SEPTIC INDUCED ACUTE KIDNEY INJURY

Soto K, Coelho S, et al.
Hospital Fernando Fonseca
## Introduction - Epidemiology

### RIFLE/AKIN Classification Scheme for AKI diagnosis

#### AKI + SEPSIS

<table>
<thead>
<tr>
<th>SIRS</th>
<th>Presence of &gt;2 of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>temperature &gt;38°C or &lt;36°C</td>
</tr>
<tr>
<td></td>
<td>heart rate &gt;90 beats/min</td>
</tr>
<tr>
<td></td>
<td>respiratory rate &gt;20 breaths/min</td>
</tr>
<tr>
<td></td>
<td>PaCO₂ &lt;32 mmHg</td>
</tr>
<tr>
<td></td>
<td>white cell count &gt;12,000 cells mm³</td>
</tr>
<tr>
<td></td>
<td>&lt;4,000 cells mm³ or with &gt;10⁵ immature (band) forms</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SEPSIS</th>
<th>Presence of confirmed or suspected infection plus ≥2 SIRS criteria</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>SEVERE SEPSIS</th>
<th>Presence of sepsis plus ≥1 organ system dysfunction</th>
</tr>
</thead>
</table>

| SEPTIC SHOCK | Presence of severe sepsis plus fluid unresponsive hypotension |

= **SEPTIC-AKI**

Absence of other clear and established, non-sepsis-related precipitants of AKI

Septic-AKI: increases in the likelihood of death, prolonged hospital stay, and increased costs of care
Septic-AKI

↔

Pathophysiology of AKI
Pathophysicsiology

Mechanisms of Lesions

- **Hemodynamics:** Vasodilation-induced glomerular hypoperfusion
  Dysregulated circulation within the peritubular network

- **Immunologic/toxic/inflammatory reactions** by systemic cytokine storm or local cytokine production + arachidonate metabolites + trombogenic ag + vasoactive substances + other mediators + neuroendocrine

- **Tubular pro-apoptotic mechanisms:** oxidative stress
  genetic process (BAX; Bcl-xL)
  immune-mediated: FasL; TNF
Pathophysiology

Hyperdynamic Sepsis

marked renal vasodilation (RVC)

marked increase in RBF

decreased creatinine clearance (CC)

Kidney International (2006) 69

HR, Heart rate; CO, cardiac output; MAP, mean arterial, RVC, Renal vascular conductance; and RBF, renal blood flow
HISTOPATHOLOGY
OF
SEPTIC AKI
There are no consistent renal histopathological changes in human or experimental septic AKI. The majority of studies reported normal histology or only mild, nonspecific changes. ATN was relatively uncommon.
Kidney lesions in septic shock go beyond those associated with simple acute tubular injury, notably capillary leukocytic infiltration and apoptosis.
## Diagnosis- Urine Microscopy

### Clinical value of urine microscopy in acute kidney injury

*Nature Reviews Nephrology, vol 5, 2009*

**ATN**
- Renal tubular epithelial cells (RTEC)
- Coarse granular, muddy brown or mixed cellular casts

**preR**
- Bland
- Occasional hyaline or fine granular casts

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![ATL](image1.png)

![Transient AKI](image2.png)
Score ≥2 is an extremely strong predictor of ATN – RR 7.3 - > PPV - NPV

The inter-observer agreement index was 99.80%. The ROC – AUC for AKI CSI to predict non-renal recovery was 0.79.
Diagnosis- Urine Microscopy

Urine Microscopy Is Associated with Severity and Worsening of Acute Kidney Injury in Hospitalized Patients

Mark A. Perazella, Steven G. Coca, Isaac E. Hall, Umo Iyamah, Madiha Koraishy, and Chirag R. Parikh

Section of Nephrology, Yale University School of Medicine, New Haven, Connecticut

Table 1. Scoring system based on number of granular casts and RTE cells

<table>
<thead>
<tr>
<th>RTE cells (per HPF)</th>
<th>Granular Casts (per LPF)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 (0 Points)</td>
</tr>
<tr>
<td>0 (0 points)</td>
<td>0</td>
</tr>
<tr>
<td>1 to 5 (1 point)</td>
<td>1</td>
</tr>
<tr>
<td>&gt;6 (2 points)</td>
<td>2</td>
</tr>
</tbody>
</table>

- The urinary sediment scores were lowest in those with stage 1 and highest in stage 3 AKI
- Was significantly associated with increased risk of worsening AKI – RR 7.3%
- Was more predictive than AKIN stage

Diagnosis-RIFLE vs AKIN criteria

Bagshaw et al. NDT 2008

No differences in mortality by the AKI definition/classification criteria. AUC 0.66 – 0.67

Cross tabulation of patients classified by AKIN vs RIFLE
Incidence: 28.5 (AKIN) - 35.5% (RIFLE)
Increased hospital mortality 36.4%.

AKIN misclassified 1,504
RIFLE 504 patients, as non-AKI

Joannidis M et al. (SAPS 3 database) Intensive Care Med 2009
Diagnosis-RIFLE vs AKIN criteria

Review

**Clinical review: RIFLE and AKIN – time for reappraisal**

Dinna N Cruz\(^1,2\), Zaccaria Ricci\(^3\) and Claudio Ronco\(^1,2\)

### RIFLE Limitations:
- GFR – equations
- Urine output
- Baseline SCr
- 48-hour timeframe

### AKIN Limitations:
- 1st SCr

*Critical Care 2009, vol 13, 3: 211*
Diagnosis- RIFLE Classification

RIFLE classification for AKI after modifications by the Acute Kidney Injury Network

Risk or Stage 1
- Creatinine Criteria: Creatinine $\geq 0.3$ mg/dL or Creatinine $\geq 150\%$ and < 200\% than baseline

Injury or Stage 2
- Creatinine Criteria: Creatinine $\geq 200\%$ and < 300\% than baseline
- Urine Output Criteria: UO < 0.5 mL/kg/h for 12 h

Failure or Stage 3
- Creatinine Criteria: Creatinine $\geq 300\%$ than baseline, or $\geq 4.0$ mg/dL and $\uparrow \geq 0.5$ mg/dL
- Urine Output Criteria: UO < 0.3 mL/kg/h for 24 h, or anuria for 12 h
- Renal Replacement Therapy

serum creatinine underestimates proved sepsis and sepsis-induced AKI by survival analysis and pathologic examination.

## Diagnosis- Serum Creatinine

### BASELINE CREATININE

<table>
<thead>
<tr>
<th>Method for estimating baseline creatinine</th>
<th>No acute kidney injury</th>
<th>Risk (%)</th>
<th>Injury (%)</th>
<th>Failure (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Crude mortality by RIFLE class (adults)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital admission</td>
<td>12.4</td>
<td>21.7</td>
<td>34.5</td>
<td>40.6</td>
</tr>
<tr>
<td>ICU admission</td>
<td>12.7</td>
<td>21.7</td>
<td>31.2</td>
<td>38.4</td>
</tr>
<tr>
<td>Lower of hospital or ICU admission</td>
<td>10.4</td>
<td>16.0</td>
<td>36.0</td>
<td>41.5</td>
</tr>
<tr>
<td>Estimate from MDRD formula</td>
<td><strong>5.7</strong></td>
<td><strong>12.7</strong></td>
<td><strong>25.2</strong></td>
<td><strong>34.9</strong></td>
</tr>
<tr>
<td>Lower of hospital or ICU admission or MDRD estimate</td>
<td>7.2</td>
<td>12.9</td>
<td>24.3</td>
<td>35.7</td>
</tr>
<tr>
<td>Nadir creatinine (first week)</td>
<td>9.7</td>
<td>13.1</td>
<td>25.9</td>
<td>30.1</td>
</tr>
<tr>
<td>Nadir creatinine (whole admission)</td>
<td>8.9</td>
<td>11.0</td>
<td>22.1</td>
<td>28.7</td>
</tr>
</tbody>
</table>

### Acute kidney injury prevalence by pediatric RIFLE class (pediatric ICU)

<table>
<thead>
<tr>
<th>Method</th>
<th>No acute kidney injury</th>
<th>Risk (%)</th>
<th>Injury (%)</th>
<th>Failure (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated creatinine clearance of 120 ml/min/1.73 m²</td>
<td>36.5</td>
<td>17.1</td>
<td>24.4</td>
<td>22.0</td>
</tr>
<tr>
<td>Estimated creatinine clearance of 100 ml/min/1.73 m²</td>
<td>17.1</td>
<td>14.6</td>
<td>36.6</td>
<td>31.7</td>
</tr>
<tr>
<td>ICU admission</td>
<td>87.9</td>
<td>7.3</td>
<td>2.4</td>
<td>2.4</td>
</tr>
<tr>
<td>Normal value for age and gender (minimum)</td>
<td>12.2</td>
<td>12.2</td>
<td>39.0</td>
<td>36.6</td>
</tr>
<tr>
<td>Normal value for age and gender (maximum)</td>
<td>46.3</td>
<td>14.6</td>
<td>17.1</td>
<td>22.0</td>
</tr>
</tbody>
</table>
Significant underestimated AKI diagnosis and severity

Using obSCr and RIFLE classification, 25.0% had AKI, similar 23.1% with AKIN classification, versus 18.3% and 15.3% respectively with eSCr.

High proportion of false negatives, either with RIFLE (43.4%) or AKIN criteria (51.8%)
Reduced Production of Creatinine Limits Its Use as Marker of Kidney Injury in Sepsis

Kent Doi, Peter S.T. Yuen, Christoph Eisner, Xuzhen Hu, Asada Leelahavanichkul, Jürgen Schnermann, and Robert A. Star

National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland


Large increases of SCr in BNx-sham; induction of sepsis + BNx significantly decreased SCr (BNx-CLP)
Serum TNF-α were higher in the BNx-CLP > BNx-sham, confirming severe sepsis

Sepsis dramatically decreased production of creatinine limiting the early detection of acute kidney injury
Treatment of sepsis with chloroquine decreased nonrenal organ injury markers but paradoxically increased serum creatinine
CYSTATIN C
Biomarkers - Cystatin C

Distribution of Serum Cystatin C levels by diagnostic group
Differential diagnosis

Submitted to CJASN - Soto K et al. 2009
Biomarkers - Cystatin C

Serum Cystatin C as severity predictor of AKI

RIFLE and GFR based on SCysC

AKIN and levels of SCysC

AUCs 0.87-0.88 - Sensitivity 80-81% and Specificity 77-80%

Submitted to CJASN - Soto K et al. 2009
Early detection of Acute Kidney Injury by serum Cystatin C

RIFLE classification: Serum cystatin C and creatinine on the three days prior to (R or F-day – 3 to R or F-day – 1) and on the day ARF was detected by creatinine (R or F-day 0) in ARF patients and controls

AUC-ROC 0.82 and 0.97 on the two days before the R-criteria

NEW BIOMARKERS
Diagnosis-Biomarkers

Biomarkers and acute kidney injury: dining with the Fisher King?

searching for the Holy Grail

✓ It should distinguish pre-renal AKI from apoptotic and necrotic injury
✓ It should be specific for renal injury in the presence of concomitant injury involving other organs
✓ It should allow timing of the onset or stage of injury
✓ It should predict outcome
✓ In the end it should act as surrogate end point useful for clinical interventional studies

We did not find the troponin, we have reached level of LDH or CK at best
New biomarkers

31 articles of biomarkers for AKI included

1. Differential diagnosis in established AKI (n=14)
   - Serum (studies)
     - Cystatin C
     - Carb Hb
     - NGAL
     - IL-18
     - GST
     - NAG
     - α-1 microglobulin
     - KIM-1
     - NHE3
     - MMP-9
   - Urine (studies)

2. Early detection (n=14)
   - Serum (studies)
     - Cystatin C
     - Pro-ANP
     - NGAL
     - Neutrophil-CD11b
   - Urine (studies)

3. Prognosis (n=9)
   - Serum (studies)
   - Urine (studies)

RRT = renal replacement therapy

Numbers of studies of biomarkers do not add up to 31 because some studies tested multiple biomarkers.

Coca SG, K Int 2008
New biomarkers in septic AKI

Few clinical studies of urinary biomarkers in AKI have included septic patients. There is promising evidence that selected biomarkers may aid in the early detection of AKI in sepsis and may have value for predicting subsequent deterioration in kidney function.


OR 6.5 AKI 24 h – AUC 0.73

Neutrophil gelatinase–associated lipocalin

NGAL
New biomarkers - NGAL

Accuracy of Neutrophil Gelatinase-Associated Lipocalin (NGAL) in Diagnosis and Prognosis in Acute Kidney Injury: A Systematic Review and Meta-analysis

Michael Haase, MD, Rinaldo Bellomo, MD, Prasad Devarajan, MD, Peter Schliattmann, MD, MSc, and Anja Haase-Fielitz, PharmD, on behalf of the NGAL Meta-analysis Investigator Group

Hierarchical summary receiver operating characteristic plot of NGAL to predict in-hospital mortality and the initiation of RRT

Overall, DOR/AUC of NGAL to predict AKI was 18.6/0.815 - In critically ill patients: 10/0.728 - pNGAL = uNGAL - Better predictive ability in children 25.4/0.930

American Journal of Kidney Diseases, 2009
New biomarkers - NGAL

Plasmatic and Urinary NGAL - Differential diagnosis

Soto K et al. 2010
New biomarkers - NGAL

Discriminative ability for AKI diagnosis

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>AUC</th>
<th>95% Cl</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNGAL: T0</td>
<td>0.809</td>
<td>0.705-0.912</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T6</td>
<td>0.813</td>
<td>0.723-0.904</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T12</td>
<td>0.816</td>
<td>0.720-0.912</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T24</td>
<td>0.794</td>
<td>0.689-0.899</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T48</td>
<td>0.796</td>
<td>0.689-0.902</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UNGAL/Creat: T0</td>
<td>0.638</td>
<td>0.511-0.765</td>
<td>0.027</td>
</tr>
<tr>
<td>T6</td>
<td>0.630</td>
<td>0.511-0.750</td>
<td>0.038</td>
</tr>
<tr>
<td>T12</td>
<td>0.699</td>
<td>0.581-0.817</td>
<td>0.001</td>
</tr>
<tr>
<td>T24</td>
<td>0.735</td>
<td>0.620-0.849</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T48</td>
<td>0.741</td>
<td>0.626-0.857</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Soto K et al. 2010
New biomarkers - pNGAL

The Effect of Grade of Acute Kidney Injury and Baseline Renal Function on pNGAL diagnostic performance
Soto K¹, Coelho S¹, Rodrigues B¹, Coelho F², Frade F², Lopes S³, Papoila AL⁴, and Devarajan P⁵
EDTA 2010

<table>
<thead>
<tr>
<th>TIME</th>
<th>AUCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKI</td>
<td>&gt;AKIN2</td>
</tr>
<tr>
<td>T0</td>
<td>0.79</td>
</tr>
<tr>
<td>T6</td>
<td>0.81</td>
</tr>
<tr>
<td>T12</td>
<td>0.80</td>
</tr>
<tr>
<td>T24</td>
<td>0.80</td>
</tr>
<tr>
<td>T48</td>
<td>0.79</td>
</tr>
</tbody>
</table>
New biomarkers - NGAL

Urine Neutrophil Gelatinase-Associated Lipocalin Moderately Predicts Acute Kidney Injury in Critically Ill Adults

Edward D. Siew,* Lorraine B. Ware,† Tebeb Gebretsadik,‡ Ayumi Shintani,‡ Karel G. M. Moons,§ Nancy Wickersham,† Frederick Bossert,† and T. Alp Ikižler*  

Prediction AKI AUC 0.71 – 0.64  
Prediction sustained AKI 0.70 – 0.66  

451 pts: 14% AKI 24 h – 19% 48 h  
AKIN criteria – 71 % Stage I  
> 50% without Baseline Cr
New biomarkers - NGAL

Plasma and urine neutrophil gelatinase-associated lipocalin in septic versus non-septic acute kidney injury in critical illness

83 AKI pts (days?): 43 septic > illness (40% Neo)
Baseline Cr = between groups
NGAL > disease severity
There was no trend over time
No difference in worsening AKI or RRT

<table>
<thead>
<tr>
<th></th>
<th>pNGAL</th>
<th>uNGAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsened AKI</td>
<td>0.71</td>
<td>0.70</td>
</tr>
<tr>
<td>RRT</td>
<td>0.78</td>
<td>0.70</td>
</tr>
<tr>
<td>Death</td>
<td>0.69</td>
<td>0.62</td>
</tr>
</tbody>
</table>

AUCs for outcomes

AUC-ROC for diagnosis septic vs non-septic AKI for: a peak plasma NGAL and b peak urine NGAL
New biomarkers – Plasma NGAL

**EARLY BIOMAKER IN ICU**

AKI diagnosis before RIFLE (N ?) 68% established AKI
For AKI at 48 h AUC-ROC 0.78 and RRT 0.82
Peak pNGAL increased with worsening AKI R = 0.554
Levels pNGAL at 24-48 NS. > with disease severity
No differences in sepsis


Values according to binary RIFLE status
Increased 48 h before RIFLE
AUC for AKI diagnosis 0.96; for RRT 0.79

Constantin JM et al Journal of Critical Care 2009
NGAL correlates with the severity and outcome of acute kidney injury, but not with renal recovery.

Correlation of NGAL serum levels in 109 AKI patients with sepsis, SOFA score, levels of CPR and CysC.
New biomarkers – Angiopoietin-2

Angiopoietin-2 in patients requiring renal replacement therapy in the ICU: relation to acute kidney injury, multiple organ dysfunction syndrome and outcome

DOI 10.1007/s00134-009-1726-7

Increase with severity of illness - Predictor of 28-day mortality at inception of RRT
The Future…

Clinical practice may soon be changing… “Lock, stock and barrel”

Joannes-Boyau Intensive Care Med 2010
Tumor necrosis factor (TNF)-like weak inducer of apoptosis (TWEAK) is a cytokine of the TNF superfamily that activates the Fn14 receptor. TWEAK may regulate cell proliferation, cell death, cell differentiation, angiogenesis and inflammation. The expression of TWEAK and Fn14 is increased in tubular cells during acute kidney injury.

Cytokine cooperation in renal tubular cell injury: The role of TWEAK

P Justo, AB Sanz, MD Sanchez-Niño, JA Winkles, C Lorz, J Egido, and A Ortiz

1Fundación Jiménez Díaz, Universidad Autónoma de Madrid and Fundación Renal Irigo Alvarez de Toledo, Madrid, Spain and 2Departments of Surgery and Physiology, Center for Vascular and Inflammatory Diseases, University of Maryland School of Medicine, Baltimore, Maryland, USA
The future

Machine Learning Technique for Early Diagnosis of Acute Kidney Injury
L. Coelho1, R. Camões1, T. Ribeiro1, A. Fantoni1, J. Costa1, G. Marques1, S. Coelho2, K. Soto2
1ISEL-DEETC, Lisbon, Portugal
2Nephrology, Hospital Fernando Fonseca EPE, Lisbon, Portugal

Three-dimensional representation of the clinical diagnosis after reduction using PCA
The End...
A 65-yr-old man presented to the emergency department with a 2-d history of dyspnea and fever.

Over the next 24 hours, the patient became more tachypneic. On transfer to the ICU, respirations were 40, heart rate 130, and BP was 84/43 mmHg.

Arterial blood gas revealed pH of 7.35, pCO2 23, pO2 65 on 31% oxygen, and calculated HCO3  19.
WBC 4000
SCr 1.1 at ED admission and 0.7 at ICU with FeNa 0.4 %.

With saline infusion: oliguric