What’s new in hemodynamic management?

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Two emerging concepts are changing our practice

- **Evolution from protocolized to individualized** management even at the early phase

- **Evolution from delayed to early use of vasopressors**

Two emerging concepts have not yet changed our practice

- **Use of beta-blockers** rather than beta-agonists

- Consideration of the **microcirculatory state**
Initial resuscitation

1. Protocolized, quantitative resuscitation of patients with sepsis-induced hypoperfusion (defined as hypotension persisting after initial fluid challenge or blood lactate $\geq 4$ mmol/L).

Goals during the first 6h of resuscitation:

(a) Central venous pressure 8-12 mmHg
(b) Mean arterial pressure (MAP) $\geq 65$ mmHg
(c) Urine output $\geq 0.5$ mL.kg$^{-1}$ h
(d) Central venous or mixed venous oxygen saturation 70 or 65%, respectively (grade 1C)
Supplemental oxygen ± endotracheal intubation and mechanical ventilation

Central venous and arterial catheterization

Sedation, paralysis (if intubated), or both

CVP
- <8 mm Hg: Crystalloid
- 8–12 mm Hg: Crystalloid, Colloid
- >12 mm Hg: Colloid

MAP
- <65 mm Hg: Vasoactive agents
- >90 mm Hg: Vasoactive agents
- >65 and <90 mm Hg: Vasoactive agents

ScvO₂
- <70%: Transfusion of red cells until hematocrit ≥30%
- ≥70%: Inotropic agents

Goals achieved

Yes: Hospital admission

No: Flowchart continues with decision points.
Reduced mortality with EGDT (30.5%) vs. control (46.5%)
Three multicenter randomized clinical trials

Arise

Goal-Directed Resuscitation for Patients with Early Septic Shock
The ARREST Investigators and the ANZICS Clinical Trials Group

Promise

Trial of Early, Goal-Directed Resuscitation for Septic Shock
Paul R. Mo Az, M.D., Tiffany M. O‘Reilly, M.D., Sarah Rotten, M.D.,
David A. Harrison, Ph.D., M. Zu Dug, Ph.D., Richard D. Smeriglio, M.D.,
Rah Jahan, B.A., sheeri O‘Reilly, Ph.D., Derek B. R. W. Dujan, M.D.,
Harrison J. Gage, M.D., Mervyn S. Ho, M.D., J.Q. Young, D.M.,
J and Kathryn A. Omar, Ph.D., for the ProCESS Investigators

Process

A Randomized Trial of Protocol-Based Care for Early Septic Shock
for ProCESS Investigators

No improved survival with EGDT
Primary **mortality** outcome of each study
Our meta-analysis does not show improved survival for patients randomised to receive EGDT compared to usual or to less invasive alternative haemodynamic resuscitation protocols.

Our findings do not support the systematic use of EGDT in the management of all patients with septic shock or its inclusion in the SSC guidelines.
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• Evolution from delayed to early use of vasopressors
  
  ➢ Duration and degree of hypotension associated with increased mortality
Hemodynamic variables related to outcome in septic shock

Time under MAP 65 mmHg

Area under MAP 65 mmHg

Best predictor of 30-day mortality
Two emerging concepts are changing our practice

- Evolution from protocolized to individualized management even at the early phase

- Evolution from delayed to early use of vasopressors
  - Duration and degree of hypotension associated with increased mortality
  - Delayed initiation of vasopressors associated with increased mortality
The later NE was initiated, the higher the mortality rate
Early versus delayed administration of norepinephrine in patients with septic shock

Xiaowu Bai, Wenkui Yu, Wu Ji, Zhiliang Lin, Shanjun Tan, Kaipeng Duan, Yi Dong, Lin Xu and Ning Li*

Critical Care 2014, 18:532

Table 5 Multivariate logistic regression analysis of independent risk factors for 28-day mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted Odds Ratio of Death</th>
<th>95% Confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to initial norepinephrine administration (h)</td>
<td>1.392</td>
<td>1.138–1.702</td>
<td>0.003</td>
</tr>
<tr>
<td>Time to initial antimicrobial treatment (h)</td>
<td>1.330</td>
<td>1.067–1.659</td>
<td>0.011</td>
</tr>
<tr>
<td>Serum lactate at septic shock onset (mmol/L)</td>
<td>1.710</td>
<td>1.174–2.537</td>
<td>0.005</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>1.243</td>
<td>1.096–1.409</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Protective factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effective antimicrobial therapy</td>
<td>0.477</td>
<td>0.231–0.982</td>
<td>0.040</td>
</tr>
<tr>
<td>Volume of intravenous fluids within 6 h (L)</td>
<td>0.676</td>
<td>0.468–0.977</td>
<td>0.033</td>
</tr>
</tbody>
</table>

Time to initial NE administration: independent predictor of mortality

.... the later, the worse
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• Evolution from delayed to early use of vasopressors
  - Duration and degree of hypotension associated with increased mortality
  - Delayed initiation of vasopressors associated with increased mortality
  - NE when initiated early, increases cardiac output by increasing preload
## Effects of NE on Cardiac Output in patients with septic shock

<table>
<thead>
<tr>
<th>Studies showing increased cardiac output with NE</th>
<th>Baseline Cardiac Index (L/min/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Martin et al Crit Care Med 1999</td>
<td>4.3</td>
</tr>
<tr>
<td>• Ledoux et al Crit Care Med 2000</td>
<td>4.7</td>
</tr>
<tr>
<td>• Jhanji et al Crit Care Med 2009</td>
<td>3.9</td>
</tr>
<tr>
<td>• Derudder et al Intensive Care Med 2007</td>
<td>3.4</td>
</tr>
<tr>
<td>• Dubin et al Crit Care 2009</td>
<td>2.9</td>
</tr>
<tr>
<td>• Georger et al Intensive Care Med 2010</td>
<td>3.1</td>
</tr>
<tr>
<td>• Hamzaoui et al Crit Care 2010</td>
<td>3.2</td>
</tr>
<tr>
<td>• Monnet et al Crit Care Med 2011</td>
<td>2.7</td>
</tr>
<tr>
<td>• Thooft et al Crit Care 2011</td>
<td>3.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Studies showing unchanged cardiac output with NE</th>
<th>Baseline Cardiac Index (L/min/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Desjars et al Crit Care Med 1987</td>
<td>5.2</td>
</tr>
<tr>
<td>• Martin et al Chest 1993</td>
<td>5.3</td>
</tr>
<tr>
<td>• Martin et al Crit Care Med 1999</td>
<td>5.7</td>
</tr>
<tr>
<td>• Albanese et al Chest 2004</td>
<td>4.7</td>
</tr>
<tr>
<td>• Albanese et al Crit Care Med 2005</td>
<td>5.1</td>
</tr>
</tbody>
</table>
• NE increases cardiac preload

• NE increases CO in preload-dependent patients

• NE reduces the degree of preload-dependency

Messages of these two studies

... as fluid infusion does

How does NE impact the venous circulation?

by blood redistribution from unstressed to stressed volume?
NE increases CO through an increase in Mean Systemic Pressure related to blood redistribution from unstressed to stressed volume.

This is a good news since unstressed volume is abnormally increased during sepsis and further overfilled by fluid loading.
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- **Evolution from delayed to early use of vasopressors**
  - Duration and degree of hypotension associated with increased mortality
  - Delayed initiation of vasopressors associated with increased mortality
  - NE when initiated early, increases cardiac output by increasing preload
  - NE when initiated early, improves microcirculation
Restoring arterial pressure with norepinephrine improves muscle tissue oxygenation assessed by near-infrared spectroscopy in severely hypotensive septic patients

| MAP mmHg | 54 ± 8 | 77 ± 9 |

StO₂

healthy volunteers
82 ± 4%

Septic shock
75 ± 9% *

p < 0.05
Early **correction** of **hypotension** resulted in **improved** muscle tissue oxygenation and **microcirculatory reserve capacities**.
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  - Duration and degree of hypotension associated with increased mortality
  - Delayed initiation of vasopressors associated with increased mortality
  - NE when initiated early, increases cardiac output by increasing preload
  - NE when initiated early, improves microcirculation
  - **Early initiation of vasopressors prevents** harmful fluid **overload**
Sepsis in European intensive care units: Results of the SOAP study*

Jean-Louis Vincent, MD, PhD, FCCM; Yasser Sakr, MB, BCh, MSc; Charles L. Sprung, MD; V. Marco Ranieri, MD; Konrad Reinhart, MD, PhD; Herwig Gerlach, MD, PhD; Rui Moreno, MD, PhD; Jean Carlet, MD, PhD; Jean-Roger Le Gall, MD; Didier Payen, MD; on behalf of the Sepsis Occurrence in Acutely Ill Patients Investigators

Crit Care Med 2006; 34:344–353

Table 7. Multivariate, forward stepwise logistic regression analysis in sepsis patients (n = 1177), with intensive care unit mortality as the dependent factor

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPS II score	extsuperscript{a} (per point increase)</td>
<td>1.0 (1.0–1.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cumulative fluid balance	extsuperscript{b} (per liter increase)</td>
<td>1.1 (1.0–1.1)</td>
<td>.001</td>
</tr>
<tr>
<td>Age (per year increase)</td>
<td>1.0 (1.0–1.0)</td>
<td>.001</td>
</tr>
<tr>
<td>Initial SOFA score (per point increase)</td>
<td>1.1 (1.0–1.1)</td>
<td>.002</td>
</tr>
<tr>
<td>Blood stream infection</td>
<td>1.7 (1.2–2.4)</td>
<td>.004</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>2.4 (1.3–4.5)</td>
<td>.008</td>
</tr>
<tr>
<td>Pseudomonas infection</td>
<td>1.6 (1.1–2.4)</td>
<td>.017</td>
</tr>
<tr>
<td>Medical admission</td>
<td>1.4 (1.0–1.8)</td>
<td>.049</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.4 (1.0–1.8)</td>
<td>.044</td>
</tr>
</tbody>
</table>
Fluid resuscitation in septic shock: A positive fluid balance and elevated central venous pressure are associated with increased mortality.

John H. Boyd, MD, FRCP(C); Jason Forbes, MD; Taka-aki Nakada, MD, PhD; Keith R. Walley, MD, FRCP(C); James A. Russell, MD, FRCP(C)

Crit Care Med 2011; 39:259–265
A positive fluid balance is an independent prognostic factor in patients with sepsis

Angela Acheampong and Jean-Louis Vincent

Critical Care (2015) 19:251
Rationale. Vasopressor therapy is required to sustain life and maintain perfusion in the face of life-threatening hypotension, even when hypovolemia has not yet been resolved.

Adequate fluid resuscitation is a fundamental aspect of the hemodynamic management of patients with septic shock and should ideally be achieved before vasopressors and inotropes are used; however, using vasopressors early as an emergency measure in patients with severe shock is frequently necessary, as when diastolic blood pressure is too low.
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Two emerging **concepts** have **not yet changed** our practice

• Use of **beta-blockers** rather than **beta-agonists**?

• Consideration of the **microcirculatory disorders**?
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 Brema, MD; Martin Westphal, MD; Sebastian Rohberg, MD; Tim Kampanakis, MD; Sandra Lijge, PhD; Alessandro Grecchioni, MD; Antonio D'Argo, MD; Fiorella D'Appolito, MD; Cristina Raffone, MD; Maria Venditti, MD; Fabio Guarnerino, MD; Massimo Grondi, MD; Luigi Trifiletti, MD; Paolo Piccorpoli, MD; Alexander Mebazza, MD; Mervyn Singer, MD, FRCP

JAMA 2013; 310:1683-1691

336 ICU patients with severe septic shock assessed for eligibility

182 Excluded
1. Heart rate <95/min
10. Previous β-blocker therapy
4. Consent denied
2. Consent unobtainable

154 Randomized

77 Randomized to receive esmolol
77 Randomized to receive usual care

77 Included in the primary analysis
77 Included in the primary analysis
Effect of Heart Rate Control With Esmolol on Hemodynamic and Clinical Outcomes in Patients With Septic Shock: A Randomized Clinical Trial

Andrea Morrelli, MD; Christian Bruna, MD; Martin Westphal, MD; Sebastian Rehberg, MD; Tim Kampschror, MD; Sandra Lages, PhD; Alessandro Giacchino, MD; Amalia Yergi, MD; Finella Rippoliti, MD; Cristina Ravone, MD; Maria Venditti, MD; Fabio Guarritini, MD; Massimo Grondi, MD; Luigi Trittapepe, MD; Paolo Picappelli, MD; Alexander Mebazza, MD; Mervyn Singer, MD, FRCP

*JAMA* 2013; 310:1683-1691

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**Adjusted survival at mean value of covariates**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Esmolol (n = 77)</th>
<th>Control (n = 77)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28 d</td>
<td>36 (49.4)</td>
<td>62 (80.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ICU</td>
<td>44 (57.1)</td>
<td>68 (88.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hospital</td>
<td>52 (67.5)</td>
<td>70 (90.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Length of ICU stay, d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>19 (11–27)</td>
<td>14 (7–25)</td>
<td>.03</td>
</tr>
<tr>
<td>Survivors', median (IQR)</td>
<td>17 (9–26)</td>
<td>21 (11–34)</td>
<td>.70</td>
</tr>
<tr>
<td>Cause of death, No./total, (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple organ failure</td>
<td>15/52 (28.8)</td>
<td>26/70 (37.1)</td>
<td></td>
</tr>
<tr>
<td>Refractory hypotension</td>
<td>32/52 (61.5)</td>
<td>44/70 (62.9)</td>
<td></td>
</tr>
<tr>
<td>Unknown cause</td>
<td>5/52 (9.8%)</td>
<td>4/70 (5.7%)</td>
<td></td>
</tr>
</tbody>
</table>

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No. at risk

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Esmolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>77</td>
<td>77</td>
<td>77</td>
</tr>
<tr>
<td>75</td>
<td>73</td>
<td>71</td>
</tr>
<tr>
<td>52</td>
<td>39</td>
<td>61</td>
</tr>
<tr>
<td>39</td>
<td>26</td>
<td>53</td>
</tr>
<tr>
<td>21</td>
<td>21</td>
<td>43</td>
</tr>
<tr>
<td>16</td>
<td>15</td>
<td>40</td>
</tr>
<tr>
<td>15</td>
<td>13</td>
<td>39</td>
</tr>
</tbody>
</table>
Esmolol prevents the sepsis-induced myocardial depression
Esmolol restores the sepsis-induced hyporeactivity of small vessels.
Esmolol up-regulate the alpha$_1$-adrenoreceptors in small vessels
Adjunction of esmolol blunted the increase in cardiac and vascular iNOS protein expression and of NF-kB expression induced by sepsis.

The adjunction of esmolol enhanced the generation of anti-inflammatory cytokines while decreasing that of pro-inflammatory cytokines.
β1-Adrenergic Inhibition Improves Cardiac and Vascular Function in Experimental Septic Shock

Antoine Kimmoun, MD; Hugnette Louis, PhD; Narimane Al Kattani, PhD; Julie Delemazure, MD; Nicolas Dessales, MD; Chaojie Wei, PhD; Pierre Yves Marie, MD, PhD; Khodor Issa, PhD; Bruno Levy, MD, PhD

Crit Care Med 2015; 43:e332–e340
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- Consideration of the microcirculatory disorders
How can the microcirculation be currently monitored at the bedside?

- OPS/SDF technology
  → visualization of sublingual microcirculation

How to evaluate the microcirculation: report of a round table conference
Daniel De Backer¹, Steven Hollenberg², Christiaan Boerma³,⁴, Peter Goedhart⁴, Gustavo Büchele¹, Gustavo Ospina-Tascon¹, Iwan Dobbe⁴ and Can Ince⁴

Critical Care 2007, 11:R101

- Functional capillary density
- Proportion of perfused vessels
- Microcirculatory flow index
- Heterogeneity index
## After initial resuscitation

<table>
<thead>
<tr>
<th></th>
<th>Patients with Sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>61 (50–72)*</td>
</tr>
<tr>
<td>Temperature, °C</td>
<td>37.0 (36.4–38.0)</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>105 (91–110)</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>71 (63–79)</td>
</tr>
<tr>
<td>Cardiac index, L/min · m²</td>
<td>3.63 (2.62–4.69)</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>97 (94–98)</td>
</tr>
<tr>
<td>SVO₂, %</td>
<td>68 (62–73)</td>
</tr>
<tr>
<td>Hemoglobin, g/dl</td>
<td>8.3 (7.4–9.9)</td>
</tr>
</tbody>
</table>
Microvascular Blood Flow Is Altered in Patients with Sepsis

Daniel De Backer, Jacques Creteur, Jean-Charles Preiser, Marc-Jacques Dubois, and Jean-Louis Vincent

Am J Respir Crit Care Med Vol 166, pp 98–104, 2002
Microvascular Blood Flow Is Altered in Patients with Sepsis

Daniel De Backer, Jacques Creteur, Jean-Charles Preiser, Marc-Jacques Dubois, and Jean-Louis Vincent

Am J Respir Crit Care Med Vol 166, pp 98–104, 2002
Cytocam-Intermittent Dark Field illumination

Microcirculatory variables measured automatically
Cytocam-IDF (incident dark field illumination) imaging for bedside monitoring of the microcirculation

Guclu Aykus1,‡‡, Gerke Veenstra1,‡‡, Claudia Scorcella2, Can Ince1 and Christiaan Boerma2

Intensive Care Medicine Experimental (2015) 3:4
Cytocam-IDF (incident dark field illumination) imaging for bedside monitoring of the microcirculation

Güclü Aykut1,2†, Gerke Veenstra1,2†, Claudia Scorcella2, Can Ince1 and Christiaan Boerma2

*Intensive Care Medicine Experimental (2015) 3:4*
How can the microcirculation be currently monitored at the bedside?

- **OPS/SDF technology**
  - visualization of sublingual microcirculation

- **NIRS technology**
  - monitoring of $O_2$ saturation in muscle microvessels
  - monitoring of $O_2$ saturation in brain microvessels

- **Laser-Doppler techniques**

- **Tissue PCO$_2$ and PCO$_2$ gap measurements**

  Tools for research but not yet for routine use
We suggest the techniques to assess regional circulation or microcirculation for research purposes only.

Recommendation Level 2; QoE low (C)
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