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Sepsis definitions: time for change

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For the Ancient Greeks, sepsis referred to rot, decay, or putrefaction. Galen and Celsus described the signs of inflammation as peripheral vasodilatation (*rubor*), fever (*calor*), pain (*dolor*), increased capillary permeability (*tumor*), and organ dysfunction (*functio laesa*).

The modern concept of sepsis has focused on the human response to invading organisms. In 1991, a North American consensus conference introduced the idea that sepsis is the host's inflammatory response to in fection.[1] For simplicity, the systemic inflammatory response syndrome (SIRS) was defined by four variables: temperature, heart rate, respiratory rate, and white blood cell count. Only minor abnormalities in these variables are needed for a patient to meet the SIRS criteria. These simple clinical criteria allowed researchers to identify patients to enrol in sepsis trials and were rapidly adopted.

However, the SIRS approach has three major problems. First, the SIRS criteria are so sensitive that up to 90% of patients admitted to an intensive care unit (ICU) meet the criteria.[2,3] SIRS can be caused by many non-infectious clinical processes, such as severe trauma, burns, pancreatitis, and ischaemic reperfusion events. If sepsis is defined by the presence of SIRS criteria plus an infection, and almost every acutely ill patient meets the SIRS criteria, then sepsis effectively equals infection. But, although all patients with sepsis have an infection, the reverse is not necessarily true—ie, not all patients with an infection have sepsis. Second, some degree of host response is actually inherent to the infection; indeed, this is an important component of the difference between infection and mere colonisation. Almost any infection—even a minor viral illness—is typically associated with fever and accompanying changes, including tachycardia, some hyperventilation, and an

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increased white cell count. This host response has beneficial aspects, and a reduced or absent reaction could suggest that the individual is immunocompromised. Third, deciphering the role of infection in the pathogenesis of SIRS has been difficult because sterile inflammation (present in, for example, severe trauma, burns, and pancreatitis) and infection can both elicit similar clinical signs of acute systemic inflammation. Moreover, several such stressors might be present simultaneously in any patient.

A second consensus conference in 2001[4] attempted to revisit the SIRS criteria but failed to come up with an easy-to-use list of variables to define sepsis. By expanding the list of potential clinical criteria, the delegates risked making the definition less specific. The delegates attempted to list major and minor criteria, as for endocarditis, but could not identify any meaningful criteria. Hence, the 1991 criteria for sepsis continue to be used.

To reach a more precise definition of sepsis than the SIRS criteria provide, we need to establish whether sepsis is the same as sterile inflammation. Several non-infectious processes that are associated with acute tissue injury and innate immune activation can induce a clinical syndrome analogous to sepsis (figure), including multiple trauma, pancreatitis, transplant rejection, and autoimmune diseases.[5] Whether this syndrome is mediated by endogenous endotoxin or by non-infectious stimuli can be very difficult to define. However, we know that sepsis arises through activation of an innate immune response to a stimulus that represents a danger to the host.[6] From a molecular perspective, the initial host response to infection does not differ appreciably from the host response to sterile inflammation from severe trauma, burns, ischaemic reperfusion injury, or other forms of tissue injury that are accompanied by cell necrosis.[5]

Work over the past few decades has shown that pattern recognition receptors, such as those of the Toll-like receptor (TLR) and the nucleotide-binding oligomerisation domain (NOD) protein families, initiate the distinct cellular responses.[6] Together these responses produce the phenotypic changes of sepsis. The receptors are activated by conserved microbial molecular structures, such as endotoxin or lipoteichoic acid. But the pattern recognition receptors used by the innate immune system to engage microbial ligands are the same receptors that recognise alarmins derived by host tissue and that are pathologically present in the extracellular environment.[5,6] For example, high mobility group box 1 (HMGB1) is released during sterile injury and signals through TLR4 to mediate organ damage, even in the absence of infection.[5]

Both invasive infection and sterile tissue necrosis thus cause immediate activation of inflammatory, coagulation, microbial clearance, and tissue repair pathways to stabilise and defend the host from further injury. Clinical signs alone fail to distinguish this sterile inflammatory response from one initiated by infection. This effect explains why the phenotype of SIRS is clinically indistinguishable in patients with severe infection and those with major injury without concomitant infection. The combined actions of both the innate and adaptive immune defences are then used to eradicate microbial invaders (sepsis) or to repair tissue (sepsis and sterile tissue injury), or both.[6] In a comparative transcriptome analysis, Xiao and colleagues[7] showed high fidelity concordance in the mitochondrial RNA signatures in leucocytes from patients immediately after severe trauma or burns, and in

people given intravenous bacterial endotoxin. These observations suggest that similar and overlapping signalling networks are activated in sterile inflammation and in invasive infection.

So where does this leave our definitions? Sepsis is not simply the host response to an infection, nor is it the same as sterile inflammation. Rather, sepsis is the host's deleterious, non-resolving inflammatory response to infection that leads to organ dysfunction. Most clinicians do not refer to patients as septic when they develop an uncomplicated mild upper-respiratory viral infection with slight fever and tachycardia. The term sepsis is usually reserved for patients with an infection who “look bad” and whose condition is severe enough that they need to be admitted to the ICU or monitored more carefully. At a Merinoff Symposium, the International Sepsis Forum wrote “sepsis is a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs”[8]—this is the very latest perception of sepsis. Importantly, pro-inflammatory and anti-inflammatory responses coexist in sepsis and can lead to immunosuppression. The response that predominates in the clinical phenotype varies across patients and over time in each patient.

How can such a dysregulated host response be defined with clinical criteria? What we actually mean when we say a patient “looks bad” is that some degree of associated organ dysfunction is already present—eg, some degree of arterial hypotension is present, the blood lactate is slightly raised, gas exchange is impaired, or the patient is obtunded or confused. A systematic review of organ function in the infected patient includes six organ systems: cardiovascular, respiratory, renal, neurological, hepatic, and coagulation.[9] Other organs, like the gut or the endocrine system, are more difficult to assess objectively. Any type of associated organ dysfunction indicates that an acute and potentially life-threatening disorder is present, which must be treated rapidly and appropriately to prevent the development of multiorgan failure and to optimise clinical outcomes.

Sepsis differs from sterile inflammation, not by the nature of the activated host response pathways or by the types of organ dysfunction, but by the presence of an underlying infectious process. The first diagnostic priority in managing a patient with sepsis is, therefore, to identify any focus of invasive infection. The range of infections that can induce sepsis is broad, and the clinical phenotype is at least partly shaped by the infecting organism. Bacterial infection can typically be diagnosed with conventional methods of culture and sensitivity, and the site of infection can be identified on the basis of clinical findings supplemented by radiographic investigations. Fungal and parasitic infections are suggested by the clinical context. Viral infections can be challenging to diagnose outside of an epidemiologically defined epidemic or pandemic, but emerging nucleic acid based assays are permitting more rapid and accurate diagnosis of viral infection. Rapid treatment with antibiotics and source control measures can assist the host in clearing the pathogen, and the therapeutic focus should be on initiation of these treatments and on maintenance of perfusion. After the host has cleared the pathogen, the clinical outcome will probably be a result of how well the complications of the residual infectious or sterile systemic inflammatory response are managed.

The terms severe sepsis and sepsis have often been used interchangeably. To clarify this situation, we believe evidence of organ dysfunction should be included in the criteria for sepsis—ie, sepsis should be defined as a systemic response to infection with the presence of some degree of organ dysfunction.

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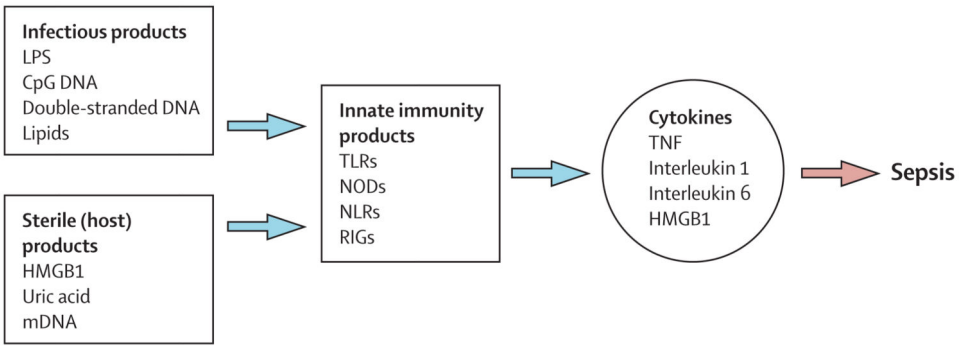

Figure. Infectious and non-infectious stimuli that activate innate immunity and cytokine release and can cause sepsis

LPS=lipopolysaccharide. HMGB1=high mobility group box 1. mDNA=mitochondrial DNA. TLR=toll-like receptor. NOD=nucleotide-binding oligomerisation domain protein. NLR=NOD-like receptor. RIG=retinoic-acid-inducible gene. TNF=tumour necrosis factor.