Acute Kidney Injury

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Objectives:
• Define and discuss acute kidney injury (AKI) as it relates to both trauma and critical care
• Compare and contrast renal biomarkers for early detection of AKI
• Discuss prevention and treatment strategies for AKI
ACUTE KIDNEY INJURY

Harry O. Senekjian, M.D.
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ACUTE KIDNEY INJURY-DEFINITION

A decrease in glomerular filtration rate (GFR) occurring over hours to days resulting in failure of the kidneys

- To excrete nitrogenous waste products
- To maintain fluid and electrolyte balance
- To metabolize and eliminate drugs
- To synthesize EPO and calcitriol
Incidence

• Approximately 7% of all hospitalized patients
• 65-70% of critically ill patients
  – RIFLE Stage F 10-20% of ICU admissions
• AKI requiring RRT: Mortality range 50-70%
• Sepsis most common cause
Acute Kidney Injury is on the rise

S.M. Bagshaw,
Div Critical Care U. Edmonton

A. Ishani, ASN 2009 and
USRDS Annual Report, 2009
**Figure 2** RIFLE criteria for diagnosing AKI

<table>
<thead>
<tr>
<th>Risk</th>
<th>Serum creatinine level</th>
<th>Urine output criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Increased serum creatinine level × 1.5</td>
<td>Urine output &lt;0.5 (ml/kg)/h for 6 h</td>
</tr>
<tr>
<td>Injury</td>
<td>Increased serum creatinine level × 2</td>
<td>Urine output &lt;0.5 (ml/kg)/h for 12 h</td>
</tr>
<tr>
<td>Failure</td>
<td>Increased serum creatinine level × 3 or serum creatinine level ≥350 μmol/l (acute rise of ≥44 μmol/l)</td>
<td>Urine output &lt;0.3 (ml/kg)/h for 24 h or anuria for 12 h</td>
</tr>
<tr>
<td>Loss</td>
<td>Persistent AKI = complete loss of renal function for &gt;4 weeks</td>
<td></td>
</tr>
<tr>
<td>ESRD</td>
<td>End-stage renal disease</td>
<td></td>
</tr>
</tbody>
</table>


### Table 1 AKIN staging system for AKI

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum creatinine criteria</th>
<th>Urine output criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Increase in serum creatinine level of ≥25 μmol/l or ≥150–200% (1.5–2-fold) from baseline</td>
<td>Change in urine output &lt;0.5 (ml/kg)/h for &gt;6 h</td>
</tr>
<tr>
<td>2</td>
<td>Increase in serum creatinine level to &gt;200–300% (&gt;2–3-fold) from baseline</td>
<td>Change in urine output &lt;0.5 (ml/kg)/h for &gt;12 h</td>
</tr>
<tr>
<td>3</td>
<td>Increase in serum creatinine level to &gt;300% (&gt;threefold) from baseline (or serum creatinine level of ≥354 μmol/l with an acute increase of at least 44 μmol/l)</td>
<td>Change in urine output &lt;0.3 (ml/kg)/h for 24 h or anuria for 12 h</td>
</tr>
</tbody>
</table>

*The AKIN modification of RIFLE criteria is a highly sensitive staging system based on data indicating that a small change in serum creatinine influences outcome. Only one criterion (serum creatinine level or urine output) has to be fulfilled to qualify for a stage. Given wide variation in indications and timing of initiation of renal replacement therapy, individuals who receive renal replacement therapy are considered to have met the criteria for stage 3 irrespective of the stage they are in at the time of initiation of renal replacement therapy. Abbreviations: AKI, acute kidney injury; AKIN, acute kidney injury network; RIFLE, Risk, Injury, Failure, Loss, and End-stage renal disease. Permission obtained from BioMed Central © Mehta, R. L. et al. Crit. Care 11, R31 (2007).*
Markers of AKI-1

Creatinine-most common, least sensitive

Nutrition ➔ Muscle mass ➔ Infection
Edema ➔ Protein metabolism
Volume of distribution ➔ Serum creatinine ➔ Hepatic function
Renal excretion
Markers of AKI-2

Cystatin-C

- 13 K Dalton proteinase produced by all nucleated cells
- Production is not influenced by race, gender or inflammation
- Eliminated strictly by GFR
- Somewhat better than serum creatinine, but still not very sensitive
- Much more expensive
Potential Biomarkers of Kidney Damage

- Urinary IL-18
- Urinary IL-6
- Urinary TNF
- Urinary Kidney Injury Molecule (KIM-1)
- Urinary Tubular Enzymes
- Urinary Proteases
- Plasma Granzyme B
- NGAL (Neutrophil Gelatinase Associated Lipocalin)
NephroCheck

- Detects the presence of insulin-like growth factor binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases (TIMP-2) in the urine.
- Provides a score to determine the risk of developing AKI within 12 hours of the test.
- Accurately detected 92% of AKI patients in one study and 76% in a second study. False positive in 50% of patients without AKI.
Defining the contribution of renal dysfunction to outcome after traumatic injury


- 3,968 patients with ISS ≥ 14
- 167 (4%) developed SCr > 2
- Mortality 2.9% vs. 34.1%
- Hospital LOS 10.9 vs. 29.1
- Ventilator days 2.4 vs. 12.7
AKI and Mortality

• Independent risk factor
• “AKI appears to increase the risk of developing severe non-renal complications that lead to death”
• Respiratory failure 20.7% vs 57.4%
• ICU mortality 14% vs 42.8%
• In-hospital mortality 7% vs 34%
Causes of AKI

Top 5
• Sepsis
• Major surgery
• Low cardiac output
• Hypovolemia
• Medications

Other common causes
• Cardiopulmonary bypass
• IAH-ACS
• Trauma
• Rhabdomyolysis
• Obstruction
Differential Diagnosis of AKI

Pre-renal
Post-renal
Intra-renal
Pre-Renal AKI

The problem may lie anywhere between the heart and the glomerulus

- LV failure
- Cardiac tamponade
- Constrictive pericarditis
- Coarctation
- Renal artery disease
- Renal vasoconstriction
- Volume depletion/hemorrhage
Urine Sodium

• In the setting of oliguria, **urine sodium below 20 mEq/L usually indicates a prerenal disorder**

• Elevated urine sodium can occur when a prerenal disorder is superimposed on intrinsic renal dysfunction (or diuretic therapy)

One of the most reliable parameters to determine difference: FENa
FENa

- FENa < 1% = Prerenal disorder
- FENa > 2% = Intrinsic renal disorder

\[ \text{FENa} = 100 \times \frac{\text{sodium}_{\text{urinary}} \times \text{creatinine}_{\text{plasma}}}{\text{sodium}_{\text{plasma}} \times \text{creatinine}_{\text{urinary}}} \]
Pre-Renal AKI

• GFR is poor, but tubules function normally
• Characterized by:
  – Concentrated urine (sg>1.020)
  – High BUN:creatinine ratio (>20)
  – Bland urine sediment
  – Avid sodium reabsorption
    • Urine sodium <20
    • FE sodium <1%
Treatment for Pre-Renal AKI

Fix the underlying problem
Post Renal AKI

• Should always be considered, even if just to dismiss it
  – Bladder outlet obstruction
  – Solitary kidney
  – Large Stones
  – Women with pelvic malignancy

• There is not much easier or less invasive test than an ultrasound
Renal Ultrasound

- Confirm number of kidneys
- Rule out obstruction
- Evaluate degree of chronicity if baseline lab values are unknown
- Measure degree of volume depletion (IVC)
Intrinsic Renal Disorders

• Impaired glomerular filtration, renal tubular dysfunction, or both
• UNa > 40 mEq/L, FENa > 2%
• Described as three entities:
  – Acute glomerulonephritis
  – Acute tubular necrosis (*most common*)
  – Acute interstitial nephritis
Intrinsic Renal AKI

• Vasculitis or glomerulonephritis
  – Characterized by proteinuria, hematuria, casts
  – Diagnosed by renal biopsy

• Acute interstitial nephritis (AIN)
  – Rash (15%), fever (27%), eosinophilia (23%)
  – Modest proteinuria
  – Most commonly drug-induced (>70%)
  – Other causes include autoimmune disease, infections
  – Definitive diagnosis by renal biopsy
## Drugs Commonly Causing AIN

<table>
<thead>
<tr>
<th>NSAID’s</th>
<th>Penicillins, cephalosporins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>Sulfa</td>
</tr>
<tr>
<td>Quinolones (Cipro)</td>
<td>H2 receptor blockers</td>
</tr>
<tr>
<td>PPI’s</td>
<td>Allopurinol</td>
</tr>
</tbody>
</table>
Acute Tubular Necrosis (ATN)

• Most common cause of AKI in hospital or ICU setting
• Sepsis and ischemia are the most common causes
• Clinical manifestations:
  – Urine output may vary from complete anuria to polyuria
  – Characterized by high urine Na (>40) and high FENa (>2%)
  – Urinalysis can demonstrate deeply pigmented granular casts and renal tubular epithelial cells
Assessment of Patients with AKI

• Careful History and Physical
  – Nephrotoxins
  – Hypotension/ischemia/sepsis
  – New medications
  – Isolated or part of a systemic process
  – Reasons for pre or post renal disease

• Urinalysis
• Renal Imaging
• Urine Electrolytes
Urine Microscopy

• Urine Microscopy
  – Examination of sediment, easy, cost-effective
• Abundant tubular epithelial cells (ATN)
• White cell casts (*interstitial nephritis*)
• Pigmented casts (*myoglobinuria*)

If unrevealing, urinary sodium determination may be helpful
Consequences of AKI

• Inability to excrete sodium water, potassium, hydrogen ion, nitrogenous wastes

• Uremic syndrome
  – Encephalopathy
  – Pericarditis
  – Platelet dysfunction
  – Immune dysfunction
Indications for Renal Replacement Therapy (RRT)

• Volume overload, usually with respiratory insufficiency
• Acidosis (pH<7.2)
• Hyperkalemia
• “Uremic symptoms”
  – Pericarditis
  – Altered mental status
  – Hyperuricemia
• Poisonings
  – Ethylene glycol, methanol, aspirin
Modes of RRT

- Intermittent hemodialysis: 3-5 hours, 3-6 times weekly
- Continuous renal replacement therapy (CRRT)
- Slow low efficiency daily dialysis (SLEDD). Hybrid of IDH and CRRT, 8-12 hours per day
- Acute peritoneal dialysis
CRRT vs IHD

• Advantages:
  – Hemodynamic stability
  – Continuous fluid removal
  – Increased alimentation
  – Elimination of inflammatory mediators
  – Better control of azotemia, fluids, electrolytes, acid/base
  – Steady state BUN and serum creatinine
  – Minimizes shifts in ICP
  – No complex machinery, relatively simple to perform
CRRT vs IHD

• Disadvantages
  – Immobilization
  – Continuous anticoagulation
  – Time and labor intensive for ICU nurses
Outcomes with CRRT vs IHD

• Meta analysis of 13 studies (n=1400)
  – Similar mortality rate: CRRT 68%, IHD 73.5%
  – Comparison difficult since mortality ranged from 33-93%
• Prospective randomized studies are difficult to perform
  – Hemodynamically unstable patients cannot tolerate IHD
  – Difficult to confine hemodynamically stable patient to bed to perform CRRT
RRT: Early vs Late

• There is no data to indicate that early initiation of RRT is associated with superior outcomes

• Risks of starting RRT too early
  – Risks of catheter placement procedure
  – Line associated sepsis
  – Immobilization
  – Prolonged ICU stay
Diuretics in AKI

Diuretics or no diuretics at nephrology consultation

<table>
<thead>
<tr>
<th>Diuretic Group</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>In hospital mortality</td>
<td>1.65 (1.05-2.55)</td>
</tr>
<tr>
<td>Non-recovery of kidney function</td>
<td>1.60 (1.14-2.53)</td>
</tr>
</tbody>
</table>
“Renal Dose” Dopamine

- No proven benefit in AKI
- Associated with harmful arrhythmias, bowel ischemia, increased myocardial oxygen consumption, decreased oxygen saturation, suppressed pituitary hormones
- Should not be routinely used
### Table 2 Long-term consequences of AKI

<table>
<thead>
<tr>
<th>Study</th>
<th>Period studied</th>
<th>No. of patients studied</th>
<th>Hospital mortality (%)</th>
<th>Renal outcome in survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turney et al.</td>
<td>1956–1988</td>
<td>1,347</td>
<td>21</td>
<td>48% with increased serum creatinine level</td>
</tr>
<tr>
<td>Chertow et al.</td>
<td>1991–1993</td>
<td>132</td>
<td>70</td>
<td>33% on chronic RRT</td>
</tr>
<tr>
<td>Brivet et al.</td>
<td>1991</td>
<td>360</td>
<td>58</td>
<td>28% have serum creatinine level &gt;129 µmol/l</td>
</tr>
<tr>
<td>Korkeila et al.</td>
<td>1989–1990</td>
<td>3,447</td>
<td>45</td>
<td>8% on chronic RRT</td>
</tr>
<tr>
<td>Mogera et al.</td>
<td>1993–1998</td>
<td>979</td>
<td>69</td>
<td>10% on chronic RRT</td>
</tr>
<tr>
<td>Liaño et al.</td>
<td>1977–1992</td>
<td>748</td>
<td>55</td>
<td>19% have abnormal renal function, 2% on chronic RRT</td>
</tr>
<tr>
<td>Palevsky et al.</td>
<td>2003–2007</td>
<td>1,124</td>
<td>49.6</td>
<td>24.6% were on RRT at day 60</td>
</tr>
<tr>
<td>Bellomo et al.</td>
<td>2005–2008</td>
<td>1,508</td>
<td>44</td>
<td>5.4% were on RRT at day 90</td>
</tr>
<tr>
<td>Van Berendonck et al.</td>
<td>2001–2004</td>
<td>595</td>
<td>50.7</td>
<td>10.3% on RRT at 2 years</td>
</tr>
</tbody>
</table>

Abbreviations: AKI, acute kidney injury; RRT, renal replacement therapy.
ESRD After AKI

P<0.0001, DF=1

No AKI

AKI

P<0.0001, DF=3

No AKI or CKD

CKD only

AKI only

AKI and CKD