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.

Recommendation for Clinical Practice

The target MAP for septic shock is 60 to 65 mm Hg, except in patients with preexisting hypertension in whom a target MAP of 80 to 85 mm Hg is recommended because of less need of renal replacement therapy, but with some increased risk of atrial fibrillation.

COMPARISONS OF VASOPRESSORS FOR SEPTIC SHOCK

An extensive 2011 Cochrane review of vasopressors for hypotensive shock analyzed data from 23 RCTs in 3212 patients (overall mortality rate of 50%; **Fig. 1**, **Table 1**). Six different vasopressors, alone or in combination with dobutamine or dopexamine, were studied in different comparisons. Norepinephrine versus dopamine, the largest comparison in 1400 patients from 6 RCTs, yielded similar mortality. Dopamine increased the risk of arrhythmias. Vasopressors used as add-on therapy in comparison with placebo were not effective either. The authors concluded that there was not sufficient evidence to prove that any of the vasopressors were superior to others and that the choice of a specific vasopressor may, therefore, be individualized and left to the discretion of the treating physicians. When discussing the implications for future research the Cochrane authors suggested that, "Maybe a more suitable approach to the treatment of shock is not the choice of a specific vasopressor but a goal directed approach (Rivers 2001). To the best of our knowledge this has not yet been assessed in a systematic way."[24] (A very recent systematic review and meta-analysis of EGDT as well as an invited accompanying editorial were reported [ICM 2105 in press] see below Early Goal-Directed Therapy for more detail.)

The 2013 Surviving Sepsis Guidelines are more prescriptive than the Cochrane Review. Norepinephrine is recommended as first choice vasopressor based on high-quality evidence. Epinephrine may be added to or substituted for norepinephrine when an additional agent is needed to maintain adequate blood pressure based on less clear evidence.[1] A Canadian intensivists' survey found that norepinephrine was the most commonly used first-line vasopressor (95% of respondents). About 80% of the respondents who selected norepinephrine as a first-line agent chose vasopressin as an alternate first-line agent.[18]

In addition to well-known adverse effects of beta-adrenergic agents on arrhythmias, tachycardia, and peripheral ischemia at high doses, there is a growing body of literature linking powerful beta-adrenergic agonists (including epinephrine) to type 2 lactic acidosis.[25–27] The recent intriguing placebo-controlled RCT showing that the beta-blocker esmolol seemed to decrease mortality of septic shock highlights the potential adverse effects of beta-adrenergic agents and the potential efficacy of esmolol.[28,29] Further multicenter RCTs of esmolol are needed before recommending it for routine clinical care.

There is a profound deficiency of vasopressin early in septic shock because of decreased output of vasopressin from the posterior pituitary gland.

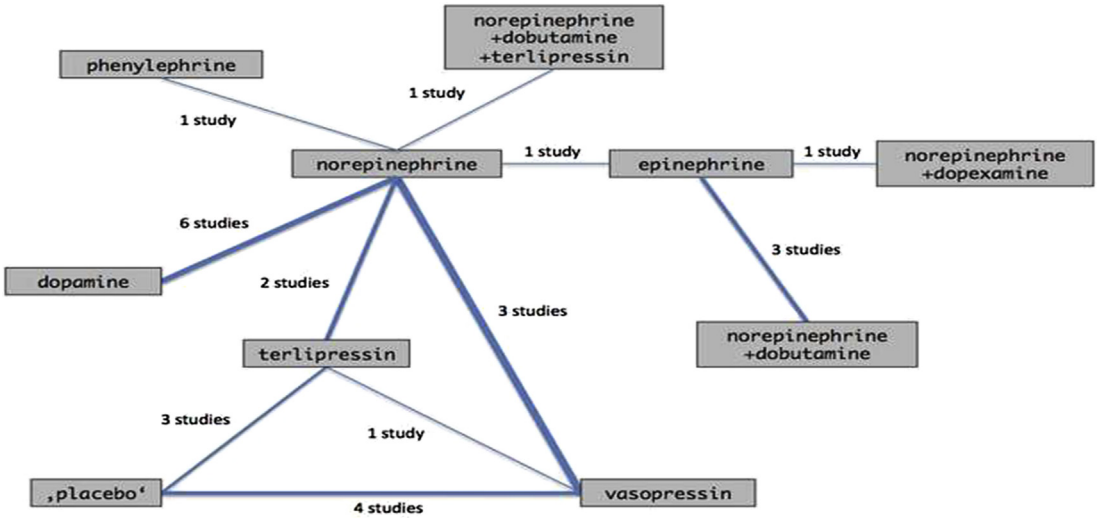

Fig. 1. Comparison of vasopressor identified from the systematic review. The 26 comparisons come from 23 studies. Line thickness is proportional to the number of included patients. (*From* Havel C, Arrich J, Losert H, et al. Vasopressors for hypotensive shock. Cochrane Database Syst Rev 2011;(5):CD003709; with permission.)

Table 1
Pivotal RCTs of vasopressors in septic shock

Author, Year	Treatment (n)	Control Intervention (n)	Treatment Mortality Rate (%)	Control Mortality Rate (%)	*P*
De Backer et al,[23] 2010	Dopamine	Norepinephrine	52.5	48.5	.10
Russell et al,[22] 2008	Vasopressin + norepinephrine	Norepinephrine	35.4	39.3	.26
Annane et al,[51] 2007	Norepinephrine + dobutamine	Epinephrine	34	40	·31
Myburgh et al,[21] 2008	Epinephrine	Norepinephrine	30.4	34.3	.49

Vasopressin has potential advantages to augment vasopressors in septic shock because small studies showed that vasopressin decreased need for vasopressors in septic shock through its direct V1a-mediated vasopressor action and indirectly because vasopressin increases responsiveness to adrenergic agents (such as norepinephrine). In the Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock (VASST) study, vasopressin plus norepinephrine had similar mortality to norepinephrine-treated patients.[22] Vasopressin is recommended as a second agent in patients who are not responsive to norepinephrine.[1] In VASST and subsequent substudies, vasopressin plus norepinephrine[22] seemed to decrease mortality in patients who had less severe septic shock and decrease risk of acute kidney injury and need for renal replacement therapy in patients at risk of acute kidney injury.[30] Furthermore, there is an interaction of vasopressin and corticosteroids (the combination was beneficial) in VASST[31] that is being validated in an ongoing RCT.[32] The Surviving Sepsis Guidelines state that vasopressin is not recommended as the single initial vasopressor and vasopressin doses higher than 0.03 to 0.04 U/min should be reserved for use when MAP targets are not attained with other vasopressor agents. We suggest that higher doses of vasopressin (>0.04 U/min) should be used only in research studies to better define the safety of these doses. No level of conviction as to the strength of the Surviving Sepsis Guidelines recommendation evidence was given despite publication of VASST, a large pivotal blinded multicenter RCT of vasopressin plus norepinephrine versus norepinephrine. Vasopressin should be titrated and weaned after a period of some hours off other vasopressors such as norepinephrine, in decrements of 0.01/U.min over 30 to 90 minutes.

A large RCT of dopamine versus norepinephrine in shock found no difference in mortality, but dopamine use was associated with increased risk of arrhythmias and increased heart rate.[23] Accordingly, dopamine should be reserved for use as an alternative vasopressor agent to norepinephrine only in highly selected patients, such patients with bradycardia and at low risk of developing arrhythmia. Phenylephrine is not recommended except in uncommon specific circumstances like norepinephrine-induced arrhythmias. Finally, low-dose dopamine should not be used for renal protection[1] because of a lack of efficacy.[33,34]

Recommendation for Clinical Practice

We recommend norepinephrine as the first-line vasopressor with epinephrine or vasopressin as a reasonable second-line vasopressor(s).

GOAL-DIRECTED THERAPIES

Clinicians and investigators have used therapies with defined goals for resuscitation, so-called EGDT of septic shock (**Table 2**). This is relevant herein because vasopressor use is embedded in EGDT so we narrow the focus of this discussion to what we have learned about vasopressors in RCTs of EGDT. In the 1990s, RCTs of supraphysiologic oxygen delivery proved unrewarding; all were negative or showed harm[35] of supraphysiologic oxygen delivery. That supernormal oxygen delivery showed no value and possibly harmful[35–37] forced reevaluation of resuscitation of septic shock. Perhaps interventions were neither early nor aggressive enough.[38–40]

Rivers and colleagues' single-center RCT compared 6 hour emergency department-initiated EGDT versus standard care (MAP >65 mm Hg, CVP 8–12 mm Hg, and urine output > 0.5 mL/kg/h). In the EGDT group, a target continuous superior vena cava oxygen saturation (SvO_2 $\geq$70%) was added. Interventions to achieve central venous oxygen saturation ($ScvO_2$) target included RBC

Table 2
Goal-directed therapy in randomized controlled trials

Study	Trial and Characteristics	Hypothesis Tested	Therapeutic Intervention	Pressure Target(s)	Hb/Hct Target (s)	Trial Results
Supernormal oxygen delivery (DO_2) Hayes et al,[35] 1994	2 center RCT n = 109 critically ill patients	Supernormal DO_2	Volume Dobutamine Dopamine	MAP >80	Hb 10	Increased mortality in intervention group
Goal-oriented hemodynamic therapy Gattinoni et al,[36] 1995	Multicentre n = 762 critically ill patients	Supernormal DO_2 (PAC CO) vs SvO_2 >70 vs normal cardiac index	Volume Dobutamine Dopamine) Nitroprusside Nitrates) Epinephrine Norepinephrine	MAP >60 Wedge <18 CVP 8–12	Hct 30	No difference in mortality
EGDT Rivers et al,[38] 2001	Single center n = 263 severe sepsis	6-h ER EGDT (continuous SvO_2) vs usual care	SvO_2 ≥70% dobutamine CVP 8–12 MAP ≥65 norepinephrine Epinephrine, dopamine, or phenylephrine	MAP >65 CVP 8–12	If SvO_2 <70% 1. RBC to Htc >30 2. Dobutamine	Mortality lower in EGDT group
Lactate clearance vs SvO_2 in early sepsis Jones et al,[85] 2010	3-center RCT n = 300 septic	$ScvO_2$ goals vs Serial lactate clearance	Crystalloids, dopamine, or norepinephrine Dobutamine depending on SvO_2 vs lactate clearance	MAP ≥65 CVP ≥8	If SvO_2 <70% RBC if Hct <30 Lactate clearance group: if lactate not decreasing RBC if Hct <30	No difference in mortality
Protocol-Based Care for Early Septic Shock The ProCESS Investigators,[13] 2014	31 centers n = 1351 severe septic patients	EGTD SvO_2 vs clinical protocol vs usual care (no protocol)	SvO_2 threshold 70% dobutamine vs ProCESS protocol: clinical protocol vs usual care	EGDT MAP ≥65 CVP 8–12 ProCESS protocol: SAP ≥100 Shock index ≥0.8 Usual care	EGDT Hct ≥30 ProCESS protocol: Hb ≥7.5 Usual care	No difference in mortality

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Table 2
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Study	Trial and Characteristics	Hypothesis Tested	Therapeutic Intervention	Pressure Target(s)	Hb/Hct Target (s)	Trial Results
Goal-Directed Resuscitation in Early Septic Shock Mouncey[14], 2015	51 centers n = 1600 severe sepsis patients	EGDT SvO_2-guided protocol vs usual care	EGDT: SvO_2 >70% dobutamine vs usual care	EGDT: MAP >65 CVP ≥8 (spontaneous ventilation) CVP ≥12 (mechanical ventilation) Usual care	EGDT: SvO_2 <70% RBC if: Hb <100 or Htc <30 Usual care	No difference in mortality
Early, Goal-Directed Resuscitation for Septic Shock ProMISe Trial Investigators,[14] 2015	56 centers n = 1243 severe sepsis patients	EGDT SvO_2 vs usual care	EGDT SvO_2 >70% dobutamine vs usual care	EGDT MAP >65 SBP >90 CVP ≥8 Usual care	EGDT: SvO_2<70% RBC if Hb <100 or dobutamine if Hb ≥100 Usual care	No difference in mortality
Levosimendan Morellia et al,[80] 2010	1 center 50 septic shock patients	Levisimendan (n = 20) vs comparator (dobutamine 5 $\mu g \cdot kg^{-1}\ min^{-1}$; control (n = 20)	Levisimendan (n = 20) vs comparator (dobutamine 5 $\mu g \cdot kg^{-1}\ min^{-1}$; control (n = 20)	NA	NA	Microcirculatory flow higher in levosimendan
Milrinone Wang et al,[84] 2015	1 center 90 severe sepsis patients control (n = 30), milrinone (n = 30), and milrinone-esmolol (n = 30)	control (n = 30) vs milrinone (n = 30) vs milrinone-esmolol (n = 30)	control (n = 30) vs milrinone (n = 30) vs milrinone-esmolol (N = 30)	NA	NA	ME lower 28-day mortality

Abbreviations: CO, cardiac output; CVP, central venous pressure; EGDT, early goal-directed therapy; ER, emergency room; Hb, hemoglobin; Hct, hematocrit; MAP, mean arterial pressure; NA, not applicable; PAC, pulmonary artery catheter; RBC, red blood cells; RCT, randomized controlled trial; SAP, systolic arterial pressure; $ScvO_2$, central venous oxygen saturation; SvO_2, mixed venous oxygen saturation; Wedge, pulmonary capillary wedge pressure.

transfusions (target Hct >30) and dobutamine. The EGDT group had significantly decreased hospital mortality (30.5 vs 46.5%; $P = .009$).

How did the intervention differ from standard care group regarding vasopressors? Vasopressors were equivalent in both groups (EGDT patients received more crystalloids, blood, and inotropic agents) during the first 6 hours. Specific vasopressor selection was not controlled or evaluated.[38] The 2008 Surviving Sepsis Guidelines incorporated EGDT and before/after case control nonrandomized trials suggested that EGDT decreased mortality.[41–43]

Rivers' EGDT was controversial because it was single center, the control mortality rate was high, and the baseline $ScvO_2$ was about 50%. Three subsequent multicenter RCTs of EGDT compared with usual care found no differences in mortality. ProCESS[13] (US-based) compared EGDT with 2 control groups (protocol-based resuscitation and usual care). The 'ProCESS protocol-based group' had a central venous catheter inserted if peripheral access was inadequate. Administration of fluids and vasopressors was guided by blood pressure targets and shock index (heart rate/systolic blood pressure). Regarding vasopressors, vasopressor choice was not prespecified. Mortality rates were similar in all groups. More vasopressors were given to the ProCESS and EGDT protocol groups than the usual care group and dobutamine was administered more in the EGDT group (8%) then in the ProCESS (1.1%) or the usual care groups (0.9%). Regarding later times, vasopressor and dobutamine use was similar from 6 to 72 hours.[13]

ARISE[44,45] (Australia/New Zealand [ANZICS]-based) RCT used Rivers' EGDT algorithm until 6 hours after randomization. Vasopressors (not guided by protocol) could include norepinephrine, epinephrine, dopamine, vasopressin, metaraminol, or phenylephrine. Prerandomization vasopressors in the EGDT and usual care groups were similar. Regarding later vasopressors, the EGDT group received more vasopressors (66.6% vs 57.8%; duration did not differ significantly) and more dobutamine (15.4% vs 2.6%) during the first 6 hours. From 6 to 72 hours, the EGDT group received more vasopressors (58.8% vs 51.5%) and dobutamine (9.5% vs 5.0%). Mortality at 28 and 90 days was similar in the EGDT and the usual-care groups (18.6% and 18.8%, respectively).

The ProMISe[14] (UK-based) RCT of $ScvO_2$ monitoring versus usual care[14] harmonized with ProCESS and ARISE for metaanalysis.[13,44] The EGDT group received more 'advanced cardiovascular support' (presumably vasopressors) and had longer ICU stay, but there was no difference in mortality (29.5% EGDT vs 29.2% usual care).

Recommendation for Clinical Practice

Recent negative EGDT RCTs have put into question the fundamental treatment paradigms of severe sepsis and septic shock, such as SvO_2 monitoring to titrate resuscitation.

IMPROVED OUTCOMES OF SEPSIS AND SEPTIC SHOCK

There is growing evidence of improved outcomes of severe sepsis and septic shock. A very large observational cohort study showed that patients in Australia and New Zealand suffering from severe sepsis and septic shock have had a remarkable improvement in outcome (from 35% to 18.4% mortality rates) over the last 12 years.[2] In the United States, Stevenson and colleagues[3] analyzed the outcomes of patients in the 'usual care' control arms of 36 severe sepsis RCTs dating back to 1991. Patients in the control arms have had progressively better outcomes over time (from 46.9% to 29%). The authors also evaluated 1993 to 2009 discharge data from Nationwide Inpatient Sample and that validated that severe sepsis mortality was decreasing.[3]

The reasons for this generalized trend toward improved survival of severe sepsis and septic shock are unclear. Levy and colleagues[46] demonstrated that patients from hospitals that had higher success rates of adoption of the Surviving Sepsis Guidelines and Bundles have improved survival compared with patients from hospitals that were less successful in the implementation of the Sepsis Guidelines and Bundles.

Some authors have questioned whether the recent decreases in mortality rates of severe sepsis and septic shock are real and only reflect changes in coding of severe sepsis in administrative databases.[47–49] Changes in hospital accreditation after publication of Rivers RCT included much greater emphasis on quality of early sepsis care in the emergency room and that could have led to much more inclusion of less severe cases of sepsis that would have been missed in prior reviews. Another possibility could be that patients with terminal diseases are now more readily given access to palliative care and are therefore no longer considered candidates for ICU admission. This would make it more likely that their deaths are classified or coded as caused by their primary terminal conditions and not sepsis. This systemic exclusion of patients with a certain upcoming mortality would significantly improve survival rates for those patients who do get admitted to an ICU.[50] Needless to say, it remains controversial whether, by how much, and why sepsis outcomes have improved.

Recommendation for Clinical Practice

Mortality of septic shock has decreased. It remains controversial whether, by how much, and why sepsis outcomes have improved.

INOTROPIC AGENT USE WHILE ON VASOPRESSORS

The Surviving Sepsis Guidelines recommend that inotropic agents should not be used to increase cardiac index to supranormal levels but that "a trial of dobutamine infusion up to 20 μg/kg/min be administered or added to vasopressors (if in use) in the presence of (a) myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output, or (b) ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and adequate MAP." This recommendation is graded 1C (strongly believed recommendation but based on low-quality evidence).[1]

The few RCTs done to evaluate the possible specific benefits of dobutamine in septic shock were structured in way that make interpretation of the role of dobutamine difficult. The biggest dobutamine RCT randomized septic patients to either receive epinephrine (n = 161) or norepinephrine plus dobutamine (n = 169). Comparison of norepinephrine and dobutamine versus epinephrine and a placebo infusion was done using a predetermined titration algorithm. Drug titration was done to maintain: mean blood pressure at 70 mm Hg or more and normal cardiac performance as assessed by various locally selected diagnostic methods (right heart catheterization, Doppler echocardiography, pulse contour cardiac output, or esophageal Doppler ultrasonography). The trial results showed mortality up to 90 days to be nearly identical (50% vs 52%) and that other outcome measures were also nearly identical in both groups. The group of patients receiving epinephrine did have persistently lower pH levels and higher initial lactic acid levels then the norepinephrine and dobutamine group.[51] Other studies comparing epinephrine administration versus a combination of norepinephrine and dobutamine (or dopexamine) were very small and provide limited clinically outcome measures that could meaningfully help to determine the usefulness of dobutamine (or dopexamine) in septic shock management.[52–54]

Recommendation for Clinical Practice

Dobutamine (or another inotropic agents such as milrinone) are needed in a minority of patients who have ventricular dysfunction during septic shock.

MONITORING PATIENTS WHO REQUIRE VASOPRESSORS

Determining which patients could potentially benefit from increased fluid administration and/or inotropic support is often difficult to decide when based only on clinical information. Because of these limitations, methods to assist in the evaluation of blood pressure and cardiac output responses to various therapeutic interventions are important and have become integral components in the treatment of septic patients. These measuring and monitoring techniques range from the very simple and easy to perform to the complex and highly specialized. A detailed analysis of these different methodologies is beyond the scope of this review, but the authors feel that this topic is so intimately associated with the use of inotropic agents that we need to at least touch on it. At the 'easy, cheap and simple' end of the diagnostic methodology spectrum the passive leg raising test, a noninvasive test, is reasonably accurate and reliable to evaluate fluid challenge responsiveness.[55] At the other end of the technology spectrum, echocardiography can be a valuable tool for the titration of fluid, vasopressor, and inotropic agents. The precise role of echocardiography in septic shock management is still not clearly established, however, because of a lack of large, rigorous, multicenter RCTs powered for mortality. Optimal selection of septic patients who should or could potentially benefit from echocardiographic assessment is limited in part by delays in availability of the equipment and variable 'around the clock' technical expertise to interpreting the images. These and other barriers have limited more widespread use of this potentially powerful technology.[56–60]

Echocardiography and other noninvasive cardiac output measurement systems are inherently safer than pulmonary artery catheter monitoring. In addition to the specific technical limitations of these systems, it remains to be seen whether 'inotropic hemodynamic optimization' using echocardiographic (or any other technology) will prove to be of significantly greater efficacy and effectiveness than usual care or whether we see a repeat of negative results of inotropic/pulmonary artery catheter–guided RCTs. The vasopressor and inotropic therapies currently recommended and used clinically to optimize hemodynamic status are similar, if not identical, to what were used in the many negative prior RCTs.[35,61,62] Ironically, the Italian esmolol RCT showed that patients given esmolol had improved survival yet cardiac outputs decreased, norepinephrine needs decreased, stroke volume increased, and glomerular filtration

rates increased. It is worth noting that patients with cardiac failure (cardiac index $\leq$2.2 and pulmonary occlusion pressures >18) were excluded from the RCT and that the average baseline cardiac index in the esmolol treated group was 4.0 versus about 3.6 in the control group.[28] Generally, these would not be patients who would be considered candidates for inotropic administration.[1] It is nevertheless difficult to accept that both beta-blockers and beta-agonists could both prove effective in the same septic patient population. Perhaps specific subgroups of patients benefit from these opposing interventions. For example, the evolutionary complexities of the stress response call for different approaches to adrenergic modulation at different stages of sepsis process?[29] More rigorous studies to discover, validate, and precisely define the responsive subgroups for inotropic versus beta-blocker treatment (eg, by clinical or biomarker selection), followed by large, well-powered RCTs are needed to better understand how and when we should use inotropic agents versus beta-blockers in septic shock.

It is also unclear as to how we should monitor inotropic response to treatment in low output states. To the best of our knowledge no RCT has convincingly and reproducibly shown vasoactive therapy guided by a 'cardiac output monitoring system(s)' to be clinically superior in terms of efficacy to decrease mortality in septic patients. Despite this lack of evidence, some now consider echocardiography to be a routine modality for cardiovascular assessment of all ICU patients[63–65] because echocardiography can discover unsuspected clinically relevant diagnostic information[66] in shock[65] and in other serious life-threatening situations.[67–70] That routine echocardiography findings improve outcome is far from certain.[71] A very detailed and comprehensive review of echocardiography in critically ill patients was recently done by The World Interactive Network Focused on Critical UltraSound.[72]

Recommendation for Clinical Practice

The passive leg raising test, a noninvasive test, is reasonably accurate and reliable to evaluate fluid challenge responsiveness. Echocardiography and other noninvasive cardiac output measurement systems are inherently safer than pulmonary artery catheter monitoring, and echocardiography can discover unsuspected clinically relevant diagnostic information in shock. More studies are required validate and define the responsive subgroups for inotropic versus beta-blocker treatment.

MILRINONE AND LEVOSIMENDAN TO SUPPLEMENT VASOPRESSORS

Milrinone[73–76] and levosimendan[77,78] are both inotropic agents that have been used, similar to dobutamine, as inotropic agents to supplement vasopressors in patients who have impaired ventricular function. Both are also vasodilators so are sometimes limited by worsening of hypotension. Neither is a beta-adrenergic agent and so do not suffer from beta-adrenergic receptor downregulation and tolerance to beat-adrenergic stimulation.

Levosimendan could have antiinflammatory and antioxidative properties, and can potentially decrease the deleterious effects of reactive oxygen species on the tissues.[79] A small RCT showed that, compared with low-dose dobutamine (5 $\mu g\ kg^{-1}min^{-1}$), levosimendan improved markers of microcirculatory blood flow.[80] Levosimendan has also been shown to control the decrease in cardiac output that can occur after vasopressin in a bovine model of septic shock.[81]

Levosimendan is now undergoing evaluation in a large in the UK.[82] This innovative RCT will assess efficacy of levosimendan to reduce acute organ dysfunction and evaluate its biological mechanisms of action in adult septic shock.

The use of inotropic agents remains controversial also because of observational propensity-scored controlled cohort studies showing that even after adjusting for baseline risks of death, use of inotropic agents is associated with increased mortality rates.[83]

Recommendation for Clinical Practice

Dobutamine (or another inotropic agents such as milrinone) are needed in a minority of patients who have ventricular dysfunction in sepsis. Levosimendan is now undergoing evaluation in a large in the UK.

SUMMARY

Regardless of the almost consistently negative RCTs, patients with septic shock may have lower mortality, but the degree and cause(s) of this change remain unknown. Perhaps priorities such as early, appropriate broad-spectrum antibiotics matters more than precise titration of specific vasopressors. We suggest that the clinician still lacks the optimal tools to assess adequacy of resuscitation and, accordingly, the need for, type, and dose(s)of vasopressors. We are aligned with international guidelines in recommending norepinephrine as first vasopressor if fluid resuscitation does not achieve resuscitation goals. Vasopressin or epinephrine may be added as second vasopressors.

Dobutamine (or another inotropic agents, such as milrinone) are needed in a minority of patients who have ventricular dysfunction in sepsis. Regarding EGDT, we recommend that routine use of EGDT including $ScvO_2$ in adult severe sepsis not be used in the developed world. Further studies of EGDT in children, in emerging countries, and/or different endpoints and algorithms would be helpful to clinicians everywhere.

Basic, translational and clinical research should have several complementary aims. First, we need to better define biomarkers of sepsis diagnosis (diagnostic biomarkers), biomarkers of improved response to vasoactive agents (predictive biomarkers), and biomarkers of prognosis (prognostic biomarkers) to better stratify patients in trials and in clinical care. Second, novel interventions such as esmolol require a better understanding of the mechanism of action in septic shock and who to treat (based on new RCTs). Third, we need a better understanding of the molecular and clinical interactions of the combinations of therapies so commonly used in septic shock (ie, vasopressors, inotropic agents, corticosteroids). Finally, we need a further understanding of novel targets to further improve outcomes of septic shock.

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