THE CCU CORNER

Early Goal-Directed Therapy for Septic Shock

BY GEORGE PHILIPPIDES, M.D., AND ERIC H. AWTRY, M.D.

The Patient

An 81-year-old diabetic man with a history of ischemic cardiomyopathy presented to the emergency department with fever, left-leg pain, fatigue, loss of appetite, and confusion 3 weeks after having coronary artery bypass graft surgery.

His temperature was 38.6° C, his BP was 90/50 mm Hg, and his heart rate 120 bpm. Oxygen saturation was 94% after administration of a 2-L/min nasal cannula. Significant physical findings included an inflamed, swollen, and tender saphenous vein–graft harvest site.

Initial laboratory results included a white blood count of 19,000 with 89% granulocytes, and hematocrit of 29.5%. Arterial blood chemistry revealed a pH of 7.32, carbon dioxide partial pressure of 40 mm Hg, and oxygen partial pressure of 88 mm Hg. Urinalysis showed multiple red blood cells and leukocytes.

Blood and urine cultures were obtained, and the patient was started on broad-spectrum antibiotics for a presumptive diagnosis of sepsis.

The Problem

Sepsis is a clinical syndrome of systemic inflammation, (temperature >38.5° C, heart rate >90 beats per minute, respiratory rate >20 breaths per minute, WBC >12,000 cells/mL) in response to a documented infection. Over 750,000 cases of sepsis and septic shock occur in the United States each year, resulting in over 200,000 deaths. Mortality due to sepsis and septic shock is about 40%-50%.

Pathophysiology of Sepsis

Left untreated, the systemic inflammatory response of sepsis can trigger an array of circulatory derangements including intravascular volume depletion, vasodilation, myocardial depression, and increased metabolism, resulting in a pathologic imbalance between tissue oxygen demand and supply. The resultant global tissue hypoxia, or shock, often precedes the development of multisystem organ failure and death. Similar to acute MI or stroke, timely diagnosis and treatment in the "golden hours" before irreversible tissue and organ damage have occurred, is the key to improving outcomes.

Therefore, most clinical guidelines, including the recently published Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2008 (Crit. Care Med. 2008;36:296-327), focus on early identification and rapid correction of hypoxemia and hypotension.

Early Management of Sepsis: The Data

All patients with sepsis should have their perfusion status carefully assessed. Clinical signs of hypoperfusion include confusion; cool, clammy, vasoconstricted skin; oliguria; and hypotension. An arterial catheter is helpful in monitoring patients with labile BP, since a sphygmomanometer is often unreliable in hypotensive patients. Because hypoperfusion can still occur in normotensive patients, a central venous catheter should be placed after initial assessment to monitor central hemodynamics, central venous oxygen saturation, and blood chemistries, and as an access port for the infusion of medications and blood products.

Once hypoperfusion has been diagnosed, aggressive "protocolized" resuscitation is crucial to staving off the development of multisystem organ failure. During the first 6 hours of resuscitation, the following goals should be targeted:

- Central venous pressure 8-12 mm Hg
- Urine output greater than 0.5 mL/kg per hour
- Mean arterial pressure (mAP) greater than 65 mm Hg
- Central venous oxygen saturation ($ScvO_2$) greater than 70%

These clinical targets were derived from a landmark trial in which 263 patients presenting to an urban ED with severe sepsis and septic shock were randomized to either standard therapy or resuscitation directed to the above goals within 6 hours of presentation. This strategy, termed early goal directed therapy (EGDT), resulted in more successful resuscitation, restoration of perfusion, and less tissue hypoxia. After 7-72 hours of treatment, patients assigned to EGDT had significantly higher mean $ScvO_2$ (70.4% vs. 65.3%), lower lactate concentration (2.0 vs. 5.1 mmol/L), higher pH (7.40 vs. 7.36), and a highly significant reduction in in-hospital mortality (30.5% vs. 46.5% (N. Engl. J. Med. 2001;345:1368-77).

Recommendations

The Boston Medical Center has adopted a similar policy of EGDT. With a specialized central venous catheter that offers continuous measurement and display of central venous/superior vena cava oxygen saturation to help guide resuscitation, 500 cc fluid boluses are administered until central venous pressure is 8-12 mm Hg and mAP is greater than 65 mm Hg.

If these goals are not achieved, pressors are recommended. If the $ScvO_2$ remains lower than 70% despite fluid and pressor infusions, then treatment with inotropes, blood transfusions, or both is considered until the 70% target $ScvO_2$ is reached.

As always, appropriate cultures are sent as soon as sepsis is suspected and broad-spectrum antibiotics are started within the hour.

Clinical Course

Despite aggressive fluid administration and resultant central venous pressure of 11 mm Hg in the ED, the patient remained oliguric and confused. Upon admission to the ICU, the mAP dropped below 65mm Hg. Intravenous dopamine was started. mAP improved to 72 mm Hg but $ScvO_2$ remained low at 60%, suggesting ongoing tissue hypoxia despite adequate BP. Because the patient had a history of cardiomyopathy and left-ventricular dysfunction, he was treated with intravenous dobutamine to increase cardiac output, and was transfused 2 units of packed red blood cells to improve peripheral oxygen delivery. After 4 hours, the $ScvO_2$ climbed to 73%.

A small abscess at the site of the saphenous vein graft harvest site was incised and drained by the surgical service. On day 2, blood cultures grew out methicillin-resistant *Staphylococcus aureus*, confirming the initial diagnosis of sepsis from a wound infection. By day 3 the patient was successfully weaned off pressors and inotropes, and by day 8 the patient was discharged to a rehabilitation facility for further IV antibiotic therapy.

The Future

Although early identification and EGDT of tissue hypoperfusion has been shown to improve survival, many modern EDs and ICUs have not yet adopted this approach. A performance improvement program using Surviving Sepsis Campaign guideline–based sepsis "bundles" has been created in an attempt to create a "global best practice" for the management of patients with severe sepsis. As of November 2007, almost 12,000 patients from 239 hospitals in 17 countries have been entered in this database. With hope, this program and implementation of other evidence-based protocols will translate to improved outcomes.

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Risk of ACS Soars in Patients With Bacterial Pneumonia

BY MIRIAM E. TUCKER
Senior Writer

WASHINGTON — The development of acute coronary syndrome was eight times more common among 206 patients hospitalized with community-acquired bacterial pneumonia than among 395 hospitalized controls in a 7-year study.

Moreover, the risk of having an acute coronary event was 45 times greater among the pneumonia patients in the first 15 days after admission—and more than 100 times greater during the first 3 days—than it was during either the previous or subsequent year.

"The association between bacterial pneumonia and the development of ACS is so striking that a causal relation is suggested," Dr. Vicente Corrales-Medina and his associates wrote in a poster presented at the jointly-held annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and the annual meeting of the Infectious Diseases Society of America (IDSA).

Several previous studies have suggested an association between acute infections—including those of the respiratory, gastrointestinal, and urinary tract—and the occurrence of ACS in the days and weeks after the infection. Most of those studies have not clearly defined or confirmed the infections, however, Dr. Corrales-Medina of the infectious diseases department of the Michael E. DeBakey VA Medical Center and Baylor College of Medicine, Houston, said in an interview.

Researchers in the current study enrolled patients hospitalized at the Houston VA Medical Center during 2000-2006. Study participants had either clinical and radiologic evidence for pneumonia and one blood culture yielding *Streptococcus pneumoniae* or *Haemophilus influenzae,* or a clinical syndrome of pneumonia, radiologic documentation of a new pulmonary infiltrate, a sputum sample showing more than 10 inflammatory cells per epithelial cell with predominance of gram-positive cocci in pairs or gram-negative coccobacilli, and a culture yielding pneumococci or *H. influenzae* with no other likely bacterial pathogens.

Case controls were patients whose reason for admission was not an elective or therapeutic procedure and whose admission diagnosis was different from pneumonia or ACS. Final diagnoses of ACS were determined by a senior cardiologist.

Of the 206 cases of pneumonia, 144 were due to *S. pneumoniae* and 62 to *H. influenzae*.

There were 22 (10.7%) cases of ACS in the group with community-acquired pneumonia (CAP) and 6 (1.5%) in the controls, a significant difference with an odds ratio of 7.8. The odds ratio was 7.0 for cases of CAP caused by *S. pneumoniae* and 9.6 for those caused by *H. influenzae*.

Dr. Corrales-Medina stated that he had no financial disclosures. ■