"PROGNOSTIC ROLE OF URINARY NEUTROPHIL GLUCOSAMINIDASE-ASSOCIATED LIPOCALIN IN CHILDREN UNDERGOING CARDIAC SURGERY FOR CHD: PRELIMINARY RESULTS".


Fondazione Toscana G.Monasterio Heart Hospital Massa and Scuola Superiore Sant’Anna, Pisa

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The interest in biomarkers of early renal damage, such as NGAL, IL-8 kidney injury molecule-1 (KIM-1) and liver-type fatty acid binding protein (L-FABP) (3,4) is progressively increased during the last few years.

Particularly NGAL has been recently tested in different physiopathologic conditions, with promising results in adults.

However, the few works recently conducted to evaluate NGAL response after paediatric cardiac surgery have shown contrasting results.
NGAL (Neutrophil Gelatinase-Associated Lipocalin) 178 aminoacid protein, 25 kDa

- Role in iron metabolism
- Role in innate immunity to bacteria
- Role in kidney development
- Role as growth factor
THE NEED FOR A TROPININ LIKE BIOMARKER FOR AKI

Nephrology 15 (2010) 419–428

Review Article

Review: Neutrophil gelatinase-associated lipocalin: A troponin-like biomarker for human acute kidney injury

PRASAD DEVARAJAN

Cincinnati Children’s Hospital Medical Center, University of Cincinnati School of Medicine, Cincinnati, Ohio, USA
The search for early markers of AKI

- NGAL should be first a early diagnostic marker of AKI, secondly serve in the stratification of AKI and possibly have also prognostic capabilities.

- It's now clear that consequences of AKI have a worrisome impact in terms of mortality, morbidity and costs, and early diagnosis may allow for an earlier treatment that may in turn ameliorate the outcome.
Neutrophil gelatinase-associated lipocalin, a siderophore-binding eukaryotic protein

Niels Borregaard* & Jack B. Cowland
Limits of actual definition of AKI

- At present time, there is an unacceptable delay in the diagnostic process of renal damage.

- The diagnosis and staging of AKI is based on serial measurements of serum creatinine.

  Plasmatic creatinine Limitations

  - functional marker, not organ specific;
  - may increase only when 50% or more of renal function is lost;
  - unable to identify sub clinical damage;
  - peak delayed (hours to days) from acute damage.
Biomarkers of Acute Kidney Injury

Vishal S. Vaidya, Michael A. Ferguson, and Joseph V. Bonventre

Potential urinary biomarkers for early diagnosis of AKI

- NAG
- β2M
- α1M
- RBP
- Cystatin C
- KIM-1
- Clusterin
- Microalbumin

NGAL
- CYR-61
- IL-18
- OPN
- FABP
- NHE3
- Fetuin A

Delayed biomarkers for kidney injury

- ↑ Serum creatinine
- ↑ Blood urea nitrogen

Definitions of AKI in children

- p-RIFLE
- AKIN (Acute Kidney Injury Network) definition.

Major difference:

1st stage (R= Risk for pRIFLE and stage 1 for AKIN) is defined by an increase of 1.5 times Scr baseline or 25% e GFR decrease from baseline.

Using the AKIN definition this stage can be additionally defined by an ≥ or equal to 0.3 mg/dl Scr increase from baseline.
<table>
<thead>
<tr>
<th>Nr</th>
<th>Age</th>
<th>AKI def.</th>
<th>AKI %</th>
<th>NGAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>311</td>
<td>1 month-18 yrs</td>
<td>P-RIFLE</td>
<td>17</td>
<td>AUC 0.71</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sens 0.43 Spec 0.85</td>
</tr>
<tr>
<td></td>
<td>JASN 2011</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>196</td>
<td>1) No AKI Group (92 pts) 3.2±0.4 yrs</td>
<td>P-RIFLE</td>
<td>51</td>
<td>AUC 0.95</td>
</tr>
<tr>
<td></td>
<td>2) AKI Group (99 pts) 4.8±0.5 yrs</td>
<td></td>
<td></td>
<td>Sens 0.82 Spec 0.9</td>
</tr>
<tr>
<td></td>
<td>Clin J Am Soc Nephrol 2008</td>
<td></td>
<td></td>
<td>Cut-off 100 ng/ml</td>
</tr>
<tr>
<td>374</td>
<td>0-18 yrs</td>
<td>AKIN</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>35 neonates</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>J Paediatric 2011</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>218</td>
<td>3 day-21.1 yrs</td>
<td>P-RIFLE</td>
<td>66</td>
<td>AUC 0.57 for creat &gt; 50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AUC 0.64 for creat &gt; 100%</td>
</tr>
</tbody>
</table>
Between December 2010 and June 2011, we prospectively enrolled 100 children undergoing cardiac surgery for CHD at a single Center.

Sample points were at 2, 6 and 12 hours after surgery.

Outcome Definition.

We used the p-RIFLE classification of AKI, that was defined as increase of 1.5 or greater of plasmatic creatinine.
Results

- Our preliminary results in 100 patients showed how NGAL peak values had a good diagnostic accuracy in the diagnosis of AKI, with an area under the ROC curve (AUC) of 0.82, a sensitivity of 71% and a specificity of 85%.

- AKI occurred in 39%
<table>
<thead>
<tr>
<th></th>
<th>All (100 pts)</th>
<th>AKI (n=39)</th>
<th>Non-AKI (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>36.58 (55.89)</td>
<td>28.88 (59.02)</td>
<td>41.83 (53.68)</td>
</tr>
<tr>
<td>Gender</td>
<td>48 F, 52 M</td>
<td>16 F, 23 M</td>
<td>32 F, 29 M</td>
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<tr>
<td>Weight (kg)</td>
<td>12.46 (13.12)</td>
<td>9.65 (13.27)</td>
<td>14.24 (13.81)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>79.98 (33.38)</td>
<td>70.4 (30.50)</td>
<td>86 (36.94)</td>
</tr>
<tr>
<td>Aristotele sc.</td>
<td>7.08 (2.16)</td>
<td>8.26 (1.91)</td>
<td>6.65 (10.4)</td>
</tr>
<tr>
<td>CPB (min)</td>
<td>108.02 (67.61)</td>
<td>141.46 (82.51)</td>
<td>87.44 (46.08)</td>
</tr>
<tr>
<td>Cross Clamp</td>
<td>47.76 (48.59)</td>
<td>79.45 (66.82)</td>
<td>46.02 (25.59)</td>
</tr>
<tr>
<td>TTE (hrs)</td>
<td>47.76 (95.92)</td>
<td>85.44 (130.57)</td>
<td>24.78 (56.61)</td>
</tr>
<tr>
<td>ICU stay (hrs)</td>
<td>72 (103.69)</td>
<td>116.34 (134.81)</td>
<td>45.69 (68.53)</td>
</tr>
<tr>
<td>Mortality</td>
<td>2 pt (2%)</td>
<td>1 pt (2.6%)</td>
<td>1 pt (1.6%)</td>
</tr>
</tbody>
</table>
Results

- The peak of NGAL values (0.30-1864 ng/L, average ± standard deviation 184.6 ± 350.9 ng/L) usually occurred at 2-6 hours post-surgery; being more frequently encountered at 2 hours.

- NGAL 2 hours significantly higher than basal values (P 0.002)

- NGAL peak preceded the one of creatinine (P 0.0049)
Correlations

- NGAL peak values positively correlated with clinical parameters: weight ($P < 0.004$), height ($P < 0.002$), CPB-time ($P < 0.001$), Aristotele score ($P < 0.003$)

- NGAL peak values positively correlated with outcome parameters: ICU stay ($P < 0.001$), Intubation time ($P < 0.001$)
However, in a multiple regression analysis model, uNGAL peak value was significantly associated ($R= 0.653$, $P<0.0001$) only with

- CEC time ($P< 0.0001$, $R= 0.607$)
- basal BNP ($R= 0.312$, $P<0.01$)
Limitations of the study

- Preliminary results
- A wider number of patient is required to drawn more accurate conclusions
Conclusions

- Urinary NGAL had an acceptable diagnostic accuracy in the early diagnosis of AKI in children undergoing cardiac surgery for CHD and may serve to identify subclinical damage otherwise unknown.

- The peak of NGAL occurred at 2-6 hours, being most common at 2 Hours, and preceding the one of serum creatinine.
Conclusions

- NGAL peak values had also a prognostic value
- The inclusion of NGAL and other biomarkers in diagnostic algorithms of children undergoing cardiac surgery may allow for a better definition and significance of AKI
- Further studies are necessary to fully evaluate the clinical usefulness and costs/benefits of NGAL in children undergoing cardiac surgery for CHD.
Thank you for your attention!