Acute Kidney Injury: Thoughts from the trenches

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Case Study

Patient Info
- 68-year-old African American female
- Pre-Op Body Weight 60 kg
- Hypertension
- COPD
- No Chronic Kidney Disease (CKD)
- Baseline SCr = 0.4 mg/dL

What are your concerns for this patient??

ICU Course
- Post-op surgery – uncomplicated bowel resection
- Abdominal Peritoneal Resection
- Sepsis Dx Post-Op Day #2
- Mechanical Ventilation
- Current SCr = 0.5 mg/dL

Acute Kidney Injury (AKI) Is Prevalent, Costly and Deadly

Incidence
- 7-18% of hospitalized patients.
- Up to 50% of critically ill patients develop some stage of AKI.

Morbidity & Mortality
- 9-times higher risk of development of Chronic Kidney Disease
- 2-times higher risk of premature death

Cost
- Estimated annual costs to US healthcare system attributable to hospital-acquired AKI is > $10 billion.

Recent Acute Kidney Injury (AKI) Definitions Have Helped Illuminate The Burden Of AKI

Acute Kidney Injury (AKI) is a rapid (typically within about 48 hours) loss of kidney function.
RIFLE/AKIN/KDIGO criteria were validated over the past decade and provide a standardized definition of AKI.
The criteria are based on increases and decreases in serum creatinine and decreases in urine output and stratify AKI into three severity levels:
1. Mild AKI (RIFLE-I or Stage 1)
2. Moderate AKI (RIFLE-I or Stage 2)
3. Severe AKI (RIFLE-F or Stage 3)
The criteria are good for epidemiological studies but difficult to apply at the bedside; AKI thus remains largely a clinical diagnosis.

AKI And Sepsis Is A Deadly Combination

Mortality in hospitalized pneumonia patients

For a typical 400 bed community hospital, the incremental resources consumed by AKI in the ICU often exceeds $25M and 8,500 bed days annually.

AKI Is Twice As Deadly As an MI

AKI potentially worse for an individual than a ST elevation myocardial infarction (STEMI)

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AKI Is Twice As Deadly As an MI

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Surgery And AKI Leads To Poor Outcomes

- Hospital Mortality
- 90-Day Mortality

Patients With AKI Have High Readmission Rates

- No AKI
- Mild (Stage 1)
- Moderate (Stage 2)
- Severe (Stage 3)

Everything is at Least 2-3 Times Worse with Moderate to Severe AKI

AKI is a Spectrum of Kidney Decline and Early Identification is Key to Potentially Stop the Progression

Suboptimal Diagnostic Tools Make AKI Improvement Difficult

Risk Assessment For AKI: An Unmet Clinical Need

Serum Creatinine
- Lagging indicator
- Only detects after 50% of kidney function loss
- Non-diagnostic for up to 52% of moderate and severe AKI

Urine Output
- Lagging indicator
- Tedious to measure
- Affected by HAI initiatives

Best Current Indicators for One Of Healthcare’s Biggest Problems: Lagging. Error Prone. Compromised by “well intended” QI.
Clinical Risk Factors For AKI Are Common But Not Reliable For Establishing The Risk Profile For An Individual Patient

A number of susceptibilities and exposures for AKI have been identified, but there is no reliable way for a clinician to use this information to establish a clear risk profile.\[^{9}\]

**Patient Risk Factors**\[^{9}\]
- Dehydration or volume depletion
- Advanced Age
- Female gender
- Black race
- CKD
- Chronic Disease (e.g. heart, lung, liver)
- Diabetes Mellitus
- Cancer
- Anemia

**Acute Risk Factors**\[^{9,11,13}\]
- Sepsis
- Pneumonia
- Cardiogenic Shock
- Major Surgery
- Cardiac Surgery
- Nephrotoxic Drugs
- Radiocontrast Agents
- Hypovolemia

A recent study stated: "AKI is potentially fatal, but in many cases reversible when appropriately managed" and "...it is reasonable to surmise that, at least in some cases, the [patient’s] outcome...may have been different if the condition [AKI] had been recognized and managed better."\[^{24}\]

**A Better Way To Identify Patients At Risk for AKI Is Paramount**

Early recognition and management of patients at risk for AKI is paramount since there are no specific therapies to reverse established AKI.\[^{9}\]

As compared to myocardial infarction, AKI may not provide early signs and symptoms sufficient to guide risk assessment.\[^{23}\]

Current methods for risk assessment are insufficient, placing substantial numbers of patients at serious risk of death and morbidity.\[^{9,26}\]

**AKI Identification in the ICU Can Be Inconsistent**

1CU physicians only identified a small proportion of the patients with AKI. Many of the severe forms of AKI, which were most associated with adverse outcomes, were missed by the physician reporting.

**Case Study**

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- COPD
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- Baseline SCr = 0.4 mg/dL

ICU Course
- Post-op surgery – uncomplicated bowel resection
- Sepsis Dx Post-Op Day #2
- Mechanical Ventilation
- Current SCr = 0.5 mg/dL

Patient Status at ICU Day 4
- Aztreonam and other antibiotics
- Pressors to maintain SBP > 100 mm Hg
- SCr = 0.9 mg/dL
- UO = 30 cc/hr (average)

**Discovery Of Novel Biomarkers For Risk Assessment For AKI**
New Technology, Advance Warning Enables Better Outcomes

What if we could get ahead of AKI? Instead of saying, “wait and see...”

• Early Warning
• Stratify Patient Risk
• Attention on “At Risk” patients
• Reduce Process Variation
• Improved Communication

Rigorous Discovery & Validation Studies Performed to Identify Biomarkers of Early AKI Risk Assessment

340 Biomarkers Evaluated including NGAL & KIM-1

Candidates identified through hypothesis based on AKI pathophysiology and evaluated individually and in combinations of 2-4 biomarkers.

Discovered in 1,200+ Patients including sepsis, shock, major surgery and trauma patients

Urinary [TIMP-2]*[IGFBP-7] stood out as the best-performing biomarkers to predict development of moderate or severe AKI within 12 hours.

Validated in 500+ Critically Ill Patients from Intended Use Population

Patients had diverse ICU admissions (surgery, sepsis, trauma) and common comorbidities (including CKD, diabetes, heart disease).

Two Novel Urinary Protein Biomarkers Stood Out as a “Renal Alarm” System

Tissue Inhibitor of Metalloproteinase-2 (TIMP-2)
Insulin-like Growth Factor Binding Protein-7 (IGFBP-7)

TIMP-2 and IGFBP-7 are:

• Biomarkers of cellular stress in the early phase of tubular cell injury caused by a wide variety of insults (inflammation, ischemia, oxidative stress, drugs, and toxins).
• Involved in G1 cell-cycle arrest that prevent cells from dividing until damage can be repaired.
• Both biomarkers appear as “alarm” proteins from other nearby cells.

This may help explain why urinary TIMP-2 and IGFBP-7 correspond to risk of AKI.

Identify Kidney Stress, Before Dysfunction Occurs

AKIRisk® Score = [TIMP-2]*[IGFBP-7]
The Clinical Cutoff Was Selected To Identify the Majority Of Patients At Risk For Moderate-Severe AKI

The NephroCheck® Test cutoff (AKIRisk® Score > 0.3) was prospectively selected prior to validation studies to achieve:

- High sensitivity and negative predictive value are important in risk assessment to ensure that:
  - The majority of patients who will develop AKI test positive
  - Few patients with a negative test result will be at risk of developing AKI

<table>
<thead>
<tr>
<th></th>
<th>Study A (408 patients)</th>
<th>Study B (126 patients)</th>
</tr>
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<tbody>
<tr>
<td>High sensitivity</td>
<td>92%</td>
<td>76%</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>96%</td>
<td>88%</td>
</tr>
<tr>
<td>High negative predictive value</td>
<td>96%</td>
<td>88%</td>
</tr>
</tbody>
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A Quantitative NephroCheck® Test Provides Confidence to Identify the Majority of Patients at Risk for AKI

- High sensitivity and negative predictive value for confidence in identifying the majority of patients at risk for AKI.

Confidence the AKIRisk® Score is not elevated due to common comorbidities such as CKD, diabetes, surgery, sepsis, and trauma.

Results from Study A and B are not statistically different (p > 0.05)

We’ve done this before...

- Ventilator Bundles
  - (Institute for Healthcare Improvement)
  - Elevation of the head
  - "Sedation vacation"
  - Stress ulcer prophylaxis
  - DVT prophylaxis
  - Daily oral decontamination

- Sepsis/Resuscitation bundle
  - (St. Mary’s Hospital, Rochester New York)
  - Measurement of lactate
  - Blood cultures before antibiotics
  - Timely administration of antibiotics
  - Fluid administration based upon CVP, MAP, and lactate
  - Vasopressor therapy
  - RBC transfusion
  - Inotropic support

Locally Developed Clinical Plans Lead to More Consistent And Timely Management of Common Critical Illnesses

...Why Not AKI?

Early Coordination of Care Among All Experts is Vital

- Clinical success stories for multidisciplinary care in acute illness
  - Sepsis
  - Chest pain
  - Rapid response teams

Evidence shows that this is important for AKI: earlier renal consultation improves outcomes

- Mortality Rate of AKI Patients by Time of Nephrology Consultation
  - Early Consultation: 6.4% 23% Increased Mortality Rate with Delayed consultation
  - Delayed Consultation: 10.2%

Diagnostic Tests and Biomarkers Play an Increasingly Important Role in Patient Care

- Acute Coronary Syndromes:

- Congestive Heart Failure:
  - BNP

- Sepsis and Infectious Diseases:
  - Lactate
  - Procalcitonin

Enhancing Patient Care
Incorporating Clinical Expertise with AKI Risk Biomarkers
Acute Kidney Injury (AKI) is a Significant Opportunity to Improve Quality of Patient Care

With dynamic measurement of the risk for AKI, there will be the opportunity to initiate timely and appropriate preventative therapies and monitoring in the ICU, for those patients who are judged to be at high risk of AKI. As well, less costly interventions are easy and reasonable to implement if risk is identified, such as considering:

- Discontinuing nephrotoxins or changing dosage
- Volume status & perfusion pressure
- Hemodynamic monitoring
- Monitoring frequency of serum creatinine and urine output
- Earlier nephrology consult.

Unlike AMI, AKI Hasn’t Had New Biomarkers Available For Over 50 Years... Until Now

<table>
<thead>
<tr>
<th>Period</th>
<th>Acute Myocardial Infarction</th>
<th>Acute Kidney Injury</th>
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</thead>
<tbody>
<tr>
<td>1960’s</td>
<td>LBB®</td>
<td>None</td>
</tr>
<tr>
<td>1970’s</td>
<td>CPA®</td>
<td>None</td>
</tr>
<tr>
<td>1980’s</td>
<td>DEA®</td>
<td>None</td>
</tr>
<tr>
<td>1990’s</td>
<td>Topco®</td>
<td>None</td>
</tr>
<tr>
<td>2000’s</td>
<td>St. Jude®</td>
<td>None</td>
</tr>
<tr>
<td>2010’s</td>
<td>The NephroCheck® Test®</td>
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Published Recommendations to Help Prevent Kidney Damage

Recent published literature has discussed the role of the NephroCheck® Test used in conjunction with clinical judgement and includes recommendations on preferred kidney sparing strategies to help prevent kidney damage.

Case Study

Patient Info
- 68-year-old African American female
- No Chronic Kidney Disease (CKD)
- COPD
- Hypertension
- Female

Current SCr = 0.5 mg/dL
Mechanical Ventilation
Abdominal Peritoneal Resection
Post-op surgery – uncomplicated bowel resection
ICU Course

Patient Status at ICU Day 4

UO = 30 cc/hr (average)
Pressors to maintain SBP > 100 mm Hg
Azreonam and other antibiotics

What might you do differently with this patient?

The “Renal Alarm” System: Don’t Act Now, Act Earlier!

The NephroCheck® Test is

- Validated in robust clinical trials
- First urinary biomarkers for risk assessment of AKI
- Highly sensitive and has acceptable specificity for risk assessment of moderate to severe AKI within the next 12 hours
- Not elevated with chronic comorbidities and non-AKI acute conditions

With the early identification of patients at risk, there is an opportunity for management strategies that may attenuate AKI severity, thereby impacting morbidity, mortality, length of stay, and cost associated with moderate to severe AKI.
The NephroCheck® Test

The NephroCheck® Test aids in identifying patients at risk for moderate to severe AKI in the next 12 hours so physicians can proactively assess the need for AKI preventative measures.

- **Identify**
  - The NephroCheck® Test provides a quantitative AKIRisk™ Score allowing the clinician to discriminate patients at risk of AKI.

- **Stratify**
  - The AKIRisk™ Score allows clinicians to triage patients into lower risk and greater risk groups for developing moderate to severe AKI in the next 12 hours.

- **Mitigate**
  - The assessment of risk 12 hours before moderate to severe AKI may clinically manifest allows the clinician to implement time sensitive kidney sparing strategies to potentially mitigate the severe consequences associated with Acute Kidney Injury.

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**Case #1**

- 78 yr old WF with a history of tobacco abuse, coronary artery disease, hyperlipidemia, chronic kidney disease and hypertension who presented with sudden severe upper back pain and a stat Chest CT with contrast detected a Acute type A aortic dissection.
- She was transferred to a level 1 Trauma hospital center where she underwent surgical repair including an aortic valve replacement.
- The aortic dissection had progressed to a location past her renal arteries placing her at risk for acute kidney injury.

- On Hospital Day #20 patient urine output increased and no further hemodialysis was required.
- Discharged to a rehabilitation facility after 27 days in hospital including 10 days in ICU.
- Renal recovery occurred and patient survived this catastrophic vascular event.

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Case #1

- Initial postoperative urine output was >0.5 cc/kg/hr and serum creatinine was unchanged.
- On postoperative Day #1 the patient developed oliguria and received several boluses of Normal Saline and Plasmanate (serum albumin) with no increase in urine output which was approximately 25 cc/hr.
- Positive fluid balance of 6.5 liters placing patient at risk for organ edema.
- On postoperative Day #2 her serum creatinine increased from 2.0 to 2.5.
Joe Skeptic MD

Not sure what we would different with the information Nephrocheck provides since we are constantly focused on protecting the kidney!

Williams reply –
• “You’re not as good as you think you are”
• “You could have done more to avoid RRT and the patient is very fortunate to have survived with renal recovery”

Do We Have a Problem With AKI?

For the year 2015 using data from our system:
• Approximately 916 cases of moderate or severe AKI
• Length of stay impact was additional 9521 days
• Cost impact estimated at 27 million dollars

Case #2 – A High Risk Nephrocheck that led to action!

• 48 yr old woman with chronic HTN, chronic abdominal pain from ulcerative colitis with multiple surgeries and intra-abdominal abscesses is admitted with abdominal pain and fever.
• Abdominal CT shows an intra-abdominal abscess that requires surgical drainage.
• Postoperatively she is in septic shock and on Norepinephrine drip.
• Nephrocheck is ordered early in postoperative course.

IU Health Protocol for Nephrocheck

- Target Patients:
  - Critically ill ICU patient ≥ 18 years of age
  - AKI
  - Acute cardiovascular compromise within the past 24 hours
  - Respiratory compromise within the past 24 hours
- Exclusion Criteria:
  - < 18 years of age
  - Known AKI
  - On RRT or on maintenance dialysis
  - Previous Renal Transplant
- Actions:
  1. Physician Orders STAT AKI Marker/Nephrocheck upon meeting inclusion criteria
  2. RN collects blood from patient venipuncture and sends to lab immediately
  3. Lab availability 24/7—results posted on EMR within one hour
  4. Physician determines appropriate action based on AKI Marker result and clinical situation

Timing of NephroCheck/AKIN Marker Sample Collection:
4-6 hour post insult (surgical, renal ischemia, sepsis, hemorrhage, or other causes of shock)
Request AKI Marker to be considered when there is a change in clinical situation or presence of an additional insult that puts the patient at risk for AKI (e.g. hypotension, blood loss).
Case #2 – A High Risk Nephrocheck that led to action!

• We pushed the patients Mean Arterial Pressure up to 85
• We used the NICOM device (Noninvasive Cardiac Output Monitor) to closely regulate the patient’s volume status.
• This target has been shown in a large Clinical Trial to reduce the development of AKI and the need for RRT.

Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial

INVESTIGATORS:

SITE:
- Single center study
- University Hospital Münster (Münster, Germany)

PATIENTS:
- 276 patients who underwent cardiac surgery (on-pump) at the University of Münster who were deemed to be at high risk for AKI.
- High risk defined as Nephrocheck® > 0.3 from discarded urine sent 4 hours after discontinuation of cardiopulmonary bypass (CPB)

TIME FRAME:
- August 2014 through December 2015.

Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial

METHODS:
- Patients at high risk (NephroCheck > 0.3) were randomized to the following arms:
  - CONTROL GROUP: Standard therapy
  - INTERVENTION GROUP: “KDIGO CT Surgical Bundle”
  - 138 patients in each group (1:1 randomization)
  - August 2014 through December 2015.
  - Powered at 80%

PRIMARY OUTCOME:
- Development of AKI 72 hours after surgery, defined by KDIGO criteria

SECONDARY OUTCOMES:
- AKI severity
- Need for dialysis
- Length of stay (LOS)
- Major Adverse Kidney Events (MAKE) at 30, 60, and 90 days

Standard Care vs. KDIGO Bundle

- Restart angiotensin converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARBs) once hemodynamics stabilized*
- Mean arterial pressure (MAP) > 65 mmHg
- Central venous pressure (CVP) between 8 and 10

*As per ACC guidelines
Hemodynamic Monitoring And Optimization Was Performed According To Strict Protocol In The KDIGO Intervention Arm

Standard of care in the control arm did not involve measurement/optimization of SVV or CI which require more sophisticated and rigorous monitoring.

SVV = stroke volume variability (high values mean volume depletion)

CI = cardiac index (low values mean low cardiac output)

MAP = mean arterial pressure (low values mean hypotension)

Optimize

Preload

Optimize

Contractility

Optimize

Afterload

Continue for 12h

Control (n=138)

Intervention (n=138)

p-value

Patients with catecholamines during intervention period, No. (%)

Dobutamine

13 (9.4)

43 (31.2)

< 0.001

Epinephrine

21 (15.2)

29 (21.2)

0.201

Norepinephrine

91 (65.9)

94 (68.1)

0.701

Volume therapy during intervention period, median (Q1, Q3), ml

Total volume

2745 (1968, 3625)

2575 (1965, 3518)

0.699

Atrial fibrillation within 12 hours, No. (%)

15 (10.9)

13 (9.4)

0.690

Hyperglycemia, No. (%)

104 (75.4)

70 (50.7)

< 0.001

ACEi and ARBs, No. (%)

42 (30.4)

15 (10.9)

< 0.001

Nephrotoxic agents, No. (%)

22 (15.9)

18 (13.0)

0.494

Contrast agents

19 (13.8)

11 (8.0)

0.122

Vancomycin, Gentamicin

6 (4.3)

9 (6.5)

0.426

Diuretics, No. (%)

113 (81.9)

103 (74.6)

0.144

Urine [TIMP-2]*[IGFBP7] at 12 h, ng/ml

0.84 (0.35, 1.57)

0.58 (0.26, 1.20)

0.045*

Intervention In [TIMP-2]*[IGFBP7] Positive Patients Was Associated With Significant Differences In Dobutamine, ACE/ARB, Hyperglycemia and 12h [TIMP-2]*[IGFBP7]

*Relative change from baseline of 12h [TIMP-2]*[IGFBP7] was not statistically different between the two arms (p > 0.05)

KDIGO Bundle Intervention Significantly Reduced AKI

Case # 3 –A negative result that matters

The implementation of a bundle of supportive measures (KDIGO CT surgery bundle) in high risk patients, identified by an elevated Nephrocheck® test, reduced the occurrence of AKI within 72 hours compared to standard care.

Patients treated with the KDIGO CT surgery bundle used more dobutamine, had a reduced rate of hyperglycemia, and a higher rate of discontinuing ACEi’s and ARBs. These patients also received better hemodynamic monitoring, which likely resulted in a more individually tailored approach to their care.

Patient randomized to the KDIGO CT surgical bundle also had lower Nephrocheck® levels at 12 hours following randomization, supporting the hypothesis that this bundle dampens tubular damage and protects against AKI.

Nephrocheck® therefore allows the bedside clinician to implement effective preventative and protective interventions well before clinical AKI develops. Physicians now have an evidence-based clinical strategy that uses commonly employed clinical therapies in high risk patients for AKI who are proactively identified by an elevated Nephrocheck® level, to prevent AKI from occurring.

Key Conclusions:

• Although the KDIGO CT bundle significantly reduced the incidence of AKI within 72 hour following surgery, it did not impact morbidity or mortality and secondary outcomes:
  • ICU LOS
  • Hospital LOS
  • MAKE

• Potential reasons for these findings:
  1. KDIGO was NOT powered to show a difference in these secondary outcomes.
  2. The rate of complications was not the same in both groups.
  3. The KDIGO criteria may not be sensitive enough to detect smaller changes in AKI.
  4. The KDIGO criteria may not be applicable to the cardiac surgery population.
  5. The KDIGO criteria may not be sensitive enough to detect smaller changes in AKI.
  6. The KDIGO criteria may not be applicable to the cardiac surgery population.

Secondary outcomes:

• 48 yr old woman with poorly controlled diabetes mellitus who presents with severe necrotizing fasciitis of the perineal region.

• She is in septic shock preoperatively on 2 vasopressors and requires source control operation.

• Postoperatively the patient has oliguria and remains in septic shock on vasopressors.

4/24/2017
Case # 3 – A negative result that matters

- Patient needed Vancomycin and a dose of Tobramycin both potentially nephrotoxic
- Patient also needed repeat CT scans with dye
- The negative Nephrocheck gave us more confidence to proceed with these interventions

Case # 4

What is your prediction regarding this patient's risk of developing Acute Kidney Injury within the next 12 hours?

1. <25%
2. 25-50%
3. 50-75%
4. 75-100%

Case # 4

- There was difficulty removing the leads secondary to severe calcification and temporary pacer was placed.
- On ICU day #1 pt exhibited signs of sepsis with low grade temperature, WBC of 21,000 and PCT was 53.
- On ICU day #2 he developed septic shock and was fluid resuscitated yet required moderate dose Norepi.
- Nephrocheck was assessed on morning rounds.

AKI risk prediction is positive
Conclusions

• Acute kidney injury is common, costly and deadly.

• There is now a new tool to help you predict which patients are at an increased risk for acute kidney injury.

• A focused effort to implement Acute Kidney Injury bundles can lead to significant quality improvement in this disease state.