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REVIEW

Challenges in the management of septic shock: a narrative review

Daniel De Backer[1*], Maurizio Cecconi[2], Jeffrey Lipman[3], Flavia Machado[4], Sheila Nainan Myatra[5], Marlies Ostermann[6], Anders Perner[7], Jean-Louis Teboul[8], Jean-Louis Vincent[9] and Keith R. Walley[10]

Abstract

While guidelines provide important information on how to approach a patient in septic shock, "many challenges remain" for the management of these patients. In this narrative review, the panel discusses the challenges in identifying the right hemodynamic target, optimization of fluid therapy, selection of vasopressor agents, identification of patients who may benefit from inotropic agents or on the contrary beta-blockade, and use of steroids. The place for microcirculation-targeted therapy is debated as well as the use of alternative techniques (blood purification) and therapies (vitamin C). The implications of hemodynamic alterations on antibiotic doses is discussed. Finally, the specific challenges in low- and middle-income countries are addressed. Ongoing trials address some of these challenges, but many uncertainties will remain, and individualized therapies based on careful clinical assessment will continue to be essential to optimizing the care of patients with septic shock.

Keywords: Hemodynamic monitoring, Cardiac output, Tissue perfusion, Vasopressors, Fluids, Steroids

Introduction

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection, and septic shock is a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than in sepsis alone [1].

The hemodynamic alterations are characterized by a profound decrease in vascular tone associated with some degree of hypovolemia (absolute, due to losses in the digestive tract or due to capillary leak, or relative, related to an increase in venous reservoir due to dilation of capacitance veins). In addition, myocardial depression may occur, altering the systolic and diastolic properties of both ventricles, potentially leading to impaired cardiac output. The decrease in vascular tone also contributes to impaired regional blood flow distribution. In addition, microcirculatory alterations occur, leading to alterations in tissue perfusion even when blood pressure and cardiac output are within target.

While guidelines provide an attractive approach [2], there remain many challenges for the management of patients with septic shock. These include issues with hemodynamic targets and therapies, as well as challenges in applying the recommended therapies. In this narrative review, the panel will discuss several of these challenges related to the management of patients with septic shock.

Selecting the right hemodynamic target

Clinicians should target providing adequate organ perfusion pressure and oxygen delivery (DO2), while limiting the side effects of any interventions used to obtain these targets.

The perfusion pressure is reflected by the mean arterial pressure (MAP) for most vital organs (e.g. brain, kidney), and diastolic arterial pressure for the left ventricle. The organ perfusion pressure also depends on the downstream pressure, i.e. central venous pressure (CVP) and interstitial pressure. To select the optimal MAP, CVP should be considered together with comorbidities

*Correspondence: ddebacke@ulb.ac.be
[1] Department of Intensive Care, CHIREC Hospitals, Université Libre de Bruxelles, Brussels, Belgium
Full author information is available at the end of the article

(including chronic hypertension), active blood loss or any intra-abdominal hypertension [3]. In septic shock, MAP should be initially targeted at 65 mmHg [2], but this should be reassessed dynamically over time. The challenge is to find markers of organ perfusion or oxygenation for adjusting MAP. Arterial pressure challenges (using acute change in vasopressor doses) could be considered, evaluating the patient's status at different MAP levels. Of note, even when organ perfusion pressure and flow are maintained, microvascular alterations may impede tissue perfusion.

Inadequate perfusion can be detected by simple markers such as increased capillary refill time (CRT) or mottling. A CRT > 3.5 s indicates poor peripheral perfusion and, if associated with hyperlactatemia, marked circulatory failure [4]. Whether resuscitation of septic shock can be guided by CRT is under investigation (NCT03078712). The challenge is in developing better tools to objectively evaluate skin perfusion.

Urine output is a good marker of shock at its onset, but not a good target for resuscitation. Indeed, it is neither sensitive nor specific to improvements in renal perfusion.

The DO2 depends on arterial blood oxygen saturation (SaO2), hemoglobin (Hb), and cardiac output (CO). No specific value of DO2 or Hb can be recommended in shock states. The mixed venous blood oxygen saturation (SvO2) helps in assessing the adequacy of DO2 to oxygen consumption. The central venous blood oxygen saturation (ScvO2) is considered a proxy for SvO2. Low ScvO2 values mean that DO2 is inadequate and that increasing CO is a therapeutic option when shock persists [5]. The challenge is in defining the optimal ScvO2 for a given patient at a given time.

The difference between venous and arterial carbon dioxide pressure (PCO2), called PCO2gap, may be useful as a target in shock states where ScvO2 is normal. In this context, a high PCO2gap (> 6 mmHg) suggests that increasing CO may be a therapeutic option. While this measurement has an important prognostic value [6], the challenge is in evaluating how therapies based on PCO2gap can influence outcome.

Lactate levels are typically > 2 mmol/L in shock states, and serial blood lactate measurements are recommended [2]. In septic shock, normalization of lactate is recommended as a goal of resuscitation [2]. However, increased blood lactate may be due to increased production, decreased clearance, or a combination of the two. Normalization of lactate can thus be delayed even if its production is decreasing due to the resolution of shock. Factors other than anaerobiosis may also increase lactate production [7]. Sustained hyperlactatemia suggests the need to reassess treatment. We need more precise guidelines on serial lactate measurements to evaluate the response to therapy.

Take home message

Guidelines provide informationon septic shock management, but challenges remain in interpretation of the studies or in applying the results.

In summary, resuscitation of macrocirculation requires a multimodal targeted approach based on defining both the optimal MAP and adequate DO2 using different markers. A significant challenge is determining the target value for each of these variables.

Optimizing fluid therapy

Fluid administration is a cornerstone in the management of hemodynamic instability [8]. Despite being a very common therapy in the ICU, optimizing fluid administration is still challenging.

The FENICE study showed extreme variability in practice worldwide in how fluid challenges are given [9]. This is true for the trigger, the type of fluid, the amount, the rate of administration, targets, and safety limits.

The decision for fluid administration is based on the recognition of inadequate perfusion, which is expected to improve after fluid administration. Though correcting hypovolemia is essential, excessive fluid loading is associated with organ dysfunction and death in patients with septic shock [10]. A more restrictive fluid administration based on more stringent criteria was not associated with worse outcome in patients with septic shock; on the contrary, worsening of acute kidney injury (AKI) appeared to be less frequent [11]. The challenge now is to better define the triggers for fluid administration.

Regardless of the criteria used to trigger fluid administration, it is recommended that fluid administration be based on bedside evidence that CO will increase if fluids are given (fluid responsiveness) [12]. The response to fluids is best predicted by dynamic indices such as pulse pressure variation, stroke volume variation, passive leg raising, or end-expiratory occlusion test. This may prevent administration of fluids to non-responders, thus avoiding the side effects of fluids in patients with no predicted benefit. The challenge is that these tests may not always be applicable.

Even in fluid responders, fluids may aggravate pulmonary edema or increase intra-abdominal pressure, or hemodilution may occur, resulting in decreased DO2. Even when DO2 increases with fluids, the effect on oxygen consumption may vary [13]. The decision to discontinue fluid administration should be based on either improved peripheral hypoperfusion, absence of fluid responsiveness, or signs of poor tolerance. The challenge lies in performing a bedside assessment of the potential benefits and risks of fluids.

When the decision to give fluids is made, it makes sense to use the smallest amount necessary to achieve the goal. While this may seem simple, we need to better define the best way to perform a fluid challenge. The response in CO depends on the dose and the rate of administration [14], and CO may only transiently increase [15].

Selection of the right type of fluid is also challenging. Multicenter randomized controlled trials (RCTs) have shown harmful effects of synthetic colloids, notably AKI [16]. Albumin is the only colloid that has been shown to be safe in most circumstances. Regarding crystalloids, buffered crystalloids may be associated with less AKI than saline, but uncertainty remains.

Of note, one of the best means of optimizing fluid therapy is to limit capillary leakage. Drugs including activated protein C, adrenomedullin, alkaline phosphatase, and selepressin have experimentally demonstrated some capacity to blunt the sepsis-associated increase in permeability.

Vasopressors: where do we stand?

Vasodilation is a central feature of septic shock. Changes in receptor signaling, excessive production of nitric oxide, and absolute or relative deficiencies of vasoactive hormones, including cortisol, vasopressin, and angiotensin II, play an important role in its pathophysiology.

The Surviving Sepsis Campaign (SSC) recommends noradrenaline as the first-choice vasopressor and vasopressin as the second-line agent [2]. Based on data from 32 trials published up to June 2014 (3544 patients), noradrenaline was associated with decreased all-cause mortality (relative risk 0.89; 95% confidence interval 0.81–0.98), which corresponds to an absolute risk reduction of 11% [17]. Compared to dopamine, noradrenaline was also associated with a lower risk of adverse events and cardiac arrhythmias [18].

While noradrenaline is an effective vasopressor, its responsiveness declines at higher doses, along with an increased risk of adverse effects. Alternatives include adrenaline, dopamine, phenylephrine, vasopressin, terlipressin, selepressin, angiotensin II, and methylene blue (Table 1). However, there is no survival advantage with these drugs compared to noradrenaline [19].

Important uncertainties remain:

1. For the majority of vasopressors, the most effective and safe dose is not known.
2. With all vasopressors, the risk of adverse events is higher in patients with intravascular volume depletion. Unfortunately, the assessment of intravascular fluid status is challenging, and the risk of inappropriate use of vasopressors is high.
3. Several RCTs have confirmed that vasopressin, selepressin, and angiotensin II increase MAP and reduce noradrenaline requirements [20, 21]. Vasopressin and angiotensin II may also have beneficial effects on renal function, and vasopressin may be associated with lower rates of atrial fibrillation. It remains controversial whether the improvement in hemodynamic variables without improvement in mortality justifies their use.

Table 1 Non-catecholamine vasopressors for hemodynamic management of vasodilatory septic shock

Drug	Rationale	Evidence from RCTs
Vasopressin	Inadequately low vasopressin concentrations in septic shock	No difference in mortality and kidney failure-free days with early addition of vasopressin to noradrenaline (VANISH) [20, 70]
	Inhibition of vasopressin secretion by corticosteroids	Reduction in noradrenaline requirements [20, 70]
Terlipressin	Synthetic vasopressin analogue with greater selectivity for the V1-receptor and longer half-life than vasopressin	Continuous infusion of low-dose terlipressin as first-line vasopressor in septic shock led to reversal of hypotension and decreased noradrenaline requirement but had no impact on mortality (TERLIVAP) [71]
		Increased risk of digital ischemia [72]
		No difference in mortality as first-line treatment compared to noradrenaline [72]
Angiotensin II	Defect of ACE in patients with severe lung injury leading to angiotensin deficiency [19, 20]	Effective increase in blood pressure in patients with vasodilatory shock but no impact on 28-day mortality (ATHOS) [21]
	Deactivation of ACE by endotoxin in gram-negative sepsis [21]	Faster liberation from RRT in angiotensin group [73]
Selepressin	Selective vasopressin V1-receptor agonist with fewer non-vascular adverse effects than vasopressin	Maintenance of blood pressure and rapid replacement of norepinephrine [74]
Methylene blue	Inhibition of NOS and soluble guanylate cyclase	Reduction of noradrenaline, adrenaline, and dopamine requirements [75]

ACE angiotensin-converting enzyme, *NOS* nitric oxide synthase, *RCT* randomized controlled trial, *RRT* renal replacement therapy. A version of the table with references is presented in the ESM

4. In septic shock, the main objective of vasopressor treatment is to improve organ perfusion. Vasopressors can have variable effects on regional blood flow and on microvascular perfusion in different organs despite acceptable systemic hemodynamic values.
5. It remains unknown whether there is a role for multimode therapy with different types of vasopressors in vasodilatory shock. This strategy may avoid the toxicity associated with high doses of a single agent.
6. What is the ideal weaning strategy for vasopressor agents? When several agents are used, which agent should be weaned first? Should accelerated strategies be promoted?

Inotropes? When? Which?

Myocardial dysfunction is observed in most patients with septic shock. Decreased systolic function is a prominent feature, providing some rationale for the use of inotropes to increase contractility. Diastolic dysfunction also occurs frequently.

The first challenge is selecting patients who may benefit from inotropes, identified by the persistence of altered tissue perfusion, together with decreased ventricular systolic function, despite adequate fluid administration. Echocardiographic assessment is desirable prior to inotropic administration in septic shock patients [8]. Inotropes will cause hypotension and tachycardia but will not significantly increase CO in hypovolemic patients. Exclusion of purulent pericarditis, isolated diastolic dysfunction, or significant valve dysfunction is advisable, as these may require more complex therapeutic approaches. Inotropes can induce or worsen atrial fibrillation and other dysrhythmias. After consideration of these potentially confounding issues, patients with significantly decreased systolic contractility may benefit from the administration of inotropes.

The second challenge is selecting the inotropic agent. Administration of dobutamine (an agent with a short half-life that may have minimal side effects at usual doses) in septic shock was proposed almost 30 years ago. The SSC guidelines suggest the use of dobutamine to treat "patients who show evidence of persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents" [2]. However, the current recommendation is considered weak, with low quality of evidence [2]. Ascertaining "adequate fluid loading" is difficult in reality. Since this recommendation does not require proof of cardiac dysfunction (e.g. echocardiography), there is a potential risk of giving dobutamine to patients with normal cardiac function and who are still hypovolemic. Some studies even suggest that dobutamine can be harmful, and vasopressor/inotrope combinations with a high beta-adrenergic component are associated with worse outcome and increased incidence of arrhythmias [22]. The calcium sensitizer levosimendan showed early promise as an inotrope in septic shock, but an RCT showed no benefit, and side effects were reported [23]; however, the inclusion did not require ventricular dysfunction, so a potential benefit of levosimendan may have been missed in these patients. Milrinone and other phosphodiesterase inhibitor inotropes may also have undesired vasodilator properties, leading to greater hypotension than with dobutamine.

Thus, the decision to give an inotropic agent may be individualized (Fig. 1). Administration of an inotrope may be regarded as a therapeutic trial, and the dose and/or agent should be adjusted according to the response. The targeted endpoint of a trial of inotrope therapy may be evidence of an improvement in tissue perfusion associated with an increase in CO. If a favorable effect is not achieved or if adverse events occur, the agent should be discontinued. Our overall challenge is that there are no trial data to support or reject the use of inotropes.

A place for beta-blockers?

Tachycardia is often present in patients with septic shock. In many instances it is related to fever or represents a compensatory mechanism engaged to preserve CO in the face of reduced stroke volume (due to hypovolemia and/or impaired contractility), and in these cases, treating the cause rather than the consequence is preferred. However, tachycardia may also be observed when stroke volume and CO are preserved, and may be related to excessive catecholamine stimulation. In these conditions, the excessive adrenergic stimulation is also considered to play a role in myocardial toxicity, metabolism, and immune function.

Experimental studies, mostly in rodents with extreme tachycardia, have shown that beta-blockers can decrease heart rate and preserve or increase stoke volume via an increase in diastolic time. These preclinical studies have shown variable effects on mortality [24, 25].

In a single-center randomized trial including 154 patients with septic shock, esmolol lowered heart rate, preserved MAP and stroke volume, and even reduced mortality [26]. Even though this study generated much enthusiasm, there were many question marks. Esmolol significantly reduced DO2 by 20%. In addition, the mortality rate in the control group was extremely high (80% at 30 days, hospital mortality 91%) in patients with normal lactate levels at inclusion. Given all these issues, administration of beta-blockers in sepsis remains experimental.

The challenge is in identifying patients who may benefit from beta-blockers. Morelli et al. [26] excluded patients with severely impaired systolic function, and most patients had a high cardiac index and normal lactate

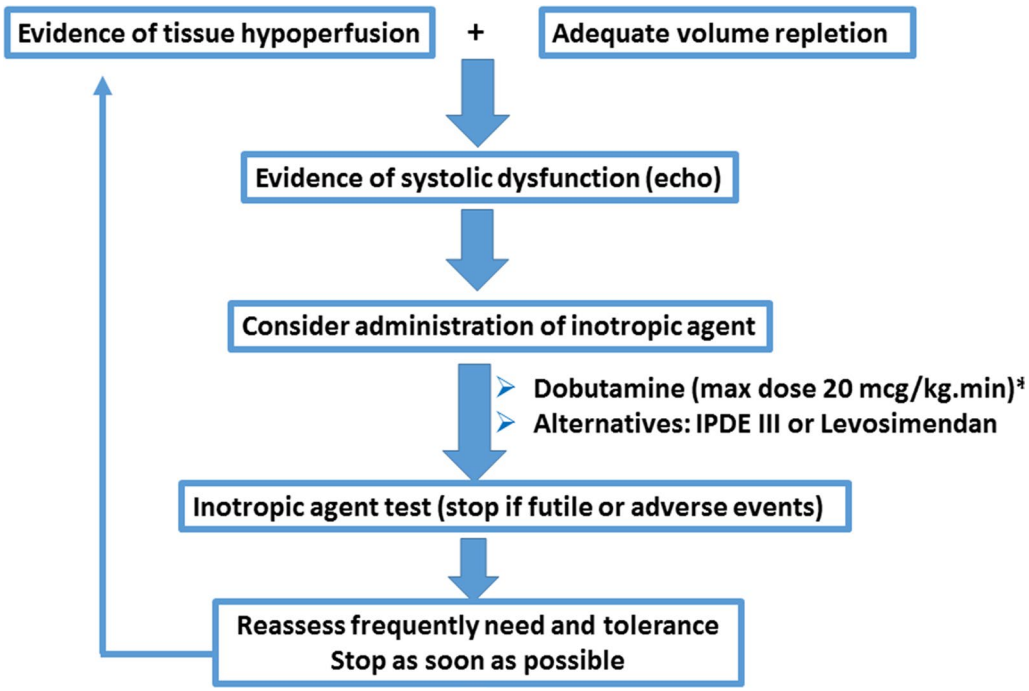

Fig. 1 A model for suggested use of inotropic agents in septic shock. Schematic algorithm for the use of inotropic agents. IPDE III denotes inhibitors of phosphodiesterase type III

levels. Some echocardiographic indices may help to identify patients in whom CO is not reduced in response to esmolol [27]. The best index has yet to be determined, but it seems that echocardiography may be useful for identifying patients who may benefit from beta-blockers.

Microcirculation-targeted therapy?

Microcirculatory abnormalities are common in patients with septic shock [28], and their duration and severity are associated with organ failure and mortality [28, 29]. Several causative mechanisms are described [30]. Heterogeneity in the capillary blood flow is the hallmark, leading to both hypoxic and over-perfused areas, making microcirculatory alterations the perfect illustration of distributive shock. Correlation between the microcirculation and systemic hemodynamics is present during early resuscitation; however, these are often later dissociated. Hence, it seems logical that monitoring of microcirculation should be used to guide therapy.

The challenges in microcirculation-targeted therapy are numerous.

First, while videomicroscopic assessment is the gold standard [31], it is presently not feasible to assess the microcirculation continuously. Technological advances facilitating continuous hands-free assessment with automatic image analysis may overcome this limitation. Therefore, surrogate markers for assessing the microcirculation are needed. Clinical indices of skin perfusion correlate poorly with the sublingual microcirculatory changes during early septic shock. Blood lactate level is often increased in patients with microvascular alterations, but its slow decrease complicates its use. An increase in PCO2gap may be a marker of microcirculatory dysfunction in septic shock, especially when SvO2 is normal [32].

Second, what is the best site for monitoring the microcirculation? Interestingly, the adequacy of sublingual microcirculation does not guarantee adequate splanchnic or renal perfusion.

Third, the intervention should recruit the microcirculation rather than further increasing flow in already perfused vessels. Fluid administration improves the microcirculation only in early (< 24 h) sepsis [33]. Though starches may have beneficial effects [34], safety concerns preclude their use. The microcirculatory effects of vasopressors [35] and dobutamine [36, 37] are variable. The baseline state of the microcirculation may help predict the response to these therapies. Though vasodilatory agents may improve microcirculation, they lack selectivity.

Finally, whether strategies to recruit the microcirculation can improve outcome is unknown, and microcirculation-targeted resuscitation trials are lacking. Before planning such a trial, specific microcirculatory

variables, their target values, and specific interventions need to be determined. Until such time, microcirculation-guided therapy in septic shock will continue to be relegated to the research arena.

Steroids: quo vadis?

The recommendations provided on the use of corticosteroids in patients with septic shock have changed over time. Three decades ago, the use of high-dose steroids was first promoted and then discouraged [38]. Around the millennium, the concept of relative adrenal insufficiency led to the administration of lower doses of hydrocortisone [39]. After the CORTICUS trial [40], corticosteroids were recommended only for patients who had severe shock unresponsiveness to fluids and vasopressor therapy [2].

In 2018, two large trials on low-dose steroids were published. The ADRENAL trial randomized 3800 mechanically ventilated ICU patients with septic shock to hydrocortisone infusion or placebo [41]. Mortality was similar between the two groups, but the time on vasopressors, on mechanical ventilation, and in the ICU was shorter in the hydrocortisone group [41, 42]. Few adverse events were registered (steroids 27 vs. placebo 6). The APROCCHSS trial randomized 1241 ICU patients who had septic shock and multiple organ failure to hydrocortisone + fludrocortisone or placebo [43]. Mortality was lower in the hydrocortisone + fludrocortisone group, as was the time on vasopressors and organ failure. Many adverse events were recorded, with no difference between groups. The two trials had different inclusion criteria and control group mortality, which may explain the differing results between them. A unifying interpretation of the two trials may be that corticosteroids are to be used only in patients with severe shock, and that the SSC recommendation should be maintained. Several design characteristics also differed between the trials, which may challenge this interpretation (Table 2).

In a systematic review of all 22 RCTs on low-dose corticosteroids in patients with septic shock [44], no effect on mortality was observed, but steroids reduced the time on vasopressors, on mechanical ventilation, and in the ICU. An interpretation of the 22 trials overall may be that low-dose corticosteroids can be used only to reduce these time-dependent process measures (Table 2).

It may be that corticosteroid use should be targeted to patients based on disease severity or genetics, that the effect depends on timing and dose, and hydrocortisone may act synergistically with other therapies (e.g. fludrocortisone, vasopressin, ascorbic acid, and thiamine) [45, 46]. In view of our incomplete understanding, further investigations are under way. Importantly, the effects on recovery, quality of life, and health economics should be assessed.

A place for alternative measures?

Alternative treatment: role of blood purification in septic shock?

The main principle in blood purification techniques is the removal of inflammatory mediators to restore a more balanced immune response. Strategies include high-volume hemofiltration (HVHF), high-cutoff membranes, and adsorption techniques, including coupled plasma filtration adsorption (CPFA).

While earlier observational studies and small trials suggested improved hemodynamics with HVHF and with polymyxin B-immobilized fiber column, subsequent RCTs showed no benefit [47, 48].

The CytoSorb® cartridge is licensed for the treatment of cytokine storm. An RCT showed a reduction in interleukin 6 levels in sepsis patients, but no improvement in mortality [49].

Evidence for lipopolysaccharide (LPS) adsorbers stems from case series showing a decrease in endotoxin level and improvement in hemodynamics [50]. However, a feasibility trial was terminated early due to problems with patient recruitment (NCT02335723).

CPFA combines the separation of plasma with a highly permeable filter, followed by sorbent adsorption of the plasma component to remove cytokines and then reinfusion of the purified plasma before hemofiltration to allow solute clearance and fluid removal. The largest RCT using this technique showed no effect on hospital mortality or ICU-free days and was stopped prematurely [51].

The challenge now is that extracorporeal blood purification removes cytokines from the blood in patients with septic shock, but this has not resulted in improved outcome. Clearly, the trials have shortcomings; it may be that timing, dose, and duration of extracorporeal blood purification techniques influence outcomes and that specific subpopulations may benefit. On the other hand, these techniques are highly invasive and have the potential to harm patients.

Alternative therapy: vitamin C?

Vitamin C serves several important physiological functions. Ascorbate, the redox form of vitamin C, is an antioxidant; it improves immune function and plays a role in the synthesis of catecholamines and vasopressin and in wound healing.

In critically ill patients, plasma ascorbate concentrations can fall to low levels [52], and high-dose parenteral ascorbic acid is usually necessary to raise plasma levels to normal [53]. Small clinical trials have demonstrated apparent feasibility of high-dose vitamin C supplementation [54, 55].

A recent retrospective single-center study found a synergistic association in the use of vitamin C with

Table 2 Challenges in interpreting recent studies on low-dose corticosteroids in patients with septic shock

Study	Characteristics	Possible interpretation	Challenges with this interpretation
ADRENAL [41]	3800 mechanically ventilated patients with septic shock randomized to hydrocortisone infusion or placebo for 7 days in 69 ICUs in five countries	Hydrocortisone does not reduce 90-day mortality in ICU patients with septic shock	Overall, patients with moderate disease severity were enrolled (control group 90-day mortality 29%)
APROCCHSS [43]	1241 patients with septic shock and multiple organ failure randomized to hydrocortisone + fludrocortisone or placebo in 34 ICUs in France	Hydrocortisone reduces 90-day mortality in ICU patients with septic shock	It started out as a 2×2 trial; 207 patients were also randomized to APC. The protocol was changed when APC was taken off the market
			Fludrocortisone was part of the intervention
			Use of etomidate, which inhibits endogenous cortisol production, was not an exclusion criterion; no data were presented on its use
			Overall, patients with high disease severity were enrolled (control group 90-day mortality 49%)
ADRENAL and APROCCHSS combined		Hydrocortisone only reduces 90-day mortality in ICU patients with septic shock who have high disease severity	In addition to disease severity, the two trials differed in many other aspects, as noted above. Any of these aspects may contribute to the differing results
Updated systematic review [44]	22 RCTs of 7297 patients with septic shock contributed to the meta-analysis and trial sequential analysis	Low-dose steroids have no effect on mortality, including no apparent effect by sub-grouping	Clinical heterogeneity, including disease severity, is difficult to control for in meta-analysis
		Low-dose steroids reduce the time on vasopressors, on mechanical ventilation, and in the ICU	We still don't know the trade-off between the potential benefits (reduced time on life-support and in ICU) and the potential harm (negative effects on recovery and QoL) from low-dose steroids in all patients with septic shock
		There are no data on the effects on QoL, recovery, or health economics	

APC activated protein C, *ICU* intensive care unit, *QoL* quality of life

hydrocortisone and thiamine, demonstrating a reduction in mortality and organ dysfunction [45]. The study is limited by its retrospective design, lack of randomization, and small sample size, but it undoubtedly raises the question of whether future research should investigate high-dose vitamin C monotherapy or focus on the synergistic administration of vitamin C with hydrocortisone and thiamine. To this end, the results of the VICTAS study, which aims to recruit 2000 patients with sepsis, are awaited (NCT03509350).

Impact of septic shock on antibiotics levels

Early recognition and adequate source control is the cornerstone of septic shock therapy. The hemodynamic alterations in sepsis (high CO/vasodilation/capillary leak) have antibiotic drug dosing implications. Optimal dosing of antibiotics in septic shock is often not achieved with current recommended doses. The challenge is in preventing underdosing while avoiding adverse effects associated with overdosing.

The first challenge is providing an adequate loading dose. Due to an increased volume of distribution of commonly used antibiotics in sepsis, it is now well established that an initial large loading dose is required—roughly 1.5 times the standard dose [56, 57].

Another challenge is knowing how much to give, especially at extremes of weight, and whether a large loading dose can cause toxicity. Aminoglycosides are rapidly bactericidal, and for maximal efficacy, peak concentrations of 10 × MIC are needed, while most of the toxicity is related to trough concentrations (as an index of total exposure). Experts advocate one or two large doses at the beginning of therapy [56], even in the presence of renal dysfunction [58]. The challenge is thus to achieve high peaks while minimizing trough concentrations under conditions of variable distribution volume and clearance.

Subsequent to a loading dose, the next challenge is optimizing further dosing when drug clearance becomes important. Sepsis can be associated with augmented renal clearance (ARC) or, on the other hand, with unstable, rapidly changing renal dysfunction [57–60]. We can envisage four different renal clearance scenarios, each necessitating different dosing requirements for antibiotics cleared by the kidneys—beta-lactams, aminoglycosides, glycopeptides, and colistin—as illustrated in Fig. 2.

ARC is thought to reflect increased renal blood flow in patients with normal renal function. Younger patients (e.g. those with pneumonia or head injury) are more prone to developing ARC [59, 61], but it can occur in other patients as well. Measurement of renal clearance may help to identify these patients. In such patients, while higher daily dosing is important, we believe that therapeutic drug monitoring should be used as an aid

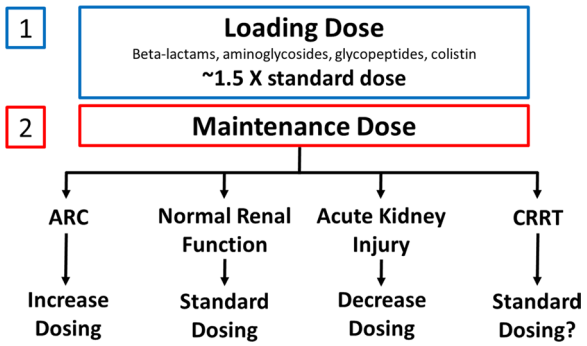

Fig. 2 Antibiotic challenges. Loading doses for hydrophilic antibiotics should be given independently of subsequent dosing, which needs to be adjusted according to altered clearance

to dosing for most antibiotics in the ICU, especially as renal function can change over time. In patients on renal replacement therapy (RRT), underdosing may occur, and higher doses of beta-lactams are probably a better option than the risk of underdosing [58].

Can we improve dosing intervals? For beta-lactams, requiring significant time above MIC for optimal efficacy, higher daily doses are best administered by shortening dosing intervals. While the administration of continuous or extended infusions may help improve outcomes by keeping trough concentrations high, especially in the presence of resistance [62], not all data are congruent [63].

Specific challenges in LMIC

Hemodynamic management of septic shock is challenging in resource-poor areas, where life-sustaining therapies such as mechanical ventilation and RRT are not always available and ICU beds are scarce. Even the less expensive therapies such as antibiotics or vasopressors and laboratory exams such as lactate are not widely available. Although this is especially critical in low-income countries in Africa and Asia, inequality is omnipresent, and some areas even in middle-income countries face severe resource limitations [64].

Monitoring tools, including those for assessing fluid responsiveness, may be lacking, and targets of resuscitation are largely based on clinical parameters. While clinical parameters such as urine output, level of consciousness, or CRT provide inexpensive alternatives for the assessment of peripheral tissue perfusion, they are rather nonspecific and need to be validated. The findings of the recently completed ANDROMEDA-SHOCK Study (NCT03078712) in Latin America, which compared two resuscitation strategies based on blood lactate levels and CRT, may throw light on this issue. Echocardiography,

Table 3 Potential solutions to the various challenges in the management of septic shock

Variables/problem	Challenges/uncertainties	Potential solutions to the challenge	Challenges with the potential solutions/ remaining questions
Selecting the right hemodynamic target			
Arterial pressure	What is the best MAP for this patient?	Consider CVP and abdominal pressure	Difficult to find indices of organ perfusion which respond rapidly to changes in MAP
		Consider comorbidities (including previous hypertension)	Potential toxicity/adverse events with higher doses of vasopressors
		Consider MAP challenges	
Skin markers of tissue hypoperfusion (CRT, skin temperature, mottling)	Can these be used to guide resuscitation?	Randomized trial completed with CRT (NCT03078712—results presented at LIVES 2018)	Uncertainty whether they are useful when combined with other variables
	Which one is best?		Do they reflect perfusion of other organs?
			Lack of correlation with etiology of alteration
$SvO_2/ScvO_2$	Randomized trials showed that targeting $ScvO_2 > 70\%$ failed to improve outcome	Individualize therapy	Uncertainty in how to define the optimal $ScvO_2$ value of an individual patient at a given time
		Combine with other variables of tissue hypoperfusion	
Veno-arterial difference in PCO_2	Can resuscitation therapies based on PCO_2gap improve outcome?	Awaiting randomized trials	What interventions are best to manipulate/ improve PCO_2gap?
			Should PCO_2gap be improved or normalized, and over what period of time?
Lactate-guided therapy	Should we target lactate reduction (and which magnitude) or lactate normalization?	Awaiting randomized trials	Could there be a benefit when combined with other markers?
			Do results differ when separating hypoxic from non-hypoxic source of lactate?
Optimizing fluid therapy			
Use dynamic indices to predict fluid responsiveness before fluid administration	Many limitations prevent the use of these tests in individual patients (i.e. low tidal volume)	Perform an alternative dynamic test	Gray zone issue
		Add maneuver such as transient increase in tidal volume	Predictive performance is often lower in practice than in original studies
			Persistent limitation in applicability
			Do not always discriminate fluid responsiveness from right ventricular dysfunction
Fluid challenge to optimize fluid administration	What is the best method of performing a fluid challenge?	Small size studies suggest administration of 4 ml/kg crystalloids over 30 min	What is the best threshold for defining fluid responders?
		Ideally, response in CO or end-tidal CO_2 should be evaluated in mechanically ventilated patients	How reliable is the evaluation of the response based on surrogate markers when CO measurements are not available?
			What are the best indices for identifying fluid intolerance?
			What is the duration of the effects?

Table 3 (continued)

Variables/problem	Challenges/uncertainties	Potential solutions to the challenge	Challenges with the potential solutions/ remaining questions
Determination of the best fluid resuscitation strategy	Should we use lower or higher fluid volumes?	Randomized trials ongoing	Interaction with the use of vasopressors?
			Do the different triggers and targets affect outcome?
Selection of type of fluid	Should we use saline or balanced crystalloids?	Randomized trials under way	Should the choice of crystalloid solution be guided by sodium/chloride measurements?
Vasopressor therapy/selection of vasopressor agent			
Norepinephrine as first line, vasopressin and angiotensin as potential alternatives	While head to head comparisons failed to demonstrate a difference in outcome, what is the best combination strategy, if any?	Rapid evaluation of the response to the first agent and addition of an agent of another class if the response is inadequate	What is the threshold dose for each agent before adding another agent?
			Are there specific conditions that should prompt the use of one agent versus the other?
Inotropes			
Inotropic agents may increase CO in the context of sepsis-induced myocardial depression	How to identify patients who may benefit from administration of inotropic agents?	Patients with impaired tissue perfusion related to a low CO due to impaired contractility are most likely to benefit from inotropic agents	What dose of which agent and for what duration?
		Awaiting randomized trials	Triggers and targets?
			How to titrate?
A place for beta-blockers?			
Esmolol limits tachycardia and may have beneficial effects in selected patients with septic shock	Can the effects of the original report be reproduced in other trials?	Confirmatory trials under way	Which echo variables should be used to identify patients who are/are not likely to benefit from beta-blockers?
	How to identify patients who may potentially benefit from esmolol?	Using echocardiography in patients with tachycardia to confirm adequate cardiac function and absence of fluid responsiveness	Any role for alternative drugs (i.e. ivabradine, clonidine,…)?
Microcirculation-targeted therapies			
Microcirculation is the key determinant of tissue perfusion, and microvascular alterations are associated with a poor outcome	Can we use surrogate markers to evaluate the microcirculation?	Veno-arterial difference in PCO_2 is inversely correlated with microvascular perfusion	If microcirculation can be easily monitored (either directly or with surrogates), could microcirculation-targeted therapy improve outcome?
	What site to monitor with videomicroscopes?	Sublingual area is thought to be one of the most representative	
	Which interventions can be used to improve the microcirculation?	Several interventions improve the microcirculation but their effects have considerable individual variability	
	What level can be considered adequate?		

Table 3 (continued)

Variables/problem	Challenges/uncertainties	Potential solutions to the challenge	Challenges with the potential solutions/ remaining questions
Corticosteroids			
Hydrocortisone facilitates shock reversal and is associated with variable effects on survival	What are the effects of steroids on recovery?	Long-term evaluation is under way in some of the trials	Are the current hydrocortisone doses adequate?
	What are the reasons for divergent effects on survival?	Shock severity and genetic profile may help to identify patients who may benefit most from steroids	If beneficial, for how long should they be administered?
Blood purification techniques			
Diverse blood purification techniques have shown variable effects on hemodynamics and outcome	Is there a role for blood purification techniques?	Registries may be useful to better characterize patient selection and response before conducting randomized trials	What is the optimal timing and number of sessions?
	If yes, are some technologies better than others?		What is the impact of blood purification techniques on antibiotic dosages?
	Should patients be selected based on severity and hemodynamic criteria or plasma levels of cytokines/endotoxin?		What is the best anticoagulation strategy?
Role of vitamin C			
A before-and-after single-center study suggests that vitamin C (+ thiamine and hydrocortisone) may be associated with improved outcome	What is the impact of co-administration of thiamine and hydrocortisone?	Randomized trials ongoing	What is the ideal dose (and duration) of vitamin C?
	What explains the effects?		Should vitamin C be limited to shock patients only?
Impact of septic shock on antibiotic levels			
Early adequate antibiotic therapy is essential	Plasma antibiotic levels are frequently inadequate in patients with septic shock due to an increased volume of distribution and renal hyperfiltration	Drug therapeutic monitoring	Do plasma levels reflect tissue levels?
		Use of higher doses of aminoglycosides	How to best monitor potential adverse effects?
		Prolonged or continuous infusion of beta-lactams	
Specific challenges in low- and middle-income countries			
Monitoring tools are often lacking	Can evidence-based medicine and guidelines (mostly driven by data from developed countries) be applied in LMIC?	Develop simple and inexpensive clinical tools to evaluate tissue perfusion	Can resuscitation strategies be based on simple clinical indices of tissue perfusion?
Organ support technologies often lacking in very low-income countries		Adapt resuscitation strategies to the level of organ support available (reevaluate the benefit/risk of each intervention in this context)	Should antibiotic strategies differ in LMIC?
Disease presentation may differ		Perform observational trials to better characterize septic shock in LMIC	

MAP mean arterial pressure, *CVP* central venous pressure, *CRT* capillary refill time, SvO_2 mixed venous oxygen saturation, $ScvO_2$ central venous oxygen saturation, PCO_2gap veno-arterial differences in PCO_2, *CO* cardiac output, *LMIC* low- and middle-income countries

although requiring some initial expenditure, is attractive and relatively inexpensive to perform, enabling rapid assessment of volume status, cardiac function, and the presence of lung edema [3]. The availability of equipment and trained personnel may vary. Invasive and less-invasive hemodynamic monitoring may be available in some but not all facilities [64].

Optimizing fluid therapy in areas with limited access to oxygen and mechanical ventilation constitutes a challenge. Administration of a predefined amount of fluids may be detrimental [65, 66]. Determination of the triggers and safety limits is crucial in these setting. Studies showed that patients received predefined amounts of fluids (totaling approximately 70 ml/kg) even if pressure was restored, stopping infusion only if there were clear signs of pulmonary edema [66]. Generalization of these findings may be limited, and these results cannot be translated to other settings using clear goals of resuscitation [67].

The challenge in LMIC is not just that of limited resources due to funding, but also the lack of adequately trained personnel, wide variation in clinical practices, and knowledge gaps. The absence of epidemiological and clinical data is also a challenge. If resources are scarce, wise choices are needed both with respect to clinical practices and in settling research questions focusing on local priorities. Building research capacity, with the necessary funding, is a key point. Recently established research networks will contribute to improving the quality of clinical trials and finding appropriate answers for LMIC [68, 69].

Conclusions

While the current literature and guidelines provide important information, many challenges remain for the management of patients with septic shock (Table 3). Although further trial data may provide clearer guidance in some areas (i.e. steroids, fluids types and volumes, and alternative therapies), patients require individualized therapies based on careful assessment, particularly where uncertainties remain (e.g. the assessment of benefit vs. risk of fluids and inotropic agents). The challenge will be to test individualized approaches in randomized trials to obtain the best possible evidence.

Electronic supplementary material

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Author details

[1] Department of Intensive Care, CHIREC Hospitals, Université Libre de Bruxelles, Brussels, Belgium. [2] Department Anaesthesia and Intensive Care Units, IRCCS Istituto Clinico Humanitas, Humanitas University, Milan, Italy. [3] Intensive Care Services, Royal Brisbane and Women's Hospital and The University of Queensland Centre for Clinical Research, Brisbane, Australia. [4] Anesthesiology, Pain and Intensive Care Department, Federal University of Sao Paulo, São Paulo, Brazil. [5] Department of Anaesthesiology, Critical Care and Pain, Tata Memorial Hospital, Mumbai, India. [6] Department of Intensive Care, King's College London, Guy's & St Thomas' Hospital, London, UK. [7] Department of Intensive Care, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark. [8] Medical Intensive Care Unit, Bicetre Hospital, Paris-South University Hospitals, Inserm UMR_S999, Paris-South University, Le Kremlin-Bicêtre, France. [9] Department of Intensive Care, Erasme University Hospital, Université Libre de Bruxelles, Brussels, Belgium. [10] Centre for Heart Lung Innovation, University of British Columbia, Vancouver, Canada.

Compliance with ethical standards

Conflicts of interest

Daniel De Backer: consultant to and material for studies by Edwards Lifesciences. Maurizio Cecconi: consultancy for Edwards Lifesciences, LiDCO, Cheetah, Masimo. Jeffrey Lipman: MSD (Australia)—Antibacterials Advisory Board; honoraria for lectures—Pfizer South Africa, MSD South Africa; committee—Pfizer International 2018 Anti-Infectives. Flavia Machado: member of steering committee for BASIC study, for which drug was supplied by Baxter. Sheila Nainan Myatra: no conflict of interest. Marlies Ostermann: research funding from Ja Jolla Pharma. Anders Perner: Dept. of Intensive Care at Rigshospitalet has received support for research from CSL Behring, Fresenius Kabi, and Ferring Pharmaceutical. Jean-Louis Teboul: member of the medical advisory board of Pulsion/Getinge (Germany). Jean Louis Vincent: no conflict of interest. Keith Walley: no conflict of interest.

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