Neonatal AKI from Bench to Bedside

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Disclosure

- Safety committee for new device for Baxter
Learning Objectives

- Understand incidence of etiology of AKI in infants
- Understand non dialytic treatments of AKI
- Understand dialytic treatments of AKI
AKI: Definition and Diagnosis

- Abrupt reduction in GFR
- Differential diagnosis includes:
  - Pre-renal
    - Volume depletion; cardiac dysfunction
  - Renal
    - Vascular; glomerular; tubular; interstitial
  - Post-renal
    - Obstruction
- Complex, multi-factorial physiology
Neonatal AKI: Special Challenges

- Specific stresses unique to the neonate
  - Different renal physiology in newborn
- Risks associated with neonatal illness and its treatment
  - Low birth weight; fluid loss; infection; drugs
- Our ignorance of details in neonatal AKI
  - Do we really know which babies have AKI?
Neonatal Water Balance is Different

- Immature tubule
- Diminished aquaporin function
- Normal excretion ability
- Lower capacity to retain free water
  - Concentrating capacity improves with development
- Risk for greater water loss with illness, prematurity
Transepidermal Water Loss

- Preterm insensible loss is higher
  - Skin, respiratory tract
  - 15x higher in preterm compared to term
- Highest immediately after birth
- Clinical maneuvers to limit water loss
  - Closed incubator
  - Humidification
  - Skin care
Risk Factors for Neonatal AKI

- Very low birthweight
- Congenital Heart Dz
- Cardiac bypass
- ECMO
- The depressed or asphyxiated infant
- Renal anomalies (CAKUT)
- Hypotension or hypoperfusion
- Infection/sepsis
- Drugs
- Umbilical catheterization
- Multi-organ disease
AKI After Congenital Heart Surgery

- 430 infants
  - <90 days (median 7d)
  - 34w – term
  - Median weight 3.1kg
- Heart surgery for congenital defects

AKI After Congenital Heart Surgery

PostOp AKI: N=225

PostOp AKI 52%

No AKI 48%

Stage 1
135

Stage 2
59

Stage 3
31

Neonatal AKI from Nephrotoxin Exposure

- 107 VLBW infants over 1 year (2011-12)
- 93 (87%) exposed to at least one nephrotoxic medication
  - Mean number of meds: 1.64
  - Median number of meds: 2
- AKI rate in study: 28/107 (26%)
  - All were exposed to nephrotoxic meds; those without nephrotoxins did not get AKI

Rhone et al. J Matern Fetal Neo Med 2014
Dialysis Dose and Outcome

• Conclusions:
  – Minimum UF rates should be ~ 35 ml/kg/hr
  – Survivors had lower BUNs than non-survivors prior to commencement of hemofiltration

425 patients
Endpoint = survival 15 days after D/C HF

146 UF rate 20ml/kg/hr
Survival significantly lower in this group compared to the others

139 UF rate 35ml/kg/hr
p=0.0007

140 UF rate 45ml/kg/hr
p=0.0013
26.9% of all patients

11.6% of all patients

3.5% of all patients

* 28-day outcome data are missed by participating centers, outcome-associated analysis excluded these patients.
Incidence and outcomes of neonatal acute kidney injury (AWAKEN): a multicentre, multinational, observational cohort study


Published on September 7th, 2017 - Lancet: Child and Adolescents - online first
AWAKEN methods

- Multi-center retrospective cohort study
  - 24 level 2-4 NICUs
  - All NICU admissions from Jan 1 - March 31, 201

- Inclusion criteria
  - Admission during the study period
  - Provision of at least 48 hours of IV fluids
AWAKEN: Breakdown of Screened vs. Enrolled

Total Number of Patients Screened
(n = 4273)

Enrolled
(n = 2162)

- Less than 2 SCr and no UOP
  (n = 140)
- Final Sample
  (n = 2022)

Not Enrolled*
(n = 2111)

- Not admitted to NICU during study period
  (n = 60)
- No IVFs for at least 48 hours
  (n = 1793)
AKI Incidence in AWAKEN study

All Enrolled Neonates

- No AKI: 70%
- AKI: 30%
AKI Incidence by GA

- 41% (N=273)
- 14%
- 45%
Infants with either AKI had higher mortality rate compared to those Without AKI

AKI: 59/605 (9.7%) vs. NO AKI: 20/1417 (1.4%)
p < 0.0001
AKI Prevalence in ECMO

- Neonates - 25% (Askenazi 2011)
  - ELSO registry ~8000 non-cardiac neonates
- Congenital diaphragmatic hernia - 71% (Gadepalli 2011)
- Congenital hearts - 72% (Smith 2009)
- Pediatric respiratory - 63% (ELSO DB 2011)

AKI on ECMO is associated with increased mortality, controlling for confounders (Askenazi 2012)

AKI on pediatric ECMO: OR 24.0 (4.2-137)
Support of AKI

- Non dialytic
- Dialytic
Management of Established AKI: Pharmacotherapy

**Attempted Therapies**
- Diuretics
- Mannitol
- Dopamine
- Fenoldopam
- Glucocorticoids
- Atrial natriuretic peptide
- N-acetylcysteine (other than contrast-induced AKI)
- Uric acid manipulation

**Definitive Therapies**
- Hmmm . . . . . .
Prophylaxis of Neonatal AKI

- **Theophylline** may protect asphyxiated infants against AKI:

  ![Relative Risk Chart](chart.png)

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>RR (95% CI)</th>
<th>Events, theophylline</th>
<th>Events, control</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jenik (2000)</td>
<td>0.30 (0.12, 0.78)</td>
<td>4/24</td>
<td>15/27</td>
<td>26.03</td>
</tr>
<tr>
<td>Bakr (2005)</td>
<td>0.42 (0.18, 0.96)</td>
<td>5/20</td>
<td>12/20</td>
<td>22.12</td>
</tr>
<tr>
<td>Bhat (2006)</td>
<td>0.42 (0.23, 0.77)</td>
<td>10/40</td>
<td>18/30</td>
<td>37.92</td>
</tr>
<tr>
<td>Eslami (2009)</td>
<td>0.28 (0.07, 1.14)</td>
<td>2/17</td>
<td>8/19</td>
<td>13.93</td>
</tr>
<tr>
<td>Overall</td>
<td>0.37 (0.24, 0.56)</td>
<td>21/101</td>
<td>53/96</td>
<td>100.00</td>
</tr>
</tbody>
</table>

*Al-Wassia et al. J Perinatol 2013*
Uric Acid

- Uric Acid is elevated in
  - Dehydration
  - AKI and CKD
  - Tumor Lysis Syndrome

- Treatment of elevated uric acid may improve renal function in AKI

- Lessons from the Tumor lysis literature
  - Allopurinol vs Rasburicase
Fig 3. Mean uric acid and creatinine levels (± standard error of the mean) evolution during rasburicase treatment.

Methods

- 7 infants
  - 34 ± 55 days (range 3-155 days)
  - 3.2 ± 1.2 kg (range 2.7-5.7 kg)

- AKI due to
  - HIE 3/7, sepsis with AKI 3/7, ATN 1/7

- Initial evaluation demonstrated normal urinalysis and renal ultrasound. Prior to use of Rasburicase no infant had responded to volume, diuretics nor vasopressor agents.
# Base line Data

<table>
<thead>
<tr>
<th>Parameter (nl)</th>
<th>Day 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cr mg/dl (0.3)</td>
<td>3.2 ± 2</td>
</tr>
<tr>
<td>BUN mg/dl (10)</td>
<td>58 ± 57</td>
</tr>
<tr>
<td>Phos mg/dl (6)</td>
<td>6 ± 1.5</td>
</tr>
<tr>
<td>K mmol/l (3-5)</td>
<td>4.1 ± 0.8</td>
</tr>
<tr>
<td>Ca mg/dl (8-9)</td>
<td>8.6 ± 1.6</td>
</tr>
<tr>
<td>Uric Acid mg/dl (&lt; 6)</td>
<td>13.6 ± 4.5</td>
</tr>
<tr>
<td>Urine out put mls/kg/hr</td>
<td>2.4 ± 1.2</td>
</tr>
<tr>
<td>Syst/Dias-average</td>
<td>81/44</td>
</tr>
</tbody>
</table>
Initial data

- Urine output /24 hrs
  - All pts had fluid overload despite urine output of 2.4 mls/kg/hr with no benefit from vaso-pressor agents nor diuretics

- Due to elevation of uric acid, a single dose of Rasburicase (0.17 mg/kg/dose) was administered IV
Data before and after Rasburicase
(avg ± SD; * p < 0.05)

<table>
<thead>
<tr>
<th>Parameter (nl)</th>
<th>Day 0</th>
<th>Day 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cr mg/dl (0.3)</td>
<td>3.2 ± 2</td>
<td>2.0 ± 1.2 *</td>
</tr>
<tr>
<td>BUN mg/dl (10)</td>
<td>58 ± 57</td>
<td>31 ± 18</td>
</tr>
<tr>
<td>Phos mg/dl (6)</td>
<td>6 ± 1.5</td>
<td>6.4 ± 1.5</td>
</tr>
<tr>
<td>K mmol/l (3-5)</td>
<td>4.1 ± 0.8</td>
<td>3.6 ± 0.8</td>
</tr>
<tr>
<td>Ca mg/dl (8-9)</td>
<td>8.6 ± 1.6</td>
<td>8.5 ± 1.4</td>
</tr>
<tr>
<td>Uric Acid mg/dl (&lt; 6)</td>
<td>13.6 ± 4.5</td>
<td>0.9 ± 0.6 *</td>
</tr>
<tr>
<td>Urine out put mls/kg/hr</td>
<td>2.4 ± 1.2</td>
<td>5.9 ± 1.8 *</td>
</tr>
<tr>
<td>Syst/Dias-average</td>
<td>81/44</td>
<td>83/48</td>
</tr>
</tbody>
</table>
Long Term Follow up

- 2/7 infants died of sepsis
- No infants required RRT
- The remaining 5/7 infants were discharged and have varying degree of CKD
Mode of Dialysis

- PD (standard and continuous flow)
- HD (standard and High Flux)
- CRRT
  - CVWH
  - CHHD
  - CWHDHFD
- SLED
- RRT on ECMO
Pediatric Data-Continuous PD

- Compared to Std PD increase in Net UF and Net Solute clearance with less intra-abdominal elevated pressure

Raaijmakers et al  
<table>
<thead>
<tr>
<th>PATIENT SIZE</th>
<th>CATHETER SIZE &amp; SOURCE</th>
<th>SITE OF INSERTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEONATE</td>
<td>Dual-Lumen 7.0 French (COOK/MEDCOMP)</td>
<td>Femoral vein</td>
</tr>
<tr>
<td>3-6 KG</td>
<td>Dual-Lumen 7.0 French (COOK/MEDCOMP)</td>
<td>Internal/External-Jugular, Subclavian or Femoral vein</td>
</tr>
<tr>
<td>6-30 KG</td>
<td>Dual-Lumen 8.0 French (KENDALL/ARROW)</td>
<td>Internal/External-Jugular, Subclavian or Femoral vein</td>
</tr>
<tr>
<td>&gt;15-KG</td>
<td>Dual-Lumen 9.0 French (MEDCOMP)</td>
<td>Internal/External-Jugular, Subclavian or Femoral vein</td>
</tr>
<tr>
<td>&gt;30 KG</td>
<td>Dual-Lumen 10.0 French (KENDALL, ARROW)</td>
<td>Internal/External-Jugular, Subclavian or Femoral vein</td>
</tr>
<tr>
<td>&gt;30 KG</td>
<td>Triple-Lumen 12 French (KENDALL/ ARROW)</td>
<td>Internal/External-Jugular, Subclavian or Femoral vein</td>
</tr>
</tbody>
</table>
HD-Std or High Flux

- Access-as above
- Equipment-multiple machines
- Solutions-online production
- Heater-online
- Anticoagulation-heparin or none
Hemo Dialysis Machine Evolution

- Drake-Willock: 1960s
- Travenol RSP: 1960s
- Seratron: 1979
- Cobe Centry: 1980s
- Cobe C3: 1990s-2000s
- Fresenius 2008h: 2000s
CRRT

- Access-as above
- Equipment-multiple machines
- Solutions-industry produced bicarbonate based with or without calcium
- Heater-online
- Anticoagulation-heparin, citrate, prostacyclin (www.pcrrt.com)
CRRT Machines: Modern Generation
SLED

- Access-Same as CRRT and HD
- Equipment-Fresenius system
  - Same lines as use in HD
  - Same membrane as used in HD
  - Can be diffusive and or convective
- Solutions-On line production
- Heater-on line
- Anticoagulation-heparin or citrate
How do you do it?

- The use of a dedicated CRRT machines improves UF accuracy and solute clearance then SCUF alone.

Diagram:
- IV pump/urometer based system
- Hemofilter
- Roller pump
- Commercial CRRT system
- ECMO bladder
Which modality is the best?
Dialysis Dose

Adapted from Gotch et al. Kidney Int 2000;58:S3-18
Pediatric Data-PD

- Recommendations of use of PD in situations

- Recommendations of use of PD in situations of limited resources
  - Vasudevan et al Modality of choice for RRT for children with AKI Indian J Nephrol 2012 22121-124
Pediatric Data-Continuous PD

- Compared to Std PD, increase in Net UF and Net Solute clearance with less intra-abdominal elevated pressure

Raaijmakers et al
Pediatric Data-CRRT

- Optimal use in situations of:
  - Hemodynamic compromise
  - Hyper metabolic states
  - Sepsis
Stem Cell Transplant: ppCRRT

- 51 patients in ppCRRT with SCT
- Mean %FO = 12.41 ± 3.7%.
- 45% survival
  - Convection: 17/29 survived (59%)
  - Diffusion: 6/22 (27%), p<0.05
- Survival lower in MODS and ventilated patients

Pediatric Data-SLED

- Using Fresenius System with Dialysis or Dialysis with Convection (filtration)
- 14 children with 16 sessions ~ 8 hrs
- Heparin anticoagulation
- UF and Solute clearance achieved in 80%
- Cost compared to CRRT (SLED 69 $ vs CVVH 235$)
- Chia-Ying Lee et al, Peds Neph 2012 27:2301-2309
Pediatric Data-HD

- Best used in situations of
  - Hemodynamic stability
  - Intoxication
  - Inborn error of metabolism in concert with CRRT
Ammonia Clearance

Ammonia (micromol/l)

HD Begins

HD Ends

HF Begins

HF Ends

Time (hours)
## RRT Modalities

<table>
<thead>
<tr>
<th>Modality</th>
<th>CRRT</th>
<th>SLED</th>
<th>HD (standard or HF)</th>
<th>PD</th>
<th>Continuous Flow PD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BFR</strong></td>
<td>3-5 mls/kg/min access dependent</td>
<td>3-5 mls/kg/min access dependent</td>
<td>3-5 mls/kg/min access dependent</td>
<td>10-20 mls/kg/pass</td>
<td>10-20 mls/kg/hr</td>
</tr>
<tr>
<td><strong>Dialysis Flow Rate</strong></td>
<td>0-4 liters/hr</td>
<td>6 liters/hr</td>
<td>30-50 liters/hr</td>
<td>0.5-2 liters/hr</td>
<td>0.5-2 liters/hr</td>
</tr>
<tr>
<td><strong>Convective Flow Rate</strong></td>
<td>0-4 liters/hr</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Systemic Anticoagulation</strong></td>
<td>Heparin or citrate</td>
<td>Heparin or citrate</td>
<td>Heparin or none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td><strong>Thermic control</strong></td>
<td>Yes</td>
<td>yes</td>
<td>yes</td>
<td>partial</td>
<td>partial</td>
</tr>
<tr>
<td><strong>Ultrafiltration control</strong></td>
<td>Yes</td>
<td>yes</td>
<td>yes</td>
<td>partial</td>
<td>partial</td>
</tr>
<tr>
<td><strong>Solutions</strong></td>
<td>Industry made</td>
<td>On Line production</td>
<td>On Line production</td>
<td>Industry made</td>
<td>Industry made</td>
</tr>
<tr>
<td><strong>Drug clearance</strong></td>
<td>Continuous</td>
<td>Intermittent</td>
<td>Intermittent</td>
<td>Continuous</td>
<td>Continuous</td>
</tr>
<tr>
<td><strong>Nutritional clearance</strong></td>
<td>Continuous</td>
<td>Intermittent</td>
<td>Intermittent</td>
<td>Continuous</td>
<td>Continuous</td>
</tr>
</tbody>
</table>
Conclusion

- The optimal mode of RRT for AKI in infants is based upon local experience and expertise.
- Data to date does not exist nor will exist in the future of an optimal RRT mode in most AKI situations.
- Do what you do well and it will work!
Thank you

- Timothy.bunchman@vcuhealth.org
- pedscrrt@gmail.com
- www.pcrrt.com
  - Contains all talks given at the PCRRT meetings from 2000 to the most recent in 2017 in Orlando that occurred 2 weeks ago
The Vulnerable Neonatal Kidney
Session 2
Case Discussion

Chairs
- Rupesh Raina, M.D.
- Carolyn Abitbol, M.D.
- Robert Cunningham, M.D.
- James Prebis, M.D.

Discussants
- Carolyn Abitbol, M.D.
- Tim Bunchman, M.D.
- Deepa Chand, M.D., MHSA
Unique Challenges with Neonatal Kidney Failure

- Recognizing and defining the disease
- Collaboration with Neonatologists, Intensivists, Nephrologists, Nursing, the Institutions and Industry
- Adaptation and Innovation
- Education and propagation.
Case Vignette

One week old term infant with acute kidney injury and tubular necrosis with perinatal asphyxia associated with placental abruption and chorioamnionitis.

Potential Questions

- What are renal support options?
- What are challenges associated with neonatal RRT?
- What modalities could be considered?
- Is PD an option?
- What are the issues with Neonatal hemodialysis?
Unique Challenges with Neonatal Kidney Failure

PATIENT
- Small size
- Gestational Age
  - Active nephrogenesis
  - Developmental immaturity
- Recognition
- Underlying Cause(s) and severity of renal failure
- Control of Fluid/volume status
- Co-morbidities with multi-organ failure

RESOURCES
- Available equipment
- Protective & supportive environment
- Experienced and skilled physician & nursing staff, intensivists, surgeons
- Ethical sensitivity and compassion for recognizing futility.
Early Therapeutic Options
Preventive and Pre-emptive therapies

- **Vasoactive support**
  - *Dopamine & dobutamine*

- **Fluid Management**
  - *Recognition of capillary leak*
  - *Avoidance of excessive colloids*
  - *Recognize Critical Edema (10%=Increased Mortality)*

- **Avoidance of Nephrotoxic Drugs**

- **Diuretics**

- **Methylxanthines**
  - *Aminophylline*
  - *Caffeine*

- **Free Radical Scavengers & Antioxidants**
  - *N-acetylcysteine*
  - *Lipophilic Co-enzyme Q-10*
  - *Carnitine*
Indications for Renal Replacement Therapy

- 15 percent or greater fluid overload
- Oliguria not responsive to diuretics
- Escalating ventilatory requirements, especially if related to volume status (prior to intubation is preferred when possible)
- Need for adequate nutrition, especially when nutrition is compromised by fluid restriction or electrolyte abnormalities
- Need for provision of large volumes of medications or blood products in a patient already >10 percent fluid overloaded
- BUN between 80 and 100 mg/dL
- Life-threatening metabolic derangements (eg, hyperkalemia or hyperammonemia) that are refractory to medical management
Modalities of Treatment

- Peritoneal Dialysis (PD): Both convective and diffusion-based solute clearance
- Intermittent Hemodialysis (HD): Both convective and diffusion-based solute clearance
- Continuous renal replacement therapies (CRRT) including:
  - Continuous venovenous hemodialysis (CVVHD): Predominantly diffusion-based solute clearance
  - Continuous venovenous hemofiltration (CVVH): Predominantly convective-based solute clearance
  - Continuous venovenous hemodiafiltration (CVVHDF): Both convective and diffusion-based solute clearance
- Therapeutic Plasma Exchange (TPE):
- Extracorporeal membrane oxygenation (ECMO) with Tandem CRRT or slow continuous ultrafiltration (SCUF), slow low efficiency hemodialysis (SLED).
NEONATAL AKI: TO PD OR NOT TO PD (WHILE HOPING FOR PEE)

Deepa H. Chand, MD, MHSA
Associate Medical Director,
Patient Safety and Pharmacovigilance, AbbVie
Associate Visiting Professor, Department of Pediatrics,
University of Illinois College of Medicine
Key Principles of PD

- Must have perfusion to the peritoneum
  - *Cannot filter blood if blood flow is not adequate*
- Must have PD access placed
  - *PD catheter v. feeding tube*
- Can only remove fluid in the intravascular space
PD complications

- Complications of PD
  - *Hemorrhage*
    - Transient (menses)
    - Supportive therapy
  - *Hernia*
    - Inguinal, umbilical, or incisional
    - More common with midline approach v. paramedial
    - Higher incidence in young males (patent processus vaginalis)
  - *Leak*
    - Usually post-operative
    - Suspend PD if possible
  - *Hydrothorax*
    - Rare, but usually right sided
    - Presumed to be due to bleb surfacing on diaphragm which ruptures
    - Congenital diaphragmatic defect
    - Convert to HD, repair defect prior to reinitiation of PD
PD Complications

- Protein losses via PD catheter
  - Anticipate this and adjust feeds accordingly

- Insufficient ultrafiltration
  - Restore perfusion if deficient
  - Fluid restriction
  - Can try diuretics, but do not force

- Inadequate clearance
  - Need to monitor electrolytes carefully and frequently
    - Including Magnesium, especially if calcium is low
  - Reassess nutritional needs
PD complications

- Peritonitis
  - *Cloudy effluent, poor feeding, temperature instability, hemodynamic instability*
  - *Obtain effluent sample sterile fashion*
    - WBC > $100 \times 10^6$/$L$ with >50% PMN
    - Gram stain, culture, sensitivities
    - CBC, blood culture, ± CRP
  - *Empiric antibiotics*
    - IP cefepime as monotherapy
    - 1\textsuperscript{st} generation cephalosporin/vancomycin + 3\textsuperscript{rd} generation cephalosporin/aminoglycoside
    - Tailor therapy based on culture and sensitivities and continued for 10-14 days
PD complications

- Complications of PD
  - *Catheter obstruction*
    - Often due to omentum
    - Can be due to fibrin, protein, or blood
      - Consider tPA
  - *Catheter migration*
    - Can be due to constipation, placement issues
    - Reposition catheter interventionally
  - *Cuff extrusion*
    - Can be due to cuff placement, torque on catheter, infection
    - Can shave cuff and monitor
Adapting Adult Machines to Infants and Small Children

- Vascular access required
- Blood flow rates limited
- Blood prime
- AN69 Membrane with “Bradykinin release”
Smaller circuits for smaller patients: improving renal support therapy with Aquadex™

David Askenazi¹ · Daryl Ingram² · Suzanne White² · Monica Cramer¹ · Santiago Borasino³ · Carl Coghill⁴ · Lynn Dill¹,² · Frank Tenney¹ · Dan Feig¹ · Sahar Fathallah-Shaykh¹


- NO blood prime (ECV<35 ml)
- Small caliber vascular access
- Low blood flow rates
- SCUF + CVVH
- Available in the USA
- Relatively inexpensive
Continuous renal replacement therapy in neonates and small infants: development and first-in-human use of a miniaturised machine (CARPEDIEM)

Claudio Ronco, Francesco Garzotto, Alessandra Brendolan, Monica Zanella, Massimo Bellettato, Stefania Vedovato, Fabio Chiarenza, Zaccaria Ricci, Stuart L Goldstein

Lancet 2014; 383: 1807-13

- Developed for use for infants and small children.
- ECV 25 to 45 ml with different size filters
- Provides convection and diffusion
- Not available ion the USA
Just because you can doesn’t mean you should...

- Need to provide all options
  - Need to include family in decision making
  - Provide best and worst case scenarios, including the spectrum
  - Care conferences and family centered rounds
    - Include palliative care and all specialists
  - Do not forget about QOL
    - Is the patient going to have neurological sequelae, pulmonary sequelae, organ damage, future need for surgeries?
    - The QOL is not just for the patient, but also the family
Questions to Consider

- If starting RRT, what is the endpoint?
- Is the patient hemodynamically stable enough to tolerate RRT?
- Can nutrition, medical management be optimized?
- Can fluid management be optimized?
- Is the team in agreement to start RRT?
So...

Which option would you choose?

- Hemodialysis
- Continuous renal replacement therapy
- Peritoneal dialysis
- Palliative care
RESEARCH ARTICLE

Treatment of AKI in developing and developed countries: An international survey of pediatric dialysis modalities

Rupesh Raina¹,²,*, Abigail M. Chauvin³, Timothy Bunchman⁴, David Askenazi⁵, Akash Deep⁶, Michael J. Ensley⁷, Vinod Krishnappa⁸, Sidharth Kumar Sethi⁹

<table>
<thead>
<tr>
<th></th>
<th>Developing Countries</th>
<th>Developed Countries</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Availability of pediatric nephrologist</td>
<td>35.4% (17/48)</td>
<td>100% (175/175)</td>
<td>0.000</td>
</tr>
<tr>
<td>Availability of dedicated pediatric dialysis unit</td>
<td>33.3% (16/48)</td>
<td>91% (159/175)</td>
<td>0.000</td>
</tr>
<tr>
<td>Institute’s dialysis modality of choice in infants PD</td>
<td>68.5% (33/48)</td>
<td>5.7% (10/175)</td>
<td>0.000</td>
</tr>
<tr>
<td>HD</td>
<td>12.5% (6/48)</td>
<td>72% (126/175)</td>
<td>0.000</td>
</tr>
<tr>
<td>CRRT</td>
<td>10.4% (5/48)</td>
<td>24% (42/175)</td>
<td>0.041</td>
</tr>
<tr>
<td>SLED</td>
<td>8.3% (4/48)</td>
<td>1.1% (2/175)</td>
<td>0.006</td>
</tr>
</tbody>
</table>
CRRT in the Neonate
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Disclosure

- Safety committee for new device for Baxter
Learning Objectives

- Understand the present options for CRRT in infants
- Understand the future options of CRRT in infants
- Understand the risks and limitations around CRRT in infants
Overview

- What equipment is needed for neonatal CRRT
  - Machines
  - Access

- What are the complications of Neonatal CRRT

- In the US is there anything approved?
arterial line

Venous line

CaCl infusion line/or TPN/or Med line

“arterial” line

Venous line
<table>
<thead>
<tr>
<th>PATIENT SIZE</th>
<th>CATHETER SIZE &amp; SOURCE</th>
<th>SITE OF INSERTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEONATE</td>
<td>Dual-Lumen 7.0 French (COOK/MEDCOMP)</td>
<td>Femoral vein</td>
</tr>
<tr>
<td>3-6 KG</td>
<td>Dual-Lumen 7.0 French (COOK/MEDCOMP)</td>
<td>Internal/External-Jugular, Subclavian or Femoral vein</td>
</tr>
<tr>
<td>6-30 KG</td>
<td>Dual-Lumen 8.0 French (KENDALL/ARROW)</td>
<td>Internal/External-Jugular, Subclavian or Femoral vein</td>
</tr>
<tr>
<td>&gt;15-KG</td>
<td>Dual-Lumen 9.0 French (MEDCOMP)</td>
<td>Internal/External-Jugular, Subclavian or Femoral vein</td>
</tr>
<tr>
<td>&gt;30 KG</td>
<td>Dual-Lumen 10.0 French (KENDALL, ARROW)</td>
<td>Internal/External-Jugular, Subclavian or Femoral vein</td>
</tr>
<tr>
<td>&gt;30 KG</td>
<td>Triple-Lumen 12 French (KENDALL/ARROW)</td>
<td>Internal/External-Jugular, Subclavian or Femoral vein</td>
</tr>
</tbody>
</table>

**UVC/ UAC not effective access**
CRRT

- Access-as above
- Equipment-multiple machines
- Solutions-industry produced bicarbonate based with or without calcium
- Heater-online
- Anticoagulation-heparin, citrate, prostacyclin (www.pcrrt.com)
CRRT Machines: Modern Generation
Machines and circuit volumes

- Primsaflex
  - 93-150 mls with AN69 membrane (M series)
- B Braun Diapact
  - 100-180 mls all with Polysulphone
- NxStage
  - 83-183 mls all with Polysulphone
- Nikkiso
  - 90-150 mls all with Polysulphone
Complications of CRRT

- Circuit volumes with need for blood priming
- Themic control
- UF accuracy
- Medication/nutritional clearance
So the circuit volume is high, just blood prime

- Components of blood bank blood
  - pH of 6.4
  - Ica of 0.02 mmol/l
  - K load

- Membrane reactions
Membranes Compatibility

- Complement activated reaction to blood/hemodialysis membrane interaction that causes
  - leukopenia
  - thrombocytopenia
  - increased Alveolar-Arterial gradient to pulmonary sequestration resulting in hypoxia
Membranes Compatibility

- Use of more biocompatible membranes (e.g., AN-69 polyacrylonitrile marketed as the M60 or M100) results in less complement activation.

- Hemodialysis data has shown that biocompatible membranes (e.g., AN69 membrane) improve survival in ARF, have a shorter time to recovery of renal function, and is less associated with oliguria.
Membranes Compatibility

- AN-69 membranes have been associated with “Bradykinin Release Syndrome” in patients on ACE inhibitors.
- This “Bradykinin Release Syndrome” may be pH dependent.
- But what about its use in CRRT?
Plasma kallikrein activity kinetics with AN69 membrane: Influence of diluted plasma pH

Plasma Kallikrein (UKK/l)

- pH = 7.2
- pH = 7.4
- pH = 7.6
- pH = 7.8
Bradykinin Release Syndrome
(Brophy et al, AM J Kid Dis, June 2001)

- What is the link
  - Blood bank blood has
    - ICa of 0.04 mmol/l
    - K+ of 40-60 mEq/l
    - pH of 6.4
  - Therefore we hypothesize that if this is a pH blood reaction either we buffer the blood or bypass the membrane
Negating the Bradykinin Factor

(Hackbarth et al Pediatr Nephrol. 2005 Sep;20(9):1328-33)

Z-BUF Modality and Bradykinin Levels

![Graph showing Z-BUF modality and Bradykinin levels over time. The graph includes lines for CVVH Bradykinin, CVVHD Bradykinin, CVVHD pH, and CVVH pH. The x-axis represents time (minutes) ranging from 0 to 60, and the y-axis represents Bradykinin levels (pg/ml) ranging from 0 to 120. The pH values are also shown on the right y-axis ranging from 6.20 to 7.60.]

The graph illustrates the changes in Bradykinin levels over time for different modalities, along with the corresponding pH values.
Complications of CRRT

- Thermic control
  - Significant risk of hypothermia
- UF accuracy
  - Most within 1-2% accurate
- Medication/nutritional clearance
  - Disproportional clearance of amino acids and most meds due to large surface area of membrane compared to infant small size
What is coming in the future

- Smaller circuits
- Improved access
- CFPD
Pediatric Data-Continuous PD

- Compared to Std PD, increase in Net UF and Net Solute clearance with less intra-abdominal elevated pressure

What is in the future

You can’t touch this

(MC Hammer)
Prismaflex Device with HF 20 Set

60 mls volume

- Blood flow (ml/min) 10-100
- Dialysate flow (ml/h) 50-2500
- Subst-flow rate (ml/h) 20-1000
- Subst.prebp (ml/h) 30-1000
- Volume reduction (ml/h) 10-2000
- Heparin-Infusion (ml/h) 0.5-5.0

• Treatment options
  • SCUF
  • CVVH
  • CVVHD
  • CVVHDF
  • CVVHDF pre+postdil

Not available in the US
Well published in Singapore, Austria
CARPEDIEM 27 mls
SO

- Vascular access and machinery make extracorporeal therapies difficult in these small children.
- As CRRT machines become miniaturized advancement in vascular access will be needed.
## RRT Modalities

<table>
<thead>
<tr>
<th>Modality</th>
<th>CRRT</th>
<th>SLED</th>
<th>HD (standard or HF)</th>
<th>PD</th>
<th>Continuous Flow PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>BFR</td>
<td>3-5 mls/kg/min access dependent</td>
<td>3-5 mls/kg/min access dependent</td>
<td>3-5 mls/kg/min access dependent</td>
<td>10-20 mls/kg/pass</td>
<td>10-20 mls/kg/hr</td>
</tr>
<tr>
<td>Dialysis Flow Rate</td>
<td>0-4 liters/hr</td>
<td>6 liters/hr</td>
<td>30-50 liters/hr</td>
<td>0.5-2 liters/hr</td>
<td>0.5-2 liters/hr</td>
</tr>
<tr>
<td>Convective Flow Rate</td>
<td>0-4 liters/hr</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Systemic Anticoagulation</td>
<td>Heparin or citrate</td>
<td>Heparin or citrate</td>
<td>Heparin or none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Thermic control</td>
<td>Yes</td>
<td>yes</td>
<td>yes</td>
<td>partial</td>
<td>partial</td>
</tr>
<tr>
<td>Ultrafiltration control</td>
<td>Yes</td>
<td>yes</td>
<td>yes</td>
<td>partial</td>
<td>partial</td>
</tr>
<tr>
<td>Solutions</td>
<td>Industry made</td>
<td>On Line production</td>
<td>On Line production</td>
<td>Industry made</td>
<td>Industry made</td>
</tr>
<tr>
<td>Drug clearance</td>
<td>Continuous</td>
<td>Intermittent</td>
<td>Intermittent</td>
<td>Continuous</td>
<td>Continuous</td>
</tr>
<tr>
<td>Nutritional clearance</td>
<td>Continuous</td>
<td>Intermittent</td>
<td>Intermittent</td>
<td>Continuous</td>
<td>Continuous</td>
</tr>
</tbody>
</table>
Summary

- Neonatal/infant CRRT difficult due to
  - Machines not scaled to size of these children
  - Access not available for these smaller children
  - Frequency of use of CRRT
- Easier to do in consort with ECMO
- Can be done but great attention at bedside needed