Tuesday Conference

12/27/2012
Objectives:

- An overview of MG-related AKI pathogenesis.
- Who is at risk.
- Heme Oxygenase-1 role.
- Some of the crush victims management guidelines.

- Other subjects like prophylaxis and fluid management of acute renal failure in traumatic rhabdomyolysis are not discussed.
51yo AA male no significant PMH, p/w fever, nausea, vomiting, diarrhea, dark urine, and abdominal pain started few days prior to presentation and associated with decreased urine output.

No hx of drugs, no OTC meds.

FH: NC.

On exam:
- Vitals: on admission: stable HD, no fever, BP: 120/65
- Chest: diffuse rhonchi and wheezing
- Extremeties: no edema, skin rash, or tenderness.
- CV: regular, no rubs
- Abd: soft, mild epigastric tenderness, no rebound, guarding
<table>
<thead>
<tr>
<th>Date</th>
<th>Cr</th>
<th>BUN</th>
<th>Ca</th>
<th>po4</th>
<th>K</th>
<th>iPTH</th>
<th>25 vit D</th>
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</thead>
<tbody>
<tr>
<td>7/16</td>
<td>3</td>
<td>35</td>
<td>5.7</td>
<td>11.9</td>
<td>5</td>
<td>668</td>
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<td>7/17</td>
<td></td>
<td></td>
<td>4.5</td>
<td>13</td>
<td></td>
<td></td>
<td>16.3</td>
</tr>
<tr>
<td>7/24</td>
<td>10.4</td>
<td>103</td>
<td>8.5</td>
<td>5.3</td>
<td>4.6</td>
<td>174</td>
<td></td>
</tr>
<tr>
<td>8/8</td>
<td>8.7</td>
<td>45</td>
<td>11.1</td>
<td>5.9</td>
<td>4.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9/27</td>
<td>1.7</td>
<td>19</td>
<td>9.4</td>
<td>3.4</td>
<td>4.3</td>
<td></td>
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</table>
- CXR: infiltrate LLL.
- urine legionella antigen positive.
- Pt also with CPK >600K
- Of note pt's legs were non-tender
- Pt also found to be hypocalcemic to 5.7 and hyperphosphatemic to 11.9, with Cr of 3, indicating acute kidney injury, likely 2/2 rhabdomyolysis, and legionella.
He was initially anuric until 7/26 when he began urinating again. Since then pt continues on HD MWF with modest improvement in urination.

pt found to be urine legionella Ag positive with evidence of PNA on CXR, thought to be primary cause of his rhabdomyolysis.

Pt was started on azithromycin for legionella pneumonia. Levaquin was added per ID recs.
The release and subsequent deposition of myoglobin (Mb) in the kidneys results in acute renal failure (ARF) in up to 40% of cases of rhabdomyolysis and accounts for 7% of cases of ARF in the US.
Myoglobin metabolism

- MW: 17KD
- Half life: 1-3 hs
- Clearance RES, kidneys.
- Loosely bound to a2-globulin.
- Effective renal threshold in plasma >0.5-1.5 mg/dl
- Insensitive marker due to short life, CK is better.
Pathophysiology:

Bywaters et al. were the first to establish a definite pathophysiologic relationship between crush injury, myoglobinuria, and acute tubular necrosis.

BMJ 1941;1:427
Hypovolemic/renal ischemia:
One of the most important and earliest events occurring after glycerol injection is a reduction in RBF.

Venkatachalam et al. 1976.
Renal vasoconstriction:
due to interplay among a number of vasoconstricting /vasodilating systems:
- increased sympathetic activity, RAS,
- reduced nitric oxide production,
- suppressed renal prostaglandin production,
- increased plasma vasopressin concentration,
- glomerular microthrombi and reduced nitric oxide activity
Animal trials observations

- after glycerol-induced ARF glomerular NO is decreased as NO scavenged by heme proteins (high affinity to NO) leading to a decrease in NO activity and oxidation to nitrite.

- Uninephrectomy partially protects renal function against glycerol-induced ARF and this protection may be based on an increase in glomerular NO synthesis.

*Canadian Journal of Physiology and Pharmacology, 2000, 78(6): 476-482*
Myoglobin nephrotoxicity

- There is now accumulating evidence that renal injury, caused by lipid peroxidation may be more important.

- Early observation proposed free iron to cause in vivo injury (Fenton reactions):
  - $F_2^+$ catalyzes formation of hydroxyl radicals, initiating lipid peroxidation.

- Caveat: role in vivo is questionable and weak.
F2-isoprostanes are a group of prostanoids formed by the action of free radicals on arachidonic acid independent of cyclooxygenase.

These compounds are sensitive markers of lipid peroxidation in vivo and are also potent vasoconstrictors, via thromboxane-like receptors and possibly by enhancing endothelin release.

The F2-isoprostanes have been shown to be elevated in the urine and kidneys of such animals and in the urine of patients with rhabdomyolysis.

(Lancet 1999;353:1241)
The heme group in Mb is capable of redox cycling between different oxidation states (ferrous, Fe2+; ferric, Fe3+, and ferryl, Fe4+) and the latter species can initiate lipid peroxidation without the need to invoke free iron and Fenton reactions.

Cimetidine
Desferrioxamine
NO
Alkalization

- Importantly, alkalization of the urine protects against renal failure, significantly suppresses the urinary excretion of F$_2$-IsoPs, supporting a causative link between oxidant injury and the renal dysfunction.

- Alkalization protects against renal failure is not by increasing solubility of Mb as previously proposed, but is consistent with stabilization of the highly reactive ferryl-Mb.
Effect of pH on MetMb-induced formation of F2-IsoPs in LDL. Three LDL preparations were incubated with 5 μm MetMb for 24 h at the pH specified.

Effect of alkalization on renal function and urinary F2-IsoP excretion in rats with rhabdomyolysis.

Nath et al demonstrated that the renal production of heme oxygenase-1 gene is upregulated exclusively in distal parts of the nephron while the proximal tubule sustains much of the injury also suggests a renoprotective effect.
Ironically, cytoprotective properties of HO are derived from products, carbon monoxide (CO) and bile pigments.
Notably, while the clinical toxicity of CO is clearly recognized, much smaller quantities of CO are remarkably cytoprotective, antiapoptotic, vasorelaxant, and anti-inflammatory.

Bile pigments, long regarded as contributors to renal disease are now recognized as anti-inflammatory and antioxidant when present in low concentrations.
There are data suggest that plasma and urinary HO-1 levels may serve as biomarkers of AKI and intrarenal HO-1 gene activity.

HO-1 mRNA is upregulated in kidney, but not in liver, lung, or spleen 24 hours after induction of glycerol or cisplatin AKI. To assess possible extrarenal sites of HO-1 production that could contribute to circulating or urinary HO-1 levels, HO-1 mRNA levels...
Plasma HO-1 concentrations reflect intrarenal HO-1 activity after glycerol-induced renal injury.

Zager R A et al. JASN 2012;23:1048-1057
Tubular obstruction:

The concurrent volume depletion and renal vasoconstriction enhance its concentration

- Early views of the mechanism of the renal failure in rhabdomyolysis saw Mb as an inert precipitant causing tubular obstruction and secondary organ dysfunction. Tubular obstruction has been inferred by the presence of tubular dilatation.

- However, kidney micropuncture shows that intratubular pressures are unexpectedly low.

- These data suggest that casts may be formed as a consequence of sluggish urine flow reflecting the low GFR, rather than a cause of obstruction per se.
Who is at risk.

- Although patients with rhabdomyolysis are at increased risk of acute renal failure, little is known about the risk factors for renal failure.

- Retrospective cohort: 72 consecutive patients with rhabdomyolysis due to illicit drug use, patients with a creatine kinase greater than 25,000 U/L, hypotension, and leukocytosis were at a greater risk of developing acute renal failure, whereas hyperthermia (temperature >38.5°C) was associated with a reduced risk.

Am J Med 2004
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Severe Renal Failure (n = 17)</th>
<th>Absence of Severe Renal Failure (n = 55)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) or Mean ± SD (Range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>41.4 ± 6.0</td>
<td>37.8 ± 8.3</td>
<td>0.1</td>
</tr>
<tr>
<td>Male sex</td>
<td>17 (100)</td>
<td>48 (87)</td>
<td>0.12</td>
</tr>
<tr>
<td>African American</td>
<td>10 (59)</td>
<td>47 (85)</td>
<td>0.02</td>
</tr>
<tr>
<td>Drug used</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined heroin and cocaine</td>
<td>25 (88)</td>
<td>42 (76)</td>
<td>0.3</td>
</tr>
<tr>
<td>Heroin use alone</td>
<td>2 (12)</td>
<td>6 (11)</td>
<td>0.32</td>
</tr>
<tr>
<td>Cocaine use alone</td>
<td>0</td>
<td>7 (13)</td>
<td>0.04</td>
</tr>
<tr>
<td>Injection drug use</td>
<td>14/16 (88)</td>
<td>41/54 (74)</td>
<td>0.08</td>
</tr>
<tr>
<td>Concurrent alcohol use</td>
<td>9/15 (60)</td>
<td>17/54 (32)</td>
<td>0.002</td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td>12 (71)</td>
<td>25 (46)</td>
<td>0.08</td>
</tr>
<tr>
<td>Recent generalized seizure</td>
<td>1 (6)</td>
<td>5 (9)</td>
<td>0.67</td>
</tr>
<tr>
<td>Compartment syndrome requiring fasciotomy</td>
<td>4 (24)</td>
<td>1 (2)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hypotension (mean arterial pressure &lt;70 mm Hg)</td>
<td>5 (29)</td>
<td>4 (7)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hyperthermia (≥38.5°C)</td>
<td>2 (12)</td>
<td>23 (42)</td>
<td>0.02</td>
</tr>
<tr>
<td>Weight (kg)†</td>
<td>91 ± 19</td>
<td>76 ± 17</td>
<td>0.003</td>
</tr>
<tr>
<td>Oliguria (&lt;400 cc/d)</td>
<td>10 (59)</td>
<td>0/37 (0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hepatitis C seropositivity</td>
<td>14/16 (88)</td>
<td>40/49 (82)</td>
<td>0.59</td>
</tr>
<tr>
<td>HIV seropositivity</td>
<td>3/15 (20)</td>
<td>17/43 (40)</td>
<td>0.17</td>
</tr>
<tr>
<td>Creatine kinase &gt;25,000 U/L</td>
<td>15 (88)</td>
<td>14 (25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>5.0 (2.7–15)</td>
<td>1.8 (0.7–3.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dL)</td>
<td>51 ± 32</td>
<td>21 ± 12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>6.0 ± 1.4</td>
<td>4.3 ± 1.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High anion gap acidosis</td>
<td>12 (71)</td>
<td>15 (27)</td>
<td>0.001</td>
</tr>
<tr>
<td>Leukocyte count (1000 cells/mm³)</td>
<td>15.9 ± 5.5</td>
<td>10.8 ± 5.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>43.8 ± 8.0</td>
<td>39.9 ± 4.8</td>
<td>0.06</td>
</tr>
<tr>
<td>Urine myoglobin (moderate or large)</td>
<td>12/12 (100)</td>
<td>35/48 (73)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Am J Med 2004
Next to hyperkalaemia, the most important electrolyte disturbance is hypocalcaemia, resulting from the influx of calcium into the muscle due to functional impairment of the muscular cell membrane; it may result in paraesthaesia, tetany, seizures, hypotension, bradycardia, impaired cardiac contractility and arrhythmia. The calcium accumulated in the muscles is released back into circulation at a later stage when the muscular lesions are healing, hence creating at that time a potential for hypercalcaemia. Therefore, in crush, correction of hypocalcaemia is recommended only if it is symptomatic.

Transplant. (2012) 27(Suppl 1)
Fasciotomies:

- Unless clearly indicated by physical findings or intracompartmental pressure measurements, do not perform fasciotomies routinely to prevent compartment syndrome.
- Unless contraindicated, consider mannitol administration as a preventive measure to treat increasing intracompartmental pressures.

Dialysis treatment of crush-related AKI

Dialysis is life-saving. Make every effort to dialyze disaster crush victims when changes in fluid, electrolyte and acid–base balance develop.

For the timely initiation of dialysis, monitor victims closely for development of indications for dialysis, specifically hyperkalemia, hypervolemia and severe uremic toxicity.

Although continuous renal replacement therapy (CRRT) or peritoneal dialysis (PD) can be used depending on availability and patient needs, prefer intermittent hemodialysis (IHD) as the first choice of renal replacement therapy. Cochrane Database Syst Rev 2007: CD003773

When discontinuing dialysis support, monitor the patient closely for any clinical or laboratory deterioration that may require reinstitution of dialysis.