World Sepsis Day 2019

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Contents

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3. View and read the PDF version and watch the videos online.
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Foreword

Sepsis is a life-threatening condition estimated to affect 27–30 million people worldwide every year, resulting in more than 6–9 million deaths annually. Around the world, it is estimated that someone dies from sepsis every 3–4 seconds. Those who survive sepsis often have long-term physical or psychological sequelae reducing their quality of life. Sepsis, therefore, represents a huge personal, physical, social, and economic burden.

Caused by a dysregulated host response to infection, sepsis can affect anyone, although is more likely to occur in children, the elderly, those with chronic diseases, and compromised immune systems. It can be difficult to diagnose accurately and rapidly. Mortality rates in patients hospitalized with sepsis are in the range of 25–50% depending on various factors including the infecting microorganism, severity of disease, and specific patient characteristics such as age and prior health status. Geographical location and available resources also influence diagnosis and management such that morbidity and mortality are generally higher in lower income countries with fewer facilities.

As the pathophysiology of sepsis has been increasingly unraveled in the last few decades, so our understanding of the underlying pathophysiological processes has improved and the urgency of sepsis diagnosis and treatment has come to the fore. Sepsis can be indicated by the presence of many signs and symptoms (fever, tachycardia, tachypnea…), not all of which will be present in all individuals and none of which is specific to sepsis. As such, a keen awareness of sepsis as a possible diagnosis is vitally important. With up to 90% of sepsis cases being community-acquired, heightened public awareness of sepsis is important so that medical help is sought earlier rather than later.

Once in hospital, the search for infection should start with the five most common areas-lungs, abdomen, urinary tract, skin, and catheters. However, infection can be difficult to identify and unexplained organ dysfunction may be the only indication and should alert the clinician to the possibility of sepsis and encourage a search for an underlying infectious source. Raised levels of biomarkers, such as C-reactive protein or procalcitonin, can help support a diagnosis of sepsis, but are not routinely available everywhere. New molecular methods that can identify infection without the need for time-delaying cultures are beginning to become available and may be particularly useful in countries and centers with limited microbiologic facilities.

Once a diagnosis has been made, appropriate antimicrobial therapy should be started as soon as possible and any identified source, for example, an infected drain or an intra-abdominal abscess, removed. Fluids and vasopressor agents should be started to ensure adequate tissue perfusion and limit further organ dysfunction. Adequate oxygenation should be assured using mechanical ventilation, if necessary. International guidelines on sepsis management are available, but must be adapted to local conditions and available resources. Increasingly, we are realizing the importance of treating patients as individuals and traditional one-size-fits-all patient management is far from optimal—treatment decisions should be adjusted according to patient characteristics and response to therapy. Better techniques to help characterize and monitor the degree of sepsis response in individual patients are being developed and should help guide appropriate treatment choices in the future.

In recent years, International endeavors such as the Surviving Sepsis Campaign, the World Health Organization resolution on sepsis and the Global Sepsis Alliance have helped spread awareness of sepsis not only among healthcare professionals but also among the public. Nevertheless, the number of cases of sepsis is increasing worldwide and continuing efforts to further enhance sepsis understanding and training are essential if the global burden of sepsis is to be reduced.

In this booklet, aimed at general clinicians involved in the management of patients with sepsis in their daily practice in India, we have selected some key published articles about various aspects of the management of sepsis, written by internationally recognized experts in the field. Providing up-to-date guidance and specialist opinion, I am sure this collection will be of use to all those actively responsible for the treatment of patients with sepsis.

Happy reading!

Prof. Jean-Louis Vincent

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Critical Appraisal

REVIEW

Challenges in the management of septic shock: a narrative review

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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

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(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

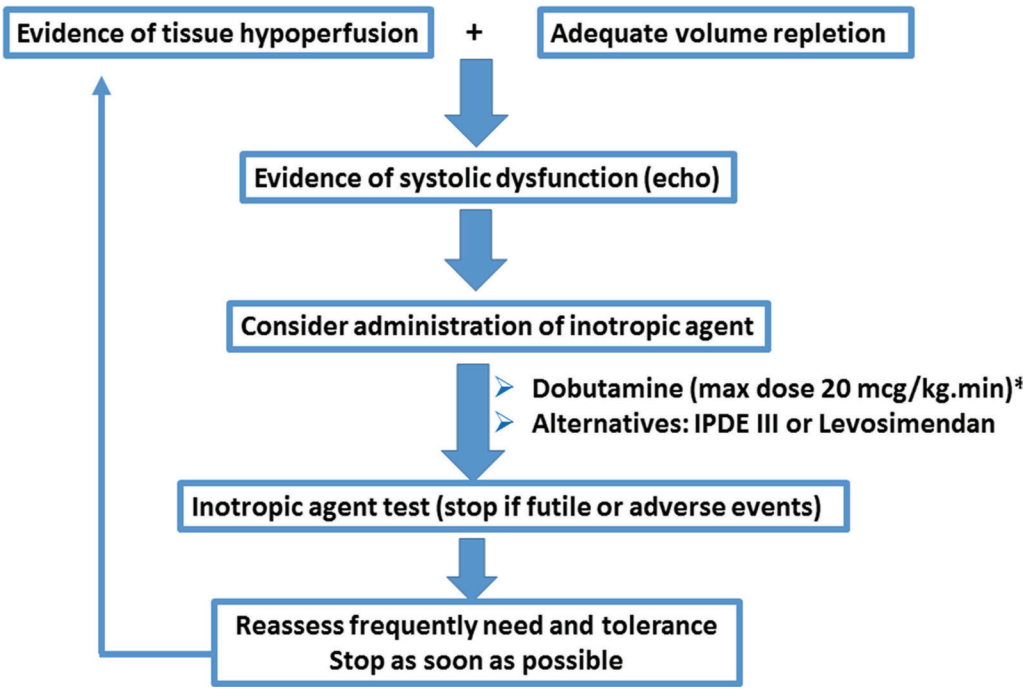

Fig. 1 A model for suggested use of inotropic agents in septic shock. Schematic algorithm for the use of inotropic agents. IPDE III denotes inhibitors of phosphodiesterase type III

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

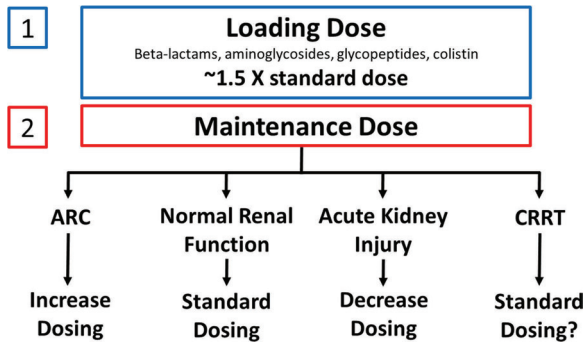

Fig. 2 Antibiotic challenges. Loading doses for hydrophilic antibiotics should be given independently of subsequent dosing, which needs to be adjusted according to altered clearance

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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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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REVIEW

Expert statement for the management of hypovolemia in sepsis

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Abstract

Hypovolemia is frequent in patients with sepsis and may contribute to worse outcome. The management of these patients is impeded by the low quality of the evidence for many of the specific components of the care. In this paper, we discuss recent advances and controversies in this field and give expert statements for the management of hypovolemia in patients with sepsis including triggers and targets for fluid therapy and volumes and types of fluid to be given. Finally, we point to unanswered questions and suggest a roadmap for future research.

Keywords: Critical care, Fluid therapy, Hemodynamics, Hypovolemia, Sepsis, Shock

Introduction

Contemporary estimates indicate that more than 19 million people develop sepsis every year and that half of these will never recover [1]; 6 million patients will die [2] and approximately 3 million will survive with cognitive and functional impairments [1]. The reasons for the overall poor outcome rates include the degree of pre-sepsis comorbidity and frailty, the severity of the acute disease, and the quality of the management by the healthcare system, i.e., timely identification and interventions against sepsis, e.g., antibiotics and source control [1, 3, 4]. Good supportive care during hospitalization and in the rehabilitation period matters [1, 3], but the evidence is low for the balance between benefits and harms for the majority of the single components of the supportive care including that for fluid management [1, 3, 5, 6]. Thus the risk of treatment-related harm is real and its avoidance of utmost importance [7–9].

Hypovolemia is likely frequent among critically ill patients including those with sepsis and septic shock [7, 10, 11]. It may be absolute (blood volume lost) or relative (blood volume redistributed); in both cases, the blood volume is insufficient to maintain vascular wall tension, mean systemic filling pressure, venous return, cardiac filling and cardiac output, and arterial blood pressure resulting in shock. In patients with sepsis the cause of hypovolemia is likely redistribution of blood volume.

In most cases, the degree of hypovolemia is difficult to assess because of lack good clinical markers. At any rate, blood volume expansion is the recommended first-line intervention in the resuscitation guidelines for patients with sepsis and septic shock [3]. It is, however, important to remember that while fluid expansion can restore a higher mean systemic filling pressure even in vasodilatory shock, in this case the pathophysiological mechanism suggests that restoring vascular tone should also be considered.

Thus guidance is provided for the management of patients with sepsis and hypovolemia, but it is still one of the most challenging tasks that clinicians face. Doing it right will make a big difference for the patient, i.e., striking the right balance between under-resuscitation and over-resuscitation and that of the benefit vs. harm of intravenous (IV) fluids and other interventions given for shock. The risk of us harming our patients with fluid therapy is real, as shown with the toxicity of synthetic colloid solutions [8, 12, 13], the potential renal impairment with

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isotonic saline [14, 15], and the increasing evidence of multiple organ impairment of fluid overload in patients with sepsis [16–18].

We have been invited by the editorial board of *Intensive Care Medicine* (the first author AP was invited and he invited the others in the group) to give expert statements about the recent advances, ongoing controversies, and current management of patients with sepsis and hypovolemia.

Recent advances and ongoing controversies

Controversies remain in many areas because of the complexity of the settings, pathophysiology, and need for multiple interventions among patients with sepsis, and the limited evidence base for the majority of recommendations. The 2016-iteration of the Surviving Sepsis Campaign (SSC) guideline issued nine specific recommendations regarding fluid therapy, many of which were based on low or very low quality of evidence [3].

Triggers and targets

The SSC guideline recommends fluid therapy as part of the resuscitation of sepsis-induced hypoperfusion, i.e., acute organ dysfunction, low blood pressure, and/or elevated plasma lactate [3]. Further, additional fluids are to be guided by repeated assessment and detection of impaired circulation using non-invasive and invasive parameters and dynamic variables to predict fluid responsiveness as available [3].

The theoretical base for these recommendations goes decades back. It may be summarized as (1) sepsis-induced organ dysfunction is, at least in part, caused by hypoperfusion, which may be caused by (2) low cardiac output and/or low blood pressure and (3) that fluids may improve cardiac output, blood pressure, and organ dysfunction and thereby patient outcomes. This pathophysiological and therapeutic construct gained further support with the publication of the original Early Goal-Directed Therapy (EGDT) trial [19]. In this trial, patients with sepsis and low blood pressure and/or elevated lactate had markedly improved outcomes with guided fluid therapy. However, in the three recent confirmatory trials, PROCESS, ARISE, and PROMISE, no improvements in outcomes were observed with EGDT vs. usual care in patients with septic shock [20]. These results appeared to hold also in different subgroups of patients including those with more severe shock defined as higher lactate values and use of vasopressor [21]. Thus, we lack good data to indicate which triggers to use to initiate fluid resuscitation in patients with sepsis.

In addition to low blood pressure and elevated lactate levels, oliguria appears to be the main trigger for fluid challenges at least in the ICU [22]. Also oliguria has been questioned as a trigger for fluid therapy because renal blood flow may be normal or even increased in patients with septic shock [23], the pathophysiology of acute kidney injury (AKI) in sepsis is complex and multifactorial [24], and systemic hemodynamic response and renal response to fluid challenge are often dissociated [25, 26]. After the initial resuscitation, fluid administration may not increase urinary output and contributes to positive fluid balance and potentially worsening of AKI in patients with septic shock [17, 27, 28].

Also clinical markers of hypoperfusion obtained by physical examination are likely to be important triggers of fluid therapy in sepsis. These markers include mottling, low skin temperature, prolonged capillary refill time, and altered consciousness [3, 29, 30]. Currently, it is unknown if the use of a single trigger or a certain combination of these triggers is better in selecting patients who benefit from fluid.

The use of markers predictive of fluid responsiveness has shown proof-of-concept [31, 32], but it is still unknown if outcomes are improved by applying these markers in the management of patients with sepsis.

Similarly, it is uncertain if outcomes are improved by the targeting of markers of circulatory failure obtained by more advanced hemodynamic monitoring in patients with septic shock [33]. Patients' outcomes were not improved by the use of central venous pressure and oxygen saturation as part of the EGDT protocol [21] or by the use of cardiac output monitoring in general ICU patients [34] or those with early shock [35]. The use of alternative strategies, such as critical care ultrasonography, has not been tested in trials of sepsis resuscitation [36], and the validity of some of the measures obtained by echocardiography should be established [37–40].

An ongoing randomized clinical trials (RCT), the TARTARE-2S trial ($n = 200$), assesses the effects of microcirculatory vs. macrocirculatory targets in patients with septic shock [41].

Volume

The SSC guideline recommends a fixed volume of 30 mL/kg of IV crystalloid solution for patients with sepsis-induced hypoperfusion [3]. This has been challenged because of the low quality of the supporting evidence and of the complex circulatory failure in sepsis—fluid loss and hypovolemia may not be prominent in all patients [42]. Furthermore, in a large prospective study a fixed dose seemed insufficient in patients with heart failure, hypothermia, or a lactate above 4.0 mmol/L [43]. Supporters of the fixed volume recommendation argue that the use of some IV fluid is standard of care, is associated with good outcomes in observational studies, and is unlikely to be harmful [44].

In recent years, at least five RCTs have tested lower vs. higher fluid resuscitation volumes in patients with sepsis (Table 1). It is challenging to pool the results of these trials because of marked heterogeneity regarding the setting, timing, and fluid dosing strategy used. However, the results suggest no or limited improvements in the markers of hypoperfusion with higher vs. lower fluid volumes and, if anything, better outcomes with lower fluid volumes. Importantly, the control groups (i.e., patients with lower fluid volumes) in all the trials did receive at least 1.5 L of fluid including that given prior to randomization (Table 1).

For the management of fluids after initial resuscitation, there are data from a recently updated systematic review [45] assessing the effects of conservative or de-resuscitation fluid strategies vs. more liberal or standard of care fluid strategies in patients with sepsis and/or ARDS. The results suggest that conservative or de-resuscitation fluid strategies results in fewer days of mechanical ventilation without an increase in mortality [45].

Taken together, we cannot make strong inferences from the data on the benefit vs. harm of higher vs. lower fluid volumes in sepsis resuscitation. But the data do highlight the urgent need for good RCTs in this area [46]. Several trial programs, CLOVERS, CLASSIC, and ARISE FLUIDS, are assessing different fluid volume protocols for resuscitation of patients with septic shock in different settings (NCT03434028) [17, 47] (Table 3).

Type of fluid

In recent years, the use of the different types of fluids has changed at the level of emergency rooms, ICUs, anesthesia units, hospital wards, hospitals, and countries [48–51]. Traditionally, colloid solutions were thought to have a markedly higher potency for plasma expansion than that of the crystalloid solutions. A recent systematic review suggested a modest gain from colloids only in this regard and showed a vast and largely unexplained heterogeneity across studies except that the colloid potency appears to have decreased over time [52].

In general, more crystalloid solutions are used now than a decade ago and among these more buffered solutions and less saline are used. Conversely, less colloid solutions are used now than 10 years ago, in particular the

Table 1 Randomized trials of fluid resuscitation of adult patients with septic shock, in which a strategy was used to obtain differences in fluid volumes between the intervention groups

Trial	Setting	Patients	Median IV fluid volumes[a]	Hypoperfusion markers[b]	Mortality[c]
CLASSIC pilot trial [17]	9 ICUs in Scandinavia	153 patients with septic shock who had received 30 mL/kg of IV fluid	Lower fluid group 0.5 L Higher fluid group 2.0 L	No differences between groups in the marker assessed	Lower fluid group 33% Higher fluid group 41%
TFM trial [71]	Single ICU in the USA	82 patients with septic shock using vasopressor > 12 h after initial resuscitation	Lower fluid group 6.2 L Higher fluid group 8.7 L	No differences between groups in the markers assessed	Lower fluid group 56% Higher fluid group 49%
EHOSS-1 trial [72]	Single ICU in France	61 patients with septic shock who had received 25 mL/kg of IV fluid	Lower fluid group 3.0 L Higher fluid group 3.3 L	No differences between groups in the markers assessed	Lower fluid group 23% Higher fluid group 47%
SSSP-1 trial [73]	Single ED in Zambia	120 patients with suspected infection, 2 positive SIRS criteria, and organ dysfunction	Lower fluid group 1.6 L Higher fluid group 2.9 L	No data published	Lower fluid group 61% Higher fluid group 64%
SSSP-2 trial [18]	Single ED in Zambia	212 patients with suspected or proven infection and hypotension	Lower fluid group 2.0 L Higher fluid group 3.5 L	Faster lactate clearance in the higher vs. the lower fluid volume group	Lower fluid group 33% Higher fluid group 48%

The above trials were identified in the literature search for a systematic review on lower vs. higher fluid resuscitation volumes in patients with sepsis [74]. The search was done in Cochrane Library, MEDLINE, EMBASE, Science Citation Index, BIOSIS, and Epistemonikos using terms related to population (sepsis, systemic inflammatory response syndrome etc.), intervention (fluid and resuscitation), and methodological filters (random and meta-analysis)

CLASSIC conservative vs. liberal approach to fluid therapy of septic shock in intensive care, *ED* emergency department, *EHOSS* early hemodynamic optimization using reload dependence during septic shock, *ICU* intensive care unit, *SSSP* simple septic shock protocol, *TMF* targeted fluid minimisation

[a] At 6 h in SSSP-1 and -2, at day 5 in CLASSIC and TMF, and at end of study in EHOSS-1; in TMF all fluids were recorded, in the other trials only resuscitation fluids were recorded

[b] Including blood pressure, vasopressor dose, lactate values/clearance, urinary output, and central venous oxygen saturation. No single trial recorded all these markers

[c] In-hospital in SSSP-1 and -2 and TMF, day 28 in EHOSS-1, and day 90 in CLASSIC

synthetic colloid solutions, hydroxyethyl starch, gelatine, and dextran. In contrast, the use of albumin is increasing [48–51]. These marked changes have occurred after the publication of RCTs and systematic reviews showing harm of hydroxyethyl starch in critically ill patients including those with sepsis [8, 13, 53, 54], the results of which were implemented in the SSC guideline [3] and in the EMA and FDA resumes on starch. The balance between benefit and harm for albumin and gelatine is less clear, but the SSC guideline suggests the use of albumin in patients requiring substantial amounts of crystalloids and to use crystalloids rather than gelatine [3]. The latter was supported in a recent network meta-analysis, in which the point estimates for gelatine vs. albumin or crystalloid did suggest increased use of renal replacement therapy with gelatine, but these were results of indirect comparisons and not statistically significant [55].

As crystalloids are the recommend first-line fluid in sepsis [3], the question now is whether we shall use saline or buffered solutions; the SSC guideline makes no recommendation of one over the other. The most informative RCTs until now are the two cluster trials comparing isotonic saline vs. buffered crystalloids in general ICU patients, SMART ($n = 15{,}802$) and SPLIT ($n = 2278$) [15, 56]. In both trials mortality was the only "truly" patient-centered outcome, relatively few patients with sepsis were enrolled, and both trials had relatively few clusters, which likely reduced their power. SMART was single-centered and open-labelled, both of which may increase the intervention effect. The results differed between the trials; SMART indicated worse renal outcomes with saline vs. buffered solutions, whereas SPLIT indicated no differences in rates of AKI or other outcomes with the use of saline vs. an acetate/gluconate-buffered solution.

Table 2 Suggested standard of care fluid resuscitation in patients with sepsis and hypovolemia as per the consensus by the expert group

Preamble	*Only few parts of the initial fluid management of patients with sepsis are supported by data from high-quality RCTs*. Therefore, an individual strategy based on the patient's history, a thorough clinical examination, and, in selected patients, more advanced hemodynamic monitoring will likely be better in identifying those who will benefit from fluids Uncertainty remains for many parts; we have higher certainty for the suggestions marked with an asterisk below
Fluid therapy	*Use fluid boluses, e.g., 250–500 mL*; stop if the circulation does not improve *Use a fixed volume to substitute documented loss* *Use crystalloid solutions*, i.e., buffered solutions or isotonic saline[a] **Do not give hydroxyethyl starch, gelatine or dextran solutions* *Aim for fluid restriction and negative fluid balances* as soon as the circulation has stabilized
Early vasopressor	*Consider early infusion of norepinephrine* in patients with severe hypotension, e.g., MAP < 50 mmHg, and in those who do not increase MAP to, e.g., 65 mmHg with the first fluid bolus. Peripheral infusion may be considered into a large vein proximal to the antecubital or popliteal fossae while waiting for central access, or if a short infusion time is expected
Restrict the use of cardiovascular depressing agents	*Consider reducing the infusion of any potential cardiovascular depressing agents* as these may suppress the compensatory mechanisms and may worsen the degree of shock (e.g., propofol, remifentanil, dexmedetomidine, and epidural anesthesia)[b]
Blood transfusion	**Transfuse at an Hb threshold of 7 g/dL* (4.3 mmol/L) unless the patient has acute myocardial ischemia, during which a higher Hb threshold may be considered
Monitoring	*Use repeated assessment of simple circulatory parameters* including blood pressure, heart rate, lactate and temperature gradients, and mottling on the extremities. If the prerequisites are fulfilled for the tests for fluid responsiveness[c], these tests may be used *Be aware*: Abnormalities in any of the above markers are not specific for hypovolemia. If they are normal, the patient is less likely to benefit from further fluid therapy *Additional diagnostics* will likely be of value in the case of unexplained or worsening shock using, e.g., echocardiography or cardiac output measurement *Safety markers*: Consider stopping fluid input in the case of worsening oxygenation or circulation during fluid resuscitation

We assessed the updated SSC guideline [3] together with other sources and applied common sense and flexibility based on patient- and setting-specific characteristics as noted in the preamble. The first version of the suggestions was drafted by the first author (AP) and circulated among all members of the group by e-mail. The suggestions were revised until consensus was obtained

Hb hemoglobin, *MAP* mean arterial pressure, *RCT* randomized clinical trial

[a] In patients with acidosis, buffered solutions may be preferred; in patients with brain injury or alkalosis, isotonic saline may be preferred

[b] These agents are frequently used in critically ill patients and have frequent or very frequent cardiovascular depressing side effects (i.e., bradycardia and/or hypotension) according to the Summary Product Characteristics (the Danish versions for the specified agents were assessed through www.produktresume.dk)

[c] The prerequisites for the valid use of the arterial waveform analyses in predicting fluid responsiveness are sinus rhythm, controlled mechanical ventilation with tidal volumes above 7 mL/kg, and deep sedation. For the valid use of passive-leg-raising test, valid assessment of changes in stroke volume is needed

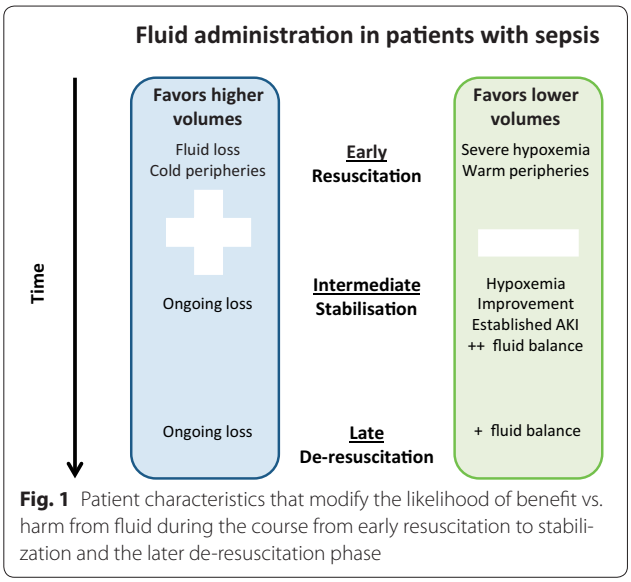

Fig. 1 Patient characteristics that modify the likelihood of benefit vs. harm from fluid during the course from early resuscitation to stabilization and the later de-resuscitation phase

Ongoing patient-level RCTs are comparing the effects of isotonic saline vs. an acetate/gluconate-buffered crystalloid on 90-day mortality in general ICU patients, the PLUS trial ($n = 8800$) [57] and the BASICS trial ($n = 11{,}000$) [58]. In the latter trial, the effect of rapid infusion rate (999 mL/h) vs. slower infusion (333 mL/h) is also assessed in a 2×2 factorial design. Another challenging concept is currently investigated in a pilot RCT of low vs. high chloride-containing fluids in patients with septic shock [59].

Vasopressor and vasodilators

Hypotension is the hallmark of septic shock and vasopressor therapy, i.e., norepinephrine, is strongly recommended [3]. When to start the infusion of norepinephrine in septic shock is still uncertain, but an early start may increase blood pressure, venous return, and cardiac output even in patients with hypovolemia [60, 61]. Early use of more vasopressor and thus less administration of fluid in vasodilatory shock, such as sepsis, has some physiological rationale. Guyton many years ago described reduced venous return and cardiac output by vasoplegia [62].

Corticosteroids increase blood pressure in patients with septic shock [63, 64], most likely through a general reduction in the degree of vasoplegia [65]. Whether steroids also increase venous return in patients with septic shock is still unsettled, but as blood pressure increases it may be that clinicians are less inclined to given fluid to patients receiving steroids.

Along these lines, the use of agents with vasodilatory potential, e.g., propofol, may worsen the degree of "hypovolemia", i.e., increase preload dependency, in patients with septic shock [66].

In clinical practice, reasons for delayed administration of norepinephrine may include the lack of invasive monitoring and/or central venous access. Administration of norepinephrine in peripheral veins is practiced, but the overall benefit vs. harm has not been thoroughly studied. There are case reports of serious adverse effects like skin and tissue necrosis after administration of peripheral norepinephrine; these risks may be minimized if the infusion is done in a large vein proximal to the antecubital or popliteal fossae for a few hours only [67, 68]. The use of peripheral norepinephrine appeared safe in an intermediate care unit case series of patients with septic shock and was associated with outcomes that were better than expected [69]. The use of early peripheral norepinephrine has been suggested in the guideline of the Canadian Association of Emergency Physicians [70].

Standard of care fluid resuscitation

In Table 2, we make expert statements on how to manage fluid resuscitation in patients with sepsis and hypovolemia by the application of the updated guidelines together with common sense and flexibility based on patient- and setting-specific characteristics. It is likely that there are characteristics that modify the likelihood of benefit vs. harm from fluid in specific patients, some of which are presented in Fig. 1.

Unanswered questions

As highlighted above, only few parts of the initial management of patients with sepsis and hypovolemia are supported by data from high-quality RCTs. Therefore, uncertainty remains for many important parts of the care of these patients. Of the nine specific recommendations regarding fluid therapy in the SSC guideline, seven were based on low or very low quality of evidence [3]. Thus, we lack high-quality data on at least seven important questions: (1) What are the triggers and targets we shall use for fluid resuscitation? (2) Shall we give fluid boluses or slower infusion? (3) Shall we give higher vs. lower fluid volumes? (4) Shall we use saline or buffered crystalloids? (5) Shall we use lactate- or acetate-buffered solutions. (6) Shall we use albumin during resuscitation? (7) Shall we use early peripheral infusion of norepinephrine in patients with sepsis?

Roadmap for future research

The major improvements in the care of these patients have come through investigator-initiated collaborative research [3]. This model of research will likely continue to be the main driver for improvements within this area.

Table 3 Large ongoing trial programs assessing different fluid volume protocols for resuscitation of patients with septic shock

Trial	Protocol	Primary outcome and sample size	Setting	Status
Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) [NCT03434028]	Vasopressor first vs. fluid first in patients with sepsis-induced hypotension	Mortality prior to discharge home within 90 days 2320 patients	Emergency departments and ICUs in the USA	Recruiting as per March 2018
Conservative vs. Liberal Approach to fluid therapy of Septic Shock in Intensive Care (CLASSIC) [17]	Restriction of all IV fluids in ICU vs. standard IV fluid therapy in patients with septic shock	Mortality at 90 days 1554 patients	ICUs in Europe	Funded, protocol approved, first patient expected to be enrolled in September 2018
Australasian Resuscitation in Sepsis Evaluation: FLUIDS or vasopressors in emergency department sepsis (ARISE FLUIDS) trial [47]	Vasopressor first vs. fluid first in patients with septic shock	Mortality at 90 days 3000 patients	Emergency departments and ICUs in Australia and New Zealand	Grant application submitted

Trial groups from around the world have embarked on trial programs to answer several of the questions above. The ongoing large trial programs on different volumes (Table 3), types (PLUS and BASICS trials), and rates of infusion (BASICS trial) are run by collaborative, academic groups from Brazil, Europe, Australasia, and North America. The growing collaboration between the trial groups will facilitate joint analyses of large data sets of patients randomized to different fluid management strategies. These efforts will directly improve the fluid therapy of patients with sepsis and will form new hypotheses to be tested in future trials.

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Compliance with ethical standards

Conflicts of interest
AP is a member of the steering committee and Danish national investigator of the Sepsis Act vasopressin trial in septic shock sponsored by Ferring Pharmaceuticals; his department is reimbursed for his time. The department also receives research funds from Fresenius Kabi (the EAT-ICU nutrition trial) and CSL Behring (the INSTINCT trial on immunoglobulins for NSTI). MCe reports being a consultant in the last 5 years for Edwards Lifesciences, LiDCO, and Cheetah Medical. The other authors report no conflicts of interest.

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CONFERENCE REPORTS AND EXPERT PANEL

Surviving sepsis campaign: research priorities for sepsis and septic shock

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Abstract

Objective: To identify research priorities in the management, epidemiology, outcome and underlying causes of sepsis and septic shock.

Design: A consensus committee of 16 international experts representing the European Society of Intensive Care Medicine and Society of Critical Care Medicine was convened at the annual meetings of both societies. Subgroups had teleconference and electronic-based discussion. The entire committee iteratively developed the entire document and recommendations.

Methods: Each committee member independently gave their top five priorities for sepsis research. A total of 88 suggestions (ESM 1 - supplemental table 1) were grouped into categories by the committee co-chairs, leading to the formation of seven subgroups: infection, fluids and vasoactive agents, adjunctive therapy, administration/epidemiology, scoring/identification, post-intensive care unit, and basic/translational science. Each subgroup had teleconferences to go over each priority followed by formal voting within each subgroup. The entire committee also voted on top priorities across all subgroups except for basic/translational science.

Results: The Surviving Sepsis Research Committee provides 26 priorities for sepsis and septic shock. Of these, the top six clinical priorities were identified and include the following questions: (1) can targeted/personalized/precision medicine approaches determine which therapies will work for which patients at which times?; (2) what are ideal endpoints for volume resuscitation and how should volume resuscitation be titrated?; (3) should rapid diagnostic tests be implemented in clinical practice?; (4) should empiric antibiotic combination therapy be used in sepsis or septic shock?; (5) what are the predictors of sepsis long-term morbidity and mortality?; and (6) what information identifies organ dysfunction?

Conclusions: While the Surviving Sepsis Campaign guidelines give multiple recommendations on the treatment of sepsis, significant knowledge gaps remain, both in bedside issues directly applicable to clinicians, as well as understanding the fundamental mechanisms underlying the development and progression of sepsis. The priorities identified represent a roadmap for research in sepsis and septic shock.

Keywords: Sepsis, Septic shock, Research, Priorities, Surviving Sepsis Campaign

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Introduction

Sepsis is life threatening organ dysfunction caused by a dysregulated host response to infection [1]. Sepsis is a global public health emergency, affecting millions of

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people worldwide, and representing one of the largest causes of death across the world [2].

The Surviving Sepsis Campaign is dedicated to reducing mortality from sepsis. The campaign has released four sets of guidelines over the last 14 years, with the most recent being published in 2016 [3]. The 2016 Surviving Sepsis Guidelines consist of 93 statements on the early management and resuscitation of sepsis and septic shock, of which 32 are strong recommendations (7 based upon high evidence, 21 based upon moderate evidence and 4 based upon low evidence), 39 are weak recommendations (7 based upon moderate evidence, 32 based upon low or very low evidence) and 18 are best practice statements. Following recommendations contained within the Surviving Sepsis guidelines has been associated with improved outcomes [4, 5]. However, gaps in the data frequently exist, leading to insufficient clarity on many elements of sepsis management and precluding recommendations on many topics. Notably, the Surviving Sepsis Campaign guidelines are designed to assist bedside practitioners in the treatment of patients with sepsis and septic shock and therefore are restricted solely to management issues.

In an attempt to determine priorities for research within the field of sepsis, the Surviving Sepsis Campaign created a research committee that was explicitly charged with developing a list of research priorities related to sepsis. The intention was to address all aspects of sepsis. Thus while bedside management of sepsis played a key role, the committee also covered topics that are not part of the guidelines, including fundamental mechanisms underlying the development and progression of sepsis and septic shock. Understanding that possibilities for research within the broad field of sepsis are nearly limitless, the goal of this document is for the Surviving Sepsis Campaign to identify research priorities for improving understanding of and outcomes from sepsis.

Methods

Sponsorship

Funding for the research priorities was provided solely by SCCM and ESICM. No outside funding was received.

Selection and organization of the committee

The presidents of ESICM and SCCM appointed seven members (including one co-chair DDB and CMC, respectively) from each society in 2016 to the committee. In addition, the co-chairs of the Surviving Sepsis Campaign guidelines (LE, AR) were added as ad hoc members to the committee. Committee members were chosen based upon expertise in a wide variety of topics related to sepsis. As such, while many of the members of the research committee were authors on the Surviving Sepsis Campaign guidelines, many were not authors, so as to include expertise in areas not covered within the guidelines. In keeping with a commitment to diversity from both SCCM and ESICM, diversity (broadly defined but including geographic, gender, profession, specialty, socioeconomic) was expressly considered when populating the committee.

Determination of research questions and priorities

Each task force member was asked to submit five research questions on any subject related to sepsis. Respondents were instructed to pick the topics they felt were most important, explicitly not restricting this to any particular area. As such, the questions were not limited to areas of patient management (as covered by the Surviving Sepsis Campaign guidelines [3]) or definitions (as covered in the recent Sepsis 3 definitions [1]). The expectation was this open-ended approach would yield questions spanning the entire potential gamut of research related to sepsis. A total of 88 questions were narrowed to 26 questions (Fig. 1) based upon a voting prioritization process detailed in supplemental methods ESM 2.

The entire committee was subsequently asked to rank their top three research priorities in order from all subgroups except basic/translational science. The reason for excluding the basic/translational subgroup from the ranking of research priorities is the committee did not feel it was possible to directly compare the other six subgroups (which relate to critically ill patients at the bedside currently) to the more mechanistic and fundamental questions asked in basic/translational science (which relate to understanding sepsis better but cannot be used at the bedside currently). Choices were weighted so that each respondent's first choice was worth three points, second choice was worth two points and third choice was

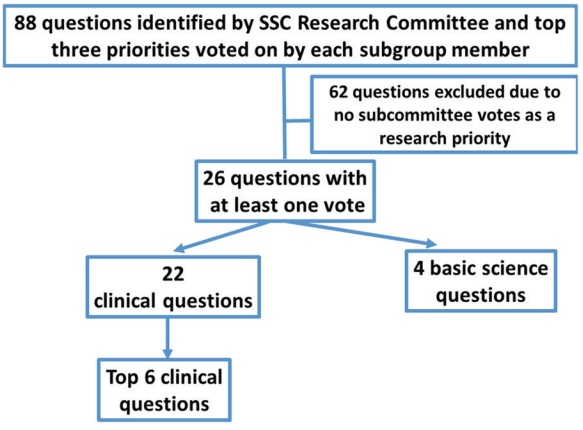

Fig. 1 Flowchart identifying process of narrowing to top research questions

Table 1 Top research priorities

Can targeted/personalized/precision medicine approaches determine which therapies will work for which patients at which times?
What are ideal endpoints for volume resuscitation and how should volume resuscitation be titrated?
Should rapid diagnostic tests be implemented in clinical practice?
Should empiric antibiotic combination therapy be used in sepsis or septic shock?
What are the predictors of sepsis long-term morbidity and mortality?
What information identifies organ dysfunction?

Table 2 Basic science questions

What mechanisms underlie sepsis-induced cellular and sub-cellular dysfunction?
How does sepsis alter bio-energetics and/or metabolism (both enhancement and failure)?
How does sepsis (and/or approaches used to manage sepsis) alter phenotypes and interactions in the host microbiome and do alterations in the microbiome effect outcomes
What mechanisms initiate, sustain and terminate recovery?

worth one point. The initial goal was to generate a top five priority list; however, a three-way tie for the fourth place resulted in the final top six priority list (Fig. 1). Of note, nine different questions received a first choice vote. A total of 13/16 first choice votes are represented in the top six priorities, and no question outside of the top six priorities received more than two votes total (and no question outside of the top six received more than a single first choice vote).

Conflict of interest policy

No industry input into the research priorities was obtained, and no industry representatives were present at any point in the process. No members of the research committee received financial compensation or honoraria of any type for their participation on the committee.

The process relied on personal disclosure in an identical manner to the Surviving Sepsis Campaign guidelines. No attempt was made by the group to seek additional information on self-reported conflict of interest.

Results

Top six research priorities

While each of the 26 research questions below were felt to be important (ESM 3), the committee felt it was appropriate to include a list of the top priorities distinct from basic/translational science. A list of the top six research priorities was therefore generated based upon a vote of the entire committee (Table 1). These priorities are not presented in order of importance, as we did not attempt to discriminate the relative importance of the top six research priorities. Although there was no intent to highlight any specific subgroups in the top priorities, they were nearly evenly distributed from the subgroups including infection (two priorities), fluids and vasoactive agents, adjunctive therapy, scoring/identification, and post-intensive care unit. The only subgroup that was not represented was administration/epidemiology. Since basic/translational science was felt to be distinct enough as to not be comparable, the four questions in this group (Table 2) were not ranked but are felt to be of equal importance in a complementary fashion.

Infections

Should empiric antibiotic combination therapy be used in sepsis or septic shock?

What is known Early institution of adequate antimicrobial therapy is associated with decreased mortality in septic patients [6, 7]. Combination therapy is defined herein as the use of two different classes (usually of different mechanistic classes) of antimicrobial agents for a single pathogen. There are two possible reasons for using combination therapy—(a) to accelerate pathogen clearance rather than to broaden antimicrobial coverage or (b) to assure that one pathogen is sensitive to the antibiotic, in light of significant microbial resistance. The most common therapy combinations include a beta-lactam with an aminoglycoside, fluoroquinolone or macrolide. It is important to note that sensitivity of microbes to these antibiotics varies locally, and this should be taken into account prior to prescribing combination therapy. Combination therapy must be distinguished from broad spectrum antibiotics (i.e. a single gram positive agent, a single gram negative agent, a single anti-fungal agent).

A propensity-matched analysis and a meta-analysis/meta-regression analysis have been performed examining the efficacy of combination therapy when used to accelerate pathogen clearance [8, 9]. These show improved survival in patients with a mortality risk of greater than 25% but also suggest the possibility of increased mortality in patients with lower-risk of death (< 15%). Based upon this, the Surviving Sepsis Campaign guidelines suggest the use of combination therapy for the initial management of septic shock (weak recommendation, low quality of evidence) and suggest against routine combination therapy for sepsis without shock or for bacteremia (weak recommendation, low quality of evidence).

It should be noted, however, that there are significant conflicting data regarding combination therapy in bacteremia, sepsis without shock and septic shock. A randomized, open-label, parallel-group trial of 600 patients with sepsis or septic shock treated with monotherapy or combination therapy did not demonstrate a

change in organ failure or mortality between the two groups [10]. A recent meta-analysis of empirical monotherapy vs combination therapy for adult ICU patients with sepsis showed no difference in mortality or other patient-important outcomes, although the quantity and quality of data was low [11]. Similarly, a meta-analysis of monotherapy versus beta lactam-aminoglycoside combination therapy for sepsis found no difference in mortality but an increase in nephrotoxicity in the combination therapy group [12]. This is consistent with a subsequent study from the Netherlands (which has a low prevalence of antimicrobial resistance) of a short course (median length 2 days) of adjunctive empirical therapy in patients with sepsis and septic shock which found an increased incidence of renal failure but not with improved survival in patients receiving combination therapy [13]. This has led some experts to support using two agents in empiric treatment for septic shock but to de-escalate to monotherapy once susceptibilities become available [14] or to call for more evidence in light of the theoretical benefits of targeted combination therapy but the mix of supporting and non-supporting data and overall insufficient data [15].

Gaps in knowledge/critique of evidence While numerous observational trials have been performed examining combination therapy [16–20], no well-done randomized controlled trial has examined this approach in septic shock patients. Although the most recent Surviving Sepsis guidelines recommend combination therapy for septic shock (and not for sepsis) based upon these available studies for accelerated pathogen clearance [3], the evidence to support this recommendation was assessed as "low quality". The issue of broadening antibiotic coverage was not covered in the Surviving Sepsis guidelines. Guidelines on management of hospital-acquired and ventilator-associated pneumonia suggest combination therapy in some specific settings to assure that the infecting pathogen is sensitive to at least one antibiotic, but the evidence to support this weak recommendation was based upon "low-quality evidence" for ventilator-associated pneumonia and "very low-quality evidence" for hospital-acquired pneumonia [21]. Whether these apply to sepsis for non-pulmonary sources remains to be determined.

Future directions Adequately powered randomized controlled trials should directly test whether combination therapy is beneficial in order to decrease mortality in sepsis and septic shock. These studies should address whether combination therapy is beneficial when used to accelerate pathogen clearance. Separately, studies should be performed to determine whether this approach is beneficial when used to assure that one pathogen is sensitive to a prescribed antibiotic and not when used for synergistic purposes related to pathogen clearance. Since not all combinations would potentially be expected to have equivalent efficacy [22, 23], different antibiotic combinations should be tested to determine if some combinations are more effective than others or more effective than monotherapy. It is critical to note study results may be different based upon local antibiotic resistance patterns and thus must be performed in different settings.

Does optimization of antimicrobial pharmacokinetics and pharmacodynamics impact patient outcomes in sepsis?

What is known Antimicrobial pharmacokinetics (PK) and pharmacodynamics (PD) are important considerations for antibiotic success, which may be particularly relevant in critically ill patients with sepsis and septic shock [24, 25]. The pathophysiologic changes that occur in sepsis can have a major effect on PK by increasing volume of distribution as well as augmenting clearance, resulting in underdosing of antibiotics administered at conventional doses. Further, drug metabolism varies significantly in critically ill patients with sepsis which may result in failure to achieve PD targets for antimicrobials, and hence bacteriological cure. It may also promote emergence of antibiotic resistance.

Gaps in knowledge/critique of evidence Both dosing and timing recommendations for antibiotics are predominantly based on studies performed in the general population which limits their applicability in the clinical setting in patients with sepsis and septic shock where both PK and PD would be expected to be altered [26]. Even though several studies report alterations in PK/PD in patients with septic shock, the impact of this on bacteriological cure and outcome remains to be determined. Alternative approaches to conventional antimicrobial management include the use of extended or continuous administration of some antibiotics and/or higher doses. However, the risk/benefit profiles of these approaches have not been clearly established.

Future directions The factors associated with PK/PD variability to consider in critically ill patients with sepsis and septic shock need to be determined. The impact and cost-effectiveness of incorporating therapeutic drug-monitoring into daily clinical practice to adjust antibiotic dosing in patients with sepsis and septic shock needs to be determined. In addition, studies are necessary to ascertain whether continuous/extended infusion of β-lactams and/or higher doses of antibiotics provide a better bacterial cure and improve outcome. If so, research should determine whether these approaches should be used in all septic patients or only in a subset of selected patients. Ideally, an approach could be utilized in which antibiotic dosing in patients

with sepsis could be determined based on clinical characteristics and source of infection. If this is possible, it leads to the fundamental question about whether it is possible to individualize antibiotic dosing regimens for septic patients.

Should antiviral therapy be administered in the context of viral reactivation in patients with acquired immunosuppression?

What is known The immune response is commonly altered in septic patients [27], and there is growing evidence that critically ill patients may present with a state of acquired immune deficiency (sometimes referred to as immunoparalysis) [28]. Healthy people are frequently asymptomatically infected by viruses that can subsequently persist in a latent state. For instance, cytomegalovirus (CMV) infects approximately 50–80% of otherwise healthy adults, who have lifelong latency in multiple cell types following their initial asymptomatic infection [29]. Several studies have reported reactivation of viruses in critically ill patients that do not have a prior history of being immunocompromised, and this is associated with worse outcomes in critical illness [30, 31]. Notably, in a study of 560 critically ill septic patients, 161 critically-ill non-septic patients and 164 age-matched healthy controls, cumulative viral DNA detection rates in the blood included CMV (24%), Epstein–Barr (53%), herpes simplex (14%), human herpes virus-6 (10%) and TTV (78%) despite these being uncommon in both critically-ill non-septic patients and healthy controls [32]. Notably, 42.7% of septic patients had two or more viruses. These are consistent with studies specifically looking at CMV in the ICU which demonstrate active rates of 17% in non-immunosuppressed patients, mostly occurring between 4 and 12 days after ICU admission [33, 34].

A recent trial of 160 CMV-positive patients with sepsis or trauma randomized participants to receive ganciclovir or placebo. Despite lower levels of CMV reactivation in the treatment group, no difference was noted in the primary outcome (IL-6 levels) although ventilator free days were higher in the treatment group [35]. In contrast, a single center trial of 124 CMV-seropositive patients undergoing mechanical ventilation randomized patients to receive anti-CMV prophylaxis with valacyclovir or low-dose valganciclovir. While valacyclovir decreased viral reactivation in the blood (12 patients vs. 2 patients), this finding was associated with an increase in 28-day mortality in patients receiving valacyclovir (41.2% in treatment arm vs. 13.5% mortality in control arm) [36].

Gaps in knowledge/critique of evidence Viral reactivation has been shown to be associated with a worse outcome but it is unclear whether the increased risk of death is related to the underlying condition or whether the viral reactivation itself contributes to the increased risk of death. The role—if any—of either prophylaxis or treatment of CMV reactivation is not clear, being limited to small studies. Further, the role of prophylaxis or treatment of viral infections outside of CMV is understood even less.

Future directions Randomized controlled trials should be performed to delineate the role (if any) of prophylaxis against viral reactivation. Similar trials should be performed to determine if treatment, once viral reactivation occurs, confers any benefit in altering mortality and/or other patient-centric outcomes. If either strategy is beneficial, it needs to be clarified whether prophylaxis or treatment is beneficial in all septic patients or only in a subset. Further, studies need to delineate whether specific viruses (CMV, EBV, HSV, HHV-6, TTV) carry therapeutic or prognostic significance. These studies should answer the question whether viral reactivation plays a role in mediating poor outcomes or is simply a marker of worse outcomes.

Should rapid diagnostic tests be implemented in clinical practice?

What is known Sepsis is a time-sensitive condition, with delays in either diagnosis or therapy leading to increased mortality. Faster diagnosis of sepsis could potentially reduce mortality, shorten length of stay, and lower hospital costs [37, 38]. However, diagnosis of sepsis relies upon a clinician suspecting infection without the actual ability to diagnose infection in real time. A significant number of patients with sepsis never have positive cultures. In addition, even in patients whose cultures will ultimately be positive, there is a time lag of hours to days between when the sample is sent to when the positive result is obtained. Further, outside of the potential utility of biomarkers such as procalcitonin, there is little available to the clinician to determine if the infection has resolved. The inability to rapidly diagnose infection and/or to determine when the infection has cleared can lead to widespread usage of broad spectrum antibiotics [39]. Notably, despite advances in the technology available to treat septic patients, culturing techniques used for identifying infection have not changed substantially over a number of decades. Numerous rapid diagnostic tests have been tested in patients for the identification of infection. Further, numerous biomarkers have been tested for the identification or prognostication of sepsis (covered elsewhere in this manuscript).

Gaps in knowledge/critique of evidence Identification of the causative organism has traditionally involved phenotypic analysis of organisms isolated from positive cultures. However, this process can take days, during which time patients may be treated with broad-spectrum

antibiotics until positive pathogen identification becomes available (which may never happen considering that many septic patients are culture negative). In addition, it is sometimes difficult to obtain samples. For instance, sputum is not always available in septic patients with pneumonia who are not intubated, and peritoneal fluid is not always accessible in septic patients with peritonitis. Faster and more accurate pathogen identification is therefore critical [40, 41]. When a culture is flagged as positive a gram stain is performed that can potentially provide information about the type of organism responsible for the infection; however, this does not provide an acceptable level of accuracy to guide therapy. Instead, tailored therapeutic intervention relies on identification of species, which can take days using conventional techniques, and the antibiotic resistance profile will typically be available only 1–2 days after that. Further, detection of fungi, viruses, and anaerobic bacteria can be more challenging than detecting aerobic bacteria, both in terms of timing and sensitivity. Several methods to detect the implicated pathogen (bacterial DNA detection, syndromic PCR) and detection of resistant organisms and/or rapid antibiogram have recently developed [42–45]. Unfortunately, none of these techniques has been widely adopted due to a combination of factors including (but not limited to) cost, logistics and accuracy concerns.

Future directions Future research should evaluate whether existing rapid diagnostic tests facilitate diagnosis and should be implemented in clinical practice. If so, studies need to determine which techniques and/or methods are superior or if further optimization is required, which may require both technological advances and examination of test accuracy across a variety of resource settings. Importantly, the role of rapid diagnostic tests in antibiotic stewardship (when to start, how broad, when to de-escalate, when to stop) needs to be examined. Further, although it is logical to believe that rapid diagnostic tests could potentially change patient outcomes, this assumption should be formally tested. Finally, assessing the immune system and performing rapid diagnostic tests might potentially help identify both the infecting organism and the dysregulated host response simultaneously, and an integrative approach examining both microbe and host may yield critical insights that assaying each in isolation might miss.

Fluids and vasopressors

What are ideal endpoints for volume resuscitation and how should volume resuscitation be titrated?

What is known The administration of intravenous fluids to improve circulation, perfusion, and oxygen delivery is a fundamental principle in sepsis management [46]. However, the potential benefits of administering fluid must be balanced against the potential for harm due to the accumulation of fluid, such as, pulmonary edema, abdominal compartment syndrome, and tissue edema. Current recommendations from the Surviving Sepsis Campaign suggest resuscitating patients with sepsis-induced hypoperfusion with at least 30 ml/kg of IV crystalloid within the first 3 h [3]. The Surviving Sepsis bundles have been associated with improved survival in numerous large-scale studies [4, 6, 47], although the specific importance of each individual component of the bundle is unclear. It should be noted that while more rapid completion of the 3 h bundle and rapid administration of antibiotics was associated with improved outcome in a study of nearly 50,000 patients, a longer time to completion of initial fluid bolus was not associated with a change in mortality [6]. Further, the amount of fluid administered was not associated with survival differences in observational and randomized studies of early goal directed therapy [48]. Also, an early resuscitation protocol including intravenous fluids, vasopressors, blood transfusion and invasive monitoring was associated with increased mortality compared to usual care in patients with sepsis (mostly HIV) and hypotension in a developing country [49].

The fundamental reasoning for administering fluid is to improve tissue perfusion by increasing cardiac output [50]. Traditional approaches to titrating fluid administration have been based on static measures of preload [51]. Dynamic indices of preload may better predict the response to fluids but still remain underused [52]. However, there are instances where a patient will not improve despite the administration of fluids. Identifying robust clinical parameters that distinguish patients likely to positively respond to a fluid bolus from those unlikely to respond is an essential need in sepsis care. One important caveat to mention is that while there is inherent value in determining which patients will respond to fluid boluses, it is unclear whether this will result in improved outcomes.

Gaps in knowledge/critique of evidence Current approaches to determine fluid responsiveness include the application of empiric fluid boluses, static measurements, and dynamic markers. The empiric administration of a fluid bolus to determine fluid responsiveness is inherently troublesome since a substantial number of patients will not respond, potentiating harm. The worst case scenario is when this empiric administration is done without any measurement of effectiveness and tolerance which can often lead to repeat administration when the problem triggering fluid administration persists.

Static measures involve the placement of venous catheters to facilitate the measurement of central venous pressure (CVP) and pulmonary capillary occluded pressure (PAOP) and evaluate baseline and incremental changes

in pressure following fluid administration. However, fluid responsiveness on the basis of CVP has not consistently demonstrated validity as a measure of fluid responsiveness [53]. Dynamic measures include a variety of techniques to assess the change in cardiac output in response to transient changes in preload induced by ventilation or an external maneuver, prior to fluid administration. Common types of dynamic measures used in clinical practice include passive leg raise (PLR) maneuver, respiratory variation, pulse pressure variation (PPV), and stroke volume variation (SVV) [54]. However, variations in respiratory patterns or pulse pressure and stroke volume can be difficult to interpret in spontaneously breathing patients. PLR is most useful when a rapid-response cardiac output monitoring is available [55], but still requires rigorous investigation and testing.

Importantly, the determination of triggers to administer fluids after initial resuscitation as well as triggers to stop fluid resuscitation remain poorly understood. While there is a significant literature evaluating many of these methods in the peri-operative setting and in non-selected critical care patients, there is a paucity of literature comparing the various methods for assessing fluid responsiveness in patients with sepsis/septic shock. In these patients the validity of these tests may be impaired due to the impact of vasoplegia, use of low tidal volume ventilation and presence of respiratory movements or increased abdominal pressure. Furthermore, application and translation of these findings across all types of clinical settings is necessary. This includes developed countries in settings where minimal monitoring devices can be implemented (i.e. hospital wards) as well as low- and middle-income countries which account for a majority of all cases of sepsis worldwide. Clinical utility of tests for fluid responsiveness need to be reproducible and applicable in resource-limited settings.

Future directions While great progress has been made in the clinical investigation of fluid resuscitation, pressing uncertainties remain leading to the following core questions: (a) do ideal clinical parameters and endpoints for volume resuscitation exist; (b) how should volume resuscitation be titrated; (c) what is the optimal dose of initial volume bolus administration; and (d) how should the approach for volume resuscitation be modified in resource-limited settings?

In the course of routine clinical care, physiological parameters are explicitly framed to direct the administration of any therapy (e.g. anti-hypertensives for the treatment of hypertension). In contrast, ideal physiological parameters to outline therapeutic endpoints for fluid resuscitation, titration, and amount of volume are largely unknown and remain ambiguous. Traditional approaches of 30 ml/kg of initial volume bolus were founded over a decade ago, and dictate a "one size fits all" strategy of initial fluid administration [56]. While there is benefit to a standardized approach to initial fluid resuscitation (especially for clinicians relatively inexperienced in the management of septic patients), the ideal approach would be personalized pending on individual patient need.

Subsequent fluid administration is even more complicated and is often driven by various approaches The need to identify the optimal measures of fluid responsiveness directly influences the clinician's ability to determine if further volume administration may be beneficial and if the patient is likely to positively respond to fluids, and how therapy should be titrated (which amount/speed of infusion/stopping rules). Randomized, controlled trials are needed to determine if greater precision is possible to determine how much fluid can be administered as a single dose for a given patient. Additionally, these questions and approaches should be tested to identify the optimal approach in resource-limited settings. Finally, studies evaluating clinical endpoints for resuscitation should be tested in a pragmatic design to promote diffusion of findings and rapid uptake into clinical practice, particularly in resource-limited settings.

What is the optimal fluid for sepsis resuscitation?

What is known Broadly stated, large randomized, controlled, multicenter trials have found no significant difference between albumin and crystalloids. The Saline versus Albumin Fluid Evaluation (SAFE) study found no difference in 28-day mortality for patients randomized to 0.9% normal saline or 4% albumin, although there was a trend towards improved outcomes in the study for patients with sepsis in a post hoc subgroup analysis [57]. Mortality was also not different between patients receiving 20% albumin or crystalloid in a large randomized trial in patients with sepsis or septic shock (ALBIOS trial) [58]. However, while the overall study did not show a difference in outcome, subgroup analysis showed improved mortality in patients with septic shock. Multiple meta-analyses have been performed comparing albumin to crystalloid, although different populations have made combining the data challenging [59]. Together, these have led to a weak recommendation (based upon low quality evidence) in the Surviving Sepsis Campaign for using albumin in addition to crystalloids for both initial resuscitation and subsequent intravascular volume replacement in patients with both sepsis and septic shock who require substantial amounts of crystalloid [3]. Within the context of the broader categories of crystalloids and colloids, there exist distinctions between individual fluid choices [60, 61]. Hydroxyethyl starch should not be used on the basis of the increased risk for acute kidney injury

and need for renal replacement therapy, in addition to increased mortality in many meta-analyses [62–65].

There is developing interest in administering crystalloids with a balanced ion content to reduce the chloride load observed with 0.9% normal saline [66]. Crystalloid solutions, such as, Ringer's lactate and PlasmaLyte, have been studied with varying results [67]. Lactate-based chloride-free solutions have been developed and can improve cardiac output and blood pressure while achieving a negative fluid balance [68]. While numerous smaller studies have demonstrated benefit in balanced crystalloids, a randomized controlled comparing 0.9% normal saline to PlasmaLyte did not reduce the risk of acute kidney injury [69]. However, while this study is widely quoted, the majority of the patients were admitted following elective surgery, had relatively few co-morbidities, received a relatively small amount of fluid, were not septic, and the overall mortality was low. As such, the relevance of this study to septic patients is unclear. Recently, two large randomized controlled trials compared balanced crystalloids to 0.9% normal saline in 15,802 critically ill patients from 5 ICUs and 13,347 non-critically ill emergency department patients who were subsequently hospitalized outside of the ICU [70, 71]. In critically ill patients, balanced crystalloids resulted in a statistically significant 1.1% decrease in the composite outcome of death from any cause, new renal-replacement therapy or persistent renal dysfunction. While balanced crystalloids did not change the primary outcome of hospital free days in non-critically ill patients, they were associated with a statistically significant 0.9% decrease in the composite outcomes of major adverse kidney events seen in critically ill patients. Although a subgroup analysis showed a larger decrease (5.1%) in composite outcome in septic patients given balanced crystalloids, it is important to note that patients with sepsis or septic shock represented less than 15% of the ICU patients in this study [70]. Further, the percent of septic patients was not reported in the study on non-critically ill patients [71]. As such the applicability of these results to septic patients (who often require a greater amount of fluids, and suffer from a higher incidence of kidney dysfunction and have a higher risk of death) remains to be determined.

Gaps in knowledge/critique of evidence Existing trials have not sufficiently evaluated fluid administration in the full continuum of acute sepsis, including initial fluid resuscitation, subgroups of patients, and adequately controlling for bias. While the detrimental effects of small amounts of any given fluid are often negligible, significant adverse effects may arise when large amounts are administered. Many of the trials that have been conducted have administered very limited amount of fluids so that these concluded that no difference was detected. Furthermore, as the burden of sepsis is better recognized, evaluating fluid types that are widely available around the world is necessary.

Future directions The choice of fluid in early sepsis resuscitation is still largely unknown and needs to be delineated. Further, the choice of fluid once initial resuscitation has been completed is equally unclear. Despite numerous studies, the role of colloids is still unclear including when to use, how much to use, and type to use. Finally, trials distinguishing between balanced crystalloids and normal saline are necessary but these should mimic the behavior of clinicians and take into account chloride measurements and potentially stopping once hyperchloremia develops. Given the heterogeneity of sepsis etiology, subgroups of sepsis need to be further evaluated to determine if there are specific groups in which type of fluid impacts outcomes. Finally, fluid choice in resource-limited areas has not been fully described, and pragmatically designed trials are required to investigate optimal fluids in these settings.

What is the optimal approach to selection, dose titration, and escalation of vasopressor therapy?

What is known Norepinephrine has been demonstrated to be a superior vasopressor option when compared to dopamine in a broad group of patients with shock [72]. Epinephrine is also a suitable substitute as a vasopressor when inotropy is also required (similar to a combination of a norepinephrine and dobutamine). As a non-catecholamine vasopressor, vasopressin has been demonstrated to be safe as an adjunct agent to norepinephrine and to potentially improve outcome in a subgroup of patients with less severe septic shock [73]. Of note, vasopressin as a primary agent has been compared to norepinephrine, yielding no difference with regards to acute kidney injury and failing to confirm the beneficial effects in patients with less severe shock [74]. More recently, angiotensin II has demonstrated efficacy in raising mean arterial pressure (MAP) but outcome data are still lacking [75]. In contrast, non-selective inhibition of nitric oxide synthase has been shown to increase mortality [76], highlighting that evaluation of vasopressors should not be based solely on its hemodynamic effects. Finally, a higher MAP target has not been shown to be beneficial in patients in septic shock, although in a subgroup of patients with severe baseline hypertension, targeting a higher MAP is associated with less need for renal replacement therapy [77].

Gaps in knowledge/critique of evidence Studies designed over the past two decades of septic shock research have varied in design and in endpoints, making it difficult to consistently evaluate different vasopressor agents. Studies have used varying doses of vasopressor agents, resuscitation strategies, clinical endpoints, and therapeutic

escalation strategies. Trials evaluating the effects of epinephrine were markedly underpowered. Admittedly, none of these showed beneficial effects of epinephrine, but it remains to be determined whether some subgroups of patients may benefit from epinephrine usage. A common framework for how vasopressors should be studied is lacking. Trials evaluating higher versus lower MAP were always above target in the low target groups (65 mmHg). Hence, the current recommendations supporting using pressors to maintain MAP at 65 mmHg are only supported by observational data.

Future directions Essential questions remain regarding vasopressor selection, escalation of therapy, sequencing of vasopressor agents, combination regimens, and dose titration. Using the broader categories of fluid choices (crystalloids and colloids) as an analogy, a therapeutic approach comparing a catecholamine (e.g. norepinephrine) to a non-catecholamine (e.g. vasopressin, angiotensin II) to raise MAP and improve survival is necessary. Similarly, the role of epinephrine as a second line agent needs to be evaluated. Further, while angiotensin II has recently been shown to effectively increase blood pressure in patients with vasodilatory shock that do not respond to high doses of conventional pressors, the indications for this new agent remain to be determined as do its effect on outcomes. Defining an acceptable dose range of vasopressors for which to escalate therapy vs. initiate a second agent is also necessary. To accomplish this effectively requires rigorous investigation into how vasopressors are dosed and titrated. Finally, subgroups of patients should be evaluated (heart failure, essential hypertension), given the predilection of some patients to suffer adverse events of hypotension as well as those resulting from vasopressor therapy (arrhythmias or acute kidney injury).

Adjunctive therapy

Can targeted/personalized/precision medicine approaches determine which therapies will work for which patients at which times?

What is known In light of the individual variability of septic patients, traditional clinical trial results currently have an inability to predict the response to an intervention at the level of an individual. Similarly, clinical practice guidelines are based upon a composite of overall best practice for the greatest number of patients. This does not account for individual differences as an intervention in a trial that showed overall benefit could potentially be of no benefit or harm to an individual participating, whereas an intervention in a trial that showed no benefit could potentially be beneficial to a subgroup of participating patients. The pathophysiology of sepsis is a complex and dynamic process that originates from the host response to infection and varies according to (at a minimum) the genetic predisposition, immune status, age and comorbid conditions of the host, the type of pathogen and the site and extent of infection. Recent advance in omics (genomics, epigenomics, transcriptomics, proteomics, metabolomics, pharmacogenomics, microbiomics) have the potential to revolutionize care by assaying the state of an individual [78, 79]. Individual insights need not be confined to "omics"-based data, however, as important insights can be drawn from easily interpretable clinical information and by use of big data approaches that allow insight from information accessible within the ICU that might not be able to be processed by a bedside provider [80].

Gaps in knowledge/critique of evidence At present, precision medicine for sepsis remains a vision in the distance [81, 82]. There are considerable amounts of data characterizing sepsis patients according to a single biomarker, but there are limited data that broadly phenotype sepsis patients and no application of these data to influence patient care [83]. An example of an early attempt was the MONARCS trial, where sepsis patients with IL-6 levels > 1000 pg/mL were targeted for treatment with an anti-TNF monoclonal antibody [84]. Similarly, attempts at targeting corticosteroid therapy have not been successfully reproduced, yet corticosteroids are used frequently in patients with septic shock [85, 86]. Precision medicine may also rely on clinical signs. As an example, an ideal trial on inotropic agent for treating the consequences of sepsis-associated myocardial depression should include patients with signs of tissue hypoperfusion associated with a low or inadequate cardiac output related to an impairment in contractility. This is a different approach from a recent trial design that included patients in shock with minimal (if any) assessment of cardiac output and cardiac function [87].

Future directions The first step toward precision medicine in sepsis is characterizing the clinical and biological heterogeneity within the syndrome. As one example, the immune response in septic patients ranges from an exuberant pro-inflammatory cascade to a profoundly immunosuppressed phenotype, yet there is currently an inability to accurately phenotype patients at the bedside to know where an individual patient lies on the immune response spectrum. An approach that has potential immediate clinical applicability is targeting precision use of corticosteroids, to determine the right patient, the right time and the right dose, as well as monitoring for the right response to therapy.

On a longer horizon, the development of novel methods to rapidly immunophenotype patients could enable the targeted application of therapies and

monitoring of treatment response. Further, the use of both omics and big data to understand the individual response, combined potentially with the use of in silico modeling, has the potential to revolutionize the management of sepsis.

Determine the efficacy of "blood purification" therapies such as endotoxin absorbers, cytokine absorbers and plasmapheresis

What is known A number of studies address this diverse area, whose common endpoint is the elimination of bloodstream substances that are felt to be harmful. Most of the studies are relatively small, often have methodologic issues and often concentrate on the elimination of mediators as the outcome of interest rather than a clinical outcome such as mortality. A 2013 meta-analysis of 16 trials concluded that blood purification decreased mortality in sepsis compared to no blood purification. However, these results were driven mainly by hemoperfusion and plasma exchange, and pooling of all trials of blood purification for treatment of sepsis was no longer associated with lower mortality after excluding trials using polymyxin B hemoperfusion [88]. There is also a negative study pending publication using polymyxin B hemoperfusion presented at ESICM LIVES 2016 [89]. Observational data (registries) support the use of cytokine hemoadsorption but there are no randomized data at this stage.

Gaps in knowledge/critique of evidence A major issue is the heterogeneity of the techniques, as results obtained with one technique may not apply to the other techniques. The most commonly used techniques are cytokine hemoadsorption and polymyxin-b hemoperfusion, with polymyxin-b hemoperfusion being widely used in Asian countries and cytokine hemoadsorption being common in Germany. However, there are numerous knowledge gaps including characterizing what can be expected from these techniques (short term hemodynamic vs modulation of host response), characterization of the potential adverse effects (optimization of anticoagulation, pharmacokinetics of antibiotics), characterization of all molecules removed, and defining which patients (if any) may potentially benefit from these techniques and at which time during the evolution of their sepsis.

Future directions There is a clear necessity for large, well designed, definitive studies in patients with sepsis and/or septic shock, especially since blood purification strategies are currently being used in highly selective places around the world. There is concern that a large scale trial including unselected patients would more than likely be negative, exposing patients to potential side effects of extracorporeal techniques without expected benefits. The challenge to design trials include finding the correct patient population as well as incorporating the potential financial consequences, as these systems are costly.

What is the ideal method of delivering nutrition support, including route, timing and composition of nutrition support, and whether this varies by hemodynamic status?

What is known Variable results have been reported from various studies with various methodologies [90–94]. Despite nutrition support being available for many years, there is limited conclusive evidence favoring any aspect of its use. Prior studies have failed to demonstrate the efficacy of early parenteral nutrition in critically ill patients, and the most recent studies suggest early feeding, whether enteral or parenteral, may be equivalent [95]. Comparing early full enteral nutrition with limited caloric intake ("trophic feeds") one large study found only small differences in gastrointestinal intolerance without evidence of harm or benefit, whereas a smaller, more recent retrospective study on patients in septic shock suggested that trophic feeds may reduce the duration of mechanical ventilation and length of stay in the ICU [93, 96]. There are similar controversies and inconsistencies in the literature regarding micronutrient supplementation, immunonutrition, assessing feeding tolerance, feeding patients in the presence of shock, and goals of nutrition support in sepsis [97, 98].

Gaps in knowledge/critique of evidence Questions regarding timing (including when to initiate and when to stop), composition, dose and route of nutritional support therapy in sepsis are incompletely understood, as most studies have been carried out in a general critical care cohort, and not specifically in patients with sepsis/septic shock. Moreover, many of the studies have high risk of bias and are underpowered. Further, several basic aspects of enteral nutrition support remain uncertain. It is unclear if the proper goal of providing enteral nutrition is to reach a certain caloric goal or if there a superior target. There is also significant controversy about whether feeding tolerance should be measured using gastric residual volume or other indicators and whether this is impacted by type of patient (surgical vs. non-surgical). There is also a lack of clarity regarding whether nutrition formulas need to be altered in sepsis, such as with micronutrient supplementation or immunonutrition formulas. For patients with septic shock, it remains to be determined at what dose of vasopressors enteral nutrition can be provided (and if type of vasopressor impacts this), if there is a maximum tolerated dose during shock, and if there is a benefit to trophic enteral feeding (with or without parenteral nutrition) while on pressors. Finally, it is unclear how chronic comorbidities (chronic kidney

disease, diabetes mellitus, chronic respiratory failure, obesity, etc.) alter nutrition needs in sepsis.

Future directions Research should focus individually on each variable as best as practicable. A first step may be to start with timing of nutrition. Later studies can examine both dose and composition (including immunonutrition). Studies should be performed in patients with sepsis and septic shock to determine the role of hemodynamic status on each factor.

What is the role of lung protective ventilation in septic patients without ARDS?

What is known Lung protective ventilation (LPV) has been proven effective for reducing mortality and reducing the duration of mechanical ventilation in patients with ARDS [99] although aggressive recruitment maneuvers and PEEP titration have been associated with increased mortality in ARDS [100]. Observational studies suggest reductions in the development of ARDS with LPV use in patients *at risk for* ARDS but who had not yet developed the syndrome [101]. Two meta-analyses suggest that use of LPV in patients without ARDS reduces the duration of mechanical ventilation, the risk of pulmonary infection and the duration of hospitalization [102, 103]. Given the frequency of respiratory failure in sepsis, with consequent high risk for developing ARDS and its attendant complications of prolonged mechanical ventilation and mortality, optimizing the approach to mechanical ventilation could save thousands of lives and reduce healthcare costs through reductions in mechanical ventilation and ICU stay.

Gaps in knowledge/critique of evidence Current evidence is observational and is not limited to septic patients. Controlled trials in related fields such as perioperative respiratory management demonstrate benefits for the use of LPV in patients without ARDS [104]; however, their applicability to septic patients is, as yet, undetermined. The PReVENT study is currently ongoing to examine the role of LPV in critically ill adult patients for improving the number of ventilator-free days [105].

Future directions Conducting a definitive clinical trial in patients with sepsis (the most common cause of ARDS) is of significant importance.

Scoring/identification

What information identifies organ dysfunction?

What is known Clinical criteria for sepsis in the Sepsis 3 definition are based on a model where the outcome variables are either mortality or a composite of mortality and increased length of ICU stay [1, 106, 107]. The Sequential [Sepsis-related] Organ Failure Assessment (SOFA) and quick SOFA (qSOFA) are scoring systems that use clinical data as surrogates for organ dysfunction [108]. These clinical constructs are based on objective measurements that are easily obtained and are linked to outcomes that can be the result of clinical decision making (i.e., the decision to discharge from the ICU or to withdraw life-sustaining therapies). Relatively little is known, however, about the pathobiology of dysfunction in individual organ systems that is associated with these outcomes. Clinical identification is based largely on surrogates (e.g., serum creatinine, serum bilirubin, blood pressure, PaO_2/FiO_2 ratio, Glasgow coma scale, platelet count, respiratory rate). In contrast, a diagnosis such as myocardial infarction correlates serum markers (troponins, creatinine kinase subgroups) to functional studies (wall shortening on echocardiography, changes in electrocardiogram pattern) and anatomy (angiography, histology).

Gaps in knowledge/critique of the evidence Organ dysfunction cannot currently be identified with the degree of precision needed to create a diagnostic gold standard for sepsis similar to that which exists for other diseases. Absent such a standard, clinical criteria must be used to construct predictive models for sepsis. In the current state, these criteria are limited in their ability to differentiate a septic patient from a patient with other disorders. In addition, current predictive models are based on outcomes (mortality, length of stay) that themselves may be biased by subjective clinical decisions.

Future directions Studies that address the lack of gold standards for sepsis-associated organ dysfunction are needed. This will likely require translation of animal models of organ dysfunction or human markers with specific indicators of organ function. Some possible examples include myocardial wall motion on imaging, renal tubular ion pump function, hepatic synthetic pathways, real-time assessment of host immune status, histopathology, and omics-based expression patterns. The short-term translational goal will be to correlate functional findings with existing clinical markers. Ideally multiple independent assessments of organ function would be used to try to provide a comprehensive assessment of whole organ function. Gold standards for each organ would correlate with available clinical findings (laboratory, imaging, functional assessment) which would then be correlated with clinical outcomes. Clinical criteria for sepsis definitions could then be adapted to provide more precise identification of organ dysfunction. Long-term, markers of organ dysfunction that either do not exist currently or exist only in the research domain would ideally make the diagnosis of organ dysfunction more mechanistic and precise. Finally, although it is reasonable to assume that prevention or early treatment of organ dysfunction improves outcome in sepsis, clinical studies should test this supposition.

How can we screen for sepsis in varied settings?

What is known Sepsis is managed in a variety of settings, including high, low and middle-income countries, differently-equipped facilities and in and out of hospital, including pre-hospital transport. Absent a diagnostic gold standard, screening tools must either predict important outcomes or correlate with the development of a recognizable entity, as a generally agreed clinical picture of sepsis. The need to avoid missing at-risk patients is an important consideration, especially in environments where a missed opportunity to intervene may have a strong effect on outcomes. Over-triage of patients who may not have sepsis or progress to develop sepsis risks wasting resources and exposing patients to the risks of unnecessary interventional therapies. At the same time, under-triage of patients runs the risk of late identification, which is associated with increased risk of death. Both of these issues are likely exacerbated in resource-limited environments. The purpose of a good screening tool is to identify populations at risk and compel further assessment and treatment while ideally excluding those not at risk.

Gaps in knowledge/critique of the evidence Although the clinical criteria in Sepsis 3 were developed using large derivation and validation cohorts, all of the data in the primary publication are from high-income countries [106, 107]. Subsequent studies appear to validate the criteria in both low-middle and developing countries [109–111], although this is relatively limited in scope. There are also two large prospective evaluations of the predictive model in the literature from the United States and Australia [112, 113]. In addition, goals for a screening tool may vary by setting, as high-resource environments might potentially trade under-triage for better accuracy, whereas low-resource environments might benefit from initial over-triage, so as not to miss high-risk cases. Finally, the purpose of the screen—to compel further assessment and treatment—has not been adequately studied.

Future directions Existing models for sepsis screening should be refined. Further, there should not be an assumption that all environments are the same and that a "one size fits all" screening tool will work the same, independent of location. As such, the efficacy of screening tools should be tested in different environments. Ideally, this would take the form of prospective studies linked to clinically meaningful outcomes, although numerous study designs could potentially yield important information. These studies should look at triggered clinical actions which could be diagnostic or therapeutic, and whose correlation to a variety of clinically important outcomes would be determined. Research should characterize construct or predictive validity of any screening tool including sensitivity, specificity, positive predictive value and negative predictive value. Studies should consider a variety of clinically important outcomes.

How do we identify septic shock?

What is known Septic shock occurs in the setting of a physiologic state of hypoperfusion. Sepsis 3 defines septic shock as "a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality [1]." Based upon a large database analysis and a Delphi process, the Sepsis 3 taskforce identified clinical criteria for septic shock as (a) hypotension, (b) requiring vasopressors and (c) a lactate >2 [107]. While lactate typically correlates with perfusion abnormalities, it may also be associated with abnormal metabolism. Further, while Sepsis 3 (and previously Sepsis 1 and 2) includes definitions without recommendations for management, the Surviving Sepsis Campaign Guidelines give differential antibiotic recommendations for sepsis as compared to septic shock, often based on very low certainty of evidence [3].

Gaps in knowledge/critique of evidence Consensus as to what defines shock is lacking. Although many clinicians characterize shock by perfusion indices, this does not provide a clear definition based on mechanisms. Further, the clinical criteria in Sepsis 3, while based upon large database analysis, were not unanimously agreed upon by the taskforce. Although there was a clearly articulated rationale for why the clinical criteria for septic shock required hypotension, vasopressors and an elevated lactate (significantly higher mortality than any of these in isolation), many in the community continue to believe that shock should be defined as hypotension/vasopressors OR elevated lactate, rather than AND. In addition, many locations throughout the world cannot measure lactate, which leads to the question of how one identifies septic shock at the bedside if a clinician cannot measure lactate. Further, there is limited evidence comparing the metabolic and circulatory abnormalities between sepsis and septic shock, and it remains unsettled whether septic shock is truly a unique entity or simply a manifestation of a greater severity of sepsis.

Future directions Research should address the fundamental question of whether septic shock is a disorder that is distinct from sepsis. If it is, efforts should address proxies for septic shock that have predictive validity for important outcomes or construct validity for a helpful clinical entity. These proxies could be correlated to clinical presentation in an effort to identify a unique group of high risk patients. Models could be created from large databases and then prospectively validated in larger groups of patients. The impacts for diagnosis, treatment and outcomes should be prospectively assessed.

Importantly, investigation should address the question of whether septic shock needs to be treated differently than sepsis outside of the institution of vasopressors. Investigation should not rely on an outcome (mortality) that is both the independent variable (used when creating the definitions to differentiate the two entities) and the dependent variable (the most common outcome used in clinical intervention studies). Finally, the clinical criteria for septic shock in Sepsis 3 should be prospectively validated.

What in-hospital clinical information is associated with important outcomes in septic patients?

What is known Clinical criteria used to identify sepsis in patients with suspected infection are derived from the association between mortality, length of ICU stay, and a discharge diagnosis of sepsis. The construct validity is based on limited, but clinically available, criteria (SOFA or qSOFA score ≥ 2, suspected infection) and validated to a few outcomes. At the bedside, clinicians draw on a larger collection of data to make diagnostic and therapeutic decisions. Ultimately, practitioners make clinical decisions, such as limiting life-sustaining therapies and deciding to transfer patients into or out from an ICU, based on an impression of prognosis.

Gaps in knowledge/critique of evidence The new Sepsis 3 definition has substantially improved construct validity for the concept of sepsis [114]. SOFA is an older tool that predicts mortality in patient populations, although some elements of the SOFA score are outdated (such as "renal dose" dopamine). In addition, qSOFA has fairly robust validity in predicting mortality and prolonged stay in patients prior to ICU admission (although its accuracy is lower in the ICU) [112, 115–117]. However, both mortality and increased length of ICU stay are themselves influenced by clinical decision making. Many important clinical outcomes, such as cognitive dysfunction and lasting organ dysfunctions, have not been studied. It is also unclear if the variables or specific elements in SOFA need updating. The pathobiology of many (if not most) adverse outcomes in the ICU is not described.

Future directions Research is needed both in improving which clinical information is utilized and in assessing patient-centric outcomes beyond mortality and length of ICU stay (understanding that these continue to be critically important outcomes). This is far reaching as it requires enhanced understanding of what is most important out of a massive amount of data readily available to the ICU team (essentially everything in the electronic medical record), data that exist but might not be readily available (heart rate variability as an example) and data that are currently not available (a moment by moment assessment of a patient's immune status). Further, it requires a conversation between clinicians and patients/families as to what outcomes are most important. Answering the two components of this research question will therefore require studies ranging from (but not limited to) (a) animal modeling, (b) new study designs, (c) big data approaches, (d) creation of new technologies, and (e) survey and face-to-face meetings to understand what outcomes are most valued. Measures should be assessed individually and as multiple, interactive variables, to establish relationships between different organ dysfunctions.

Administration/epidemiology

Which is the optimal model of delivering sepsis care?

What is known The way in which ICUs and their larger hospitals and healthcare systems are organized and managed affects quality and efficiency in sepsis care. Further, both early recognition and early intervention in sepsis saves lives. Performance improvement efforts for sepsis are associated with improved patient outcomes. An example of this is the Surviving Sepsis Campaign bundles, in which rapid antibiotic administration and fluid resuscitation are associated with lower mortality [4, 118–121]. Sepsis performance improvement programs should optimally have multiprofessional representation (physicians, nurses, advanced practice providers, pharmacists, respiratory therapists, nutrition support specialists, administrators). Successful programs should include protocol development and implementation, targeted metrics to be evaluated, data collection, and ongoing feedback to facilitate continuous performance improvement. Ideally, sepsis performance improvement programs should be sustained over time with repeated assessment of key metrics and additional intervention if there is a failure to "hold the gain". Despite many success stories, many ICUs, hospitals and healthcare systems have been slow to adopt recommended sepsis protocols or initiate quality improvement programs because of a myriad of implementation challenges and/or financial concerns.

Gaps in knowledge/critique of evidence Although both bundles (intended for quality improvement) and guidelines (intended to help guide practice) are based on the best available evidence, they are frequently not supported by high-quality evidence. While it is known that adaptation of process of care to different health care systems around the globe is highly variable, there is a lack of understanding both in the extent of this variability and its causes. Within bundles, even if beneficial in aggregate, this does not mean that each component has equivalent efficacy (or any efficacy) and whether other critical elements are missing entirely that would potentially change outcome.

Future directions Research towards understanding which systems of sepsis screening and care delivery are

most beneficial and cost-effective in a wide variety of patient care environments is critical. This should not be limited to the ICU but include the emergency department and the wards (and potentially both pre-hospital emergency care and outpatient facilities for sepsis screening as well) [122, 123]. These can be intra-location delivery systems (i.e. ICU-specific, ED-specific), intra-hospital, intra-health care system or regionalized (such as in trauma care in many countries). Methods of determining and then tracking optimal communication, transitions of care, and multidisciplinary coordination of care will likely be critical to this effort. Determining the best tool to detect the at-risk patient with optimal sensitivity and specificity is equally important. Finally, research should attempt to determine the relative importance of each bundle component and elements should be added, deleted or modified based upon these results.

Which is the epidemiology of sepsis susceptibility and response to treatment?

What is known Sepsis is a heterogeneous syndrome. The phenotype of sepsis in an individualized patient is influenced by both specifics of the infectious process and the host response of an individual patient. Different infections will impact the host differentially, and even within a single organism, different virulence factors will induce distinct responses. The host response is equally variable, and different genetic, epigenetic, and cellular/subcellular factors lead patients to respond very differently to the identical therapy [124–130].

Gaps in knowledge/critique of evidence Although Sepsis 3 is an intellectual advance, it continues to be non-specific, and does not make distinctions between either type of infection or host response [1, 2, 131–134]. An urgent need thus exists to better characterize different subgroups of sepsis, assuming they exist (which is likely). The field of precision medicine as it relates to sepsis is still in its infancy, so an ability to characterize patients based on their biological profile rather than clinical criteria alone is not currently possible at the bedside.

Future directions Research should improve the epidemiological information of sepsis in different subgroup of patients. In the short-term, this might be based upon factors that are currently identifiable such as transplant, oncohematological, elderly, etc. In the longer term, this should be more individualized and more biological in nature. Factors that require tailoring of therapy should be assayed. This should include both pathogen factors and host factors (phenotypes, endotypes, omics, real time assessment of immune function). Ideally, this would allow clinicians to prophylax against sepsis as well as treat the syndrome in an individualized manner.

It is possible to stratify the risk of sepsis based on biomarker panels?

What is known Biomarkers are laboratory assessments used to detect and characterize diseases and improve clinical decision making. A reliable biomarker for sepsis would assist with earlier diagnosis, improve risk stratification, or improve decision making for care in septic patients [135–137]. Risk stratification and prognostication in sepsis is of particular importance because high-risk patients may benefit from earlier clinical interventions, whereas low-risk patients may benefit from not undergoing unnecessary procedures. Prognostication in sepsis is currently done mostly via clinical criteria (e.g., organ dysfunction and/or presence of shock) and blood lactate levels. While numerous biomarkers have been evaluated in sepsis, none has sufficient accuracy to be utilized in clinical practice. The most commonly used biomarker in septic patients is procalcitonin, but its utility (though still debated) is predominantly to discontinue antibiotics in septic patients when levels fall. Preliminary studies suggest stratification using omics techniques are able to identify high risk patients.

Gaps in knowledge/critique of evidence It is unclear if the absence of acceptable predictive validity in a single biomarkers means (a) we have not yet found the correct biomarker, (b) we have inadequately studied the correct biomarker, or (c) there is no single biomarker that is predictive in sepsis, owning to its heterogeneity. Omics approaches that can generate a "molecular fingerprint" for risk validation and possibly treatment are promising; however, published studies have not been validated. Further the best approach (genomics, transcriptomics, proteomics, metabolomics, epigenetic approaches, etc.) are unclear both from accuracy and feasibility in terms of timeliness and cost.

Future directions Research should continue into whether a single or multiple biomarker have acceptable predictive value to predict development or progression of sepsis, prognosis from sepsis (including need for ICU admission) and/or response to therapy. Existing preliminary studies with omics, endotypes and epigenetic analysis should be validated by research groups outside of those who developed them. Additional research should also be performed to refine and expand existing models and/or to create new biomarker/molecular fingerprints in sepsis.

Post-ICU

What is the attributable long-term morbidity and mortality from sepsis?

What is known As recognition of sepsis increases globally and compliance with best practice improves, the short-term mortality from sepsis appears to be improving,

although the degree to which this is occurring is controversial [131]. While this is obviously encouraging, this leads to an increase in the number of sepsis survivors globally, which represents an additional burden to the heath-care systems in terms of rehabilitation, long-term care and support to caregivers. It is important here to distinguish between acute mortality directly related to the initial insult and late (or post-acute) mortality in patients who survive after hospital discharge. The current knowledge about late sepsis-attributable mortality is limited. Select older data coming from high income countries suggest that sepsis survivors have worse long-term outcomes [138, 139]. A recent systematic review of 43 studies, among which only 16 had control arms to allow assessment of attributable mortality, failed to clearly demonstrate a causal relationship between sepsis and post-acute mortality [140]. This systematic review raised the alternative hypothesis that the increased mortality after sepsis was probably related to the pre-existing disease comorbidity. The review's conclusion was subsequently challenged by two well-designed studies. One study showed that mortality was increased, compared with matched non-hospitalized controls, non-septic infected hospitalized patients and patients admitted with sterile inflammatory conditions [141]. Another study demonstrated that septic patients had higher mortality than matched controls from the general population and subjects who were hospitalized for a non-septic cause [142]. Data from newer cohorts with appropriate controls have also shown that sepsis survivors have a higher risk of hospital readmission which is associated with an increased risk of death [143–145]. Since some of these readmissions are caused by ambulatory care sensitive conditions [143], it is possible that some percentage of these readmissions is preventable.

It is useful to organize the broad domain of morbidity in terms of the Post-Intensive Care Syndrome framework [146], which divides post-critical illness morbidity into (a) cognitive impairment; (b) emotional impairments; and (c) physical disability; as well as (d) increases in specific disease states. There are data to suggest sepsis causes an acute and enduring worsening of cognitive function among survivors [147, 148]. There are conflicting data on emotional impairment with some studies suggesting increased rates of psychiatric diagnoses [149] and others suggesting little change in rates of self-reported depressive symptoms [150] albeit with elevated pre-sepsis symptom burden. Multiple cohorts describe a clear high burden of psychological problems among survivors, including anxiety and post-traumatic stress disorder, regardless of whether it is pre-existing, unmasked, or truly caused by the sepsis or other critical illness [151–154]. These data are indirect, however, as they come from non-septic critically ill patients or exclusively elderly septic patients. Disability rates also appear to be increased for years in survivors of sepsis compared to their pre-ICU levels, at least among older Americans and are high in many populations, driving poor measured health-related quality of life [148, 155–158]. While there have been no systematic efforts to map the specific conditions for which septic patients are at increased risk, there are suggestions of increased rates of malignancy, readmissions for a new sepsis episode, high rates of new cardiovascular diseases and residual immune dysregulations [142, 143, 159–163]. Many septic patients develop new comorbidities such as chronic kidney failure, the mechanisms of which may be different than in patients with non-septic acute kidney injury [164]. Other potential sepsis-associated long term consequences include frailty and an altered microbiome [165, 166]. Unfortunately, many studies in this domain are vulnerable to biases from insufficient characterization of pre-sepsis levels and trajectories of illness [167].

Gaps in knowledge/critique of evidence The specific burden of sepsis morbidity is inadequately characterized, particularly in terms of treatable conditions and competing risks. In addition, while significant contributions have been made regarding the four elements of post intensive care syndrome, the literature is still conflicting at times, incomplete at times, and at risk for bias. The impact of sepsis on caregivers is also inadequately described, including ways in which caregivers provide effective support, and the ways in which supporting caregivers may improve the support of patients. Finally, low and middle-income countries harbor 85% of all sepsis cases. Although mortality rates are higher, thus generating less survivors, the burden to the heath-care system has not been characterized, which may lead to an even higher burden given that these systems are less prepared in terms of rehabilitation capacity, chronic care facilities and support to caregivers.

Future directions More studies are needed to assess the attributable mortality of sepsis (both short-term and late) assessing pre-illness trajectory, confounding factors, and appropriate control groups. Studies using advanced matching techniques to distinguish par subgroups of sepsis from those of other ill and/or critically ill patients at risk of acquiring sepsis are needed. More comprehensive studies are required to determine to what extent sepsis causes all elements of the post intensive care syndrome and whether this differs between sepsis and other causes of ICU admission. Next, understanding the causes of readmission could potentially lead to the determination of preventable causes. Finally, since pre-, intra- and post-hospital resources may play a crucial role in potentially preventable causes of long-term morbidity and mortality,

studies need to be performed in diverse settings, and not just high income countries.

What are the predictors of sepsis long-term morbidity and mortality?

What is known Evidence regarding the extent to which sepsis causes late morbidity and mortality is generally low level and has limited the measurement of a causal relationship between different groups. In 16 studies reported in a systematic review with non-sepsis controls, the main predictor variables for post-acute mortality were age, male sex, tobacco use, health-care associated pneumonia, use of immunosuppressant drugs, HIV infection, cancer, previous cardiovascular or cerebrovascular disease and the degree of organ dysfunction [140]. However, even in well-controlled studies, it is difficult to identify among these factors those related to the sepsis-attributable mortality. A recent controlled study showed that late excess mortality was higher in patients with 3 or more organ dysfunctions, even after adjusting for acute mortality differences [141]. Another recent study observed these [141] effects were significantly higher in male patients, younger patients, those with higher Charlson Comorbidity Index scores, those with higher numbers of organ failure, those admitted to intensive care units, those with shock, and those who required mechanical ventilatory support [142].

Gaps in knowledge/critique of evidence The causal relationship between sepsis and specific subsequent morbidity has been inadequately characterized. Composite outcomes such as quality of life may dilute the ability to measure specific prognostically or mechanistically relevant associations due to poor reliability [168]. It is unclear to what extent acute burden of illness under current supportive technology is correlated with longer-term burden of illness. For instance, some conditions (e.g. acute hypoxic respiratory failure) may be difficult to manage in the inpatient setting, but not strongly associated with worse long-term outcomes among those who survive the acute setting [169]. In addition, many studies do not distinguish between predictors that are prognostically relevant among survivors and those predictors that are mechanistically relevant, which can lead to selection bias.

Future directions More studies are needed to assess the sepsis attributable mortality assessing pre-illness trajectory, confounding factors, and appropriate control groups both in well-resourced setting and resource-limited settings. Approaches to rapidly retrospectively characterize patients' pre-sepsis illness and morbidity trajectory are needed, particularly methods that can use indirect measures such as patterns of past hospitalizations, nursing home use, activity as recorded in personal devices (e.g. smartphones, fitness trackers or proxy reports [170–172]. Studies using advanced matching techniques to distinguish subgroups of sepsis from those of other ill and/or critically ill patients at risk of acquiring sepsis are also needed. Finally identification of potential modifiable risk factors is important to design interventional trials.

Are there potential in-hospital interventions that can impact long term outcomes?

What is known An implication of the data reviewed in questions 1 and 2 in this section is that sepsis-attributable late morbidity and mortality might be amenable to in-hospital interventions. There is strong clinical and physiologic plausibility that interventions considered as best practice with respect to short-term outcomes will also translate into improved long-term mortality and morbidity. Credible in-hospital interventions for which long-term consequences should be considered include (but are not limited to) (a) sepsis screening and detection strategies, (b) ICU triage and use of ICU, about which there is conflicting evidence in terms of short-term mortality in the United States and France, at least among elderly patients [173, 174], (c) alternative antibiotic regimens, including empiric strategies, culture guidance, and de-escalation strategies, and the ABCDEF bundle [175]. Ultimately, however, our knowledge about the relationship between in-hospital interventions and long-terms outcomes is limited, which precludes any definitive statements about the impact of such interventions.

Gaps in knowledge/critique of evidence There is no systematic review assessing this issue and concrete evidence linking in-hospital intervention and long-term outcomes is generally lacking. In addition, there are no data from low and middle-income countries. Since previous studies suggest that compliance with best practice standards might be lower in these settings, potential associations between in-hospital interventions and long-term outcomes need to be specifically addressed in low and middle-income countries.

Future directions Epidemiological studies assessing the association of in-hospital interventions are needed with adequate controls and controlling of confounding factors and selection bias. In addition, long-term follow-up of patients undergoing randomized trials in-hospital may help to clarify whether intervening in the hospital impacts long-term outcome. Currently, most studies do not examine long-term outcomes because of either cost or feasibility issues, yet the opportunity to determine the lasting (or transient) impact of in-hospital interventions is crucial in understanding long-term patient well-being.

Are there potential post-discharge interventions that can improve outcomes?

What is known The optimal strategy for rehabilitation programs and post discharge outpatient clinics aiming to improve quality of life and long-term sepsis mortality is unknown. Two trials that addressed this issue in critically ill patients (not specifically with sepsis) failed to show improved outcomes [176, 177]. Hospital readmissions for ambulatory care sensitive conditions are more common after sepsis than after matched controls, suggesting that effective outpatient care might have an impact in reducing re-hospitalization and, consequently, might influence long-term morbidity and mortality [143]. Despite a relative paucity of evidence to support their use, there is growing use of practices targeting the critically ill, which will, by definition, capture many septic patients. In the United Kingdom, the NICE guidelines recommend a post-ICU follow-up review after 2–3 months for all adult patients who stayed in critical care for more than 4 days and were at risk of morbidity [178]. They also state that health care systems should ensure that any adult who has had a critical care stay can be reassessed if they self-refer at any time. A model integrating early, time-limited post-ICU follow-up (including nurses, physicians, physical therapists, pharmacists, social workers, and peer support) is also being disseminated across Scotland [179]. In the United States, there is growing interest in both post-ICU clinics and post-ICU peer support models [180]. A growing number of United States hospitals report focusing on sepsis as part of the Centers of Medicare and Medicaid Services (CMS) program Partnership for Patients that aims to a 12% reduction in 30-day readmissions [181].

Gaps in knowledge/critique of evidence There is no systematic review assessing this issue, nor have most of the currently adopted models been subject to rigorous comparative effectiveness research. In addition, to our knowledge there are no data from low and middle-income countries.

Future directions Studies aiming to assess the impact of rehabilitation and the long- term follow up of septic patient patients in rehabilitation clinics are needed.

Basic/translational science

What mechanisms underlie sepsis-induced cellular and sub-cellular dysfunction?

What is known Specific functional abnormalities have been reported in essentially all tissues/organs following sepsis. Some evidence suggests that sepsis causes a global defect in a basic sub-cellular function that could lead to the development of dysfunction in many different cell types irrespective of their specific function or location. For example, a defect in mitochondrial oxidative phosphorylation has been demonstrated in multiple cell types [182–184]. The resulting energy deficit could disable cell-specific functions. Conversely, each cell or type of cell may develop a specific defect or manifest dysfunction in a unique manner. For example, secretory function in monocytes and lymphocytes increases, elevating cytokine production [185], while elaboration/release of surfactant or surfactant proteins by type 2 pulmonary epithelial cells [186–188] or of hormones by endocrine or pituitary cells decrease [189–192]. Similarly, apoptosis increases in lymphocytes, dendritic cells and the gut epithelium, while apoptosis is delayed following sepsis in neutrophils (and is unaffected in multiple other cell types) [193–196]. Finally, dysfunction in a single type of cell that is present in virtually all organs could underlie cell- and organ-specific dysfunction. For example, endothelial cells, which are present in all tissues, actively produce inflammatory mediators and coagulation intermediaries during sepsis, and contribute to sepsis-induced vascular dysfunction and leak [197, 198].

Gaps in knowledge//future directions Does a global defect that is shared by multiple cell types underlie all forms of sepsis-induced cellular dysfunction? Are there unique mechanisms of dysfunction that are specific to different types of cells? Do cells of similar embryologic origin (e.g., epithelium) become dysfunctional in ways that differ from other types of cells? Do cells with similar functions (e.g., elaboration/release of proteins, lipids etc.) develop unique forms of dysfunction that differ from that of cells with different basic functions (e.g., all cells that contract)? Since endothelial cells are present in virtually all organ systems and may directly modulate organ function, does endothelial cell dysfunction underlie dysfunction in other organ system? Conversely, because crosstalk occurs between virtually all organ systems and may directly modulate organ function, is there are an overarching method in which cells communicate to cause dysfunction on other organ systems? Finally, what are the mechanisms triggering these cellular alterations and what could be the interplay with tissue hypoperfusion?

How does sepsis alter bio-energetics and/or metabolism (both enhancement and failure)?

What is known Sepsis dramatically alters bio-energetics and/or metabolism [199, 200]. Sepsis increases metabolic rate, as reflected in oxygen consumption and overall substrate utilization [201]. However, this is paradoxically associated with a reduction in ATP utilization in many tissues, which occurs in concert with maintenance of ATP abundance, suggesting that the decreased use reflects an attempt to conserve ATP availability [202, 203]. Decreased activity in electron transport chain complexes I, III, IV and ATP synthase has also been demonstrated

[183, 184]. Sepsis is also known to alter substrate preference, with a decrease in the utilization of glucose (glucose intolerance) relative to fat and protein [204, 205]. As a result, septic patients tend to be hyperglycemic. In later stages oxidation of fatty acids may also be impaired, as reflected in elevated serum levels of lipoproteins, free fatty acids and triglycerides. Glycolysis is favored over oxidative phosphorylation despite adequate oxygen availability ("aerobic glycolysis", sometimes called the Warburg Effect) [206–208]. There is accelerated catabolism of skeletal muscle and perhaps smooth muscle as well [209]. In addition, micronutrient (e.g., vitamins, trace metals) effects are also impaired, reflecting either deficiency or altered activity [210, 211]. In addition, abnormalities are noted in the level and/or effectiveness of most hormones in sepsis [192].

Gaps in knowledge/future directions Are changes in energetics observed in all cells or are they cell-type specific? Are defects affecting energetics present only in mitochondria or are there changes in other sub-cellular structures? What mechanisms mediate alterations in oxidative phosphorylation? What underlies the altered activity in specific electron transport chain complexes? What mechanisms alter sepsis-induced changes in pathway (e.g., glycolysis, beta-oxidation, nitrogen cycle), substrate (e.g., carbohydrate, fat, protein, micronutrient), and/or cell-specific (e.g., cardiomyocyte, hepatocyte etc.) metabolism? What mechanisms underlie sepsis-induced defects in endocrine activity? How does sepsis affect brain circuits that control metabolism? Since cytokines alter metabolism in incompletely understood ways, how do cytokines alter metabolic pathways (and which ones are responsible)? Do metabolic pathways influence inflammation, and if so, how?

How does sepsis (and/or approaches used to manage sepsis) alter phenotypes and interactions in the host microbiome and do alterations in the microbiome effect outcomes?

What is known The microbiome contains 40 trillion organisms, the same number of cells as in the host patient [212]. While the majority of bacterial species and diversity of the microbiome reside within the gut lumen, the microbiome includes all microorganisms residing within (mouth, lungs, gut) or on (skin) the host. Microbial diversity is enormous with 1000 different species of bacteria and over 2 million bacterial genes [212, 213]. Sepsis leads to a rapid (within 6 h) decrease in microbial diversity [214]. Whereas the most common microbe makes up 25% of the microbiome in healthy patients, a massive diversity crash causes results in the most common microbe making up 95% of the microbiome in ICU patients [215]. These changes appear to result from both the underlying disorder (sepsis) and its treatment (antibiotics), which by definition alter the microbiome [216–222]. Further, microbes alter their virulence in response to both the internal host environment (availability of phosphate) and treatments in critically ill patients (opiates) [223–225]. Bacteria in pre-clinical models of sepsis can be tricked into "believing" that the host environment is non-toxic, preventing the development of virulence factors that would ordinarily occur in sepsis, leading to survival advantage in septic rodents [226]. Microbes also possess the capacity for quorum sensing in which individual cells can work together to collectively respond to the environment [227, 228].

Gaps in knowledge/future directions What mechanisms underlie the specific, sepsis-induced changes in the microbiome? Are these reversible? If so, how? How do alterations in the microbiome affect the host response? Which components of the microbiome are responsible? Is it possible to restore a healthy microbiome in the setting of clinical therapies that continue to alter the microbiome? Does the site of bacteria within the microbiome make a difference and can specific host locations be targeted (for instance, the respiratory microbiome)? Does restoring a healthy microbiome improve outcomes in patients (note: this is more of a clinical question than a basic science question since fecal microbial transplant, probiotics, prebiotics, synbiotics and selective decontamination of the digestive disease system are currently in clinical use in select environments)?

What mechanisms initiate, sustain and terminate recovery?

What is known Aside from therapy targeting the specific infection in the ICU, treatment for sepsis is nonspecific and supportive. In spite of this, it is implicitly understood by clinicians that cells and organ systems must recover over time in sepsis survivors despite the absence of therapy aimed at cellular/organ recovery. The study of mechanisms behind recovery in sepsis has only recently become an area of focus in basic/translational sepsis research, and thus relatively little is understood. Intrinsic to recovery is the return of function at subcellular, cellular, and multicellular/organ levels, and within the immune, metabolic, endocrine, intestinal, vascular, neurologic, etc. systems. Recovery may be affected by specific mediators and systems that participate in the initiation and development of sepsis-associated responses. Examples include lipids (resolvins, lipoxins, maresins, prostanoids), autophagy, miRNAs, exosomes, and neuronal activity [190, 229–235].

Gaps in knowledge/future directions What mechanisms and specific mediators are important in recovery? What metabolic, energetic immune, endocrine, intestinal, neuronal and vascular, etc. pathways mediate recovery from dysregulated cellular and subcellular function? Can

sub-cellular, cellular and/or tissue/organ- specific dysfunction be reversed or mitigated by promoting recovery pathways and can the magnitude and time frame of this recovery be accelerated?

Conclusion

This work complements two recent publications on research priorities in sepsis. A 2017 research agenda by 11 international experts in septic shock listed 10 topics to undergo testing over the next 10 years [236]. A 2015 research roadmap by 13 international authors proposed research topics on a wide array of subjects ranging from epidemiology to molecular diagnostics [237]. It is logical that there should be some overlap between the priorities in the different manuscripts, and although each of the potential questions for this manuscript were developed independently of the other two, each previously enumerated priority is proposed in some fashion in the current recommendations. This suggests there is some degree of international consensus regarding sepsis research priorities, and multiple international groups are actively performing research on these priorities. However, the priority list detailed herein additionally includes topics that have been little covered in past efforts, including post-ICU and is broader in scope.

Ultimately, although our understanding of sepsis has greatly increased over the past 20 years, mortality remains unacceptably high. The reasons for this are multifactorial. Significant gaps in knowledge translation from existing evidence to the bedside exist, and efforts aimed to translating best practice to the bedside will almost assuredly result in better outcomes. However, even if all existing best practice standards were followed, significant knowledge gaps remain on a wide array of issues. By taking a maximally inclusive view of priorities in adult sepsis, we hope this overview will serve as a catalyst for research that needs to be performed in sepsis.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-018-5175-z) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest

Dr. DeBacker is immediate past president of the European Society of Intensive Care Medicine and has received consulting fees from Edwards Lifesciences, Fresenius Kabi, and Grifols. Dr. Deutschman is a consultant for Enlivix Therapeutix LTD. Dr. Ferrer Roca received honoraria from Toray, MSD, Pfizer and Grifols. Dr. Martin serves on a medical advisory board for Edwards Lifesciences and Grifols. Dr. Antonelli is president of the European Society of Intensive Care Medicine and received honoraria from Pfizer, Toray, Orion, and Air liquid. Dr. Evans is the current co-chair of the Surviving Sepsis Campaign guidelines committee. Dr. Kesecioglu is president-elect of the European Society of Intensive Care Medicine and has received honorarium from Xenios AG. Professor Rhodes is the current co-chair of the Surviving Sepsis Campaign guidelines committee.

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Research Update

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ORIGINAL

Health-related outcomes of critically ill patients with and without sepsis

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Abstract

Purpose: To determine differences in health-related quality of life (HRQoL), survival and healthcare resource use of critically ill adults with and without sepsis.

Methods: We conducted a primary propensity score matched analysis of patients with and without sepsis enrolled in a large multicentre clinical trial. Outcomes included HRQoL at 6 months, survival to 2 years, length of ICU and hospital admission and cost of ICU and hospital treatment to 2 years.

Results: We obtained linked data for 3442 (97.3%) of 3537 eligible patients and matched 806/905 (89.0%) patients with sepsis with 806/2537 (31.7%) without. After matching, there were no significant differences in the proportion of survivors with and without sepsis reporting problems with mobility (37.8% vs. 38.7%, $p = 0.86$), self-care (24.7% vs. 26.0%, $p = 0.44$), usual activities (44.5% vs. 46.8%, $p = 0.28$), pain/discomfort (42.4% vs. 41.6%, $p = 0.54$) and anxiety/depression (36.9% vs. 37.7%, $p = 0.68$). There was no significant difference in survival at 2 years: 482/792 (60.9%) vs. 485/799 (60.7%) (HR 1.01, 95% CI 0.86–1.18, $p = 0.94$). The initial ICU and hospital admission were longer for patients with sepsis: 10.1 ± 11.9 vs. 8.0 ± 9.8 days ($p < 0.0001$) and 22.8 ± 21.2 vs. 19.1 ± 19.0 days, ($p = 0.0003$) respectively. The cost of ICU admissions was higher for patients with sepsis: A$43,345 ± 46,263 (€35,109 ± 35,043) versus 34,844 ± 38,281 (€28,223 ± 31,007), mean difference $8501 (€6885), 95% CI $4342–12,660 (€3517 ± 10,254), $p < 0.001$ as was the total cost of hospital treatment to 2 years: A$74,120 ± 60,750 (€60,037 ± 49,207) versus A$65,806 ± 59,856 (€53,302 ± 48,483), $p = 0.005$.

Conclusions: Critically ill patients with sepsis have higher healthcare resource use and costs but similar survival and HRQoL compared to matched patients without sepsis.

Keywords: Sepsis, Post-sepsis syndrome, Post-intensive care syndrome, Long-term outcomes

Introduction

Sepsis, defined as the body's life-threatening response to infection, is a leading cause of death worldwide contributing to 1 in every 2–3 deaths in US hospitals. The annual cost of treating sepsis in the USA is estimated to be $24 billion, making it the most expensive inpatient condition to treat [1].

The World Health Organisation has designated sepsis as a global health priority and, with encouragement from the European Union Commissioner for Health, the European Sepsis Alliance was launched in March 2018 [2, 3].

Patients with sepsis who are treated in an intensive care unit (ICU) are at an increased risk of death compared to other critically ill patients [4–6]. Patients who survive sepsis commonly report reduced quality of life related to physical and cognitive impairment that impacts their ability to care for themselves and to perform usual

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activities of daily living [7–9]. "Post-sepsis syndrome" and "post-intensive care syndrome" are terms used to describe the persistent adverse effects that occur after a hospital admission for the treatment of sepsis or after an admission to an ICU for any critical illness [9, 10]. There is increasing recognition of the importance of assessing longer-term outcomes in survivors of critical illness, but it is uncertain whether such outcomes differ between survivors of critical illness who did or did not have sepsis [10, 11].

We hypothesized that critically ill patients with sepsis would have decreased survival and report decreased health-related quality of life, and increased healthcare resource use and costs compared to critically ill patients without sepsis, and this difference would persist after matching using a propensity score.

Methods

Study population and data sources

The study population was ICU patients enrolled in the Crystalloid versus Hydroxyethyl Starch Trial (CHEST), an investigator-initiated, binational, prospective, blinded randomized controlled trial that compared the effects of fluid resuscitation using hydroxyethyl starch (6% HES 130/0.4) to 0.9% sodium chloride (saline) in 7000 patients enrolled in 32 ICUs in Australia and New Zealand [12, 13].

Following ethical approval by the New South Wales Population Health Ethics Committee, we identified patients enrolled in CHEST in the Australian state of New South Wales and linked the trial dataset to government administrative health databases to capture clinical outcomes as well as healthcare resource use and associated costs for up to 2 years after trial enrolment [14]. As allowed by local regulations, we obtained written informed consent from the patient or a waiver of consent for data linkage from the approving ethics committees.

Study design

We conducted a primary propensity score matched analysis of patients with and without a pre-randomization diagnosis of sepsis after conducting an initial unmatched, unadjusted analysis [15]. From candidate variables collected at baseline in CHEST, we used variables that were considered by an expert consensus panel to be predominant risk factors associated with sepsis (eMethods), to assign patients a propensity score (ranging from 0 to 1) according to their probability of having sepsis. Matching variables were limited to those collected at the time of trial enrolment and included age, sex, weight, admission source, medical or surgical admission, trauma, creatinine concentration, heart rate, mean arterial pressure, mechanical ventilation status and Acute Physiology and Chronic Health Evaluation (APACHE) II score [16]. The study inclusion and exclusion criteria and baseline variables collected in CHEST but not used in the propensity matching are listed in the eMethods.

Take-home message

Propensity score matched critically ill patients with and without sepsis had similar health-related quality of life and survival but patients with sepsis had higher healthcare resource use and costs at 2 years.

Sepsis definitions

Patients with sepsis were prospectively identified on enrolment into CHEST using the 1992 consensus definition of sepsis: suspected infection and the presence of two or more systemic inflammatory response syndrome criteria (Box 1) [17]. Post hoc, we also classified patients as having sepsis using the Third International Consensus Definitions of Sepsis and Septic Shock (Sepsis-3) that are reported in the Supplement [18].

Box 1 Sepsis definitions

Systemic inflammatory response syndrome (SIRS) criteria definition (1992) [17]

A defined focus of infection and

Two or more SIRS criteria

Core temperature > 38 or < 36 °C

Heart rate > 90 beats per minute

Respiratory rate > 20 breaths per minute or a PaCO2 < 32 mmHg or mechanical ventilation for an acute process

White blood cell (WBC) count of > 12×10^9/L or < 4×10^9/L, or > 10% immature neutrophils

Sequential organ failure assessment (SOFA) criteria definition (2016) [18]

Suspected infection and

An acute change in SOFA score of two or more points consequent to infection[a]

[a]Baseline SOFA score assumed to be zero in patients not known to have pre-existing organ dysfunction

Clinical outcomes

Health-related quality of life at 6 months after enrolment was assessed for the whole CHEST cohort using structured telephone interviews conducted by designated trained research coordinators at participating sites. Where possible patients were interviewed in person, but where patients were incapacitated, a proxy, defined as a caregiver, spouse or relative, was interviewed.

Health-related quality of life was assessed using the EuroQol Group Association five-domain, three-level questionnaire (EQ-5D-3L) [19]. This questionnaire

measures five domains of health including mobility, self-care, usual activities, pain/discomfort and anxiety/depression and assesses each domain across three levels: no problems, some problems or extreme problems [19]. We grouped patients into two categories, those reporting no problems and those reporting some or extreme problems within each domain.

Vital status (dead or alive) 2 years after enrolment was obtained from the New South Wales registry of births, deaths and marriages.

Healthcare resource use and economic outcomes

Healthcare resource use was determined by linking the study database to the New South Wales Admitted Patient Data Collection and the Emergency Department Data Collection. Through these linkages, hospital-associated resource use was measured by assessing ICU and hospital length of stay during the initial admission and subsequent readmissions to the emergency department and to hospital within 2 years of enrolment.

Economic outcomes included the cost of ICU admissions and the cost of hospital admissions, inclusive of ICU admission costs, at 2 years after trial enrolment. Costs for ICU admissions were calculated using the New South Wales cost-of-care standards cost per bed day [20], multiplied by the length of stay in the ICU. Total hospital costs were derived from matching Australian Refined Diagnostic Related Group codes to publicly available government reimbursement figures [21]. Where the ICU admission occurred partway through the hospital stay, we adjusted costs proportionately in accordance with the amount of time spent in hospital prior to the ICU admission during which the patient was enrolled in CHEST.

Statistical analyses

We compared binary outcomes for baseline variables using the chi- square (χ^2) test and report as standardised differences. Continuous data were compared using non-parametric tests. Probability of survival was assessed by Kaplan–Meier survival analysis using the log-rank test to compare groups and reported as a hazard ratio (HR) with 95% CIs. Healthcare resource use and costs are reported as means ± standard deviations (SD) and differences assessed using the *t* test for means and the χ^2 test for proportions, reported as mean differences with 95% CI and odds ratios with 95% CIs respectively.

To conduct the propensity score matching, we created a missing value variable for instances where continuous variables (creatinine concentration, heart rate and mean arterial pressure) were not recorded. We matched patients at a ratio of 1:1 using the greedy matching method whereby a patient with sepsis is selected at random and the patient without sepsis whose propensity score is closest to that of the randomly selected sepsis patient was chosen as the control. This process was repeated until the list of patients with sepsis for whom a matched patient without sepsis could be found was exhausted (eMethods) [15].

We conducted prespecified sensitivity analyses of the survival outcome to ensure the robustness of the propensity model. We stratified by quintile of propensity score, a method to measure the equivalence of propensity score distribution within each of the five quintiles in the sepsis and non-sepsis groups [22], and applied inverse-probability treatment weighting by propensity score, where each sepsis subject receives a weight equal to the inverse of the propensity score and each control unit receives a weight equal to the inverse of one minus the propensity score [23]. We adjusted the analysis using the propensity score as a covariate. The primary results are presented without adjustment with results from sensitivity analyses reported in the Supplement.

Costs are reported in Australian dollars (A$) with Euro (€) conversions, with A$1.00 equating to EU€0.81 or US$0.96, for the period of 1 July 2012 to 30 September 2012.

Results

Of 7000 patients included in CHEST, 3537 (50.5%) were enrolled in New South Wales. Of these, 57 (1.6%) patients did not have linkage data available, 30 (0.8%) declined consent and in eight (0.2%) sepsis status at baseline was not recorded.

Of the 3442/3537 (97.3%) patients allocated a propensity score, 905/3442 (26.3%) met the 1992 consensus definitions for sepsis at baseline and 2537/3442 (73.7%) did not. We matched 806/905 (89.0%) patients with sepsis to patients without sepsis; 99/905 (10.9%) could not be matched (Fig. 1). Characteristics of patients with sepsis who could not be matched are reported in the Supplementary Appendix (eTable 1).

After matching by propensity score the baseline characteristics of the two groups were similar (Table 1 and Fig. 2); additional information on ICU admission diagnostic categories for matched patients are reported in the Supplementary Appendix (eTable 2).

At 6 months after enrolment, there was no significant difference in the proportion of matched survivors with and without sepsis reporting problems across health-related quality of life domains of mobility, self-care, usual activities, pain/discomfort and anxiety/depression (Table 2). Results for the whole cohort are reported in the Supplementary Appendix (eTable 3).

After matching by propensity score 482/792 (60.9%) with sepsis and 485/799 (60.7%) without sepsis were alive at 2 years. There was no significant difference in survival

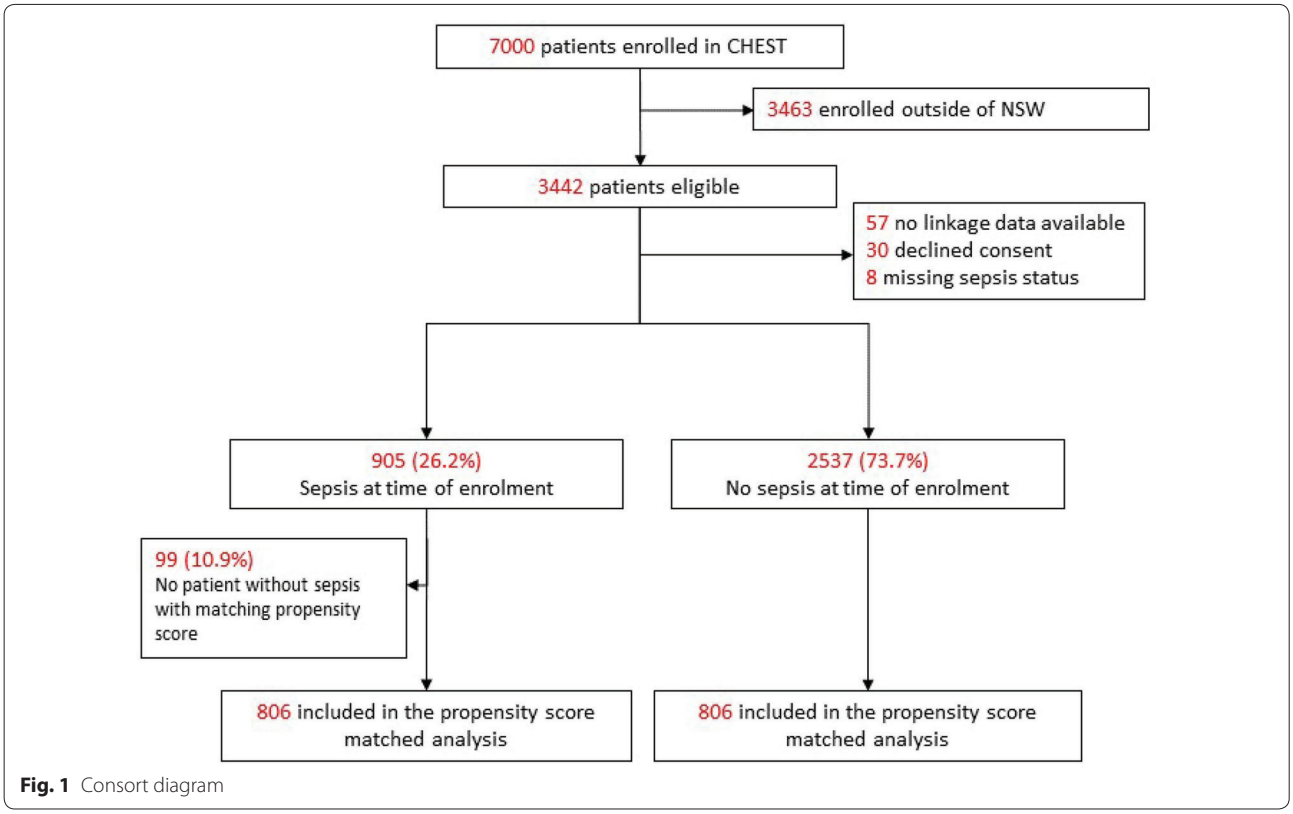

Fig. 1 Consort diagram

between the groups (HR 1.01, 95% CI 0.86–1.18, $p=0.94$) (Fig. 3). Results for the unmatched cohort are reported in the Supplementary Appendix (eFig. 1). The sensitivity analyses conducted to ensure the robustness of the propensity model provided similar results to the primary analysis (eTable 4).

The duration of the initial ICU (10.1 ± 11.9 days vs. 8.0 ± 9.8 days, mean difference 2.13, 95% CI 1.06–3.19, $p<0.0001$) and hospital (22.8 ± 21.2 days vs. 19.1 ± 19.0 days, mean difference 3.68, 95% CI 1.71–5.65, $p=0.0003$) admission were longer for patients with sepsis compared to those without sepsis (Table 3). During the 2 years after enrolment, similar proportions of patients with and without sepsis had visited an emergency department: 289/641 (45.1%) versus 305/653 (46.7%), odds ratio 0.94, 95% CI 0.75–1.17, $p=0.56$; had been readmitted to hospital 455/635 (71.7%) versus 465/644 (72.2%), odds ratio 0.97, 95% CI 0.76–1.24, $p=0.83$ and readmitted to an ICU, 90/634 (14.2%) versus 113/643 (17.6%), odds ratio 0.78, 95% CI 0.57–1.05, $p=0.10$ respectively (Table 3). The cost of the ICU admissions for patients with sepsis was significantly higher than for patients without sepsis: A$47,298 ± 53,730 (€38,311 ± 43,521) versus A$38,952 ± 46,778 (€31,551 ± 37,890), mean difference $8346 (€6760), 95% CI $3420–13,271 (€2770–10,749), $p<0.001$. The overall cost of hospital treatment to 2 years was higher in patients with sepsis: A$74,120 ± 60,750 (€60,037 ± 49,207) versus A$65,806 ± 59,856 (€53,302 ± 48,483), mean difference $8314 (€6734), 95% CI $3007–60,305 (€2436–48,847), $p=0.005$ (Table 3). Results for the unmatched cohort are reported in the Supplementary Appendix (eTable 5).

Applying the Third International Consensus Definitions of Sepsis and Septic Shock (Sepsis-3) did not alter the results (eTables 6, 7, 8, eFig. 2).

Discussion

In this analysis of critically ill patients enrolled in a fluid resuscitation trial, approximately 40% of patients with sepsis at the time of enrolment died within 2 years. Propensity score matched patients without sepsis had similar survival at 2 years. Health-related quality of life at 6 months was similar in the matched and unmatched groups. Patients with a diagnosis of sepsis at the time of trial enrolment had longer initial ICU and hospital stay which was associated with higher healthcare-associated resource use and costs. When applying the Third International Consensus Definitions of Sepsis, we found similar results.

Our study supports findings from other studies that report poor longer-term outcomes for critically ill patients [8, 24–29, 30]. Previous research which suggests

Table 1 Baseline characteristics of patients with sepsis and matched patients without sepsis

	Propensity score matched			Unmatched cohort		
	Sepsis (*N* = 806)	Non-sepsis (*N* = 806)	*p* value	Sepsis (*N* = 905)	Non-sepsis (*N* = 2537)	*p* value
Age	62.5 ± 16.9	63.1 ± 17.0	0.50	62. 8 ± 16.8	62.7 ± 17.6	0.81
Male	471 (58.4)	490 (60.8)	0.33	534 (59.0)	1579 (62.3)	0.08
Weight	79.7 ± 23.2	79.9 ± 22.8	0.88	80.3 ± 23.2	78.7 ± 20.6	0.05
Source of admission to ICU						
Emergency department	272 (33.7)	261 (32.4)	0.85	309 (34.1)	642 (25.3)	< 0.0001
Hospital floor	231 (28.7)	227 (28.2)		266 (29.4)	412 (16.3)	
Another ICU	11 (1.4)	14 (1.7)		11 (1.2)	32 (1.3)	
Another hospital	129 (16.0)	126 (15.6)		150 (16.6)	239 (9.4)	
Operating room, after emergency surgery	127 (15.8)	145 (18.0)		132 (14.6)	457 (18.0)	
Operating room, after elective surgery	36 (4.5)	33 (4.1)		37 (4.1)	751 (29.6)	
Surgical admission	162 (20.1)	172 (21.3)	0.54	162 (18.0)	1265 (50.1)	< 0.0001
Trauma	6 (0.7)	4/806 (0.5)	0.52	6 (0.7)	322 (12.7)	< 0.0001
Time from ICU admission to trial enrolment (h)	7.1 ± 31.5	9.3 ± 32.3	0.28	7.0 ± 30	8.9 ± 32.4	0.12
Physiological variables						
Creatinine (μmol/L)	111.3 (61.4)	111.0 (65.2)	0.93	115.8 (63.6)	94.5 (54.1)	< 0.0001
Heart rate (bpm)	99.5 ± 22.4	95.2 ± 23.8	0.0002	101.0 ± 22.3	85.1 ± 22.1	< 0.0001
Mean arterial pressure (mmHg)	73.8 ± 15.0	74.4 ± 16.5	0.47	73.3 ± 15.0	75.0 ± 15.8	0.006
Central venous pressure (mmHg)	11.2 ± 6.0	10.6 ± 5.5	0.29	11.2 ± 6.0	9.5 ± 5.4	< 0.0001
Lactate (mmol/L)	2.1 ± 1.6	2.3 ± 2.1	0.07	2.2 ± 1.7	2.0 ± 1.7	0.002
Mechanical ventilation	506 (62.8)	526 (65.3)	0.29	533 (59.5)	1752 (69.7)	< 0.0001
SOFA scores[a]						
Cardiovascular	1.9 ± 1.4	1.7 ± 1.4	0.03	1.9 ± 1.4	1.7 ± 1.3	0.0002
Respiratory	2.1 ± 1.1	2.0 ± 1.2	0.003	2.1 ± 1.1	1.8 ± 1.1	< 0.0001
Renal	0.7 ± 0.9	0.7 ± 0.9	0.61	0.8 ± 0.9	0.4 ± 0.7	< 0.0001
Hepatic	0.5 ± 0.8	0.4 ± 0.8	0.09	0.5 ± 0.8	0.3 ± 0.7	< 0.0001
Haematologic	0.6 ± 1.1	0.4 ± 0.8	0.0009	0.6 ± 1.1	0.4 ± 0.8	< 0.0001
Total APACHE II[b]	20.0 ± 7.4	20.4 ± 8.3	0.27	20.3 ± 7.3	17.0 ± 7.7	< 0.0001
APACHE II score ≥ 25	209 (25.9)	240 (29.8)	0.08	247 (27.4)	417 (16.5)	< 0.0001

ICU intensive care unit, *SOFA* Sequential Organ Failure Assessment, *APACHE* Acute Physiology and Chronic Health Evaluation

Values are presented as mean ± standard deviation or proportions (percentages)

[a] SOFA scores taken from the 24-h period prior to trial enrolment. Glasgow Coma Score component of SOFA scores not collected

[b] APACHE II scores taken from the 24-h period prior to trial enrolment

that sepsis is associated with higher risk of death [24] and increased healthcare resource use [25] have used a range of comparator groups based on a 'claims-based' diagnosis of sepsis, whereas we were able to include patients diagnosed with sepsis prospectively and compare these patients to other critically patients. Research which has found patients with sepsis and septic shock to have reduced longer-term health-related quality of life [8] has primarily included only patients with sepsis and septic shock, making no comparisons between other critically ill patients. Our findings suggest that despite increased hospital resource use and costs related to the initial admission episode, outcomes for patients with and without sepsis, who are matched using a propensity score at baseline, are not substantially different.

Our study has several strengths. Our patient population was taken from a large randomized controlled trial with high levels of internal and external validity. We used a number of patient-centred outcomes including health-related quality of life and survival in addition to economic indices of hospital resource use and costs obtained from an established data-linkage unit. We derived costs from validated and publicly available government reimbursement figures capturing data from patients treated in a universal access public health system. We assessed the cohort overall prior to conducting the primary analysis

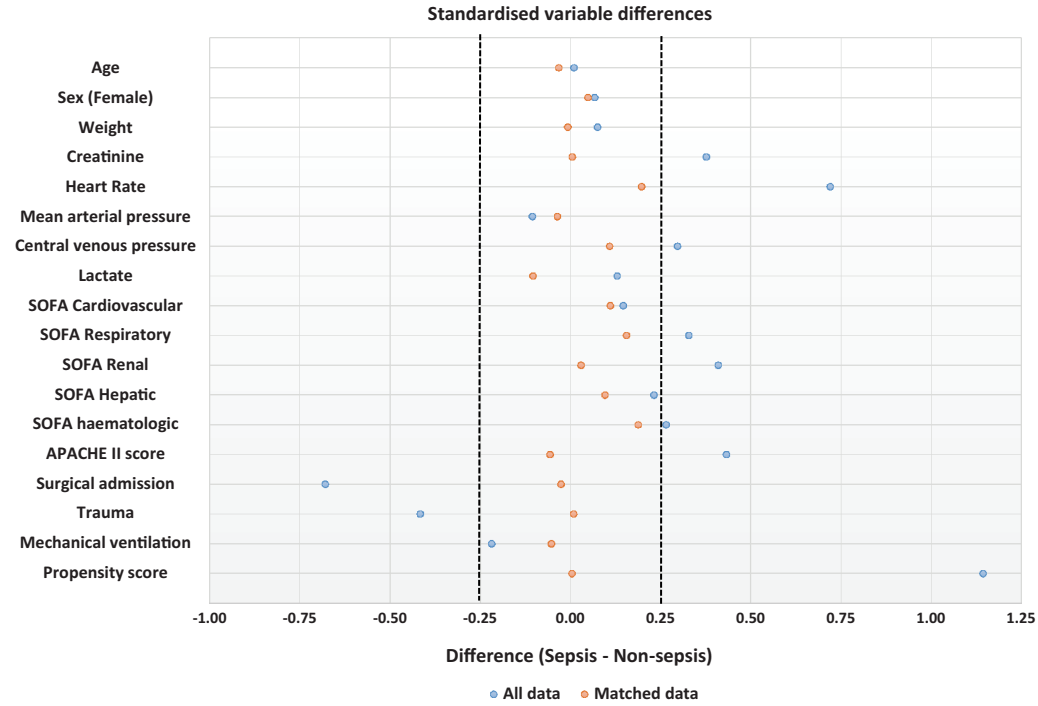

Fig. 2 Standardised differences of baseline characteristics of matched and unmatched patients

Table 2 Health-related quality of life of matched survivors at 6 months

Characteristics[a]	Sepsis *N* = 538/564 (95.4%)	Non-sepsis *N* = 549/578 (95.0%)	Odds ratio	95% CI	*p* value
Mobility					
No problems	334/537 (62.2%)	336/548 (61.3%)	0.96	0.75–1.23	0.86
Some problems/unable to walk	203/537 (37.8%)	212/548 (38.7%)			
Self-care					
No problems	404/537 (75.2%)	406/549 (74.0%)	0.94	0.74–1.23	0.44
Some problems/unable to wash or dress myself	133/537 (24.7%)	143/549 (26.0%)			
Usual activities					
No problems	298/537 (55.5%)	292/549 (53.2%)	0.91	0.72–1.16	0.28
Some problems/unable to perform	239/537 (44.5%)	257/549 (46.8%)			
Pain or discomfort					
No pain or discomfort	310/538 (57.6%)	320/548 (58.4%)	1.03	0.81–1.31	0.54
Some or extreme pain or discomfort	228/538 (42.4%)	228/548 (41.6%)			
Anxiety or depression					
Not anxious or depressed	339/537 (63.1%)	338/543 (62.2%)	0.96	0.75–1.23	0.68
Moderately or extremely anxious or depressed	198/537 (36.9%)	205/543 (37.7%)			

Health-related quality of life was measured using the EuroQol, five-dimension, three-level questionnaire

[a] Missing data: sepsis, *N* = 28/564 (4.5%); non-sepsis, *N* = 29/578 (5.0%)

and used established matching methods. We performed several sensitivity analyses to confirm the robustness of the matching.

Our study has some limitations. We collected information about sepsis status at the time of trial enrolment and could not determine whether patients developed sepsis later in their ICU stay. However, in an inception

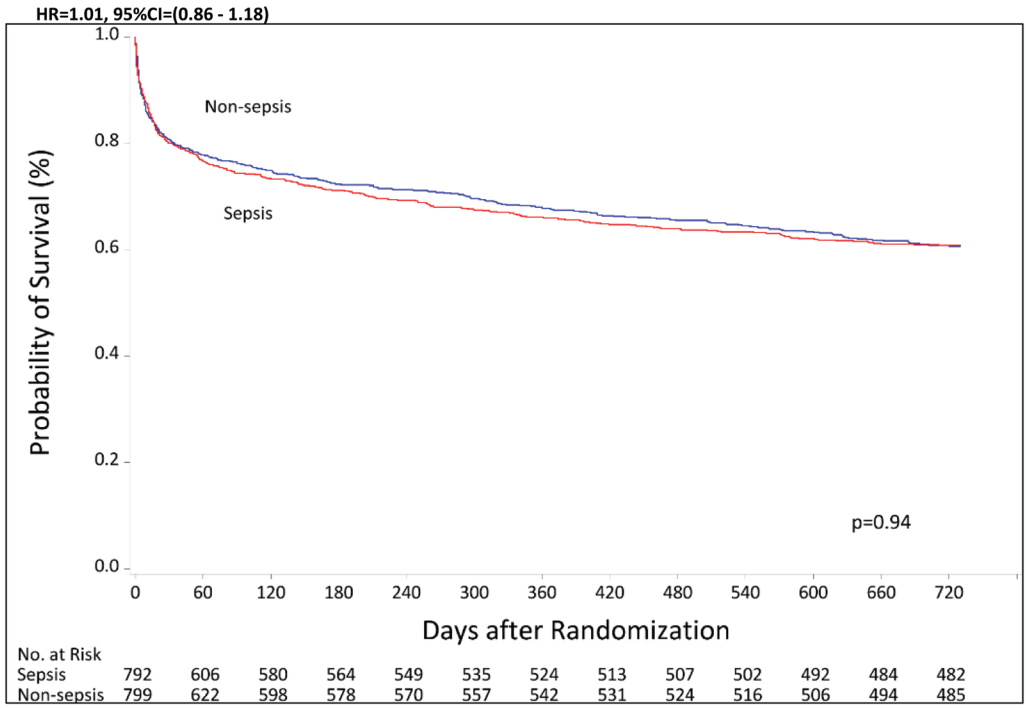

Fig. 3 Probability of survival to 2 years; propensity score matched

Table 3 Length of initial ICU and hospital admission, hospital readmissions and costs

Outcome	Propensity score matched			95% CI	*p* value
	Sepsis (*N* = 806)	Non-sepsis (*N* = 806)	Mean difference/odds ratio		
Length of initial ICU admission (days)	10.1 ± 11.9	8.0 ± 9.8	2.13	1.06–3.19	< 0.0001
Length of initial hospital admission (days)	22.8 ± 21.2	19.1 ± 19.0	3.68	1.71–5.65	0.0003
Emergency department visits after discharge[a]	289/641 (45.1)	305/653 (46.7)	0.94	0.75–1.17	0.56
Hospitalizations after discharge[b]	455/635 (71.7)	465/644 (72.2)	0.97	0.76–1.24	0.83
ICU admissions after discharge[c]	90/634 (14.2)	113/643 (17.6)	0.78	0.57–1.05	0.10
Total ICU costs to 24-months ($A)[d]	47,298 ± 53,730	38,952 ± 46,778	8346	3420–13,271	< 0.001
Hospital costs using AR-DRG to 24-months (A$)	74,120 ± 60,750	65,806 ± 59,856	8314	3007–60,305	0.005

ICU intensive care unit, *$A* Australian dollars, *AR-DRG* Australian related diagnostic group codes

Values are presented as mean ± standard deviation or proportions (percentages)

[a] Refers to visits to a public hospital emergency department in New South Wales after discharge from the initial hospital admission

[b] Refers to public hospitalisations in New South Wales after discharge from the initial hospital admission

[c] Refers to readmissions to an ICU in New South Wales after discharge from the initial ICU admission

[d] Total ICU costs derived from multiplying the length of ICU stay by the New South Wales Cost of Care Standard average cost per ICU bed day

cohort study of the epidemiology of sepsis in Australian and New Zealand ICUs, only 2.4% of patients developed sepsis more than 24 h after admission to an ICU [31], suggesting that the development of sepsis later in our patients' ICU stay would not have materially affected our findings. Matching characteristics were limited to variables collected at the time of enrolment to CHEST; we had no data on other potentially important risk factors such as pre-existing co-morbidities, frailty and other functional impairments. We were unable to propensity match 11% of patients with sepsis because there was no patient without sepsis with a comparable propensity score—with patients who had sepsis at the time of trial enrolment more likely to have higher propensity scores than patients

who did not have sepsis. Our study used linked data in New South Wales, the most populous state in Australia and therefore we were unable to quantify the number of patients enrolled in the trial in New South Wales who died or used healthcare resources outside New South Wales. As recognised in observational studies, there may be unidentified confounders not identified in the analysis.

The primary outcome for clinical trials in sepsis and other forms of critical illness has traditionally been 28- and 90-day mortality [32]. More recently, longer-term effects of sepsis and other forms of critical illness extending beyond 3 months have become apparent [24, 33]. Our findings confirm that patients who survive critical illness have poor quality of life and increased healthcare resource use and costs for at least 2 years. However, we found that the diagnosis of sepsis per se was not associated with worse clinical outcomes in comparison to matched patients without sepsis. These findings have implications for health service planning and for planning the ongoing support and treatment of survivors of sepsis and other forms of critical illness.

Future research should seek to further characterise the sequelae of sepsis and critical illness and to determine which interventions in the ICU, in the hospital after ICU discharge and later in the community may mitigate or treat the sequelae of sepsis and of critical illness in general.

Conclusions

In patients who were able to be matched, we found no demonstrable differences in longer-term outcomes in critically ill patients with sepsis in comparison to patients without sepsis, although patients with sepsis have higher healthcare-associated resource use and costs.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-018-5274-x) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest

The authors declare no conflicts of interest.

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WHAT'S NEW IN INTENSIVE CARE

Norepinephrine in septic shock

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Introduction

Norepinephrine (NE) is both an alpha1- and beta1-agonist, and is therefore able to increase vascular tone and contractility [1]. Recent guidelines recommend NE as the first-line vasopressor in septic shock [2]. However, because septic shock is a syndrome that results from a variable combination of decreased venous return, myocardial depression and decreased vascular tone, the place for NE in initial resuscitation is not straightforward.

There is no doubt that prolonged hypotension contributes to the mortality of sepsis [3], but several issues, such as when to start NE, or the optimal mean arterial pressure (MAP) target in different contexts, are still controversial [4]. This is particularly relevant since NE has a wide spectrum of effects on the cardiovascular system (Fig. 1) that could eventually increase or decrease systemic, regional or microcirculatory blood flow depending on factors such as dose, pre-existing comorbidities, preload status, severity and stage of disease, and interaction with other processes of care [1].

When to start norepinephrine

The recent Hour-1 Bundle supported by the Surviving Sepsis Campaign recommends starting vasopressors within the first hour of resuscitation if initial fluid loading does not restore minimum MAP [5]. Indeed, NE infusion can be safely started before intensive care unit (ICU) admission, even in intermediate care without intensivist supervision [6].

Early administration of NE can increase cardiac output through an increase in venous return and thus cardiac preload, but also by increasing contractility [7]. Two recent studies showed that early use of NE is associated with less fluid administration and improved outcome [8, 9]. Moreover, in a retrospective study, early initiation of NE was associated not only with less positive fluid balance but also with a shorter duration of hypotension and NE requirements [10]. In hypotensive fluid-responsive patients, NE may thus be used as an adjunct to fluids to increase cardiac output and perfusion pressure, although the exact place and timing have yet to be determined.

Norepinephrine and cardiac performance

As NE improves cardiac systolic function in the early stage of septic shock, increased left ventricular afterload does not necessarily result in a decrease in stroke volume even in patients with low left ventricular ejection fraction (< 45%) [7]. In addition to the beta1-agonist effects of NE, restoration of coronary perfusion pressure through an increase in diastolic arterial pressure, which may be particularly low in the context of vasodilatory shock [1], might contribute to a beneficial effect of NE on cardiac function. This is especially relevant for patients with coronary artery disease, who represent a large proportion of patients admitted for septic shock. Whether NE can still be beneficial for cardiac function when administered in advanced septic shock, with potential desensitization of beta1 receptors, has yet to be demonstrated.

In the early phase of septic shock, ventriculo–arterial (V–A) coupling, an important determinant of cardiovascular performance, may be impaired in more than 80% of the patients [11]. This uncoupling results in worsening cardiac energetics and performance. Guinot et al. showed that NE can improve V–A coupling and stroke volume in hypotensive post-cardiac surgery patients, although stroke volume was found to increase only in patients with preserved coupling [12].

Dynamic arterial elastance (Eadyn) also provides insight into the cardiovascular state [13]. Eadyn is a functional marker of V–A coupling that can help to indicate or adjust NE therapy. In patients with septic shock, Guinot et al. [13] demonstrated that Eadyn predicts a

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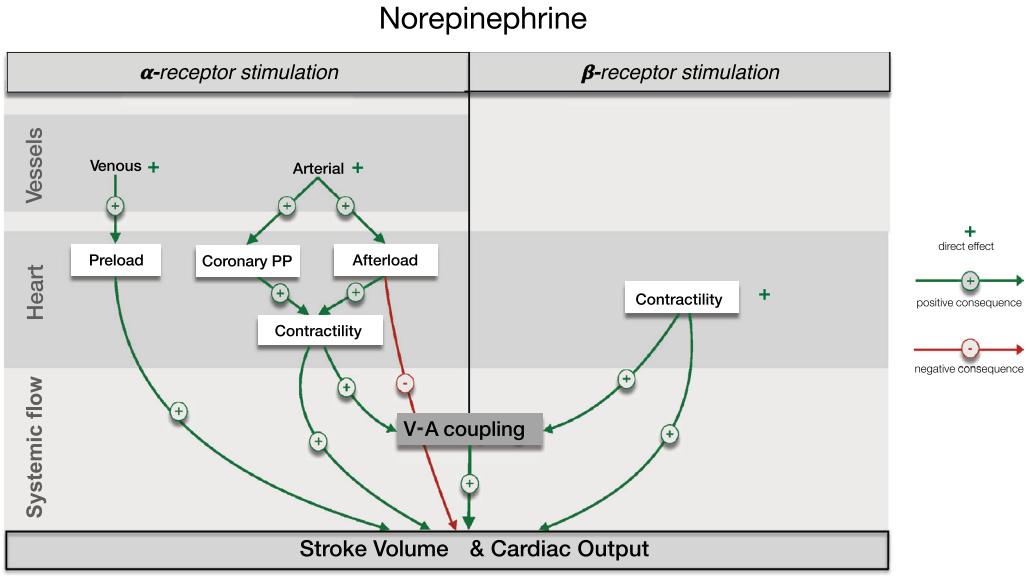

Fig. 1 Schematic representation of the potential mechanisms by which norepinephrine can modulate cardiac output and stroke volume through alpha- or beta-receptor stimulation in septic shock. *PP* perfusion pressure, *V-A* ventriculo-arterial coupling

decrease in MAP in response to a decrease in NE dosage, suggesting its potential in helping clinicians to individualize vasopressor therapy and maintain NE at the lowest necessary infusion rate.

Norepinephrine and tissue perfusion

NE can improve regional and microcirculatory flow by increasing perfusion pressure above the autoregulation threshold in hypotensive patients, but can also decrease flow by excessive vasoconstriction in high doses. This is particularly true for the microcirculation, where the final effect depends on the basal status of microcirculatory flow [1]. Unfortunately, monitors for assessing the effect of NE on regional or microcirculatory flow are not universally available. Therefore, until new research is published, current practice should be to adjust NE infusion to the lowest dose maintaining a MAP $\geq$ 65 mmHg and adequate global perfusion parameters.

Immunologic effects of norepinephrine

Norepinephrine, via both its alpha- and beta-adrenergic effects, may induce immunoparalysis. Where alpha-adrenergic receptors are linked to both pro- and anti-inflammatory actions, beta-adrenergic stimulation exerts anti-inflammatory effects [14]. Both in vitro and in vivo data suggest that NE has substantial anti-inflammatory effects and promotes bacterial growth that can be significantly mitigated by the use of beta-blockers. The clinical relevance in shock states, however, is unknown. In the early phase of shock resuscitation, adequate tissue perfusion and antibiotics may prevail over potential anti-inflammatory effects.

When and how to discontinue norepinephrine support

In septic shock patients with combined NE and vasopressin (VP) support, the discontinuation of VP first may result in faster development of hypotension then when NE is discontinued first [15]. Because NE decreases the release of VP, discontinuation of VP during NE infusion might result in persistently depressed VP levels, resulting in hypotension. The potential role of monitoring Eadyn to guide the reduction of NE infusion [15] appears more impractical than bedside clinical testing.

Directions for further hemodynamic research

Following current recommendations, NE is initially adjusted to maintain a MAP $\geq$ 65 mmHg, but guidelines have established no superior limit, and MAP is typically managed in the range of 65–85 mmHg in the usual clinical setting. However, minor changes in the rate of NE infusion within these limits could significantly influence a range of cardiac function-related parameters including preload, afterload, contractility and V–A coupling, with potential detrimental consequences. Thus, it appears necessary to test a two-step NE titration strategy in septic shock: the first step aimed at achieving a minimum organ perfusion pressure, and then further adjustments focused on the dose associated with the best cardiac performance. In addition, the optimal criteria for initiation

of NE should be addressed, with a focus on the relationship between heart rate and diastolic blood pressure as an indirect assessment of the severity of vascular tone depression.

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WHAT'S NEW IN INTENSIVE CARE

Immunoglobulins and sepsis

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Introduction

Intravenous immunoglobulins are considered as potential adjuvant therapy in sepsis patients. We present a narrative review of recent research into the associations between immunoglobulins and sepsis.

Immunoglobulins and free light chains

Immunoglobulins are glycoproteins secreted by plasma cells. Each immunoglobulin molecule monomer consists of identical heavy and light chain pairs held together by electrostatic forces and disulphide bonds. Based on their heavy chain, there are five immunoglobulin isotypes namely IgG, IgA, IgM, IgD and IgE [1]. There are two types of light chains (kappa and lambda), which are also present in circulation independent of whole immunoglobulin molecules, referred to as free light chains (FLC). The variable regions of immunoglobulin molecules enable cross-linking to bacterial and other antigens (antigen binding). The constant region transduces signals in response to antigen binding (effector function). IgG has four subclasses (IgG1, IgG2, IgG3 and IgG4) and the main functions are secondary antibody responses, opsonisation and complement activation. IgA has two subclasses (IgA1, IgA2) and the main function is mucosal immunity. The key functions of IgM are complement activation and primary antibody responses.

Low immunoglobulins and high free light chains are common in sepsis

Low immunoglobulin concentrations [2] as well as abnormally high FLC levels [3] are seen in most adult sepsis patients. Although low IgG is the commonest quantitative immunoglobulin abnormality in sepsis, a number of reasons explain why low IgG alone does not increase the risk of death in sepsis patients [2]. First, the nadir of immunoglobulin drop is often seen on day 3 following sepsis diagnosis [2, 3]. Second, low levels of multiple endogenous immunoglobulins (IgG1, IgM and IgA) may be required to increase the risk of death [2–4]. Third, the association between low immunoglobulins and mortality is observed in sepsis patients with less severe organ dysfunction [5]. These reasons suggest that the risk of death caused by low immunoglobulins is either lower than other stronger risk factors such as organ dysfunction/comorbidity in sepsis patients or that our understanding of the mechanisms behind this high prevalence of low immunoglobulins in sepsis is incomplete. For example, endothelial abnormalities in sepsis include endothelial dysfunction and endothelial apoptosis leading to leaky capillaries. IgG and albumin are recycled through the Fc neonatal receptors in endothelial cells. There may also be impaired immunoglobulin recycling and leak of immunoglobulin into the extravascular space resulting in low immunoglobulin levels [1]. Immunoglobulin consumption secondary to pathogen opsonisation and neutralisation of toxins could also contribute to low immunoglobulin levels. There is impaired in vitro IgM production by lymphocytes from sepsis patients [6]. In health, light chains are produced in excess of heavy chains. Raised light chains are surrogates for new immunoglobulin production [7]. Therefore, the observation that low immunoglobulin levels with concurrent raised FLC levels suggest impaired immunoglobulin assembly [3]. Importantly, raised FLC levels in sepsis could also result from release of stored light chains during accelerated B-lymphocyte death [8] and impaired excretion due to renal dysfunction, independent of immunoglobulin assembly.

Intravenous immunoglobulins and previous clinical trials in adults with sepsis

Intravenous immunoglobulins are produced by pooling together of serum immunoglobulins from multiple

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donors. There are two types of intravenous immunoglobulin products—IVIG containing only IgG and IVIGAM containing IgG, IgA and IgM. The newer IVIGAM products contain higher levels of IgM. The manufacturing processes, concentrations of different immunoglobulins and the herd immunity of the donors influence the therapeutic effects of IVIG/IVIGAM [1]. The pleiotropic immunomodulatory properties of IVIG are mediated through Fc gamma receptors (FcγR), scavenging of mediators, by negating the biological effects of B-lymphocyte apoptosis and replenishing low immunoglobulins in sepsis [1]. Infection and sepsis increase leukocyte FcγR expression. As the relative expression of inhibitory FcγRIIB versus stimulatory FcγR in sepsis patients is unknown, the extent of immunomodulation with IVIG/IVIGAM therapy may unpredictably differ between patients.

Systematic reviews of randomized controlled trials (RCTs) have showed potential benefits of IVIG/IGAM in sepsis, but important limitations preclude their utilization as a standard of care therapy in sepsis patients [9, 10]. Key limitations include variable trial quality, uncertainty around best responder characteristics, the ideal preparation IVIG vs IVIGAM, or the dosage regimen, timing, duration of therapy, low product availability and lack of cost-effectiveness data (Table 1) [9, 10]. Importantly, although IVIG are often used in sepsis from group A streptococcus infection, the level of evidence that could support such recommendation is lower than for the overall population of patients with sepsis [9, 10]. In addition, IVIG/IVIGAM therapy is associated with adverse reactions such as fever, headache, thromboembolic events, renal dysfunction, aseptic meningoencephalitis, anaphylaxis and detrimental effects of the positive fluid balance on outcomes such as respiratory dysfunction [9, 10]. These issues also highlight the need for better designed IVIG/IVIGAM trials.

Designing future intravenous immunoglobulins trials in sepsis

Sepsis is a heterogeneous illness. Sepsis characteristics such as site of infection and organ dysfunction influence mortality differently [11]. Sepsis-related host responses differ by site of infection [12]. These differences may lead to different IVIG/IVGAM treatment effects in trials. These differences could also inform IVIG/IVIGAM treatment responder characteristics (predictive enrichment) or identify subpopulations (such as patients with exaggerated inflammation) who benefit the most in future trials [13]. As the biological rationale for IVIG/IVIGAM therapy is immunomodulation, the highest tolerated dose with the greatest potential effect needs to be determined. Phase II clinical trials looking at identifying dominant mechanisms affecting endogenous immunoglobulin pathways could also inform future trials. For example, patients with low levels of immunoglobulins

Table 1 Reasons precluding the current use of IVIG/IVGAM in sepsis [9]

Parameter	Explanation from previous trials
Trial quality	Many of these trials were small, were prone to bias primarily due to lack of blinding, had suboptimal adverse event reporting and had low quality when evaluated using standard RCT quality assessment instruments
Population	The trial populations varied in specific characteristics such as infection site, illness severity and organ dysfunction. In meta-analysis of trials, patients with higher illness severity (severe sepsis and shock vs. sepsis) were more likely to benefit from IVIG/IVIGAM therapy
Product	In meta-analysis of trials, IVIGAM had a higher treatment effect compared to IVIG, albeit with significant between trial heterogeneity. Thus, the ideal therapeutic product to use in sepsis patients is unknown. Further, the IVIG/IVIGAM products used differed between trials and this may have contributed to differences in the beneficial (and/or adverse) immunomodulatory effects
Dosing, timing and duration of therapy	Trials have tested widely different IVIG/IVIGAM doses (between 0.2 and 2 g/kg) and different treatment durations (from 2 to 7 days). At low doses only replacement of low immunoglobulin levels is achieved. For immunomodulation, doses greater than 0.5 g/kg are required. In meta-analysis of trials, patients receiving higher doses ($\geq$ 1 vs. < 1 g/kg) over a longer period (more than 2 days) may benefit more from IVIG/IVIGAM therapy
Mechanism of action	Exact mechanism(s) by which intravenous immunoglobulins provide benefit to sepsis patients are unclear. Therefore, no trial to date had targeted or evaluated specific mechanisms, other than generic improvements in inflammation
Adverse effects	Although IVIG/IVIGAM products have several adverse effects well observed in clinical studies. Some of the adverse effects overlap with sepsis manifestations and as such the safety of these products still remains uncertain
Availability and costs	IVIG/IVGAM being a blood product coming from several human donors, its production is resource intensive, costly and limited in capacity. The cost-effectiveness of IVIG/IVIGAM in sepsis remains uncertain
Standard of care	Most trials were conducted more than a decade ago, when the standard of early sepsis management (resuscitation goals, fluids and antibiotic therapy) were different. Therefore, an argument often highlighted is that the IVIG/IVIGAM treatment effects were observed in the context of a suboptimal early sepsis care

with concurrently raised free light chains imply impaired immunoglobulin production which may be a major mechanism contributing to death in sepsis. Interventional cohort studies highlight the potential utility of immunoglobulin therapy in patients with multidrug-resistant bacterial infections [14] and in patients with sepsis-associated coagulopathy [15], which should be followed through to inform future immunoglobulin trials in sepsis.

Conclusions

Immunoglobulin and B-lymphocyte homeostasis is acutely altered in sepsis. Despite biological plausibility, further trials addressing the limitations in current evidence base are required prior to using intravenous immunoglobulins as adjuvant therapy for sepsis patients.

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Author contributions

All authors developed the outline. MSH wrote the first draft. All authors contributed to the critical revision of the manuscript for important intellectual content.

Compliance with ethical standards

Conflicts of interest

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EDITORIAL

How I treat septic shock

Jean-Louis Vincent*

Introduction

Septic shock is the worst form of sepsis, associated with acute circulatory failure and hyperlactatemia [1, 2]. Septic shock is an emergency, with every aspect of management a matter not of hours but of minutes, so I make sure my team has enough people to complete all the necessary interventions efficiently and effectively, under my leadership. My patient management is based on the three major components shown in Fig. 1; importantly, infection and hemodynamic management must be performed simultaneously.

Infection management

Antibiotics are effective, so it makes sense to administer them as quickly as possible. I use the antibiotics most likely to cover all potential organisms but this does not mean that I give every patient broad-spectrum antibiotics. For example, in our hospital, patients with community-acquired peritonitis can be effectively treated initially with amoxicillin/clavulanic acid. Nevertheless, combination therapy is currently advised in septic shock; I usually add amikacin (I do not trust quinolones very much in critically ill patients), sometimes only for a single dose. Of course, if there is any possibility of staphylococcal infection, even in our unit where methicillin-resistant *Staphylococcus aureus* (MRSA) is no longer common, I add vancomycin. Every member of the team knows that all possible samples for culture must be rapidly obtained before antibiotics are given.

When the source of infection is not evident, I reassess the "big five" likely culprits—lungs, abdomen, urinary tract, skin, and catheters—and encourage the nurses to be involved in the search, particularly for skin and catheter-related infection, as they usually look at these better than we do! If a procedure needs to be done, e.g., surgical drainage or catheter removal, I make sure it is done as soon as possible, personally engaging with operating room or interventional radiology staff when necessary.

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Hemodynamic management

Hemodynamic management is conducted in four phases, summarized by the letters SOSD—salvage, optimization, stabilization, and de-escalation [1]; importantly, each phase has a different duration and durations vary in different patients.

S for salvage

In this initial resuscitation phase, my goal is to urgently restore some degree of organ perfusion. Fluids and vasopressor agents are given quickly before much monitoring equipment has been set up. I do not follow any specific protocol for fluid administration, but usually give a first liter (adapted roughly according to the patient's body weight) of intravenous fluid at a fast rate. I then give 1 l/h for a brief period, during initial monitoring with echocardiography. If the condition is severe, I introduce a central venous catheter (or rather, invite a junior doctor to do so!). These two interventions can be achieved in less than 30 min in all patients.

I usually use a crystalloid as my initial fluid and prefer balanced solutions (Ringer's lactate or PlasmaLyte). If I use normal saline (in patients without severe acidosis), I check chloride levels regularly (at least after each liter of saline solution) [3] to ensure hyperchloremia does not develop. In patients with hypoalbuminemia (typically albumin levels < 2.2 g/dl, although there is no strict cut-off) who are already edematous (e.g., patients with decompensated cirrhosis), I may use albumin.

I use norepinephrine as the vasopressor of choice and start it at virtually the same time as fluids. I do not believe we need to wait for the response to fluids to be evaluated before we start vasopressor therapy. I individualize the doses of norepinephrine needed to achieve an adequate mean arterial pressure (not 65 mmHg for

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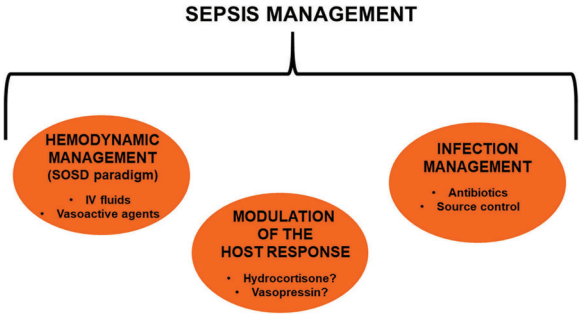

Fig. 1 The three components of septic shock management. *SOSD* salvage, optimization, stabilization, and de-escalation

everyone!). Dopamine should no longer be used. I also avoid epinephrine because I am concerned that it is more arrhythmogenic, may reduce splanchnic blood flow, and may alter cellular metabolism.

O for optimization

Fluid administration must be optimized to ensure adequate tissue perfusion by increasing cardiac output while limiting increase in filling pressures and development of edema. In all patients, I use repeated fluid challenges to guide ongoing fluid administration. For a fluid challenge, I give a small amount of fluid (100–200 ml) over 10 min and watch the dynamic effect on cardiac output and central venous pressure (CVP) [4]. A minimal change in CVP along with an increase in cardiac output suggests that fluid is beneficial and fluids are continued. A large increase in CVP with little change in cardiac output indicates poor fluid tolerance and fluid infusion is immediately stopped. In mechanically ventilated patients who have no spontaneous breathing, I assess the pulse pressure variation (usually visually) or stroke volume variation (using pulse contour analysis) but this situation is rare, because we try to minimize sedative use in our unit. In patients with complex hemodynamic conditions, I still use a pulmonary artery catheter in addition to repeated echocardiographic evaluations, according to the current guidelines [5].

If signs of altered tissue perfusion persist but fluids are no longer tolerated (i.e., there is an increase in cardiac filling without an increase in cardiac output), I add a small dose of dobutamine (3–5 μg/kg/min is usually sufficient) [6]. Severe peripheral vasoconstriction is an incentive to give it. Despite the negative studies on early goal-directed therapy [7], I check the central venous oxygen saturation ($ScvO_2$), because a low value (<70%) can help support the decision to give some dobutamine or a blood transfusion if the hemoglobin concentration is decreased [8]. I measure blood lactate levels every hour during shock [9] to check they are decreasing. If lactate levels stagnate or even increase, I reconsider my strategy and may contact the surgeon or the radiologist to reassess source control.

S for stabilization

This period is best summarized simply by the four letters, STOP. The patient is improving, so we stop fluid resuscitation and move to maintenance fluids. Vasopressor doses are stable or can already start to be decreased.

D for de-escalation

The patient is now clearly improving, so we wean from vasopressor agents and limit fluid intake. If the patient does not eliminate any excess fluid, I give diuretics [or add ultrafiltration as part of renal replacement therapy (RRT)], but this is a rare event. Some people call this phase "de-resuscitation", but this term is inappropriate, because it suggests a backward step to the time prior to resuscitation.

Modulation of host response and other aspects of patient management

Our ability to modulate the host response is still limited. In patients with *severe* septic shock, I believe there is now good evidence that administration of moderate doses of hydrocortisone (200 mg/day in four doses) improves outcomes [10]. I do not believe that fludrocortisone is necessary. I consider vasopressin as a form of compensation for relative vasopressin deficiency and prescribe it at limited doses (0.03 U/min) in the rare cases when vascular tone is extremely reduced, i.e., when hypotension persists in the presence of a high cardiac output. Some people overuse vasopressin, forgetting it can be very harmful if cardiac output is not elevated.

I add vitamins only in cases of malnutrition and I do not give selenium. I avoid enteral nutrition during the shock phase, because there is a risk of gut ischemia. Unless contraindicated, I start nutritional support during the stabilization phase.

Conclusion

Patients with septic shock require rapid, effective, and complete management by a trained group of individuals. Every minute counts to limit organ dysfunction, and good treatment can make a clear difference in complication rates and survival. Many factors, including bacterial pathogenicity, the time course, and various host features such as immune status and comorbidities, can influence outcomes. Hence, I apply individualized treatment, guided by appropriate monitoring systems. Because of the complex nature of these patients and the need for

multiple, diverse, and rapid management strategies, a team approach is required 24 h a day, 7 days a week.

Compliance with ethical standards

Conflicts of interest
The author has no conflicts of interest to declare related to this manuscript.

Ethical approval
This article does not contain any studies with human participants or animals performed by the author.

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FOCUS EDITORIAL

Focus on sepsis: new concepts and findings in sepsis care

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Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. It affects over 30 million people worldwide and represents one of the top causes of death. The Surviving Sepsis Campaign (SSC) guidelines undoubtedly improved the process of care and outcomes in the past decade. The last version of the guidelines was recently published in the journal [1]. As key messages, the Surviving Sepsis Campaign recommends "antimicrobial therapy in the first hour", and "aggressive fluid resuscitation during the first 24 h of management". Hypotensive patients with lactate level of 4 mMol/L or more should receive an immediate crystalloid of more than 30 mL/kg within 3 h and repeated bolus as needed.

Translation of the guidelines to resource-limited settings is hampered by the limited availability of skilled staff, equipment, and laboratory support, compounded by infrastructure and logistical challenges. Subsequently, recommendations relating to core elements of general supportive care for patients with sepsis in these settings have been developed [2]. However, evidence of their efficacy in resource-limited settings are lacking and may differ from trials conducted in other settings.

As a recent example, Andrews et al. [3] randomly assigned patients with sepsis and hypotension in Zambia to be treated using either (1) an early resuscitation protocol including intravenous fluid bolus administration with monitoring of jugular venous pressure, respiratory rate, and arterial oxygen saturation and treatment with vasopressors targeting mean arterial pressure ($\geq$65 mmHg) and blood transfusion (for patients with a hemoglobin level $<$7 g/dL), or (2) usual care in which treating clinicians determined hemodynamic management. Paradoxically the early resuscitation protocol increased hospital mortality from 34/103 (33%) to 51/106 patients (48.1%) [between-group difference, 15.1% (95% CI 2.0%–28.3%)].

Even in high income countries, gaps in the data frequently exist, leading to insufficient clarity on many elements of sepsis management and precluding recommendations on many topics (Table 1). In a retrospective analysis of a large multicenter US database, Marik et al. questioned the impact of a large fluid loading after initial resuscitation on prognosis [4]. They evaluated 35,135 patients with a diagnosis of severe sepsis or septic shock, and identified that a low volume resuscitation (1–4.99 L) was associated with a reduction in mortality of $-$0.7% per litre (95% CI $-$1.0%, $-$0.4% $p=0.02$). However, in patients receiving high volume resuscitation (5 to $\geq$9 L), the mortality increased by 2.3% (95% CI 2.0, 2.5%; $p=0.0003$) for each additional liter above 5 L. This result strongly questioned the dogma of an extra-large fluid loading during the first hours. Another large epidemiological study in the emergency department was not able to demonstrate a survival benefit of an increase of the amount of fluid received in case of severe sepsis and septic shock [5]. Finally, severe weight gain in patients with shock was independently associated with increased mortality in patients who survived the first 3 days [6].

These results altogether suggested that fluid overload is rapidly deleterious and that fluid loading after initial resuscitation should be lower than usually recommended, and guided not only on macrocirculatory, but also microcirculatory parameters.

In an attempt to determine priorities for research within the field of sepsis, the SSC created a new research committee which came up with a list of six questions to be answered in the near future [7], that were quite consistent with priorities set up by another recent

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Table 1 Uncertainties in sepsis

1.	Optimal amount of initial fluids in sepsis-induced hypoperfusion
2.	Ideal clinical parameters and endpoints for volume resuscitation
3.	Time-to-initiation of empirical antibiotics in patients with sepsis without shock
4.	Role of rapid microbiological diagnostic tests in the management of sepsis
5.	Selection of patients for treatment with adjunctive therapies
6.	Efficacy and feasibility of treatment recommendations in resource-limited countries

international expert consensus [8]. Among the top six priorities, five included the ICU stay and included scoring/identification, appropriate therapy of infection, fluids and vasoactive agents, and adjunctive therapy.

Some recent developments are targeting the adjunctive therapy. Several extracorporeal devices have been developed to remove endotoxin, cytokines and other sepsis mediators from the circulation. However, the studies evaluating these devices have been limited and heterogeneous; therefore, further research is warranted [9]. Another potentially interesting therapeutic target in sepsis might be the blood coagulation, in order to counteract excessive coagulation activation. In that perspective, thrombomodulin, which combines anticoagulant and anti-inflammatory effects, represents a promising therapeutic option [10]. Interestingly, in the different clinical trials that evaluate this drug, the rate of bleeding complications was generally relatively low, suggesting that despite major coagulation disorders, anticoagulation of patients with sepsis is quite safe. Thrombomodulin trials have so far allocated anticoagulant treatments to a selected subset of septic patients on the basis of coagulopathy criteria. Following encouraging results of a phase II trial, a larger Phase III study with 800 randomized patients (SCARLET trial, EudraCT number 2012-002251-42) was recently completed, and its results are pending.

In before-after studies, educational and training programs are able to improve the appropriateness of antimicrobial therapy in sepsis [11]. These initiatives clearly improved the process of care, but have not demonstrated any positive impact on outcome. The reduction of the time before initiation of antimicrobial therapy by means of a multifaceted intervention was tested in a cluster-randomized trial involving 4183 patients with sepsis or septic shock [12]. Although the risk of death increased by 2% per hour of delay of the antimicrobial therapy start, and by 1% per hour of delay of the source control, the intervention was not able to reduce neither the median time to antimicrobial therapy (1.5 vs. 2.0 h, $p = 0.41$), nor the mortality. One possible explanation is that immediate antimicrobial therapy may be instrumental in septic shock but of a lesser importance in sepsis, as suggested by two large epidemiological studies [5, 13]. The absence of benefit of early antimicrobial therapy may have been related with the diagnostic uncertainty regarding sepsis and the possible harm associated with unnecessary antibiotics such as toxic or allergic reactions and emergence of bacterial resistance.

The management of multidrug-resistant bacteria (MDRB) in the intensive care setting is more than ever challenging due to their sustained diffusion in healthcare settings and, for some of them, in the community setting [14]. The control of MDRB requires antibiotic stewardship programs that should include faster diagnostic spanning antibiotic resistance, in addition to pathogen identification, and a better assessment of pharmacokinetics parameters. New antibiotics active on MDRB (especially Gram-negative rods) are also urgently needed [15].

The resident microbes of the gut serve essential metabolic and immunomodulatory functions. Profound alterations of richness and diversity of the gut microbiota have been described in ICU patients largely due to antimicrobial exposure [16], but also to many other drugs including antiviral and antiprotozoan therapies [17]. These alterations may favor the emergence of pathogenic bacteria (so called pathobiota) and may contribute to immune dysregulation and multiple organ failure in sepsis.

In a recent cohort, Freedberg et al. showed that at admission in ICU, the intestinal dominance of *Enterococcus* as determined by 16S profiling was associated with a higher risk of infections and increased mortality [18]. In addition, they also observed that the detection of reads assigned to *Escherichia coli*, *Pseudomonas* spp., *Klebsiella* spp. and *Clostridium difficile* was associated with a higher risk of infections caused by those bacteria. While assessing the risk of infections caused by MDRB using clinical parameters remains unsatisfactory [19], the findings of Freedberg et al. suggest that considering specific microbiological traits of the patients could be of help.

Hence, the control and modulation of the intestinal microbiota is a promising approach. As an unaltered microbiota could be associated with a better outcome in ICU patients, some drugs aiming at preventing the impact of antibiotics on the intestinal microbiota could be made available in the coming years, such as gut-delivered active charcoal [20] or recombinant beta-lactamases.

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