**ACUTE RENAL FAILURE IN CHILDREN**

**PREVIOUS DEFINITION:** Sudden (hours, days) reduction in renal function of at least 50%, characterized by rising serum levels of waste products (creatinine, urea), disturbances in water/electrolyte balance and urine amount and composition.

*Irit Krause, M.D. Schneider’s Children Medical Center*

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**ACUTE KIDNEY INJURY NEW DEFINITION**

Modified RIFLE criteria in critically ill children with acute kidney injury

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Estimated CCI</th>
<th>Urine Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>RISK</td>
<td>eCCI decrease by 25%</td>
<td>&lt;0.5 ml/kg/h for 8 h</td>
</tr>
<tr>
<td>INJURY</td>
<td>eCCI decrease by 50%</td>
<td>&lt;0.5 ml/kg/h for 16 h</td>
</tr>
<tr>
<td>FAILURE</td>
<td>eCCI decrease by 75% or eCcr &lt;35 ml/min/1.73 m²</td>
<td>&lt;0.3 ml/kg/h for 24 h or anuric for 12 h</td>
</tr>
<tr>
<td>LOSS</td>
<td>Persistent failure &gt;4 weeks</td>
<td></td>
</tr>
<tr>
<td>END STAGE</td>
<td>End-stage renal disease (persistent failure &gt;3 months)</td>
<td></td>
</tr>
</tbody>
</table>

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**Causes of acute kidney injury in children**

- **Prerenal causes** (decreased effective blood volume)
  - Altered systemic hemodynamics
  - dehydration
  - blood loss
  - third space losses (burns)
  - vasodilatation (septic shock, anaphylaxis, drugs)
  - hypoalbuminemia (liver disease, nephrotic syndrome, protein loosing enteropathy)
  - heart failure

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**Causes of AKI - cont**

- **Altered local hemodinamics**
  - renal vein thrombosis
  - renal artery stenosis/thrombosis
Intrinsic Renal Diseases (1)

- **Glomerular** (acute glomerulonephritis)
  - Vasculitis (Wegener’s, microscopic polyangiitis)
  - HUS
  - Immune mediated
    - Post infectious
    - Henoch-Schönlein purpura, IgA nephropathy
    - SLE
    - Membranoproliferative GN
    - anti-GBM associated GN (including Goodpasture)

Intrinsic Renal Diseases (2)

- **Tubulointerstitial**
  - Acute tubular necrosis
  - Infectious/parainfectious
  - Drug related
  - Infiltrative (malignancies)

- **Exogenous**
  - Drugs (aminoglycosides, amphotericin, NSAIDs)
  - Contrast media
  - Rare causes: heavy metals, methoxyflurane, ethyleneglycol

- **Nephrotoxicity**
  - Endogenous
  - Myoglobin
  - Hemoglobin
  - Uric acid
  - Oxalate

Postrenal Causes

- Obstruction by tumor
- Retroperitoneal fibrosis
- Obstruction by calculi
- Functional obstruction (neurogenic bladder)
- Iatrogenic (following urological operation)

Causes of Renal Failure According to Incidence

<table>
<thead>
<tr>
<th>Cause</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATN</td>
<td>120</td>
<td>23.3</td>
</tr>
<tr>
<td>HUS</td>
<td>108</td>
<td>21.0</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>65</td>
<td>12.6</td>
</tr>
<tr>
<td>“Intrinsic renal disease”</td>
<td>44</td>
<td>8.5</td>
</tr>
<tr>
<td>Urinary obstruction</td>
<td>17</td>
<td>3.3</td>
</tr>
<tr>
<td>Postoperative</td>
<td>35</td>
<td>6.8</td>
</tr>
<tr>
<td>Sepsis</td>
<td>32</td>
<td>6.2</td>
</tr>
<tr>
<td>Ischemic/Prerenal</td>
<td>23</td>
<td>4.5</td>
</tr>
<tr>
<td>Other</td>
<td>71</td>
<td>13.8</td>
</tr>
<tr>
<td>Total</td>
<td>515</td>
<td>100</td>
</tr>
</tbody>
</table>

(Pediatric Nephrology (2002) 17; 61-69)
Acute Tubular Necrosis

- The most common cause of AKI
  - Ischemic
  - Nephrotoxic
  - Secondary to glomerular disease

NSAID – kidney enemy!

Pathophysiology of Ischemic Acute Renal Failure

Ischemic Injury

- ATP↓
- Cytoskeleton
- Cell swelling
- Intracellular Ca↑
- Activation of phospholipases proteases endonucleases
- Activation of leukocytes, thymocytes
cytokines↑
Adhesion molecules

- Oxygen radicals
- mesangial contraction
- NO
- endothelin cast formation

Cell damage
Diagnosis

- Acute vs chronic renal failure
- History, previous tests
- Growth
- Kidney size
- Anemia
- Renal osteodystrophy

Prerenal vs. Intrinsic Renal Damage

<table>
<thead>
<tr>
<th></th>
<th>Response to fluid therapy</th>
<th>Fe of Na</th>
<th>Urinary Osmolality</th>
<th>Urinary output</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PreRenal</strong></td>
<td>Improvement</td>
<td>&lt; 1%</td>
<td>&gt; 400 mOsmol/l</td>
<td>Low</td>
</tr>
<tr>
<td><strong>ATN</strong></td>
<td>No improvement</td>
<td>&gt; 1%</td>
<td>&lt; 400 mOsmol/l</td>
<td>Variable</td>
</tr>
</tbody>
</table>

Fractional excretion of sodium = urinary sodium x serum creatinine/serum sodium x urinary creatinine x 100% (normal <1%)

Treatment (1) - General Principles

- Treating the cause
  - Fluid balance including regular weighing
  - Evaluation of intravascular volume and effective blood volume (clinical, CVP)
- Avoidance of further renal damage
  - hypoxia
  - hypovolemia
  - nephrotoxic drugs
  - contrast material
- Adjustment of drug dosage according to the degree of renal dysfunction
- Nutrition

- Urine sediment – important!
- Urine electrolytes, including creatinine – important!
- Keep some urine for further tests!
- Ultrasound
- Plain abdomen X-ray
- Specific tests according to the suspected cause (serological investigations)
### Treatment (2) – Drug Therapy

#### Hyperkalemia
- Glucose 0.5 gm/kg
- Insulin 0.3 units/gm glucose over 2h
- Sodium bicarbonate 1-3mEq/kg and by titration
- Calcium globionate/gluconate (10%) 0.2-0.5mL/kg over 2-5 minutes
- Salbutamol nabalised intravenous 4-5mcg/kg over 15 min
- Kayexalate (sodium polystyrene sulfonate) 1-2 gr/kg in solution of sorbitol 20% PO or in solution of glucose 10% PR every 4 hours

#### Hyperphosphatemia
- Phosphor binders (calcium carbonate) with meals

#### Hypocalcemia
- Ca supplements PO or IV

#### Acidosis
- sodium bicarbonate (IV continuous- preferable)

### Treatments pointed to improve outcome

**Dopamine** (“renal dose” 2-5µg/kg/min)
- D1-dopaminergic receptors → vasodilatation, natriuresis
- No definitive studies showing improved outcome in ARF
- Placebo controlled randomized study of low-dose dopamine in adult critically ill patients with early renal dysfunction did not confer clinically significant protection from renal failure.
- No studies in children
- **Adverse effects**
  - suppression of respiratory drive
  - increased cardiac output and myocardial oxygen consumption
  - triggering of arrhythmias
  - hypokalemia
- High dose dopamine is indicated in cardiac dysfunction

**Diuretics- Furoseamade**
- No studies in children.
- In adults with ARF there is no hard data regarding the benefit of furoseamide.
- Larger doses in children are not more effective. Dosage should not exceed 10mg/kg/day
- Preference to slow infusion
- **Adverse effects**
  - hypokalemia
  - hypomagnesemia
  - hypercalciuria
  - hearing loss
  - intravascular volume depletition
Diuretics- Mannitol

- Acts as osmotic diuretic in proximal tubule, increases plasma osmolality and intravascular volume.
- Dose: 0.5-1 gr/kg over 30-60 min.
- Data regarding the effectiveness of mannitol is contradictory.
- In a controlled study of pediatric kidney transplant patients- benefit was shown for mannitol given just prior to clamp removal during the surgery.

Natriuretic peptides

- One study showed beneficial effect in ANF.
- Very large multicentral study showed no beneficial effect in patients with oliguric ARF.

Albumin
- No survival benefit in critically ill patients with ARF.

Calcium channel antagonists
- Have been shown to reduce the incidence of ATN following renal transplantation
- Clinical use in post-ischemic ARF is not established.

Future

- Fenoldopam mesylate– selective D1-dopaminergic receptor agonist.
- Melanocyte stimulating factor- anti-inflammatory activity, direct effect on tubules.
- Free radical scavengers.
- IGF-1?
Renal Replacement Therapy

- **Absolute indications for dialysis**
  - Fluid overload with pulmonary congestion/heart failure/uncontrollable hypertension.
  - Hyperkalemia
  - Acidosis
  - Hypocalcemia
  - Uremia (encephalopathy, bleeding, pericarditis)
  - Intoxications
- **Relative indications**
  - Nutritional support impossible due to fluid restriction
  - Very high urea (>300mg%).
- **Timing**

Choice of Dialysis

- Assessment of patient's clinical status and specific problems
- Access
- Experience

Peritoneal Dialysis

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>easy access</td>
<td>slow clearance</td>
</tr>
<tr>
<td>little equipment, easy to operate</td>
<td>distention of abdomen</td>
</tr>
<tr>
<td>safe in hemodynamically unstable patients</td>
<td>hyperglycemia</td>
</tr>
<tr>
<td>continuous, gradual ultrafiltration and solute clearance</td>
<td>leak around the catheter</td>
</tr>
<tr>
<td>may provide calories and protein (nutraneal)</td>
<td>infection</td>
</tr>
<tr>
<td>not expensive</td>
<td>hypothermia</td>
</tr>
</tbody>
</table>

Intermittent Hemodialysis

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>rapid fluid and solute clearance</td>
<td>access difficult to achieve in very little children</td>
</tr>
<tr>
<td>bedside insertion of access</td>
<td>need for fluid restriction</td>
</tr>
<tr>
<td></td>
<td>hyperglycemia</td>
</tr>
<tr>
<td></td>
<td>large volume changes not safe in hemodynamically unstable patients</td>
</tr>
<tr>
<td></td>
<td>disequilibrium syndrome</td>
</tr>
<tr>
<td></td>
<td>systemic anticoagulation</td>
</tr>
<tr>
<td></td>
<td>access thrombosis</td>
</tr>
<tr>
<td></td>
<td>infection</td>
</tr>
</tbody>
</table>
Malignant Hypertension

Presence of severe hypertension along with complications:

- papilledema
- neurological
- congestive heart failure

Outcome

- Mortality: 35-73% in patients requiring dialysis
- Prognostic factors
  - Cause of ARF
  - Presence of multiorgan failure
  - Age
  - Hypoalbuminemia
  - Early dialysis?
  - More aggressive dialysis?

Hypertensive Emergencies

- Measurement of blood pressure
- Classification of hypertension by age groups

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Age (yr)</th>
<th>Systolic/Diastolic (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Significant</td>
</tr>
<tr>
<td>Newborn</td>
<td></td>
<td>104</td>
</tr>
<tr>
<td>Infant</td>
<td>&lt;2</td>
<td>112/74</td>
</tr>
<tr>
<td>Children</td>
<td>3-5</td>
<td>116/76</td>
</tr>
<tr>
<td></td>
<td>6-9</td>
<td>122/78</td>
</tr>
<tr>
<td></td>
<td>10-12</td>
<td>126/82</td>
</tr>
<tr>
<td>Adolescents</td>
<td>13-15</td>
<td>136/86</td>
</tr>
<tr>
<td></td>
<td>16-18</td>
<td>149/92</td>
</tr>
</tbody>
</table>

Etiology of Hypertensive Emergencies in Children and Adolescents (1)

- Renal
  - Acute glomerulonephritis
  - Hemolytic uremic syndrome
  - Acute renal failure due to other causes
  - Acute hydronephrosis
  - Chronic renal failure
  - Renal artery disease
  - Renal vein thrombosis
  - Trauma to the kidney
  - Post transplantation
  - Cardiac
  - Coarctation of aorta
Etiology of Hypertensive Emergencies in Children and Adolescents (2)

- CNS
  - Increased intracranial pressure
  - Endocrinological
  - Pheochromocytoma
  - Thyroid storm

- Exogenious agents
  - Amphetamins
  - Drug withdrawal from anti-hypertensive therapy
  - Corticosteroid therapy

Treatment Goals

- To treat complications and reduce BP.
- General guidelines: reduce BP by one third of the difference between the normal and the elevated values during first 6-8 hours or until resolution of symptoms.

Main Drug Groups for Treatment of Hypertension (1)

- **Calcium channel blockers**
  - **Nifedipine** (Adalat, Pressolat, Osmoadalat)
  - **Felodipine** (Penedil)
  - **Amlodipine** (Norvasc)
  - **Nicardipine**

- **Beta blockers**
  - **Propranolol** (Deralin) nonselective
  - **Atenolol** (Normiten) selective

- **Central α-adrenergic agonists**
  - **Clonidine** (Clonirit)

- **Peripheral α-blockers**
  - **Prazosin** (Hypotense, Minipress)

- **α and β blockers**
  - **Labetalol**

Main Drug Groups for Treatment of Hypertension (2)

- **ACE inhibitors**
  - **Captopril** (Capoten)
  - **Enalapril** (Convertin)

- **Angiotensin II receptor antagonists**
  - **Losartan** (Ocsaar)

- **Vasodilators**
  - **Hydralazine**
  - **Minoxidil**
  - **Sodium nitroprusside**
  - **Diazoxide**

- **Diuretics**
  - **Loop diuretics**
    - **Furosemide** (Fusid)
  - **Thiazides**
    - **Hydrochlorothiazide** (Disothiazide)
    - **Metolazone** (Zaroxolyn)
  - **Potassium sparing**
    - **Spironolactone** (Aldospirone, Aldactone)
## Treatment of Hypertensive Emergencies in Children

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nifedipine</strong></td>
<td>0.25-1mg/kg/dose PO (not sublingual)</td>
</tr>
<tr>
<td><strong>Hydralazine</strong></td>
<td>0.15-0.25 mg/kg/dose IV may be repeated every 15 min</td>
</tr>
<tr>
<td><strong>Sodium nitroprusside</strong></td>
<td>0.5-1µg/kg/min IV</td>
</tr>
<tr>
<td><strong>Captopril</strong></td>
<td>0.1-0.2 mg/kg PO q6h</td>
</tr>
<tr>
<td><strong>Diazoxide</strong></td>
<td>1-5mg/kg IV (rapid bolus or continuous infusion)</td>
</tr>
<tr>
<td><strong>Labetalol</strong></td>
<td>0.3-1mg/kg/dose IV (may be given by continuous infusion 0.4-1mg/kg/hr)</td>
</tr>
</tbody>
</table>