Acute Kidney Injury

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What is AKI?

Sudden loss of renal function, over hr-days, with derangement(s) in fluid balance, acid base & electrolytes

KDIGO Clinical Practice Guidelines for Acute Kidney Injury
Kidney International 2012
Serum Creatinine versus Urine output

Serum creatinine: pitfalls
- Varies: age, gender, muscle
- Rises after 50% function lost
- Volume overload & creatinine
- Tubular secretion overestimates function
- Does not depict decline in function immediately
- Methods of estimation
- Easily dialyzed

Urine output
- Duration & episodes have prognostic value
- Enables early diagnosis
- Improves management
- Useful chiefly in PICU

The canary in the coal mine
Emphasis on early recognition

Any of the following

Increase in creatinine by $\geq 0.3$ mg/dl within 48 hr

Increase in creatinine to $\geq 1.5$ times baseline, known or presumed to have occurred within prior 7 d

Urine volume $< 0.5$ ml/kg/hr for 6 hr
Conceptual model for AKI

Stages defined by creatinine and urine output are surrogates

Antecedents
Intermediate Stage
AKI
Outcomes

Markers such as NGAL, KIM-1, and IL-18 are surrogates

RIFLE Severity of AKI

- **Risk**: Increased creatinine $\times 1.5$ or GFR decrease $>25%$
- **Injury**: Increased creatinine $\times 2$ or GFR decrease $>50%$
- **Failure**: Increased creatinine $\times 3$ or GFR decrease $>75%$ or creatinine $\geq 4$ mg per 100 ml (acute rise of $\geq 0.5$ mg per 100 ml/dl)

<table>
<thead>
<tr>
<th>GFR criteria</th>
<th>Urine output criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased creatinine $\times 1.5$ or GFR decrease $&gt;25%$</td>
<td>UO $&lt;0.5$ ml kg$^{-1}$ h$^{-1}$ $\times 6,$ h</td>
</tr>
<tr>
<td>Increased creatinine $\times 2$ or GFR decrease $&gt;50%$</td>
<td>UO $&lt;0.5$ ml kg$^{-1}$ h$^{-1}$ $\times 12,$ h</td>
</tr>
<tr>
<td>Increased creatinine $\times 3$ or GFR decrease $&gt;75%$ or creatinine $\geq 4$ mg per 100 ml (acute rise of $\geq 0.5$ mg per 100 ml/dl)</td>
<td>UO $&lt;0.3$ ml kg$^{-1}$ h$^{-1}$ $\times 24,$ h or anuria $\times 12,$ h</td>
</tr>
</tbody>
</table>

**High sensitivity**

**High specificity**

- **Loss**: Persistent ARF = complete loss of renal function $>4$ weeks
- **ESRD**: End-stage renal disease
# Severity of AKI

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum creatinine</th>
<th>Urine output</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5–1.9 times baseline OR ( \geq 0.3 \text{ mg/dl} \ (\geq 26.5 \text{ μmol/l}) ) increase</td>
<td>(&lt; 0.5 \text{ ml/kg/h for 6–12 hours})</td>
</tr>
<tr>
<td>2</td>
<td>2.0–2.9 times baseline</td>
<td>(&lt; 0.5 \text{ ml/kg/h for } \geq 12 \text{ hours})</td>
</tr>
<tr>
<td>3</td>
<td>3.0 times baseline OR Increase in serum creatinine to ( \geq 4.0 \text{ mg/dl} \ (\geq 353.6 \text{ μmol/l}) ) OR Initiation of renal replacement therapy OR, In patients (&lt; 18 \text{ years}), decrease in eGFR to (&lt; 35 \text{ ml/min per 1.73 m}^2)</td>
<td>(&lt; 0.3 \text{ ml/kg/h for } \geq 24 \text{ hours}) OR Anuria for ( \geq 12 \text{ hours})</td>
</tr>
</tbody>
</table>
RIFLE & stepwise increase in mortality

KI 2008; 73, 538-546

24 studies (2004-07); 71000 patients

<table>
<thead>
<tr>
<th>AKI level</th>
<th>RR [95% CI] mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>2.40 [1.9, 3.0]</td>
</tr>
<tr>
<td>Injury</td>
<td>4.15 [3.1, 5.5]</td>
</tr>
<tr>
<td>Failure</td>
<td>6.37 [5.1, 7.9]</td>
</tr>
</tbody>
</table>

P <0.0001; vs. non-AKI
Validated in children

7-fold higher mortality in children with heart failure & creatinine rise of >0.3

Intensive Care Med 2008;34:1713

**AKI @ admission to PICU: 5x increased mortality**

**AKI during admission: 9x mortality; 4x stay**

Schneider Crit Care Med 2010;38:933

**Adjusted OR for death: Risk 2.9 (0.8,11); Injury/Failure 3 (1,8)**

Akcan-Arikan Kidney Int 2007; 71:1028

**Incident AKI in 19.4 cases per 1000 patient days**

**Higher stages AKI: increased mortality & prolonged hospital stay**

Mehta Indian Pediatr 2012;49: 537-42

**AKI affects PICU mortality**

Nat Rev Nephrol 2010;6:393
# Etiology of ARF (%)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>35</td>
<td>17</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>HUS</td>
<td>-</td>
<td>36</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>25</td>
<td>19</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>GN</td>
<td>30</td>
<td>13</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Obstruction</td>
<td>3</td>
<td>3</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

**Causes vary with age; determine mortality**

- Incident AKI 15%
- AKI @ admission 5.5%
  - HUS
  - Septicemia
  - Rapidly progressive GN
  - Dehydration

References:
- Indian Pediatr 2012, 49: 537-42
AKI: Profile, Outcome

Ankara Ped Neph 2009;24:1379

100 [‘03-08] median 7-yr
Marrow transplant 27%;
GN 14%; dehydration 10%;
cardiac surgery; multiple 31%
Dialysis 45%; mortality 31%
Outcome related to AKI
stage; underlying cause

Thailand Pediatr 2006;118: 786

1982-2004; n=318; mean 7 yr
Sepsis (21%), hypovolemia,
GN, SLE, infections
Mortality 42%; declining

<table>
<thead>
<tr>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Dengue</td>
</tr>
<tr>
<td>Scrub typhus</td>
</tr>
<tr>
<td>Leptospirosis</td>
</tr>
<tr>
<td>Malaria</td>
</tr>
<tr>
<td>Acute glomerular diseases</td>
</tr>
<tr>
<td>Underlying renal diseases</td>
</tr>
<tr>
<td>Underlying cardiac diseases</td>
</tr>
<tr>
<td>Envenomations</td>
</tr>
<tr>
<td>Haemolytic uraemic syndrome</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
<tr>
<td>Others*</td>
</tr>
</tbody>
</table>

Data from Krishnamurthy and colleagues.*Includes children with hepatorenal syndrome, diabetic ketoacidosis, hypoxic ischaemic injury, acute lymphoblastic leukaemia, intracranial haemorrhage with shock, and poisonings (organophosphorus and endosulfan).

Table: Most important causes of 166 cases of paediatric acute kidney injury in South India
**Tropical infections & AKI**

**Malaria**

AKI 1-4%; in 60% with severe malaria

Mortality 25-45%

Acute tubular necrosis
Interstitial nephritis
Mesangioproliferative GN
Blackwater fever
Thrombotic microangiopathy

**Dengue**

AKI 0.3-5%

Acute tubular necrosis
Mesangioproliferative GN
Hemolytic uremic syndrome

**Leptospirosis**

Non oliguric renal failure, transaminitis

Acute tubular necrosis; interstitial nephritis
Mesangioproliferative GN
Envenomation & AKI

Snake bites (vipers, sea snakes) cause 50,000 deaths/yr
Hemolysis, hemoglobinuria, rhabdomyolysis
Tubular necrosis; interstitial nephritis, GN, arteritis
Antivenom; maintain urine flow; alkalization

Acute renal failure following wasp sting (children) 14%

Hornet attacks: hemolysis, rhabdomyolysis
38 of 65 (59%) patients AKI
Vietnam. NDT 2010;25:1146
Contrast Nephropathy

High- ~2000 mOsm/kg
Low- 600-800
Iso-osmolal 290; less toxic

Minimum contrast volume
Saline/ bicarbonate-based @ 1.0 mL/kg/min for 3-12 h before & 6-12 h after contrast exposure
Urine output (1.5 ml/kg/h)

Algorithm for patients receiving iodinated contrast media

Meta-analysis (16 studies) Iso- vs. low-osmolar media. J Am Coll Cardiol 2006;48:692
Volume of contrast. J Am Coll Cardiol 2007;50:584
Thrombotic Microangiopathy
Thrombocytopenia, hemolysis & schistocytes

Thrombotic Microangiopathy

Hemolytic Uremic Syndromes

Thrombotic Thrombocytopenia Purpura

Typical HUS
Atypical HUS
Alternate Complement Pathway Abnormality
Secondary HUS
Idiopathic HUS

Toxin Associated
Stem Cell Transplant
Pregnancy/HELLP
Drug Associated
Malignant Hypertension
Septicemia/DIC
Autoimmune Disorders
Malignancy
Streptococcal Infection
The new ‘H’ in HUS
Anti-factor H associated HUS

6-10% of atypical HUS in children
Peak age 7-12 years
Antibodies develop on a genetic background

During 2007 & 2013: 246 patients from 26 centers
Anti-CFH antibodies in 138 (56%)
Specific therapies possible

Prompt plasma exchanges and immunosuppressive treatment improves the outcomes of anti-factor H autoantibody-associated hemolytic uremic syndrome in children
The contrasting characteristics of acute kidney injury in developed and developing countries

Jorge Cerdá*, Arvind Bagga, Vijay Kher and Rajasekara M Chakravarthi

March 2008; 4:138-53

**Developed nations:** AKI chiefly in ICU; older population; multiorgan failure & sepsis; high mortality

**Developing world:** AKI in the young; single diseases [gastroenteritis, malaria, sepsis, leptospirosis, HUS, enzyme deficiencies]
**Evaluation**

Blood counts
Urea, creatinine, electrolytes, calcium, phosphate
Blood pH, bicarbonate

**Urinalysis:** sodium, osmolality, FE sodium

Chest X-ray; ECG
Abdominal ultrasonography

**Determine etiology**

**HUS:** Smear, platelets, reticulocytes, LDH; C3; shigatoxin

**GN:** ASO, C3, ANA, ANCA

**Thrombosis:** Doppler ultrasonography

Renal biopsy
## KDIGO Clinical Practice Guidelines for AKI

Kidney International 2012

<table>
<thead>
<tr>
<th>High Risk</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinue all nephrotoxic agents when possible</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Ensure volume status and perfusion pressure</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Consider functional hemodynamic monitoring</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Monitor Serum creatinine and urine output</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Avoid hyperglycemia</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Consider alternatives to radiocontrast procedures</td>
<td>Non-invasive diagnostic workup</td>
<td>Consider invasive diagnostic workup</td>
<td>Check for changes in drug dosing</td>
</tr>
<tr>
<td></td>
<td>Consider Renal Replacement Therapy</td>
<td>Consider ICU admission</td>
<td>Avoid subclavain catheters if possible</td>
</tr>
</tbody>
</table>
Surviving Sepsis Guidelines: Fluids

Early goal directed therapy: prevents AKI

Saline & albumin as good

Hexastarch & AKI

Persistent overload: hypoxia, ARDS

Judicious fluid removal

EGDT (6 hr of dx)

- MAP >65 mm Hg
- CVP 8-12 mm
- Venous saturation 80%
- Urine output >0.5 ml/kg/h

EGDT Collaborative Group. NEJM 2001;345: 1368
Preventing nephrotoxicity

Aminoglycosides
Use suitable, less nephrotoxic alternatives (2A)
Administer as single dose daily regimen (2B)
Monitor drug levels if using multiple doses (1A) or single-daily dose for more than 48-hr (2C)
Use topical or local route, when feasible (2B)

Amphotericin B
Use lipid formulations rather than conventional (2A)
Azoles and/or echinocandins, if equal efficacy assumed (1A)

Dose modification in renal failure
Loop diuretics for AKI

Frusemide: No benefits in prevention & treating AKI
Do not improve survival, recovery of renal function

High doses: increased ototoxicity

Recommend not using diuretics to prevent AKI (1B)
Suggest not using diuretics to treat AKI, except management of volume overload (2C)
Suggest not using diuretics to enhance renal recovery, or to reduce duration or frequency of RRT (2B)

Crit Care Resusc 2007; 9: 60-68
Renal vasodilators

**Low dose Dopamine**
- Increases RBF & GFR
- Does **not** prevent/alter course
- Tachycardia, myocardial & tissue ischemia
- **No role in preventing AKI**

The myth. JAPI 2002; 50: 571-575

**Fenoldopam**
- Reduced RRT (OR 0.4); mortality (OR 0.5)
- Lower creatinine; less AKI [than dopamine]

Blinded RCT. Crit Care Med 2005; 33: 2451
Fenoldopam vs. dopamine. Crit Care Med 2006;34:707

Recommend **not** using dopamine to prevent or treat AKI (1A)
Suggest **not** using fenoldopam to prevent or treat AKI (2C)

Suggest **not** using ANP to prevent or treat AKI (2B)
Delivery of nutrition: A challenge

High catabolism & energy needs; dialysis losses
Enteral nutrition preferred; fortification

Table 9.1  Recommended protein intake and estimated protein losses during dialysis therapy for acute renal failure

<table>
<thead>
<tr>
<th>Age (weight range)</th>
<th>RDI</th>
<th>Estimated PD losses</th>
<th>Estimated HD losses</th>
<th>Estimated CRRT losses</th>
<th>Daily protein intake goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant (≤10 kg)</td>
<td>1.6–2.2</td>
<td>2.0–4.0</td>
<td>0.5–1.0</td>
<td>2.0–3.0</td>
<td>2.0–6.0</td>
</tr>
<tr>
<td>Small child (&gt;10 and ≤25 kg)</td>
<td>1.0–1.2</td>
<td>2.0–3.0</td>
<td>0.5–1.0</td>
<td>2.0–3.0</td>
<td>1.0–3.0</td>
</tr>
<tr>
<td>Older child (&gt;25 and ≤40 kg)</td>
<td>0.8–1.2</td>
<td>1.0–2.0</td>
<td>0.5–1.0</td>
<td>2.0–3.0</td>
<td>1.0–3.0</td>
</tr>
<tr>
<td>Adolescent (&gt;40 kg)</td>
<td>0.8–1.0</td>
<td>1.0–2.0</td>
<td>0.5–1.0</td>
<td>2.0–3.0</td>
<td>1.0–3.0</td>
</tr>
</tbody>
</table>

Adapted from [4]
Values are expressed as grams of protein kg⁻¹ day⁻¹. RDI recommended dietary intake for normal children, PD peritoneal dialysis, HD hemodialysis, CRRT continuous renal replacement therapy

Table 9.2  Recommendations for oral water-soluble vitamin supplementation in acute kidney injury and composition of pediatric and adult parenteral vitamin preparations

<table>
<thead>
<tr>
<th>Supplement</th>
<th>ASPEN recommendation</th>
<th>ASPEN enteral dose</th>
<th>M.V.I. pediatric for infusion</th>
<th>M.V.I. adult for infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiamine</td>
<td>Recommended</td>
<td>0.2–1 mg day⁻¹</td>
<td>1.2 mg</td>
<td>6 mg</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>Recommended</td>
<td>0.3–1 mg day⁻¹</td>
<td>1.4 mg</td>
<td>3.6 mg</td>
</tr>
<tr>
<td>Pyridoxine</td>
<td>Recommended</td>
<td>6.25–50 mg day⁻¹</td>
<td>1 mg</td>
<td>6 mg</td>
</tr>
<tr>
<td>Folate</td>
<td>Recommended</td>
<td>0.4–1 mg day⁻¹</td>
<td>140μg</td>
<td>600μg</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>Recommended</td>
<td>0.5–2.5 μg day⁻¹</td>
<td>1 μg</td>
<td>5 μg</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Caution</td>
<td>≤60 mg day⁻¹</td>
<td>80 mg</td>
<td>200 μg</td>
</tr>
</tbody>
</table>

Guidelines on Nutrition

Intake >20-30 kcal/kg/d (2C)

Avoid restricting proteins to prevent/delay RRT (2D)

Suggest administering protein at
0.8-1.0 g/kg/d in noncatabolic patients not on dialysis
1.0-1.5 g/kg/d in patients with AKI on RRT
Up to 1.7 g/kg/d in those on CRRT, hypercatabolic (2D)

Provide nutrition preferably by enteral route (2C)
Management of complications

Fluid overload
Pulmonary edema
Hypertension
Metabolic acidosis
Hyperkalemia
Hyponatremia
Severe anemia
Hyperphosphatemia
Begin renal replacement therapy early

Uremia
Late initiation BUN >76: high risk of death
Multicentric; adults
CJASN 2006;5:915

CVVH dosing requirements
Lower BUN @ initiation: better outcome
Lancet 2000; 356:26

Fluid overload
116 patients; 39% sepsis
<20% overload: 59% survival
>20% overload: 40% survival
P<0.002
PRISM similar
Goldstein, ppCRRT. KI 2005; 67: 653

Fluid overload >15%
Independent risk factor for mortality

Fluid overload = fluid in (L) - fluid out (L) x 100
weight @ admission (kg)
Initiate RRT *emergently* if life-threatening fluid, electrolyte and acid-base imbalance exist (Not Graded)

Consider the *broad clinical context*, the presence of conditions that can be modified with RRT, and *trends* of laboratory tests — when making the decision to start RRT (Not Graded)
Choice of RRT depends on clinical features, location & expertise

Peritoneal dialysis: prefer if isolated ARF; universally available
Hemodialysis: efficient; nursing expertise
Hemofiltration: increasingly used in PICU; enables nutrition; risks of bleeding

Table 1 Advantages and disadvantages of various modalities of renal replacement therapy for acute renal failure (CVVH continuous venovenous hemofiltration, CVVHDF continuous venovenous hemodiafiltration)

<table>
<thead>
<tr>
<th>Type</th>
<th>Complexity</th>
<th>Use in hypotension</th>
<th>Efficiency</th>
<th>Volume control</th>
<th>Anticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peritoneal dialysis</td>
<td>Low</td>
<td>Yes</td>
<td>Moderate</td>
<td>Moderate</td>
<td>No</td>
</tr>
<tr>
<td>Intermittent hemodialysis</td>
<td>Moderate</td>
<td>No</td>
<td>High</td>
<td>Moderate</td>
<td>Yes</td>
</tr>
<tr>
<td>CVVH</td>
<td>Moderate</td>
<td>Yes</td>
<td>Moderate</td>
<td>Good</td>
<td>Yes</td>
</tr>
<tr>
<td>CVVHDF</td>
<td>High</td>
<td>Yes</td>
<td>High</td>
<td>Good</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Patients with AKI need follow up

Evaluate patients at 3-mo after AKI
Manage patients with CKD as per guidelines
Consider patients without CKD as being at increased risk
AKI: Conclusions

Early recognition; judicious therapy
Varied & evolving etiology
Limited role of pharmacological interventions
Determining etiology enables specific therapy
Prompt initiation of RRT (not mode, nor dose) effects outcomes
Need prolonged follow up
Pre-Congress CME

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