Acute Kidney Injury in Sepsis

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Disclosures

• I have received speaking, consultation and grant fees from
  • Baxter
  • BBraun
  • Edwards Lifesciences
Septic AKI is the most common form of severe AKI in developed countries.
It makes up >50% of all cases of severe AKI in ICU.
If combined with the need to deliver RRT, it carries a >50% mortality.
There is no specific therapy. Only treatment of septic focus and supportive care.
A major problem in developing therapies arises from our limited understanding of its pathogenesis.
Why limited understanding?

- Can’t get tissue
- Can’t monitor global blood flow
- Can’t monitor regional renal blood flow
- Urinary flow is of limited information
- Urinary biochemistry is of limited value
- Urinary microscopy is of limited value
- Functional measured become abnormal only when >50% of function is lost
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

MAP-SC
HR-SC
CO-SC
In experimental gram negative bacteremia with AKI, RBF increased and renal vascular resistance decreased with simultaneous oliguria and loss of GFR.

In early (first 24 hours) experimental hyperdynamic sepsis loss of GFR occurs with renal hyperemia and vasodilatation.
Hypothesis

- Like other vascular beds the renal bed vasodilates in severe sepsis
- Efferent arteriolar vasodilatation may cause such loss of GFR
- Septic ARF is at least initially a hyperemic not an ischemic form of AKI
- Loss of function (loss of GFR) is due to decreased filtration pressure
- If true.... vasoconstrictors should improve GFR in septic ARF
If efferent vasodilation were true....pharmacologic efferent vasconstriction should improve function
Flow goes down
Proof of concept

- In early hyperdynamic mammalian sepsis or septic shock function (GFR) can be lost in the presence of increased RBF and renal vasodilatation.
- Ang II seems to help function.

Does this happens 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 and Smith H in J Lab Clin Invest 1945)
So...global flow appears dissociated from function...

- What is the mechanism for such dissociation?
- Is it really efferent arteriolar vasodilatation?
- What is happening inside the kidney?
- Is this a model dependent finding?
Measurement of renal blood flow by phase-contrast magnetic resonance imaging during septic acute kidney injury: A pilot investigation

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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 function (GFR)!
Microcirculatory changes as the cause of loss of function
Cortical and Medullary Tissue Perfusion and Oxygenation in Experimental Septic Acute Kidney Injury

Paolo Calzavacca, MD, PhD¹,²,³,⁴; Roger G. Evans, PhD⁵; Michael Bailey, PhD⁶; Rinaldo Bellomo, MD, PhD²,³; Clive N. May, PhD¹

(Crit Care Med 2015)
The septic kidney: global renal blood flow
Intra-renal oxygenation
Cortico-medullary dissociation

Knowing global
Or even intra-renal blood flow says little about medullary oxygenation

Also simultaneous major fall in GFR!
Shunting in Renal Microvasculature of the Rat: A Scanning Electron Microscopic Study of Corrosion Casts

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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.
Intrarenal and urinary oxygenation during norepinephrine resuscitation in ovine septic acute kidney injury

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![Graphs showing changes in urinary flow, plasma creatinine, creatinine clearance, and fractional Na+ excretion over time.](image_url)
Urinary O2 below 20 mmHg with norepinephrine infusion
PuO2 in patients with Septic AKI

PuO2 is similar to what is seen in septic sheep
Objectives: The histopathologic changes associated with septic acute kidney injury are poorly understood, in part, because of the lack of biopsy data in humans. Animal models of septic acute kidney injury may help define such changes. Therefore, we performed a systematic review of the histopathologic changes found in modern experimental septic acute kidney injury models.

Data Sources: MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature, and PubMed (from January 2007 to February 2015).
455 potentially relevant citations identified and screened for retrieval

154 citations excluded
   - Not relevant type of articles (n=103)
   - Not experimental study (n=2)
   - Cell culture experiments (n=10)
   - Study about other organ (n=39)

301 unique abstracts retrieved for detailed evaluation of study design

129 abstracts excluded
   - No use of sepsis model (n=112)
   - Sepsis with other diseases (n=10)
   - Two-hit model; sepsis + hemorrhage (n=4)
   - No acute kidney injury (n=3)

172 unique articles retrieved for detailed evaluation of study detail

70 articles excluded
   - No description of histopathology (n=63)
   - Number of animals (n=7)

102 articles included in systematic review

Figure 1. Flow diagram summarizing article selection and reasons for exclusion.
There are tubular changes but they are "bland" given the loss of GFR

Figure 4. Percentage of acute tubular necrosis (ATN) and other histopathologic changes in septic acute kidney injury. ATN (n = 184 animals), vacuolization (n = 423), loss of brush border (n = 250), swelling (n = 243), sloughing (n = 60), cast formation (n = 127), tubular dilation (n = 183), and leukocyte infiltration (n = 205).
Mechanisms of Cardiac and Renal Dysfunction in Patients Dying of Sepsis

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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.
**Rationale:** It is unclear how septic shock causes acute kidney injury (AKI) and whether this is associated with histological change.

**Objectives:** We aimed to determine the nature and extent of changes in renal structure and function over time in an ovine model of septic shock.

**Methods:** Fifteen sheep were instrumented with a renal artery flow probe and renal vein cannula. Ten were given intravenous *Escherichia coli* to induce septic shock, and five acted as controls. Animals were mechanically ventilated for 48 hours, while receiving protocol-guided parenteral fluids and a norepinephrine infusion to maintain mean arterial pressure. Renal biopsies were taken every 24 hours or whenever animals were oliguric for 2 hours. A renal pathologist, blinded to tissue source, systematically quantified histological appearance by light and electron microscopy for 31 prespecified structural changes.
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<td>Non Septic</td>
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<td>Septic</td>
<td>Non Septic</td>
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<td>Time of biopsy after E. coli</td>
<td>0 hrs</td>
<td>0 hrs</td>
<td>24 hrs</td>
<td>21 ± 4 hrs</td>
<td>48 hrs</td>
<td>42 ± 10 hrs</td>
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<td>Number of animals biopsied</td>
<td>n=5</td>
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<td>n=5</td>
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<td>Urine Output preceding each biopsy (mL/kg/hr)</td>
<td>1.5 ± 0.8</td>
<td>0.6 ± 0.5</td>
<td>1.8 ± 1.1</td>
<td>0.3 ± 0.4</td>
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**Necrosis**

- 1st Biopsy
- 2nd Biopsy
- 3rd Biopsy

** Basement Membrane Thickening**

- 1st Biopsy
- 2nd Biopsy
- 3rd Biopsy
B

Mesangial Expansion (EM) *

Basement Membrane Deposit

Basement Membrane Thinning

Basement Membrane Thick (EM)
Global renal blood flow in Gram negative sepsis may initially be high driven by decreased vascular resistance.

What drives such vasodilatation remains unknown but may include shunting and efferent vasodilatation.

Human data suggest that global blood flow and function are dissociated and both renal blood flow and function are dissociated from histology and that ATN is uncommon.
Knowing about the macro-circulation may not be enough and AKI may mostly be a disease of the micro-circulation.

Urinary O2 may provide a window on such microcirculatory changes.

But if they exist and we can indirectly observe their consequences on medullary O2, can we manipulate them?