Marrying Structure with Function: The Impact of Novel Renal Biomarkers on Drug Therapy Use

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Disclosure

All planners, presenters, and reviewers of this session report no financial relationships relevant to this activity.
Learning Objectives

• Identify limitations of existing renal biomarkers
• Explain a method for using cystatin C, to improve medication dosing
Ideal Renal Biomarker

- Easily, rapidly and inexpensively measured
- Detect kidney damage or decreased GFR to a greater degree than current clinical models
- Specific and unaffected by other diseases
- Present early in the course of the disease
- Proportional response to disease severity
Existing Biomarkers

**Urine output**
- Relatively easy to measure
- Issues when not strict I/O
- Affected by diuretics and hypovolemia
- Qualitative rather than quantitative
- Delayed response

**Serum creatinine**
- Relatively easy to measure
- Widely available and integrated into care
- Numerous non-renal confounders (e.g. skeletal muscle mass, diet)
- Delayed response
Spectrum of Kidney Disease

No kidney disease $\rightarrow$ ↑ AKI risk $\rightarrow$ Kidney damage $\rightarrow$ ↓ GFR $\rightarrow$ Kidney failure $\rightarrow$ Morbidity, mortality

Need for new biomarkers to:
- Better estimate GFR for dosing
- Facilitate earlier detection of AKI
Classes of Novel Biomarkers

No kidney disease → ↑ AKI risk → Kidney damage → ↓ GFR → Kidney failure → Morbidity, mortality

Structural Markers (e.g. NGAL, KIM-1, L-FABP, IL-18, TIMP-2, IGFBP7)

Functional Markers (cystatin C, beta-trace protein, beta-2 microglobulin, proenkephalin)
Measured GFR

- Generally considered the “gold” standard
- Exogenous compound that is filtered, not secreted/reabsorbed and quantitate its elimination (e.g. inulin, iothalamate, iohexol)
- Single moment in time, often requires urine collection
- Back leak from tubules in AKI
- Generally reserved for research and outpatient use
# Functional Markers for eGFR

<table>
<thead>
<tr>
<th>Attributes</th>
<th>Ideal</th>
<th>SCr</th>
<th>CysC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endogenous</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Easily, rapidly, inexpensively measured</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Detects even small GFR changes</td>
<td>✔</td>
<td>?</td>
<td>✔</td>
</tr>
<tr>
<td>Quick response to changing GFR</td>
<td>✔</td>
<td>❌</td>
<td>?</td>
</tr>
<tr>
<td>Few confounders</td>
<td>✔</td>
<td>❌</td>
<td>?</td>
</tr>
</tbody>
</table>

GFR: Glomerular filtration rate; SCr: Serum creatinine; CysC: Cystatin C

## Medication Use and CysC

<table>
<thead>
<tr>
<th>Studied Medications</th>
<th>No. of Studies</th>
<th>Renal Elimination (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>7</td>
<td>&gt;80</td>
</tr>
<tr>
<td>Arbekacin</td>
<td>1</td>
<td>~50</td>
</tr>
<tr>
<td>Amikacin</td>
<td>1</td>
<td>68-80</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>1</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>2</td>
<td>96</td>
</tr>
<tr>
<td>Topotecan</td>
<td>1</td>
<td>~50</td>
</tr>
<tr>
<td>Digoxin</td>
<td>3</td>
<td>79-83</td>
</tr>
</tbody>
</table>

## Vancomycin Use and CysC

<table>
<thead>
<tr>
<th>Ref.</th>
<th>N</th>
<th>SCr</th>
<th>CysC</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>[1]</td>
<td>65</td>
<td>UCrCl</td>
<td>Flodin</td>
<td>- Heterogeneity in equations</td>
</tr>
<tr>
<td>[2]</td>
<td>165</td>
<td>CG</td>
<td>Hoek</td>
<td>- CysC associated vancomycin level and drug clearance</td>
</tr>
<tr>
<td>[3]</td>
<td>25</td>
<td>CG</td>
<td>Hoek</td>
<td>- Drug clearance better predicted by CysC than SCr in most studies</td>
</tr>
<tr>
<td>[5]</td>
<td>24</td>
<td>CG</td>
<td>Larsson</td>
<td>- Limited bedside applicability, more simulated models and population studies</td>
</tr>
<tr>
<td>[6]</td>
<td>678</td>
<td>CG</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>[7]</td>
<td>37</td>
<td>Many</td>
<td>CKD-EPI</td>
<td></td>
</tr>
<tr>
<td>[8]</td>
<td>130</td>
<td>CG</td>
<td>Larsson</td>
<td></td>
</tr>
</tbody>
</table>

References:

Vancomycin Dosing at Mayo

- Establish target for source of infection (10-15 or 15-20 mcg/mL)
- Maintenance dose: 15-20 mg/kg
  - 20-25 mg/kg loading dose could be considered
- Interval

<table>
<thead>
<tr>
<th>CrCl (mL/min)</th>
<th>Dosing Interval (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 90</td>
<td>q8 hours</td>
</tr>
<tr>
<td>70-90</td>
<td>q12 hours (q8h if target 15-20 mcg/mL)</td>
</tr>
<tr>
<td>35-69</td>
<td>q24 hours (q12h if severe infection)</td>
</tr>
<tr>
<td>21-34</td>
<td>q48 hours (q24h if severe infection)</td>
</tr>
</tbody>
</table>
Vancomycin Dosing

Baseline (SCr and cystatin C collection)

Steady-state trough

Goal trough range

Vancomycin level (mg/L)

Vancomycin Dose 1

Dose 2

Dose 3

Dose 4

Time
# Multivariate Models

<table>
<thead>
<tr>
<th>CrCl with Cockcroft-Gault Model</th>
<th>$R^2$</th>
<th>Predicted Trough Achievement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-trough total dose</td>
<td>0.269</td>
<td>33 (26-40%)</td>
</tr>
<tr>
<td>Dosing interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl (mL/min)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CKD EPI$_{Cr-CysC}$ Model</th>
<th>$R^2$</th>
<th>Predicted Trough Achievement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-trough total dose</td>
<td>0.580</td>
<td>54 (45-61%)</td>
</tr>
<tr>
<td>Dosing interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CKD-EPI$_{Cr-CysC}$ (mL/min)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## New Nomogram

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>eGFR (CKD-EPI&lt;sub&gt;cr-cys&lt;/sub&gt; mL/min)</th>
<th>Goal 10-15 mg/L</th>
<th>Goal 15-20 mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>70-79</td>
<td>60-69</td>
<td>70-79</td>
<td>80-89</td>
</tr>
<tr>
<td></td>
<td>1500 q24</td>
<td>1200 q12</td>
<td>1500 q24</td>
</tr>
<tr>
<td></td>
<td>800 q12</td>
<td>1200 q12</td>
<td>1500 q24</td>
</tr>
<tr>
<td></td>
<td>1200 q12</td>
<td>1200 q12</td>
<td>1500 q24</td>
</tr>
<tr>
<td>80-89</td>
<td>70-79</td>
<td>1500 q24</td>
<td>1200 q12</td>
</tr>
<tr>
<td></td>
<td>800 q12</td>
<td>1200 q12</td>
<td>1500 q24</td>
</tr>
<tr>
<td></td>
<td>1200 q12</td>
<td>1200 q12</td>
<td>1500 q24</td>
</tr>
<tr>
<td>90-99</td>
<td>80-89</td>
<td>1500 q24</td>
<td>1200 q12</td>
</tr>
<tr>
<td></td>
<td>1500 q24</td>
<td>1200 q12</td>
<td>1500 q24</td>
</tr>
<tr>
<td></td>
<td>1200 q12</td>
<td>1200 q12</td>
<td>1500 q24</td>
</tr>
<tr>
<td></td>
<td>1200 q12</td>
<td>1200 q12</td>
<td>1500 q24</td>
</tr>
</tbody>
</table>
New Nomogram: Candidacy

**Inclusion**
- ≥ 18 years
- Hospitalized in one of three ICUs under evaluation
- Prescribed intravenous vancomycin
- Consistent regimen planned with 8, 12, or 24 hour dosing interval

**Exclusion**
- > 1 dose before ICU admission
- GFR < 20 mL/min
- Dialysis-dependent
- Inappropriate candidate for scheduled dosing (i.e. AKI)
- Weight < 40 kg
- BMI > 40 kg/m²

Implementation Logistics

Patient eligibility and need for first vancomycin dose assessed

CysC added to stored serum or drawn

Pharmacist-directed dosing and communication

Steady state level checked

De-escalation and adjustments per usual practice

Patient Example

- 63yo white male, 99 kg, BMI 31.6 kg/m²
  - Goal trough 15-20 mcg/mL (pneumonia)
  - SCr 0.7 mg/dL, CrCl\textsubscript{Cockcroft-Gault} = 151 mL/min
  - Corresponding dose: 15-20 mg/kg q8h (1500-2000 mg q8h)
  - Observed trough: 29.7 mg/L
Example Case

- 63yo white male, 99 kg, BMI 31.6 kg/m²
  - SCr 0.7 mg/dL
  - Cystatin C 2.02 mg/L
- CKD EPI\textsubscript{cr-cysC} 67 mL/min
- New dose: 1200 mg q12h


https://www.kidney.org/professionals/kdoqi/gfr_calculator
Comparative Study

• Cohort study
  – Novel dosing nomogram vs historical control with SCr dosing
• Primary endpoint
  – Initial steady state therapeutic vancomycin trough
• Secondary endpoints
  – Clinical failure, in confirmed gram-positive infections
  – ICU, hospital length of stay, 28-day mortality
  – Nephrotoxicity

Trough Distribution

Target Achievement

<table>
<thead>
<tr>
<th>Percent of Patients</th>
<th>Control</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>52%</td>
<td>50%</td>
</tr>
<tr>
<td>Subtherapeutic</td>
<td>28%</td>
<td>36%</td>
</tr>
<tr>
<td>Therapeutic</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>Supratherapeutic</td>
<td>14%</td>
<td></td>
</tr>
</tbody>
</table>

## Secondary Endpoints

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control (N = 264)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Intervention (N = 135)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite of nephrotoxicity or death within 7 days of vancomycin (N; %)</td>
<td>38 (14)</td>
<td>17 (13)</td>
<td>0.62</td>
</tr>
<tr>
<td>Treatment failure at day 7 (N; %)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>37 (34)</td>
<td>12 (29)</td>
<td>0.50</td>
</tr>
<tr>
<td>In MRSA patients (N; %)</td>
<td>8 (30)</td>
<td>3 (33)</td>
<td>1.00</td>
</tr>
<tr>
<td>Intensive care unit length of stay (days)</td>
<td>2.5 (1.3, 6.5)</td>
<td>2.9 (1.5, 6.4)</td>
<td>0.78</td>
</tr>
<tr>
<td>Hospital length of stay (days)</td>
<td>10.9 (5.6, 20.2)</td>
<td>10.3 (6.2, 32.0)</td>
<td>0.16</td>
</tr>
<tr>
<td>28-day all-cause mortality (N; %)</td>
<td>35 (13)</td>
<td>24 (18)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

AKI: acute kidney injury; RRT: renal replacement therapy

<sup>a</sup>: Values expressed as median (IQR) unless noted

<sup>b</sup>: N (%) of the 150 individuals (Control: N = 108; Intervention: N = 42) with confirmed gram-positive infections

Pearls and Key Takeaways

• SCr and UOP have numerous limitations as renal biomarkers
• Operationalizing anything other than SCr-based renal dosing is a multidisciplinary effort
• Automation where possible (lab draw, calculations, resultant dose)
• NKF Calculator can be used to calculate CKD EPI_{cr-cysC} eGFR (mL/min)
• Drug specific dosing models are needed rather than blind application of a different eGFR formula
• No GFR estimate should replace good clinical judgement
Marrying Structure with Function: The Impact of Novel Renal Biomarkers on Drug Therapy Use

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University of Pittsburgh College of Pharmacy, Pittsburgh, PA
Objectives

• Summarize the role for structural biomarkers for the early detection of drug-induced kidney disease (DIKD).
• Explain the application of the structural biomarkers currently available in the United States.
Structural Biomarkers

- Damage biomarkers
  - Indicate injury or at least cellular distress
- Proteins
  - Synthesis is upregulated during AKI
  - Molecules released from injured or distressed cells
  - Byproducts whose filtration, reabsorption or secretion are altered by kidney damage
- So, increase in biomarker concentration (blood, urine) indicative of concern
Characteristics of Structural Biomarkers

**Ideal Characteristics**

1. Easily measured
2. Present early in the course of the disease
3. Detect to a greater degree
4. Unaffected by other diseases
5. Proportional response to severity

**Biomarkers**

1. Urine and serum
2. Major advantage
3. ? Accuracy of detection
4. Affected by other diseases; varies by biomarker
5. ? Severity
<table>
<thead>
<tr>
<th>Advantage</th>
<th>Example of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine and serum</td>
<td>NGAL: cisplatin induced nephrotoxicity; 4 of 6 studies positive; more favorable for urine than serum; similar for KIM-1 NAG: heterogeneity in reporting (i.e. different unit of measurement)</td>
</tr>
<tr>
<td>Presents earlier than current biomarkers</td>
<td>NGAL: evaluated amphotericin inducted AKI and compared NGAL to SCr; NGAL detected AKI 1.7-3.2 days sooner</td>
</tr>
<tr>
<td>Detect to a greater degree</td>
<td>NGAL: higher for AKI-related to NSAIDs than hypovolemia and type 1 hepatorenal syndrome and lower than acute tubular necrosis</td>
</tr>
<tr>
<td>Affected by other diseases</td>
<td>NGAL: may be elevated in sepsis, malignancy, CKD, UTIs TIMP-2•IGFBP7: may be elevated in diabetes</td>
</tr>
<tr>
<td>Severity</td>
<td>KIM-1: higher concentration more kidney damage TIMP-2•IGFBP7: moderate risk &gt; 0.3 to ≤ 2.0 &amp; high &gt; 2.0</td>
</tr>
</tbody>
</table>
Role of Biomarkers and Drug Management

Individualized risk based adjustment
Adjust renally excreted medications
Avoid/Withdraw nephrotoxins
Avoid/Withdraw Meds with renovascular effect

Biomarker assessment
AKI
Biomarker assessment

Medication introduction/Re-introduction
Consider new renoprotective medications

Adapted from Chawla LS et al. Nat Rev Nephrol 2017;13:241-57
Which structural renal biomarker(s) are commercially available in the United States?

A. Liver fatty acid binding protein (L-FABP)
B. Tissue inhibitor of metalloproteinase-2 plus insulin-like growth factor binding protein 7 (TIMP-2•IGFBP7)
C. Neutrophil gelatinase-associated lipocalin (NGAL)
D. Kidney injury molecule-1 (KIM-1)
E. All of the above
TIMP-2-IGFBP7 (NephroCheck®)

- “Cell-cycle arrest” markers detected in urine

Kidney sustains an insult (e.g. hypoperfusion)

Pause in replication to prevent damaged cells from dividing

TIMP-2 and IGFBP7 released

Detected in the urine, signal risk for cell damage and AKI

TIMP-2:IGFBP7
(NephroCheck®)

- **Sapphire study: Discovery and Validation**
  - Clinical variables (including SCr): AUC 0.81
  - Clinical variables + TIMP-2:IGFBP7: AUC 0.87

- **Opal study: Established clinical cut-offs**
  - Moderate risk > 0.3-2.0: 4+ fold higher risk
  - High risk >2.0: 10+ fold higher risk

Single-center, randomized trial of 276 cardiac surgery patients with TIMP-2·IGFBP7 ≥0.3

138 control patients
138 intervention patients

Primary Endpoint: Any AKI at 72-h

Any AKI: 72%
Stage II/III: 45%

Any AKI: 55%
Stage II/III: 30%

KDIGO Bundle
- Avoid nephrotoxins
- Withhold ACEI/ARB
- Monitor SCr/UOP
- Glucose < 150 mg/dL
- Limit IV contrast
- Optimize volume status/hemodynamics

NephroCheck® Rapid Response Team

Clinical Stratification
- Low Risk
- Medium Risk
- High Risk

Laboratory Stratification
- TIMP-2·IGFBP7
  - ≤ 0.3
  - > 0.3 to ≤ 2.0
  - > 2.0

Monitor, prevent
- Consult Neph., d/c nephrotoxins, optimize perfusion with fluids and vasopressors, consider dialysis

Monitor, non-invasive tests, optimize fluid status and perfusion, avoid nephrotoxins, informal nephrology consult

Case: A.B.

- 74 y.o. male admitted for septic shock due to a urinary tract infection (UTI)
- PMH: Alcoholic cirrhosis, stroke with hemiparesis and urethrocutaneous fistula with recurrent UTIs
- Fluids, vasopressors, cultures were drawn
- Starting cefepime, gentamicin, vancomycin

Renal assessment
- Serum creatinine (SCr) 0.8 mg/dL (eGFR 92 mL/min)
- Urine output (UOP) 20 mL/h x 4h (0.25 mL/kg/hr)
What statement best characterizes the use of TIMP-2•IGFBP7 in A.B.?

A. TIMP-2•IGFBP7 is not indicated for use in A.B. given his baseline risk for AKI
B. TIMP-2•IGFBP7 is indicated in A.B. to estimate GFR for renally-dosed medications
C. TIMP-2•IGFBP7 is indicated in A.B. and a level >2.0 would justify holding gentamicin
D. TIMP-2•IGFBP7 is indicated in A.B and requires daily monitoring to optimize medication use
Case: A.B.

**Clinical Stratification**
- Low Risk
- High Risk
- Very High Risk

**Laboratory Stratification**
- ≤ 0.3
- > 0.3 to ≤ 2.0
- > 2.0

**TIMP-2**
- ● IGFBP7

**Follow SCr/UOP, consider volume replacement, gentamicin benefit > risk, re-evaluate in 12-hours**

**Follow SCr/UOP, urinalysis, evaluate fluid status and perfusion, critically determine whether gentamicin is needed**

**Consult nephrology, gentamicin risk > benefit, consider fluids and vasopressors, more closely monitor and adjust doses**
Key Takeaways

• Key Takeaway #1
  – Structural biomarkers offer advantages over current clinical models. Data are promising for biomarker use to detect drug induced kidney disease but standard use is premature.

• Key Takeaway #2
  – Data demonstrate TIMP-2•IGFBP7 is associated with cell distress and suggestive of AKI in the next 12-24 hours. Clinical data on the benefit of adjusting medications using this information is needed.
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