Drug Induced Kidney Injury: Prevention and Management Strategies

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Nephrology & Hypertension
The Heart Institute
NINJA

ephrotoxic
injury
gated by
ust-in-time
ction
Conflicts of Interest

• Baxter Healthcare
  – Speaker’s Bureau
  – Grant support
  – Consultant

• Consultant
  – AM Pharma
  – Akebia
  – Astute Medical
  – Bellco
  – Biporto
  – MediBeacon
  – Otuska
High Level Rationale for NINJA

• One of the most common causes of AKI in non-critically ill hospitalized children

• A portion of NTMx-AKI goes unnoticed due to lack of systematic kidney function surveillance in exposed children
  – Multiple studies show SCr measured at least every four days only 50% of the time in children receiving multiple NTMx

• NTMx-AKI may be a potentially modifiable adverse safety event if
  – At-risk patients are identified
  – Systematic SCr monitoring is instituted reliably in at-risk patients
  – AKI is avoided and/or mitigated by reducing unnecessary NTMx exposure
NINJA Vision Statement

Children should only get the nephrotoxic medications they need for the duration they need them.
- Patients receiving IV AG > 5 days
- Primary renal diagnoses excluded
- One year of study
  - 557 children
  - 95% > 3 months of age
  - AKI occurred in
- SCr measured at least q4 days only 50% of the time
350 non-critically ill children with AKI by pRIFLE
350 matched children without AKI
38 potential NTMx
Compared NTMx exposure rate between AKI vs. non-AKI patients
86% exposed to at least 1 NTMx
Patients with AKI had 1.7 OR for exposure to a NTMx
PPV for AKI doubles for patient with 3+ NTMx
Background

Nephrotoxic medication (NTMx)-associated Acute Kidney Injury (AKI) is one of the most common causes of AKI in hospitalized children.
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Recent studies demonstrate that NTMx-AKI occurs at higher than previously recognized rates.
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Background

Nephrotoxic medication (NTMx)-associated Acute Kidney Injury (AKI) is one of the most common causes of AKI in hospitalized children. Recent studies demonstrate that NTMx-AKI occurs at higher than previously recognized rates. A portion of NTMx-AKI goes unnoticed due to lack of kidney function surveillance in susceptible children.

Hypothesis:

More reliable surveillance of NTMx exposure and injury would demonstrate that rates of AKI are high, and that... an epidemic exists.
Objectives of NINJA

- Develop and EHR-based AKI screening intervention to assess changes in AKI prevalence, or duration (intensity)

- **RELIABLY QUANTIFY** the rate of High NTMx exposure and NTMx-AKI in the non-critical care population.
High NTMx-exposure Criteria

Patient receiving 3 or more nephrotoxic medications (NTMx) concomitantly*

or

On an aminoglycoside for 3 or more days

*IV radiology contrast, amphotericin, or cidofovir in previous week is counted for the week following administration
# Nephrotoxic Medication List

## Table 1: List of Nephrotoxic Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Medication</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>Enalaprilat</td>
<td>Mesalamine</td>
</tr>
<tr>
<td>Ambisome&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Foscarnet</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Amikacin</td>
<td>Gadopentetate dimeglumine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Nafcillin</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>Gadoxetate disodium&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Piperacillin/tazobactam</td>
</tr>
<tr>
<td>Captopril</td>
<td>Ganciclovir</td>
<td>Piperacillin</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>Gentamicin</td>
<td>Sirolimus</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>Ibuprofen</td>
<td>Sulfasalazine</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>Ifosfamide</td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>Iodixanol&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Ticarcillin/clavulanic acid</td>
</tr>
<tr>
<td>Cidofovir&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Iohexol&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Tobramycin</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Iopamidol&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Topiramate</td>
</tr>
<tr>
<td>Colistimethate</td>
<td>Ioversol&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Valacyclovir</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Ketonolac</td>
<td>Valganciclovir</td>
</tr>
<tr>
<td>Dapsone</td>
<td>Lisinopril</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Lithium</td>
<td>Zonisamide</td>
</tr>
</tbody>
</table>

<sup>a</sup> Medications counted for 7 days after administration toward exposure.
### TABLE 2  pRIFLE SCr-Based AKI Criteria

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>eCCI decrease by 25%</td>
</tr>
<tr>
<td>Injury</td>
<td>eCCI decrease by 50%</td>
</tr>
<tr>
<td>Failure</td>
<td>eCCI decrease by 75% or eCCI &lt; 35 mL/min/1.73 m²</td>
</tr>
<tr>
<td>Loss</td>
<td>Persistent failure &gt; 4 wk</td>
</tr>
<tr>
<td>End stage</td>
<td>End-stage renal disease (persistent failure &gt; 3 mo)</td>
</tr>
</tbody>
</table>

eCCI, estimated creatinine clearance.

\(^{a}\) eCCI derived for the Schwartz equation as previously described.\(^{13}\)
# Outcome Measures

## TABLE 3  Outcome Measures and Definitions

<table>
<thead>
<tr>
<th>Measure Name</th>
<th>Numerator</th>
<th>Denominator</th>
<th>Clinical Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>High NTMx exposure prevalence rate (per 1000 patient-days)</td>
<td>Number of new patients with high NTMx exposure in the calendar week of study</td>
<td>The total number of noncritically ill patient hospital days standardized per 1000 patient days in the calendar week of study</td>
<td>This measure generates a normalized rate of high NTMx exposure cases per study week.</td>
</tr>
<tr>
<td>AKI prevalence rate (per 1000 patient-days)</td>
<td>Number of patients with high NTMx exposure who developed AKI in the calendar week of study</td>
<td>The total number of noncritically ill patient hospital days standardized per 1000 patient days in the calendar week of study</td>
<td>This measure generates a normalized rate of AKI cases per study week.</td>
</tr>
<tr>
<td>Rate of patients with high NTMx exposure who develop AKI (%)</td>
<td>Number of patients who develop AKI&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Number of new patients with high NTMx exposure in the calendar week of study</td>
<td>This measure generates the fraction of patients with high NTMx exposure who develop AKI.</td>
</tr>
<tr>
<td>AKI intensity rate (per 100 susceptible patient days)</td>
<td>Number of days patients have AKI</td>
<td>The total number of susceptible patient days standardized per 100 susceptible-days</td>
<td>This measure depicts a normalized duration of AKI per susceptible days.</td>
</tr>
</tbody>
</table>

NTMx, nephrotoxic medication.

<sup>a</sup> AKI development factors into the numerator of the week that the patient became susceptible if AKI develops in a different calendar week than when a patient became susceptible.

*Pediatrics* 2013;132:e756–e767
The Process

Pharmacists create/receive daily reports, verify & validate

Provide SCr screening suggestions if necessary

Data Analyst compiles registry from Pharmacist reports...

...and generate metrics, run charts

Share with AKI team, leadership, other stakeholders
AKI Surveillance Algorithm

High Exposure NTMx Patient Identified

Daily SCr collected, exposure status monitored

Patient sustained AKI

Yes

AKI lasts ≥30 days

Yes

No

Patient returns to baseline

Yes

Baseline lasts ≥25 days

Yes

No

High NTMx Exposure

No

Yes

Continue SCr surveillance

High NTMx exposure

Yes

No

Continue surveillance for 2 more days

CLOSED (end surveillance)
AKI Surveillance Algorithm

Meets High NTMx Exposure Criteria
AKI Surveillance Algorithm

Injury surveillance loop

- High Exposure NTMx Patient Identified
  - Daily SCr collected, exposure status monitored
  - Patient sustained AKI
    - Yes: AKI lasts ≥30 days
      - Yes: High NTMx Exposure
        - No: Close surveillance for 2 more days
      - No: Patient returns to baseline
        - Yes: Baseline lasts ≥25 days
          - Yes: High NTMx Exposure
            - No: Close surveillance for 2 more days
        - No: Continue SCr surveillance
          - Yes: High NTMx exposure
            - No: Close surveillance for 2 more days
    - No: Continue SCr surveillance
  - No: Continue SCr surveillance
AKI Surveillance Algorithm

High Exposure NTMx Patient Identified → Daily SCr collected, exposure status monitored → Patient sustained AKI → AKI lasts ≥30 days (Yes, go to end surveillance; No, continue SCr surveillance)

Yes: AKI lasts ≥30 days → End surveillance

No: Patient returns to baseline → Baseline lasts ≥25 days (Yes, go to end surveillance; No, continue surveillance for 2 more days)

Yes: Baseline lasts ≥25 days → High NTMx Exposure (No, go to end surveillance)

No: High NTMx Exposure → Yes: High NTMx exposure → Continue surveillance for 2 more days (No, go to end surveillance)

Exposure surveillance loop
AKI Surveillance Algorithm

High Exposure NTMx Patient Identified → Daily SCr collected, exposure status monitored → Patient sustained AKI → AKI lasts ≥30 days → Yes → End Surveillance

No → Patient returns to baseline → Baseline lasts ≥25 days → Yes → End Surveillance

No → High NTMx Exposure → Yes → End Surveillance

No → Continue SCr surveillance

Yes → High NTMx exposure → Yes → Continue surveillance for 2 more days

No → End Surveillance
Electronic Health Record Identification of Nephrotoxin Exposure and Associated Acute Kidney Injury


*Pediatrics;* originally published online August 12, 2013;
DOI: 10.1542/peds.2013-0794
99% compliance with daily SCr monitoring in all high NTMx-exposed patients

Data span June 2, 2011 – June 4, 2012
Distribution of High NTMx Medications and Medications associated with AKI

- % High NTMx exposures involving each medication
- % AKI episodes involving each medication

Medications:
- AntiViral
- CN/mTOR
- Amphotericin
- Piperacillin/tazobactam
- ACE Inhibitor
- Vancomycin
- IV Aminoglycoside
- Iodinated Contrast
- NSAID
- Other Antibiotic
- Methotrexate
- Mesalamine

Pediatrics 2013;132:e756–e767
Distribution of High NTMx Medications and Medications associated with AKI

<table>
<thead>
<tr>
<th>Medications</th>
<th>% High NTMx exposures involving each medication</th>
<th>% AKI episodes involving each medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>AntiViral</td>
<td>27.1</td>
<td></td>
</tr>
<tr>
<td>CN/mTOR</td>
<td>24.9</td>
<td></td>
</tr>
<tr>
<td>Amphotericin</td>
<td>20.3</td>
<td></td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>17.7</td>
<td></td>
</tr>
<tr>
<td>ACE Inhibitor</td>
<td>15.2</td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>11.4</td>
<td></td>
</tr>
<tr>
<td>IV Aminoglycoside</td>
<td>6.4</td>
<td></td>
</tr>
<tr>
<td>Iodinated Contrast</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>NSAI D</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>Other Antibiotic</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>Mesalamine</td>
<td>0.2</td>
<td></td>
</tr>
</tbody>
</table>

*Pediatrics* 2013;132:e756–e767
Initial AKI prevalence rates 10-fold higher than CAUTI rates and 3-fold higher than CLBSI rates at CCHMC
AKI intensity decreases in Year 1 of the project by 42%
A sustained quality improvement program reduces nephrotoxic medication-associated acute kidney injury

High NTMx Exposure Rate per 1000 Non-ICU Patient Days

Week Ending

- BiWeekly High NTMx Exposure Rate
- Mean High NTMx Exposure Rate
- Control Limits

*Kidney International* (2016) *90*, 212–221;
A sustained quality improvement program reduces nephrotoxic medication-associated acute kidney injury

Stuart L. Goldstein¹, Theresa Mottes¹, Kendria Simpson¹, Cynthia Barclay², Stephen Muething³, David B. Haslam⁴ and Eric S. Kirkendall⁵

**AKI Rate per 1000 Non-ICU Patient Days**

(Using μ chart)

Week Ending

- BiWeekly AKI Rate
- Average AKI Rate
- Control Limits

Cincinnati Children’s
A sustained quality improvement program reduces nephrotoxic medication-associated acute kidney injury

Stuart L. Goldstein¹, Theresa Mottes¹, Kendria Simpson¹, Cynthia Barclay², Stephen Muething³, David B. Haslam⁴ and Eric S. Kirkendall⁵

### Adverse Events Avoided

<table>
<thead>
<tr>
<th>Measure</th>
<th>2011*</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015*</th>
<th>Aggregate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annualized Non-Critically Ill Patient Days</td>
<td>97,065(26,133)</td>
<td>91,363</td>
<td>90,627</td>
<td>99,076</td>
<td>109,968(27,492)</td>
<td>334,691 Census Days</td>
</tr>
<tr>
<td>(Actual Count)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annualized Number Of Patient Exposures</td>
<td>1,129(304)</td>
<td>969</td>
<td>837</td>
<td>960</td>
<td>692</td>
<td>3,243 Patient Exposures</td>
</tr>
<tr>
<td>(Actual Count)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annualized Number Of Patients With AKI</td>
<td>271(73)</td>
<td>168</td>
<td>141</td>
<td>159</td>
<td>116</td>
<td>575 Patients With AKI</td>
</tr>
<tr>
<td>(Actual Count)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Exposures Avoided</td>
<td>N/A</td>
<td>108</td>
<td>200</td>
<td>219</td>
<td>106</td>
<td>633 Avoided Exposures</td>
</tr>
<tr>
<td>Patients With AKI Avoided</td>
<td>N/A</td>
<td>105</td>
<td>113</td>
<td>134</td>
<td>46</td>
<td>398 Avoided AKI Events</td>
</tr>
</tbody>
</table>

* Data presented for partial year. Annualized values represent if data were extrapolated to full time period. Study period in 2011 (Sept – Dec), in 2015 (January – March). All aggregate data are actual count.
Cost Implications – A Theoretical Model

• Costs incurred
  – Daily creatinine
  – Prolonged hospital admission for AKI detection
  – Follow up clinic and labs since AKI detected
  – Medications to slow CKD progression

• Potential cost savings (earlier detection)
  – AKI avoided
  – CKD avoided
  – ESRD avoided
Dissemination of NINJA

• Disseminate NINJA implementation at nine pediatric hospitals

• Measure the impact of NINJA on NTMx-AKI in participating hospitals

• Assess the association between context measures, including network participation, and reduction in NTMx-AKI by individual hospitals across the network
NINJA

ephrotoxic injury

just-in-time action

University of Michigan
C.S. Mott Children’s Hospital

Cincinnati Children's

DELAFARE

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CHILDREN'S CENTER

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UAB BLAZERS

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KC Royals

UCLA

Cincinnati Children’s
Rate of Nephrotoxic Medication (NTMx) associated Acute Kidney Injury (AKI) per 1000 Non-ICU Patient Days

Grant Centers Only

AKI Rate

Median AKI Rate

Goal

Maturity Detection System

Cincinnati Children's
Next for NINJA

• Accepted by the Solutions for Patient Safety as the next Hospital Acquired Condition
• Will roll out to another 15 centers in 2017 and disseminate SPS wide in 2018
• Use NINJA as the foundation for more translational work
  – Risk stratification
  – Biomarker integration
  – Sub-population assessment
Urinary kidney injury biomarkers and tobramycin clearance among children and young adults with cystic fibrosis: a population pharmacokinetic analysis

Kevin J. Downes\textsuperscript{1,2*}, Min Dong\textsuperscript{2}, Tsuyoshi Fukuda\textsuperscript{2,3}, John P. Clancy\textsuperscript{3,4}, Christopher Haffner\textsuperscript{5}, Michael R. Bennett\textsuperscript{5}, Alexander A. Vinks\textsuperscript{2,3} and Stuart L. Goldstein\textsuperscript{3,5}

\textsuperscript{1}Division of Infectious Diseases, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH, USA; \textsuperscript{2}Division of Clinical Pharmacology, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH, USA; \textsuperscript{3}Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA; \textsuperscript{4}Division of Pulmonology, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH, USA; \textsuperscript{5}Division of Nephrology and Hypertension, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH, USA
Table 2. Between-subject correlations of weighted average biomarker concentrations and individual PK parameter estimates\(^a\)

<table>
<thead>
<tr>
<th>Biomarker (^b)</th>
<th>$C_{\text{max}}$ regression coefficient</th>
<th>$P$ value</th>
<th>$\text{AUC}_{0-24}$ regression coefficient</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGAL</td>
<td>0.07</td>
<td>0.57</td>
<td>0.46</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NGAL/UCr</td>
<td>0.19</td>
<td>0.15</td>
<td>0.33</td>
<td>0.009</td>
</tr>
<tr>
<td>RBP</td>
<td>−0.19</td>
<td>0.16</td>
<td>0.15</td>
<td>0.25</td>
</tr>
<tr>
<td>RBP/UCr</td>
<td>−0.15</td>
<td>0.26</td>
<td>0.03</td>
<td>0.80</td>
</tr>
<tr>
<td>KIM-1</td>
<td>0.19</td>
<td>0.14</td>
<td>0.13</td>
<td>0.32</td>
</tr>
<tr>
<td>KIM-1/UCr</td>
<td>0.29</td>
<td>0.02</td>
<td>−0.08</td>
<td>0.53</td>
</tr>
</tbody>
</table>

\(^a\)Analyses performed using 186 PK estimates and biomarker pairs, accounting for repeated measurements during 60 tobramycin courses.

\(^b\)Biomarkers log-transformed for comparisons.
So..... CAN NINJA WORK IN THE ICU?

• NO!
  – NINJA raised awareness of NTMx-AKI by increasing surveillance in at-risk non-ICU patients
    • AKI risk is already high in the ICU
    • Aren’t we already monitoring for AKI daily anyway in the ICU?
    • Don’t all ICU patients get at least 3 NTMx the femtosecond they roll in the door?

• MAYBE!
  – Are pharmacists in the ICU armed and supported to
    • Make medication recommendations/dosing adjustments based on risk?
    • Highlight the need to minimize “unnecessary” NTMx?
    • Look up organism antimicrobial susceptibility?
Acknowledgements

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• Stephen Muething, MD
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• Jason Olivea
• Devesh Dahale
• Cynthia Barclay, PharmD
NINJA

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