European Journal of Internal Medicine xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Rethinking the concept of sepsis and septic shock

Joana A. Cabrita[a], Isabel Pinheiro[a], L. Menezes Falcão[a,b,*]

[a] Hospital de Santa Maria/CHLN, Portugal
[b] Faculdade de Medicina de Lisboa, Portugal

ARTICLE INFO

Keywords:
SIRS
Sepsis
qSOFA
SOFA

ABSTRACT

Sepsis is a major global health problem and represents a challenge for physicians all over the world. The knowledge of sepsis and septic shock is a topic of interest among the scientific community and society in general.

New guidelines for management of sepsis and septic shock were developed in 2016, providing an update on this area. In Sepsis-3 new definitions for sepsis and septic shock were published.

The purpose of this narrative review is to discuss and compare the new criteria of 2016 with the old criteria, purposing at the same time an alternative approach for this topic. SOFA criteria (Sequential Organ Failure Assessment Score) are more complete, but too extensive and usually difficult to apply outside the intensive care units, therefore inducing potentially delay in the proper treatment.

We purpose combined criteria for the selection of sepsis patients. Initially, we could apply qSOFA (quick Sepsis Related Organ Failure Assessment) criteria, due to its easy application, associated with the SIRS (systemic inflammatory response syndrome) criteria, allowing to select the patients who are infected and need faster treatment. In that way we would use the best of old and newest criteria, allowing the early selection of patients who are infected and require faster treatment, while the search for a better and faster tool continues.

1. Introduction

The core of what physicians hope to prevent and to treat remains the same: they want the best outcomes for their patients. Sepsis and septic shock are life-threatening conditions that remain huge causes of death and morbidity causing organ dysfunction from mild to severe. Early management and appropriate treatment are essential to improve outcomes and reduce morbidity [1].

Tachypnea, tachycardia, and fever are known to be associated with life-threatening conditions. Accumulated clinical knowledge advocates SIRS as systemic manifestations of infection, distinct from local signs [2]. Traditionally, diagnosis of sepsis was based on the presence of two or more positive SIRS criteria due to infection. Recently published Sepsis-3 criteria put more emphasis on organ dysfunction caused by infection in the definition of sepsis. However no gold standard for sepsis diagnosis exists [3]. The purpose of this narrative review is to discuss and compare the new criteria of 2016 with the old criteria, purposing at the same time an alternative approach for this topic.

It is known that the mortality due to infection with SIRS is 7 to 9% but the mortality caused by infection with organ disfunction is the major concern of physicians. The main point is how SIRS can be useful to identify patients with life-threatening organ dysfunction caused by infection. Past knowledge appears to consider SIRS as the concept capable to identify those patients [2].

Current management of sepsis includes antimicrobial agents to tackle the underlying infection, optimization of intravascular volume to improve stroke volume, vasopressors to counteract vasoplegic shock and high-quality supportive care. Nowadays proper treatment combined with novel therapeutic approaches are the main tools used to continue decreasing the impact of sepsis [4]. Early diagnosis is paramount.

2. Historical overview

The authors review the historical concepts of SIRS and sepsis throughout the years in order to understand their changes, strong points and limitations.

2.1. SIRS and sepsis -1 definitions

The first definition of sepsis was published in 1992 consensus document, and was based on the presence of a suspected or proven infection with two or more criteria of the Systemic Inflammatory Response Syndrome. In this document, severe sepsis indicated the presence of organ failure, and septic shock was defined by the presence of acute circulatory failure and arterial hypotension (Table 1) [5, 6].

* Corresponding author at: Hospital de Santa Maria/CHLN, Portugal.
E-mail address: luis.falcao@chln.min-saude.pt (L. Menezes Falcão).

https://doi.org/10.1016/j.ejim.2018.06.002
Received 7 February 2018; Received in revised form 23 May 2018; Accepted 4 June 2018

Table 1
Definitions for sepsis-1 and organ failure and guidelines for the use of innovative therapies in sepsis (1991) [6].

Infection	Microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms
Bacteremia	The presence of viable bacteria in the blood
Systemic inflammatory response syndrome (SIRS)	The systemic inflammatory response to a variety of severe clinical insults. The response is manifested by two or more of the following conditions: (1) Temperature > 38 °C or < 36 °C; (2) Heart rate > 90 beats per minute; (3) Respiratory rate > 20 breaths per minute or $PaC0_2$ < 32 mmHg; and (4) White blood cell count > 12,000/cu mm, < 4000/cu mm, or > 10% immature (band) forms
Sepsis	The systemic response to infection, manifested by two or more of the following conditions as a result of infection: (1) Temperature > 38 °C or < 36 °C; (2) Heart rate > 90 beats per minute; (3) Respiratory rate > 20 breaths per minute or $PaCO_2$ < 32 mmHg; *and* white blood cell count > 12,000/cu mm, < 4000/cu mm, or > 10% immature (band) forms.
Severe sepsis	Sepsis associated with organ dysfunction, hypoperfusion or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria, acute alteration in mental status.
Septic shock	Sepsis-induced with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured.
Sepsis-induced hypotension	A systolic blood pressure < 90 mmHg or a reduction of ≥40 mmHg from baseline in the absence of other causes for hypotension.
Multiple organ dysfunction syndrome (MODS)	Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.

2.2. 2001 improvement

New variables were added in 2001 to identify systemic response to infection, on grounds of considering SIRS criteria to be too sensible and poorly specific. The task force recognized that some bedside examination findings and laboratory tests were significant and indicative of organ dysfunction, as general parameters (fever, hypothermia, heart rate, tachypnea, altered mental status, significant edema, hyperglycemia), inflammatory, hemodynamic, organ dysfunction and tissue perfusion parameters. However, old diagnostic criteria for sepsis continued to be used - the 2001 task force did not make a revision to the definition [7, 8]. The definitions of sepsis, septic shock, and organ dysfunction have remained unchanged for more than two decades [9].

2.3. 2016 and sepsis-3

In 2016, with the new definitions of Sepsis-3 (see Table 2), new guidelines were published in the Surviving Sepsis Campaign. Sepsis is now defined as a life-threatening organ condition caused by a dysregulated host response to infection, and septic shock is a subset of sepsis in which circulatory and cellular/metabolic abnormalities are serious enough to increase mortality. The term severe sepsis is not used in new definitions [9, 10].

SIRS criteria will continue to be useful in everyday routine of infection diagnosis because they reflect a proper response from the organism to the threat. Sepsis criteria are more complex than SIRS criteria implying surveillance and other kinds of intervention [9].

Sepsis-3 included the SOFA score. At the same time, the task force also introduced a quick version of SOFA, the qSOFA score, which should be used in the emergency department. An increase of 2 or more points in qSOFA score is associated with 3 to 14-fold increase in hospital mortality and creates the suspicion of sepsis, conducting to early patient support (Tables 3–5) [7, 9].

Table 2
New terms and definitions (Sepsis-3) [9].

- Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.
- Organ dysfunction can be identified as an acute change 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 an overall mortality risk of approximately 10% in a general hospital population with suspected infection. Even patients presenting 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 ≤ 100 mmHg, or respiratory rate ≥ 22/min.
- Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are severe enough to substantially increase mortality.
- Patients with septic shock can be identified by means of a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥65 mmHg and having a serum lactate level > 2 mmol/L (18 mg/dL) despite adequate volume resuscitation.
- With these criteria, hospital mortality is in excess of 40%.

Abbreviations: MAP, mean arterial pressure; qSOFA, quick SOFA; SOFA: Sequential [Sepsis-related] Organ Failure Assessment.; ICU, Intensive Care Unit

3. Methods

The authors performed a PubMed search on November 29, 2017 with the terms ‘sepsis’, ‘septic shock’, ‘severe sepsis’, ‘Systemic Inflammatory Response Syndrome’, selecting articles with the original definitions of sepsis (Sepsis-1, Sepsis-2 and Sepsis-3) and those that have been published in the last 12 months. A total of 493 articles were obtained, and further selection was performed, eliminating those who were case reports, drug effects, paediatrical, biochemical, immunological and nursing articles. A total of 119 articles remained which were subsequently selected by the title and abstract. 24 articles were included and their results analyzed.

4. Results and discussion

4.1. SIRS and sepsis

Infections begin with an inoculum followed by local and eventually system-wide host response, the last recognized as SIRS. Organ dysfunction, multiple organ dysfunction and shock may occur. There is a continuous spectrum of the illness and waiting for life-threatening organ dysfunction may delay early antibiotic and fluid administration. Timing is important to sepsis treatment [2]. Furthermore, organ dysfunction may emerge for reasons other than sepsis [7].

Steven Q. Simpson recommends that SIRS should remain an