Renal failure in sepsis and septic shock

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Incidence and predictors of ARF


ARF + Sepsis

- Incidence:
  - 3-d after the beginning of sepsis: 16-24%
  - pH < 7.30 = 6 times
  - S. Creatinine > 1 mg/dl = 7.5 times

ARF + Sepsis

- RRT: 6 times higher mortality
- fluids and vasoactive drugs
- LOS
- ventilator days
- mortality
**GFR Criteria**

- Increased S. Creat x 1.5 or GFR decrease >25%
- Increased S. Creat x 1.5 or GFR decrease >50%
- Increased S. Creat x 3 or GFR decrease >75% or S. Creat >4mg/dl

**U O Criteria**

- UO <0.5ml/kg/h x 6h
- UO <0.5ml/kg/h x 12hr
- UO < 0.3ml/kg/h x 24hr or anuria >12h

**RIFLE Criteria**

- Risk
- Injury
- Failure
- Loss
- ESKD

- Persistent ARF**, complete loss of kidney function > 4 weeks
- End Stage Kidney Disease > 3 months

**High Sensitivity**

**High Specificity**
<table>
<thead>
<tr>
<th>AKI stage</th>
<th>Serum Creatinine criteria</th>
<th>Urine output criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5-1.9 times baseline OR ≥0.3 mg/dl (≥ 26.5 μmol/l) increase</td>
<td>&lt;0.5 ml/kg/h for 6-12 hours</td>
</tr>
<tr>
<td>2</td>
<td>2.0-2.9 times baseline</td>
<td>&lt;0.5 ml/kg/h for ≥12 hours</td>
</tr>
<tr>
<td>3</td>
<td>3.0 times baseline S. creatinine to ≥4.0 mg/dl initiation of RRT patients &lt;18 years, eGFR to &lt;35 ml/min per 1.73 m²</td>
<td>&lt;0.3 ml/kg/h for ≥ 24 hours OR Anuria for ≥12 hours</td>
</tr>
</tbody>
</table>
Can AKI in turn be a cause of sepsis?

<table>
<thead>
<tr>
<th>Number 618</th>
<th>Sepsis before AKI</th>
<th>Sepsis after AKI</th>
<th>Sepsis free AKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>patients</td>
<td>174 (28%)</td>
<td>243 (40%)</td>
<td>194 (32%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mortality</th>
<th>48%</th>
<th>44%</th>
<th>21%</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRT</td>
<td>72%</td>
<td>70%</td>
<td>50%</td>
</tr>
<tr>
<td>LOS</td>
<td>38</td>
<td>37</td>
<td>27</td>
</tr>
<tr>
<td>Renal recovery</td>
<td>46</td>
<td>43</td>
<td>52</td>
</tr>
</tbody>
</table>

Conclusion: Sepsis frequently develops after AKI and portends a poor prognosis, with high mortality rates and relatively long LOS.
Pathogenesis of AKI in Sepsis

Ischemic insult

Hemodynamic changes
- Hypoperfusion
- Global and regional
- Ischemia reperfusion
- microthrombi

Systemic Inflammation
- LPS/Endotoxin
- Direct/Indirect cytokines
  - hypoxia
  - oxidative stress toxicity
  - NO
  - endothelial dysfunction

Renal cell injury
- Sublethal injury
- Apoptosis and necrosis

Sepsis
- Toxins
  - Exogenous
  - Heme proteins
  - Antibiotics
  - Contrast media
  - Vasopressors

Renal repair and regeneration

Cell loss
Why Renal failure is bad in sepsis

- Uremia impairs
  - immune system leading to pneumonia and sepsis
  - cytokine regulation, and vascular permeability
  - Impaired monocyte cytokine production

- AKI requiring dialysis
  - increased risk of bacteremia
  - endocarditis through CVC or PD
  - increases length of stay in the hospital
Functional biomarkers
- serum creatinine
- Cystatin C

Damage biomarkers
- urinary albumin
- neutrophil gelatinase-associated lipocalin
- interleukin-18
- KIM-1 (Kidney injury molecule-1)
- L-FABP (Liver-type Fatty acid-binding protein-1)
- TIMP-2 (Tissue inhibitor of metalloproteinases-2)
- IGFBP7 (Insulin-like growth factor binding protein7)

Rise in S. Creatinine is late feature
Management of ARF in septic shock

1. Prevent: Antibiotics induced ARF
2. antibiotics
3. Volume expansion
4. Vasopressor of choice
5. Insulin: normalization of blood glucose
6. Inhibit inflammatory mediators
7. Renal replacement therapy
Prevent: Antibiotics induced ARF

- **Aminoglycosides**
  - incidence of ARF 5-25%
  - monitoring? (rise in trough!)
  - thrice-daily regime vs once daily
    - ARF = 24% to 5%

- **Antifungal agent**
  - Fluid hydration
  - liposomal vs conventional amphotericin B
    - ARF = 12% vs 26%
Antibiotic administration

Early administration with in an hour or < 6 hours

Acute kidney injury in septic shock: clinical outcomes and impact of duration of hypotension prior to initiation of antimicrobial therapy

Intensive Care Med 2009

4,532 patients with septic shock (1989 to 2005)

Early AKI 64.4% (< 24 hr after onset of hypotension)

Delay in administration of antibiotics

Increased incidence of AKI

Increased mortality
Volume expansion to prevent ARF

- **Surviving Sepsis Campaign**
  - Early Goal-directed Therapy: volume and pressor
  - MAP 65 mmHg
  - CVP 8 to 12 mmHg (12 to 15 mm Hg in IPPV)


Higher CVP in the first 24 hours of ICU admission with septic shock was associated with increased risk for development or persistence of AKI over the next 5 days.
Simon Finfer: *A comparison of albumin and saline for fluid resuscitation in the ICU (SAFE) trial.*


<table>
<thead>
<tr>
<th></th>
<th>Albumin</th>
<th>Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>3497</td>
<td>3500</td>
</tr>
<tr>
<td>Mortality (28-d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>20.9%</td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td>21.1%</td>
<td></td>
</tr>
</tbody>
</table>

No Difference

Between single organ and MODS
Number of days spent in ICU
Mechanical ventilation
**Incidence of renal impairment**
Duration of renal replacement therapy
Which Crystalloid?


Conclusion: Implementation of chloride-restrictive strategy in ICU was associated with a significant decrease in the incidence of AKI and use of RRT.

Annals of Surgery 2012 Editorial

Intravenous 0.9% Saline and General Surgical Patients
A problem, Not a Solution
Dileeep N. Lobo, DM, FRCS, FACS

Editorial

Should “Normal” Saline Be Our Usual Choice in Normal Surgical Patients? Anesth Analg 2013
Colloids and ARF


Fluid resuscitation with HES in patients with sepsis is associated with an increased incidence of AKI and use of RRT: a systematic review and meta-analysis of the literature. J Crit Care 2014

Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis. JAMA 2013

Conclusion: Septic patients treated with HES

Develop more AKI
Require more RRT
Increased risk of mortality
Vasopressor of choice: Norepinephrine


- Venoconstriction (increasing preload)
- Arterial constriction
- Positive inotropy (improved cardiac output)
- Improved renal perfusion
### Intensive Insulin Therapy in critically ill


<table>
<thead>
<tr>
<th></th>
<th>Conventional</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number = 1548</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>783</td>
<td>765</td>
</tr>
<tr>
<td>BSL mmol/L</td>
<td>10 to 11</td>
<td>4.4 to 6.1</td>
</tr>
<tr>
<td>Death</td>
<td>63 (8%)</td>
<td>35 (4.6%)</td>
</tr>
<tr>
<td><strong>Renal impairment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine &gt;221 μmol/L</td>
<td>96 (12.3%)</td>
<td>69 (9%)</td>
</tr>
<tr>
<td>BUN &gt; 19.2 mmol/L</td>
<td>88 (11.2%)</td>
<td>59 (7.7%)</td>
</tr>
<tr>
<td>RRT</td>
<td>64 (8.2%)</td>
<td>37 (4.8%)</td>
</tr>
</tbody>
</table>
Hemodynamic stability: HD or CRRT?

- Intermittent versus Continuous RRT
  No difference: Hypotension or need for Vasopressor
  Lower likelihood of chronic dialysis with CRRT

- Early or late CRRT
  No Difference

- High volume ultrafiltration
  No difference renal recovery or 28-d mortality

- Extracorporeal inflammatory mediator removal
  No difference renal recovery or 28-d mortality
Future: Prevention and treatment of Acute Renal Failure in Sepsis

- Identify high-risk patients at earlier stages of renal injury
- Targeted treatment of AKI
- Novel biomarker and imaging studies for early injury
- Surveillance of septic AKI in hospitalized patients
Question?

145 septic AKI patients
CVVHF or EDHF

CVVHF: higher recovery of renal function (50.77% vs 32.50%)
Faster renal recovery (17.26 d vs 25.46 d)
Mortality similar
Increased risk of hypophosphatemia

Conclusions: Patients undergoing CVVHF had significantly improved renal recovery. The patients with septic AKI had similar 60-day all-cause mortality rates, regardless of type of RRT.
Extracorporeal inflammatory mediator removal

- Removal of Cytokines and nonselective mediators

Problems
- removal of inflammatory and antiinflammatory mediators
- cytokines: removal by absorption. rapid saturation: dialyser
- high endogenous turnover of cytokines

- requirement: highly permeable membrane (sieving coefficient 1)
- high UF rate (more than 2 L/h)
- half-life of the substance is > 60 min

Conclusion: It is unclear which mediators should be removed at which time point and under which conditions
ARF is heterogeneous
sepsis ± radiocontrast ± ischemia ± drugs
treatment of ARF in sepsis: gloomy

**Take home message**

**Fluids**
- no consensus (volume)

**Diuretics**
- oliguric to nonoliguric

**RRT**
- no difference between
  - CRRT vs IHD

**Normoglycemia**

**Vasopressor**

**Say NO!**

- dopamine
- nitric oxide
- ANP
- anti TNF-α
- PAF
- inhibition of AA
- growth hormone

**Say Yes**
Pathophysiology of ARF in sepsis

- Release of inflammatory mediators
- Leukocyte-endothelial interactions
- Dysfunction: coagulation / fibrinolytic cascade
- Release of oxygen radicals
- Dominance of vasoconstrictory substances
- Rennin-angiotensin + vasopressin
- Epinephrine and norepinephrine

Medulla
Inhibition of Platelet-Activating Factor

LPS and TNF-α

- mesangial cells
- leukocytes
- endothelial cells

Synthesis of PAF

- Vasoactive
- Platelet aggregating
- Pro-inflammatory

Serum
Urine
GFR
Endothelin antagonism

Endotoxin and TNF-α

Endothelin-1 (ET-1)

Vasoconstrictor

RBF and GFR.

Animals: Not encouraging
Humans: No studies
Norepinephrine vs Dopamine

Martin C et al. *Norepinephrine or dopamine for the treatment of hyperdynamic septic shock.*
*Chest* 1993; 103: 1826-1831

- **dopamine** = 2.5 to 25 μcg /kg/min
- **norepinephrine** = 0.5 to 5.0 μcg /kg/min

**Target Values:** SVRI > 1,100 or MBP > 80 mm Hg,
CI > 4.0 L/min/m², DO₂I > 550, VO₂I > 150ml/min/m²

Responders **dopamine** 31 % **norepinephrine** 93 %

**Conclusion:** *norepinephrine was more effective than dopamine to reverse the abnormalities of septic shock.*
Can Vasopressin reduce the need for vasopressor?

Secretion: Posterior pituitary activation of $V_{ia}$ receptor: $\uparrow$ SVR, urine output

vasopressin deficiency in septic shock


Anesthesiology 2002; 96:576-582 (RCT = 24)

DB-RCT 4-h norepinephrine or vasopressin

Conclusion: *short-term vasopressin infusion spared vasopressor use and improved renal function*
Fraction of patients who developed AKI as a function of minimum blood pressure in the 48-hour target window. N = 3,658 (34% AKI).

Hypotension as a Risk Factor for Acute Kidney Injury in ICU Patients
Fraction of patients who developed AKI as a function of hypotension duration in the target 48-hour window using various MAP values as thresholds. A third of the 3613 patients included in this plot developed AKI, as indicated by the black dashed line. Prolonged hypotension increased the incidence of AKI in these patients. The duration of hypotension associated with a 5% increase in AKI incidence (indicated by the dotted blue line) varies with severity of hypotension (see text).
Hypotension as a Risk Factor for Acute Kidney Injury in ICU Patients

Mean arterial blood pressure up to 3 days prior to AKI onset for the AKI cohort, or prior to the last creatinine measurement time for the no AKI group. Plot shows mean and standard error of patients’ median MAP in 3-hour bins. Circadian variations are apparent and reflect the timing of the creatinine measurements, which are usually taken in the early morning.
Acute renal failure in sepsis

Presentation

Hospital acquired

1. Sepsis → AKI
2. Sepsis → AKI → Sepsis + AKI
3. AKI → Sepsis
Hemodynamic stability:
Intermittent HD or CRRT?


No difference: Hypotension or need for Vasopressor
Early or delayed RRT


Number 106 patients

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Mode</th>
<th>HF /day per 24hr</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>35</td>
<td>high-volume HF</td>
<td>72–96 L</td>
<td>74.3%</td>
</tr>
<tr>
<td>35</td>
<td>early low-volume HF</td>
<td>24–36 L</td>
<td>68.8%</td>
</tr>
<tr>
<td>36</td>
<td>late low-volume HF</td>
<td>24–36 L</td>
<td>75%</td>
</tr>
</tbody>
</table>

Conclusion: Critically ill patients with oliguric ARF, survival at 28 days and recovery of renal function were not improved using high ultrafiltrate volumes or early initiation of hemofiltration
Which is better CRRT or IHD?


Conclusion: Compared with intermittent HD, initiation of CRRT in critically ill adults with AKI is associated with a lower likelihood of chronic dialysis.
High-volume hemofiltration (HVHF)


<table>
<thead>
<tr>
<th>N = 425</th>
<th>20 mL/h/kg</th>
<th>35 mL/kg/h</th>
<th>45 mL/kg/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>41%</td>
<td>57%</td>
<td>58%</td>
</tr>
</tbody>
</table>

Bouman CS et al. *Effects of early high-volume CVVH on survival and recovery of renal function in IC patients with ARF.* Crit Care Med 2003; 30:2205 (Number = 106)

No difference renal recovery or 28-d mortality

**Conclusion:** at present HVHF is not recommended