Le sepsis:
Des urgences aux soins intensifs

Daniel De Backer

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Professor of Intensive Care, Université Libre de Bruxelles
Past-President European Society of Intensive Care Medicine
Inspired from....

- **55 experts**
- **5 sections**
  - Hemodynamics
  - Infection
  - Adjunctive therapies
  - Metabolic
  - Ventilation
Surviving Sepsis Guidelines
A Continuous Move Toward Better Care of Patients With Sepsis

Sepsis is a life-threatening condition that affects more than 1 million patients a year in the United States and even more patients around the globe and is one of the leading causes of death. Since the Declaration of Barcelona in 2002, the European Society of Intensive Care Medicine and the Society of Critical Care Medicine (SCCM) have launched several initiatives to decrease the mortality of patients with sepsis. The Surviving Sepsis Campaign (SSC) was established in 2004 as the first international initiative to reduce mortality from sepsis. The SSC guidelines in 2008 focused on shorter time to treatment with antibiotics and rapid administration of fluid resuscitation, and in 2016 the revised SSC guidelines expanded the recommendations to the field of critical care. The new SSC guidelines and recommendations are available at https://www.sccm.org/Portals/0/Documents/activities/SSC/SSC_Guidelines_2016.pdf.

Another important advance is that the new guidelines recommend the use of dynamic (ie, pulse or stroke volume variations induced by mechanical ventilation or passive leg raise test) over static variables (index) for the assessment of cardiac output. Dynamic indices are associated with reduced mortality compared with static indices. Although dynamic indices are not as widely available, the SSC guidelines recommend them as the preferred method for assessing cardiac output. The SSC guidelines also recommend early recognition and treatment of sepsis-related organ dysfunction to improve outcomes. Early recognition and treatment of sepsis-related organ dysfunction may include early administration of vasopressors, fluid resuscitation, and administration of antibiotics.
Le sepsis aux urgences

1. Comment reconnaître ?
Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection.
Le sepsis: comment reconnaître?

➢ Suspecter une infection…

➢ Détecter une dysfonction d’organe…
Organ dysfunction is characterized clinically by a change in SOFA score $\geq 2$ related to the episode of new infection.
Sepsis = infection + 2 qSOFA points
Assessment of Clinical Criteria for Sepsis For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Seymour C et al
JAMA 315:762; 2016

SOFA in the ICU

- SIRS
- SOFA
- qSOFA

Outside the ICU encounters
N = 66,522
AUROC in-hospital mortality

- SIRS
- SOFA
- qSOFA

qSOFA outside the ICU

- Respiratory rate ≥ 22 bpm
- Altered mentation
- Systolic blood pressure ≤ 100 mmHg
Le sepsis: comment reconnaître?

➢ Suspecter une infection…
  ➢ Signes cliniques habituels…T°/GB/CRP…

➢ Détecter une dysfonction d’organe…
  ➢ qSOFA 2
  ➢ 2 pts dysfonction d’organe
  ➢ Signes biologiques
Evaluation of skin perfusion
The Mottling Score

Mottling score

5

4

3

2

1

SCORE 2

SCORE 4

Ait Oufella et al
ICM 37:801;2011
The Mottling Score

N=60 / H6
Le sepsis aux urgences

1. Comment reconnaître ?
2. Prise en charge
Le sepsis aux urgences: 
Prise en charge

- Identifier / Contrôler la source
- Antibiotiques

- Traitement supportif
D. ANTIMICROBIAL THERAPY

1. We recommend that administration of IV antimicrobials be initiated as soon as possible after recognition and within 1 h for both sepsis and septic shock (strong recommendation, moderate quality of evidence; grade applies to both conditions).
Time to Treatment and Mortality during Mandated Emergency Care for Sepsis


NY state 49331 pts
149 hosp
HEMODYNAMIC RESUSCITATION
Fluids at the different stages of shock

**Salvage**
- Obtain a minimal acceptable blood pressure
- Perform lifesaving measures

**Optimization**
- Provide adequate oxygen availability
- Optimize cardiac output, $\text{SvO}_2$, lactate

**Stabilization**
- Provide organ support
- Minimize complications

**De-escalation**
- Wean from vasoactive agents
- Achieve a negative fluid balance


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A. INITIAL RESUSCITATION

2. We recommend that, in the resuscitation from sepsis-induced hypoperfusion, at least 30 mL/kg of IV crystalloid fluid be given within the first 3 h (strong recommendation, low quality of evidence).
New bundles

**SPECIAL EDITORIAL**

The Surviving Sepsis Campaign Bundle: 2018 update

- Measure lactate level. Remeasure if initial lactate is >2 mmol/L.
- Obtain blood cultures prior to administration of antibiotics.
- Administer broad-spectrum antibiotics.
- Begin rapid administration of 30ml/kg crystalloid for hypotension or lactate ≥4 mmol/L.
- Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥65 mm Hg.

*“Time zero” or “time of presentation” is defined as the time of triage in the Emergency Department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of sepsis (formerly severe sepsis) or septic shock ascertained through chart review.*

**Fig. 1** Hour-1 Surviving Sepsis Campaign Bundle of Care
Prompt Administration of Antibiotics and Fluids in the Treatment of Sepsis: A Murine Trial

B

Fluids

C

Antibiotics

D

Fluids and Antibiotics

- Fluids at criteria
- No treatment

- Abx+fluids at criteria
- Abx+fluids–2 hour delay
- Abx+fluids–4 hour delay
Not too much but also not limited....

9190 pts with sepsis

Liu V et al
Annals ATS 2013
Effect of an Early Resuscitation Protocol on In-hospital Mortality Among Adults With Sepsis and Hypotension
A Randomized Clinical Trial

212 patients in Zambia
Patients randomized to the sepsis protocol received hemodynamic management for the first 6 hours after enrollment. An initial 2-L bolus of intravenous isotonic crystalloid was administered within 1 hour of enrollment, followed by an additional 2 L over the subsequent 4 hours. After each liter of intravenous fluid was administered, an investigator or study nurse measured arterial oxygen saturation, respiratory rate, and JVP (details appear in the eMethods in Supplement 2). If the arterial oxygen saturation decreased by 3%, the respiratory rate increased by 5 breaths per minute, or JVP reached 3 cm or greater above the sternal angle, fluid infusion was discontinued. The sepsis protocol limited intravenous fluid administration to a total of 4 L, including any fluid given in the ED prior to enrollment.

$\approx 70 \text{ ml/kg}$

$\Rightarrow$ Patients were reassessed for tolerance, but not for indication!
Influenza preparedness in low-resource settings: a look at oxygen delivery in 12 African countries

Janeil Belle¹, Hillary Cohen², Nahoko Shindo³, Matthew Lim⁴, Adriana Velazquez-Berumen⁵, Jean-Bosco Ndihokubwayo⁶, Meena Cherian⁷

¹Duke University School of Medicine, Durham, NC, USA
²Maimonides Medical Center, Department of Emergency Medicine, Brooklyn, NY, USA
³-⁵World Health Organization Headquarters, Geneva, Switzerland,
⁶World Health Organization Regional Office for Africa, Brazzaville, Congo

<table>
<thead>
<tr>
<th></th>
<th>Electricity</th>
<th>Generator</th>
<th>Any oxygen source</th>
<th>Oxygen Cylinder</th>
<th>Oxygen Concentrator</th>
<th>Face mask and tubing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Always available</td>
<td>81 (35.1)</td>
<td>127 (56.7)</td>
<td>99 (43.8)</td>
<td>66 (29.1)</td>
<td>55 (24.6)</td>
<td>75 (34.3)</td>
</tr>
<tr>
<td>Sometimes available</td>
<td>112 (48.5)</td>
<td>59 (26.3)</td>
<td>71 (31.4)</td>
<td>55 (22.9)</td>
<td>64 (28.6)</td>
<td>79 (37.6)</td>
</tr>
<tr>
<td>Not available</td>
<td>38 (16.5)</td>
<td>38 (17.0)</td>
<td>56 (24.8)</td>
<td>109 (48.0)</td>
<td>105 (46.9)</td>
<td>65 (31.0)</td>
</tr>
</tbody>
</table>

The following countries participated in the situational analysis: Ethiopia, The Gambia, Ghana, Kenya, Liberia, Malawi, Mali, Nigeria, Sierra Leone, Sao Tome and Principe, United Republic of Tanzania, and Uganda. Allopathic health facilities, community
Caution: the delay in fluid administration may be related to lower initial severity.
Time to Treatment and Mortality during Mandated Emergency Care for Sepsis


The New England Journal of Medicine

Original Article

OR hospital mortality for each hour delay

OR hospital mortality for each hour delay

NY state
49331 pts
149 hosp
Le sepsis aux soins intensifs: Prise en charge

➢ Identifier / Contrôler la source
➢ Antibiotiques
➢ Traitement supportif
➢ Are we happy with the prescribed antibiotics?

➢ Are we happy with source control?
DALI: Defining Antibiotic Levels in Intensive Care Unit Patients: Are Current β-Lactam Antibiotic Doses Sufficient for Critically Ill Patients?

Jason A. Roberts,1,2 Sanjoy K. Paul,3,4 Murat Akova,5 Matteo Bassetti,6 Jan J. De Waele,7 George Dimopoulos,3 Kirsi-Maija Kaukonen,9 Despoina Koulenti,1,8 Claude Martin,10,11 Philippe Montravers,12 Jordi Rello,13 Andrew Rhodes,14 Therese Starr,2 Steven C. Wallis,1 and Jeffrey Lipman;1,2 for the DALI Study

Table 3. Antibiotic Data for Achievement of Pharmacokinetic/Pharmacodynamic Targetsa in Critically Ill Patients

<table>
<thead>
<tr>
<th>Dosing and PK/PD Data</th>
<th>Amoxicillin (n = 71)</th>
<th>Ampicillin (n = 18)</th>
<th>Cefazolin (n = 14)</th>
<th>Cefepime (n = 14)</th>
<th>Ceftriaxone (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage per 24 h</td>
<td>6.0 (3.5–6.0)</td>
<td>12.0 (8.3–12.0)</td>
<td>3.0 (3.0–4.0)</td>
<td>6.0 (5.0–6.0)</td>
<td>2.0 (2.0–4.0)</td>
</tr>
<tr>
<td>50% f T&gt;MIC achieved</td>
<td>52.1%</td>
<td>55.6%</td>
<td>100.0%</td>
<td>78.6%</td>
<td>97.0%</td>
</tr>
<tr>
<td>50% f T&gt;4×MIC achieved</td>
<td>16.9%</td>
<td>27.8%</td>
<td>50.0%</td>
<td>50.0%</td>
<td>93.9%</td>
</tr>
<tr>
<td>100% f T&gt;MIC achieved</td>
<td>18.3%</td>
<td>33.3%</td>
<td>78.6%</td>
<td>78.6%</td>
<td>93.9%</td>
</tr>
<tr>
<td>100% f T&gt;4×MIC achieved</td>
<td>11.3%</td>
<td>22.2%</td>
<td>14.3%</td>
<td>71.4%</td>
<td>87.9%</td>
</tr>
</tbody>
</table>
6. We suggest empiric combination therapy (using at least two antibiotics of different antimicrobial classes) aimed at the most likely bacterial pathogen(s) for the initial management of septic shock (weak recommendation, low quality of evidence).

*Combination therapy*

The use of multiple antibiotics (usually of different mechanistic classes) with the specific intent of covering the known or suspected pathogen(s) with more than one antibiotic (e.g., piperacillin/tazobactam and an aminoglycoside or fluoroquinolone for gram-negative pathogens) to accelerate pathogen clearance rather than to broaden antimicrobial coverage. Other proposed applications of combination therapy include inhibition of bacterial toxin production (e.g., clindamycin with β-lactams for streptococcal toxic shock) or potential immune modulatory effects (macrolides with a β-lactam for pneumococcal pneumonia).
10. We suggest that an antimicrobial treatment duration of 7–10 days is adequate for most serious infections associated with sepsis and septic shock (weak recommendation, low quality of evidence).
13. We recommend daily assessment for de-escalation of antimicrobial therapy in patients with sepsis and septic shock (BPS).
# Resuscitation targets at the different stages of shock

<table>
<thead>
<tr>
<th>Phase Focus</th>
<th>Salvage</th>
<th>Optimization</th>
<th>Stabilization</th>
<th>De-escalation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obtain a minimal acceptable blood pressure</td>
<td>Provide adequate oxygen availability</td>
<td>Provide organ support</td>
<td>Wean from vasoactive agents</td>
</tr>
<tr>
<td></td>
<td>Perform lifesaving measures</td>
<td>Optimize cardiac output, (S\overline{o}_2), lactate</td>
<td>Minimize complications</td>
<td>Achieve a negative fluid balance</td>
</tr>
</tbody>
</table>

Vincent JL and De Backer D
NEJM 369:1726; 2013
A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators

<table>
<thead>
<tr>
<th>Study</th>
<th>Events,</th>
<th>Events,</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>EGDT</td>
<td>control</td>
</tr>
<tr>
<td>Rivers et al. (2001)</td>
<td>0.52 (0.31, 0.86)</td>
<td>38/130</td>
<td>59/133</td>
</tr>
<tr>
<td>Jones et al. (2010)</td>
<td>1.47 (0.82, 2.60)</td>
<td>34/150</td>
<td>25/150</td>
</tr>
<tr>
<td>ProCESS Investigators (2014)</td>
<td>1.17 (0.88, 1.55)</td>
<td>92/439</td>
<td>167/902</td>
</tr>
<tr>
<td>ARISE Investigators (2014)</td>
<td>0.98 (0.76, 1.26)</td>
<td>147/792</td>
<td>150/796</td>
</tr>
<tr>
<td>ProMISe Investigators (2015)</td>
<td>1.02 (0.80, 1.30)</td>
<td>184/623</td>
<td>181/620</td>
</tr>
<tr>
<td>Overall (I-squared = 56.7%, p = 0.055)</td>
<td>1.01 (0.88, 1.16)</td>
<td>495/2134</td>
<td>582/2601</td>
</tr>
</tbody>
</table>

Favours EGDT Favours control
The concept remains valid

Patient identification is crucial

The classical EGDT may be applied when better hemodynamic strategies cannot be used

Whenever possible use advance hemodynamic monitoring tools to optimize tissue perfusion
What is the right amount of fluids after the salvage phase?
Fluids and cardiac output

Muller L et al
Anesthesiology
115:541; 2011

39 critically ill patients
CVP as a target?
Extreme CVP values provide some information even if all indices of preload poorly predict fluid responsiveness!
CVP: Never an optimal prediction but still some reasonable guidance if nothing better can be used.

<table>
<thead>
<tr>
<th>CVP cut-off point (mmHg)</th>
<th>Number of data sets for the CVP ranges given</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;2: 72</td>
<td>64 % (39–89)</td>
<td>52 % (49–55)</td>
</tr>
<tr>
<td>2</td>
<td>2–3: 125</td>
<td>65 % (54–76)</td>
<td>53 % (50–56)</td>
</tr>
<tr>
<td>4</td>
<td>4–5: 163</td>
<td>64 % (57–71)</td>
<td>55 % (52–59)</td>
</tr>
<tr>
<td>6</td>
<td>6–7: 177</td>
<td>59 % (54–65)</td>
<td>57 % (54–61)</td>
</tr>
<tr>
<td>8</td>
<td>8–9: 187</td>
<td>56 % (52–61)</td>
<td>59 % (56–63)</td>
</tr>
<tr>
<td>10</td>
<td>10–11: 161</td>
<td>53 % (50–57)</td>
<td>61 % (56–66)</td>
</tr>
<tr>
<td>12</td>
<td>12–13: 108</td>
<td>51 % (47–54)</td>
<td>61 % (55–67)</td>
</tr>
<tr>
<td>14</td>
<td>14–15: 79</td>
<td>50 % (47–53)</td>
<td>66 % (58–73)</td>
</tr>
<tr>
<td>16</td>
<td>16–17: 39</td>
<td>49 % (46–52)</td>
<td>64 % (54–75)</td>
</tr>
<tr>
<td>18</td>
<td>18–19: 22</td>
<td>48 % (45–51)</td>
<td>59 % (44–75)</td>
</tr>
<tr>
<td>20</td>
<td>&gt;19: 15</td>
<td>48 % (45–51)</td>
<td>53 % (28–79)</td>
</tr>
</tbody>
</table>

1148 pts
The increase in CVP does not indicate the response to fluids
We should individualize fluid therapy!
#### Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level</th>
<th>QoE</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>28. We recommend that commonly used preload measures (such as CVP or PAOP or end diastolic area or global end diastolic volume) alone should not be used to guide fluid resuscitation</td>
<td>Level 1</td>
<td>QoE moderate (B)</td>
<td>Recommendation</td>
</tr>
<tr>
<td>29. We recommend not to target any absolute value of ventricular filling pressure or volume</td>
<td>Level 1</td>
<td>QoE moderate (B)</td>
<td>Recommendation</td>
</tr>
<tr>
<td>30. We recommend that fluid resuscitation should be guided by more than one single hemodynamic variable</td>
<td>Ungraded</td>
<td></td>
<td>Best practice</td>
</tr>
<tr>
<td>We recommend using dynamic over static variables to predict fluid responsiveness, when applicable</td>
<td>Level 1</td>
<td>QoE moderate (B)</td>
<td>Recommendation</td>
</tr>
</tbody>
</table>
Preload dependence indices to titrate volume expansion during septic shock: a randomized controlled trial

Time: \( p < 0.001 \)
Treatment arm: NS
Interaction: \( p < 0.01 \)

Cumulative probability of survival

\( p = 0.07 \)

NUMBER AT RISK
- Control: 30, 25, 23, 20, 19, 16
- Preload dependence: 30, 26, 26, 25, 24, 24
The best way to administer fluids

Perfusion issue that may respond to fluids

Prediction of the response to fluids

Fluid challenge to assess response (incl. and tolerance) to fluids
Pay attention to the response of the patient
Fluid challenges in intensive care: the FENICE study

A global inception cohort study

Fluid administration post fluid challenge

Percentage receiving further fluid administration

- Positive response
- Uncertain response
- Negative response

N = 2213
Do fluids correct hypotension in septic shock?
The increase in arterial pressure depends on vascular tone and the impact on cardiac output.

In sepsis, the low vascular tone limits the increase in arterial pressure in response to fluids.
Does correction of hypotension with vasopressors affect tissue perfusion?
Correction of hypotension improves urine output and renal function in septic patients

MAP 50 => 78 mmHg

Patients with septic shock (n=14)
When to introduce vasopressors?

Early introduction of vasopressors may decrease later need for fluids
Early introduction of norepi decreased fluids requirements

Sennoun N et al
CCM 35:1736;2007

Rats / LPS

Fluids
Late NE
Early NE

ml

Category 1

++

0
5
10
15
20
25
30

Rats / LPS
Duration of hypotension before initiation of vasopressor agents is associated with poor outcome

Bai X et al
Crit Care 2014

213 pts with septic shock
Which blood pressure target?
High vs Low MAP?

73-75
65-70 VS 80-85 mmHg

Target 65-70

798 pts septic shock

Asfar P et al
NEJM 2014
High vs Low MAP?

65-70 VS 80-85 mmHg

➢ But lower incidence of AKI with high MAP in previously hypertensive patients
➢ Higher rate of arrhythmias and AMI in high MAP

798 pts septic shock
High variability in response to increase in MAP

Renal Doppler

11 pts septic shock
MAP target?

- 65 mmHg as a starting point
- Higher levels can be considered in some patients but the response to a higher target level should be evaluated => «MAP challenge»
- However, the «MAP challenge» should take place only after having optimized other aspects of perfusion.
Select the right vasopressor agent!
Norepinephrine vs Dopamine in shock (SOAP investigators)

De Backer et al
NEJM 362: 779; 2010

N = 1679

* p<0.05
Norepinephrine vs Dopamine in shock (SOAP investigators)

* p<0.05

De Backer et al
NEJM 362: 779; 2010
Norepinephrine vs Dopamine in shock (SOAP investigators)

De Backer et al
NEJM 362: 779; 2010

Arrhythmias
N = 200

P < 0.001

DOPA vs NOREPI

Atr fib
Ventr tachyc
Ventr fib
Norepinephrine vs Dopamine in shock (SOAP investigators)

De Backer et al
NEJM 362: 779; 2010

P=0.07 by log-rank test

<table>
<thead>
<tr>
<th>Days since Randomization</th>
<th>No. at Risk Norepinephrine</th>
<th>No. at Risk Dopamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>821</td>
<td>858</td>
</tr>
<tr>
<td>4</td>
<td>617</td>
<td>611</td>
</tr>
<tr>
<td>8</td>
<td>553</td>
<td>546</td>
</tr>
<tr>
<td>12</td>
<td>504</td>
<td>494</td>
</tr>
<tr>
<td>16</td>
<td>467</td>
<td>452</td>
</tr>
<tr>
<td>20</td>
<td>432</td>
<td>426</td>
</tr>
<tr>
<td>24</td>
<td>412</td>
<td>407</td>
</tr>
<tr>
<td>28</td>
<td>394</td>
<td>386</td>
</tr>
</tbody>
</table>
# Dopamine vs norepinephrine in septic shock

A meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Norepinephrine</th>
<th>Dopamine</th>
<th>RR [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Event</td>
<td>Total</td>
<td>Event</td>
</tr>
<tr>
<td>Martin et al.</td>
<td>7</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>Marik et al.</td>
<td>5</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Ruokonen et al.</td>
<td>4</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Mathur et al.</td>
<td>14</td>
<td>25</td>
<td>19</td>
</tr>
<tr>
<td>De Backer et al.</td>
<td>249</td>
<td>502</td>
<td>291</td>
</tr>
<tr>
<td>Patel et al.</td>
<td>51</td>
<td>118</td>
<td>67</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>330</td>
<td>676</td>
<td>396</td>
</tr>
</tbody>
</table>
Shifting from norepi to phenylephrine + dopamine was associated with increased mortality.
G. VASOACTIVE MEDICATIONS

1. We recommend norepinephrine as the first-choice vasopressor (strong recommendation, moderate quality of evidence).

2. We suggest adding either vasopressin (up to 0.03 U/min) (weak recommendation, moderate quality of evidence) or epinephrine (weak recommendation, low quality of evidence) to norepinephrine with the intent of raising MAP to target, or adding vasopressin (up to 0.03 U/min) (weak recommendation, moderate quality of evidence) to decrease norepinephrine dosage.
What to do if the patient is not responding to norepinephrine?

\[ \alpha = \alpha \]

Adding another alpha adrenergic agent (i.e. epinephrine) would not increase blood pressure more than increasing the dose of norepinephrine…
Norepinephrine vs Epinephrine

Myburgh et al
ICM 34:2226;2008

280 pts
Levy B et al
CCM 2011

30 pts cardiogenic shock

Norepi + dobu VS Epi
EPI vs NOREPI (±DOBU)

330 pts septic shock

Death rate: 52 % vs 37%  p=0.25
Vasoconstriction

↑ intracellular calcium in vascular smooth muscle cells

Vasoconstriction

Differences arise due to receptor sensitivity and disposition in the vascular system, as well as stimulation of other receptors (beta/V2...).
802 septic shock pts

VASST
Russell et al
NEJM 358:877;2008
Mortality (%) according to severity at baseline

More severe n= 400 (NE > 15 mcg/min)
Less severe n= 378 (NE < 15 mcg/min)

(15 mcg/min ~0.19 - 0.21 mcg/kg.min for 80-70kg pts)
A double-blind randomised controlled trial of vasopressin (up to 0.06 u/min) vs noradrenaline within 6h of onset of septic shock.

Norepi dose at randomization: 0.16 [0.10-0.31] mcg/kg.min
Terlipressin

Half-Life 6h

Bolus 0.5 – 1 mg /8-6h

Infusion 20 – 160 µg/h

O’Brien A Singer M Lancet 2002
Lange M et al ICM 2009

Morelli A Crit Care 2009
Liu Z et al ICM 2018
Terlipressin versus norepinephrine as infusion in patients with septic shock: a multicentre, randomised, double-blinded trial

Zi-Meng Liu, Juan Chen, Qiuye Kou, Qinhan Lin, Xiaobo Huang, Zhanhong Tang, Yan Kang, Ke Li, Lixin Zhou, Qing Song, Tongwen Sun, Ling Zhao, Xue Wang, Xiandi He, Chunting Wang, Benquan Wu, Jiandong Lin, Shiying Yuan, Qin Gu, Kejian Qian, Xianqing Shi, Yongwen Feng, Aihua Lin, Xiaoshun He, Study Group of investigators and Xiang-Dong Guan

N=617
Terlipressin versus norepinephrine as infusion in patients with septic shock: a multicentre, randomised, double-blinded trial

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<table>
<thead>
<tr>
<th>Variable</th>
<th>Norepinephrine group (N = 266)</th>
<th>Terlipressin group (N = 260)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-day mortality N (%)</td>
<td>101/266 (38%)</td>
<td>104/260 (40%)</td>
<td>0.633</td>
</tr>
<tr>
<td>Days alive and free of vasopressor</td>
<td>14.66 ± 11.13</td>
<td>15.50 ± 11.14</td>
<td>0.424</td>
</tr>
<tr>
<td>Change of SOFA score from D0 to D7</td>
<td>−6 (−10 to 5)</td>
<td>−7 (−11 to 3)</td>
<td>0.123</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Norepinephrine group (n = 266)</th>
<th>Terlipressin group (n = 260)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myocardial infarction or ischaemia</td>
<td>4 (1.39%)</td>
<td>2 (0.68%)</td>
<td>0.45</td>
</tr>
<tr>
<td>Life-threatening arrhythmia</td>
<td>6 (2.08%)</td>
<td>7 (2.38%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Acute mesenteric ischaemia</td>
<td>1 (0.35%)</td>
<td>3 (1.02%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Hyponatraemia</td>
<td>18 (6.25%)</td>
<td>25 (8.5%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Digital ischaemia</td>
<td>1 (0.35%)</td>
<td>33 (12.6%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1 (0.35%)</td>
<td>8 (2.72%)</td>
<td>0.037</td>
</tr>
<tr>
<td>Overall</td>
<td>31 (11.65%)</td>
<td>78 (30%)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

N=617
A role for angiotensin II in septic shock?
Administration of AGII decreases the need for norepinephrine

20 pts distributive shock
The primary end point was the response with respect to mean arterial pressure at hour 3, with response defined as a mean arterial pressure of 75 mm Hg or higher or an increase in mean arterial pressure from baseline of at least 10 mm Hg, without an increase in the dose of background vasopressors. The mean values of triplicate deter-

<table>
<thead>
<tr>
<th>End Point</th>
<th>Angiotensin II (N=163)</th>
<th>Placebo (N=158)</th>
<th>Odds or Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary efficacy end point: MAP response at hour 3 — no. (%) †</td>
<td>114 (69.9)</td>
<td>37 (23.4)</td>
<td>Odds ratio, 7.95 (4.76–13.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary efficacy end points</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change in cardiovascular SOFA score at hour 48‡</td>
<td>-1.75±1.77</td>
<td>-1.28±1.65</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Mean change in total SOFA score at hour 48§</td>
<td>1.05±5.50</td>
<td>1.04±5.34</td>
<td>0.49</td>
<td></td>
</tr>
<tr>
<td>Additional end points</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change in norepinephrine-equivalent dose from baseline to hour 3¶</td>
<td>-0.03±0.10</td>
<td>0.03±0.23</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality at day 7 — no. (%)</td>
<td>47 (29)</td>
<td>55 (35)</td>
<td>Hazard ratio, 0.78 (0.53–1.16)</td>
<td>0.22</td>
</tr>
<tr>
<td>All-cause mortality at day 28 — no. (%)</td>
<td>75 (46)</td>
<td>85 (54)</td>
<td>Hazard ratio, 0.78 (0.57–1.07)</td>
<td>0.12</td>
</tr>
</tbody>
</table>
Nitric oxide inhibition?
LNNMA IN PATIENTS WITH SEPTIC SHOCK

Lopez et al
CCM 32:21;2004

Placebo
LNNMA

Survival Distribution Function

Day of Study

0 3 7 14 21 28 35 42 49 56 63 70 77 84 90

Log-Rank Test p=<.001
Wilcoxon Test p=<.001
**VASOPRESSOR SUPPORT IN SHOCK**

- Norepinephrine as the 1st choice agent
- Vasopressin as an alternative.
- Angiotensin appears to be promising in septic shock but more data are needed.
- If one drug seems of limited efficacy, add a second agent of another class rather than another agent of same class.
And steroids....
500 pts septic shock

Sprung et al
NEJM 358:111;2008

CORTICUS

Shock reversal
EFFECT ON OUTCOME

Annane et al
JAMA 288:862; 2001

300 Patients in septic shock
500 pts septic shock
ADRENAL

Outcome

3800 pts septic shock

Hazard ratio for death, 0.95 (95% CI, 0.84–1.07)
P = 0.42

Venkatesh et al
NEJM 378:798;2018
1241 pts septic shock
Norepi (epi) dose at randomization

- Annane JAMA 2002: 1.1 (0.9) mcg/kg.min
- APPROACHES 2018: 1.2 mcg/kg.min
- CORTICUS 2008: ~0.5 mcg/kg.min
- VANISH 2016: 0.16 [0.10-0.31] mcg/kg.min
- ADRENAL 2018: 50% <0.2 mcg/kg.min
Inotropic agents: Why?
Myocardial depression in patients with septic shock

Reversible alteration in contractility

In vitro myocardial muscle

Parillo J et al
JCI 76:1539;1985
Reversible myocardial depression in patients with septic shock

Echographic evaluation of LVEF in patients with septic shock

\[ \text{Cl} = 0.05 \times \text{LVEF} + 0.73 \]

=> Inotropic agents should not be used to correct a low EF
Inotropic agents: Which?
EFFECT OF DOBUTAMINE

Vincent et al
CCM 18:689;1990

Dobutamine
5 mcg/kg.min

L/min.M²

P<0.01

Cardiac index

DDB USI
An increase in cardiac output is not always achieved by an increased contractility

Jellena et al
CCM 34:2392;2006

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Dobu Max</th>
<th>End</th>
<th>Baseline</th>
<th>Dobu Max</th>
<th>End</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ΔSVI &gt; 10% (n = 5)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>105 (77–114)</td>
<td>103 (83–132)</td>
<td>94 (87–119)</td>
<td>97 (67–123)</td>
<td>116 (76–135)</td>
<td>105 (69–125)</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>78 (78–94)</td>
<td>88 (79–98)</td>
<td>78 (77–94)</td>
<td>72 (65–91)</td>
<td>85 (60–77)</td>
<td>88 (68–81)</td>
</tr>
<tr>
<td>MPAP, mm Hg</td>
<td>30 (27–40)</td>
<td>35 (23–36)</td>
<td>30 (28–40)</td>
<td>27 (16–41)</td>
<td>24 (18–39)</td>
<td>26 (18–44)</td>
</tr>
<tr>
<td>PAOP, mm Hg</td>
<td>18 (15–22)</td>
<td>15 (11–23)</td>
<td>18 (15–24)</td>
<td>15 (10–19)</td>
<td>15 (12–19)</td>
<td>14 (10–20)</td>
</tr>
<tr>
<td>RAP, mm Hg</td>
<td>12 (8–24)</td>
<td>10 (6–21)</td>
<td>10 (7–20)</td>
<td>12 (7–21)</td>
<td>13 (8–21)</td>
<td>13 (6–18)</td>
</tr>
<tr>
<td>SVI, mL·m⁻²</td>
<td>49 (25–55)</td>
<td>56 (31–66)</td>
<td>46 (27–55)</td>
<td>52 (31–80)</td>
<td>44 (26–76)</td>
<td>50 (26–78)</td>
</tr>
<tr>
<td>CI, L·min⁻¹·m⁻²</td>
<td>4.3 (2.9–5.6)</td>
<td>5.4 (3.3–7.5)</td>
<td>4.8 (2.5–5.2)</td>
<td>4.4 (2.8–7.7)</td>
<td>4.9 (2.8–6.9)</td>
<td>4.6 (2.8–7.7)</td>
</tr>
<tr>
<td><strong>ΔSVI ≤ 10% (n = 14)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVSVI, g·m⁻²</td>
<td>41 (25–56)</td>
<td>65 (25–75)</td>
<td>46 (26–55)</td>
<td>41 (25–55)</td>
<td>31 (17–57)</td>
<td>36 (17–49)</td>
</tr>
<tr>
<td>Pao₂, mm Hg</td>
<td>122 (78–100)</td>
<td>93 (68–118)</td>
<td>108 (82–116)</td>
<td>102 (70–102)</td>
<td>88 (71–120)</td>
<td>84 (58–115)</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>98 (97–99)</td>
<td>97 (96–97)</td>
<td>97 (95–98)</td>
<td>97 (95–99)</td>
<td>96 (93–98)</td>
<td>97 (93–98)</td>
</tr>
<tr>
<td>Pvo₂, mm Hg</td>
<td>44 (36–45)</td>
<td>44 (40–48)</td>
<td>42 (36–44)</td>
<td>44 (36–48)</td>
<td>46 (34–57)</td>
<td>46 (32–54)</td>
</tr>
<tr>
<td>Svo₂, %</td>
<td>72 (69–77)</td>
<td>79 (74–81)</td>
<td>71 (68–74)</td>
<td>77 (58–83)</td>
<td>76 (60–85)</td>
<td>79 (60–87)</td>
</tr>
<tr>
<td>DoI, mL·min⁻¹·m⁻²</td>
<td>601 (398–744)</td>
<td>622 (466–979)</td>
<td>571 (430–676)</td>
<td>560 (423–855)</td>
<td>628 (394–977)</td>
<td>630 (485–967)</td>
</tr>
<tr>
<td>VoI, mL·min⁻¹·m⁻²</td>
<td>159 (125–179)</td>
<td>143 (125–179)</td>
<td>155 (123–175)</td>
<td>127 (86–263)</td>
<td>141 (100–198)</td>
<td>130 (85–226)</td>
</tr>
<tr>
<td>O₂ER, %</td>
<td>27 (21–31)</td>
<td>22 (21–31)</td>
<td>27 (24–32)</td>
<td>22 (16–38)</td>
<td>20 (17–36)</td>
<td>19 (17–36)</td>
</tr>
<tr>
<td>DPTI/SPTI</td>
<td>1.02 (0.77–1.2)</td>
<td>0.97 (0.7–1.1)</td>
<td>0.97 (0.63–1.14)</td>
<td>0.96 (0.59–1.46)</td>
<td>0.81 (0.5–1.41)</td>
<td>0.85 (0.59–1.45)</td>
</tr>
<tr>
<td>PWI, mL O₂·min/100 g⁻¹</td>
<td>9.0 (8.0–10.8)</td>
<td>11.9 (8.6–13.3)</td>
<td>9.4 (8.7–10.7)</td>
<td>8.7 (6.1–11.1)</td>
<td>8.5 (6.5–11.8)</td>
<td>8.4 (6.6–11.5)</td>
</tr>
</tbody>
</table>

19 patients with septic shock
## EFFECT OF LEVOSIMENDAN

<table>
<thead>
<tr>
<th></th>
<th>Levosimendan</th>
<th>Dobutamine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>24 h</td>
</tr>
<tr>
<td>EDVI (ml m⁻¹)</td>
<td>75.8±23.8</td>
<td>66.2±24.6***</td>
</tr>
<tr>
<td>ESVI (ml m⁻¹)</td>
<td>46.7±21.9</td>
<td>36.9±19.4***</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>37.1±3.0</td>
<td>45.4±8.4*</td>
</tr>
</tbody>
</table>

*p<0.05 baseline vs. 24 h, **p<0.05 levosimendan vs. dobutamine after 24 h

Morelli et al
ICM 31:638;2006
### EFFECT OF LEVOSIMENDAN

<table>
<thead>
<tr>
<th></th>
<th>Levosimendan</th>
<th>Dobutamine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>24 h</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>114±8.3</td>
<td>115±10.5</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>76.2±2.8</td>
<td>75.0±3.3</td>
</tr>
<tr>
<td>MPAP (mmHg)</td>
<td>26.2±2.4</td>
<td>23.1±2.4***</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>13.5±1.4</td>
<td>12.3±1.5*</td>
</tr>
<tr>
<td>PAOP (mmHg)</td>
<td>16.8±1.2**</td>
<td>12.0±0.6***</td>
</tr>
<tr>
<td>SI (ml m⁻²)</td>
<td>36.6±2.9**</td>
<td>39.1±4.1*</td>
</tr>
<tr>
<td>CI (l min⁻¹ m⁻²)</td>
<td>4.1±0.2</td>
<td>4.5±0.2*</td>
</tr>
<tr>
<td>SVRI (dyne s⁻¹ cm⁻⁵ m⁻²)</td>
<td>1238±100</td>
<td>1181±114</td>
</tr>
<tr>
<td>PVRI (dyne s⁻¹ cm⁻⁵ m⁻²)</td>
<td>226±56</td>
<td>202±45</td>
</tr>
<tr>
<td>DO₂I (ml min⁻¹ m⁻²)</td>
<td>715±58</td>
<td>746±59*</td>
</tr>
<tr>
<td>VO₂I (ml min⁻¹ m⁻²)</td>
<td>223±36</td>
<td>239±32*</td>
</tr>
<tr>
<td>LVSWI (g m⁻¹ m⁻²)</td>
<td>29.6±2.8</td>
<td>33.9±3.7***</td>
</tr>
</tbody>
</table>

|                | Baseline     | 24 h       |
| Troponin cTnI (ng/ml)     | 0.14±0.07    | 0.13±0.06***|
| GMP (%)         | –            | +55.3±20.1***|
| ΔP sub g sub a sub CO₂ (mmHg) | 15.3±1.1**   | 11.9±1.3****|
| Arterial lactate (mmol l⁻¹) | 4.9±1.2     | 3±0.7****   |
| Creatinine clearence (ml min⁻¹) | 43.9±12.8    | 72.1±16.2****|
| Urinary output (ml 24 h⁻¹)  | –            | 2028±461****|
| Fluid perfused (ml 24 h⁻¹)  | –            | 5907±330*** |
| Norepinephrine rate (µg kg⁻1 min⁻¹) | 0.22±0.07  | 0.22±0.06 |

*p<0.05 baseline vs. 24 h, **p<0.05 levosimendan vs. dobutamine at baseline, ***p<0.05 levosimendan vs. dobutamine after 24 h
Levosimendan in sepsis

Adult patients who had septic shock and had received vasopressors for at least 4 hours were eligible for inclusion. Detailed inclusion and exclusion criteria are provided in the full article. The study found no evaluation of cardiac output and no evaluation of contractility.

➢ No evaluation of cardiac output
➢ No evaluation of contractility
Select the right hemodynamic tool
Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine

<table>
<thead>
<tr>
<th>No.</th>
<th>Statement/recommendation</th>
<th>GRADE level of recommendation; quality of evidence</th>
<th>Type of statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>We recommend further hemodynamic assessment (such as assessing cardiac function) to determine the type of shock if the clinical examination does not lead to a clear diagnosis</td>
<td>Ungraded</td>
<td>Best practice</td>
</tr>
<tr>
<td>14</td>
<td>We suggest that, when further hemodynamic assessment is needed, echocardiography is the preferred modality to initially evaluate the type of shock as opposed to more invasive technologies</td>
<td>Level 2; QoE moderate (B)</td>
<td>Recommendation</td>
</tr>
<tr>
<td>15</td>
<td>In complex patients, we suggest to additionally use pulmonary artery catheterization or transpulmonary thermodilution to determine the type of shock</td>
<td>Level 2; QoE low (C)</td>
<td>Recommendation</td>
</tr>
</tbody>
</table>
CIRCULATORY FAILURE

Central line
- CVP
- ScvO2
- PvaCO2

ECHO

Arterial line
- AP
- PPV
- Lactate

Rapid improvement

No improvement
Complex cases

Expect and reevaluate

PAC
TPTD

EVLW
GEDV
PAP
PAOP

CONFERENCE REPORTS AND EXPERT PANEL
Less invasive hemodynamic monitoring in critically ill patients
ICM 2016
Initial assessment

Echocardiography

- Hypovolemia Distributive
  - TPTD

- ARDS or Cardiac dysfunction without RV impairment
  - TPTD or PAC

- ARDS or Cardiac dysfunction with RV impairment
  - PAC or TPTD + Echo

Once a day or significant hemodynamic changes detected by monitoring

Repeat Echocardiography
What is the resuscitation goal?

**Early phase**

<table>
<thead>
<tr>
<th>Salvaage</th>
<th>Optimization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obtain a minimal acceptable blood pressure</td>
<td>Provide adequate oxygen availability</td>
</tr>
<tr>
<td>Perform lifesaving measures</td>
<td>Optimize cardiac output, $S\text{vo}_2$, lactate</td>
</tr>
</tbody>
</table>

**Later stages**

<table>
<thead>
<tr>
<th>Stabilization</th>
<th>De-escalation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provide organ support</td>
<td>Wean from vasoactive agents</td>
</tr>
<tr>
<td>Minimize complications</td>
<td>Achieve a negative fluid balance</td>
</tr>
</tbody>
</table>