Acute Kidney Injury

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Outline

• Scope
• Definition
• Tools to diagnose
• Etiology
• Treatments
Why is this important?

• AKI occurs in 10-20% hospitalized patients
  – 40-60% ICU patients

• 5% of ICU patients with AKI require renal replacement therapy (50% mortality).

• AKI is associated with an increased risk for *de novo* CKD, CKD progression, and in some cases death.
Acute Kidney Injury Definition

**RIFLE**

- **Risk**
  - Increased Cr x 1.5 or GFR decreases >25%
  - Increased Cr x 2 or GFR decreases >50%
  - Increased Cr x 3 or GFR decreases >75% or Cr ≥ 4 mg/dl (with acute rise of ≥ 0.5 mg/dl)

- **Injury**
  - UO <0.5 ml/kg/hr x 6 hr

- **Failure**
  - UO <0.5 ml/kg/hr x 12 hr

- **Loss**
  - UO <0.3 ml/kg/hr x 24 hr or anuria x 12 hr

- **ESRD**
  - Persistent ARF = complete loss of renal function for > 4 weeks

- **2004**

**AKIN**

- **Cr Criteria**
  - Increased Cr x 1.5 or ≥0.3 mg/dl

- **Urine Output (UO) Criteria**
  - UO <0.5 ml/kg/hr x 6 hr

- **Stage 1**
  - Increased Cr x 2
  - UO <0.5 ml/kg/hr x 12 hr

- **Stage 2**
  - Increased Cr x 2
  - UO <0.3 ml/kg/hr x 24 hr or anuria x 12 hr

- **Stage 3**
  - Increased Cr x 3 or Cr ≥ 4 mg/dl (with acute rise of ≥ 0.5 mg/dl)
  - UO <0.3 ml/kg/hr x 24 hr or anuria x 12 hr

2007

Patients who receive renal replacement therapy (RRT) are considered to have met the criteria for stage 3 irrespective of the stage that they are in at the time of commencement of RRT.
KDIGO Definition of AKI 2012

- Increase in SCr by $\geq 0.3\text{mg/dL}$ within 48 hours
- Increase in SCr to $\geq 1.5 \times$ baseline, known or presumed to have occurred within prior 7 days
- Urine volume $< 0.5\text{mL/kg/h}$ for 6 hours

<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&lt;br&gt;$\text{OR} &gt; 0.3\text{ mg/dL}$ increase</td>
<td>$&lt;0.5\text{mL/kg/h}$ for 6-12h</td>
</tr>
<tr>
<td>2</td>
<td>2.0–2.9 $\times$ baseline</td>
<td>$&lt;0.5\text{mL/kg/h}$ for &gt;12h</td>
</tr>
<tr>
<td>3</td>
<td>3.0 $\times$ baseline&lt;br&gt;$\text{OR} &gt; 4.0\text{ mg/dL}$ increase&lt;br&gt;$\text{OR}$ Initiation of RRT</td>
<td>$&lt;0.3\text{mL/kg/h}$ for &gt;24h&lt;br&gt;$\text{OR}$ Anuria for &gt;12h</td>
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</tbody>
</table>
Limitations of Serum Creatinine

• Low Sensitivity – cellular injury that does not affect GFR
• Low Specificity – creatinine can increase/decrease without change in GFR
• Delayed – rise is seen 2-3 days after drop in GFR
• Fluid therapy – may dilute serum creatinine delaying diagnosis
• Inter-laboratory Variation
Work-up

- Basic Metabolic Panel
- Urinalysis with micro
- Fractional excretion of sodium (and/or Urea)
- Urine protein to creatinine ratio (UPC)*
- Autoimmune and infectious serology
- Renal ultrasound
- Renal Biopsy
Urinalysis – Cells

Isomorphic RBCs

Dysmorphic RBCs

Renal Tubular Epithelial Cells (RTE)

Squamous Epithelial Cells

WBCs
Urinalysis - Casts

- Granular
- RBC
- RTE
- WBC
Fractional Excretion of Na/Urea

\[ FENa = \frac{UNa \times SCr}{SNa \times UCr} \times 100\% \]

\[ FEUrea = \frac{UUN \times SCr}{BUN \times UCr} \times 100\% \]

- FENa < 1% suggests prerenal disease, where reabsorption of almost all of the filtered Na is an appropriate response to decreased renal perfusion.

- FENa > 2% percent usually indicates ATN

- FEUN < 35% suggests prerenal disease

- FEUN can be more accurate than the FENa in patients receiving diuretics when the FENa is higher than expected for clinical prerenal disease
Fractional Excretion of Na - Limitations

- The FENa criterion of less than 1% to diagnose prerenal disease applies **only** to patients with a marked reduction in GFR and oliguria.

- Single measurements of SCr may not provide an accurate estimate of the GFR.

- There are other causes of AKI other than prerenal disease in which the FENa can be less than 1%.

- The FENa may be above 1% when prerenal disease occurs in patients with CKD or any cause of sodium wasting, such as diuretic therapy.
Renal Ultrasound

- Low yield in patients without risk factors or clinical concern for obstruction
- Risk Factors - history of hydronephrosis, recurrent urinary tract infections, a diagnosis consistent with obstruction, non-black race.
  - AND absence of: exposure to nephrotoxins, congestive heart failure, or prerenal AKI
- RUS in AKI – 10-15% with hydronephrosis, but only 3-5% requiring intervention.
# Risk Factors for AKI

<table>
<thead>
<tr>
<th>Exposures</th>
<th>Susceptibilities</th>
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</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>Dehydration or volume depletion</td>
</tr>
<tr>
<td>Critical illness</td>
<td>Advanced age</td>
</tr>
<tr>
<td>Circulatory shock</td>
<td>Female gender</td>
</tr>
<tr>
<td>Burns</td>
<td>Black race</td>
</tr>
<tr>
<td>Trauma</td>
<td>CKD</td>
</tr>
<tr>
<td>Cardiac surgery (especially with CPB)</td>
<td>Chronic diseases (heart, lung, liver)</td>
</tr>
<tr>
<td>Major noncardiac surgery</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Nephrotoxic drugs</td>
<td>Cancer</td>
</tr>
<tr>
<td>Radiocontrast agents</td>
<td>Anemia</td>
</tr>
<tr>
<td>Poisonous plants and animals</td>
<td></td>
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</tbody>
</table>

CKD, chronic kidney disease; CPB, cardiopulmonary bypass.
Etiologies

AKI

Prerenal

Intrinsic

Postrenal

Acute Tubular Necrosis

Acute Interstitial Nephritis

Acute GN

Acute Vascular Syndromes

Intratubular Obstruction
Etiologies

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Postrenal

Intratubular Obstruction
Prerenal AKI

Volume Depletion

Congestive Heart Failure
Liver Failure
Sepsis

Incr Vasoconstriction
• ↑ Angiotensin II
• ↑ Adrenergic stim.
• ↑ Vasopressin

Decr Vasodilation
• ↓ Prostaglandins
• ↓ Nitric Oxide

Renal Hypoperfusion
Volume Depletion

• Isotonic Fluid Volume Deficit
  – Serum Na level remains wnl

• Decreased Cardiac Output
  – Decreased blood pressure, decreased organ/tissue perfusion

• Compensation
  – Neural – baro/chemoreceptors -> ↑SNS, ↑RR
  – Hormonal – renin (RAAS), epi/norepi, ADH
Volume Depletion

• Extra-Renal Losses
  – Blood loss, third-spaced fluids, NPO, AMS
  – GI – vomiting, diarrhea,
  – Skin – excessive sweating, extensive burns, fever

• Renal Losses
  – Intrinsic – salt-wasting, DI, diuretic phase of AKI
  – Extrinsic – excess diuretics, osmotic diuresis
Impaired Autoregulation can lead to “normotensive” prerenal AKI

Abuelo 2007 NEJM
Congestive Heart Failure

- Pulmonary hypertension
- RV failure

- Venous Congestion
  - ↑ Renal venous pressure
  - ↑ Intra-abdominal pressure
  - ↑ Renal interstitial pressure

- Cardiac Output
- Peripheral vascular resistance
- Arterial Underfilling

- Neurohormonal Activation
  - ↑ SNS activity
  - ↑ RAAS activity
  - ↑ AVP release

- Renal Hemodynamics and Renal Salt/Water Excretion

- Myocardial Depressant Factor
Peripheral and splanchnic vasodilatation with inadequate increase in cardiac output

Activation of RAAS, SNS, Vasopressin

Renal Vasoconstriction
Salt/Water Retention

Ascites / Edema

HRS

SBP
Hemorrhage
Infection
Over Diuresis
Large vol para
Prerenal AKI Treatment

• Correction of volume depletion (crystalloids)
• Discontinuation or Dose Adjustment
  – NSAIDS
  – RAAS inhibitors
  – CNIs
• Mgmt of “Effective” Volume Depletion
  – Diuresis in CHF
  – Improving MAP in HRS treatment
  – Antibiotics in Sepsis
• Recognize and Treat Abd Compartment Syndrome
Etiologies

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Acute Tubular Necrosis

Acute Interstitial Nephritis

Acute GN

Acute Vascular Syndromes

Intratubular Obstruction

Postrenal
Intrinsic Renal

**Vasculature**
- Vasoconstriction
- Focal ischemia
- Vasodilation
- Thrombosis
- Coagulation
- Inflammation
- Intermittent flow

**Microenvironment**
- Innate immunity
- Adaptive immunity
- Cellular dysfunction
- Paracrine factors
- Autocrine factors

**Tubules**
- Apoptosis
- Necrosis
- Mitochondrial dysfunction
- Back-leak
- Detachment
- Obstruction

**Systemic factors**
- Proinflammatory cytokines
- Antiinflammatory cytokines
Acute Tubular Necrosis

• Ischemic
  – Prolonged prerenal azotemia
  – Hypotension, shock
  – Cardiopulmonary arrest
  – Cardiopulmonary bypass

• Septic
  – Cytokine mediated inflammation
  – Endothelial stress/injury

• Nephrotoxic
  – Abx (aminoglycosides, vancomycin, amphotericin)
  – Chemotherapy (cisplatin, mtx)
  – Contrast?
Sepsis-related AKI/ATN

Mechanisms

- Pro-Inflammatory state
- Cytokine-mediated Cell Injury
- Systemic Vasodilation
- Impaired Microcirculation
Toxins

There is no role for pre- or post-HD for prevention of CIN
Acute Interstitial Nephritis

• Lymphocytic infiltration of the interstitium
  – Drugs (Abx, PPIs, NSAIDs, furosemide, etc)
  – Infection
  – Malignancy
  – Systemic Diseases (SLE, Sjogren’s, TINU, etc)
• Classic Triad (rare) – fever + rash + eosinophilia
• Pyuria, WBC Casts
• Role of glucocorticoids is uncertain (no RTCs)
Urine Eos?

<table>
<thead>
<tr>
<th></th>
<th>Drug Induced-AIN</th>
<th>All Etiologies of AIN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All cases (n=548)</td>
<td>Pyuria (n=452)</td>
</tr>
<tr>
<td></td>
<td>&gt;1%</td>
<td>&gt;5%</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>35.6</td>
<td>23.3</td>
</tr>
<tr>
<td>Specificity</td>
<td>68.2</td>
<td>91.2</td>
</tr>
<tr>
<td>PPV</td>
<td>14.7</td>
<td>28.8</td>
</tr>
<tr>
<td>NPV</td>
<td>87.3</td>
<td>88.6</td>
</tr>
<tr>
<td>Positive LR</td>
<td>1.1</td>
<td>2.6</td>
</tr>
<tr>
<td>Negative LR</td>
<td>0.9</td>
<td>0.8</td>
</tr>
</tbody>
</table>
Glomerulopathies

• **Nephritic (proliferative) pattern** is an *active* urine microscopy with RBC casts and/or dysmorphic red cells and a variable degree of albuminuria.

• **Nephrotic (non-proliferative) pattern** is proteinuria, usually in the nephrotic range (>3.5 g per 24 hours), and an *inactive* microscopy with very few cells or casts.*
Glomerulopathies

General Pathogenic Mechanisms

- Structural GBM Abnormalities
  - Thin Basement Membrane
  - Alports
- Endothelial Injury / Thrombosis
- Antibody-Mediated
  - Anti-GBM
  - ANCA Vasculitis
- Complement Dysregulation
  - MPGN
  - Atypical HUS
  - C3 Glomerulopathy
- Immune Complex-Mediated
  - Membranous
  - Lupus Nephritis
- Podocyte Injury
  - MCD
  - FSGS

IgAN
Acute Vascular Syndromes

• Thrombotic Microangiopathy (TMA)
  – Hemolytic Uremic Syndrome (HUS)
    • Diarrhea, Shiga/Vero Toxin associated
    • Supportive Care, Dialysis if indicated
  – Thrombotic Thrombocytopenic Purpura (TTP)
    • ADAMS13 Deficiency (autoimmune or hereditary)
    • Autoimmune - Supportive care, PLEX, adjuvant steroids/rituximab, rare splenectomy
  – Atypical HUS (aHUS)
    • Complement dysregulation (hereditary or acquired)
    • Supportive care, PLEX, immunosuppression, Eculizumab
Intra Tubular Obstruction

- Protein
  - Myeloma light chain cast nephropathy

- Crystals
  - Uric acid
  - Oxalate
  - Medications
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Intratubular Obstruction

Postrenal
Post-Renal AKI

- Obstruction within the kidney leading to dilatation of individual calyces or caliectasis
  - stones, transitional cell carcinoma, blood clots, and sloughed papillae
- Obstruction at or distal to the renal pelvis leading to pelviectasis, hydronephrosis/ureter
  - stones, malignancy, external compression, blood clots, infection (fungus ball), bladder dysfunction
A. Stone in renal pelvis
B. Caliectasis
C. Lymphomatous infiltration
Urinary Tract Obstruction

Symptoms
• Pain
• Change in UOP
• Hypertension
• Hematuria

Lab Findings
• Elevated creatinine
• Hyperkalemia / RTA
• Hematuria/pyuria

Treatment = Relieve the pressure!
• Percutaneous nephrostomy (PCN)
• Ureteral stent / Lithotripsy
• Foley / Suprapubic Catheter
Natural History AKI

1 - FULL RECOVERY

2 - AKI TO CKD

3 - ACUTE-ON-CHRONIC KIDNEY DISEASE

4 - AKI TO ESRD

RENAI FUNCTION

TIME
Natural History AKI

**Risk Factors**
- Age
- Race / Ethnicity
- Genetic Factors
- Diabetes Mellitus
- Hypertension
- Metabolic syndrome

**Disease Modifiers**
- Severity of AKI
- Duration of AKI
- No. of Episodes
- Stage of CKD
- Proteinuria

**Outcomes**
- Cardiovascular events
- Kidney Events
- ESRD
- Disability
- Diminished QOL
- Death
References

- KDIGO Clinical Practice Guideline for Acute Kidney Injury