Septic Shock: Pharmacologic Agents for Hemodynamic Support

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Objectives

• Define septic shock and briefly review pathophysiology
• Outline receptor selectivity and physiologic functions
• Examine guidelines and recommendations
• Compare vasopressors used in septic shock
• Distinguish which patients benefit from corticosteroids
• Summarize the when and why of vasopressors, inotropes, and steroids
Agents of Interest

- Norepinephrine
- Dopamine
- Epinephrine
- Vasopressin
- Phenylephrine
- Dobutamine
- Hydrocortisone
Septic Shock

Definition
• Hypotension refractory to adequate fluid resuscitation

Pathophysiology
• ↓ intravascular volume (capillary leakage)
• ↓ arteriole resistance
• ↑ venous capacitance
• ↓ cardiac contractility
# Receptor Types & Physiological Function

<table>
<thead>
<tr>
<th>Vasoconstriction</th>
<th>Heart Rate</th>
<th>Splanchnic Blood Flow</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>α</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>β</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>V</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td></td>
<td></td>
<td>↑</td>
</tr>
</tbody>
</table>

Basic and Clinical Pharmacology 11th ed
Spectrum of Activity

α

Phenylephrine
Norepinephrine
Epinephrine

β

Dobutamine
Relative Receptor Activity

<table>
<thead>
<tr>
<th></th>
<th>α</th>
<th>β</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>+++</td>
<td>+++</td>
<td>0</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>+++</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>+++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>+/-</td>
<td>+++</td>
<td>0</td>
</tr>
<tr>
<td>Dopamine</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

α ≈ β
α >> β
α >>>>> β
β >>>>> α

Adopted from:
Tintinalli’s Emergency Medicine
Basic and Clinical Pharmacology 11th ed.

R. Phillip Dellinger, MD; Mitchell M. Levy, MD; Andrew Rhodes, MB BS; Djillali Annane, MD; Herwig Gerlach, MD, PhD; Steven M. Opal, MD; Jonathan E. Sevinsky, MD; Charles L. Sprung, MD; Ivor S. Douglas, MD; Roman Jaeschke, MD; Tiffany M. Osborn, MD, MPH; Mark E. Nunnally, MD; Sean R. Townsend, MD; Konrad Reinhart, MD; Ruth M. Kleinpell, PhD, RN-CS; Derek C. Angus, MD, MPH; Clifford S. Deutschman, MD, MS; Flavia R. Machado, MD, PhD; Gordon D. Rubenfeld, MD; Steven A. Webb, MB BS, PhD; Richard J. Beale, MB BS; Jean-Louis Vincent, MD, PhD; Rui Moreno, MD, PhD; and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup*
Grading of Recommendations

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>1</td>
<td>Strong</td>
</tr>
<tr>
<td>2</td>
<td>Weak</td>
</tr>
<tr>
<td>A</td>
<td>High</td>
</tr>
<tr>
<td>B</td>
<td>Moderate</td>
</tr>
<tr>
<td>C</td>
<td>Low</td>
</tr>
<tr>
<td>D</td>
<td>Very Low</td>
</tr>
</tbody>
</table>

Surviving Sepsis, CCM 2013
Surviving Septic Shock: Vasopressors

1. Target a MAP of 65 mmHg (1C)
Vascular Beds

![Graph showing the relationship between blood flow and perfusion pressure, with a line labeled 'autoregulation'.]
Evaluating Tissue Perfusion

- Mean Arterial Pressure (MAP)
- Blood Pressure
- Lactate
- SvO₂
- Urinary Output
- Skin perfusion
- Mental status
Surviving Septic Shock: Vasopressors

2. Norepinephrine as first choice (1B)
Norepinephrine

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Initial Rate</th>
<th>Adjustment</th>
<th>Soft Max</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>4mg / 250ml D5W</td>
<td>5</td>
<td>2-5 every 5 min</td>
<td>30</td>
<td>mcg / min</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>α</th>
<th>β</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>+++</td>
<td>++</td>
<td>0</td>
</tr>
</tbody>
</table>

- α and β activity, but **prominently α**
- Vasoconstriction with opposing β
- Little change in heart rate

*Basic and Clinical Pharmacology 11th ed*
Dopamine

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Initial Rate</th>
<th>Adjustment</th>
<th>Max Rate</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREMIX (800mg / 500ml D5W)</td>
<td>8-10</td>
<td>5 every 3-5 min</td>
<td>20</td>
<td>mcg / kg / min</td>
</tr>
</tbody>
</table>

Dose-Dependent Pharmacological Profile

- **Low**: <5 mcg / kg / min  →  $D$
- **Intermediate**: 5-10 mcg / kg / min  →  $\beta + D$
- **High**: >10 mcg / kg / min  →  $\alpha + \beta + D$

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*Basic and Clinical Pharmacology 11th ed*
Norepinephrine vs. Dopamine

- **De Backer, et al. 2010**
  - Not specific to “septic shock”
  - No difference in rate of death
  - Greater adverse events with dopamine

- **Vasu, et al. 2012**
  - Systemic Review, 6 RCT’s
  - Pooled analysis favored norepinephrine
  - More adverse effects with dopamine
  - Short term mortality favoring norepinephrine

- **De Backer, et al. 2012**
  - Meta-analysis
  - Dopamine increased mortality

*De Backer, et al. NEJM 2010
De Backer, et al. CCM 2012
3. Epinephrine can be substituted for or added to norepinephrine for adequate blood pressure (2B)
Epinephrine

- Hyperlactatemia
- May decrease splanchnic circulation
- No evidence of difference from norepinephrine

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<th>Adjustment</th>
<th>Soft Max</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>4mg / 250ml NS</td>
<td>5</td>
<td>1-2 every 3-5 min</td>
<td>20</td>
<td>mcg / min</td>
</tr>
</tbody>
</table>

α +++ β +++ D 0
Surviving Septic Shock: Vasopressors

4. Vasopressin can be added to norepinephrine to raise MAP or decrease norepinephrine (Ungraded)

5. Not recommended as initial single agent, and higher doses only for salvage therapy (Ungraded)
**Vasopressin**

- Relative vasopressin deficiency
- Norepinephrine dose sparing effect
- VASST trial
  - no difference in outcome
  - $<15 \text{ mcg/min of NE}$, better survival
  - More digital ischemia with vasopressin

<table>
<thead>
<tr>
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<th>Initial Rate</th>
<th>Adjustment</th>
<th>Max Rate</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 units / 250ml NS</td>
<td>0.03</td>
<td>rare</td>
<td>0.04</td>
<td>units / min</td>
</tr>
</tbody>
</table>

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Surviving Septic Shock: Vasopressors

6. Dopamine as an alternative in select patients (2C)
## Dopamine

<table>
<thead>
<tr>
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<th>Initial Rate</th>
<th>Adjustment</th>
<th>Max Rate</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREMIX (800mg / 500ml D5W)</td>
<td>8-10</td>
<td>5 every 3-5 min</td>
<td>20</td>
<td>mcg / kg / min</td>
</tr>
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</table>

• Selected Patients
  • Low risk of tachyarrhythmia’s
  • Absolute or relative bradycardia

• Balance with risk of adverse arrhythmias
Surviving Septic Shock: Vasopressors

7. Phenylephrine not recommended with few exceptions (1C)
Phenylephrine

### Exceptions for use
1. Norepinephrine → serious arrhythmias
2. Cardiac output is known to be high
3. Added for salvage therapy

### Caution
- Can decrease stroke volume, cause bradycardia

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<th>Soft Max</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>50mg / 250ml NS</td>
<td>100</td>
<td>10-50 every 5 min</td>
<td>300</td>
<td>mcg / min</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>α</th>
<th>β</th>
<th>D</th>
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</thead>
<tbody>
<tr>
<td>+++</td>
<td>0</td>
<td>0</td>
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Surviving Sepsis, CCM 2013
Basic and Clinical Pharmacology 11th ed
Surviving Septic Shock: Vasopressors

8. Do not use low-dose dopamine for renal protection (1A)
Low Dose Dopamine

- <5 mcg/kg/min
- May increase renal blood flow and UOP
- No difference in outcomes, may induce harm
- Bellomo, et al. 2000 (RCT)
  - No difference in peak serum creatinine
  - Does not confer renal protection
- Kellum, et al. 2001 (meta-analysis)
  - 58 studies
  - Did not prevent mortality, onset of AKI, or dialysis

Bellomo, et al. 2000
Kellum, et al. 2001
Surviving Septic Shock: Inotropic Therapy

1. Dobutamine in addition to vasopressor for myocardial dysfunction or ongoing hypoperfusion *despite* volume and MAP (1C)

2. Do not push supranormal, predetermined cardiac index (1B)
Dobutamine

• Mixed α stimulation/blockade
• Systemic vasodilation
• Myocardial contractility
• Minimal heart rate changes

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<th>Adjustment</th>
<th>Max Rate</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREMIX (500mg / 250ml NS)</td>
<td>2</td>
<td>2.5-5 q5-10 min</td>
<td>20</td>
<td>mcg / kg / min</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>α</th>
<th>β</th>
<th>D</th>
</tr>
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<tbody>
<tr>
<td>+/-</td>
<td>++++</td>
<td>0</td>
</tr>
</tbody>
</table>
Surviving Septic Shock: Corticosteroids

1. Only add hydrocortisone if refractory to fluids and vasopressors (2C)

2. Suggest against use of ACTH stimulation test (2B)
Surviving Septic Shock: Corticosteroids

3. Taper off when vasopressors no longer required (2D)

4. Not for treatment of sepsis without shock (1D)

5. Continuous infusion over bolus (2D)
Steroid Activity

- Glucocorticoid
- Mineralocorticoid

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Equivalent Dose</th>
<th>Anti-inflammatory</th>
<th>Mineralocorticoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>20 mg</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Prednisone</td>
<td>5 mg</td>
<td>4</td>
<td>0.6</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>4 mg</td>
<td>5</td>
<td>0.25</td>
</tr>
<tr>
<td>Dexamethosone</td>
<td>0.8 mg</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>-</td>
<td>0</td>
<td>125</td>
</tr>
</tbody>
</table>

Basic and Clinical Pharmacology 11th ed
Corticosteroids

  • French multicenter RCT (specific to refractory septic shock)
  • Significant shock reversal and reduction in mortality
  • No significant difference in responders vs non-responders

• CORTICUS trial, 2008.
  • Enrolled patients without sustained shock, lower risk of death
  • Decrease time to shock resolution, but no mortality benefit
  • Patient that persisted <90 SBP at 1 day, despite fluids and vasopressors
    • 11.2% absolute reduction in mortality in steroid group

Annane, et al. JAMA 2002
Sprung, et al. NEJM 2008
Continuous versus Bolus

• Hydrocortisone 200 mg/day
  • 200 mg / 24h continuous infusion or...
  • 50 mg every 6h

• Concerns for “peak effect” with bolus
  • Hyperglycemia, hypernatremia

• Reality
  • Glucose peak levels ~150 mg/dl in study
  • No significant individual variability found
  • No association with patient outcomes
  • Continuous infusion not current clinical practice

Weber-Carstens Study

Summary

• Vasopressors when refractory to adequate fluids
• Receptor activity plays a major role in agent selection, with norepinephrine being the first line for a vast majority of patients
• Vasopressin added upon escalation of norepinephrine may spare dosing, offer less side effects, and add possible survival benefit
• Dopamine, Dobutamine, and Phenylephrine are appropriate for only select patients or salvage therapy
• Corticosteroids when refractory to fluids and vasopressors