Laboratory’s Role in Acute Kidney Injury (AKI) Risk Assessment

Denise Uettwiller-Geiger, Ph.D., DLM(ASCP)
Director of Laboratory Services and Clinical Trials
John T. Mather Memorial Hospital
Port Jefferson, New York, USA 11777
dgeiger@matherhospital.org
Disclosure

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• Astute Speakers Bureau

• No other COI regarding this presentation
Presentation Objectives

- Describe the laboratory’s role in Acute Kidney Injury (AKI) risk assessment
- Gain insight on how new biomarkers can improve clinical decisions and provide high value patient outcomes
- Examine clinical research and applications of novel biomarkers for the assessment of AKI
Scope of the Problem
Scope of the Problem

- 7500 dollars (3 to 14,000 per admission excess hospital costs) per year
- 9,000,000,000 dollars/year
- 3.5% of admissions
- 300,000 people die in the United States annually from AKI
- 1.2 million people per year get AKI during a hospital stay
- Your length of stay increases, on average, by 3.5 days if you get AKI
- Odds of death: Unadjusted, Age adjusted, Multivariable
- Change in serum creatinine (mg/dl): 0.3–0.4, 0.3–0.4, 1.0–1.9, ≥2.0
- Death rate/year: Prostate cancer, Breast cancer, Heart failure, Diabetes, AKI
- Death rate more than breast cancer, prostate cancer, heart failure, and diabetes, combined

Source: Kidney Int © 2013 International Society of Nephrology
Acute Kidney Injury

US Healthcare costs for AKI
$10 billion a year

G. M. Chertow et al. J. Am. Soc. Nephrol. 16 2005
The Challenges
Acute Kidney Injury (AKI): Unmet Clinical Needs

- Rapid, sensitive and specific test
- To identify, treat and manage patients
- Prevent irreversible kidney damage
- Recognize AKI onset rapidly
By The Time AKI Is Diagnosed With Functional Markers, It May Be Too Late

Functional Biomarkers
Serum Creatinine, Urine Output

Stress/Injury → Decreased Function

Asymptomatic → Symptomatic (Diagnosis)

The Ideal Marker(s) of AKI

Performance Requirements

• AKI specific
• Sensitive for the detection of clinically significant AKI
• Capable of estimating the extent of the damage
• Rapid kinetics
• Prognostic for short and long term outcomes of AKI
• Solid analytical performance
• Fast TAT, easy to measure, and cost effective
New Biomarkers for AKI

TIMP-2
(Tissue-inhibitor of Metalloproteinase-2)
and
IGFPB-7
(Insulin-like Growth Factor-Binding Protein-7)
Tissue Inhibitor of Metalloproteinase (TIMP-2)

- Inhibitor of the matrix metalloproteinases, (degradation of the extracellular matrix)
- Suppresses proliferation of endothelial cells
- Inhibits protease activity in tissues undergoing remodeling of extracellular matrix
- Implicated in epithelial cell-cycle arrest
Insulin-Like Growth Factor Binding Protein-7 (IGFBP-7)

• Regulation of tissue availability of IGFs
• Stimulates cell adhesion
• Implicated in epithelial cell-cycle arrest
Discovery – Validation Path

Human Clinical Studies

Animal Model Studies

Pathophysiology
Physical and Biochemical Changes

AKI Biomarker Discovery

Identify Candidate Biomarkers and Select Subset
(340 markers)

Create and Validate Immunoassay
Nephrocheck® AKIRisk™ Score

Sapphire Clinical Study
Clinical Studies

Discovery

and

Sapphire Validation
TIMP-2 and IGFBP-7 Outperform Existing Biomarkers

AUC for [TIMP-2]\-[IGFBP-7] was significantly greater than any existing biomarkers

Modified from Kashani et al. Critical Care 2013, 17:R25
[TIMP-2]•[IGFBP-7] Has a Compelling Specificity Profile

Urine NGAL (ng/mL)

[TIMP-2]•[IGFBP-7] (ng/mL)^2/1000

Kashani et al. Critical Care 2013, 17:R25
TIMP-2 and IGFBP-7 Work Well in Important Subgroups

**Sepsis**

- [TIMP-2]•[IGFBP7]
- Urine TIMP-2
- Urine IGFBP7
- Urine NGAL
- Plasma Cystatin C
- Urine KIM-1
- Plasma NGAL
- Urine IL-18
- Urine pi-GST
- Urine L-FABP

**Surgery**

- [TIMP-2]•[IGFBP7]
- Urine TIMP-2
- Urine IGFBP7
- Urine NGAL
- Plasma Cystatin C
- Urine KIM-1
- Plasma NGAL
- Urine IL-18
- Urine pi-GST
- Urine L-FABP

AUC (with 95% CI)

Modified from Kashani et al. Critical Care 2013, 17:R25
Apparently Healthy Donors vs. AKI
Assay Performance Metrics
Design Goals for TIMP-2 and IGFBP-7

- Quantitative in urine
- Multiplexed design; TIMP-2 and IGFBP-7 assays in a single test device
- Assess risk of AKI in the next 12 hours
- Provide results in <20 minutes
- CV’s less than or equal to 15 percent
Clinical Assay - Intended Use

• The NEPHROCHECK® Test System is an in vitro diagnostic device that quantitatively measures TIMP-2 and IGFBP-7 proteins associated with kidney function in human urine by fluorescence immunoassay on the ASTUTE140® Meter.

• The test is intended 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.

• This test is intended to be used in patients 21 years of age or older.
NEPHROCHECK® Test Process

- Fresh or thawed urine
- Single-use cartridge
- Sandwich immunoassay
- Results in < 25 minutes
- Bench top device
- Available STAT
- Reported as AKI Score units = (ng/ml)^2/1000
  [TIMP-2]•[IGFBP-7]
The Clinical Cutoff at AKIRisk™ Score > 0.3 Identifies The Majority Of Patients At Risk For AKI

Results from Study A and B are not statistically different (p>0.05)

<table>
<thead>
<tr>
<th>Study</th>
<th>Sensitivity</th>
<th>Negative Predictive Value (NPV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (408 patients)</td>
<td>92%</td>
<td>96%</td>
</tr>
<tr>
<td>B (126 patients)</td>
<td>76%</td>
<td>88%</td>
</tr>
</tbody>
</table>
# The Reportable Range and Reference Ranges

<table>
<thead>
<tr>
<th>Result</th>
<th>Reportable Range*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKIRisk™ Score</td>
<td>0.04-10.00*</td>
</tr>
</tbody>
</table>

AKIRisk™ Scores that are outside the above reportable range are reported as either “< 0.04” or “> 10.00” by the ASTUTE140® Meter. If the AKIRisk™ Score is > 10.00, the specimen should not be diluted for retesting.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Gender</th>
<th>Number of Subjects</th>
<th>AKIRisk™ Score Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apparently Healthy subjects</td>
<td>All</td>
<td>378</td>
<td>0.04 - 2.25</td>
</tr>
<tr>
<td>Subjects with stable chronic morbidities</td>
<td>All</td>
<td>372</td>
<td>0.05 - 2.20</td>
</tr>
<tr>
<td>Intended Use subjects with No AKI (Study A)</td>
<td>All</td>
<td>337</td>
<td>0.04 - 2.62</td>
</tr>
<tr>
<td>Intended Use subjects with AKI (Study A)</td>
<td>All</td>
<td>71</td>
<td>0.10 - 8.47</td>
</tr>
</tbody>
</table>
## Analytical Sensitivity

<table>
<thead>
<tr>
<th>BIOMARKER</th>
<th>LIMIT OF BLANK</th>
<th>LIMIT OF DETECTION</th>
<th>LIMIT OF QUANTITATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKIRisk™ Score</td>
<td>0.0002</td>
<td>0.002</td>
<td>0.002</td>
</tr>
</tbody>
</table>

# Precision

<table>
<thead>
<tr>
<th>Sample</th>
<th>Sample S2</th>
<th>Sample S3</th>
<th>Sample S4</th>
<th>Sample S5</th>
<th>Sample S6</th>
<th>Sample S7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean AKIRisk™ Score</td>
<td>0.04</td>
<td>0.14</td>
<td>0.30</td>
<td>0.56</td>
<td>4.61</td>
<td>8.55</td>
</tr>
<tr>
<td>Total CV</td>
<td>18.0%</td>
<td>11.0%</td>
<td>10.4%</td>
<td>10.9%</td>
<td>9.1%</td>
<td>11.7%</td>
</tr>
</tbody>
</table>

AKIRisk™ Score cutoff at 0.3

- Total CV represents overall results from 3 lots of NephroCheck Test kits measured at 3 testing sites under intended use conditions.
- Samples (S2-S7) spanned the reportable range of the AKIRisk™ Score; each sample was tested for at least 20 days, 2 test runs per day, 2 replicates per test run.

Source: John T. Mather Memorial Hospital, Astute Medical, and Pacific Rim
Interfering Substances and Potential Cross Reactants

Three substances showed substantial interference (bias exceeding 10%)

- Urinary albumin at concentrations above 125 mg/dL and at concentrations above 3000 mg/dL cause an invalid test result†

- Urinary bilirubin at concentrations above 7.2 mg/dL ‡

- Methylene blue at concentrations above 0.49 mg/L


†Fewer than 1% of the intended use patients enrolled in clinical studies A and B exhibited albumin levels that exceeded 125 mg/dL; therefore it is not expected that interfering levels of albumin will be encountered often.

‡None of the intended use patients enrolled in clinical studies A and B exhibited bilirubin levels that exceeded 7.2 mg/dL; therefore it is not expected that interfering levels of bilirubin will be encountered often.
## Cross-Reactivity with Related Proteins

<table>
<thead>
<tr>
<th>Potential Cross-Reactant</th>
<th>Cross-Reactant Concentration (ng/mL)</th>
<th>TIMP-2 % Cross-reactivity</th>
<th>IGFBP-7 % Cross-reactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-1</td>
<td>1500</td>
<td>--</td>
<td>0</td>
</tr>
<tr>
<td>IGF-2</td>
<td>1500</td>
<td>--</td>
<td>0</td>
</tr>
<tr>
<td>IGFBP-1</td>
<td>100</td>
<td>--</td>
<td>-1.1%</td>
</tr>
<tr>
<td>IGFBP-2</td>
<td>250</td>
<td>--</td>
<td>-0.8%</td>
</tr>
<tr>
<td>TIMP-1</td>
<td>3000</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>TIMP-3</td>
<td>2500</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>TIMP-4</td>
<td>600</td>
<td>0</td>
<td>--</td>
</tr>
</tbody>
</table>
Key Questions to Consider before Using a New Biomarker

- Reveal novel mechanisms of AKI?
- Incrementally better than known biomarkers?
- Improves decision making when combined with known biomarkers?
- Helps determine patient management strategies?
- Changes clinical practice?
Laboratory Value
Adding Value with Lab Tests

• Goal is to improve patient outcomes while reducing the cost per episode of care.

• Lab can spend a bit more money, but contribute to millions in cost savings.
The Role of Biomarkers and Outcomes in AKI

• Important risk assessment information
• Actionable information
• Novel biomarkers outperform existing tests
• There must be a clear understanding of exactly what information biomarkers can provide, and how this will impact care
Making the Financial Case at Mather Balancing Healthcare Costs

Assumptions

• 2015 ICU/CCU admissions- 1627 patients
• 50% of ICU/CCU admissions- 813 patients
• $7500 per admission excess hospital costs
• Cost of AKI Risk Score test- $70
Making the Financial Case at Mather
Balancing Healthcare Costs

Excess Cost of AKI in Critically Ill
$6,097,500

Cost of Testing
$56,910

Saving: $6,040,590
Think About the Impact your Lab can have on AKI
Wrap up

Thank you!

Questions?????