We Want To Pump You Up!: Out of Hospital Use of Pressors

Code3 Conference 2014

Jacob B. Keeperman, MD

Assistant Professor of Anesthesiology and Emergency Medicine
Department of Anesthesiology, Division of Critical Care Medicine
Division of Emergency Medicine, Section of EMS
Washington University School of Medicine
Saint Louis, Missouri

Medical Director
Air Evac Lifeteam
Disclosures

• I have no financial disclosures to report.
What we will cover...

Vasopressor of Choice for Septic Shock

Targets for Vasopressor Therapy

Clinical Application
What pressor does your agency carry?
What is the vasopressor of choice for septic shock?

Patient Characteristics

Effects on Regional Vascular Beds

Clinical Trial Results
BP = CO \times SVR

BLOOD PRESSURE \neq BLOOD FLOW
Pulmonary hypertension?
ARDS?
HOCM?
EF 20%?
Cardiac valves?
Perioperative MI?
Mesenteric ischemia?
SHOCK PROFILE IN SEPSIS

HYPOVOLEMIC
- Capillary leak (exacerbated by venodilation)
- Poor cardiac filling

DISTRIBUTIVE

Macrovascular:
- Arterial hypotension
- Shunting to “vital” organs
- Regional hypoperfusion

Microvascular:
- Vasodilation
- Precapillary shunting
- Impaired microvascular flow
- Microvascular thromboses

Mitochondrial dysfunction:
- Impaired oxygen utilization
- “Cytopathic hypoxia”

CARDIOGENIC
- Myocardial depression (decreased ejection fraction)
- Modulated by ventricular dilation to maintain stroke volume
What is the vasopressor of choice for septic shock?
Clinical Trials & Outcome data. Do we have any?
Effect of norepinephrine on the outcome of septic shock

Martin et al, Crit Care Med 2000
Comparison of Dopamine and Norepinephrine in the Treatment of Shock

Daniel De Backer, M.D., Ph.D., Patrick Biston, M.D., Jacques Devriendt, M.D., Christian Madl, M.D., Didier Chocrod, M.D., Cesar Aldecoa, M.D., Alexandre Brasseur, M.D., Pierre Defrance, M.D., Philippe Gottignies, M.D., and Jean-Louis Vincent, M.D., Ph.D., for the SOAP II Investigators*
<table>
<thead>
<tr>
<th>Time Period</th>
<th>Dopamine (%)</th>
<th>NE (%)</th>
<th>Odds Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU</td>
<td>50.2</td>
<td>45.9</td>
<td>1.19</td>
<td>0.07</td>
</tr>
<tr>
<td>Hospital</td>
<td>59.4</td>
<td>56.6</td>
<td>1.12</td>
<td>0.24</td>
</tr>
<tr>
<td>28 Days</td>
<td>52.5</td>
<td>48.5</td>
<td>1.17</td>
<td>0.10</td>
</tr>
<tr>
<td>6 Month</td>
<td>63.8</td>
<td>62.9</td>
<td>1.06</td>
<td>0.71</td>
</tr>
<tr>
<td>12 Month</td>
<td>65.9</td>
<td>63.0</td>
<td>1.15</td>
<td>0.34</td>
</tr>
</tbody>
</table>
Figure 3. Forest Plot for Predefined Subgroup Analysis According to Type of Shock.

A total of 1044 patients were in septic shock (542 in the dopamine group and 502 in the norepinephrine group), 280 were in cardiogenic shock (135 in the dopamine group and 145 in the norepinephrine group), and 263 were in hypovolemic shock (138 in the dopamine group and 125 in the norepinephrine group). The P value for interaction was 0.87.
In summary, although the rate of death did not differ significantly between the group of patients treated with dopamine and the group treated with norepinephrine, this study raises serious concerns about the safety of dopamine therapy, since dopamine, as compared with norepinephrine, was associated with more arrhythmias and with an increased rate of death in the subgroup of patients with cardiogenic shock.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dopamine (N = 858)</th>
<th>Norepinephrine (N = 821)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Support-free days through day 28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasopressors not needed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial drug</td>
<td>11.0±12.1</td>
<td>12.5±12.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Open-label vasopressors</td>
<td>12.6±12.3</td>
<td>14.2±12.3</td>
<td>0.007</td>
</tr>
<tr>
<td>Mechanical ventilation not needed</td>
<td>8.5±11.2</td>
<td>9.5±11.4</td>
<td>0.13</td>
</tr>
<tr>
<td>Renal support not needed</td>
<td>12.8±12.4</td>
<td>14.0±12.3</td>
<td>0.07</td>
</tr>
<tr>
<td>Intensive care not needed</td>
<td>8.1±10.3</td>
<td>8.5±10.3</td>
<td>0.43</td>
</tr>
<tr>
<td>Length of stay — no. of days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Interquartile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interquartile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cause of death in ho</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refractory shock</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdrawal or w</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain death or s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrhythmias —</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>10 (1.2)</td>
<td>4 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction — no. (%)</td>
<td>19 (2.2)</td>
<td>25 (3.0)</td>
<td>0.29</td>
</tr>
<tr>
<td>New infectious episode</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of episodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>0–1</td>
<td>0–1</td>
<td></td>
</tr>
<tr>
<td>Patients with at least one episode — no. (%)</td>
<td>674 (78.6)</td>
<td>619 (75.4)</td>
<td>0.35</td>
</tr>
<tr>
<td>Skin ischemia — no. (%)</td>
<td>56 (6.5)</td>
<td>34 (4.1)</td>
<td>0.09</td>
</tr>
<tr>
<td>Mild†</td>
<td>46 (5.4)</td>
<td>28 (3.4)</td>
<td></td>
</tr>
<tr>
<td>Severe‡</td>
<td>10 (1.2)</td>
<td>6 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Arterial occlusion — no. (%)§</td>
<td>21 (2.7)</td>
<td>20 (2.4)</td>
<td>0.12</td>
</tr>
<tr>
<td>Arms or fingers</td>
<td>5 (0.6)</td>
<td>1 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Legs</td>
<td>7 (0.8)</td>
<td>13 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Bowel</td>
<td>11 (1.3)</td>
<td>6 (0.7)</td>
<td></td>
</tr>
</tbody>
</table>
Dopamine versus norepinephrine in the treatment of septic shock: A meta-analysis *

Daniel De Backer, MD, PhD; Cesar Aldecoa, MD; Hassane Njimi, MSc, PhD; Jean-Louis Vincent, MD, PhD, FCCM

Objectives: There has long been controversy about the possible superiority of norepinephrine compared to dopamine in the treatment of shock. The objective was to evaluate the effects of norepinephrine and dopamine on outcome and adverse events in patients with septic shock.

Data Sources: A systematic search of the MEDLINE, Embase, Scopus, and CENTRAL databases, and of Google Scholar, up to June 30, 2011.

Study Selection and Data Extraction: All studies providing information on the outcome of patients with septic shock treated with dopamine compared to norepinephrine were included. Observational and randomized trials were analyzed separately. Because time of outcome assessment varied among trials, we evaluated 28-day mortality or closest estimate. Heterogeneity among trials was assessed using the Cochrane Q homogeneity test. A Forest plot was constructed and the aggregate relative risk of death was computed. Potential publication bias was evaluated using funnel plots.

Methods and Main Results: We retrieved five observational (1,360 patients) and six randomized (1,408 patients) trials, totaling 2,768 patients (1,474 who received norepinephrine and 1,294 who received dopamine). In observational studies, among which there was significant heterogeneity ($p < .001$), there was no difference in mortality (relative risk, 1.09; confidence interval, 0.84–1.41; $p = .72$). A sensitivity analysis identified one trial as being responsible for the heterogeneity; after exclusion of that trial, no heterogeneity was observed and dopamine administration was associated with an increased risk of death (relative risk, 1.23; confidence interval, 1.05–1.43; $p < .01$). In randomized trials, for which no heterogeneity or publication bias was detected ($p = .77$), dopamine was associated with an increased risk of death (relative risk, 1.12; confidence interval, 1.01–1.20; $p = .035$). In the two trials that reported arrhythmias, these were more frequent with dopamine than with norepinephrine (relative risk, 2.34; confidence interval, 1.46–3.77; $p = .001$).

Conclusions: In patients with septic shock, dopamine administration is associated with greater mortality and a higher incidence of arrhythmic events compared to norepinephrine administration. (Crit Care Med 2012; 40:725–730)

Key Words: adrenergic agents; adverse effects; mortality; outcome; vasopressor
<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>Overall</td>
<td>330</td>
<td>676</td>
<td>396</td>
</tr>
</tbody>
</table>
Vasopressor started, now what?
Restore perfusion to vital organs
Increasing MAP?

Bourgoin et al
CCM 2005, 33, 780-786
Increasing MAP?

Bourgoin et al
CCM 2005, 33, 780-786
Increasing MAP from 65 to 85 mmHg

• Does not significantly improve:
  ▪ systemic oxygen metabolism (DO2/VO2)
  ▪ skin microcirculatory blood flow
  ▪ urine output, UF, CrCl, Cr
  ▪ splanchnic perfusion
  ▪ lactate clearance

LeDoux et al, Crit Care Med 2000
Bourgoin et al, Crit Care Med 2005
Clinical Application
Fluids or colloids (B)
Dopamine or Norepinephrine first choice (C)
Phenylephrine or Epinephrine second choice (D)
Vasopressin for refractory shock (D)
Dobutamine as inotrope (C)
• Fluids or colloids (1B)
• Fluid challenge (1C)
• Dopamine or Norepinephrine first choice (1C)
• Epinephrine second choice (2B)
• Vasopressin in refractory shock (2C)
• Dobutamine as inotrope (1C)

R. Phillip Dellinger, MD¹; Mitchell M. Levy, MD²; Andrew Rhodes, MB BS³; Djillali Annane, MD⁴; Herwig Gerlach, MD, PhD⁵; Steven M. Opal, MD⁶; Jonathan E. Sevransky, MD⁷; Charles L. Sprung, MD⁸; Ivor S. Douglas, MD⁹; Roman Jaeschke, MD¹⁰; Tiffany M. Osborn, MD, MPH¹¹; Mark E. Nunnally, MD¹²; Sean R. Townsend, MD¹³; Konrad Reinhart, MD¹⁴; Ruth M. Kleinpell, PhD, RN-CS¹⁵; Derek C. Angus, MD, MPH¹⁶; Clifford S. Deutschman, MD, MS¹⁷; Flavia R. Machado, MD, PhD¹⁸; Gordon D. Rubenfeld, MD¹⁹; Steven A. Webb, MB BS, PhD²⁰; Richard J. Beale, MB BS²¹; Jean-Louis Vincent, MD, PhD²²; Rui Moreno, MD, PhD²³; and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup*
2012 Guidelines

Recommendations: Hemodynamic Support and Adjunctive Therapy

1. Crystalloids as the initial fluid of choice in the resuscitation of severe sepsis and septic shock (grade 1B).
2. Against the use of hydroxyethyl starches for fluid resuscitation of severe sepsis and septic shock (grade 1B).
3. Albumin in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids (grade 2C).
4. Initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with suspicion of hypovolemia to achieve a minimum of 30mL/kg of crystalloids (a portion of this may be albumin equivalent). More rapid administration and greater amounts of fluid may be needed in some patients (grade 1C).
5. Fluid challenge technique be applied wherein fluid administration is continued as long as there is hemodynamic improvement either based on dynamic (e.g., change in pulse pressure, stroke volume variation) or static (e.g., arterial pressure, heart rate) variables (UG).
2012 Guidelines

Recommendations: Hemodynamic Support and Adjunctive Therapy

Vasopressor therapy initially to target a mean arterial pressure (MAP) of 65 mm Hg (grade 1C).

- **Norepinephrine as the first choice vasopressor** (grade 1B).
- **Epinephrine** (added to and potentially substituted for norepinephrine) when an additional agent is needed to maintain adequate blood pressure (grade 2B).

Vasopressin 0.03 units/minute can be added to norepinephrine (NE) with intent of either raising MAP or decreasing NE dosage (UG).

Low dose vasopressin is not recommended as the single initial vasopressor for treatment of sepsis-induced hypotension and vasopressin doses higher than 0.03-0.04 units/minute should be reserved for salvage therapy (failure to achieve adequate MAP with other vasopressor agents) (UG).

- **Dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients** (eg, patients with low risk of tachyarrhythmias and absolute or relative bradycardia) (grade 2C).

Phenylephrine is not recommended in the treatment of septic shock except in circumstances where (a) norepinephrine is associated with serious arrhythmias, (b) cardiac output is known to be high and blood pressure persistently low or (c) as salvage therapy when combined inotrope/vasopressor drugs and low dose vasopressin have failed to achieve MAP target (grade 1C).

Low-dose dopamine should not be used for renal protection (grade 1A).

All patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available (UG).
How do I give it?

• Is dopamine safer to give via PIV than norepinephrine?
  – There is no evidence to suggest that
  – What evidence is there?
How do I give it?

• My patients do not have central lines
How do I give it?
Central or Peripheral Catheters for Initial Venous Access of ICU Patients: A Randomized Controlled Trial

Jean-Damien Ricard, MD, PhD1,2; Laurence Salomon, MD, PhD3; Alexandre Boyer, MD4; Guillaume Thiery, MD5; Agnes Meybeck, MD1; Carine Roy, MSc6; Blandine Pasquet, MSc6; Eric Le Mièvre, MD1; Didier Dreyfuss, MD1,2

- RCT
- PIV vs CVC
- Analyzed by ITT
- Results – less major complications with CVC rather than PIV (0.64 vs 1.04, p<0.02)
- The majority of complications in the PIV group were the inability to insert a PIV
What we want to know:

• Were there extravasation injuries in the PIV group?
  – Included very high doses
    • Up to 2 mg/hr (33.3 mcg/min) of norepinephrine or epinephrine
    • Up to 10 mg/kg/min of dopamine or dobutamine
  – 19 patients in the PIV group had extravasation
    • None of them required anything more than observation and conservative treatment*
What does the study mean?

• You can give pressors via PIV

• There are risks with all pressors (including dopamine)

• We need to investigate the use of pressors via IO
What if there is extravasation?

• If patient is relying on the pressor, infuse via new access (IV, IO)
• Aspirate from the IV that infiltrated
• Give phentolamine (Regitine)
  – Comes 5 mg / 1 mL
  – Place in 9 mL NS
  – Dose: 0.1 – 0.2 mg/kg (up to 10 mg)
  – Inject a few mLs via the infiltrated catheter and the remaining SQ around the borders of the extravasation
• Consult plastic surgery
Push-Dose-Pressors

- Term coined by Scott Weingart, MD
- Used by OB anesthesia for a long time
- Quick bolus of vasopressor during duress
Push-Dose-Pressors

• Idea
  – Hypotension should be corrected quickly
  – Push drugs result in hypotension, so push drugs should be used to correct hypotension
  – Typically use phenylephrine or epinephrine
  – You might be able to use norepinephrine (we need a study)
Push-Dose-Pressors

EPINEPHRINE

• Receptors: Alpha and beta
• Mixing:
  – 1 mL of epinephrine from cardiac epinephrine ampule (100 mcg/mL)
  – 9 mL of normal saline in 10 mL syringe
  – 10 mL of epinephrine 10 mcg/mL (same concentration as lidocaine with epi)
• Dose: 0.5 - 2 mL q 2-5 minutes

*** Do NOT give cardiac arrest dose (1 mg) to patients with a pulse
Push-Dose-Pressors

PHENYLEPHRINE

• Receptors: Pure alpha
  – No intrinsic inotropy
  – May cause increased coronary perfusion which may increase CO
  – I only use it in tachycardic patients

• Mixing
  – 1 ml phenylephrine from vial (10 mg/mL)
  – Inject into 100 mL bag normal saline
  – Phenylephrine 100 mcg/mL

• Dose: 0.5 - 2 mL q 2 - 5 minutes
Push-Dose-Pressors

• Pit-falls
  – Errors in mixing

• Solution
  – Pre-mixed syringes
Conclusions

• Fill the tank first
• The first line pressor choice should be norepinephrine (Levophed)
• Pressors can be given via peripheral IV
• Need to evaluate pressors via IO
• Push-dose-pressors are coming to the out-of-hospital setting
References

• EMCrit
References

Acknowledgements
Thank you!!!

Code3 Conference Planning Committee

Please let me know if you have any questions:
keepermanj@wusm.wustl.edu