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Systemic inflammatory response syndrome (SIRS)

Where did it come from and is it still relevant today?

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The concept of a systemic inflammatory response syndrome (SIRS) to describe the complex pathophysiologic response to an insult such as infection, trauma, burns, pancreatitis, or a variety of other injuries came from a 1991 consensus conference charged with the task of developing an easy-to-apply set of clinical parameters to aid in the early identification of potential candidates to enter into clinical trials to evaluate new treatments for sepsis. There was recognition that a diverse group of injuries produced a common inflammatory response in the host and provided attractive targets for new anti-inflammatory molecules designed to prevent further propagation and/or provide specific treatment. Effective application of these new anti-inflammatory strategies necessitated identification of early clinical markers that could be assessed in real-time and were likely to define a population of patients that would have a beneficial response to the targeted intervention. It was felt that early clinical manifestations might be more readily available to clinicians than more sophisticated and specific assays for inflammatory substances that were systemically released by the network of injurious inflammatory events. Therefore, the early definition of a systemic inflammatory response syndrome (SIRS) was built upon a foundation of basic clinical and laboratory abnormalities that were readily available in almost all clinical settings. With further refinement, it was hoped, that this definition would have a high degree of sensitivity, coupled with a reasonable degree of specificity. This manuscript reviews the derivation, application, utilization, potential benefits, and speculation regarding the future of the SIRS definition.

Introduction

The concept of a systemic inflammatory response syndrome (SIRS) to describe the complex pathophysiologic response to an insult such as infection, trauma, burns, pancreatitis, or a variety of other injuries came from an American College of Chest Physicians/Society of Critical Care Medicine-sponsored sepsis definitions consensus conference held in Chicago, IL in August 1991.[1] The conference participants were charged with the task of defining an easy to apply set of clinical parameters to aid in the early identification of potential candidates to enter into clinical trials to investigating new innovative treatment strategies for sepsis. There was recognition that there was a great deal of ambiguity and lack of clarity in the current clinical definition of sepsis used in clinical discussions, design of research trials, and communication in the medical literature.[1-4] The explosion of new advancements in the field of biotechnology coupled with an enhanced understanding of the complex pathophysiologic processes felt to be responsible for the clinical syndrome known as sepsis, gave birth to a plethora of new agents designed to inhibit, bind, block, or neutralize the villainous mediators that were felt to be responsible for the network of events that culminated in the clinical manifestations and organ dysfunction(s) seen in the septic patient.[5-7] It was also anticipated that the use of these new strategic "antimediators, receptor blockers, anti-inflammatory agents, etc." would improve patient survival and decrease morbidity in the critically ill infected patient.[5,6] Most researchers in the field recognized the importance of interrupting these inflammatory pathways as early as possible in order to achieve success and it was therefore necessary to have the ability to recognize the septic patient at the earliest possible time point, if this strategy was going to have a potential to produce the desired benefit. This premise was the major goal of the 1991 consensus conference.[1] This discussion will focus on the rationale for the SIRS definition, the application of SIRS in clinical research and patient management, the potential benefits associated with using the definition, the emergence of the term systemic inflammatory response syndrome (SIRS), and speculation as to the future of the SIRS definition. This review will only discuss the sepsis and SIRS definition in adults over the age of 18, as the complex and changing physiology of young children pose additional challenges to using target heart rates, respiratory rates, and other clinical parameters in the definition.

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Need for a Consensus Definition of Sepsis

Recognition that the systemic inflammatory response to infection or sepsis was likely similar to the systemic inflammatory response to a group of diverse injuries and perturbations, such as burns, trauma, pancreatitis, etc. focused attention toward developing effective strategies to limit the excessive inflammatory response in the host and produce improved outcome.[1,5,6] The identification of various pro-inflammatory compounds, such as endotoxin, cytokines, products of arachidonic acid metabolism, coupled with the demonstration that a clinical syndrome resembling sepsis could be produced by injecting these molecules

into human volunteers or experimental animals, fueled a mission to identify specific agents to inhibit, block, neutralize, or limit the potential destructive effects of these compounds.[8-12] As new products were developed and readied for clinical trial, it became necessary to have a means to identify those patients who were most likely to benefit from this intervention. The need for a diagnostic tool with a reasonable degree of certainty for identifying a relatively homogenous population of patients with possible sepsis who might be amenable to treatment with the anti-inflammatory treatment strategies prompted the desire to have a clinical definition of sepsis that did not require sophisticated or time consuming tests and could be utilized in hospitals of all sizes and locations.[1] Hence the driving force behind the 1991 consensus conference was to improve trial design coupled with adding clarity to the literature which was full of varied definitions of sepsis and septic shock.

While most would agree that sepsis is defined as a systemic inflammatory response to the presence of a documented infection, this definition has not been uniformly accepted or used in clinical practice.[2] Prior to 1992, a diagnosis of sepsis often required evidence of positive blood cultures or confirmation of a documented infection with a microorganism, and in many circumstances also required the presence of shock or hypotension.[2] Some clinicians had the belief that the definition of sepsis, like pornography, was in the eyes of the beholder.[2] Sepsis was felt to be easily recognizable by the trained clinician and did not require a formal definition.[2] The ambiguity in the definitions of the time coupled with the recognition that early treatment would likely improve survival also supported the drive to agree on a consensus definition. Varied definitions impeded the appreciation of the literature concerning sepsis and made it difficult to define the incidence and prevalence or perform a meta-analysis of sepsis studies since there was often little uniformity in the definitions employed or patient populations studied.

Development of SIRS Definition

The clinical definition of sepsis that emerged from the consensus conference sponsored by the American College of Chest Physicians and the Society of Critical Care Medicine was met with mixed reactions.[1,13] While the goals of the consensus conference were to produce an operational definition of severe sepsis and septic shock that would allow scientists to effectively communicate in the literature using a standard definition and to create a definition that could easily be used in clinical trials evaluating new therapeutic strategies for the treatment of severe sepsis and septic shock, the lack of specificity seemed to bring out more doubters than supporters.[13] Most clinicians understood the goal of the definition was to facilitate early identification of potential patients for inclusion in therapeutic trials and that it was mandatory for the diagnostic tool to use easily obtained laboratory results and/or clinical parameters that were readily and rapidly available to all clinicians. The common early clinical manifestations seen in septic patients, fever, mental status changes, tachypnea, tachycardia, hypotension, leukocytosis, thrombocytopenia, and coagulation abnormalities were considered for inclusion in the definition.[2,14,15] The conference participants drew on past experience with clinical trial design in sepsis and eventually proposed changes in body temperature, heart rate, respiratory rate (including evidence of hyperventilation and/or the use of mechanical ventilatory support as a consequence of sepsis), and white blood cell count (too high, too low, or an increase in immature "band" neutrophils) as components of the definition, as they are all rapidly available and easy to define as present or absent.[1]

The conference participants also recognized that these clinical parameters are not unique to the septic patient and these alterations may be present in a diverse group of clinical disorders that result in a pro-inflammatory response.[1] These parameters were chosen to be quite sensitive, so as to include all potential patients with a pro-inflammatory response, but they clearly lacked specificity for a specific clinical disorder or for the presence of infection.[1,13] An important requirement for the parameters included in the definition was that the clinical abnormalities had to result from a documented infection or in a clinical setting with a high suspicion for infection as the cause of the change.[1] There was also the realization that the patient population that would be amenable to these new therapeutic strategies would typically be more acutely ill and cared for in an intensive care unit, often related to the presence of organ dysfunction or perfusion abnormalities.[1] Again, it was an important requirement of the definition that the decreased perfusion or organ dysfunction(s) were the result of the systemic reaction to the infectious insult.[1] Hypoperfusion and organ dysfunction could be clinically manifested in a number of ways such as, mental status changes, oliguria, hypotension, hypoxemia, or lactic acidosis.[1] When the septic patient manifests evidence of a "shock state" with hemodynamic alterations and/or acidosis the condition would be termed septic shock.[1] The group also defined sepsis related multiple organ dysfunction syndrome (MODS) as the presence of altered organ function in an acutely ill septic patients such that homeostasis cannot be maintained without intervention.[1]

The decision to require 2 of the 4 criteria to identify sepsis was based on an evaluation of the diagnostic sensitivity of using either 2, 3, or 4 of the criteria in the acute physiology and chronic health evaluation (APACHE) database to identify those individuals with a clinical diagnosis of sepsis.[16] Using 2 of the 4 criteria produced a highly sensitive tool for identifying septic patients.[16] When this definition was used in the setting of noninfectious inflammatory disease or in the setting of burn injury, pancreatitis, trauma, or other insults that can evoke a pro-inflammatory response, the systemic inflammatory response syndrome or SIRS response was defined and was also further defined as severe SIRS when organ dysfunction and/or hypoperfusion resulted from the systemic response.[1] Similarly, SIRS shock and SIRS related MODS were defined as in the sepsis definition.[1]

Clinical Impact of SIRS

Despite concern that the criteria incorporated in the sepsis and SIRS definitions lacked specificity for a clinically meaningful diagnosis, the definition gained favor with trialists and has been used in a large number of prospective, controlled, clinical

trials designed to evaluate novel therapies aimed at the patient population with severe sepsis and/or severe SIRS.[5,6,17,18] The SIRS parameters happened to be incorporated into the inclusion criteria for a prospective, randomized, double-blind clinical trial evaluating high dose steroid treatment of severe sepsis and septic shock patients and appeared to function quite well.[19] These criteria identified a population of patients that were clinically similar to patients with defined sepsis and an identifiable cause of infection.[20] Those noninfected patients who met the inclusion criteria seemed to be indistinguishable from those with sepsis from a defined infection and gave rise to the term "septic syndrome" that had a defined mortality rate based on clinical sequelae irrespective of whether there was a gram-positive, gram-negative, or no identifiable infection.[20] Two of the four criteria were suggested as necessary to define sepsis, since this optimized the sensitivity of the definition.[1,16] However, it should be noted that the patients encountered in the critical care setting with sepsis actually have severe sepsis (sepsis with organ dysfunction) and most often have septic shock or severe sepsis with multiple organ dysfunction.[1]

Additional support for this proposed definition came from the University of Iowa intensive care units where the mortality rate was found to increase in relationship to the number of SIRS criteria that were present and as a patient moved along a continuum from sepsis to severe sepsis to septic shock, there was also an increase in associated mortality rate.[21] This observation appeared to provide proof that this consensus definition had utility in identifying a population of patients with critical illness with a defined mortality rate and an increase in mortality as a patient moved down the continuum from sepsis to severe sepsis to septic shock.[21] Further endorsement of the utility of this clinical sepsis and SIRS definition came from the second International Sepsis Definition Consensus Conference held in 2001 in Washington, DC, which brought together representatives from the Society of Critical Care Medicine, the European Society of Intensive Care Medicine, the American College of Chest Physicians, the American Thoracic Society, and the Surgical Infection Society in an effort to enhance the specificity of the 1991 definition.[22] This conference proposed additional criteria to enhance a clinician's ability to recognize a septic patient, but also re-affirmed the utility of the SIRS criteria as a major component of the sepsis diagnosis.[22] This conference also proposed a conceptual framework, similar to oncology, for the staging of sepsis using the PIRO acronym (predisposition, insult or infection, response, and organ dysfunction).[22] The evolution of the changing definition of sepsis can be reviewed in **Table 1**.

By far the major demonstration of support for the utility of the sepsis and SIRS criteria is the observation that this definition or a close variant of the definition has been used in the vast majority of clinical investigative trials to evaluate new therapeutic agents for the management of patients with severe sepsis and septic shock for the past 20 years. The consensus definition has also facilitated studies to evaluate the incidence of severe sepsis over time, as well as, outcome comparisons to evaluate the impact of therapeutic strategies over time.[23-25] A uniform definition has identified that there are increasing numbers of septic patients each year in the US and that the number of deaths per year remains disturbingly high, despite improvements in care and our understanding of the pathophysiologic process.[23-25] Sepsis and its various adverse sequelae, such as septic shock, acute respiratory distress syndrome (ARDS), and multiple organ dysfunction (MODS) continue to be among the most common causes of death in the noncoronary intensive care unit.[2-4] In 1994–1995 discharge coding data with extrapolation to the entire United States speculated that there would be close to a million cases of severe sepsis each year by 2010.[23] A number of factors contribute to this rise, including an increased awareness of the diagnosis, an increased number of elderly and/or immunocompromised patients who have an increased susceptibility for the development of infection.[2] There continues to be an increased use of aggressive chemotherapeutic and immunosuppressive therapies, as well as invasive procedures that compromise normal host defense mechanisms and defensive barriers. There is also an ever increasing number of microorganisms that have developed resistance to commonly employed antimicrobial regimens.[2]

Potential Benefits of the SIRS Definition

The major benefit of the SIRS and sepsis definition was the enhanced ability to compare clinical trial results since the inclusion and exclusion criteria have been remarkably similar over the past couple of decades. The use of similar populations of study patients allows for comparison of the placebo groups to identify trends in sepsis/SIRS outcomes and determine the impact of standard treatment over time.[23-26] While some may criticize the practice of continuing to use a definition that has failed to identify a population of patients that will benefit from a new strategic intervention, demonstrating that the placebo group mortality has improved over time as demonstrated in the PROWESS and PROWESS Shock studies, gives the clinician an appreciation of the therapeutic impact related to changes in management such as early goal directed therapy, early antibiotic administration, and improved adherence to therapeutic regimens with the use of treatment "bundles of care".[27-35]

Another benefit of a consensus definition has been improved discussions in the literature, at medical meetings, and on daily rounds since we are all speaking a common language. The definition is easy to use at the bedside and does not require sophisticated equipment, expensive assays, inordinate amounts of time, or specific expertise. The definition uses the common clinical parameters we collect throughout the day and it is very easy and quick to obtain a white blood cell determination. While we will all agree that the current definition is way too sensitive and lacks specificity to identify a homogenous population of patients, it may well be that this very sensitive definition may be necessary for blockade of the septic network at an early enough point in time to produce the desired beneficial outcomes. Hopefully, technology will catch up in rapid fashion with point of care tests to identify the circulating mediator or marker that will add the necessary specificity to make the definition useful in the therapeutic management of the septic or SIRS patient. At present there is a growing list of potential biomarkers, some that were included in the 2001 consensus definition, that alone or in combination

Table 1. Changing sepsis definition over time

Sepsis definition prior to 1980	1980s severe sepsis and septic shock definition	Sepsis syndrome definition	1991 consensus conference definition	2001 consensus conference definition
Sepsis and **Septicemia** often included **Septic Shock**: clinically patient had bacteremia and manifested hypotension or required vasopressor support	-Clinical evidence of infection	-Presumed or documented infection	**Systemic inflammatory response syndrome (SIRS)**	-Documented or suspected infection
	-Fever >38 °C, rectal or hypothermia <35.6 °C	-Temperature <96 °F or >101 °F	Manifested by two or more of the following in response to a variety of clinical insults:	-Fever (core temperature >38.3 °C)
	-Tachycardia >90 bpm	-Tachycardia >90 bpm	-Temperature >38 °C or <36 °C	-Hypothermia (core temperature <36 °C)
	-Tachypnea >20 bpm	-Tachypnea >20 bpm	-HR >90 bpm	-Heart rate >90/min or >2 SD above normal value for age
	-At least one manifestation of inadequate organ perfusion or organ dysfunction	-Evidence of at least 1 end-organ with dysfunction:	-RR >20 bpm or P_aCO_2 <32 mmHg	-Tachypnea
	a) Altered mentation	a) Poor or altered cerebral function	-WBC >12 000 mm^3, <4000 mm^3, or >10% immature (band) forms	-Altered mental status
	b) Hypoxemia (P_aO_2 <75 mmHg)	b) P_aO_2 <75 torr	**Sepsis**	-Significant edema or positive fluid balance
	c) Elevated lactate	c) Elevated plasma lactate	Systemic response to infection manifested by two or more of the following in response to a variety of clinical insults:	-Hyperglycemia in the absence of diabetes
	d) Oliguria (urine output <30 ml or 0.5 ml/kg for at least 1 h)	d) Oliguria (urine output <30 ml/h or <0.5 ml/kg/h)	-Temperature >38 °C or <36 °C	-WBC >12 000/μL
		e) Systolic blood pressure <90 mmHg or >40 mmHg drop from baseline systolic blood pressure	-HR >90 bpm	-WBC <4000/μL
			-RR >20 bpm or P_aCO_2 <32 mmHg	-Normal WBC with >10% band or immature forms
			-WBC >12 000 mm^3, <4000 mm^3, or >10% immature (band) forms	-Elevated CRP

Adapted and modified from references 1, 2, 4, 19, 20, and 22.

just may be able to improve the diagnostic capability of a sepsis definition.[36] If such a discriminating biomarker(s) can be confirmed to provide specificity for the diagnosis of sepsis, the next task will be to simplify the testing so that it is available at the bedside or with such rapid turnaround time, such as troponin assays, that it can be part of the diagnostic algorithm.

SIRS as a Therapeutic Target

Late in his career, Roger Bone proposed a new paradigm to explain the pathogenesis of the septic process, taking into account the complexity and chaotic nature of the septic response. The septic network of events was viewed as a complex, overlapping network of interactions designed to help the body handle the severe assault of infection.[37] He recognized that this process, while intended to benefit the host, could potentially cause severe injury that could culminate in death. He suggested there were a series of 5 stages to the sepsis cascade that could eventually result in multiple organ dysfunction/failure if not properly countered by a compensatory anti-inflammatory response.[37] The initial stage was the local reaction at the site of the infection or injury. This pro-inflammatory response is designed to limit the initial injury and prevent spread. The response will generate stage 2, the early compensatory anti-inflammatory response (CARS), to

Table 1. Changing sepsis definition over time (continued)

Sepsis definition prior to 1980	1980s severe sepsis and septic shock definition	Sepsis syndrome definition	1991 consensus conference definition	2001 consensus conference definition
			Severe sepsis	-Elevated PCT
			Sepsis with organ dysfunction or hypoperfusion. Abnormalities may include, but not limited to, lactic acidosis, oliguria, or an acute alteration in mental status	-SBP <90 mmHg
			Septic shock	-MAP <70 mmHg
			Sepsis induced hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities	-SBP decrease >40 mmHg from baseline
			Septic induced hypotension: a systolic BP <90 mmHg or a reduction of ≥40 mmHg from baseline in the absence of other causes of hypotension	-S_vO_2 >70%
			Multiple organ dysfunction syndrome (MODS)	-C.I. > 3.5 L/min/M^2
			The presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention	-P_aO_2/F_IO_2 <300
				-Urine output <0.5 mL/kg/h or <45 mmol/L for at least 2 h
				-Creatinine increase >0.5 mg/dL
				-INR >1.5, aPTT >60 s
				-Ileus: absent bowel sounds
				-Platelet count <100 000/μL
				-Total bilirubin >4 mg/dL or 70 mmol/L
				-Increased lactate >1 mmol/L
				-Mottling or decreased capillary refill

Adapted and modified from references 1, 2, 4, 19, 20, and 22.

maintain immunologic balance. The third stage occurs when the vigor of the pro-inflammatory SIRS response predominates over the CARS response and results in progressive endothelial dysfunction, increased microvascular permeability and produces a coagulopathy, along with activation of the coagulation system. The fourth stage occurs when the compensatory anti-inflammatory response (CARS) becomes excessive and can result in immunosuppression or immune paralysis. An exaggerated CARS response can make the individual susceptible to nosocomial or secondary infections which can re-initiate the septic cascade. The fifth stage is marked by multiple organ dysfunction/failure and has been termed immunologic dissonance and is manifest as an inappropriate or out of balance immune system that results from persistent dysregulation of the SIRS and CARS response.[37]

There were numerous multicentered, prospective, controlled clinical trials conducted in the 1990s and early 2000s to try to identify the "silver bullet" for sepsis management.[5,14,20,38-40] The preclinical and early clinical studies had identified a host of potential molecules that could be blocked, neutralized, removed, or even augmented to improve the outcome of patients with severe sepsis and septic shock.[5,6,9,39] The 1991 Sepsis Consensus Conference sepsis/SIRS definition appeared as an inclusion criteria in almost every trial.[5,6] To some extent, this complex interaction and the intricacies of timing, dose, and pre-existing comorbid conditions helped explain the lack of benefit of the new therapeutic agents which had appeared so promising during pre-clinical and early phase clinical trials.[40-42] Some speculate that had a more specific definition been used to create a more homogenous study population, some of the exciting investigational therapies may have actually been granted approval for use in the management of severe sepsis and septic shock.

Is It Time for a Change in the SIRS Definition?

The overly sensitive sepsis/SIRS definitions that lack clinical specificity have recently been the subject of a "viewpoint" article in *Lancet*.[43] The authors argue that there are three major problems associated with the current SIRS definition: (1) the definition is too sensitive and almost all patients in the intensive care unit meet the definition, (2) the current definition does not differentiate the normal beneficial host response from a pathologic host response that produces organ dysfunction, and (3) there is difficulty determining the role of infection in this inflammatory response and the recognition that a similar inflammatory response can result from noninfectious insults.[43] Dr Vincent and co-authors suggest that "sepsis is the host's deleterious, nonresolving inflammatory response to infection that leads to organ dysfunction."[43] This sepsis definition is similar to the consensus conference definition of severe sepsis and severe SIRS which require the presence of new or worsening organ dysfunction as a consequence of the over-exuberant inflammatory response to infection or insult, respectively.[1] All of the definitions of sepsis and SIRS since the late 1980s have included the concept of a deleterious response to an infection or insult that results in organ dysfunction and/or failure as a consequence of this response (see **Table 1**).

The Future of SIRS: Where Do We Go from Here

Severe sepsis and SIRS remain important conditions that consume resources, lead to complications, and drastically change lives of afflicted patients. While a larger number of septic patients will survive their illness, these individuals demonstrate an increased mortality rate over the next 8 years compared with age-matched nonseptic critical care survivors.[26] Every day in the ICU clinicians diagnose and treat complicated septic and SIRS patients and struggle to prevent the complications of critical illness and to define what population to give selected innovative therapeutic strategies.

The consensus conference definition for sepsis and SIRS was well intentioned and served as a template for future refinements which came from the second international consensus conference. Even with these refinements, the definition lacked enough specificity to satisfy all of its critics and may be responsible, at least in part, for the failure of some of the innovative therapeutic strategies to improve outcome in the severe septic patient.[40-42,44] While our current consensus conference definition for sepsis and SIRS has marked limitations, it still seems to be the most functional tool for early identification and intervention in the population of interest. Undoubtedly, there will be scientific breakthroughs in our understanding of mechanisms and pathophysiology that will lead to a more refined diagnosis, perhaps coupled with specific biomarkers and/or PCR technology.[44,45] This enhanced tool may allow for an even earlier identification of the septic patient and perhaps define the cause of the infection and its innate resistance properties. To more readily define benefit of new innovative strategies to block, inhibit, neutralize, or enhance the effect of various "mediators" that are likely instrumental in the injury process will require that a more homogeneous study population be identified, as well as, identify abnormal levels of the mediator to be manipulated by the treatment strategy. In time, there is no doubt that this scenario will be feasible and this will change the paradigm for diagnosis and management of a variety of disease processes. Until such time, however, we are left with the simple, overly sensitive consensus definition that we can easily apply at the patient's bedside. In time "son of SIRS" will come to the rescue and improve the diagnostic ability and hopefully patient outcomes.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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