How to resuscitate the patient in early sepsis?

A physiological approach

J.G. van der Hoeven, Nijmegen
Disclosure interests speaker

<table>
<thead>
<tr>
<th>(potential) conflict of interest</th>
<th>None / See below</th>
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<tbody>
<tr>
<td>Potentially relevant relationships with companies</td>
<td>Company names</td>
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<tr>
<td>• Sponsorship or grant for research</td>
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<td>• Fee or other (financial) compensation</td>
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<td>• Shareholder</td>
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<td>• Other relationship, ........</td>
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Overall it must be simple...

Host response → Septic Shock

Circulatory failure that results in inadequate cellular oxygen utilization

Treatment goal...

Restore tissue oxygenation
Unfortunately…

- Inadequate O\(_2\) delivery on a macrocirculatory level
- Inadequate O\(_2\) delivery on a microcirculatory level
- Inadequate O\(_2\) utilization (mitochondrial dysfunction)

**Oxygen delivery (DO\(_2\)) = CO × Hb × SaO\(_2\)**
Arterial and venous vasodilatation
Increased capillary permeability

Absolute/relative hypovolemia

Cardiodepressant factors
Microcirculatory disturbances

Systolic/diastolic dysfunction

Increased NO, vasopressin deficiency, IDO activation

Vasodilatation Hypotension

Insufficient perfusion pressure / low DO₂
Change in $P_{ra}$ and $P_{pericard}$ after fluid challenge

$\Delta P_{ra} = 0.99 \Delta P_{pericard} + 0.69$

Cardiac surgery
$N = 9$
FC op to 2.1 L

Taberg JV. Circulation 1986;3: 428-432
Normal RV works below its stressed volume

Conformational changes

Increase in MSFP and venous return
Important consequence

- If increasing RV volume increases RV preload and thus RV distending pressure, the RV is either hypertrophied with diastolic dysfunction or over distended as in acute cor pulmonale.

Any increase in CVP is abnormal!
Hagen-Poiseuille equation

\[ \text{Flow} = \frac{\Delta P \times r^4}{\eta \times L} \]
Does CVP ↑ play a role in organ hypoperfusion?

- **Arterial constriction**

- **Low oncotic pressure**
  - Increased capillary permeability
  - Plasma protein leak
  - Hypoalbuminaemia

- **Normal interstitium**

- **Interstitial oedema**

- **Normal oncotic pressure**

- **Slower loss of fluid from vasculature**

- **Rapid vascular refilling with fluid removal**

- **Normal**

- **MAP**

- **CVP**

- **Systemic inflammation**

- **Rapid loss of fluid from vasculature**

- **Slow vascular refilling with fluid removal**

- **Fluid therapy**

- **Ultrafiltration**
Septic patient

- CVP will increase due to
  - Excessive fluid loading
  - RV constraint due to increased pericardial pressure (MV)
  - Diastolic and systolic RV dysfunction
CVP and septic AKI

- Sepsis (N = 137) - retrospective study design
- Relation systemic hemodynamics and AKI
Increased CVP associated with ↓ microcirculatory perfusion
"VIP" treatment

Increase systemic oxygen delivery

• Ensure sufficient oxygenation - no evidence that hyperoxia is harmful in circulatory shock

• Fluid therapy depending on resuscitation phase (SOSD) - salvage - optimization - stabilization - de-escalation

• Restore a minimal tissue perfusion pressure
SOSD

Salvage
25 - 30 mL/kg “No monitoring”

Optimization
Based on Fluid responsiveness

Stabilization
Neutral fluid balance

De-escalation
Negative fluid balance
Passive leg raising (meta-analysis 1)

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Specificity</th>
<th>AUC</th>
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</thead>
<tbody>
<tr>
<td>86%</td>
<td>92%</td>
<td>0.95</td>
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</tbody>
</table>

Unaffected by ventilation mode, fluid type, PLR starting position

Abdominal hypertension?

Measure between 30 - 90 seconds after leg raising

Cherpanath TGV. Crit Care Med 2016;44:981-991
Passive leg raising
(meta-analysis 2)

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>AUC</th>
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<tbody>
<tr>
<td>N = 21</td>
<td>85%</td>
<td>91%</td>
<td>0.95</td>
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<tr>
<td>Total 991 patients</td>
<td></td>
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</table>

In both studies AUC with CO changes >> PP changes

Monnet X. Intensive Care Med 2016
Mini fluid challenge

N = 50

M1
VTI

M2
VTI

M3
VTI

10 sec

50 cc

15 min

450 cc

Wu Y. Crit Care 2014;18:R108
Transfusion in septic shock

Transfusion in septic shock

Restrictive (4.3 mmol/l)  Liberal (5.6 mmol/l)

<table>
<thead>
<tr>
<th></th>
<th>Mortality D 90</th>
<th>Ischemic events</th>
<th>Life support D 5</th>
<th>Life support D 28</th>
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</thead>
<tbody>
<tr>
<td>N = 998</td>
<td>43</td>
<td>45</td>
<td>64.4</td>
<td>62.2</td>
</tr>
<tr>
<td>N = 998</td>
<td>7.2</td>
<td>8</td>
<td>0.47</td>
<td>0.14</td>
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MAP in septic shock

SEPSIS PAM


N = 776

Less AKI/RRT in high MAP group with previous hypertension

Personalized medicine
When to start NE?

When MAP is inadequate

Preload (mm Hg)

CO (l/min)

Mortality Odds Ratio

Pressor Delay Decile Range (hrs)

Bai X. Crit Care 2014;18:R532
Beck V. Crit Care 2014;18:R97
Dynamic arterial elastance = ratio PPV/SVV during single MV breath

MAP responders defined by increase MAP ≥ 10%
Norepinephrine optimal vasopressor?

Stolk RF. Am J Respir Crit Care Med 2016;194:550-558
Myocardial depression

30 - 50%

• Rapid increase in filling pressures without increase in cardiac output - cardiac ultrasound

• Highly susceptible for NE induced excessive afterload increase

• Milrinone/Enoximone or Dobutamine
Diastolic heart failure with tachycardia?

- Esmolol group
  - Higher SVI
  - Higher LVSWI
  - Lower NE dose
  - Less volume therapy

![Graph showing mortality over study days](image)

Log rank statistic, 22.795; df, 1; P value < .001

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Control</th>
<th>Esmolol</th>
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<tr>
<td>0</td>
<td>77</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>52</td>
<td>73</td>
</tr>
<tr>
<td>10</td>
<td>39</td>
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<td>25</td>
<td>16</td>
<td>40</td>
</tr>
<tr>
<td>30</td>
<td>15</td>
<td>39</td>
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No. at risk

Morelli A. JAMA 2013;310:1683-1691
Potential therapies for the microcirculation

Fluid therapy

Proportion perfused vessels

- $\leq 24$ hrs
- $> 48$ hrs

Variable effects

Improvement with severe derangements but worsening when nearly normal

Vasopressors

Vasodilators?

Dobutamine has no effect after resuscitation of macrocirculation

Nitroglycerine has no effect after resuscitation of macrocirculation

Experimental???

Dexmedetomidine

Ospina-Tascon G. Intensive Care Med 2010;36:949-955


Boerma EC. Crit Care Med 2010;38:93-100
Beyond hemodynamics - early metabolic therapy to improve mitochondrial function

- Thiamine (cofactor for PDH)
- Ascorbic acid, tocopherol, selenium and zinc
- Coenzyme Q10, L-carnitine, caffeine, melatonin

No definite evidence yet
My recommendations

- Besides early fluid resuscitation early vasopressor therapy may be beneficial
- For a number of reasons the goals of resuscitation should be established with the lowest possible CVP
- Optimization of fluid therapy should probably be guided by tests of fluid responsiveness
- Resuscitate both the macro- and the microcirculation
- At least for the first 3 days make a daily echocardiogram and treat myocardial dysfunction accordingly