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Review Article

Recognizing and Management of Septic Shock in ER

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Abstract

Introduction: Sepsis is considered to be a relatively common presentation that is frequently encountered by physicians in the emergency department and is a common cause of admissions into the intensive care units and death.

Aim of Work: From this point of view, we will be discussing some practical points of sepsis triage, early resuscitation, hemodynamic status monitoring, and the goal of resuscitation for patients with sepsis in the emergency department according to the currently published and most recent evidence.

Methodology: We did a systematic search for sepsis using PubMed search engine and Google Scholar search engine. The terms used in the search were: Sepsis, Septic shock, emergency department, management.

Conclusions: The new definition of sepsis is the dysregulation of a host's response to infection as an organ dysfunction score that is higher than 2. Septic shock is generally defined as continuous decreased blood pressure, that requires a vasopressor to keep hemodynamic stability, and hyperlactatemia (serum lactate more than 2 mmol/L). The concept of septic shock is thought to be because of an inflammatory process that causes changes in vessel permeability and cardiac dysfunction rather than volume depletion. The qSOFA, which is recommended as the standard sepsis screening tool in the Sepsis-3 guidelines, had relatively low sensitivity when used in the emergency department.

Keywords:*Sepsis; Septic Shock; Emergency Department; Management*

Introduction

Sepsis is considered to be a relatively common presentation that is frequently encountered by physicians in the emergency department and is a common cause of admissions into the intensive care units and death [1]. Despite that there are detailed sepsis guidelines,

mortality rates caused by sepsis around the world are still very high and can reach forty-six percent [2]. Therefore, early detection, rapid resuscitation, early administration of antibiotics, and eradication of the infection source are the most important management steps during the delivery of high-quality care to patients with sepsis. As sepsis is routinely defined as the presence of a dysregulated host response to infection and causes organ dysfunction that could not be detected by superficial evaluation, triage and detection of sepsis in the emergency department could be a difficult challenge [3].

Providing early hemodynamic resuscitation is considered essential in the management of sepsis. Providing under fluid resuscitation or over fluid resuscitation could both cause unfavorable patients outcomes. Assessment of the patient's hemodynamic status and response is the considered crucial during sepsis management in the emergency department. From this point of view, we will be discussing some practical points of sepsis triage, early resuscitation, hemodynamic status monitoring, and the goal of resuscitation for patients with sepsis in the emergency department according to the currently published and most recent evidence.

Methodology

We did a systematic search for sepsis using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles. The terms used in the search were: Sepsis, Septic shock, emergency department, management.

New and old definitions of sepsis: how does it matter for sepsis triage?

The presence of systemic inflammatory response syndrome (SIRS) - which is defined as increased body temperature that is higher than 38°C or that is less than 36°C, heart rate that is more than 90 beats per minute, respiratory rate that is more than twenty breaths per minute, and white blood cell count that is higher than 12,000/nm^3 or that has more than ten percent immature neutrophils - has been frequently used as a part of the criteria for sepsis for many years. However, a more recent study demonstrated that older patients and immunocompromised patients with sepsis might show an absence of fever and manifest with leukopenia instead of leukocytosis, while increased heart rate, tachypnea, and hyperthermia are not generally specific for the presence of an underlying infection. For these mentioned reasons, the SIRS criteria are insufficient and not specific to confirm the diagnosis of sepsis [4].

The new definition of sepsis based on Sepsis-3 pays significant attention to the presence of organs dysfunction and organs hypoperfusion rather than only focusing on the presence of inflammation. As a result, the term "severe sepsis" was deleted from the definition. Consequently, the sepsis task force suggested the use of a new definition of sepsis as the presence of a life-threatening organs dysfunction, that is defined by a resulting organ failure assessment (SOFA) score that is two or higher. Septic shock was then defined as the need for the administration of a vasopressor to keep a mean arterial pressure of at least sixty-five mmHg and a serum lactate concentration that is two mmol/L (> 18 mg/dL) with the absence of hypovolemia that could elevate mortality rates to up to forty percent. However, the SOFA score still needs the presence of several laboratory results that are not available in most cases in the triage area of an emergency department. The time needed to get these investigations results could potentially lead to delayed diagnosis of a patient with sepsis.

Consequently, the quick SOFA (qSOFA) score was proposed in Sepsis-314 and is defined as a tool that predicts the risk of death and extended intensive care unit admission, but it is not used to stand alone as an early warning signal of sepsis or detect patients who should be moved to the intensive care unit [5]. In fact, two cohort studies that were published recently demonstrated that the validity of the qSOFA score criteria, which includes assessing altered mental status (Glasgow Coma Scale score that is less than fifteen), respiratory rate that is higher than twenty-two, systolic blood pressure that is less than 100 mmHg, and with the presence or absence of serum lactate that is greater than two mmol/L, were relatively good predicting factors that predicted hospital mortality accurately and similar to the SOFA score [6]. On the other hand, outside the intensive care unit sepsis group, thirty percent had no SIRS criteria and forty-one percent had no SOFA points. Another recent systematic review and data from a published meta-analysis demonstrated that the qSOFA outside the intensive care unit showed very low sensitivity (about fifty percent) when used as a screening tool within the emergency department [7].

On the other hand, the National Early Warning Score (NEWS) and Modified Early Warning Score (MEWS), that depend on the clinical parameters of temperature of the body, respiratory rate, heart rate, oxygen saturation rates, systolic blood pressure, and level of consciousness, were found to have higher feasibility for the monitoring and early detection of septic patients in both the emergency department and outside the intensive care unit. Recent data seem to demonstrate that the sensitivity of the NEWS criteria is significantly better than the MEWS and qSOFA scores. The sensitivity of a NEWS score that is more than five can be as high as seventy-nine percent, which is similar to the SIRS criteria that is higher than two (sensitivity of eighty percent) and higher than a qSOFA score that is higher than two (a sensitivity of seventy-four percent). When the sensitivity was compared as regards the rates of in-hospital mortality, the NEWS score that is higher than five, the MEWS score that is higher than five, the qSOFA score that is higher than two, and the SIRS criteria that is higher than two showed sensitivities of ninety-five percent, seventy-one percent, sixty-eight percent, and ninety-three percent, respectively [8].

To sum up, the new definition of sepsis focuses on the presence of organs dysfunction and decreased perfusion. SIRS criterion was removed from the sepsis clinical syndrome definition and is not a part of the definition of septic shock, which is now defined as a subtype of sepsis. On the other hand, the new sepsis-3 definition is still not free of controversy. There are many debates on whether the new definition, that depends on the presence of organs dysfunction, could fail in early detection and delayed resuscitation of patients with sepsis. The qSOFA score is, actually, not a part of the definition of sepsis and could not be used as a screening tool for sepsis. Despite this, it must still alert clinicians to those patients who are in real need for more evaluation of the presence of organs dysfunction. NEWS score is considered to be better than the MEWS score as a screening tool for patients with sepsis patients [6]. On the other hand, the Surviving Sepsis Campaign (SSC) guidelines do not suggest the use of any specific screening tool for patients with sepsis [9].

Fluid resuscitation in sepsis: time, types, and dose

For many years, the use of fluid resuscitation has been suggested to be the first and main priority when treating patients with septic shock [3]. The pathophysiology of septic shock is because of the increase in insensible fluid loss, the alteration of venous capacitance, and the development of vascular leakage that causes generating a case of "relative hypovolemia". Thus, fluid administration in patients with sepsis might be different among different the phases of sepsis and the choice of the fluid and the volume of resuscitation can affect the patient's outcome [10].

Understanding the 4 phases of septic shock

A more recent conceptual model of circulatory shock was published, and it defines the four different phases of resuscitation as the following: rescue, optimization, stabilization, and de-escalation [11]. The phase of 'rescue' which is also known as the 'life-threatening phase', develops within minutes to hours and is characterized by the presence of relatively strong vasodilation and leads to a case of decreased blood pressure and dysfunctional organ perfusion. During the first three-to-six hours following the initiation of therapy, fluid resuscitation is the main aim for early and sufficient fluid administration to prevent the development of cardiovascular collapse and subsequent death.

Early goal-directed therapy (EGDT) has been also advised for a decade as the gold standard protocol for resuscitation of patients with septic shock based on SSC [12]. Results published from three international independent multicenter studies demonstrated the absence of any benefits of Early goal-directed therapy over general standard care [13]. Many published systematic reviews and meta-analyses previously reported that Early goal-directed therapy does not significantly reduce mortality rates when compared to standard conventional care. In addition, a previous study demonstrated an even worse outcomes in the Early goal-directed therapy group when compared to the standard conventional care group. The Sepsis Campaign Guidelines advises for the immediate fluid administration at a dose of thirty mL/kg of IV crystalloid fluid in all patients with sepsis who show decreased blood pressure or elevated lactate concentrations. On the other hand, the aim of administration of fluids must be individualized and made on a case basis. An assessment of the patient's need for fluid administration could be achieved using several methods, including the fluid challenge test, the passive leg raise test, and the end-expiratory occlusion test.

The 'optimization' phase, which is also known as the ischemia and reperfusion phase, develops within hours. During this time, strict evaluation of the intravascular volume status and determination of the necessity for additional administration of fluids are essential. The ideal fluid resuscitation in this phase is still considered widely controversial. Several previous studies have demonstrated higher mortality rates in the group who received a bolus of fluids [14], whereas another previous study demonstrated the presence of an association between higher fluid balance and higher mortality rates in patients with sepsis [15]. Responsiveness to fluids is usually defined as a significant change in the stroke volume or cardiac output of approximately fifteen percent following the administration of a bolus fluids dose. The routine administration of invasive cardiac output monitoring devices, including the central venous catheter and pulmonary artery catheter, have been found to be linked to several risks without the presence of significant actual benefits. Current studies demonstrate relatively low sensitivity and specificity of using central venous pressure (CVP) for the assessment of volume status and response to fluids in patients who developed shock [16].

Some studies provided solid evidence that using the passive leg raising test and the end-expiratory occlusion test can possibly predict volume responsiveness. The velocity time integral (VTI) is another possible parameter that can be used for prediction of volume response in patients with sepsis that could be done using bedside echocardiography. A previous study that evaluated patients with the presence or absence of mechanical ventilation for intensive care unit patients who have shock showed that there is about a twelve percent alteration in the velocity time integral and this had a sensitivity and specificity of seventy-seven percent and a hundred percent, respectively, for a more than fifteen percent elevation in cardiac output following administration of fluid with an associated area under the curve of ninety-six percent. The caval index is generally calculated as the highest diameter on expiration minus the least diameter on inspiration divided by IVC max. Some evidence showed that the IVC diameter might be used to predict central venous pressure in intubated, mechanically ventilated patients and in spontaneously breathing patients [17]. A previous meta-analysis of right studies reported that the pool sensitivity and specificity of the caval index to be used in the prediction of volume responsiveness in shock patients were seventy-six percent and eighty-six percent, respectively, and the caval index performance was even higher in patients who were on mechanical ventilation than in patients who were spontaneously breathing patients [18].

As soon as sufficient intravascular volume status has been recovered, rapid administration of vasopressor therapy in the setting of fluid-refractory shock is essential in a timely-manner. Delayed administration of vasopressor therapy could cause excessive fluid resuscitation and higher morbidity and mortality rates. Mortality elevations of up to five percent were estimated to happen for every one hour of delay in the administration of vasopressor treatment [19]. The choice of the initial vasopressor therapy in the setting of a septic shock is norepinephrine, which starts at a dose of 0.5 mcg/kg/minute [19].

The 'stabilization' phase in sepsis often happens within a few days and following the optimization of fluids which is clinically demonstrated by a maintenance of a stable hemodynamic status. The aim of this phase is to maintain the intravascular volume, replace the continuous loss of fluids loss, support the body organs and especially dysfunctional organs, and avoid the development of any iatrogenic harm with unnecessary IV administration of fluids [20]. This step evaluates the sufficiency of organ perfusion and microcirculatory resuscitation is essential. Several previous studies demonstrated that a high central venous pressure (that is higher than eight mmHg) can be linked to a long period of mechanical ventilation, longer hospital admissions, kidney injuries, less pO_2/FiO_2, and higher mortality rates [21]. A $ScvO_2$ that is between seventy percent and eighty-nine percent could indicate the presence of a sufficient VO_2/DO_2 balance, whereas a supra-normal $ScvO_2$ value that is higher than ninety-percent indicates poor utilization of oxygen, tissue dysoxia and it is linked to relatively higher mortality rates. The use of lactate and lactate clearance can be the best option to date. Multiple studies demonstrated lower mortality rates when achieving the lactate clearance [22]. As soon as the end point of the resuscitation process is achieved, daily fluid balance must be strictly observed and maintenance of fluids must be used only to cover daily requirements that include insensible fluid loss and digestive tract loss [23].

The 'de-escalation' phase in sepsis is generally characterized by the occurrence of organ recovery and weaning from the mechanical ventilation and vasopressors administration. Excessive fluid balance in this phase is strongly associated with mortality [24]. The aim of

this phase is to maintain a negative fluid balance.63 More recently, several clinical studies have shown an independent correlation between a higher positive fluid balance and elevated mortality rates in patients who had sepsis [25].

A moderate fluid administration strategy encompasses avoiding fluid overloading and decreasing fluid overload is an essential component for better survival rates. Initiation of fluid removal process must be carefully performed without leading to the development of decrease blood pressure decreasing the cardiac output. The main risk in this phase is being too aggressive in cessation of fluids administration which might lead to the development of hemodynamic deterioration. To prevent the development of this problem, assessing preload responsiveness could be important [26].

Time is crucial!!

Time is considered to be one of the most essential concerns when performing fluid resuscitation. Many previous studies have demonstrated that delays in administrating proper fluid resuscitation is strongly associated with higher mortality rates [27]. This finding was later confirmed by a cohort study that studied more than eleven thousand patients with sepsis and showed the presence of significant mortality benefit associated with early fluid administration that is within thirty minutes following diagnosis of sepsis. The mortality rate was lower in the group that received fluids within less than thirty minutes (eighteen percent) when compared to the group that received fluid after more than thirty minutes (twenty-five percent) [28].

Type of fluid: colloid versus crystalloid

Fluids administration to achieve resuscitation plays the most important role in the management of patients with septic who are in the acute phase of their disease. Despite this, the gold standard of intravenous fluids for patients with sepsis remains to be highly controversial. The ideal fluid resuscitation in patients with sepsis must be physiologically assessed according to the improvement in the patient's outcome and a in a cost-effective way.

Normal saline solution (NSS) has been used for fluids resuscitation as the main choice of treatment in patients with septic shock for decades. Normal saline solution is isotonic to extracellular fluid, but it contains more chloride levels than normal plasma. Hartmann's solution, lactated Ringer's solution (LRS), and Plasma-Lyte, on the other hand, might be mildly hypotonic when compared to the extracellular fluid, but these fluids provide relatively more physiologic ions and control of pH status [29]. A previously published randomized, cross-over study showed a decrease in renal cortical perfusion and renal blood flow in healthy individuals who received a two-liter bolus of Normal saline solution [30]. Another retrospective study that analyzed about two thousand patients who were admitted in the intensive care unit showed that hyperchloremia at seventy-two hours following admission to the intensive care unit was strongly correlated with mortality rates and every five mEq/L increase of serum chloride levels was linked a more elevation in mortality rates [31].

Lactated Ringer's solution, Hartmann's solution, and Plasma-Lyte solutions are frequently known as balanced crystalloids as they have relatively lower levels of chloride ions when compared to normal saline. lactated Ringer's solution is considered to be better than Normal saline solution in regards of acid balance and has demonstrated improvement in survival outcomes in patients with sepsis [32]. The lactate in Lactated Ringer's solution is normally metabolized in the liver to release bicarbonate which acts as the key buffer in preventing the development of acidosis without increasing the levels of circulating lactic acid in septic patients who enter a state of hypoperfusion [33].

Conclusions

The new definition of sepsis is the dysregulation of a host's response to infection as an organ dysfunction score that is higher than 2. Septic shock is generally defined as continuous decreased blood pressure, that requires a vasopressor to keep hemodynamic stability, and hyperlactatemia (serum lactate more than 2 mmol/L). The concept of septic shock is thought to be because of an inflammatory process that causes changes in vessel permeability and cardiac dysfunction rather than volume depletion. The qSOFA, which is recommended as the standard sepsis screening tool in the Sepsis-3 guidelines, had relatively low sensitivity when used in the emergency department. NEWS score was demonstrated to be better than the MEWS score and qSOFA score as screening tools for sepsis in the emergency depart-

ment. The lower mortality benefits of early fluid resuscitation within thirty minutes following diagnosis is superior to the type of fluid resuscitation. Optimized volume resuscitation is the second priority for sepsis shock resuscitation to decrease mortality rates. The type of fluid that is administrated, whether crystalloid or colloid is still a matter of debates. while albumin resuscitation in sepsis has tended to be superior to a crystalloid solution without statistical significance. LRS is recommended in first-line treatment of sepsis resuscitation rather than NSS due to the benefit of lower mortality and renal replacement therapy. CVP is not a single good indicator to evaluate fluid responsiveness. However, if CVP monitoring is needed, the CVP should be kept lower than eight mmHg. Lactate clearance can be used as a goal targeted therapy as well as $ScvO_2$. Bedside echocardiography to evaluate VTI seems to be the best parameter to guide fluid resuscitation in the emergency department with high sensitivity and specificity. Early antibiotic treatment within one hour to eliminate the source of infection is still recommended. Clinicians who care for sepsis patients should use various physiologic parameters to adjust fluid resuscitation rather than rely on a single parameter.

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