Pediatric AKI and Application of Biomarkers

Arnold O. Beckman Conference
Michael Zappitelli MD, MSc

Most AKI is ATN and multifactorial
• Glomerular
• Tubular
• Vascular
• Interstitial

Child AKI disease model
Overview

1. Pediatric AKI – common and associated with poor outcomes
2. Opportunities for AKI biomarkers in children
3. Review of some published pediatric AKI biomarker data
4. Future directions

Definition in children

<table>
<thead>
<tr>
<th>Stage</th>
<th>Acute SCr rise</th>
<th>Acute UO drop</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5-3 times baseline OR ≥0.3 mg/dl (≥20.5 μmol/l) increase</td>
<td>&lt;0.5 mg/dl/h for 9-12 hours</td>
</tr>
<tr>
<td>2</td>
<td>2.0-3.8 times baseline</td>
<td>&lt;0.5 mg/dl/h for ≥12 hours</td>
</tr>
<tr>
<td>3</td>
<td>3.0 times baseline OR increase in serum creatinine to ≥4.0 mg/dl (≥358 μmol/l) OR OR Initiation of renal replacement therapy OR, in patients &lt;18 years, decrease in aGFR to &lt;30 ml/min per 1.73 m²</td>
<td>&lt;0.3 mg/dl/h for ≥24 hours OR Anuria for ≥12 hours</td>
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KDIGO

Reframing timing of rise

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<th>Acute SCr rise</th>
<th>Acute UO drop</th>
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Incidence of RRT-AKI

- Canada: ~1%
- USA: ~1-3%
- Caribbean: ~6%
- Africa: 1-2%
- Australia & New Zealand: ~4%

RRT-AKI Mortality high everywhere

- Canada: 50-60%
- USA: 40-45%
- Caribbean: 25-50% 42-67%
- Africa: 36% 40% 33-65% 64%

AKI child populations

At risk

- Pre-operative cardiac Sx
- ICU Admission
- Aminoglycoside start
- Chemotherapy start

Clinical data collection
- Blood collection
- Urine collection
- Follow-up
**Incidence: PICU full cohort studies**

- **USA**
  - N=3396
  - No severe CKD
  - Creat
  - ~10%

- **Turkey**
  - N=189
  - No severe CKD
  - Creat
  - ~40%

**Schneider et al, Ped Crit Care, 2010**


**Incidence: PICU partial cohort studies**

- **Canada**
  - N=2196
  - ≥12 hours Creat
  - ~18%

- **North India**
  - N=486
  - ≥24 hours, NO severe Admx AKI Creat
  - ~20%

- **South India**
  - N=215
  - ≥48 hours Creat + Urine
  - ~30%

- **North India**
  - N=486
  - >48 hours Creat + Urine
  - ~60%

**Plotz et al, Intens Care Med, 2008**

**Alkandari et al, Crit Care, 2011**

**Mehra, et al, Ind Ped, 2012**

**Krisnamoorthy, et al, Ind J Ped, 2012**

**AKI OCCURS EARLY IN THE ICU**

Figure 1 | Distribution of the day of admission that subjects reached pRIFLEmax (n = 123) and pRIFLE F stratum (n = 31). Confirmed in several other larger epidemiologic cohort studies
Does a 50% SCr rise really matter?

• In repeated studies last 5 years:
  • AKI independently associated with:
    • PICU mortality
    • Length of stay
    • Duration of mechanical ventilation

• Gr: AKI associated with:
  • PICU LOS
  • Hospital LOS
  • Longer ventilation

Difficult to REALLY know if independent of illness severity

Confirmed: several retrospective and prospective PICU studies

Incidence: Cardiac

2 Canadian studies (646)
  Morgan, J Ped, 2012
  Zappitelli, J, 2009

4 US studies (1194)
  Manrique, Ped Anesth, 2009
  Li, Crit Care Med, 2011
  Bender, J Thor Card Surg, 2012

1 Hungarian study (1510)
  Toth, Card Anethes, 2012

1 Indian study (124)
  Sethi, Clin Exp Nephrol, 2011

Day of Occurrence of AKI
Does a 50% SCR rise really matter?

Risk Factors for and Outcomes of Acute Kidney Injury in Neonates Undergoing Complex Cardiac Surgery

Does a 50% SCR rise really matter?

TRIBE-AKI, multi-centre cardiac: Li et al, CCM 2011

Table 4. Association of outcomes with development of acute kidney injury

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Acute Kidney Injury</th>
<th>No Acute Kidney Injury</th>
<th>Adjusted Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRIBE-AKI</td>
<td>Mammmen group, Pediatr Nephrol, 2013</td>
<td>AKIN Stage 3: Longer PICU stay</td>
<td>Mortality</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.55 (1.12)</td>
<td>1.00 (1.00)</td>
<td>1.55 (1.12)</td>
<td>0.96 (-)</td>
</tr>
<tr>
<td></td>
<td>(1.00, 1.12)</td>
<td>(1.00, 1.00)</td>
<td>(1.00, 1.00)</td>
<td>(.70, 1)</td>
</tr>
</tbody>
</table>

Cardiac surgery setting

Table 1. Risk factors for postoperative cardiac surgery acute kidney injury, identified using multivariate models in the last 3 years

<table>
<thead>
<tr>
<th>Reference</th>
<th>Odds Ratio (95% CI)</th>
<th>Significance in multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zappitelli, Pediatr Nephrol, 2013</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>
Patients developing acute kidney injury

Bypass time (minutes)

<table>
<thead>
<tr>
<th>Bypass time (minutes)</th>
<th>0-60</th>
<th>61-90</th>
<th>91-120</th>
<th>121-180</th>
<th>&gt;180</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Patients developing</td>
<td>5</td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>AKI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adj OR: 1
Adj OR: 2.14
Adj OR: 2.47
Adj OR: 3.20
Adj OR: 7.57

Confidence intervals:
(B.43, 21.52)
(1.38, 7.44)
(1.08, 5.65)
(1.38, 7.44)
(2.62, 21.92)

Adjusted for age, RACHS-1 score and site

AKI (or recognition) may be increasing

Comparison of the incidences of general pediatric admissions and ARF cases according to year

THAILAND

“Community-acquired AKI” in children

Urinary biomarkers to detect acute kidney injury in the pediatric emergency center

Prospective observation cohort of children admitted to the Texas Children’s Hospital ED Jan-Apr 2009

Serum creatinine an urine ordered?
Consent obtained?
Included: n=252
Only 27% had baseline SCR available

7% had AKI defined by pRIFLE criteria
What do we know about non ICU AKI?

Incidence and etiology of acute kidney injury in Southern India

Indian J Pediatr

Incidence:
- Nephrotoxins
- Aminoglycosides ≥5 days
  - N=557

Zappitelli et al, NDT, 2011

Increasing numbers (≥3) of NTM used
Increases risk for AKI in non-ICU children
Moffett & Goldstein, CJASN, 2011

Confirmed MCH prospective study (n~160) – 40%

Does a 50% Scr rise really matter?

Houston AG cohort (≥5 days): AKI associated with longer LOS & costs

Zappitelli et al, NDT, 2012
Acute renal damage with cancer therapy

- **Chemotherapies**: Cisplatin, Ifosfamide, CsA?
- **Stem cell transplant**: Myeloablation, Irradiation, Post-immunosuppresion, GVHD?
- **Infection**: Sepsis, ABx
- **Kidney attack**: TTP, TLS

**Acute renal damage with cancer therapy**

AKI post stem-cell transplant: ~20%, wide range

Renal function following hematological stem cell transplantation in childhood

Fig. 1: Acute renal failure in 22 children after hematological stem cell transplantation (HSCT). The onset of acute renal injury (empty bars) and doubling of serum creatinine (filled bars) are shown.

**Acute renal damage with cancer therapy**

Risk factors for acute kidney injury in patients undergoing allogeneic hematopoietic stem cell transplantation

Prospective evaluation of acute and chronic renal function in children following matched related donor hematopoietic stem cell transplantation

- **China**: ~30% AKI, Grade 3-5 (p<0.001)
- **Turkey**: ~42% AKI

Fig. 1: Survival in patients with acute kidney injury. There is a significant difference between the patients who had "no AKI" and "Grade 2 AKI" (p<0.05).
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**AKI child populations**

At risk

- Pre-operative cardiac Sx
- ICU Admission
- Aminoglycoside start
- Chemotherapy start

Clinical data collection

- Blood collection
- Urine collection

Follow-up
TRIBE AKI cardiac surgery

Early diagnosis

Pre-operative Consider clinical risk models
Immediate post-operative Consider pre-op & intra-op clinical risk models

Prognosis
At the time of AKI
Severity of renal injury

Pre-operative AKI prediction:
SCr, CysC, eGFR

Pre-op clinical model:
Age, gender, RACHS-1, CPB time, study site.

AKI
AUC = 0.73 (0.67, 0.80)

Stage 2+ AKI
AUC = 0.79 (0.70, 0.87)

Pre-operative AKI prediction:
CysC, eGFR in children not predictive

OR

2.5
2
1.5
1
0.5
0

Stage 1+
Stage 2+

Pre-op CysC
Pre-op eGFR

*
GFR in children – not simple

TRIBE AKI cardiac surgery

Early diagnosis

Pre-operative
Consider clinical risk models

Immediate post-operative
Consider pre-op & intra-op clinical risk models

Prognosis
At the time of AKI
Severity of renal injury

Post-operative AKI prediction:
early SCr rise

IL-18

uNGAL

pNGAL
Post-operative AKI prediction: NGAL & IL-18

How have biomarkers been doing?

Mishra et al, Lancet, 2005
Single centre, cardiac

Parikh et al, JASN, 2012
Multi-centre, cardiac

Table 3. Risk classification for severe AKI, based on clinical model and biomarkers

<table>
<thead>
<tr>
<th>First Postoperative Biomarker</th>
<th>NRI</th>
<th>IDI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Value (SE)</td>
<td>P</td>
</tr>
<tr>
<td>Urine IL-18 (pg/ml)</td>
<td>0.22 (0.09)</td>
<td>0.02</td>
</tr>
<tr>
<td>Urine NGAL (ng/ml)</td>
<td>0.17 (0.08)</td>
<td>0.02</td>
</tr>
<tr>
<td>Plasma NGAL (ng/ml)</td>
<td>0.14 (0.06)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Table 1. Categorical MFI and IFR of clinical model with post-operative biomarkers in children

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>CAT</th>
<th>MFI</th>
<th>Overall</th>
<th>P Value</th>
<th>IFR</th>
<th>CAT</th>
<th>MFI</th>
<th>Overall</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver (KID)</td>
<td>0.02</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
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<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Liver (GOT)</td>
<td>0.02</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
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<td>0.02</td>
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<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Liver (GPT)</td>
<td>0.02</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
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<tr>
<td>Lung (GPT)</td>
<td>0.02</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
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KID = Kidney Injury Molecule-1; GOT = Glutamic Oxaloacetic Transaminase; GPT = Glutamic Pyruvic Transaminase; IFR = Immune Function Ratio

Table 2. Biomarker combinations in children

<table>
<thead>
<tr>
<th>Biomarker Combination</th>
<th>Day 1</th>
<th>Day 2</th>
</tr>
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<tr>
<td>Liver (KID)</td>
<td>0.00</td>
<td>0.00</td>
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<td>Lung (KID)</td>
<td>0.00</td>
<td>0.00</td>
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<tr>
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<tr>
<td>Lung (GPT)</td>
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<td>0.00</td>
</tr>
<tr>
<td>Liver (GAL)</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Lung (GAL)</td>
<td>0.00</td>
<td>0.00</td>
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<tr>
<td>Liver (PRG)</td>
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<td>0.00</td>
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<tr>
<td>Lung (PRG)</td>
<td>0.00</td>
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Table 3. Preoperative stage 1 and 2 MFI association with Clinical and Cytotoxic. is adjusted with no intravenous preoperative MFI count

<table>
<thead>
<tr>
<th>Stage</th>
<th>MFI (Mean±SD)</th>
<th>% With stage 1</th>
<th>% With stage 2</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>3.5 (5.2)</td>
<td>1.0</td>
<td>0.3</td>
</tr>
<tr>
<td>2</td>
<td>2.2 (3.1)</td>
<td>1.0</td>
<td>0.3</td>
</tr>
<tr>
<td>3</td>
<td>1.2 (2.1)</td>
<td>1.0</td>
<td>0.3</td>
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% Cytotoxic

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<tbody>
<tr>
<td>1</td>
<td>1.2 (2.1)</td>
<td>1.0</td>
<td>0.3</td>
</tr>
<tr>
<td>2</td>
<td>0.2 (1.1)</td>
<td>1.0</td>
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% Cytotoxic

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<td>1.0</td>
<td>0.3</td>
</tr>
<tr>
<td>2</td>
<td>0.2 (1.1)</td>
<td>1.0</td>
<td>0.3</td>
</tr>
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Non-cardiac PICU setting

Much more challenging

No "pre-operative" assessment

Many patients arrive with AKI: mild, moderate or severe

Many patients arrive with high SCr – not all AKI.

Biomarkers may help distinguish: but who to measure in?

How have biomarkers been doing?

Very high risk PICU: 80% AKI
Zappitelli et al, CCM, 2007

Lower risk PICU: ~40% AKI
Zappitelli et al, unpublished

**WHAT HAPPENED?**

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>AUC (95% CI)</th>
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<tbody>
<tr>
<td>Urine NGAL</td>
<td>0.61 (0.46 – 0.76)</td>
</tr>
<tr>
<td>Urine IL-18</td>
<td>0.69 (0.55 - 0.82)</td>
</tr>
<tr>
<td>Urine KIM-1</td>
<td>0.49 (0.33 – 0.64)</td>
</tr>
</tbody>
</table>
Nephrotoxicity
Zappitelli et al, ASN poster, 2012
Children treated with Tobramycin
Pi-GST on the 1st day of AKI

AUC = 0.72
95% CI 0.55-0.88

Focus is on QUICK and SIMPLE assessment
Intent is to have an index / threshold risk with HIGH NPV
No Renal Angina: HIGHLY likely NOT to develop AKI
Do NOT study biomarker performance
Do NOT use biomarkers to predict AKI (future)

Renal Angina
Stuart L. Goldstein* and Lakhmir S. Chawla†

Putting it to the test!
At risk
PICU day 1
RA yes or no?
PICU day 3
Outcome: Sever AKI (St 2)
AKI scenarios
At risk

Improved biomarker performance
Better performed clinical trials
Improved AKI outcomes

Cardiac surgery patients at risk for AKI
Clinical/biomarker risk profile
Low Risk
High Risk
Standard Care
Preventive Rx
Active Avoidance

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