Vasopressors During Sepsis: Selection and Targets

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KEYWORDS

• Vasopressors • Norepinephrine • Epinephrine • Vasopressin • Dobutamine • Milrinone • Septic shock • Sepsis

KEY POINTS

- Urgent resuscitation using intravenous fluids and vasopressors is a universally accepted early intervention in septic shock.
- Randomized controlled trials (RCTs) have compared different types of vasopressors, use of vasopressors with inotropic agents, and mean arterial pressure targets.
- RCTs of early goal-directed therapy (EGDT) to optimize oxygen delivery by use of fluids, vasopressors, inotropic agents, and red blood cell transfusion(s) have been studied extensively.
- Recent negative EGDT RCTs have put into question fundamental treatment paradigms of severe sepsis and septic shock such as SvO_2 monitoring to titrate resuscitation.
- Better biomarkers of sepsis diagnosis, biomarkers of improved response to vasoactive agents, and biomarkers of prognosis are needed to stratify patients in trials and in clinical care.

INTRODUCTION

Septic shock is the most serious complication of sepsis and requires emergent recognition and treatment. Considerable efforts have been made to evaluate different therapies for septic shock, but consensus is far from established. Coinciding with improvements in optimal management of septic shock, there is a trend toward improved survival of septic patients.[1–3] Many different strategies of fluid replacement,[4] monitoring[5,6] vasopressor use, and combinations of therapies or goal-directed therapies have now been assessed in large pivotal randomized controlled trials (RCTs). The complexity of the literature prompted various groups to create the Surviving Sepsis Campaign Guidelines in 2004.[7] The most recent version of The Surviving Sepsis Campaign guidelines attempt to organize available information up to 2012 into practical guidelines and bundles.[1] More recent updates can be found at www.survivingsepsis.org. Herein, we review questions, answers, and clinical application for selection of vasopressor support in septic shock. We focus on high-level evidence RCTs despite concerns that such evidence does not routinely lead to changes in practice.[8,9] We then proceed to discuss exciting new targets under investigation.

HYPOTENSION, SHOCK, AND MEASUREMENT OF ARTERIAL PRESSURE

Sepsis-mediated hypotension is the clinical manifestation of the interactions of venous and arterial vasoplegia, hypovolemia and myocardial depression.

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The 2001 Society of Critical Care Medicine/European Society of Intensive Care Medicine/American College of Chest Physicians/American Trauma Society/Surgical Infection Society International Sepsis Definitions Conference defined severe sepsis as sepsis complicated by organ dysfunction. Septic shock refers to a state of acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes. In this 2001 consensus hypotension is defined by a systolic arterial pressure of less than 90 mm Hg, a mean arterial pressure (MAP) of less than 60, or a decrease in systolic blood pressure of 40 mm Hg from baseline, despite adequate volume resuscitation, in the absence of other causes for hypotension.[10]

How should arterial pressure be measured and monitored?[1,11,12] The 2013 Surviving Sepsis Guidelines recommend that patients who are receiving vasopressors have an arterial catheter[1] yet 2 very recent large RCT of early goal-directed therapy (EGDT) did not mandate this in their study protocol.[13,14] Arterial catheters are often suggested because pressure measured invasively can differ from noninvasive blood pressure measurement and this can, therefore, alter clinical decisions. These differences between invasive versus noninvasive arterial pressure are somewhat minimized by using MAP.[15,16] Dorman and colleagues[17] showed that patients receiving high doses of norepinephrine could have clinically meaningful differences in MAP and systolic arterial pressure when comparing invasive radial and femoral blood pressures. Using femoral instead of radial arterial pressure resulted in frequent and meaningful reductions in vasopressor support.[17] Furthermore, nurses and physicians in the intensive care unit (ICU) sometimes chose to disregard radial arterial pressure readings in favor of noninvasive blood pressure when radial artery catheters gave 'positional readings' or were otherwise deemed unreliable. Few if any of the studies mentioned in this review seem to have mentioned or taken into consideration faulty radial artery blood pressure measurements in their interpretation of the data. This seems a little surprising, considering that so much emphasis is put on that one hemodynamic measurement.

Recommendation for Clinical Practice

Noninvasive blood pressure monitoring is indicated for most patients requiring vasopressors.

WHAT IS THE TARGET MEAN ARTERIAL PRESSURE FOR SEPTIC SHOCK?

Recent reviews and guidelines have recommended 65 mm Hg as the threshold MAP below which therapies to increase MAP should be started[1,11,12] based on knowledge of physiology and expert opinion. A scenario-based questionnaire reported in 2011 of Canadian Intensivists seemed to demonstrate that intensivists are using vasopressors in a relatively homogenous way. MAP was the most commonly used and initiation of vasopressors was usually begun when the MAP was less than 60 mm Hg and target MAP was about 65 mm Hg. Intensivists almost uniformly raised targeted MAP for patients with severe chronic hypertension and past cerebrovascular injury with known vascular stenosis. MAP target modifications for other comorbidities were less frequent or less consistent. Digital cyanosis or livido reticularis prompted almost one-half of clinicians to lower vasopressors, whereas low urine output and the doubling of the creatinine motivated about one-third of respondents to increase vasopressors.[18]

Because blood pressure target recommendations were historically based on low quality evidence Asfar and colleagues[19] designed and completed an important large multicenter RCT of 776 patients with septic shock randomized to a high target MAP (80–85 mm Hg) or to a low target MAP group (60–65 mm Hg) for 5 days. Fluid administration was equivalent in both groups and significantly higher doses of vasopressors were used in the high MAP target group. Both the low and high MAP groups exceeded their target MAP. Survival at 28 days (primary end point) and 90 days was not different. Atrial fibrillation was more frequent in the high MAP group, but strokes were not evaluated as an endpoint. In the prospectively defined group of patients with hypertension (about 40% of enrolled patients had baseline hypertension), those that were assigned to the high MAP group had significantly less renal dysfunction and renal replacement therapy.[19] This RCT leads us to suggest that routinely targeting a high MAP in septic shock is not warranted because high MAP target did not lower mortality but increased de novo atrial fibrillation.[20] Second, a high MAP target may decrease incidence of acute kidney injury and need for renal replacement therapy (number needed to treat of 9.5 to prevent 1 patient from needing renal replacement therapy) in patients with hypertension. Interestingly, fluid resuscitation varies widely between RCTs of septic shock. Asfar and colleagues[19] used less fluid and higher doses of norepinephrine than was used in some other trials,[21,22] but used less norepinephrine and similar fluids when compared with 1 other trial.[23] This variability in fluid use suggests that, as with vasopressors and many things in septic shock management, optimal fluid use is far from an exact science.