Recent advances in CRRT

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Pediatric AKI epidemiology and demographics

• Since the majority of patients receiving CRRT are critically ill children with AKI, it is important to understand AKI epidemiology which has changed over the past several decades.

• **1980** → Hemolytic uremic syndrome and other primary renal diseases, sepsis, and burns as the most common causes of pediatric AKI

• **Recently** → congenital heart disease (and corrective surgery), acute tubular necrosis (ATN), sepsis, and administration of nephrotoxic medications

→ Thus, many children with AKI now commonly have one or more co-morbid conditions

Pediatric RRT Epidemiology

- In 1995, 45% of pediatric centers in US ranked PD and 18% ranked CRRT as the most common modality used for initial AKI treatment.

- In 1999, 31% of centers chose PD versus 36% of centers reported CRRT as their primary initial modality for AKI treatment

→ The use of CRRT for initial AKI treatment is increasing!

Semin Dial. 2011
Dialysis in children

- Peritoneal dialysis
- Intermittent hemodialysis using pediatric hemofilter
- Pediatric CRRT- A first choice treatment for the critically ill children
Choice of various modalities of RRT

- Influenced by

1) Clinical status of patients
   - Hemodynamic instability → PD or CRRT than HD
   - VLBW → PD than HD

2) Specific indication of RRT
   - Inborn errors of metabolism (hyperammonemia) → CRRT

3) Underlying cause of ARF
   - Severe rhabdomyolysis with myoglobinuric ARF → CRRT

4) Clinical expertise available at each center
   - CRRT or HD nurses
CRRT in Pediatrics

• Requires an understanding of several considerations which are unique to therapy in pediatric patients including:

(1) Extracorporeal blood volume concerns
(2) The need for circuit blood priming
(3) Adaptation of equipment and prescriptions designed for adult-size patients
(4) The use of CRRT to manage conditions unique to pediatric patients, such as inborn errors of metabolism.

→ multidisciplinary team approach is important
Indications for CRRT

- Hemodynamically unstable patients with the following diagnoses may be candidates for CRRT:
  - Complications associated with AKI (90%)
    - fluid overload, uremia (encephalopathy, bleeding, pericarditis)
    - life-threatening electrolyte imbalance (hyperK, acidosis)
  - Major burns with compromised renal function
  - Drug overdose, intoxication (2%)
  - Inborn errors of metabolism (4%)

- There is no clear consensus on when CRRT should be started, though most experts tend to favor earlier starts over later ones.
Inborn errors of metabolism

• Patients with suspected inborn errors of metabolism should receive care at centers with the capacity to deliver either hemodialysis or CRRT.

• Ammonia clearance with peritoneal dialysis is inadequate, and this therapy should only be used as a last resort if no other RRT modality is available!!

• HD vs. CRRT ➔ consider hemodynamics!

• If CRRT is used in this situation, it is imperative to deliver higher clearance rates, on the order of 8,000 ml/h/1.73 m² ➔ replace electrolytes

• Equally efficacious (CVVH, CVVHD, CVVHDF)
Vascular Access

• Common sites for venous access include the internal jugular, subclavian and femoral veins.

• Dual lumen (Newborn: 7F, 3-6kg: 7 Fr, 6-30kg: 8 Fr, > 15 kg: 9 Fr, > 30kg: 10Fr – 13.5 Fr)

• The CRRT access must not be located close to other vascular access used for infusion of drugs or nutrition.
Vascular Access

- ppCRRT Registry demonstrated significantly lower circuit survival rates when
  - CRRT was delivered via: 5 and 7 French catheters
  - Catheters placed in the femoral versus internal jugular veins
  - A convective versus diffusive small clearance modality (CVVH/CVVHDF vs. CVVHD)

- Complication: air embolism or hemorrhage.

- Consideration for the potential long-term vascular needs of patients who may be expected to develop chronic kidney disease (CKD)

Semin Dial. 2011
CRRT prescription: Blood flow rate

• Blood flow rate (BFR): 3-10 ml/kg/min

• Older CRRT machines, such as Prisma system® (Gambro), have a maximal Qb → 180 ml/min.

• Higher blood flow rates (10–12 ml/kg/min) are usually necessary in neonates and small infants: 4kg → 40 ml/kg/min

• 30–80 ml/min in neonates and small infants
• 50–100 ml/min in infants 10–20 kg
• 100–150 ml/min in larger children
• 150–250 ml/min in adolescents.
CRRT prescription: Blood flow rate

• Many patients will not tolerate maximal blood flow at the initiation of CRRT and, in general,

→ It is best to advance $Q_b$ to the targeted rate over 20–30 min!
CRRT prescription: dialysate and replacement rate

- Prescribed urea nitrogen clearance:

  (1) Dialysate rate: 2 liter/1.73 m2/hr (min 500 ml/hr – max 2500 ml/hr) → 25 mL/kg/hr

  (2) Replacement rate: 2 liter/1.73 m2/hr (min 100 ml/hr – max 2000 ml/hr) → Predilution/postdilution

  (3) Net fluid removal rate: oral/IVF rate + TPN rate + desired net hourly fluid deficit

  A delivered dose → 85–100% of the prescribed dose.
The RENAL Replacement Therapy Study demonstrated equivalent survival in patients receiving higher-intensity (33.4 ± 12.8 ml/kg/h) and lower-intensity (22 ± 17.8 ml/kg/h) CRRT.

CRRT dose and considerations

- Higher-intensity CRRT has been associated both with the development of hypophosphatemia, hypokalemia and with excessive amino acid losses
  - P and K replacement and amino acid intake to 2.5–3 g/kg/day

- Higher CRRT doses may be associated with supernormal drug clearance rates
  - a reduced effective dose of most of these agents (antibiotics or vasoactive drugs)
Anticoagulation & CRRT

- Anticoagulation is needed in CRRT because the clotting cascades are activated when the blood touches the non-endothelial surfaces of the tubing and filter.

- CRRT can be run without anticoagulation, but filters last much longer if some form of anticoagulation is used.

- The physician must consider the relative risks of anticoagulation and choose the safest option for the patient.

- Options for anticoagulation include Heparin, Citrate, and no anticoagulation, nafamostat mesilate
No Anticoagulation

- Platelet count < 50,000/mm3
- INR > 2.0
- aPTT > 60 seconds
- actively bleeding or with an active bleeding episode in the last 24 hours
- severe hepatic dysfunction or recent liver transplantation
- within 24 hours post cardiopulmonary bypass
Heparin

- **Loading dose**: 10-20 units/kg prior to connecting Pt to CRRT
- **Maintenance dose**: 10-20 units/kg/hr
- **Check ACT on the venous side of hemofilter**: q 2-3 hr → q 4 hr
- **Maintain ACT**: 170-220 sec
Citrate anticoagulation

- Regional anticoagulation of the filter can be achieved through the use of Citrate.

- Citrate inhibits clotting by binding Calcium, a key cofactor in many steps of the clotting cascade.

- Since citrate is a small molecule, majority of the calcium–citrate complex is freely filtered and lost in the effluent.

    → Therefore, a systemic calcium infusion is necessary to replace the calcium lost with citrate.

- Any calcium–citrate complex remaining then returns to the patient and is metabolized to bicarbonate by the liver, kidney and skeletal muscle.
Citrate anticoagulation

- When Citrate anticoagulation is used, dialysate and replacement fluids must be calcium free.
Nafamostat mesilate

• Nafamostat is a synthetic serine protease inhibitor which inhibits activated coagulation factors thrombin, Xa and XIIa, kallikrein, and plasmin in addition to platelet.

• It is considered that nafamostat acts as a regional anticoagulant because of its very short anticoagulation effect.

• In addition, about 40% of nafamostat is removed by dialysis and/or convection in the extracorporeal circuit and is then rapidly degraded by esterases in the liver and blood.

➔ Maintenance dose: 0.1-0.5 mg/kg/hr
Complications of CRRT

- Bleeding

- Hypothermia → warming lines in small infants (avoiding body temperatures of less than 35°C)

- Electrolyte Imbalances: Hypokalemia, Hypophosphatemia

- Acid-Base Imbalances

- Infection

- Clotting in the circuit -> significant blood loss

- Nutrition problems

- Problems in drug effectiveness
Drug dosing

• Monitoring of plasma concentration especially for drugs with a narrow therapeutic index, i.e. digoxin, vancomycin, aminoglycosides

• Overdose is preferable for drugs with a wide therapeutic index (e.g., betalactam antibiotics)

• Monitor clinical effects of drugs with pharmacodynamic effects (e.g., cardiovascular agents, sedatives, analgesics)
Nutrition

• Important for not only proper growth but also minimizing morbidity and mortality.

• A significant amount of amino acids are lost during CRRT.

• Non-dialytic setting of AKI: protein requirements → about 1.5 g/kg/day.

• Patients on CRRT require protein administration of 3-4 g/kg/day in order to maintain adequate nitrogen balance.

• Adequate vitamin and trace element supplementation
CRRT outcomes

• Dependent on the underlying disease state and co-morbid conditions, the indication for initiation, and a range of clinical criteria.

• Large observational studies in adult patients: mortality in adults with AKI severe enough to require CRRT is 50–80%.

• Greater mortality risk → vasopressor support, mechanical ventilation, sepsis, severity of illness, failure of organs in addition to the kidney (heart, liver, GI, brain, lungs), and greater positive fluid balance.

Pediatr Nephrol. 2012
## CRRT outcomes

Data from Department of Pediatrics, Yonsei Univ.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survivors (n=11)</th>
<th>Nonsurvivors (n=21)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>8.4±4.7</td>
<td>7.1±4.9</td>
<td>0.457</td>
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<tr>
<td>Body weight (kg)</td>
<td>24.8±11.9</td>
<td>26.4±16.4</td>
<td>0.907</td>
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<tr>
<td>%FO at CRRT</td>
<td>5.2±6.0</td>
<td>15.0±8.9</td>
<td>0.002</td>
</tr>
<tr>
<td>PRISM III score at CRRT</td>
<td>9.8±5.3</td>
<td>26.7±7.6</td>
<td>&lt;0.0001</td>
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<tr>
<td>Maximum pressor number</td>
<td>2.1±1.2</td>
<td>3.0±1.0</td>
<td>0.038</td>
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<tr>
<td>Number of organ failure</td>
<td>2.9±1.0</td>
<td>3.3±1.0</td>
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<td>CRP on CRRT</td>
<td>11.5±13.1</td>
<td>6.0±10.5</td>
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<tr>
<td>Days on CRRT</td>
<td>12.0±9.6</td>
<td>7.6±7.0</td>
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<td>ICU days to CRRT</td>
<td>4.1±7.8</td>
<td>3.6±7.3</td>
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<tr>
<td>BUN at CRRT (mg/dL)</td>
<td>37.6±24.1</td>
<td>39.6±22.1</td>
<td>0.696</td>
</tr>
<tr>
<td>eGFR at CRRT (mL/min/1.73m²)</td>
<td>73.6±54.4</td>
<td>51.5±40.3</td>
<td>0.434</td>
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<tr>
<td>Urine output at CRRT (mL/kg/hour)</td>
<td>2.2±2.1</td>
<td>1.7±1.6</td>
<td>0.667</td>
</tr>
</tbody>
</table>

*J Korean Soc Pediatr Nephrol. 2007*
ECMO and CRRT

- Many patients who require ECMO develop AKI and fluid overload.

→ CRRT can effectively and safely be used to treat uremia and fluid overload which is refractory to other interventions.

*However, the methods of connection has not been established yet!*
Plasmapheresis with CRRT

• Plasma exchange on the Prismaflex system
→ plasma filtration with simultaneous infusion of a replacement solution.

• During TPE, plasma is removed through the large-pore membrane of plasma filter, while fresh plasma or other types of colloid solutions are infused post-plasma filter to replace the plasma removed.
As a technology of CRRT and clinical practice has been advanced, experiences using CRRT on small infants and neonates have increased.

Recently, the Cardio-Renal Pediatric Dialysis Emergency Machine (CARPEDIEM) CRRT machine was introduced

- a project developed by the Department of Nephrology and International Renal Research Institute of the San Bortolo Hospital in Vicenza (IRRIV)

- provide various treatment modalities and support for multiple organ dysfunction in neonates and small infants
Low priming volume of the circuit (less than 30 mL), miniaturised roller pumps, and accurate ultrafiltration control via calibrated scales with a precision of 1 g.

In-vitro tests confirmed that both hardware and software met the specifications.

We treated a 2.9 kg neonate with haemorrhagic shock, multiple organ dysfunction, and severe fluid overload for more than 400 h with the CARPEDIEM, using continuous venovenous haemofiltration, single-pass albumin dialysis, blood exchange, and plasma exchange.

The patient’s 65% fluid overload, raised creatinine and bilirubin concentrations, and severe acidosis were all managed safely and effectively.

Despite the severity of the illness, organ function was restored and the neonate survived and was discharged from hospital with only mild renal insufficiency that did not require renal replacement therapy.
Conclusions

• CRRT can replace excretory renal function with a minimum of hemodynamic instability in critically ill patients.

→ became the preferred modality to treat AKI and fluid overload in critically ill children!!

• CRRT allows for optimal alimentation and administration of fluids and medications that would be limited if intermittent therapies were used.

• Optimal outcomes are dependent upon a well-educated and cohesive multidisciplinary team.
Conclusions

- However, there are many limitations in clinical practice such as
  (1) Vascular access
  (2) Bleeding complications
  (3) Lack of neonate-specific devices.

- Moreover, the data on pharmacokinetics of drugs and nutrition in children receiving CRRT are lacking.

- Considering the rarity of pediatric AKI, multicenter study is required to perform prospective randomized trials to evaluate the effect of CRRT dose and modality on patient outcome and to assess CRRT pharmacokinetics in the future.