

# Vasoactive drugs for vasodilatory shock in ICU

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## Purpose of review

Vasoactive drugs are the mainstay of hemodynamic management of vasodilatory shock when fluids fail to restore adequate tissue perfusion. In this review, studies published during the past year that increase our understanding of the use of vasoactive drugs in the ICU are discussed.

## Recent findings

The Vasopressin and Septic Shock Trial did not find a difference between low-dose vasopressin and norepinephrine vs. norepinephrine alone in the hemodynamic support of septic shock, suggesting that either approach is reasonable. However, vasopressin may be beneficial in the less severe septic shock subgroup. In this study, patients who were also treated with corticosteroids, vasopressin, compared with norepinephrine, were associated with significantly decreased mortality. Epinephrine, phenylephrine and terlipressin can be used safely in the ICU setting as first-line therapy for septic shock. The incidence of global left ventricular hypokinesia in patients with septic shock is 60%, much higher than previously described. Although dobutamine remains the gold standard therapy for septic myocardial depression, combined milrinone and metoprolol therapy may be an effective alternative therapy.

## Summary

Current evidence does not support a clear recommendation of one vasopressor over another; indeed norepinephrine, vasopressin, terlipressin, phenylephrine and epinephrine may be used safely with similar survival outcomes.

## Keywords

corticosteroids, dobutamine, epinephrine, metoprolol, milrinone, norepinephrine, phenylephrine, sepsis syndrome, septic shock, terlipressin, vasopressin

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## Introduction

The purpose of vasoactive drug therapy in the ICU setting is to restore tissue perfusion in shock states. Hypovolemic, cardiogenic and obstructive forms of shock are characterized by decreased cardiac output, arterial pressure and profound vasoconstriction in the peripheral circulation. In vasodilatory shock, there is a complex interaction between pathologic vasodilation, relative and absolute hypovolemia, myocardial depression and altered blood flow distribution, which occur as a consequence of the inflammatory response to injury [1]. Sepsis is the most frequent cause of vasodilatory shock; however, vasodilatory shock is a consequence of significant organ injury and is also the final common pathway for prolonged and severe shock of any cause [2].

The hemodynamic management of shock is aimed at maintaining oxygen delivery above a critical threshold and increasing mean arterial pressure (MAP) to a level that allows appropriate distribution of cardiac output to

allow adequate individual organ perfusion. Vasoactive drug therapy in the treatment of shock states aims to increase oxygen delivery or increase organ perfusion pressure or both. Ventricular function can also be decreased in vasodilatory shock states either from a previous condition or from myocardial depression due to sepsis. Because oxygen delivery is dependent on cardiac output, the successful resuscitation of septic shock patients depends on identifying left and right ventricular dysfunction and correcting it by the use of inotropic agents [3] with attention to appropriate preload and afterload conditions.

Although many vasopressors have been used since the 1940s, until recently few controlled clinical trials have directly compared these agents or documented improved outcomes due to their use [4]. Thus, the manner in which these agents are commonly used in the past was based on expert opinion, animal data and the use of surrogate end points such as tissue oxygenation as a proxy for decreased morbidity and mortality.

## Specific vasopressor agents

An evidence-based consensus of vasopressor and inotropic support in septic shock was published in 2008 by a subcommittee of the Surviving Sepsis Campaign [5\*\*]. In this context, we examine additional recent evidence regarding use of vasoactive agents that has been published in the last year.

### Vasopressin

Vasopressin is an endogenously released stress hormone that is important during shock. The rationale for its use in the ICU is that there is a vasopressin deficiency in vasodilatory shock and that exogenously administered vasopressin can restore vascular tone [2].

#### *What is the role of vasopressin in septic shock?*

The Vasopressin and Septic Shock Trial (VASST) was a multicenter, randomized, blinded trial of vasopressin vs. norepinephrine [6\*\*]. Patients having septic shock were allocated to either low-dose vasopressin (0.01–0.03 U/min) or norepinephrine infusion (5–15 µg/min) in addition to open-label vasopressors. All vasopressors were titrated and weaned according to protocols to maintain a target blood pressure. Patients were analyzed according to the *a priori* strata of more severe and less severe septic shock, based on the level of vasopressor use at baseline. A total of 779 patients were randomized and infused with the study drug (vasopressin  $n = 397$ , norepinephrine  $n = 382$ ). The study was prospectively powered to detect an absolute difference in 28-day mortality of 10% from an expected 60%. The observed mortality rates were considerably lower than predicted in the vasopressin and norepinephrine groups, compared with previous reports perhaps because of overall improvements in the care of patients who have septic shock.

There was no difference in the primary outcome, 28-day mortality, between vasopressin (35.4%) and norepinephrine (39.3%,  $P = 0.26$ ). There were no differences in the overall rates of serious adverse events. In the prospectively defined stratum of less severe septic shock in VASST, mortality was significantly lower in the vasopressin-treated group at 28 days (26.5 vs. 35.7%,  $P = 0.05$ ). VASST confirmed the relative deficiency of vasopressin in septic shock and low-dose vasopressin infusion (0.01–0.03 U/min) restored plasma vasopressin to an appropriate level in septic shock.

In summary, the VASST did not find a difference between low-dose vasopressin with norepinephrine and norepinephrine alone suggesting that either approach is reasonable. However, vasopressin may be beneficial in the less severe septic shock subgroup (patients on  $<15$  µg/min norepinephrine at baseline).

### Epinephrine

Epinephrine is a potent  $\alpha$ -adrenergic and  $\beta$ -adrenergic agent that is not considered first-line therapy for septic shock due to its detrimental effects on regional circulation and blood lactate levels [1]. The Surviving Sepsis guidelines suggest that epinephrine should be reserved for cases of extreme hemodynamic collapse [5\*\*]. However, epinephrine continues to be widely used, particularly in low-income countries where alternative, more expensive drugs such as norepinephrine are restricted or unavailable.

#### *Is there a difference between norepinephrine and epinephrine in management of septic shock?*

To address this question, the CAT study investigators conducted a multicenter randomized controlled trial of norepinephrine vs. epinephrine in septic shock [7\*]. In four ICUs, 280 patients requiring vasopressor support for any reason were randomized to receive either epinephrine or norepinephrine. There was no difference in the primary outcome (MAP) or the secondary outcomes (28-day or 90-day mortality). The findings were the same in the *a priori* subgroup of patients with severe sepsis at baseline (no difference in outcomes). Epinephrine was associated with the development of significant tachycardia, lactic acidosis and increased insulin requirements for the first 24 h of the study, after which there was no difference between the two drugs. The authors conclude that either norepinephrine or epinephrine can be used effectively in the ICU and that the use of epinephrine presents a cost-effective alternative to norepinephrine in low-income countries.

### Phenylephrine

Previous findings suggest that a delayed administration of phenylephrine replacing norepinephrine in septic shock patients causes a more pronounced hepatosplanchnic vasoconstriction as compared with norepinephrine. In a prospective, randomized controlled trial, 32 septic shock patients were randomly allocated to treatment with either norepinephrine or phenylephrine infusion [8\*]. Data from right heart catheterization, a thermodilution catheter, gastric tonometry, acid–base homeostasis, as well as creatinine clearance and cardiac troponin were obtained at baseline and after 12 h. No differences were found in any of the investigated parameters. This study suggests there are no differences in terms of cardiopulmonary performance, global oxygen transport and regional hemodynamics when phenylephrine was administered instead of norepinephrine in the initial hemodynamic support of septic shock.

### Terlipressin

Terlipressin, an analogue of vasopressin with a longer duration of action, is under investigation for the treatment of hypotension not responsive to conventional

vasopressor therapy. The half-life of terlipressin is 6 h, and the duration of action is 2–10 h, compared with the short half-life of vasopressin (6 min) and duration of action (30–60 min). The disadvantage terlipressin has over vasopressin is that once a bolus of terlipressin is given, its effects cannot be reversed easily, as with a continuous infusion of vasopressin. However, vasopressin is not available in every country.

The DOBUPRESS study [9<sup>\*</sup>] was conducted to study the effects of short-term simultaneous infusion of dobutamine and terlipressin in patients with septic shock. The patients were randomized to either sole norepinephrine infusion (control,  $n=20$ ); a single dose of terlipressin 1 mg ( $n=19$ ); or a single dose of terlipressin 1 mg followed by dobutamine infusion titrated to reverse the anticipated reduction in central venous oxygen saturation ( $S_{vo_2}$ ;  $n=20$ ). Terlipressin (with and without dobutamine) infusion preserved MAP, while allowing a reduction in norepinephrine.  $S_{vo_2}$  decreased with terlipressin and this effect was reversed by dobutamine. Generalization of the results of this study is limited by its use of surrogate outcomes.

Preliminary clinical data suggest that continuous infusion (rather than bolus dosing) of terlipressin (1.3  $\mu\text{g}/\text{kg}/\text{h}$ ) may be as safe as vasopressin (0.03 U/min) or norepinephrine (15  $\mu\text{g}/\text{min}$ ) when given as first-line vasopressor in septic shock patients [10<sup>\*</sup>]; however, to date, no large-scale clinical trials have evaluated this. Currently, the Terlipressin and Septic Shock Trial (TESS-1) is underway [11]. Patients are being randomized to low-dose or ultra-low-dose terlipressin in comparison with standard treatment with norepinephrine. Hopefully, this study will shed more light on the safety of continuous terlipressin as first-line therapy in septic shock.

### Dopamine

Preliminary reports of a randomized controlled trial of dopamine vs. norepinephrine in septic shock by the Brussels group of investigators suggest no significant difference in survival outcome [12]. Dopamine was associated with increased heart rate and possibly with increased incidence of adverse cardiac events associated with more  $\beta$ -adrenergic stimulation compared with norepinephrine. Publication of final results is anticipated soon. A further phase III randomized trial of dopamine vs. norepinephrine for the treatment of vasopressor-dependent septic shock is currently recruiting participants [13].

### Vasopressor interaction with corticosteroid treatment

The Corticosteroid Therapy of Septic Shock (CORTICUS) study prospectively tested for a difference in mortality between septic shock patients treated with corticosteroids vs. placebo [14<sup>\*\*</sup>]. This study demonstrated no difference in survival. However, the results

confirmed the known corticosteroid potentiation of adrenergic signaling pathways. That is, the need for catecholamine vasopressors was reversed more rapidly in the hydrocortisone-treated group.

A posthoc analysis of the VASST patients also suggested that corticosteroid treatment of septic shock patients who were treated with norepinephrine was not beneficial [15<sup>\*\*</sup>]. However, the combination of low-dose vasopressin and corticosteroids was associated with decreased mortality and organ dysfunction compared with norepinephrine and corticosteroids. Among the 779 patients enrolled, 589 were treated with a moderate dose of corticosteroids. There was a statistically significant interaction between vasopressin infusion and corticosteroid treatment ( $P=0.008$ ). In patients who had septic shock and were also treated with corticosteroids, vasopressin, compared with norepinephrine, was associated with significantly decreased mortality (35.9 vs. 44.7%, respectively,  $P=0.03$ ). In contrast, in patients who did not receive corticosteroids, vasopressin was associated with a trend toward increased mortality compared with norepinephrine (33.7 vs. 21.3%, respectively,  $P=0.06$ ). In patients who received vasopressin infusion, use of corticosteroids significantly increased plasma vasopressin levels by 33% at 6 h ( $P=0.006$ ) to 67% at 24 h ( $P=0.025$ ) compared with patients who did not receive corticosteroids.

We suggest that a new trial of vasopressin (vs. control) and corticosteroids (vs. placebo) in a factorial design is warranted. In the editorial accompanying this publication, Annane [16] recommended that given the apparent increased mortality with vasopressin infusion in corticosteroid-free patients, neither corticosteroids nor vasopressin should be used in patients with mild septic shock (basal rate of death of 25–30%).

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### Inotropic agents in ICU

Myocardial dysfunction frequently accompanies severe sepsis and septic shock. Myocardial dysfunction does not appear to be due to myocardial hypoperfusion but due to an intramyocardial inflammatory response triggered by ligands for myocardial toll-like receptors [17], and by circulating inflammatory mediators, including the cytokines tumor necrosis factor- $\alpha$  and IL-1 $\beta$ . At a cellular level, reduced myocardial contractility seems to be induced by both nitric oxide-dependent and nitric oxide-independent mechanisms [18], involves apoptotic pathways, depends on molecules in the edematous extracellular myocardial matrix binding cellular adhesion molecules expressed on activated cardiomyocytes [19], with final alteration in intracellular calcium flux due to changes in the S100A8 and A9 group of calcium handling molecules [20].

The true incidence of acute left ventricular hypokinesia in septic shock was recently investigated [21<sup>•</sup>]. During a 3-year period, 67 patients having septic shock and who were free from previous cardiac disease were studied by transesophageal echocardiography. Primary global left ventricular hypokinesia, defined as a left ventricular ejection fraction (LVEF) of less than 45% at admission was present in 26 patients. Secondary global left ventricular hypokinesia defined as LVEF of less than 45% observed in a patient previously in the normal range was observed at day 2 or 3 in 14 patients treated with norepinephrine. Thus, the overall incidence of global left ventricular hypokinesia in patients with septic shock and no prior cardiac history was 60%, much higher than previously described.

### Dobutamine

Dobutamine is a  $\beta$ -adrenergic agent that remains the 'gold standard' inotropic agent in the treatment of septic shock. In the Surviving Sepsis Campaign [5<sup>••</sup>], dobutamine is recommended as the first-line therapy for myocardial dysfunction as suggested by elevated cardiac filling pressures and low-cardiac output (grade 1C).

Recently,  $\beta$ -blocker therapy has been cautiously used in an effort to reduce tachycardia in septic shock patients requiring inotropic therapy. A retrospective analysis of milrinone and enteral metoprolol therapy in patients with septic myocardial depression [22<sup>•</sup>] reported that low doses of enteral metoprolol in combination with phosphodiesterase inhibitors are feasible in patients with septic shock and cardiac depression but no overt heart failure. Metoprolol blunted the tachycardia associated with milrinone therapy and was associated with a fall in central venous pressure, and norepinephrine, vasopressin and milrinone dosages (all  $P < 0.001$ ). Cardiac index and cardiac power index remained unchanged, whereas stroke volume index increased ( $P = 0.002$ ). The authors suggest that future prospective controlled trials on the use of  $\beta$ -blockers for septic cardiomyopathy and their influence on proinflammatory cytokines are warranted.

### Conclusion

The hemodynamic management of vasodilatory shock often requires use of vasoactive agents, after adequate fluid resuscitation, in order to preserve tissue perfusion. Current evidence does not support recommendation of one vasopressor over another; indeed, norepinephrine, vasopressin, terlipressin, phenylephrine and epinephrine may be used safely with similar survival outcomes. There may be a benefit to using vasopressin in low-dose in combination with corticosteroids; however, this approach needs further study. Dobutamine remains the mainstay

of inotropic therapy; however, preliminary data suggest that combination metoprolol and milrinone may be beneficial.

## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 459–450).

- 1 Beale RJ, Hollenberg SM, Vincent JL, Parrillo JE. Vasopressor and inotropic support in septic shock: an evidence-based review. *Crit Care Med* 2004; 32:S455–S465.
- 2 Landry DW, Oliver JA. The pathogenesis of vasodilatory shock. *N Engl J Med* 2001; 345:588–595.
- 3 Rivers E, Nguyen B, Havstad S, *et al.* Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368–1377.
- 4 Mullner M, Urbaneck B, Havel C, *et al.* Vasopressors for shock. *Cochrane Database Syst Rev* 2004;CD003709.
- 5 Dellinger RP, Levy MM, Carlet JM, *et al.* Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008; 36:296–327.
- This review reports a consensus of opinion regarding the vasoactive management of septic shock, based on available evidence.
- 6 Russell JA, Walley KR, Singer J, *et al.* Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med* 2008; 358:877–887.
- Although low-dose vasopressin did not reduce mortality compared with norepinephrine among septic shock patients, vasopressin is well tolerated and may be beneficial in patients having less severe septic shock. This study also confirmed the deficiency of endogenous vasopressin levels in septic shock and that infusion of 0.03 U/min restored serum vasopressin levels to an appropriate level for shock.
- 7 Myburgh JA, Higgins A, Jovanovska A, *et al.*, CAT Study investigators. A comparison of epinephrine and norepinephrine in critically ill patients. *Intensive Care Med* 2008; 34:2226–2234.
- This randomized controlled trial found no difference in outcomes between epinephrine and norepinephrine in the treatment of septic shock.
- 8 Morelli A, Ertmer C, Rehberg S, *et al.* Phenylephrine versus norepinephrine for initial hemodynamic support of patients with septic shock: a randomized, controlled trial. *Crit Care* 2008; 12:R143.
- This study suggests that there are no differences in cardiopulmonary performance, global oxygen transport and regional hemodynamics between phenylephrine and norepinephrine in the hemodynamic support of septic shock.
- 9 Morelli A, Ertmer C, Lange M, *et al.* Effects of short-term simultaneous infusion of dobutamine and terlipressin in patients with septic shock: the DOBUPRESS study. *Br J Anaesth* 2008; 100:494–503.
- This is the first randomized controlled trial showing that terlipressin bolus administration reduces norepinephrine requirements in septic shock patients; however, high doses of dobutamine are needed to reverse the terlipressin-linked cardiovascular effects.
- 10 Ertmer C, Rehberg S, Morelli A, Westphal M. Current place of vasopressin analogues in the treatment of septic shock. *Curr Infect Dis Rep* 2008; 10:362–367.
- This review summarizes the effects of vasopressin and terlipressin in the treatment of septic shock and gives recommendations for the practical use of vasopressin analogues.
- 11 Westphal M, Rehberg S, Ertmer C, Andrea M. Terlipressin – more than just a prodrug of lysine vasopressin? *Crit Care Med* 2009; 37:1135–1136.
- 12 Vincent JL. Is the current management of severe sepsis and septic shock really evidence based? *PLoS Med* 2006; 3:e346.
- 13 Dopamine versus norepinephrine for the treatment of vasopressor dependent septic shock on world wide web URL. <http://clinicaltrials.gov/ct2/show/NCT00604019?term=NCT00604019&rank=1>.
- 14 Sprung CL, Annane D, Keh D, *et al.* Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008; 358:111–124.
- Although corticosteroids did not decrease mortality of patients having septic shock, and cannot be recommended, hydrocortisone may have a role among patients who are vasopressor unresponsive.

- 15** Russell JA, Walley KR, Gordon AC, *et al.* Interaction of vasopressin infusion, corticosteroid treatment, and mortality of septic shock. *Crit Care Med* 2009; 37:811–818.

This substudy of VASST found an interaction between vasopressin and corticosteroids. The combination of low-dose vasopressin and corticosteroids was associated with decreased mortality and organ dysfunction compared with norepinephrine and corticosteroids.

- 16** Annane D. Vasopressin plus corticosteroids: the shock duo! *Crit Care Med* 2009; 37:1126–1127.
- 17** Boyd JH, Mathur S, Wang Y, *et al.* Toll-like receptor stimulation in cardiomyocytes decreases contractility and initiates an NF-kappa B dependent inflammatory response. *Cardiovasc Res* 2006; 72:384–393.
- 18** Court O, Kumar A, Parrillo JE. Clinical review: myocardial depression in sepsis and septic shock. *Crit Care* 2002; 6:500–508.
- 19** Boyd JH, Chau EH, Tokunaga C, *et al.* Fibrinogen decreases cardiomyocyte contractility through an ICAM-1-dependent mechanism. *Crit Care* 2008; 12:R2.

- 20** Boyd JH, Kan B, Roberts H, *et al.* S100A8 and S100A9 mediate endotoxin-induced cardiomyocyte dysfunction via the receptor for advanced glycation end products. *Circ Res* 2008; 102:1239–1246.

- 21** Vieillard-Baron A, Caille V, Charron C, *et al.* Actual incidence of global left ventricular hypokinesia in adult septic shock. *Crit Care Med* 2008; 36:1701–1706.

Global left ventricular hypokinesia is more frequent in septic shock than previously known and can be unmasked by norepinephrine treatment.

- 22** Schmittinger CA, Dunser MW, Haller M, *et al.* Combined milrinone and enteral metoprolol therapy in patients with septic myocardial depression. *Crit Care* 2008; 12:R99.

Low doses of metoprolol in combination with phosphodiesterase inhibitors are feasible in patients with septic shock and cardiac depression but no overt heart failure.  $\beta$ -Blockers in the setting of septic cardiomyopathy may have a role.