

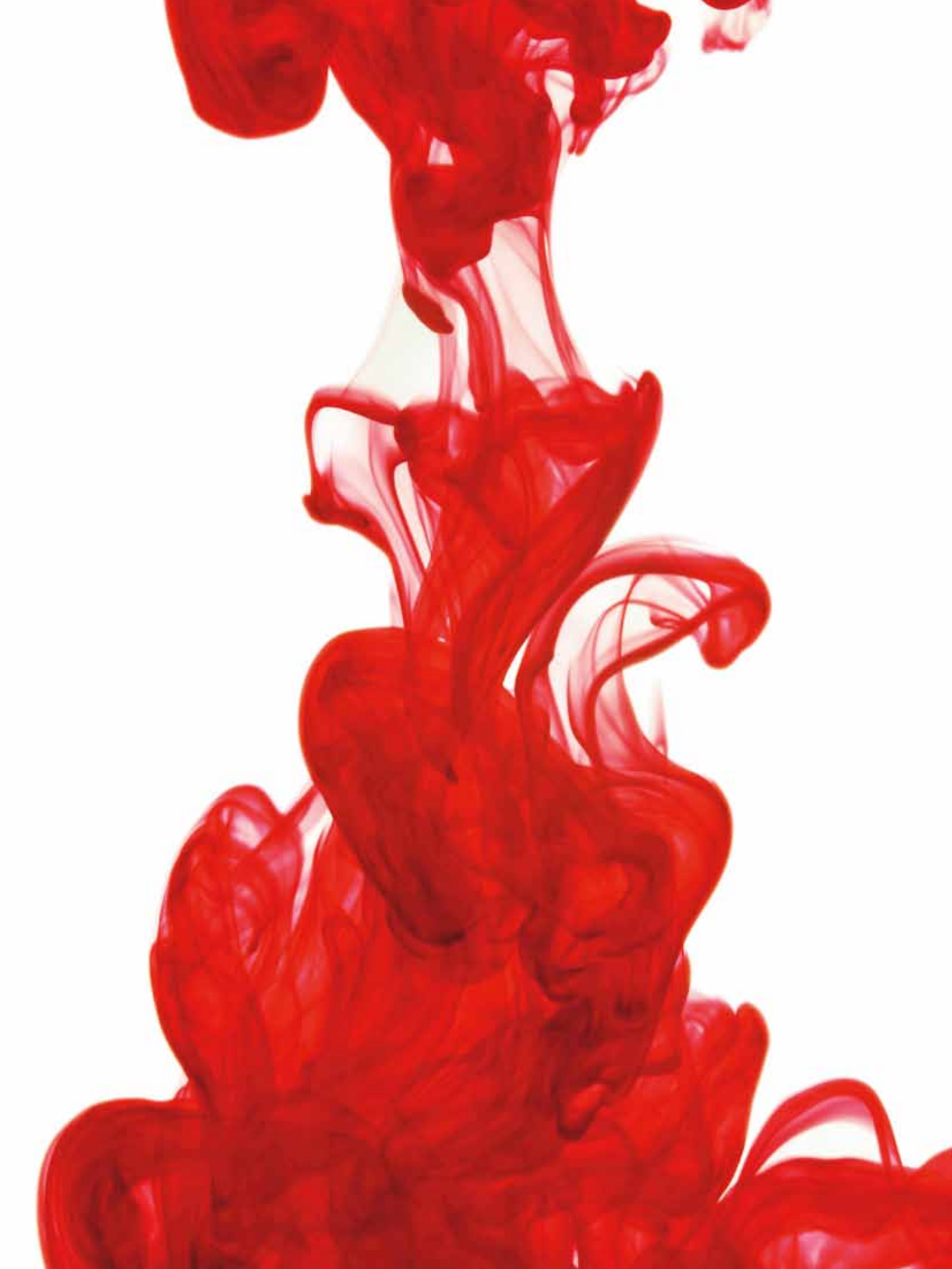
# A New Aid for Identifying Sepsis

**Sameh Fahmy**

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# A New Aid for Identifying Sepsis

The measurement of BRAHMS procalcitonin, a diagnostic biomarker, aids clinicians in identifying patients with sepsis and has also been shown to reduce unnecessary antibiotic use. The positive outcomes experienced at hospitals such as the Swedish Covenant Hospital in Chicago, Illinois, USA, are confirmed by several clinical trials, including a recent large, multicenter study conducted in Switzerland.

By Sameh Fahmy, MS

A patient in the intensive care unit (ICU) has a fever, a rapid heart rate, an elevated respiratory rate, or an abnormal white blood cell count. These symptoms could herald the onset of sepsis, a life-threatening systemic inflammatory response to infection, or they could be the result of trauma or a host of other conditions. Results from blood cultures have a high rate of false negatives – 40 percent in one study<sup>1</sup> – and will not be available for up to 72 hours. The clock is ticking, and every hour of delayed treatment increases the likelihood of death.<sup>2</sup> Inappropriate antibiotic use can cause adverse side effects for the patient and encourage the development of drug-resistant bacteria

Fortunately, there is a better option. By measuring serum levels of the protein procalcitonin (PCT), clinicians can identify patients at risk for sepsis early and begin treatment when it is most likely to be effective.

The BRAHMS PCT assay is available on the Siemens ADVIA Centaur<sup>®</sup> XP and ADVIA Centaur CP Immunoassay Systems.\* This PCT assay also allows clinicians to monitor response to treatment and tailor antibiotic therapy accordingly.

“PCT gives you more confidence in your decision-making about when to start antibiotics, when antibiotics are not working, and when to stop antibiotics,” says Eric Gluck, MD, Director of Critical Care Services at Chicago’s Swedish Covenant Hospital and Professor of Medicine at Finch University of Health Sciences/The Chicago Medical School. “Nothing else correlates with those three endpoints as well as PCT does.”

Swedish Covenant, a 323-bed academic hospital, has been using the BRAHMS PCT assay on Kryptor<sup>®</sup> since 2007 and has seen significant decreases in antibiotic usage in the ICU and a decreased average length of stay in patients with sepsis. Performance evaluation trials of

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BRAHMS PCT on ADVIA Centaur XP were conducted at Swedish Covenant using performance evaluation-only reagents, calibrators, and controls. Several studies<sup>3-8</sup> within the past decade have shown the benefits of BRAHMS PCT guidance in reducing unnecessary antibiotic usage as well as associated adverse side effects, including a large multicenter clinical trial recently published in the *Journal of the American Medical Association (JAMA)*.<sup>9</sup>

## A Growing Threat

An estimated 215,000 annual deaths are attributed to sepsis in the United States alone, making it more deadly than common cancers such as lung cancer, colon cancer, and breast cancer. Worldwide, 18 million cases occur annually, with an average cost per patient of US\$22,100.<sup>10</sup> An aging population and the increasing use of invasive procedures are making sepsis even more common, with the rate of sepsis increasing by an estimated 1.5 percent every year.<sup>10</sup> A rapid and accurate diagnostic tool is critical, because the prognosis for patients with sepsis is best when the condition is recognized and treated early.<sup>11</sup> If a patient progresses to severe sepsis, defined as sepsis and organ dysfunction, mortality can jump to 52 percent. If a patient enters septic shock, the mortality rate can jump to 82 percent.<sup>12</sup> “The data has demonstrated very clearly that the sooner you start antibiotics, the better the outcomes will be,” says Gluck.

## Rapid, Accurate Diagnosis

PCT is a protein that is normally produced in small amounts in the thyroid gland. In patients with sepsis, however, the protein is produced in large quantities by the liver, kidney, fat cells, and muscle. Increasing serum PCT concentrations indicate increased severity of infection and a worse prognosis for the patient. Using the ADVIA Centaur XP and ADVIA Centaur CP Systems\*, clinicians can receive results in less than 30 minutes. Swedish Covenant began using the BRAHMS PCT assay on Kryptor in 2007 after conducting clinical trials to

# “Patients in the BRAHMS PCT group had a 30-percent reduction in the rate of antibiotic-related side effects.”

Philipp Schuetz, MD, Department of Emergency Medicine,  
Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA

assess its sensitivity and specificity. “We found that the assay had a sensitivity of 91 percent in the identification of patients who were septic and a specificity of 98 percent to identify patients who do not have sepsis,” Gluck said. “And that was better than anything else that we had available to us at the bedside in our hospital – none of the blood tests or physical findings got us anywhere near those kind of results.”

Gluck says that in many cases, patients would have received a much later diagnosis of sepsis and would have likely had a worse outcome had it not been for the PCT assay. One patient, for example, was brought to the emergency department by family members after intentionally overdosing on prescription medications. An elevated white blood cell count was thought to be the result of stress of the overdose. However, the treating physician ran a PCT assay to corroborate the finding, now a routine practice at Swedish Covenant. An elevated PCT level strongly suggested infection, so the patient was given antibiotics. When results from blood cultures became available the next day and were followed by an ultrasound, it became clear that the patient had cholecystitis, or inflammation of the gallbladder, accompanied by infection. “In this particular patient, I’m not sure if we would have ever made the diagnosis,” Gluck says, “because the patient couldn’t give us a history.”

## Measurable Reductions in Antibiotic Use

A large-scale, multicenter trial recently published in *JAMA*, led by Philipp Schuetz, MD, University Hospital in

Basel, Switzerland, showed that the use of BRAHMS PCT can help rule out bacterial infection, especially in patients with chronic obstructive pulmonary disease (COPD) and bronchitis, and reduce the duration of antibiotic use in patients with diagnosed infection. Schuetz says that while previous studies were consistent with these findings, they were not large enough to assess whether patients treated with PCT-based guidelines had comparable rates of disease-related complications. To answer that question, Schuetz and a team of researchers compared treatment based on PCT guidance against standard care in a randomized controlled trial involving more than 1,300 patients with lower respiratory tract infections at six tertiary care hospitals in Switzerland. According to the study’s guidelines, antibiotics were strongly discouraged if PCT was less than 0.1 µg/L, discouraged if levels were 0.25 µg/L or lower, encouraged if PCT was higher than 0.25 µg/L and strongly encouraged if levels were above 0.5 µg/L. Overruling of the guidelines was possible by prespecified criteria, such as immediate need for ICU admission or respiratory or hemodynamic instability. In patients given antibiotics, PCT measurements were repeated after three, five, and seven days of treatment. The guidelines recommended stopping antibiotics if PCT levels decreased by 80 percent.

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## Summary

### Challenge:

- Identifying patients with sepsis early, when treatment is most likely to be effective
- Reducing the high cost associated with treating patients with severe sepsis and septic shock
- Differentiating sepsis from other inflammatory diseases, trauma, and other conditions, whose symptoms can mimic sepsis
- Reducing unnecessary antibiotic usage and its associated costs and side effects

### Solution:

- Measurement of serum levels of the biomarker BRAHMS procalcitonin, allowing physicians to rapidly identify patients with sepsis
- Early identification of sepsis using procalcitonin, allowing for treatment to be initiated sooner, potentially reducing costly complications associated with sepsis
- Measuring procalcitonin levels, helping rule out bacterial infection in patients whose symptoms mimic those of sepsis
- Negative BRAHMS PCT result indicates that antibiotics may not be necessary; in patients with bacterial infection, serial measurement of PCT helps guide treatment, helping ensure that patients receive optimum duration of antibiotics

### Result:

- Patients receive appropriate treatment quickly, improving likelihood of survival<sup>2</sup>
- Early and appropriate treatment for sepsis may result in reduced co-morbidities, with potential cost savings associated with shorter lengths of stay<sup>7</sup>
- Antibiotics given only to patients who need them, and for optimum duration, resulting<sup>5, 6, 7, 9</sup> in reduction of adverse side effects and minimization of potential for the development of drug resistant bacteria<sup>9</sup>
- Inappropriate antibiotic usage dramatically reduced<sup>5, 6, 7, 9</sup>, resulting in potential cost savings, fewer adverse side effects<sup>9</sup>, and potentially shorter lengths of ICU stay<sup>7</sup>

those treated without knowledge of procalcitonin levels, the risk for adverse events was the same,” says Schuetz, who is currently engaged in research at the Department of Emergency Medicine at Beth Israel Deaconess Medical Center in Boston, Massachusetts, USA. “Patients had the same mortality, they had the same ICU admissions rate, and – importantly – they had the same rate of recurrent infections.”

Notably, the researchers also found that patients in the procalcitonin group had an average antibiotic exposure nearly 35 percent less than the control group. Schuetz points out that the pattern of reduction varied depending on diagnosis. The study found that patients with pneumonia were treated with fewer days of antibiotics than the control group, while patients with exacerbations of chronic obstructive pulmonary disease (COPD) and bronchitis were less likely to have antibiotics initiated than the control group.

The reduction in antibiotic use also translated to better patient care. Schuetz points out that patients in the PCT group had a 30-percent reduction in the rate of antibiotic-related side effects such as nausea, diarrhea, and rash.

## Integrating PCT into Clinical Routines

BRAHMS PCT guidance has also been shown to be useful in reducing antibiotic use in primary care settings, and preliminary data from Gluck and his colleagues suggest that measuring PCT when a patient presents to the emergency department can reduce unnecessary blood cultures.

Administering the assay is inexpensive, Gluck notes, especially when compared to the high cost of treating a septic patient and the potential cost savings from reductions in antibiotic use and shorter lengths of stays.

Although the data regarding the value of PCT guidance are convincing, both Schuetz and Gluck acknowledge that physicians are initially hesitant to alter well-established treatment practices.

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Eric Gluck, MD, Director of Critical Care Services, Swedish Covenant Hospital, Chicago, Illinois, USA

“In the beginning, you have to reassure physicians that the algorithm is safe,” Schuetz says, “but once physicians start using it, they realize that what they have been doing for all of these years – over-treating patients with antibiotics – was not necessary.”

Gluck introduced his colleagues at the hospital to the BRAHMS Kryptor PCT assay in a large, general instruction session that covered the benefits of the assay and emphasized that it does not replace medical judgment or other diagnostic tests. The assay, he

explained, is a tool to help physicians make more informed decisions. An initial utilization in the ICU was later expanded to infectious disease physicians, the emergency department, and eventually to the entire hospital. Gluck says that Swedish Covenant has so much confidence in the assay that it has implemented a hospital-wide policy indicating that physicians should discontinue antibiotics if PCT levels are negative in two measurements 24 hours apart.

“One of the most important dictums in medical ethics is ‘do no harm,’” Gluck notes. “And by treating patients with antibiotics when they don’t need them, you’re exposing them to some possibility of harm. So, it makes my conscience much clearer to know that when I leave the hospital, I have significantly reduced the number of patients who receive unnecessary antibiotics. And it also makes me feel comfortable that in the likelihood that the patient needs antibiotics, I will know about it as fast or faster than anybody else practicing critical care medicine.”

*Sameh Fahmy, MS, is an award-winning freelance medical and technology journalist based in Athens, Georgia, USA.*

## Sepsis by the Numbers

Sepsis is not a specific disease, but rather a continuum of events triggered by the body’s inflammatory immune response to bacterial, fungal, parasitic, or viral infections. The statistics below demonstrate the high toll it exacts.

- Approximately 18 million sepsis cases estimated yearly worldwide<sup>1</sup>
- Sepsis affects more than 35 percent of ICU patients<sup>1</sup> and manifests in approximately 2/3 of these patients as severe sepsis or septic shock<sup>13</sup>
- Approximately 28.6 percent average overall mortality for sepsis, severe sepsis, and septic shock<sup>12</sup>
- Up to 82 percent mortality for patients with septic shock<sup>12</sup>
- Once a patient is in septic shock, survival rates can drop 7.6 percent for every hour that antibiotic therapy is delayed<sup>2</sup>
- U.S. estimated cost exceeds US\$17 billion annually, with average cost per patient of US\$22,100<sup>10</sup>
- Incidence of sepsis is increasing by approximately 1.5 percent per year and is expected to continue growing as the population ages<sup>10</sup>

- <sup>1</sup> Vincent J.L., et al. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med.* 2006 Feb; 34(2):344-53.
- <sup>2</sup> Kumar A. et al. Duration of hypotension prior to initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med.* 2006; 34(6):1593.
- <sup>3</sup> Briel M., Schuetz P., Mueller B., et al. Procalcitonin-guided antibiotic use vs a standard approach for acute respiratory tract infections in primary care. *Arch Intern Med.* 2008; 168(18):2000-2007.
- <sup>4</sup> Briel M., Christ-Crain M., Young J., et al. Procalcitonin-guided antibiotic use versus a standard approach for acute respiratory tract infections in primary care. *BMC Fam Pract.* 2005; 6:34.
- <sup>5</sup> Christ-Crain M., Jaccard-Stolz D., Bingisser R., et al. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections. *Lancet.* 2004; 363(9409):600-607.
- <sup>6</sup> Christ-Crain M., Stolz D., Bingisser R., et al. Procalcitonin guidance of antibiotic therapy in community acquired pneumonia: a randomized trial. *Am J Respir Crit Care Med.* 2006; 174(1):84-93.
- <sup>7</sup> Nobre V., Harbarth S., Graf J.D., et al. Use of procalcitonin to shorten antibiotic treatment duration in septic patients. *Am J Respir Crit Care Med.* 2008; 177(5):498-505.
- <sup>8</sup> Stolz D., Christ-Crain M., Bingisser R., et al. Antibiotic treatment of exacerbations of COPD. *Chest.* 2007; 131(1):9-19.
- <sup>9</sup> Schuetz P., et al. Effect of procalcitonin-based guidelines vs. standard guidelines on antibiotic use in lower respiratory tract infections. *JAMA.* 2009; 302(10):1059-1066.
- <sup>10</sup> Angus D.C., Linde-Zwirble W.T., Lidicker J., Clermont G., Carcillo J., Pinsky M.R. Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. *Crit Care Med.* 2001; 29(7):1303-1310.
- <sup>11</sup> Rivers E., et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *NEJM.* 2001; 345(19):1368-77.
- <sup>12</sup> Salvo L., et al. The Italian sepsis study: preliminary results on the incidence and evolution of SIRS, sepsis, severe sepsis, and septic shock. *Intensive Care Med.* 1995; 21 Suppl 2:S244-9.
- <sup>13</sup> Kumar A. et al. Duration of hypotension prior to initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med.* 2006; 34(6):1953
- <sup>14</sup> Brun-Buisson C. The epidemiology of the systemic inflammatory response. *Int Care Med.* 2000; 26:s64-74.
- <sup>15</sup> Vincent J.L., et al. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med.* 2006 Feb; 34(2):344-53.
- <sup>16</sup> Alberti C., et al. Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. *Int Care Med.* 2002; 28:108-21.

### Further Information

[www.siemens.com/sepsis](http://www.siemens.com/sepsis)

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#### **Global Siemens Headquarters**

Siemens AG  
Wittelsbacherplatz 2  
80333 Muenchen  
Germany

#### **Global Siemens Healthcare Headquarters**

Siemens AG  
Healthcare Sector  
Henkestrasse 127  
91052 Erlangen  
Germany  
Phone: +49 9131 84-0  
[www.siemens.com/healthcare](http://www.siemens.com/healthcare)

#### **Global Division**

Siemens Healthcare Diagnostics Inc.  
1717 Deerfield Road  
Deerfield, IL 60015-0778  
USA  
[www.siemens.com/diagnostics](http://www.siemens.com/diagnostics)

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