Chapter 1

Fluid Resuscitation in Septic Patients

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Abstract

Sepsis is a systemic inflammatory response to severe infection that is one of the most common causes of death in critically ill patients in non-coronary intensive care units (ICU). It is well established that fluid resuscitation is a central component of sepsis management and that early fluid resuscitation of septic patients reduces the sepsis-related morbidity and mortality. Several clinical trials have demonstrated the effects of different types of fluid in septic patients’ resuscitation but up to now, there is no consensus over which type of fluid resuscitation should be considered ideal as therapy to septic patients. Resuscitation fluids can be separated based on their composition into crystalloids and colloids. According to different clinical trials, crystalloid solutions seem to be the most appropriate type of fluids for initial resuscitation of septic shock patients. Thus, further clinical studies on the use of fluid resuscitation in septic patients are needed.

Background

Sepsis is one of the most common causes of death in critically ill patients in non-coronary intensive care units (ICU) [1]. In the United States, sepsis accounts for 10% of ICU admissions. The mortality rates have decreased along the years and nowadays is around 25%. Seventeen percent of septicemia or sepsis hospitalizations ended in death, whereas only 2% of other hospitalizations did [2]. Despite significant advances in intensive care treatment over the last years, septic shock remains associated with high mortality rates [3].
Sepsis was first described as a presence of infection (presumed or proven) associated with at least two of four systemic inflammatory response syndrome (SIRS) criteria. Septic shock was defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation [4,5]. However, in 2016, The European Society of Intensive Care Medicine and the Society of Critical Care Medicine (SCCM) published new consensus definitions of sepsis. Thus, now sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection and septic shock is defined as a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality [6]. The differences between the most recently and the first sepsis clinical criteria are listed in table 1.

Pathophysiology

Sepsis can initiate not only through the direct dissemination of pathogens into the bloodstream but also indirectly, as a consequence of traumas, postsurgical complications, hemorrhagic shock and burn [7].

The bacterial sepsis are the most causes of sepsis; most of cases are caused by Gram-negative bacteria (60%) and the remainder of Gram-positive bacteria [8].

Traditionally, sepsis was defined as an excessive systemic proinflammatory reaction but recently, it has been proposed that the proinflammatory stage is followed or overlapped by a prolonged state of immunosuppression [9]. Sepsis has been shown to develop a release of inflammatory mediators in response to an infection that exceeds the limits of the local environment, leading to an imbalance between pro-inflammatory and anti-inflammatory responses, becoming intensified and subsequently dysregulated [10]. This immune process results in an excessive release of cytokines, chemokines and other inflammatory regulators [10].

Several cell types, including neutrophils, B cells, monocytes and macrophages, play important role in initial phase of infection. These through induction of early response genes such as TNF-α and IL-6 rapidly produce cytokines and chemokines, amplifying the inflammatory response. Dendritic cells and lymphocytes are the next cells activated in the coordination of later phases of the immune response [11].

Table 1: New and Old Criteria to Sepsis and Septic Shock diagnosis

<table>
<thead>
<tr>
<th>Old Criteria</th>
<th>New Criteria</th>
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</thead>
<tbody>
<tr>
<td><strong>Sepsis diagnosis</strong></td>
<td><strong>Suspicious/documented infection associated with 2 or 3 changes in qSOF A (quick Sepsis-related Organ Failure Assessment) score that include hypotension (systolic blood pressure ≤100mmHg), altered mental status and tachypnea (respiratory rate &gt; 22/min).</strong></td>
</tr>
<tr>
<td>Tachypnea</td>
<td>Tachypnea</td>
</tr>
<tr>
<td>Fever (&gt;38.3°C)</td>
<td>Suspicious/documented infection associated with 2 or 3 changes in qSOF A (quick Sepsis-related Organ Failure Assessment) score that include hypotension (systolic blood pressure ≤100mmHg), altered mental status and tachypnea (respiratory rate &gt; 22/min).</td>
</tr>
<tr>
<td>Hypothermia (core temperature &lt; 38°C)</td>
<td></td>
</tr>
<tr>
<td>Leukocytosis (White blood cells count &gt;12,000 µL⁻¹)</td>
<td>Leukocytosis (White blood cells count &gt;12,000 µL⁻¹)</td>
</tr>
<tr>
<td>Leukopenia (White blood cells count &lt;4,000 µL⁻¹)</td>
<td>Leukopenia (White blood cells count &lt;4,000 µL⁻¹)</td>
</tr>
<tr>
<td>Arterial hypoxemia (PaO₂/FiO₂ &lt;300)</td>
<td>Arterial hypoxemia (PaO₂/FiO₂ &lt;300)</td>
</tr>
<tr>
<td>Thrombocytopenia (platelet count &lt;100,000 µL⁻¹)</td>
<td>Thrombocytopenia (platelet count &lt;100,000 µL⁻¹)</td>
</tr>
<tr>
<td>Hyperglycemia (plasma glucose &gt;140 mg/dL or 7.7 mmol/L) in absence of diabetes</td>
<td>Hyperglycemia (plasma glucose &gt;140 mg/dL or 7.7 mmol/L) in absence of diabetes</td>
</tr>
<tr>
<td>Hypolactatemia (≤1 mmol/L)</td>
<td>Hypolactatemia (≤1 mmol/L)</td>
</tr>
</tbody>
</table>

| Septic Shock diagnosis |
|------------------------|----------------|
| Sepsis-induced hypoperfusion: | Sepsis associated with: |
| Hypotension (systolic blood pressure < 90 mmHg, despite adequate fluid resuscitation) | Persisting hypotension requiring vasopressors to maintain MAP ≥65 mm Hg. |
| Blood lactate>2 mmol/L, despite adequate volume resuscitation | Blood lactate>2 mmol/L, despite adequate volume resuscitation |
The pathogen recognition occurs in specific cell surface receptors, such as Toll-like receptors (TLRs). The TLR activation leads to recruit of several proteins, including LBP, CD14 and myeloid differentiation protein-2 (MD-2), leading to activation of various transcription factors such as NF-κB and MAPK, which lead to mRNA production of pro- and anti-inflammatory mediators [12-14]. This inflammatory response, when persistent, can lead to organ damage/dysfunction and consequently patient’s death (Figure 1).

*Figure 1*: Sepsis pathophysiology. After infection, the first recruited cells in inflammatory process are macrophages. The endotoxin (LPS) attaches to an LPS-binding protein (LBP) complex and connects to the Toll-like receptor 4 (TLR4) in order to generate an intracellular immune response. The presence of both a cellular wall CD 14 receptor and a cell wall linked MD2 is necessary for adequate stimulation. The intracellular TLR domain binds to the IL-1 receptor-associated kinase (IRA K) in a process facilitated by adapter proteins such as MyD88 (myeloid differentiation protein 88) which induces TNF receptor-associated factor-6 (TRAF6), leading to nuclear translocation of transcription factors as MAPK and nuclear factor-κB (NF-κB) and subsequent activation of cytokine gene promoters.

Among the various mechanisms of innate immunity of the host, cytokines play a major role in regulating the immune response to infection and are responsible for triggering the inflammation [15]. Many cells, including leukocytes, epithelial cells and endothelial cells are responsible to cytokine production [11,15]. Cytokines contribute to the recruitment of leucocytes towards the site of infection and exert their effects on targets by binding to cell surface receptors. However, a dysregulated cytokine release may lead to endothelial dysfunction associated with hypotension and edema, which are frequent findings in septic patients [16].

Despite considerable knowledge of the pathophysiology of the sepsis, clinical trials using different interventions such as immunotherapy has shown negative results, and mortality rates in sepsis remain high [17]. Currently, the main treatment for patients who present with septic shock is fluid resuscitation. Until now, therapy for sepsis has been mostly supportive, and efficient treatments are needed [18].

**Fluid Resuscitation**

The main characteristic of sepsis is systemic vasodilation, with frequently absolute hypovolemia. In addition, the inflammatory response leads to capillary leakage during which the intravascular volume leaks into the interstitium, causing volume depletion leading to decreased organ perfusion and organ failure [19,20].
The fluid resuscitation restores intravascular volume preventing hemodynamics changes and avoid tissue injury. On the other hand, some studies have showed that patients treated with positive fluid balance have presented poor outcomes besides of decreased lung function, poor gut perfusion, increase in abdominal pressure and increased mortality risk [21,22]. Therefore, previous studies have demonstrated that an adequate fluid resuscitation is an important treatment of sepsis [23,24]. The most recent Surviving Sepsis Campaign guideline recommend 30 cc/kg of crystalloid within the first 3 h for hypovolemic septic patient [5].

Despite extensively used in clinical practice, there has been no consensus on the optimal type and amount of fluid is appropriate during volume resuscitation of septic patients.

**Types of Fluid**

Resuscitation fluids can be separated based on their composition into crystalloids and colloids. Crystalloid solutions are composed of molecules that can diffuse across cell membranes. They are solutions containing water, inorganic ions and small molecules. Crystalloids are used to replace fluids such as blood lost in trauma and in prehospital care, in order to provide expansion supporting the restoration of blood pressure. They can be divided into balanced and unbalanced fluids [24,25].

Unbalanced fluids, such as normal saline (NS), are isotonic to plasma and receive that denomination, because they have a strong ion difference of zero, as opposed to plasma and balanced fluids such as Ringer’s Lactate and Ringer’s Acetate, that were developed to resemble the composition of plasma [26].

Colloids are substances that do not diffuse through vascular membranes due to their high molecule weight, and thus, are limited to the intravascular space. These fluids have higher capacity of intravascular expansion and a higher oncotic pressure when compared to crystalloids. Colloids exert an osmotic effect drawing fluid from both the interstitial and intracellular compartments, expanding the vascular compartment and effectively reducing edema especially in pulmonary and cerebral tissues [27-29].

In the following sections, we will discuss the different types of fluids available for septic shock resuscitation. Table 2 and Table 3 compares the composition and characteristics of mainly crystalloids and colloids used in septic patients.
Table 2: The main crystalloid solution used in septic patients and their characteristics.

<table>
<thead>
<tr>
<th>Solution</th>
<th>Osmolarity (mOsm/L)</th>
<th>pH (mol/L)</th>
<th>Electrolytes (mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9% Saline</td>
<td>308</td>
<td>5.7</td>
<td>Na⁺ 154, Cl⁻ 154, K⁺ 0, Ca++ 0</td>
</tr>
<tr>
<td>Ringer’s Lactate</td>
<td>273</td>
<td>6.5</td>
<td>Na⁺ 130, Cl⁻ 109, K⁺ 4, Ca++ 3</td>
</tr>
<tr>
<td>Ringer’s Acetate</td>
<td>275</td>
<td>6.7</td>
<td>Na⁺ 1280, Cl⁻ 1280, K⁺ 0, Ca++ 0</td>
</tr>
<tr>
<td>Hypertonic Saline</td>
<td>2400</td>
<td>5.9</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: The main colloids solution used in septic patients and their characteristics.

<table>
<thead>
<tr>
<th>Solution</th>
<th>Osmolarity (mOsm/L)</th>
<th>Oncotic pressure (mmHg)</th>
<th>Plasma expansion (%)</th>
<th>Electrolytes (mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HES</td>
<td>300-326</td>
<td>23-82</td>
<td>100-160</td>
<td>Na⁺ 154, Cl⁻ 154</td>
</tr>
<tr>
<td>Albumin 4%</td>
<td>300</td>
<td>19-30</td>
<td>70-100</td>
<td>Na⁺ 140, Cl⁻ 128</td>
</tr>
</tbody>
</table>

Litmus has reported benefits of albumin based on its physiological effects in nitric oxide modulation, primarily binding and transportation of various substances in the blood; which may be of particular relevance in critically ill patients, and not only to regulate osmotic pressure as other resuscitation fluids [30,31].

The beneficial effects of resuscitation using albumin in patients with severe sepsis remains to be clarified. A subgroup analysis among septic patients enrolled in the Saline versus Albumin Fluid Evaluation (SAFE) study, where authors have compared albumin and saline for fluid resuscitation in Intensive Care Units (ICU), showed a tendency of mortality reduction in favor to albumin when compared to normal saline. In patients with severe sepsis, the mortality rate in those who received albumin was 30.7%, compared with a mortality rate of 35.3% of those who received normal saline [32,33]. More recently, the ALBIOS study (Volume Replacement With Albumin in Severe Sepsis) randomized 1,818 severe sepsis and septic shock patients to receive either 300mL of 20% albumin plus crystalloid or to receive crystalloid alone from randomisation until day 28, or ICU discharge, aiming to maintain serum albumin ≥30g/L. However, no statistically significant difference in 28-day mortality between the two groups was observed in this study [34].

Taken together, the findings of both studies suggest a potential beneficial effect of albumin for resuscitation of septic patients during the initial admission period to the

Colloids

Albumin

Albumin is the most used colloid with a strong resuscitation effect. In addition, albumin has anti-inflammatory property and have been shown to be fluid sparing and decrease mortality in the subset of septic patients [20].
ICU. However, at present, this remains the only evidence-based indication for albumin administration.

**Hydroxyethyl Starch**

Hydroxyethyl starch (HES) is a semisynthetic colloid solution derived from chemically modified plant starch. The HES is commonly used for restrictive fluid strategy due to a high plasma expansion capacity with lower volume administration. There are different HES solutions that vary in the average molecular weight of the starch molecule, the degree of hydroxyethyl substitution of the starch molecule, and the concentration of the solution [29,35].

HES is the only semisynthetic colloid for which large trials enrolling patients with sepsis have been conducted. The larger Scandinavian Starch for Severe Sepsis/Septic Shock (6S) trial compared the use of HES and Ringer’s Lactate as fluid resuscitation in 804 patients with severe sepsis. The authors have concluded that patients who received HES had a higher risk of death at 90 days, were more likely to receive renal-replacement therapy and had fewer days alive without renal-replacement therapy and fewer days alive out of the hospital when compared to Ringer’s Lactate [36].

The 2004 Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) trial comparing Ringer’s Lactate and 10% HES 200/0.5 among 537 patients with severe sepsis was stopped early for increased acute kidney injury (34.9% vs 22.8%; P 5 .002) and a trend toward increased 90-day mortality (41.0% vs 33.9%; P 5 .09) with HES [37].

Thus based on fact that these studies do not support the efficacy of HES in fluid resuscitation of septic patients the use of HES in the treatment of critically ill patients, specifically in those with sepsis should be avoided.

**Crystalloids**

**Normal Saline**

Normal saline is the most commonly prescribed fluid therapy for sepsis in the United States. It is considered an isotonic solution, with osmolality closer to the plasma osmolality (287 mOsm/kg) [30,38]. Several studies have demonstrated the adverse effects of saline-induced hyperchloremic metabolic acidosis on blood pressure in septic patient [39-41]. Besides the hyperchloremic acidosis, large amounts of normal saline infusion can compromise coagulation, kidney function and the immunologic response [38].

Because of these findings, the role of normal saline in the treatment of septic patients is suffering re-evaluation and “balanced” crystalloids (e.g. Ringer’s lactate and Ringer’s acetate) may offer a safer alternative in these patients.

**Ringer’s Lactate**

Balanced solutions have been proposed as an alternative to normal saline. Ringer’s Lactate is a mild hypotonic solution (273 mOsm/L) and has potassium and calcium
in its composition [38]. They have an electrolyte content more closely resembling that of plasma including a much lower chloride concentration than normal saline [42].

Several studies have demonstrated the benefit of balanced fluids therapies in septic patients. The retrospective study published by Raghunathan et al, performed in 50,000 septic patients, showed a decreased mortality rate in patients who received any balanced crystalloid compared with those who received unbalanced crystalloids such as normal saline [43]. Additionally, Rochwerger et al performed a meta-analysis investigating the effect of different fluid therapies on mortality in septic patients and suggested that balanced crystalloids were associated with increased survival in septic patients compared with normal saline [44].

However, in the sepsis literature, data comparing other crystalloids to Ringer’s Lactate are lacking. Some studies have shown problems associated with the use of Ringer’s Lactate as inability to use lactate as a marker of hypoxia and the fact that lactate may increase oxygen consumption [45]. Furthermore, Ringer’s Lactate cannot be used in patients with lactic acidosis and is often contraindicated in septic patients, who have a hepatic disruption of lactate clearance [24].

**Hypertonic Saline**

The beneficial effects of hypertonic saline were first described by Velasco and colleagues in the treatment of hemorrhagic shock [46]. Next, innumerous studies showing that hypertonicity affects the immune system, preventing bacterial translocation, improving blood volume expansion, and decreasing pulmonary neutrophil infiltration and lung injury [8,46–48]. These benefits were attributed to diminished leukocyte-endothelial cell interaction.

Fluid resuscitation with hypertonic saline (NaCl 7.5%) was postulated to achieve hemodynamic normalization by recruitment of fluid from the intracellular space, thereby limiting interstitial edema. Thus, the use of hypertonic saline as fluid resuscitation has been described as a promising therapeutical agent mainly by the diminished amount of fluid necessary [49].

Previous studies in hypovolemic shock and pancreatitis indicated that infusion of hypertonic saline reduced the production of pro-inflammatory cytokines and increased the production of anti-inflammatory cytokines, such as IL-10 [8,50–52]. Other studies using hypertonic saline in the setting of sepsis have reported hemodynamic improvements, which lead to better tissue perfusion and reduced necrosis and inflammation. Recent clinical trial using hypertonic saline (7.5% NaCl) noted an improvement in cardiac contractility and vascular tone in patients receiving hypertonic saline compared to normal saline [8].

Although the use of hypertonic saline resuscitation presents benefits in controlling the inflammatory process and in reducing mortality in experimental models, clini-
Clinical trials have failed to demonstrate reduced mortality in hemorrhagic shock and trauma [47,53,54]. The trial performed by Bulger et al. [53] failed to observe survival benefits after 28 days in trauma patients who received hypertonic fluid compared with normal saline. On the other hand, studies of septic patients have revealed that although hypertonic saline resuscitation did not produce survival rate improvements, it decreased the incidence of multiple organ failure and improved hemodynamic parameters; therefore, the effectiveness of HS treatment in the clinical setting has been inconsistent [47,53].

A recent study published by Petroni and colleagues using an experimental model of sepsis-induced acute lung injury inflammatory have showed that the therapeutic window for hypertonic saline resuscitation benefits is very small: close to 15 min after the injury and after that, the fluid resuscitation using hypertonic saline was associated with aggravated pulmonary inflammation and tissue damage. This narrow period is an important limitation for the use of HS in clinical practice. Thus, further clinical studies will be necessary in order to establish the therapeutic benefits of fluid resuscitation with hypertonic saline in septic patients [47].

**Conclusion**

Despite extensive study, there is no consensus over which type of fluid resuscitation should be considered ideal as therapy to septic patients. Crystalloids remain the clinician’s choice for sepsis resuscitation fluid because they are widely available, inexpensive, and have not been shown to result in worse outcomes. Balanced crystalloids such as Ringer’s Lactate are probably superior to normal saline, but further prospective studies are necessary. Albumin appears to be equivalent to crystalloids in terms of outcomes, but it has an issue due to higher cost. Hydroxyethyl starches seem to increase mortality and acute kidney injury in septic patients and are no longer indicated in the treatment of this patient population. There is very limited clinical data regarding the use of hypertonic saline in septic patients. Thus, there is a need for further research on the use of fluid resuscitation in septic patients to develop evidence-based guidelines for future clinical decision making.

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