Acute Kidney Injury—Update on Mechanisms and Management

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Bodies Revealed Exhibition
Outside Activities

• Consultant/Equity:
  – Eunoia Biotech
  – Boston Clinical Research Institute

• Intellectual Property
  – Angiopoietins in critical diseases

• Royalties
  – Up-To-Date

• Paid Travel
  – American Society of Nephrology (Program Cmte, AKI Highlights Faculty)
Objectives

• Understand the footprint of AKI in local and global settings

• Discuss barriers to therapeutic progress in the AKI field

• Become familiar with emerging considerations in patient care
Outline

• Impacts of AKI
  – Global
  – Attributable morbidity/mortality

• “Avoid nephrotoxins...”
  – Is there even a pathway or process to target?

• Clinical management
  – Not too little, but then what?
RIFLE
- STAGE 1: 1.5 fold $\uparrow$ serum creatinine (risk)
- STAGE 2: 2.0 fold $\uparrow$ serum creatinine (injury)
- STAGE 3: 3.0 fold $\uparrow$ serum creatinine (failure)

AKIN
- STAGE 1: 1.5-2.0 fold $\uparrow$ serum creatinine
- STAGE 2: >2.0-3.0 fold $\uparrow$ serum creatinine
- STAGE 3: >3.0 fold $\uparrow$ serum creatinine

KDIGO
- STAGE 1: 1.5-1.9 fold $\uparrow$ serum creatinine
- STAGE 2: 2.0-2.9 fold $\uparrow$ serum creatinine
- STAGE 3: $\geq$3.0 fold $\uparrow$ serum creatinine or dialysis
The figure illustrates the pooled AKI-associated mortality rate (95% CI) across different stages and dialysis requirements. The mortality rates are as follows:

- Overall (KDIGO-equivalent): 23.0%
- Stage 1 (Risk): 15.9%
- Stage 2 (Injury): 28.5%
- Stage 3 (Failure): 47.8%
- Dialysis Requirement: 49.4%

The table below provides the number of studies and patients with AKI for each category:

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of Studies</th>
<th>No. of Patients with AKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (KDIGO-equivalent)</td>
<td>110</td>
<td>429,535</td>
</tr>
<tr>
<td>Stage 1 (Risk)</td>
<td>26</td>
<td>8,226</td>
</tr>
<tr>
<td>Stage 2 (Injury)</td>
<td>25</td>
<td>42,354</td>
</tr>
<tr>
<td>Stage 3 (Failure)</td>
<td>25</td>
<td>42,354</td>
</tr>
<tr>
<td>Dialysis Requirement</td>
<td>31</td>
<td>6,534</td>
</tr>
</tbody>
</table>

Source: Susantitaphong, et al. CJASN 2013
$7500
(3 to 14,000) per admission excess hospital costs
$9,000,000,000/year

3.5% of admissions

Your length of stay increases, on average, by 3.5 days if you get AKI

300,000 People die in the United States annually from AKI

1.2 Million people per year get AKI during a hospital stay

Death rate more than breast cancer, prostate cancer, heart failure, and diabetes, combined
Based on population incidence of AKI 2100 per million

Lewington, et al. Kid Intl 2013
AKI drives CKD: a VA study

Chawla and Kimmel. Kid Intl 2012
Repeated AKI and mortality: diabetics

Thakar, et al. CJASN 2008
Evidence that AKI Kills

- “Pure” AKI cases
  - Case-control study in Contrast Induced Nephropathy (Levy, et al. JAMA 1996)
  - Adjusted odds ratio death 5.5

- Multivariate Analysis in ICUs
  - Cross-sectional, one-day prevalence study enrolled 3877 ICU subjects of whom 415 had severe sepsis/septic shock (Oppert, et al. NDT 2008)
  - Adjusted odds ratio death 2.11
Natural History of “ATN”

Liano, et al. KI 2007
Episode of ATN

- \(~50\%\) Full
- \(~40\%\) Partial
- \(~10\%\) ESRD

*20-60\% ATN sufferers die before d/c depending on case series, comorbidities

Liano, et al. KI 2007
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Renal Blood Flow = 1440 L/d
Glomerular filtrate = 140L/d
UOP = 1L/d
Why does the resorptive apparatus interact with filtration

- **Ex #1**: In pregnancy, GFR increases from ~140L/day to ~220 L/day → contrary to popular opinion, pregnant women do NOT urinate 80L/day

- **Ex #2**: Since reabsorption is an energy-requiring process (Na-coupled transport), imagine an overloaded tubule being unable to slow GFR
Why does the resorptive apparatus interact with filtration

- Ex #1: In pregnancy, GFR increases from ~140L/day to ~220 L/day → contrary to popular opinion, pregnant women do NOT urinate 80L/day = GLOMERULOTUBULAR BALANCE

- Ex #2: Since reabsorption is an energy-requiring process (Na-coupled transport), imagine an overloaded tubule being unable to slow GFR = TUBULOGLOMERULAR FEEDBACK
IMMUNE RESPONSE

Bonventre and Yang. JCI 2012
Even in Mice, AKI differs in Form...

Cortex and OSOM
Scant Cell Death
Proximal Tubule

Ischemia-Reperfusion
Surgical Sepsis
Cisplatin

Miyaji, et al. Kid Intl 2003
Parikh Lab unpublished
Sublethal injury in experimental sepsis

Cr 0.8

Cr 1.8

BUN ~80

BUN ~15
