Improving the gold standard:
Can urine biomarkers help refine AKI definition in premature infants?

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Background

- Urine biomarkers may improve our ability to detect organ damage and provide insight on injury/repair mechanisms(1).
- Serum creatinine (SCr)-based AKI definitions carry important limitations. Besides the usual limitations to SCr, it is even more challenging in neonates(2).
- At birth, serum creatinine (SCr) reflects maternal creatinine and decreases over time depending on gestational age.
- In the first week of life, newborns lose up to 15% of their weight – fluid changes can affect SCr values.
- We and others have shown that adjusting SCr for fluid balance can improve the ability to prognosticate clinical outcomes in neonatal(3), pediatric(4) and adult cohorts(5).
- Because urine biomarker values are associated with gestational age, urine biomarkers studies in premature infants must account for differences in gestational age (GA)(6).

Methods

Population:
- 113 VLBW Infants (birth weight ≤1200 g or GA ≤31 weeks) were prospectively followed between February 2012 to June 2013
- Acute kidney injury (AKI) definitions
  - SCr values were prospectively collected on days 1, 2, 3, 4, and 14; and combined with clinically measured SCr.
  - The traditional KDIGO SCr-based definition was used
    - AKI was defined if SCr ≥ 0.3 mg/dl or ≥ 150-200%
    - Lowest previous value was used as the baseline for each SCr value
  - The FA-SCr definition use the same criteria as above after SCr was fluid adjusted
    - FA-SCr = SCr x [TBW + (current weight – birth weight)]/TBW, where total body weight (TBW) = 0.8 x weight in kg.

Urine Biomarkers
- Urine was collected during the first 4 days using cuddlebuns diapers.
- Average number of urines obtained was 3 (range 1-5).
- Biomarker analysis was performed for 14 urine biomarkers, using the MesoScale Discovery (MSD) Human Kidney Injury Panels 3 and 5.
- Samples were controlled for urine creatinine (Ucr) measured by LC/MS Statistical Analysis
- Logistic regression was used to construct the receiver operating characteristic (ROC) and calculate the area under the curve (AUC) for each biomarker on days 1-4, and 14 and its predictive characteristic for the two AKI definition outcomes, after controlling for gestational age (GA).

Table 1: Distribution of AKI outcomes

<table>
<thead>
<tr>
<th>AKI (FA-SCr)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>AKI (SCr)</td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

Table 2: Cohort Demographics and Outcomes by SCr and FA-SCr (N=113)

<table>
<thead>
<tr>
<th>Demographics</th>
<th>SCr (N=84)</th>
<th>SCr AKI (N=29)</th>
<th>P-value†</th>
<th>No FA-SCr AKI (N=94)</th>
<th>FA-SCr AKI (N=19)</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA (weeks)</td>
<td>27.9(2.4)</td>
<td>26.7(2.3)</td>
<td>0.01</td>
<td>27.8(2.2)</td>
<td>26.6(2.1)</td>
<td>0.04</td>
</tr>
<tr>
<td>Apgar 1 minute</td>
<td>4.2(2.4)</td>
<td>4.2(2.6)</td>
<td>0.8</td>
<td>4.2(2.3)</td>
<td>3.7(2.7)</td>
<td>0.7</td>
</tr>
<tr>
<td>Apgar 5 minute</td>
<td>6.8(1.8)</td>
<td>6.4(1.8)</td>
<td>0.3</td>
<td>6.8(1.7)</td>
<td>6.1(2.3)</td>
<td>0.1</td>
</tr>
<tr>
<td>Gender (male, %)</td>
<td>44(54)</td>
<td>12(38)</td>
<td>0.2</td>
<td>47(50)</td>
<td>8(42)</td>
<td>0.5</td>
</tr>
<tr>
<td>Race (N, %)</td>
<td>0.8</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>33(40)</td>
<td>13(45)</td>
<td>0.4</td>
<td>42(45)</td>
<td>15(79)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>44(52)</td>
<td>16(52)</td>
<td>0.2</td>
<td>45(48)</td>
<td>15(79)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>7(8)</td>
<td>0</td>
<td>0.002</td>
<td>10(11)</td>
<td>2(11)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

P-values estimated from t-test where means and SDs are given, †else Mantel-Haenszel X²

Conclusions

- The incidence of AKI was 29/113 (26%) and 19/113 (17%) for SCr and FA-SCr based definition, respectively.
- The performance of the biomarker was enhanced by incorporating the FA-SCr AKI definition in most biomarkers on most days (figure 1) and see attached table for in-depth values.
- Of all biomarkers for all days and definitions, urine neutrophil gelatinase-associated lipocalin (NGAL) on day 4 for fluid-corrected AKI performed best (AUC adjusted for GA = 0.861).

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