Diagnosis and Management of Acute Kidney Injury

Jeffrey S. Berns, MD
University of Pennsylvania School of Medicine

RIFLE Criteria for Classification of AKI

Class determined by worst of GFR or UO criteria

AKIN Classification

Table 1 Proposed classification/vaing system for acute kidney injury, based on modification of RIFLE criteria.

<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 of ≥264 μmol/L (3.0 mg/dl) OR to 150-200% of baseline</td>
<td>&lt;0.5 mg/dl/kg for &lt;12h</td>
</tr>
<tr>
<td>2</td>
<td>Increase to &gt;300-500% of baseline (2–3 fold)</td>
<td>&lt;0.5 mg/dl/kg for &lt;12h</td>
</tr>
<tr>
<td>3</td>
<td>Increase to &gt;500% of baseline (≥4-fold) or serum creatinine (≥344 μmol/L) with an acute rise of at least 44 μmol/L (0.5 mg/dl)</td>
<td>≤0.3 mg/dl/kg for 24h OR anuria for 12h</td>
</tr>
</tbody>
</table>

Only one criterion/endpoint (serum or urine output) needs to be fulfilled to qualify for a stage. Patients who receive renal replacement therapy are considered to have met the criteria for Stage 3, regardless of the stage they are in at the time of commencement of renal replacement therapy. Permission obtained from Blood Purification. D Mehta et al., 2007. Clin Care 1 (831).
Acute Kidney Injury - Definition

Abrupt (within 48 hours) reduction in kidney function

An absolute increase in serum creatinine of > 0.3 mg/dl or a percentage increase of > 50% or oliguria (UO < 0.5 ml/kg/hr for > 6 hours)

Acute Kidney Injury Network, 2005

Audience Response 1

What is the most common cause of AKI in hospitalized patients (not in ICU)?
A. Prerenal azotemia
B. Hepatorenal syndrome
C. Contrast induced AKI
D. Sepsis
E. Drug-induced AIN

Common Causes of AKI in the Hospital

• Prerenal azotemia--Hypovolemia
• Ischemic/septic ATN
• Contrast-induced AKI
• Hepatorenal syndrome
• Nephrotoxins
  – ATN
  – AIN
• Atheroemboli

AKI and GFR Assessment

Serum creatinine also affected by:
- Age
- Muscle mass
- Liver disease
- Acute illness
- Diet
- Medications: trimethoprim, cimetidine, antibiotics
Risk Factors for AKI

- Baseline CKD
- Older age
- CHF
- Diabetes mellitus
- Hypovolemia
- Multiple “hits”

Impact of AKI

10-24% increase in serum creatinine → 2-fold increase in mortality
25-49% increase in serum creatinine → 3-fold increase in mortality
> 50% increase in serum creatinine → 6-fold increase in mortality

Even small, completely reversible increases in serum creatinine are associated with increased mortality

AKI also increases risk of progressive CKD and ESRD

Even small, completely reversible increases in serum creatinine are associated with increased mortality

AKI Increases Risk of CKD and ESRD

PRERENAL ACUTE KIDNEY INJURY

Functional Causes

- Cardiac
  - Infarction, arrhythmias, valvular disease, tamponade, cardiomyopathy, severe HTN
- Volume Depletion
  - Hemorrhage
  - Gastrointestinal - vomiting, diarrhea, fistulae
  - Renal - diuretics, salt-wasting disorders
- Redistribution of Extracellular Fluid
  - Hypoalbuminemic states
  - Vasodilation - sepsis, antihypertensive drugs
  - Physical causes - peritonitis, 3rd spacing, crush injury
PRERENAL ACUTE KIDNEY INJURY
Structural Causes

- Renal Artery
  - Embolism
    - Atrial Fibrillation
    - Atherosclerotic Renal Artery Stenosis
    - Dissection
    - Trauma
- Renal Vein
  - Thrombosis

ACUTE KIDNEY INJURY
Acute Tubular Necrosis

- Post - Ischemic
- Heme Pigments
  - Myoglobinuria
  - Hemoglobinuria
- Nephrotoxins
  - Antibiotics
  - Contrast media
  - Heavy Metals
  - Poisons
  - Etc....
ACUTE KIDNEY INJURY
Primary Renal Diseases

• Acute Glomerulonephritis
• Acute Interstitial Nephritis
• Vasculopathy / Vasculitis
  – Microscopic polyarteritis
  – HUS-TTP
  – Malignant hypertension

Audience Response 2

• What of the following best distinguishes ATN from prerenal azotemia?
  A. Urine Na
  B. FE urea nitrogen
  C. Urine microscopic examination
  D. BUN/creatinine ratio
  E. Urine NGAL level

ACUTE KIDNEY INJURY
Urinary Indices

\[
\text{FENa} = \frac{\text{excreted Na}}{\text{filtered Na}} \times \frac{\text{UNaV}}{\text{PNa}} X \frac{\text{UCrV}}{\text{PCr}} X 100 \%
\]

Pathophysiology of Ischemic ATN
ACUTE KIDNEY INJURY
Fractional Excretion of Urea

- \[\text{FEUrea} = \frac{\text{Uurea nitrogen/BUN}}{\text{UCr/PCr}} \times 100\]
- FENa may be >1% despite pre-renal status—ie, “false positive” for ATN—in some patients on diuretics
- Unlike Na, urea reabsorption is not affected by diuretic administration
- In presence of “low renal perfusion”, urea reabsorption is maximal
- FEUrea < 35% suggests prerenal azotemia

Diagnostic Value of UA in ATN

- Don’t rely on clinical lab UA
- When viewed by a nephrologist, RTE cells and coarse granular casts predict:
  - ATN vs. prerenal azotemia
  - Higher AKIN stage
  - Worsening kidney function
  - Greater likelihood of needing dialysis
  - Death

URINARY SEDIMENT

- Dysmorphic RBC and RBC Casts
  - Acute Glomerulonephritis
  - Vasculitis
- WBC Cells and WBC Casts
  - Acute Pyelonephritis
  - Allergic Interstitial Nephritis
  - Especially if eosinophilia seen
- Crystalluria
  - Uric Acid - Tumor Lysis Syndrome

ACUTE KIDNEY INJURY
Urine Volume

- Anuria (< 100 ml/day)
  - Acute bilateral arterial or venous occlusion
  - Bilateral cortical necrosis
  - Acute glomerulonephritis (severe)
  - Obstruction (complete)
  - ATN (rare)
- Oliguria (100 to 500 ml/day)
  - ATN
  - Prerenal azotemia
- Non-Oliguria (> 500 ml/day)
  - ATN
  - Obstruction (partial)
Biomarkers and AKI

- Cystatin-C
- N-acetyl-β-glucosaminidase
- Kidney Injury Molecule-1 (KIM-1)
- Neutrophil Gelatinase Associate Lipocacin (NGAL)
- Interleukin (IL)-18
- Netrin-1
- Fatty Acid Binding Protein

Urinary NGAL as AKI Biomarker in the ED

- Urine NGAL helped distinguish AKI from other creatinine elevations and predicted in-patient outcome
- All markers had high NPV if (-)
- Only uNGAL had PPV > 0.90 if (+)

Toxic Nephropathies

- Therapeutic and diagnostic agents
- Alternative and complementary products
- Environmental exposures
- High renal blood flow and renal epithelial cell transport lead to high toxin exposure

Toxic Nephropathies

- Renal hypoperfusion/ischemia – diuretics, other antihypertensive agents
- GN – pamidronate, VEGF inhibitors, anabolic steroids, gold
- Vasculitis—cocaine, amphetamines, anti-TNFα therapy, propylthiourical, infliximab
- ATN – zolendronic acid, aminoglycosides, Chinese herbs
- Acute/chronic interstitial nephritis—TNTC
- Nephrolithiasis/crystalluria—acyclovir, indinavir, sodium phosphate, ephedra
- TTP—quinine, clopidogrel, mitomycin, cyclosporine, bevacizumab
AKI in Cirrhosis

• Interpret serum creatinine with caution—GFR very often < 50% predicted
• Prerenal azotemia is much more common than HRS
• Urine indices usually of little—UA microscopic is helpful

Hepatorenal Syndrome

• HRS-1: rapidly progressive AKI (inpatients)
  – median survival 2 weeks
• HRS-2: more slowly progressive AKI (outpatients)
  – median survival 6 months

Hepatorenal Syndrome--

Treatment

• Stop diuretics
• IV 0.9% saline and/or albumin 1 g/kg
• Vasoconstrictors:
  – Best data with terlipressin—not available in US
  – Midodrine 5-15 mg orally tid + octreotide 100-200 mcg sc tid+
    albumin 50-100 g/d (off-label use)
    • Trial of 7-14 days, should see increase BP and UO, decrease in serum
      creatinine
    • May improve short term (15-day) but not longer term mortality
• Albumin dialysis (????)
• Liver transplant is only definitive therapy

ACUTE KIDNEY INJURY

Contrast Media

• Prevalence
  – Less than 1% in patients with normal renal function
  – Increases significantly with reduced GFR
• Risk Factors
  – Reduced GFR
  – Diabetes mellitus
  – Volume of contrast media
  – Type of contrast media (?)
  – Multiple myeloma (?)
CONTRAST-INDUCED AKI
Clinical Characteristics
- Onset - 24 to 48 hrs after contrast exposure
- Duration - 5 to 7 days
- Non-oliguric (majority)
- Dialysis – rarely needed
- Urinalysis - dirty brown casts, RTE cells and casts
- Low FENa

CONTRAST MEDIA ACUTE KIDNEY INJURY
Prophylactic Strategies
- Use intravascular contrast only when necessary
- Hydration - NS or bicarbonate
- N-acetylcysteine (?)
- Minimize contrast volume
- Choice of contrast media (?)

Atheroemboli
- May account for 3-10% of AKI
- Angiography, vascular surgery, anticoagulation, spontaneous
- Risk factors:
  - Male sex
  - Age > 60 yrs
  - White > African American
  - Tobacco use
  - Diabetes mellitus
  - Atherosclerotic disease
  - AAA

Images from Scolari and Ravani, Lancet 2010

Note inflammatory response
- Anemia, leukocytosis, elevated ESR and CRP
- UA: proteinuria (usually low-grade but can be nephritic)
- Eosinophilia, eosinophiluria
- Hypocomplementemia

Atheroemboli
- Acute, subacute, chronic kidney injury
- Hypertension—often severe
- Livedo reticularis
- Blue toes, digital ulcers, purpura
- GI infarction, bleeding, pain
- MI
- TIA, stroke, spinal cord infarction
- Retinal emboli
- Anorexia, weight loss, fever

Images from Scolari and Ravani, Lancet 2010
ACUTE INTERSTITIAL NEPHRITIS

- Drugs (>75%)
  - Beta-lactam antibiotics
  - Trimethoprim-Sulfamethoxazole
  - Quinolones
  - Vancomycin, sulfonamides
  - NSAIDs
  - Proton Pump Inhibitors
  - Phenytoin, Allopurinol, many others

- Infection (5-10%)
  - Viruses, M.TB, various bacteria

- Idiopathic
  - TINU, anti-TBM

- Systemic diseases
  - SLE, Sarcoidosis, Sjogren

ALLERGIC INTERSTITIAL NEPHRITIS

Clinical Characteristics

- Fever
- Rash
- Arthralgia
- Eosinophilia
- Urinalysis
  - Hematuria - usually microscopic; rarely microscopic
  - Pyuria - sterile
  - Eosinophiluria

ALLERGIC INTERSTITIAL NEPHRITIS

- Based on retrospective data:
  - Final serum creatinine is lower with steroid treatment (4-6 weeks)
  - The longer the delay to start steroids, less likely to recover kidney function
  - Steroid treatment associated with lower likelihood of requiring dialysis

Audience Response 3

- What of the following reduces severity and improves outcomes of hospital-acquired AKI?
  A. Dopamine
  B. Mannitol
  C. Diuretics
  D. A and C
  E. None of the above
Pharmacologic Interventions
Proven to Improve Ischemic/Septic AKI

Meta-analysis: Diuretics in ARF
Ho et al BMJ 2006

- 9 studies with 549 patients
  - 3 for prevention of ARF
    - Cardiac surgery, cardiac angiography, major general/vascular surgery
  - 6 for treatment of ARF
- Variety of doses: 1 mg/h to 3400 mg/d
- No reduction in:
  - hospital mortality (RR 1.11; 0.92-1.33)
  - requirement for RRT (RR 0.99; 0.8-1.22)
  - number of dialysis sessions (-0.48; -1.45-0.5)
  - proportion of patients with persistent oliguria (0.54; 0.18-1.61)
- Not even one single RCT has shown benefit
- Increased risk of temporary deafness and tinnitus
- At least one cohort study suggests increased mortality risk

Pharmacologic Interventions that Don’t Improve Ischemic/Septic AKI

- Diuretics
- Dopamine
- ANP
- Fenoldopam (+/-)
- Mannitol
- Corticosteroids
- Pentoxifylline
- N-acetylcysteine
- Etc…

Pre-op Patients and AKI

- Delay OR after cardiac cath
- Stop ACEi and ARB (?)
- Benefit of statins (?)
- Assess GFR—don’t rely on serum creatinine
- Be careful with medication dosing
**Indications for RRT in AKI**

- **Absolute**—or you waited too long
  - Pericarditis
  - Uremic sepsis
  - Intractable hyperkalemia, acidosis, volume overload
  - No specific BUN or creatinine
- **Relative**
  - Oliguria of “some” duration
  - “Worrisome” electrolytes or azotemia level
  - Volume overload
- **Contraindication**
  - Nearly dead or going to die regardless of what we do
  - Patient/family wishes

**Renal Replacement Therapy Options**

- Intermittent HD (IHD)
- SCUF
- CVVH
- CVVHD
- CVVHDF
- SLED, EDD
- Peritoneal Dialysis
- None

**Does Dialysis Timing, Frequency, or Modality Matter?**

- When best to start dialysis remains unclear
  - Some evidence that “early” may be better than “late” but still controversial
- Daily HD may be better than less frequent HD in catabolic and hemodynamically unstable patients
- Studies have not demonstrated benefit of CRRT over HD—even in hemodynamically unstable ICU patients

**Conclusions and Summary**

- AKI is associated with bad outcomes
  - Even if mild and reversible
- Diagnosis most often the result of a careful history and PE
  - Labs much less useful in most patients
- No effective treatments once AKI is established
- Prevention and early recognition are key
- Importance in prevention is recognition of reduced GFR as risk—but don’t rely on serum creatinine!
- Check medication dosing as GFR goes up and down
- Various dialysis options
  - Not dialyzing is OK in appropriate circumstances
THANKS