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# The Great Flood: An Exploration of Fluid Resuscitation in Sepsis

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# The Great Flood: An Exploration of Fluid Resuscitation in Sepsis

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## I. Abstract

Sepsis and septic shock continue to be major causes of in-hospital mortality.[1] The World Health Organization (WHO) declared sepsis as a global health top priority as of 2017.[1] To combat sepsis mortality, the Surviving Sepsis Campaign (SSC) released the first set of guidelines in 2004 and continues to publish treatment guidelines, updating the guidelines every four years based on emerging evidence.[2] The 2018 update to the 2016 guidelines contains an Hour-1 Bundle released by the SSC, which includes a rapid infusion of a 30 ml/kg fluid bolus as a strong recommendation with low quality evidence.[3] Recently, studies have challenged this recommendation, demonstrating complications due to fluid overload when following the guideline.[4,5] This continues to be a source of controversy, as the fluid bolus is included in the Centers for Medicare and Medicaid Services SEP-1 performance measure, requiring healthcare practitioners to administer the bolus despite the risks of harm.[5] A literature review was conducted utilizing PubMed to explore the following question: in adult patients with sepsis or septic shock, does initially administering at least 30 ml/kg of fluid improve morbidity and mortality compared to other treatment modalities, such as a fluid restrictive approach or early introduction of vasopressors? The null hypothesis was that there would be no difference amongst treatment modalities. This review revealed that giving a standard 30 ml/kg fluid bolus may be harmful, potentially leading to poorer outcomes. Alternative fluid administration approaches are discussed.

## II. Introduction

Throughout history, sepsis has been a challenge to patients and healthcare providers alike. The term "sepsis" dates back as far as the times of Hippocrates, who considered sepsis to be the process of faster rotting flesh and wounds.[1] In more recent times, sepsis has been considered one of the top global health priorities by the World Health Organization.[1] Sepsis affects over 750,000 patients a year, over 210,000 of which will die as a result.[6] Roughly 15% of patients with sepsis progress into septic shock, accounting for 10% of intensive care unit (ICU) admissions and carries a 35% to 50% mortality rate.[6,7] One study estimated the mortality of patients in septic shock to be as high as 40% to 80%.[8] As one can imagine, the cost of care and mortality is directly proportional to the severity of the patient's sepsis.[8] Not only is sepsis a condition of high mortality but also associated with high costs. The healthcare cost associated with sepsis in the United States is more than $20.3 billion annually and rising.[7] From 2012 to 2018 alone, the cost of caring for septic patients more than doubled, rising from $6.0 billion to $13.4 billion annually.[9]

As knowledge of sepsis pathophysiology increases, the definition has evolved. In 1991, the systemic inflammatory response syndrome (SIRS) criteria was introduced.[7] In 2015, the Centers for Medicare and Medicaid Services (CMS) instituted an all-or-none sepsis bundle (SEP-1) to promote high quality and cost effective care of sepsis patients.[10] In 2016, the International Consensus Sepsis-3 issued updated definitions for both sepsis and septic shock.[11] Sepsis is defined as life-threatening dysfunction resulting from dysregulated host response to an infection.[11] Septic shock is then defined as a subset of sepsis with the characteristics of profound circulatory, cellular, and metabolic abnormalities.[7] Clinically, high risk sepsis can be identified using the SIRS criteria or a qSOFA score of two or more points, while septic shock can be

identified using a mean arterial pressure (MAP) of 65 mmHg or greater and a serum lactate of 2 mmol/L or greater in the absence of hypovolemia.[7]

To help combat sepsis in patients, the Surviving Sepsis Campaign (SSC) was launched in 2002 with the Barcelona Declaration.[2] This collaborative mission amongst the European Society of Intensive Care Medicine (ESICM), the International Sepsis Forum (ISF), and the Society of Critical Care Medicine (SCCM) aimed to reduce the mortality of sepsis by 25% through the development of evidence-based guidelines.[2] The 2018 update to the 2016 SSC guidelines introduced the Hour-1 Bundle consisting of measuring serum lactate levels, obtaining blood cultures, rapidly infusing 30 ml/kg crystalloid for hypotension or lactate levels of 4 mmol/L or greater, and administering vasopressors if the patient is hypotensive during or after fluid resuscitation with a MAP goal of 65 mmHg or greater.[3]

As more research has been conducted analyzing the outcomes of septic patients, the rapid administration of at least 30 ml/kg crystalloid fluid bolus given within the first three hours has been questioned.[5] This came as a strong recommendation with low quality evidence from the SSC 2016 guidelines.[12] Recent studies have shown that this bolus commonly results in fluid overload and a harmful sequelae, leading to increased interventions and greater mortality.[5,13] In some states, such as New York, practitioners are required by the SEP-1 mandate to administer the 30 ml/kg fluid bolus to septic patients or face a malpractice lawsuit, despite the risk of further harm to the patient.[5] In cases of patients with pneumonia or acute lung injury who are septic, this means the patients are intubated and placed on a mechanical ventilator, so they can receive the potentially harmful fluid bolus.[14] This potentially goes against the ethical principles of nonmaleficence that is carried by medical providers.

It is within the realm of conflicting guidelines and disagreements that the focus of this paper arises. The research paper is intended to review current medical literature to answer the following question: in adult patients with sepsis or septic shock, does initially administering at least 30 ml/kg of fluid improve morbidity and mortality compared to other treatment modalities, such as a fluid restrictive approach or early introduction of vasopressors? The null hypothesis of this review is that there is no significant difference in morbidity and mortality despite the different treatment modalities. The objectives of this paper include a brief overview of the pathophysiology of sepsis; an overview of current Surviving Sepsis Campaign recommendations, origins, and critiques; a review of fluid management principles of sepsis and septic shock; a review of post-fluid administration physiology; and an overview of fluid resuscitation approaches, complications, and outcomes in sepsis and septic shock.

## III. Literature Review

### Brief Pathophysiology of Sepsis

The pathophysiology of sepsis in patients involves a complex cascade of multisystem organ dysfunction as a result of systemic infection.[15] As the pathophysiology of sepsis has been described in detail elsewhere, a brief overview is provided for this paper.[15-16] While some patients mount a proper immune response to an antigen and will clear the infection without further complications or deterioration, others enter into a dysregulated state of the immune response.[15] This can progress into patient deterioration leading to septic shock and eventually death without prompt intervention.[15] Previously, a "cytokine storm" of inflammatory mediators was thought to be the cause of this dysregulation.[15] However, recent studies suggest that both proinflammatory as well as anti-inflammatory mediators are released in a septic state, each playing a role in the dysfunction.[15] An excess of proinflammatory mediators released in the

bloodstream can cause systemic damage to the endothelial tissue of the vasculature.[15] This can lead to hyperpermeability of blood vessels secondary to the loss of barrier function of the endothelial lining.[16] Multi-system organ failure can develop as a result and can lead to death.[15] Almost every body system is ultimately affected, including the cardiovascular, pulmonary, renal, hematological, gastrointestinal, endocrine, and neurological systems.[5,15]

In the cardiovascular system, pathologic arterial and venodilation can lead to potentially life-threatening hypotension, as seen in septic shock.[15] Hypotension in septic patients results from decreased venous return (decreased preload), loss of intravascular volume due to third spacing of intravascular fluid (tissue edema), and myocardial depression, which is seen in up to 60% of septic patients.[15] The cause is multifactorial involving inflammatory cytokines, nitrous oxide released by damaged endothelial tissue, and hyperpermeability of the vasculature.[5,15,16] In addition to a low MAP, patients in early stages of septic shock can either exhibit a high cardiac output state (hyperdynamic circulatory shock) or low cardiac output state (sepsis with severe hypovolemia or sepsis-induced cardiomyopathy).[17] One important component of the vascular dysfunction seen in septic patients is the endothelial glycocalyx.[16] Normally acting as an "endothelial gatekeeper," early shedding of this important layer in sepsis causes disruption of the endothelial tissue, resulting in damage to the endothelial cells and ultimately dysfunction.[18] The loss of the barrier function normally provided by the endothelial glycocalyx is a key component contributing organ dysfunction seen in sepsis.[16]

In the pulmonary system, increased permeability of the alveolar and capillary endothelium results in the accumulation of fluid in the lungs.[15] This noncardiogenic pulmonary edema can ultimately progress into acute respiratory distress syndrome (ARDS) in up to 7% of patients with sepsis.[15] The accumulation of fluid in the patient's lungs impairs their ability to

oxygenate and ventilate properly, resulting in hypoxia and further potentiating metabolic acidosis.[15]

In the renal system, acute kidney injury (AKI) may occur in patients with sepsis, contributing to morbidity and mortality.[15] Subsets of patients, such as those who are of advanced age or have underlying chronic kidney disease and/or cardiovascular disease, are at higher risk for developing AKI with sepsis.[15] Multiple factors contribute to the development of AKI in sepsis patients, including endothelial dysfunction, inflammation of the renal parenchyma, and obstruction of the renal tubules from debris as a result of apoptosis.[15] Initial prevention of AKI in sepsis patients is essential, and the risk can be minimized with prompt correction of hypotension and avoiding other potentiating factors, such as unnecessary nephrotoxic medications.[15]

In addition to those listed above, other body systems are affected in sepsis. Hematologically, sepsis can cause anemia, leukocytosis, neutropenia, thrombocytopenia, and in severe cases, disseminated intravascular coagulation (DIC).[15] In the gastrointestinal system, liver failure can develop secondary to septic shock, increasing the mortality risk for the patient.[15] Occurring in less than 2% of patients with sepsis, liver failure is thought to arise from parenchymal hypoxia.[15] Other manifestations include cholestasis, coagulopathies, and hyperammonemia leading to hepatic encephalopathy.[15] Hyperglycemia is commonly seen in patients with sepsis, caused by elevation in glucagon, catecholamines, cortisol, and other factors as part of the stress response.[15] Clinical hypothyroidism may also be seen as the result of impairment of the hypothalamic-pituitary-thyroid axis.[15] Lastly, sepsis can have profound impacts on the neurological system as a result of systemic dysfunction, spanning from altered mental status, sleep disturbance, agitation and hallucinations to seizures, which occur secondary

to encephalopathy and more.[15] Due to the wide variety of systemic pathology, it is important for clinicians to rapidly recognize a septic patient and initiate prompt treatment to minimize the sequelae caused by sepsis.

Surviving Sepsis Campaign Recommendations

In 2016, the Surviving Sepsis Campaign (SSC) released its most recent recommendations with a subsequent update in 2018.[3,12] Although there are many recommendations regarding treatment and care, the focus for this paper will remain on the resuscitation aspect of septic patients, involving fluid resuscitation and the use of vasopressors. One of the most notable changes in the 2018 update is the replacement of the three and six hour treatment bundles with a single Hour-1 Bundle.[3] This was made to promote rapid resuscitation and management in these patients.[10] "Time zero" is a term synonymous with time of presentation and is used to describe the timeframe from which interventions should be performed.[3] The Surviving Sepsis Campaign's focus on rapid diagnosis and immediate action in treating septic patients was the result of studies which showed an association between increased bundle compliance and decreased mortality in septic patients.[3]

The focus of the Hour-1 Bundle remains on obtaining initial lactate levels and blood cultures, administering broad-spectrum antibiotics, beginning a rapid infusion of 30 ml/kg crystalloid for hypotension or lactate $\geq$ 4 mmol/L, and administering vasopressors if the patient is hypotensive during or after fluid administration with a goal MAP of $\geq$ 65 mmHg.[3] Studies have demonstrated improved outcomes, such as mortality, with proper adherence to the SSC bundles; however, the specific benefit of each component in the bundle remains less clear.[19]

According to the SSC 2018 update, the rapid infusion of 30 ml/kg of crystalloid should be completed in the first three hours of care.[3] The evidence for the rapid administration of 30

ml/kg of crystalloid is of low quality, yet carries a strong recommendation.[3] The 2018 update also stressed that due to evidence suggesting harm with a sustained positive fluid balance in septic patients, caution should be used when administering additional fluids beyond the initial rapid infusion of cyrstalloid.[3] In regards to vasopressors, the recommendations are to initiate a vasopressor if the patient remains hypotensive during the first hour of the fluid resuscitation to maintain a MAP ≥ 65 mmHg.[3] Based on studies examining the benefits of individual vasopressors, norepinephrine is recommended as a first-line vasopressor.[3] If the patient remains hypotensive despite fluid and norepinephrine infusions, other vasopressors such as epinephrine and vasopressin may be considered.[3]

Origins of the Surviving Sepsis Campaign Recommendations

Before analyzing the outcomes of the recommended 30 ml/kg bolus of intravenous fluids, it is important to understand where this SSC recommendation originated. In 2001, Rivers *et al*. conducted a single-center randomized controlled trial (RCT) evaluating the efficacy of early goal-directed therapy (EGDT) versus standard therapy in septic patients prior to admission into the ICU.[19] In this study, the authors concluded that there was a significant benefit in patient outcome by using aggressive fluid resuscitation to achieve macrocirculation goals of central venous pressure (CVP) of 8 mmHg or greater and MAP of 65 mmHg or greater and microcirculation goals of a central venous oxygen saturation ($SvO_2$) at 70% or greater.[19] The aggressive fluid resuscitation approach resulted in a reduction of mortality from 46.5% to 30.5%.[19] The subsequent endorsement of this study by the SSC started a new era of aggressive fluid resuscitation in sepsis patients.[5]

Following this study, the Trial of Early Goal-Directed Resuscitation Septic Shock (ProMISe), Protocol-based Care for Early Septic Shock (ProCESS), and Goal-Directed

Resuscitation for Patients with Early Septic Shock (ARISE) trials were conducted to evaluate the efficacy of the EGDT endorsed by the SSC.[20-22] All three of these trials showed no significant reduction in mortality while following the EGDT protocol.[20-22] In support of the guidelines of EGDT, the International Multicenter Prevalence Study on Sepsis (IMPreSS) study showed a reduction in mortality by 40% when in compliance with the guidelines.[5] In addition, Levy *et al.* showed that increased compliance with the guidelines resulted in a reduction in mortality in septic patients.[5] It is important to note, however, that these studies were uncontrolled longitudinal observational studies, which inherently weakens the conclusions drawn. Furthermore, they did not assess the effect of fluid administration independently but rather as part of the overall sepsis treatment bundle.[5] Another large study that focused on independently assessing variables, including the time of fluid bolus administration, found there was no change in mortality with faster fluid administration (3 hours compared to 12 hours).[23] An additional study demonstrated patients who received more than five liters of fluid during the first day in the hospital had a significantly increased risk of death.[5] These conflicting results call into question the efficacy of administering a rapid 30 ml/kg crystalloid bolus to patients with sepsis.

Critiques of the Surviving Sepsis Campaign Recommendations

Conflicting results from studies evaluating the SSC guidelines for administering a rapid fluid bolus of crystalloid point out the inherent vagueness to it. There is no mention within the guideline of whether the patient's actual weight, predicted weight, or ideal body weight should be used in the calculation.[3,12] This could potentially result in fluid overload for patients with obesity or, conversely, under-resuscitation of patients who are extremely underweight. Considering the guideline has a fixed volume of 30 ml/kg, this all-or-nothing approach can potentially cause harm associated with fluid overload.[5] One study found that the SSC guidelines

led to evidence of fluid overload in 67% of patients, of which 48% of patients still had fluid overload on day three.[13] This resulted in increased medical interventions, such as thoracentesis, paracentesis, diuretic use, and ultrafiltration, in addition to increased hospital mortality.[13] Due to the lack of scientific evidence and potential harm to patients, blindly administering at least 30 ml/kg of crystalloid fluid within the first three hours, as required by the CMS in their performance measures in the SEP-1 mandate, has been questioned.[10]

## Fluid Management Principles of Sepsis and Septic Shock

The main goal of fluid resuscitation in sepsis and septic shock is to replenish the lost intravascular volume, improve tissue perfusion and oxygenation, and reverse organ dysfunction.[7] Per the Surviving Sepsis Campaign recommendations, this should be completed by an infusion of 30 ml/kg crystalloid over three hours.[3,12] Conceptually, increasing the intravascular volume will increase preload and translate into a higher cardiac output and a higher MAP.[7] Studies suggest that a MAP $\geq$ 65 mmHg is necessary to maintain proper organ perfusion and maximize survival.[12]

Within medical literature, the terms fluid bolus, challenge, balance, and overload are commonly used. Fundamentally, a fluid bolus and a fluid challenge can be used synonymously. Fluid bolus itself refers to a discrete amount of fluid given to a patient over a specified amount of time.[17] A fluid challenge refers to a dynamic test in which a fluid bolus is administered and physiologic effects are simultaneously monitored.[17] Fluid balance refers to the net fluid accumulation in the body.[24] Simply, it is calculated by measuring all inputs and outputs over a certain period of time.[24] Fluid overload is used to describe a fluid state in patients that have too much fluid accumulation.[24] More specifically, fluid overload can be defined as greater than 10% fluid accumulation, which has been associated with worse patient outcomes.[24] It can be

calculated by dividing the patient's fluid balance by the patient's baseline body weight, then multiplying it by 100%.[17]

Generally, fluid resuscitation in patients with sepsis and septic shock should be divided into four phases: rescue, optimization, stabilization, de-escalation.[7] In the rescue phase, initial fluid resuscitation is initiated to combat hypoperfusion.[7] Next, during the optimization phase, the need for additional fluid boluses should be evaluated and administered to optimize cardiac output and tissue perfusion, while weighing the benefits and risks.[7] During the stabilization phase, usually occurring 24 to 48 hours after the onset of septic shock, an effort should be made to achieve a neutral or slightly negative fluid balance in patients.[7] Finally, the de-escalation phase is characterized by resolving organ dysfunction and shock, and aggressive fluid removal strategies should be used.[7] Because the aim of this paper is on the initial resuscitation of patients with sepsis or septic shock, the focus will remain on the resuscitation phase.

Post-fluid Administration Physiology

Currently, there are very limited randomized controlled trials focused on the physiological effects of fluid resuscitation in septic patients.[25] In a review performed by Glassford *et al*., researchers looked at physiological effects immediately post-infusion of a fluid bolus at timeframes of 30, 60, and over 60 minutes.[25] In six of the studies included in the review, the reported cardiac index increased after receiving a fluid bolus by a median of 800 ml/min/$m^2$ (range: 0 to 1,300 ml/min/$m^2$), while the median heart rate decreased by two beats per minute (bpm) (range: 0 to 10 bpm reduction).[25] The median increase in MAP was 7 mmHg (range: 1 to 15.2 mmHg), while the median increase in CVP was 3.2 mmHg (range: 2.3 to 5.2mmHg).[25] At 30 minutes post-administration, the cardiac index was increased by a median of 300 ml/min/$m^2$ (range: -400 to 600 ml/min/$m^2$), the median heart rate was reduced by 2 bpm

(range: 11  reduction to 0.3 bpm increase), the median MAP was increased by 7.5 mmHg (range: 3 to 11 mmHg), and the CVP was increased by 3 mmHg (range: 2 to 5.25 mmHg).[25] Finally, at 60 minutes post-administration, the cardiac index was increased by a median of 300 ml/min/$m^2$ (range: -300 to 400 ml/min/$m^2$), the heart rate decreased by 1 bpm (range: 11 bpm reduction to 2 bpm increase), the median change in MAP was a 3 mmHg increase (range: 2 to 7 mmHg), and the median CVP increase was 2 mmHg (range: 1 to 3 mmHg).[25] While this review was important as it attempted to quantify physiologic changes after a fluid bolus in sepsis patients, the heterogeneity of studies was high, varying in fluid type (crystalloid versus colloid), definition of bolus volume, and other elements.[25] However, the review was able to demonstrate that fluids can help raise the cardiac index, decrease heart rate, increase MAP, and increase CVP, though these changes are relatively transient.[25] Other studies have demonstrated that during this first fluid bolus, cardiac output will increase in almost all cases.[17] After the initial bolus, subsequent fluid administration may be harmful, since preload responsiveness is unlikely.[17]

## Approaches to Fluid Administration in Sepsis and Septic Shock

Throughout the past couple decades, researchers have explored several different approaches to administering intravenous fluids to septic patients as well as how to quantify a patient's response.[17,19] Large randomized controlled multicenter trials have established that there is no difference in patient outcome between colloid versus crystalloid solution administration to septic patients.[3,19] Regardless, this led the SSC to recommend that crystalloid solution be used as the resuscitation fluid of choice.[3] Furthermore, recent studies suggest that the use of a balanced crystalloid, such as lactated ringers or Plasma-Lyte, decreases the risk of renal injury, hyperchloremia, metabolic acidosis, and may lower mortality.[7]

Optimal therapeutic endpoints for fluid resuscitation remain unclear and are subjects of controversy.[4-6] Although early goal-directed therapy (EGDT) is endorsed by the SSC and was initially shown to improve outcomes, it has since been questioned, and other methods for guiding fluid resuscitation have been proposed.[17] Traditionally, the goal of resuscitation was to optimize CVP to 8 to 12 mmHg for non-ventilated patients or 12 to 15 mmHg for patients on a ventilator.[26] More recently, the use of invasive monitoring to evaluate CVP and pulmonary capillary wedge pressure (PCWP) to guide fluid responsiveness in patients has been questioned, showing no improvement in outcomes and may even be dangerous, especially in severe septic shock.[17,24] In one study, it was found that following an EGDT protocol led to fluid overload in 67% of patients after 24 hours.[13]

Researchers have advocated to move away from static measurements such as CVP, which is found to be accurate in only half of cases, to an approach using dynamic measurements.[7] One example of a dynamic measurement approach is administering either a small fluid bolus or passively raising the patient's legs while simultaneously lowering the patient from a semirecumbent position to supine.[7] Raising the patient's legs has been shown to act as a small "fluid challenge," shifting 200 to 300 milliliters of blood from the lower extremities into the central circulation. Subsequent cardiac output is measured by a variety of means, including thermodilution, echocardiography, or pulse pressure variation.[7] The measurement can then be used to determine volume responsiveness. Quantitatively, volume responsiveness can be defined as an increase of stroke volume or cardiac output by 10% to 15% after a 200 to 500 milliliters fluid bolus.[27] While one meta-analysis found a risk reduction in death of -2.9% in ICU patients resuscitated with a volume-responsiveness approach, only a subset of the sample patients were

septic.[27] In fact, another study suggests that this "volume-responsiveness approach" showed no difference in mortality compared to standard resuscitation strategies.[27]

Another data point that can be used to guide fluid resuscitation is lactate levels.[7] Trending serum lactate values has been shown to decrease the high mortality rate associated with septic patients with levels > 4 mmol/L.[7] In sepsis, lactate levels rise as a result of increased anaerobic respiration from hypoxic tissues, accelerated glycolysis due to the body's stress response, medications administered (such epinephrine or beta-2 agonists), or liver failure.[7] Intuitively, effective fluid resuscitation will result in down-trending lactate levels as tissue oxygenation is optimized.[7]

Recently, a study published in 2020 investigated an alternative method to guide resuscitation involving the use of skin perfusion parameters, such as capillary refill time, distal skin temperatures, and skin mottling as a surrogate for visceral organ perfusion.[28] The study concluded that capillary refill times better reflected organ perfusion compared to serum lactate levels.[28] In addition, using skin perfusion parameters resulted in lower fluid volumes administered to patients and lower lactate levels at 48 and 72 hours.[28] Although reported mortality was lower as well, this was not found to be statistically significant.[28]

Liberal Versus Restrictive Approach to Fluid Administration

Initial resuscitation of septic patients with intravenous fluids remains a mainstay of current treatment.[29] Over the past two decades, two predominant strategies of fluid administration have emerged: a liberal fluid approach and a restrictive fluid approach.[29] In the liberal fluid approach, larger volumes of crystalloid fluids are administered. The volumes of fluid vary greatly but generally consist of 50 to75 ml/kg.[29] In the restrictive approach, fluids are given in smaller amounts of ≤ 30 ml/kg of crystalloid.[29] Due to the emergence of data

illustrating the prevalence and potential dangers of a positive fluid balance in septic patients, a new wave of studies seeking to shift the paradigm away from large volume resuscitation have occurred.[29]

As researchers continue to investigate different fluid treatment modalities in septic patients, approaches continue to be generally categorized into the two different groups: liberal fluid approach and restrictive fluid approach.[29] Importantly, definitions vary widely from study to study regarding the definition of a liberal versus restrictive approach and at what point during resuscitation the patients are enrolled in the study. This can potentially skew results if not closely examined. For example, some studies referring to a restrictive approach may only enroll patients into the restrictive treatment group after they have already received the recommended 30 ml/kg crystalloid fluid bolus. In contrast, another study may enroll patients into the restrictive group from triage in the emergency department (ED) and begin the restrictive fluids approach immediately. Due to this inconsistency, careful attention to the methods of studies is important.

Generally speaking, a liberal fluid approach is most commonly utilized in the ED in the United States, consisting of an intravenous fluids (typically 50 to 75 ml/kg) over several hours to treat hypotension in septic patients.[29] Resuscitation endpoints are based on SSC recommendations derived from EGDT.[29] Vasopressors are administered to patients who are profoundly hypotensive or those who remain hypotensive despite fluid therapy.[29] As mentioned previously, early studies initially supported the use of a liberal fluid approach when treating septic patients.[29] However, more recent data has challenged this approach, citing questionable efficacy and dangers, such as fluid overload.[5,30]

In contrast, a restrictive fluid approach involves smaller volumes of fluid (typically $\leq 30$ ml/kg) and earlier introduction of vasopressors to reduce vasodilation and improve perfusion of

the patient's tissues.[29] Data has shown that large fluid boluses only transiently increase intravascular volume and cardiac output, ultimately leading to downstream complications such as tissue edema and organ dysfunction.[29] With this in mind, a fluid restrictive approach aims to minimize the harmful sequelae caused by large fluid boluses.

Fluid Overload Complications

Understanding the dangers of fluid overload in patients with sepsis is fundamental in making a clinical decision as to when to begin fluid administration, at what volume, and when to discontinue the infusion. According to one study, fluid overload was observed in 67% of patients in the first 24 hours and in 48% of patients on day three using an EGDT approach.[13] This led to increased fluid-related medical interventions, such as thoracentesis, paracentesis, diuretic administration, and ultrafiltration for fluid removal.[13] Lastly, the study showed an increased mortality with the use of an EDGT approach.[13] Due to the high incidence of fluid overload and the associated increase in mortality, it is important to understand the complications that can occur in order to recognize and minimize their effects.

Fluid overload in septic patients can lead to worsening multisystem dysfunction and adverse outcomes.[5] This further dysfunction can be found in the cardiovascular, pulmonary, central nervous system, renal system, gastrointestinal system, and hepatic system.[5,31] Physiologically, large volume resuscitation may potentiate damage and shedding of the endothelial glycocalyx, especially when it is infused rapidly.[5] Moreover, one study found that the volume of resuscitation fluids was independently associated with the degree of glycocalyx degradation and, ultimately, in-hospital mortality.[5] These complications lead to longer ICU stays, increased days on the mechanical ventilator, increased medical interventions, and higher mortality.[5]

Interestingly, it has been shown that an increase in fluid can actually cause more cardiac dysfunction and the need for an increased amount of vasopressors in patients with sepsis.[5] The Fluid Expansion As Supportive Therapy (FEAST) trial, during which pediatric patients were randomized to receive 40 ml/kg of saline, albumin, or no fluid resuscitation, was stopped early after a 40% increase in mortality that occurred in the fluid treatment group of the study.[5] It was later determined the cause of increased death in the fluid treatment group was not due to fluid overload itself but because of delayed cardiovascular collapse and refractory shock.[5] In 2017, the results of an RCT in Zambia showed that despite greater amounts of fluids received, patients required greater usage of vasopressors and ultimately experienced higher mortality than the usual treatment group (58% versus 36%, respectively).[32] In a hyperdynamic sheep model, it was found that a large fluid bolus prior to administration of a vasopressor resulted in increased cardiac output and MAP as expected; however, a simultaneous drop in systemic vascular resistance was noted.[5] Animals also showed signs of resistance to vasopressors along with increased evidence of myocardial and glycocalyx damage reflected by elevated troponin and hyaluronan levels.[5]

Given the harm that can occur from potentially causing the septic patient to become fluid overloaded, fluid restrictive approaches arose. During the Refresh Fluid Resuscitation in Suspected Sepsis Associated Hypotension (REFRESH) trial in 2018, patients were randomly assigned to either a usual care group or a fluid restrictive group.[33] The fluid restrictive protocol for septic patients with hypotension involved early introduction of a vasopressor paired with a small 250 milliliter fluid bolus.[33] At the conclusion of this trial, there was a 30% reduction in the total fluid volume received in the first 24 hours and significant positive change in outcome.[33] In addition, the fluid restriction did not result in longer vasopressor use.[33] Therefore, this may be a feasible alternative to the standard 30 ml/kg fluid bolus seen in the SSC guidelines, which would

decrease the potential for harm secondary to fluid overload. Similar results were seen in the Restrictive IV Fluid Trial in Severe Sepsis and Septic Shock (RIFTS) trial, in which no increase in mortality, organ failure, or adverse events were noted.[34]

Early Norepinephrine Administration

To further investigate the optimal treatment for patients with sepsis and septic shock, studies have been conducted to analyze the effect of introducing early vasopressors during the initial resuscitation period of treatment. The administration of an early vasopressor, specifically norepinephrine as a first line vasopressor, aims to restore the vascular tone in septic shock to help maintain a MAP ≥ 65 mmHg to ensure organ perfusion.[35] Studies have shown that after the very early phase of sepsis, only half of patients are fluid-responsive.[35] The 2016 SSC guidelines recommend that vasopressors be used if a patient is rapidly deteriorating or when initial fluid bolus administration fails to maintain a MAP ≥ 65 mmHg.[12] While some advocate for the early administration of norepinephrine, there is limited data in the literature investigating how the timing of vasopressor administration affects mortality and other patient outcomes.[36,38] The goals of early norepinephrine administration are to prevent prolonged severe hypotension, increase cardiac output through increased preload, improve microcirculation and tissue oxygenation, prevent fluid overload, and improve outcomes.[36]

Studies have demonstrated that both the degree and duration of hypotension are crucial in maximizing patient outcomes in septic shock.[36] In addition, fluid administration alone may not be sufficient to correct severe hypotension.[36] Adding a potent vasoconstrictor, such as norepinephrine, may shorten the time to correction, therefore shorting the duration of hypotension.[36] The shorter time to correction of severe hypotension can be attributed to norepinephrine's effects on the vasculature. At low doses of norepinephrine (less than 2

mcg/min), beta-1 agonist effects may be more pronounced, while at higher doses (higher than 3 mcg/min), alpha-1 agonist effects predominate.[36] The stimulation of these receptors have been shown to increase cardiac output when administered early, leading to increased blood pressure, organ perfusion, and ultimately improved outcomes.[36] In a study that looked at patients who have been resuscitated in less than three hours by standard treatment whose MAP remained below 65 mmHg, echocardiographic variables were obtained to address the effects of norepinephrine administration.[36] Following administration of norepinephrine, an increase in right and left ventricular systolic function was observed in addition to increased cardiac output.[36] Interestingly, experimental data has shown a time-dependent effect on beta-1 stimulation, during which an early potentiated beta-1 response was seen followed by a downregulation phase, suggesting that the greatest benefit from increased contractility is seen in the early phase of septic shock.[36]

Early norepinephrine administration may even be beneficial in hypotensive patients with a MAP slightly greater than 65 mmHg but who have a low diastolic arterial pressure (DAP).[38] Although a low DAP can be due to other physiological causes such as bradycardia or arterial stiffness, it is most likely due to the decreased arterial tone in septic patients.[38] Therefore, norepinephrine can be administered to augment vessel tone and increase cardiac output through increased preload.[36] This may be especially beneficial in septic patients with a history of coronary artery disease, as a higher DAP can increase coronary perfusion and help prevent ischemia.[38]

The Early Use of Norepinephrine in Septic Shock Resuscitation (CENSER) trial, a single center, randomized, double-blinded, placebo-controlled clinical trial, investigated the effects of early norepinephrine administration on septic shock control.[39] This was defined as a MAP $\geq$ 65

mmHg, urine flow ≥ 0.5 ml/kg/h for 2 consecutive hours, or decreased serum lactate ≥ 10% from baseline.[39] At the conclusion of the trial, it was found that patients in the early norepinephrine group had a higher frequency of shock control compared to the control group (76.1% versus 48.4%).[39] It is important to note that in this study, patients received a standard 30 ml/kg normal saline bolus prior to randomization.[39]

Previously, concerns for impaired microcirculation secondary to norepinephrine administration have been brought up; however, recent data suggests that microcirculation may actually improve.[36, 40] In a study by Georger *et al.*, researchers found that the tissue oxygen saturation ($StO_2$) recovery curve slope improved after increasing MAP with the administration of norepinephrine in septic shock patients.[36] Even when the MAP ≥ 65 mmHg, clinical studies showed increasing the MAP to ≥ 85 mmHg did not impair microcirculation after norepinephrine administration.[36]

As mentioned previously, a positive fluid balance is associated with an increased mortality rate in patients with septic shock. This is due to tissue edema, damage to the endothelial glycocalyx, increased venous pressure, and hemodilution. Early administration of norepinephrine has been shown to decrease the fluid requirements of patients in septic shock, minimizing the risks of fluid overload.[40]

The optimal timing of early administration of norepinephrine remains unclear.[40] The widespread acceptance of initially administering 30 ml/kg of crystalloid prior to consideration of a vasopressor is reflected in many studies that randomize patients only after they have received a fluid bolus.[40] However, recent studies have questioned the clinical benefit of fluid bolus administration in patients with septic shock.[40] In fact, recent experimental data suggests that fluid resuscitation preceding the start of vasopressors is associated with higher lactic acid levels

and paradoxical increase in vasopressor dose and duration requirements compared to the immediate start of a vasopressor without previous fluid administration.[40]

In one retrospective cohort study intended to determine the effects of vasopressors administered before or after 6 hours from admission, researchers found that the 30-day mortality was higher in patients who received vasopressors after 6 hours (51.1% versus 25%).[38] In addition, although the data did not show any difference in vasopressor dose at the 24-hour mark, patients who received earlier vasopressors had more vasopressor-free hours by the 72-hour mark of care (34.5 hour versus 13.1 hour).[38] Lastly, early vasopressor administration shortened the time it took to reach a target MAP of ≥ 65 mmHg.[38]

A randomized controlled trial involving patients in septic shock found that patients who received a norepinephrine infusion between 20 to 30 minutes (early group) had quicker restoration of blood pressure, better lactate clearance, and lower mortality rates compared to those who received the infusion 120 to 180 minutes (late group) after admission to the emergency department (28.1% versus 54.4%, respectively).[36] The early group received crystalloid fluids concurrently with the norepinephrine infusion, while the late group received a standard 30 ml/kg targeted fluid resuscitation.[36]

A prospective study addressing the effects of early vasopressor administration showed similar results.[40] In this study, patients were categorized based on whether or not they received a vasopressor prior or within one hour of their first fluid bolus of crystalloid.[40] In the group that received early vasopressors, there was a smaller volume of resuscitation fluid received in the first 8 hours (1100 versus 2600 milliliters) with no significant increase in acute renal failure.[40] Due to this, there was also a lower net fluid balance at 8 and 24 hours.[40] Finally, there was a significant reduction in mortality compared to the delayed vasopressor group.[40]

## IV. Methods

Sepsis and Septic Shock Background Information

To gain an understanding of the current treatment options for sepsis and septic shock, a search was performed in UpToDate using the phrase "Treatment of Sepsis in Adult Patients." This led to the article named "Evaluation and Management of Suspected Sepsis and Septic Shock in Adults." Additionally, a search utilizing PubMed was performed with the following search phrases, selecting articles published in the last five years: "Surviving Sepsis Campaign;" "SEP-1;" "WHO Sepsis Global Health;" "SEPSIS-3;" "Epidemiology AND Sepsis;" and "Cost of Sepsis."

Fluid Administration in Sepsis and Septic Shock

To obtain information regarding the administration of fluids in sepsis, a PubMed search was performed using the following search terms: "Fluid Management AND Sepsis;" "Fluid Administration AND Sepsis;" "Fluid Resuscitation AND Sepsis;" "Volume Resuscitation AND Sepsis;" "Volume Administration AND Sepsis;" "Fluid Overload AND Sepsis;" "Harms of Fluid Overload AND sepsis;" "Treatment of Sepsis;" "Surviving Sepsis Campaign AND Outcomes;" "Restrictive AND Fluid AND Sepsis;" "Initial resuscitation AND sepsis;" "Fluid Approach to Sepsis;" "Early Norepinephrine AND Sepsis;" and "Early Vasopressor* AND Sepsis." The search was again performed using the same terms listed above but "sepsis" was replaced with "septic shock." To acquire a variety of articles, reviews, systematic reviews, randomized controlled trials, clinical trials, and meta-analyses were included. The search date range for all PubMed searches was modified to articles published from 2010 to 2020, with an emphasis in selecting articles published in the past five years.

**V. Discussion**

Sepsis and septic shock continues to carry an in-hospital mortality rate of 25 to 50%, posing a challenge to patients and healthcare providers alike.[2,3] This complex condition also carries a high cost burden on the healthcare system, costing roughly $20.3 billion annually.[3] In an effort to decrease the mortality of sepsis by 25%, the European Society of Intensive Care Medicine (ESICM), International Sepsis Forum (ISF), and Society of Critical Care Medicine (SCCM) developed the Surviving Sepsis Campaign (SSC) guidelines, releasing them in 2004.[9] As part of their 2018 update of the 2016 guidelines, the Hour-1 Bundle included a recommendation to immediately start a rapid infusion of 30 ml/kg crystalloid to be completed within three hours.[3] This came as a strong recommendation with low quality evidence.[10] The evidence for these guidelines came from a limited number of interventional and observational studies, and recent studies have challenged the data.[3,5]

Studies suggest that blindly giving the fluid bolus, as recommended by the SSC guidelines, commonly results in a positive fluid balance, leading to complications, greater need for medical interventions, longer ICU stays, and greater mortality.[13] Some argue this is partly due to the vagueness of the recommendations themselves.[5,10] For example, it is unclear whether the 30 ml/kg should be based off of the patient's actual weight, estimated weight, or ideal body weight.[10] Hospital ICUs may not have beds that can weigh patients, and the ones that do may not provide an accurate weight. In addition, the patients who are obese may end up receiving harmful amounts of fluid if their actual weight is utilized in the calculation.[5] It has also been shown that staff in the ICU are notoriously unreliable when estimating patients' weights.[5] This poses an obvious risk, as over- or under-estimating a patient's weight can quickly cause incorrect dosing of the fluid bolus. This is particularly important in patients with comorbidities such as

congestive heart failure.[10] Blindly administering a 30 ml/kg fluid bolus can be especially dangerous in states, such as New York, where practitioners are mandated per the CMS SEP-1 quality control measures to administer 30 ml/kg to septic patients as part of their care, or they face a possible malpractice lawsuit.[5] In fact, some organizations, such as the Infectious Diseases Society of America (IDSA), do not endorse the SSC guidelines, as they are not in favor of an all-or-none type of approach to sepsis and septic shock.[10]

Instead of a rigid treatment approach, some studies advocate for a more individualized approach to fluid resuscitation in patients. The SSC guidelines are based on EGDT, which is supported by researchers such as Rivers *et al.*[19] However, this approach has been scrutinized, as well as studies suggesting that there are safer alternatives that can be used as resuscitative endpoints.[7,27] For example, some studies recommend that dynamic measures be used, such as cardiac output, to better gauge fluid responsiveness.[7] Using dynamic measures in conjunction with small fluid challenges of 250 to 500 milliliters of crystalloid creates a more tailored approach and can decrease the risk of fluid overload in patients. Studies have shown that only half of sepsis patients are fluid responsive at baseline.[35] Multiple boluses of fluid have also been shown to be ineffective at improving hemodynamic parameters.[35] In addition, the physiologic effects of a fluid bolus have been shown to be only transient effects on parameters, such as cardiac output and MAP.[25] Additional dynamic measures have been studied that may hold promise as a surrogate for organ perfusion, such as skin perfusion.[28]

Researchers continue to investigate different fluid approaches, including utilizing a fluid restrictive versus a liberal fluid approach. Despite the importance of this research, there are issues regarding these two approaches. First, there is a lack of uniformity amongst definitions across the medical literature, specifically what is considered restrictive versus liberal. While

some restrictive approaches involve minimizing fluids from the moment a patient is triaged, other studies begin enrollment after the patient has already received a 30 ml/kg fluid bolus. This may lead to some confusion and heterogeneity in review studies. However, studies have shown that a restrictive approach is both feasible and safe for patients, minimizing positive fluid balances, minimizing fluid overload complications, and ultimately improving outcomes.[5,32,33]

Another variable that must be considered during fluid resuscitation of septic patients is the addition of vasopressors. Recent data has alleviated concerns about early administration of vasopressors, in particular norepinephrine, proving that early administration of vasopressors either after a small fluid challenge or concurrently with a fluid bolus can improve outcomes.[37,38,40] Additionally, early vasopressor administration actually decreases the amount of fluid required to maintain a MAP $\geq$ 65 mmHg, results in smaller doses of vasopressors required to maintain an adequate MAP, and can result in serum lactate clearance.[37,38,40] This ultimately shortens the time a patient experiences hypotension, leading to less organ dysfunction.[37] Due to a limited number of trials available in the literature, more studies are needed to evaluate the optimal timing of vasopressor administration to maximize benefit and decrease mortality.

**VI. Conclusion**

Given the associated high mortality and high cost in the healthcare system, sepsis and septic shock remain one of the top global health priorities.[1] Due to the complexity of the pathophysiology of sepsis and septic shock, there are many different components to treatment, making studying each component as independent variables difficult. Although guidelines have been published outlining recommended treatments, more research needs to be conducted.[4] The SSC guidelines are certainly a step in the right direction to improve the care provided to sepsis and septic shock patients. However, as more research is completed and the knowledge base

grows, these guidelines need to evolve to reflect current data and optimize patient outcomes. In addition, a more tailored approach to fluid resuscitation may provide benefit by reducing fluid overload and improving patient outcomes.

It is clear that clinicians must be cautious when administering fluid boluses to septic patients, as it may lead to further organ dysfunction, additional medical interventions, and even higher mortality compared to a restrictive fluid approach. By administering small fluid challenges of 250 to 500 milliliters crystalloid and using dynamic measures, such as cardiac output, to monitor the patient's response, it can minimize a positive fluid balance and help minimize fluid overload complications. Adding vasopressors early in the resuscitation can also decrease the need for fluids to maintain adequate perfusion and minimize the time necessary to correct hypotension in septic shock patients. It is still unknown, however, what the optimal volume of fluid administered should be or at what time during resuscitation vasopressors should be initiated to maximize patient outcomes, so further research is needed.

In order to continue improving the medical knowledge surrounding fluid administered to patients with sepsis and septic shock, a consensus on the definitions of restrictive and liberal fluid approaches needs to be established. As mentioned previously, different studies enroll patients into the trials at different points in their care. Specifically, studies vary on whether patients are enrolled before or after an initial fluid bolus has already been administered. To truly compare these approaches, studies need to use specific definitions and consistent timing of fluid bolus initiation to adequately evaluate the different approaches and increase homogeneity amongst studies. Another layer of complexity in study design is ensuring that these trials are conducted in a manner that can evaluate each approach as an independent variable rather than as part of different treatment arms seen in many studies on this topic. Ideally, these studies can be

designed as randomized controlled trials with two treatment approaches. This may be difficult as there are many different treatment options being studied for the care of septic patients, and fluid administration is a small piece of the overall puzzle. In addition, future trials should evaluate and establish the ideal approach to be used to accurately measure the response to the fluid bolus. These parameters need to be both practical and accurate. Lastly, more research focused on the use of early vasopressors should be conducted compared to fluid bolus administration, as early data has shown promise in improving outcomes and decreasing complications associated with fluid overload.

Currently, the Crystalloid Liberal Or Vasopressor Early Resuscitation in Sepsis (CLOVERS) trial is being conducted comparing these strategies.[29] This randomized multicenter trial aims to determine the outcomes of a restrictive versus liberal fluid approach in the first 24 hours among adult patients in the United States.[29] The primary outcome of this study is focused on in-hospital mortality to day 90, with secondary outcomes of ventilator-free days, and organ-failure free days until day 28.[29] Although this is one example of a current trial being conducted, similar studies will help to provide valuable insight, which will continue to improve the care delivered to sepsis and septic shock patients.

The care of sepsis and septic shock patients can be equally as complicated as the pathophysiology involved in the condition itself. Thus far, great strides have been made in the medical community attempting to lower the high mortality rate, but future research is required to continue this positive trend. As more data becomes available, it is important for clinicians caring for sepsis and septic shock patients to keep up to date on medical literature to ensure the best care is provided to these patients. Although fluid administration is only one facet in the overall

care of sepsis and septic shock patients, its potential to affect downstream sequelae make it an essential component of resuscitation and improving morbidity and mortality.

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