MRSA: HOSPITALS CAN DO MORE

Although several recent journal articles have reported rapidly rising rates of methicillin-resistant Staphylococcus aureus (MRSA) infections, a poll of infection prevention professionals shows more could be done to prevent the spread of the dangerous bacterium in hospitals.

Of the 2,100 Association for Infection Control Professionals (APIC) members who responded to a June 2007 poll, 59% reported adopting APIC-recommended measures to eliminate transmission, but half of them also said their institutions could increase compliance with hand-hygiene protocols, better barrier precautions, and other MRSA control measures. Among the 41% who said their healthcare facility had not taken any new steps toward better MRSA control, half cited lack of support from hospital leadership and lack of resources as the reason.

The poll was conducted to determine if hospitals had adopted additional measures to prevent MRSA since a more scientific November-December 2006 survey, detailed in the December 2007 issue of the American Journal of Infection Control, reported that 46 out of every 1,000 inpatients were either colonized or infected by MRSA. “That figure is a minimum estimate,” wrote the researchers from APIC, Jason and Jarvis Associates (Hilton Head, S.C.), and Sharp Memorial Hospital, the University of California San Diego Health and Human Services Agency, and the University of California San Diego in San Diego, Calif. “The team’s figure is based on responses from respondents reporting on 7,994 MRSA colonized and infected patients at 1,237 hospitals, and is 8.5 fold higher than previous estimates that used different methodology. Data suggest that about 70% of isolates were more consistent with healthcare-associated MRSA, rather than that acquired in the community (Am J Infect Control 2007; 35: 631–637).

More information is available at www.apic.org.

CAN DO MORE

Sepsis can quickly turn severe—and fatal—when accompanied by organ dysfunction or failure. A range of clinical conditions caused by the body’s systemic response to an infection, sepsis strikes an estimated 750,000 people in the U.S. annually and kills 30–35% of them. While sepsis sometimes arises from an infection in an otherwise healthy person, all hospital patients are at risk. But identifying patients with sepsis is difficult because its clinical signs can mimic other conditions. And now, hospitals are seeing more cases of sepsis in part due to increasing numbers of immunosuppressed cancer and transplant patients. Early diagnosis is the key to saving more lives, but results from culture alone can take up to 48 hours. Consequently, some labs have started to offer faster tests for sepsis markers to speed diagnosis.

Currently, just three tests have been specifically cleared by the FDA for sepsis, The first, the Endotoxin Activity Assay (EAA), was cleared in 2003, and is marketed by Spectral Diagnostics (Toronto, Canada). The manual BRAHMS PCT LI A assay, developed by Brahms Diagnostics (Annapolis, Md.), was cleared in January 2005. The newest, the VIDAS BRAHMS PCT Assay, was cleared in October. Marketed by

IN THIS ISSUE

Lab 2008: Improving Health Care

8 Drugs-of-abuse Testing

11 New Products

12 Industry Profiles

13 Washington Profiles

14 Diagnostic Profiles

15 News from the FDA

See Sepsis, continued on page 3

Genetic Testing Oversight

Is More Regulation Needed?

BY PHIL KIBAK

As far back as 1997, a task force created by the National Institutes of Health—Department of Energy Working Group on Ethical, Legal and Social Implications of Human Genome Research suggested that CLIA requirements were inadequate to ensure the overall quality of genetic testing because they were not specifically designed for emerging molecular genetic tests. Now, a decade later, the adequacy of the current regulatory oversight of genetic testing has again been called into question by the Secretary’s Advisory Committee on Genetics, Health, and Society (SACGHS), a group that provides policy advice to the Department of Health and Human Services (HHS) on the broad array of complex medical, ethical, legal, and social issues raised by the development and use of genetic technologies. In November, the group released a draft report with new recommendations regarding government oversight of genetic testing in which members concluded that there are significant and potentially harmful gaps in the current system. The report urges the HHS Secretary to take steps that would enhance interagency coordination of the activities associated with the oversight of genetic testing, including policy and resource development, education, regulation, and knowledge generation.

But this recent criticism of the current federal oversight of genetic testing in clinical labs may be more of the same. Responding to a 2006 petition filed by the Genetics and Public Policy Center, Public Citizen, and the Genetic Alliance calling for the agency to strengthen standards for genetic testing laboratories, CMS wrote in August 2007 that there was insufficient evidence to establish a new genetics specialty under CLIA. The agency said it will continue to vigorously apply existing

See Genetic Testing, continued on page 5
Sepsis is not a specific disease, but rather a continuum of events triggered by the body’s inflammatory immune responses to a bacterial, viral, fungal, or parasitic infection. For many years, understanding of sepsis was limited in part by disagreement over its definition and lack of common terminology for the syndrome. In the early 1990s, a better definition emerged and clinicians started to approach sepsis as a continuum of clinical events. In 1992, a consensus statement issued by the American College of Chest Physicians and the Society of Critical Care Medicine recognized progressive stages of sepsis, beginning with the initial systemic inflammatory response (SIRS), to infection. According to the consensus statement, sepsis occurs when SIRS compromises one or more vital organs and can lead to septic shock, which is marked by low blood pressure that does not respond to standard treatment, problems in vital organs, and oxygen deprivation. About half of patients who suffer septic shock die. In 2003, researchers at Henry Ford Hospital in Detroit, Michigan showed that early, goal-directed therapy can improve sepsis mortality rates (NEJM 2001, 345: 1368–1377).

PCT: An Up and Coming Marker? PCT, the prohormone of calcitonin, is a small, 13-24 kDa protein that is usually undetectable in plasma. It surges in response to bacterial infections, but not those of viral origin. With FDA’s October clearance of the automated bioMérieux test, which is appropriate for emergency or stat testing, PCT could become a convenient aid in sepsis diagnosis. The test is intended for critically ill patients upon admission to the intensive care unit (ICU) and assesses risk for progression to sepsis and septic shock in conjunction with other laboratory findings and clinical assessments.

The first PCT test was marketed in Europe in 1996 by Brahms Diagnostica LLC (Berlin, Germany), and a manual version of the test has been sold in the U.S. since 2005. According to Jonas Leichter, Brahms’ Director of Marketing, the company has also submitted a more sensitive version of the test to the FDA that runs on its Kryptor automated platform and has licensed its technology to two other companies, Roche Diagnostics (Indianapolis, Ind.) plans to develop a PCT test for its Elecsys system and submit it under the 510(k) process in the second quarter of 2008, and Siemens Medical Solutions (Tarrytown, N.Y.) recently announced an agreement with Brahms to develop an assay for its ADVIA Centaur Immunoassay System.

For More Information
- Patrick St. Louis’ online expert access presentation on sepsis is available at www.aacc.org/AACC/event/expert_access/2007/OCT07.
- The Surviving Sepsis campaign offers background information about the syndrome, links to treatment guidelines, and information about educational opportunities at www.survivingsepsis.org.

How Deadly is Sepsis? Despite advances in treatment of infectious diseases and clinical care, severe sepsis remains a major killer. U.S. mortality rates for severe sepsis exceed those for acute myocardial infarction and common cancers.

### Disease
- **Severe Sepsis**: 215,000
- **Acute Myocardial Infarction**: 193,000
- **Lung Cancer**: 156,000
- **Colon Cancer**: 57,000
- **Breast Cancer**: 42,000

### Number of Deaths Annually
- 0
- 50,000
- 100,000
- 150,000
- 200,000
- 250,000

Source: www.sepsis.com

PCT as Diagnostic Tool
While its function in the process that stimulates sepsis isn’t well-understood, PCT may mediate the inflammatory response, according to St. Louis. PCT rises in response to a clinically relevant, systemic bacterial infection within 3 to 6 hours, according to Cynthia Fowler, MD, bioMérieux Senior Medical Director. The molecule has a 24-hour half-life, so if a patient is being successfully treated with antibiotics, PCT levels should drop by half every 24 hours. “PCT is a snapshot in time. It’s analogous to serial testing of cardiac enzymes,” Fowler explained. “You can repeat the test and compare to the previous result. The direction in which the PCT is going can be a useful indication of the patient’s response to therapy and progression of disease.”

Hundreds of studies have explored PCT’s ability to identify sepsis, while a growing body of data shows it has a role in guiding therapy. In one recent paper, researches wrote that PCT helped to substantially reduce antibiotic use in 302 patients with community-acquired pneumonia, half of whom received treatment according to PCT results. PCT guidance reduced both the duration and the number of antibiotic prescriptions, with 85% of the PCT group receiving them, versus 99% of the usual care group. The median duration for the PCT group was 5 days, versus 12 days for the usual care group. After adjustment for the Pneumonia Severity Index, the hazard ratio of antibiotic discontinuation was higher in the PCT group than in the control group (3.2; 95% CI, 2.5–4.2) (American Journal of Respiratory and Critical Care Medicine 2006; 174: 84-92). Another study of 208 Swiss patients hospitalized for COPD exacerbation concludes that PCT guidance “offers a sustained advantage over standard therapy in reducing antibiotic use for up to 6 months” (Chest 2007; 131: 9–19). Authors of an accompanying editorial noted the need for replications of the results in multi-center trials in the U.S.

Not all research has been flattering to PCT, however. A meta-analysis published last year by a research team at University of Sydney, led by Benjamin Tang, MD, concluded that “procalcitonin cannot reliably differentiate sepsis from other, non-infectious causes of systemic inflammatory response syndrome” and that “the widespread use of the procalcitonin test for sepsis diagnosis in critical care settings” is not supported by the findings (Lancet Infectious Disease 2007; 7: 210–217). In a response to that study, a letter from Beat Müller, MD, and colleagues from University Hospital in Basel, Switzerland, noted that there is no “gold standard to differentiate infections from non-infectious causes in patients with SIRS,” and therefore all observational studies are prone to a potential bias. St. Louis agrees with Müller’s stance. “Given the variability of the PCT data, as well as that of all the other prospective markers, it is not impossible to come to this conclusion for any marker currently available,” he remarked.

PCT vs. CRP
CRP is a popular inflammation marker because it is easy and cheap and at about $3 per result, according to St. Louis, while PCT is much more expensive, $25–$40. PCT and CRP are of roughly equal utility, according to St. Louis’s presentation. He pointed out that both markers are normally absent or very low in serum, have variable utility for diagnosis and prediction of severity and outcome, and have somewhat variable cutoffs. But PCT has a slight diagnostic edge over CRP, in St. Louis’s opinion. As part of a research team that conducted a meta-analysis of studies examining PCT’s diagnostic value, he found PCT was better than CRP for differentiating bacterial from noninfectious causes of inflammation, with PCT levels showing a sensitivity of 88% (95% CI, 80%–93%) versus 75% (95% CI, 62%–84%) for CRP. PCT’s specificity was 81% (95% CI, 67%–90%) versus 67% (95% CI, 56%–77%) for CRP. The sensitivity for differentiating bacterial from viral infections was also higher for PCT markers, 92% (95% CI, 86%–95%) versus 86% (95% CI, 65%–95%), while the molecules’ specificities were comparable at 73% (95% CI, 42%–91%) and 70% (95% CI, 19%–96%), respectively (Clinical Infectious Diseases 2004; 39:206–217).

Slides that accompanied St. Louis’ presentation point to a meta-analysis that examined 15 studies using both markers and concluded that the ROC curves for procalcitonin were better. In the 15 studies using both markers, the Q* value was 0.78 for PCT, versus 0.71 for CRP. Based on these findings, researchers concluded that PCT should be included in diagnostic guidelines for sepsis and in clinical practice in intensive care units (Critical Care Medicine 2006; 34:1996–2003).

In a more recent study of 82 patients with intraperitoneally proven secondary peritonitis, European researchers from five sites concluded that “procalcitonin monitoring is a fast and reliable approach to assessing septic multiorgan dysfunction syndrome and overall prognosis in secondary peritonitis. This single-test marker improves stratification of patients who will develop clinically relevant complications” (Archives of Surgery 2007; 142:134–142).

PCT has yet to become a popular diagnostic tool for sepsis in the U.S., as it is in bioMérieux (Durham, N.C.), it uses technology developed and licensed by Brahms and runs in just 20 minutes on bioMérieux’s automated VIDAS platform. These and other tests are intended for use in conjunction with culture, but often are much more expensive than culture alone. Lab directors considering these and other sepsis marker tests must consider not only speed and cost, but also the test’s ability to aid diagnosis, determine whether patients will benefit from antimicrobial therapy, and monitor a patient’s response to interventions.

But the central question surrounding sepsis markers is their clinical utility. “Do we have markers that aid in good medical practice—diagnosis, prognosis, and monitoring? There is no individual marker that addresses any of these questions with 100% certainty,” explained Patrick St. Louis, PhD, Director, MDS Pharma Services Central Laboratory in Mississauga, Ontario. St. Louis recently gave an online presentation about sepsis on AACC’s Web site (See Box).
Tailoring Therapy with EAA

In one study, 57.2% of 857 American, Canadian, or European patients admitted to ICUs had either intermediate or high endotoxin activity. For patients with low, intermediate, and high EA levels, rates of severe sepsis were 4.9%, 9.2%, and 13.2%, respectively, while ICU mortality in those groups was 10.9%, 13.2%, and 16.8%, respectively (Journal of Infectious Diseases 2004; 190: 527–534).

Tailoring Therapy with EAA

Recently published research suggests that EAA may one day be used to tailor therapy for patients with severe sepsis. A pilot study of 345 ICU patients by researchers at Spectral Diagnostics, University of Toronto, and University of Ottawa found that variable EA activity occurred independently of infection status and was a marker of increased severity of illness (Shock 2007, 28: 524–529).

Meanwhile, the Japanese healthcare system has embraced a sepsis therapy that relies on EAA results. Foster noted that some hospitals in Japan are conducting a dialysis process that strips endotoxin from the blood. A Japanese company, Eisai (Ridgefield Park, N.J.), is also integrating EAA into drug development (See Sidebar).

However, EAA has its detractors, too. “Endotoxin is difficult to measure, so it hasn’t caught on in clinical labs. Traditionally Gram-negative bacteria has been seen as a primary culprit behind sepsis and these organisms produce endotoxin,” explained James Versalovic, MD, PhD, Director of the Division of Molecular Pathology and the Microbiology Laboratories at Texas Children’s Hospital and Associate Professor of Pathology at Baylor College of Medicine in Houston. He is using arrays to design a test that identifies multiple eukaryotic alges of sepsis. “Plus there are organisms, like Gram-positive bacteria and fungi, that can cause sepsis but may not produce endotoxin,” said Versalovic.

Working Toward a Multi-Marker assay

At least one diagnostic manufacturer is combining markers for sepsis diagnosis. Biosite (San Diego, Calif.), now being acquired by Inverness Medical Innovations (Waltham, Mass.), is developing a multi-marker panel. A team at Henry Ford Hospital in Detroit, led by Emanuel P. Rivers, MD, Director of Research in the Department of Emergency Medicine, help the company to develop the panel, which includes neutrophil gelatinase-associated lipocalin (NGAL), C-reactive protein (CRP), and macrophage inflammatory protein-1 (MIP-3). Rivers, who discussed the panel during a Biosite-sponsored presentation at the AACC’s 2007 Annual Meeting last July, said the panel is intended as a point-of-care test to assess risk of sepsis progression within 72 hours of emergency department presentation. The multi-marker assay is the result of an extensive Biosite screening program that evaluated about 150 possible markers for both their ability to detect sepsis and risk stratify patients. The company has launched a prospective multicenter study involving 1,000 patients at 10 U.S. centers to validate the clinical utility of the data and compile it for submission to the FDA, according to Rivers. He noted, however, that panel is now undergoing refinement and the markers could change.

NGAL, one of the panel’s potential markers, is also being used as an experimental marker of acute kidney injury, the most common cause of sepsis in the ICU. Right now, acute kidney injury is usually a delayed diagnosis based on serum creatinine levels, which can vary considerably among individuals and require many days to reach a steady state, according to Prasad Devarajan, MD, Professor of Pediatrics and Director of Nephrology at Cincinnati Children’s Hospital Medical Center, who also spoke at Biosite’s event. His institution holds an exclusive license for NGAL to detect acute kidney injury and is developing a urine test for Abbott Diagnostics (Abbott Park, Ill.) and a plasma version for Biosite. Both assays detect the rise of NGAL within 2 to 6 hours of an event that leads to acute kidney injury.

No Clear Winner

With no one sepsis marker clearly recognized as the preferred marker, whatever emerges must be able to alleviate the huge burden sepsis creates for the healthcare system. Spectral’s Foster likened the current landscape of sepsis diagnostics to the state of cardiac markers prior to troponin. “Right now, sepsis care is in the same zone that cardiac care was before troponin became the leading test in diagnosis of acute myocardial infarction. Patients are dying at high rates. There are many markers, but no one test is dominant and so far, uptake in the U.S. has been slow. These markers need to be used and challenged to determine the best fit into the differential diagnosis of sepsis,” he explained. Those in the sepsis field are hopeful that research will yield tools that better diagnose the condition, guide therapy, and save more lives.