Practice Based Learning in CRRT: The Science and the Art
Pediatric Session

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Objectives

• Brief Epidemiology
• Challenges with Pediatric CRRT
  • Indications
  • Prescription
  • Vascular Access
  • Dose
  • Anticoagulation
  • Fluid Removal
• Outcomes
AKI Epidemiology in children

• Clarity in last 2-3 years due to 2 large pediatric studies

  • **AWARE** - The Assessment of **Worldwide Acute Kidney Injury, Renal Angina and Epidemiology**
    • 32 PICUs across 4 continents enrolled 5,297 children

  • **AWAKEN** - The Assessment of **Worldwide Acute Kidney injury Epidemiology in Neonates**
    • 24 NICUS across 4 countries enrolled 2,162 neonates
4,683 patients had complete data and were evaluated

- Ages 3 months to 25 years
- AKI developed in 26.9% of children admitted to ICU
- Moderate/Severe AKI (KDIGO Stage 2/3) in 11.6%
- Use of creatinine criteria alone missed 67.2% of AKI

Stage 2/3 AKI independently associated w/ poor outcomes

- Mortality 11% vs 2.5% (p<0.001)
- Adjusted OR for death if Stage 2/3 AKI 1.77 [1.17 – 2.68]
- Increased need for mechanical ventilation and RRT
• 2,022 patients had complete data and were evaluated
  • Age = 0 (gestational ages 22-36+ weeks)
  • AKI developed in 25.2% of eligible neonates
  • Moderate/Severe AKI (KDIGO Stage 2/3) in 15.7%
  • Use of creatinine criteria alone missed at least 33.7% of AKI

• AKI independently associated w/ poor outcomes
  • Mortality 8.4% vs. 2.4% (p<0.001)
  • Length of Stay 44.3±49.4 vs. 27.5±26.5 (p<0.001)
Indications
Indications for Pediatric RRT

• Fluid Overload (hypervolemia with pulmonary edema/respiratory failure) and/or electrolyte (metabolic) imbalance
• Uremia with bleeding and/or encephalopathy
• Acuity/Degree of Kidney Injury
  • reduction in GFR/elevated creatinine
  • reduction in urine output
• Intoxications, Inborn errors of Metabolism (IEM)
• Nutritional support

Timing of Pediatric RRT

• No adequate definition for “timing of initiation”
• Absence of a generally accepted, validated and applied AKI definition has impeded the adequate investigation of this question
• The decision to initiate RRT affected by
  • strongly held physician beliefs
  • Patient characteristics: age, race, illness acuity, and co-morbidities.
  • Organizational characteristics: country, type of institution, type of ICU, type of physician or insurance provider, and perceived cost of therapy.

Fluid Accumulation and Survival

Fluid Overload Threshold: Multivariate analysis ppCRRT Registry

Indication/Timing Recommendations

• Give plenty of fluids early
• Monitor critically ill patient’s cumulative fluid overload
• Consider initiation of renal support therapy when a patient reaches 10%
• What is the trajectory of the FO?
Vascular Access
Pediatric: Vascular Access

• CRITICAL for successful therapy
• Influences
  • Adequacy
  • Filter life
  • Staff satisfaction
Catheter Size

• Catheter Selection is determined by patient size and desired blood flow rate

• Recommended Blood Flow Rate
  • 3 – 5 mL/kg/min
# Blood Flow Ranges

<table>
<thead>
<tr>
<th>Patient weight (kg)</th>
<th>Minimum blood flow rate [mL/min (mL/h); 3–5 mL/kg/min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>100 (6000)</td>
</tr>
<tr>
<td>25</td>
<td>125 (7500)</td>
</tr>
<tr>
<td>30</td>
<td>150 (9000)</td>
</tr>
<tr>
<td>35</td>
<td>175 (10,500)</td>
</tr>
<tr>
<td>40</td>
<td>200 (12,000)</td>
</tr>
<tr>
<td>45</td>
<td>225 (13,500)</td>
</tr>
<tr>
<td>&gt;50</td>
<td>250 (15,000)</td>
</tr>
</tbody>
</table>
# Pediatric CRRT Vascular Access

## ppCRRT Registry Data

### 60-Hour Circuit Survival Rates

<table>
<thead>
<tr>
<th>Catheter Size*</th>
<th>Number of Patients</th>
<th>% Survival at 60 hours *</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>6</td>
<td>0 (p &lt;0.0000)</td>
</tr>
<tr>
<td>7</td>
<td>57</td>
<td>43 (p &lt; 0.002)</td>
</tr>
<tr>
<td>8</td>
<td>65</td>
<td>55 (NS)</td>
</tr>
<tr>
<td>9</td>
<td>35</td>
<td>51 (p &lt; 0.002)</td>
</tr>
<tr>
<td>10</td>
<td>46</td>
<td>53 (NS)</td>
</tr>
<tr>
<td>11.5</td>
<td>71</td>
<td>57 (NS)</td>
</tr>
<tr>
<td>12.5</td>
<td>64</td>
<td>60 (NS)</td>
</tr>
</tbody>
</table>

| Insertion Site H | | |
|------------------|-------------------|
| Internal Jugular | 58                | 60 (p < 0.05) |
| Subclavian       | 31                | 51 (NS)       |
| Femoral          | 260               | 52 (NS)       |

- **376 Patients**
- **1574 circuits**
  - Femoral 69%
  - IJ 16%
  - Sub-Clavian 8%
  - Not Specified 7%

*Hackbarth et al: IJAIO 30:1116-21, 2007*
Pediatric CRRT Vascular Access Survival ppCRRT Registry Data

Hackbarth et al: IJAIO 30:1116-21, 2007
Pediatric Vascular Access Options

<table>
<thead>
<tr>
<th>Patient Size</th>
<th>Catheter Size</th>
<th>Expected Blood Flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates</td>
<td>7 Fr or 2 single lumen</td>
<td>35 mL/min</td>
</tr>
<tr>
<td>3 – 6 Kg</td>
<td>7 Fr (~ 22 ga lumens)</td>
<td>35 mL/min</td>
</tr>
<tr>
<td>6 – 12 Kg</td>
<td>8 Fr (~ 20 ga lumens)</td>
<td>65 mL/min</td>
</tr>
<tr>
<td>12 – 20 Kg</td>
<td>9 Fr (~ 18 ga lumens)</td>
<td>125 mL/min</td>
</tr>
<tr>
<td>20 – 30 Kg</td>
<td>10 Fr (~ 16 ga lumens)</td>
<td>220 mL/min</td>
</tr>
<tr>
<td>&gt; 30 Kg</td>
<td>10 – 12 Fr (~ 14 ga lumens)</td>
<td>330 mL/min</td>
</tr>
</tbody>
</table>

Adapted from Cincinnati Children’s Hospital Center for Acute Care Nephrology
Acute Dialysis/CRRT/Pheresis Access Guideline
Summary: Vascular Access for Pediatric CRRT

• Put in the largest and shortest catheter when possible
  • Caveat: short femoral catheters have been shown to have high rate of recirculation in adult patients. (Little et al. AJKD 2000;36:1135-9)

• The IJ site is preferable (over femoral) when clinical situation allows

• Avoid 5Fr Catheters
Filters
Pediatric: CRRT Filter Choice

**Prismaflex Sets**
- **HF1000**
  - Set volume is 165 mL
  - Polyarylethersulfone (PAES)
  - Biocompatible
- **M100**
  - Set volume is 152 mL
  - Acrylonitrile (AN69)
  - Bradykinin release syndrome
- **M60**
  - Set volume is 93 mL
  - AN69
  - Bradykinin release syndrome

**Non-Set Filters**
- **Tubing**
  - Pediatric blood sets
  - Neonate blood sets
- **Filters**
  - RenalFlo II 400, 700, 1200
  - Diacap
  - Others
Dosing
The “Ronco Study”

- Improved survival in all patients with convective clearance of 35mL/kg/hr
- Trend towards improved survival in septic patients with convective clearance of 45mL/kg/hr
THE ATN STUDY

1124 adults in the ICU
563 had intensive therapy
561 had less-intensive therapy

<table>
<thead>
<tr>
<th>SOFA &lt; 2</th>
<th>IHD 3x weekly</th>
<th>IHD 6x weekly</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOFA &gt; 2</td>
<td>CRRT 20 ml/kg/hour</td>
<td>CRRT 35 ml/kg/hour</td>
</tr>
</tbody>
</table>

Sepsis-related Organ Failure Assessment score
The ATN Study
The RENAL Study

Figure 2. Kaplan–Meier Estimates of the Probability of Death.
Mortality at 28 days was similar in the higher-intensity and lower-intensity treatment groups (38.5% and 36.9%, respectively), and mortality at 90 days was the same (44.7%) in both groups.
CRRT Dose

• Absolutely, positively no studies in children
• In most studies all clearance is lumped
  • Dialysate, replacement, ultrafiltration = effluent = dose
• Three main dose studies in adults
• High dose (35-45mL/kg/hr) vs. Low dose (25mL/kg/hr)
  • “The Ronco Study” - more clearance better
  • “The VA/NIH Trial” - more clearance no better
  • “The RENAL Trial” - more clearance no better
• To the best of my knowledge adults will tell you there’s no need to go higher than 25mL/kg/hr
CRRT Dose Considerations

• So many factors contribute to the fact that delivered clearances are less than prescribed

• The downsides to higher clearance are
  • Cost
  • Hypophosphatemia (in the adult studies)
  • High clearance rates for amino acids and meds

• We tend to modify our fluids to approximate serum

• Often recommend dosing meds for normal renal function

• Administer aggressive nutritional supplementation
Pediatric Recommendations: Modality/Dose

• Modality
  • Machine Dependent
  • CVVHDF
    • Pre-Replacement
    • Post-Replacement (May be required)
    • Dialysate

• Dose
  • 2000 mL/hour/1.73 m²
  • 25-35 mL/kg/hour
Prescription Summary

• Blood Flow Rate: 3-5 mL/kg/min
• Dose: 2000 mL/1.73 m2/hour
  • CVVH – All replacement
  • CVVH-D – All dialysate
  • CVVH-DF – Combine replacement and dialysate
• Solution: Commercially available
  • Additives as necessary
  • Reduce errors by prescribing same bag composition (when possible)
Priming Techniques
Pediatrics' Challenge

4 Kg Infant
ECBV ~ 300 mL

1/3 of the patient blood volume outside the body
Blood Prime

• Circuit volume > 10-15% patient blood volume
  • Smaller patients (e.g. <10-15kg) require blood priming to prevent hypotension/hemodilution

• Caevet for AN 69 membranes
  • Bradykinin Release Syndrome
Risk Associated with Packed RBC

- HYPOCALCEMIC (Citrate)
- ACIDIC (Citrate)
- HYPERKALEMIC (Shelf-life)
- Without Platelets
  - Every prime you start CRRT platelets count drop
- Without Coagulation factors
  - Every prime you start CRRT coagulation factor drop.
- Rapid transfusion
  - Every prime results in an exchange transfusion in 10 min
Bradykinin Release Syndrome – AN69

• Exquisitely pH sensitive – ASSOCIATED with blood priming
• Mucosal congestion, bronchospasm, hypotension at start of CRRT
• Resolves with discontinuation of CRRT
• Thought to be related to bradykinin release when patient’s blood contacts hemofilter
• Associated with AN-69 membrane
• Protocols in place to avoid this
Blood Prime Techniques

- Techniques to prevent hypotension/hemodilution
  - Bypass Procedure
  - Bicarbonate Buffer Procedure
  - Z-Buff Procedure
  - Machine Blood Procedure
  - Circuit to Circuit Procedures
  - ~ 20 other variations
Bypass Blood Prime

Modified from Brophy, et al. AJKD, 2001
Waste Recirculation Plan:
Qb 200ml/min
Qd ~40ml/min
Time 7.5 min

Normalize pH

Normalize $K^+$

Machine Blood Prime

PRBC

Waste

Bicarbonate

CCHMC Procedure, 2012
Blood Prime

- PRBC
- NaHCO3
- Calcium Gluconate
- Waste NS Bag
- Blood Flow = 20 ml / min

Brophy et al. AJKD 2001
Blood Prime

Brophy et al. AJKD 2001
Circuit to Circuit

• Indications
  • Changing blood primed circuits

• Benefits
  • Decrease exposure to blood products
  • Decrease incidence of BRS (pH)
  • Decrease time off circuit
Circuit-to-Circuit Prime – Method 1
Circuit-to-Circuit
Cross-Prime – Method 2
Other Variation

• Albumin/Blood Prime
• Blood mixed to HCT 35-40%
• Blood transfusion (vs Blood priming)
• Other medications/additives given during the prime procedure

What is your institution doing?
Neonatal Options

• Adaptation of UF machines
  • Lower circuit volume
  • Lower blood flow rates
  • Smaller filter
Traditional Use of Aquadex

- FDA approved for ultrafiltration in 2007
- 33 cc circuit volume
- 4 kg = 10 % ECV
Adapted Aquadex

Prescription
- Blood flow at 40 ml/min
- CRRT solution additives at 30 ml/kg/hr
- Heparin anticoagulation
Children’s of Alabama (Dec 2013 – April 2015)

• 12 children received CVVH on Aquadex™
  • 5 in CICU and 7 in NICU
  • 9 for AKI and 3 for severe congenital CKD
  • median age at initiation = 30 days (IQR = 13, 38 days)
  • median weight at initiation was 3.4 kg (IQR = 3.0 – 4.3 kg)

• Access
  • double lumen vascular access (n=9) (4 = 8F; 4 = 7F; 1 = 6F)
  • 2 x single lumen catheters in 3 with congenital heart disease had 2 single lumen catheters.

• The median duration = 14.5 days (IQR = 10, 22.8 days).
Children’s of Alabama (Dec 2013 – April 2015)

• 101 circuits – 261 days
  • 12 new starts
  • 89 restarts
    • 59 (61%) circuits lasted 72 hours

• Prime
  • 80% Blood Prime
    • ECV > 10% (<4 kg)
    • pRBC + NaHC03 + CaCl 80% for Saline prime in 20%
    • Cross prime circuit for routine change out
  • 20% Saline Prime
Anticoagulation
Calcium is necessary for each event in the cascade.

Heparin acts in conjunction with ATIII on thrombin and FIX, FX, FXII.
Pediatric: Anticoagulation

• Crucial step in delivering the prescribed dose (reducing downtime)
• Critically ill patients are at risk for both increased and decreased clot formation simultaneously
Pediatric: Anticoagulation

• Citrate
• Heparin
• No anticoagulation
  • 50-100mL flushes every hour or continuous infusion
  • Poor circuit survival for the most part (unable to deliver therapy)
  • Hepatic dysfunction
Multi-centre evaluation of anticoagulation in patients receiving continuous renal replacement therapy (CRRT)

Patrick D. Brophy¹, Michael J. G. Somers², Michelle A. Baum², Jordan M. Symons³, Nancy McAfee³, James D. Fortenberry⁴, Kristine Rogers⁴, Joni Barnett⁵, Douglas Blowey⁶, Cheryl Baker⁷, Timothy E. Bunchman⁸ and Stuart L. Goldstein⁹

• 138 Patients in multicenter registry study
  • 442 circuits
  • Circuit survival time evaluated for three anticoagulation strategies
    • Heparin (52% of circuits)
    • Regional citrate (36% of circuits)
    • No anticoagulation (12% of circuits)
Anticoagulation

No anticoagulation
Not a good option

Anticoagulation: Heparin

• Systemic Anticoagulant
• Risk of iatrogenic hemorrhage
• Can use other extracorporeal circuit heparinization
  • ECMO – heparization targets are adequate for CRRT
  • VAD – heparization targets are adequate for CRRT
• Can utilize LMWH if patient is already on it as well
Heparin Protocol

• Heparin infusion prior to filter
• Post filter monitoring
• Heparin adjustment based upon parameters
• Bolus with 10-20 units/kg
• Infuse heparin at 10-20 units/kg/hr
• Adjust post filter ACT 180-200 seconds or PT
  • Decrease target by 40 sec if using iSTAT ACT
• Interval of checking is local standard and varies from 1-4 hr increments
Anticoagulation: Citrate

• Coagulation cascade is Ca dependent
  • Citrate infused immediately post arterial lumen of catheter
  • Citrate binds calcium in blood, interfering with coagulation
  • Downstream circuit is effectively anticoagulated
  • Normocalcemia restored by infusing CaCl systemically

• Ionized calcium levels in the circuit and patient are used to titrate citrate and calcium chloride infusion rates
Citrate Protocol

• Citrate infusion rate 1.5-2x blood flow rate
  • Liver failure infusion rate ~ 50-70% of standard (unable to metabolize calcium citrate)
  • Target circuit iCal 0.25-0.3

• Calcium chloride infusion rate 40-50% the citrate rate
  • Target patient iCal 1.1-1.3
Citrate

**Advantages**
- Extremely effective
- FFP administration has no effect on anticoagulation
- POC ICa monitoring rapid (3min)

**Disadvantages**
- Arterial limb not anticoagulated
- Metabolic alkalosis
- Hepatic failure may result in acidosis
- Citrate accumulation
- Potential need for central line for CaCl administration
- POC restrictions
Citrate Toxicity (Accumulation)

- Liver metabolizes Calcium Citrate
- Liver dysfunction leads to decreased metabolism
- Calcium citrate builds up in body
  - Patient ionized calcium remains the same
  - Total calcium increases
Citrate Toxicity

• Techniques to mitigate citrate toxicity
  • Increase clearance
  • Reset citrate/calcium at lower infusion rates
  • Increase circuit iCal target
  • Reduce Qb (less citrate required)
  • Replace replacement fluid with NS
  • Heparin (wholesale switch or low dose infusion into arterial lumen with higher circuit iCal range)
  • Look the other way
Considerations

• Multiple Citrate protocol published

• Summarized
  • Citrate is calculated by the blood flow rate
  • Calcium can be calculated by the blood flow rate or the citrate rate
  • Calcium concentrations vary from institutions
    • 8 mg/mL
    • 10 mg/mL
    • 20 mg/mL
    • 100 mg/mL
  • When adapting, ensure the rates and concentrations match your institution
Summary: Anticoagulation for Pediatric CRRT

• Heparin or citrate is better than no anticoagulation (even in liver failure, DIC, etc)

• Citrate has fewer bleeding complications

• Circuit survival means less downtime hence more delivered therapy

• Pick institutional strategy and learn to use it well
Fluid Removal Rates
Pediatric: Ultrafiltration

• What to consider when choosing a UF rate (Patient Fluid Removal Rate)
  • Current fluid balance status
  • Increased fluid needs – i.e. nutrition, blood products, medications
  • Desired 24 hour goal
  • Current hemodynamics
Basic Components and Formula

• Intake – all IV fluids, blood products, enteral feeds, IV medications, PO medications

• Output – urine, chest tubes, nasogastric tubes, bleeding, stool, drains

• Speak the same language
  • Desired fluid status
  • Net loss (negative fluid balance)
  • Net gain (positive fluid balance)
  • Even
Net Fluid Removal Rates Recommendations

• 1-3% of body weight per day
  • 10 kg patient = 12 mL/hour Max Net Removal
  • Actual removal rate would be 12 + Intake

• 1-2 mL/kg/hour
  • 10 kg patient = 10 mL/hour Max Net Removal
  • Actual removal rate would be 10 + Intake
What Would You Do? #1

What modality should I use?

• Whatever your center uses
  • 21% (CVVH), 48%(CVVHD), and 30% (CVVHDF)

• Targeted clearance
  • Hyperammonemia in NICU (CVVHD)
  • Middle molecular wt drugs (Vanc overdose, CVVH)
  • Magic cytokine clearance (CVVH)

What Would You Do? #2
I started CRRT and the blood pressure is zero

• Calcium
  • Almost always a good idea. Citrate and blood products lower serum calcium

• Volume
  • If the patient is small or patient is very volume sensitive

• Bicarb
  • If the patient is acidotic or does poorly with acidosis

• Epinephrine
  • If plans A through C don’t work
What Would You Do? #3
The patient is acidotic, can I add bicarb?

• Yes. But it may not solve the problem.
• Adding bicarb
  • Sort of like a rich man’s bicarb drip.
  • Doesn’t correct the underlying cause
  • Can cause hypernatremia
  • If ventilation is compromised it may make the bicarb better, the CO2 worse, and the pH unchanged
What Would You Do? #4
Yikes, the bicarb is 42. Can you take the bicarb out?

• Yes. If it’s been added, removing it will help.

• But if we never added any…it’s not the problem
  • Removing bicarb requires custom solutions
  • Labor and time intensive for pharmacy
  • Prone to erroneous compositions

• The alkalosis is almost always related to something that isn’t CRRT
  • Citrate (vast majority of the time)
  • TPN
What Would You Do? #5

I cranked the UF because the Intensivist said the patient was puffy and needed to look less puffy by signouts. Now the patient looks “not good”

• There’s a reason the patient is on CRRT
  • They are unstable and intolerant of fluid shifts
  • Remove fluid slowly as tolerated
  • If you overshoot, the resuscitation may leave you worse than you started
  • Big volumes (PRBCs) need to be removed over time

• If you aren’t happy with the UF, change the patient’s physiology
  • Pressors
What Would You Do? #6

My unstable 5yo with liver failure has a BUN of 105 and a creatinine of 1.2 -- should I start CRRT?

• How’s the urine output?
• Is the patient on maximal diuretics?
  • Is the patient on too much diuretic?
• How’s the blood pressure?
• Is the pt requiring or going to require tons of fluid? Are you restricting nutrition?
• Is the patient getting better or worse?
What Would You Do? #7

My unstable 8yo stem cell recipient is 16% fluid overloaded -- should I start CRRT?

• How’s the urine output?
• Is the patient on maximal diuretics?
• How’s the blood pressure?
• Is the pt requiring or going to require tons of fluid? Are you restricting nutrition?
• Is the patient getting better or worse?
• Does CRRT start with a C?