

## Sepsis: Improving the odds

Sepsis is a syndrome that is defined as a systemic inflammatory response to an infection. Sepsis can result in significant morbidity and can be fatal. Early diagnosis of sepsis and of the underlying cause is still a significant clinical challenge. Delaying diagnosis by as little as one hour decreases patient survival, so there is a critical need for faster tools that can aid clinicians in the diagnosis of this potentially fatal condition.

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## The scope of the problem

Sepsis strikes an estimated 750,000 adults in the US annually, killing 30 to 35 percent, with a reported 215,000 deaths per year.<sup>1</sup> There are another 400,000 US pediatric cases a year. The mortality rate is similar internationally. At an average of \$20,000 to \$30,000 per case in the US (141 percent higher than the average hospital cost), the cost of sepsis is estimated at \$17 billion annually.<sup>2</sup> Despite significant advances in treatment of infectious disease and improvements in clinical care, severe sepsis remains a major killer. The annual US mortality rate for severe sepsis exceeds those for acute myocardial infarction (AMI) and common cancers (Figure 1). Heart attacks, lung cancer, HIV/AIDS all are recognized as major medical issues and receive vast amounts of publicity. But sepsis, which has largely remained out of the public eye, has moved up to top these better-known conditions.

## What is sepsis?

Sepsis is not a specific disease, but rather a continuum of events triggered by the body's inflammatory immune responses to bacterial, viral, fungal, or parasitic infections. It develops in a series of events in which the body's normal immune response is ineffective, and possibly even harmful to the patient. Any trauma, burns, surgery, hemorrhage, or infections will result in an activation of the immune system and release of immune activators. In healthy individuals, the immune system deals effectively with threats, mounting a competent immune response that frequently results in control of the infection, often supported by appropriate treatment. In immunocompromised individuals, we may see an overreaction or an insufficient reaction of the immune system that may cause serious consequences.

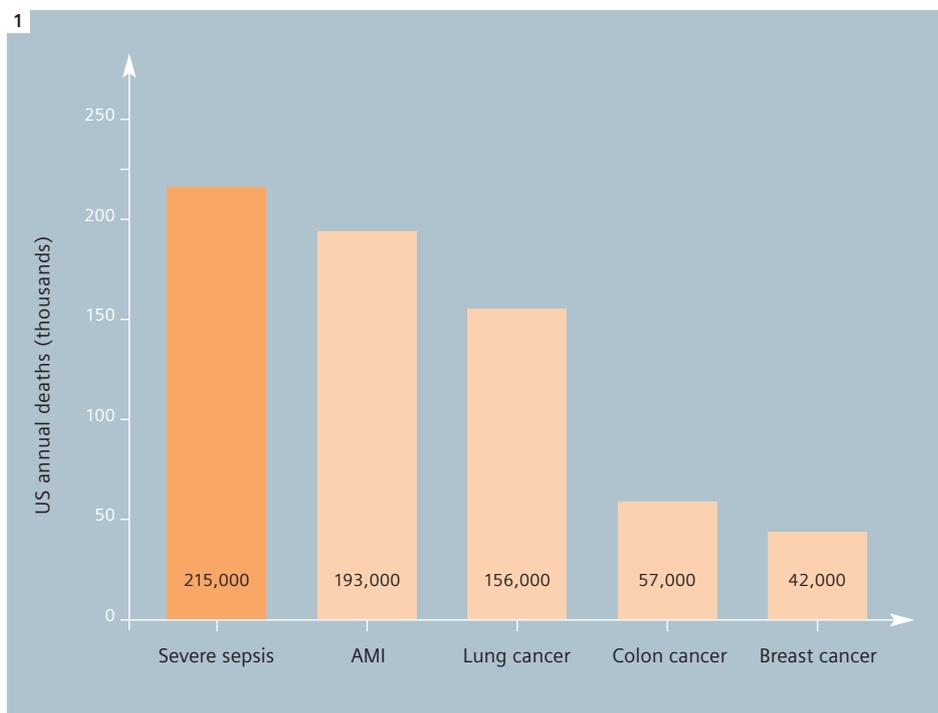
A consensus definition published in 1992 by the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) recognizes the progressive stages of sepsis.<sup>3, 4</sup> Sepsis starts with a systemic inflammatory response syndrome (SIRS) caused by an infection. SIRS is defined as the presence of two or more of the following: body

temperature greater than 38.3 °C or lower than 36 °C; increased heart rate of greater than 90 beats/minute, respiratory rate greater than 30 breaths/minute; and abnormal leukocyte count: either leukocytosis (white blood cell [WBC] count greater than 12,000 cells/mm<sup>3</sup>) or leucopenia (WBC count less than 4000 cells/mm<sup>3</sup>).

Sepsis can progress to severe sepsis and septic shock. Severe sepsis is defined as sepsis accompanied by perfusion abnormalities and organ dysfunction. Many patients may have dysfunction of multiple organs (multiple organ dysfunction syndrome, MODS) or failure of multiple organs. Septic shock is defined as severe sepsis with hypotension that does not respond to adequate fluid replacement. Progression from sepsis to severe sepsis or septic shock is associated with an increased mortality risk for the patient. Thus interrupting this progression through early diagnosis and appropriate treatment is critical.

## The need for earlier detection

The 28-day mortality rate in Figure 2 shows that the mortality increases during the progression to septic shock. In patients with infection/trauma, one-month mortality is approximately 10 percent. Progression to SIRS increases that risk to 20 percent, and progression to sepsis with documented infection will result in 40 percent. The mortality rate dramatically increases to 80 percent when a patient enters septic shock.<sup>5, 6</sup> Once a patient becomes septic, the survival rate drops 6 percent every hour. The diagnostic paradigm "early detection equals better outcomes" holds true for severe sepsis and septic shock. Sepsis is the clinical evidence of infection and the systemic response to infection. In sepsis where bloodstream infection is present, bacteremia accounts for about 80 percent of cases, followed by fungemia, parasitemia, viremia, and other causes.



**1 Mortality rates of major killers in the United States**  
(Reference: [www.sepsis.com](http://www.sepsis.com))

Sepsis is exacerbated by trauma, burns, surgery, increased age, comorbid illness, and a compromised immune system. Before diagnosing the cause of sepsis, intensive care unit (ICU) patients are often put on a cocktail of antibiotics. Once blood culture results are available, which may take from 48 to 72 hours, the antibiotic regimen is adjusted accordingly. An integration of sepsis markers into the diagnostic process may shorten time to detection, increase the accuracy of the clinical diagnosis of sepsis, and may result in earlier treatment.

### The development of sepsis

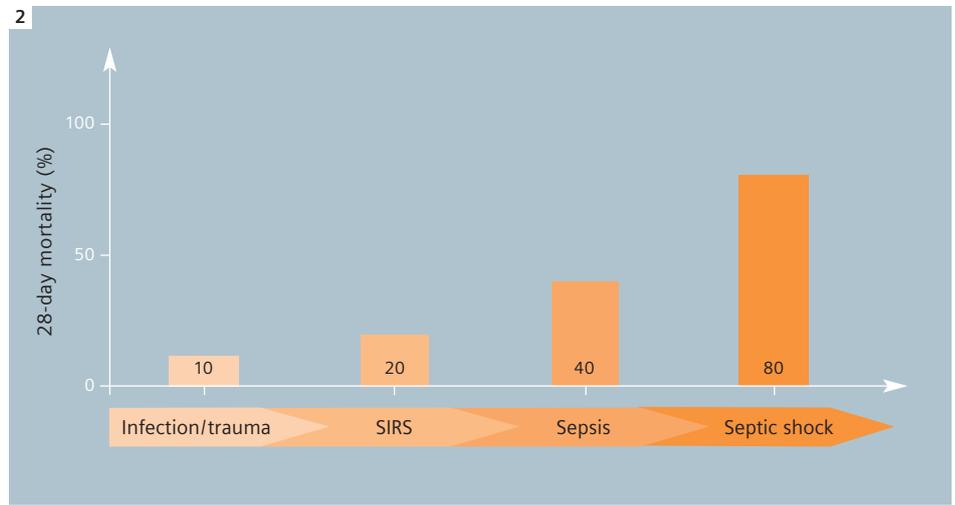
The mechanism of sepsis lies in the interaction of various cytokines, biochemical analytes that play a role in moderating the immune system (Figure 3). When the body senses an infection, proinflammatory cytokines such as IL-6, IL-8, tumor necrosis factor (TNF), etc. are released, signaling cells to flood the area and combat the invading organisms. In immunocompetent (healthy) individuals, anti-inflammatory cytokines such as IL-10 control inflammation, causing it to subside after successfully fighting the infection. In sepsis, however, the interaction between these two signals becomes skewed. A hypoactive (insufficient) inflammatory response can allow the infection to spread completely out of control. Hyperactive inflammation can cause harm to bodily tissues and can disrupt organ function. The precise balance of the immune system is the key to success; sepsis compromises this balance.

### Some promising markers

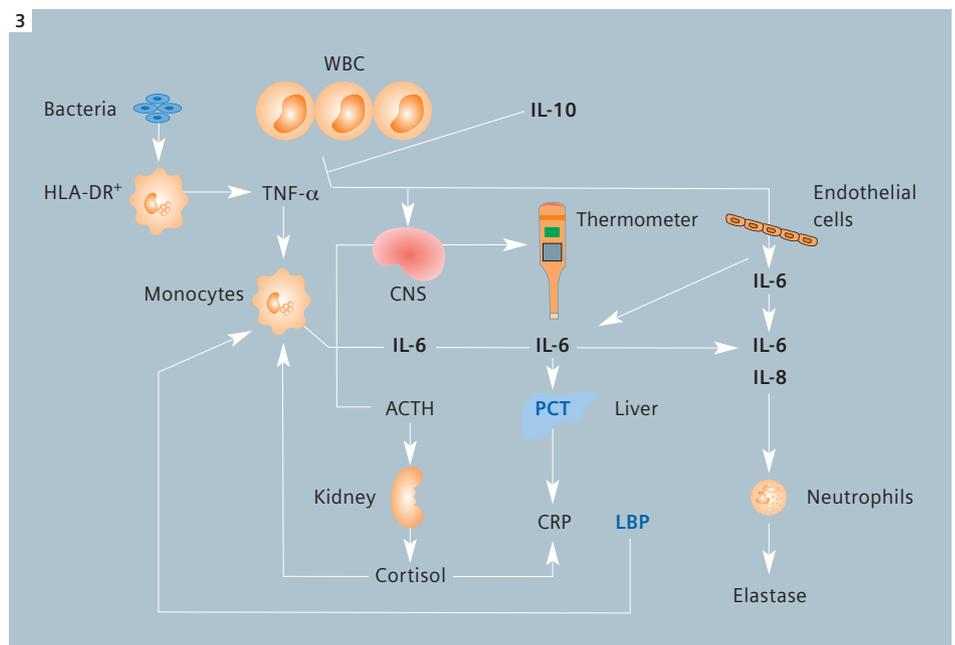
Recent studies have examined various analytes that show promise as markers for identifying septic patients. Procalcitonin (PCT) is currently at the forefront of sepsis research and is proving helpful in reducing the number of false positives in the diagnosis of sepsis. PCT is the precursor of calcitonin, a hormone that is produced in the thyroid gland. It is absent from the blood of healthy individuals. During an infection and subsequent inflammatory response, however, PCT levels increase exponentially over a wide range. This change occurs within hours, providing a valuable and timely snapshot

for identifying affected patients. Such an obvious spike may help diagnose sepsis, or at the very least rule out sepsis from consideration. PCT may also be helpful in monitoring patient treatment as it has a half-life of about 24 hours. Changes can be detected in serum PCT within hours, making it fast enough for clinical use. Antibiotic doses can be progressively adjusted as indicated by PCT velocity, which can reduce costs for hospitals and allow

patients to avoid potentially harmful side effects.<sup>7</sup> PCT has also been shown to predict mortality rates in critically ill patients.<sup>8</sup> This should allow physicians to triage patients, allowing proper decision making and a more beneficial therapeutic approach. B·R·A·H·M·S AG, based in Berlin, Germany, has recently developed and released a PCT assay for the rapid diagnosis of sepsis. Siemens Healthcare Diagnostics, as well as a few other companies, has entered



**2 The progression from infection to septic shock: 28-day mortality rate**  
SIRS, systemic inflammatory response syndrome (Reference: www.sepsis.com)



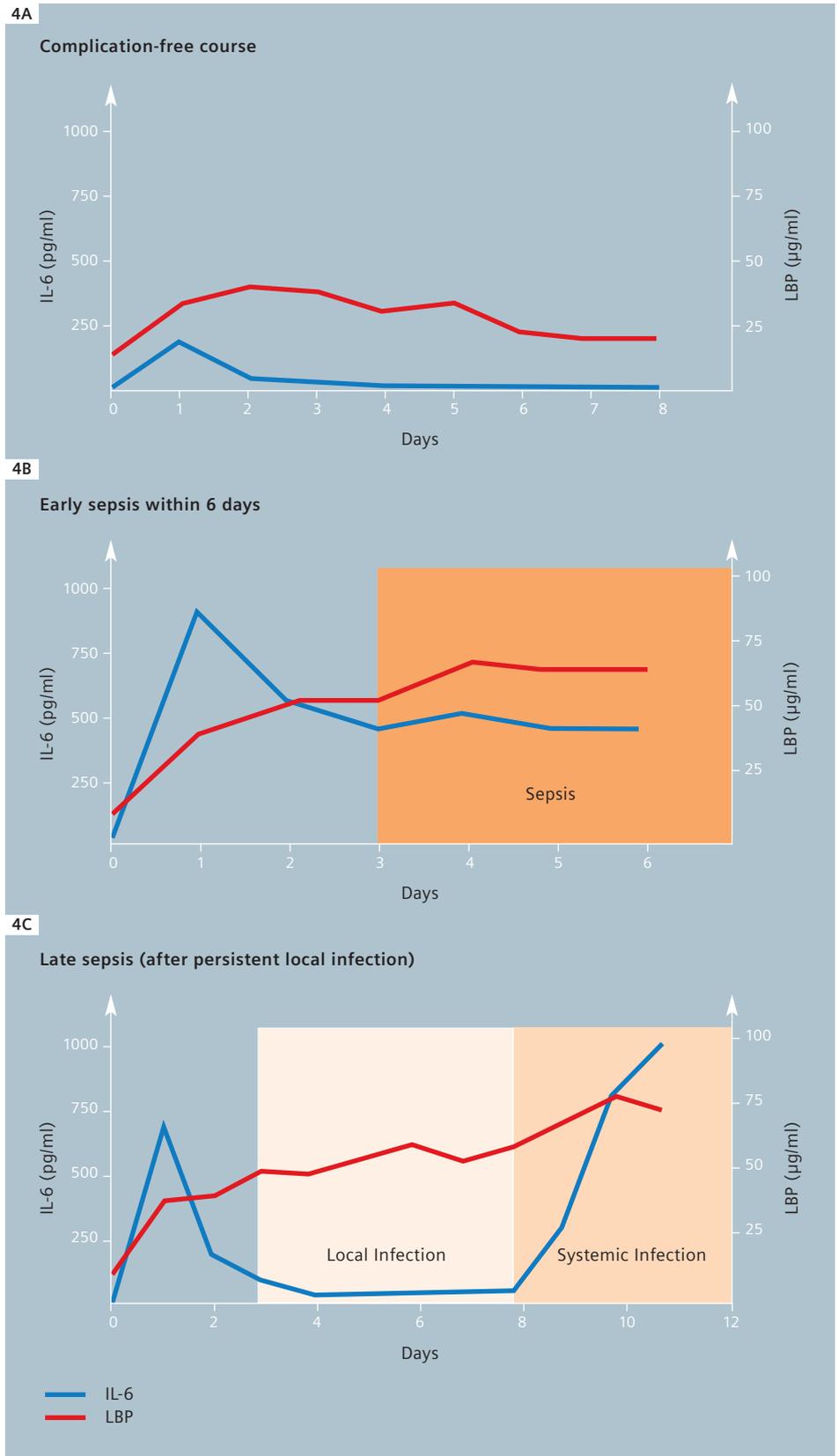
**3 Cytokine network in sepsis**  
ACTH, adrenocorticotropin; CNS, central nervous system; CRP, C-reactive protein; IL, interleukin; LBP, lipopolysaccharide binding protein; PCT, procalcitonin; TNF-α, tumor necrosis factor alpha; WBC, white blood cell (leukocyte)

into cooperation with B·R·A·H·M·S and plans to release a PCT assay on the Siemens immunoassay platforms. Another commonly researched marker for sepsis is IL-6, a proinflammatory cytokine that is released during the onset of an infection. IL-6 levels peak a few hours after inflammation begins and return to normal after a few days of successful immune response (Figure 4a).

In a septic patient, however, the IL-6 levels are significantly increased when compared to a normal response (Figure 4b). After this spike, IL-6 levels stay at abnormally high values, indicating sepsis. These levels may increase again in the case of new infections, or if a local infection becomes systemic. In data collected by Prof. van Griensven,<sup>9</sup> the IL-6 concentration around 150 pg/ml is the discrimination point between local and systemic inflammation. Unfortunately, reliance upon a single measurement often leaves a gray area of false positives and false negatives. The differentiation between local and systemic infections is clinically significant and is made possible by utilizing a second marker in conjunction with IL-6.

This second marker is lipopolysaccharide binding protein (LBP), a protein found on the membrane of cells that binds to structures found on the exterior of various strains of gram-negative bacteria. LBP allows the immune system to recognize the bacterial infection and respond accordingly. During a controlled infection, the LBP levels rise slightly and return to normal after a few days (Figure 4a). These levels increase steadily for a few days during the course of sepsis (Figure 4b). By itself, LBP does not provide significant clinical value; it is nonspecific, and its levels vary among different patients. Thus, LBP alone does not show promise as a diagnostic tool for differentiating between noninfectious SIRS and sepsis.<sup>10</sup> However, when used along with IL-6, it can provide physicians with valuable information. The diagnostic question is, "Is it an local infection, SIRS, or sepsis?"

LBP can provide vital information to help distinguish between local and systemic infections. IL-6 levels may peak and then decline to an inconclusive level, providing little to no information about the status of the infection. However, IL-6 kinetics combined with LBP may provide information whether the infection has spread and become systemic (Figure 4c).



**4 Kinetics of IL-6 and LBP in a surgical patient**  
 IL-6, interleukin 6; LBP, lipopolysaccharide binding protein



Changes can be detected in serum PCT within hours, making it fast enough for clinical use.

Alone, IL-6 is considered a marker of inflammation and LBP a marker of infection. As demonstrated in Figure 4, the combined use of these markers may allow differentiation between SIRS and different levels of sepsis. With the 28-day mortality rate doubling from infection to SIRS and again to sepsis and septic shock as seen in Figure 2, the utility of an IL-6/LBP combination might be helpful for patients such as trauma patients who are at risk for sepsis.

As Dr. Martijn van Griensven concluded in his study, "These parameters together (IL-6 and LBP) allow more differentiated approach for the treatment of multiple trauma patients."<sup>9</sup>

How can this novel approach support therapeutic decision making in patient stratification, determine effectiveness of therapy, and guide the duration of therapy? For patient stratification, we need to decide which patients will require surgical intervention, which patients are at risk to develop infectious complications, and which patients will require antibiotic treatment. Cytokine algorithms can help determine the effectiveness of therapy, either by successful surgical intervention or response to antibiotic treatment. Cytokine kinetics is a tool that may aid

clinicians in assessing the success or failure of antibiotic therapy, and may facilitate earlier implementation of therapeutic changes when needed.

### What needs to happen next

Sepsis has a high mortality rate exceeding that of acute myocardial infarction and common cancers. An important step is increasing public awareness through education. Effective education can make patients and their families effective partners with healthcare providers in the fight against sepsis. Faster and more reliable markers for sepsis need to be developed. This area shows promise. The novel immune monitoring concept shown in Figure 4 involves utilization of a number of cytokines to differentiate between local and systemic infection. The central question surrounding sepsis markers is their clinical utility. Do we have tests that can contribute to good medical practice – in diagnosis, prognosis, and patient monitoring?

As noted earlier, the lethality of sepsis is a consequence of an excessive immunological dysfunction. Immune function monitoring using markers like IL-6, LBP

and PCT can facilitate early recognition of posttraumatic complications, and the early detection of local infection and systemic infection. All of this has tremendous therapeutic implications, and we are hopeful that future research may yield tools that aid in diagnosis, guide therapy and save lives.

A European study documented that over 35 percent of patients were septic sometime during their ICU stay.<sup>11</sup> The question is, "Why?" Infections are common in hospitalized patients and spread easily in the hospital environment. Most hospital personnel are not at risk, as their immune systems can handle the stress. ICU patients, however, cannot cope. Their immune response has already been compromised and contracting an infection can lead to sepsis and death.

Appropriate hand hygiene in clinical settings can mitigate the spread of infection. Another study reported that as few as 30 to 50 percent of healthcare personnel have maintained the recommended hand-washing practice in the past.<sup>12</sup> Antibiotic treatment of catheters has been shown to prevent infection and sepsis.<sup>13</sup> For the prevention of sepsis in infants, screening and treating both mother and child for group B strepto-



coccus (GBS) has been a key. Prophylaxis of GBS has been proven to reduce the rate of sepsis in preterm and term infants.<sup>14</sup>

## Surviving sepsis campaign

The Surviving Sepsis Campaign (SSC), a creation of the European Society of Intensive Care Medicine, the International Sepsis Forum, and the Society of Critical Care Medicine, has published specific guidelines for hospitals dealing with septic patients.<sup>15</sup> The SSC seeks to reduce the incidence of sepsis by 25 percent by 2009 (for more information on the goals of the SSC, visit the website [www.survivingsepsis.org](http://www.survivingsepsis.org)).

## Summary

Sepsis continues to be an important clinical challenge. The use of markers that can aid in the earlier diagnosis of sepsis and its underlying cause is an excellent strategy for decreasing its associated morbidity and mortality and optimizing patient outcomes.

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