Pressors in Septic Shock

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INTRODUCTION

• Sepsis is a clinical syndrome characterized by systemic inflammation due to infection.
• There is a continuum of severity ranging from sepsis to severe sepsis and septic shock.
• Over 1,665,000 cases of sepsis occur in the United States each year, with a mortality rate up to 50%
THERAPEUTIC PRIORITIES

• The **early** administration of fluids and antibiotics are the cornerstone of management for patients with severe sepsis and septic shock.

• Therapeutic priorities for patients with severe sepsis or septic shock include:
  ● Early initiation of supportive care to correct physiologic abnormalities, such as hypoxemia and hypotension.
  ● Distinguishing sepsis from systemic inflammatory response syndrome (SIRS) because, if an infection exists, it must be identified and treated as soon as possible. This may require appropriate antibiotics as well as a surgical procedure (eg, drainage).
Hypotension

- Hypotension is the most common indicator that perfusion is inadequate (e.g., systolic blood pressure [SBP] < 90 mmHg, mean arterial pressure < 70 mmHg, decrease in SBP > 40 mmHg).

Therefore, it is important that the blood pressure be assessed early and often. Because a sphygmomanometer may be unreliable in hypotensive patients, an arterial catheter may be inserted if blood pressure is labile or restoration of arterial perfusion pressures is expected to be a protracted process.
High versus Low Blood-Pressure Target in Patients with Septic Shock

BACKGROUND
The Surviving Sepsis Campaign recommends targeting a mean arterial pressure of at least 65 mm Hg during initial resuscitation of patients with septic shock. However, whether this blood-pressure target is more or less effective than a higher target is unknown.

METHODS
In a multicenter, open-label trial, we randomly assigned shock to undergo resuscitation with a mean arterial pressure of 85 mm Hg (high-target group) or 65 to 70 mm Hg (low-target group). The primary end point was mortality at day 28.

RESULTS
At 28 days, there was no significant between-group difference in mortality. However, deaths reported in 142 of 388 patients in the high-target group (36.7%) were significantly higher than those in the low-target group (23.1%) (risk difference, 13.6%; 95% CI, 5.3% to 21.9%; P = .001). There was no significant difference in mortality at either 28 or 90 days. (Funded by the French Ministry of Health; SEPSISPAM ClinicalTrials.gov number, NCT01149278.)
Intravenous fluids

- In patients with sepsis, intravascular hypovolemia is typical and may be severe, requiring rapid fluid resuscitation.
- **Volume** — The optimal volume of resuscitative fluid is unknown. As examples, two studies of early goal directed therapy (EGDT) reported mean infusion volumes that ranged from 3 to 5 liters.
- The volume of fluid that was administered within the initial six hours of presentation was targeted to set physiologic endpoints (eg, mean arterial pressure).
Vasopressors

- Vasopressors are second line agents in the treatment of severe sepsis and septic shock; intravenous fluids are preferred as long as they increase perfusion without seriously impairing gas exchange.
- However, intravenous vasopressors are useful in patients who remain hypotensive despite adequate fluid resuscitation or who develop cardiogenic pulmonary edema.
• Vasopressor administration is required for persistent hypotension once adequate intravascular volume expansion has been achieved.

• Persistent hypotension is typically defined as *systolic blood pressure lower than 90 mm Hg* or *MAP lower than 65 mm Hg* with altered tissue perfusion.

• The mean blood pressure required for adequate splanchnic and renal perfusion (*MAP, 60 or 65 mm Hg*) is based on clinical indices of organ function.
Background

- Vasopressors are class of drugs that elevate Mean Arterial Pressure (MAP) by inducing vasoconstriction.

- Inotropes increase cardiac contractility.

- Many drugs have both vasopressor and inotropic effects.

- Vasopressors are indicated for a decrease of >30 mmHg from baseline systolic blood pressure or MAP <60 mmHg, when either condition results in end-organ dysfunction secondary to hypoperfusion.
Endogenous catecholamine synthesis
<table>
<thead>
<tr>
<th>Receptor</th>
<th>Location</th>
<th>Effect</th>
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<tbody>
<tr>
<td><strong>Alpha-1 Adrenergic</strong></td>
<td>Vascular wall</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td></td>
<td>Heart</td>
<td>Increase duration of contraction without increased chronotropy</td>
</tr>
<tr>
<td><strong>Beta Adrenergic</strong></td>
<td></td>
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</tr>
<tr>
<td>Beta-1</td>
<td>Heart</td>
<td>↑Inotropy and chronotropy</td>
</tr>
<tr>
<td>Beta-2</td>
<td>Blood vessels</td>
<td>Vasodilation</td>
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<tr>
<td><strong>Dopamine</strong></td>
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<tr>
<td></td>
<td>Renal</td>
<td>Vasodilation</td>
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<tr>
<td></td>
<td>Splanchnic (mesenteric)</td>
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<td></td>
<td>Coronary</td>
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<td></td>
<td>Cerebral</td>
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<tr>
<td><strong>Subtype</strong></td>
<td></td>
<td>Vasoconstriction</td>
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</tbody>
</table>
## Vasoactive Medication Receptor Activity and Clinical Effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>Alpha-1</th>
<th>Beta-1</th>
<th>Beta-2</th>
<th>Dopaminergic</th>
<th>Predominant Clinical Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neosynephrine (Phenylephrine)</td>
<td>***</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>SVR ↑ ↑, CO ↔/↑</td>
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<tr>
<td>Levophed (Norepinephrine)</td>
<td>***</td>
<td>**</td>
<td>0</td>
<td>0</td>
<td>SVR ↑ ↑, CO ↔/↑</td>
</tr>
<tr>
<td>Adrenalin (Epinephrine)</td>
<td>***</td>
<td>***</td>
<td>**</td>
<td>0</td>
<td>CO ↑ ↑, SVR ↓ (low dose) SVR/↑ (higher dose)</td>
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<tr>
<td>Intropin (Dopamine)</td>
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<tr>
<td>0.5 to 2</td>
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<td>0</td>
<td>**</td>
<td>CO</td>
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<tr>
<td>5 to 10</td>
<td>*</td>
<td>**</td>
<td>0</td>
<td>**</td>
<td>CO ↑, SVR ↑</td>
</tr>
<tr>
<td>10 to 20</td>
<td>**</td>
<td>**</td>
<td>0</td>
<td>**</td>
<td>SVR ↑ ↑</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>0/*</td>
<td>***</td>
<td>**</td>
<td>0</td>
<td>CO ↑, SVR ↓</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>0</td>
<td>***</td>
<td>***</td>
<td>0</td>
<td>CO ↑, SVR ↓</td>
</tr>
</tbody>
</table>

*** Very Strong Effect, ** Moderate effect, * Weak effect, 0 No effect.
Objective Summary

• Understand the vasopressor and inotropic agent receptor physiology
  – Alpha-1, Beta-1, and Beta-2 adrenergic receptors induce vasoconstriction, inotropy plus chronotropy, and vasodilation, respectively.
  – Dopamine receptors induce vasodilation (one subtype induces norepinephrine release and vasoconstriction).
• In most patients with severe septic shock, **norepinephrine** is preferred.
• However, **phenylephrine** (a pure alpha-adrenergic agonist) may be useful when tachycardia or arrhythmias preclude the use of agents with beta-adrenergic activity (eg, norepinephrine).
VASST

- Vasopressin (0.03 un/hr) v. NE in septic shock
- No significant difference in mortality at 28 days
- Decreased mortality in patients with less severe septic shock (lowest quartile of arterial lactate)
- Vaso + corticosteroids decreased mortality v. NE + corticosteroids
- Conclusion: May be effective in patients with less severe septic shock already receiving NE
Patients receiving NE had best survival rate on all days of hospital stay (p<0.001)

Mortality strongly associated with high lactate and low urine output

“NE was associated with a highly significant decrease in hospital mortality. The data contradict the notion that norepinephrine potentiates end organ hypoperfusion through excessive vasoconstriction

CONCLUSIONS

Although there was no significant difference in the rate of death between patients with shock who were treated with dopamine as the first-line vasopressor agent and those who were treated with norepinephrine, the use of dopamine was associated with a greater number of adverse events.

(ClinicalTrials.gov number, NCT00314704.)
52.5% dopa vs. 48.5% norepi OR 1.17 (0.97 to 1.42); P=0.10

Figure 2. Kaplan–Meier Curves for 28-Day Survival in the Intention-to-Treat Population.
First-line agents: norepinephrine vs dopamine

- The recommended first-line agent for septic shock is norepinephrine, preferably administered through a central catheter.\cite{14,59} Norepinephrine has predominant alpha-receptor agonist effects and results in potent peripheral arterial vasoconstriction without significantly increasing heart rate or cardiac output. The dosage range for norepinephrine is 5-20 µg/min, and it is not based on the weight of the patient.

- Norepinephrine is preferred to dopamine for managing septic shock because dopamine is known to cause unfavorable flow distribution (more arrhythmias). In this setting, norepinephrine has been shown to be both significantly safer and somewhat more effective.

- In a systematic review of randomized controlled trials, norepinephrine was significantly superior to dopamine in improving both in-hospital and 28-day mortality in septic shock patients.\cite{81} In a meta-analysis that evaluated these 2 agents in the setting of septic shock, the investigators determined that in comparison with dopamine, epinephrine was associated with a decreased risk of death and a lower incidence of arrhythmic events.\cite{82}
Second-line agents

• Second-line vasopressors appropriate for patients who have persistent hypotension despite maximal doses of norepinephrine or dopamine are epinephrine, phenylephrine, and vasopressin.
• In theory, norepinephrine is the ideal vasopressor in the setting of warm shock, wherein peripheral vasodilation exists in association with normal or increased cardiac output. The typical patient with warm shock has warm extremities but exhibits systemic hypotension and tachycardia, the results of decreased systemic vascular resistance.
• Dopamine should be used only in certain highly specific situations, such as when there is a low risk of tachyarrhythmias and bradycardia. Treatment usually begins at 5-10 µg/kg/min IV, and the infusion is adjusted according to the blood pressure and other hemodynamic parameters. Often, patients may require high dosages of dopamine (up to 20 µg/kg/min). Low-dose dopamine is not recommended for renal protection. [14, 59]
Norepinephrine

- Increased CO,
- Venoconstriction,
- Arteriolar constriction
- Less impaired splanchnic/renal perfusion
- Improves RV
Results A total of 39 patients survived for 28 days after admission to the intensive care unit. The variables independently associated with 28-day mortality in multivariable models included low urine flow, high lactate levels, high organ failure score, high prothrombin time, and need for epinephrine cotreatment. The reason, dose, and duration of norepinephrine administration did not have prognostic significance. Scores greater than 40 on the Acute Physiology and Chronic Health Evaluation II, bicarbonate levels less than 9.0 mEq/L, or receipt of an epinephrine dose of 0.25 μg/kg per minute or greater were associated with 100% mortality.

Conclusions Although the cause of shock and treatment with norepinephrine were not predictive of death when high doses of the drug were deemed necessary, rescue treatment with high-dose norepinephrine is futile in patients with severe disease and metabolic acidemia.
Epinephrine

- clearly increases MAP in patients unresponsive to other vasopressors, mainly by virtue of its potent inotropic effects on the heart; thus, it should probably be the first alternative agent considered in patients with septic shock who show a poor clinical response to norepinephrine or dopamine.\textsuperscript{[14, 59]} Adverse effects include tachyarrhythmias, myocardial and splanchnic ischemia, and increased systemic lactate concentrations.
Phenylephrine

- exerts a pure alpha-receptor agonist effect, which results in potent vasoconstriction, albeit at the expense of depressed myocardial contractility and heart rate. Phenylephrine may be considered a first-line agent in patients with extreme tachycardia; its pure alpha-receptor activity will not result in increased chronotropy.\cite{83}
Vasopressin (ADH),

- It has been proposed for use in septic shock because it is an endogenous peptide with potent vasoactive effects and its circulating levels are depressed in septic shock. According to the 2012 Surviving Sepsis Campaign guidelines, vasopressin should not be the single initial vasopressor but should be reserved for salvage therapy.\(^{[14]}\) After first-line treatment, 0.03 U/min of vasopressin may be added to norepinephrine, with an anticipated effect equivalent to that of norepinephrine alone.\(^{[14, 59]}\)
Characteristics of the vasopressors

• Norepinephrine is a potent alpha-adrenergic agonist with minimal beta-adrenergic agonist effects. It can increase blood pressure successfully in patients with sepsis who remain hypotensive after fluid resuscitation and dopamine. The dosage may range from 0.2 to 1.5 µg/kg/min, and dosages as high as 3.3 µg/kg/min have been used because of the alpha-receptor downregulation in sepsis.

• In patients with sepsis, indices of regional perfusion (e.g., urine flow) and lactate concentration have improved after norepinephrine infusion. Several studies have found that a significantly greater percentage of patients treated with norepinephrine were resuscitated successfully, in comparison with patients treated with dopamine.\[81, 82\] Therefore, norepinephrine should be used early and should not be withheld as a last resort in patients with severe sepsis who are in shock.

• Concerns about compromising splanchnic tissue oxygenation have not been borne out by the data; the studies have confirmed no deleterious effects on splanchnic oxygen consumption and hepatic glucose production, provided that adequate cardiac output is maintained.
Dopamine

- A precursor of norepinephrine and epinephrine, dopamine has varying effects, according to the doses infused. At lower doses, it has a much greater effect on beta receptors; at higher doses, it has more alpha-receptor effects and increases peripheral vasoconstriction.
- Dosages range from 2 to 20 µg/kg/min. A dosage lower than 5 µg/kg/min results in vasodilation of renal, mesenteric, and coronary beds.\(^{[14]}\) At a dosage of 5-10 µg/kg/min, beta\(_1\) -adrenergic effects induce an increase in cardiac contractility and heart rate. At dosages of about 10 µg/kg/min, alpha-adrenergic effects lead to arterial vasoconstriction and elevation in blood pressure.\(^{[14]}\)
- Dopamine is effective for optimizing MAP in patients with septic shock who remain hypotensive after volume resuscitation. The blood pressure increases primarily as a result of the drug’s inotropic effect, which is useful in patients who have concomitant reductions in cardiac function.
- Dopamine may be particularly useful in the setting of cold shock, where peripheral vasoconstriction exists (cold extremities) and cardiac output is too low to maintain tissue perfusion. Undesirable effects include tachycardia, increased pulmonary shunting, the potential to decrease splanchnic perfusion, and an increase in pulmonary arterial wedge pressure (PAWP).
- Low-dose (renal-dose) dopamine has been studied. Dopamine at a dosage of 2-3 µg/kg/min is known to initiate diuresis by increasing renal blood flow in healthy animals and volunteers; however, several well-designed clinical trials have not found such regimens to have any beneficial effects on renal blood flow and function in the setting of circulatory shock of any etiology.
- Multiple studies also have not shown prophylactic or therapeutic low-dose dopamine administration to have any beneficial effect in patients with sepsis who are critically ill. In view of the real side effects of dopamine infusion, the use of renal-dose dopamine should be abandoned.
Epinephrine

- Epinephrine can increase MAP by increasing cardiac index and stroke volume, as well as by increasing systemic vascular resistance and heart rate. This agent may increase oxygen delivery and oxygen consumption. The use of epinephrine is recommended only in patients who are unresponsive to traditional agents. The undesirable effects of epinephrine include the following:
  - An increase in systemic and regional lactate concentrations
  - The potential to produce myocardial ischemia and promote development of arrhythmias
  - Reduced splanchnic flow
Phenylephrine

- is a selective alpha_1 -adrenergic receptor agonist that is used primarily in anesthesia to increase blood pressure. Although the data are limited, studies have found phenylephrine to increase MAP in patients who were septic and hypotensive with increased oxygen consumption. However, concern remains about this agent’s potential to reduce cardiac output and lower heart rate in patients with sepsis. Phenylephrine may be a good choice when tachyarrhythmias limit therapy with other agents.
Vasopressin

- is synthesized in the hypothalamus and excreted by the posterior pituitary. In contrast to endogenous catecholamines (e.g., norepinephrine), whose serum levels are universally high in septic shock, vasopressin stores are limited and its levels are low.\[^{[84]}\] Furthermore, catecholamine effectiveness on vascular smooth muscle cells is inhibited by the activation of ATP-dependent potassium channels and NO.
• Several small clinical trials have shown that low-dose vasopressin increases MAP and decreases the requirement for catecholamines while maintaining mesenteric and renal perfusion.\[^{84}\] However, a large, randomized trial (the Vasopressin and Septic Shock Trial [VASST]) did not find mortality to be significantly lower in patients who received vasopressin in addition to norepinephrine than in those who received norepinephrine alone, even though vasopressin reduced the requirement for norepinephrine.\[^{85}\]
Overall, the major adverse effects attributed to vasopressin (myocardial ischemia, cardiac arrest, mesenteric, and digital ischemia) were not significantly increased in the trial; however, patients with known coronary artery disease or congestive heart failure were excluded from the study. The incidence of digital ischemia was higher with vasopressin use. Because the mean time to receiving the drug in VASST was 12 hours, this study does not address the use of vasopressin in early sepsis resuscitation.
Dobutamine

- is an inotropic agent that stimulates beta receptors and results in increased cardiac output. In theory, it can enhance tissue oxygen delivery in patients with septic shock who have received adequate fluid resuscitation and vasopressor support. In EGDT, dobutamine is recommended if there is evidence of tissue hypoperfusion (central venous oxygen saturation \([\text{ScvO}_2]\) < 70 mm Hg) after CVP, MAP, and hematocrit goals have been met.

- The 2012 Surviving Sepsis Campaign guidelines recommend administration of dobutamine dosages up to 20 µg/kg/min only in the presence of myocardial dysfunction or persistent hypoperfusion despite adequate fluid resuscitation and adequate MAP.\(^\text{[14]}\)
Dobutamine

β agonist: inotrope, tachycardia, increased myocardial VO2?

B2 activity: Leads to vasodilation and aferload reduction
Milrinone

Phosphodiesterase III inhibitor
Positive inotrope
Afterload reduction
Improved diastolic function
# Adverse Reactions

<table>
<thead>
<tr>
<th></th>
<th>Epinephrine</th>
<th>Norepinephrine</th>
<th>Dopamine</th>
<th>Dobutamine</th>
<th>Vasopressin</th>
<th>Phenylephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachycardia</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
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<tr>
<td>Arrhythmias</td>
<td>x</td>
<td></td>
<td>High doses</td>
<td>x</td>
<td>x (ventricular)</td>
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<tr>
<td>Increased myocardial O2 demand</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
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<tr>
<td>Decreased perfusion to vital organs</td>
<td>x</td>
<td>x</td>
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<td>x (less)</td>
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<td>Nausea/vomiting</td>
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<tr>
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<td>x (contains sulfites)</td>
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<tr>
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<td>x</td>
<td>x</td>
<td>x</td>
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</table>
Glucocorticoids

- Glucocorticoids have long been investigated as therapeutic agents in sepsis because the pathogenesis of sepsis involves an intense and potentially deleterious host inflammatory response. Evidence from randomized trials suggest that corticosteroid therapy is most likely to be beneficial in patients who have severe septic shock (defined as a systolic blood pressure <90 mmHg) that is unresponsive to adequate fluid resuscitation and vasopressor administration.
References

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