Incidence: Acute Kidney Injury (AKI)*

*AKI is the new (2012) consensus term for acute renal failure (ARF)

Xue et al JASN 2006
**Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT**

**Mortality Related to Severe Sepsis and Septic Shock Among Critically Ill Patients in Australia and New Zealand, 2000-2012**

Kirsu-Maija Kaukonen, MD, PhD, EDIC; Michael Bailey, PhD; Satoshi Suzuki, MD; David Pilcher, FCICM; Rinaldo Bellomo, MD, PhD

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**IMPORTANCE** Severe sepsis and septic shock are major causes of mortality in intensive care unit (ICU) patients. It is unknown whether progress has been made in decreasing their mortality rate.

**OBJECTIVE** To describe changes in mortality for severe sepsis with and without shock in ICU patients.

**DESIGN, SETTING, AND PARTICIPANTS** Retrospective, observational study from 2000 to 2012 including 101,064 patients with severe sepsis from 171 ICUs with various patient case mix in Australia and New Zealand.

**MAIN OUTCOMES AND MEASURES** Hospital outcome (mortality and discharge to home, to other hospital, or to rehabilitation).
Table 1. Characteristics and Outcomes in Severe Sepsis

<table>
<thead>
<tr>
<th></th>
<th>All Patients (N = 101,064)</th>
<th>Without Comorbidities(^a) (n = 64,149)</th>
<th>With Comorbidities(^a) (n = 36,915)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (95% CI), y</td>
<td>63.5 (63.3–63.6)</td>
<td>62.3 (62.2–62.5)</td>
<td>65.4 (65.3–65.6)</td>
</tr>
<tr>
<td>Male sex</td>
<td>54 (54-54)</td>
<td>53 (52-53)</td>
<td>56 (56-57)</td>
</tr>
<tr>
<td>Sepsis as admission diagnosis</td>
<td>52 (52-52)</td>
<td>50 (49-50)</td>
<td>57 (56-57)</td>
</tr>
<tr>
<td>Infection as admission diagnosis</td>
<td>48 (48-48)</td>
<td>50 (50-51)</td>
<td>43 (43-44)</td>
</tr>
<tr>
<td>APACHE III score, mean (95% CI)</td>
<td>70.9 (70.7–71.1)</td>
<td>66.6 (66.3–66.8)</td>
<td>78.4 (78.1–78.7)</td>
</tr>
<tr>
<td>APACHE III risk of death, median (IQR), %</td>
<td>21.2 (8.6–46.3)</td>
<td>16.8 (6.8–37.9)</td>
<td>30.6 (13.9–58.0)</td>
</tr>
<tr>
<td>Mechanical ventilation in ICU</td>
<td>50 (50-50)</td>
<td>52 (52-52)</td>
<td>45 (45-46)</td>
</tr>
<tr>
<td>Length of stay, median (IQR), d</td>
<td>3.2 (1.6–6.9)</td>
<td>3.2 (1.6–7.0)</td>
<td>3.1 (1.6–6.8)</td>
</tr>
<tr>
<td>ICU</td>
<td>13.5 (7.0–25.9)</td>
<td>13.2 (7.0–25.5)</td>
<td>13.8 (7.0–26.9)</td>
</tr>
<tr>
<td>Hospital</td>
<td>4 (4–4)</td>
<td>3 (3–3)</td>
<td>6 (6–7)</td>
</tr>
<tr>
<td>Limitation of treatment</td>
<td>16 (16–16)</td>
<td>13 (13–13)</td>
<td>22 (22–23)</td>
</tr>
<tr>
<td>ICU mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>24 (24–24)</td>
<td>19 (19–19)</td>
<td>33 (33–34)</td>
</tr>
<tr>
<td>Discharge to home</td>
<td>57 (57–57)</td>
<td>61 (60–61)</td>
<td>51 (50–51)</td>
</tr>
<tr>
<td>Discharge to rehabilitation(^b)</td>
<td>7 (7–7)</td>
<td>8 (8–8)</td>
<td>6 (6–6)</td>
</tr>
<tr>
<td>Discharge to other hospital</td>
<td>11 (11–11)</td>
<td>12 (12–12)</td>
<td>10 (9–10)</td>
</tr>
<tr>
<td>Subgroups</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>49 (49–49)</td>
<td>50 (50–51)</td>
<td>48 (47–48)</td>
</tr>
<tr>
<td>Septic shock</td>
<td>51 (51–51)</td>
<td>50 (49–50)</td>
<td>52 (52–53)</td>
</tr>
<tr>
<td>Medical admissions</td>
<td>77 (77–77)</td>
<td>75 (74–75)</td>
<td>82 (82–82)</td>
</tr>
<tr>
<td>Surgical admissions</td>
<td>23 (23–23)</td>
<td>25 (25–26)</td>
<td>18 (18–18)</td>
</tr>
<tr>
<td>Respiratory failure(^c)</td>
<td>45 (45–45)</td>
<td>48 (47–48)</td>
<td>40 (39–40)</td>
</tr>
<tr>
<td>Acute renal failure(^d)</td>
<td>17 (17–17)</td>
<td>15 (15–15)</td>
<td>20 (20–21)</td>
</tr>
</tbody>
</table>

Incidence of severe AKI on day 1
Acute Renal Failure in Critically Ill Patients
A Multinational, Multicenter Study

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John A. Kellum, MD
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Context Although acute renal failure (ARF) is believed to be common in the setting of critical illness and is associated with a high risk of death, little is known about its epidemiology and outcome or how these vary in different regions of the world.

Objectives To determine the period prevalence of ARF in intensive care unit (ICU) patients in multiple countries; to characterize differences in etiology, illness severity, and clinical practice; and to determine the impact of these differences on patient outcomes.

Design, Setting, and Patients Prospective observational study of ICU patients who either were treated with renal replacement therapy (RRT) or fulfilled at least 1 of the predefined criteria for ARF from September 2000 to December 2001 at 54 hospitals in 23 countries.

Main Outcome Measures Occurrence of ARF, factors contributing to etiology, illness severity, treatment, need for renal support after hospital discharge, and hospital mortality.

Results Of 29,269 critically ill patients admitted during the study period, 1,738 (5.7%; 95% confidence interval [CI], 5.5%-6.0%) had ARF during their ICU stay, including 1,260 who were treated with RRT. The most common contributing factor to ARF was septic shock (47.5%; 95% CI, 45.2%-49.5%). Approximately 30% of patients had preadmission renal dysfunction. Overall hospital mortality was 60.3% (95% CI, 58.0%-

Contributing factors (n = 1726)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septic shock</td>
<td>820 (47.5)</td>
</tr>
<tr>
<td>Major surgery</td>
<td>592 (34.3)</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>465 (26.9)</td>
</tr>
<tr>
<td>Hypovolemia</td>
<td>442 (25.6)</td>
</tr>
<tr>
<td>Drug-induced</td>
<td>328 (19.0)</td>
</tr>
<tr>
<td>Hepatorenal syndrome</td>
<td>99 (5.7)</td>
</tr>
<tr>
<td>Obstructive uropathy</td>
<td>45 (2.6)</td>
</tr>
<tr>
<td>Other</td>
<td>211 (12.2)</td>
</tr>
</tbody>
</table>
Things we really, honestly know about septic AKI

- AKI is common in septic ICU patients
- Septic AKI is responsible for about 50% of ARF in ICU
- Septic AKI is, therefore, relatively common. We should worry about it and try to understand it.
What do we mean by AKI?

- In the clinic by AKI we actually mean “loss of small solute clearance” (urea/creatinine increase in blood) and/or low urine output.
- This \textit{implies} loss of GFR.
- So...clinically we actually mean “\text{likely acute decrease in GFR}”.
- \textit{So...why does it happen?}
Why does GFR fall in sepsis?

- I thought we did not know, but luckily the **NEJM told us** (Schrier RW, Wang W. Acute renal failure in sepsis.(Review) N Engl J Med 2004; 2004; 351: 159-169)

- “...early in sepsis-related AKI, the predominant pathogenetic factor is renal vasoconstriction with intact tubular function....”
Current Dogma: Renal vasoconstriction is the first major pathogenetic event in septic AKI

- But...hang on ..in the same article: “....the hemodynamic hallmark of sepsis is **generalized arterial vasodilatation**.....”
- So... which one is true?
- **Vasoconstriction or vasodilatation?**
- It can only be vasoconstriction, right?
- How else would GFR fall?
- Well...actually......
Vasomotor GFR control: Logical principles

- GFR can decrease **if the afferent arteriole constricts** no matter with the efferent does.
- GFR can decrease **if the efferent arteriole dilates** even if the afferent stays the same.
- GFR can decrease **if the afferent arteriole dilates** but the efferent arteriole dilates even more.
- All can logically cause loss of glomerular filtration pressure.
Haemodynamic measurements in conscious sheep

- Systolic, diastolic, mean arterial pressure
- Central venous pressure
- Cardiac output, heart rate, stroke volume, maximum aortic flow, dF/dt
- Regional flows and conductances
- Urinary flow
Example of induction of sepsis: hemodynamics

Induce sepsis with E. Coli

Study period

CVP 0 to 2 mmHg
Renal vasconstriction in early sepsis???

Intensive Care Med 2003; 31: 2509-13
Impact of general anaesthesia

Figure 2c

Crit Care Med 2003; 31: 2509-13
Impact of general anaesthesia

Figure 2d

Pre sepsis  Septic Control  Norepinephrine

% Changes in Medullary Flow

Sheep 1  Sheep 2  Sheep 3  Sheep 4  Sheep 5  Sheep 6  Sheep 7  Sheep 8
Renal Blood Flow and Septic AKI

- Once we simulated the hemodynamics of human sepsis, RBF increased and renal vascular resistance decreased with simultaneous oliguria and loss of GFR.
- When we simulated profound septic shock, infusion of a powerful vasoconstrictor (norepinephrine) increased RBF and UO.
- In early (first 24 hours) experimental hyperdynamic sepsis loss of GFR occurs with renal hyperemia and vasodilatation.
New (old) Hypothesis

- Like other vascular beds the renal bed **vasodilates** in severe sepsis
- **Efferent arteriolar vasodilatation** causes loss of GFR
- Septic ARF is **at least initially** a *hyperemic* not an ischemic form of AKI
- If true... **vasoconstrictors should improve GFR in septic ARF in man**
If efferent vasodilation were true…pharmacologic efferent vasconstriction should fix things
Flow goes down
Renal blood flow in experimental septic acute renal failure

C Langenberg¹, L Wan², M Egi², CN May³ and R Bellomo²

¹Department of Nephrology, Charité Campus Mitte, Berlin, Germany; ²Department of Intensive Care and Department of Medicine, Austin Hospital and University of Melbourne, Heidelberg, Melbourne, Australia and ³Howard Florey Institute, University of Melbourne, Parkville, Melbourne, Australia
Extended sepsis

- In an extended hyperdynamic sepsis model of septic AKI:
  - 1. Creatinine increased 3 times
  - 2. RBF increased 3 times
  - 3. Renal vascular conductance increased 3 times
  - **Dissociation between flow and function!**
Proof of concept

- In early hyperdynamic mammalian sepsis or septic shock GFR can be lost in the presence of increased RBF and renal vasodilatation. Vasoconstrictors seem to help function.

Does this happen in man?
RBF in human sepsis with AKI

- Only one series in the last 40 years!
True Renal Plasma Flow (TRPF) in early sepsis

- TRPF = 154% of normal
- TPRF tightly correlated with CO
- Similar findings in humans given “pyrogen” (Combos et al. Circulation 1967; 36: 555-569)
All this was already described by Homer Smith
J Clin Invest 1945; 24: 749-758

"Derivatives of bacterial protein...lead to...a marked increase in renal blood flow, reduction in arterial pressure and an increase in cardiac index......renal hyperemia occurred in each instance studied...."
FIG. 1. SUBJECT P. H. THE SYSTEMIC AND RENAL CIRCULATORY EFFECTS OF THE PYOGENIC REACTION, NORMAL, MALE, 52 YEARS

BP, blood pressure (Hamilton manometer) in mm. Hg, the thick line being the mean pressure; HR, heart rate; SV, stroke volume in ml.; CI, cardiac index (ballistocardiograph) in liters per minute per square meter of body surface; R, peripheral resistance in dyne cm.\(^{-4}\) sec.; FF, filtration fraction (fraction of renal plasma flow filtered at the glomerulus); Cm, mannitol clearance (glomerular filtration rate in ml. per minute); Cd, diodrast clearance (renal plasma flow in ml. per minute). Values of the renal fraction (per cent of the cardiac output passing through the kidneys) are inserted below each diodrast clearance period figure; \(\degree F\), rectal temperature in degrees of Fahrenheit. The arrows at the top of the figure indicate times at which hemodynamic data were obtained. All subjects described here were premedicated with amidopyrine.
So...global flow is dissociated from function...and from histology...which is also dissociated from function in sheep and man!

- What is the mechanism for such dissociation?
- Is it really efferent arteriolar vasodilatation?
- What is happening inside the kidney?
- **Is there intra-renal shunting?**
Ultrastructural demonstration of a connection between afferent and efferent juxtamedullary glomerular arterioles

Arne Ljungqvist

Institute of Pathology, Karolinska Sjukhuset, Stockholm, Sweden

In the juxtamedullary unit, the previous observation of a direct vascular connection between the afferent and efferent vessels bypassing the glomerular tuft was confirmed. In a previous report [3], it was emphasized that in the uninjected specimen the lumen of this connecting segment is usually collapsed and that this explains why the connecting segment has been demonstrated only by workers using injection techniques [1-3, 12, 13]. This view was further
Look at this vessel!

Renal Vasculature

Glomerulus

Afferent arteriole

Efferent arteriole
The functional significance of the continuous jux-tamedullary vessel as a glomerular bypass mechanism for medullary blood flow has been discussed in detail previously [1]. The present observation that the wall of the connecting segment is devoid of smooth muscle cells suggests that this will largely passively convey the blood from the afferent to the efferent arteriole, although a certain contractile activity may well be exerted by the lacis cells to judge from their cytoplasmic
Shunting in Renal Microvasculature of the Rat: A Scanning Electron Microscopic Study of Corrosion Casts

D. CASELLAS AND A. MIMRAN
Department of Medicine D, CHR Saint-Charles, Montpellier, France
Fig. 7. Corrosion cast of a juxtamedullary glomerulus (539 g body weight). An agglomerular vessel (AV) arises from the afferent arteriole (AA) at the glomerular vascular pole. Note the presence of an efferent arteriole (EA). Bar: 100 μm. VR, vasa recta.
Fig. 2. Glomerular and peritubular microvascular connections. 3-D reconstruction of the outer portion of a surface glomeruli in a Munich-Wistar Fromter rat using 2-photon microscopy to acquire individual 1-μm planes. A 150-kDa fluorescent dextran provides the fluorescence detected only within the arteriole and capillary/venous microvasculature. Note the many connections between surface vessels and capillaries. Additional studies will be needed to interrelate the functional and anatomic aspects of these vessels and their importance in AKI.
Microcirculation: What happens in sepsis?
Long-term measurement of renal cortical and medullary tissue oxygenation and perfusion in unanesthetized sheep

Paolo Calzavacca,1,2,3 Roger G. Evans,4 Michael Bailey,5 Yugeesh R. Lankadeva,1 Rinaldo Bellomo,2 and Clive N. May1
Cortical and Medullary Tissue Perfusion and Oxygenation in Experimental Septic Acute Kidney Injury

Paolo Calzavacca (MD, PhD)\textsuperscript{1,3}, Roger G. Evans (PhD)\textsuperscript{4}, Michael Bailey\textsuperscript{5} (PhD), Rinaldo Bellomo (MD, PhD)\textsuperscript{5}, Clive N. May (PhD)\textsuperscript{1}

\begin{center}
\hspace{1cm}
\begin{tabular}{cc}
\textbf{E. coli} & \textbf{E. coli} \\
\end{tabular}
\end{center}

\begin{center}
\hspace{1cm}
\begin{tabular}{cc}
Mean Arterial Pressure (mmHg) & Heart Rate (bpm) \\
\end{tabular}
\end{center}

\begin{center}
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\begin{tabular}{cc}
Time (hours) & Time (hours) \\
\end{tabular}
\end{center}

\begin{center}
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\begin{tabular}{cc}
Total Peripheral Conductance (mL/min/mmHg) & Cardiac Output (L/min) \\
\end{tabular}
\end{center}

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\textbullet & \textbullet \\
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\end{tabular}
\end{center}
Cortico-medullary dissociation in flow and tO2
Loss of GFR

Oliguria

Decreased Na re-absorption
Increased O2 delivery

Unchanged O2 consumption

Decreased O2 extraction
Does medullary hypoxia cause structural tubular injury?
Renal Histopathology During Experimental Septic Acute Kidney Injury and Recovery

Christoph Langenberg, MD, PhD¹; Glenda Gobe, PhD²; Sally Hood, MSc¹; Clive N. May, PhD¹; Rinaldo Bellomo, MD, PhD³

Objectives: Our understanding of septic acute kidney injury is limited. We therefore assessed renal histopathological changes induced by septic acute kidney injury and their evolution during recovery.

Design: Prospective experimental study.

Setting: Physiology Research Institute.

Subjects: Twenty-two Merino sheep.

Intervention: We induced septic acute kidney injury by continuous IV infusion of *Escherichia coli*. We studied histology, immunohistochemistry, markers of apoptosis, and expression of nitric oxide synthase isoforms and hypoxia-inducible factor-1α. Analysis was performed on kidneys from normal sheep, sheep with septic acute kidney injury, and sheep after recovery from septic acute kidney injury.
DISCUSSION
Histopathological and biochemical changes, including measurement of markers of apoptosis, NOS isoforms, and HIF-1α, were assessed in the renal cortex and medulla from normal sheep, sheep after 48 hours of severe hyperdynamic sepsis, and sheep after 48-hour recovery from sepsis. Septic AKI was severe with a close to four-fold increase in serum creatinine over 48 hours. In spite of this, renal histopathology in septic animals and in animals after recovery from sepsis was indistinguishable from that in normal animals. In particular, we found no evidence of ATN or immunohistochemical evidence of macrophage or fibroblast infiltration, caspase activation, or neutrophil gelatinase-associated lipocalin expression. We also quantified apoptosis and found no increases in the septic AKI or recovery groups. Finally, we found that cortical, but not medullary, expression of all NOS isoforms was increased during septic AKI compared with the normal and recovery groups and that nNOS expression correlated with RBF. Although cortical HIF-1α expression also increased in septic AKI, it showed no correlation with RBF.
### Table 1. Human studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>Cause</th>
<th>AKI Definition</th>
<th>Method</th>
<th>AKI/Patients (%)</th>
<th>ATN (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hotchkiss [10]</td>
<td>Sepsis/septic shock</td>
<td>SCr&gt;2mg/dL and UO&lt;20mL/kg/hr x 6 hr</td>
<td>PM</td>
<td>12/20 (60)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Sato T [12]</td>
<td>Sepsis</td>
<td>NA</td>
<td>PM</td>
<td>6/6 (100)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Mustonen [9]</td>
<td>Sepsis/shock/hypovolemia</td>
<td>NA</td>
<td>Biopsy</td>
<td>57/57 (100)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Rosenberg [11]</td>
<td>Sepsis</td>
<td>SCr&gt;3.5mg/dL and U/P osm &gt;1</td>
<td>Biopsy</td>
<td>1/1 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Zappacosta [13]</td>
<td>Sepsis</td>
<td>NA</td>
<td>Biopsy</td>
<td>1/1 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Diaz de Leon [14]</td>
<td>Severe sepsis</td>
<td>SCr, Urine Output, U/P osm (not specified)</td>
<td>Biopsy</td>
<td>107/332 (32)</td>
<td>20 (50)</td>
</tr>
</tbody>
</table>

### Table 2. Primate studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>Cause</th>
<th>AKI/Animals (%)</th>
<th>ATN (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carraway [17]</td>
<td>Heat shocked E. Coli and live E. Coli</td>
<td>6/6 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Coalson [16]</td>
<td>E.coli endotoxin infusion</td>
<td>4/4 (100)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Coalson [15]</td>
<td>Live E. Coli infusion</td>
<td>3/8 (38)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Welty-Wolf [18]</td>
<td>Heat shocked E. Coli and live E. Coli/gentamicin administration</td>
<td>6/6 (100)</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Reference</td>
<td>Induction of sepsis</td>
<td>ATN</td>
<td></td>
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<tr>
<td>-----------</td>
<td>--------------------------------------------</td>
<td>-----</td>
<td></td>
</tr>
<tr>
<td>[32]</td>
<td>Salmonella enteritidis endotoxin</td>
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<td>[33]</td>
<td>CLP/LPS</td>
<td>yes</td>
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<td>[34]</td>
<td>E. coli</td>
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<tr>
<td>[35]</td>
<td>LPS induced sepsis</td>
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<td>[36]</td>
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<td>LPS induced sepsis</td>
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<td>[38]</td>
<td>E. coli septicemia</td>
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<td>[39]</td>
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<td>[40]</td>
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<td>[41]</td>
<td>CLP</td>
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<tr>
<td>[42]</td>
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<td>[35]</td>
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<tr>
<td>[43]</td>
<td>LPS induced sepsis</td>
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</table>
Mechanisms of Cardiac and Renal Dysfunction in Patients Dying of Sepsis

Osamu Takasu*, Joseph P. Gaut*, Eizo Watanabe, Kathleen To, R. Eliot Fagley, Brian Sato, Steve Jarman, Igor R. Efimov, Deborah L. Janks, Anil Srivastava, Sam B. Bhayani, Anne Drewry, Paul E. Swanson, and Richard S. Hotchkiss

Am J Respir Crit Care Med Vol 187, Iss. 5, pp 509–517, Mar 1, 2013

patients with sepsis-induced cardiac and renal failure. The vast majority of septic patients (32 of 38) were in shock, requiring the use of inotropic agents and/or vasopressors to maintain adequate mean arterial pressure and/or oxygen delivery (Table
Renal tubular injury is common in sepsis but presents focally; renal tubular regeneration possibly driven by mTOR also appears to be occurring. Renal tubular cell death occurs by necrosis and not by apoptosis or autophagy. Calcium phosphate crystals occur in renal tubules in approximately 50% of patients and may be contributing to renal failure. Although in some septic patients the degree of renal tubular injury was sufficient to explain renal failure, in most septic patients the majority of renal tubular cells appeared normal by light microscopy. Thus, the degree of cell injury and death may not account for the severity of renal failure in all patients with sepsis. This suggests that much of the organ injury is potentially reversible and that efforts to control infection and improve host immunity could decrease mortality.
What about bioenergetic failure despite high flows?
Renal Flow and Mean Arterial Pressure change over time in Septic Coil sheep

1st Injection of E. coli
2nd Injection of E. coli

IV KCl

IJAO 2005
Start

Sepsis

Immediately After CA

15 minutes of CA
Renal bioenergetics during early gram-negative mammalian sepsis and angiotensin II infusion

No bioenergetic Problems even with vasoconstrictors Like Angiotensin II
Measurement of renal blood flow by phase-contrast magnetic resonance imaging during septic acute kidney injury: A pilot investigation

John R. Prowle, MB, BChir, MRCP, FFICM; Maurice P. Molan, MBBS, FRACR; Emma Hornsey, BSc; Rinaldo Bellomo, MD, FCICM

Objective: In septic patients, decreased renal perfusion is considered to play a major role in the pathogenesis of acute kidney injury. However, the accurate measurement of renal blood flow in such patients is problematic and invasive. We sought to overcome such obstacles by measuring renal blood flow in septic patients with acute kidney injury using cine phase-contrast magnetic resonance imaging.

Design: Pilot observational study.

Setting: University-affiliated general adult intensive care unit.

Patients: Ten adult patients with established septic acute kidney injury and 11 normal volunteers.

Interventions: Cine phase-contrast magnetic resonance imaging measurement of renal blood flow and cardiac output.

Measurements and Main Results: The median age of the study patients was 62.5 yrs and eight were male. At the time of magnetic resonance imaging, eight patients were mechanically ventilated, nine were on continuous hemofiltration, and five required vasoressors. Cine phase-contrast magnetic resonance imaging examinations were carried out without complication. Median renal blood flow was 482 mL/min (range 335–1137) in septic acute kidney injury and 1260 mL/min (range 791–1750) in healthy controls ($p = .003$). Renal blood flow indexed to body surface area was 244 mL/min/m$^2$ (range 165–662) in septic acute kidney injury and 525 mL/min/m$^2$ (range 438–869) in controls ($p = .004$). In patients with septic acute kidney injury, median cardiac index was 3.5 L/min/m$^2$ (range 1.6–8.7), and median renal fraction of cardiac output was only 7.1% (range 4.4–10.8). There was no rank correlation between renal blood flow index and creatinine clearance in patients with septic acute kidney injury ($r = .26, p = .45$).

Conclusions: Cine phase-contrast magnetic resonance imaging can be used to noninvasively and safely assess renal perfusion during critical illness in man. Near-simultaneous accurate measurement of cardiac output enables organ blood flow to be assessed in the context of the global circulation. Renal blood flow seems consistently reduced as a fraction of cardiac output in established septic acute kidney injury. Cine phase-contrast magnetic resonance imaging may be a valuable tool to further investigate renal blood flow and the effects of therapies on renal blood flow in critical illness. (Crit Care Med 2012; 40:000–000)

Key Words: acute kidney injury; cine phase-contrast; critical care; magnetic resonance imaging; renal blood flow; sepsis
Oops...renal blood flow is dissociated from GFR!
Renal Blood Flow Index

ml/min/m²

AKI 1  AKI 2  AKI 3  AKI 4  AKI 5  AKI 6  AKI 7  AKI 8  HRS 1  HRS 2  Normals

Arrows indicate significant differences in renal blood flow index between groups.
Toll-Like Receptor 4 Inhibitor TAK-242 Attenuates Acute Kidney Injury in Endotoxemic Sheep

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Background: This study was conducted to investigate the role of toll-like receptor 4 (TLR4) in mediating acute kidney injury in endotoxemic sheep using the selective TLR4 inhibitor TAK-242.

Methods: A randomized, controlled, experimental study was performed with 20 adult Texel crossbred sheep. Before an Escherichia coli lipopolysaccharide infusion (3 μg · kg⁻¹ · h⁻¹ for 24 h), sheep were randomized to receive a bolus dose (2 mg/kg), followed by a continuous infusion (4 mg · kg⁻¹ · 24 h⁻¹) of either TAK-242 (n = 7) or vehicle (n = 7). A third group of lipopolysaccharide-treated sheep (n = 6) received norepinephrine, titrated to maintain baseline arterial blood pressure.
Conclusions

- Global renal blood flow in sepsis may initially be high driven by renal vasodilatation.
- What drives such vasodilatation remains unknown.
- Function, microvascular flow, tissue O2 and histology are dissociated.
- They may be dissociated because of decreased filtration pressure or because of shunting or both.
- Knowing about the macro-circulation is not enough and AKI may mostly be a disease of the micro-circulation.
Is it all about hemodynamics?

- If it is, all we need to do is constricts the efferent arteriole (without constricting the afferent arteriole)
- It seems far too "simple"
- Sepsis is a complex and toxic state
- This data only relates to the first 24-48 hrs
- It is mostly from models
- Much more is likely to be at work
We generally do not know or understand the histology or pathogenesis of AKI in man.

However, we need to consider treating septic AKI as a specific entity.

We need to stop pretending that experimental total ischemia (renal artery clamp) models of AKI tell us what happens in septic AKI.

We need to start questioning old paradigms.
Reflections for those who still believe that ischemia causes septic AKI, that giving more fluid will fix things, and that ATN is the histology of AKI

- The difficulties lie not in new ideas, but in escaping old ones... which ramify into every corner of our minds (John Maynard Keynes)
- Doubt is not a pleasant condition, but certainty is absurd (Voltaire)
- Doubt is one of the names of intelligence (Jorge Luis Borges)