Fluid Resuscitation in Sepsis

Subjects: Critical Care Medicine

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The importance of fluid resuscitation therapy during the early stages of sepsis management is a well-established principle. Current Surviving Sepsis Campaign (SSC) guidelines recommend the early administration of intravenous crystalloid fluids for sepsis-related hypotension or hyperlactatemia due to tissue hypoperfusion, within the first 3 h of resuscitation and suggest using balanced solutions (BSs) instead of normal saline (NS) for the management of patients with sepsis or septic shock.

Keywords: fluids ; resuscitation ; sepsis

1. Introduction

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection, whereas septic shock is a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities are associated with a higher risk of mortality than with sepsis alone [1]. Although the exact worldwide burden of sepsis is difficult to ascertain, it certainly represents a major global health issue. In 2017, there was an estimate of 48.9 million cases of sepsis; during the same year, 11 million sepsis-related deaths were reported worldwide, representing almost 20% of global deaths [2]. Between 1990 and 2017, age-standardized sepsis incidence fell by 37% and mortality decreased by 52.8% [2]. Despite these trends, sepsis still remains a major cause of death worldwide. Interestingly, there are significant regional disparities in sepsis-related incidence and mortality, with approximately 85% of sepsis cases and sepsis-related deaths occurring in low- and middle-income countries [2].

The management of sepsis has not significantly changed over the past 40 years. Current guidelines recommend the early administration of antibiotics and intravenous (IV) fluids, in addition to source control and the judicious use of vasopressors [3]. Fluid resuscitation therapy represents one of the cornerstones of sepsis management [3]. Understanding the pathophysiology of sepsis is crucial in order to determine the role of intensive fluid administration in the initial phase of septic shock.

Although there is a consensus on the need for adequate fluid therapy in sepsis and despite the multiple recent clinical trials examining fluid management in sepsis, the ideal fluid management strategy is still controversial and elusive, as there are no clear guidelines about the optimal fluid resuscitation in critically ill patients with sepsis.

2. Fluid Resuscitation in Sepsis

Despite the scientific advances of the last 20 years, sepsis management has not changed drastically, apart from the introduction of the bundles, which designate multiple interventions that should be completed within a specific time frame. After initial airway and respiratory stabilization, sepsis bundle should be performed within the first 3 h of presentation. The SSC 2021 bundle includes fluid resuscitation, antibiotic administration, lactate measurement and obtainment of cultures [3]. Vasopressors should be initiated if the patient remains hypotensive despite adequate fluid resuscitation [3]. However, a group of 34 European Society of Intensive Care Medicine (ESICM) experts recently suggested to start vasopressors early, before full completion of fluid resuscitation [4]. In the revision of the Surviving Sepsis Campaign (SSC) guidelines in 2018, the 3 and 6 h bundles were combined into a single “1-h bundle” where fluid resuscitation is required in all patients without exception [5]. The implementation of these sepsis protocols in clinical practice have led to decreased sepsis mortality [6].

Fluid resuscitation remains an integral part of sepsis management, since it was first employed during the European cholera epidemic as early as 1830 [7]. The following years, fluid resuscitation was used to treat hypovolemia and restore tissue perfusion pressure in order to improve oxygen transport to cells [8]. Previous versions of SSC guidelines recommended a quantitative resuscitation protocol, that was based entirely on the early goal-directed therapy (EGDT) study [9]. This landmark study showed the benefit of early and aggressive fluid resuscitation in the mortality and the

maintenance of a CVP of 8–12 mmHg and a central venous oxygen saturation ($S_{CV}O2$) of at least 70% [9]. The era of a time-sensitive bundled care was then introduced in sepsis. However, subsequent multi-center randomized controlled trials (RCTs) failed to reproduce the benefits observed in the EGDT trial [10].

There is a growing scepticism regarding aggressive fluid resuscitation, since this approach may lead to massive fluid overload and, inevitably, to adverse outcomes [11]. An increasing number of studies have associated fluid overload to worse outcomes and increased mortality in septic patients [12][13][14]. Current SSC guidelines recommend the early administration of 30 mL/kg of IV fluids for sepsis-related hypotension or a lactate ≥ 4 mmol/L, within the first 3 h of resuscitation [3]. This recommendation remains weak, as it is based on low-quality evidence. Infusing an initial 1 L bolus over the first 30 min and administrating the remainder volume of fluid resuscitation with repeated bolus infusions is an acceptable approach [15]. A proposed algorithm about fluid resuscitation in patients with sepsis is shown in **Figure 1** [3][16][17]. Four distinct phases of IV fluid therapy have been proposed: resuscitation, optimization, stabilization, and evacuation (ROSE), which are all crucial steps in sepsis management (**Figure 2**) [18]. In addition, specific strategies for fluid minimization and de-escalation or de-resuscitation have been reported, demonstrating that fluid restriction is associated with improved outcomes [19][20].

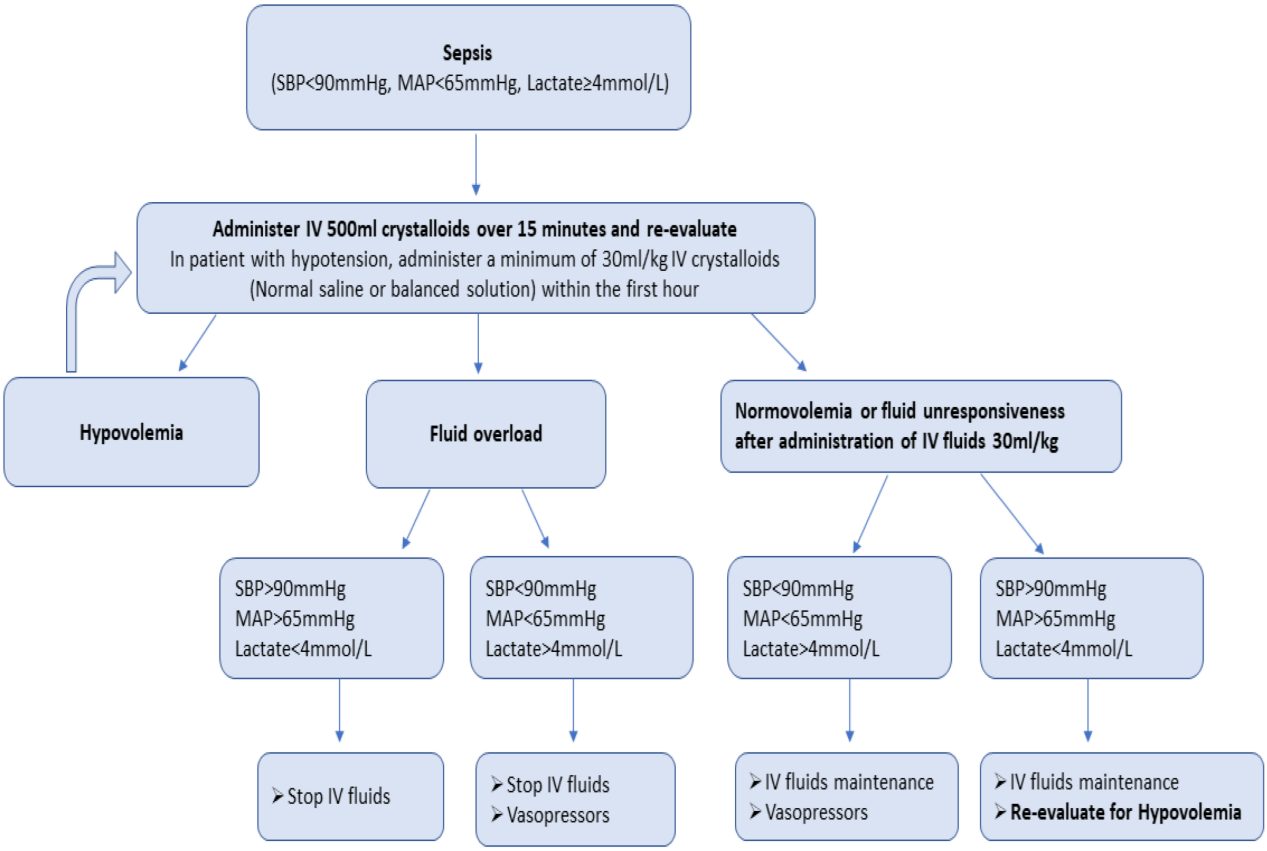

Figure 1. Proposed algorithm of fluid resuscitation in patients with sepsis.

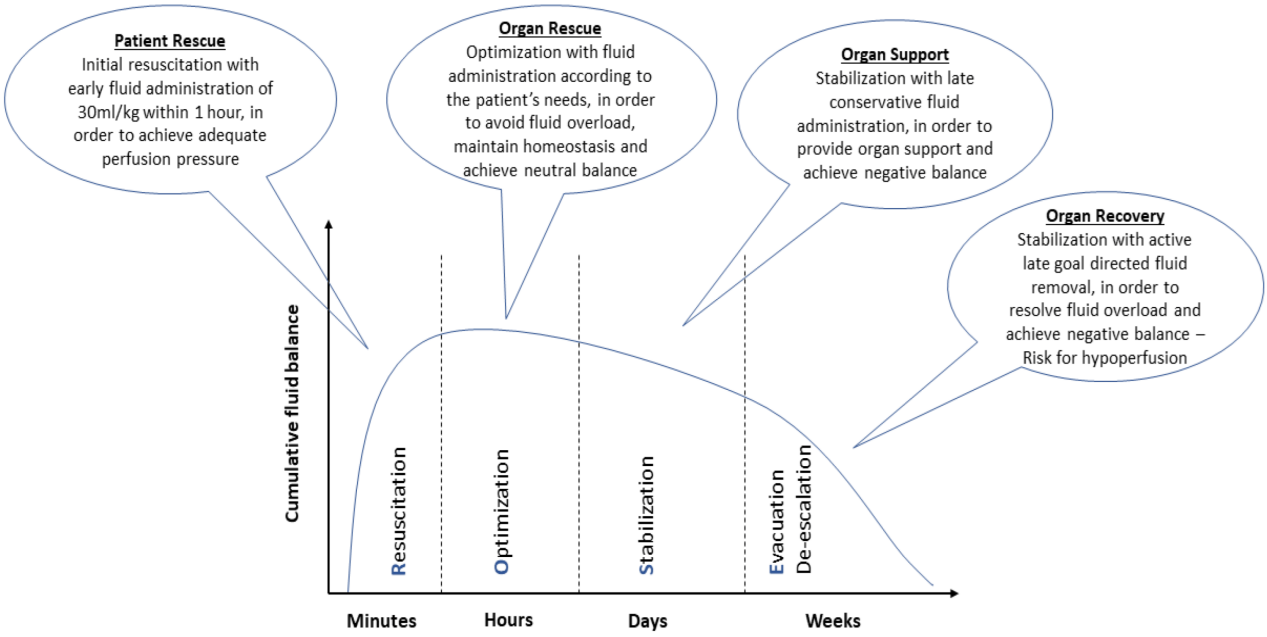

Figure 2. Characteristics of the four distinct phases of intravenous fluid therapy: resuscitation, optimization, stabilization, and evacuation (ROSE).

The 2021 SSC guidelines suggest the use of crystalloid fluids [3]. However, different types of fluids have been proposed. Colloids, including albumin and semisynthetic colloids, such as hydroxyethyl starch (HES), dextrans, and gelatins, were commonly used in the past. Several studies which examined their use in septic patients recommend against the administration of HES and other semisynthetic colloids [21][22][23][24][25]. HES use has been associated with acute kidney injury and the need for renal replacement therapy, as well as with increased mortality [25]. Gelatins have been found to increase anaphylaxis, renal failure, bleeding, and mortality [26]. Hence, the side effects of semisynthetic colloids far outweigh any potential benefits and, according to the SSC guidelines, their use should be avoided in sepsis management [3].

Current SSC guidelines suggest using albumin in septic patients who received large volumes of crystalloids over using crystalloids alone [3]. Albumin is not recommended as the first-line fluid for resuscitation in sepsis due to the lack of proven benefit and its higher cost compared to crystalloids [3]. However, two RCTs, the Saline versus Albumin Fluid Evaluation (SAFE) and the Albumin Italian Outcome Sepsis (ALBIOS) study, as well as a meta-analysis of randomized clinical trials, compared the effect of albumin and crystalloid use in patients with sepsis or septic shock, and showed a trend towards reduced mortality and improved outcomes in the albumin group, without observing serious side effects [27][28][29].

In septic patients, human albumin solution can be given for two indications: to restore or expand intravascular volume and to supplement serum albumin in the septic patients with hypoalbuminemia [30]. In addition, human albumin acts as the most significant modulator of plasma oncotic pressure, which is typically in the 25–30 mmHg range. This is a major endogenous antioxidant agent and a major binding protein of several endogenous compounds and drugs [30]. Albumin appears to have important immunomodulatory effects that likely impact the host inflammatory response in critical illness [30]. The time, dose, and concentration of the albumin, as well as the determination of a specific target for serum albumin level remains controversial. Of note, in the ALBIOS trial, albumin was administered as a 20% solution, with a treatment goal of a serum albumin concentration of 30 g/L until intensive care unit (ICU) discharge or 28 days [28].

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