New diagnostic tests for acute kidney injury

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Disclosures

• Research support and speaking fees
  – Alere
  – Baxter
Objectives

• To discuss the rationale for novel diagnostic tools in AKI
• To present data on promising AKI biomarkers
• To demonstrate the integration of biomarkers into recently completed clinical trials
Objectives

• To discuss the rationale for novel diagnostic tools in AKI
• To present data on promising AKI biomarkers
• To present studies that integrated novel AKI biomarkers
I thought we already knew how to diagnose AKI!

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<th>Serum creatinine change from baseline*</th>
<th>Urine output (mL/kg/hr)</th>
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<tr>
<td>I</td>
<td>1.5-2x or 27 µmol/L</td>
<td>&lt; 0.5 x 6 hours</td>
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<td>II</td>
<td>2-3x</td>
<td>&lt; 0.5 x 12 hours</td>
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<td>III</td>
<td>&gt; 3x baseline or if sCr &gt; 354 µmol/L, a rise of 27 µmol/L</td>
<td>&lt; 0.3 x 24 hours or anuria x 12 hours</td>
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KDIGO Guidelines for AKI, 2012
The shortcomings of serum creatinine

- insensitive to the nephron site most susceptible to injury
- sCr is a marker of glomerular filtration, not tubular function
- rise in sCr may occur well after time of injury
  - Could this explain the lack of effective therapies for established AKI?
The shortcomings of urine output

• severe oliguria may be an appropriate physiologic response in a variety of settings

• urine volume is dependent on solute/volume intake

• confounded by structural injury to collecting system
Objectives

• To discuss the rationale for novel diagnostic tools in AKI
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• To present studies that integrated novel AKI biomarkers
An abundance of candidate biomarkers

- gamma-glutamyl-transpeptidase
- lactate dehydrogenase
- glutathione S-transferase
- N-acetyl-beta-glucosaminidase
- alkaline phosphatase
- alpha1-microglobulin
- beta2-microglobulin
- retinol-binding protein
- adenosine deaminase-binding protein
- cystatin C (urine and plasma)
- kidney injury molecule-1
- neutrophil gelatinase-associated lipocalin (NGAL, urine and plasma)
- Interleukin-18
- liver-type fatty acid-binding protein
- microRNA-210
- angiotensinogen
- isoform 3 of the sodium-hydrogen exchanger
- insulin-like growth factor-binding protein 7 (IGFBP-7)
- tissue inhibitor of metalloproteinases-2 (TIMP-2)
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How can biomarkers help us?

• Before AKI is diagnosed….assist in the early identification of kidney injury
  – Facilitate triage of patients for early intervention

• After AKI is diagnosed….risk stratify patients who are destined to have poor clinical outcomes
  – Facilitate triage of patients for therapies that may alter outcomes in established AKI

• As a marker of therapeutic response in trials examining novel interventions to prevent AKI

• Discerning between etiologies of elevated serum creatinine
Biomarkers for the early diagnosis of AKI: NGAL

- 25 kDa protein
- markedly upregulated in animal models of ischemia
- induced shortly following ischemia in various epithelial cells, including loop of Henle and collecting ducts
- potentially useful as a plasma and urine marker
NGAL in Cardiac Surgery

- 71 children undergoing cardiac surgery
- excluded if history of renal insufficiency, diabetes, receipt of nephrotoxic agents
- AKI - defined as increase in SCr by > 50% - occurred in 28% of patients

Mishra et. al. *Lancet* 2005
The performance of NGAL

At a cutoff of 25 µg/L, urine NGAL measured 2 hours post-CPB had Sn and Sp approaching 100%
How do biomarkers perform in the adult cardiac surgery population?

• TRIBE-AKI Collaborative
• prospective multicentre cohort (n=1219) study of patients undergoing cardiac surgery
• High risk features for AKI (≥ 1 of):
  – emergency surgery
  – preoperative serum creatinine > 177 μmol/L
  – LV ejection fraction < 35%
  – age > 70 years
  – diabetes mellitus
  – combined CABG and valve surgery
  – repeat revascularization surgery

Parikh et al JASN 2011
TRIBE-AKI Collaborative

- AKI defined as doubling in sCr or receipt of acute dialysis (n=60, ~5% of participants)
- 18 (1.5%) needed dialysis
- 20 (1.6%) died
- Tested 3 candidate biomarkers postoperatively shortly after patient arrived in ICU

Parikh et al JASN 2011
Plasma NGAL

Risk of AKI (%) vs. Plasma NGAL (ng/mL) Quintiles

- Q1: (<105) n=236, 1.7%
- Q2: (105-158) n=236, 2.1%
- Q3: (158-218) n=237, 4.6%
- Q4: (218-292) n=236, 3.4%
- Q5: (>293) n=236, 11.9%

P for trend < .0001

Parikh et al JASN 2011
Urine NGAL

Parikh et al JASN 2011
Urine Interleukin-18

Parikh et al JASN 2011
The incremental yield of the biomarkers

AUC of clinical model* = 0.69

- Add uIL-18: Revised AUC = 0.76*, NRI = 0.25*
- Add pNGAL: Revised AUC = 0.75*, NRI = 0.18*
- Add uNGAL: Revised AUC = 0.73, NRI = 0.14

* = p < 0.05

Clinical model included age, gender, race, CPB time, nonelective surgery, preoperative GFR, DM, HTN

Parikh et al JASN 2011
The bottom line for TRIBE-AKI

- Plasma NGAL and urine IL-18 appear to perform well and add incremental predictive capacity over and above pre-existing knowledge for AKI following cardiac surgery.
- Cardiac surgery is unique: clear, fixed time of injury.
- Severe AKI is rare.
- Patients do well.
- How do biomarkers work predict AKI in a general ICU?
NGAL in an unselected ICU population

- 632 consecutive patients over a 6-month period in a single ICU in Erasmus, Netherlands
- 27% developed AKI
- 4% received dialysis

De Gues et al  AJRCCM 2011
Performance of NGAL: Diagnosis of AKI

De Gues et al. AJRCCM 2011

Urine NGAL

Plasma NGAL

AUC 0.77 ± 0.05

AUC 0.80 ± 0.04
The new kid on the block

- Tissue Inhibitor of Metalloproteinase-2 (TIMP2) and Insulin-like Growth Factor Binding Protein-7 (IGFBP7)
- Identified through an extensive search for potential AKI biomarkers
- inducers of $G_1$ cell-cycle arrest

Kashani et al Crit Care 2013
NephroCheck

• Approved by FDA in September 2014

Courtesy of Astute Medical
NephroCheck approval by FDA

• "... to be used in conjunction with clinical evaluation in patients who currently have, or have had within the past 24 hours, acute cardiovascular and/or respiratory compromise and are ICU patients, as an aid in the risk assessment for moderate or severe acute kidney injury (AKI) within 12 hours of patient assessment..."
Performance of urinary [TIMP-2]*[IGFBP7]

- 408 critically ill patients at 23 sites with either no AKI or AKI-Stage 1
- Collected urine and plasma within 24 hours of ICU admission
- Outcome of interest: KDIGO Stage 2-3 AKI within 12 hours as adjudicated by a committee of 3 nephrologists
- 71 (17%) developed the outcome

Bihorac et al AJRCCM 2014
Bihorac et al AJRCCM 2014

AUC = 0.82 (0.76-0.88)

<table>
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<tr>
<th>Cutoff value, (ng/ml)$^2$/1000</th>
<th>Sensitivity, %</th>
<th>Specificity, % (95% CI)</th>
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<tbody>
<tr>
<td>0.3</td>
<td>92 (85-98)</td>
<td>46 (41-52)</td>
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<tr>
<td>2.0</td>
<td>37 (26-47)</td>
<td>95 (93-97)</td>
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The incremental value of urine $[\text{TIMP-2}]^*\text{[IGFBP7]}$

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<th>Variable</th>
<th>Without Urinary $[\text{TIMP-2}]^*\text{[IGFBP7]}$</th>
<th>With Urinary $[\text{TIMP-2}]^*\text{[IGFBP7]}$</th>
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<td>Enrollment serum creatinine, $\uparrow$ per unit log</td>
<td>2.36 (0.74–7.50)</td>
<td>2.45 (0.68–8.84)</td>
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<td>APACHE III score (nonrenal), per unit</td>
<td>1.02 (1.01–1.03)$\uparrow$</td>
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<td>Body mass index, per kg/m$^2$</td>
<td>1.05 (1.02–1.08)$\uparrow$</td>
<td>1.07 (1.04–1.11)$\uparrow$</td>
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<td>Urinary $[\text{TIMP-2}]^*\text{[IGFBP7]}$ test, $\uparrow$ per unit log</td>
<td>Not included</td>
<td>16.5 (7.6–35.5)$\uparrow$</td>
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<td>Area under the curve (95% CI)</td>
<td>0.70 (0.63–0.76)$\uparrow$</td>
<td>0.86 (0.80–0.90)$\uparrow$</td>
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Bihorac et al AJRCCM 2014
Prognosticating AKI progression

• Once AKI is established, how do you know who will progress (ie, go to Stage 3, require RRT, die)?

• Vital knowledge to help decide on enrollment in trials evaluating AKI interventions
Back to the TRIBE Study

• 380 patients with Stage I-II AKI following cardiac surgery
• 45 (12%) had progression of AKI
• Biomarkers evaluated on the first day the patient met criteria for AKI

Koyner et al JASN 2012
Biomarkers to forecast the progression of AKI

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<th>Cut Points</th>
<th>N</th>
<th>AKI Progression (%)</th>
<th>P for Trend</th>
<th>Unadjusted OR (95% CI)</th>
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Koyner et al JASN 2012
AKI prognosis: The value of urine [TIMP-2]*[IGFBP7]

Koyner et al JASN 2015
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• To present data on promising AKI biomarkers
• To present studies that integrated novel AKI biomarkers
The integration of biomarkers into clinical research

- STARRT-AKI pilot trial
- 100-patient RCT to evaluate the feasibility and safety of conducting a definitive trial of accelerated vs standard initiation of RRT in AKI

Wald et al. *Kidney Int* 2015
Inclusion criteria for the STARRT-AKI pilot

1- Age ≥ 18 years
2- Admission to a critical care unit
3- Evidence of severe AKI based on 2 of the following three criteria:
   - doubling of serum creatinine
   - urine output < 6 mL/kg over previous 12 hours
   - whole blood neutrophil gelatinase associated lipocalin (NGAL) > 400 ng/mL
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<th>Baseline characteristics</th>
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<td>Accelerated ((n = 48))</td>
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<td>Age, years</td>
<td>62.2 ± 11.9</td>
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<tr>
<td>Women</td>
<td>13 (27)</td>
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<tr>
<td>Baseline eGFR, ml/min per 1.73 m²</td>
<td>74.8 ± 33.9</td>
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<td>Hypertension</td>
<td>23 (48)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>19 (40)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Cardiopulmonary bypass in past 7 days</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>26 (54)</td>
</tr>
<tr>
<td>Receipt of IV contrast in past 7 days</td>
<td>11 (23)</td>
</tr>
<tr>
<td>SOFA score</td>
<td>13.3 ± 2.5</td>
</tr>
<tr>
<td>The 24-h urine output, ml (^a)</td>
<td>355 (196–528)</td>
</tr>
<tr>
<td>Cumulative fluid balance, ml (^b)</td>
<td>514 (2420–7006)</td>
</tr>
<tr>
<td>Mechanically ventilated</td>
<td>45 (94)</td>
</tr>
<tr>
<td>Receipt of vasopressor(s)</td>
<td>42 (88)</td>
</tr>
<tr>
<td>Serum creatinine, (\mu)mol/l</td>
<td>286 (237–355)</td>
</tr>
<tr>
<td>Whole-blood NGAL, ng/ml</td>
<td>&gt; 1300 (774–&gt;1300)</td>
</tr>
<tr>
<td>Urea (^b), mmol/l</td>
<td>17.7 (12.0–22.7)</td>
</tr>
<tr>
<td>Potassium (^a), mmol/l</td>
<td>4.3 ± 0.7</td>
</tr>
<tr>
<td>Bicarbonate (^b), mmol/l</td>
<td>20.1 ± 4.5</td>
</tr>
<tr>
<td>Hemoglobin, g/l</td>
<td>92 ± 18</td>
</tr>
<tr>
<td>White blood cells, (\times 10^9)/l</td>
<td>16.1 ± 11.7</td>
</tr>
</tbody>
</table>
Early vs late initiation of renal replacement therapy in critically ill patients with AKI (ELAIN) Trial

Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury
The ELAIN Randomized Clinical Clinical Trial

Alexander Zarbock, MD; John A. Kellum, MD; Christoph Schmidt, MD; Hugo Van Aken, MD; Carola Wempe, PhD; Hermann Pavenstädt, MD; Andreea Boanta, MD; Joachim Gerß, PhD; Melanie Meersch, MD

Zarbock et al JAMA 2016
NGAL in ELAIN

- KDIGO *Stage 2* AKI
- Plasma NGAL > 150 ng/mL
- One of:
  - sepsis
  - vasopressors
  - refractory fluid overload
  - non-renal organ failure

Zarbock et al *JAMA* 2016
**ELAIN: Baseline characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Early strategy (n=112)</th>
<th>Delayed strategy (n=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (SD), yrs</td>
<td>66 (14)</td>
<td>68 (13)</td>
</tr>
<tr>
<td>Women, %</td>
<td>30</td>
<td>43</td>
</tr>
<tr>
<td>CKD, %</td>
<td>38</td>
<td>45</td>
</tr>
<tr>
<td>SOFA (SD)</td>
<td>16 (2)</td>
<td>16 (2)</td>
</tr>
<tr>
<td>Mechanical ventilation, %</td>
<td>88</td>
<td>88</td>
</tr>
<tr>
<td>Vasopressor, %</td>
<td>86</td>
<td>91</td>
</tr>
<tr>
<td>Serum creatinine (SD), µmol/L</td>
<td>172 (57)</td>
<td>177 (97)</td>
</tr>
<tr>
<td>Oligoanuria, %</td>
<td>70</td>
<td>68</td>
</tr>
<tr>
<td>NGAL (IQR), ng/mL</td>
<td>490 (350-822)</td>
<td>619 (382-941)</td>
</tr>
</tbody>
</table>

Zarbock et al JAMA 2016
NGAL in ELAIN

- > 90% of patients in the delayed arm progressed to RRT
- Was NGAL the key factor in identifying a population that was at risk of progressing?

Zarbock et al JAMA 2016
Conclusions

- novel biomarkers hold promise as alternatives or complements to traditional diagnostic tools in AKI
- the optimal biomarker would be widely validated, have well-defined performance characteristics and be measurable at the point-of-care
- But important limitations exist at present
Limitations of currently available biomarkers

• early “success” has not always been sustained
• limited evidence that they offer incremental knowledge
• none of the currently available AKI biomarkers is ready for integration into a clinical trial protocol
Thank you for your attention

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