Open Access Emergency Medicine

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REVIEW

Septic shock in the ER: diagnostic and management challenges

This article was published in the following Dove Press journal:
Open Access Emergency Medicine

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Abstract: Sepsis is a common presentation in the emergency department and a common cause of intensive care unit admissions and death. Accurate triage, rapid recognition, early resuscitation, early antibiotics, and eradication of the source of infection are the key components in delivering quality sepsis care. Evaluation of the patient's volume status, optimal hemodynamic resuscitation, and evaluation of patient response is crucial for sepsis management in the emergency department.

Keywords: sepsis, Sepsis-3, resuscitation, lactate, fluid responsiveness

Introduction

Sepsis is a common presentation in the emergency department and common cause of intensive care unit admissions and death.[1,2] Even though, there is a sepsis campaign guideline, the mortality from sepsis worldwide is still high at 34–46%.[3,4] Rapid recognition, early resuscitation, early antibiotics, and eradication of the source of infection are the key components in delivering quality sepsis care.[5–7] Since sepsis[8] is defined as a dysregulated host response to infection and causes organ dysfunction which cannot be diagnosed by superficial assessment, triage and recognizing sepsis in the emergency department can be a challenge.

Early and optimal hemodynamic resuscitation is crucial. Either under or over fluid resuscitation can lead to an unfavorable patient outcome. Evaluation of the patient's volume status and response is the cornerstone for sepsis management in the emergency department.

From this point of view, we discuss some practical points of sepsis triage, initial resuscitation, hemodynamic monitoring, and the target end point of resuscitation for sepsis patients in the emergency department based on the current evidence.

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

Systemic inflammatory response syndrome (SIRS) – body temperature >38°C or <36°C, heart rate >90 beats/min, respiratory rate >20 breaths/min, and white blood cell count >12,000/nm^3 or >10% immature neutrophils – has been used as part of the definition of sepsis for decades.[9,10] A recent study shows that the elderly and immunocompromised patients may have an absence of fever and present with leukopenia instead of leukocytosis, meanwhile tachycardia, increased respiratory rate, and high body temperature are not specific for infection. For these reasons, the SIRS criteria are inadequate and not specific to make a diagnosis of sepsis.[11–13]

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DovePress
http://doi.org/10.2147/OAEM.S166086

The new definition of sepsis according to Sepsis-3 pays attention to organ dysfunction and hypoperfusion rather than an inflammation.[14] Subsequently, the term "severe sepsis" was removed from the definition.[8] Therefore, the sepsis task force proposed a new definition of sepsis as a life-threatening organ dysfunction, which is defined by a sequential organ failure assessment (SOFA) score ≥2 (Table 1). Septic shock was defined as the need for a vasopressor to maintain a mean arterial pressure of at least 65 mmHg and serum lactate level over 2 mmol/L (>18 mg/dL) in the absence of hypovolemia which can increase the mortality rate to 40%.[15]

However, the SOFA score needs several laboratory results which mostly are not available in the triage area of an emergency department. The time needed to obtain the test results can cause delayed detection of a septic patient.

The quick SOFA (qSOFA) score (Box 1) was introduced in Sepsis-3[14] and is a tool to predict risk of death and extended ICU stay, but it is not designed to stand alone as an early warning signal of sepsis or identify which patients should be transferred to the ICU.[16,17] Two recent cohort studies found that the validity of the qSOFA score criteria, that includes altered mental status (Glasgow Coma Scale score <15), respiratory rate >22, systolic blood pressure <100 mmHg, and with and without serum lactate greater than >2 mmol/L, were good indicators to predict hospital mortality equally as well as the SOFA score.[14,18] Unfortunately, outside the ICU sepsis group, 30% had no SIRS criteria and 41% had no SOFA points. A recent systematic review and data from a meta-analysis showed that the qSOFA outside the ICU had poor sensitivity (0.51) when used as a screening tool in the emergency department.[19,20] Meanwhile, the National Early Warning Score (NEWS) (Table 2) and Modified Early Warning Score (MEWS) (Table 3), which are based on the clinical parameters of body temperature, heart rate, respiratory rate, oxygen saturation, systolic blood pressure, and level of consciousness, were shown to be more feasible for monitoring and early recognition of septic patients in both the emergency department and outside the ICU. Recent data seem to indicate that the sensitivity of the NEWS criteria is superior to the MEWS and qSOFA scores. The sensitivity of a NEWS ≥5 is 79%, which is similar to the SIRS criteria ≥2 (sensitivity 80%) and higher than qSOFA ≥2 (sensitivity 74%). NEWS had a similar AUROC (AUROC =0.65; 95% CI, 0.61 to 0.68) to qSOFA (AUROC =0.62; 95% CI, 0.59 to 0.66).[21] When the sensitivity was compared for in-hospital mortality, the NEWS ≥5, MEWS ≥5, qSOFA ≥2, and SIRS ≥2 criteria had sensitivities of 95.1%, 71.4%, 68.7%, and 93.8%, respectively.[22]

In summary, the new definition of sepsis focuses on organ dysfunction and hypoperfusion. SIRS was removed from the sepsis clinical syndrome and is not a part of the definition of

Table 1 SOFA score

SOFA score	0	1	2	3	4
Respiration PaO_2/FiO_2 or SaO_2/FiO_2 mmHg	>400	<400 221–301	<300 142–220	<200 67–141	<100 <67
Coagulation Platelets 10^3/ mm^3	>150	<150	<100	<50	<20
Liver Bilirubin (mg/dL)	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Cardiovascular Hypotension	No hypotension	MAP <70	Dopamine ≤5 or any	Dopamine >5 or norepinephrine ≤0.1	Dopamine >15 or norepinephrine >0.1
CNS Glasgow Coma Scale	15	13–14	10–12	6–9	<6
Renal Creatinine (mg/dL) or urine output (mL/d)	<1.2	1.2–1.9	2.0–3.4	3.5–4.9 or <500	>5.0 or <200

Abbreviations: SOFA, sequential organ failure assessment; PaO_2, partial pressure arterial oxygen; FiO2, fraction of inspired oxygen; SaO_2, arterial oxygen saturation; PaO_2/FiO_2, ratio of arterial oxygen partial pressure to fractional inspired oxygen; SaO_2/FiO_2, ratio of arterial oxygen saturation to fractional inspired oxygen; CNS, central nervous system.

Box 1 Quick sequential organ failure assessment

- Criteria
- Abnormal mental status
- Respiratory rate ≥22
- Systolic blood pressure ≤100 mmHg

sepsis and septic shock is now defined as a subset of sepsis.[14] However, the new sepsis-3 definition is not without controversy. There is debate about whether the new definition, which relies on organ dysfunction, can fail in early recognition and delayed resuscitation of sepsis patients. The qSOFA score is not a part of the definition of sepsis and cannot be used as a sepsis screening tool. However, it should alert clinicians to patients who are in need of further assessment of organ dysfunction. NEWS is superior to MEWS as a screening tool for sepsis patients.[18] However, the Surviving Sepsis Campaign (SSC) guideline does not recommend any specific tool for screening septic patients.[14]

Fluid resuscitation in sepsis: time, types, and dose

For decades, fluid resuscitation has been recommended as the first priority to treat septic shock.[5,8,23] The physiology of septic shock is due to increased insensible fluid loss, alteration of venous capacitance, and vascular leakage that results in generating "relative hypovolemia".[24] Therefore, fluid management in sepsis may differ between the phases of sepsis and fluid choice and the volume of resuscitation affects the patient's outcome.[25]

Understanding the 4 phases of septic shock

A recent conceptual model of circulatory shock was published, and it identifies the 4 phases of resuscitation as rescue, optimization, stabilization, and de-escalation.[26]

The rescue phase or life-threatening phase occurs within minutes to hours characterized by strong vasodilation and causes hypotension and impaired organ perfusion. During the first 3 to 6 hrs after initiation of therapy, fluid resuscitation is the aim for early and adequate fluid administration to prevent cardiovascular collapse and death. Early goal-directed therapy (EGDT) has been recommended for a decade as the best standard protocol for resuscitation of septic shock patients according to the SSC.[9,23] Results from three international independent multicenter trials (ProCESS, ARISE, and ProMISe)[8,27,28] showed no benefit of EGDT over standard care. Many systematic reviews and meta-analyses reported that EGDT does not decrease mortality compared with conventional care.[29–33] Furthermore, one study showed a worse outcome in the EGDT group compared to conventional care.[34] The Sepsis Campaign Guideline 2018[35]

Table 2 National Early Warning Score (NEWS)

Physiological parameters	3	2	1	0	1	2	3
Respiration rate	≤8		9–11	12–20		21–24	≥25
Oxygen saturations	≤91	92–93	94–95	≥96			
Any supplemental oxygen		Yes		No			
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Heart rate/min	≤40		41–50	51–90	91–110	111–130	≥131
Level of consciousness				Alert			Verbal, Ppain, or unresponsive

Table 3 Modified Early Warning Score (MEWS)

Score	+3	+2	+1	0	+1	+2	+3
Respiratory rate/min		<9		9–14	15–20	21–29	≥30
Pulse rate/min		≤40	41–50	51–100	101–110	111–129	≥130
Systolic blood pressure (mmHg)	≤70	71–80	81–100	101–199		≥200	
Temperature (°C)		≤35	35.1–36	36.1–38	38.1–38.5	>38.5	
Central nervous system			New confusion/agitation	Alert	React to voice	React to pain	Unresponsive

recommends immediate fluid administration at a dose of 30 mL/kg of intravenous crystalloid fluid in all septic patients who have hypotension or an elevated lactate level. However, the goal of fluid administration should be individualized. An evaluation of the need for fluid can be achieved by many methods, such as the fluid challenge test, the passive leg raise test, and the end-expiratory occlusion test.[36]

The optimization phase, which is also referred to as the ischemia and reperfusion phase, occurs within hours. During this time, careful assessment of the intravascular volume status and determination of the need for further fluid administration are crucial. Optimum fluid resuscitation in this phase is still being debated. Some studies showed a higher mortality rate in the fluid bolus group,[37] while another study showed a relationship between increased fluid balance and increased mortality in septic patients.[38] Fluid responsiveness is determined by a change in the stroke volume or cardiac output (CO) of approximately 12–15% after a bolus dose of fluid administration.[39] The routine use of invasive CO monitoring devices, such as central venous catheter and pulmonary artery catheter, have been associated with risks without significant benefits.[40] Current data show poor sensitivity and specificity of central venous pressure (CVP) to evaluate volume status and fluid response in shock patients.[41,42] Some studies gave evidence that the passive leg raising test and the end-expiratory occlusion test have potential to predict volume responsiveness.[43–46] The velocity time integral (VTI) is another parameter to predict volume response in septic patients which can be done by bedside echocardiography. Lamia et al[47] studied patients with and without mechanical ventilation for ICU patients with shock and demonstrated that a 12.5% change in the VTI had a sensitivity and specificity of 77% and 100%, respectively, for a >15% increase in CO following fluid loading with an associated area under the curve of 0.96. The caval index can be calculated as the maximum diameter on expiration (IVC max) minus the minimum diameter on inspiration (IVC min) divided by IVC max. Some research demonstrated that the IVC diameter may predict CVP in intubated, mechanically ventilated patients and in spontaneously breathing patients.[48–50] A meta-analysis from 8 studies reported that the pool sensitivity and specificity of the caval index to predict volume responsiveness in shock patients were 76% and 86%, respectively, and the caval index performance was better in patients on mechanical ventilation than in spontaneously breathing patients.[51]

Once adequate intravascular volume status has been achieved, rapid administration of vasopressor therapy in the setting of fluid-refractory shock is a time-critical intervention. Delayed initiation of vasopressor therapy can lead to excessive fluid resuscitation and increased morbidity and mortality. Mortality increases of 5.3% were estimated to occur for every 1 hr delay in vasopressor initiation.[52] Initial vasopressor choice in septic shock is norepinephrine, starting at a dose of 0.5 mcg/kg/min.[53]

The stabilization phase usual occurs within a few days and after optimized fluid was given which is manifested by a stable hemodynamic state. The goal of this phase is to maintain intravascular volume, replace ongoing fluid loss, support organ dysfunction, and avoid iatrogenic harm with unnecessary intravenous fluid administration.[54] This step assesses the adequacy of organ perfusion and microcirculatory resuscitation is crucial. Several studies demonstrated that a high CVP (≥8 mmHg) could be associated with prolonged mechanical ventilation, longer hospital length of stay, kidney injury, lower pO_2/FiO_2, and increased mortality.[55,56] A $ScvO_2$ between 70% and 89% would suggest an adequate VO_2/DO_2 balance, while a supranormal $ScvO_2$ value ≥90% suggests poor oxygen utilization, tissue dysoxia, and it is associated with mortality.[57] The use of lactate and lactate clearance (([initial lactate – 6 hrs lactate]/initial lactate) x 100)) seem to be the best options to date.[58] Multiple studies showed a lower mortality by achieving the lactate clearance.[58–60] Once the end point of resuscitation is achieved, daily fluid balance should be closely monitored and maintenance fluid should be given only to cover daily needs including insensible fluid loss and gastrointestinal loss.[61]

The de-escalation phase is characterized by organ recovery and weaning from mechanical ventilation and vasopressor support. Excessive fluid balance in this phase is significantly related to mortality.[55,62] The goal of this phase is to achieve an overall negative fluid balance.[63] Recently, more clinical studies have demonstrated an independent association between an increased positive fluid balance and increased mortality in patients with sepsis.[38,64,65] One randomized study showed that aggressive fluid loading was associated with a significant increase in the risk of death.[37]

A moderate fluid management strategy encompasses the avoidance of fluid loading and getting rid of fluid overload is a key component for improved survival.[36] Starting fluid removal should be done carefully without

inducing hypotension and reducing CO.[66] The risk in this phase is to be too aggressive in discontinuing fluids which may cause hemodynamic deterioration. To avoid this problem, testing preload responsiveness might be useful.[36]

Time is crucial!!

One of the most important concerns of fluid resuscitation is time. Many studies have shown that delayed fluid resuscitation is related to mortality.[67–69] This was confirmed by a cohort study in 11,182 sepsis patients which demonstrated the mortality benefit of early fluid resuscitation within 30 mins after diagnosis. The mortality rate was lower in the <30-min group (17.8%) than in the >30-min group (24.5%).[70] In a recent study that evaluated the effects of Ringer's lactate solution or 4% albumin on the microvascular circulation, fluid administration improved microvascular perfusion in the early but not in the late phase of sepsis.[71] This gave assurance that the type of fluid used is likely to be less important than timing.[71,72]

Type of fluid: colloid versus crystalloid

Fluid resuscitation plays a major role in septic shock patients in the acute phase. However, the best choice of intravenous fluid for sepsis patients has been debated. Ideal fluid resuscitation in sepsis should be physiologically balanced with improvement in the patient's outcome in a cost-effective manner.

Normal saline solution (NSS) has been used for volume resuscitation as standard treatment in shock patients for decades.[73,74] NSS is isotonic to extracellular fluid, but contains a higher chloride concentration than plasma. Hartmann's solution, lactated Ringer's solution (LRS), and Plasma-Lyte may be slightly hypotonic to extracellular fluid, but these solutions provide more physiologic ions and pH control.[24] A randomized, double-blind crossover study demonstrated a reduction of renal cortical perfusion and renal blood flow by magnetic resonance imaging in healthy volunteers who received a 2-L bolus of NSS.[75] Another retrospective analysis of 1,940 ICU patients found that hyperchloremia at 72 hrs after ICU admission was significantly associated with mortality and every 5 mEq/L increase of serum chloride concentration was associated with a further increase in mortality.[76] Both experimental[77,78] and clinical[79,80] studies suggested that resuscitation with normal saline has detrimental effects on the kidneys, acid–base balance, and electrolyte homeostasis, and may affect tissue perfusion.[81] A prospective pilot study in a single ICU, which implemented a chloride-restricted fluid policy, found a significant decrease in acute kidney injury and the reduced need for renal replacement therapy although mortality was unchanged.[82]

LRS, Hartmann's solution, and Plasma-Lyte are commonly known as balanced crystalloids because they have lower concentrations of chloride ions compared to normal saline.[24] LRS is considered to be superior to NSS in terms of acid balance and has shown to improve survival in septic patients.[83,84] The lactate in LRS is metabolized in the liver to form bicarbonate which is the key buffer in preventing acidosis without increasing the circulating lactic acid concentration in patients who are in the state of hypoperfusion.[85,86]

Recently, a cohort study in SIRS patients[87] and a prospective observational study in abdominal surgery patients[88] reported the same results from a comparison between Plasma-Lyte and NSS. Plasma-Lyte was associated with lower rates of acute respiratory failure, coagulopathy, electrolyte abnormality, and renal failure, in addition to a shorter length of hospital stay and lower in-hospital mortality.

Albumin and hydroxyethyl starch (HES) are considered to be colloid solutions. Albumin is commonly used and recommended in septic patients due to the anti-inflammatory effect, fluid sparing, and may decrease mortality in septic shock patients.[89,90] Sepsis guidelines (Grade 2C) currently suggest that albumin should be considered as a resuscitation fluid in patients with severe sepsis, particularly if those patients are not responding to crystalloid infusion.[23,91] However, the benefits of using albumin for resuscitation in septic patients need to be clarified. A subgroup analysis among septic patients in the Saline versus Albumin Fluid Evaluation study (SAFE)[89] showed significant mortality reduction in the albumin group with a mortality rate of 30.7% compared with 35.3% in the NSS group. The Albumin Italian Outcome Sepsis study (ALBIOS)[92] randomized 1,818 severe sepsis and septic shock patients and showed no statistically significant difference in the 28-day mortality between the albumin and NSS groups. A third trial, Early Albumin Resuscitation During Septic Shock (EARSS), randomized septic shock patients who received vasopressin within 8 hrs were administered 100 mL of 20% albumin or 0.9% NSS 100 mL every 8 hrs for 3 days. Among 798 patients, vasopressor-free days were higher in the albumin group (24.1% vs 26.3%) without improvement of 28-day mortality.

HES is a semisynthetic colloid solution derived from chemically modified plant starch. An HES solution contains molecules of various different molecular weights that range from 70 to 670 kDa[93] and has been associated with several problems, such as altered hemostasis, immunological consequence, and altered renal function.[94] In 2004, the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) trial[95] had to stop early due to a trend of increased 90-day mortality (41.0% vs 33.9%) and increased acute kidney injury with HES 200/0.5 (34.9% vs 22.8%) compared with the LRS group. Later, the larger Scandinavian Starch for Severe Sepsis/Septic Shock (6S) trial compared the use of HES and LRS as resuscitation fluids in 804 septic patients and showed the same results as the VISEP trial. The author concluded that patients who received HES had a higher risk of death at 90 days and were more likely to need renal-replacement therapy compared to LRS.[96] The harmful effects of HES were later confirmed further in the CRYSTMAS, CHEST, and CRISTAL studies.[97–99] The latest systematic review and meta-analysis affirmed that HES was related to acute kidney injury and mortality.[100]

Conclusion

The new concept of sepsis is dysregulation of a host's response to infection defined as an organ dysfunction score ≥2.[8] Septic shock is defined as persistent hypotension, which needs a vasopressor to maintain hemodynamic stability, and hyperlactatemia (serum lactate ≥2 mmol/L).[23] The concept of septic shock is believed to be due to an inflammatory process that causes changes in vessel permeability and cardiac dysfunction rather than volume depletion.[101,102] The qSOFA, which is recommended as the standard sepsis screening tool in the Sepsis-3 guideline,[23] had poor sensitivity when used in the ED.[19,20] NEWS was shown to be superior to MEWS and qSOFA as screening tools for sepsis in the ED.[22] The lower mortality benefit of early fluid resuscitation within 30 mins after diagnosis is superior to the type of fluid resuscitation.[70,72] Optimized volume resuscitation is the second priority for sepsis shock resuscitation to decrease mortality.[37,103] The type of fluid, whether crystalloid or colloid is still controversial[92] while albumin resuscitation in sepsis has tended to be superior to a crystalloid solution without statistical significance.[89] LRS is recommended in first-line treatment of sepsis resuscitation rather than NSS due to the benefit of lower mortality[80] and renal replacement therapy.[82] CVP is not a single good indicator to evaluate fluid responsiveness.[104,105] However, if CVP monitoring is needed, the CVP should be kept lower than 8 mmHg.[55] Lactate clearance can be used as a goal targeted therapy as well as $ScvO_2$.[106,107] Bedside echocardiography to evaluate VTI seems to be the best parameter to guide fluid resuscitation in the ED with high sensitivity and specificity.[108,109] Early antibiotic treatment within 1 hr to eliminate the source of infection is still recommended.[5–8] Physicians who care for sepsis patients should use various physiologic parameters to adjust fluid resuscitation rather than rely on a single parameter.

Disclosure

The authors report no conflicts of interest in this work.

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