Sooner, smarter—new strategies against sepsis

Ann Griswold, PhD

July 2013—When it comes to fighting sepsis, the ingenuity of the laboratory is indispensable.

At the front line of the fight are physicians, who largely rely on guidelines issued by the Surviving Sepsis Campaign. But where the SSC guidelines end, a critical phase of the fight begins.

Laboratories, as incubators of innovative technologies, are constantly formulating fresh ways to improve the accuracy and reporting of sepsis diagnoses, and to uncover essential details about the identities and antibiotic susceptibilities of offending pathogens. And at the end of the day, laboratories are in an ideal position to track the impact of new technologies on patient outcomes. In these three areas—diagnoses, details, and impact—laboratories are striking back against sepsis.

The SSC guidelines, updated in 2012 to reflect changes in the clinical landscape since the 2008 version was issued, harness the expertise of 30 clinical organizations worldwide in a bid to improve patient survival (Dellinger RP, et al. *Crit Care Med*. 2013;41[2]:580–637). According to the SSC, the use of evidence-based treatment regimens known as sepsis care bundles—groups of interventions performed in a certain time frame—could save as many as 400,000 lives if just half of the eligible patients are treated at 10,000 participating hospitals. The hope, of course, is that the actual numbers will far outrun this estimate.

Dr. Dellinger

The 2012 guidelines contain several key updates from previous versions, says first author R. Phillip Dellinger, MD, director of critical care at Cooper University Hospital and a professor of medicine at Cooper Medical School of Rowan University, Camden, NJ. Most of the updates pertain to clinicians and pharmacists, Dr. Dellinger notes, but a handful of recommendations are targeted to clinical laboratories. The new guidelines suggest using the 1,3 beta-D-glucan assay and the mannan and anti-mannan antibody assays when exploring candidiasis as a differential diagnosis.

New levels for certain physiologic targets, such as glucose, are also described in the updated guidelines. The SSC previously recommended moderate glycemic control, using insulin therapy as needed to keep blood glucose levels below 150 mg/dL. But the new guidelines account for recent findings that an upper limit of 180 mg/dL can be just as effective while also reducing the risk of hypoglycemia. “We’re now recommending more liberal glucose control because we think that if you try to keep it too low, you’ll induce hypoglycemia in too many patients and push outcomes in a negative direction,” Dr. Dellinger explains.

Most notably, the revised guidelines tighten the timeline for detecting sepsis and initiating antibiotic therapy. Though the guidelines have long emphasized the need to collect a patient blood sample before initiating therapy, Dr. Dellinger notes, the authors changed the wording in the 2012 guidelines to ensure that patients receive antibiotics promptly, as studies have shown a 7.6 percent drop in survival for every hour that antibiotics are withheld from a patient with septic shock. “You should never wait longer than 45 minutes to get a blood culture,” Dr. Dellinger says. “If you’ll have to wait more than 45 minutes to collect a culture sample, you should go ahead and empirically give antibiotics.”

Similarly, whereas previous guidelines allowed six hours from patient presentation to the first measurement of lactate, a telltale marker of severe sepsis and septic shock, the 2012 guidelines cut that time in half, recommending a first lactate measurement within three hours of presentation and again after six hours to determine if resuscitation efforts were successful.

“We suggest using lactate normalization as a target for resuscitation,” Dr. Dellinger explains. “If someone has severe sepsis and their initial serum lactate is elevated, you want to resuscitate them with fluids, normalize their blood pressure, ensure good oxygen levels, and increase tissue perfusion to totally normalize lactate—that’s a new recommendation for 2012.” To better accommodate the new recommendation, laboratories will need to use a rapid and robust lactate assay; some emergency departments may prefer the use of blood gas analyzers to measure lactate levels closer to the bedside.

Dr. Woodworth

Though lactate is a useful indicator of severe sepsis and septic shock, and has proved valuable to physicians, the biomarker’s utility is limited, says Alison Woodworth, PhD, director of esoteric chemistry and associate director of clinical chemistry, Vanderbilt University Medical Center, and assistant professor of pathology, microbiology, and immunology, Vanderbilt School of Medicine. “Essentially, lactate is released when your tissues start to lose oxygen. If it is elevated in a patient with systemic inflammation, it is likely that he or she has severe sepsis, but it is not very useful for finding patients early in the sepsis pathobiological process because they haven’t yet had significant organ failure or oxygen deprivation.”

Clinicians are faced with the impossible task of searching for sepsis among patients who present with bits and pieces of the condition: lethargy, general aches and pains, fever, shortness of breath, rapid heart rate, and other symptoms that mimic unrelated inflammatory ailments. Blood cultures can take from 16 hours to three days to reveal answers. Researchers like Dr. Woodworth are searching for biomarkers that can identify an infectious agent early in the process, and quickly.

There’s just one problem, Dr. Woodworth says: So far, the FDA has cleared only single biomarkers for use in guiding the early diagnosis of sepsis, before culture results are in. But patients with sepsis may present differently—physiological indicators vary—depending on the pathogen involved and whether the patient has comorbidities. “It’s becoming clear that one biomarker is not going to be the answer for diagnosing sepsis,” Dr. Woodworth says. “That’s where biomarker panels come in.”

The advantage of multimarker panels lies in their flexibility. “The idea is to identify patients at each stage of the sepsis cascade, from the early upregulation of proinflammatory cytokines to the eventual development of organ failure, so that clinicians can diagnose and treat patients more precisely,” she explains. “When you choose biomarkers that are upregulated at different phases and combine them into a prediction model, it provides far superior diagnostic strength compared with any single marker available right now.” Dr. Woodworth is developing a sepsis biomarker panel designed to run on an existing immunoassay platform, allowing for the rapid measurement of inflammatory markers within hours of an infectious insult. The possibilities are enticing, she says.

“If you had a panel that could distinguish among patients with sepsis, severe sepsis, septic shock, or an inflammatory response that is unrelated to infection, you could immediately triage these patients and treat them accordingly,” Dr. Woodworth explains. Conceivably, such a panel could be used throughout the course of a patient’s admission to track therapy response.

Though such panels are in development, they're a long way from FDA approval and have not yet been optimized to identify specific pathogens. Dr. Woodworth is exploring the use of biomarkers to identify bacterial agents of community-acquired pneumonia. But even if her efforts succeed, laborious culture systems will continue to be in demand until researchers hit upon a method of using biomarkers to determine antibiotic susceptibility profiles, she notes.

In the meantime, the new SSC guidelines focus on the indicators available now. Two FDA-cleared biomarkers, procalcitonin and C-reactive protein, are included as part of the criteria for diagnosing sepsis (in line with the 2003 SCCM/ESCIM/ACP/ATS/SIS Sepsis Definitions Conference). Previous versions of the guidelines noted that procalcitonin, a peptide upregulated in response to proinflammatory cytokines, does not reliably distinguish patients with sepsis from patients with inflammatory conditions unrelated to infection. "We, however, now suggest the use of procalcitonin and other biomarkers, not as a reason to start antibiotics but as variables in the decision to stop," Dr. Dellinger says, noting that recent literature has shown that low procalcitonin levels can guide discontinuation of antibiotic therapy during the recovery from sepsis.

Dr. Woodworth agrees that procalcitonin as well as CRP can inform the decision to discontinue antibiotic therapy, but she worries about their inclusion in the diagnostic criteria. That said, she notes the markers might offer additional value in predicting prognosis, as recent studies suggest that elevated procalcitonin and CRP concentrations are associated with increased mortality.

"The biomarkers that are available right now are OK, but they have a lot of limitations," Dr. Woodworth says. "Sepsis is not one disease, like diabetes. It's a syndrome that can be caused by many different things." Multimarker panels, she says, are unsurpassed in their ability to capture this diversity.

When a patient presents with symptoms of sepsis, two sets of blood culture samples—one to support aerobic and another to support anaerobic growth—are collected within the first 45 minutes, and laboratory tests are ordered to assess levels of lactate, CRP, and procalcitonin. After that point, however, the SSC guidelines offer little guidance for clinical laboratories. In the hours and days that follow, physicians devote their efforts to resuscitating and stabilizing the patient, while clinical laboratories work to detect growth in culture, identify the pathogen, and determine antibiotic susceptibilities.

Dr. Wolk

"In that way, the guidelines aren't accounting for what happens after the first four to six hours," says Donna M. Wolk, MHA, PhD, D(ABMM), system director of the microbiology laboratory at Geisinger Medical Laboratories, Danville, Pa., and director of the Center for Infectious Disease Diagnostics and Research at Weis Research Center. "Microbiology laboratory efforts can still save people's lives after that point if we apply the right technology." In particular, rapid reporting of blood culture results allows patients to transition from broad-spectrum antibiotics to less toxic and more targeted therapies that can improve outcomes, Dr. Wolk notes.

The importance of timely blood culture processing and reporting has not been addressed in the SSC's guidelines, Dr. Dellinger says. "Perhaps that literature should be pursued in the next rendition of the guidelines. We did not have any clinical laboratory representation on the guidelines committee. That should also likely occur in the next revision."

A recent Q-Probes study on the timeliness and accuracy of reporting preliminary blood culture results found that most laboratories achieve admirable turnaround times, with a median time of 45 minutes from detection of a

positive blood culture to reporting of preliminary Gram stain results.

“The sooner you identify what the pathogen is and adjust the treatment, the better the outcome. Our study showed that laboratories by and large do a pretty good job of accomplishing that goal,” says study author Ron B. Schifman, MD, chief of diagnostics, Southern Arizona VA Healthcare System, and associate professor of pathology, University of Arizona College of Medicine.

While the rapid turnaround times did not come as a surprise to Dr. Schifman, he says the study did turn up several unexpected findings about the use of technology to monitor blood cultures. “There were 64 laboratories in the Q-Probes study, and every one of them used a continuous-monitoring blood culture system,” Dr. Schifman says. “Based on the labs that participated, it seems this technology has more or less penetrated the lab community, which is a good thing because these systems have been shown to be very reliable and much faster in terms of detecting bacteremia with greater productivity than some of the other systems out there.”

Dr. Schifman

While 100 percent of the labs used continuous-monitoring systems, the study found that almost a third of the labs did not make full use of the technology. “With these systems, you can get a positive signal anytime during a 24-hour period. But some of the laboratories—more than I expected—were not sufficiently staffed on evenings during the week or nights on the weekend to process that blood culture when it first signaled as positive,” Dr. Schifman says.

As a result, several hours might pass before the positive culture is removed from the machine and subjected to Gram staining. That delay lengthened the overall median turnaround time for those labs to two hours, compared with just 37 minutes for labs that provided around-the-clock coverage. “That’s an area for improvement,” Dr. Schifman says. “Laboratories that are not processing blood cultures on a continuous basis might need to revisit this issue and see if there’s some way they might make that happen.” Labs might find it difficult to follow this recommendation in the face of tough financial pressures, he adds, but the authors encourage labs to be resourceful. Telepathology, for example, might help overcome the challenges of understaffing or lack of expertise during certain times of day.
Interestingly, the study found no differences between the accuracy of Gram stain results when a nonspecialist versus specialist microbiologist processed the positive blood culture samples. In fact, among more than 5,000 blood cultures, the authors found a very low (1.2 percent) rate of discordance between the results of preliminary Gram staining and the final blood culture results.

“Most of the discordances were mixed cultures,” says Q-Probes coauthor Frederick A. Meier, MD, senior staff pathologist at Henry Ford Hospital in Detroit and director of regional laboratory services, Henry Ford Health System. “It’s not that nonspecialists were misinterpreting Gram stains.”

For laboratories to maintain such high Gram stain interpretation quality, the authors recommend that laboratories track the accuracy of their initial blood culture Gram stain results. The Q-Probes study also highlighted the value to laboratories of setting and monitoring turnaround time goals for processing and reporting, and of monitoring the efficiency of their efforts to report preliminary blood culture Gram stain results as critical values. “Of our 64 participating institutions, laboratories that set goals reached better levels of performance than those who didn’t,” Dr. Meier says.

Dr. Meier

He adds, “A lab that monitors blood culture incubators 24/7, sets itself goals for rapid Gram stain performance and reporting, and monitors the correlation between the Gram stain and the final diagnosis is doing its part to maintain quality in positive blood culture initial detection, characterization, and reporting.”

After the preliminary blood culture results are reported, laboratories work quickly to identify the pathogen and determine its antibiotic susceptibility profile.

“When you have something that’s positive in the continuous-monitoring blood culture system, you have several options,” says Vincent LaBombardi, PhD, director of microbiology at New York Hospital-Queens, Flushing, NY. Various technologies—existing ones and those to come—aim to provide more information in a shorter time with less complexity compared with previous methods.

Newer technologies tend to channel the power of multiplex PCR, which generally provides more targets in a shorter time compared with nonmultiplex assays. “Instead of one target per test, we now have many targets per test in the same amount of time—and in some cases less time—than it took to perform the manual or singleplex methods,” Dr. Wolk says. Nanosphere’s Verigene Gram-Positive Blood Culture Test, for example, is an automated multiplex test capable of detecting nine species of gram-positive bacteria commonly associated with bloodstream infections, as well as four genera and three antibiotic resistance genes within about 2.5 hours of obtaining a positive blood culture test. A Gram-Negative Blood Culture Test, also FDA-approved, detects five species, four genera, and six resistance genes in less than two hours. And in June, the FDA cleared BioFire’s blood culture ID panel for the FilmArray instrument, which relies on multiplex PCR to test for 24 pathogens and four resistance genes in about one hour.

AdvanDx’s PNA FISH testing algorithm was among the first FDA-cleared systems for the rapid detection of bacteria and yeast from blood culture bottles. The PNA FISH assay uses fluorescent probes to illuminate species-specific rRNA sequences in whole cells within 90 minutes.

Dr. LaBombardi

Other technologies have not been FDA cleared but are available for research use only. Europe and Canada have approved the use of Bruker’s IVD MALDI Biotyper for the rapid identification of microorganisms via MALDI-TOF analysis, for example.
Still other technologies are in prototype form and have yet to hit the clinical arena. Accelerate Diagnostics, of Tucson, Ariz., is working on a prototype of an instrument called the BACcel, designed to identify organisms and provide susceptibility testing directly from a positive blood culture in a two- to six-hour window.

Though these technologies are rapid and informative, most lack the ability to assess antibiotic susceptibility, and those that have this ability often require up to 24 hours to yield results. Dr. LaBombardi considers the VITEK 2 by bioMérieux among the fastest systems to combine pathogen identification with antibiotic susceptibility profiling.

“Some of the other growth-based systems have to incubate overnight, so essentially it doesn’t make a difference when you set them up because you’re not going to get a result until the following day.”

By streamlining the VITEK 2 workflow, Dr. LaBombardi’s group at a hospital he was with previously greatly reduced the time needed to transition patients to targeted antibiotic therapies. In particular, his group began placing primary plates or subcultures into the machine continually throughout the day, rather than batch loading at the end of each shift.

To expedite the reporting of results, particularly with regard to drug-resistant organisms, Dr. LaBombardi initiated a feature he calls autoposting. As soon as an isolate is identified and susceptibility tests are complete, the results go through an advanced expert system to confirm that the isolate identification is consistent with the organism’s susceptibility profile. Results that pass this internal screen are automatically sent across the interface and posted to the lab and hospital information systems. Contradictory results are held back for manual review.

“As soon as I can see the results, our clinicians can see the results,” Dr. LaBombardi says. “So instead of having a result the following morning, by the time the technologists get around to reading the result and sending it across the interface, the results are now available the same afternoon the isolate is set up.”

Dr. LaBombardi’s group further customized the machine to flag some of the antibiotic resistance mechanisms commonly reported in New York. “If I have an organism producing a carbapenemase, for example, I don’t want to hold that back for review. I want that sent across right away, because for us that’s quite common. If you’re somewhere else in the country, it might not be that commonplace and you might want to look at it beforehand. But in this case, we need to trust the instrument.”

These relatively simple changes in workflow brought dramatic results at his former hospital. “Before we started autoposting, 36 percent of our isolates of *Klebsiella pneumoniae* produced carbapenemase,” Dr. LaBombardi estimates. “One year after implementation, we were down to 23 percent. And the year after that, we were down to 21 percent. We made a significant decrease in our rates of resistant isolates because the patients could be placed in context precautions right away.”

Physicians quickly latched onto the efficiency of autoposting, Dr. LaBombardi recalls. “Clinicians would comment to me that they became used to looking for results in the afternoons. So when they were around the computer, they knew to check and see what was new. We changed their whole way of doing business.”

Innovative technologies and workflows continue to change the landscape of clinical pathology, Dr. Wolk says, but with them comes greater responsibility. Dr. Wolk uses the term “interventional diagnostics” to describe the recent push to monitor the effects of new technologies on patient outcomes, such as might result from shortening the time to when a patient receives targeted antimicrobial therapy. This information can, in turn, be used to generate evidence-based clinical microbiology practices. “These practices will drastically improve the way we assess new technology, moving from a model where we assess accuracy with no metrics to prove patient benefit, to a model in which patient benefit metrics become the norm.”

Those metrics involve tracking morbidity, mortality, health care cost, length of hospital stay, duration of antibiotic or antiviral treatment, and other factors before and after the technology is implemented, she explains. “It’s a statistical approach—rather than presuming, ‘We have this new technology so we should test for all of these microbes just because we have the tools,’ maybe we should rapidly and critically examine the impact to patient care.”

From where Dr. Wolk stands, the future of pathology and laboratory medicine will call for greater ownership of the postanalytical impact of laboratory tests, ranging from improvements in patient care to reductions in health care costs and increased adoption of antibiotic stewardship. “Laboratories spend a lot of time and effort examining analytical and preanalytical phases of testing,” Dr. Wolk notes. “But from my perspective, the larger impact will come from our postanalytical footprint—it’s in this phase that we can prove these new laboratory tests are actually worth what we’re paying for them.”

In her lifetime, she hopes, “we’ll have an ability to prove the laboratory impact in ways we never could before.”

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