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Review Article

What is new in Sepsis?

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Abstract

The consensus definition generalized in 1991 and revisited in 2001 described sepsis as a clinical syndrome defined by the presence of both infection and a systemic inflammatory response. Septic shock is defined as a state of circulatory failure associated with infection in the absence of other causes. This systemic inflammatory syndrome was not very specific to identify early sepsis, even if there is suspected or proven microbial etiology. So, The Third International consensus definition for sepsis and septic shock defined in a manner sufficient enough to create awareness about early diagnosis of sepsis and septic shock among health care professionals, so that mortality in sepsis can be reduced to some extent with proper intervention.

Discussion

In 1991, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) convened a Consensus Conference, to define the systemic inflammatory response to infection, which is a progressive injurious process that falls under the generalized term 'sepsis' and includes sepsis-associated organ dysfunction as well.[1] Systemic inflammatory response syndrome (SIRS) results from a systemic activation of the innate immune response regardless of cause. It was hypothesized that SIRS is triggered by localized or generalized infection, trauma, thermal injury or sterile inflammatory

process like acute pancreatitis. SIRS is considered to be present when patients have more than one of the clinical findings like

- ✓ Body temperature higher than 38oC or lower than 36oC
- ✓ Heart rate higher than 90/min
- ✓ Hyperventilation evidenced by respiratory rate higher than 20/min or PaCO2 lower than 32mm/Hg
- ✓ White blood cell count higher than 12,000 cells/cmm or lower than 4,000cells/cmm.

Bone et al defined sepsis as SIRS plus infection. Severe sepsis as sepsis associated with organ dysfunction, hypoperfusion or hypotension. Septic shock as sepsis with arterial hypotension despite adequate fluid resuscitation. These definitions were widely used in practice and served as a basis for numerous clinical trials, which provided a need to revisit and modify 1992 definition. Thus a conference was held in Washington D.C in december 2001 and included 29 participants from Europe and North America. Prior to convening, five subgroups were formed to evaluate the signs and symptoms of sepsis, cell markers, microbiological data and coagulation parameters. This manuscript serves as the final report of 2001 International Sepsis Definitions Conference.[2] (Table 1)

Any two of the SIRS criteria which is based on suspected or proved infection was enough to consider the diagnosis of early sepsis. In this group of patients, Internists and physicians used to observe that patients presenting with tachypnoea and mental changes especially alteration of the sensorium based on Glasgow Coma Scale (GCS) < 15 can progress to severe sepsis with ARDS or multiorgan failure. The other groups of patients with only fever and tachycardia may not progress to severe sepsis, but still they are grouped under sepsis, if they are suspected to have an infective etiology. The changes in white cell count, body temperature and heart rate reflects only inflammation. SIRS criteria do not necessarily indicate a dysregulated life threatening host response. The sensitivity, face validity, and construct validity of the rule of using two or more SIRS criteria for the diagnosis of severe sepsis in the first 24 hours after ICU admission were studied and found that the SIRS-criteria rule missed one patient in eight with severe sepsis. Such patients with SIRS negative severe sepsis had lower but still substantial mortality, as compared with patients with SIRS-positive sepsis. The incidence, proportion, and mortality decreased over time almost identically to the rates among patients with SIRS positive sepsis.[3]

Similarly SIRS can not be abandoned, because of the fact that this criteria of SIRS is present in various non infectious condition like acute pancreatitis, post pump cardiotomy syndrome and burns. That is the reason why the task force of the 3rd international consensus definition for sepsis and septic shock (Sepsis - 3) sought to differentiate sepsis from uncomplicated infection and also to modify the definition of sepsis and septic shock which is quite often not a continuum of the initial infection.

Obviously in sepsis these are three elements.

1) INFECTION

2) HOST RESPONSE

3) ORGAN DYSFUNCTION

Hence early recognition is important for practicing Physician at the level of primary care or outside the hospital (for public as well as practitioners), emergency department and hospital ward settings. Early recognition is important because prompt management as outlined in surviving sepsis campaign 2012 guidelines may improve the final outcome.[4] **(Table 2)**

The new definition of sepsis as per the 3rd International consensus definition for sepsis and septic shock.[5] (**Table 3)**

Table 1 Diagnostic criteria for sepsis

Infection
Documented or suspected and some of the following
General parameters
Fever (core temperature >38.3^{o}C)
Hypothermia (core temperature <36^{o}C)
Heart rate >90 beats/min or >2SD above the normal range for age
Tachypnea >30 breaths/min
Altered mental status
Significant edema or positive fluid balance (>20ml/kg over 24h)
Hyperglycemia (plasma glucose >110mg/dl or 7.7mM/l) in the absence of diabetes
Inflammatory parameters
Leukocytosis (WBC > 12,000/µl)
Leukopenia (WBC < 4,000/µl)
Normal WBC count with 10% immature forms
Plasma C reactive protein >2SD above the normal value
Plasma procalcitonin >2 SD above the normal value
Hemodynamic parameters
Arterial hypotension (systolic BP <90mmHg, mean arterial pressure <70, or systolic BP decrease >40mmHg in adults or <2SD below normal for age)
Mixed venous oxygen saturation >70%
Cardiac Index >3.51 L/min/m^2
Organ dysfunction parameters
Arterial hypoxemia (PaO_2/FiO_2 <300)
Acute oliguria (urine output <0.5ml/kg/hr or 45nM/l for at least 2h)
Creatinine increase ≥0.5mg/dl
Coagulation abnormalities (INR >1.5 or aPTT >60s)
Ileus (Absent bowel sounds)
Thrombocytopenia (platelet count <1,00,000/µl)
Hyperbilirubinemia (plasma total bilirubin >4mg/dl or 70mmol/l)
Tissue perfusion parameters
Hyperlactatemia (>3 mmol/l)
Decreased capillary refill or mottling

Table 2: Some facts about sepsis

- Sepsis is the primary cause of death from infection, especially if not recognized and treated promptly. It is independent from positive or negative SIRS criteria. Its recognition mandates urgent attention.
- Sepsis is a syndrome shaped by pathogen factors and host factors (Eg: sex, age,race, comorbidities, environmental and other genetic determinants) with characteristics that evolve over time. What differentiates sepsis from infection is an aberrant or dysregulated host response and presence of organ dysfunction.
- Sepsis induced organ dysfunction may be occult. Therefore, its presence should be considered in any patient with infection. Conversely, unrecognized infection may be cause of new onset organ dysfunction. Any unexplained organ dysfunction should thus raise the possibility of underlying infection.
- The clinical and biological phenotype of sepsis can be modified by preexisting illness, long standing illness, medication and interventions and immunological status
- Specific infections may result in local organ dysfunction without generating dysregulated systemic host response

Table 3: The new definition of sepsis as per the 3rd International consensus definition for sepsis and septic shock

New Terms and Definitions

- Sepsis is defined as life threatening organ dysfunction caused by a dysregulated host response to infection.
- Organ dysfunction can be identified as an acute changes in total SOFA score ≥2 points consequent to the infection.
- The baseline SOFA score can be assumed to be zero in patients not known to have preexisting organ dysfunction.
- A SOFA score 2 reflects overall mortality risk of approximately 10% in a general hospital population with suspected infection. Even patients presenting with modest dysfunction can deteriorate further, emphasizing the seriousness of this condition and the need for prompt and appropriate intervention, if not already being instituted.
- In lay terms, sepsis is a life threatening condition that arises when the body's response to an infection injures its own tissues and organs.
- Patients with suspected infection who are likely to have a prolonged ICU stay or to die in the hospital can be promptly identified at the bedside with qSOFA, ie.
  - Alteration in mental status
  - Systolic blood pressure < 100mmHg
  - Respiratory rate >22/min.
- Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.
- Patients with septic shock can be identified with a clinical concept of sepsis with persisting hypotension requiring vasopressors to maintain MAP > 65mmHg and having a serum lactate level of >2nmol/lit (18 mg/dl) despite adequate volume resuscitation. With these criteria hospital mortality is in excess of 40%.

SOFA score: SOFA score is useful to clinically characterize a septic patient and has a well validated relationship with mortality risk. It requires investigations like liver function test, renal function test apart from complete blood count, PaO_2/FiO_2 and Glasgow Coma Scale. It is a scoring system to determine the extent of organ dysfunction or rate of failure.[6,7]

SOFA scoring system and LODS are still useful in the ICU setting. This is not quick enough to categorize the patient with dysregulated host response. Hence the task force evaluated and developed a clinical criteria

that will be easily identifiable in patients with sepsis especially in prehospital area, emergency department and general wards. After considering SIRS criteria, SOFA scoring system, and Logistic organ dysfunction score (LODS), a new scoring system was considered i.e qSOFA. It has three clinical criteria.

1. Altered mentation (GCS < 15)
2. Systolic BP ≤ 100mmHg
3. Respiratory rate of ≥22 /min
4. qSOFA is quick SOFA, since it is easy to diagnose clinically without laboratory evaluation. Sepsis is likely if 2 or more qSOFA criteria is present. At 2 points mortality is increased 3-fold, at 3 points by 14-fold. Among encounters with suspected sepsis in ICU, SOFA and LODS had statistically greater predictive value compared with SIRS criteria. Outside of the ICU, a simple model qSOFA as described above had statistically greater predictive value than SOFA score. The task force suggested that qSOFA criteria can be assessed quickly and used to investigate early enough for organ dysfunction, increase the frequency of monitoring and also to suspect infectious etiology in a noninfectious condition with hypotension. It was however statistically inferior compared to SOFA for encounter in the ICU and has a statistically lower content validity as a measure of multi organ dysfunction. Thus the task force recommended use of SOFA score of 2 points or more in encounters with infection as a criteria for sepsis and use of qSOFA in non-ICU settings to consider the possibility of sepsis.[5] In both cases (≥ 2 qSOFA criteria or ≥ 2 SOFA points) intensified monitoring, special diagnostics and therapy should be initiated promptly.

Definition of Septic shock

The septic shock is defined as a subset of sepsis in which underlying circulatory, cellular and metabolism abnormalities are associated with greater risk of mortality than sepsis alone.

The task force favored a definition that is fit enough to differentiate septic shock from cardiovascular dysfunction alone and to recognize the importance of cellular abnormalities and much likelihood of death than sepsis alone. Hence in 2015 clinical criteria has been proposed for septic shock.

1. Apart from sepsis, hypotension should be reported as a mean arterial pressure of less than 65mmHg. Systolic BP was used as a qSOFA criteria, because it was most widely recorded in the electronic health record data.
2. Elevated lactate level >2nmol/L (18mg/dl) despite adequate fluid resuscitation is reflective of cellular dysfunction.[8] In sepsis hyperlactemia is a reasonable marker of illness severity with higher levels predictive of higher mortality.[9]

Insufficient tissue oxygen delivery, impaired aerobic respiration, accelerated aerobic glycolysis and reduced hepatic clearance also contribute to the elevated lactate level.[10] Both hypotension and hyperlactemia together encompasses cellular dysfunction and cardiovascular compromise. It is associated with significantly higher risk adjusted mortality. The proposed definition and criteria of septic shock differ from prior definitions in 2 respects: (1) the need for both a serum lactate level and vasopressor - dependent hypotension (ie, cardiovascular SOFA score ≥2) instead of either alone and (2) a lower serum lactate level cutoff of 2 mmol/L vs 4 mmol/L as currently used in the SSC definitions. In the new septic shock definition, an increase in serum lactate level is positioned as a proxy for a cellular metabolic abnormality, and as a variable independently associated with acute mortality (predictive validity), which is consistent with the literature. An elevated serum lactate level is not specific for cellular dysfunction in sepsis but has face validity given the lack of a superior yet readily available alternative.[8]

Sepsis finally is a life threatening condition that arises when the body's response to infection injures its own

tissues. The new definition proposed does probably endorses and emphasize that sepsis if not detected early, may end fatally despite various advances in the management of infection.

Controversies and Limitations

The PIRO system for staging sepsis based on predisposition, insult (Infection), response and organ dysfunction is not included, as this article is likely to exceed the limitation. In developing countries the facility for serum lactate measurement is not readily available in all the centers. In such situation a working diagnosis of septic shock is necessary and may be done using fluid resistant hypotension and other criteria consistent with tissue hypoperfusion like delayed capillary refill.[11] The task force also wished to stress that SIRS criteria may still remain useful for the identification of infection. qSOFA can be applied at bedside without need for blood investigations and is hoped that it will facilitate prompt identification of infection that poses a greater threat to life.

Conclusion

Components of SIRS are nearly ubiquitous in hospitalized patients and occur in many benign conditions both related and not related to infection that is not adequately specific for the diagnosis for sepsis.[12] The idea behind new definition is to facilitate early detection of sepsis, instead of SIRS with suspected microbial infection as a basis of definition of sepsis. The new definition of sepsis as evidence of infection plus life threatening organ dysfunction clinically characterized by an acute change of 2 points or more in SOFA score will be helpful in recognizing sepsis at an early stage for general practitioners, physicians and other specialties.

Conflicts of Interest - None
Financial Disclosure - None

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