AKI and CRRT in the Neonate

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We hope to cover

- Epidemiology of AKI / RRT
- Technical Aspects of RRT in the newborn
- RRT in the setting of In-Born Error of Metabolism
Epidemiology of AKI / RRT

- How do we define neonatal AKI?
- How often does AKI happen?
- What are the outcomes after AKI / RRT?
## GFR by Inulin Clearance

<table>
<thead>
<tr>
<th>AGE</th>
<th>ml/min/1.73m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 days</td>
<td>14.0±5</td>
</tr>
<tr>
<td>1-7 days</td>
<td>18.7±5.5</td>
</tr>
<tr>
<td>4-8 days</td>
<td>44.3±9.3</td>
</tr>
<tr>
<td>3-13 days</td>
<td>47.8±10.7</td>
</tr>
<tr>
<td>1.5 – 4 mo</td>
<td>67.4±16.6</td>
</tr>
</tbody>
</table>
### GFR by Inulin Clearance

<table>
<thead>
<tr>
<th>Term infants</th>
<th>ml/min/1.3m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
<td></td>
</tr>
<tr>
<td>1-3 days</td>
<td>20.8±5.0</td>
</tr>
<tr>
<td>4-14 days</td>
<td>36.8±7.2</td>
</tr>
<tr>
<td>1-3 mo.</td>
<td>85.3 + 35.1</td>
</tr>
<tr>
<td>4-6 mo.</td>
<td>87.4±22.3</td>
</tr>
<tr>
<td>7-12 mo.</td>
<td>96.2+12.2</td>
</tr>
<tr>
<td>1-2 years</td>
<td>105.2±17.3</td>
</tr>
</tbody>
</table>

Schwartz G, Furth S. Pediatric Nephrology Feb 2007
Background - Glomerular Filtration Rate (GFR)

Background – GFR in infants

Background – GFR in infants

Finney: Arch Dis of Children 2000
Background – GFR in infants

Finney: Arch Dis of Children 2000
How should we define AKI in Newborns?

- SCr of 1.5 mg/dl - historically
- Need for dialysis - historically

?
Problems with Creatinine as a marker of AKI

- SCr is a marker of function – not injury
- SCr may not change until 25-50% of the kidney function has been lost
- SCr will overestimate renal function due to tubular secretion of creatinine.
- SCr varies by muscle mass, hydration status, sex, age and gender
- Once a patient receives dialysis, SCr can no longer be used to assess kidney function since SCr is easily dialyzed.
Additional problems with SCr in neonatal AKI

- SCr in the first few days of life reflects mother
- Normal kidney development in healthy term infants begins eight weeks of gestation and continues until 34 weeks of gestation
Populations of Neonates at Risk for AKI in Newborns

- Premature Infant who lives in the NICU for first 3 months of life
- Term infant who is born under distress due to ischemia and/or infection
- Infant who needs cardiopulmonary bypass (CPB) for repair of congenital heart disease.
- Infant who requires Extra-Corporeal Membrane Oxygenation (ECMO)
Epidemiology of Premature Infants
Neonatal Outcomes

Changes in mortality, morbidity, and morbidity-free survival
NICHD Neonatal Research Network centers
AJOG : Feb 2007
18-month Prospective Study on Neonatal AKI in Premature Infants

- February 2008 -- August 2009
- RNICU (UAB) and Children’s Hospital of Alabama
- Serum Creatinine
  - Measured on remnant samples (blood gas) run by mass spectrometry – 10 ul
  - Ordered by clinician

Koralkar et al. Pediatric Research 2011
## Neonatal AKI Definition

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum Creatinine</th>
</tr>
</thead>
</table>
| I     | ↑ SCr ≥ 0.3 mg/dl from previous value within 48 hours  
       | ↑ SCr ≥ 150-200% from previous value |
| II    | ↑ SCr ≥ 200%-300% from previous value |
| III   | ↑ SCr ≥ 300 % from previous value or  
       | SCr ≥ 2.5 mg/dl  
       | Receipt of Renal Replacement Therapy |
AKI any time

AKI 0 (83%)
AKI 1 (4%)
AKI 2 (4%)
AKI 3 (9%)

Koralkar et al. *Pediatric Research* 2011
### Difference in Survival between infants with AKI and without AKI.

<table>
<thead>
<tr>
<th>AKI Category</th>
<th>Survival</th>
<th>Death</th>
<th>Crude HR (95% CI)</th>
<th>Adj** HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AKI</td>
<td>203</td>
<td>26</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
Epidemiology of Sick Term Newborns
AKI in Asphyxiated Newborns

- APGAR ≤ 6 pick up most cases of renal failure
- Definition of AKI = SCr ≥ 1.5 mg/dl

Results

- AKI incidence = 50-60%
- AKI is non-oliguric in 60-80%
- Mortality in AKI = 17-25%

Gupta Indian Pediatr 2005;42(9):928-34
Agras PI: Ren Fail 26:305-309, 2004
AKI in newborns with low 5 minute APGAR - SUMMARY

- AKI happens in 50-60% of those with 5-minute Apgar \( \leq 6 \)
- Non-oliguric AKI is common
- Mortality in those with AKI 15-25%
Epidemiology of Infant who undergoes CPB surgery

Single Center Studies – different populations, definitions and interventions

- Estimated incidence of AKI – 30-40%
- Studies report high mortality rate ranging from 20-79% in those with AKI.

Reviewed in:
Coming soon.....ASSESS AKI

- The assessment, serial evaluation, and subsequent sequelae of acute kidney injury.
Epidemiology of Infant who receives ECMO
Outcomes in CRRT/ EMCO in Neonates

- Conflicting Reports
CRRT/ECMO in Cardiac Newborns

- Shah SA et al. ASAIO J 2005
  - 41/84 (48.9%) post-operative congenital heart disease patients with AKI
    - CVVH NOT associated with:
      - Ability to wean off ECMO
      - Survival to discharge

  - 26/74 (35%) post-operative congenital heart disease patients
    - Hemofiltration = 5.01 X increased risk of death
CRRT/ECMO – Noncardiac Children

  - Case-control study
    - Cases 26/86 - received CVVH for >24 hours
    - Controls 26 – no CVVH
  - Significant differences in fluid balance
  - Significant treatment differences
  - No difference in survival or vent days during or after ECMO
CRRT/ECMO Outcomes

  - 15/35 neonatal and pediatric survived
    - 14/15 (93%) RENAL RECOVERY
    - 1/15 (7%) – Wegener’s
Extracorporeal Life Support Organization (ELSO) Registry

- Most US ECLS (extracorporeal life support) centers enrolled since 1990
  - 1998-2008 data
  - 8958 patients age ≤ 30 days
    - Non-Survivors = 2182 (27.4%)
    - Survivor = 5776 (72.6%)

Askenazi et al. Pediatric Critical Care Medicine 2010 (in press)
Extracorporeal Life Support Organization (ELSO) Registry

- AKI Categorically defined
  - Complication code of SCr ≥ 1.5 mg/dl or
  - ICD-9 code of Acute renal failure

- Dialysis
  - CPT codes used

- Survival

- Demographics, Complications, Co-Morbidities and Interventions

Askenazi et al. Pediatric Critical Care Medicine 2010 (in press)
ELSO Registry - Neonates

Askenazi et al. Pediatric Critical Care Medicine 2010 (in press)
ELSO Registry - Neonates

Number of Survivors

<table>
<thead>
<tr>
<th>Neither</th>
<th>RRT</th>
<th>SCr &gt; 1.5 mg/dl</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>4734</td>
<td>817</td>
<td>116</td>
<td>109</td>
</tr>
</tbody>
</table>

Askenazi et al. Pediatric Critical Care Medicine 2010 (in press)
ELSO Registry

Table: Neonatal Mortality given AKI/ RRT*

<table>
<thead>
<tr>
<th></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>2.0 (2.3, 2.7)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* adjusted for age, days before ECLS, hours ECLS, pre-ECLS (duration vent, pH, pH<7.2, arrest), FiO2 at 24 hrs. AKI, RRT, CPR/Heart arrest, center category, sex, brain, seizure, pulmonary hemorrhage, infection, liver, % dialysis category, mode category, diaphragmatic hernia, meconium aspiration, pulmonary hypertension.

Askenazi et al. Pediatric Critical Care Medicine 2010 (in press)
Outcomes in neonates receive RRT
Survival by Diagnosis

Survivors

TOTALS: N=85; Survivors=32

36% Congen Ht Dz
71% Metabolic
15% Multiorg Dysfxn
42% Sepsis
22% Liver failure
0 Malignancy
50% Congen Neph Synd
0 Congen Diaph Hernia
50% HUS
50% Ht Failure
100% Obstr Urop
0 Renal Dyspl
60% Other

ppCRRT Data of Infants <1 Month: Demographic Information

- 35 children
  - 22 boys, 13 girls
  - Median age 8 days old
    - Youngest <1 day
  - Median weight 3.2 kg
    - Smallest 1.3 kg
## ppCRRT Data of Infants < 1 Month: Indications for CRRT

<table>
<thead>
<tr>
<th>Indication</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid Overload and Electrolyte Imbalance</td>
<td>13</td>
</tr>
<tr>
<td>Fluid Overload Only</td>
<td>6</td>
</tr>
<tr>
<td>Electrolyte Imbalance Only</td>
<td>5</td>
</tr>
<tr>
<td>Other (Endogenous Toxin Removal)</td>
<td>11</td>
</tr>
</tbody>
</table>

N=35
## ppCRRT Data of Infants < 1 Month: Primary Disease Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inborn Error of Metabolism</td>
<td>11</td>
</tr>
<tr>
<td>Cardiac</td>
<td>8</td>
</tr>
<tr>
<td>Sepsis</td>
<td>4</td>
</tr>
<tr>
<td>Hepatic</td>
<td>3</td>
</tr>
<tr>
<td>Ischemic ATN</td>
<td>3</td>
</tr>
<tr>
<td>Renal</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
</tr>
</tbody>
</table>

N=35
ppCRRT Data: Infants < 1 Month Overall Survival

N = 35

57% Non-Survivors
43% Survivors
ppCRRT Data of Infants < 1 Mo: Survival by Disease Category

- **Inborn Error**: 73% survivors
- **Cardiac**: 25% survivors
- **Sepsis**: 0% survivors
- **Hepatic**: 0% survivors
- **Ischemic ATN**: 33% survivors
- **Renal**: 100% survivors
- **Other**: 33% survivors

Totals: N=35  Survivors=15
CRRT in Infants <10Kg: Outcome

- Patients ≤10kg: 38% Survival, 85 N, 32 Survivors
- Patients 3-10kg: 41% Survival, 69 N, 28 Survivors
- Patients ≤3kg: 25% Survival, 16 N, 4 Survivors

Objectives

- How do we define acute kidney injury in neonates?
- How often does AKI happen?
- Is AKI associated with bad outcomes?
Objectives

- How do we define acute kidney injury in neonates?
- How often does AKI happen?
  - ~ 50% in those with APGARs <= 6
  - ~ 20% of the time in those < 1500 grams
  - ~ 45% -- if BW < 750 grams or ≤ 26 wks GA
- Is AKI associated with bad outcomes?
Objectives

- How do we define acute kidney injury in neonates?
- How often does AKI happen in premies?
- Does AKI predict outcomes in this population? **YES !!! Is very strongly associated?**
CRRT in Neonates: Technical Issues

- Challenges
- Access
- Hardware
- Blood Primes
- Prescription
- Anticoagulation
Neonatal CRRT: Ronco, 1984
CRRT for Neonates: 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
- Limited outcome data
Potential Complications of Neonatal CRRT

- Volume related problems
- Biochemical and nutritional problems
- Hemorrhage, infection
- Thermic loss
- Technical problems
- Logistical problems
Vascular Access in Neonates
CRRT Access in the Newborn: What are your choices

- Size and type
- Location
Flow

- **Pousielle’s Law**
  \[ Q = \frac{\Delta P \pi r^4}{8 \eta l} \]

- Smaller diameters = greater resistance to flow
- Longer lengths = greater resistance to flow
- Decreasing the diameter by 1/5th is the same as doubling the length
CRRT Access in the Newborn: What are your choices

- Size and type
  - Hemodialysis Line: 7 Fr/ 8Fr DLC
  - Two single lumen lines:
    - 5 Fr catheters or introducers
  - Umbilical lines:
    - 5 Fr UAC; 7 Fr UVC
Vascular Access

Shorter life span for 7 and 9 French catheters (p< 0.002)

Hackbarth R et al: *IJAIO* 30:1116-21, 2007
CRRT in Newborns < 10kg

Goldstein SL et al: *IJAIO* 2006
CRRT Access in the Newborn: What are your choices

- **Location**
  - Femoral
  - Subclavian
  - Internal Jugular
  - Umbilical
ppCRRT Data of Infants < 1 Month: Vascular Access Location

- Femoral: 29%
- Internal Jugular: 53%
- Subclavian: 9%
- Other: 9%

N = 35
Vascular Access - Femoral

Pros:
- Accessible under almost any conditions
- Easier to maintain hemostasis

Cons:
- Potential for kinking
- More recirculation
- Thrombosis
- Problematic flow with increased abdominal pressures
Vascular Access – Subclavian

- Pros:
  - Shorter catheter/better flow
  - Less recirculation

- Cons:
  - Potential for kinking
  - Difficult hemostasis
  - Potential for venous narrowing

- **Pros:**
  - Shorter catheter/better flow
  - Less recirculation

- **Cons:**
  - Difficult hemostasis
  - Catheter length problematic in small infants
Vascular Access – Umbilical

■ Pros:
  □ Bedside procedure
  □ Neonatologists love them

■ Cons:
  □ They don’t work!
Shorter life span for Femoral and Subclavian (p<0.05)

Summary: Access in Neonates

- Don’t use a 5 French catheter
- 8 F catheter. 7 F catheter in really small ones
- Choose the largest diameter that is safe
- Choose the minimum length possible
- Right IJ is optimal??
- “Without access, you may as well stay home”
- What type of access do surgeon’s get for ECMO?
- 8 F cuffed IJ is standard at our institution
  - Smallest baby – Hyperammononemia – 1.7 kg
CRRT for Neonates
The Hardware
Question

- Which current machinery in North America is approved for CRRT in Neonates?
None
CRRT Machines: Current Generation
# CRRT Filter Sets for Prisma

<table>
<thead>
<tr>
<th></th>
<th>Surface Area</th>
<th>Priming Volume</th>
<th>Membrane</th>
</tr>
</thead>
<tbody>
<tr>
<td>M-10*</td>
<td>0.042m²</td>
<td>50ml</td>
<td>AN-69</td>
</tr>
<tr>
<td>M-60</td>
<td>0.6m²</td>
<td>90ml</td>
<td>AN-69</td>
</tr>
<tr>
<td>M-100</td>
<td>0.9m²</td>
<td>107ml</td>
<td>AN-69</td>
</tr>
<tr>
<td>HF-1000</td>
<td>1.15m²</td>
<td>128ml</td>
<td>Polyarylethersulfone (PAES)</td>
</tr>
</tbody>
</table>

* Not available in US
Thermal Regulation

- Hotline® blood warming tubing
- Place at venous return to patient
- Leave on at set temperature of 39 °C
- Treat temp elevations if they occur
Blood Prime for Neonatal CRRT
Pediatric CRRT Circuit Priming

- Heparinized (5000 units/L) for most patients
- Smaller patients require blood priming to prevent hypotension/hemodilution
  - Circuit volume $\geq$ 10-15% patient blood volume

Example
- 5 kg infant: Blood Volume = 400 cc (80/kg)
- Prisma circuit (extracorporeal volume = 92 ml)
- Therefore 24% extracorporeal volume
Added Risk for PRBC prime

- Electrolyte abnormalities
- Bradykinin Surge
Added Risk for PRBC prime

- **Packed RBCs**
  - HYPOCALCEMIC
    - Citrate
  - HYPERKALEMERIC
  - LYSIS OF CELLS
  - ACIDIC

- Protocols for initiation of CRRT use NaHCO3 and Calcium infusions around the time of initiation
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
  - Most common with AN-69 membranes
- Exquisitely pH sensitive
Technique Modifications to Prevent Bradykinin Release Syndrome

- **Buffered system**
  - THAM, NaBicarb
    - To PRBCs?
    - To membrane?

- **BABY Buffer Technique**
  - Run PRBCs into patient and use baby’s blood to prime the circuit (rather use a pH of 7.4 than 6.8)

- **Recirculation system**
  - recirculate blood prime against dialysate

- **Using other than AN-69 membrane**
Baby Buffer Technique

Blood Flow = 10 ml / min

Brophy et al. AJKD 2001
Baby Buffer Technique

Blood Flow = 10 ml / min

Brophy et al. AJKD 2001
Baby Buffer Technique

Brophy et al. AJKD 2001
Pre dialysis of blood prime in continuous hemodialysis normalizes pH and electrolytes

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

Normalize pH
Normalize K⁺
Neonatal Double CRRT Restart

- Potentially less blood exposure
- Decrease risk of Blood Transfusion
- Need several more hands
Neonatal Double CRRT Restart
Neonatal Double CRRT Restart
Neonatal CRRT Prescription
Neonatal solute clearances limited only by vascular access/maximum blood flow rate.

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 Options

- Citrate
- Heparin
Heparin: Special concern in infants

- Systemic heparinization increases risk of cerebral, pulmonary hemorrhage in patients already at high risk for those complications.
Citrate: Special concerns in infants:

• Hyperglycemia when ACD-A citrate is used.
• Effects of long-term citrate (and possibly calcium) accumulation on neonates and older children unknown.
• Premature infants have decreased citrate metabolism – consider starting at lower doses of citrate (similar to folks with liver failure)
ECMO and CRRT in the Neonate
How do you do it?
CRRT on ECMO

“Homemade” system connected to the ECMO circuit

- IV infusion pumps used to control ultrafiltrate
- (if replacement desired) IV infusion pump to add replacement fluids
- Several sites to hook into circuit each with drawbacks (shunting, bubble trap, flows)
ECMO/CRRT Homemade System
ECMO/CRRT Homemade System
CRRT on ECMO

- Standard dialysis machines
- In series with ECMO before bladder
ECMO/CRRT: RRT System
## ECMO and CRRT

<table>
<thead>
<tr>
<th></th>
<th>Hemofilter</th>
<th>CRRT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ultrafiltration control</strong></td>
<td>IV pump controlled</td>
<td>CRRT machine controlled</td>
</tr>
<tr>
<td><strong>Metabolic Control</strong></td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td><strong>ECMO Flow</strong></td>
<td>Blood Shunt - decrease ECMO flow or decreased PaO2 to patient</td>
<td>NO systemic changes</td>
</tr>
<tr>
<td><strong>Anti-coagulation</strong></td>
<td>Heparin</td>
<td>Heparin</td>
</tr>
</tbody>
</table>
CRRT on ECMO

- Anti-coagulation – Heparin
- Circuit prime
  - Can use saline prime even in tiny ones
- Watch out for too much ultrafiltration!
  - UF error hard to spot in context of hemodynamic stability provided by ECMO
  - Decreasing ECMO flows for no good reason
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:
  - 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 $\rightarrow$ 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 isovaleric 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
  - Qb = 10-30 ml/min
  - Qdialysis = 1-5 liters/hr

- 50% reduction times
  - CRRT – 2.1 to 15 hrs
    (Qb dependent)
  - PD – 6.5 to 36 hrs
    (shorter dwell times)
- Clearance linear at Qb/Qd ≤ 0.5
- Clearance at high Qb is dependent on Qd
- Association between efficacy of dialytic toxin removal and outcome

RENAL REPLACEMENT THERAPY IN THE TREATMENT OF CONFIRMED OR SUSPECTED INBORN ERRORS OF METABOLISM

Kevin D. McBryde, MD, David B. Kershaw, MD, Timothy E. Bunchman, MD, Norma J. Maxvold, MD, Theresa A. Mottes, RN, Timothy L. Kudelka, RN, BSN, and Patrick D. Brophy, MD

- 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= 2000ml/1.73m2/hr
    - infant = 0.21 m2 ; Qd = 240 ml/hr
    - clearance is limited by Qd
- Goal ammonia <200 umol/L
18 patients
21 treatments
- 14/21 received HD
  - 7 received conversion to CVVHD
  - Duration 1-3 days (mean 1.7+/−0.8)
- 6 received CVVHD
  - 3 received HD
  - Duration 1 to 9 days (mean 3.7+/−4.6)
- 1 received PD
  - Duration 2 days
Most common “complication” (HD or CVVHD): hypotension
- 15 of 21 treatment required vasopressor support
10/18 patients developed AKI
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<table>
<thead>
<tr>
<th>Demographic variable</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>14/4</td>
</tr>
<tr>
<td>Age (mo)</td>
<td>$56.2 \pm 71.0$ (2d–17 y)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>$18.5 \pm 19.2$ (1.5–52.5)</td>
</tr>
<tr>
<td>Duration of RRT (d)</td>
<td>$6.1 \pm 9.8$ (1–44)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>$1.0 \pm 0.8$ (0.3–3.1)</td>
</tr>
<tr>
<td>Ammonia at presentation (µmol/L)</td>
<td>$500.2 \pm 509.2$ (37–1869)</td>
</tr>
<tr>
<td>Ammonia at initiation of RRT (µmol/L)</td>
<td>$721.4 \pm 467.2$ (54–1650)</td>
</tr>
<tr>
<td>Time to RRT (d)</td>
<td>$1.65 \pm 2.42$ (2h–10 d)</td>
</tr>
<tr>
<td>Time for medical therapy</td>
<td>$1.57 \pm 2.44$ (0–10 d)</td>
</tr>
</tbody>
</table>
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/$1.73m^2$/hour

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**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>

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

- Evaluate prognostic indicators for 10 hyperammonemic 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
Neurological outcome better with shorter duration of coma prior to RRT (<22 hr)
Neurological outcome no different with duration of coma during CRRT
Neurological outcome not affected by RRT modality of rapidity of NH₃ clearance
HD hampered by hypotension limiting Qb
The Prospective Pediatric CRRT (ppCRRT) Registry

- First patient enrolled on 1/1/01
- 376 patients entered into database as of 07/31/05 (study end)
- 342 with complete data
- >60,000 hours of CRRT

- Texas Children’s
- Boston Children’s
- Seattle Children’s
- UAB
- University of Michigan
- Mercy Children’s, KC
- Egleston Children’s, Atlanta

- All Children’s, Tampa
- DC Children’s
- Columbus Children’s
- Packard Children’s, Stanford
- DeVos Children’s, Grand Rapids
Table 5. Principal diagnoses and survival

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n</th>
<th>Survivors</th>
<th>% Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>81</td>
<td>48</td>
<td>59</td>
</tr>
<tr>
<td>Bone marrow transplant</td>
<td>55</td>
<td>25</td>
<td>45</td>
</tr>
<tr>
<td>Cardiac disease/ transplant</td>
<td>41</td>
<td>21</td>
<td>51</td>
</tr>
<tr>
<td>Renal disease</td>
<td>32</td>
<td>27</td>
<td>84</td>
</tr>
<tr>
<td>Liver disease/ transplant</td>
<td>29</td>
<td>9</td>
<td>31</td>
</tr>
<tr>
<td>Malignancy (no tumor lysis syndrome)</td>
<td>29</td>
<td>14</td>
<td>48</td>
</tr>
<tr>
<td>Ischemia/shock</td>
<td>19</td>
<td>13</td>
<td>68</td>
</tr>
<tr>
<td>Inborn error of metabolism</td>
<td>15</td>
<td>11</td>
<td>73</td>
</tr>
<tr>
<td>Drug intoxication</td>
<td>13</td>
<td>13</td>
<td>100</td>
</tr>
<tr>
<td>Tumor lysis syndrome</td>
<td>12</td>
<td>10</td>
<td>83</td>
</tr>
<tr>
<td>Pulmonary disease/ transplant</td>
<td>11</td>
<td>5</td>
<td>45</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
<td>5</td>
<td>71</td>
</tr>
</tbody>
</table>

\(^a\) P (\(\chi^2\)) < 0.001.
The ppCRRT and Inborn Errors: Patient Data

- 13 infants (M:F – 8:5) treated with CRRT
- Mean age: 7 days
- All initiated within one day of ICU stay
- Mean weight: 2.9 kg
- Pressor # at CRRT initiation
  - 1 = 15.4%
  - 2 = 15.4%
  - 3 = 23.1%

Walters S: in preparation
The ppCRRT and Inborn Errors: Circuit Data

<table>
<thead>
<tr>
<th>N=38 filters</th>
<th>Mean ± SD (median, range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qb (ml/min)</td>
<td>37 ± 13 (35, 20-60)</td>
</tr>
<tr>
<td>Qd (L/1.73m2/hr)</td>
<td>6.2 ± 3.8 (5.1, 1.8 -17.2)</td>
</tr>
<tr>
<td>Circuit life (hr)</td>
<td>16.4 ± 18.8 (12, 1 – 88)</td>
</tr>
<tr>
<td>Heparin: Citrate: No</td>
<td>22:13:3</td>
</tr>
</tbody>
</table>
## The ppCRRT and Inborn Errors: Outcome Data

<table>
<thead>
<tr>
<th></th>
<th>Survivors (8)</th>
<th>Non-Survivors (5)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance (L/1.73m²/hr)</td>
<td>5.9 ± 3.8</td>
<td>5.4 ± 2.6</td>
<td>0.79</td>
</tr>
<tr>
<td>Pt Size (kg)</td>
<td>3.1 ± 0.9</td>
<td>2.9 ± 0.9</td>
<td>0.91</td>
</tr>
<tr>
<td>Initial Circuit Survival (hrs)</td>
<td>13 ± 16</td>
<td>10.4 ± 11</td>
<td>0.44</td>
</tr>
<tr>
<td>Pressor # &lt;2</td>
<td>6/8</td>
<td>2/5</td>
<td>0.24</td>
</tr>
</tbody>
</table>
RRT intervention

- Child was electively intubated for airway protection
- Foley catheter placed for use for urine collection and accurate I/O
- Na Pheylacetate, 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

- **Ammonia (micromol/l)** vs. **Time (hours)**

- **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

Time (hours)

Ammonia (micromol/l)
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

![Bar chart showing solute clearance in different filters and for different substances: Ammonia, NaPheny, NaBenz.](image)
Newborn AKI and CRRT: Summary

- Neonatal AKI is common and is associated with poor outcomes.
- Neonatal CRRT is something we can do
  - Can be life-saving for critically ill infants
  - Careful planning with institution, program, and individuals improves care
  - Technical challenges can be met
  - Cooperation, communication, and collaboration will increase our success
Thank You!