PRE-RENAL AKI: DOES IT LEAD TO ATN

Sushma Bhusal
9.9.14
CASE PRESENTATION

• **CC**: 31 AAM presented with Fatigue, malaise and body aches x 10 days

• **HPI:**
  ✓ STD testing done 2 weeks prior, all results negative
  ✓ Symptoms started the following day
  ✓ No clear precipitating cause

• **ROS:**
  ✓ Nausea, vomiting, poor po intake X 1 week
  ✓ Constipation x 1 week
  ✓ Low urine volume but no other urinary symptoms
  ✓ 1 pint of Vodka daily to help him sleep, last drink 4 days PTA
CASE PRESENTATION

• PMH: HTN, PTSD, ETOH use, Tobacco Use

• PSH: None

• FH: DM, HTN in Mom

• Social: Unemployed, Cigarette smoking, 1 pint ETOH daily, sexually active with one partner (polygamous)
CASE PRESENTATION

• Allergies: None

• Home Medications: Stopped one week prior
  ✓ Cholecalciferol 1000U po daily
  ✓ Folic acid 1 mg po daily
  ✓ Thiamine 100 mg po daily
  ✓ Lisinopril 20 mg/HCTZ 25 mg po daily
COURSE PRIOR TO RENAL TEAM EVALUATION

- Presenting Vitals: T 98.4, BP 81/54, HR 118, RR 15, O2 sat 100% RA
- Found with AKI, no obstruction on NCCT
- Patient deemed to be hypovolemic and given 2L of IV fluids
PHYSICAL EXAM

• Vitals: T 98.6, BP 116/74, HR 85, RR 18, O2 sat 100% RA
• General: Alert, oriented, no acute distress
• HEENT: oral mucosa dry
• CVS: S1S2+, RRR, no murmurs/rubs/gallops
• Resp: CTABL
• Abdomen: soft, non tender, non distended, BS+ all quadrants
• Back: No CVA tenderness
• Skin: No rash
• Ext: no joint swelling, edema
LABS

CBC

<table>
<thead>
<tr>
<th></th>
<th>6.2</th>
<th>10.6</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>31.0</td>
<td>320</td>
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</table>

BMP

<table>
<thead>
<tr>
<th></th>
<th>135</th>
<th>85</th>
<th>108</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>4.9</td>
<td>20</td>
<td>24.5</td>
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</tbody>
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ABG: pH - 7.27 PCO2 30  Po2 - 125

CPK : 51, Trop neg

Calcium – 10.5

Lactate: 0.6
LABS

• **Urine studies**
  - UA: cloudy, SG 1.018, pH 5.0, prot 1+, nit -, LE small, no blood
  - Urine microscopy: hyaline casts, wbc 17, rbc 1
  - Urine lytes: Na 32, K 14, Cl 24, Urea 238
  - FENa: > 2%
  - U P/Cr: 0.7/316

• Urine tox: negative
IMAGING

• CXR: No acute Cardiopulmonary disease

• NCCT Abdomen and Pelvis Without contrast: Unremarkable, kidneys normal size, no hydronephrosis or calculus
DIFFERENTIALS: PRE–RENAL AKI

• Hypovolemia
  • Blood loss, GI loss, Skin
  • 3rd Space (bowel, pancreatitis, edema)
• Cardiovascular: low cardiac output
• Distributive (decreased SVR)
  • Sepsis
  • Hepatorenal
  • Vasodilators
• Renal
  • Renal artery stenosis
  • Drugs (ACE inhibitors, non-steroidal)
  • Rapid lowering of BP in severe hypertension
DIFFERENTIALS: ATN

- Ischemia
- Toxins: Myoglobin, Aminoglycosides, Radio-contrast agents
- Interstitial Nephritis
- Acute Glomerulonephritis and Vasculitis

- *Post Renal*
HOSPITAL COURSE

• Patient improved with IV fluids, total of 5 L

• Labs as shown

• Discharged to be followed up in clinic, never did x 2

• At discharge the diagnosis was pre-renal renal failure
## HOSPITAL COURSE

<table>
<thead>
<tr>
<th>DATE</th>
<th>BUN</th>
<th>Na</th>
<th>K</th>
<th>Cl</th>
<th>AG</th>
<th>CO2</th>
<th>Creat</th>
<th>Ca</th>
<th>Hb</th>
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<td>135</td>
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<td>20</td>
<td>24.9</td>
<td>10.9</td>
<td>10.6</td>
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<td>7/1/14</td>
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<td>137</td>
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<td>97</td>
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<td>16</td>
<td>23.4</td>
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<tr>
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<td>9.5</td>
<td>9.5</td>
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<td>4.2</td>
<td>94</td>
<td>12</td>
<td>36</td>
<td>3.7</td>
<td>100</td>
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<tr>
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<td>14</td>
<td>147</td>
<td>4.1</td>
<td>105</td>
<td>10</td>
<td>32</td>
<td>1.2</td>
<td>8.8</td>
<td>9.3</td>
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<tr>
<td>8/21/14</td>
<td>11</td>
<td>147</td>
<td>3.7</td>
<td>107</td>
<td>7</td>
<td>33</td>
<td>1.0</td>
<td>9.5</td>
<td>10.9</td>
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OBJECTIVES

1. Pathophysiology of pre-renal AKI: Failure of auto regulation
2. ATN: Is pre-renal failure a cause (difference in opinion)
3. Biomarkers in AKI: In brief
Pathophysiology of Pre-Renal AKI
AUTO-REGULATION OF RENAL BLOOD FLOW

1. Myogenic stretch Reflex

2. Tubulo-Glomerular feedback

3. Angiotensin II
TUBULO-GLOMERULAR FEEDBACK

Okusa. Contrib Nephrol, 2011
AUTO-REGULATION OF RENAL BLOOD FLOW

Reduced Renal Perfusion Pressure → Myogenic Reflex & Tubuloglomerular Feedback → Angiotensin II → \( R_E \) → Maintenance of PGF → Maintenance of GPF → \( R_A \) → Maintenance of GFR

Badr NEJM, Sept 8, 1998
IMPAIRED AUTO-REGULATION

Abuelo NEJM, Aug 2007

[Image showing a graph with normal autoregulation of GFR and normotensive renal failure, illustrating the relationship between GFR and mean arterial pressure.]
Failures to increase efferent arteriolar resistance

- ACEI
- ARBS

Renal Artery Stenosis

Failures to decrease afferent arteriolar resistance

1. Structural changes
   - Old age
   - Atherosclerosis
   - Ch HTN
   - CKD
   - Malignant HTN

2. Reduced vasodilatory PG
   - NSAIDs
   - Cox 2 inhibitors

3. Afferent art vasoconstriction
   - Sepsis
   - Hypercalcemia
   - HRS
   - CNI
   - Radiocontrast

Adapted from Abuelo NEJM, Aug 2007
C Decreased perfusion pressure in the presence of NSAIDs

Decreased vasodilatory prostaglandins

Increased angiotensin II

Low GFR

D Decreased perfusion pressure in the presence of ACEI or ARB

Slightly increased vasodilatory prostaglandins

Decreased angiotensin II

Low GFR
PRE-RENAL AZOTEMIA: A FLAWED PARADIGM IN CRITICALLY ILL SEPTIC PATIENTS?

Contrib Nephrol 2007; 156: 1-9
Bellomo et al
PRE-RENAL AZOTEMIA: A FLAWED PARADIGM

• Widely known concept

• Applied to describe two overlapping processes:
  • Trigger outside the kidney
  • No parenchymal disease, functional, rapidly reversible, if not: ATN (structural)
  • Assumption: Cannot arise denovo
PRE-RENAL AZOTEMIA: A FLAWED PARADIGM

Questions before concept is accepted

1. How does one know when pre-renal AKI becomes ATN

2. How much structural injury needed to be able to say kidney has transitioned from pre-renal to ATN

3. Treatment implications of accurate classification

4. Availability of experimental data that these pathophysiological states exist in severe sepsis
WHEN DOES PRE-RENAL AKI BECOMES ATN

- No consensus criteria defining either ATN or Pre-renal AKI
- When no line can be defined, how to know when crossed
- Biopsy vs clinical course: No biopsies available
- What duration of progressive pre renal azotemia before
HOW MUCH STRUCTURAL INJURY NEEDED

• If ATN assumed patchy, how many necrotic cells to call ATN

• ? No. of necrotic cells correlate with duration and ability to resolve quickly

• Can both coexist

• What is rapid response to treatment ?
TREATMENT IMPLICATIONS OF ACCURATE CLASSIFICATION

• Academic rather than clinical

• ? Classification guides clinicians to appropriate treatments
AVAILABILITY OF EXPERIMENTAL DATA

- Urine analytes and derived variables can D/D between ATN and Pre-renal AKI: Not supported by histopath

- Tubular casts: viable cells, not “necrotic”

- Animal studies: urinary chemistries due to loss of cell polarity and translocation of ATPase, not cell death

- Urinary findings may D/D sustained from rapidly resolving AKI: May be true in ward patients
Biomarkers: Where do we stand?
BIOMARKERS OF AKI

• AKI still remains a cause of significant morbidity and mortality

• Barriers to translating animal studies to patients:
  ✓ heterogeneity with regards to underlying etiology
  ✓ Comorbidities
  ✓ complex pathophysiology
  ✓ late timing of experimental interventions

• Search for “kidney troponin” still on

• Current Biomarkers: NGAL, KIM1, L-FABP, IL8, Cystatin C, TIMP-2, IGFBP7
Urinary neutrophil gelatinase-associated lipocalin distinguishes pre-renal from intrinsic renal failure and predicts outcomes

Eugenia Singer¹,²,³, Antje Elger¹,², Saban Elitok², Ralph Kettritz¹,², Thomas Nickolas⁴, Jonathan Barasch⁴, Friedrich C. Luft¹,², and Kai M. Schmidt-Ott¹,²,#

¹Experimental and Clinical Research Center, a joint institution of the Charité Medical Faculty and the Max-Delbrück Center for Molecular Medicine, Berlin, Germany

²Department of Nephrology and Hypertension, Franz-Volhard Clinic, Helios Clinics Berlin, Germany

⁴Department of Medicine, Columbia University College of Physicians and Surgeons, New York, NY, USA
METHODS

• Prospective study, 161 patients

• **Inclusion Criteria**: All patients hospitalized with AKI

• **Exclusion criteria**: no baseline Cr, inadequate follow up or post obstructive renal failure

• Urinary NGAL levels checked at enrollment and 2 days later along with other parameters

• **Composite outcome**: Step up of RIFLE, RRT, Death
Figure 1. Study flow diagram
SUB STRATIFICATION OF RIFLE SEVERITY BY NGAL LEVELS

**In-hospital dialysis initiation (%)**

**In-hospital mortality (%)**

**In-hospital dialysis initiation or mortality (%)**

- **NGAL ≤ 104 μg/L**
- **NGAL > 104 μg/L**
- **All patients**
Singer et al.

- RIFLE stepup (p=0.013)
- Dialysis initiation (p<0.001)
- Mortality (p=0.004)
- Composite outcome (p<0.001)

Percentage of subgroup displaying prospective outcome:

- <47 (n=43)
- 47-104 (n=32)
- 104-426 (n=38)
- >426 (n=32)

## AUC FOR DIFFERENT BIOMARKERS

<table>
<thead>
<tr>
<th>Test</th>
<th>Diagnosis of intrinsic AKI (vs pre-renal AKI)</th>
<th>Prediction of composite outcome (unfavorable clinical course)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>U-NGAL</strong></td>
<td>0.87 (0.81-0.94) ***</td>
<td>0.71 (0.62-0.8) ***</td>
</tr>
<tr>
<td><strong>U-NGAL/U Cr</strong></td>
<td>0.89 (0.82-0.95) ***</td>
<td>0.71 (0.62-0.8) ***</td>
</tr>
<tr>
<td>Serum Cr</td>
<td>0.74(0.63-0.84) ***, #</td>
<td>0.61(0.51-0.71) *, &amp;</td>
</tr>
<tr>
<td><strong>RIFLE Class</strong></td>
<td>0.72 (0.62-0.82) ***, #</td>
<td>0.56(0.47-0.66) #</td>
</tr>
<tr>
<td><strong>FCreatinine</strong></td>
<td>0.59(0.48-0.71) #</td>
<td>0.49(0.38-0.6) #</td>
</tr>
<tr>
<td><strong>FENa</strong></td>
<td>0.54(0.42-0.65) #</td>
<td>0.45(0.34-0.55) #</td>
</tr>
<tr>
<td><strong>BUN/Cr</strong></td>
<td>0.71(0.59-0.82) *,#</td>
<td>0.48(0.37-0.58) #</td>
</tr>
</tbody>
</table>
Some biomarkers of acute kidney injury are increased in pre-renal acute injury

Maryam Nejat¹, John W. Pickering¹, Prasad Devarajan², Joseph V. Bonventre³, Charles L. Edelstein⁴, Robert J. Walker⁵ and Zoltán H. Endre¹,⁶

*Kidney International* (2012) 81, 1254–1262

Kidney Biomarkers and Differential Diagnosis of Patients With Cirrhosis and Acute Kidney Injury

Justin M. Belcher,¹,²,³ Arun J. Sanyal,⁴ Aldo J. Peixoto,²,⁵ Mark A. Perazella,²,⁵ Joseph Lim,⁶ Heather Thiessen-Philbrook,⁷ Naheed Ansari,⁸ Steven G. Coca,¹,²,³ Guadalupe Garcia-Tsao,⁵,⁶ and Chirag R. Parikh,¹,²,³ for the TRIBE-AKI Consortium

*Hepatology* 2014;60:622-632
CONCLUSIONS

• Our patient was a classic case of pre-renal renal failure by any criteria !!

• Hope to see biomarkers in our clinical practice