

# 1

## Definition of Sepsis and Non-infectious SIRS

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### 1.1

#### Introduction

The word “sepsis” has its origins in the word “σήψις”, which is the original Greek word for decomposition or putrefaction, and has been used in that context since before Hippocrates [1, 2]. However, although the word, sepsis, has been used for more than 2700 years, it is only relatively recently that we have begun to understand the pathophysiology of sepsis in any depth [3]. With this new insight into the mechanisms underlying sepsis has come the potential for new and improved therapeutic interventions, and simultaneously a realization that the available terminology and definitions of sepsis were confusing and inadequate. In this chapter, I will outline progress in the field of sepsis definitions, and discuss possible approaches for the future.

### 1.2

#### Sepsis Syndrome

In 1989, Roger Bone [4] proposed the term “sepsis syndrome”, defining it as hypothermia (temperature less than 96 °F (35.5 °C)) or hyperthermia (greater than 101 °F (38.3 °C)), tachycardia (greater than 90 beat/min), tachypnea (greater than 20 breaths/min), clinical evidence of an infection site, and at least one end-organ demonstrating inadequate perfusion or dysfunction. This terminology was somewhat redundant as sepsis was already a known syndrome, and is no longer used, having being replaced by the term “severe sepsis”.

### 1.3

#### Systemic Inflammatory Response Syndrome

In 1991, a Consensus Conference was held by the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) to

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create a “set of definitions that could be applied to patients with sepsis and its sequelae” [5]. The goal of the conference was to provide a “framework” to define the systemic inflammatory response to infection, and by so doing to improve the early diagnosis of sepsis, thus allowing earlier therapeutic intervention. It was realized that the lack of a single definition for sepsis created difficulties in identifying patients, particularly for clinical trials, and it was believed that having a single, universally accepted definition would facilitate ongoing research in this field.

It had been recognized that the same systemic response seen in patients with severe infections, could also occur in patients without infection but with other inflammatory processes, e.g. pancreatitis, multiple trauma, ischemia, burns, etc. and the consensus conference believed it was necessary to introduce new terminology to define such patients. The key aspect of the consensus conference definitions was, therefore, the introduction of the term Systemic Inflammatory Response Syndrome or SIRS to define this phenomenon. SIRS was defined as being the presence of more than one of four clinical criteria:

1. Body temperature greater than 38 °C or less than 36 °C
2. Heart rate greater than 90 beats/min
3. Respiratory rate greater than 20 breaths/min or hyperventilation with a PaCO<sub>2</sub> less than 32 mmHg
4. White blood cell count >12000/mm<sup>3</sup>, <4000/mm<sup>3</sup>, or with >10% immature neutrophils.

The combination of SIRS with a confirmed infectious process was then called sepsis. Severe sepsis was defined as sepsis associated with organ dysfunction, hypoperfusion abnormality, or sepsis-induced hypotension, and septic shock was defined as severe sepsis with sepsis-induced hypotension persisting despite adequate fluid resuscitation.

The SIRS approach was rapidly adopted by many and has been widely used to define populations of patients for inclusion in clinical trials. However, not all have considered the SIRS criteria useful, arguing that they are too sensitive and non-specific to be of any real use in clinical diagnosis or in the clinical trial setting [6]. Indeed, most intensive care unit (ICU) patients and many general ward patients meet the SIRS criteria [7–11]; in the recent Sepsis Occurrence in Acutely ill Patients (SOAP) study, 93% of ICU admissions had at least two SIRS criteria at some point during their ICU stay [11]. In addition, a “diagnosis” of SIRS provides no real information regarding the underlying disease process; each of the SIRS criteria can be present in many conditions. For example, fever can be present in sepsis, after myocardial infarction or pulmonary embolism, or post-operatively. Similarly tachycardia and tachypnea may be present in sepsis, but also in heart failure, anemia, respiratory failure, hypovolemia, etc. A raised white blood cell count can be present in many other diseases encountered in ICU patients, including trauma, heart failure, pancreatitis,

hemorrhage, and pulmonary edema. The presence of the SIRS criteria generally reflects an appropriate adaptative response to a physiologic insult rather than an abnormality and certainly does not constitute a separate disease entity [12].

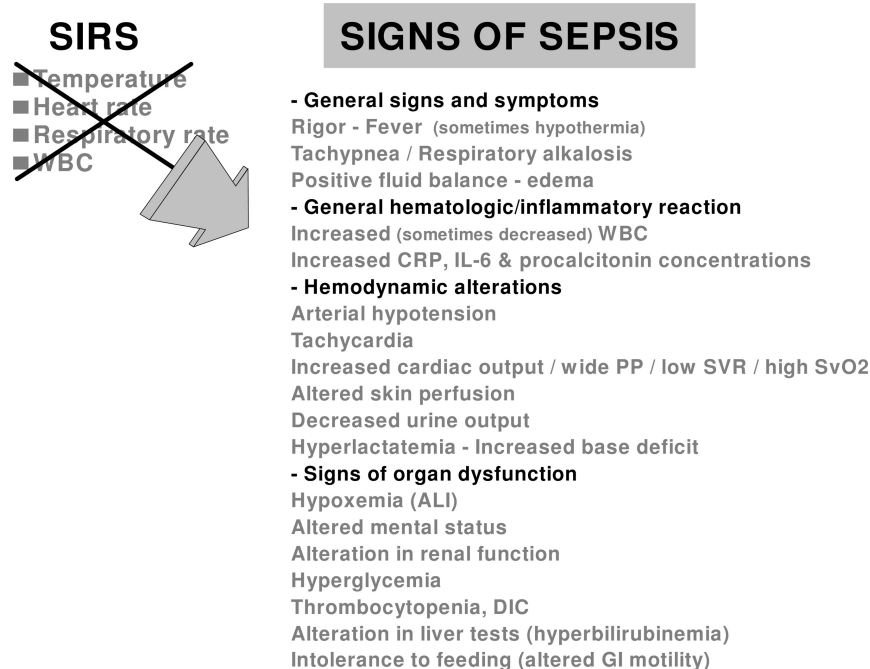
#### 1.4 Sepsis Markers

Despite the 1991 ACCP/SCCM consensus conference definitions, a survey of 1058 ICU physicians in 2000 reported that many of the participants remained concerned about the lack of a common definition, with only 22% of intensivists giving the consensus conference definition when asked to define sepsis [13]. With continuing advances in our understanding of sepsis pathophysiology, identification of various proposed sepsis markers, and persistent uncertainty and disagreement about the usefulness of the SIRS criteria, a Sepsis Definitions conference was convened in 2001 to re-evaluate and update definitions (Table 1.1) [14]. The conference included 29 participants from Europe and North America, and was sponsored by several leading intensive care societies.

The participants at this conference concluded that the SIRS criteria were indeed too sensitive and non-specific and that, in preference to the SIRS criteria, an expanded list of signs and symptoms of sepsis should be used to reflect the clinical response to infection (Figure 1.1). However, unfortunately, no marker is 100% specific for sepsis and diagnosis must, at present, rely on the presence of a combination of clinical symptoms and signs and available markers. Various markers have been proposed over the years. Cytokine levels may seem an obvious choice as cytokines are key mediators of the inflammatory response to sepsis. Raised levels of certain cytokines have been well documented in patients with sepsis and some have been correlated with outcome [15–18]. However, no cytokine is specific for sepsis, and not all cytokine levels are raised at all time points during the course of the disease. For example, tumor

**Table 1.1** Current definitions of infection and sepsis [14].

Infection	A pathologic process caused by the invasion of normally sterile tissue or fluid by pathogenic or potentially pathogenic microorganisms.
Sepsis	The presence of infection, documented or strongly suspected, with a systemic inflammatory response, as indicated by the presence of some of the features in Figure 1.2.
Severe sepsis	Sepsis complicated by organ dysfunction.
Sepsic shock	Severe sepsis complicated by acute circulatory failure characterized by persistent arterial hypotension, despite adequate volume resuscitation, and unexplained by other causes.



**Figure 1.1** Proposed change from SIRS to a longer list of signs for the diagnosis of sepsis [14].

necrosis factor (TNF) levels are raised early in the course of sepsis, but raised levels are also found in other conditions including acute pancreatitis [19], trauma [20], myocardial infarction [21], and heart failure [22], and later in the disease process levels may fall. The same is seen with other cytokines including interleukin (IL)-6, although this is generally the cytokine whose levels are most consistently raised in sepsis. Other markers of inflammation have also been suggested as being of use in the diagnosis of sepsis and some, such as C-reactive protein (CRP), are in common use, particularly in Europe. CRP has been shown to be a useful indicator of the presence of sepsis [23], and more indicative of infection than the white cell count or fever [24]. CRP levels >17 mg/dl have been suggested as providing a means of separating patients with sepsis from those with a non-septic inflammatory response due to trauma [25]. More recently, procalcitonin has been proposed as a marker of infection [26–28], but may be more useful as an indicator of the severity of infection rather than as a marker of the presence of infection *per se* [29]. Procalcitonin levels have been used to guide therapy in patients with lower respiratory tract infections, community-acquired pneumonia, and exacerbations of chronic obstructive pulmonary disease [30–32]; whether they could also be used to guide therapy in general populations of patients with sepsis remains to be determined.

Many other molecules have been suggested as markers of sepsis, but again all are markers of inflammation rather than infection, and none are specific for sepsis. The development of multiplex technology now allows the presence of multiple markers to be detected from a single blood sample, enabling a so-called “sepsis profile” to be constructed for individual patients. Bozza and colleagues recently reported the results of a preliminary study in 60 patients with severe sepsis using a multiplex assay that included the levels of 17 cytokines [33]. These authors were able to identify cytokine profiles associated with an increased risk of early and late death and with evolution of organ dysfunction. Clearly further study is needed but multiplex profiling of ICU patients may offer an effective means of monitoring the severity of sepsis.

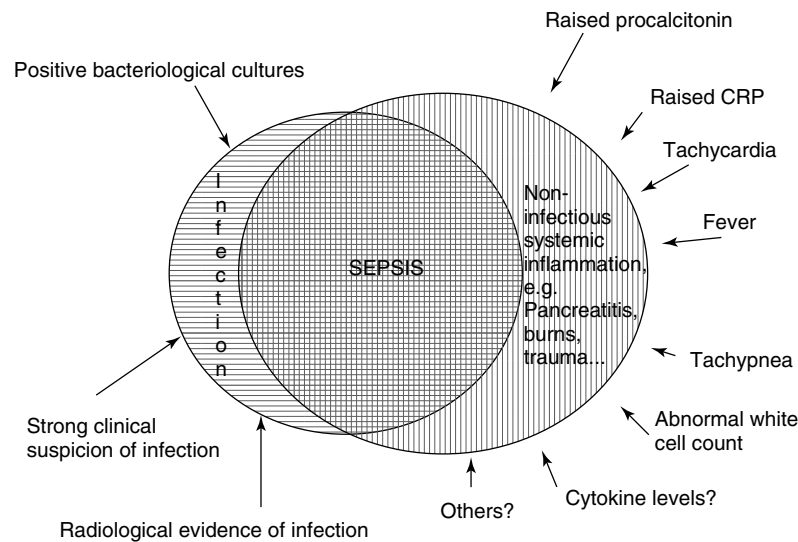
Importantly, the list of suggested markers proposed by the participants in the Definitions Conference should be considered as a guide to diagnosis – not all patients with sepsis will have all the markers included on the list, but their presence should be used to raise suspicion of sepsis and to encourage a continued, repeated, or more thorough search for an infectious focus. As research continues and more potential markers are identified, this list may be adapted and expanded.

By these new definitions [14], sepsis is thus defined as the presence of infection plus some of the listed signs and symptoms of sepsis (Table 1.1). Severe sepsis is defined as sepsis complicated by organ dysfunction, and septic shock is severe sepsis with acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes.

## 1.5 Inflammation versus Infection

Importantly, sepsis, whichever official definition is used, represents the body’s systemic response to severe infection, and thus true sepsis can only be present if there is an associated infection (Figure 1.2). It is important to differentiate patients with sepsis from those with SIRS, as treatments may be very different, e.g. antibiotics should not be given to all patients with SIRS, but only to those with clinical and/or bacteriological evidence of infection. However, infection can be difficult to diagnose, particularly in the ICU patient who has already received, or is receiving, antibiotics, and has multiple risk factors for infection and often several concurrent disease processes. In the recent SOAP study, 40% of patients classified as having sepsis had negative culture results [34]. Nevertheless, negative cultures do not necessarily mean that no infection is present, but may just reflect our inability to detect or locate it. Hence, sepsis may be defined as being strongly suspected without microbiological confirmation [14].

Various attempts have been made to improve the diagnosis of infection. The biphasic activated partial thromboplastin time (aPTT) may provide a means of differentiating sepsis from systemic inflammation. Chopin *et al.* [35] recently reported that the biphasic waveform had 90% sensitivity and 92% negative



**Figure 1.2** Sepsis represents the presence of infection accompanied by a systemic inflammatory response.

predictive value for differentiating severe sepsis and septic shock from SIRS or sepsis. Others have suggested that gene profiling or protein profiling could be used to distinguish SIRS due to infection from non-infectious SIRS. Using mass spectrometry techniques, Lissauer *et al.* recently reported that there were 134 different unique proteins between patients with non-infectious SIRS and those with sepsis [36]. Over 20% of these proteins were related to the complement or coagulation systems. The same group also reported that patients with sepsis had different gene expression profiles compared to patients with non-infectious SIRS; of the 54 613 gene probes evaluated, there were 459 unique gene differences between the two groups of patients, functionally involved in four major areas: innate immunity, cytokine receptors, T cell differentiation, and protein synthesis regulation [37]. Importantly, in both these studies [36, 37], the differences between patients with non-infectious SIRS and those with sepsis were already present before sepsis was clinically apparent.

An alternative approach is the development of scores that combine several variables. Peres Bota *et al.* [38] developed an infection probability score, which uses six variables (body temperature, heart rate, respiratory rate, white blood cell, CRP, and SOFA), to assess the likelihood of infection, resulting in a score from 0–26 (Table 1.2). Infection was absent in 90% of ICU patients when the score was below a cut-off value of 14. A recent prospective study supported the good predictive value of the IPS (Infection Probability Score) for a diagnosis of infection, and suggested that changes in IPS over time may be useful in following the response to antimicrobial therapy [39].

**Table 1.2** Infection probability score (IPS) [38].

	IPS points						
	0	1	2	3	6	8	12
BT (°C)	≤37.5		>37.5				
HR (beats/min)	≤81					81–140	>140
RR (breaths/min)	≤25	>25					
WBC ( $\times 10^3/\text{mm}^3$ )	5–12	>12		<5			
CRP (mg/dl)	≤6				>6		
SOFA score	≤5		>5				

BT, body temperature; HR, heart rate; RR, respiratory rate;  
WBC, white blood cell; CRP, C-reactive protein; SOFA,  
sequential organ failure assessment.

In addition to improving the diagnosis of infection in general, a consensus conference was organized by the International Sepsis Forum to provide definitions for specific infections [40]. Definitions were developed for the six most frequent causes of infections in septic patients: pneumonia, bloodstream infections (including infective endocarditis), intravascular catheter-related sepsis, intra-abdominal infections, urosepsis, and surgical wound infections. The main aim of these definitions is to facilitate patient selection for inclusion in clinical trials; by classifying patients into prospectively defined infection categories, treatments could be more specifically targeted. However, such definitions could also potentially be used as a framework for guiding diagnostic or therapeutic decisions.

## 1.6 Conclusion

Clear definitions of sepsis are important clinically in facilitating accurate diagnosis and appropriate treatment. Clear definitions are also important for the purposes of clinical trials, insuring that only patients who do have sepsis are enrolled, reducing the risks of misclassification bias. New markers specific for infection rather than inflammation need to be developed, but currently physicians must rely on the presence of a number of signs and markers of sepsis in their diagnosis; no one variable alone is sufficient. Multiplex technology or combinations of elements in scoring systems are two approaches that can improve the diagnosis of sepsis, but further research is needed in this field. Current definitions may need to be adapted as new techniques or markers are identified that can usefully differentiate between sepsis and non-infectious inflammation.

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