Acute renal failure in sepsis

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Sepsis and mortality

Netherlands 8500 - 9000 cases of severe sepsis/yr
## ARF in sepsis

<table>
<thead>
<tr>
<th></th>
<th>Moderate sepsis</th>
<th>Severe sepsis</th>
<th>Septic shock</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute renal failure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive culture</td>
<td>19%</td>
<td>23%</td>
<td>51%</td>
</tr>
<tr>
<td>Negative culture</td>
<td>5%</td>
<td>16%</td>
<td>38%</td>
</tr>
<tr>
<td><strong>ARDS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive culture</td>
<td>6%</td>
<td>8%</td>
<td>18%</td>
</tr>
<tr>
<td>Negative culture</td>
<td>3%</td>
<td>4%</td>
<td>18%</td>
</tr>
</tbody>
</table>
ARF in sepsis

- Mortality 50 - 70%
- Pathophysiology is complex and includes hemodynamic changes and renal inflammation
- Predominant afferent constriction
- High risk with NSAID's, ACEi
- Tubular function initially intact

Schrier RW. N Engl J Med 2004;351:159-169
Renal blood flow in human sepsis

<table>
<thead>
<tr>
<th>PAH-RPF/true RPF (n/n)</th>
<th>PAH-RPF (ml/min)</th>
<th>True RPF (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 (0)</td>
<td>-</td>
<td>690</td>
</tr>
<tr>
<td>40 (11)</td>
<td>475</td>
<td>1116</td>
</tr>
<tr>
<td>22 (6)</td>
<td>474</td>
<td>1238</td>
</tr>
</tbody>
</table>

True RPF includes renal vein sampling for PAH - normal RPF 600 - 700 ml/min)
Renal blood flow after endotoxin infusion

Schaller G. Crit Care Med 2007;35:1869-1875
Hypothesis from animal experiments

- Sepsis
- iNOS ↑
- eNOS ↓
- Cellular damage
- NO ↑
- Local inflammation
- Cellular damage
- **Urine**
  - Creatinine and urea → Clearance
  - GST-α and GST-π (ELISA)
  - NO metabolites (nitrate, nitrite)

- **Blood**
  - Creatinine and urea → Clearance
  - Cytokines (TNF-α, IL-β)
  - C-Reactive Protein
  - Leukocytes and trombocytes
  - NO metabolites (nitrate, nitrite)

**Isolation**
- Protein
- RNA
- Western blot
- Real Time PCR
- Expression iNOS
Early renal damage

Correlation between cumulative NOx excretion and GST A1
(r = 0.67, p = 0.013)

NOx excretion and renal damage

Correlation between cumulative NOx excretion and GST A1 only after LPS ($r = 0.67$, $p = 0.013$)

Human septic shock

A

B

**Kidney function**

<table>
<thead>
<tr>
<th></th>
<th>Time</th>
<th>AP (n=10)</th>
<th>Placebo (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total urine volume (ml)</td>
<td>0-24 h</td>
<td>1876 [940-2227]</td>
<td>1470 [1115-2775]</td>
</tr>
<tr>
<td>Protein excretion (mg/day)</td>
<td>0-24 h</td>
<td>454 [330-533]</td>
<td>447 [414-769]</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>Baseline</td>
<td>54 [24-84]</td>
<td>80 [77-91]</td>
</tr>
<tr>
<td></td>
<td>0-24 h</td>
<td>76 [25-101] *</td>
<td>59 [45-59]</td>
</tr>
</tbody>
</table>

Data are expressed as median [25-75% range]. *P<0.05, significantly different compared to the placebo group.

Methylene blue

- Nine patients with norepinephrine refractory septic shock
- Infusion of methylene blue 1 mg/kg/hr for 4 hrs
- 90% decrease in urinary NO metabolites
- Decrease in GST-A1 and GST-P1 of 45 and 70%
- Increase in creatinine clearance of 51%
What does not work?

- Frusemide
- Low dose dopamine
- N-Acetyl Cysteine
Autoregulation

Normal autoregulation of GFR

Normotensive renal failure

GFR (% of normal rate)

Mean Arterial Pressure (mm Hg)
Optimal MAP in sepsis

<table>
<thead>
<tr>
<th></th>
<th>MAP 65</th>
<th>MAP 75</th>
<th>MAP 85</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate (mmol/l)</td>
<td>3.1 ± 0.9</td>
<td>2.9 ± 0.8</td>
<td>3.0 ± 0.9</td>
</tr>
<tr>
<td>Urine (ml/hr)</td>
<td>49 ± 18</td>
<td>56 ± 21</td>
<td>43 ± 13</td>
</tr>
<tr>
<td>Capillary blood flow (ml/min/100 gr)</td>
<td>6.0 ± 1.6</td>
<td>5.8 ± 1.2</td>
<td>5.3 ± 0.9</td>
</tr>
<tr>
<td>PiCO2 (mm Hg)</td>
<td>41 ± 2</td>
<td>47 ± 2</td>
<td>46 ± 2</td>
</tr>
<tr>
<td>Pa-PiCO2 (mm Hg)</td>
<td>13 ± 3</td>
<td>17 ± 3</td>
<td>16 ± 3</td>
</tr>
</tbody>
</table>

LeDoux D. Crit Care Med 2000;28:2729-2732
Optimal MAP in sepsis

Bourgoin A. Crit Care Med 2005;33:780-786
Renal Resistive Index

Renal resistive index (PSV-EDV)/PSV

Deruddre S. Intensive Care Med 2007;33:1557-1562
Conclusions

• Local renal iNOS activation and NO production play a possible role in sepsis-induced acute kidney injury

• This opens new possibilities for the prevention and treatment of acute kidney injury

• Second study with alkaline phosphatase recently started