

New concepts of sepsis and their practical value

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INTRODUCTION

In an effort to identify a cohort of patients who might benefit from the early administration of novel therapies designed to modulate the endogenous host inflammatory response, an expert consensus conference of the American College of Chest Physicians and the Society of Critical Care [1] coined the phrase systemic inflammatory response syndrome (SIRS) to describe a clinical syndrome believed to be the result of an overly activated inflammatory response. This new definition recognized the important role that endogenous mediators of systemic inflammation play in sepsis, which was no longer regarded as being caused by microbial pathogenicity factors alone [2].

The clinical signs of sepsis, such as fever, tachycardia, tachypnea and leucocytosis, are common responses to systemic infection. A trigger-response concept of sepsis emerged, in which bacteria were seen as the trigger, with the pathophysiology being the response to that trigger. It was now recognized that sepsis involved both microbial and pathophysiological events, and this powerful concept allowed clinicians to see the role of infection in the common inflammatory response [2]. For example, uninfected trauma patients and those with intra-abdominal infection had similar clinical courses, both groups developing multiple organ failure with identical microscopic pathology [3] – autodestructive inflammation which seemed to be independent of infection. Also, in animal studies it was found that the severity of the physiological response

was a better predictor of outcome than the microbial challenge [4].

THE CONSENSUS CONFERENCE DEFINITION FOR SIRS AND MODS

The criteria proposed by the ACCP/SCCM are given in Table 1. Two or more criteria are needed for meeting the definition of systemic inflammatory response syndrome (SIRS). There are differences with previous definitions; as can be seen in Table 2 the definition of sepsis syndrome by Bone et al [5] has a more rigorous definition than severe sepsis, requiring the presence of three screening criteria (as opposed to any two of four in SIRS but, for purposes of clinical study, the two have been considered equivalent [6]).

It is recognized that there is a progression in the disease state from SIRS/sepsis to severe SIRS/severe

Table 1 Systemic inflammatory response syndrome (SIRS)

Two or more
(1) Temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$
(2) Heart rate $>90/\text{min}$
(3) Respiratory rate $>20/\text{min}$
or
Pa $\text{PCO}_2 <32$ torr
(4) WBC $>12,000$ cells/ mm^3 , $<4,000$ cells/ mm^3
or $<10\%$ band forms
ACCP/SCCM, 1992 (1).

Table 2 Sepsis syndrome

Clinical evidence of infection
Rectal temperature $>38.3^{\circ}$ or $<35.6^{\circ}\text{C}$
Respiratory rate $>20/\text{min}$
Heart rate $>90/\text{min}$
One of the following: Alteration in mental status
Hypoxemia ($\text{PaO}_2 <72$ torr)
Oliguria (<30 ml/hour)

Data from Bone et al [5].

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sepsis in the presence of acute organ dysfunction, hypotension or hypoperfusion. The next step in the progression is sterile shock/septic shock present when there is hypotension that is unresponsive to resuscitation with fluids.

Multiple organ dysfunction syndrome (MODS) is the recognized diminished organ dysfunction associated with acute illness, in which organ function is not capable of maintaining homeostasis. The dysfunction can be absolute or relative but is more readily identified as a gradual change over time. When several organs fail to maintain their function, MODS can be said to have complicated the SIRS. The various stages must be seen as phases in a continuum of increasing disturbance of homeostasis. Although these definitions were not meant to represent prognostic indicators, an index of the usefulness of the syndrome definitions could be related to morbidity and mortality, independently for age and underlying disease, so that patients with these syndromes would be more sick and more likely to die than patients without [1,7,8].

Several scoring systems have been introduced to assess the physiologic response, but the variables must be weighted carefully so that increasing score values correlate with worsening prognosis. Examples of such scoring methods are the acute physiology and chronic health evaluation (APACHE) [9], the simplified acute physiologic score (SAPS II) [10] and the mortality probability model (MPM II) [11]. The Apache system is the most widely used system for assessing acute physiologic disturbances. The pathophysiology scored is that which predicts the greater mortality risk in patients with differing initiating events or diagnoses. The latest version, APACHE III, provides updated risk assessment for the first seven days of illness [12].

Mild degrees of organ dysfunction are common in SIRS but the untreated patients may develop severe organ failure, which is associated with poor outcome. The simultaneous failure of two organs is associated with widely differing prognosis depending on the combination of organs involved, ranging from 20% mortality for combined cardiovascular and haematological failure to 76% mortality for combined cardiovascular and central nervous system failure [13].

The various methods of grading organ dysfunction have been recently reviewed for the development of a new score of organ failure. This MOD score considers six organ systems [14] (Table 3). The function of each organ is weighted on a scale from 0 to 4. The weighting was developed in one half of a surgical ICU population and validated in the other half. For each variable a 0 value was associated with <5% mortality while a value of 4 represented severe dysfunction and a mortality of >50% for patients managed in the ICU.

Table 3 MOD score^a

System	Parameter	0	4
Respiratory	P(O ₂)/FI(O ₂) ratio	>300	≤75
Renal	Serum creatinine (μmol/L)	≤100	>500
Hepatic	Serum bilirubin (μmol/L)	≤20	>240
Cardiovascular	PAR ^b	≤10	>30
Hematological	Platelet count		
Neurological	Glasgow coma S	15	≤6

^a Adapted from Marshall et al [14].

^b Pressure-adjusted heart rate: Heart rate × (R atrial pressure/mean arterial pressure).

THE MEDIATORS

After an injection of bacteria or endotoxin, certain cytokines appear briefly in circulating blood. The classical sequence is tumor necrosis factor alpha (TNF alpha) followed by interleukins 1 (IL-1), 6 (IL-6) and 8 (IL-8). These cytokines have been named the pro-inflammatory or alarm cytokines because they appear first. They, and other factors, mediate various responses including the activation of numerous cell populations and release of secondary cytokines and growth factors.

It is important to understand whether the same mediator is activated by different triggers and if different mediators are associated with different pathophysiological responses. Does the pathophysiological response to infection differ from the response to other triggers? There are certain differences: infection induces more TNF alpha than does physical trauma, which releases more IL-6 and IL-8 [2]. Thus primary infection is associated with higher fever than in trauma, probably because of the different balance of mediators produced. Hypovolemic and hypotensive patients, however, often suffer initially from hypothermia and leucopenia whether triggered by infection or trauma. Initial differences in mediator pattern result in different clinical presentations, but within hours or days it is clinically no longer possible to associate these responses with specific triggers [2].

Approaching the problem from a different standpoint, attempts to correlate measurements of circulating cytokines with pathophysiological changes and with prognosis have not been entirely successful. The concentrations of these mediators vary very widely probably because they have short half-lives in the circulation and most are localized within the inflamed body compartments where they cannot readily be measured [2].

THE ACUTE PHASE RESPONSE

This may be seen as the primary part of the systemic inflammatory response. The principal alarm cytokines

cause fever and stimulate the pituitary to release stress hormones. They also stimulate the liver to synthesize a number of acute phase proteins such as C-reactive protein, fibrinogen and major anti-proteases [15]. IL-6 is the principal signal for the hepatic acute phase response. At the site of injury numerous mediators cause pain, vasodilatation and increased vascular permeability, and attract granulocytes to the site.

The acute phase response involves additional mechanisms which reverse the inflammatory response. IL-4 and IL-10 can turn off monocyte-macrophage production of TNF alfa, IL-1, IL-6 and IL-8, and therefore have potent anti-inflammatory action. In addition the acute phase response produces antagonists to the TNF receptor and IL-1 receptor, which bind the circulating cytokine or block receptors on target cells. The early events also induce the production of cortisone. Through the combined action of these mechanisms and others the acute phase response is attenuated and the homeostatic mechanisms return to normal. This process takes several days and it is best seen in patients after major surgery. Fever resolves after two to three days, bowel function is restored after three to four days and the patient can soon return to full oral intake. The extent of the pro- and anti-inflammatory events is proportional to the magnitude of the insult. Constitutional factors, both genetic and acquired, may cause particular patients to overreact or respond inadequately. The pro- and anti-inflammatory mechanisms are often disregulated for reasons that are poorly understood [2].

LIMITATIONS OF THE NEW DEFINITIONS OF SEPSIS

The above definitions have allowed some uniformity necessary to deepen insight into the epidemiology of the systemic inflammatory response, but the usefulness of the criteria for these definitions remains unproved.

SIRS is too sensitive and not specific; examples of this oversensitivity are 'running for the bus' and 'the flu' [16] and it is clear that they should not be applied in the absence of clinical judgement. The definitions of sepsis have failed to identify a subgroup with an increased risk of death and, in fact, they have not been helpful in clinical practice nor in clinical trial design [16].

In some studies [17], the frequency of positive microbiological results did not increase with an increasing number of SIRS criteria; the increasing mortality could be attributed to a more harmful response rather than to a higher frequency of infection. In other populations [18], SIRS criteria appear to be little more than abbreviated generic severity scores of illness measure – a variation on APACHE II or the

Injury Severity Scoring System – and this observation should be expected: the four physiologic variables that define SIRS (tachycardia, tachypnea, hyper- or hypothermia, and leucocytosis or leucopenia) are all components of APACHE II, as are acidosis, altered mentation, and hypotension, which are variables that characterize severe sepsis and septic shock [19].

The definition of 'sepsis syndrome' as originally defined by Bone et al [5], prior to the consensus definitions, included alterations in mental status as a criterion. Bossink et al's data [17] confirmed that mental changes may be early clinical features of infection and they could be reintroduced, by virtue of their prognostic value, in the sepsis definitions. SIRS and sepsis definitions could be further refined to include hypoalbuminemia to improve the ability of identifying febrile patients who have a harmful host response to infection [17]. The prospect of discriminating the maladaptive consequences of the host response from its beneficial effects remains elusive [19] and more research would be necessary to better define a patient group likely to respond to a treatment intervention in a predictable and useful manner [20].

Table 4 Diagnostic and prognostic value of plasma procalcitonin (PCT) levels in sepsis

	Daily plasma measurements in ICU patients			
	SIRS n=18	S n=14	SS n=21	Sh n=25
PCT ^a	0.6	3.5	6.2	21.3
ICU mortality	28%	14%	19%	64%

S: sepsis; SS: severe sepsis; Sh: septic shock.

^aValues on admission (day 1).

Data from Pugin et al [21].

Despite these negative views concerning the clinical value of the new definitions of sepsis, studies continue to show interest in using them; a recent report on the diagnostic and prognostic value of plasma procalcitonin levels in human sepsis, appears to revalidate the utility of the definition of SIRS and sepsis: in a group of 78 intensive care patients prospectively followed (Table 4), no difference in clinical variables was observed between SIRS and septic patients. Procalcitonin levels, however, had a 97% sensitivity and a 78% specificity in differentiating patients with SIRS from those with sepsis. Also, all patients who died never had procalcitonin levels below 1.1 ng/ml [21].

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