|| ISSN(online): 2589-8698 || ISSN(print): 2589-868X ||
International Journal of Medical and Biomedical Studies
Available Online at www.ijmbs.info
NLM (National Library of Medicine ID: 101738825)
Index Copernicus Value 2021: 70.61
Review Article Volume 6, Issue 12; December: 2022; Page No. 32-40

Recent Advances in Fluids and Electrolyte Management in Sepsis

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Article Info: Received 22 November 2022; Accepted 18 December 2022

DOI: https://doi.org/10.32553/ijmbs.v6i12.2633

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Conflict of interest: No conflict of interest.

Abstract

Sepsis condition can cause life-threatening complications including organ dysfunction, circulatory failure, or mortality. Electrolyte abnormalities, including hyperkalaemia, hyponatremia, hypophosphatemia, and hypocalcaemia, have been observed in the later stages of sepsis due to cellular damage or ion channel dysfunction. Fluid resuscitation has been suggested as the common intervention to improve the patient's condition when in septic shock. Fluids can help in an enhanced distribution of both intravascular and extravascular compartments, thereby increasing cardiac output. Timely fluid administration has shown improved survival rates with fewer severe microcirculatory alterations and mitochondrial dysfunctions. Fluid and electrolyte management is an effective strategy for treating sepsis but certain factors including timing, dosage, type of fluid and the health status of the individual needs to be carefully considered. Early intervention therapy seems to be effective in individuals with sepsis and has minimized the requirement for additional fluid administration. Certain aspects of fluid management including the future potentiality of dynamic fluid responsiveness and the role of albumin administration in sepsis treatment still need to be clarified. This review focuses on the updated management strategies that can be used for fluid and electrolyte management in individuals with sepsis.

Keywords: Sepsis; Fluid resuscitation; electrolyte replacement therapy; albumin; intravenous therapy; septic shock

Highlights

- In patients with sepsis, fluid resuscitation has been an effective intervention and earlier administration of therapy has minimized the need for additional fluid administration.

Future research lends scope for improvement and advancements in electrolyte replacement therapy, effects of resuscitation, the effectiveness of fluid responsiveness and role of albumin in fluid management.

Introduction

Sepsis is a condition of dysregulated systemic reaction to an infection that can cause life-threatening complications including organ dysfunction, circulatory failure, or mortality in the worst-case scenario. (1) Sepsis is one of the common causes for ICU hospitalization and a meta-analysis study found that the incidence rate of sepsis was 288 cases per 100000 person-years. (2)

Septic shock is a subtype of sepsis characterized by hemodynamic alterations that happen as a result of impaired tissue perfusion. Fluid resuscitation has been suggested as the common intervention to improve the patient's condition when in septic shock. Timely fluid administration has shown improved survival rates with fewer severe microcirculatory alterations and mitochondrial dysfunctions. (3) (4) Fluids can help in the enhanced distribution of

compartments, both intravascular and extravascular, thereby increasing cardiac output. Timely expansion of the plasma volume through fluid resuscitation can prevent tissue hypoxia and preserve the organ's functioning. However, the distribution of fluids depends on electrolyte content, oncotic properties of infused fluids, and microvascular permeability.

In addition to fluid imbalance, electrolyte abnormalities are common in individuals with sepsis. Hydro-electrolyte balance is critical for maintaining homeostasis and also plays an important role in tissue perfusion and protecting cellular functions. Electrolyte abnormalities, including hyperkalaemia, hyponatremia, hypophosphatemia, and hypocalcaemia, have been observed in the later stages of sepsis due to cellular damage or ion channel dysfunction. Few studies have also demonstrated that a minor change in electrolyte content can elevate cellular damage in septic patients. (5)

Improper fluid and electrolyte management in individuals with sepsis can lead to dehydration, hyperosmolarity, renal failure, oedema, pulmonary dysfunction, congestive heart failure, intraventricular haemorrhage, and electrolyte abnormalities. Therefore, fluid and electrolyte management is an imperative aspect of treatment in individuals with sepsis. There are still arguments regarding the best management process to be followed for fluid and electrolyte imbalance in sepsis. This review focuses on the updated management strategies that can be used for fluid and electrolyte management in individuals with sepsis.

Recent advances in fluid and electrolyte management

1. Intravenous fluid therapy (IV fluid therapy)/Restricted infusion therapy

Intravenous fluid therapy is one of the commonly used therapies that help to maintain homeostasis in septic patients. (6) The usage of IV fluid therapy mainly depends on the signs and indications shown by the patient. It is mainly employed when patients in critical condition exhibit severe hypovolemia, sepsis, oliguria, or hemodynamic alterations. (7)

Vincent and De Backer (Figure 1) have recently described the four different clinical phases of fluid therapy during the time of severe illness in patients. (6) This new framework enables to design an individualized fluid therapy according to the patient's requirements and responsiveness as a seriously ill patient can have widely varying fluid requirements. Monitoring the patient at each stage can help to propose the appropriate fluid requirement for each patient.

Apart from following this framework, fluid management should be designed in such a way as to optimize tissue perfusion and reduce the risk of organ failure. Comorbidities including renal dysfunction and cardiac complications have to be taken into consideration as they also dictate the amount and type of fluid to be used. Proper fluid de-escalation and mobilization have to be performed accordingly to prevent cumulative effects of fluid administration including fluid accumulation. (8) When medications are provided via intravenous fluids, it is best to restrict the volume of IV fluids, however overt fluid and electrolyte damages can be corrected according to the required IV volumes. (9)

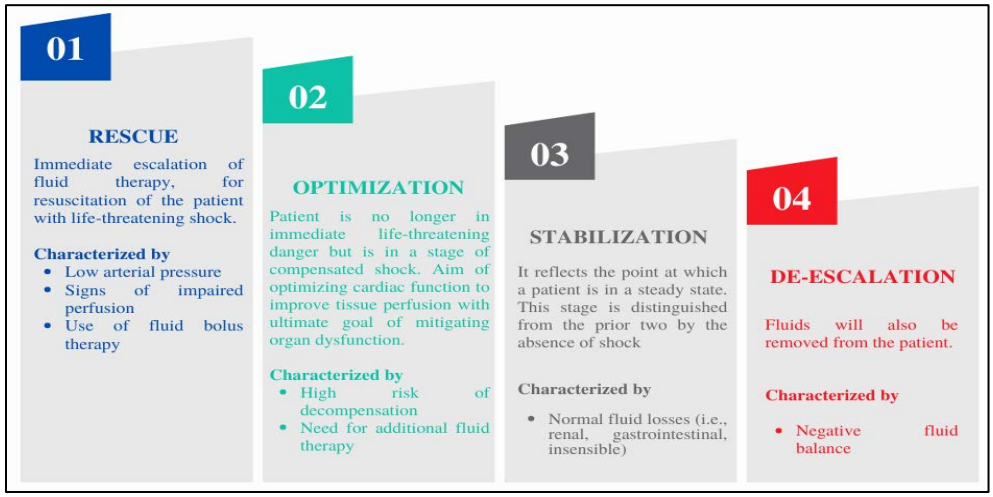

Figure 1: Stages of fluid resuscitation

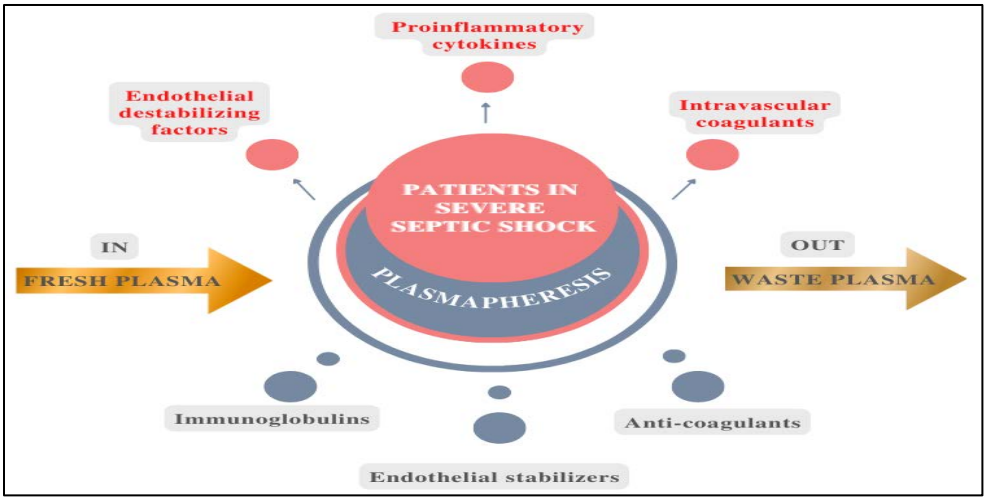

Figure 2: Mechanisms targeted by Plasma replacement therapy

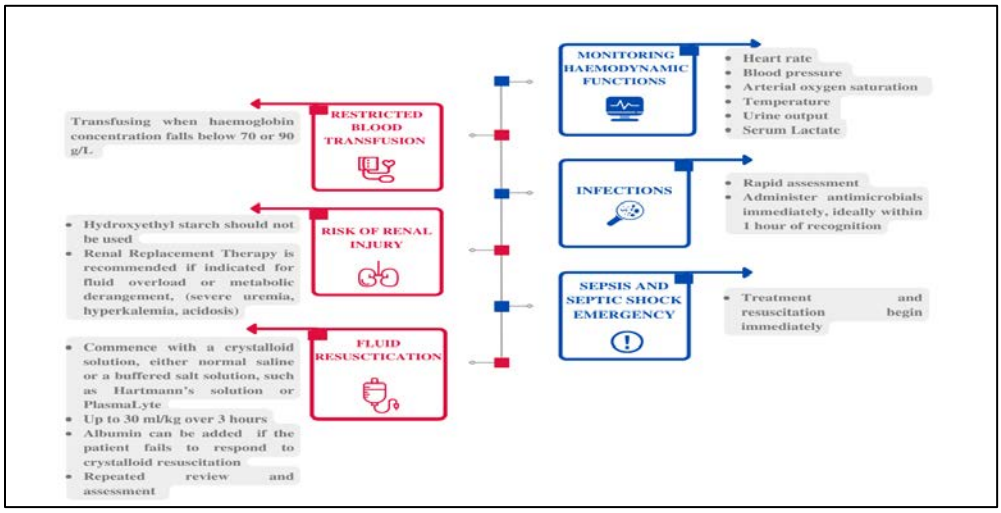

Figure 3: Guidelines and recommendations for fluid and electrolyte management in sepsis

Early target-controlled plasma volume replacement

Early target-controlled and individualized plasma volume replacement can be used to achieve hemodynamic stability and proper oxygenation of tissues which is highly necessary in the case of individuals with sepsis. (10) (11) Recent studies have suggested that plasma volume replacement should be done according to flow-based parameters and passive leg-raising (PLR) tests that can accurately predict volume responsiveness. PLR functions as a reversible self-volume challenge for 250ml of blood and the hemodynamic changes that occur between 30 to 90s after the PLR test can predict the volume responsiveness in the given clinical setting. (12) (13) (14) Plasma replacement therapy aims to target different molecular mechanisms in order to relieve a patient from septic shock as illustrated in Figure 2.

The selection criteria for suitable fluids required for plasma replacement therapy still face a lot of debate. The suitable fluids which are frequently used are crystalloid solutions and colloid solutions. The crystalloid solution is mainly composed of water and electrolytes that diffuse into the interstitial space and can cause oedema while the colloid solutions are unable to pass through the semi-permeable biological membranes because of their macromolecular size. The particles present in colloid solutions can exert colloid osmotic pressure which retains the water in intravascular space. This postulates the fact that lower volumes of colloidal solutions are required compared to crystalloid solutions to achieve stable hemodynamics. (15) (16)

Plasma volume replacement has been considered the last resort in the case of patients who have undergone a septic shock. Several studies (17) (18) (19) (20) have found that plasma replacement is associated with reduced mortality rates, endothelial injuries, and improved organ functioning. An individualized and target-controlled plasma replacement therapy has been shown to have minimized the risk of harmful fluid overload. (21) (22) However, it has to be noted that plasma replacement can have adverse reactions including transfusion-related acute lung injury (TRALI) which can lead to mortality in severe cases. Another known condition, Transfusion-associated cardiac overload (TACO) (23) can also occur in the case of severely ill patients who typically presents with acute respiratory distress and tachycardia. Apart from these concerns, the limited availability of plasma is also a looming concern as females are not allowed to donate plasma. Identification of the necessary plasma components beneficial for the treatment has paramount importance and it varies according to the health status of the individual. An improved understanding of the mechanism of action of plasma is warranted to understand the efficacy of plasma for treating individuals with sepsis. (24) Even though plasma replacement has shown preliminary good results, certain factoring parameters including the dosage, timing, duration, and replacement fluids have to be standardized by conducting further trials.

2. Albumin Replacement therapy

The utility of albumin replacement therapy is still unclear. The current evidence suggests that the administration of albumin to individuals with sepsis or those who are in a septic shock is a reliable strategy. (25) The SAFE (26) and ALBIOS trials (27) suggested that using albumin instead of saline was safer as it lowered the mortality rates and the total volume of fluids required for fluid resuscitation also reduced considerably. However, it was noticed in the ALBIOS trial that the use of albumin to treat hypoalbuminemia was not successful even though it improved hemodynamic stability. A recent propensity score-matched cohort study (28) concluded that using albumin during the initial hours of resuscitation did not deliver any beneficial results in individuals with sepsis. Furthermore, opting for albumin replacement therapy is not affordable due to the high relative

cost of albumin. Questions regarding the dosage, concentration, and target serum albumin levels have to be answered before clinically putting this therapy into practice. The clinical benefits and parameters of albumin replacement therapy in individuals with sepsis warrants further investigation and confirmation.

3. Blood transfusion Treatment

Organ dysfunction or failure is common in septic patients and blood transfusion is often performed to restore the RBC delivery and oxygenation in the tissues. The effect of blood transfusion in tissue microcirculation of individuals with sepsis is yet to be deciphered. (29) It is recommended that RBC transfusion be performed only when the haemoglobin concentration is below $7gdL^{-1}$ in adults in the absence of severe hypoxemia, myocardial ischemia, or acute haemorrhage. (30) Blood transfusion is highly restricted in septic patients as they are highly susceptible to the transfusion-related risk of infection which can even lead to mortality in later stages. The immunomodulating effects of blood transfusion can lead to adverse outcomes in patients. A retrospective study found a correlation between the number of RBCs transfused and the onset of secondary infections in individuals with sepsis. (23) The storage period of RBCs is an important confounding factor that can help to estimate the risk rate of infection. Another study (31) found that a restrictive transfusion threshold can significantly reduce exposure to blood products. However, further studies are required to understand ways in which the secondary infection caused by blood transfusion can be restricted.

4. Electrolyte infusion treatment

Electrolyte management is a crucial aspect of sepsis treatment. Chances of electrolyte (phosphorus, sodium, potassium, calcium) imbalance are common during the early stages of sepsis. A study conducted by Harbi et al (32) found a strong correlation between hypophosphatemia and mortality in severely ill septic patients. A low serum phosphate level can deteriorate the hemodynamic instability resulting in decreased myocardial contractility and the occurrence of cardiac arrhythmias in patients. Phosphate replacement (33) therapy has been shown to have reduced the incidence of cardiac arrhythmias, especially in patients who are in the early stage of sepsis. Future investigations should focus on analysing the additional benefits of phosphate replacement therapy apart from reducing the risk of cardiac arrhythmias in seriously ill patients and further studies are required to understand the reasons why phosphate replacement therapy is not beneficial in the later stages of sepsis as in the initial stages.

5. Blood Purification Treatment

Blood purification treatment is considered an additional supportive therapy for individuals with sepsis. One of the most studied methods is hemoadsorption where the blood is passed through adsorbent membranes (polymyxin B is the commonly used adsorbent membrane) for the removal of the endotoxins. A meta-analysis studied the efficacy of hemoadsorption and found that this technique reduced mortality rates in individuals with sepsis. Blood purification can be also performed via coupled plasma filtration adsorption (CPFA), which is a combination of plasma filtration and hemadsorption, however, this did not yield any promising results as the hemoadsorption. (34)

Guidelines and recommendations for fluid and electrolyte management in sepsis

The Surviving Sepsis Campaign (SSC) has not released any specific guidelines or recommendations pertaining to fluid and electrolyte management in individuals with sepsis. However, the general guidelines and recommendations provided by SSC can help physicians to take the required decisions for selecting and designing the appropriate treatment for individuals with sepsis. Some of the guidelines critical for fluid and electrolyte management in individuals with sepsis are given in figure 3. (10) (11)

It is already understood that fluid resuscitation is the cornerstone for sepsis treatment. Fluid management in sepsis varies widely with practice. Several studies have been conducted to compare the adverse reactions and mortality rates associated with sepsis treatments, evaluate the efficacy of resuscitation fluids, and estimate the reliability and success rates of different sepsis treatments. Table 1 consolidates the major interventions found by different studies conducted to evaluate the status of fluids and electrolytes management in sepsis.

Research study	**Remarks**	**Ref**
Fluid response evaluation	● Personalized monitoring can increase proper fluid resuscitation ● Dynamic fluid responsiveness is directly correlated with improved patient outcomes	(35)
Fluid management and renal function	● Restrictive fluid management was not associated with kidney dysfunction in patients suffering from malaria. ● Crystalloid administration (2-3ml/kg) during the initial 24 hours without bolus therapy is recommended	(36)
Effect of albumin on patients with severe sepsis	● Albumin administration reduced the risk of organ dysfunction including renal failure compared to saline ● Mortality rate also decreased in severe individuals with sepsis with albumin administration	(37)
Effect of albumin replacement in patients with septic shock	● The survival rate did not show any improvement with albumin replacement therapy at 28 and 90 days.	(27)
Conservative fluid management in sepsis	● The conservative fluid management did not affect the daily mean fluid balance (500ml) in patients with sepsis	(38)
Effect of therapeutic plasma exchange in individuals with sepsis	● Early institution of therapeutic plasma exchange may contribute to better outcomes in patients with sepsis-induced multisystem organ failure	(38)
Effect of therapeutic plasma exchange in patients with severe sepsis and septic shock	● Early institution of therapeutic plasma exchange can lead to better hemodynamic stability in patients with severe sepsis and septic shock	(39)
Role of restrictive Intravenous fluid therapy in patients with sepsis and septic shock	● Restrictive fluid therapy did not show any negative outcomes in septic patients with a decrease in hours of mechanical ventilation	(40)

Conclusion

Fluid and electrolyte management is an effective strategy for treating sepsis. This strategy depends on certain factors including timing (initial or middle stage), dosage (e.g., albumin, potassium), type of fluid (crystalloid or colloidal solutions), and the health status of the individual. Early intervention therapy has minimized additional fluid administration which seems to be effective in individuals with sepsis. Certain aspects of fluid management including the future potentiality of dynamic fluid responsiveness and the role of albumin administration in sepsis treatment still need to be clarified. Future research lends scope improvement in electrolyte replacement therapy, effects of resuscitation, the effectiveness of fluid

responsiveness, the role of albumin, and standardization of composition of the preferred fluids for resuscitation in individuals with sepsis.

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