Evolving Concepts in Sepsis Definitions

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• Sepsis • Septic shock • PIRO • Diagnosis • Infection

To be able to give a clear name or label to a specific collection of signs and symptoms is important for physicians and patients alike. Having an exact diagnosis helps to identify particular groups of patients, to better understand the underlying disease process, and provides a more defined target for appropriate treatment. However, to be able to reach an accurate diagnosis, and hence, offer optimal medical therapy, a precise definition of the disease process in question is required. Over the years many disease processes have become well defined and are fairly easy to diagnose with the appropriate set of symptoms and test results. For example, acute myocardial infarction is associated with typical symptoms (eg, chest pain), signs (eg, abnormal electrocardiogram), and biomarkers (eg, raised blood troponin levels); patients meeting these criteria can be offered immediate and appropriate therapy. Imprecise definitions of disease limit the ability to form a specific, correct diagnosis and attempts to institute or study therapies in such situations are unlikely to be of benefit and may cause harm.

In sepsis, attempts have also been made to provide clear and accurate definitions, but these efforts have not met with universal support. In 2004, a survey of 1058 physicians, including 529 intensivists, noted that only 17% of those interviewed agreed on any one definition.[1] Sepsis is a complex process that can affect any individual and can originate from multiple sites and be caused by multiple microorganisms. Sepsis can present with a multitude of signs and symptoms, none of which are specific for sepsis and all of which can vary among patients and within the same patient over time. These symptoms can vary in severity from a mild, short-lived fever to fatal septic shock. Faced with such complexity and variation, it may be that a single, simple definition for sepsis will never be possible and we should focus on types of infection rather than on sepsis per se.

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PREVIOUS AND CURRENT DEFINITIONS OF SEPSIS

Sepsis is derived from "σηψις," the original Greek word for the decomposition of animal or vegetable organic matter.[2] First used more than 2700 years ago by Homer, it was only approximately 100 years ago that the link between bacteria and systemic signs of disease was made;[3] sepsis then became almost synonymous with severe infection. More recently, as the role of the immune response has become clearer, we have realized that what we had called sepsis is in fact a host response to the invading microorganism rather than any specific feature of the microorganism itself. Indeed, sepsis can be initiated by any microorganism, whether it is bacterial, fungal, viral, parasitic, or by microbial products and toxins, and is then propagated by a complex network of inflammatory mediators and cellular dysfunction.

The Sepsis Syndrome

One of the first attempts to establish a set of clinical parameters to define patients who have severe sepsis came in 1989 when Roger Bone and colleagues[4] proposed the term "sepsis syndrome." Sepsis syndrome was defined as hypothermia (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 breath/min); clinical evidence of an infection site; and the presence of at least one end-organ demonstrating inadequate perfusion or dysfunction expressed as poor or altered cerebral function, hypoxemia (PaO_2 less than 75 torr on room air), elevated plasma lactate, or oliguria (urine output less than 30 mL/h or 0.5 mL/kg body weight/h without corrective therapy). However, although it has been used as an entry criterion for clinical trials,[5,6] sepsis syndrome does not successfully define a homogeneous group of patients.

Systemic Inflammatory Response Syndrome and Multiple Organ Dysfunction Syndrome

Systemic inflammatory response syndrome

Following on from the sepsis syndrome, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) convened a Consensus Conference in 1991 in an attempt to create a set of standardized definitions.[7] Thirty-five experts in the field of sepsis were gathered together to provide a framework to define the systemic inflammatory response to infection (ie, sepsis). The end result of this conference was the introduction of the term "systemic inflammatory response syndrome" (SIRS). It had been recognized for some time that the same inflammatory response to infection could also occur in response to other conditions, including acute pancreatitis, trauma, ischemia/reperfusion injury, and burns. SIRS was an attempt to differentiate sepsis from these noninfectious causes.

According to the ACCP-SCCM Consensus Conference,[7] infection was defined as a microbial phenomenon characterized by the invasion of microorganisms or microbial toxins into normally sterile tissues. SIRS was defined, by consensus, as the presence of at least two of four clinical criteria:

- Body temperature >38°C or <36°C
- Heart rate >90 beats/min
- Respiratory rate >20 breaths/min or hyperventilation with a $PaCO_2$ <32 mmHg
- White blood cell count WBC >12,000/mm^3, <4000/mm^3, or with >10% immature neutrophils

SIRS represented a systemic inflammatory response of any etiology, including sepsis, which was therefore defined by the presence of SIRS in association with

a confirmed infection. Sepsis associated with organ dysfunction, hypoperfusion abnormality, or sepsis-induced hypotension was called severe sepsis, and septic shock was defined as severe sepsis with sepsis-induced hypotension persisting despite adequate fluid resuscitation.

The SIRS approach was rapidly adopted and has been widely used to define populations of patients in interventional clinical trials. Trzeciak and colleagues[8] reported that 69% of clinical trials in sepsis published between 1993 and 2001 used the Consensus Conference definitions. Similarly, Veloso and colleagues[9] reported that 10 of the 11 multicenter, randomized controlled trials of new therapeutic interventions in adult patients who had severe sepsis published between January 2000 and December 2007, used SIRS as part of the entrance criteria. Nevertheless, in the survey of 1058 physicians, including 529 intensivists, conducted by Poeze and colleagues[1] in 2000, only 5% (22% of the intensivists) gave the ACCP/SCCM definition when asked to define sepsis.

Although the SIRS criteria do have the prognostic value of defining a group of patients who are at an increased risk of developing complications and with increased mortality,[10,11,12] they have been criticized for being too sensitive and nonspecific to be of much clinical use.[13] Most ICU patients and many general ward patients meet the SIRS criteria.[12,14,15,16] In the Sepsis Occurrence in Acutely ill Patients study, 93% of ICU admissions had at least two SIRS criteria at some point during their ICU stay.[12] Moreover, each of the SIRS criteria can be present in many different conditions, so that a label of SIRS provides little or no information about the underlying disease process. For example, fever can be present in sepsis, but also after myocardial infarction, pulmonary embolism, or postoperatively; tachycardia and tachypnea may be present in heart failure, anemia, respiratory failure, hypovolemia, sepsis, and so forth; a raised white blood cell count can be present in many diseases encountered in ICU patients, including trauma, heart failure, pancreatitis, hemorrhage, and pulmonary edema. The use of the SIRS criteria to define septic shock was also unrealistic. Any type of shock is associated with hyperventilation (to compensate for the lactic acidosis), tachycardia (either to compensate for a decreased stroke volume or to achieve a supranormal cardiac output), and an increased white blood cell count (as part of the stress response). The body temperature is often within the normal range in septic shock. Accordingly, the SIRS criteria cannot separate septic from other types of shock. Furthermore, patients who meet the SIRS criteria have a wide range of disease severity, and hence, likely mortality.

Use of the SIRS criteria to identify patients for enrollment in clinical trials has been disappointing, and has likely contributed to the negativity of almost all these trials. Indeed, use of SIRS for entrance into clinical trials generates a very heterogeneous group of patients with multiple underlying pathologies and disease severity; while some patients in such a mixed population may well benefit from the intervention, it is likely that others will not, thus diluting out any beneficial effect.

Multiple organ dysfunction syndrome

With the realization that severe sepsis is frequently associated with the development of multiple organ dysfunction and that multiple organ failure is the most common cause of death in patients who have severe sepsis, the 1991 ACCP-SCCM Consensus Conference also introduced the term ‘‘multiple organ dysfunction syndrome’’ (MODS). MODS was defined as ‘‘the presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.’’[7] Many systems have since been developed to characterize and quantify MODS, including the

sequential organ failure assessment,[17] and are increasingly used as measures of morbidity in clinical trials.

2001 Sepsis Definitions Conference

With advances in our understanding of sepsis pathogenesis and pathophysiology and with continued dissatisfaction with available definitions of sepsis, a Consensus Sepsis Definitions Conference of 29 international experts in the field of sepsis was convened in 2001 under the auspices of SCCM, the European Society of Intensive Care Medicine, ACCP, and the Surgical Infection Societies.[18] The conference participants concluded that the definitions of sepsis, severe sepsis, and septic shock, as defined in the 1991 North American Consensus Conference,[7] may still be useful in clinical practice and for research purposes. The key change was in the use of the SIRS criteria, which were considered too sensitive and nonspecific. The participants suggested that other signs and symptoms be added to better reflect the clinical response to infection (**Box 1**). Sepsis is now defined as the presence of infection plus some of the listed signs and symptoms of sepsis. Severe sepsis is now defined as sepsis complicated by organ dysfunction and septic shock is defined as severe sepsis with acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes. Importantly, the list of signs of sepsis is meant as a guide, not all patients who have sepsis will have all the signs and symptoms listed, and many patients who do not have sepsis will have several of them. In addition, the list will change as new biomarkers are identified. These signs of sepsis should be considered as alarm signals that suggest the possibility of an infection and when combined with microbiological results and other evidence of organ involvement, can help in decisions regarding the need for antibiotics (**Fig. 1**).

THE PREDISPOSITION-INFECTION-RESPONSE-ORGAN DYSFUNCTION APPROACH

The inflammatory response to sepsis can vary in course and outcome depending on individual patients characteristics (eg, age, genetic makeup, pre-existing comorbidities) and characteristics of the infecting organism, including virulence, origin, and inoculum (**Fig. 2**). As such, sepsis could be said to be an umbrella term covering a group of diseases rather than being a single disease in its own right. Indeed, the consideration of sepsis as a single entity rather than as a syndrome associated with a complex group of diseases has been given as a key explanation for the apparent failure of most clinical trials in sepsis.[19,20] This assumption has led to the inclusion into clinical trials of heterogeneous groups of patients who are unlikely to respond similarly to the single intervention being trialed.[21] In this context, sepsis has been compared with cancer. Much as sepsis is the inflammatory response to infection but is heterogeneous in its origins, targets, and prognosis, so cancer is the uncontrolled proliferation of abnormal cells that is again heterogeneous in its origins, targets, and prognosis. No oncologist would offer the same treatment to patients who have breast cancer, as to patients who have leukemia or malignant melanoma. Likewise, treatment may depend on the type of cellular proliferation. Yet in sepsis trials, potential new therapies have been expected to work in widely heterogeneous groups of patients. Unlike sepsis, oncologists rapidly took this idea on board and began defining patients not only as having cancer but according to the specific origin, type, and stage of the cancer, enabling homogeneous groups of patients to be identified and effective interventions for each of those groups to be developed and introduced. Recognition that patients who have more severe forms

Box 1
Move from 1991 systemic inflammatory response syndrome criteria to expanded list of signs and symptoms in 2001 Sepsis Definitions Conference

SIRS criteria

- Fever/hypothermia
- Tachycardia
- Tachypnea
- Altered white blood cell count

Sepsis Definitions Conference

General signs and symptoms

- Fever/hypothermia
- Tachypnea/respiratory alkalosis
- Positive fluid balance/edema

General inflammatory reaction

- Altered white blood cell count
- Increased biomarker (C-reactive protein (CRP), IL-6, PCT) concentrations

Hemodynamic alterations

- Arterial hypotension
- Tachycardia
- Increased cardiac output/low systemic vascular resistance (SVR)/high SvO2
- Altered skin perfusion
- Decreased urine output
- Hyperlactatemia (increased base deficit)

Signs of organ dysfunction

- Hypoxemia
- Coagulation abnormalities
- Altered mental status
- Hyperglycemia
- Thrombocytopenia, disseminated intravascular coagulation
- Altered liver function (hyperbilirubinemia)
- Intolerance to feeding (altered gastrointestinal motility)

Abbreviation: PCT, procalcitonin.

of cancer needed different treatments and had different prognoses led to the development of the tumor, nodes, metastases (TNM) grading system to classify patients who have cancer.[22] Patients who have a tumor, therefore, receive a specific classification (eg, T2, N1, M0) for that tumor. The TNM classification is then linked to

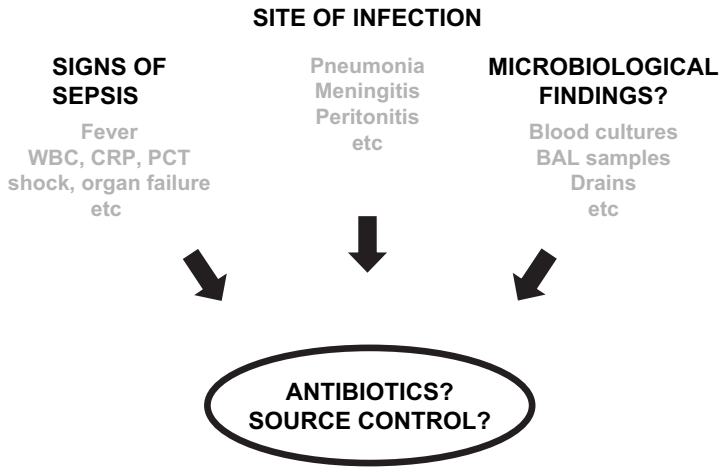

Fig. 1. The three components used clinically to decide whether or not to give antibiotics or effect a source control. The presence of increasing numbers of components supports a diagnosis of sepsis and a need for antimicrobial therapy. For example, a positive bronchoalveolar lavage (BAL) culture may suggest infection, but could be colonization; however, if patients also have a fever and radiological signs supporting a diagnosis of pneumonia, the case for antibiotics is much clearer.

a stage, usually from I to IV, which stratifies patients according to their likely prognosis and the probability that they will respond to a particular therapy.

Participants at the Sepsis Definitions Conference believed that a similar mechanism could be useful to characterize and stage the host response to infection,[18] and

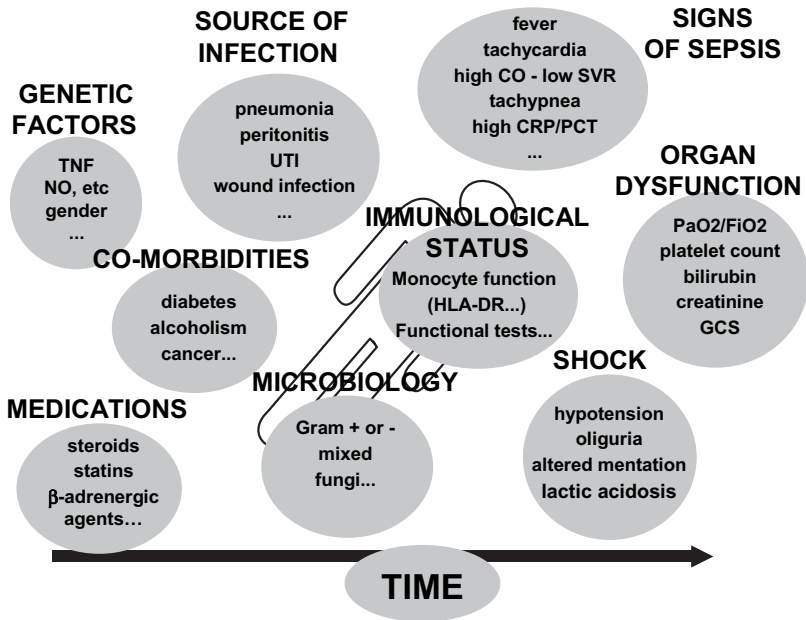

Fig. 2. Some examples of the heterogeneity of patients who have sepsis. GCS, Glasgow Coma Scale. CO, cardiac outfit.

suggested the PIRO grading system whereby patients could be stratified according to four key aspects: predisposing factors, the insult or infection, the host response, and organ dysfunction (**Table 1**). The PIRO system offers a possible means of forming more homogeneous subgroups of patients who have sepsis, who could then receive better targeted interventions with the prospect of real therapeutic advances.

Several groups have already attempted to apply the PIRO system clinically (**Table 2**).[23,24,25,26] Moreno and colleagues[23] used the Simplified Acute Physiology Score (SAPS) 3 database to develop a model based on the PIRO system which could be used to predict mortality in patients who have sepsis. Multivariate analysis was used for each of the four PIRO components to select weight variables significantly associated with hospital mortality. The authors felt it was not possible to separate host response from the resulting organ dysfunction, so they combined these two components. Calibration and discrimination were reported as good and the authors suggested that, although further prospective validation is needed, the proposed SAPS 3 PIRO system could be used to stratify patients at,or shortly after, ICU admission to enable better selection of management according to the risk of death. The PIRO performed better than the SAPS 3 admission score (area under the receiver operating characteristics curve [AUC] 0.77 versus 0.74).

In a prospective, observational study, Lisboa and colleagues[24] again used multivariate logistic regression to identify variables for each PIRO category that were independently associated with ICU mortality in patients who had ventilator-associated pneumonia (VAP). Lisboa and colleagues developed a four-point score, with one point for each component. Mortality increased with increasing score: a score of 0 was associated with a mortality rate of 9.8%, increasing to 93.3% for patients with a score of 4. The VAP-PIRO score outperformed the Acute Physiology and Chronic Health Evaluation (APACHE) II score (area under the curve [AUC] 0.81 versus 0.53, $P<.001$).

Rello and colleagues[25] reported the results of a cohort study to develop a tool based on the PIRO system which could enable the stratification of critically ill patients who had community-acquired pneumonia (CAP) into mortality risk groups, and to compare its performance with other predictive systems. Variables were selected from the

Table 1
Some suggested clinical and laboratory variables for the four components of the PIRO grading system

	Laboratory	Clinical
Predisposing factors	Genetic polymorphisms	Age, pre-existing diseases (eg, alcoholism, diabetes, cirrhosis), sex, steroid or immunosuppressive therapy, religious and cultural beliefs
Infection	Microbiology (infecting organism, virulence, antimicrobial sensitivities)	Site (pneumonia, peritonitis, catheter), type (hospital-acquired versus community-acquired)
Response	White blood cell count, prothrombin time, APTT, blood lactate levels, biomarkers (eg, CRP, PCT)	Temperature, heart rate, blood pressure, cardiac output, and so forth
Organ dysfunction	PaO_2/FiO_2, serum creatinine, serum bilirubin, platelet count	Blood pressure, urine output, Glasgow Coma Scale

Table 2
Components selected for use in PIRO scores in four recent studies

Moreno et al[23]	
P	Age, source of admission, comorbidities (cancer, cirrhosis, AIDS), length of stay before ICU admission, reason for admission (cardiac arrest)
I	Nosocomial, extended, respiratory, fungal
R & O	Organ dysfunction (renal, coagulation), organ failure (cardiovascular, respiratory, central nervous system, coagulation, renal)
Lisboa et al[24]	
P	Chronic obstructive pulmonary disease (COPD), heart failure, immunocompromised, cirrhosis, chronic renal failure
I	Bacteremia
R	Hypotension
O	Acute respiratory distress syndrome (ARDS)
Rello et al[25]	
P	Age, COPD, immunocompromised
I	Bacteremia, multilobar opacities on chest X ray
R	Shock, severe hypoxemia
O	Acute renal failure, ARDS
Rubulotta et al[26]	
P	Age, chronic liver disease, congestive cardiomyopathy
I	Community-acquired urinary tract infection, Gram-positive, Gram-negative, other community-acquired infection, nosocomial infection, fungal nonabdominal infection, fungal abdominal infection
R	Tachycardia, tachypnea
O	Number of organ failures

current literature as being most significant in the prognosis of patients who have CAP or because they were considered to have clinical importance. A score of 1 was given for each variable present giving a total possible score of 8. The mean PIRO score was significantly higher in nonsurvivors than in survivors and mortality rate increased with increasing PIRO score, such that patients who had a PIRO score of 7 had 100% mortality. According to the observed mortality for each PIRO score, patients were stratified into four levels of risk: Low, mild, high, and very high. By Cox regression analysis, mild (hazard ratio [HR] 1.8; 95% CI 1.1–2.9; $P<.05$), high (HR 3.1; 95% CI = 2.0–4.7; $P<.001$) and very high (HR 6.3; 95% CI = 4.2–9.4; $P<.001$) grades of risk were associated with a higher risk of death. Higher PIRO scores were also associated with increased length of ICU stay and duration of mechanical ventilation. The PIRO score again predicted mortality better than the APACHE II score (AUC 0.88 versus 0.75, $P<.001$).

Most recently, Rubulotta and colleagues[26] used two large sepsis databases to generate and validate a version of the PIRO staging model risk stratification in severe sepsis. Using a logistic regression technique, variables were included in the score to give a 0 to 4 point score for each of the PIRO components (0–1 for R) and hence a total score range of 0 to 13 (see **Table 2**). The correlations of the PIRO total score and in-hospital mortality rates were 0.974 ($P<.0001$) and 0.998 ($P<.0001$) in the two databases tested. The AUC was 0.70 compared with 0.69 for the APACHE II score. The authors suggest that although the proposed model should be seen as a ‘‘preliminary,

hypothesis generating version," it could potentially be used to stratify patients for inclusion into a severe sepsis trial, as a prospectively defined subgroup analysis outcome variable for future clinical trials, and to determine prognosis and individual treatment recommendations for individual patients suffering from severe sepsis.

These studies provide some insight into how the PIRO system could potentially be used in the future to characterize patients who have sepsis. Clearly, further study is needed before this approach can be widely adopted, but even in these early examples, the scores performed better than other predictive models, such as APACHE and SAPS. These studies also demonstrate how the system will need to be adapted to fit specific groups of patients, much as the TNM system is adjusted to specific cancers.[27] Importantly, using the PIRO system for clinical trial inclusion would necessitate a shift from the large heterogeneous studies of today to much smaller studies targeting more specific and clearly defined and characterized groups of patients. Although this could be seen as a threat by the pharmaceutical industry as the potential market would be seen to be smaller and the intervention therefore potentially less lucrative, this approach has been used with success in oncology,[21] and indeed the chances of a positive result would be greater if the intervention were more appropriately targeted.

SUMMARY

Developing effective therapies for any disease process relies on the ability to clearly define the population of patients who will benefit from that intervention. Advances in our understanding of sepsis pathogenesis have made it clear that the global definition or concept of sepsis as a single, homogeneous disease process is inadequate. The idea that all patients who have severe sepsis will respond positively to any single therapeutic intervention is probably too simple, although some interventions may target more general pathways and be globally beneficial. For example, drotrecogin alfa (activated) was shown to be effective at reducing mortality in a clinical trial with a heterogeneous patient population,[28] although even here positive results were restricted to patients who had severe sepsis, highlighting the importance of being able to better characterize patients. Our approach to sepsis and its definition has evolved as we increasingly recognize the complex nature of the process and the importance of targeting treatments according to individual patients' characteristics. Clinical variables are too sensitive and nonspecific and improved biologic and biochemical tools need to be incorporated into current definitions to provide precise and accurate methods of diagnosis. Systems, such as PIRO, that can characterize patients according to their likely prognosis and response to a specific therapy need to be further developed so that treatments can be appropriately directed for individual patients.

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