

INTRODUCTION

“Nothing endures but change” – eternal words by Heraclitus echo around, as the medical community endeavours to imbibe the revised definitions and diagnostic algorithms of “Sepsis-3”, the Third International Consensus Definitions for Sepsis and Septic Shock released by European Society of Intensive Care Medicine (ESICM) and the Society of Critical Care Medicine (SCCM) in 2016.

Despite advances in intensive care and antimicrobial therapy, in last two decades, Sepsis continues to be the leading cause of death from infection. Sepsis, as a syndrome, refers to the complex interplay of pathogen’s virulence and host’s immune response leading to multifaceted changes in the host’s physiology and biochemical milieu that ultimately lead to organ dysfunction. The details of pathophysiology behind this complicated phenomenon remain poorly understood and the heterogeneity of presentation, course and outcome make it a daunting task to arrive at a precise consensus definition and diagnostic criterion.

BACKGROUND

The first definition of sepsis originated in 1992, and was defined as presence of at least two out of the four Systemic Inflammatory Response Syndrome (SIRS) criteria (Table 1). The definition lacked specificity and was revised in 2002, wherein a revised set of laboratory and clinical parameters were added to the criteria to define sepsis and organ dysfunction. In this revision organ dysfunction during sepsis was labeled as ‘Severe Sepsis’ and persistent hypotension despite fluid resuscitation was called ‘Septic Shock’. However, in the last decade the epidemiological as well as clinical utility of these definitions were questioned leading to formulation of a 19-member-Task Force commissioned under the aegis of ESICM and SCCM, in the year 2014. The Task-Force came out with the new definitions and the classification criteria

Table 1: SIRS

Systemic inflammatory response syndrome (SIRS) in adults requires 2 or more of the following :

1. Temperature >38 C or <36 C
2. Pulse >90 /min
3. RR >20 /min or PaCO₂ <32 mmHg
4. WBC count $>12,000$ /cmm or <4000 /cmm or $>10\%$ immature band forms

in 2016, now called “Sepsis-3”. This nomenclature and the authors of Sepsis-3 also emphasise that this is “a work in progress”. With the existing knowledge, understanding and evidence, it is impossible to work-out the “perfect definition” and classification criteria with acceptable sensitivity and specificity in all settings. With continued research and experience, as new evidence and information surfaces, it is hoped that the future generations of “sepsis definitions” will be closer to perfection than the existing one. This article will dwell upon these new changes, their basis and the concerns.

WHY WAS THE CHANGE REQUIRED?

An acceptable criteria for “sepsis” should have multiple characteristics, namely - reliability (valid for all kinds of settings, at all times without significant intra-observer and inter-observer variations), content validity (measure represents every single facet of the condition), construct validity (should be able to measure what they purport to measure), criterion validity (should improve upon the existing standards), measurement burden (economic, pragmatic and safe), and timeliness (should not delay the clinical care). The existing standards of defining and diagnosing sepsis, severe sepsis and septic shock had several pitfalls leading to conceptual misinterpretations as well as heterogeneity in surveillance studies and clinical trials.

1. Problems with existing definition and SIRS criteria: The earlier proposition of defining sepsis with “the presence (probable or documented) of infection together with systemic manifestations of infection” and the qualifying criteria of presence of “at least two SIRS features” were deceptive because even uncomplicated infections may have systemic manifestations and SIRS features (as an appropriate host adaptive response). This created an illusory increase in the number of sepsis cases reported in epidemiological and statistical surveys and downplayed the severity of the condition. The SIRS criteria were found to be lacking both sensitivity and specificity.
 - a. A large number of patients in acute medical and surgical wards with infective illnesses would satisfy SIRS criteria without really being septic. These (fever, leukocytosis, tachycardia or tachypnoea) may represent appropriate host responses rather than a “dysregulated” one that can cause organ-dysfunction. Studies conducted in the West have shown that 68-93% patients admitted to acute and

critical care wards may have 2 or more SIRS criteria positive, at some point during their stay in the hospital.

- b. Similarly, a considerable number of septic patients may not have 2 or more SIRS criteria positive. It has been shown that 1 in 8 ICU patients with infection and organ dysfunction do not have 2 or more SIRS criteria.
 - c. Also, the effect of pre-existing co-morbidities on SIRS parameters had not been addressed.
2. Limitations of "Septic shock" definition: The existing definition of "septic shock" focussed only on circulatory failure without taking into account the role of cellular metabolism dysfunction in sepsis. The existing criteria do not satisfactorily differentiate mere cardiovascular dysfunction from the more complicated and sinister "septic shock".
 3. Absence of screening tool: The importance of early suspicion of sepsis in the pre-hospital and emergency room setting cannot be over-emphasised as it has been unequivocally shown that early and appropriateness of treatment has significant bearing on outcomes. It was vital to formulate a screening tool that can assist the practitioners in the non-ICU environment to suspect sepsis early. Such a tool should be based on point-of-care assessment and thus SIRS did not fit the requirement.

SEPSIS 3: NEW DEFINITIONS AND CRITERIA

Aim of the New Definition and Criteria

The aims of the new definition and criteria are to assist medical practitioners to recognize septic patients early in the pre-hospital, emergency department as well as in-hospital setting and equally important to aid researchers in designing clinical trials and reporting epidemiological analyses.

The endpoint for formulating the new criteria was increased specificity for predicting mortality or ICU stay of > 3 days.

Definition of Sepsis

"A 'life-threatening organ dysfunction due to a dysregulated host response to infection'".

The earlier "SIRS criteria" in the definition of sepsis has been removed. More importantly, the new definition emphasizes that in septic patients the normal immunopathological host response becomes maladaptive creating disturbance in the homeostatic milieu, which will ultimately cause life-threatening organ dysfunction. It is this stormy host response that the future trials are likely to be focused on.

Diagnosis of Sepsis

The organ dysfunction in sepsis is recommended to be identified by 'an acute change in total SOFA score (Sequential or Sepsis-related Organ Failure Assessment) ≥ 2 points consequent to infection'. Such a criterion reflects an overall mortality rate of approximately 10%.

The baseline (SOFA) score (Table 2) is assumed zero unless the patient has a previously known co-morbidity (e.g. cirrhosis, chronic kidney disease, etc.) In ICU patients with suspected infection, SOFA was found to be a superior predictor of mortality in sepsis patients compared to SIRS, Logistic Organ Dysfunction System (LODS) score and other scores. The term "severe sepsis" which was earlier defined as "sepsis with evidence of organ definition" has now been removed because firstly, it is a misnomer considering that all septic patients are "severe" considering the high mortality and morbidity in "true sepsis" and secondly, because organ dysfunction as evidenced by SOFA score is now essential to label "sepsis".

Screening Tool

The Task Force also gave a screening tool for the pre-hospital or emergency room setting, for early identification of "potential septic" patients using an abridged SOFA score called qSOFA (for Quick SOFA). The qSOFA score (Table 3) eliminates the laboratory parameters of the detailed SOFA score and focuses on only three clinical variables - hypotension (systolic blood pressure ≤ 100 mmHg), altered mental status and tachypnea (respiratory rate > 22 /min): the presence of at least two of these criteria strongly predicts the likelihood of poor outcome in patients with clinical suspicion of sepsis in the non-ICU environment. It is reiterated that the role of qSOFA is only to raise suspicion of Sepsis. It is not a part of the definition of Sepsis. A patient with infection may have positive qSOFA but not fulfill the definition of sepsis because the parameters in qSOFA are different from the SOFA score (compare tables 2 and 3). Also, patient may have sepsis without fulfilling qSOFA because all organ dysfunctions (like coagulation/renal function) are not represented in qSOFA. Thus, qSOFA, although still unvalidated, appears to be a robust sepsis-screening tool in the pre-ICU setting but is not to be used to define sepsis or to rule it out. Its role is to encourage early suspicion of sepsis and prompt further action.

Septic Shock

Sepsis-3 has defined septic shock as a 'subset of sepsis where underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality'.

For making the diagnosis of septic shock the patient with sepsis should have the need for vasopressors to obtain a MAP ≥ 65 mmHg and an increase in lactate concentration > 2 mmol/L, despite adequate fluid resuscitation. This new definition differentiates septic shock from other forms of circulatory shock and reiterates the devastating impact of sepsis-induced cellular metabolism abnormalities. With these criteria, the in-hospital mortality of septic shock exceeds 40%.

To increase the awareness about this life threatening condition and to encourage its early identification and treatment, the Task Force also endorsed a lay definition of sepsis as 'a life-threatening condition that arises when the body's response to infection injures its own tissue'.

Table 2: SOFA Score

Organ System score	0	1	2	3	4
Respiration PaO ₂ /FiO ₂ , mmHg(kPa)	≥400 (53.3)	<400 (53.3)	<300(40)	<200 (26.7)with respiratory support	<100 (13.3) with respiratory support
Coagulation Platelets, x10 ³ /μL	≥150	>150	>100	>50	>20
Hepatic Bilirubin, mg/dL	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
CNS Glasgow Coma Scale	15	13-14	10-12	6-9	<6
Cardiovasc.	MAP ≥70 mmHg	MAP <70 mmHg	Dopamine <5.0 or dobutamine (any dose) ^a	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1 ^a	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1 ^a
Renal Serum creatinine, μmol/l mg/dL	<1.2	1.2-1.9	2.0-3.4	3.5-4.9	>5.0 or dialysis
Or urine output				Or <500 mL/24h	Or <200 mL/24h

Abbreviations: FIO₂, fraction of inspired oxygen; MAP, mean arterial pressure; PaO₂, partial pressure of oxygen.

^a Catecholamine doses are given as μg/kg/min for at least 1 hour.

The PaO₂/FiO₂ ratio is calculated without reference to the use or mode of mechanical ventilation, and without reference to the use or level of PEEP.

Glasgow Coma Score - For the patient receiving sedation or muscle relaxants, normal function is assumed unless there is evidence of intrinsically altered mentation).

Table 3: qSOFA score

2 or more of:

1. Hypotension: SBP less than or equal to 100 mmHg
2. Altered mental status (any GCS less than 15)
3. Tachypnoea: Respiratory rate greater than or equal to 22

CONCERNS WITH "SEPSIS-3"

The Taskforce for Sepsis-3 admits that consensus could not be arrived at on all points, considering the complexity of syndrome, lacunae in knowledge and wide variations in clinical infrastructures and practices. Thus, few pragmatic compromises had to be made to facilitate generalizability and applicability. Following are the limitations of the new definitions/criteria which, though seemingly trivial, must be made note of before implementing the definitions in practice and research.

1. The data utilized to formulate the sepsis-3 consensus definitions is primarily from Europe and United States. Data from the low-middle group nations is lacking. Though extrapolation seems intuitive, differences in the infection spectrum and the hospital infrastructure and set-up, poses questions on the validity of these definitions in the Indian setting. More validation studies, using Indian data are required to endorse the new definitions.
2. The screening-tool qSOFA has been arrived at

from retrospective analysis of limited data. The evidence to support its usefulness as a sensitive tool to pick-up the diverse presentations of sepsis is lacking. A patient with isolated hypotension or altered mentation with underlying evidence of infection may be classified as uncomplicated infection (not having sepsis) which is potentially perilous. It is also unclear how to use qSOFA in patients with pre-existing illnesses that may affect the three parameters used (example - old stroke). Additionally, the qSOFA is recommended for non-ICU settings. In the intubated and the mechanically ventilated patient, or in the patient with psychotropic substance abuse, an appropriate tool is still required. These patients are paradoxically at a higher risk for developing sepsis.

3. The new criteria for defining sepsis may miss an evolving sepsis (when it is eminently treatable) and pick it up only at an advanced stage (after frank organ dysfunction has set in) and may thus delay the institution of prompt appropriate management. Since the endpoint of Sepsis-3 was predicting increased mortality and ICU stay beyond 3 days, this definition may encourage "waiting" rather than prompt aggressive management.
4. SOFA score needs to be revised in sync with existing practice guidelines. For example, in the cardiovascular score the order of introduction of

vasopressors is not in concordance with the existing guidelines.

5. Septic shock has been defined by the presence of hypotension and hyperlactatemia. This approach may tend to miss cases of pre-shock or early shock that may have one of the two conditions and not both (hypotension with normal lactates or vice versa). Even with well-established shock pathology, it is well known that there is a subset of patients that do not develop hyperlactatemia. Additionally, serum lactate measurement may not be available in all care settings. The authors of sepsis-3 justify this concern by stating that presence of both the parameters significantly increases the mortality, compared to presence of only one of them. This does not imply that the energetic treatment will not be offered to patients with early or pre-shock. The definition will however have an important statistical role in designing clinical trials and studying epidemiological aspects of sepsis presentation and management outcomes.

CONCLUSION

It is clear that the “Sepsis-3” does not address all the expected objectives of a “perfect” definition and “gold standard” criteria, which should ideally have unquestionable acceptability in clinical care, research, surveillance, and also quality improvement and audit. However, the adaptation of the new definitions will lay the foundation for further studies in the complex field of sepsis and will allow homogeneity in recruitment and pooling of data for generation of quality evidence. As of now, it is prudent to adapt to Sepsis-3 but hold strongly on to sound clinical judgment, in clinical care, which takes precedence over any guideline, scoring or criteria. With developments in genetics, genomics, immunology, and cellular biology, the understanding of sepsis syndrome

is likely to improve and lead to sub-division into patho-physiologically distinct entities with targeted therapies. Thus, Sepsis-4 may incorporate specific biomarkers in its definition giving it a vital clinical role apart from being a mere epidemiological tool.

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