


## NARRATIVE REVIEW



# Current practice and evolving concepts in septic shock resuscitation

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### Abstract

Clinical and pathophysiological understanding of septic shock has progressed exponentially in the previous decades, translating into a steady decrease in septic shock-related morbidity and mortality. Even though large randomized, controlled trials have addressed fundamental aspects of septic shock resuscitation, many questions still exist. In this review, we will describe the current standards of septic shock resuscitation, but the emphasis will be placed on evolving concepts in different domains such as clinical resuscitation targets, adequate use of fluids and vasoactive drugs, refractory shock, and the use of extracorporeal therapies. Multiple research opportunities remain open, and collaborative endeavors should be performed to fill in these gaps.

**Keywords:** Sepsis, Intensive care, Vasoactive drugs, Fluids, Fluid resuscitation, Treatment

### Introduction

A recent review addressed current and evolving standards of care for patients with acute respiratory distress syndrome [1], a condition where simple rules to avoid ventilatory-induced lung injury can be recommended. In the field of septic shock, there is a lack of solid evidence in almost every aspect of care. Several randomized, controlled trials (RCTs) have addressed the proper use and place of the pillars of hemodynamic resuscitation such as fluids, vasopressors, and inotropes, but no intervention was associated with a significant effect on survival [2]. This also holds true for monitoring devices as these by themselves cannot change outcome and thus, their

effectiveness relies on the proper use of adequate protocols that deal with relevant clinical abnormalities. While the role of new vasopressors or inotropes is still uncertain, new concepts in fluid resuscitation have been slowly introduced.

In this narrative review, we provide an update on different domains of septic shock resuscitation including the devices used to monitor the effect of different interventions. The basis is current practice with emphasis on evolving concepts in the monitoring and management of septic shock (Fig. 1).

### Current practice

Current practice, although heterogenous, mostly follows Surviving Sepsis Campaign (SSC) guidelines [3], especially in the emergency department.

### Clinical targets

Septic shock is characterized by an abnormal distribution of blood flow associated with vasodilation due to

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vasoplegia that is associated with the release of mediators due to the innate immune response to the infection, resulting in microvascular injury and inadequate tissue oxygen supply and abnormal cell metabolism. Several mechanisms may contribute to the decrease in venous return in these conditions. Most important is the venous pooling of blood that can be further complicated by poor fluid intake or increased losses during the early phase of illness. In addition, endothelial damage resulting in a capillary leak into the interstitium may further worsen venous return and, thus, macrocirculatory perfusion. The presence of cardiac dysfunction (due to sepsis-related myocardial depression, pulmonary hypertension, or a decreased myocardial perfusion in most severe cases) may further compromise hemodynamics.

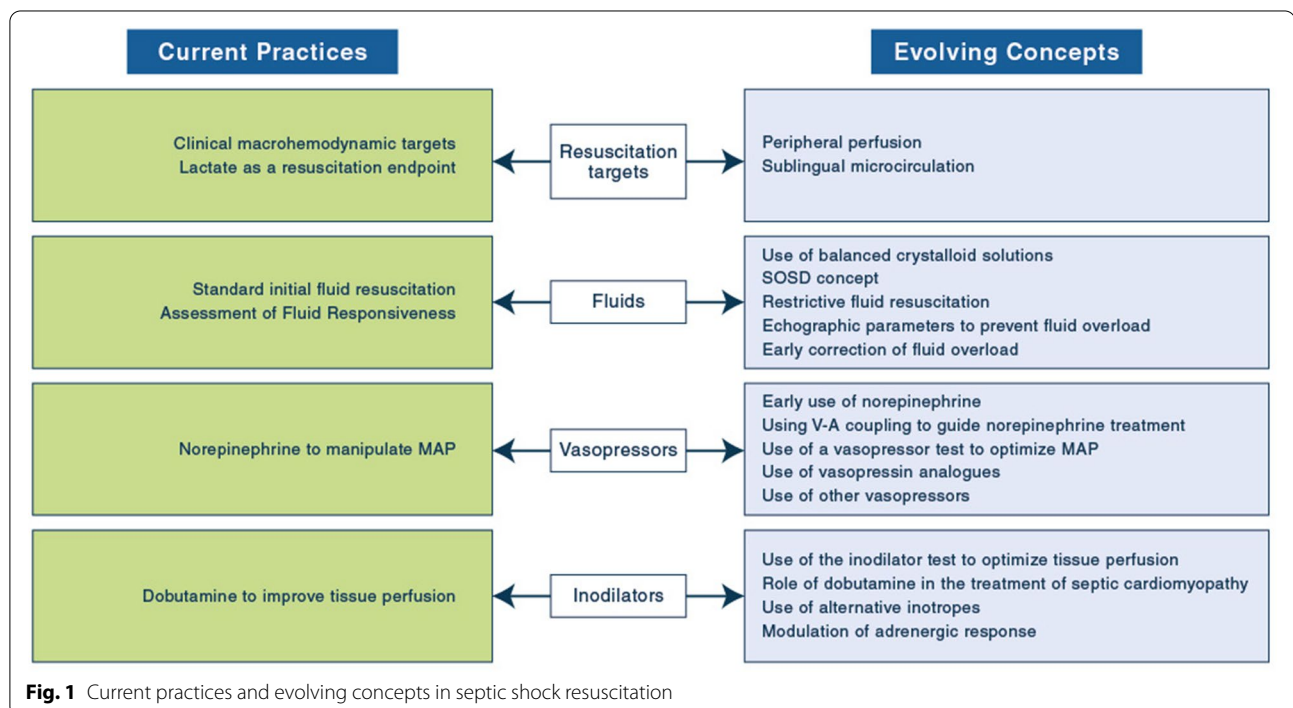
The clinical picture of shock usually reveals a mixture of hypotension (usually requiring vasopressors), altered tissue perfusion (abnormal skin perfusion, altered mentation, decreased urine output), and increased lactate levels [4]. As resolution of these clinical signs indicates shock reversal, they may be used as resuscitation endpoints. Although lactate-based resuscitation has been shown effective [5], the complexity of using lactate levels and blood pressure as a target has been recently highlighted and this general approach needs individualization [6–8]. An overview of the different aspects of hemodynamic and perfusion monitoring is presented in Table 1.

### Take-home message

Septic shock treatment standards have evolved in the past decades, alongside with deeper physiological and clinical understanding of the disease. In this review, we present both the current practice and evolving concepts related to different clinical domains of septic shock resuscitation.

### Initial fluid resuscitation and fluid responsiveness

Fluid resuscitation in septic shock is an effective intervention to increase venous return, and thus cardiac output (CO) and oxygen transport [9]. The key element in fluid resuscitation is the adequacy of volume and timing in combination with the monitoring of the result to prevent fluid overload [10]. As the aim of fluid resuscitation in a shock state is to reverse tissue hypoperfusion, timely fluid resuscitation is critical. The SSC guidelines for adults recommend to start resuscitation immediately upon recognition and suggest to use at least 30 ml/kg to be completed within 3 h of recognition [3]. As fluids should only be used in patients likely to respond with an increase in CO (fluid responders) dynamic assessment of fluid responsiveness is important [11]. As only 50–60% of the patients in the early phase of septic shock are fluid responders [10, 12] and 25% may already be fluid unresponsive after an initial fluid resuscitation [13], over-treatment (and, thus, possible harm) is possible in a significant number of patients. This recommended dose of 30 ml/kg is only based on observational evidence



**Table 1 Current practice and evolving concepts in hemodynamic and perfusion monitoring**

Current practices		Problems/drawbacks	Evolving concepts	Challenges and remaining questions
<b>Hemodynamics</b>				
Arterial blood pressure	Arterial catheter	Invasive (major complications are rare) requires meticulous leveling and zeroing of the pressure transducer	Hemodynamics Non-invasive monitoring technologies	Role of improved sensor technology, signal stability, and measurement performance not established
	SSC recommends MAP 65 mmHg as initial lower intervention threshold (then individual target)	Initial blood pressure target not individualized	Defining individualized blood pressure targets	Need to establish the causality between hypotension and outcomes and to investigate optimal individual intervention thresholds Need for methods to monitor regional blood pressure Unclear how blood pressure autoregulation is influenced by different diseases in critically ill patients Need to determine the best therapeutic interventions for different causes of hypotension
Central venous pressure	Central venous catheter	Invasive Often misused as guide for fluid resuscitation		
Cardiac output	Pulmonary artery catheter (pulmonary artery thermodilution)	Invasive	Non-invasive monitoring technologies; continued monitoring after ICU discharge (ward monitoring)	Improving sensor technology, signal stability, and measurement performance
	Pulse wave analysis (arterial catheter)	Measurement performance in patients with marked alterations in vascular tone Optimal/adequate target values remain elusive	Individualized goal-directed therapy (personalized medicine)	Need to identify the best target variables for goal-directed therapy Need to evaluate adaptive goal-directed therapy concepts (adapting to hemodynamic changes in the course of the disease) Need for evidence that individualized goal-directed therapy improves outcomes
Fluid responsiveness	Dynamic cardiac preload variables (PPV, SW) Passive leg raising Fluid challenge	Cannot be used in most ICU patients Needs to be skillfully performed and requires continuous CO monitoring Risk of excessive fluid administration		
Cardiac anatomy and function	Beside echocardiography	Operator dependent Only available for one patient at a time Intermittent		
			Sepsis phenotypes/hemodynamic clusters/	Need to develop a clinical systematic approach to disclose hemodynamic phenotypes that allow to individualize initial resuscitation
			Dynamic elastance/V–A coupling	Need to establish real contribution to clinical decisions and management

Table 1 (continued)

	Current practices	Problems/drawbacks	Evolving concepts	Challenges and remaining questions
<b>Perfusion</b>				
Lactate	SSC recommended resuscitation goal	Multiple sources Non-hypoxic related causes may pre-dominate in clinical practice Slow kinetics of recovery Not useful for assessing response to fast acting interventions such as fluid bolus often misused as trigger for fluid administration	Perfusion Regional/microcirculatory assessment	Tools are of limited value outside research settings Technical limitations for performance or interpretation for ICG, RRI, etc. Slow development of software for MC analysis Expanded analysis of MC: RBC velocity, glycolyx, patterns of MC dysfunction
ScvO <sub>2</sub>	indicator of DO <sub>2</sub> /VO <sub>2</sub> relationship	Superior vena cava territory: rapid normalization after sedation/intubation Normal or supranormal values in severe microcirculatory dysfunction Represents metabolic stress more than perfusion by itself Confusion on role after negative major trials when tested as a target	Multimodal assessment	Each variable (ScvO <sub>2</sub> and Pv-aCO <sub>2</sub> ) represents different physiological aspects that provide complementary information in the decision-making process Has yet to demonstrate impact on physiological outcomes or treatment intensity The best way to combine variables for decision-making is unknown
Pv-aCO <sub>2</sub>	Indirect marker of systemic blood flow	Does not directly represent tissue hypoxia Can be normal in the presence of tissue hypoxia with preserved or high systemic flow Controversy on relative role of systemic blood flow or microcirculatory dysfunction Impact of the Haldane effect on the relationship between CO <sub>2</sub> content and pCO <sub>2</sub>		
Peripheral perfusion CRT	Marker of tissue perfusion and hyperadrenergia	Inter-rater variability for CRT assessment Doubts on the best cut-off value for CRT No study on kinetics of response of mottling score Unclear relationship with hepatosplanchnic perfusion	Development of optical devices that may allow continuous assessment of peripheral perfusion	To demonstrate if continuous assessment is superior to an intermittent one in different aspects considering the inherent loss of simplicity and universal availability

SSC Surviving Sepsis Campaign, MAP mean arterial pressure, ICU intensive care unit, PPV pulse pressure variation, SW stroke volume variation, ICG indocyanine green, RRI renal resistive index, MC microcirculation, RBC red blood cell, ScvO<sub>2</sub> central venous oxygen saturation, DO<sub>2</sub> oxygen delivery, VO<sub>2</sub> oxygen uptake, Pv-qCO<sub>2</sub> difference between central venous carbon dioxide pressure and arterial carbon dioxide pressure, CRT capillary refill time

and is controversial as individualization is warranted where continued fluid administration might be needed in patients with a favorable clinical and hemodynamic response [8, 14].

Testing for fluid responsiveness is not indicated where hypovolemia and low venous return is obvious (e.g., hemorrhage) and reaching a state of fluid unresponsiveness is used as an absolute stopping point for use of fluids rather than an endpoint of fluid resuscitation. Although assessing fluid responsiveness has limitations, a recent study in septic shock patients showed that testing for fluid responsiveness was possible in more than 80% of patients [13]. Three approaches have been advocated to assess fluid responsiveness. First, actually testing the system by infusing a given volume of fluid in a short period of time while monitoring CO and tissue perfusion [15]. A second approach is to assess fluid responsiveness where venous return is potentially recruited using a physical/mechanical intervention. Examples of these are the passive leg raising (PLR) test, end-expiratory hold or increasing tidal volume (6–8 ml/kg) in mechanically ventilated patients or a more continuous way using stroke volume variation (SVV) or pulse pressure variation (PPV). All of these techniques have been shown to be valuable in the right context but still have limitations [11, 16]. Finally, echo-derived variations in the superior vena cava represent a more reliable method, when compared to the inferior vena cava, with less limitations although this requires a more invasive trans-esophageal echocardiography [17].

As the effects of the infused fluids may wear off rapidly [18], the parameters used to assess the efficacy of the fluid resuscitation need to be closely monitored.

Fluid unresponsiveness on the other hand could be used to safely remove fluids in the hemodynamically stable patient [19].

### **Vasoactive drug use**

Norepinephrine is currently the vasopressor of first choice [3]. Administration of norepinephrine not only increases mean arterial pressure (MAP) but also its beta-1 adrenergic effects together with an increase in venous return, it may increase CO and tissue perfusion [20–23].

Dobutamine is the inotropic agent of reference in the acutely ill patient given its clinical response and favorable onset and offset of action [24]. A limited dose of dobutamine reliably increases blood flow and microcirculatory perfusion, without significantly affecting arterial pressure [25]. Current use is mostly indicated when signs of altered tissue perfusion following fluid resuscitation persist [3]. Although tachycardia may complicate the use of dobutamine this usually is a marker of (relative) hypovolemia. Dobutamine should, thus, be avoided in patients

with evident hypovolemia as the associated vasodilation may also induce profound hypotension.

The use of vasopressin is variable in usual practice despite its physiological rationale. Given the distribution of V1a receptors in the kidney, vasopressin may maintain renal perfusion better than norepinephrine [26]. This positive effect did not result in improved mortality in large clinical trials although it seemed to benefit patients with less severe shock [27, 28]. A meta-analysis showed that vasopressin use was associated with a decrease in the requirement for renal replacement therapy, a trend to lower 90-day mortality, but more complications like digital ischemia [29]. Currently, it is recommended to add vasopressin to a low-to-moderate dose of norepinephrine (0.25–0.5 mcg/kg min) when MAP is still inadequate instead of using it as a first-line drug [30]. Other beneficial effects expected of the use of vasopressin, that drive clinical use, are reduced rates of tachyarrhythmias.

## **Evolving concepts**

### **New potential resuscitation targets**

#### ***Peripheral perfusion***

The skin territory lacks auto-regulatory blood flow control and therefore, sympathetic activation impairs skin perfusion during circulatory dysfunction, a phenomenon that can be evaluated by peripheral perfusion assessment. For long, indicators of abnormal peripheral perfusion have been associated with increased morbidity and mortality [31, 32]. A cold clammy skin, mottling or prolonged capillary refill time (CRT) has been suggested as a clinical trigger for fluid resuscitation in patients with septic shock [33]. Moreover, the excellent prognosis associated with CRT normalization, its rapid response time to fluid loading, its relative simplicity, its availability in resource-limited settings, and its capacity to change in parallel with perfusion of physiologically relevant territories such as the hepatosplanchnic region constitute strong reasons to consider CRT as an important target for fluid resuscitation in septic shock patients. A recent trial found that CRT-targeted resuscitation was associated with a lower mortality (34.9% vs. 43.4%,  $p=0.06$ ), beneficial effects on organ dysfunction, and less intensity of treatment [13], supported by a subsequent Bayesian analysis [34]. Although limited evidence of prospective studies is present to date, the recent SSC guideline [3] has also adopted the use of CRT to guide resuscitation in addition to the other parameters of tissue perfusion. Evolving markers of tissue perfusion/oxygenation like veno-arterial PCO<sub>2</sub> difference and the central venous–arterial carbon dioxide to arterial–venous oxygen content ratio, have shown an association with outcome parameters [35, 36] but they still lack sufficient clinical evidence of benefit when used in early resuscitation.

### **The microcirculation**

Over the past decade, the sublingual microcirculatory alterations during shock and its resuscitation have been shown to be closely related to outcome. In addition, parameters of microcirculatory perfusion amendable to the optimization of tissue perfusion have been identified [37]. The latter being the ultimate goal of resuscitation [4]. It would, thus, be meaningful to use these parameters as an endpoint for the use of fluids and vasoactive agents as has been shown in various small studies confirming the beneficial effects of fluids and vasoactives (norepinephrine, inotropes/inodilators and vasodilators) but also drugs targeting the endothelium more specifically [38]. An important element of these studies is the observation by Dubin et al. [25]. When analyzing all patients, norepinephrine did not improve microcirculatory blood flow; however, in patients with abnormal microcirculatory perfusion, norepinephrine did improve perfusion underscoring the fact that resuscitation should be individualized and recruitment of the microcirculation might contain targets beyond MAP and CO [39].

From a physiological point of view, it is clear that the hemoglobin level is an important determinant of tissue oxygenation [40], much more than convective flow, meaning that care should be taken to avoid dilutional anemia during fluid resuscitation [41]. The recent introduction of the microcirculatory parameter named tissue red blood cell perfusion (tRBCp), which is based on microcirculatory analysis and combines the diffusional capacity and the convective capacity of red blood cell flow and oxygen delivery in the microcirculation may provide an effective resuscitation end point [42]. Evolving concepts of resuscitation could, thus, be the use of blood transfusion and vasodilating agents. However, despite these physiological sound arguments, it is still unclear whether these interventions affect clinically relevant outcome measures.

Another aspect of using microcirculatory perfusion to guide resuscitation of septic shock patients is the objective interpretation of the images. In this respect, the availability of fast and accurate software could enhance the use of the sublingual microcirculation at the bedside [42, 43].

### **Evolving concepts in fluid resuscitation**

#### **Type of fluids**

Crystalloids remain the mainstream fluid for sepsis resuscitation. Balanced (“low chloride”) solutions are increasingly used in clinical practice and may be more beneficial, especially when started in the very early phase (emergency department) of septic shock resuscitation [44, 45]. Several aspects of fluid resuscitation remain unresolved and will still evolve in the coming years. First, the effect

of chloride in the fluids administered, potentially inducing hyperchloremia which can be harmful [46]. Although a recent trial failed to find a significant benefit in favor of a balanced solution when compared to high-chloride saline this was in the absence of induced hyperchloremia [47].

The use of albumin in early resuscitation also remains a topic of debate. Although the recent SSC guideline recommends using albumin when a large volume of crystalloids has been used during resuscitation the evidence is moderate as no study has shown a mortality benefit in one-size-fits-all studies [3]. Given the physiologic rationale and the limited benefit shown in RCTs (lower net fluid balance, higher blood pressure), future studies should focus on these aspects in selected patient groups. Besides the fluid composition other important questions remain, including the optimal rate of infusion and the temperature of the fluid [47].

#### **SOSD concept**

The salvage, optimization, stabilization and de-escalation (SOSD) concept has been introduced to describe the different stages of shock resuscitation [48]. In the salvage phase, the focus is on increasing blood pressure in hypotensive patients using fluid resuscitation and the start of vasopressors when the MAP or diastolic arterial pressure (DAP) is critically low. The optimization phase is focused on tissue perfusion and oxygen delivery. Stabilization and de-escalation are crucial periods in which decreases in fluid balances and weaning of vasoactive medication should be achieved while maintaining adequate tissue perfusion. However, studies determining how to best guide de-escalation and the effects on outcome parameters are lacking.

#### **Restrictive fluid resuscitation and timely removal of excessive fluids**

As true hypovolemia is often not present in septic shock patients, especially in those already hospitalized, fluid administration should be individualized, incorporating etiology, clinical context, existence of comorbidities and side effects, rather than using a fixed volume. Recent data suggest that starting vasopressors simultaneously with fluids or following a very limited fluid resuscitation is associated with beneficial effects (Table 2) while a delayed start has been associated with increased mortality [49]. The simultaneous start of fluids and vasopressors is associated with the use of less fluids, a lower net fluid balance, shortened duration of hypotension and lower incidence of pulmonary edema and new onset arrhythmias [50–52]. Although these possible beneficial effects did not result in decreased mortality in a RCT [51], a systematic review incorporating both observational and randomized trials showed decreased short-term mortality [52]. While

**Table 2 Potential reasons for immediate (or concomitant) start of vasopressors during early resuscitation of sepsis-related cardiovascular dysfunction**

Problem	Effect	Setting	Potential benefit of early start of vasopressors
Time of hypotension and outcomes	Prolonged hypotension is related with worse clinical outcomes	Clinical	Shortening time of hypotension
Low preload / low myocardial contractility	Decreased cardiac output	Clinical/experimental	Mobilization of blood volume from the non-stressed to the stressed circulatory compartment Increasing myocardial contractility Optimization of ventriculo-arterial coupling
Low diastolic pressure	Altered myocardial perfusion	Clinical	Severe hypotension derived from serious vasodilation is unlikely to be reversed by simple fluid administration
Low microcirculatory driving pressure	Altered convective microcirculatory blood flow	Clinical	Correcting hypotension improves microcirculatory blood flow Nevertheless, increasing vasopressor dose can derange microcirculatory blood flow when baseline microcirculation is already corrected
Altered splanchnic flow	Decreased splanchnic perfusion	Experimental	Early combination of fluids and vasopressors might be superior at restoring mesenteric blood flow and tissue oxygenation compared to fluid resuscitation alone Nevertheless, isolated use of vasopressors might worsen splanchnic flow
Using a pre-defined fixed volume of resuscitation fluids	Paradoxical increase in vasopressor requirements	Experimental	A very early vasopressor start might decrease subsequent need for fluid therapy

sufficient clinical evidence favoring the early start of vasopressors is currently lacking, the possible beneficial hemodynamic effects should be considered in early septic shock resuscitation and warrant further interventional studies. Fluid resuscitation based on markers of peripheral perfusion seems to be safe and has been associated with a decreased net fluid balance [13, 33]. Cautious use of fluids is warranted and constant reassessment of the benefit/risk ratio should be part of the resuscitation protocol as rational and restrictive fluid administration may decrease fluid overload [53].

Fluid overload can be estimated using the change in body weight (or net fluid balance) and is frequently associated with evidence of organ dysfunction (weaning related heart failure, organ edema, intraabdominal hypertension, acute kidney injury, etc.) resulting in increased morbidity (increased duration of mechanical ventilation (MV) and length of stay) and mortality [54].

Removal of excess fluid following stabilization of the patient, thus, seems rational. However, this is still an evolving concept as guidelines on how to execute this in clinical practice are lacking [54, 55]. Frequently used interventions include the use of diuretics [56] or renal replacement therapy [57]. As this may induce excessive fluid removal possibly resulting in hypovolemia

and regional hypoperfusion [54] other more physiology driven approaches are needed. The diagnosis of fluid unresponsiveness in stabilized patients has been successfully used to start removal of fluids [19] and use of ultrasound to guide fluid removal showed improved efficiency [58], whereas the use of continuous fluid removal, using renal replacement therapy, has been associated with improved outcome [57]. Given these scarce data, further studies in both patients on continuous renal replacement therapy or without kidney injury are warranted.

#### **Evolving concepts in vasopressor use**

##### ***Use of norepinephrine according to vasomotor tone***

Decreased vasomotor tone is a common characteristic of sepsis-related hypotension. A low diastolic blood pressure (DAP) frequently indicates a state of vasodilation and the use of the diastolic shock index (ratio between DAP and heart rate) [59], may optimize the early use of vasopressors.

The coupling between the pump and the vasculature (ventriculo-arterial coupling, VAC) assessed by the ratio between arterial elastance (Ea) and end-systolic elastance (Ees) [60] might be used to predict and monitor the effect of norepinephrine on myocardial performance [12] and VAC [21] and may detect drug-induced uncoupling [61].

At present, these parameters require complex monitoring and modeling and cannot be easily used at the bedside. However, the ratio between PPV and SVV reflecting a dynamic arterial elastance ( $E_{a_{dyn}}$ ) can be obtained at the bedside using an arterial catheter and pulse contour analysis [62] and may help to identify patients who will increase MAP when CO is increased by a fluid challenge [63]. The  $E_{a_{dyn}}$  may also assist weaning from vasopressor support in the de-escalation phase [48] as it may identify patients who tolerate weaning off norepinephrine without developing hypotension [64]. Although variables of vasomotor tone and VAC have the potential to facilitate adequate use of fluids and vasopressors at the bedside further studies are required to develop protocols on ensuring efficacy in septic shock resuscitation.

The effects of norepinephrine also extend to the venous circulation by increasing mean systemic filling pressure, and thus venous return and CO [65]. The effect of norepinephrine on alpha and beta adrenergic receptors in the myocardium increases contractility facilitating the increase in venous return.

The extent to which the increased CO and MAP also contribute to improvement of microcirculatory perfusion is variable, depending on the balance between the improvement in organ perfusion pressure and a potential deterioration in driving pressure at the level of the microcirculation. This was shown in two studies. First, the effect of increasing MAP with norepinephrine on microcirculatory perfusion was dependent on the baseline state of the microcirculation [25]. Second, the optimal MAP varied between individuals and was independent of previous hypertension [66]. Given this variable effect of norepinephrine on important elements of tissue perfusion a challenge of the system by temporarily increasing the norepinephrine dose to reach a higher MAP could optimize resuscitation. In a RCT, subgroup analysis showed that previously hypertensive patients might benefit from a higher MAP [67]. This also applies to patients without previous hypertension [25, 66]. A large study in elderly patients ( $\geq 65$  years) allocated to relative hypotension (MAP 60–65 mmHg) showed no overall significant effect on mortality when compared to usual care but a possible beneficial effect in a subgroup analysis of chronic hypertensive patients [68]. Therefore, a higher MAP target might not benefit all chronic hypertensive patients.

Therefore, a vasopressor test, whereby the MAP is increased and the effect on tissue perfusion is monitored (CRT, urine output, lactate, limb/cardiac ischemia, arrhythmias, etc.), seems a logical step in the resuscitation of patients who have not improved with initial treatment. This concept was first introduced in the ANDROMEDA-SHOCK study in previously hypertensive patients without improvement of peripheral

perfusion or decrease of lactate levels following initial treatment targeted to a MAP of 65 mmHg [13]. Following the results of the recent study on the effects of maintaining a higher MAP [67] in septic shock patients, the norepinephrine dose was increased to reach a MAP 80–85 mmHg (depending on the randomization group) while monitoring the effect on peripheral perfusion (1 h later) or lactate levels (2 h later). When the target was reached the higher MAP level was maintained, if the target could not be met, the MAP was returned to baseline level.

Although the tools used in these clinical interventions are not new the context in which these are now increasingly used in clinical practice have evolved. However, as the effects on outcome parameters have not been established, these are not part of current guidelines and, thus, require further studies.

#### *Use of vasopressin analogs in septic shock*

The current use of vasopressin is mainly as an adjunct to norepinephrine when a pre-defined dose is reached. Vasopressin is usually added at a pre-defined dose [3], aiming to further increase MAP when required while sparing additional adrenergic burden.

Other vasopressin analogs have been studied. Given the relative advantages of terlipressin (greater V1a-receptor selectivity) and even the possibility to use intermittent bolus treatment (given the long half-life), it has been compared to norepinephrine [69]. However, the study did not find a difference in mortality but a higher incidence of adverse events (30% terlipressin, 12% norepinephrine) like digital ischemia [69]. Selepressin is an even more selective V1a agonist than terlipressin. Its use in experimental models and in a phase II randomized study was associated with reduced fluid requirements and edema formation [70]. These benefits did not translate into clinical benefit as selepressin was similarly effective (mortality and vasopressor- and ventilator free days) compared to placebo in a Phase 2b/3 randomized study; however, adverse ischemic events were higher in the selepressin group when compared to norepinephrine alone [71]. Currently, selepressin is not yet approved for clinical use and given the outcome of the studies using terlipressin, its use is currently not recommended.

#### *Use of other vasopressors*

In the renin–angiotensin–aldosterone system, angiotensin II (ATII) has vasoconstrictive effects. Relative deficiency of ATII has been associated with worse outcomes in septic shock. The use of ATII in septic shock increases blood pressure and decreases the need of standard vasopressors without an effect on outcome [72]. However, as many as 30% of the patients did not respond to ATII.



Interestingly in a post hoc analysis, patients with acute kidney injury requiring renal replacement therapy and elevated renin levels had a significant mortality benefit even if MAP did not respond to angiotensin II [73, 74]. Additional studies are required for clear recommendation on clinical use.

Methylene blue (MB) improves hemodynamics by reducing excessive production of nitric oxide by blocking guanylate cyclase. However, only small-sized studies have been conducted with conflicting results; thus, its use cannot be recommended currently [75, 76].

The use of these agents in patients requiring high-dose adrenergic agents to maintain MAP should be further evaluated in clinical studies.

## **Evolving concepts in inotrope use**

### **Dobutamine**

Cardiomyopathy in septic shock is frequently present and whether this leads to inadequate tissue perfusion depends on the interplay between the effect of contractility and state of vasoplegia (afterload) both induced by the septic process [77]. The use of repeated echocardiography combined with clinical, hemodynamic, and biological variables is, therefore, crucial to detect, monitor and treat septic cardiomyopathy where dobutamine is the current recommended first-line inotrope for its treatment [24]. A recent study using hemodynamic profiling identified characteristics of patients with septic cardiomyopathy who might benefit from inotropic treatment [78]. Dobutamine benefitted 18% of these patients, characterized by a low left ventricular ejection fraction (LVEF) (<40%) and low aortic velocity time integral (VTI) as a measure of stroke volume [78]. Effective dobutamine treatment is characterized by improvement in clinical status together with an increase in LVEF and VTI, and without an increase or even a decrease in heart rate [79].

So, adequately selecting patients likely to benefit or trialing dobutamine treatment and monitoring its effects may represent a better approach and could facilitate individualization. A recent network meta-analysis found dobutamine to be significantly associated with reduced mortality in patients with severe sepsis or septic shock (OR for dobutamine vs placebo 0.30; 95% CI 0.09–0.99) [80]. More evidence is expected from an ongoing multicenter trial (ClinicalTrials.gov ID: NCT04166331) studying the effectiveness of dobutamine in improving tissue hypoperfusion and its associated organ dysfunctions in patients with septic shock and septic cardiomyopathy.

Outside of the cardiac dysfunction context, improving CO may result in improved tissue perfusion. Earlier studies have shown that adding low dose (5 mcg/kg min) dobutamine to current treatment showed not only improvements in macro- but also in microcirculatory

flow, the latter even being independent of the effect on CO [81, 82]. The latter could have been related to the vasodilatory actions of dobutamine. However, the effects may vary and there is no single agent that has been shown to reproducibly lead to improved macro/microvascular flow [83, 84], and side effects may complicate the use of dobutamine, underscoring the trialing approach [84].

This trialing approach using a limited dose of dobutamine was recently introduced in septic shock patients (similar to the vasopressor test described earlier) [13] as an inodilator test. It involved administering a 5 mcg/kg min infusion for a limited time (see previous description) after which the effect on the target parameter was assessed. If beneficial, the infusion would be maintained.

It is clear that while dobutamine may have beneficial effects on tissue perfusion its timing, dosing and effect on outcome parameters in specific hemodynamic profiles in septic shock have not yet been clarified.

### *Use of alternative inotropes*

Calcium sensitizers (e.g., levosimendan) and phosphodiesterase-3 inhibitors (e.g., milrinone and enoximone) exhibit inotropic and vasodilatory effects.

In general, addition of levosimendan to standard treatment without clear impairment in cardiac function is not associated with improved morbidity or mortality even when biochemical evidence of cardiac injury is present [85]. This underscores that manipulating cardiac function should be triggered by a clinical problem (i.e., abnormal tissue perfusion) and not just by the presence of myocardial injury or even a low CO [77] as in those cases the side effects might outweigh any benefit. In this context, levosimendan has been associated with a lower likelihood of successful weaning from MV and a higher risk of supraventricular tachyarrhythmia [85]. In addition, levosimendan does not provide clear benefit over the use of dobutamine [86]. A theoretical advantage of levosimendan could be in patients admitted with sepsis in whom beta-blocker therapy contributes to the inadequate cardiac function.

Although experimental studies have shown possible benefit from the use of phosphodiesterase-3 inhibitors, clinical studies on outcomes in patients are scarce [83]. Although these might represent a typical example of an inodilator, the long half-life and the unpredictable effects on MAP limit its use in the already typically vasoplegic septic shock patients.

From the current studies available, it is clear that the use of vasopressors and inotropes in patients with septic shock is in need of more profound evidence of indication and benefit [87].

### The concept of adrenergic modulation

A sustained hyperadrenergic response in septic shock and the use of adrenergic agents has been associated with adverse hemodynamic, microcirculatory, metabolic, and pro-inflammatory effects [88, 89]. Adrenergic modulation has a favorable impact on several physiological and clinical outcome parameters in septic shock. Dexmedetomidine ( $\alpha_2$ -agonist) attenuates the sympathetic response to stress, and decreases epinephrine levels without adverse consequences for tissue perfusion. Experimental studies have found anti-inflammatory effects and improvement in microcirculatory flow, and exogenous lactate clearance [88]. Also, clinical studies have reported faster resolution of the hyperlactatemia [90]. Recent studies also showed that dexmedetomidine may reduce norepinephrine requirements; however, the impact on major outcomes has yet to be demonstrated [91, 92]. The supporting evidence for the use of  $\beta$ -blockers in sepsis is relatively weak. Experimental studies have shown favorable effects on heart rate, and some hemodynamic, inflammatory, metabolic variables, including a decrease in blood lactate levels [88]. The effect of esmolol on intrinsic myocardial function and vascular responsiveness is still controversial [93]. A clinical challenge in septic shock patients with persistent tachycardia is to distinguish a compensatory origin (low stroke volume) from maladaptive sympathetic overstimulation as in the former context beta blockers could be detrimental in the former. In the latter, beta blockers may decrease myocardial  $O_2$  consumption, increase diastolic filling and systemic flow and improve VAC [94]. Ongoing studies try to identify

the best predictors of a favorable response to beta blockers. Till the results of these studies are available, the use of beta blocker in septic shock cannot be recommended [93].

### Evolving concepts in refractory shock

Refractory septic shock is a life-threatening condition that is best defined by a state in which escalation of vasoactive therapy does not restore adequate tissue perfusion. At the bedside, this can be recognized by persistent hypotension and hypoperfusion in the absence of hypovolemia, while the patient is receiving more than 0.25  $\mu\text{g}/\text{kg}$  min of norepinephrine [95]. Multiple factors may favor the onset of refractory shock (Table 3). Timely identification of refractory shock and the provoking factors may reduce the urge to increase vasopressors at the risk of severe side effects that may further worsen the clinical condition. It is important to recognize the difference between severely decreased vasopressor responsiveness and complications like for instance LV outflow tract obstruction due to high vasopressor support. Therefore, echocardiography should always accompany the diagnosis of refractory shock. In the absence of these complications, adjuvant therapies may benefit the patient. Various treatments have been studied and shown variable effects. Whilst the benefit of hydrocortisone in specific patients has been established the role of vitamins is less clear [96, 97]. In addition, non-adrenergic vasopressors (vasopressin, angiotensin 2) and drugs targeting endothelial factors (NO-scavenger/inhibitors, MB, endothelin), have shown clinical effects that might be beneficial but their impact

**Table 3 Potential factors contributing to refractory septic shock**

Factors	Mechanisms
Core Temperature > 39 °C	Increase in cell metabolism and oxygen demand Decrease in sympathetic vasomotor tone
Age > 80 years	Senescent endothelial cells and vascular smooth muscle cells are associated with decreased vasomotor tone and decreased sensitivity to alpha-agonists
Drugs	Sedative drugs decrease sympathetic drive to vascular smooth muscles with subsequent decrease in vasomotor tone NO-donors trigger relaxation of vascular smooth muscles
Acidosis: pH < 7.20	Acidosis is associated with impaired vascular smooth muscles metabolism and contractility and decreased coupling of alpha-agonists to alpha receptors Acidosis triggers adenosine triphosphate-sensitive potassium channels present in smooth muscle cells, preventing calcium entry
Hyperglycemia	Insulin resistance and decreased glucose uptake by vascular smooth muscles reduce vasomotor tone
Hypocalcemia	Decreased intra-cellular calcium concentration results in decreased smooth muscles contractility
Critical illness-related corticosteroid insufficiency OR adrenal insufficiency	Decreased cortisol results in decreased contractility of vascular smooth muscles and in decreased coupling between alpha-agonists and alpha-adrenergic receptors
Vasopressin deficiency	Loss of vasopressin mediated vascular smooth muscles contractility and decreased sensitivity to alpha-agonists
Thiamine, vitamin C deficiencies	Decrease in the coupling of alpha-agonists to alpha-adrenergic receptors

NO nitric oxide

**Table 4 Extracorporeal techniques used in sepsis**

Technique	Main principle	Main components removed	Selected RCTs in sepsis	Potential harm
<b>Hemofiltration (HF)</b>				
High volume HF	Convection	Pro- and anti-inflammatory mediators up to 45 kDa	Joannes-Boyau et al. [105] No mortality benefit	Invasiveness of the procedure Risk of infection Hemodynamic instability Fluid overload when using replacement therapies Loss of nutrients, trace elements and drugs Loss of albumin, nutrients and drugs Adsorption of specific drugs
High cut-off HF	Convection	Pro- and anti-inflammatory mediators including molecules > 65 kDa	Atan et al. [104] No benefit	See above
<b>Adsorption techniques</b>				
Hemoperfusion	Passage of blood through haemofilter or sorbent containing cartridge where mediators are adsorbed (allowing removal of larger molecular weights compared to convection)	Cytosorb®: most cytokines, myoglobin, PAMPs and DAMPs but not endotoxin and IL-10 Polymyxin B immobilized fiber columns: endotoxin Modified AN69 membrane: cytokines, endotoxin LPS adsorber: removal of LPS and endotoxin	Schädler et al. [103] No benefit Dellinger et al. [102] No mortality benefit No published RCT Lipcsey et al. 2020 [106] Terminated early; no mortality benefit	See above
<b>Coupled plasma filtration/adsorption</b>				
	Combination of high cut-off filter which separates the plasma from blood, and plasma then flows through an adsorber before being returned to the circuit where all blood undergoes conventional HF	Pro- and anti-inflammatory mediators	Garbero et al. [109] Terminated early due to adverse events	See above
<b>Apheresis techniques</b>				
Plasmapheresis	Removal of harmful circulatory molecules and/or replacement of protective plasma proteins that counteract effects of inflammation	Removal of cytokines, endotoxin and inflammatory mediators and replenishment of immunoglobulins and coagulation factors	Busund et al. 2002 [107] No significant effect on 28-day mortality	See above
Affinity apheresis	Use of heparin or lectin columns which bind microorganisms	Pathogens	No RCTs completed so far	See above
Selective cytopheresis	Use of synthetic biomimetic membrane that binds activated leukocytes	Activated leukocytes	Tumlin et al. [108] No mortality benefit	See above

HF hemofiltration, DAMPs danger associated molecular patterns, LPS lipopolysaccharide, PAMPs pathogen-associated molecular patterns, RCT randomized controlled trial, TNF tumor necrosis factor

on outcome remains to be determined [98]. Other studies have focused on individualizing treatment and identifying the response to vasoactive medication and corticosteroids that may vary in specific patients [99–101].

Extracorporeal blood purification techniques (ECBPT) offer a theoretical benefit of removing mediators and establishing immune homeostasis. Many studies have been performed (Table 4) [102–109]. However, as the immune response in sepsis is an individual process and, thus, cytokine profiles vary significantly between different sepsis phenotypes, the success of ECBPT is difficult to predict [110, 111]. In addition, adverse effects, including inadvertent removal of nutrients, trace elements and drugs have been reported with ECBPT [112] and the clinical benefit from these techniques remains controversial (Table 4) and requires further studies [113].

A ultimate rescue therapy for septic shock patients with refractory LV failure could be hemodynamic support with venous-arterial extracorporeal membrane oxygenation (VA-ECMO). A recent systematic review and meta-analysis indicated that especially septic shock patients with a very low LVEF might benefit [114].

Many treatments listed in this section lack sufficient clinical evidence and so general recommendations cannot be made. The use of these treatments should, thus, be individualized in which careful consideration should be given to the problem at hand in relation to the likelihood of benefit and harm of the intervention.

## Conclusions

In this review, we have discussed current practice and evolving concepts in septic shock resuscitation. While the pillars of hemodynamic resuscitation have not changed in general, there is new information on how to optimize fluid administration and the use of vasoactive drugs. The lack of solid evidence in all fields is of growing concern, and this precludes to make strong recommendations for most interventions.

A broad research agenda focusing on individualization and phenotyping of septic shock patients using combined efforts of the different excellence groups is, therefore, imperative.

## Supplementary Information

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## Abbreviations

RCT: Randomized controlled trials; SSC: Surviving Sepsis Campaign; CO: Cardiac output; PLR: Passive leg raising test; SVV: Stroke volume variation; PPV: Pulse pressure variation; MAP: Mean arterial pressure; LV: Left ventricular; CRT: Capillary refill time; ICU: Intensive care unit; tRBCp: Tissue red blood cell perfusion; SOSD: Salvage, optimization, stabilization, de-escalation; DAP: Diastolic arterial pressure; ScvO<sub>2</sub>: Central venous oxygenation; MV: Mechanical ventilation; VAC: Ventriculo-arterial coupling; Ea: Arterial elastance; Ees: End-systolic elastance; Ea<sub>dyn</sub>: Dynamic arterial elastance; ATII: Angiotensin II; MB: Methylene

blue; LVEF: Left ventricular ejection fraction; VTI: Aortic velocity time integral; ECBPT: Extracorporeal blood purification techniques; VA-ECMO: Venous-arterial extracorporeal membrane oxygenation.

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GH, JB, EK and DDB conceived the manuscript; DA, JB, RC, MC, DDB, AD, LE, MNG, OH, GH, EK, CI, BL, XM, GOT, MO, MP, JR, BS, TWLS, JLT, AVB, JLV, FGZ drafted specific parts of the manuscript, critically revised and approved its final contents.

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