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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

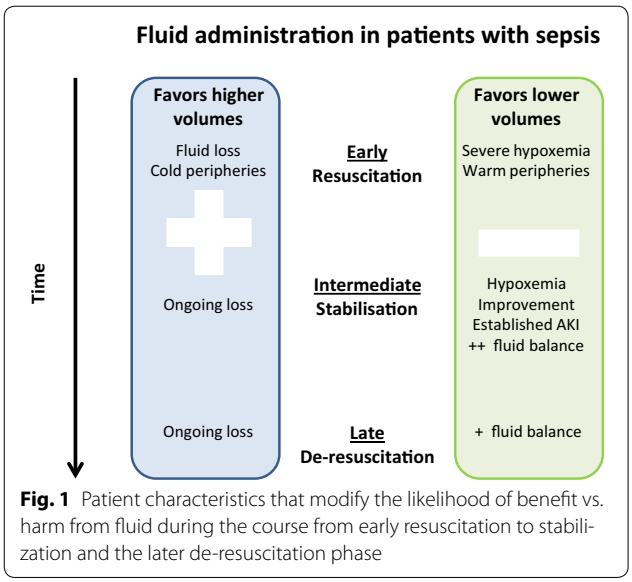

Fig. 1 Patient characteristics that modify the likelihood of benefit vs. harm from fluid during the course from early resuscitation to stabilization and the later de-resuscitation phase

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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