Siemens Healthcare Diagnostics, the leading clinical diagnostics company, is committed to providing clinicians with the vital information they need for the accurate diagnosis, treatment and monitoring of patients. Our comprehensive portfolio of performance-driven systems, unmatched menu offering and IT solutions, in conjunction with highly responsive service, is designed to streamline workflow, enhance operational efficiency and support improved patient care.

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IL-6 and LBP: Detection of Infection, Inflammation, and Sepsis

Answers for life.

SIEMENS

Defining Sepsis

Siemens Healthcare Diagnostics is taking an active lead in providing answers to challenges facing intensive care medicine and postsurgical care medicine. By offering biomarkers such as IL-6 and LBP that can be used to help identify patients at risk of progression to sepsis, severe sepsis, and septic shock early in the inflammatory and infective processes, the Siemens portfolio of assays may well provide an innovative approach to monitoring inflammation, infection, and sepsis. Several studies have also indicated that these markers can be an asset in neonatal and pediatric intensive care medicine, and may also be of value in emergency medicine and in outpatient care.

A clinical definition of sepsis was first proposed by Roger Bone in 1989: "Sepsis is an invasion of microorganisms and/or their toxins through the bloodstream in collaboration with the reactions of the organism to this invasion." In 1991 at the Conference of the American College of Chest Physicians (ACCP) and The Society of Critical Care Medicine (SCCM),[1] Bone's definition was expanded to incorporate the role of the systemic inflammatory response syndrome (SIRS) in both the infectious and noninfectious origins of sepsis. The definitions and working model of sepsis were reevaluated and confirmed at the International Sepsis Definitions Conference of the 2001 SCCM/ESICM/ACCP/ATS/SIS (Table 1), although it was recognized that "the signs and symptoms of sepsis are more varied than the initial criteria established in 1991." [2] A model for defining the stages of sepsis was presented (Figure 1), and the PIRO system was proposed for refining sepsis staging and outcome prediction (Table 2). The overarching conference consensus was that the refined definition, diagnostic criteria and staging models should facilitate better bedside diagnosis.

Although biomarker inclusion in guidelines was considered premature at the time, more recent studies suggest that including information derived from biomarkers can aid in diagnosis and risk assessment.

Table 1. Diagnostic criteria for sepsis, severe sepsis, and septic shock.

Infection, documented or suspected, and some of the following	**General variables** • Fever (>38.3°C) • Hypothermia (core temp. <36°C) • Heart rate >90/min or >2 SD above the normal value for age • Tachypnea • Altered mental status • Significant edema or positive fluid balance (>20 mL/kg over 24 hrs) • Hyperglycemia (plasma glucose >140 mg/dL or 7.7 mmol/L) in the absence of diabetes	**Inflammatory variables** • Leukocytosis (WBC count >12,000/µL) • Leukopenia (WBC count <4,000/µL) • Normal WBC count with >10% bands (immature forms) • Plasma C-reactive protein >2 SD above normal • Plasma procalcitonin >2 SD above the normal value	**Hemodynamic variables** At least one indicator of arterial hypotension **Adult:** • SBP <90 mm Hg • MAP <70 mm Hg • SBP decrease >40 mm Hg **Pediatric:** • <2 SD below normal for age
Organ dysfunction variables	• Arterial hypoxemia ($Pa_{O_2}/FI_{O_{10}}$ <300) • Acute oliguria (urine output <0.5 mL/kg/h or 45 mmol/L for at least 2 h, despite adequate fluid resuscitation) • Creatinine increase >0.5 mg/dL or 44.2 µmol/L • Coagulation abnormalities (INR >1.5 or a PTT >60 sec) • Ileus (absent bowel sounds) • Thrombocytopenia (platelet count <100,000/µL) • Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 µmol/L)		
Tissue perfusion variables	• Hyperlactatemia (> upper limit of lab normal) • Decreased capillary refill or mottling		
Pediatric diagnostic criteria	**Signs and symptoms of inflammation plus:** • Infection with hyper- or hypothermia (rectal temperature >38.5°C or <35°C) • Tachycardia (may be absent in hypothermic patients) **And at last one of the following:** • Indications of altered organ function • Altered mental status • Hypoxemia • Increased serum lactate level • Bounding pulse		

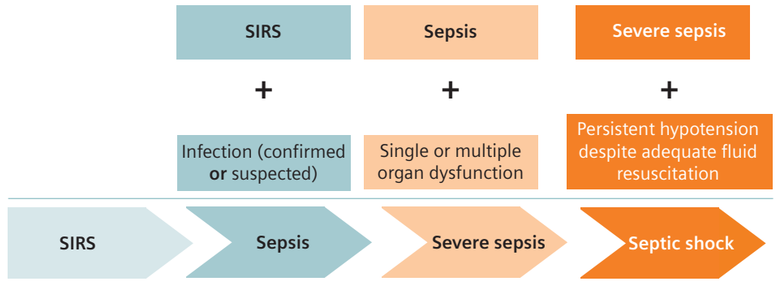


Figure 1. The sepsis continuum.

Table 2. The PIRO model.

Definition	Explanation/examples
Predisposition	• Premorbid illness with reduced probability of short-term survival (e.g., cancer, CVD, pulmonary disease) • Reversibility of disease • Cultural or religious beliefs • Genetic polymorphism resulting in a more aggressive inflammatory response • Age • Sex
Insult infection	• Culture and sensitivity of infecting pathogens • Pathogen detection and identification • Location and extent of infection
Response	• SIRS • Other signs of sepsis • Shock • Prognostic/severity determination by biomarkers (e.g., IL-6, LBP, PCT)
Organ dysfunction	• Number of failing organs • Extent of dysfunction as determined by composite score (e.g., MODS, SOFA, LODS, PEMOD, PELOD)

The first Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock were published in 2004.[3] The protocols in this publication were reevaluated and updated in 2008, and several recommendations for early intervention and care were presented.[4] Kit bundles laying out protocols for treatment and management of severe sepsis and sepsis are available at: http://survivingsepsis.com/implement/bundles.

The Clinical Dilemma

- According to recent estimates, over 18 million cases of sepsis occur worldwide annually, and at least 1/3 of these cases escalate to severe sepsis or septic shock.[2]
- Sepsis affects over 35% of ICU patients, and approximately 2/3 of these patients have severe sepsis or septic shock.[5,6]
- Sepsis is one of the most prevalent causes of morbidity and mortality in the ICU.[7,8]
- Mortality for septic shock can exceed 50%.[5]
- Overall mortality for sepsis (~30%)[8] is approximately 3 to 4 times greater than in-hospital mortality for acute myocardial infarction (~6% to ~12%).[9–12]
- The cost of treating patients with severe sepsis is very high and rises dramatically when ICU treatment and life-support equipment is required (Table 3).[10–23]
- The cost of treating nonsurvivors is typically greater than the cost for treating survivors.[10–23]
- Sepsis costs can account for up to 42% of total ICU expenditures.[13]
- Increasing patient age, greater use of invasive devices, and more complex surgical procedures have led to an increase in the incidence of sepsis.[3]

Table 3. Incidence and financial burden of sepsis.

Country	~ Total severe sepsis	Total pop (million)	Publication year	# per 100,000 pop.	% ICU pop.	Median LOS [a] (days)	Mean cost/case	National cost, (local currency, million)
Australia[14]	15,000[b]	20.1	2003	77	11.8	7[c]	N/A	N/A
US (total)[15]	751,000	278.1	2001	300	11.8[16]	20[d]	$22,100	$16,700
US (pediatric)[17]	42,364		2003	56	N/A	31[d]	$40,600	$1,970
UK[18]	27,926	54.8	2003	51	27.1	3.56[c] 18[d]	€3,802 – €17,963[19]	N/A
Norway[20]	2,121	4.5	1999	50	N/A	16.1[d]	€35,906[21]	N/A
The Netherlands[22]	9,000	16	2001	54	11	13.3[d]	€I9,500[23]	€168.6[23]
Germany[24]	44,000 – 95,000	82	2002	54 – 116	N/A	16.6[c]	€23,297	€3,647 – €7,874[e]
France[25,26]	56,540	59.6	2005	95	14.6 – 16.6	25[c]	€22 800	N/A
Brazil[27]	N/A	176	2001-2	35.6[f]	6.3	4[c]	N/A	N/A

[a] LOS = length of stay; in most cases, average LOS longer for survivors than for nonsurvivors
[b] Extrapolated from total number of annual cases
[c] ICU population only
[d] Hospital population
[e] Direct and indirect costs
[f] Per 1000 patient-days

In October 2002, during the congress of the European Society of Intensive Care Medicine in Barcelona, clinicians from all over the world published a declaration that drew attention to the alarmingly high rate of sepsis mortality. Their goal was to reduce the death rate from sepsis by 25% over 5 years. The resulting Surviving Sepsis campaign emphasizes the importance of rapid recognition and medical response.

Necessity of Early Diagnosis

It is difficult to diagnose sepsis early, when intervention can be most effective. Without a single, definitive diagnostic test, the clinician must rely on a combination of laboratory and clinical information to make the diagnosis. Thus, the biggest impediments to achieving the Surviving Sepsis goals are the difficulties in diagnosing sepsis, distinguishing sepsis from SIRS, and predicting which patients with SIRS or a localized infection are likely to develop a more dangerous septic response. While several illness severity models have been proposed, most rely heavily on events that are generally not observed until sepsis has progressed to septic shock. Currently, sepsis most frequently is not diagnosed until after organ dysfunction or failure is already evident, when it is much more difficult to treat and the patient is more likely to suffer a negative outcome.[4]

Early diagnosis of infection and sepsis is essential:

- Early detection and treatment of local infection can prevent systemic spread.
- The odds ratio of death increases by 7.6% for every hour of delay of appropriate treatment in septic shock (Figure 2).
- An accurate estimation of the extent and the origin of excessive inflammation could help direct effective and specific treatment.
- As with most diseases, early treatment is likely to be less expensive and more effective than if the disease is more advanced or severe.

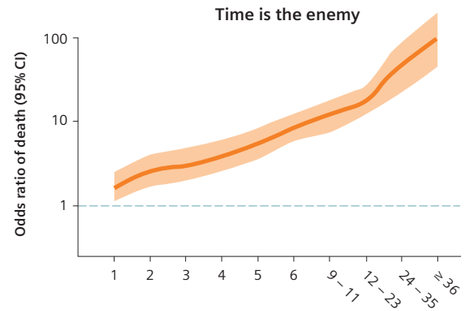
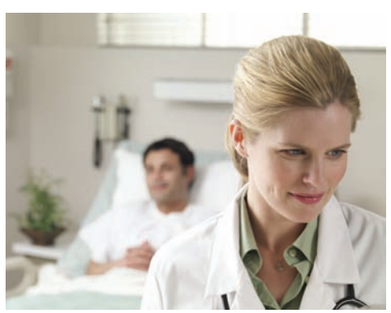


Figure 2. The risk of death increases when appropriate treatment is delayed: every hour of delayed treatment decreased survival by 7.6% (colored background indicates the 95% CI).[28]



Innovative Diagnostics

Measurement of interleukin-6* (IL-6), a marker of acute inflammation, and lipopolysaccharide-binding protein* (LBP), a transport molecule that recognizes bacterial and fungal invaders, can provide valuable information to clinicians about the extent of a patient's inflammation and the potential severity of infection. Used together, these assays can help reveal a clearer clinical picture of immune status in patients being monitored for postsurgical or posttraumatic infection, and potentially sound an alarm before other signs and symptoms become apparent.

*CE marked. For research use only in the US.

IL-6

IL-6 is an early indicator of inflammatory response to illness or injury. It rises within hours of substantial injury or infection (Figure 3). With a half-life of 45 minutes, IL-6 can be monitored to reveal if a patient is suffering an acute response to surgery, trauma, or infection, and if the response is waning slowly or rapidly, which can help to predict the patient's risks and prognosis.[29–31]

- IL-6 can help to predict infection at the onset of a new fever before microbiological culture results are available[32] and can alert the clinician that the patient has a greater postsurgical sepsis risk before other signs and symptoms appear.[33]
- IL-6 levels can help predict if a patient with hospital-acquired pneumonia is likely to progress to septic shock.[34]
- Elevated IL-6 can indicate late-onset neonatal sepsis 1–2 days before sepsis manifests clinically.[35]
- IL-6 levels are predictive of outcome.[29,30]
- IL-6 can be measured quickly and easily on the IMMULITE® random access automated systems under routine or emergency circumstances. The assay is calibrated to the WHO 1st IS 89/548 IL-6 standard.

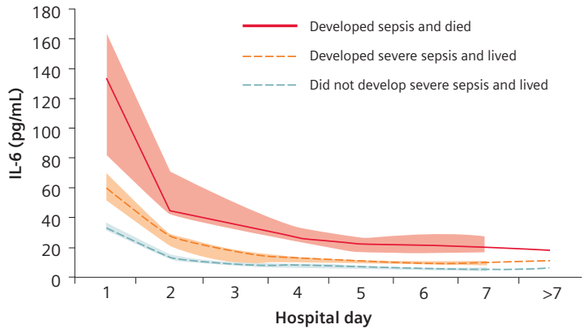


Figure 3. IL-6 kinetics and association with mortality (colored backgrounds indicate the 95% CIs).[29]

LBP

LBP is a well-documented mediator molecule of the immune system. It is induced within a few hours of exposure to gram-positive and gram-negative bacteria, and also rises in the presence of pathogenic fungi (Figure 4).[36] LBP kinetics are shown in Figure 5.[37]

- An increased LBP level above the normal reference level can alert the clinician to the onset of a severe local infection, a systemic bacterial or fungal infection, or septicemia.[38]
- LBP can assist in differentiation between bacterial or fungal sources of infection vs. other pathogenic or aseptic causes of inflammation (e.g., viral, parasitic, trauma, surgery, pancreatitis).[39]
- LBP can indicate infection in neutropenic patients.[40]
- LBP may be the best indicator of early- and late-onset neonatal sepsis.[41,42]
- A new study suggests that LBP may be a useful aid for differentiating between pneumonia and bronchitis in a community healthcare setting.[43]
- LBP levels are predictive of outcome, including lung injury and death, and serial measurements may help to alert the clinician to patients who could benefit from extra vigilance and early intervention.[44]

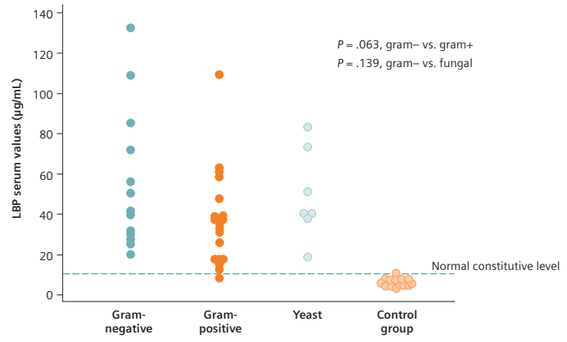


Figure 4. LBP rises in gram-positive, gram-negative, and fungal infections.[39]

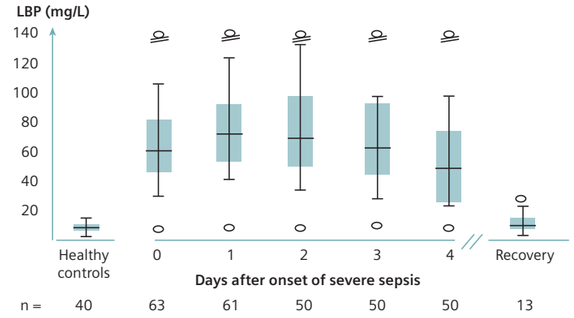


Figure 5. LBP kinetics.[37]

Case Studies

Graphs showing daily LBP and IL-6 profiles monitored in three general surgical patients illustrate how these biomarkers can reflect patient infection and immune function status (reference ranges: IL-6, <10 pg/mL; LBP, <15 mg/mL) (Figures 6–8).

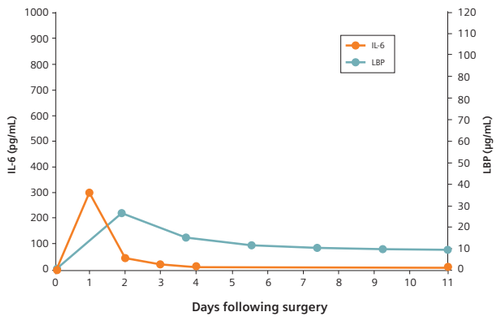


Figure 6. Patient 1 with a complication-free course following surgery (day 0 = surgery).

- Day 1: Moderate IL-6 increase at day 1 (postsurgery).
- Day 2: Fast decrease of IL-6 to almost normal values, moderate LBP increase (postsurgery).
- Day 3: Constant decrease of LBP levels after surgery, tendency to normalization.

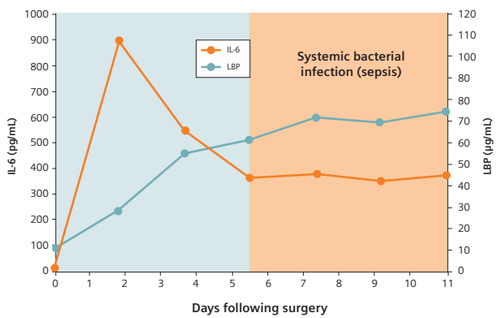


Figure 7. Patient 2 developed sepsis within 6 days of surgery.

- Day 1: Significant IL-6 increase (hyperinflammatory response >500 pg/mL).
- Day 3: Decreased IL-6, but levels still >100 pg/mL, indicating persistent systemic inflammation.
- Day 4: Significant and persistent increase of LBP accompanied by persistently high levels of IL-6.

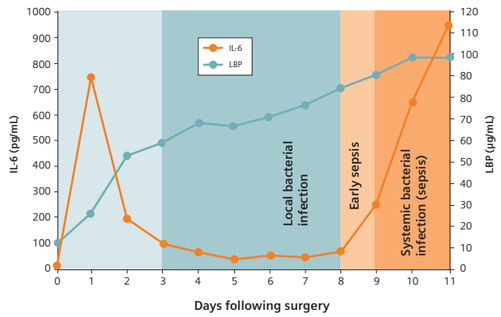


Figure 8. Patient 3 developed sepsis after several days of persistent local infection.

- Day 1: Significant IL-6 increase (hyperinflammatory response >500 pg/mL).
- Day 2: Continuous and steady increase of LBP, reflecting persistent local infection.
- Day 3: Decreasing IL-6 to levels of <100 pg/mL, but persistent systemic inflammation (IL-6 levels 15 to150 pg/mL).
- Day 9: IL-6 increase >100 pg/mL and high levels of LBP signalling onset of sepsis.

Reducing ICU Costs

Sepsis is a costly disease with a significant impact on national healthcare systems (Table 3) because of the number of interventions and medications required, and because of the extended time sepsis patients remain in the hospital. The necessity of ICU care increases hospitalization costs over extended general ward care as well. Reducing the average patient stay could lead to tremendous savings. Monitoring infection and immune function using IL-6 and LBP can make an important contribution to these efforts because it provides the clinician with valuable decision-making tools and the possibility of detecting sepsis earlier, when treatment might be easier to administer and more effective.

The following example highlights the annual costs of sepsis estimated within the German healthcare system for a 400-bed hospital (Figure 9).

Standard ICU care for a septic patient costs €1,318 per day, and the average patient stay is 17 days.[24]

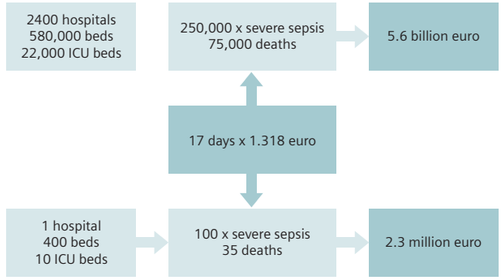


Figure 9. Annual cost of sepsis in Germany.

Monitoring 100 patients with IL-6 and LBP each day for 17 days would cost well less than €50,000 per year, which corresponds to less than 1.5% of the current total expense for sepsis patient care. Assuming that infection and immune function monitoring, with associated therapeutic results, can reduce the average patient stay from 17 to 16 days (a minimum expectation), the expenses would be reduced by 6%, or nearly 5 times the investment in laboratory diagnostics.

Monitoring of infection and immune function, however, offers much more than financial benefits:

- Earlier recognition of postsurgical and posttraumatic complications and risks[45]
- Earlier detection of local infection (which can be crucial for avoiding sepsis)
- Earlier detection of systemic infection.

A lead time of 1 to 2 days provides the clinician with extra time to effectively treat the patient. Important therapy decisions can be made earlier, leading to a reduction in follow-up costs:

- Earlier microbial culturing and identification
- Earlier treatment of local infection by surgery or antibiotic treatment
- Earlier verification of the success of antibiotic treatment.

Earlier detection and treatment may prevent the development of severe sepsis or septic shock, further reducing cost of care and improving patient outcome as well as quality of life.

Conclusion

Siemens Healthcare Diagnostics offers an extensive portfolio of tools, including IL-6 and LBP immunoassays, that can aid in sepsis diagnosis and care in the contexts of inflammation/anti-inflammation and immunocompetence, hemostasis, blood gas, hematology, microbiology, and clinical chemistry. An early and accurate diagnosis can save precious time, expense, and most importantly, lives.

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