Acute Kidney Injury 2016
Case Vignettes

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Why Spend 45 minutes talking about AKI?

A. Most honored and recognized organ in the world
B. The Kidney is the most important organ of the body
C. Mortality from Kidney disease is a global epidemic
D. You really need more time to sleep
E. Kidney ??? I thought this was a Cardiology lecture !
Global Burden of AKI

23.2% incidence of AKI in hospitalized patients
13.3 million cases per year
11.3 million are in low-income countries
1.7 million deaths / year
In Hospital Daily Burden of AKI for Nephrologists

Koyner JL. Am J Kid Dis 2014 Sep;64(3):394-401
Worldwide Incidence of AKI for Hospitalized Patients

Mortality of 22%
Risk of AKI By Age and Race: The U.S. Experience

Skyrocketing rates of AKI in the elderly especially in black patients
Population incidence of dialysis-requiring AKI in the United States by age groups from 2000 to 2009

Severity of AKI is increasing!!!
Additional Hospital Charges from AKI: Based on Change in Creatinine from Baseline


In England - Yearly cost of AKI 1.7 billion dollars in 2010-11
AKI and Systemic Disease:

Traditional Model

- Loss of GFR
  - Na + Water Overload
  - Acid Base Disorders
  - Electrolyte Abnormalities
  - Pulmonary Edema
  - Cardiac Dysfunction
  - Immune deficiency
  - CNS disease

Current Theory

- Loss of GFR
  - Cytokine Release
  - IL-1, IL-6, TNF-α
  - Sympathetic Stimulation
  - Upregulation of Adhesion Molecules
  - Increased oxidative stress
Clinical Consequences of AKI

AKI

Immune Dysfunction

Sepsis

Multiorgan Failure
Discharge Status of Patients after AKI

- Home: 45.0%
- Institution: 31.1%
- Death: 10.2%
- Other: 7.4%
- Hospice: 4.8%
- ESRD: 1.4%
Post Discharge Mortality after AKI

LaFrance J-P, J Am Soc Nephrol 2010;21;345

OR = 1.4 for death after AKI discharge
AKI and the risk of CKD

- The worse the severity of AKI the higher the risk of CKD
- The greater the number of AKI episodes – the higher the risk of CKD
Effect of AKI on CKD

Dear JW. Kidney Intern 2008:74;7
**Mechanism of AKI associated CKD**

- Mal-adaptive repair of AKI leads to progressive fibrosis
  - Epigenetic transformation of cells to myofibroblasts (EMT)
  - Ischemic injury
  - In ATN, the loss of vascular density varies between 30 and 50%
  - The loss of vascular reserve may be one of the key components of the development of fibrosis after injury.
What is the origin of myofibroblasts in the kidney?

A variety of cell types transform themselves into myofibroblasts under the influence of cytokines leading to CKD.
**Interim Summary**

**AKI : Epidemiology**

- AKI is a common clinical situation facing both subspecialists and primary care physicians in the hospital setting
  - Increasing incidence / severity
  - Higher risk in the elderly / black race
- The development of AKI carries a significant economic impact not only for the acute event but also in the management of the long term complications of AKI
  - CKD
  - ESRD
  - Hospital re-admissions
- Short and long term mortality is significantly increased in patients with AKI
International Society of Nephrology’s 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): a human rights case for nephrology

Ravindra L. Mehta*, Jorge Cerdá*, Emmanuel A. Burdmann*, Marcello Tonelli*, Guillermo García-García, Vivekanand Jha, Paweena Susantitaphong, Michael Rocco, Raymond Vanholder, Mehmet Sukru Sever, Dinna Cruz, Bertrand Jaber, Norbert H. Lameire, Raúl Lombardi, Andrew Lewington, John Feehally, Fredric Finkelstein, Nathan Levin, Neesh Pannu, Bernadette Thomas, Elijah Aronoff-Spencer, Giuseppe Remuzzi

Mehta R. Lancet 2015; 385: 2616–43
The 5 Rs of the ISN Campaign: 0by25

**Risk**
- Toolkits and training for risk assessment and recognition in three-tiered service model
  - Peripheral village health centre
  - Secondary district hospital or clinic
  - Tertiary care hospital in urban area

**Rehabilitation**
- Follow-up after AKI at local level based on the same group that educates and trains
- Point-of-care testing
- Telemedicine supported

**Recognition**
- Training and methods that can be deployed at periphery
  - Clinical
  - Point-of-care testing
  - Telemedicine accessibility

**Renal support**
- Protocol-driven management adapted to local resources and customs
  - Hub-and-spoke setup
  - Telemedicine enabled
  - Protocol-driven transfer to tertiary centres
  - Peritoneal dialysis

**Response**
- Development of small renal-functional units
  - Point-of-care testing
  - Development of specialised tertiary hospital centres that are telemedicine enabled
  - Protocols for care based on local resources
Deaths that occur secondary to public health issues such as unclean water and diarrhoea, endemic infections (eg, leptospirosis), and environmental exposures (eg, snakebites)—all of which are complicated by AKI

Deaths that occur from absent or delayed recognition of AKI because of inaccessibility of laboratory studies, inadequate response to diagnosis of AKI, or iatrogenic factors - use of non-steroidal antiinflammatory drugs (NSAIDs), nephrotoxic antibiotics, and exposure to contrast agents.

Deaths due to the absence of dialysis support to treat life threatening hyperkalemia, fluid overload, and acidosis.
Followup of AKI by Nephrology

Only 19% of patients with AKI see a nephrologist within 1 year of discharge.

- Nephrology visit after Stage 1 or Stage 2 AKI: 11.9%
- Nephrology visit after Stage 3 AKI (Dialysis): 30%
- Cardiology visit after MI: 76%

Chawla L. Kidney International (2012) 82, 516–524
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 times baseline (7 days) OR ≥0.3 mg/dl (≥26.5 mmol/l) increase (48 hours)</td>
<td>&lt;0.5 ml/kg/h for 6–12 hours</td>
</tr>
<tr>
<td>2</td>
<td>2.0–2.9 times baseline</td>
<td>&lt;0.5 ml/kg/h for ≥12 hours</td>
</tr>
<tr>
<td>3</td>
<td>3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dl (≥353.6 mmol/l) OR Initiation of renal replacement therapy</td>
<td>&lt;0.3 ml/kg/h for ≥24 hours OR Anuria for ≥12 hours</td>
</tr>
</tbody>
</table>

**KDIGO :**

Kidney Disease Improving Global Outcomes

**KDIGO Clinical Practice Guideline for Acute Kidney Injury**
And now even Hepatology has adopted our Guidelines for Hepatorenal Syndrome

1996: Original International Ascites Club Criteria for HRS
Doubling of the serum creatinine
Creatinine > 1.5 mg/dl

2004: KDIGO AKI definition
Creatinine increase by 0.3 mg/dl

2007: ICA proposed changes to amend AKI diagnosis in HRS
to fit the KDIGO definition

2015: ICA adopts the new diagnostic criteria for AKI in cirrhosis as a creatinine change of 0.3 mg/dl

Diagnosis of AKI

International Club of Ascites

Acute kidney injury

• Rise in serum creatinine of ≥50% from baseline, or a rise of serum creatinine by ≥26.4 μmol/l (0.3 mg/dl) in <48 h
  • HRS type I is a specific form of acute kidney injury
The lack of accuracy of the current eGFR equations for GFR > 60 cc/min makes them insensitive to detect the majority of cases of AKI.

No criteria have been developed for the use of the CKD-EPI formula in the diagnosis of AKI.
Caveat

Pre-Renal Azotemia

Not Considered true AKI
Immediately reversible with hydration
No short or long term consequences

Renal

True AKI
Associated with cellular injury
Significant short and long term morbidity and mortality and risk of CKD

Post Renal
Etiologies of AKI after Correction of Pre-Renal Azotemia

In-Hospital
- ATN: 74%
- Interstitial Nephritis: 6%
- Obstruction: 14%
- Glomerulonephritis: 6%

Outpatient
- ATN: 42%
- Interstitial Nephritis: 28%
- Obstruction: 20%
- Glomerulonephritis: 10%
Case Presentation

- 75 year Caucasian female presents to the ER with an acute coronary syndrome
- Must be taken to the Cath lab for an urgent catheterization

PMH
Type II Diabetes for 15 years
HTN X 10 years
GERD
DJD
Recent UTI 1 week ago

Medications
Metformin
Cimetidine
Procardia XL
Enalapril
Bactrim DS x 3 days (just finished)

<table>
<thead>
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<td>12</td>
<td></td>
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<tr>
<td>Cr</td>
<td>1.4</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>eGFR</td>
<td>37</td>
<td>62</td>
<td></td>
</tr>
</tbody>
</table>
What is your assessment of this woman’s kidney function at baseline? Is it normal?

1. Yes, her creatinine was normal (< 1.5 mg/dl)
2. No, she had AKI
3. No, she had CKD
4. Sorry, I’m not awake yet
5. What is CKD?

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Diagnosis of Renal Disease

Acute Kidney Injury (AKI)
- Changes in Serum Creatinine
  (days to weeks)

Chronic Kidney Disease (CKD)
- Changes in GFR
  (3 months)
<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR(CKD-EPI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>At Increased Risk</td>
<td>&gt; 90 with CKD risk factors</td>
</tr>
<tr>
<td>1</td>
<td>Chronic kidney damage with normal GFR</td>
<td>&gt; 90</td>
</tr>
<tr>
<td>2</td>
<td>Mild ↓ GFR</td>
<td>60 - 89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate ↓ GFR</td>
<td>30 – 59</td>
</tr>
<tr>
<td>4</td>
<td>Severe ↓ GFR</td>
<td>15 – 29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney Failure</td>
<td>&lt; 15 or dialysis</td>
</tr>
</tbody>
</table>
Changes in Kidney Function with Age
“Renal Senescence”

Rate of decline 0.1 cc/min/yr < 40 years old
Rate of decline 0.8 cc/min/yr > 40 years old

Males

Females
Diagnosis of CKD: Based on 3 Parameters

- Structural
- GFR
- Albuminuria
Differentiating Acute Kidney Injury and Chronic Kidney Disease

Radiologic Appearance of the kidney

Urinary Sediment
Renal Ultrasound

Size and Appearance DO MATTER!

• Size
  – No change in size during AKI
  – Decrease in size with CKD due to fibrosis
  – Normal > 11 cm
    • Decrease in size < 10 cm
Renal Ultrasound

• Echogenicity
  – Compare the echo texture of the kidneys to the liver
  – Specific echogenic kidneys zones can be defined due to the presence of glomeruli and tubules while the liver is more homogeneous
  – A clear differentiation is usually seen due to the difference in density of the tubules between the cortex and the medulla of the kidneys

• Corticomedullary differentiation
Normal vs. CKD

AKI

- Small / Abnormal (< 10 cm)
- Increased Echogenicity
- Loss of corticomedullary junction

CKD

- Small / Abnormal (< 10 cm)
- Increased Echogenicity
- Loss of corticomedullary junction

And ........The Resistive index !!

By ultrasound doppler – values > 0.80 (normal < 0.65)
indicate more severe injury
Waxy Casts

Indicative of Chronic Kidney Disease (CKD)
Question

What is your assessment of this woman’s kidney function at baseline?

1. Yes, her creatinine was normal (< 1.5 mg/dl)
2. No, she had AKI
3. No, she had CKD
4. Sorry, I’m not awake yet
5. What is CKD?

But, In the absence of microalbuminuria or proteinuria, this level of GFR is likely not a significant risk for progressive kidney disease or increased CV risk.
**Question**

What is your assessment of this woman’s kidney function right now before the catheterization?

1. She has AKI from Metformin
2. She has AKI from Cimetidine
3. She has AKI from Enalapril
4. She has AKI from Bactrim
5. She has AKI from all of the above
6. Something else ..........

### Laboratory Values

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Lactic Acidosis: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with GLUCOPHAGE (metformin hydrochloride) or GLUCOPHAGE XR (metformin hydrochloride); when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 μg/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypo perfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient’s age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking GLUCOPHAGE or GLUCOPHAGE XR and by use of the minimum effective dose of GLUCOPHAGE or GLUCOPHAGE XR. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. GLUCOPHAGE or GLUCOPHAGE XR treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, GLUCOPHAGE and GLUCOPHAGE XR should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, GLUCOPHAGE and GLUCOPHAGE XR should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking GLUCOPHAGE or GLUCOPHAGE XR, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, GLUCOPHAGE and GLUCOPHAGE XR should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure (see also PRECAUTIONS).

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgia, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradycardiac arrhythmias with more marked acidosis. The patient and the patient’s physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur (see also PRECAUTIONS). GLUCOPHAGE and GLUCOPHAGE XR should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose, and if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized, an elevated level of GLUCOPHAGE or GLUCOPHAGE XR gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking GLUCOPHAGE or GLUCOPHAGE XR do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling. (See also PRECAUTIONS.)

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking GLUCOPHAGE or GLUCOPHAGE XR, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery. (See also CONTRAINDICATIONS and PRECAUTIONS.)
Metformin Induced Lactic Acidosis: A Persistent Concern

Hung SC. Lancet Diabetes Endocrinology 2015 Aug;3(8):605-14

But ...Metformin is not directly nephrotoxic
ACEI / ARB AKI

- Not directly nephrotoxic
- Decrease intraglomerular pressure and may result in a slight but stable rise in the serum creatinine < 0.5 mg/dl
- AKI only in the presence of
  - Bilateral renal artery stenosis
  - Pre-existing AKI and volume depletion
  - Acute ischemic insult
    - Hypotension
    - Contrast exposure
Drug Induced Hyperkalemia

- RAAS inhibition
  - Renin inhibitors
  - ACEI
  - AII receptor inhibitors
  - Aldosterone blockade
- Trimethoprim (resembles amiloride)
  - Bactrim
- NSAIDs
- Heparin
- Non selective β blockers : β2 blockers
Pseudo-AKI

Bactrim

Cimetidine
Serum Creatinine

- **End product of muscle metabolism**
  - Cyclic anhydride of creatine (nonenzymatic)
- **Creatine is synthesized in the liver and stored in muscle** (creatine phosphokinase - CPK)
  - Also ingested orally and localized to muscle
- **Renal excretion of Creatinine**
  - Filtration – GFR (85%)
  - Proximal Tubular secretion (15%)
Spurious Elevations of Serum Creatinine with Normal Renal Function

Impaired tubular secretion

• **Trimethoprim**
  – Bactrim (Trimethoprim and Sulfamethoxazole)
  – 15 – 35% increase

• **Cimetidine (Tagamet)**
  – 20% increase
  – No increase with other H-2 antagonists

Caveat

In these cases the BUN/Cr ratio will be < 10
In AKI the ratio is 15:1
In Pre-Renal Azotemia the ratio is > 20:1
**Question**

What is your assessment of this woman’s kidney function right now?

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<td>BUN/Cr</td>
<td>6.4</td>
<td>15</td>
</tr>
</tbody>
</table>

*Pseudo – AKI = Trimethoprim*
Case Presentation

- 75 year Caucasian female with Stage 2 CKD presents to the ER with an acute coronary syndrome
- She underwent a cardiac catheterization and had a drug eluting stent placed in the LAD
- The day after the catheterization the following labs were obtained

<table>
<thead>
<tr>
<th>Urinalysis</th>
<th>Pre Cath</th>
<th>Post Cath</th>
</tr>
</thead>
<tbody>
<tr>
<td>FENA</td>
<td>140</td>
<td>140</td>
</tr>
<tr>
<td>Specific gravity</td>
<td>5.5</td>
<td>5.8</td>
</tr>
<tr>
<td>Cl</td>
<td>104</td>
<td>101</td>
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<tr>
<td>eGFR</td>
<td>1.4</td>
<td>2.0</td>
</tr>
<tr>
<td>Urine Na</td>
<td>45</td>
<td>24</td>
</tr>
</tbody>
</table>
**Laboratory Evaluation of AKI**

<table>
<thead>
<tr>
<th>Urinalysis</th>
<th>Pre-renal Azotemia</th>
<th>Pre-Renal Azotemia with CKD or Diuretics</th>
<th>ATN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine Sodium</td>
<td>&lt; 20</td>
<td>&gt;40</td>
<td>&gt; 40</td>
</tr>
<tr>
<td>Specific gravity</td>
<td>1.015</td>
<td>1.010</td>
<td>1.010</td>
</tr>
<tr>
<td>FENA</td>
<td>&lt; 1%</td>
<td>&gt; 2%</td>
<td>&gt; 2%</td>
</tr>
</tbody>
</table>

Sp Gravity = 1.010 = Isosthenuria
(Urine that is neither concentrated or dilute)
Question

Could anything have been done to prevent the ATN from CIN: Contrast Nephrotoxicity?

1. High dose saline infusion
2. High dose bicarbonate infusion
3. Mucomyst- N Acetylcysteine
4. Diuretics + Hydration
5. Dialysis immediately after the procedure
6. Prayer

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Radiocontrast

• Nephrotoxicity
  – Proximal tubular damage - ATN
  – Pathogenesis
    • Increased adenosine
    • Direct cytotoxicity

• Clinical
  – Reversible AKI
  – Begins within 24-48 hours post-exposure
  – Non-oliguric
  – Severity of injury requiring dialysis only in patients with baseline creatinine > 4 mg/dl
    • risk of dialysis among all patients receiving contrast < 1%
What does not work: Diuretics!

Multiple trials / Multiple meta-analysis

No benefit in altering the outcome of AKI

Ho KM. Anaesthesia 2010; 65: 283–293
N Acetyl Cysteine:
15 Minutes of Fame is almost over

Joint Guidelines of the ACC/AHA do not recommend using acetylcysteine

However if NAC is to be used – high dose 1200 BID is recommended
Dialysis to Prevent CIN:
15 Minutes of Fame ARE over

Just say NO!
## Type and Volume of Contrast Matters

**Low Osmolar vs Isosmolar**

### Classification of Contrast Dyes

<table>
<thead>
<tr>
<th>Type of Contrast Medium</th>
<th>Osmolality</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-Osmolar Contrast Medium (HOCM)</td>
<td>Osmolality ≈ 1500 mOsm</td>
<td></td>
</tr>
<tr>
<td>Diatrizoate (Gastrografin, Hypeaque, Urografin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iothalamate (Conray)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-Osmolar Contrast Medium (LOCM)</td>
<td>Osmolality ≈ 320-800 mOsm</td>
<td>Higher rate of AKI vs IOCM</td>
</tr>
<tr>
<td>Iohexol (Omnipaque)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ioxaglate (Hexabrix)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ioversol (Optiray)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iomeprol (Imeron)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iopromide (Ultravist)</td>
<td></td>
<td>Similar rate of AKI vs IOCM</td>
</tr>
<tr>
<td>Iopamidol (Isovue, Iopamiro, Iopamiron, Niopam)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iso-Osmolar Contrast Medium (IOCM)</td>
<td>Osmolality = 290 mOsm</td>
<td></td>
</tr>
<tr>
<td>Iodixanol (Visipaque)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Preferred*
Volume of Contrast and CIN

![Graph showing the incidence of CIN across different quartiles of contrast volume.]

- Quartile I: 4.4% (14 ± 4 mL)
- Quartile II: 10.9% (23 ± 2 mL)
- Quartile III: 15.2% (34 ± 6 mL)
- Quartile IV: 29.8% (61 ± 12 mL)

Population incidence of CIN was 4.4% with a P value of 0.005.
Saline vs Bicarbonate

- **Uptodate**
  - **Hydration is essential**
  - No preference to type of fluid used
  - **Emergency procedure**
    - 3 cc/kg over 1 hour followed by 1-1.5 cc/kg/hr for 6 hours
  - **Non emergency procedures**
    - 1 cc/kg/hr for 6 hours prior and continue for 6-12 hours post
Early high-dose rosuvastatin administered in addition to standard CI-AKI preventive measures (hydration and iso-osmolar contrast medium administration) reduced the incidence of renal injury by 55%.

(J Am Coll Cardiol 2014;63:71–9)
### Statins for Preventing CIN

**Favorable Meta Analysis Data**

#### Table: Study or Subgroup Data

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.1.1 Statins vs placebo/no statin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abaci 2015</td>
<td>6</td>
<td>103</td>
<td>0.68</td>
<td>[0.25, 1.84]</td>
</tr>
<tr>
<td>de Oliveira 2012</td>
<td>6</td>
<td>67</td>
<td>1.22</td>
<td>[0.39, 3.80]</td>
</tr>
<tr>
<td>Han 2014</td>
<td>34</td>
<td>1498</td>
<td>0.59</td>
<td>[0.39, 0.89]</td>
</tr>
<tr>
<td>Jo 2008</td>
<td>3</td>
<td>118</td>
<td>0.75</td>
<td>[0.17, 3.28]</td>
</tr>
<tr>
<td>Leoncini 2014</td>
<td>17</td>
<td>252</td>
<td>0.45</td>
<td>[0.26, 0.77]</td>
</tr>
<tr>
<td>Li 2012</td>
<td>2</td>
<td>78</td>
<td>0.16</td>
<td>[0.04, 0.70]</td>
</tr>
<tr>
<td>Ozhan 2010</td>
<td>2</td>
<td>60</td>
<td>0.33</td>
<td>[0.07, 1.54]</td>
</tr>
<tr>
<td>Patti 2011</td>
<td>6</td>
<td>120</td>
<td>0.38</td>
<td>[0.15, 0.93]</td>
</tr>
<tr>
<td>Qiao 2015</td>
<td>2</td>
<td>60</td>
<td>1.00</td>
<td>[0.15, 6.87]</td>
</tr>
<tr>
<td>Quintavalle 2012</td>
<td>7</td>
<td>202</td>
<td>0.45</td>
<td>[0.19, 1.07]</td>
</tr>
<tr>
<td>Sanei 2014</td>
<td>5</td>
<td>115</td>
<td>0.88</td>
<td>[0.28, 2.79]</td>
</tr>
<tr>
<td>Shehata 2015</td>
<td>5</td>
<td>65</td>
<td>0.38</td>
<td>[0.15, 1.02]</td>
</tr>
<tr>
<td>Tosic 2010</td>
<td>15</td>
<td>152</td>
<td>0.94</td>
<td>[0.48, 1.83]</td>
</tr>
<tr>
<td>Yun 2014</td>
<td>55</td>
<td>408</td>
<td>0.72</td>
<td>[0.52, 0.99]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>3298</td>
<td>3339</td>
<td>0.61</td>
<td>[0.51, 0.74]</td>
</tr>
</tbody>
</table>

#### Total events: 165 vs 281

Heterogeneity: $\tau^2 = 0.00$, $\chi^2 = 12.29$, df = 13 ($P = 0.50$); $I^2 = 0$

Test for overall effect: $Z = 5.18$ ($P < 0.00001$)

#### 1.1.2 High-dose vs lower-dose statins

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cao 2012</td>
<td>6</td>
<td>90</td>
<td>0.33</td>
<td>[0.14, 0.80]</td>
</tr>
<tr>
<td>Han 2013</td>
<td>1</td>
<td>73</td>
<td>0.18</td>
<td>[0.02, 1.61]</td>
</tr>
<tr>
<td>Jia 2009</td>
<td>6</td>
<td>113</td>
<td>0.34</td>
<td>[0.14, 0.82]</td>
</tr>
<tr>
<td>Zhou 2009</td>
<td>0</td>
<td>50</td>
<td>0.14</td>
<td>[0.01, 2.70]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>326</td>
<td>309</td>
<td>0.31</td>
<td>[0.17, 0.56]</td>
</tr>
</tbody>
</table>

#### Total events: 13 vs 43

Heterogeneity: $\tau^2 = 0.00$, $\chi^2 = 0.56$, df = 3 ($P = 0.91$); $I^2 = 0$

Test for overall effect: $Z = 3.90$ ($P < 0.00001$)

Total (95% CI): 3624 vs 3648

Heterogeneity: $\tau^2 = 0.01$, $\chi^2 = 17.57$, df = 17 ($P = 0.42$); $I^2 = 3$

Test for overall effect: $Z = 5.95$ ($P < 0.00001$)

Test for subgroup differences: $\chi^2 = 4.66$, df = 1 ($P = 0.03$), $I^2 = 78.5$
The use of high dose statin pre-procedure appears to be reno-protective for contrast nephropathy.
Question

Could anything have been done to prevent CIN: Contrast Nephrotoxicity?

1. High dose saline infusion
2. High dose bicarbonate infusion
3. Mucomyst
4. Diuretics + Hydration
5. Dialysis immediately after the procedure
6. Prayer

BUT … Statins look VERY promising

<table>
<thead>
<tr>
<th></th>
<th>Pre Cath</th>
<th>Post Cath</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>140</td>
<td>140</td>
</tr>
<tr>
<td>K</td>
<td>5.5</td>
<td>5.8</td>
</tr>
<tr>
<td>Cl</td>
<td>104</td>
<td>101</td>
</tr>
<tr>
<td>HCO3</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>BUN</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>Cr</td>
<td>1.4</td>
<td>2.0</td>
</tr>
<tr>
<td>eGFR</td>
<td>37</td>
<td>24</td>
</tr>
</tbody>
</table>
**Question**

- If this patient after cardiac catheterization had this rash on her legs what alternative diagnosis would you consider as a cause of AKI?
  1. Interstitial Nephritis
  2. Pre-renal azotemia
  3. TTP
  4. Atheroembolism
  5. Acute vasculitis
  6. Zika Virus
  7. I’m an internist! Consult Dermatology!!!
Renal Syndromes

- Blood Vessels
  - Vasculitis

- Glomeruli
  - Glomerulonephritis

- Tubules
  - Tubular Necrosis

- Interstitium
  - Interstitial Nephritis
Acute Allergic Interstitial Nephritis

- Characterized by predominant involvement of the renal interstitial compartment by
  - Interstitial edema
  - Interstitial cellular infiltrate
    - T lymphocytes
    - Monocytes
    - Eosinophils
    - Plasma cells
    - Neutrophils
Normal

Extensive T cell infiltrate

Interstitial Nephritis
Acute Interstitial Nephritis
Common Drugs

- PPI – proton pump inhibitors
- NSAIDs
  - Both COX-1 and COX-2 inhibitors
- Ampicillin / PCN
- Cephalosporin
- Rifampin
- Sulfonamides
  - Furosemide
  - Bumetanide
  - Thiazide diuretics
  - Trimethoprim-Sulfamethoxazole
- Cimetidine
- Allopurinol
- Ciprofloxacin

Most common etiology in the U.S.
# Acute Interstitial Nephritis

## Typical Course

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time of onset</strong></td>
<td><strong>7-10 days</strong></td>
</tr>
<tr>
<td><strong>Fever</strong></td>
<td><strong>80%</strong></td>
</tr>
<tr>
<td><strong>Rash</strong></td>
<td><strong>70%</strong></td>
</tr>
<tr>
<td><strong>Eosinophilia</strong></td>
<td><strong>50%</strong></td>
</tr>
<tr>
<td><strong>Proteinuria</strong></td>
<td><strong>&lt; 2g</strong></td>
</tr>
<tr>
<td><strong>Recovery Period</strong></td>
<td><strong>1-2 Weeks</strong></td>
</tr>
</tbody>
</table>

Except PPIs and NSAIDs that rarely cause eosinophilia, fever, rash and result in AKI over weeks / months.
Caveat

AIN is usually accompanied by the triad of 

Maculopapular rash / Fever / Eosinophilia
Test Pearl

• Any patient case where they present AKI with a CBC that shows eosinophilia – (always look at the differential)
  – That is Interstitial Nephritis !!!!
  – Treatment requires immediate discontinuation of the offending drug and sometimes Steroids
Cardiac Catheterization
**Atheroembolic Disease**

- Acute release of cholesterol crystals from an ulcerative plaque leading to downstream end organ injury

*Cholesterol clefts in an atheroma of the aorta*

Cardiac catheterization is the most common cause for the traumatic release of these crystals
Atheroembolic Disease

Kidney

Toes

Skin

Retina

Ischemia

“Purple” Toes

Livido

Hollenhorst Plaques
Question

If this patient after cardiac catheterization had this rash on her legs what alternative diagnosis would you consider as a cause of AKI?

1. Interstitial Nephritis
2. Pre-renal azotemia
3. TTP
4. Atheroembolism ✅
5. Acute vasculitis
6. Zika Virus
7. I’m an internist! Consult Dermatology!!!
Nephrology Case –
The Workup Dilemma

- 60 year male – office visit
- Complained of abdominal pain – RUQ
- Sent for Abdominal x-ray and ultrasound

PMH

- Type II DM X 20 years
- Stage 4 CKD
  - eGFR 20 cc/min
  - Creatinine 4 mg/dl
Nephrology Case – The Workup Dilemma

- **X-ray**
  - Normal bowel gas pattern
- **Ultrasound**
  - Solid/cystic mass left lobe of the liver
  - Report recommendation
    - “clinical correlation – lesion highly suspicious for malignancy. MRI with gadolinium recommended”
Now we know IV contrast is nephrotoxic – but what about an MRI with Gadolinium?

1. Perfectly safe – no nephrotoxicity
2. Terrible choice – just as nephrotoxic as IV contrast – causes ATN
3. A little safer – not as nephrotoxic as IV contrast – but instead of ATN it may cause Allergic Interstitial Nephritis
4. Call a Lawyer – it can cause amyloidosis in CKD patients
5. Call 1-800-sue-adoc: it can cause Nephrogenic Systemic Fibrosis in CKD patients
Gadolinium

- Non ionic hyperosmolar contrast agent used for MRI studies
- Excreted unchanged in the urine
  - Half life increases 10X with CKD
- Free gadolinium ($\text{Gd}^{3+}$) can bind to tissue anions forming insoluble complexes
- 5 approved chelates used clinically
  - Magnevist, Multihance, Omniscan, Optimark, ProHance
Nephrogenic Systemic Fibrosis (NSF)

- Recently identified fibrosing disorder only seen in:
  - Patients with renal failure
    - CKD
    - Hemodialysis
    - Peritoneal dialysis
  - Exposure to gadolinium
- First cases identified in 1997
  - > 200 cases reported
  - No gender / race / age / geographic predilection
  - Higher risk in peritoneal dialysis patients
Nephrogenic Systemic Fibrosis
Nephrogenic Systemic Fibrosis (NSF)

- Clinical Manifestations
  - Interval from exposure to disease onset
    - 2 weeks to 18 months
  - Skin
    - Peripheral involvement first then central distribution
    - Ankles / hands first then thighs / forearms
    - Cobblestone appearance
      - Burning / pain sensation
      - Thick / firm texture
      - Scleromyxedema-like
      - Fixed contractures of the joints
Nephrogenic Systemic Fibrosis (NSF)

Clinical Manifestations
- Systemic Fibrosis
  - Muscle
  - Lung
  - Myocardium
  - Heart valves

Outcome
- Chronic / unremitting course
- Mortality – 30%
- Stabilization or improvement only with recovery of renal function
Nephrogenic Systemic Fibrosis (NSF)

Prevention

- In hemodialysis patients
  - Hemodialysis immediately after the administration followed by a second treatment at 24 hours
- In peritoneal dialysis patients
  - Switch to hemodialysis (as above)
  - Rapid CAPD exchanges for 2 days
- In Stage 4 CKD
  - Hemodialysis as above
- In Stage 3 CKD
  - Unknown risk
  - Avoidance recommended and the role of dialysis after exposure is not clear
Questions

• We know IV contrast is nephrotoxic – but what about Gadolinium?
  1. Perfectly safe – no nephrotoxic
  2. Terrible choice – just as nephrotoxic as IV contrast – causes ATN
  3. A little safer – not as nephrotoxic as IV contrast – but instead of ATN it may cause Allergic Interstitial Nephritis
  4. Call a Lawyer – it can cause amyloidosis in CKD patients

Call 1-800-sue-adoc : it can cause Nephrogenic Systemic Fibrosis in CKD patients
Question

- Your patient has now turned 50 years old and to celebrate you have scheduled him for a colonoscopy
- PMH
  - Diabetes Mellitus
  - Stage 3 CKD
  - HTN
- The test showed a hyperplastic polyp that was biopsied and removed
- Approximately 3 months later he doesn’t feel well and goes to the ER where the following labs are found

<table>
<thead>
<tr>
<th></th>
<th>Now</th>
<th>3 m ago</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>140</td>
<td>138</td>
</tr>
<tr>
<td>K</td>
<td>5.5</td>
<td>4.6</td>
</tr>
<tr>
<td>Cl</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>HCO3</td>
<td>21</td>
<td>24</td>
</tr>
<tr>
<td>BUN</td>
<td>40</td>
<td>25</td>
</tr>
<tr>
<td>Cr</td>
<td>2.4</td>
<td>1.5</td>
</tr>
<tr>
<td>eGFR</td>
<td>30</td>
<td>54</td>
</tr>
</tbody>
</table>
Question

What happened ???

A. This is the natural progression of DM

B. This is the natural progression of anyone with Stage 3 CKD – it is progressive over time

C. Must be using some NSAID or unreported nephrotoxin

D. The biopsy of the polyp may have led to a microperforation and now is causing early sepsis

E. Something else ......

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<td>eGFR</td>
<td>30</td>
<td>54</td>
</tr>
</tbody>
</table>
This is his abdominal x-ray
Attention Colonoscopy Patients!

Acute Kidney Injuries

Associated with:
Oral Sodium Phosphate (OSP) Used Prior To Colonoscopies

If You Are Suffering Kidney Injury After Taking Visicol, OsmoPrep or Other OSP Products - Read Here!

You may be entitled to compensation!

- Any Kidney Injuries occurring after colonoscopy

Do you suffer from the following symptoms?

- Malaise, lethargy, or drowsiness
- Decreased amount of urine
- Swelling of the ankles, feet and legs

If you or a loved one has suffered a kidney injury or is experiencing any of the above-mentioned side effects after taking an OSP product, call our OSP legal information center now! Delay may affect your legal rights.
Calcium Phosphate Nephrocalcinosis

- Hypercalcemia and Hypercalciuria
  - Sarcoid
  - HPTH
  - Vitamin D excess
  - Milk alkali

- Hypercalciuria Without Hypercalcemia
  - Medullary Sponge Kidney
  - Type I RTA
  - Chronic loop Diuretic Use
  - Bartter’s Syndrome
  - Dent’s Disease
  - Lowe’s Disease

- Hyperphosphaturia
  - Tumoral Calcinosis
  - Oral Sodium Phosphate
  - Tumor Lysis Syndrome
Phosphate Induced Nephrocalcinosis

- Related to the use of oral sodium phosphate containing hyperosmolar laxatives used for bowel cleansing prior to colonoscopies

Hyperphosphatemia

Hyperphosphaturia
Phosphate Induced Nephrocalcinosis

Acute Reversible Kidney Injury

Acute (Chronic) Phosphate Nephropathy

Persistent elevation of the creatinine > 1 year after exposure to OSP for a colonoscopy
**Acute Phosphate Nephropathy**

- Serum phosphate levels > 7.0 mg/dl in 30-40% of patients
  - Exacerbated by
    - volume depletion
    - CKD
    - ACEI/ARB
- **Pathology**
  - Precipitation of calcium phosphate restricted to distal tubule and collecting ducts
  - Associated with both an acute and chronic interstitial fibrosis
Acute Phosphate Nephropathy

- FDA has placed a black box warning on OSP - 2008
  - Removed from over the counter sales
- Available by prescription only
  - (Visicol, Osmoprep)

Polyethylene glycol preps are safe
Be cautious in the use of these preps in patients with advanced CKD
Question

What happened ???

A. This is the natural progression of DM
B. This is the natural progression of anyone with Stage 3 CKD – it is progressive over time
C. Must be using some NSAID or unreported nephrotoxin
D. The biopsy of the polyp may have led to a microperforation and now is causing early sepsis
E. Something else ........

Acute Phosphate Nephropathy
Can ATN be reversed? NO!

Supportive care only

Nothing will improve the recovery

It needs to run it’s course over 7-14 days
Primary Care physicians need to know that …..

- AKI is increasing in frequency and intensity
- AKI is not only an economic burden but leads to higher patient mortality and a higher risk of CKD
- Familiarity with the KDIGO criteria for AKI is essential
- ATN is the most cause of AKI but be aware of the possibility of Allergic Interstitial nephritis or exogenous toxin exposure
- Maintaining a high urine output may be an important preventive tool for avoiding contrast nephropathy
- Be aware of the risk of gadolinium in CKD patients
- PPIs should be considered as important causes of insidious AIN
- Watch out for oral Na phosphates and AKI after colonoscopies
And Remember

The Most Important Organ of the Body is the Kidney!