Nephrotoxic Acute Kidney Injury: Prevention and Management

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Disclosures

- None
“Nephrologists are by necessity practicing pharmacologists”

Outline

- What is nephrotoxic AKI (NTMx-AKI)?
  - Background, epidemiology
- NTMx-AKI is reversible. Should I even care beyond that?
  - Outcomes
- But I can’t stop patients from getting these medications for their underlying disease.
  - Strategies for prevention
Drug-induced Nephrotoxicity

- One of the commonest causes of AKI in non-critically ill hospitalized children
- Not always recognized
  - Non-oliguric
  - Lack of systematic kidney function surveillance in exposed children
# Table 1. Clinical Variables for Pediatric Patients With ARF Stratified by Age

<table>
<thead>
<tr>
<th>Age (no. of patients)</th>
<th>GFR</th>
<th>Survival</th>
<th>ICU Stay/LOS</th>
<th>RRT*</th>
<th>Most Common ARF Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-30 d (62)</td>
<td>11.5 + 9.8</td>
<td>34 (56)</td>
<td>59 (97), 46</td>
<td>34 (58)</td>
<td>Ischemic 16 (26)</td>
</tr>
<tr>
<td>1-12 mo (37)</td>
<td>18.4 + 14.3</td>
<td>22 (59)</td>
<td>32 (86), 26</td>
<td>10 (32)</td>
<td>Ischemic 13 (35)</td>
</tr>
<tr>
<td>1-5 y (43)</td>
<td>32.9 + 20.1</td>
<td>36 (84)</td>
<td>30 (70), 21</td>
<td>8 (27)</td>
<td>Ischemic 10 (23)</td>
</tr>
<tr>
<td>6-15 y (83)</td>
<td>29.3 + 20.4</td>
<td>61 (73)</td>
<td>49 (59), 18</td>
<td>28 (57)</td>
<td>Nephrotoxins 22 (26)</td>
</tr>
<tr>
<td>16-21 y (29)</td>
<td>35.5 + 17</td>
<td>23 (79)</td>
<td>15 (52), 23</td>
<td>8 (53)</td>
<td>Nephrotoxins 6 (21)</td>
</tr>
<tr>
<td>Total (254)</td>
<td>35.2 + 39.2</td>
<td>176 (70)</td>
<td>185 (73), 26</td>
<td>80 (43)</td>
<td>Ischemic 45 (22)</td>
</tr>
</tbody>
</table>

NOTE. Values expressed as mean ± SD or number (percent).
Abbreviation: LOS, average length of ICU stay in days.
*Percentages reflect fraction of patients admitted to the ICU that required RRT.
Patients receiving IV AG > 5 days

Primary renal diagnoses excluded

557 children over 1 year
- 95% > 3 months of age

AKI occurred in 33% by pRIFLE and 20% by AKIN

SCr measured q4 ~ 50% of the time

Prospective study

100 patients receiving IV AG > 7 days

Excluded known CKD or impaired renal function at baseline

AKI occurred in 62% by pRIFLE and 42% by AKIN

SCr measured twice a week
• Retrospective case control study
  • 357 non-critically ill children with AKI by pRIFLE matched with 357 children without AKI
• 86% of the entire group was exposed to \( \geq 1 \) NTMx
• Patients with AKI had a greater number of median NTMx exposures, doses and days of therapy
• Patients with AKI had 1.7 OR of exposure to NTMx
Nephrotoxic Medications and Associated Acute Kidney Injury in very Low Birth Weight Infants

Barhight M¹•, Altaye M², Gist KM³, Isemann B⁴, Goldstein SL⁵, and Akinbi H⁶

• Retrospective chart review of 276 infants <30 weeks postmenstrual age and/or <1500 g birth weight
• 233 (84%) received NTMx
• AKI by KDIGO occurred in 21 (9%)
• Patients with AKI were exposed to a median of 5 NTMx compared to 2 in those without AKI
• Median duration of exposure was 12 days (vs 5 days in those without AKI)
• What is nephrotoxic AKI (NTMx-AKI)?
  • Background, epidemiology
• NTMx-AKI is reversible. Should I even care beyond that?
  • Outcomes
• But I can’t stop patients from getting these medications for their underlying disease.
  • Strategies for prevention
• Retrospective case control study
• 100 patients with NTMx-AKI assessed at ≥ 6 months after AKI episode
• Matched with patients who received NTMx but did not develop AKI
• Review of electronic health record
  • Nephrology Clinic visit (y/n)
  • Serum creatinine
  • Urine for protein and creatinine
  • Cystatin C
  • GFR estimation from serum creatinine and/or CysC

<table>
<thead>
<tr>
<th></th>
<th>Before AKI</th>
<th>Hospital DC</th>
<th>6 months post-AKI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>eGFR (ml/min/1.73m²)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;90</td>
<td>0/100</td>
<td>22/92 (5-92)</td>
<td>18/77 (5-88)</td>
</tr>
<tr>
<td>90-150</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;150</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cystatin C eGFR (ml/min/1.73m²)</strong></td>
<td></td>
<td>N/A</td>
<td>80+ 23</td>
</tr>
<tr>
<td><strong>Urine protein/creat &gt;0.2</strong></td>
<td></td>
<td>N/A</td>
<td>27/34</td>
</tr>
</tbody>
</table>

At 6 months post-AKI

- 29/77 patients with hypertension
- 15/77 seen by a nephrologist
- Only 42% with complete CKD assessment
Acute Kidney Injury Associated with High Nephrotoxic Medication Exposure Leads to Chronic Kidney Disease after 6 Months

Shina Menon, MD\textsuperscript{1}, Eric S. Kirkendall, MD\textsuperscript{2}, Hovi Nguyen, MPH\textsuperscript{1}, and Stuart L. Goldstein, MD\textsuperscript{1}

DOES NEPHROTOXIC MEDICATION ASSOCIATED AKI CAUSE CKD?
• What is nephrotoxic AKI (NTMx-AKI)?
  • Background, epidemiology
• NTMx-AKI is reversible. Should I even care beyond that?
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• But I can’t stop patients from getting these medications for their underlying disease.
  • Strategies for prevention
Strategies for prevention

- Awareness of risk factors
- Improving recognition of NTMx-AKI
  - Be a NINJA
  - Using biomarkers
- Tailored management (precision medicine)
Know your enemy: Drug related risk factors

• Inherent nephrotoxic potential: aminoglycosides, amphotericin, NSAID, ACEI and ARB, antiviral, and anticancer drugs
• Dose dependence
• Prolonged duration of treatment
• Frequency of administration
• Rate and route of administration
Patient related risk factors

- Prematurity
- Pre-existing CKD
- Intravascular volume depletion
- Sepsis
- Other concomitant nephrotoxic medications
- Hypoalbuminemia
- Impaired acid-base homeostasis
Children should only get the nephrotoxic medications they need for the duration they need them.
Study Design

- Hypothesis: More reliable surveillance of NTMx exposure and injury would demonstrate that rates of AKI are high.
- Aims: Develop an 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

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

or

On an aminoglycoside for 3 or more days

### 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>Ambisomea</td>
<td>Foscarne</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Amikacin</td>
<td>Gadopentetate dimegluminea</td>
<td>Nafcillin</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>Gadobenate disodiuma</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>Cefazidime</td>
<td>Ifosfamide</td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>Iodixanola</td>
<td>Ticarcillin/clavulanic acid</td>
</tr>
<tr>
<td>Cidofovira</td>
<td>Iohexola</td>
<td>Tobramycin</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Iopamidola</td>
<td>Topiramate</td>
</tr>
<tr>
<td>Colistimethate</td>
<td>Ioversola</td>
<td>Valacyclovir</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Ketorolac</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>

*a Medications counted for 7 days after administration toward exposure.
99% compliance with daily SCr monitoring in all high NTMx-exposed patients
AKI intensity decreased by 42% in Year 1

Associated with 908 AKI days avoided in one year
• Prospective QI project from Sep 2011 through March 2015
• 1749 patients and 2358 separate hospital admissions
  • 3243 episodes of NTMx exposure
  • 575 individual AKI episodes
• NTMx exposure rate decreased by 38% (11.63–7.24 exposures/1000 patient days)
• AKI rate decreased by 64% (2.96–1.06 episodes/1000 patient days)
• Estimated 633 exposures and 398 AKI episodes avoided
Rate of Nephrotoxic Medication (NTMx) associated with Acute Kidney Injury (AKI) per 1000 Non-ICU Patient Days

<table>
<thead>
<tr>
<th>Date Range</th>
<th>AKI Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/1-10/14, 2014</td>
<td>0.7848</td>
</tr>
<tr>
<td>11/15-11/30, 2014</td>
<td>0.7848</td>
</tr>
<tr>
<td>1/1-1/14, 2015</td>
<td>0.7848</td>
</tr>
<tr>
<td>2/15-2/28, 2015</td>
<td>0.7736</td>
</tr>
<tr>
<td>3/29-4/11, 2015</td>
<td>0.8842</td>
</tr>
<tr>
<td>5/10-5/23, 2015</td>
<td>0.8807</td>
</tr>
<tr>
<td>6/21-7/4, 2015</td>
<td>0.9906</td>
</tr>
<tr>
<td>8/2-8/15, 2015</td>
<td>1.2081</td>
</tr>
<tr>
<td>9/13-9/26, 2015</td>
<td>1.4802</td>
</tr>
<tr>
<td>10/25-11/7, 2015</td>
<td>0.8792</td>
</tr>
<tr>
<td>12/6-12/19, 2015</td>
<td>1.2914</td>
</tr>
<tr>
<td>1/17-1/30, 2016</td>
<td>1.1896</td>
</tr>
<tr>
<td>2/28-3/12, 2016</td>
<td>0.9997</td>
</tr>
<tr>
<td>4/10-4/23, 2016</td>
<td>1.3382</td>
</tr>
<tr>
<td>5/22-6/4, 2016</td>
<td>0.899</td>
</tr>
<tr>
<td>7/3-7/16, 2016</td>
<td>2.273</td>
</tr>
<tr>
<td>8/14-8/27, 2016</td>
<td>0.9627</td>
</tr>
<tr>
<td>9/8-10/8, 2016</td>
<td>1.758</td>
</tr>
<tr>
<td>11/19-12/2, 2016</td>
<td>1.1407</td>
</tr>
<tr>
<td>12/31-1/13, 2017</td>
<td>1.3331</td>
</tr>
</tbody>
</table>

Maturity Detection System

Seattle Children's Hospital • Research • Foundation
UW Medicine
UW School of Medicine
Pilot study of once-daily IV tobramycin in 37 patients with CF

Assessed SCr and urinary biomarkers including NGAL, KIM-1

Urinary NGAL (not SCr) was strongly associated with tobramycin clearance
Pre-Hydration in NTMx Therapy

CF patient admitted for bronchopneumonia and IV antibiotics

Starting NTMx? NO

Initiate appropriate therapy

Starting NTMx? YES

Urinalysis resulted? NO

Wait for urinalysis results before initiating therapy

Initiate IV nephrotoxic antibiotics and continue IVF overnight for protection

Urinalysis resulted? YES

Specific gravity ≤1.010? NO

Start hydration and continue to hydrate until specific gravity ≤1.010

Specific gravity ≤1.010? YES

END
Electronic Health Record–Enabled Big-Data Approaches to Nephrotoxin-Associated Acute Kidney Injury Risk Prediction

Scott M. Sutherland*

<table>
<thead>
<tr>
<th>EHR Cohort</th>
<th>Patients</th>
<th>AKI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EHR Cohort</td>
<td>2.5 million</td>
<td>2.2%</td>
</tr>
<tr>
<td>Age 40-60</td>
<td>750,000</td>
<td>1.9%</td>
</tr>
<tr>
<td>Male</td>
<td>310,000</td>
<td>2.8%</td>
</tr>
<tr>
<td>Male Aged 40-60 Stem Cell Transplant</td>
<td>5,000</td>
<td>14%</td>
</tr>
<tr>
<td>Male Aged 40-60 Stem Cell Transplant Acyclovir/Tacrolimus</td>
<td>3,500</td>
<td>22%</td>
</tr>
<tr>
<td>Male Aged 40-60 Stem Cell Transplant Acyclovir/Tacrolimus Amphotericin</td>
<td>1,500</td>
<td>39%</td>
</tr>
</tbody>
</table>
Conclusions

- NTMx-AKI is common
- It increases morbidity, hospital length of stay, cost of admission
- It may have long term impact
- And it can be prevented
Acknowledgements
Thank you