Vasopressors for shock

Background Reviews and Observational Studies


- The literature on prevalence, etiology and mortality of shock in the field is inadequate.
- Estimated prehospital prevalence of hypotension is 20/1000 EMS contacts and the prevalence of shock is 10-20/1000 EMS contacts.
- In-hospital mortality was 33-52%


- Retrospective observational study of 67 patients with septic shock treated by EMS in Australia Northern Territory (MD-RN flight crew).
- 91% admitted to ICU, 13% 28-day mortality.
- Vasopressors started in field in 89% of patients: 12% Epinephrine, 21% Norepinephrine, 40% meteraminol, multiple agents 14%.
- No comparison of vasopressors. State meteraminol was most common because of ‘ease of use peripherally’. And ‘It is common practice to start peripheral vasopressors such as meteraminol or adrenaline in shorter cases in which a ‘scoop and run’ approach may be been favoured to reach definitive care quickly and central access may be more time consuming.’

Finfer and Vincent 2013. - Circulatory Shock. (NEJM review)

- Norepinephrine is first-line
- Reserve Epinephrine as second-line for severe cases. Rational: no benefit found over NE, may be associated with increased arrhythmia, can increase lactate levels and decrease splanchnic blood flow.
- Do not recommend dopamine for treatment of patients with shock. Rational: no benefit found over NE, more arrhythmias, increased 28-day mortality in cardiogenic shock and possibly increased mortality in septic shock.

Norepinephrine vs Epinephrine

Levy 2011. – Comparison of norepinephrine-dobutamine to epinephrine for hemodynamics, lactate metabolism, and organ function variables in cardiogenic shock.

Design: Randomized
Setting: ICU (France)
N: 33
Included: cardiogenic shock refractory to dopamine-dobutamine
Excluded: acute MIs
Outcome: HD parameters, 28-day mortality

Findings:
- Epinephrine as effective for hemodynamic effects.
- No difference in mortality.
- Epinephrine associated with transient increased lactic acidosis.
- Epinephrine had more dysrhythmias (3 vs 0).
- Concluded that norepi-dobu was a more effective, safer strategy.


Design: Randomized
Setting: ICU (France)
N: 330
Included: adult patients in septic shock
Excluded: Pregnancy, obstructive CMP, AMI, PE, advanced ca or malignant hemopathy or AIDS with decision for palliative care, persistent neutropenia, enrolment in another trial
Outcome: 28-day all cause mortality

Findings:
- No difference in mortality at ICU discharge, hospital discharge, 28-days, or 90-days
- No difference in time to hemodynamic effects
- No difference in time to vasopressor withdrawal
- No difference in adverse events
- Some delay in normalization of pH and lactate in Epi group compared to NE/Dobu

Myburgh 2008. – A Comparison of Epinephrine and Norepinephrine in critically ill patients.

Design: Randomized
Setting: ICU (Australia)
N: 280
Included: Patients 18-80 judged by treating MD to require infusion of either epinephrine or norepinephrine
Excluded: Cardiac arrest, anaphylaxis, pheo or hypoadrenal, pts on MAOI, or those likely to die within 24 hours
Outcome: Time to achieve goal MAP for >24 hours off pressors (default 70mmHg but per treating MD). Secondary 28- and 90-day mortality.

Findings:
- No difference in time to sustained goal MAP, 28- or 90-day mortality.
- Epinephrine associated with tachycardia and lactic acidosis and increased insulin requirements sustained for first 24-hours of treatment and then no difference. Did cause withdrawal of some patients.
- No difference in tachydysrhythmias or other adverse events.


Design: Randomized  
Setting: ICU (France)  
N: 22  
Included: Adult patients in septic shock  
Excluded: Pregnancy, history of esophageal or gastric disease or surgery  
Outcome: Gastric mucosal blood flow. Hemodynamic variables and lactate also measured.

Findings:
- Same effect on MAP.  
- At same MAPs, NE/Dopexamine increased gastric perfusion more than Epinephrine.  
- Epinephrine induced greater heart rate, cardiac output, oxygen delivery and oxygen consumption.  
- Increased lactate with epinephrine.

Norepinephrine vs Dopamine

De Backer 2010. – Comparison of Dopamine vs Norepinephrine in the Treatment of Shock.

Design: Randomized  
Setting: ICU (Europe)  
N: 1679  
Included: Adult patients in persistent shock after fluids  
Excluded: Patients already receiving vasopressor >4 hours, serious dysrhythmia, brain death  
Outcome: 28-day mortality. Many secondary endpoints including time to effect, HDs, adverse events...
Findings:
- No difference in 28-day mortality, or death in ICU, 6 or 12 months.
- Death from refractory shock more frequent in dopamine group.
- In predefined subgroups, higher 28-day mortality in cardiogenic shock with dopamine.
- Significantly higher rate of dysrhythmias causing withdrawal of study drug in Dopamine vs Norepinephrine (6.1% vs 1.6%)

**Patel 2010.** Efficacy and Safety of Dopamine Versus Norepinephrine in the Management of Septic Shock.

Design: Randomized  
Setting: ICU  
N: 252  
Included: Adult patients with septic shock.  
Excluded: Other causes of shock, allergy to DA or NE, already receiving vasopressor >6 hrs  
Outcome: 28-day mortality. Secondary outcomes: LOS, adverse events, organ dysfunction.

Findings:
- No difference in 28-day mortality.  
- More dysrhythmias with dopamine (19% vs 3%). Arrhythmia was a significant predictor of outcome.

**Meta-Analyses**

**Avni 2015.** Vasopressors for the Treatment of Septic Shock: Systematic Review and Meta-Analysis

Design: Meta-Analysis  
N: 32 trials; 3544 patients  
Included: Randomized studies comparing vasopressors for the treatment of adult patients with septic shock  
Outcome: All-cause mortality. Secondary outcomes included other clinical and hemodynamic parameters.

Findings:
- Norepinephrine was associated with decreased all-cause mortality compared with dopamine, ARR 11%. Excluding DeBacker study did not alter results.  
- Norepinephrine was associated with lower risk of adverse events and cardiac arrhythmias compared to dopamine.
• No mortality benefit was demonstrated for comparisons of norepinephrine to epinephrine (RR 0.96, 95% CI 0.77–1.21).
• No other mortality benefit with other vasopressors found.
• Hemodynamic data were similar between the different vasopressors.
• There was some advantage for norepinephrine in central venous pressure, urinary output, and blood lactate levels.


Findings:
• 28 RCTs comparing vasopressors current to June 2015.
• No differences in mortality with any comparisons (range of evidence high to very low).
• More dysrhythmias with dopamine compared to norepinephrine (high-quality of evidence).

Conclusions:
• Dopamine increases the risk of arrhythmias compared with norepinephrine and might increase mortality.
• Otherwise evidence of any other differences between any of the 6 vasopressors examined is insufficient
• NE vs DA had high quality evidence and low risk of bias
• Moderate to very low quality of evidence for other comparisons

Guidelines


Design: International consensus committee of experts
Recommendations regarding vasopressors:
• Recommend norepinephrine as the first-choice vasopressor (strong recommendation, moderate quality of evidence).
• Suggest adding either vasopressin (up to 0.03 U/min) (weak recommendation, moderate quality of evidence) or epinephrine (weak recommendation, low quality of evidence) to norepinephrine with the intent of raising MAP to target, or adding vasopressin (up to 0.03 U/min) (weak recommendation, moderate quality of evidence) to decrease norepinephrine dosage.

Design: Expert panel from French Intensive Care Society (SRLF)

Recommendations regarding vasopressors:

- Norepinephrine should be used to restore perfusion pressure during cardiogenic shock (strong agreement).
- Epinephrine can be a therapeutic alternative to the combination of dobutamine and norepinephrine, but is associated with a greater risk of arrhythmia, tachycardia, and hyperlactemia (weak agreement).
  - Based on Levy 2011. (above) and Perez 2014 – NE effects on 25 patients in cardiogenic shock from AMI, improved HD and reduced lactate.

Summary of Evidence

- Literature does not support the use of Dopamine as first-line agent for shock.
- Studies of low-moderate quality (sample size issues) in ICU patients show equivalent effect for norepinephrine (+-dobutamine) vs epinephrine drip.
- There are no studies of patient outcome comparing vasopressors in PH setting.
- There are no studies comparing push-dose epi to initial norepinephrine drip.