Advances in the Pathogenesis and Management of Acute Kidney Injury (AKI)

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Director, Nephrology Clinical Laboratory
CEO, Dialysis Unit
Cincinnati Children’s Hospital Medical Center

New York Academy of Medicine, 3/22/13
Objectives

- Understand the epidemiology of pediatric acute kidney injury (AKI)
- Understand recent advances in the pathogenesis of AKI
- Understand the role of novel biomarkers for the diagnosis of AKI
- Understand the emerging therapeutic options for AKI
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• Understand the epidemiology of pediatric acute kidney injury (AKI)
• Understand recent advances in the pathogenesis of AKI
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• Understand the emerging therapeutic options for AKI
AKI – A Standardized Definition

- Increase in serum creatinine by $\geq 0.3 \text{ mg/dl}$ within 48 hours; OR
- Increase in serum creatinine to $\geq 1.5$ times the baseline within the prior 7 days; OR
- Urine volume $< 0.5 \text{ ml/kg/hour}$ for 6 hours
### AKI – A Standardized Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum Creatinine</th>
<th>Urine Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5 to 1.9 times baseline, OR ≥ 0.3 mg/dl increase from baseline</td>
<td>&lt; 0.5 ml/kg/hour for 6-12 hours</td>
</tr>
<tr>
<td>2</td>
<td>2.0 to 2.9 times baseline</td>
<td>&lt; 0.5 ml/kg/hour for ≥ 12 hours</td>
</tr>
<tr>
<td>3</td>
<td>≥ 3.0 times baseline, OR ≥ 4 mg/dl</td>
<td>&lt; 0.3 ml/kg/hour for ≥ 24 hours, OR anuria ≥ 12 hours</td>
</tr>
</tbody>
</table>

*KDIGO, Kidney Int Suppl 2:19-36, 2012*

*Devarajan, Curr Pediatr Rep, 2012*
Pediatric AKI – Common And Serious

- Afflicts 30-35% of children admitted to pediatric ICUs
- Independently associated with longer ICU stay, mechanical ventilation, and a persistently high mortality rate of 30-40%

Goldstein/Devarajan, Nat Rev Nephrol 6:393-394, 2010
Shneider, Crit Care Med 38:933-939, 2010
Pediatric AKI – Common And Serious

- Afflicts 40-50% of children undergoing cardiac surgery
- Independently associated with longer ICU stay, mechanical ventilation, and a 5-10 fold greater risk of death

Goldstein/Devarajan, Nat Rev Nephrol 6:393-394, 2010
Li, Crit Care Med 39:1493-1499, 2011
Blinder, JTCVS 143:368-374, 2012
Aydin, ATS ePub, 2012
Pediatric AKI – Changing Epidemiology

- No longer primary glomerular diseases
- Most commonly a hospital-acquired complication of other systemic illnesses
- Most commonly as a result of sepsis, congenital heart disease, other critical illness, nephrotoxins
- Children with AKI die of, and not merely with AKI

Goldstein/Devarajan, Nat Rev Nephrol 6:393-394, 2010
Duzova, Pediatr Nephrol 25:1453-61, 2010
Moffett, CJASN 6:856-63, 2011
Pediatric AKI – Ironic, even Tragic

- Largely a hospital-acquired disease
- Largely a result of improved critical care, and improved management of other organ failures
- Current diagnostic AKI markers are delayed
- Promising novel therapies cannot even be tested until better diagnostic markers become available
- Current AKI supportive care (including dialysis) is delayed

AKI: Delayed Diagnosis

- Serum creatinine is the current “gold standard” for AKI diagnosis, but is highly problematic.
- Normal serum creatinine varies widely with age, gender, diet, muscle mass, muscle metabolism, medications, and hydration status.
- In AKI, serum creatinine can take several days to reach a new steady state.
- More than 50% of kidney function may be lost before serum creatinine even begins to rise.

Devarajan, Biomarkers Med 4:265-80, 2010
## AKI versus AMI – Similar Incidence

<table>
<thead>
<tr>
<th>Period</th>
<th>Acute Myocardial Infarction</th>
<th>Acute Kidney Injury</th>
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<td>1960s</td>
<td>LDH</td>
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<tr>
<td>1970s</td>
<td>CPK, myoglobin</td>
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<td>CK-MB</td>
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<td>2000s</td>
<td>Troponin I</td>
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Early Damage Markers
Multiple Therapies
50% ↓ Mortality

*Kellum, JAMA 307(21):2265-6, 2012*
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<td>Serum creatinine</td>
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- **Early Damage Markers**
  - Multiple Therapies
  - 50% ↓ Mortality

- **Delayed Functional Marker**
  - Supportive Care
  - High Mortality

*Need early damage markers for better treatment of AKI*

*Devarajan, Biomarkers Med 4:265-80, 2010*
### Interventions that prevent AKI in animals

<table>
<thead>
<tr>
<th>Paradigm</th>
<th>Before Injury</th>
<th>Soon After Injury (before SCr rises)</th>
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<tbody>
<tr>
<td><strong>Vasodilators</strong></td>
<td>Diuretics, Mannitol, Dopamine, Calcium Channel Blocker, Endothelin Antag</td>
<td>ACE inh, ANP, Dopamine, BNP Endothelin Antag</td>
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<tr>
<td><strong>Growth Factors</strong></td>
<td>IGF-1, EGF, HGF NGAL, p53 inh BMP agonists</td>
<td>IGF-1, NGAL, p53 inh BMP agonists</td>
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<tr>
<td><strong>Antioxidants/ Anti-inflammatory</strong></td>
<td>N-acetylcysteine, Iron chelators</td>
<td>ICAM-1 ab, α-MSH Iron chelators</td>
</tr>
</tbody>
</table>

*The paucity of early damage biomarkers has crippled our ability to institute timely therapy in humans*

*Devaraj, Biomarkers Med 4:265-80, 2010*
So How Do We Get Out Of The Dark Ages in AKI??

- A better understanding of the early pathogenesis and clinical continuum of AKI
- Listen carefully to what the kidney is trying to tell us
Objectives

• Understand the epidemiology of pediatric acute kidney injury (AKI)
• **Understand recent advances in the pathogenesis of AKI**
• Understand the role of novel biomarkers for the diagnosis of AKI
• Understand the emerging therapeutic options for AKI
Biochemistry of AKI

Devarajan JASN 17:1503-20, 2006
Clinical Continuum of AKI

Devarajan, Biomarkers Med 4:265-80, 2010
AKI: Morphologic and Clinical Continuum

Normal

- Normal Epithelium
- Proliferation & Differentiation
- Dedifferentiation of Viable Cells

Damage

- Insult
- Recovery
- Loss of brush border and cell polarity

↑ S Creat

- Nucleus & Apoptosis
- Kidney failure
- Sloughing & Obstruction

↓ GFR

- Cytokine release

PMN

- B cell

Macrophage

- Microvascular Congestion
Objectives

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How Are AKI Biomarkers Discovered?
Phase 1: Listen to the Kidney

- The early adaptive response of the stressed kidney itself is providing us with biomarkers that inform pathophysiology and, serendipitously, the early diagnosis:
  - Neutrophil gelatinase-associated lipocalin (NGAL)
  - Interleukin 18 (IL-18)
  - Kidney injury molecule 1 (KIM-1)
  - Liver type fatty acid binding protein (L-FABP)

Reference:
Devarajan, NEJM 358(3):312, 2008
NGAL: Discovery Phase (Phase 1)

- **Neutrophil gelatinase-associated lipocalin**
- Normally very small amounts in kidney tubules
- The most upregulated gene in the kidney by gene expression profiling, soon after ischemic or nephrotoxic AKI
- Protein product highly over-expressed and easily detected in the kidney, urine and plasma during early phases of AKI in animal and human models

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*Supavekin et al, Kidney Int 63:1714-24, 2003 (ischemia)*
*Kieran et al, Kidney Int 64:480-492, 2003 (ischemia)*
*Amin et al, Environ Health Perspect 112:465-479, 2004 (cisplatin)*
*Yuen et al, Physiol Genomics 25:375-386, 2006 (ischemia & HgCl)*
*Grigoryev et al, J Am Soc Nephrol Jan 30, 2008 (ischemia)*
Phase 1: Kidney NGAL in Ischemic AKI

- Mouse Ischemia
- 30 min ischemia
- S creat ↑ 24 h
- Kidney NGAL ↑ 3 h
- NGAL in tubule lumen

Mishra et al, JASN 15:3073-82, 2004
Phase 1: Urine NGAL in Ischemic AKI

- Mouse Ischemia
- 30 min ischemia
- S creat ↑ 24 h
- Urine NAG ↑ 8 h
- Urine β2M ↑ 8 h
- Urine NGAL ↑ 2 h

Mishra et al, JASN 15:3073-82, 2004
Phase 2 Transition: Human NGAL ELISA

- Sandwich monoclonal ELISA for human NGAL
- Inter- and intra-assay coefficient variations 5%
- Linear relationship in the 1-1000 ng/ml range

Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery

Jaya Mishra*, Catherine Dent*, Ridwan Tarabishi*, Mark M Mitsnefes, Qing Ma, Caitlin Kelly, Stacey M Ruff, Kamyar Zahedi, Mingyuan Shao, Judy Bean, Kiyoshi Mori, Jonathan Barasch, Prasad Devorajan

Lancet 2005; 365: 1231-38
See Comment page 1205
Phase 2: Urine NGAL (ELISA) as an Early AKI Biomarker after Cardiac Surgery

AKI = 50% or greater increase in serum creatinine from baseline

*Mishra et al, Lancet 365:1231-1238, 2005*
Phase 2: Urine NGAL (ELISA) as an Early AKI Biomarker: ROC Curve

For 2 hour urine NGAL, AUC = 0.99 for prediction of AKI

Mishra et al, Lancet 365:1231-1238, 2005
Phase 2: Plasma NGAL (ELISA) as an Early AKI Biomarker after Cardiac Surgery

AKI = 50% or greater increase in serum creatinine from baseline

Mishra et al, Lancet 365:1231-1238, 2005
Phase 2: Plasma NGAL (ELISA) as an Early AKI Biomarker: ROC Curve

For 2 hour plasma NGAL, AUC = 0.91 for prediction of AKI

*Mishra et al, Lancet 365:1231-1238, 2005*
Phase 2 Meta-analysis: NGAL for Early Diagnosis of AKI in Diverse AKI Settings – Rigor for Translation

<table>
<thead>
<tr>
<th>Biomarker Name</th>
<th>Cardiopulmonary Bypass (CPB)</th>
<th>Contrast induced Nephropathy (CIN)</th>
<th>Kidney Transplant (Tx)</th>
<th>ICU or ED Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGAL</td>
<td>2 hr post CPB 2 days pre AKI 0.8 (1-9)</td>
<td>2 hr post contrast 1-2 days pre AKI 0.88</td>
<td>12 hr post tx 2-3 days pre DGF 0.90</td>
<td>2 days pre AKI 0.85</td>
</tr>
</tbody>
</table>

AKI = 50% or greater increase in serum creatinine from baseline

Post CPB meta-analysis: 1154 subjects, 304 events

(1) Mishra et al, Lancet 2005, 365:1231-8 (U+P; n=71; AKI=20; AUC 0.91-0.99)
(2) Wagener et al, Anesthesiol 2006, 105: 485-91 (U; n=81; AKI=16; AUC 0.78)
(3) Portilla et al, KI 2008, 4:465-72 (U; n=40; AKI=20; AUC 1.0)
(4) Parikh et al, KI 2006, 70:199-203 (U; n=55; AKI=20; AUC 0.95)
(5) Koyner et al, KI 2008, 74:1059-69 (U; n=72; AKI=34; AUC 0.71)
(6) Xin et al, Ren Fail 2008, 30:904-13 (U; n=33; AKI=9; High S/S)
(7) Dent et al, Crit Care 2007, 11(6):R127 (P; n=120; AKI=45; AUC 0.96)
(8) Bennett et al, CJASN 2008, 3:665-73 (U; n=196; AKI=99; AUC 0.95)
(9) Wagener et al, AJKD 2008, 52:425-33 (U; n=426; AKI=85; AUC 0.61)

Haase, Devarajan et al, AJKD 54(6):1012-24, 2009
Phase 2: Plasma NGAL Clinical POC Kit

TRIAGE® NGAL KIT
Biosite Inc.

- Tests for cardiac markers
- Adapted for NGAL testing
- 15 min results - whole blood
- Compact, portable
- Simple, easy to use
- Undergoing clinical testing

* Currently not for sale in US
Phase 2: Urine NGAL Clinical Platform

- Abbott Diagnostics
- ARCHITECT: Standardized clinical platform

* Currently not for sale in US
Explosion of Phase 2 NGAL Studies

- NGAL for AKI Prediction
  - Cardiac Surgery
  - ICU/ER
  - Kidney Transplant
  - Contrast Nephropathy
  - Sepsis
- NGAL for AKI Staging
- NGAL for AKI Differential Diagnosis
- NGAL for AKI Prognosis
## NGAL For AKI Prediction After Cardiac Surgery

<table>
<thead>
<tr>
<th>Author</th>
<th>Publication</th>
<th>Patients</th>
<th>AKI Events</th>
<th>Plasma/Urine</th>
<th>AUC</th>
<th>Sens</th>
<th>Spec</th>
<th>Avg Peak</th>
<th>Cut-off</th>
<th>Comments</th>
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<tr>
<td>Mishra</td>
<td>Lancet 2005</td>
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<td>20</td>
<td>Urine</td>
<td>0.99</td>
<td>100</td>
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<td>50</td>
<td>AKI = RIFLE R or greater</td>
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<td>Wagener</td>
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<td>81</td>
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<td>Urine</td>
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<td>Bennett</td>
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<td>90</td>
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<td>2924</td>
<td>433</td>
<td>&gt;0.5 mg/dl Creat increase</td>
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<td>Han</td>
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**NGAL Totals**

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<tr>
<th>Patients</th>
<th>Total</th>
<th>Sens</th>
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<th>Avg Peak</th>
<th>Cut-off</th>
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NGAL For AKI Prediction In ER/ICU Setting

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NGAL Totals: 19 patients, 7234 AKI events, 1488 plasma/urine samples. AUC 0.83, Sensitivity 77%, Specificity 82%, Average Peak 705, Cutoff 128.
Explosion of Phase 2 NGAL Studies

- NGAL for AKI Prediction
  - Cardiac Surgery
  - ICU/ER
  - Kidney Transplant
  - Contrast Nephropathy
  - Sepsis
- NGAL for AKI Staging
- NGAL for AKI Differential Diagnosis
- NGAL for AKI Prognosis
Phase 2 Meta-analysis: Early NGAL Measurements Predict Subsequent Need For Dialysis in ICU

Phase 2 Meta-analysis: Early NGAL Measurements Predict In-hospital Mortality in AKI in ICU

Ref.

Wagener et al., 2006 [15]b
Wagener et al., 2008 [33]b
Bennett et al., 2008 [16]b
Koyner et al., 2008 [22]a
Koyner et al., 2008 [22]b
Nickolas et al., 2008 [14]b
Cruz et al., 2008 [36]a

Total mortality prediction

AUC-ROC

Phase 3 Transition: “Added Value”: Outcome of NGAL(+) Creat(-) “Subclinical AKI” in ICU Subjects

The Outcome of Neutrophil Gelatinase-Associated Lipocalin-Positive Subclinical Acute Kidney Injury

A Multicenter Pooled Analysis of Prospective Studies

Michael Haase, MD,*† Prasad Devarajan, MD,‡ Anja Haase-Fielitz, PHARMaD,*†
Phase 3 Transition: “Added Value”: Outcome of NGAL(+) Creat(-) “Subclinical AKI” in ICU

Haase, Devarajan et al, JACC 57:1752-61, 2011
Phase 3 Transition: “Added Value”: Outcome of NGAL(+) Creat(-) “Subclinical AKI” in ICU

Haase, Devarajan et al, JACC 57:1752-61, 2011
<table>
<thead>
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<th>Functional Criteria</th>
<th>Biomarker Criteria</th>
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<td>RIFLE-R or AKIN-1</td>
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<tr>
<td>RIFLE-I or AKIN-2</td>
<td>+++</td>
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<td>RIFLE-F or AKIN-3</td>
<td>+++++</td>
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Diagnostic and Prognostic Stratification in the Emergency Department Using Urinary Biomarkers of Nephron Damage
A Multicenter Prospective Cohort Study

Thomas L. Nickolas, MD, MS,* Kai M. Schmidt-Ott, MD,†‡ Pietro Canetta, MD,*

<table>
<thead>
<tr>
<th>Urinary Biomarker</th>
<th>AUC-ROC (95% CI)</th>
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<tr>
<td>uNGAL</td>
<td>0.81 (0.76–0.86)</td>
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<td>uKIM-1</td>
<td>0.71 (0.65–0.76)*</td>
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<tr>
<td>uIL-18</td>
<td>0.64 (0.57–0.70)†</td>
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<tr>
<td>uL-FABP</td>
<td>0.70 (0.65–0.76)†</td>
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## Biomarkers to Refine AKI Classification

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<th>Increased Biomarker</th>
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<tr>
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<td>-</td>
<td>Transient Azotemia</td>
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<tr>
<td>+</td>
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<td>Intrinsic AKI</td>
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</table>
Biomarkers in Early AKI – Cut-offs Approach

- Measure only if AKI is clinically suspected
- Low levels (NGAL < 50 ng/ml)
  - Low risk of AKI, repeat measures if clinical suspicion persists
- Grey Zone (NGAL 50-150 ng/ml)
  - Indeterminate, repeat measures if clinical suspicion persists
- Moderately high levels (NGAL 150-300 ng/ml)
  - High Sensitivity for AKI, monitor fluids and kidney function, avoid nephrotoxins, consider early interventions if clinical risk factors present
- Very high levels (NGAL >300 ng/ml)
  - High Specificity for AKI, implement early interventions

Cut-offs depend on assay used
Biomarkers for Timing of AKI

Fold Increase in Concentration

Time post-CPB

NGAL (0.95)

Marker (AUC)
Biomarkers for Timing of AKI

- **NGAL (0.95)**
- **L-FABP (0.8)**
- **IL-18 (0.75)**

Marker (AUC)
Biomarkers for Timing of AKI

- **NGAL (0.95)**
- **L-FABP (0.8)**
- **IL-18 (0.75)**
- **KIM-1 (0.83)**
- **CREAT**

Marker (AUC)
Initiation: vasoconstriction, ATP depletion, oxidant and labile iron generation

Extension: apoptosis and necrosis, inflammatory response

Maintenance: ongoing injury, dedifferentiation, regeneration, repair

Pathophys:

- **Initiation:** vasoconstriction, ATP depletion, oxidant and labile iron generation
- **Extension:** apoptosis and necrosis, inflammatory response
- **Maintenance:** ongoing injury, dedifferentiation, regeneration, repair

Therapy:

- **Vasodilators, ATP donors**
- **Anti-oxidants, Fe Chelator**
- **Anti-inflammatory, Anti-apoptotic, Stem cells**
- **Growth factors, Stem cells, RRT, renal devices**
Objectives

• Understand the epidemiology of pediatric acute kidney injury (AKI)
• Understand recent advances in the pathogenesis of AKI
• Understand the role of novel biomarkers for the diagnosis of AKI
• Understand the emerging therapeutic options for AKI
Biochemistry of AKI

Iron

Devarajan JASN 17:1503-20, 2006
Emerging Pharmacotherapies for AKI

- Iron chelators
  - Deferiprone

- Apoptosis inhibitors
  - p53 siRNA

- Vasodilators
  - Fenoldopam
Emerging Pharmacotherapies for AKI

Devarajan JASN 17:1503-20, 2006

Anti-inflammatory
α-MSH analog

Normal Epithelium

Insult → Recovery

Loss of brush border and cell polarity

Proliferation & Differentiation

Necrosis & Apoptosis

Dedifferentiation of Viable Cells

Sloughing & Obstruction

Microvascular Congestion

PMN

B cell

Macrophage

Stem Cells
Outline - Emerging Options for AKI Therapy

- Apoptosis inhibitors
  - p53 siRNA

- Iron chelators
  - Deferiprone

- Anti-inflammatory agents
  - Alpha-melanocyte stimulating hormone (α-MSH) analog

- Repair agents
  - Mesenchymal stem cells

All are currently undergoing clinical trials
AKI: p53 siRNA – Animal Studies

Molitoris JASN 20:1754-64, 2009
AKI: p53 siRNA – Human Studies

• Completed a Phase I/IIa, randomized, double-blind, trial of the safety and pharmacokinetics of p53 siRNA in adults undergoing cardiovascular surgery
  • Single IV injection within 4 hours of bypass
  • Pharmacokinetics during first 24 hours
  • Follow up for safety and dose limiting toxicities until hospital discharge and then by phone at 6 and 12 months post surgery

Quark Pharmaceuticals
ClinicalTrials.gov NCT00554359
p53 siRNA – What they’re not telling you ...

**p53 – “guardian of the genome”**
- Tumor suppressor
- Prevents gene mutations
- Conserves genome stability

**p53 - “policeman of cell damage”**
- Activates DNA repair
- Promotes apoptosis of the irreparably damaged cells

p53 inhibition may result in excessive proliferation of damaged cells and accumulation of mutations – both renal and extra-renal
Outline - Emerging Options for AKI Therapy

- Apoptosis inhibitors
  - p53 siRNA

- Iron chelators
  - Deferiprone

- Anti-inflammatory agents
  - Alpha-melanocyte stimulating hormone (a-MSH) analog

- Repair agents
  - Mesenchymal stem cells

All are currently undergoing clinical trials
Deferiprone Iron Chelator in AKI

- FDA-approved as an oral therapy to treat thalassemia patients with iron overload due to blood transfusions
- Completed Phase II randomized, double-blind, placebo-controlled trial to assess efficacy and safety of oral deferiprone (given before and then BID for 8 days after angiography)
  - primary outcome: change in novel AKI biomarkers
  - secondary outcome: change in serum creatinine

CorMedix
ClinicalTrials.gov NCT01146925
Deferiprone – What they’re not telling you ..

- Efficiency of targeting an orally administered chelator to the toxic ferric iron in renal tubules in AKI (vasoconstriction)
- Systemic side effects of generalized iron chelation - other iron chelators (deferoxamine) cause systemic hypotension
- Black box warning – neutropenia and agranulocytosis
- May lead to progressive hepatic fibrosis
Outline - Emerging Options for AKI Therapy

- Apoptosis inhibitors
  - p53 siRNA

- Iron chelators
  - Deferiprone

- Anti-inflammatory agents
  - Alpha-melanocyte stimulating hormone (α-MSH) analog

- Repair agents
  - Mesenchymal stem cells

All are currently undergoing clinical trials
AKI: $\alpha$-MSH – Animal Studies

- Potent anti-inflammatory and anti-apoptotic cytokine
- Decreases several pro-inflammatory cytokines (TNF-$\alpha$, IL-10), neutrophil adhesion molecules, and nitric oxide production
- Protects from AKI due to ischemia-reperfusion, nephrotoxins, and sepsis

Star PNAS 1995; 92:8016-20
Chiao JCI 1997; 99:1165-72
AKI: $\alpha$-MSH – Human Studies

- Completed a multicenter Phase II, randomized, double-blind, placebo-controlled, safety and efficacy trial in adults undergoing high-risk cardiovascular surgery
  - Primary outcome: safety and tolerability - analysis of adverse events, serious adverse events, and changes in laboratory parameters over 90 days
  - Primary outcome: efficacy – serum creatinine changes over 7 days

Action Pharma/Abbott
ClinicalTrials.gov NCT01256372
α-MSH – What they’re not telling you ....

- Efficiency of targeting an IV agent to the renal tubules in AKI (vasoconstriction)
- Systemic side effects
- Effects of blocking anti-inflammatory cytokines
- Effects of blocking systemic apoptosis (excessive proliferation of damaged or malignant cells)
Outline - Emerging Options for AKI Therapy

- Apoptosis inhibitors
  - p53 siRNA

- Iron chelators
  - Deferiprone

- Anti-inflammatory agents
  - Alpha-melanocyte stimulating hormone (α-MSH) analog

- Repair agents
  - Mesenchymal stem cells

All are currently undergoing clinical trials
AKI: Modified MSCs – Human Studies

- Recruiting for a multicenter, double-blind, placebo-controlled, Phase II study of AC607 for the treatment of AKI after cardiac surgery (0.5 mg/dl or greater rise in serum creatinine within 24 hours of CPB)
- Single IV administration of AC607 or vehicle
- Primary outcome: time to kidney recovery
- Secondary outcome: mortality or dialysis within 90 days

AlloCure
ClinicalTrials.gov NCT01602328
MSCs – What they’re not telling you ....

- Efficiency of targeting an IV agent to the renal tubules in AKI (vasoconstriction)
- Homing to other organs
- Effects of blocking systemic apoptosis (excessive proliferation of damaged or malignant cells)
Summary - Emerging Options for AKI Therapy

- Apoptosis inhibitors
  - p53 siRNA
  - BMP receptor ligands
- Iron chelators
  - Deferiprone
- Anti-inflammatory agents
  - Alpha-melanocyte stimulating hormone (α-MSH) analog
  - Recombinant Alkaline Phosphatase
- Repair agents
  - Modified mesenchymal stem cells
- Devices
  - Benephit intrarenal drug delivery catheter
  - Renal Assist Device

Currently undergoing clinical trials
### Pediatric AKI Trials in ClinicalTrials.gov

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AKI: No Magic Bullet Yet ......
AKI: The Future is Bright ......
Summary – Exciting Times!

1. Biologically plausible early damage biomarkers of AKI such as NGAL, KIM-1, L-FABP and IL-18 are now becoming available

2. Early measurements of damage biomarkers predict development of AKI and its adverse outcomes

3. Biomarkers should be used in the context of the clinical setting, and should improve upon clinical scores

4. Future studies should utilize early damage biomarkers as entry criteria for promising AKI therapeutic trials in the appropriate clinical context
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