

Volume Resuscitation in Sepsis

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Abstract

Fluid resuscitation in sepsis is the subject of long and complicated debate. Recent research has called into question several entrenched clinical positions. Currently, crystalloid, titrated to specific hemodynamic parameters is the leading modality of resuscitation in early shock. Central venous pressure, mean arterial pressure, and oxygen saturation of mixed venous blood are the indices which measure the adequacy of fluid resuscitation therapy. Lack of more accurate and earlier predictors of sufficient fluid resuscitation precludes even more effective therapeutic measures. In this review we examine the current evidence that drives fluid resuscitation therapy.

Keywords: Sepsis; Volume resuscitation; Central venous pressure; Mixed venous saturation; Lactic acid

Introduction

Cardiovascular system performance in early sepsis exhibits low systemic vascular resistance, increased endothelial leakage, microcirculation impairment, and aberrant cardiac function [1]. The first two conditions create a state in which profound depletion of intravascular volume is present [2,3]. This is further enhanced by large evaporative and gastrointestinal fluid losses. As a result hemodynamic stability and organ system functions are compromised. Currently, there are two primary means to correct the function of the cardiovascular system: fluid resuscitation and vasoactive medications [1]. Repletion of the intravascular volume is an initial and mandatory step in resuscitation of the septic patient [1,4,5]. Insufficient fluid resuscitation hampers the clinical efficacy of the pressors and may lead to worsening lactic acidosis [6]. On the other hand, excessive fluid resuscitation leads to expansion of the interstitial volume, which, in the setting of enhanced endothelial leak, seen in sepsis, hampers the delivery of the oxygen to the tissue and increases the risk of the end-organ damage [5,7].

This review examines the few aspects of early fluid resuscitation in sepsis. We focused on the pathophysiology of the intravascular volume depletion, indices of successful fluid resuscitation, and strategy for treatment. Our review is not intended as thorough review of the vast body of evidence, but a targeted analysis of common concepts of fluid management strategies sepsis. For this review, we decided to leave off the critical aspects of oxygen delivery and utilization by end-organs during sepsis. Instead, we focused on several controversial issues related strictly to volume resuscitation with the goal of pinpointing limitations in our current understanding of the physiology of sepsis and prevailing rationale for treatment. We believe that this approach is more beneficial since it provides the reader with the background necessary to re-examine the current thinking on fluid resuscitation strategies.

Pathophysiology of intravascular volume depletion

The immune system is frequently perceived as the sole driver of the pathology of sepsis [1,5,8,9]. Currently, the prevailing belief is that release of cytokines, free radical oxygen species, and vasoactive modulators results in an excessive drop in blood pressure. The resulting hypotension impairs delivery of oxygen to the tissues. As a consequence, the less efficient anaerobic metabolism becomes the main energy-generating source. In organs with high-energy demands production of ATP by anaerobic mechanisms may not be sufficient to sustain the cellular integrity resulting in end organ dysfunction and eventual failure [5].

Hypotension in sepsis has multifactorial origins [1,5,10]. The most appropriate therapy should aim at correction of underlying pathology. However, the ability of the clinician to identify the driving force behind the hypotension is elusive. One of the most common mechanisms is depletion of intravascular volume. There are several pathways by which this can occur.

There are several mechanism involved in the septic shock related hypotension. First, there is expansion of the capacity of the cardiovascular system. Predominantly, this is a consequence of enhanced vascular compliance [11,12]. Increased arterial compliance coupled with decreased systemic vascular resistance produce hypotension by rapidly expanding the circulatory capacitance [13]. The resulting venous pooling of blood, which contributes to the overall volume depletion, can only be effectively counteracted with fluid loading [12,14]. Such a fluid loading improve hemodynamic on the "macrovascular" levels but it may have adverse effect on microcirculation. Concomitantly, a major source of the absolute loss of fluid is increased capillary permeability [3,15-18]. Commonly, the net movement of the fluid out of capillaries is governed by Starling equation [19]. This concept has been modified several times [20,21]. It is elegant but it is unclear how to apply it in clinical decision making since several variables of the Sterling equation change in sepsis. The increase in the filtration coefficient (due to increased number of pores) of the vascular epithelium leads to excessive seepage of fluid to the extravascular space [16]. Degradation of glycocalyx is enhanced leading to increased permeability [22]. Moreover, massive fluid loading, and sepsis itself, effectively lowers the serum level of intravascular proteins/albumins further exacerbating escape of the fluid from intravascular space resulting in increased in extravascular water in some, but not, all studies [3,23,24]. This force counteracts the hydrostatic pressure from Sterling equation potentially restoring the balance of fluid exchange. On the other hand, capillary hydrostatic pressure is mostly determined by the pressure difference between post-arterioles pressure and pre-venule pressure which is particularly difficult to estimate in setting of low sepsis-related SVR [18]. Furthermore, in

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sepsis the relationship between mean arterial pressure and adequacy of microcirculation seems to be abolished [25]. Another confounding variable is that total surface area of microcirculation and function of the lymphatics are frequently underappreciated in shock [19,26]. To take all these variables into account is very complex task that is further hampered by the lack of tools to measure them. This model allows for conceptualization of several changes occurring in the sepsis but it is unclear how to apply its principle in management of sepsis. Hence, we focus on measuring the adequacy of the intravascular volume to the capacitance of the vascular bed. If there is a mismatch cardiac output will diminish since the heart is operating on the non-optimal part of the curve. Loading patient with the fluid should increase stroke volume. However, such a strategy is problematic given that in sepsis not only preload but also left ventricular stroke index (a measure of ventricular performance), and left ventricular end-diastolic pressure (diastolic function of the heart) are severely affected, adding to the difficulty of predicting the effect of fluid load on the cardiac performance [2,10,27-29]. These complex interactions force clinician to perform "a clinical experiment" with fluid loading and subsequent assessment of the changes in cardiac output. Alternatively, physician is trying to meet the "resuscitation goal".

Goal of fluid resuscitation in sepsis

The history of fluid resuscitation in sepsis reflects an evolving understanding of its pathophysiology. Currently, the Surviving Sepsis campaign recommends fluid resuscitation of sepsis patients to a CVP of 8-12 mm Hg; MAP greater or equal to 65 mm Hg; urine output greater or equal to 0.5 ml kg⁻¹hr⁻¹; and central venous oxygen saturation greater or equal to 70%, or mixed venous oxygen saturation greater or equal to 65%.

According to the guidelines, CVP is considered to be an indicator of right ventricle preload and thus overall intravascular fluid status. However, the value of CVP depends on several dynamic variables like: degree of diastolic dysfunction of the heart, positive end expiratory pressure and compliance of the lungs, as well as position of the measuring probe [30,31]. It is easy to state that patient is volume depleted if CVP equals zero, but if the value is 15 cm H₂O several possibilities have to be considered. Volume overcorrection, worsening heart performance, and/or change in lung compliance are some possible scenarios that could be reflected as a high CVP even though suboptimal right ventricle loading is present. Some propose to evaluate the trend, but that incorrectly assumes that other variables affecting CVP are static. So it is not surprising that randomized trials and meta-analysis have failed to confirm its clinical utility [31,32]. A better assessment of ventricular preload and fluid responsiveness is provided by direct measurement of the cardiac output and preload using advanced hemodynamic monitoring techniques or transthoracic echocardiography [7,29,33-36].

Another measure commonly used in the ICU to guide treatment of septic patients is the central oxygen saturation (SvO₂) [1,4,5]. It is an important marker reflecting the global balance between oxygen delivery and consumption since inadequate delivery of oxygen will result in higher extraction ratio [1,9]. In "idealized" sepsis, with high throughput state, this value can be artificially high and thus underestimate the true volume deficit of the patient. In contrast if the patient has pre-existing condition which makes his cardiac output low at baseline, SvO₂ can be low to begin with and thus give an overestimation of volume deficit [1,9]. Finally, given that SvO₂ is global measure of tissue oxygen extraction it is not sensitive enough to detect regional variation and/or deficits in tissue oxygen utilization. Since regional aberration of flow results in organ damage, SvO₂ is not sensitive enough to provide useful information before multiple organ failure occurs. However, it was shown that SvO₂ can be utilized to guide the therapy in early sepsis [4,37,38].

Using a mean arterial pressure value of 65mmHg as threshold reflecting adequate perfusion is supported by some evidence based research [6]. This is the loading pressure seen by precapillaries but in the settings of low SVR it is unclear how it translates into effective perfusion. Interestingly, Trzeciak et al found that when measured at early time points flow velocity correlated with the MAP. Additionally ScvO₂ was found to correlate inversely with flow velocity. Interestingly these correlations only held for the early time-points and were found to not be statistically significant at later time-points. These results are in contrast with observation that adding pressor in sepsis did not affect microcirculation [25]. Such differences are reflected by the hypothesis that in early/acute sepsis organ failure is a consequence of perfusion failure, while late-phase sepsis organ failure may be related to bioenergetic failure due to mitochondrial dysfunction [1,9].

Lactate production during sepsis is thought to represent lack of oxygen delivery to tissues secondary to hypo-perfusion [6]. Since targeting early clearance of lactate has shown to confer a mortality benefit to septic patients it is logical to ask if this value can be used to monitor the effectiveness of resuscitative efforts [39,40]. Given the relative ease and technical simplicity of measuring lactate levels versus ScvO₂, the assessment of lactate clearance may be more practical and cost effective way to improve the current monitoring approach of septic patients in the ICU. One has to bear in mind that lactate levels are depended not only of the perfusion mismatch but also on liver function among other variables.

The poor reliability of existing markers to accurately reflect volume status during resuscitation underscores how little we know about the mechanism by which fluid resuscitation works. On the one hand fluid loading results in an increase of extravascular pressure while clinicians routinely witness anasarca patients with multiorgan failure. Alternatively, it would be interesting to see what the regional perfusion to a given organ system is in these patients, and how much of this is responsible for organ failure.

Type of Fluid

In the last decade the only randomized controlled trial which looked at fluid resuscitation during sepsis introduced the concept of Early Goal Directed Therapy (EGDT). In this study Rivers et al concluded that aggressive fluid resuscitation initiated upon identification at the Emergency Department, and continued for six hours, results in significant short and long term benefits including lower mortality, as well as prevention of sudden cardiovascular collapse [4]. The 2008 Surviving Sepsis Campaign did not address the issue as to which type of fluid is preferred for resuscitation during sepsis or septic shock [5,41]. As a result no clear consensus currently exists as to which type of fluid or fluids provide a clear benefit for septic patients.

IV fluids used for resuscitation can be classified into several main categories: colloids, crystalloids, and blood products. Crystalloid use is currently favored [42]. Colloids have theoretical advantage of staying predominantly intravascularly. This assumes an intact endothelial barrier, which is severely malfunctioning in sepsis. This was tested in randomized controlled trial of the Saline versus Albumin Fluid Evaluation (SAFE) study comparing normal saline to albumin as a resuscitation fluid [43]. This study did not showed strong advantage for using of albumin over crystalloids. This is in line with several metaanalyses [44]. The type of crystalloids to use is also the subject of serious debate with data suggesting the Lactate Ringer results in less acidosis vs normal saline [45].

It is worth mentioning the use of packed red blood cell transfusions in conjunction with EGDT. Theoretically, PRBCs could rapidly replete the intravascular space and at the same time increase the oxygen

carrying capacity. A study published in 2010 by Fuler et al looked at the supplementation of EGDT with PRBC's transfusion. Not only they did not see a statistically significant change in mortality, they did report a statistically significant increase in days on mechanical ventilation and increased length of stay for the group receiving PRBC's [46]. This study adds to the mounting evidence reflecting the deleterious effects of transfusing critically ill individuals.

Summary

Sepsis is a dynamic process with each patient having its own set of variables whose interplay determine the course and final outcome of his/her illness. Understanding these individual differences is crucial in developing therapeutic approaches tailored specifically current clinical situation of the patient. This review has highlighted some of the current issues intensivists face every day when dealing with septic patients. It highlights the need for larger, definitive studies in order to achieve a consensus with regards to the best fluid therapy as well as reliable broadly applicable outcome measurements such as lactate clearance levels.

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