Assay Could Speed Diagnosis of Bacterial Sepsis

BY JEFF EVANS

A testing method that uses positive blood cultures and an automated DNA-based polymerase chain reaction and microarray system accurately identified bacteria in sepsis much faster than a standard culture-based process.

The test identified bacterial species in patients with suspected sepsis with 95% sensitivity and 99% specificity, with a mean turnaround time of 23 hours—compared with 41.5-48 hours for the standard culture-based method, according to a report.

Although the sepsis assay is a "major advance" that encompasses the best of nucleic acid and standard culture-based methods, it is unknown whether determining the species of a pathogen 18 hours earlier than usual will "translate into demonstrable clinical benefit commensurate to the cost of undertaking the additional test," commented Dr. Shin Lin of Stanford (Calif.) University and Dr. Samuel Yang of Johns Hopkins University, Baltimore, who were not involved in the study (Lancet 2009 Dec. 10 [doi:10.1016/S0140-6736(09)61791-8]).

In the study, Dr. Päivi Tissari of the Helsinki University Hospital Laboratory and colleagues tested the Prove-it sepsis assay, manufactured by Helsinki-based Mobidiag, against standard blood culture and pathogen identification. The analysis included 3,318 blood samples from patients with suspected sepsis at two large academic medical centers (Lancet 2009 Dec. 10 [doi:10.1016/S0140-6736(09)61569-5]).

The assay identifies more than 50 species of gram-positive and gram-negative bacteria that cause most cases of sepsis. A total of 2,107 blood culture samples tested positive, including 1,807 that were covered by the sepsis assay. The researchers compared DNA sequences of topoisomerase and 16S rRNA genes and original microbiologic laboratory data for samples when the results differed between the assay and standard blood culture method.

For organisms that could be detected with the sepsis assay, the results of the assay were between 93% and 100% concordant with the results of blood culturing for all species except one. The assay identified 133 of the 163 coagulase-negative staphylococci that were identified through blood culture.

False-positive results were identified in 52 of the 3,318 samples put through the assay. Those 52 false positives included 34 that were due to contamination or software failure, 11 with more bacterial species detected than with conventional blood culture, 3 with *Staphylococcus epidermidis* reported, 3 attributed to cross-hybridization between species, and 1 sample in which the assay also detected *Bacteroides fragilis*.

False-negative results occurred in 34 samples due to inadequate sensitivity for certain species, and in 60 samples because the sepsis assay did not detect all the bacteria it should have. The assay also had difficulty in resolving species in polymicrobial samples.

The median difference in turnaround time between the Prove-it assay and the reference method for 39 samples was 18 hours 19 minutes.

The assay provided 100% sensitivity and specificity for methicillin-resistant *Staphylococcus aureus*, although it is the only type of antibiotic resistance testing that can be performed with the assay.

"The Prove-it sepsis assay cannot replace standard methods but could have a role alongside them," Dr. Lin and Dr. Yang wrote.

Five of the investigators are employees of Mobidiag, which provided the equipment and reagents for the assay. None of the other researchers had conflicts of interest. Dr. Lin and Dr. Yang had no conflicts of interest to report. The study was performed without outside funding. ■

MY TAKE

Sepsis Assay Requires More Study

As Dr. Lin and Dr. Yang note, until someone shows that being able to diagnose bacterial sepsis 18 hours faster makes a difference in patient care, it's not clear that this assay would be a clinically important advance.

One could speculate about other possible benefits, such as reductions in empiric antibiotic use, antibiotic exposure and resistance, or costs for medication and lab testing. But someone needs to demonstrate such benefits. Otherwise, who cares?

FRANK MICHOTA, M.D., *is the Director of Academic Affairs in the Department of Hospital Medicine at the Cleveland Clinic. He reports no relevant conflicts of interest.*

Ceftaroline Shows Promise In the Treatment of CAP

BY DOUG BRUNK

SAN FRANCISCO — Ceftaroline demonstrated a higher clinical cure rate, compared with ceftriaxone in patients hospitalized with community-acquired pneumonia, according to combined results from two phase III studies.

A parenteral, broad-spectrum cephalosporin being developed by Forest Laboratories and AstraZeneca, ceftaroline "has a similar spectrum of activity as ceftriaxone, but it adds additional coverage against resistant gram-positive [organisms] that cause pneumonia in increasing frequency," Dr. Paul Eckburg said in an interview during a poster session at the annual meeting of the Interscience Conference on Antimicrobial Agents and Chemotherapy.

The researchers enrolled 1,228 hospitalized patients with community-acquired pneumonia who required IV therapy; 614 received ceftaroline 600 mg every 12 hours and 614 received ceftriaxone (Rocephin) 1 gram every 24 hours. Each group was treated for 5-7 days. The mean age of patients was 61 years and 63% were male, Dr. Eckburg and his associates reported.

The primary objective of the two clinical trials was to determine noninferiority in the clinical cure rate with ceftaroline, compared with ceftriaxone (Rocephin) at 8-15 days after therapy. Of the 1,228 patients in the two trials, 908 met clinically evaluable criteria; they had clinical cure rates of 84.3% with ceftaroline and 77.7% with ceftriaxone.

"What surprised us was that the clinical cure rates were much higher in the ceftaroline arm than what we expected," commented Dr. Eckburg, director of anti-infective development at Cerexa Inc., the wholly owned anti-infectives subsidiary of Forest Laboratories Inc. "We expected to see very similar cure rates."

Among the 1,153 patients in the modified intent-to-treat efficacy group (limited to patients with class III and IV pneumonia), the overall clinical cure rates for ceftaroline and ceftriaxone were 82.6%and 76.6%.

Both drugs were well tolerated in the trials. Diarrhea was the most common adverse event (4.2% in ceftaroline users vs. 2.6% in ceftriaxone users), followed by headache (3.4% vs. 1.5%) and insomnia (3.1% vs. 2.3%).

"The bottom line is that we now have a new drug that shows similar efficacy to an older drug, ceftriaxone, but it offers additional coverage against emerging resistant pathogens," Dr. Eckburg said.

The study was supported by Forest Laboratories. ■

Nonsustained Hypotension May Be Red Flag in Sepsis Treatment

BY BRUCE JANCIN

NEW ORLEANS — Nonsustained hypotension in emergency department patients with sepsis was associated with a threefold increased rate of in-hospital mortality in a large prospective study.

"Clinicians should consider any hypotension in the setting of sepsis to herald worse outcome. This knowledge should impart reluctance to dismiss nonsustained hypotension—including a single measurement—as not clinically significant or meaningful," Dr. Michael Marchick said at the annual meeting of the Society for Academic Emergency Medicine.

Dr. Marchick reported on a randomly obtained single-center study population consisting of 700 adults hospitalized with a primary diagnosis of sepsis. None had clinically overt shock as defined by need for vasopressors in the ED or systolic blood pressure below 100 mm Hg sustained for 1 hour or longer, and none had experienced significant trauma within the 24 hours prior to their enrollment in the study.

The lower the blood pressure nadir attained in the ED in this septic population, the greater the associated in-hospital mortality, noted Dr. Marchick of Carolinas Medical Center, Charlotte, N.C. (See box.)

In-hospital mortality occurred in 3.6% of 550 septic patients with no hypotension, 9.3% of 86 patients with a single transient hypotensive episode, and 10.9% of 64 patients with multiple episodes.

In a multivariate regression analysis that adjusted for acute organ dysfunction, comorbidities, and demographic variables, nonsustained hypotension emerged as the strongest risk factor for in-hospital mortality, conferring 2.7-fold increased risk, he said. ■