Diagnosis and Management of Acute Kidney Injury

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Period Prevalence of Acute Renal Failure and Mortality by Country

<table>
<thead>
<tr>
<th>Country</th>
<th>No. of Patients</th>
<th>No. of Deaths</th>
<th>Prevalence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>50</td>
<td>5</td>
<td>100%</td>
<td>40%</td>
</tr>
<tr>
<td>Canada</td>
<td>40</td>
<td>4</td>
<td>100%</td>
<td>30%</td>
</tr>
<tr>
<td>Japan</td>
<td>30</td>
<td>3</td>
<td>100%</td>
<td>20%</td>
</tr>
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</table>

The annual incidence of community acquired AKI—both dialysis—requiring and not—is increasing > 7% per year in the US.

RIFLE Criteria for Classification of AKI

- **GFR Criteria**
  - Acute or chronic decrease in GFR by ≥25% or serum creatinine ≥1.5 x ULN
  - Decreased absolute GFR by ≥25% or serum creatinine ≥1.5 x ULN
- **Urine Output Criteria**
  - Decreased UO (UO < 0.5 mL/kg/h for 6 hours)
  - UO < 0.5 mL/kg/h for 12 hours

Severity determined by worst of GFR or UO criteria:
- Risk
- Injury
- Failure
- Losses
- ESRD
- ESRD - > 3 months

The table and chart provide detailed information on the prevalence and mortality of acute renal failure across different countries, highlighting the increasing trend in the US.
AKIN Classification

Table 1: Proposed classification/staging 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 to 1.5x baseline (0.3 mg/dl OR to 150-299% of baseline)</td>
<td>&lt;0.5 ml/kg/hr for &gt;4 h</td>
</tr>
<tr>
<td>2</td>
<td>Increase to &gt;200% of baseline (&gt;0.5 mg/dl)</td>
<td>&lt;0.5 ml/kg/hr &gt; 12 h</td>
</tr>
<tr>
<td>3F</td>
<td>Increase to &gt;200% of baseline (&gt;3 mg/dl) or serum creatinine &gt;5.0 mg/dl (444 μmol/L) with an acute rise of at least 4.4 mg/dl</td>
<td>&lt;0.5 ml/kg/hr for 24 h OR acute for 12 h</td>
</tr>
</tbody>
</table>

Only one criterion (serum creatinine or urine output) needs to be fulfilled to qualify for a stage. Variables that may affect renal replacement therapy are considered to have met this criteria for “Stage 3.” Exceptions of the stage had they gone in at the time of commencement of renal replacement therapy. Permission obtained from Oxford Centre for Clinical>All Life Ltd, (2005) Crit Care 11:R1.

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

AKI and GFR Assessment

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

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

Risk Factors for AKI

• Baseline CKD
  – Albuminuria level
• Older age
• CHF
• Diabetes mellitus
• Hypovolemia
• Multiple “hits”

[Graph showing adjusted HR for AKI]
Impact of AKI

10-24% increase in serum creatinine $\rightarrow$ 2-fold increase in mortality
25-49% increase in serum creatinine $\rightarrow$ 3-fold increase in mortality
$> 50\%$ increase in serum creatinine $\rightarrow$ 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.

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

"Cardiorenal Syndrome"
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

Pathophysiology of Ischemic ATN
**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**

<table>
<thead>
<tr>
<th>UOsm (mOsm/L)</th>
<th>UNa (mEq/L)</th>
<th>FENa = \frac{\text{excreted Na}}{\text{filtered Na}} \times \frac{\text{UNa/V}}{\text{PNa} / \text{UCr/V}}</th>
<th>X 100 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td>40</td>
<td>ATN</td>
<td>1.0</td>
</tr>
<tr>
<td>500</td>
<td>20</td>
<td>PR</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**ACUTE KIDNEY INJURY**

**Fractional Excretion of Urea**

- \frac{\text{Urea nitrogen/BUN}}{\text{UCr/PCr}} \times \text{X 100}

- FENa may be >1% despite pre-renal status—i.e., “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 eosinophiluria 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)

More likely to need dialysis and die
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
• Only uNGAL had PPV > 0.90

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 – zoledronic acid, aminoglycosides, Chinese herbs
- Acute/chronic interstitial nephritis—TNIC
- 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
  - Cirrhosis with ascites
  - Sustained increase in serum creatinine concentration to a level greater than 2.5 mg/dl (226 μmol/L) in less than 2 weeks
  - No improvement in serum creatinine (decrease to 1.5 mg/dl or less) after at least 2 days of diuretic withdrawal and expansion of plasma volume with albumin (1 g/kg body weight/day up to a maximum of 100 g/day)
  - Absence of shock
  - No current or recent treatment with nephrotoxic drugs or vasodilators
  - Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microscopic hematuria (>50 red blood cells per high-power field), or abnormal renal ultrasonography
Hepatorenal Syndrome--
Treatment

- Stop diuretics
- IV 0.9% saline and/or albumin 1 g/kg

- Vasoconstictors:
  - 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

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

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

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, Sjögren

ALLERGIC INTERSTITIAL NEPHRITIS

Clinical Characteristics

- Fever
- Rash
- Arthralgia
- Eosinophilia
- Urinalysis
  - Hematuria - usually microscopic; rarely macroscopic
  - 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

Pharmacologic Interventions that Don’t Improve Ischemic/Septic AKI

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

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 seizure
  - 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

ESRD and Death after “Minor” AKI following MI

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Conclusions and Summary

• The annual incidence of AKI is rising > 7% per year

• AKI is associated with bad outcomes
  – Even if mild and reversible
  – Mortality
  – CKD-ESRD
  – Poor QoL and functional status

• Diagnosis most often the result of a careful history and PE
  – Labs much less useful in most patients

Conclusions and Summary

• 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

QUESTIONS??