Review Article

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Hemodynamic management of septic shock: Beyond of the SSC guidelines

Running title: Hemodynamic management of septic shock

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Abstract

Although the SSC Guidelines provide a standardized and generalized guidance, they are less individualized. This review focuses on recent updates in the hemodynamic management of septic shock. Monitoring and intervention for septic shock should be personalized according to the phase of shock. In the salvage phase, fluid resuscitation and vasopressors should be given to provide tissue perfusion for life-saving. During the optimization phase, tissue perfusion should be optimized. In the stabilization and de-escalation phases, minimal fluid infusion and safe fluid removal should be performed, respectively, while preserving organ perfusion. There is a controversy on the use of restrictive versus liberal fluid strategies after initial resuscitation. Fluid administration after initial resuscitation should depend on the patient's fluid responsiveness and require individualized management. A number of dynamic tests have been proposed to monitor fluid responsiveness, which help clinicians decide whether to give fluid or not. The optimal timing for the initiation of vasopressors is unknown. Recent data suggest that early vasopressor initiation should be considered. Inotropes can be considered in patients with decreased cardiac contractility associated with impaired tissue perfusion despite adequate volume status and arterial blood pressure. Veno-arterial ECMO should be considered for refractory septic shock with severe cardiac systolic dysfunction.

Keywords: Septic shock, Resuscitation, Fluid responsiveness, Vasopressor, Extracorporeal membrane oxygenation

Capsule Summary

What is already known:
The Surviving Sepsis Campaign Guidelines provide a standardized and generalized guidance based on randomized controlled trials that investigate the patient's response to one intervention. Sepsis is a complex condition with variable clinical course, patient phenotype and the response to treatment. Therefore, a “one-size-fits-all” management based on the guidelines may not be appropriate for all patients.
What is new in the current study:

Hemodynamic monitoring and fluid management should be personalized according to the phase of shock. There is a controversy on the use of restrictive versus liberal fluid strategies after initial resuscitation. Fluid administration after initial resuscitation should be determined by the patient's fluid responsiveness. Recent data suggest early initiation of vasopressor if blood pressure is not restored after initial fluid resuscitation. Veno-arterial ECMO can be considered for refractory septic shock with severe cardiac systolic dysfunction.
Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality [1]. Despite advances in sepsis care, sepsis remains a major cause of morbidity and mortality worldwide, including in Korea. In 2017, an estimated 48.9 million sepsis cases were recorded worldwide and 11.0 million sepsis-related deaths were reported, representing 19.7% of all global deaths [2, 3].

To reduce the morbidity and mortality associated with sepsis, the Surviving Sepsis Campaign (SSC) Guidelines were first launched in 2002 by the European Society of Intensive Care Medicine, the International Sepsis Forum, and the Society of Critical Care Medicine. Since then, it has been regularly updated based on new research findings and clinical experiences [4]. While the guidelines provide a standardized and generalized guidance, they are supported by evidence mainly based on randomized controlled trials (RCTs) that investigate the patient's response to one intervention. However, recent large RCT studies failed to show a difference in mortality overall [5-7]. The reason for this is the fact that these RCT studies have not considered the characteristics of individual patients that may affect their response to specific interventions. Given that sepsis is a complex condition with variable clinical course, patient phenotype and the response to treatment, a “one-size-fits-all” management may not be appropriate for all patients. In this respect, the evidence-based SSC guidelines appear to be less individualized. Future sepsis treatment should be individualized based on the diversity of sepsis. This narrative review focuses on recent updates in the personalized hemodynamic management of septic shock which have not been covered in the SSC guidelines.

Personalized hemodynamic management

Hemodynamic support remains the cornerstone in the management of septic shock. There are different phases in the management of shock: salvage, optimization, stabilization, and de-escalation
phases [8]. Monitoring and intervention for each phase of septic shock should be personalized according to the phase of shock (Fig. 1) [9].

1. Personalized hemodynamic monitoring

1) Salvage phase

In the salvage phase, the goal of treatment is to provide tissue perfusion for life-saving. Mean arterial pressure (MAP) ≥ 65 mmHg and diastolic arterial pressure ≥ 45mmHg should be achieved. Clinical assessment has a role in identifying patients who may respond to fluids and assessing their response [10]. Altered clinical signs, including hypotension, tachycardia or bradycardia, cold extremities, skin mottling, increased capillary refill time (CRT) and oliguria are important warning signals indicating tissue hypoperfusion is occurring, but these cannot reliably indicate whether cardiac output (CO) is low or high, nor indicate the source of the hemodynamic alteration [11]. For this purpose, physicians should perform additional evaluations such as lactate measurement and echocardiography. If cardiac impairment is suspected or patient fails to respond to fluid therapy, bedside echocardiography is the only useful tool for rapid estimation of cardiac dysfunction along with the identification of the cause of low CO. Blood lactate level is also useful to identify impairment in tissue perfusion [9].

2) Optimization phase

During the optimization phase, the goal is to optimize tissue perfusion. In addition to the monitoring tools in the salvages phase, central venous oxygen saturation (ScvO₂) or mixed venous oxygen saturation (SvO₂) and venous-to-arterial carbon dioxide difference (Pv-aCO₂) may be used for the estimation of tissue perfusion [9]. ScvO₂ or SvO₂ reflects the balance between the actual oxygen consumption and tissue oxygen delivery. A low ScvO₂ indicates inadequate O₂ delivery in if hemoglobin and arterial O₂ saturation are within normal ranges [9]. Pv-aCO₂, defined as the difference between mixed-venous and arterial CO₂ partial pressures, is inversely related to CO. Increased Pv-aCO₂ reflects decreased microvascular blood flow during early phases of resuscitation of
septic shock [12]. It is important to note that there are differences in normalization rate between monitoring tools. In an observational study, monitoring tools such as ScvO2, Pv-aCO2, and CRT were already normal in more than 70% of survivors at 6 h, whereas lactate presented a much slower normalization rate decreasing significantly at 6 h compared to that of baseline but with only 52% of patients achieving normality at 24 h [12]. Therefore, it is preferable to use several monitoring tools in combination rather than using only one monitoring tool. Transpulmonary thermodilution (TPTD), advanced monitoring tool, provides continuous and real time monitoring of cardiac output. It estimates the end-diastolic volume and systolic function of the four cardiac chambers. It also measures extravascular lung water (EVLW), which quantifies the volume of pulmonary edema, and pulmonary vascular permeability, which quantifies the degree of a pulmonary capillary leak [13, 14]. Transpulmonary thermodilution should be considered in patients with severe septic shock.

3) Stabilization phase
In the stabilization phase, the goal is to preserve organ perfusion and to prevent organ dysfunction. Cardiac dysfunction and volume overload are common at this stage, and hemodynamic tools already in use can continue to be used. In particular, repeated echocardiography may be helpful to recognize the development of right ventricular dysfunction [9].

4) De-escalation phase
Finally, in the de-escalation phase, the goal is to achieve negative fluid balance by weaning vasoactive drugs and promoting spontaneous polyuria or by inducing fluid clearance using diuretics or ultrafiltration. Monitoring can be minimized. Tissue perfusion and fluid responsiveness should be evaluated prior to fluid removal. When hypoperfusion occurs, de-escalation should be stopped [9].

2. Fluid management after initial resuscitation
For patients with sepsis induced hypoperfusion or septic shock, the SSC guidelines suggest that at least 30 mL/kg of intravenous crystalloid fluid should be given within the first 3 h of resuscitation.[4] This fixed volume of initial resuscitation was mainly based on several large RCT trials [5, 7, 15-18]. However, the SSC guidelines suggest no recommendation for fluid administration in patients with sepsis and septic shock who still have signs of hypoperfusion and volume depletion after initial resuscitation, and that fluid resuscitation should be given only if patients present with signs of hypoperfusion. The guidelines emphasize that fluid administration after the initial fluid bolus should be guided by perfusion parameters as well as a response in hemodynamic variables [4]. Liberal fluid administration may have detrimental effects by causing edema in vital organs, leading to organ dysfunction and impairment of oxygen delivery, but the restrictive fluid strategy primarily relies on vasopressors to reverse hypotension and maintain perfusion limiting fluid administration [19].

Observational clinical studies and randomized trials showed harmful effects including kidney injury, respiratory failure, or high mortality. These studies suggest that a restrictive fluid strategy is potentially superior to a liberal fluid strategy [20-24]. Recently, the results of two RCT studies related to restrictive versus liberal fluid strategies after initial resuscitation have been published. In CLASSIC trial, the restrictive fluid group received intravenous fluids bolus of 250 to 500 ml if the patient had severe hypoperfusion, which was defined as a plasma lactate value of at least 4 mmol/L, a mean arterial pressure below 50 mmHg despite infusion of a vasopressor or an inotropic agent, mottling score >2 (on a scale of 0 to 5, with higher scores indicating a greater area of mottling), or a urinary output of less than 0.1 ml/kg/hr during the first 2 hours after randomization. In the standard fluid group, no upper limit of fluid administration was set. The study found that intravenous fluid restriction did not cause fewer deaths at 90 days than standard intravenous fluid therapy [25]. In CLOVERS trial, patients with sepsis-induced hypotension refractory to initial treatment with 1 to 3 liters of intravenous fluid were enrolled. There was no difference in 90-day mortality and adverse outcomes between the restrictive fluid strategy (prioritizing vaspressors and lower intravenous fluid volumes) and the liberal fluid strategy (prioritizing higher volumes of intravenous fluids before vasopressor use) [26]. These studies showed that restrictive fluid therapy is not superior to liberal
fluid therapy. This means that fluid administration after initial resuscitation may vary depending on the patient's fluid responsiveness and require individualized management. A comprehensive evaluation including tissue perfusion monitoring, benefits and risks of fluid infusion, and fluid responsiveness should be done to achieve individualized fluid management, which should be preferred over a restrictive or liberal fluid strategy [13].

3. Tests to predict fluid responsiveness

The goal of fluid administration in patients with septic shock is to increase cardiac output and tissue perfusion. However, fluid infusion can cause deleterious effect of fluid overload without increase in cardiac output. In an observational cohort study, only two thirds of patients with septic shock were fluid responders [27]. Therefore, patients not responding to volume expansion may experience fluid overload [28]. Fluid overload has been shown to cause enhanced shedding of the endothelial glycocalyx. Disruption of glycocalyx increases vascular permeability, leading to tissue edema [29]. To prevent a harmful effect of fluid overload, predicting fluid responsiveness should be the first step of fluid strategy. Fluid responsiveness refers to a set of bedside tests that reversibly increase the preload status of the heart, allowing the clinician to assess if this manipulation determines a significant increase in CO [30]. Fluid responsiveness is commonly defined as a stroke volume (SV) increase of at least 10% following a fluid bolus of 200–500 mL in 10–15 min [31, 32]. For this purpose, static measurements of preloads, including central venous pressure, inferior vena cava (IVC) diameter, and arterial pressure, have been used for decades, but are unreliable. Strong evidence suggests that these traditional uses should be abandoned [31-35]. In the last two decades, a number of dynamic tests have been proposed to establish and monitor fluid responsiveness (Table 1). These dynamic tests use heart-to-lung interactions, passive leg raising, or mini-fluid challenges to induce short-term changes in cardiac preloads and observe their effects on CO [31, 36]. All have some limitations, but they are frequently complementary, which helps clinicians to take the decision to give fluid or not [31, 36].

In 2018, expert statement proposed an individualized fluid treatment based on a repeated bolus of
250–500 mL of IV crystalloids with the continuous monitoring of fluid responsiveness and the early administration of vasopressors if circulation fails to improve [37]. Since it is impractical to standardize the amount of fluid according to each patient, an individualized strategy of resuscitation based on fluid responsiveness is preferable.

On the other hand, fluid unresponsiveness could be used to safely remove fluids in the hemodynamically stable patient [38].

Table 1. Tests predicting fluid responsiveness

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<tr>
<th>Test</th>
<th>Advantages</th>
<th>Limitations</th>
<th>Threshold</th>
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<tbody>
<tr>
<td>PPV/SVV</td>
<td>Require no maneuver</td>
<td>Cannot be used in case of spontaneous breathing, cardiac arrhythmias, low Vt/ lung compliance</td>
<td>≥ 12%</td>
</tr>
<tr>
<td>PLR</td>
<td>No fluid infusion</td>
<td>Requires a direct measurement of CO/SV</td>
<td>CO ≥ 10%</td>
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<td></td>
<td>Works regardless of breathing activity, cardiac rhythm, Vt, lung compliance</td>
<td></td>
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<tr>
<td>EEO test</td>
<td>Easy to perform</td>
<td>Requires a direct measurement of CO/SV</td>
<td>CO ≥ 5%</td>
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<td></td>
<td>Works regardless of breathing activity, cardiac rhythm, Vt, lung compliance</td>
<td>Requires mechanical ventilation</td>
<td></td>
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<tr>
<td>Vt challenge</td>
<td>Requires no</td>
<td>Requires mechanical ventilation</td>
<td>PPV ≥ 1 to</td>
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<td>Measurement</td>
<td>Required in position</td>
<td>Spontaneous breathing</td>
<td>Requires transesophageal Doppler</td>
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<tr>
<td>IVC diameter variation</td>
<td>Requires no measurement in CO/SV</td>
<td>Cannot be used in spontaneous breathing, low Vt/lung compliance</td>
<td>≥ 12%</td>
</tr>
<tr>
<td>SVC diameter variation</td>
<td>Requires no measurement in CO/SV</td>
<td>Cannot be used in spontaneous breathing, low Vt/lung compliance</td>
<td>≥ 12 to 36%</td>
</tr>
<tr>
<td>Mini-fluid challenge</td>
<td>Easy to perform</td>
<td>Requires a precise technique for measuring CO</td>
<td>CO ≥ 5%</td>
</tr>
<tr>
<td>Trendelenburg maneuver</td>
<td>No fluid infusion</td>
<td>Possible gastric reflux</td>
<td>CO ≥ 8 to 10%</td>
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Timing of initiation of vasoactive agents in septic shock
Septic shock results in shedding of the vascular endothelial glycocalyx and endothelial damage, which leads to increased permeability, diffuse alterations in microvascular perfusion, and vasodilation due to marked decrease in vascular tone [29]. Hypotension in patients with septic shock is known to be associated with increased mortality [38, 39]. Vasoactive agents play a crucial role in septic shock management by modulating vascular tone and enhancing myocardial contractility. Vasoactive agents possess varying abilities to constrict or dilate blood vessels and enhance myocardial contractility (Fig. 2) [40]. The selection of vasoactive agents is tailored to the individual patient's hemodynamic profile and specific needs to achieve optimal cardiovascular stability and tissue perfusion. The SSC guidelines recommend norepinephrine as first-line vasopressor to maintain a target MAP of 65 mmHg for initial resuscitation [4]. Norepinephrine is both the α-1 and β-1 adrenergic agonist that predominantly enhances vascular filling pressure and redistributing blood flow via its vasoconstrictive effect, and myocardial contractility [41]. In septic shock patients, a decrease in norepinephrine dose resulted in a more significant decrease in mean systemic pressure than a decrease in resistance to venous return, leading to a decrease in venous return [42].

Timely initiation of vasopressors with fluid resuscitation is a key component in the management of septic shock. However, optimal timing for the initiation of vasopressors has not been known. There are no recommendations on the timing of initiation of vasoactive agents for septic shock treatment in the SSC guidelines. Recent data showed an association between delayed therapy and increased mortality, and suggested that early initiation of vasopressor should be considered [38, 43, 44]. The 2018 SSC hour-1 bundle, which recommends vasopressor therapy within the first hour during or after volume resuscitation if blood pressure is not restored after initial fluid resuscitation to achieve MAP of ≥ 65 mm Hg [45]. In a retrospective study, every 1-hour delay in norepinephrine initiation during the first 6 hours after septic shock onset was associated with a 5.3% increase in mortality. Twenty-eight day mortality rates were significantly higher when norepinephrine administration was started more than or equal to 2 hours after septic shock onset compared to less than 2 hours [43]. A very early start of vasopressor within/before the next hour of the first resuscitative fluid load was related with
significant lower net fluid balances, and was also associated with a significant reduction in the risk of death at 28-day mortality [46]. Early high-dose vasopressor within the first 6 hours of shock is associated with lower mortality [47]. In a systematic review and meta-analysis, early initiation of norepinephrine in patients with septic shock was associated with decreased short-term mortality, shorter time to achieved target MAP, and less volume of intravenous fluids within 6 hr [48]. In the CENSER trial, a single-center, prospective, double-blind, placebo-controlled trial, early vasopressor group received norepinephrine at 1.5 hr compared to 3 hr in the standard treatment group. Shock control rate at 6 hr, which was the primary endpoint, was met in 76.1% of patients in the early vasopressor group compared to 48.4% in the standard group ($p < 0.001$), while there was no difference in 28-day mortality [49]. In contrast, earlier vasopressor use with a restrictive fluid strategy did not result in significantly lower (or higher) mortality before discharge home by day 90 than later vasopressor use with a liberal fluid strategy [26]. Similarly, vasopressor initiation within 1 hr of fluid loading was associated with higher 28-day mortality in patients with septic shock [50]. Diastolic arterial pressure (DAP) and diastolic shock index (DSI), defined as the ratio between heart rate and DAP, may be used to guide the timing of vasopressor initiation in septic shock. It seems logical to initiate vasopressors when a very low DAP < 45 mmHg or DSI > 2, which indicates severe vasodilation [51]. A retrospective observational study showed that in patients with the high DSI (≥2.0) and high lactate (≥2.5 mmol/L), an early start of vasopressor therapy was associated with decreased 28-day mortality [52]. These data suggest that norepinephrine should be initiated early, ideally within 1 hr of shock onset, and post adequate fluid resuscitation. DSI and lactate can help guide the appropriate time to initiate vasopressor therapy in septic shock [53]. The SSC guidelines suggest adding vasopressin instead of escalating the dose of norepinephrine for adults with septic shock on norepinephrine with inadequate MAP levels. However, the timing of vasopressin initiation is not well described in the literature. In the VASST trial, there was no difference in 28-day mortality, but subgroup analyses identified a mortality benefit with the use of vasopressin in less severe septic shock patients, who were those with a norepinephrine dose at
randomization ≤ 15 mcg/min and those with a lactate concentration at randomization of ≤ 1.4 mmol/L

[54]. A retrospective, observational study, higher norepinephrine-equivalent dose at vasopressin initiation and higher lactate concentration at vasopressin initiation were each associated higher in-hospital mortality in patients with septic shock [55]. These data indicate that vasopressin should be initiated when patients are on low norepinephrine-equivalent doses or have low lactate concentrations. While the SSC guidelines suggest vasopressin initiation when norepinephrine dose is in the range of 0.25–0.5 mcg/kg/min [4], vasopressin initiation may be considered before norepinephrine-equivalent doses exceed 0.1-0.2 mcg/kg/min (10–15 mcg/min) [53].

Epinephrine should be considered as a third-line treatment for septic shock, and its use should be limited to those cases with inadequate MAP levels despite norepinephrine and vasopressin administration [4]. The specific norepinephrine equivalent dose at which epinephrine should be added in septic shock is unknown. One study identified the optimal norepinephrine equivalent dose range for initiating epinephrine as 37 to 133 mcg/min. In this dose range, 29% of patients achieved hemodynamic stability with the initiation of epinephrine while 15% of patients who had epinephrine initiated outside of this dose range achieved hemodynamic stability (p = 0.03) [56].

Inotropes

Sepsis-induced cardiomyopathy (SCM) is a reversible myocardial dysfunction caused by sepsis. The prevalence of SCM varies from 10% to 70%. Studies defining SCM as an EF of <45% have generally reported a prevalence of 30–50% [57]. Inotropes can be considered in patients with decreased cardiac contractility associated with impaired tissue perfusion. The SSC guidelines suggest either adding dobutamine to norepinephrine or using epinephrine alone for adults with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and arterial blood pressure [4]. Adverse effects (tachyarrhythmia, increased heart rate, hypotension, and myocardial oxygen consumption) and specific risks (hypertrophic cardiomyopathy, myocardial ischemia) should be carefully investigated and the risk/benefit of intervention should be evaluated [9]. Milrinone is a phosphodiesterase inhibitor, which increase intracellular cyclic AMP leading to inotropic effects.
independent of β-adrenergic receptors [16]. It could be effective in patients recently on β-blockers [58]. Experts suggest a stepwise approach of inotropics. First, starting a limited dose of dobutamine (2.5 to 5 mcg/kg/min) and evaluate efficacy and tolerance. If there is still severe contractility impairment, higher doses (up to 20 mcg/kg/min) may be considered. Second, substitute or add enoximone or milrinone and evaluate efficacy and tolerance. Third, substitute or add levosimendan in cases of severe impairment. At each step, improvement in cardiac function and CO, resolution of tissue hypoperfusion and tolerance (e.g., lack of tachycardia, arrhythmias, etc.) should be evaluated. As soon as the situation improves, weaning of inotropics should be attempted [9]. However, the SSC guidelines suggest against using levosimendan as it was not superior to dobutamine in adults with sepsis in terms of mortality [4, 59].

**Timing of initiation of corticosteroid in septic shock**

Sepsis results in disruption of the hypothalamic–pituitary–adrenal axis, which may translate into cardiovascular and other organ dysfunction, and eventually an increase in the risk of death. Corticosteroid is known to improve cardiovascular function via sodium and water retention, restore systemic vascular resistance, and decrease organ failure [60]. Three recent large RCTs have shown that corticosteroids accelerate the resolution of shocks, but there was no clear effect on short-term or long-term mortality [61-63]. The SSC guidelines suggest using IV corticosteroids in patients with septic shock and ongoing requirements for vasopressor therapy [4]. Although there is no clear recommendation with regard to the time of initiation of corticosteroids in septic shock patients, the early initiation of corticosteroid therapy in sepsis, specifically within 24 hr of shock, despite adequate fluid resuscitation and vasopressor administration (norepinephrine-equivalent dose of 0.5–1 mcg/kg/min) is reasonable [53]. A retrospective cohort study showed decreased ICU mortality when hydrocortisone was administered within 0-6 hr after shock onset compared to > 48 hr after shock onset (OR 0.6, 95% CI 0.4-0.8) and suggested that hydrocortisone should be started within the first 12 hr after shock onset [64].
A recent multicenter, propensity score-weighted observational cohort study \((n = 198)\) evaluated early (within 12 hr of vasopressor initiation) versus late (after 12 hr of vasopressor initiation) low-dose corticosteroid initiation in septic shock and identified that early initiation was associated with shorter time to vasopressor discontinuation compared with late (40.7 vs. 60.6 hr; \(p = 0.0002\)) [65]. The SSC guidelines suggest that corticosteroid administration is commenced at least 4 hr after vasopressor initiation and at norepinephrine or epinephrine dose of at least 0.25 mcg/kg/min [4].

**Veno-arterial ECMO in septic shock**

While the SSC guidelines suggest using veno-venous (VV) ECMO when conventional mechanical ventilation fails for sepsis-induced severe ARDS, there is no suggestion of veno-arterial (VA) ECMO in septic shock complicated by SCM [4]. Most early studies of VA-ECMO for refractory septic shock complicated by SCM reported low survival rates and poor outcomes [66]. A recent retrospective, multicenter study showed that patients with severe sepsis-induced cardiogenic shock treated with VA-ECMO had a large and significant improvement in survival compared with controls not receiving ECMO (60% vs 25%, \(p < 0.0001\)) [67]. A meta-analysis of 468 patients placed on VA-ECMO for refractory septic shock showed an overall survival of 36% and significantly higher survival in patients with EF < 20% compared to those with EF > 35% (62% vs. 32.1%, \(p = 0.05\)) [68]. Therefore, VA-ECMO should be considered as a bridge therapy to recovery for refractory septic shock with severe cardiac systolic dysfunction and end-organ hypoperfusion. However, VA-ECMO should not be used for isolated vasodilatory septic shock without significant myocardial dysfunction [66].

**Summary**

Sepsis is a complex condition with variable clinical course, patient phenotype and the response to treatment. Personalized hemodynamic monitoring and fluid responsiveness based on the phase of septic shock are essential in septic shock management to assess the patient’s cardiovascular status,
guide fluid resuscitation, determine the need and timing for vasopressors and inotropic agents, and optimize tissue perfusion, which leads to improved outcomes in septic shock.
References


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32. Monnet X, Teboul JL. My patient has received fluid. How to assess its efficacy and side effects? Ann Intensive Care 2018;8:54.


**Figure legend**

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<td><strong>Targets</strong></td>
<td>• MAP ≥ 65 mmHg</td>
<td>• Optimal MAP</td>
<td>• Preserve tissue perfusion</td>
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<td>• DAP ≥ 45 mmHg</td>
<td>• Tissue perfusion &amp; oxygen</td>
<td>• Minimized fluid</td>
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Fig. 1. Hemodynamic monitoring, targets, and interventions at the different phases of shock

CRT, capillary refill time; MAP, mean arterial pressure; DAP, diastolic arterial pressure; SvO₂, mixed venous oxygen saturation; ScvO₂, central venous oxygen saturation; PväCO₂, venous to arterial carbon dioxide difference; EVLW, extravascular lung water; TPTD, transpulmonary thermodilution.
Fig. 2. Vasoactive agents and their effects