Diagnosis and Management of Acute Kidney Injury in Children

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Disclosure
Select either a or b and make applicable to your situation.
a. I have no relationships with commercial companies to disclose.

Learning Objectives
At the end of this presentation the participant will be able to:
1. Correctly recognize and diagnose common causes of AKI in children.
2. Recognize common complications of AKI in children.

Presentation Outline
• Normal renal development and glomerular function.
• Definition and epidemiology of acute kidney injury (AKI).
• Pathophysiologic mechanisms in AKI.
• Diagnosis and management of AKI.
• Morbidity and mortality of AKI.
• Future AKI research.

Human Kidney Development
- The metanephros is the direct precursor of the adult kidney.
  - Mesenchyme
    • Glomerulus
    • Proximal tubule
    • Loop of Henle
  - Ureteric Bud
    • Ureter
    • Collecting ducts

Kadioglu, Am J Rad 2010

Human Kidney Development
- Nephrogenesis is complete by 36 weeks’ gestation in humans.
- Humans have between 0.7-1 x 10^6 glomeruli in each kidney.
- Combined adult kidney weight is ~300gm (0.5% of body weight).

Avner, Pediatric Nephrology, 6th Edition
Development of Renal Blood Flow and Glomerular Filtration

- Fetal RBF is only 3-7% of cardiac output.
- Postnatal RBF doubles by 2 weeks after birth.
- By 2 years of age, RBF reaches mature levels (~20% of cardiac output).

Rubin, JCI 1949

Normal GFR:
- E.g. 70kg adult
- Blood volume ~ 5L
- Cardiac output ~ 5L/min
- RBF ~20% of 5L/min
- ~1L/min

Renal plasma flow:
- RBF*(1-Hct)
  - 1L/min*(1-40%) ~ 0.6L/min

Filtration fraction
- ~20% * 600mL/min
- GFR ~ 120mL/min

Kidneyatlas.org

Estimation of GFR

- Ideal GFR marker
  - Freely filtered by the glomerulus.
  - Not secreted or reabsorbed by the tubules.
  - Not metabolized by the kidney.

- Inulin – “gold standard”
  - Not useful in clinical settings:
    - Difficult to obtain and prepare.
    - Requires a continuous infusion.
    - Measurement methods are not routinely available.

• GFR ~ clearance of inulin
  - \( C_{\text{In}} = \frac{(U_{\text{In}} \times V)}{P_{\text{In}}} \)

Creatinine as a Marker of GFR

- Creatinine
  - Normal product of muscle breakdown.
  - Relatively constant daily production rate.
  - Production is a function of muscle mass:
    - ~50 mg Cr from 1 kg muscle
    - Boys: 15-20 mg/kg/day
    - Girls: 10-15 mg/kg/day

Wyss, Phys Rev 2000

Formula to Estimate GFR in Children

- Schwartz formula
  - GFR ~ Cr clearance
  - \( \text{GFR} = \frac{k \times \text{Height (cm)} \times \text{S}_{\text{Cr}} \text{ (mg/dl)}}{\text{Age}} \)
  - \( k \) values:
    - < 1 year: 0.45
    - 1-12 yrs: 0.55
    - >12 yrs, F: 0.55
    - >12 yrs, M: 0.7
  - GFR adjusted for body surface area, so units are ml/min/1.73m²

Schwartz, Ped 1976

Formulas to Estimate GFR in Adults

- Cockcroft-Gault:
  - (140 – age) × body weight/plasma creatinine × 72
  - (× 0.85 if female)

- Modified Diet in Renal Disease:
  - 175 × plasma creatinine
    -1.154 × age
    -0.203 (× 0.742 if female; × 1.21 if black)

- CKD-EPI:
  - for men with a plasma creatinine ≤0.9 :
    - (plasma creatinine/0.9)^(-1.154 × age-1.203) × 0.742
  - for women:
    - (plasma creatinine/0.9)^(-1.154 × age-1.203) × 1.21
  - for black men:
    - (plasma creatinine/0.9)^(-1.154 × age-1.203) × 1.63
  - for white or other:
    - (plasma creatinine/0.9)^(-1.154 × age-1.203) × 1.41

Michels, CJASN 2010
Normal Creatinine Values in Children

Acute Kidney Injury
- Definition
- Epidemiology
- Pathophysiology

Definition of AKI
- Abrupt decrease in glomerular filtration rate.
- Consensus on a clear clinical definition is still lacking.
  - To increase sensitivity of the diagnosis of AKI.
  - To improve epidemiologic data.
  - To predict outcomes of AKI.

Epidemiology of AKI
- Adult data:
  - Uchino, JAMA 2005
    - Prospective observational study of 29,269 adult ICU patients.
    - Period prevalence for severe acute renal failure was 5.7%.
    - 72.5% of severe renal failure required dialysis.
    - Mortality was 60.3%.
    - Risk factors for worse outcomes:
      - Vasopressor use, mech. Ventilation, sepsis, cardiogenic/septic shock, hepatorenal syndrome

Pediatric RIFLE Criteria
- Acute Dialysis Quality Initiative developed the RIFLE criteria in 2002
  - To standardize the definition of AKI.
  - Based on changes in creatinine clearance and urine output.
  - Modified for pediatric use (pRIFLE)

Epidemiology of AKI in Children

<table>
<thead>
<tr>
<th>Table 1: Pediatric-modified RIFLE (pRIFLE) criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
</tr>
<tr>
<td>GFR  125 mL/min/1.73 m²</td>
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<tr>
<td>GFR  50-125 mL/min/1.73 m²</td>
</tr>
<tr>
<td>GFR  10-49 mL/min/1.73 m²</td>
</tr>
<tr>
<td>GFR  0-10 mL/min/1.73 m²</td>
</tr>
</tbody>
</table>

Hsu, Ped Neph 2010
Pathophysiology of AKI

Pre-renal AKI
- The most common cause of AKI.
- Due to inadequate intravascular volume.
  - GI fluid loss
    - Vomiting, diarrhea, NG suction
  - Blood loss
    - Surgery, trauma, GI bleeding
  - Insensible fluid loss
    - Burns, hyperthermia

- Renal losses
  - Diuresis, diabetes insipidus, salt wasting nephropathy
- Decreased effective intravascular volume
  - Nephrotic syndrome, sepsis, heart failure, liver failure

Intrinsic AKI
- Ischemic ATN
  - Severe volume/blood loss
- Toxic ATN
  - Drugs (aminoglycosides, NSAIDs, IV contrast, cisplatin, ifosfamide)
  - Exogenous toxins
    - Ethylene glycol, methanol, heavy metals, toxic mushrooms
- Endogenous toxins
  - Myoglobin, hemoglobin, uric acid

Diagnostic Approach to AKI
- Pre-renal
  - Decreased intravascular volume
  - Decreased effective intravascular volume
- Intrinsic
  - Ischemic acute tubular necrosis (ATN)
  - Toxic ATN
  - Glomerulonephritis
  - Interstitial nephritis
  - Vascular lesions
  - Infection
- Post-renal
  - Ureteral obstruction
  - Urethral obstruction

Acute Kidney Injury
- Diagnosis
- Management
**Post-Renal AKI**
- Ureteral obstruction
  - Ureteropelvic junction obstruction
  - Ureterovesical junction obstruction
  - Urolithiasis
- Urethral obstruction
  - Posterior urethral valve
- Extrinsic mass compression (i.e. tumor, hematoma, abscess)

**Clinical Evaluation of AKI**
- **History:**
  - Decreased urine output
  - Volume loss
  - Vomiting, diarrhea
  - Respiratory symptoms
  - Dyspnea, hemoptysis
  - Cardiac disease
  - Fever
  - Abdominal pain, dysuria
  - Hematuria
  - Swelling
  - Extremities, joints
  - Skin lesions, pallor
  - Trauma, hemorrhage
  - Seizure
  - Medications
  - Chronic kidney disease
- **Physical Exam:**
  - Vital signs
  - Weight change, fever, tachycardia
  - Hypertension, tachypnea
  - Altered mental status
  - Periorbital edema
  - Mucous membranes
  - Dry, pale
  - Oropharyngeal lesions
  - Tonsillitis, oral ulcers
  - Heart and Lung sounds
  - Abdominal exam
  - Asymmetry, mass, tenderness
  - Edema, joint swelling/pain
  - Petechiae, purpura, skin turgor, capillary refill, jaundice

**Laboratory Evaluation of AKI**
- **Urinalysis**
  - Dysmorphic RBCs, RBC casts
  - Glomerulonephritis
  - WBC casts
  - Pyelonephritis
  - + Blood but no RBCs
  - Rhabdomyolysis, hemolysis
  - Eosinophils
  - Interstitial nephritis
  - Proteinuria
- **Serum biochemistry**
  - Hyponatremia
  - Hyperkalemia
  - Metabolic acidosis
  - Hyperphosphatemia
  - Azotemia
- **Blood cell counts**
  - Leukocytosis
  - Sepsis
  - Anemia
  - Hemolysis
  - Thrombocytopenia
  - HUS, TTP, DIC
- **Serologic testing**
  - Hypocomplementemia
    - PSGN, MPGN, SLE
  - ASO, anti-DNAse B
  - PSGN
  - ANA, anti-dsDNA
  - SLE
  - ANCA
    - Wegener’s, MPA
  - Anti-GBM Ab
    - Goodpasture’s
  - HUS
    - ADAMTS-13

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*Images courtesy of Kidneyatlas.org.*
Radiologic Evaluation of AKI

- Imaging studies
  - Renal ultrasound
    - Determine renal and bladder anatomy
    - Detect obstruction or mass
    - Assess blood flow
  - Dimercaptosuccinic acid (DMSA) scan

| Common Clinical Findings in Different Types of AKI |
|---------------------------------|-----------------|-----------------|
| **Pre-Renal** | **Intrinsic** | **Post-Renal** |
| History | Vomiting, diarrhea | Dehydration | Decreased urine output |
| Dehydration | Ischemic insult | Urinary urgency |
| Hemorrhage | Toxins/medication | Abdominal mass |
| Decreased urine output | Hematuria, Fever, Rash |
| **Physical Exam** | Dry membranes | Hypertension | Hypertension |
| Hypertension | Lack of tears | Edema | Edema |
| Edema | Tachycardia, delayed cap. refill | Respiratory rates | Palpable bladder |
| Respiratory rales | Increased skin turgor | Purpura, petechiae | Palpable mass |

Common Investigative Findings in Different Types of AKI

<table>
<thead>
<tr>
<th>Pre-Renal</th>
<th>Intrinsic</th>
<th>Post-Renal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinalysis</td>
<td>Dysmorphic RBCs, casts</td>
<td></td>
</tr>
<tr>
<td>Urine Specific Gravity &gt;1.025</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine Osmolality &gt;500 mOsm</td>
<td>&lt;350 mOsm</td>
<td>&lt;350 mOsm</td>
</tr>
<tr>
<td>Urine Na &lt;10 mEq/L</td>
<td>&gt;30 mEq/L</td>
<td>&gt;30 mEq/L</td>
</tr>
<tr>
<td>FENa &lt;1%</td>
<td>&gt;2%</td>
<td>&gt;2%</td>
</tr>
<tr>
<td>FEUrea &lt;35%</td>
<td>&gt;50%</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>Serum BUN-Cr &gt;20:1</td>
<td>10-20:1</td>
<td>10-20:1</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>Empty bladder</td>
<td>Increased echogenicity</td>
</tr>
</tbody>
</table>

General Management of AKI

- Determination of GFR
  - Severity of AKI
  - Drug dosing
- Fluid management
- Electrolyte abnormalities
- Acidosis
- Blood pressure
- Renal replacement therapy

Management of Pre-Renal AKI

- Fluid resuscitation
  - Isotonic fluid
  - Up to 60 ml/kg in 1-2 hrs
  - Reassess for response
    - Pulses
    - Perfusion
    - Mental status
    - Urine output
- Correct the underlying etiology.

Management of Intrinsic AKI

- Estimation of GFR
  - To determine the severity of AKI.
  - To determine the rate of decline/recovery.
  - To determine drug dosing.
- Schwartz equation
  \[ k \times \text{Height (cm)} / S_C (\text{mg/dl}) \]
Management of Intrinsic AKI

- Fluid management
  - Determination of the patient’s volume status is crucial.
  - History, weight, blood pressure, physical exam findings.
  - Daily maintenance fluid requirement = UOP + IL
  - Patients with hypervolemia and oliguria/anuria need to be fluid restricted.
  - IL ~ 400 ml/m²/day or ~ 1/3 daily maintenance.

- Diuresis
  - Furosemide (Lasix)
    - Effective as monotherapy, need higher doses with worsened kidney function.
    - Adverse effects: hypokalemia, ototoxicity, contraction alkalosis.
  - Thiazides (Chlorothiazide (Diuril), Hydrochlorothiazide)
    - Can be used as an adjunct to loop diuretics.
    - Minimally effective when GFR <30 ml/min.
    - Adverse effects: hypokalemia, hypercalcemia, hyperuricemia.
  - Metolazone – “thiazide-like” diuretic
    - Several times more potent than thiazides.
    - Dosing: 0.1-0.2 mg/kg/dose PO Q12-24 hours.

- Electrolyte abnormalities
  - Hyperkalemia
    - Increased potassium load
    - Cellular shifts
    - Impaired excretion
    - Symptoms
      - Weakness, paresthesias,
    - Complications
      - Arrhythmias
      - Death
  - Medical Treatment of Hyperkalemia
    - 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
    - Calcium gluconate
      - 10% CaGluc 0.5-1 ml/kg IV over 5-10 min; preferably via central line
    - Sodium bicarbonate
      - 1-2 meq/kg IV over 30-60 min
    - Furosemide
      - 1-2 mg/kg IV over 30-60 min
    - Kayexalate
      - 1 gm/kg PO/PR; removes potassium from the body

- Metabolic Acidosis
  - Usually a wide gap acidosis
  - Treatment
    - NaHCO₃ 1-2 meq/kg IV over 30-60 min
    - Complications: hypocalcemia

- Blood pressure
  - Hypotension
    - Replace volume, give pressors
  - Hypertension
    - Severe: >99th + 5mmHg
    - Hypertensive emergency
      - Symptomatic or evidence of end-organ damage
      - Nausea, vomiting, altered mental status, seizure
    - Treatment goal
      - BP reduction by 25% over 8 hours, then normalization (BP < 90°) over next 24-48 hours
Management of Intrinsic AKI

- Medical treatment of severe hypertension
  - Labetalol 0.2-1 mg/kg/dose IV Q6 hours
    - relative contraindication in asthma and overt heart failure
  - Hydralazine 0.2-0.6 mg/kg/dose IV Q4 hours
    - reflex tachycardia
  - Nicardipine 0.5-4 mcg/kg/min IV infusion
    - reflex tachycardia
  - Esmolol 100-500 mcg/kg/min IV infusion
    - bradycardia
  - Sodium Nitroprusside 0.5-10 mcg/kg/min IV infusion
    - monitor cyanide levels, give with sodium thiosulfate

- Imaging
  - Renal ultrasound
    - Increased echogenicity
    - Abnormal vascular flow
  - DMSA

- Renal replacement
  - Indications
    - Acidosis
    - Electrolyte abnormalities
    - Intoxications
    - Overload (fluid)
    - Uremia
  - Advantages
    - Effective for fluid and metabolite removal.
    - Short treatment time.
  - Disadvantages
    - Requires vascular catheter and systemic heparin.
    - Volume/solute shifts may not be tolerated.

- Hemodialysis
  - Continuous therapy.
  - Useful for hemodynamically unstable patients.
  - Requires vascular catheter and anticoagulation.
  - Requires abdominal catheter.
  - Contraindicated with intraabdominal pathology.
  - Requires vascular catheter and anticoagulation.
  - Labor intensive.

- Peritoneal Dialysis
  - Requires abdominal catheter.
  - Contraindicated with intraabdominal pathology.

Renal Replacement Therapy

Management of Post-Renal AKI

- Relief of the obstruction.
- Monitor for post-obstructive diuresis and salt-wasting.

Acute Kidney Injury

- Morbidity and Mortality
- Future Research
Morbidity and Mortality in AKI

- AKI is associated with increased in-hospital morbidity and mortality in adults.
  - In hospitalized adults, a 25% increase in serum Cr -> relative risk of death 1.8; 50% increase -> RR of death 6.9 (Coca, AJKD 2007)
- Paucity of pediatric data in the literature.
- Prospective study of 110 ICU admissions with AKI (Bresolin, PedNeph 2009)
  - 37 deaths (31 from multiorgan failure, 6 from septic shock)
  - Factors that increased the risk of mortality:
    - Oliguria/anuria, dialysis, hypotension, need for pressors, mechanical ventilation, multiorgan failure, lactic acidosis.

Morbidity and Mortality in AKI

- Primary versus secondary etiologies of AKI
  - Survival rates higher with primary renal disease
    - 66.7% vs 52.5% (Hayes, J Crit Care 2009)
  - 90% vs 51% (Foland, Crit Care Med 2004)
  - 81% vs 43% (Bunchman, Ped Neph 2001)

Morbidity and Mortality in AKI

Long Term Outcomes in Pediatric AKI

- Askenazi, Kidney Int 2006
  - 174 pediatric patients with in-hospital AKI and survived to discharge
  - 3-5 year survival after discharge was 79.9%
  - 66.5% of deaths were in the first year after discharge
  - 21% of survivors had at least one sign of persistent renal injury
    - Microalbuminuria, decreased GFR, hypertension, or hyperfiltration
  - 9% developed end stage kidney disease
Future AKI Research

- AKI epidemiologic data
- Earlier markers of AKI
  - Cystatin C
  - Kidney injury molecule-1 (KIM-1)
  - Neutrophil gelatinase-associated lipocalin (NGAL)
- AKI therapies
  - Inhibitors of oxidative stress
  - Stem cell therapy

Cystatin C and KIM-1 Predict AKI in Adult Cardiac Surgery Patients

Urine NGAL Predicts Severe AKI After Pediatric Cardiac Surgery

Future AKI Research

- The incidence and prevalence of AKI in children may be underestimated, and further studies are needed to clearly define AKI and determine its burden.
- Early detection of AKI may be beneficial, and more sensitive biomarkers need to be developed.
- Development of biomarkers to predict those patients who will be at higher risk for AKI may help to decrease its occurrence.
- There are currently no therapies to slow or reverse kidney damage in AKI, and these need to be developed.