Sepsis and Non-infectious Systemic Inflammation

From Biology to Critical Care

Edited by
Jean-Marc Cavaillon and
Christophe Adire

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Preface

In 1519 when Lucrece Borgia succumbed to puerperal septicemia while she was giving birth to her seventh child, probably no doctor could explain the events. It was only in 1847 that Ignaz Semmelweis understood the possible reasons for the high percentage of deaths due to puerperal septicemia, and he was the first to define the antiseptic methods required to reduce mortality in his hospital in Vienna. In 1879, Louis Pasteur further promoted antiseptic methods, and identified the presence of common bacteria in the bloodstream of these patients. Circa 1904, Sir William Osler offered a quite provocative definition of sepsis when, including the potential deleterious effects of the inflammatory response, he wrote: 'Except on few occasions, the patient appears to die from the body's response to infection rather than from it'. More recently, Roger Bone redefined sepsis, and with others, introduced the concept of 'systemic inflammatory response syndrome' (SIRS), a clinical setting that mimics many pathophysiologic observations made in sepsis but in the absence of infection. Nowadays, the discovery of endogenous 'alarmins' or 'danger associated molecular patterns' (DAMPs) that share similar receptors with exogenous 'pathogen associated molecular patterns' (PAMPs) partially explains the similarity between sepsis and non-infectious SIRS. Bone also introduced the concept of 'compensatory anti-inflammatory response syndrome' (CARS) to explain the consequences of the altered immune status observed among sepsis and non-infectious SIRS patients.

Interestingly, systemic inflammatory responses share many similarities whatever their infectious or non-infectious origin. Despite many years of intensive basic and clinical research which has increased our understanding of the ongoing processes, establishing better therapeutic strategies appeared to be the main approach to improving survival rather than the development of specific new treatments targeted at an intrinsic mechanism. We felt that this was an appropriate time to offer an overview of all the new insights into this syndrome, regardless of whether it has originated from an infectious process or from any other cause. It therefore seemed logical to report on the state-of-the art in this increasingly frequent clinical presentation from an epidemiologic, mechaninistic, and predisposal standpoint, and on the experimental models that will help to further decipher, and hopefully define new treatments for this

dreadful syndrome. Accordingly, we have asked the most distinguished and prominent doctors and scientists in the field to contribute their expertise to the discussion of many of the important aspects and treatment of sepsis and SIRS.

Paris and Saint-Denis — *Jean-Marc Cavaillon*
July 2008 — *Christophe Adrie*

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PART I
Clinical Aspects of Sepsis and SIRS

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

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 $PaCO_2$ less than 32 mmHg
4. White blood cell count $>12000/mm^3$, $<4000/mm^3$, 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.
Septic shock	Severe sepsis complicated by acute circulatory failure characterized by persistent arterial hypotension, despite adequate volume resuscitation, and unexplained by other causes.

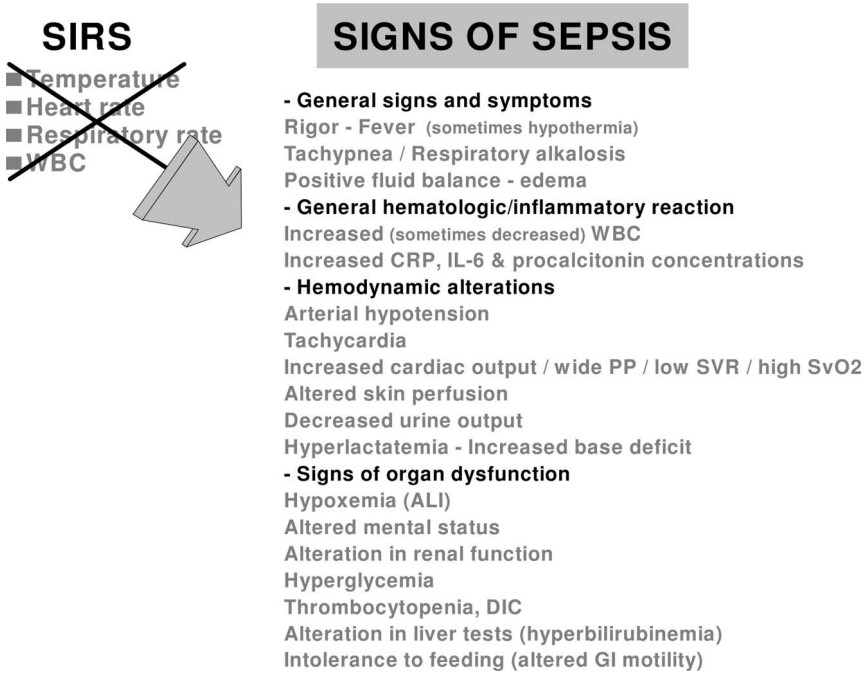

Figure 1.1 Proposed change from SIRS to a longer list of signs for the diagnosis of sepsis [14].

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.