Sepsis-3

Abdul Hakeem Al Hashim, MD, FRCPC
Senior Consultant
Internal Medicine & Critical Care
Sultan Qaboos University Hospital
Topics

• Definition of Sepsis

• Resuscitation strategy

• Use of Vasopressors
History

ACC autopsy conference

Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis

 THE ACCP/SCCM CONSENSUS CONFERENCE COMMITTEE:
Roger C. Bone, M.D., F.C.C.P., Chairman
Robert A. Balk, M.D., F.C.C.P.
Frank B. Cerra, M.D.
R. Phillip Dellinger, M.D., F.C.C.P.
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William A. Knaus, M.D.
Roland M. H. Schein, M.D.
William J. Sibbald, M.D., F.C.C.P.

2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference

Mitchell M. Levy, MD, FCCP; Mitchell P. Fink, MD, FCCP; John C. Marshall, MD; Edward Abraham, MD; Derek Angus, MD, MPH, FCCP; Deborah Cook, MD, FCCP; Jonathan Cohen, MD; Steven M. Opal, MD; Jean-Louis Vincent, MD, FCCP, PhD; Graham Ramsay, MD; For the International Sepsis Definitions Conference
Septic Shock Definitions

1991
Sepsis induced hypotension, persistent despite fluid resuscitation along with hypoperfusion & organ dysfunction

2001
State of acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes

2016
Sepsis-3
Task of:
- Intensivists
- ID
- Surgery
- Pulmonary medicine
Old Definition

**SIRS**: (2 or more of:) 1) Temperature >38 or < 36°C 2) HR > 90/min 3) RR > 20/min or PaCO2 < 32 mmHg 4) WBC > 11,000 or < 4,000 or > 10% immature (band) forms

**Sepsis**: SIRS with definitive evidence of infection

**Severe Sepsis**: Sepsis with organ dysfunction, hypoperfusion or hypotension

**Septic shock**: Sepsis with hypotension despite adequate fluid resuscitation
Old definition

**SIRS**: (2 or more of:)

1) Temperature >38 or < 36°C
2) HR > 90/min
3) RR > 20/min or PaCO₂ < 32 mmHg
4) WBC > 11,000 or < 4,000 or > 10% immature (band) forms

Old definition

• **Severe Sepsis**: Sepsis with organ dysfunction, hypoperfusion or hypotension

• **Mortality:**
  - Australia 22%
  - Germany 60.5%
  - The Netherlands 60%
The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH
Sepsis 2016: Definition

• **Sepsis:**

  a *life-threatening organ dysfunction* caused by a *dysregulated* host response to *infection*
Clinical Criteria of Sepsis

- Sepsis: Infection with organ dysfunction

Organ Dysfunction: Acute change in total SOFA score ≥ 2 from baseline
(Previous healthy patient: take baseline SOFA as zero)

SOFA: Sequential (Sepsis-related) Organ Failure Assessment
## SOFA score

### Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score\(^a\)

<table>
<thead>
<tr>
<th>System</th>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\text{PaO}_2/\text{FiO}_2, \text{mm Hg (kPa)})</td>
<td>(\geq 400 (53.3))</td>
<td>(&lt;400 (53.3))</td>
<td>(&lt;300 (40))</td>
<td>(&lt;200 (26.7)) with respiratory support</td>
<td>(&lt;100 (13.3)) with respiratory support</td>
<td></td>
</tr>
<tr>
<td><strong>Coagulation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets, (\times 10^3/\mu\text{L})</td>
<td>(\geq 150)</td>
<td>(&lt;150)</td>
<td>(&lt;100)</td>
<td>(&lt;50)</td>
<td>(&lt;20)</td>
<td></td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin, mg/dL ((\mu\text{mol/L}))</td>
<td>(&lt;1.2 (20))</td>
<td>(1.2-1.9 (20-32))</td>
<td>(2.0-5.9 (33-101))</td>
<td>(6.0-11.9 (102-204))</td>
<td>(&gt;12.0 (204))</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (\geq 70 \text{mm Hg})</td>
<td>MAP (&lt;70 \text{mm Hg})</td>
<td>Dopamine &lt;5 or dobutamine (any dose)(^b)</td>
<td>Dopamine 5.1-15 or epinephrine (\leq 0.1) or norepinephrine (\leq 0.1)(^b)</td>
<td>Dopamine &gt;15 or epinephrine &gt;0.1 or norepinephrine &gt;0.1(^b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Central nervous system</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glasgow Coma Scale score(^c)</td>
<td>15</td>
<td>13-14</td>
<td>10-12</td>
<td>6-9</td>
<td>(&lt;6)</td>
<td></td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine, mg/dL ((\mu\text{mol/L}))</td>
<td>(&lt;1.2 (110))</td>
<td>(1.2-1.9 (110-170))</td>
<td>(2.0-3.4 (171-299))</td>
<td>(3.5-4.9 (300-440))</td>
<td>(&gt;5.0 (440))</td>
<td></td>
</tr>
<tr>
<td>Urine output, mL/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(&lt;500)</td>
<td>(&lt;200)</td>
</tr>
</tbody>
</table>

**Abbreviations:** \(\text{FiO}_2\), fraction of inspired oxygen; MAP, mean arterial pressure; \(\text{PaO}_2\), partial pressure of oxygen.

\(^a\) Adapted from Vincent et al.\(^{27}\)

\(^b\) Catecholamine doses are given as \(\mu\text{g/kg/min}\) for at least 1 hour.

\(^c\) Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.
Scoring

Outside ICU; qSOFA has similar predictive validity to more complex scores

Outside the ICU, consider Sepsis if:
Infection + ≥ 2 qSOFA points
gSOFA

- Respiratory Rate
- Mental Status
- Systolic BP

HAT
- Hypotension \((sBP \leq 100)\)
- Altered mental status
- Tachypnia \((RR \geq 22/\text{min})\)
Important

- qSOFA doesn’t define sepsis

- A predictor of increase ICU stay and mortality
Clinical Criteria

Patients with suspected infection

qSOFA $\geq 2$?

YES

Assess for evidence of organ dysfunction

SOFA $\geq 2$?

YES

Sepsis

SOFA Variables:
- PaO2/FiO2 ratio
- Glasgow Coma Scale score
- Mean arterial pressure
- Administration of vasopressors with type and dose rate of infusion
- Serum creatinine or urine output
- Bilirubin
- Platelet count
Sepsis Shock

• **Sepsis**: a life-threatening organ dysfunction caused by a dysregulated host response to infection

• **Septic Shock**: a subset of sepsis in which profound circulatory, cellular & metabolic abnormalities are associated with a **greater risk of mortality**
Septic Shock 2016

• Who are those sickest patients with higher mortality??

• What clinical criteria?

  - Circulatory dysfunction
  - Cellular / Metabolic
Cellular/ Metabolic: lactate
## In hospital Mortality

<table>
<thead>
<tr>
<th>Patients</th>
<th>Hospital Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Hypotension &amp; Lactate &lt; 2</td>
<td>18.7</td>
</tr>
<tr>
<td>Lactate &gt; 2 only</td>
<td>25.7</td>
</tr>
<tr>
<td>Hypotension only</td>
<td>30.1</td>
</tr>
<tr>
<td>Hypotension + Lactate &gt; 2</td>
<td>42.3</td>
</tr>
</tbody>
</table>
Septic Shock

Sepsis

Despite adequate fluid resuscitation:
1) Vasopressors required to maintain MAP ≥ 65 mmHg &
2) Serum lactate ≥ 2 mmol/L

YES

Septic Shock
Sepsis & Septic Shock

- **SIRS**
  - Non specific

- **Severe Sepsis**
  - Confusing
  - Use sepsis mostly
Sepsis & Septic Shock

• New sepsis ≈ old severe sepsis

(with better defined criteria of organ dysfunction {SOFA} )

• Septic shock: bad sepsis with higher mortality
New definition

• Not widely accepted or endorsed
  - Emergency medicine societies
  - American College of Chest Physicians

- No change recommended for regulatory agencies and hospital Quality dept

Why?
New criteria criticism

- Sepsis I – II: Suspected Infection + (SIRS)
- Sepsis III: Suspected Infection + (qSOFA + SOFA)
- qSOFA & SOFA are mortality indicator

In ER, you want to identify patients at risk
**SIRS vs qSOFA**

<table>
<thead>
<tr>
<th>Test</th>
<th>Area under ROC curve</th>
<th>Sensitivity for Mortality %</th>
<th>Specificity for Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIRS ≥ 2</td>
<td>0.76</td>
<td>64</td>
<td>65</td>
</tr>
<tr>
<td>SOFA ≥ 2</td>
<td>0.79</td>
<td>68</td>
<td>67</td>
</tr>
<tr>
<td>qSOFA ≥ 2</td>
<td>0.81</td>
<td>55</td>
<td>84</td>
</tr>
</tbody>
</table>

*Patient with suspected infection*

- qSOFA ≥ 2? (see A)
  - Yes
    - Assess for evidence of organ dysfunction
      - SOFA ≥ 2? (see B)
        - Yes
          - Monitor clinical condition; reevaluate for possible sepsis if clinically indicated
        - No
          - Sepsis
    - No
      - Monitor clinical condition; reevaluate for possible sepsis if clinically indicated
  - No
    - Sepsis still suspected?
      - Yes
        - Monitor clinical condition; reevaluate for possible sepsis if clinically indicated
      - No
        - Monitor clinical condition; reevaluate for possible sepsis if clinically indicated
New Criteria Criticism

• **qSOFA**: screening with low BP (too late?)

• **SOFA score**:
  - Asking too much?
  - Questions about their sensitivity / specificity (no prospective studies)
  - What about centers with limited resources?
  - Not all ICUs use SOFA score

• **Lactate**
  Not all hospitals measure lactate
Steps of new sepsis

- **1\textsuperscript{st} step**: Identification of infection, culture, and antibiotic administration
- **2\textsuperscript{nd} step**: screening of organ dysfunction and management of sepsis: qSOFA / SOFA
  
  Three-hour bundle elements

- **3\textsuperscript{rd} step**: Identification and management of initial hypotension:
  
  Crystalloid 30 mL / kg
  
  Reassessment of tissue perfusion / volume responsiveness

**SIRS still has a role**

Note: No change in pathobiology or management
Sepsis definition 3.0
Topics

• Definition of Sepsis

• Resuscitation strategy

• Use of Vasopressors
Early Goal Directed Therapy? 
Resuscitation
EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

EMANUEL RIVERS, M.D., M.P.H., BRYANT NGUYEN, M.D., SUZANNE HAVSTAD, M.A., JULIE RESSLER, B.S., ALEXANDRIA MUZZIN, B.S., BERNHARD KNOBLICH, M.D., EDWARD PETERSON, PH.D., AND MICHAEL TOMLANOVICH, M.D., FOR THE EARLY GOAL-DIRECTED THERAPY COLLABORATIVE GROUP*
Management of septic shock

Supplemental oxygen ± endotracheal intubation and mechanical ventilation

Central venous and arterial catheterization

Sedation, paralysis (if intubated), or both

CVP

< 8 mm Hg

Crystalloid

Colloid

8–12 mm Hg

MAP

< 65 mm Hg

Vasoactive agents

> 90 mm Hg

Transfusion of red cells until hematocrit ≥ 30%

≥ 85 and ≤ 90 mm Hg

ScvO2

< 70%

Inotropic agents

≥ 70%

Goals achieved

No

Yes

Hospital admission
EGDT in severe sepsis and septic shock

- In-hospital mortality (all patients) vs Standard Therapy
- 28-day mortality: EGT 49.2% vs Standard Therapy 33.3%
- 60-day mortality: EGT 50% vs Standard Therapy

p=0.01*  
NNT 6

Rivers et al. NEJM 2002;345:1368
Management of septic shock

Supplemental oxygen ± endotracheal intubation and mechanical ventilation

Central venous and arterial catheterization

Sedation, paralysis (if intubated), or both

CVP

< 3 mm Hg

2-12 mm Hg

Crystalloid

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

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

The ProCESS Investigators*

<table>
<thead>
<tr>
<th>Table 1. Characteristics of the Patients at Baseline.*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristic</strong></td>
</tr>
<tr>
<td>Age — yr†</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
</tr>
<tr>
<td>Residence before admission — no. (%)‡</td>
</tr>
</tbody>
</table>
Figure S2. – Protocol for Standard Therapy.

1. Supplemental oxygen ± endotracheal intubation and mechanical ventilation

2. 2 large bore (18 g or larger) IV’s (Central line if unable to achieve)

3. Sedation, analgesia, +/- or paralysis (if intubated)

4. 500-1000 ml fluid bolus* (min. initial total fluid = 2 L*, unless fluid replete/overload)
A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*

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

A Cumulative In-Hospital Mortality to 60 Days

No. at Risk
- Protocol-based EGDT: 439, 373, 356, 348, 347, 347, 347
- Protocol-based standard therapy: 446, 389, 376, 368, 366, 366, 365
- Usual care: 456, 396, 376, 371, 371, 371, 370

P = 0.52 by log-rank test
A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*
Does it mean no Central line?

- Unstable patients need central line for:
  - Multiple drug infusions
  - Vasopressor infusion
  - Central venous saturation (SvO2)
Does it mean no central line?
Management of septic shock

1. Supplemental oxygen ± endotracheal intubation and mechanical ventilation
2. Central venous and arterial catheterization
3. Sedation, paralysis (if intubated), or both
   - CVP
   - 8–12 mm Hg
   - <8 mm Hg
   - Crystalloid
   - Colloid
Albumin Replacement in Patients with Severe Sepsis or Septic Shock

Pietro Caironi, M.D., Gianni Tognoni, M.D., Serge Masson, Ph.D., Roberto Fumagalli, M.D., Antonio Pesenti, M.D., Marilena Romero, Ph.D., Caterina Fanizza, M.Stat., Luisa Caspani, M.D., Stefano Faenza, M.D., Giacomo Grasselli, M.D., Gaetano Iapichino, M.D., Massimo Antonelli, M.D., Vieri Parrini, M.D., Gilberto Fiore, M.D., Roberto Latini, M.D., and Luciano Gattinoni, M.D., for the ALBIOS Study Investigators*
Crystalloids vs Colloids

A meta-analysis of 56 randomized trials found no overall difference in mortality between crystalloids and artificial colloids (modified gelatins, HES, dextran) when used for initial fluid resuscitation (125). Information from 3 randomized trials (n = 704 patients with severe sepsis/septic shock) did not show survival benefit with use of heta-, hexa-, or pentastarches compared to other fluids (RR, 1.15; 95% CI, 0.95–1.39; random effect, I² = 0%) (126–128). However, these solutions increased the risk of acute kidney injury (RR, 1.60; 95% CI, 1.26–2.04; I² = 0%) (126–128).
Management of septic shock

- CVP:
  - < 8 mm Hg: Crystalloid, Colloid
  - 8–12 mm Hg
  - > 90 mm Hg: Vasoactive agents

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

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

- Goals achieved:
  - No: Continue treatment
  - Yes: Hospital admission
SvO2
Management of septic shock

- **CVP**
  - < 8 mm Hg: Crystalloid, Colloid
  - 8–12 mm Hg
    - **MAP**
      - < 65 mm Hg: Vasopressors
      - > 90 mm Hg
        - **ScvO₂**
          - < 70%: Transfusion of red cells until hematocrit ≥ 30%
          - ≥ 70%
            - **Goals achieved**
              - Yes: Hospital admission
              - No: Inotropic agents

What is the target BP?

High versus Low Blood-Pressure Target in Patients with Septic Shock

Pierre Asfar, M.D., Ph.D., Ferhat Meziani, M.D., Ph.D., Jean-François Hamel, M.D., Fabien Grelon, M.D., Bruno Megarbane, M.D., Ph.D., Nadia Anguel, M.D., Jean-Paul Mira, M.D., Ph.D., Pierre-François Dequin, M.D., Ph.D., Soizic Gergaud, M.D., Nicolas Weiss, M.D., Ph.D., François Legay, M.D., Yves Le Tulzo, M.D., Ph.D., Marie Conrad, M.D., René Robert, M.D., Ph.D., Frédéric Gonzalez, M.D., Christophe Guitton, M.D., Ph.D., Fabienne Tamion, M.D., Ph.D., Jean-Marie Tonnelier, M.D., Pierre Guezennec, M.D., Thierry Van Der Linden, M.D., Antoine Vieillard-Baron, M.D., Ph.D., Eric Mariotte, M.D., Gaël Pradel, M.D., Olivier Lesieur, M.D., Jean-Damien Ricard, M.D., Ph.D., Fabien Hervé, M.D., Damien Du Cheyron, M.D., Ph.D., Claude Guerin, M.D., Ph.D., Alain Mercat, M.D., Ph.D., Jean-Louis Teboul, M.D., Ph.D., and Peter Radermacher, M.D., Ph.D. for the SEPSISPAM Investigators*
SEPSISPAM

• Randomized trial of 776 patients with septic shock in France
• High target (MAP 80-85) vs Low MAP (65-70) x 5 days.
• Inclusion:
  – >18
  – Refractory shock
  – Septic shock < 6 hours
  – Norepinephrine > 0.1mcg/kg/min
High versus Low Blood-Pressure Target in Patients with Septic Shock

**No. at Risk**
- Low target: 379, 256, 233, 225
- High target: 375, 249, 227, 219
High versus Low Blood-Pressure Target in Patients with Septic Shock

Table 2. Clinical Results, Primary and Secondary Outcomes, and Serious Adverse Events.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low-Target Group (N = 388)</th>
<th>High-Target Group (N = 388)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative fluid intake from day 1 to day 5 — liters</td>
<td>10.0 (5.8–14.0)</td>
<td>10.5 (5.5–14.0)</td>
<td>0.89</td>
</tr>
<tr>
<td>Cumulative urine output from day 1 to day 5 — liters</td>
<td>6.7 (2.9–10.7)</td>
<td>6.9 (2.4–10.7)</td>
<td>0.87</td>
</tr>
<tr>
<td>Cumulative fluid balance from day 1 to day 5 — liters</td>
<td>2.8 (0.0–6.2)</td>
<td>2.4 (0.0–6.0)</td>
<td>0.74</td>
</tr>
<tr>
<td>Median dose of norepinephrine (NOR) — µg/kg/min</td>
<td>161 (41.5)</td>
<td>150 (38.7)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

- **Doubling of plasma creatinine**
  - Low-Target: 90/173 (52.0)
  - High-Target: 65/167 (38.9)
  - P Value: 0.02

- **Renal-replacement therapy from day 1 to day 7**
  - Low-Target: 139 (35.8)
  - High-Target: 130 (33.5)
  - P Value: 0.50

- **Chronic hypertension**
  - Low-Target: 66/215 (30.7)
  - High-Target: 77/221 (34.8)
  - P Value: 0.36

- **Renal-replacement therapy from day 1 to day 7**
  - Low-Target: 73/173 (42.2)
  - High-Target: 53/167 (31.7)
  - P Value: 0.046
Target BP

• At least MAP 65 mmHg
• Probably higher value if:
  - Hx of chronic HTN
  - Increased abdominal pressure
  - Initial renal impairment
Management of septic shock

- CVP: 
  - < 8 mm Hg: Crystalloid
  - 8-12 mm Hg: Colloid
  - ≥ 65 mm Hg and ≤ 90 mm Hg:
    - < 65 mm Hg: Vasoactive agents
    - ≥ 90 mm Hg: No

- MAP: 
  - < 65 mm Hg: Vasoactive agents
  - ≥ 65 mm Hg: Yes

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

- Goals achieved: 
  - No: Inotropic agents
  - Yes: Hospital admission
Lower versus Higher Hemoglobin Threshold for Transfusion in Septic Shock

Lars B. Holst, M.D., Nicolai Haase, M.D., Ph.D., Jørn Wetterslev, M.D., Ph.D.,
TRISS trial

- Multicenter, randomized control trial
- 1005 patients
- Low Hb threshold \((7 \text{ g/dl})\) and High Threshold \((9 \text{ g/dl})\)
TRISS trial

• **Inclusion:**
  - Septic Shock
  - > 18 years
  - Hb < 9g/dl

• **Exclusion:**
  - Active Bleeding.
  - Acute coronary syndrome
  - Prior transfusion in the ICU.
  - Reaction to transfusion.
TRISS trial

Blood Hemoglobin (g/dl)

Days since Randomization

Baseline 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28

Higher hemoglobin threshold

Lower hemoglobin threshold
TRISS trial

![Graph showing the probability of survival over days since randomization for two hemoglobin thresholds. The graph shows that the lower hemoglobin threshold has a higher probability of survival compared to the higher hemoglobin threshold. The P-value is 0.41.]
Management of septic shock

1. Supplemental oxygen ± endotracheal intubation and mechanical ventilation
2. Central venous and arterial catheterization
3. Sedation, paralysis (if intubated), or both
   - **CVP**
     - <8 mm Hg: Crystalloid
     - 8-12 mm Hg
     - >90 mm Hg: Vasoactive agents
   - **MAP**
     - <65 mm Hg: Vasoactive agents
     - >90 mm Hg: Crystalloid
   - **ScvO₂**
     - <70%: Transfusion of red cells until hematocrit ≥30%
     - ≥70%
6. **Goals achieved**
   - No
   - Yes: Hospital admission
Sepsis

- Primarily treat sepsis with IV fluids
- Use crystalloids
- MAP $> 65$ mmHg adequate
- Early antibiotics (within 1 hour)
- Hb threshold 7 is adequate
- No use of ScvO2
Topics

• Definition of Sepsis

• Resuscitation strategy

• Use of Vasopressors
Pharmacotherapy Update on the Use of Vasopressors and Inotropes in the Intensive Care Unit

Jacob C. Jentzer, MD¹,⁵, James C. Coons, PharmD¹,²,⁶, Christopher B. Link, MD¹, and Mark Schmidhofer, MD³,⁴

Abstract
This paper summarizes the pharmacologic properties of vasoactive medications used in the treatment of shock, including the inotropes and vasopressors. The clinical application of these therapies is discussed and recent studies describing their use and associated outcomes are also reported. Comprehension of hemodynamic principles and adrenergic and non-adrenergic receptor pharmacology has become increasingly important as treatment of severe forms of shock becomes more complex.
Direct inotropic effects

NO

Vasoconstrictors
Phenylephrine
Vasopressin

YES

Inoconstrictors
Norepinephrine
Epinephrine
Dopamine

Vasodilators
Nitroglycerine
Nitroprusside
Nesiritide

Inodilators
Dobutamine
Milrinone

INOTROPES

Peripheral vascular effects

Vasoconstriction

Vasodilation
Vasopressor therapy initially to target MAP 65mmHg
Comparison of Dopamine and Norepinephrine in the Treatment of Shock

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Vasopressors

No. at Risk
Norepinephrine  821  617  553  504  467  432  412  394
Dopamine  858  611  546  494  452  426  407  386

P=0.07 by log-rank test

Days since Randomization

Probability of Survival (%)

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Vasopressors

![Hazard Ratio (95% CI)](image)

- **Type of shock**
  - Hypovolemic
  - Cardiogenic
  - Septic
  - All patients

- **Hazard Ratio (95% CI)**
  - Norepinephrine Better
  - Dopamine Better

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Norepinephrine VS Dopamine

Dopamine increases MAP and cardiac output, primarily due to an increase in stroke volume and heart rate. Norepinephrine increases MAP due to its vasoconstrictive effects, with little change in heart rate and less increase in stroke volume compared with dopamine. Norepinephrine is more potent than dopamine and may be more effective at reversing hypotension in patients with septic shock. Dopamine may be particularly useful in...
Norepinephrine VS DA

effects. However, information from five randomized trials \( (n = 1993 \) patients with septic shock) comparing norepinephrine to dopamine does not support the routine use of dopamine in the management of septic shock (136, 149–152). Indeed, the relative risk of short-term mortality was 0.91 (95% CI, 0.84–1.00; fixed effect; \( I^2 = 0\% \)) in favor of norepinephrine. A recent meta-analysis showed dopamine was associated with an increased risk (RR, 1.10 [1.01–1.20]; \( p = 0.035 \)); in the two trials that reported
• Improves systemic blood pressure
• Does not substantially worsen end-organ ischemia in most studies of crystalloid-resuscitated septic shock patients
• Equivalent efficacy in increasing mean arterial pressure, oxygen consumption, and oxygen delivery compared with other catecholamine pressors
• Gastric pH has been observed to increase (not decrease)
• 778 patients with septic shock randomly assigned to either low dose vasopressin (0.01 to 0.03 units per minute) norepinephrine (5 to 15 mcg per minute)
• similar 28-day and 90-day mortality rates, similar incidence of serious adverse events

Vasopressin and Septic Shock Trial (VASST)
Vasopressors

1st choice: Norepinephrine &/or Epinephrine /Vasopressin

Dopamine in ONLY highly selected patients; Absolute bradycardia
Thanks

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