Acute Kidney Injury: Raising Awareness

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AKI Outline
- Epidemiology
- Definitions and Classification of AKI
- Diagnosis and Evaluation
- Treatment and Management of AKI
- Current Status of Quality of Care

Epidemiology

AKI Impact

Worldwide, 2,000,000 people will die this year with AKI!

- AKI Incidence (KDIGO definition)
  - 21% of all hospital admissions
  - Over 50% of ICU patients
- AKI is a major risk factor for CKD and ESRD, even after initial recovery of renal function
- AKI is an independent risk factor for mortality

Mehta RL et al. Lancet 2015
Pannu et al. CJASN 2013
Cerda, et al. CJASN 2015

1.2 million People per year get AKI during a Hospital stay
300,000 people die in the US annually from AKI

More than breast cancer, prostate cancer, heart failure and diabetes, combined

Your length of stay in the hospital increases by 12.5 days (3.5 times) if you get AKI

$7,500 cost of hospital admission
$59,000,000,000 per year
3.5% Admissions
What is the mortality of ICU patients with AKI who require dialytic therapy?

A. < 10%
B. 10 to 30%
C. 30 to 50%
D. Over 50%

Definition and Classification

Definition

- >35 different AKI definitions existed with a variety of incidence rates, risk factors, and morbidity and mortality rates
- Staging system needed to stratify patients for accurate identification and prognostication

www.ADQI.net

Using RIFLE, Patients with AKI Have Poorer Outcomes

- 5,383 patients
- Analysis of 71,000 pts/13 studies to validate RIFLE

Mild AKI with poor outcomes
Mortality Risk in Hospitalized Patients

Kidney Disease: Improving Global Outcomes Initiative (KDIGO) AKI Guidelines: Definition of AKI

- AKI is defined as any of the following (Not Graded):
  - Increase in Scr by ≥0.3 mg/dl within 48 hours; or
  - Increase in Scr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
  - Urine volume <0.5 ml/kg/h for 6 hours
- The Dx of AKI must be established using this criteria before staging

Kidney Disease: Improving Global Outcomes Initiative (KDIGO) AKI Guidelines: Definition 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 × baseline OR ≥ 0.3 mg/dL</td>
<td>&lt;0.5 ml/kg/hr for 6-12 hrs</td>
</tr>
<tr>
<td>2</td>
<td>2.0 - 2.9× baseline</td>
<td>&lt;0.5 ml/kg/hr ≥ 12 hrs</td>
</tr>
<tr>
<td>3</td>
<td>3.0 times baseline OR increase in Cr to ≥4.0 mg/dL OR Initiation of RRT</td>
<td>&lt;0.3 ml/kg/hr ≥ 24 hrs OR Anuria ≥ 12 hrs</td>
</tr>
</tbody>
</table>

Diagnosis and Evaluation

Classification of the Etiologies of AKI

Non-ICU

- Acute Tubular Necrosis
- Acute Interstitial Nephritis
- Acute GN
- Acute Vascular Syndromes
- Intratubular Obstruction

ICU

- Acute on-chronic ARF
- Obstructive ARF
- Other AKI
ICU associated AKI

Sepsis / Infection
Acute Lung Injury
Mech. Vent

Chronic Kidney Disease
Comorbidities (DM, HTN, etc.)

Drug Metabolism
Ischemia / Reperfusion
Nephrotoxins & Contrast

“Standard” Initial Diagnostic Evaluation of AKI
- Clinical history
- Physical exam
- Medication/nephrotoxin history
- Labs
  - Complete blood count (CBC)
  - Serum biochemistries
  - Urine electrolytes
  - Urinalysis with microscopy
  - Renal ultrasound
  - Trends

Evaluation of Cause of AKI

<table>
<thead>
<tr>
<th>Condition</th>
<th>BUN/creatinine ratio</th>
<th>Urine Osmolality (mOsm/kg H2O)</th>
<th>Urine Sodium (mEq/L)</th>
<th>FeNa</th>
<th>Urinalysis and Microscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prerenal</td>
<td>&gt; 20:1</td>
<td>&gt; 500</td>
<td>&lt; 20</td>
<td>&lt; 1%</td>
<td>Specific gravity &gt; 1.020 Normal or hyaline casts</td>
</tr>
<tr>
<td>ATN</td>
<td>10:1</td>
<td>500</td>
<td>&gt; 40</td>
<td>&gt; 2%</td>
<td>Specific gravity &gt; 1.010 Mucus / hyaline casts and tubular epithelial casts</td>
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<tr>
<td>ARF</td>
<td>Variable</td>
<td>500</td>
<td>&gt; 40</td>
<td>&gt; 2%</td>
<td>Microproteinuria, leukocytes, erythrocyte casts, eosinophils</td>
</tr>
<tr>
<td>Acute GN</td>
<td>Variable</td>
<td>Variable, &gt; 500</td>
<td>Variable</td>
<td>Variable, &lt; 1%</td>
<td>Proteinuria, granulocytes, erythrocyte casts, eosinophils</td>
</tr>
<tr>
<td>Intratubular obstruction</td>
<td>Variable</td>
<td>Variable, &gt; 500</td>
<td>Variable</td>
<td>Variable, &gt; 20</td>
<td>Crystals or RBCs, granular casts in proximal tubules</td>
</tr>
<tr>
<td>Acute vascular syndromes</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
<td>Hematuria</td>
</tr>
<tr>
<td>Postrenal</td>
<td>&gt; 20:1</td>
<td>Variable, &gt; 500</td>
<td>Variable, &gt; 20</td>
<td>Variable, &gt; 20</td>
<td></td>
</tr>
</tbody>
</table>

Pitfalls of FeNa
- Only reliable in oliguria
- Pre-existing CKD: FeNa even without tubular injury
- Poor sensitivity with diuretics use (use FEUrea)
- Affected by recent Na-containing IV fluid administration

Etiologies of FeNa < 1% OTHER than pre-renal AKI
- Hepatorenal syndrome
- Contrast nephropathy
- Rhabdomyolysis
- Acute glomerulonephritis
- Early obstructive uropathy

Pitfalls of Serum Creatinine
- SCr influenced by age, muscle mass, gender, race
- SCr does not reflect presence or absence of structural injury
- Rise in SCr delayed by 2-3 days after injury
- Fluid therapy may dilute SCr and delay diagnosis
- Inter-laboratory variation in measuring SCr, and bilirubin and other compounds interfere with the colorimetric modified Jaffe assay

Relationship Between GFR and Creatinine

GFR (mL/min)

Serum Creatinine (mg/dL)

Days

Conceptual Model for AKI

**IDEAL BIOMARKER**
- Predict and diagnose AKI early (before increase in Scr)
- Identify the primary location of injury
- Pinpoint the type (pre-renal, AKI, CKD), duration and severity of AKI
- Identify the etiology of AKI
- Predict clinical outcomes (dialysis, death, LOS)
- Monitor response to intervention and treatment
- Expedite the drug development process (safety)

Current use of biomarkers in acute kidney injury: report and summary of recommendations from the 10th Acute Dialysis Quality Initiative consensus conference

Patrick T. Murray,1,5 Duranta L. Mabula,4,1 Andrew Shue,2,3,8 Eystein Roncar,4,1 Zoltan Erdélyi,3,4,1 John A. Kellum,1 Lahimr S. Dhawan,1,8 Sena Cruz,1,8 Can Inca,1,8 Mark D. Okusa3 and For the ADQI 10 working group

Biomarkers after AKI

**Early Detection**

**Urinary Biomarkers Associated with Tubular Damage**

New Paradigm for the Spectrum of AKI

**No AKI**
- Scr (-)
- Biomarker (-)

**Structural AKI**
- (Damage without Loss of Function)
- Scr (-)
- Biomarker (+)

**Functional AKI**
- (Loss of Function without Damage)
- Scr (+)
- Biomarker (-)

**Intrinsic AKI**
- (Damage + Loss of Function)
- Scr (+)
- Biomarker (+)

"Pre-Renal Azotemia"

"Intrinsic AKI"

**The Search for a Kidney Troponin**

Adapted from Koyner and Parikh-Brenner and Rector’s The Kidney

Courtesy of J. Koyner

"Sub-clinical AKI"

"Excellent" 1.0 - 0.85
"Very Good" 0.85 - 0.75
"Good" 0.75 - 0.65
"Fair" 0.65 - 0.50
"Poor" < 0.50

P=NS
Are some biomarkers “better”?  

**TIMP-2 \*IGFBP7-FDA Approved 2014**

Cutoffs Values for AKI Progression

<table>
<thead>
<tr>
<th>TIMP-2</th>
<th>IGFBP7</th>
<th>Cutoff (ng/mL1/1000)</th>
<th>Sens., %</th>
<th>Spec., %</th>
<th>-LR</th>
<th>+LR</th>
<th>NPV, %</th>
<th>PPV, %</th>
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</thead>
<tbody>
<tr>
<td>0.3</td>
<td>2.0</td>
<td>89/82-94</td>
<td>50/47-63</td>
<td>0.22/0.11-0.35</td>
<td>1.79/1.63-1.97</td>
<td>97/96-99</td>
<td>18/17-20</td>
<td></td>
</tr>
<tr>
<td>0.6</td>
<td>1.0</td>
<td>42/33-51</td>
<td>95/93-96</td>
<td>0.62/0.51-0.71</td>
<td>7.69/5.57-10.88</td>
<td>93/92-94</td>
<td>49/41-58</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Kashani et al. Crit Care 2013—data courtesy of Astute medical

**The NEPHROCHECK® Test System Components**

**AJKD Perspective**

Clinical Use of the Urine Biomarker (TIMP-2 \* IGFBP7) for Acute Kidney Injury Risk Assessment

**Development and Standardization of a Furosemide Stress Test to Predict the Severity of Acute Kidney Injury**

- 77 patients multi-center trial
- Challenging those with early AKI w/ a one time dose of:
  - 1 mg/ kg (loop naive)
  - 1.5 mg/kg (prior loop exposure)
- Exam Urine output following FST
- Primary Endpoint: Progression to Stage 3
**Biomarker Summary**

- Biomarkers of AKI used in conjunction with serum creatinine predict progression of AKI
- Several biomarkers of AKI are associated with long-term adverse outcomes with TIMP2*IGFBP7’s effects being specific to those with AKI
- FST used in conjunction with biomarkers and serum creatinine – predict those patients at highest risk for the worst patient outcomes

**Interventions in AKI**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Biological rationale</th>
<th>Animal experiments</th>
<th>Uncontrolled human data</th>
<th>Small RCT</th>
<th>Large RCT</th>
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</thead>
<tbody>
<tr>
<td>Loop diuretics</td>
<td>Present</td>
<td>Favorable</td>
<td>Favorable</td>
<td>Negative</td>
<td>N/A</td>
</tr>
<tr>
<td>Low-dose dopamine</td>
<td>Present</td>
<td>Favorable</td>
<td>Favorable</td>
<td>Variable</td>
<td>Negative</td>
</tr>
<tr>
<td>Mannitol</td>
<td>Present</td>
<td>Favorable</td>
<td>Favorable</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Ca antagonist</td>
<td>Present</td>
<td>Favorable</td>
<td>Favorable</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Thromboxane antagonist</td>
<td>Present</td>
<td>Favorable</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Thromboxane antagonist</td>
<td>Present</td>
<td>Favorable</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Natriuretic peptide</td>
<td>Present</td>
<td>Favorable</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>α-receptor antagonist</td>
<td>Present</td>
<td>N/A</td>
<td>Positive</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Endothelin antagonist</td>
<td>Present</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Saline</td>
<td>Present</td>
<td>Favorable</td>
<td>Favorable</td>
<td>Positive</td>
<td>N/A</td>
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<tr>
<td>NAC</td>
<td>Present</td>
<td>Favorable</td>
<td>Positive</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Non-ionic media</td>
<td>Present</td>
<td>Favorable</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
</tbody>
</table>

**The only FDA approved treatment of AKI is dialysis**

**Prevention of ATN**

- Recognition of underlying risk factors
  - Diabetes
  - CKD
  - Age
  - Cardiac/liver dysfunction
- Early recognition is key
  - Changes in creatinine are a late manifestation of renal injury
  - A “normal” normal serum creatinine may reflect significant renal insufficiency, particularly in the elderly
- Maintenance of renal perfusion
- Avoidance of nephrotoxins

**Global Organizations**

- International Society of Nephrology “0 by 25” – no patient deaths due to untreated AKI by 2025 to improve the diagnosis and treatment of global AKI
- Kidney Disease: Improving Global Outcomes Initiative (KDIGO)
- Acute Dialysis Quality Initiative (ADQI)
- AKI Network
- National Institute for Health and Care Excellence (NICE)
A 74-yr-old man with DM, HTN, CKD, and a baseline serum creatinine of 1.7 mg/dl undergoes coronary angiography. Forty-eight hours after the procedure, his serum creatinine is 1.8 mg/dl. One week later, he is readmitted to the hospital with abdominal and lower extremity muscle pains. His serum creatinine is 3.6 mg/dl. His amylase is elevated at 320 U/L, with a creatinine kinase of 470 U/L. His urine specific gravity is 1.012, with 1+ blood and 2+ protein by dipstick. Microscopic examination reveals 3 to 5 RBCs per HPF, rare WBCs, and a moderate number of fine granular casts.

Which ONE of the following is the MOST likely cause of his AKI?

A. Contrast nephropathy
B. Atheroembolic disease
C. Myoglobinuric AKI
D. Prerenal azotemia
E. Vasculitis
Atheroembolic Disease: Renal Manifestations

- Renal infarction
- Acute kidney injury
- Subacute kidney injury
- Exacerbation of hypertension
- Proteinuria (may be nephrotic)
- Hematuria

Atheroembolic Disease: Laboratory Features

- Serum chemistries
  - BUN and creatinine
  - Amylase
  - CPK
  - LFTs
- Hematology
  - Leukocytosis
  - Eosinophilia
  - Anemia
  - Thrombocytopenia
- Serologic
  - ESR
  - Serum complement
- Urine
  - Eosinophiluria
  - Proteinuria
  - Hematuria
  - Pyuria

Atheroembolic Disease: Treatment

- Avoid anticoagulation
- Avoid vascular interventions
- ACE inhibitors / angiotensin receptor blockers
- Statin therapy
- Nutrition support
- Dialysis for management of volume status and uremia
- Role of steroid therapy is uncertain

Contrast Media-Nephrotoxicity

- Increase in serum creatinine occurs within 24 to 48 hours following contrast exposure
- Systemic hypoxemia
- Hypovolemia
- Osmotic load
- Blood flow
- Oxygen delivery
- Oxygen consumption
- Direct cellular toxicity
- Renal medullary hypoxia

Rudnick et al. Seminars in Nephrology 17:15-26, 1997

Risk Factors for Contrast-Associated AKI

- Patient Related
  - Preexisting CKD
  - Diabetes mellitus
  - Intravascular volume depletion
  - Reduced cardiac output
  - Concomitant nephrotoxins
- Procedure related
  - Increased dose of radiocontrast
  - Multiple procedures within 72 hours
  - Intra-arterial administration
  - Type of radiocontrast

Recommendations for Prevention of Contrast-Associated AKI

- Identify high risk patients
- Use lowest risk contrast in high-risk population
- Volume expand with isotonic crystalloid
- No benefit to bicarbonate as compared to saline
- Optimal protocol for fluid administration uncertain
- Do not use N-acetylcysteine
- Role of statins is uncertain
- Discontinue NSAIDs and other nephrotoxic drugs
A 57-year-old man is evaluated for a diagnosis of AKI. He was diagnosed with GERD 3 weeks ago and was prescribed omeprazole. Several days ago he noticed lower extremity swelling and decreased frequency of urination. Laboratory evaluation showed a serum creatinine level of 2.2 mg/dL (194.5 µmol/L). Medical history is otherwise unremarkable, and he takes no other medications. He reports no allergies.

On physical examination, the patient is afebrile, blood pressure is 135/77 mm Hg, pulse rate is 88/min, and respiration rate is 12/min. There is no rash. Cardiac examination and estimated central venous pressure are normal. The lungs are clear. Lower extremity edema to the ankles is present bilaterally.

Dipstick urinalysis reveals blood and trace protein, and urine sediment is notable for 5-10 erythrocytes/hpf, 10-20 leukocytes/hpf, and 1 leukocyte cast.

In addition to discontinuing omeprazole, which of the following is the most appropriate next step in management?

A. Kidney biopsy
B. Oral glucocorticoids
C. Repeat kidney function testing in 5 to 7 days
D. Urine eosinophil testing

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**Acute Interstitial Nephritis**

- **Clinical Suspicion**
  - Fever, Rash
  - Culprit Drug or Disease Process

- **Blood Tests**
  - Increased serum creatinine
  - Leukocytosis, eosinophilia, anemia, elevated ESR, transaminitis

- **Urine Studies**
  - Dipstick/low grade proteinuria
  - Pyuria, hematuria, WBC casts
  - Eosinophiluria

- **Kidney Biopsy**

**The triad of Fever, Rash and Eosinophilia: <5-10%**

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**Acute Interstitial Nephritis - Summary**

- Most commonly drug induced
- Complete “classic” triad is rarely present
- Common urinary findings include
  - Pyuria
  - Hematuria
  - WBC casts
- Eosinophiluria neither sensitive nor specific
- Primary treatment is discontinuation of offending agent/treatment of underlying etiology
- Role of glucocorticoids remain uncertain

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**Current Status of Quality of Care in AKI**

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**Acute Interstitial Nephritis Urine Sediment**

White Blood Cell Cast

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**Acute Interstitial Nephritis: Eosinophilia**

<table>
<thead>
<tr>
<th>Drug Induced-AIN</th>
<th>All cases (n=548)</th>
<th>Pyuria (n=452)</th>
<th>All Etiologies of AIN</th>
<th>All cases (566)</th>
<th>Pyuria (467)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;1%</td>
<td>&gt;5%</td>
<td>&gt;1%</td>
<td>&gt;5%</td>
<td>&gt;1%</td>
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<tr>
<td>Sensitivity</td>
<td>35.6</td>
<td>23.3</td>
<td>44.8</td>
<td>29.3</td>
<td>30.6</td>
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<tr>
<td>Specificity</td>
<td>68.2</td>
<td>91.2</td>
<td>61.7</td>
<td>89.3</td>
<td>68.2</td>
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<td>PPV</td>
<td>14.7</td>
<td>28.8</td>
<td>14.7</td>
<td>28.8</td>
<td>15.6</td>
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<tr>
<td>NPV</td>
<td>87.3</td>
<td>88.6</td>
<td>88.4</td>
<td>89.6</td>
<td>83.7</td>
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<tr>
<td>Positive LR</td>
<td>1.1</td>
<td>2.6</td>
<td>1.2</td>
<td>2.7</td>
<td>0.97</td>
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<tr>
<td>Negative LR</td>
<td>0.0</td>
<td>0.8</td>
<td>0.9</td>
<td>0.8</td>
<td>1.01</td>
</tr>
</tbody>
</table>

Insensitive test with specificity and positive LR only potentially acceptable using Urine Eos >5% cutoff in setting of high pretest probability

Muriithi AK, et al. CJASN 2013; 8: 1857-1862
Quality in AKI: Time Has Come!

AKI has CLEAR gaps in quality of care!

- Wide variability in the treatment of AKI
- Lack of reliable systems and processes for the detection and management of AKI
- Major imperative to focus on developing clinical quality measures (QMs) to track and report on care for AKI patients and identify best practices to improve outcomes
- Need to standardize systems and processes to prevent, detect, and manage AKI
Early identification of patients at increased risk for AKI is key for preventive strategies.

Early diagnosis of AKI for interventions to minimize further renal injury.

Interventions to correct reversible factors.

Availability, timing, type and dose of RRT.

Post-discharge care of patients with AKI.

Next Steps....

1. Risk Identification (i.e., education tools, EMR, Renal Angina Index)
2. Early recognition/detection/[disruptive] alerting (i.e., educational tools, check lists, EMR)
3. Response (i.e., clinical decision support, care bundles, FST)
4. Renal support (i.e., RRT prescription/delivery)
5. Rehabilitation (i.e., kidney recovery, discharge checklists, AKI survivor clinic)

AKI Summary

- AKI is bad
  - Up to 65% of critically ill patients develop AKI
  - Patients with AKI are at increased risk for death, CKD and ESRD

- AKI definition is now standardized and accepted
  - The degree of AKI classified by KDIGO criteria correlates with mortality in a progressive fashion

- AKI is not a disease
  - AKI is a syndrome caused by numerous etiologies
  - Basic management strategies can be done if we can identify patients at risk for AKI

AKI Summary

- Methods for earlier diagnosis of AKI and its progression may result in improved outcomes by facilitating targeted and timely treatment of AKI

- There is no treatment of ATN and prevention of precipitating factors is paramount

- Higher quality of care in AKI involves risk identification, recognition, diagnosis, investigation, monitoring, management, and post-AKI follow up