Vasopressor Therapy in Sepsis

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Objectives

• After completion of this module, participants will:
  – Compare catecholamine and vasopressors for patients with septic shock
  – Describe the initial vasopressor of choice for patients with septic shock
  – Explain the literature for vasopressor therapy in patients with septic shock

New Definitions

Sepsis
• Life-threatening organ dysfunction caused by a dysregulated host response to infection
  – Defined by qSOFA + SOFA scores
  – Emphasizes organ dysfunction
  – De-emphasizes non-specific systemic inflammation
  – No more "severe sepsis"

Septic shock
• Persistent hypotension requiring vasopressors AND lactate > 2
  • A subset of sepsis in which underlying circulator and cellular/metabolic abnormalities are profound enough to substantially increase mortality
  – Hypotension = MAP < 65
  – Combination of ↓ BP and ↑ lactate:
    » Significantly higher risk-adjusted mortality for combo (42.3%) vs. for pressors alone (30.7%), lactate > 2 alone (25.7%)


Vasopressors / Inotropics

<table>
<thead>
<tr>
<th>Agent</th>
<th>α</th>
<th>β</th>
<th>DA</th>
<th>DO</th>
<th>VO</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>10-15 mg/kg</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>2-30 mcg/min</td>
<td>6-20 mcg/kg</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>1-10 mcg/kg</td>
<td>10-20 mcg/kg</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>0.04 Units/min</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>0.04 Units/min</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>2-10 mcg/kg</td>
<td>2-10 mcg/kg</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

Activity ranges from no activity (0) or maximal activity (++++) or ?? when activity is unknown; DA = dopaminergic; DO = O2 deliver; VO = O2 consumption; pHi = intestinal pH

SOAP study evaluated the epidemiology of sepsis in Europe

• P, MC, observational study
• Objective
  – Whether dopamine administration influenced outcome in septic shock in the SOAP cohort
• Included adult patients admitted from 5/1 – 5/15/2002
• Evaluated all vasopressors, alone and in combination
• Baseline characteristics similar with exception of increased HF in dopamine group
• 1058 patients (14.7% septic shock)
  – 375 = dopamine
  – 683 = No dopamine

Comparison of Shock

Table 5. Summary of a multivariable forward stepwise logistic regression analysis with intensive care unit outcome as the dependent factor in patients with shock due to any cause and those with septic shock.

<table>
<thead>
<tr>
<th>Shock Due to Any Cause*</th>
<th>Septic Shock*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Odds Ratio (95% CI)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>1.02 (1.00–1.03)</td>
</tr>
<tr>
<td>Blood Urea</td>
<td>1.02 (1.00–1.03)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>2.46 (1.57–3.82)</td>
</tr>
<tr>
<td>Blood pH</td>
<td>0.94 (0.90–0.99)</td>
</tr>
<tr>
<td>Hemodynamic assistance</td>
<td>1.42 (1.05–2.91)</td>
</tr>
<tr>
<td>Number of hypotensive episodes</td>
<td>1.07 (1.00–1.05)</td>
</tr>
</tbody>
</table>

p, confidence interval; SAPS, Sequential Organ Failure Assessment.

Norepinephrine vs Dopamine Summary

Table 6. Dopamine versus Norepinephrine for the Treatment of Septic Shock

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Blood Pressure</th>
<th>Heart Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
</tbody>
</table>

Vasopressors – Surviving Sepsis Campaign 2016

- Norepinephrine should be considered first line agent for most patients
  - Strong recommendation, moderate quality of evidence
  - Norepinephrine is more potent than dopamine & may be more effective in reversing hypotension in septic shock

- Dopamine may be an alternative to norepinephrine in selected patients (low risk of tachyarrhythmias and absolute or relative bradycardia)
  - Weak recommendation, low quality of evidence

Norepinephrine vs. Epinephrine

- P, R, MC, DB
- October 1999 to December 2004
  - 330 patients enrolled
- Objective
  - 28 day all-cause mortality
  - 90 day mortality
- Inclusion criteria
  - Septic shock
  - Vasopressor dependent shock after fluid
- Exclusion criteria
  - Pregnancy
  - AMI
  - Obstructive cardiomyopathy
  - PE
Mortality

<table>
<thead>
<tr>
<th></th>
<th>Epinephrine (n=161)</th>
<th>Norepinephrine plus dobutamine (n=163)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>At day 7</td>
<td>80 (51%)</td>
<td>34 (20%)</td>
<td>0.30</td>
</tr>
<tr>
<td>At day 14</td>
<td>56 (34%)</td>
<td>64 (34%)</td>
<td>0.48</td>
</tr>
<tr>
<td>At day 28</td>
<td>64 (40%)</td>
<td>58 (34%)</td>
<td>0.31</td>
</tr>
<tr>
<td>At discharge from ICU</td>
<td>75 (42%)</td>
<td>77 (44%)</td>
<td>0.69</td>
</tr>
<tr>
<td>At discharge from hospital</td>
<td>84 (52%)</td>
<td>82 (49%)</td>
<td>0.53</td>
</tr>
<tr>
<td>At day 90</td>
<td>84 (52%)</td>
<td>85 (50%)</td>
<td>0.73</td>
</tr>
</tbody>
</table>

Data are number of deaths (%).

Table 3: All-case mortality rates

Epinephrine

- Can be added to norepinephrine to increase BP or decrease norepinephrine doses
  - Weak recommendation; LOE
- Considered as effective as norepinephrine for BP
-Transient increase in lactate
  - May interfere with lactate clearance
- Increase in HR compared to norepinephrine
- No difference in mortality
- Potential to decrease coronary and mesenteric blood flow
Vasopressin

- Low-dose vasopressin can be added to norepinephrine to increase MAP and decrease norepinephrine dose
  - Doses up to 0.03 units/min
  - Weak recommendation, LQE
- May decrease CO/CI? (dose related?)
- Potential to decrease coronary and mesenteric blood flow
- Not recommended as single initial agent and doses greater than 0.03-0.04 units/min are considered salvage therapy
  - Higher doses associated with more ADE
- Should be titrated off after catecholamine has been D/C'd

VASST – Vasopressin vs Norepinephrine

28-day Mortality

- **P=0.26**
- **39%** Norepinephrine
- **35%** Vasopressin

VASST – Vasopressin vs Norepinephrine

28-day Mortality

- **Patients with More Severe Septic Shock (NE ≥ 15 mcg/min)** (43%)
- **Patients with Less Severe Septic Shock (NE < 15 mcg/min)** (36%)

- **NE = 396, VP = 382**
- 778 enrolled

Vasopressin

- Treatment
  - VP started at 0.01 units/min titrated to max of 0.03 units/min
  - NE started at 5 mcg/min titrated to > 15 mcg/min
  - VP weaned off 8 hours after catecholamine
- Primary endpoint: 28-day mortality

Dobutamine

- Dobutamine can be added to vasopressor
  - Evidence of persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents
  - Weak recommendation, LQE
- Dobutamine should not be used to increase CI to supranormal levels
- Dobutamine may decrease BP due to B2 effects
- Should be titrated to CI or ScvO2
- Max dose 20 mcg/kg/min
**Vasopressors / Inotropics**

Surviving Sepsis Campaign 2016

- Maintain MAP ≥ 65 mmHg
- Norepinephrine initial vasopressor of choice
- Epinephrine as second line agent
- Vasopressin as third line agent; not recommended for mono-therapy
- Dopamine in select patients (low risk of tachyarrhythmias and bradycardia)
- Phenytoin not recommended, except in select indications
  - 1) Norepi associated arrhythmias; 2) CO is high and BP low; 3) salvage therapy
- Do not use low-dose dopamine for renal protection
- Use dobutamine with myocardial dysfunction
- Do not increase hemodynamics (cardiac index) to supranormal values


**Interprofessional Education Module to Learn, Teach, and Optimize the Treatment of Sepsis**

- Jeffrey P. Gonzales, PharmD
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- Renee Dixon, MD
- Joan M. Davenport, RN, PhD
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- Tracey Wilson, DNP
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- Nimeet Kapoor, RN
- Peter P. Olivieri, MD