Marker May Help Tailor Antibiotic Use in CAP

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MONTREAL — In community-acquired pneumonia, overuse of broad-spectrum antibiotics can be curbed with the help of biologic markers such as procalcitonin, according to Dr. Jean Chastre of the Hôpital de la Pitié-Salpêtrière, Paris.

Blood levels of procalcitonin (PCT) rise in patients with bacterial infections but remain fairly low in those with viral infections, and PCT levels decrease as the bacterial infection subsides. Measuring PCT levels thus aids decisions about whether to prescribe antibiotics, what type to prescribe, and for how long, said Dr. Chastre at an international conference on community-acquired pneumonia (CAP) that was sponsored by the International Society of Chemotherapy. "We use antibiotics for too long for too many patients, and in doing so are favoring the emergence of resistant strains," he said in an interview.

"The more antibiotics we use, the more resistance we are going to see," Dr. Jean-Claude Pechère agreed in an interview. In his presentation, he outlined a 2004 study in which PCT-guided therapy for lower respiratory tract infections significantly reduced antibiotic use, compared with standard care (Lancet 2004;363:600-7). "With these biomarkers, we suddenly realized we could cut antibiotic consumption almost in half. In Europe, we are speaking of millions of patients," said Dr. Pechère, a professor of medicine at the University of Geneva.

Although a PCT assay is approved in Europe, it is still not widely available, and it is even less so in North America, according Dr. Thomas File, a professor of internal medicine and head of infectious diseases at Northeastern Ohio Universities, Rootstown. "There are a few places where they have it available in the [emergency department], but in most places it takes several hours to get the result back—maybe even a day," Dr. File said in an interview. Because initiation of antibiotic therapy is recommended within hours of a diagnosis of bacterial CAP, a PCT assay may not be practical for guiding initial treatment decisions, he said. "It's probably going to be more helpful in making decisions about duration of therapy, or changing therapy."

For example, antibiotics can be stopped if the PCT results suggest that bacterial infection is unlikely, explained Dr. Chastre, who has received research funding and is a speaker for Brahms Diagnostics LLC, which makes a PCT assay. Or, therapy could be shortened if serial PCT measurements suggest a rapid response. "It's probably possible, even in severe pulmonary infection, to shorten the duration of antibiotics to 5 or 7 days if the PCT is decreasing very rapidly," Dr. Chastre said.

European guidelines recommend that empiric therapy for bacterial CAP should provide coverage against the most common pathogen (*Streptococcus pneumoniae*) but not atypical pathogens, whereas North American experts favor a wider spectrum of coverage that includes the atypicals. PCT-guided therapy could allow European physicians to continue with less complete initial coverage by identifying the nonresponders who need expanded therapy, Dr. Pechère said.

In the future, it may even be possible to use PCT levels to distinguish typical from atypical CAP pathogens, he added, citing one study that noted lower levels in hospitalized CAP patients infected with typical, compared with atypical, bacteria (Infection 2000;28:68-73). But a more recent study concluded PCT levels were not predictive of type of pathogen (Clin. Microbiol. Infect. 2007;13:153-61).

Dr. Chastre said that in evaluating the severity and progression of pneumonia, PCT levels should always be considered in conjunction with other clinical parameters. "This marker is not 100% sensitive in some patients because, even with very severe disease, some people can have low levels," he said, citing his own study showing low PCT levels in some patients with ventilator-associated pneumonia (Am. J. Respir. Crit. Care Med. 2005;171:48-53).

The reverse can also be true, with high levels of PCT seen in nonseptic conditions such as trauma, cardiogenic shock, and heat stroke, among others, he said. ■

Deaths in MRSA, Pneumonia May Have Involved a Toxin

MONTREAL — The high mortality in community-acquired pneumonia caused by methicillin-resistant *Staphylococcus aureus* may be largely due to Panton-Valentine leukocidin toxin, according to Dr. Ian Gould, consultant microbiologist at the University of Aberdeen (Scotland).

Thus, efforts to control the infection should probably focus on the toxin as well as the bacteria, Dr. Gould said at an international conference on community-acquired pneumonia (CAP).

"Switching off toxin production is probably a major issue because it's mainly a toxin-induced disease," he said in an interview at the meeting. "Even if the antibiotics can kill the bug, the toxin's still there and that's what's doing the damage."

Panton-Valentine leukocidin (PVL) toxin is produced mostly by community-acquired, as opposed to hospital-acquired, strains of methicillin-resistant *S. aureus* (MRSA). And the prevalence is increasing, Dr. Gould said.

"Clearly, there have been big changes in the epidemiology of community-acquired MRSA, and now there are quite a few epidemic strains that produce PVL," he said. In fact, according to a recent report from the Centers for Disease Control, the majority of reported community-acquired MRSA infections are PVL-producing strains (MMWR 2007;56:325-9; see accompanying story). However, although most of these infections involve skin and soft tissue and are "relatively mild," according to Dr. Gould, "more and more commonly, we're seeing very severe respiratory disease associated with community-acquired MRSA PVL strains." In the recent CDC report of 10 cases of MRSA-associated CAP, all isolates were positive for PVL toxin.

"This is an organism that causes severe pneumonia," said Dr. Coleman Rotstein, who also presented at the meeting, which was sponsored by the International Society of Chemotherapy. The key features of CAP caused by MRSA are empyema and necrotizing pneumonia, said Dr. Rotstein, professor of medicine at McMaster University, Hamilton, Ont.

He and other experts at the meeting agreed that treatment options are limited.

"When it comes to treatment, we are standing in the dark, with a case mortality in the published literature of around 75%," Dr. Gould said. "It's like going back to the influenza epidemic after the First World War, when there were no antibiotics."

"For these new MRSA CAP etiologies, the present arsenal of antibiotics is unfortunately insufficient," said Dr. Ethan Rubenstein, who also presented at the meeting. "Evidently, the β-lactams are useless, and vancomycin is associated with unfavorable clinical results even when used in higher doses," said Dr. Rubenstein, professor and head of infectious diseases at the University of Manitoba, Winnipeg.

According to Dr. Gould, high-dose clindamycin or linezolid are good options not only for their antibacterial effects but also because of their potential ability to lower PVL production. "[Intravenous] immunoglobulin is also well recognized as an adjunct, but I don't know if there's much evidence for its effect—although there are PVL antibodies in it," he said. In addition, gentamicin is indicated for patients who are bacteremic.

"We haven't seen the end of this story. This is a highly adaptable, rapidly developing organism … things are going to get worse here before they get better," Dr. Gould said. ■

Implement New Community-Acquired Pneumonia Guidelines Judiciously

MONTREAL — New guidelines for the management of community-acquired pneumonia provide an excellent framework for site-of-care decisions, but they must be augmented with a good dose of clinical judgment, according to Glenn Tillotson, Ph.D.

The consensus guidelines from the Infectious Diseases Society of America and the American Thoracic Society hinge on two severity scoring systems to aid in the decision about whether to hospitalize patients with community-acquired pneumonia (CAP) or treat them as outpatients (CID 2007;44[suppl. 2]:S29).

However, although the well-established Pneumonia Severity Index (PSI) and the CURB-65 (confusion, uremia, respiratory rate, blood pressure, age 65 years or older) scoring systems are excellent tools, "clinical judgment based on more subjective criteria should override the rules," Dr. Tillotson said at an international conference on community-acquired pneumonia.

This advice is especially true for patients on either end of the age spectrum. Disease severity scoring systems adequately classify most patients with CAP into either hospital or outpatient treatment, but such systems may be less reliable for young adults (aged 17-40 years) and the frail elderly, said Dr. Tillotson, who is executive director of scientific affairs at Replidyne Inc.

He outlined one study of young CAP patients (median age 20 years) in which previous pulmonary disease, initial vital signs, and lab values were not predictive of mortality or length of stay (Chest 2006;130[suppl.]:105S). On the other end of the age spectrum, another study found that in frail elderly patients with CAP, chronic comorbidities were not predictive of disease severity (Chest 2006;130[suppl.]:105S). "The factors we tend to lean on should not necessarily drive our decisions, especially in these populations," he said.

Dr. Tillotson emphasized that although there may be a need for more specific scoring systems for CAP patients who are either young or frail and elderly, the science of scoring systems must always bow to the art of clinical judgment for all CAP patients.

"It's not always possible to articulate what marks a stay-at-home type patient versus someone who needs to go to hospital. There may be occasions when you should admit someone—not because they're severely ill, but simply because they need some TLC. One or 2 days in hospital could make all the difference in getting them back to normal, rather than giving them similar management in the community without someone there looking after them," he said in an interview.

To illustrate this point, he noted a study of almost 2,000 low-risk CAP patients in which 45% were treated as inpatients (J. Gen. Intern. Med. 2006;21:745-52). Among the hospitalized patients, about one-fifth had no identifiable risk factor according to the PSI disease severity scoring system. "My take is that an overnight stay in hospital can sometimes just get somebody over that hump. They're feeling sick; they have chest pains, fever, and coughing. They're not really sick enough to be admitted, but 24 hours in an observation ward can make a big difference," he said.

Weighing against this sentiment, however, are the known risks associated with hospitalization. "It's often better to manage someone in the community because they're less likely to acquire resistant pathogens, or they're less likely to have thromboembolic events. There's always a balance," Dr. Tillotson said. ■