Hemodynamic support of the septic patient

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Clinical “standard”? 

- What are typical “macro measurements” in the modern ICU? 
  - Static or dynamic pressure and flow-derived hemodynamic variables, pulse oximetry, capnometry, ScvO₂, etc. 
  - Therapeutic decisions are commonly based on these parameters. 
  - Traditionally well established and represent a clinical “standard.”

- What are the right targets (e.g., cardiac output, MAP)?
- What are the best concepts regarding management of macro-hemodynamics (e.g., early vs. late, standardized vs. individualized)?
Fluids and hemodynamic stabilization

- What do the guidelines say?

**Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012**

- Initial resuscitation (within 6 hours) and hemodynamic stabilization
- *Within six hours means: fast*

*Dellinger et al, Intensive Care Med. 2013 Feb;39(2):165-228*
Reduced 90-day mortality with colloid therapy in general and HES specifically.

Less ventilatory days and less need of vasopressor agents.

No significant difference between groups regarding need of RRT. (Ananne et al, JAMA 2013)

Hemodynamic Support and Adjunctive Therapy (Table 6)

G. Fluid Therapy of Severe Sepsis

1. **We recommend crystalloids** be used as the initial fluid of choice in the resuscitation of severe sepsis and septic shock (grade 1B).

2. **We recommend against the use of hydroxyethyl starches (HES)** for fluid resuscitation of severe sepsis and septic shock (grade 1B). (This recommendation is based on the results of the VISEP [128], CRystMas [122], 6S [123], and CHEST [124] trials. The results of the recently completed CRYSTAL trial were not considered.)

- Crystalloids are the fluid of choice [1B]
- Initial infusion of 30 mL/kg BW → “fluid challenge” [1C]
- If colloids are necessary → albumin [2C]
- Effects of volume judged by
  - static parameters (HR, MAP) and [UG]
  - dynamic parameters (PPV, SVV) [UG]
An everyday situation...

- A critically ill patient suffers from an acute drop in blood pressure
- Decision to administer an intravenous fluid bolus (e.g. 1L crystalloid)
- In combination with norepinephrine, the mean arterial blood pressure (MAP) increases again to 80 mmHg
Problem: We are “traditionally biased” and believe that our personal hemodynamic targets and beliefs are simply the best

- But is an increase in MAP or cardiac output following an intervention always and without exceptions beneficial?
- The patient’s “baseline” condition and associated co-morbidities might be more important than just numbers on a screen
- Consider that the resuscitation regimen that rescues one patient might not be beneficial in another one ...
What happened in 2001...?

You are right, the Rivers-study was published!
Randomized, controlled clinical trial

- 263 patients with severe sepsis or septic shock
- Patients were randomly assigned to receive either early goal-directed therapy (EGDT) or standard therapy within the first six hours
- EGDT included macro-hemodynamics (MAP, CVP) and $\text{ScvO}_2$

- **In-hospital mortality:** 30.5% (EGDT) vs. 46.5% (standard)
- **Conclusion:** EGDT provides significant benefits in patients with severe sepsis and septic shock
Early goal directed therapy

- State-of-the-art in sepsis therapy for more than a decade
- Should one question an established concept?
Multicenter, randomized controlled clinical trial
1341 patients with early septic shock
Randomization to receive either
→ Protocol-based EGDT (n=439)
→ Protocol-based standard therapy (n=446)
→ Usual care (n=456)

Primary endpoint: 60-day in-hospital mortality
Secondary endpoints: long term mortality, need for organ support
- **Protocol-based EGDT**: Similar to Rivers, included measurement of CVP, ScvO$_2$ & administration of red blood cells and inotropic agents

- **Protocol-based standard therapy**: No indication for central venous catheter; administration of fluids and vasopressors according to blood pressure and shock index; assessment of fluid status by clinical judgment

- **Usual care**: Bed-side providers directed all care without prompted actions from study coordinator
Results

No significant differences between groups concerning the primary endpoint, i.e. 60-day mortality
A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*

N ENGL J MED 370;18 NEJM.ORG MAY 1, 2014

A Cumulative In-Hospital Mortality to 60 Days

P = 0.52 by log-rank test

Days

Mortality (%)

Protocol-based EGDT
Protocol-based standard therapy
Usual care
Results

- No significant differences between groups regarding the primary endpoint, i.e. 60-day mortality.
- No significant differences between groups regarding 1-year mortality and need for organ support.
A Randomized Trial of Protocol-Based Care for Early Septic Shock

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N ENGL J MED 370;18  NEJM.ORG  MAY 1, 2014

B  Cumulative Mortality to 1 Yr

Mortality (%)

P=0.70 by log-rank test, 90 days
P=0.92 by log-rank test, 1 yr

Days
Conclusion

In this multicenter trial, a protocol-based resuscitation in patients with septic shock did not improve outcome
Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZICS Clinical Trials Group*

DOI: 10.1056/NEJMoal404380
Goal-Directed Resuscitation for Patients with Early Septic Shock

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DOI: 10.1056/NEJMoa1404380

CONCLUSIONS

In critically ill patients presenting to the emergency department with early septic shock, EGDT did not reduce all-cause mortality at 90 days. (Funded by the National Health and Medical Research Council of Australia and the Alfred Foundation; ARISE ClinicalTrials.gov number, NCT00975793.)
My personal conclusion is and remains

If there is a problem: Fix it as soon as possible to avoid consecutive (collateral) damages

Don’t think too much. You’ll create a problem that wasn’t even there in the first place.
How much pressure is needed?
What do the guidelines say?


1. We recommend that vasopressor therapy initially target a MAP of 65 mmHg (grade 1C).

2. We recommend norepinephrine as the first-choice vasopressor (grade 1B).

3. We suggest epinephrine (added to and potentially substituted for norepinephrine) when an additional agent is needed to maintain adequate blood pressure (grade 2B).
Physiological facts have to be kept in mind

- Pressure is not flow!

- A high blood pressure is no guaranty for organ perfusion

- The key determinants of tissue oxygenation and organ perfusion are convection and diffusion

- The “best” blood pressure is still a matter of debate
What about a three step approach?

**Step One**
Target minimum MAP (45-50 mmHg) to preserve heart and brain perfusion

**Step Two**
Target tissue perfusion-based endpoints irrespective of MAP <65 mmHg (permissive hypotension)

**Step Three**
Target single-organ (renal) perfusion

Setting and objective

- Post-hoc analysis of a multicenter trial with 290 septic patients
- To determine the association between a $\text{MAP} \geq 70 \text{ mmHg}$, vasopressor load, mortality and disease-related events

Results

- MAP levels $\geq 70 \text{ mmHg}$ did not improve survival in this trial
- Mean vasopressor load was associated with mortality, disease-related events and organ failure

Conclusion

- Increasing MAP $> 70 \text{ mmHg}$ by higher vasopressor dosages may increase mortality in septic patients
AFTER 5 YEARS
High versus Low Blood-Pressure Target in Patients with Septic Shock

SEPSISPAM Investigators*

- Multicenter open-label trial
- 776 patients with septic shock were randomly assigned to undergo resuscitation with either
  - MAP target 80-85 mmHg (high-target group, n=167) or
  - MAP target 65-70 mmHg (low-target group, n=173)
- Primary endpoint: 28-day mortality
- Secondary endpoints: 90-day mortality, organ dysfunction, LOS
High versus Low Blood-Pressure Target in Patients with Septic Shock
High versus Low Blood-Pressure Target in Patients with Septic Shock

SEPSISpAM Investigators*

- **Results:**
  - No significant differences between groups (high vs. low MAP) in 28-day mortality (36.6 vs. 34%; \( p=0.57 \)) and 90-day mortality (43.8 vs 42.3%; \( p=0.74 \))
  - Higher rate of atrial fibrillation within high-target group (6.7 vs. 2.8%, \( p=0.02 \))
  - Higher plasma creatinine concentrations and need for RRT in patients with chronic hypertension allocated to the low MAP group
High versus Low Blood-Pressure Target in Patients with Septic Shock

SEPSISPAM Investigators*

<table>
<thead>
<tr>
<th>Renal function</th>
<th>Low MAP</th>
<th>High MAP</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doubling of plasma creatinine</td>
<td>161 (41.5)</td>
<td>150 (38.7)</td>
<td>0.42</td>
</tr>
<tr>
<td>No chronic hypertension</td>
<td>71/215 (33.0)</td>
<td>85/221 (38.5)</td>
<td>0.32</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>90/173 (52.0)</td>
<td>65/167 (38.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Renal-replacement therapy from day 1 to day 7</td>
<td>139 (35.8)</td>
<td>130 (33.5)</td>
<td>0.50</td>
</tr>
<tr>
<td>No chronic hypertension</td>
<td>66/215 (30.7)</td>
<td>77/221 (34.8)</td>
<td>0.36</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>73/173 (42.2)</td>
<td>53/167 (31.7)</td>
<td>0.046</td>
</tr>
</tbody>
</table>

However, the use of RRT had no negative influence on survival!
• Conclusions
  
  • No significant differences were recorded between high-target and low-target groups regarding 28-day and 90-day mortality in patients with septic shock.
  
  • Since the use of renal replacement therapy did not negatively impact on survival, a MAP of 70 mmHg seems to represent a rational target in septic shock patients.
Beta blockade... A new crazy therapeutic option?
Effect of Heart Rate Control With Esmolol on Hemodynamic and Clinical Outcomes in Patients With Septic Shock
A Randomized Clinical Trial

Andrea Morelli, MD; Christian Ertmer, MD; Martin Westphal, MD; Sebastian Rehberg, MD; Tim Kampmeier, MD; Sandra Ligges, PhD; Alessandra Orecchioni, MD; Annalia D’Egidio, MD; Fiorella D’Ippoliti, MD; Cristina Raffone, MD; Mario Venditti, MD; Fabio Guarracino, MD; Massimo Girardis, MD; Luigi Tritapepe, MD; Paolo Pietropaoli, MD; Alexander Mebazaa, MD; Mervyn Singer, MD, FRCP

- Open-label randomized phase II study
- 154 patients with septic shock were randomly received
  → titrated continuous esmolol to maintain HR 80-94/min during ICU stay (esmolol group, n=77)
  → standard treatment (control group, n=77)
- Primary endpoint: Reduction of heart rate
- Secondary endpoints: Hemodynamics, organ functions, NE dosage and mortality
• **Results:**
  • Significant improvement in hemodynamic variables (HR, SVI, LVSWI) and fluid requirements (each p<0.05)
  • Significant improvement of 28-day survival
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Adjusted survival at mean value of covariates

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Control</th>
<th>Esmolol</th>
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<tbody>
<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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<tr>
<td>25</td>
<td>16</td>
<td>40</td>
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<td>30</td>
<td>15</td>
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</tr>
</tbody>
</table>

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Summary I

- One size does not fit all: A regimen that helps one patient might not be beneficial for another one.

- Anyway, there should be pressure AND flow in a living patient.

- Co-morbidities and the underlying pathophysiology should be taken into account to apply the “right” therapeutic intervention.

- Medicine evolves, and old traditions need to be challenged.
Summary II

- Monitoring of the macro level helps to complete the overall hemodynamic picture
- Since shock is a failure of the macro- and microcirculation, both should be monitored and targeted
- Macro and micro are the “yin and yang of hemodynamic monitoring”
Pathophysiology of sepsis

- Massive release of mediators ("cytokine storm") in response to an infection leading to
  - capillary leakage
  - vasodilatation in periphery vessels
  - vasoconstriction in pulmonary vessels

- Consecutive impairment of organ systems
  - Lung (ARDS)
  - Kidney (septic kidney injury)
  - Intestine
  - Heart (septic cardiomyopathy)
  - Brain (septic encephalopathy)
  - Coagulation
Hemodynamic stabilization

- In the initial phase of sepsis, there are only two options to maintain or re-establish hemodynamic stability:
  - Fluids (e.g. crystalloids, colloids)
  - Vasoactive agents (e.g. Norepinephrine, Dobutamine)
Physiology works – even in patients

- The microcirculation may be uncoupled from the macrocirculation
- MAP and cardiac output may not be well correlated either

“Leaving blood pressure cosmetics behind and moving forward to permissive hypotension and a tissue perfusion-based approach”

Differentiated control of deranged nitric oxide metabolism: a therapeutic option in sepsis?

Corinna Lupp*¹, Silke Baasner¹, Can Ince², Frank Nocken¹, John F Stover¹ and Martin Westphal¹³