Acute Kidney Injury

May 2014
Kathleen D. Liu, MD, PhD

What I’m not going to tell you

- Acute renal failure/acute kidney injury is associated with an increased risk of death
- Despite many efforts, we have no therapies to treat or prevent acute kidney injury

What’s “hot” in AKI

- Can we identify “at risk” patients?
- Impact of fluid management on AKI
- Medication dosing in patients with AKI

Comparison of RIFLE, AKIN and KDIGO Definitions and Staging of AKI

<table>
<thead>
<tr>
<th></th>
<th>RIFLE definition</th>
<th>AKIN definition</th>
<th>KDIGO definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>staging</td>
<td>Increase in Scr by ≥1.5 times baseline within 7 days</td>
<td>Increase in Scr by 0.3 mg/dL or ≥1.5 times baseline within 48 hours</td>
<td>Increase in Scr by 0.3 mg/dL within 48 hours; or Increase in Scr by ≥1.5 times baseline within 7 days</td>
</tr>
<tr>
<td>R</td>
<td>Increase in Scr by 1.5 - &lt;2.0 times baseline</td>
<td>Increase in Scr by ≥2.0 - &lt;3.0 times baseline</td>
<td>Increase in Scr by ≥2.0 - &lt;3.0 times baseline</td>
</tr>
<tr>
<td>I</td>
<td>Increase in Scr by 2.0 - &lt;3.0 times baseline</td>
<td>Increase in Scr by ≥3.0 times baseline</td>
<td>Increase in Scr by ≥3.0 times baseline</td>
</tr>
</tbody>
</table>
**KDIGO Classification**

<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; or ≥0.3 mg/dL increase</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 &gt;12 hours</td>
</tr>
<tr>
<td>3</td>
<td>≥3.0 times baseline; or increase to ≥4.0 mg/dL; or initiation of RRT; or in patients &lt; 18 years, decrease in eGFR to &lt; 35 mL/min/1.73 m²</td>
<td>&lt;0.3 mL/kg/h for ≥24 hours; or Anuria for ≥12 hours</td>
</tr>
</tbody>
</table>

**Stage-based Management of AKI**

- Discontinue all nephrotoxic agents when possible
- Ensure volume status and perfusion pressure
- Consider functional hemodynamic monitoring
- Monitor serum creatinine and urine output
- Avoid hyperkalemia
- Consider alternatives to radiocontrast procedures

**Identifying patients at risk: Low urine output?**

- Exclude patients with KDIGO stage II or III before hour 12 by SCR criteria
- 96 hours after septic shock onset

**What’s “hot” in AKI?**

- Can we identify “at risk” patients?
- Impact of fluid management on AKI
- Medication dosing in patients with AKI

*Leedahl et al, CJASN 2014*
Identifying patients at risk: Low urine output?

Identifying patients at risk: Low urine output?

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OR (95% CI)</th>
<th>P Value</th>
<th>AUC (95% CI)</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>KDIGO stage II or III</td>
<td>1.47 (1.03 to 2.08)</td>
<td>&lt;0.05</td>
<td>0.74 (0.67 to 0.82)</td>
<td>1.6 (1.33 to 1.94)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SCr level (mg/dl)</td>
<td>1.07 (1.04 to 1.11)</td>
<td>&lt;0.01</td>
<td>0.79 (0.72 to 0.87)</td>
<td>1.02 (1.02 to 1.12)</td>
<td>0.36</td>
</tr>
<tr>
<td>APACHE III score, per unit</td>
<td>1.03 (1.00 to 1.07)</td>
<td>0.38</td>
<td>0.70 (0.64 to 0.77)</td>
<td>0.99 (0.96 to 1.03)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Leedahl et al, CJASN 2014

“Renal Angina: Right concept, wrong name?”

• “This term is derived from the Latin word angina, where it refers to an acute throat infection (quinsy)…. Although there are many clinical syndromes beyond cardiac angina (angina pectoris) that use the term angina….all of these are characterized by pain. Thus, the term renal angina is incorrect from an etymologic standpoint and should be abandoned.”

Palevsky, CJASN 2014

In ACS, we do not use troponin to predict MI!

In “renal angina” studies, common to use low urine output or elevated serum creatinine to predict...lower urine output or more elevated serum creatinine

Palevsky, CJASN 2014
Identifying patients at risk: Biomarkers?

Postop cardiac surgery patients with established baseline Cr
AKI defined by Cr criteria only

Parikh, JASN 2011

Identifying patients at risk: Biomarkers?

What’s “hot” in AKI

- Can we identify “at risk” patients?
- Impact of fluid management on AKI
  - Volume overload
  - Hydroxyethyl starch
  - Chloride-rich fluids
- Medication dosing in patients with AKI

Identifying patients at risk: TIMP-2/IGFBP7

- Panel developed by company, following FDA pipeline for new diagnostic
- What is being “predicted”?
  - “Adjudicated AKI” BUT AKI defined as doubling of serum Cr or UOP < 0.5 mL/kg/h x 12 hours
  - No comment in paper about how many met based on serum Cr vs UOP criteria
Chloride rich solutions and AKI

- Rationale: Hyperchloremia can lead to renal vasoconstriction with associated reductions in GFR
- Pre/post study:
  - 0.9% NS
  - Hartmann solution
  - 4% gelatin
  - Plasmalyte-148
  - 4% albumin
  - 20% salt-poor albumin

Yunas et al, JAMA 2012

Limitations

- Multiple interventions: unclear which component of intervention was associated with change in AKI
- Other temporal changes in care?
Chloride rich solutions and AKI

- Results are intriguing and warrant repeating/study in other contexts
- With some exceptions, use balanced salt solutions rather than isotonic saline
What’s “hot” in AKI

• Can we identify “at risk” patients?
• Impact of fluid management on AKI
• Medication dosing in patients with AKI
  – Dosing related to RRT
  – Vigilance is needed in “at risk” patients!
  – Impact of illness on CrCl/eGFR estimation

Issues with drug dosing for RRT

• Specifics of RRT are not standardized
  – Modality: IHD, CRRT, SLED/PIRRT
  – Dose: Blood flow/dialysate flow rate, treatment time [other features like filter type are fairly standard now]
• Critically ill patients may have large differences in volume of distribution, protein binding, endogenous hepatic/renal clearance

Classification of Antibacterial Activity

<table>
<thead>
<tr>
<th>Time-Dependent</th>
<th>Concentration-Dependent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-lactams</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Fluoroquinolones</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Daptomycin</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Metronidazole</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Telithromycin</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>Vancomycin</td>
</tr>
</tbody>
</table>

Pharmacodynamic Interactions
Failure to achieve PK/PD targets is common with CRRT

Table 3: Probability of time the concentration is four times MIC attainment for Pseudomonas spp.

<table>
<thead>
<tr>
<th>Antibiotic, daily dose (number of patients)</th>
<th>Time period (number of series)</th>
<th>PK/PD target attainment (number of series %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEM 1 g</td>
<td>48 (n = 22)</td>
<td>10 (45%)</td>
</tr>
<tr>
<td></td>
<td>Day ≤ 48 hours (n = 7)</td>
<td>5 (22%)</td>
</tr>
<tr>
<td></td>
<td>Days &gt; 48 hours (n = 15)</td>
<td>15 (70%)</td>
</tr>
<tr>
<td>TDP 4 g</td>
<td>48 (n = 22)</td>
<td>10 (45%)</td>
</tr>
<tr>
<td></td>
<td>Day ≤ 48 hours (n = 10)</td>
<td>10 (50%)</td>
</tr>
<tr>
<td></td>
<td>Days &gt; 48 hours (n = 18)</td>
<td>8 (45%)</td>
</tr>
<tr>
<td>ETP 2 g</td>
<td>48 (n = 15)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Day ≤ 48 hours (n = 10)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Days &gt; 48 hours (n = 5)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>CTR 2 g</td>
<td>48 (n = 15)</td>
<td>5 (33%)</td>
</tr>
<tr>
<td></td>
<td>Day ≤ 48 hours (n = 10)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Days &gt; 48 hours (n = 5)</td>
<td>5 (33%)</td>
</tr>
</tbody>
</table>

Seyler, Crit Care, 2011

Our ability to predict clearance is poor

Table 4: Multivariate linear regression analysis of factors contributing to ADEs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume of distribution Vd 3</td>
<td>-0.50</td>
<td>0.08</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>1.01</td>
<td>0.03</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.10</td>
<td>0.00</td>
</tr>
<tr>
<td>CRRT filter</td>
<td>0.05</td>
<td>0.23</td>
</tr>
<tr>
<td>Elevation constant Kd</td>
<td>0.08</td>
<td>0.46</td>
</tr>
<tr>
<td>Baseline Cr</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Bauer et al, CJASN 2012

Recovery from AKI is another opportunity for adverse drug events

Many potential ADEs are preventable

- 44% of subjects experienced a potential ADE or ADE
- 66% assessed as preventable

Cox, CJASN 2014
Cr generation is affected by critical illness – impact on eGFR/CrCl

Drug dosing: Practical suggestions

- Use therapeutic drug monitoring where feasible (vancomycin, aminoglycosides)
- Patients rarely die of antibiotic overdosing, but they are likely to die of antibiotic underdosing (though there are sequelae to overdosing as well)
- Guidelines are useful, but recognize that they are based on limited data
Drug dosing: Practical suggestions

- IHD: high flux therapy, but short, so reasonable to dose/redose many drugs after dialysis
- CRRT: continuous rate of clearance, so typically dose for clearance of 10-30 cc/min (probably sticking to the high side of this)
- SLED: depending on duration of therapy and type of antibiotic, may need to consider different dosing regimens on/off therapy....

Drug dosing: Practical suggestions

- Be vigilant for changes in renal function and proactive about medication dosing
- In patients with prolonged illness, consider timed measurements of creatinine clearance to assess renal function
- Work closely with pharmacy to manage high risk patients

Summary

- A lot of interest in “at risk” patients but many studies are methodologically problematic
- Fluid management in AKI is area of major interest
  – Fluid overload
  – Avoidance of HES, chloride containing solutions
- Drug dosing in AKI is problematic for many reasons, including varying clearance with RRT, failure to recognize AKI or recovery from AKI, and changes in Cr production