The Grading of Sepsis – Why we Need New Definitions

H. Gerlach

Vivantes – Klinikum Neukoelln, Dept. of Anesthesiology and Critical Care, Berlin, Germany

Sepsis is a major cause of death worldwide, with a large impact on mortality in the intensive care unit. It has been estimated that every day around 1,400 patients die on the ICU as a result of sepsis. Recent progress in sepsis research has been able to improve the knowledge about the basic pathophysiological processes of sepsis. However, in daily ICU practice it remains difficult to identify and treat sepsis, and its related conditions, adequately. Apparently the mortality rate of sepsis has not improved in recent decades. Therefore, concerns remain about the lack of consistent definitions and understanding about sepsis among the global medical community. A proposition for the definition of sepsis and related syndromes was made in 1991 by the American College of Chest Physicians and the Society of Critical Care Medicine (ACCP/SCCM). The goals were to provide a conceptual and a practical framework to define the systemic inflammatory response to infection, which is a progressive injurious process that falls under the generalized term “sepsis” and includes sepsis-associated organ dysfunction as well [1]. Another objective of the conference participants was that the broad definitions they proposed would improve the ability of clinicians at the bedside to detect the condition and thus allow timely and appropriate monitoring, testing and treatment. These definitions would advance the sepsis research agenda by encouraging the "standardization of research protocols". Although these definitions were based upon expert opinion, the recommendations have not found unequivocal acceptance. However, these definitions have since then been used for research purposes investigating new therapeutic modalities, in essentially all intervention trials [1].

The report from the ACCP/SCCM Consensus Conference that was published in 1992 introduced into common parlance a new term, SIRS, which was the acronym for the Systemic Inflammatory Response Syndrome. This term was introduced to denote the constellation of findings that result from systemic activation of the innate immune response, irrespective of the cause. The concept was that SIRS could be triggered by localized or generalized infections, trauma, thermal injury, or sterile inflammatory processes, such as acute pancreatitis. From an operational standpoint, SIRS was considered to be present when patients had more than one of the following clinical findings: body temperature >38 °C or <36 °C; heart rate >90 min^{-1}; hyperventilation as evidence by respiratory rate >20 min^{-1} or $PaCO_2$ <32 mm Hg; and

white blood cell count >12,000 cells μL^{-1} or <4,000 μL^{-1}. Since the initial report, the SIRS concept has been adopted by clinicians and investigators. A MEDLINE search from January 1992 through May 2002, yielded almost 800 publications that mentioned the term SIRS in either the title or the abstract.

The inflammatory events responsible for clinical derangements such as severe infection, sepsis, or septic shock are thought to be similar. Initially manifested by the systemic inflammatory response syndrome (SIRS), these events lead to circulatory instability with respiratory distress according to the extent of infection and/or the intensity of the host response, culminating in single or multiple organ dysfunction syndromes (MODS). A major factor contributing to the belief that mediation of septic shock proceeds via well-defined molecular and cellular pathways irrespective of microbial taxonomy is the extensive database concerning bacterial septic shock syndromes. For Gram-negative bacteremia or endotoxinemia, data are especially compelling to causally link excessive production or prolonged activity of host-derived pro-inflammatory cytokine mediators with the intravascular inflammation, cardiopulmonary dysfunction, and organ injury characteristic of septic shock.

In septic shock, the amount of inflammatory markers like interleukin 6 and 8 were found to correlate with disease severity and worse outcome, and soluble E-selectin reflects endothelial activation. Furthermore, circulating neutrophils express markers of activation (complement receptor 3 (CD11b/CD18) and high affinity Fcγ-receptor I (CD64)). An overwhelming production of nitric oxide mediates peripheral vasodilation, catecholamine resistance, tissue hypoxia, and cardiomyopathy. Increased plasma NOx formation as the main breakdown product of cytokine-induced nitric oxide metabolism was found to correlate with shock severity, organ failure, and outcome. However, experimental sepsis models and a recent phase III study with L-arginine analogue N^G-monomethyl-L-arginine (L-NMMA) strongly indicate that excessive and nonspecific blocking of nitric oxide synthases (NOS) is fatal, stressing the importance of cytoprotective and regulative properties of maintained basal nitric oxide production. Therefore, selective inhibition of inducible (i)NOS might be more effective. In contrast to nonspecific competitive inhibitors of nitric oxide synthesis (L-arginine analogues, isothioureas), glucocorticoids inhibit iNOS but not the constitutively expressed endothelial nitric oxide synthase. Inhibition of nitric oxide formation by glucocorticoids was demonstrated *in vitro* at different levels: transcription, translation, substrate or enzyme cofactor availability, and calpain-induced iNOS degradation.

The paradigm of cytokine overexpression-mediated shock has been and still is the base for many therapies being evaluated in clinical trials which seek to suppress such endogenous cytokine activity. Besides anti-TNF-α strategies, these interventions have also included the preemptive neutralization of stimulatory bacterial endotoxins present in the circulation, transcriptional repression of cytokine gene expression within host defense leukocytes, and antagonism of IL-1 with a recombinant form of the soluble receptor protein. These intervention trials for septic shock most often have been predicated on successful preclinical studies, even if such earlier success occurred only when agents were used as prophylaxis in animal studies. It should not be surprising that these strategies often fail to improve outcome when administered after an endotoxin challenge, or as post-infection therapy.

The reasons for such failure are perhaps most evident in those patients with postsurgical or immunosuppression-related septic shock. In general, the pathogenetic sequence and role of cytokine overexpression have not been validated for special subgroups of sepsis, e.g. fungal sepsis, despite widespread evidence that these organisms are increasingly responsible for nosocomial septic shock and lethal disseminated infections in the critically ill. Since the pathogenetic mechanisms of fungal septic shock differ fundamentally from TNF-α-mediated bacterial septic shock syndromes, it has to be proposed that the general concept of cytokine overexpression-mediated septic shock is overly simplistic, and in particular is not consistently valid for special subgroups of patients. Recent data pertain to the potential therapeutic value of enhancing host defense by upregulating cytokine expression: Amphotericin B, a current mainstay in the management of disseminated fungal infections, has immunomodulatory effects including induction of TNF-α, and fluconazole, another antimycotic drug, synergizes with IL-1. These phenomena may explain their pyrogenic properties, and suggest that stimulation of host defense cytokine gene transcription may be an important part of their overall therapeutic efficacy in addition to their microbicidal disruption of fungal cell walls. Similar results were found for GM-CSF, and preliminary clinical studies demonstrated a beneficial effect of exogenous GM-CSF in high-dose chemotherapy patients.

After the failure of multiple immunomodulatory studies to reduce morbidity and mortality of clinical sepsis, reconsideration of the pathogenesis of sepsis has taken place. Although it is recognized that inflammatory cytokines play a major role in the pathogenesis of sepsis, this does not necessarily guarantee success of therapies targeting any one of the mediators involved. Patients during sepsis may undergo various stages of disease, in each of which pro- or anti-inflammatory processes predominate. In addition, different subgroups of infections, e.g. fungal sepsis, have other characteristics compared to bacterial infections. Finally, patients with special diseases including high-dose chemotherapy leading to severe immunosuppression exert systemic cytokine patterns, which may differ fundamentally from other patient groups. Hence, determining the stage of disease may be helpful in identifying the indications of inhibiting or augmenting certain aspects of the inflammatory response. In some cases, where harmful effects of leukocytes outweigh their efficiency in killing microorganisms, inhibiting strategies may be beneficial. This seems to be the case in bacterial meningitis, where rapid sequestration of neutrophils in the brain produce irreversible tissue injury and death. However, inhibiting leukocyte function does not seem to be beneficial in cases where control of local or systemic infection seems to be crucial in reducing mortality. Increasing neutrophil function and numbers during sepsis, especially in severely immunocompromised patients, seems to be associated with an overall favorable outcome.

In conclusion, host response to infections includes endothelial damage, consisting of procoagulatory activation, increased adhesion of leukocytes, hyperpermeability, and vasodilation. These mechanisms take part in the compartmentalization of inflammation, which plays a crucial role to inhibit systemic spreading. In severe sepsis and septic shock, imbalance between pro- and anti-inflammatory activity leads to disturbed macro- and microcirculation. New therapeutic approaches include inhibition of hyperinflammation, modulation of coagulation and fibrinolysis, protocols for

improving hemodynamics and metabolism, and specific blockade of mediators. Future experimental and clinical studies may help define under which circumstances inhibiting or augmenting endogenous mediators may be a helpful adjunctive therapy for sepsis – another reason for defining a new grading system for this disease.

In 2001, several North American and European intensive care societies agreed to revisit the definitions for sepsis and related conditions. This conference was sponsored by the SCCM, ESICM, ACCP, American Thoracic Society (ATS), and the Surgical Infection Society (SIS). Each of these groups provided an official representative to the conference. The overall goals of the conference were threefold. The first was to review the strengths and weaknesses of the current definitions of sepsis and related conditions. The second goal was to identify ways to improve the current definitions. The third goal was to begin to identify ways to increase the accuracy, reliability and/or clinical utility of the diagnosis of sepsis. The conference was attended by 29 participants from Europe and North America. In advance of the conference, five subgroups were formed to evaluate the following areas: signs and symptoms of sepsis, cell markers, cytokines, microbiologic data, and coagulation parameters. These subgroups, corresponded electronically prior to the conference, and met in person during the conference. A spokesperson for each group presented the deliberation of each group to all conference participants during a plenary session.

As in 1992, sepsis was regarded to be the clinical syndrome defined by the presence of both **infection** and a **systemic inflammatory response**. In considering whether the diagnostic criteria for infection or systemic inflammation should be revised, the group sought to adhere to the following principles. First, the criteria should be broadly useful to both clinicians caring for patients at the bedside and to researchers designing observational studies and clinical trials to improve our understanding of sepsis and its optimal treatment. Second, the criteria should be sensitive enough to identify most patients with the syndrome, minimally sacrificing specificity (since there will inevitably be some sacrificing of specificity). Third, the criteria should not be so cumbersome that clinicians will find them hard to remember or to apply. Fourth, any laboratory-dependent criteria should use assays that either are widely available now or are likely to be generally available in the near future. Fifth, the criteria should be applicable to both adult and pediatric patients [2].

Despite the definitions for sepsis, severe sepsis and septic shock, these terms do not allow for precise characterization and staging of patients with this condition. A clinically useful staging system stratifies patients with a disease by both their baseline risk of an adverse outcome and their potential to respond to therapy. Such systems, both formal and informal, are widely used in clinical medicine. Perhaps the best-developed and most explicit approach to disease stratification has evolved in oncology. The TNM system classifies malignant tumors based on descriptors for the primary tumor itself (T), metastases to regional lymph nodes (N), and distant metastases (M). Each domain is graded to denote the extent of pathologic involvement. For any given tumor type, survival tends to correlate with certain TNM subgroups.

Using a variation of the TNM approach, the development of a classification scheme for sepsis was envisioned – called **PIRO** – that will stratify patients on the basis of

their **P**redisposing conditions, the nature and extent of the **I**nsult (or in the case of sepsis, **I**nfection), the nature and magnitude of the host **R**esponse, and the degree of concomitant **O**rgan dysfunction. It is important to emphasize that the PIRO concept presented herein is rudimentary; extensive testing and further refinement will be needed before it can be considered ready for routine application in clinical practice.

Predisposition

Premorbid factors have a substantial impact on outcome in sepsis, modifying both the disease process and the approach taken to therapy. This point is emphasized by recent data showing that genetic factors play a greater role in determining the risk of premature mortality due to sepsis than they do in influencing the risk of premature death from other common conditions, such as cancer or cardiovascular diseases. Beyond genetic variability, however, the management of patients with sepsis, and hence the outcome of the disease, is clearly influenced by factors such as the premorbid health status of the patient, the reversibility of concomitant diseases, and a host of religious and cultural forces that shape the approach toward therapy. It is also important to appreciate that these multiple predisposing factors could influence both the *incidence* and the *outcome* in similar or conflicting ways. They could also pose separate or different risks for each of the different stages of infection, response, and organ dysfunction. For example, immunosuppression may increase a person's risk of infection, decrease the magnitude of that person's inflammatory response, and have no direct influence on organ dysfunction. Similarly, a genetic polymorphism such as the TNF2 allele may result in a more aggressive inflammatory response to an invading organism. This might decrease a person's risk of infection but increase that person's risk of an overly exuberant, and potentially harmful, inflammatory response should she become infected.

Infection

The site, type, and extent of the infection have a significant impact on prognosis. A bilateral bronchopneumonia is a more extensive process than a localized pneumonia, and a generalized fecal peritonitis is a more extensive process than an appendicitis. By studying mortality rates among patients randomized to receive placebo in recent randomized clinical trials of new agents for the adjuvant treatment of sepsis, it is apparent that pneumonia and intra-abdominal infections are associated with a higher risk of mortality than are urinary tract infections. Patients with secondary nosocomial bacteremia experience a higher mortality than those with catheter-related or primary bacteremia. Similarly, there is evidence that the endogenous host response to Gram-positive organisms differs from that evoked by Gram-negative organisms. Early studies with antibodies directed against endotoxin, for example, suggested that benefit was greatest in patients with Gram-negative infec-

tion or endotoxemia, but that treatment might be harmful to patients with Gram-positive infection.

Response

In general, novel therapies for sepsis target the host response, rather than the infecting organism. The host response has proven to be difficult to characterize. Putative biologic markers of response severity include circulating levels of PCT, IL-6 and many others. When a new mediator is identified, epidemiologic studies will be required to determine whether measurements of the compound can be useful for staging patients. Furthermore, the optimal set of biologic markers for staging sepsis may depend upon the nature of the therapeutic decision to be made. For example, an indicator of dysregulation of the coagulation system might be more valuable for making a decision about whether to institute therapy with drotrecogin alfa (activated), whereas a marker of adrenal dysfunction might be more useful for determining whether to institute therapy with hydrocortisone.

Organ Dysfunction

By analogy with the TNM system, the presence of organ dysfunction in sepsis is similar to the presence of metastatic disease in cancer. Certainly, the severity of organ dysfunction is an important determinant of prognosis in sepsis. Whether the severity of organ dysfunction can aid in therapeutic stratification is less clear. Nevertheless, there is some evidence that neutralization of TNF, an early mediator in the inflammatory cascade, is more effective in patients without significant organ dysfunction, whereas drotrecogin alpha (activated) may provide more benefit to patients with greater as compared to lesser disease burden. The modern organ failure scores can be used to quantitatively describe the degree of organ dysfunction developing over the course of critical illness.
The potential utility of the proposed PIRO model lies in being able to discriminate morbidity arising from infection from morbidity arising from the *response* to infection. Interventions that modulate the response may impact adversely on the ability to contain an infection; conversely interventions that target the infection are unlikely to be beneficial if the morbidity impact is being driven by the host response. Premorbid conditions establish a baseline risk, independent of the infectious process, while acquired organ dysfunction is an outcome to be prevented [2].

References

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