Current Concepts and Controversies in Pediatric Acute Kidney Injury

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* Normal Kidney Function
* Epidemiology of AKI
* Definition of AKI
* Diagnostic Evaluation of AKI
* Questions and Controversies
  * Diuretics
  * Renal Replacement Therapy (RRT)
  * Contrast-Induced AKI
* Why Do We Care?
* What Can We Do Better?

Functions of the Kidney

* Waste removal
* Fluid homeostasis
* Electrolyte homeostasis
* Acid-base homeostasis
* Blood pressure regulation
* Erythropoiesis
* Gluconeogenesis

Nephrology is Fun!
Development of Renal Blood Flow and Glomerular Filtration

- Normal GFR:
  - Eq. 70kg adult
  - Blood volume ~ 5l
  - Cardiac output ~ 5l/min
  - RBF ~ 200ml of 5l/min
  - ~3ml/min
  - Renal plasma flow:
    - 200ml/min
    - 200ml/min~(0.6xGFR) ~ 1.44ml/min
  - Filtration fraction
    - ~20% of blood/min
  - GFR ~ 120ml/min

Creatinine as a Marker of GFR

- Creatinine
  - Normal product of muscle breakdown.
  - Relatively constant daily production rate.
  - Production is a function of muscle mass.
  - ~105 mg/1.73m^2 from 1 kg muscle
  - Males: 1.05 mg/kg/day
  - Females: 1.0 mg/kg/day

Creatinine as a Marker of GFR

- Creatinine clearance = GFR
- Schwartz formula for kids
  - CrCl = 5 x Height (cm) 
  - Serum Cr (mg/dl)

Epidemiology of Acute Kidney Injury

- Worldwide incidence of AKI is increasing
- In children, reported incidence ranges from ~20-60% of all hospitalizations
- Large-scale data is still lacking overall
- Linked to increased short- and long-term mortality

Worldwide Incidence of AKI

- Source: Various studies and reports.
AKI in Hospitalized Children in the US
- 2009 Kids Inpatient Database
- >5 million discharges
- ICD-9 search
- AKI in >5,000 hospitalizations
- AKI associated with:
  - Having more diagnoses
  - Having more procedures
  - Sepsis
  - Shock
  - Respiratory failure
- Corresponded with CPE in Am Soc Nephrol

Incidence of AKI in the PICU
- Analyzed 8,560 admissions
  - Non-OLT transplant
  - 33.8% AKI during ICU course
  - 6.4% had AKI on admit
  - 60% developed within hours
  - 62.4% had severe AKI
  - Askenazi et al, Ped Neph 2009

Incidence of AKI in the CICU
- Buchholz et al, Pediatrics 2014
- TRIBE-AKI consortium
- Prospective study, 305 patients
- 52% developed AKI after cardiac surgery
- Pinho et al, World J Ped Cong Heart Surg 2014
  - Retrospective study, 95 neonates
  - 45% had AKI post-operatively
  - AKI associated with CPB time, prep-aminoglycoside use, small kidneys, other factors

Incidence of AKI in the NICU
- Prior studies reported incidences ranging from 20-65%
  - Did not use standardized diagnostic criteria
  - Most cases had perinatal asphyxia or shock
  - Askarian et al, Ped Neuh 2009

Incidence of AKI in Pediatric Oncology
- Fisher et al, Ped Blood Cancer 2010
- 83% pediatric AML patients
- ICD-9 code search
  - 55% had AKI in the first year
  - AKI associated with older age, black race, longer vincristine or carboplatin exposure
  - 66 newly diagnosed pediatric ALL patients 2009-2013
  - 45% developed AKI in the first 90 days
  - Associated with older age
Definition of and Diagnostic Approach to AKI

Definition of AKI

Clinical Evaluation of AKI

Diagnostic Approach to AKI
**Laboratory Findings in AKI**

<table>
<thead>
<tr>
<th>Test</th>
<th>Prerenal AKI</th>
<th>Intrinsic AKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine specific gravity</td>
<td>&gt; 1,020</td>
<td>≤ 1,000</td>
</tr>
<tr>
<td>Serum sodium, mEq/L</td>
<td>&lt; 20</td>
<td>&gt; 80</td>
</tr>
<tr>
<td>Fractional excretion of sodium</td>
<td>&lt; 1% (nephates &lt; 2.5%)</td>
<td>&gt; 2% (nephates &gt; 2.5%)</td>
</tr>
<tr>
<td>Fractional excretion of urea</td>
<td>&lt; 35%</td>
<td>&gt; 50%</td>
</tr>
<tr>
<td>Urine osmolality, mOsm/kg</td>
<td>&gt; 600</td>
<td>&lt; 350</td>
</tr>
<tr>
<td>Urea nitrogen--creatinine ratio</td>
<td>&gt; 20</td>
<td>10-15</td>
</tr>
</tbody>
</table>

**Fractional Excretion of Stuff**

- **Rental clearance of any substance Z**
  \[ \frac{U_z \times V}{P_z} \]

- **Fractional Excretion of Sodium**
  \[ \frac{P_{Na} \times (P_C \times V)}{P_C} \times 100\% \]

**Pitfalls in the Evaluation of AKI**

- FENa less useful in patients receiving diuretics
- PTNuria can be used instead
- Changes in serum Cr lag behind the actual clinical course
- Serum Cr could be worsening while the patient is actually improving

**Serum creatinine is an insensitive marker of AKI**

**Laboratory Diagnostic Clues in AKI**

- **Urine analysis**
  - Dysmorphic RBCs, RBC casts
  - Glomerulonephritis
  - WBC casts
  - Pyelonephritis
  - Blood but no RBCs
  - Tubulointerstitial nephritis
  - Proteinuria
Laboratory Diagnostic Clues in AKI

- Blood cell counts
- Leukocytosis
- Sepsis
- Anemia
- Blood loss, Hemolysis
- Thrombocytopenia
  - HUS, TTP, DIC

Questions and Controversies in AKI Management

General Management of AKI

- Determine severity of AKI
- Drug therapy
- Fluid management
- Electrolyte abnormalities
- Acidosis
- Blood pressure
- Renal replacement therapy

Medical Treatment of Acute Hyperkalemia

- Calcium gluconate
  - 10% CalGlu 1-2 mEq/kg IV over 5-10 min; preferably via central line
- Albuterol
  - 2.5 mg nebulized dose; rapid onset of action
- Dextrose
  - 25% glucose 2 ml/Kg IV + regular insulin 0.1 u/kg; rapid onset of action
- Sodium bicarbonate
  - 1 ml/kg IV over 30-60 min
- Furosemide
  - 1 mg/kg IV; removes potassium from the body
- Sodium polystyrene sulfonate (Kayexalate)
  - 1 g/ml PO/PR; removes potassium from the body

Diuretics in AKI

- Are diuretics harmful in AKI?
- Is furosemide useful in treating AKI?
- Can furosemide be used to prevent AKI?
Are Diuretics Harmful in AKI?
- Melton et al, JAMA 2002
- Retrospective cohort
- Diuretic use was associated with increased risk of death or non-recovery of function
- Increased risk was borne largely by patients receiving furosemide

| Table 3: Effect of Diuretics on Mortality and Non-recovery of Renal Function Compared With No Diuretic Use * |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Variable                                         | Univariate                                       | Multivariate                                    |
| Mortality                                        | Crude OR (95% CI)                                | Crude OR (95% CI)                                |
| Develop AKI                                      | 1.56 (1.31-1.85)                                 | 1.48 (1.26-1.73)                                 |
| Develop AKI + mortality                         | 1.50 (1.25-1.80)                                 | 1.50 (1.25-1.80)                                 |
| Nondiuretic                                       | Univariate (OR)                                  | Multivariate                                    |
| Develop AKI                                      | 1.10 (0.86-1.39)                                 | 1.10 (0.86-1.39)                                 |
| Develop AKI + mortality                         | 1.10 (0.86-1.39)                                 | 1.10 (0.86-1.39)                                 |

Can Furosemide Be Used to Prevent AKI?

Is Furosemide Useful in Treating AKI?
- van der Voort et al, Crit Care Med 2009
- Single center, double blinded RCT
  - Furosemide vs placebo
  - Increased urine output with furosemide
  - No effect on duration of AKI or frequency of renal recovery

| Table 3: Results of the multivariable analysis of factors associated with mortality free day |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Clinical Variables                              | Regression Coeff (95% CI)                        | Regression Coeff (95% CI)                        |
| Intensive Care                                  | 0.96 (0.82-1.11)                                 | 0.96 (0.82-1.11)                                 |
| Intensive Care + mortality                      | 0.89 (0.75-1.05)                                 | 0.89 (0.75-1.05)                                 |
| Nondiuretic                                       | Regression Coeff (95% CI)                        | Regression Coeff (95% CI)                        |
| Intensive Care                                  | 0.95 (0.81-1.11)                                 | 0.95 (0.81-1.11)                                 |
| Intensive Care + mortality                      | 0.89 (0.75-1.05)                                 | 0.89 (0.75-1.05)                                 |
Furosemide Stress Test
- Test to predict progression of disease in ICU patients with AKI
- 77 patients, given an IV dose of Furosemide 1.5mg/kg
- Urine output <200ml in the first 2 hours was predictive of progression to severe AKI

Summary of Diuretic Use in AKI
- Diuretics do not cause death
- Diuretics are not useful for preventing AKI, decreasing duration of AKI, or improving renal recovery with AKI
- Diuretics can increase urine output in some patients with AKI

Renal Replacement Therapy in AKI
- When to start?
- What modality?

When To Start RRT in AKI?
- AKIKI trial
  - Gaudry et al, NEJM 2016
  - Multicenter RCT
  - ICU305 Stage 3 and mechanical ventilation or catecholamine use
  - Early RRT (n=351)
    - Within 6 hours of AKI
  - Late RRT (n=308)
    - Absolute indication or oliguria >72 hours

When To Start RRT in AKI?
- No difference in 60 day mortality 48.5% vs 49.7%
- Higher number of RRT-free days in delayed group
- No difference in vent-free days or vasopressor-free days between the 2 groups
- Higher number of catheter-related bloodstream infections in early group
When To Start RRT in AKI?

- **ELAIN trial**
  - Zarbock et al, JAMA 2016
- Randomized controlled trial
  - KDIGO Stage 2 and NGAL >350 ng/mL
- Early CRRT (n=112)
  - UOP < 5 ml/kg/1.73m²/hr or Cr increase >2x baseline
- Late CRRT (n=115)
  - UOP < 5 ml/kg/1.73m²/hr or Cr increase >3x baseline or absolute RRT indication

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Which RRT Modality in AKI?

- **Vissonneau et al, Lancet 2006**
- Multicenter RC
- 360 adult ICU patients
- No difference in 60 day survival
- Low overall survival at 31%
- Hemodynamic tolerance was the same in both groups
- Concluded no survival benefit for CRRT vs HD
- Pitfalls: underpowered, unplanned, high early mortality 28%, lower CRRT dose, unblinded identifying HD group mortality lower

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When To Start RRT in AKI?

- **Primary outcome**
  - 30 day mortality 33.3% vs 54.7%, *p* = 0.03
- **Significant Secondary outcomes**
  - Shorter RRT duration 9 vs 25 days, *p* = 0.04
  - Shorter duration of mechanical ventilation, 125.5 vs 181.3 days, *p* = 0.002
  - Shorter hospital stay 51 vs 82 days, *p* = 0.001

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Which RRT Modality in AKI?

- **Earlier randomized controlled trials:**
  - Mehta et al, Kidney Int 2001, 156 adult ICU patients, multicenter
    - Increased mortality with CRRT, no difference in renal function recovery
  - CRRT group had higher severity of illness
  - Concluded no survival benefit for CRRT over HD, but noted fewer patients in CRRT group, did not control for time to receipt of RRT, dialysis dose, fluid status, hemodynamic support
  - Augustin et al, Am J Kid Dis 2002, 80 adult ICU patients, single center
    - Adjusted for severity of illness
    - Noted lower MAPs in HD group, no effect on survival
    - Better volume control with CRRT
    - Concluded no difference between CRRT or HD in survival, preservation of urine output, or renal recovery, suggested that the study was underpowered and the use of low-dose mannitol and lower CRRT dose

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When To Start RRT in AKI?

- **Modem et al, Crit Care Med 2014**
- Retrospective, single center
- 390 Pediatric ICU patients
- 180 survivors
- 210 non-survivors
- Overall mortality 47%
- Early (55 days) CRRT initiation associated with lower mortality
Which RRT Modality in AKI?

- Single center RRT
- 242 adult ICU patients
- Excluded advanced CKD patients
- Daily HD v/cRRT
- Accounted for CRRT dosing
- No difference in mortality
- No difference in RRT days, vasopressor days, vent days, hospital stay
- Pitfall: underpowered, more modality switching in CRRT group.

Summary of RRT in AKI

- When to start?
  - When there is an indication.
- Which modality to use?
  - Depends on the patient.
- RRT needs to be individualized for each patient.
  - Underlying disease process
  - Indication for RRT
  - Centers available resources and experience

Contrast Imaging and AKI

- What is the role of dialysis in iodinated IV contrast CT imaging?
- Is gadolinium IV contrast MRI contraindicated in AKI?

Mechanisms of Iodinated Contrast-Induced AKI

Iodinated IV Contrast-induced AKI

- Risk of CI-AKI
  - GFR >45 ml/min/1.73 m²
    - Low to non-existent
  - GFR 30-44 ml/min/1.73 m²
    - Borderline
  - GFR <30 ml/min/1.73 m²
    - Substantially increased to no risk

- Risk of contrast-related complications is low
  - Volume overload
  - Pulmonary edema
  - Heart failure
  - Anaphylaxis
KDIGO Guidelines on Contrast-Induced AKI

4.1. Define and stage AKI after administration of intravascular contrast media as per recommendations 2.1.1-2.1.2. (Not Graded)
4.1.1. In individuals who develop changes in kidney function after administration of intravascular contrast media, evaluate for CI-AKI as well as for other possible causes of AKI. (Not Graded)
4.2. Assess the risk for CI-AKI and, in particular, screen for pre-existing impairment of kidney function in all patients who are considered for a procedure that requires intravascular (i.e., IV) administration of iodinated contrast media. (Not Graded)
4.3. Consider alternative imaging methods in patients at increased risk for CI-AKI. (Not Graded)
4.3.1. Use the lowest possible dose of contrast medium in patients at risk for CI-AKI. (Not Graded)
4.4. We recommend using either low-osmolar or low-osmolar iodinated contrast media, rather than high-osmolar iodinated contrast media, in patients at increased risk of CI-AKI. (BII)
4.5. We recommend using low-osmolar contrast media in patients at increased risk of CI-AKI. (BII)
4.6. We recommend using non-ionic contrast media, in patients at increased risk of CI-AKI. (BII)
4.7. No specific iodine dose or non-ionic contrast media formulation should be used to prevent CI-AKI. (BII)
4.8. We recommend not using mannitol to prevent CI-AKI. (CII)
4.9. We recommend not using furosemide to prevent CI-AKI. (BII)
4.10. We recommend not using prophylactic potassium hydroxyacetate (300 mg/kg) or hemofiltration (111) for contrast media removal in patients at increased risk for CI-AKI. (CII)

Gadolinium in AKI

- Major concern is nephrogenic systemic fibrosis
- Mechanism unknown
- Risk highest in chronic dialysis patients, >2.5%
- Shabana et al, Am J Roentgen 2008
- Adverse effects such as nephrotoxicity or allergic reaction are rare

Gadolinium in AKI

- Treatment: no proven effective therapies
  - Kidney transplantation
  - Extracorporeal photopheresis
  - UV A phototherapy
  - Plasmapheresis
- Course
  - Progressive
  - Can lead to contractures, loss of mobility, and death
- Recommendations:
  - Avoid in patients with AKI, dialysis, or GFR <30 ml/min/1.73 m²
  - Consider hemodialysis immediately after if no other options, although there is no data to support this

AKI and Long-Term Sequelae

- Mammen et al, Am J Kid Dis 2012
- PICU survivors who had AKI
- 1/3 of patients, 3 year follow up
- 28% had severe AKI
  - 6.5% of those required dialysis
- 38% of the total cohort developed GFR <30 ml/min/1.73 m²
- 9.5% developed proteinuria, 3.2% developed hypertension
- Garg et al, JAMA 2003
- Pediatric HUS long-term outcomes
- Metaanalysis - 3400 patients
- Median 4.4 year follow-up
- ESRD/death 12% (range ~30%)
- GFR <10, hypertension, or proteinuria 25% (range ~64%)
Life Expectancy in Pediatric End-Stage Renal Disease

Mortality Rates in Pediatric ESRD

<table>
<thead>
<tr>
<th>ESRD Type</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-dialysis</td>
<td>6.4</td>
</tr>
<tr>
<td>Dialysis Stage 1</td>
<td>0.5</td>
</tr>
<tr>
<td>Dialysis Stage 2</td>
<td>0.8</td>
</tr>
<tr>
<td>Dialysis Stage 3</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Causes of Death in Pediatric ESRD

- Hypertension
- Infection
- Cardiovascular Disease
- Neoplasms

Fluid Overload and Mortality in AKI

Targeted Therapies in AKI

What Can We Do Better?

Early Detection of AKI
Collaborative Research

"Cliff Analogy" – Levels of Health Intervention

Thank You