Sepsis: A Re-Look At Updates In 2019

Dr Gautam Rawal1*, Dr Raj Kumar2, Dr Sankalp Yadav3, Dr Prashant Kumar4,
Ms Sujana R5

1Associate Consultant-Respiratory Intensive Care, Max Super Specialty Hospital, Saket, New Delhi, India.
2Principal Consultant and Incharge-Respiratory Intensive Care, Max Super Specialty Hospital, Saket, New Delhi, India.
3General Duty Medical Officer-II, Department of Medicine & TB, Chest Clinic Moti Nagar, North Delhi Municipal Corporation, New Delhi, India.
4Consultant-Respiratory Intensive Care, Max Super Specialty Hospital, Saket, New Delhi, India
5Nursing Quality, Max Super Specialty Hospital, Saket, New Delhi, India.

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ABSTRACT

Sepsis remains the one of the leading causes of mortality and morbidity worldwide. Though there have been continuous advancements in its understanding and management, it remains a deadly entity. The latest definition of sepsis given by the Sepsis-3 guidelines in the year 2016, stated sepsis to be a life-threatening organ dysfunction due to dysregulated host response to infection. The new recommendations include the use of balanced fluids for resuscitation, nor-ephinephrine as the first vasopressor of choice, steroids use in septic shock refractory to fluid resuscitation and vasopressors, using Sequential Organ Failure Assessment (SOFA) score for rapid identification of patients with sepsis, quick SOFA (qSOFA) score to identify patients at risk of sepsis outside intensive care unit, and new the therapeutic options of angiotensin II, vitamin C, and thiamine that need further validation in managing sepsis.
INTRODUCTION:
Sepsis still remains a dreaded entity worldwide due to its high lethality. There are estimated 19 million sepsis cases per year worldwide and approximately 1.5 million cases each year in the United States [1-3]. Sepsis is responsible for greater than 30% in-hospital mortality despite the advancements in understanding of sepsis and better critical care facilities [1-3]. The mortality associated with the septic shock is even greater, estimated to be as high as 50% [4]. Sepsis affects people of all ages; however, approximately 49% of patients with sepsis fall in the age group of 65–84 years, usually affecting those with weakened immune system, chronic or debilitating diseases, infants and patients with traumatic injury [5]. The economic burden of sepsis in United States is estimated to be more than $20 billion per year and about $55 million each day [6].

In this review, we will outline the evolution of definition of sepsis, data regarding intravenous (IV) fluid administration, the use of steroids, and new drug therapies including vitamin C, thiamine, and angiotensin 2. Although it is unclear which of these will be practice changing, they raise important concerns in the management of sepsis.

Definition:
The definition of sepsis has been constantly evolving. It was first described in 1991 (Sepsis-1), when the consensus developed that systemic inflammatory response syndrome (SIRS) to infection would be called sepsis [7]. In the year 2012, Sepsis-2 guidelines defined sepsis as the presence (probable or documented) of infection together with systemic manifestations of infection [7]. In the year 2016, the Third International Consensus Definitions Task Force published the ‘The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) defining sepsis as a life-threatening organ dysfunction caused by a dysregulated host response to infection [7, 8]. This new definition eliminated the SIRS criteria and highlighted the three main critical components of sepsis: 1) the presence of infection, 2) the abnormal regulation of the host response to infection and 3) the resulting organ system dysfunction as a result of the host response [7, 8]. The Sepsis 3 guidelines focused on organ dysfunction as the most critical component in the diagnosis of sepsis. The ‘life-threatening organ dysfunction’ in patients with presumed or suspected infection was identified by an increase (from baseline) in the Sequential Organ Failure Assessment (SOFA) score [Table 1] of two points or more in patients in an intensive care unit (ICU) and quick SOFA (qSOFA) score [Table 2] of two or more for patients outside of the ICU [7, 8].

The assessment of sepsis at presentation was done by assuming that the baseline SOFA score is zero (unless the patient had known organ dysfunction which was pre-existing before the onset of current infection). The assessment of sepsis at presentation was done by assuming that the baseline SOFA score is zero (unless the patient had known organ dysfunction which was pre-existing before the onset of current infection). It was also observed that the patients who had an increase of 2 or more in the SOFA score had an estimated in-hospital mortality of 10% due to sepsis and two to twenty-five times higher risk of death as compared with patients with a SOFA score of <2 [1].

| Table 1: The Sequential Organ Failure Assessment (SOFA) score |
|-----------------|-------|-----|-----|-----|
| SOFA score      | 1     | 2   | 3   | 4   |
| Respiration PaO2/FiO2 (mm Hg) | <400 | <300 | <200 with respiratory support | <100 with respiratory support |
| Coagulation Platelets ×10^9/mm³ | <150 | <100 | <50 | <20 |
| Liver Bilirubin (mg/dL) | 1.2-1.9 | 2.0-5.9 | 6.0-11.9 | >12.0 |
Septic shock

Septic shock has been defined in several ways in guidelines depending on the chosen clinical variables to characterize the organ dysfunction associated and hypotension. The Sepsis 2 (2012 taskforce) defined the septic shock as sepsis-induced hypotension that persists despite adequate fluid resuscitation. Sepsis-induced tissue hypoperfusion was defined as hypotension (systolic blood pressure (SBP) <90 mm Hg, mean arterial pressure (MAP) <70 mm Hg, or SBP decrease >40 mm Hg or less than 2 SD below normal for age in the absence of other causes), elevated lactate (>1 mmol/L) or oliguria (urine output <0.5 mL/kg/hour for 2 hours despite fluid resuscitation) secondary to infection.

The 2016 Sepsis 3 guidelines defined the septic shock as sepsis with persistent hypotension requiring vasopressors to maintain MAP ≥65 mm Hg and having a serum lactate >2 mmol/L (18 mg/dL) despite adequate volume resuscitation.

Early goal directed therapy and the surviving sepsis campaign

The early goal-directed therapy (EGDT) proposed by Rivers et al in 2001 became the mainstay of the approach to a patient with sepsis with a reported increased survival chances compared to those treated on a protocol versus standard therapy (46.5% vs 30.5% respectively) [9]. The EGDT (fluid resuscitation to aim central venous pressure (CVP), mean arterial pressure (MAP), urine output and mixed venous oxygen saturation) was adopted by the Surviving sepsis campaign guidelines [10]. Subsequently over the next few years the various randomized controlled trials and their meta-analysis failed to demonstrate the same benefit of EGDT as by Rivers et al [11].

Initial resuscitation

The 2012 surviving sepsis guidelines recommended a protocolized approach for resuscitation of patients having sepsis related hypoperfusion which was...
defined as hypotension persistent after initial fluid challenge or lactate ≥4 mmol/L [10]. This approach for resuscitation for a patient in sepsis or septic shock was through achieving the specific set of goals (or the care bundles) to be met from the time of presentation in the first 3 hours and by 6 hours. A strong correlation has been observed between the time-to-completion of the 3-hour bundle with mortality with an increased OR of 1.04 for each hour of delay [12].

**Three-hour and 6-hour sepsis bundles:**

Within 3 hours of presentation:
- Measure serum lactate
- Acquire blood cultures (preferably paired)
- Fluid bolus 30 mL/kg crystalloid for hypotension and lactate ≥4 mmol/L

Within 6 hours of presentation:
- In case of persistent hypotension (MAP < 65 mm Hg) despite adequate fluid resuscitation, consider adding vasopressors
- Frequent re-assessment of volume status and tissue perfusion in patients with persistent hypotension and/or initial lactate ≥4 mmol/L
- Aim for normalization of lactate

The 2016 guideline Sepsis 3 update continues to emphasize on the initial resuscitation with a 30 mL/kg crystalloid bolus within the first 3 hours of presentation followed by reassessment of the patient’s physiological parameters namely blood pressure, heart rate, capillary refill, arterial oxygen saturation and urine output [2]. The new guidelines do not recommend to achieve the targets such as CVP of 8–12 mm Hg, and an ScVO2 of 70% or SV02 (mixed venous oxygen saturation) of 65%, as was recommended in the previous guidelines [10]. This change in the goal is the result of the recent clinical trials (PROMISE [13], ARISE [14], PROCESS [15]) that questioned the use and benefit of EGDT.

The latest guidelines recommend that after the initial bolus, resuscitation to be guided by dynamic assessment of fluid responsiveness (includes response to straight leg raise, stroke volume variation and pulse pressure variation) or bedside ultrasound [2]. It is also recommended to obtain a serum lactate in the first 3 hours of presentation with a goal of normalizing it by 6 hours. The patient should be initiated on vasopressors at 6 hours if he/she continues to be hypotensive with MAP ≤ 65 mmHg despite initial resuscitation [16].

**Intravenous fluid therapy**

The 2016 Sepsis 3 guidelines suggest that either balanced crystalloids or normal saline is acceptable for initial fluid resuscitation [16]. In cases where high volume crystalloid is required, albumin should be considered in addition to crystalloids. Fluids should be used judiciously to avoid the complications such as pulmonary edema and volume overload and fluid resuscitation can be discontinued when there is no longer a physiological response [16]. The use of hydroxyethyl starches is discouraged [16].

**Vasopressors**

The recommendations for vasoactive medications in 2016 guidelines are similar to the 2012 guidelines [16]. The use of Norepinephrine continues to be the first-line agent for blood pressure support in septic shock. Vasopressin is initiated at a dose of 0.04 units/minute for decreasing the dose of norepinephrine or augment the MAP with goal MAP ≥ 65 mm Hg. Epinephrine is recommended as the second-line agent for use in patients with septic shock. Dopamine is considered instead of norepinephrine only in patients having relative or absolute bradycardia, with a low risk to develop tachyarrhythmias. Dobutamine is recommended for patients with persistent hypoperfusion despite adequate intravascular volume and vasopressor administration. In the 2016 update of sepsis management, phenylephrine is now no longer recommended for treatment of septic shock.

**Steroids in critical illness**

The use of steroids in sepsis is a common, but unresolved controversial practice. It is known fact that secretion and response of mineralocorticoid and glucocorticoid is altered during sepsis, but the arguments persist for and against the steroid administration in sepsis. The initiation of steroids helps to reduce vasoconstrictor use and improve SOFA scores [17], and also may improve mortality in septic shock [18, 19]. Steroids do have adverse effect of causing hypernatremia, hyperglycemia, and neuromuscular weakness [17]. The SCCM guidelines continue to recommend the use of intravenous hydrocortisone for septic shock unresponsive to
adequate fluid resuscitation and vasopressor administration [16, 17].

**Angiotensin II: the new vasopressor**

The main approach to maintain arterial blood pressure in septic shock (after judicious resuscitation) is by the use of vasoactive/vasoconstrictor agents which aim to reverse pathologic vasodilation. Currently, the vasoconstrictors used in septic shock are norepinephrine, vasopressin, and epinephrine [16]. The Angiotensin II is a non-catecholamine vasopressor that preferentially causes vasoconstriction. The use of Angiotensin II is emerging as an effective therapy to increase the blood pressure in patients with septic/vasodilatory shock without an increase in adverse effects related to the catecholamines (ATHOS 3 trial) [20]. Angiotensin II rapidly increases blood pressure by direct vasoconstriction, increasing catecholamine release by the adrenal medulla and thus increasing the sympathetic discharge [20]. The slow and persistent increase in blood pressure by Angiotensin II is by causing direct renal vasoconstriction, increase in renal sodium reabsorption and renal sympathetic tone [20]. The use of Angiotensin II does come with some adverse effects of increased venous and arterial thrombosis or thromboembolic events.

**Vitamin C and Thiamine**

Vitamin C and thiamine have shown some promising results as new therapies for sepsis. Vitamin C: Studies have shown that the vitamin C plays a vital role in maintaining the integrity of the endothelium and the deficiency of vitamin C may contribute to capillary leak, therefore the administration of vitamin C can be beneficial in sepsis, burns and trauma [23-26]. Thiamine (vitamin B1): It has been observed that in sepsis the depletion of thiamine levels is common [27]. The deficiency of thiamine may contribute to metabolic impairments in mitochondria and is a cause of lactic acidosis [28] and its repletion may help in increased lactate clearance [28, 29]. The data published in a recent study suggests that the combination of intravenous vitamin C and thiamine along with hydrocortisone have a synergistic action and help in improving the functional and metabolic circulatory impairments in septic shock [30]. The cause of concern is that high dose of vitamin C recommended in sepsis can precipitate oxalate formation causing worsening of renal failure [30]. Thought the data looks promising for the use of combination of vitamin C and thiamine along with hydrocortisone, more studies are required to validate and reproduce the same beneficial results in septic shock.

**CONCLUSION:**

The advances in clinical approach to sepsis are a continuous process. The new definition of sepsis in the Sepsis 3 guidelines stating the sepsis as a dysregulated host response to infection causing life threatening organ damage helps to further understand sepsis and its complications The Sepsis 3 re-looked at the established prevalent therapies for sepsis such as administration of intravenous fluids and steroids. There are studies to suggest the new therapies in sepsis which include the roles of angiotensin II, vitamin C and thiamine. Among the intravenous fluids, the use of balanced crystalloids seems to be superior option over the hyperchloremic solutions. Steroid administration has always been controversial; however, it helps to reverse the septic shock if used early in patients. Angiotensin II is a new non-catecholamine vasoconstrictor to increase blood pressure in shock, but carries a risk of prothrombotic state. Vitamin C and thiamine have shown to improve the metabolic abnormalities but still need further validation studies before being put in routine use.

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