
<td>70%</td>
</tr>
</tbody>
</table>

Positive tests for COVID-19 per 1,000 residents by ZIP code as of April 28.
Resource Surge

- Consumables (filters, cartridges, dialysate for CRRT)
- CRRT machines – increased from 24 to 40
- Increased staffing needs
  - Increased bedside dialysis for COVID+ patients
  - Staff quarantines and infections
  - Cardiac perfusionists assistance for management of CRRT machines
  - Agency HD nurses
- Expansion of clinical services
  - Geolocalized model with careful census tracking to allow rapid reconfiguration
  - Expansion of services to limit individual census and provider fatigue
Development of Decision Support Tools
allowed for changes to be informed by census and utilization rates

CUIMC Census Tracker

Enterprise wide supplies Tracker

Shared CRRT Protocol Tracker

CRRT Sharing Protocol

- Patients needing RRT exceeded CRRT and bedside HD availability
- RRT huddle to allow resource allocation across geolocalized services
- Created a shared protocol for CVVHD using a 24 hr on/off cycle
  - Limited machine downtime and nursing burden for change
  - Fewer logistical challenges of moving machines between patients across units
  - Change timed to follow a daily CRRT huddle to review resource availability
Consumable Tracking

- High cartridge turnover with increased clotting events and sharing protocol
  - Clear anticoagulation protocol
  - Tracker for monitoring available supplies and projected needed
- Increased dialysate consumption with sharing protocol
  - Track available supplies
  - Developed rounding tool to ensure to partial dialysate bag wastage
  - Use of SCUF for pts needing volume management only
  - Generation of dialysate for CVVHD using a regular HD machine

Lessons Learned

- Development of tracking tools to track census and resource availability
- Daily RRT huddle to manage allocation of RRT resources across services
- Expanded geolocalized clinical services and census tracking
- Flexible RRT delivery model
  - Shared CRRT protocols
  - Acute PD
  - Increased bedside HD
COVID-19 Pandemic
Dialysis Workload at Ochsner Medical Center

[Graph showing the dialysis workload over time, with categories such as COVID-19+ PUI, COVID-19 Death, COVID-19 precaut, D/c'ed+ Cumm.]

COVID-19 Pandemic
Dialysis Workload at Ochsner Medical Center

Dialysis Machines Pre-COVID-19 Inventory
- 38 Fresenius K/K2 (IHD, SLED)
- 6 PrismaFlex (CVVHDF)
- 25 ROs
- Total: 44 RRT + 25 ROs

COVID-19-driven Acquisitions
- 10 Fresenius K2 (IHD, SLED) (used 4)
- 4 PrismaFlex (CVVHDF) (used 4)
- 10 PrisMax (CVVHDF)
- 10 ROs (used 4)
- Total: 68 RRT + 35 ROs

≈ 50% Expansion → 20% True Growth in Activity

COVID-19 Pandemic
SLED platform at Ochsner Medical Center

Advantages
- High dialysis dose delivery, more pts treated per week
- Not dependent on dialysate solutions
- Run by ICU nurses

Limitations
- RO machines needed
- Faster than CVVHDF
- If ICU nurse not trained, long 1-1 RRT nurse needed
COVID-19 Pandemic
Dialysis Nurse Deficit

• Recruited administrators with prior training as RRT nurse
• Hiring of 10 agency nurses
• Cross-training of 3 perfusionists
• Virtual training of 10 ICU nurses

https://healthcaresalariesguide.com/

COVID-19 Pandemic
Dialysis Access

• Optimization of acute HD catheter placement
• Teams in charge
• 11 Fr, 12 Fr, 13 Fr, 14 Fr
• Dual lumen vs. trialysis catheters
• Heparin lock (5000 U/ml vs 1000 U/ml) vs TPA
COVID-19 Pandemic
Consult Team Workforce

- Added 1 Attending Physician (from 2 to 3)
- Kept 1 APP Inpatient (less ESRD Outpt.)
- 2 Fellows volunteered to help in Consults
- 1 GI Fellow helped on 1 weekend
- Doubled IM Resident support for weekends
- 1 Attending worked as ICU Sub-Attending

≈ 33% Growth

Acknowledgements

- Department of Nephrology at Ochsner Medical Center
- Dialysis nurses
- Kenneth Chauvin (ADU Nurse Manager) and Dr. P. Blemur (ADU Director)
- Fellows, Nurse Practitioners and Faculty
- Residents and Medical students
- ICU personnel, RTs, ICU nurses
- Hospital administration

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Questions

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American Society of Nephrology (ASN)

Closing Remarks

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Summary

- RRT resources were/are stretched thin during COVID pandemic
- Important to plan for the next surge/crisis
  - Inventory of available equipment
  - Available modalities
  - Available nursing resources
  - Anticoagulation strategies – heparin, citrate, other protocols
- Discuss with hospital administrators regarding projections
- Plan for worst case scenario