CRRT in the Newborn: Principles and Practical Issues

David Askenazi MD MSPH

Jordan M Symons MD
Outline of the Presentation

• Acute kidney injury in the neonate
• Technical aspects of CRRT for the newborn
• CRRT for the neonate with metabolic disorders
• CRRT for intoxications
Acute Kidney Injury in the Neonate: Definitions and Epidemiology

David Askenazi MD MSPH
Background

- How do we define Acute Kidney Injury in Neonates?
- How often does AKI happen in neonates?
- If so, what is the effect?
- What if you look in the urine?
Definition of AKI

• A biological disturbance which results in a sudden deterioration of one or more functions of the kidney.
SCr-based definitions for AKI

• Small elevations of SCr are associated with mortality in numerous populations
• SCr is a surrogate of FUNCTION not INJURY
• SCr overestimates renal function due to tubular secretion of creatinine
• SCr varies by muscle mass, hydration status, sex, age, bilirubin level, medications
SCr-based definitions for Neonatal AKI

Normal Creatinine levels x gestational age

Gallini F: Pediatric Nephrology 2000 (15); 119-124
SCr-based definitions for AKI

• RIFLE (2005), AKIN (2008), KDIGO (2011)
  – Categorical definitions of AKI
  – Stage 1, 2 and 3
  – Either SCr and/or urine output criteria
Definition of Neonatal AKI

Table 1: Neonatal AKI definition

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No change or rise &lt; 0.3 mg/dl</td>
</tr>
<tr>
<td>1</td>
<td>$\uparrow$ SCr $\geq 0.3$ mg/dl or $\uparrow$ SCr $\geq 150$-$200%$ from baseline</td>
</tr>
<tr>
<td>2</td>
<td>$\uparrow$ SCr to $\geq 200$-$300%$ from baseline</td>
</tr>
<tr>
<td>3</td>
<td>$\uparrow$ SCr to $\geq 300%$ from baseline or SCr $\geq 2.5$ mg/dl or Receipt of dialysis</td>
</tr>
</tbody>
</table>

Baseline SCr will be defined as the lowest previous SCr
Neonatal AKI

Premature Neonate

Cardiopulmonary Bypass

Sick Newborn in the NICU

ECMO

Asphyxiated Infant

How Do you Define AKI?

How Often Does it Happen?

What happens to those with AKI?
18-month Prospective Study on Neonatal AKI in Premature Infants
## Difference in Survival between infants with AKI and without AKI

<table>
<thead>
<tr>
<th>AKI Category</th>
<th>Survival N = 203</th>
<th>Death N = 26</th>
<th>Crude HR</th>
<th>Adj** HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AKI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No AKI</td>
<td>179</td>
<td>9</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Any AKI</td>
<td>24</td>
<td>17</td>
<td>9.3 (4.1, 21.0)</td>
<td>2.3 (0.9, 5.8)</td>
</tr>
<tr>
<td>AKI 1</td>
<td>7</td>
<td>3</td>
<td>6.8 (1.8, 25.0)</td>
<td>2.5 (0.6, 9.8)</td>
</tr>
<tr>
<td>AKI 2</td>
<td>7</td>
<td>3</td>
<td>6.1 (1.6, 22.2)</td>
<td>1.6 (0.4, 6.1)</td>
</tr>
<tr>
<td>AKI 3</td>
<td>10</td>
<td>11</td>
<td>12.4 (5.1, 30.1)</td>
<td>2.8 (1.0, 7.9)</td>
</tr>
</tbody>
</table>

**controlled for Gestational age, Birth weight, High frequency ventilation**
Sick infant admitted to the NICU

• Prospective cohort study
• Neonates admitted to Level 2 or 3 NICU
  – No congenital anomalies of the kidney
  – Birth weight > 2000 grams
  – 5 minute Apgar ≤ 7
• 9 / 58 (16%) had AKI

Askenazi et. al. Abstract at ASN 2011 - Philadelphia
Sick infant admitted to the NICU

Outcomes of Infants with and without AKI

<table>
<thead>
<tr>
<th></th>
<th>No AKI (n=49)</th>
<th>AKI (n=9)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 3 weight</td>
<td>2683 ± 781</td>
<td>3890 ± 1314</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% Fluid Change*</td>
<td>-2.8 ± 7.0</td>
<td>12.0 ± 14.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>at Day 3 of life</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DC Weight</td>
<td>2913 ± 750</td>
<td>3719 ± 1315</td>
<td>0.01</td>
</tr>
<tr>
<td>Survive</td>
<td>49 / 49 (100)</td>
<td>7 / 9 (77.8)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

% fluid change at day 3 = [1 - (wt @ day 3/ birthweight)] * 100

Askenazi et. al. Abstract at ASN 2011 - Philadelphia
AKI after Perinatal Depression

• Three observational studies in newborns
  – Term infants w/ 5-minute APGAR scores ≤6
  – Definition of AKI (SCr ≥1.5 mg/dl).
  – Findings
    • Incidence of AKI = 47-66%
    • Mortality in those with AKI worse than no AKI

Karlowicz, Pediatr Nephrol 1995
Agras Pl:. Ren Fail, 2004
Infant who receives ECMO

• Retrospective chart review of infants with congenital diaphragmatic hernia on ECMO
  – 48/68 patients (71%) had AKI by the RIFLE
  – Patients with Severe AKI “failure”
    • Increased time on ECMO
    • Decreased ventilator free days
    • Decreased survival
      27.3% vs. 80% without AKI, \( P = .001 \)

Askenazi et al. Pediatric Critical Medicine 2011
**ELSO Registry**

<table>
<thead>
<tr>
<th>Table: Neonatal Mortality given AKI/ RRT</th>
<th>OR (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>5.8 (4.9, 6.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adjusted*</td>
<td>3.2 (2.6, 4.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RRT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>3.5 (3.0, 3.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adjusted*</td>
<td>1.9 (1.6, 2.2)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* adjusted for age, hours ECLS, pre-ECLS (duration vent, pH, pH<7.2, handbagging, arrest, FiO2) Ventilator type at 24hr. AKI, RRT, CPR/Heart arrest, sex, brain, seizure, pulmonary hemorrhage, liver, diaphragmatic hernia, meconium aspiration, pulmonary hypertension.
Infant who undergoes Cardio-pulmonary Bypass Surgery

- Retrospective chart review of 430 infants
  - <90 days, median age 7 days) with CHD.
- AKI was defined using a modified AKIN definition
  - urine output criteria included)
- 225/ 430 (52%) infants with AKI

Infant who undergoes Cardio-pulmonary Bypass Surgery

Incidence of AKI

- NO AKI
- AKI stage 1

Infant who undergoes Cardio-pulmonary Bypass Surgery

- AKI of all stages was associated with longer ICU

- AKI stages 2 and 3
  - Associated with increased mechanical ventilation
  - Associated with increased post-operative inotropic therapy.

- AKI was associated with higher mortality
  - 27/225 (12%) vs. 6/205 (3%) \( P < 0.001 \)
    - Stage 2 OR for death = 5.1 (95% CI = 1.7 – 15.2), \( P = 0.004 \)
    - Stage 3 OR for death = 9.5 (95% CI = 2.9 – 30.7), \( P = 0.0002 \)

Outcomes in neonates receive RRT
Survival by Diagnosis


Totals:  N=85; Survivors=32
ppCRRT Data of Infants < 10 kg:

ppCRRT data - unpublished
ppCRRT Data of Infants < 10 kg:

<table>
<thead>
<tr>
<th></th>
<th>Survivors N = 36</th>
<th>Non-Survivors N = 48</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Gender</td>
<td>21/36 (58%)</td>
<td>30/48 (63%)</td>
<td>0.82</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>5.0</td>
<td>5.2</td>
<td>0.71</td>
</tr>
<tr>
<td>Age (days)</td>
<td>255</td>
<td>335</td>
<td>0.68</td>
</tr>
</tbody>
</table>

ppCRRT data - unpublished
ppCRRT Data of Infants < 10 kg

Primary Diagnoses

- Primary Sepsis: 35%
- GI/Hepatic Disease: 21%
- Cardiac Disease: 19%
- Inborn Error of Metabolism: 15%
- Primary Pulmonary Process: 10%

ppCRRT data - unpublished
ppCRRT Data of Infants < 10 kg: Demographic Information

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Survivor</th>
<th>Non-Survivor</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Airway Pressure (at CRRT Conclusion)</td>
<td>11</td>
<td>20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pressor Dependency (throughout CRRT)</td>
<td>36%</td>
<td>69%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>GI/Hepatic disease (present at CRRT start)</td>
<td>8%</td>
<td>31%</td>
<td>0.01</td>
</tr>
<tr>
<td>Urine output (ml/kg/hr) (at CRRT start)</td>
<td>2.4</td>
<td>1.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Multiorgan system failure</td>
<td>68%</td>
<td>91%</td>
<td>0.04</td>
</tr>
<tr>
<td>PRISM score (at ICU admit)</td>
<td>16</td>
<td>21</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

ppCRRT data - unpublished
Survival Differences by Fluid Overload in Infants < 10 kg enrolled in ppCRRT

ppCRRT data - unpublished
What if we look in the urine?
### Baseline Values of AKI Biomarkers Vary by Gestational Age.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N=52</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NGAL (ng/mL)</td>
<td>351</td>
<td>231</td>
<td>145</td>
<td>85</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(271, 456)</td>
<td>(161, 333)</td>
<td>(96, 218)</td>
<td>(53, 134)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-18 (pg/mL)</td>
<td>42</td>
<td>41</td>
<td>30</td>
<td>67</td>
<td>0.57</td>
</tr>
<tr>
<td>(2.0 , 67)</td>
<td>(21, 81)</td>
<td>(14, 63)</td>
<td>(29, 155)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KIM-1 (pg/mL)</td>
<td>226</td>
<td>158</td>
<td>155</td>
<td>143</td>
<td>0.04</td>
</tr>
<tr>
<td>(184, 277)</td>
<td>(117, 212)</td>
<td>(112, 213)</td>
<td>(99, 207)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cys-C (ng/mL)</td>
<td>911</td>
<td>457</td>
<td>230</td>
<td>133</td>
<td>0.01</td>
</tr>
<tr>
<td>(570, 1454)</td>
<td>(195, 1069)</td>
<td>(87, 608)</td>
<td>(27, 657)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPN (ng/mL)</td>
<td>177</td>
<td>121</td>
<td>145</td>
<td>83.5</td>
<td>0.13</td>
</tr>
<tr>
<td>(142, 221)</td>
<td>(81, 181)</td>
<td>(92, 229)</td>
<td>(40, 177)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B2mG (ug/mL)</td>
<td>0.8</td>
<td>1.0</td>
<td>0.9</td>
<td>0.3</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>(0.7, 1.0)</td>
<td>(0.7, 1.4)</td>
<td>(0.6, 1.3)</td>
<td>(0.1, 0.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Geometric Mean (95% confidence interval) for all urine measurements

N = number of subjects

Askenazi et al. Pediatric Research July 2011 (Vol. 70 (3))
Urine AKI Biomarkers predict AKI in Children after Cardiopulmonary Bypass
Urine Biomarkers Predict AKI in VLBW Infants

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>No AKI (n = 21)</th>
<th>AKI (n = 9)</th>
<th>p-value</th>
<th>ROC AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGAL*</td>
<td>458 (210,587)</td>
<td>985 (452,1398)</td>
<td>0.01</td>
<td>0.80</td>
</tr>
<tr>
<td>KIM-1*</td>
<td>835 (311,775)</td>
<td>867 (252,1145)</td>
<td>0.90</td>
<td>0.50</td>
</tr>
<tr>
<td>IL-18*</td>
<td>307 (73,399)</td>
<td>754 (90,975)</td>
<td>0.43</td>
<td>0.60</td>
</tr>
<tr>
<td>Osteopontin*</td>
<td>217 (115,280)</td>
<td>468 (247,655)</td>
<td>&lt;0.01</td>
<td>0.83</td>
</tr>
<tr>
<td>Cystatin C *</td>
<td>2150 (219,3930)</td>
<td>3889 (2130,5790)</td>
<td>&lt;0.06</td>
<td>0.73</td>
</tr>
<tr>
<td>β₂ MG (µg/mL)</td>
<td>2.1 (0.9,2.7)</td>
<td>1.5 (1.2,1.7)</td>
<td>&lt;0.06</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Askenazi et al. J Ped July 2011
Urine Biomarkers Predict Mortality in VLBW Infants

<table>
<thead>
<tr>
<th></th>
<th>Survivors (n = 100)</th>
<th>Non-Survivors (n = 23)</th>
<th>p-value</th>
<th>ROC AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGAL</td>
<td>395 (189,662)</td>
<td>493 (283,1484)</td>
<td>0.11</td>
<td>0.61</td>
</tr>
<tr>
<td>KIM-1</td>
<td>263.9 (147,549)</td>
<td>385 (231,1028)</td>
<td>&lt;0.03</td>
<td>0.65</td>
</tr>
<tr>
<td>IL-18</td>
<td>162 (55,435)</td>
<td>158 (84,450)</td>
<td>0.64</td>
<td>0.47</td>
</tr>
<tr>
<td>Osteopontin</td>
<td>230 (112,371)</td>
<td>482 (281,631)</td>
<td>&lt;0.01</td>
<td>0.78</td>
</tr>
<tr>
<td>Cystatin C</td>
<td>2030 (717,4459)</td>
<td>1884 (400,4589)</td>
<td>0.87</td>
<td>0.51</td>
</tr>
<tr>
<td>β2 MG (μg/mL)</td>
<td>1.8 (1.1, 2.5)</td>
<td>1.7 (0.9, 3.0)</td>
<td>1.0</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Askenazi et al. J Ped July 2011
<table>
<thead>
<tr>
<th>Urine Biomarkers in Term Neonates with Perinatal Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td>NGAL (pg/mL)</td>
</tr>
<tr>
<td>Cys C (pg/mL)</td>
</tr>
<tr>
<td>Osteopontin (pg/mL)</td>
</tr>
<tr>
<td>EGF (pg/mL)</td>
</tr>
<tr>
<td>Uromodulin (pg/mL)</td>
</tr>
<tr>
<td>Albumin (pg/mL)</td>
</tr>
<tr>
<td>B2Mg (pg/mL)</td>
</tr>
<tr>
<td>KIM-1 (pg/mL)</td>
</tr>
</tbody>
</table>
Biomarkers of AKI in Term Newborns

- Cohort of term Neonates with 5 min Apgar ≤ 7
- Cases - 9 AKI
- Controls - 24 no AKI
- Urine NGAL at DOL 1 - 3

Askenazi et al. CRRT meeting Abstract 2012
CRRT for the Newborn: Special Issues Regarding Technique

Jordan M Symons MD
CRRT for Infants: A Series of Challenges

- Small patient with small blood volume
- Equipment designed for bigger people
- No specific protocols
- Complications may be magnified
- No clear guidelines
Potential Complications of Infant CRRT

- Volume related problems
- Biochemical and nutritional problems
- Hemorrhage
- Infection
- Thermic loss
- Technical problems
- Logistical problems
- Medico-legal problems
Infant CRRT: Choices for Vascular Access

- Single-lumen 5Fr (2 caths)  Can’t find ‘em & don’t work
- Double-lumen 7 Fr
- Triple-lumen 7 Fr  Not so good
- Umbilical catheters  Suboptimal
- Double-lumen 8Fr permanent
Circuit Survival by Catheter Size

Hackbarth R et al: IJA/O December 2007
Neonatal CRRT Prescription
Neonatal CRRT Prescription: Too Much of a Good Thing?

• Neonatal solute clearances limited only by vascular access
• Rapid depletion of electrolytes, amino acids, water soluble vitamins, trace minerals.
• Supplementation guidelines are needed!
Amino acid losses

- 6 pediatric patients
- Prospective crossover design
- Caloric intake 20-30% above energy expenditure.
- Protein 1.5 g/kg/day
- 2 L/hr/1.73 m2 of dialysate or filtered replacement fluid
- Amino acid clearances were greater on CVVH than CVVHD
- Amino acid loss on CVVH and CVVHD was similar (12.50 ± 1.29 g/day/1.73 m2 vs. 11.61 ± 1.86 g/day/1.73 m2), representing 12% and 11%, respectively, of the daily protein intake.

Choosing $Q_B$ for Pediatric CRRT

Choose blood flow rate ($Q_B$) of 3-5ml/kg/min, or:

- 0-10 kg: 25-50ml/min
- 11-20kg: 80-100ml/min
- 21-50kg: 100-150ml/min
- >50kg: 150-180ml/min

CRRT device may affect choices for $Q_B$
Anticoagulation for Infant CRRT

- Heparin
- Citrate
- Nothing
- ? Other things ?
Blood Prime for Neonatal CRRT
Blood Prime for Pediatric CRRT

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

• Example
  – 5 kg infant : Blood Volume = 400 cc (80/kg)
  – Extracorporeal circuit volume = 100 ml
  – Therefore 25% extracorporeal volume

• Technique: prime first with saline, then blood/albumin mix to Hct of ~35%
Blood Prime Increases Risks

- Blood product exposure – possibly repeated
- Biochemical imbalances
  - HYPOCALCEMIA
    - Citrate anticoagulant in the PRBCs
  - HYPERKALEMIA
    - K+ release from RBCs – more over time (older unit)
  - ACIDEDEMIA
- Increases risk for bradykinin release syndrome
Bradykinin Release Syndrome

- 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
- Exquisitely pH sensitive
- Associated with AN-69 membrane
Technique Modifications to Prevent Bradykinin Release Syndrome

- Buffered system: add CaCl, NaBicarb to PRBCs
- Bypass system: prime with saline, run PRBCs into patient on venous return line
- Recirculation system: recirculate blood prime against dialysate
- Double CRRT restart (cross-prime)
Bypass System to Prevent Bradykinin Release Syndrome

Recirculation System to Prevent Bradykinin Release Syndrome

Recirculation Plan:
Qb 200ml/min
Qd ~40ml/min
Time 7.5 min

Normalize pH

Normalize K+

Neonatal Double CRRT Restart

- “Cross prime” from active circuit to new circuit
- No new units of blood from blood bank
- Blood in system already equilibrated to patient
- Need several more hands
- Only good for restarts when current circuit still functioning
Neonatal Double CRRT Restart
Neonatal Double CRRT Restart
Simple Systems to Limit Likelihood of Bradykinin Release Syndrome

Don’t prime on with blood
Don’t use the AN-69 membrane
CRRT Machines
“WARNING: Only intended for patients weighing 20 kilograms or more.”

“Just pull off the sticker”

“Explain it to the family”

“Get a new device”

“Stand in front of it all day long”
A Dedicated Neonatal CRRT Machine?

- Lines and filters to limit extracorporeal blood volume
- Hardware and software accurate for low flows and low UF volumes
- Dedicated rather than adapted
- Safe and reliable

Claudio Ronco with the Cardio Renal Pediatric Dialysis Emergency Machine (CARPEDIEM)
The Infant with Inborn Error of Metabolism: Role of CRRT

David Askenazi MD MSPH
Inborn Errors of Metabolism

- Example
- Background
- DDx
- Goals of therapy
- Toxin Removal Procedure
Inborn Error of Metabolism

- 2.9 kg infant presents at 48 hours of life with lethargy.
- Child is afebrile, BP is 75/40, HR of 130 BPM, RR of 50 BPM
- On exam “floppy” infant with poor neurologic tone
Inborn Error of Metabolism

• Normal laboratory data shows of
  – H/H of 15/45; Cr of 0.9 mg/dl (maternal), K of 4.3 mg/dl, Ca of 9.5 mg/dl, Phos of 6.0 mg/dl (nl)

• Abnormal laboratory data shows
  – CO2 of 14 mg/dl and a ammonia of 1533 micromls/l (nl < 40)
Presentation

• Lethargy and poor feeding
  – Initial thought sepsis
• Respiratory distress or apnea
  – Central in origin from encephalopathy
  – Tachypnea
    • Metabolic acidosis (organic aciduria)
    • Central hyperventilation -> resp alkalosis (urea cycle defect)
• Acute metabolic encephalopathy
  – Toxic effects of accumulating metabolites in the CNS
  – Seizures, abnormal muscle tone
  – Cerebral edema, intracranial hemorrhage occasionally
DDX - Infant Hyperammonemia

- Urea cycle disorders
- Transient hyperammonemia of the newborn
- Organic acidemias
- Fatty acid oxidation defects (older infant)
- Severe liver parenchymal or vascular disease
Inborn Errors of Metabolism

• Abnormality or absence of enzyme or cofactor leading to accumulation or deficiency of specific metabolite
• Affect 1 in 30,000 to 40,000 live births
• Optimal outcome depends on early recognition, prompt evaluation and treatment
• Neurological prognosis related to *DURATION* of coma and peak NH3 level
Why is ammonia bad for the brain?

“Because ammonia is what you clean your table with….”

Stuart Goldstein
2/25/2010
Goals in treatment

• Diagnosis (sending the labs: Genetics Service)

• Decrease Toxin Production
  – Discontinuation of protein intake
  – Prevent catabolism
    • IV glucose
    • insulin

• Removal of accumulating metabolites
  – Organic acid intermediates
  – Ammonia
Decrease Toxin Production

- Branched chain organic acidemias
  - High calorie, protein free nutrition
  - Hydration
  - Slow correction of acidosis
  - Insulin to treat catabolism
  - L-carnitine supplementation
  - Vitamin B12 (MMA) or Biotin (carboxylase deficiency)
  - L-glycine if suspect iso-valeric acidemia (particular odor)
Decrease Toxin Production

- **Urea cycle defects**
  - Parenteral high energy, protein free nutrition
  - Sodium benzoate and sodium phenylbutyrate
  - Hydration
  - L arginine supplement if diagnosis unknown
  - L carnitine supplement while on sodium benzoate
  - Avoid glucocorticoids, valproic acid
  - Mannitol is ineffective for treatment of cerebral edema
Toxin Removal Procedures

• Extracorporeal therapies
  – Exchange transfusion
  – Peritoneal dialysis
  – CRRT
  – Hemodialysis
Toxin Removal Procedures

• Exchange transfusions
  – Inadequate removal procedure for metabolites distributed throughout TBW
Toxin Removal Procedures

• Peritoneal dialysis
  – Superior efficacy over exchange transfusions
  – 40-50ml/kg exchanges Q 1 hr cycles repeated over 24-36 hrs
  – Not preferred modality because of slow rate of removal
Toxin Removal Procedures

- Hemodialysis
  - Most effective/rapid method for small solute removal
  - May require multiple sessions due to rebound in circulation of toxic metabolites
  - IV phosphorus/potassium supplementation needed since patients do not have renal failure
  - Potential for hemodynamic instability with UF inaccuracies
Toxin Removal Procedures

• CRRT
  – Tolerated better in infants with hemodynamic instability, multiorgan failure, hypercatabolic state
  – Removal of toxins within hours and allow for early reintroduction of protein
  – Less risk for rebound
  – **Current recommendations**: Patients with very high ammonia should receive HD prior to CRRT
PD versus CRRT comparison

- CVVHD (7) vs. peritoneal dialysis (5)
- Patients Jan 1988-Dec 1997 with first metabolic crisis during first 4 weeks of life
- Between 1988-1993 PD
  - 15-30ml/kg fill volume
  - Dwell time 30-60 minutes
- After 1993 CVVHD
  - $Q_b = 10-30$ ml/min
  - $Q_{dialysis} = 1-5$ liters/hr

EFFECT OF BLOOD AND DIALYSATE FLOW ON IN VITRO AMMONIA CLEARANCE IN CVVHD (from Schaefer et al, 1999).

- RRT at University of Michigan from 1991 to 2000 for control of metabolic disturbances
- Diagnoses: urea cycle defects, organic acidurias, Reyes syndrome
- HD
  - Qb 5-10 ml/kg/min
  - Qd = 500 ml/min = 30,000 ml/hr
- CVVHD
  - Qb 5-8 ml/kg/min
  - Qd = 2000 ml/1.73 m2/hr
    - infant = 0.21 m2; Qd = 240 ml/hr
    - clearance is limited by Qd
- Goal ammonia <200 umol/L
Survivors received RRT earlier

- Time to RRT termination: HD $4.4 \pm 1.1$ hours, CRRT $78 \pm 69.4$ hours, $p<0.03$
- Patients who received CRRT required longer treatment and had worse outcome
  - Qd only $2000$ ml/1.73m2/hour

Table II. Clinical characteristics and outcomes overall and by class of metabolic disorder

<table>
<thead>
<tr>
<th>Overall study patients</th>
<th>Survivors (n = 9 treatments; 7 patients)</th>
<th>Nonsurvivors (n = 12 treatments; 11 patients)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mo)</td>
<td>$65.7 \pm 72.2$</td>
<td>$49.1 \pm 72.4$</td>
<td>.25</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>$22.8 \pm 22.3$</td>
<td>$15.3 \pm 16.8$</td>
<td>.65</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>6/1</td>
<td>9/3</td>
<td></td>
</tr>
<tr>
<td>$S_Cr$ at initiation of RRT (mg/dL)</td>
<td>$0.7 \pm 0.2$</td>
<td>$1.2 \pm 0.9$</td>
<td>.33</td>
</tr>
<tr>
<td>Time to RRT (d)</td>
<td>$0.5 \pm 0.5$</td>
<td>$2.5 \pm 2.9$</td>
<td>.06</td>
</tr>
<tr>
<td>Duration of medical therapy (d)</td>
<td>$0.4 \pm 0.3$</td>
<td>$2.5 \pm 3.0$</td>
<td>.06</td>
</tr>
<tr>
<td>Plasma ammonia at admission (μmol/L)</td>
<td>$464.0 \pm 336.2$</td>
<td>$527.3 \pm 622.8$</td>
<td>.65</td>
</tr>
<tr>
<td>Plasma ammonia at initiation (μmol/L)</td>
<td>$651.0 \pm 361.3$</td>
<td>$791.9 \pm 567.7$</td>
<td>.60</td>
</tr>
<tr>
<td>Duration of RRT (d)</td>
<td>$3.8 \pm 3.6$</td>
<td>$8.0 \pm 12.6$</td>
<td>.76</td>
</tr>
<tr>
<td>2-Year patient survival (Y/N/U)</td>
<td>5/1/1</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Neurologic impairment (Y/N/U)</td>
<td>3/3/1</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

The Journal of Pediatrics • June 2006
Extracorporeal dialysis in neonatal hyperammonemia: modalities and prognostic indicators

- Evaluate prognostic indicators for 10 hyperammonememic infants
  - 4 received CAVHD
  - 4 received CVVHD
  - 2 received HD

- Prescribed clearance
  - CAVHD: $Q_d = 500 \text{ ml/hr}$
  - CVVHD: $Q_d = 2000 \text{ ml/hr}$
  - HD: $Q_d = 500 \text{ ml/min}$

- Clearance calculated $K = Q_b \times (C_i - C_o)C_i$
  - $C_i$ ammonia concentration at filter inlet
  - $C_o$ ammonia concentration at filter outlet
RRT intervention

- Child was electively intubated for airway protection
- Foley catheter placed for use for urine collection and accurate I/O
- Na Pheyacetate, Na Benzoate, Arginine Cl, Carnitine were all begun once urine and plasma amino and organic acids obtained.
RRT intervention

• A 7 Fr 10 cm MedComp “softline” dual lumen vascular access placed
• HD begun using a blood prime and a Phoenix (Gambro)
  – BRF of 70 mls/min (~ 22 mls/kg/min)
  – DFR of 500 mls/min with a physiologic K and Phos bath
• Ammonia levels collected at 1 hr intervals
Ammonia Clearance

Time (hours)

Ammonia (micromol/l)

HD Begins

HD Ends
RRT intervention

• At 2 hours of HD the ammonia was ~ 200 micromls/l and HD was exchanged for CVVHDF (Gambro Prisma M 60 membrane) using the same vascular access
• A blood prime bypass maneuver was performed
• Replacement rate of 2 liters per hour and a dialysate rate of 1 liter per hour
• (HD clearance was 30 l/hr now decreased to 3 l/hr)
Ammonia Clearance

- HD Begins
- HD Ends
- HF Begins
- HF Ends

Ammonia (micromol/l) vs. Time (hours)
RRT intervention

• A few practical comments
• Ammonia is non-osmolar so no risk of dialysate disequilibrium exists
• In Born Error of metabolism infants appear to be polyuric so keeping them intubated and keeping them “wet” is important
Drug clearance

• Where as ammonia is a small molecular wt compound Na Phenylacetate and Na Benzoate are also small, non protein bound

• So will your therapy clear the drug?
Solute Clearance in I E M

![Graph showing solute clearance in different filters and dialysis modes](image-url)
Management of Acute Intoxication: Can We Use CRRT?

Jordan M Symons MD
Neonatal Intoxication

- A rare event
- Iatrogenic
- Principles from hyperammonemia (an “endogenous intoxication”) apply
- Some molecules are more readily removed than others
Creatinine 113 D
Urea 60 D
Glucose 180 D
Vit. B$_{12}$ 1,355 D
$\beta2$-M 11,800 D
Albumin 66,000 D
IgG 150,000 D

Membrane Selectivity
RRT for Intoxication: Points to Consider

• Size of molecule
• Protein binding of molecule
• Volume of distribution of molecule
  – Relates to compartment localization, ability to access the molecule
CRRT for Intoxication: A Reasonable Choice?

**MAYBE**
- Effective method for molecular clearance
  - Urea, creatinine, electrolytes
- Everything else seems to come out
  - “I need to go up on all my drips”

**MAYBE NOT**
- Diffusion: only small molecules
- Convection: only up to membrane cut-off
- Protein-bound, intra-cellular: little/no access
- “Isn’t it too slow to treat an intoxication?”
Rate of Mass Transfer with Hemodialysis

• Higher blood flow gives higher clearance

• At low flow:
  – $K \approx Q_B$
  – Big or small dialyzers the same

• In neonates:
  – Low blood flow is the rule
Rate of Mass Transfer in CRRT

- Infused fluid rate (dialysate, replacement), not blood flow, is limiting factor
- Greatly increasing fluid flow rates will increase clearance
- Can we approximate HD?

CRRT and Protein-Bound Molecules

- RRT removes molecules in aqueous phase of blood
- Protein bound molecules considered “undialyzable”
- Albumin-enhanced dialysis can permit removal of protein-bound substances
CRRT and Protein-Bound Molecules

- RRT removes molecules in aqueous phase of blood
- Protein bound molecules considered “undialyzable”
- Albumin-enhanced dialysis can permit removal of protein-bound substances
Logistical Issues for Infant CRRT

- Infrequently performed procedure in neonatal units
- Vascular access can be difficult to organize and obtain
- Neonatology staff may be unfamiliar with equipment, procedure, risks
- Written procedures may improve coordination and results of therapy
Neonatal CRRT in Seattle: How to Handle a Rare Procedure

Developed an Acute Initiation Checklist defining specific roles/actions for:

– Neonatal ICU MD
– Nephrology MD
– Neonatal ICU RN
– Dialysis RN
– IV access MD
Acute Initiation Checklist: Example

Neonatal ICU Nurse

- **Time Zero:**
  - Move pt to room with dialysis water
  - Get orders from resident for IV fluids to keep access open
- **20 – 40 min:**
  - Meet MD; discuss RRT plan
- **60 – 120 min:**
  - Meet ICU team

Dialysis Nurse

- **10 – 60 min:**
  - Arrive and begin setup
- **20 – 40 min:**
  - Meet MD; discuss RRT plan
- **60 – 120 min:**
  - Complete prime; ready for access
  - Begin RRT
  - Meet ICU team
Acute Initiation Checklist: Example

**Nephrology MD**
- **Time Zero:**
  - Contact dialysis nurse to start RRT urgently
- **10 – 20 min:**
  - Bring catheters to ICU
  - Enter orders for RRT
- **20 – 40 min:**
  - Meet ICU MDs & RNs, discuss plan
- **60 – 120 min:**
  - Present in ICU for initiation
  - Meet ICU team

**IV Access MD**
- **10 – 30 min:**
  - Arrive and begin insertion of dialysis access
- **60 min (or when circuit is ready for Rx):**
  - Complete insertion of access
  - Connect ports to heparin IV solutions
State of the Art for Infant CRRT: Summary

• CRRT can be an effective therapy for even the smallest patients
• Overall survival comparable to larger children - skewed to selected diagnoses
• Neonates with metabolic disorders or intoxications may benefit from CRRT
• Multiple challenges remain on several fronts
• The possibility of a dedicated device for neonates may open further options
Thanks!