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COLLEGE OF AMERICAN PATHOLOGISTS

Triple play in lab's MALDI-TOF efforts

Karen Titus

When James Musser, MD, PhD, and colleagues at Houston's The Methodist Hospital submitted a study for publication this fall (to "one of the prestigious weeklies based in a northeastern part of the country," says Dr. Musser), they were prepared to answer questions from reviewers.

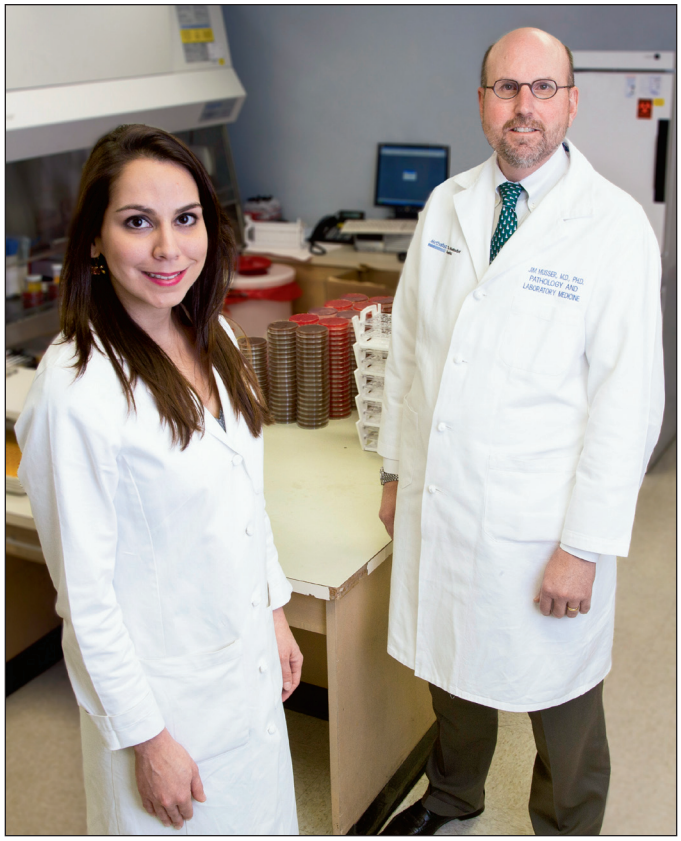
The study tackled rapid pathogen identification and antimicrobial stewardship—topics near and dear to the hearts of microbiology laboratories, infectious disease specialists, pharmacists, and anyone scared silly by the book *Rising Plague*. In an era when antibiotics seem to be applied as liberally as sheep dip, looking at ways to use them more judiciously would merit national discussion.

The study (since published in early online release Dec. 6 in the *Archives of Pathology & Laboratory Medicine*) used MALDI-TOF mass spectrometry to quickly identify gram-negative bloodstream infections directly from positive blood culture bottles. This was followed immediately by direct antimicrobial agent susceptibility testing. The lab then put the information into the hands of an ID pharmacist, who made herself available 24/7.

All of it impressive. But when the study landed at the aforementioned weekly, the main reviewer's primary reaction was less a question than a statement. "Which was, 'You changed multiple things,'" says Dr. Musser, chair of pathology and genomic medicine, The Methodist Hospital System.

"Our response was: 'Absolutely.'"

Changing three processes simultaneously, as Dr. Musser has learned, can be a difficult mental leap for some to make. Others who've read the paper responded similarly to the journal reviewer, he says: *But, but, but, but, you didn't change just one thing. So we can't precisely determine....* That, of course, was precisely the point. Incremental changes, while helpful, tend to bring small improvements; if labs want to see big gains, they'll have to start making equally big changes, he says.



Bruce Bennett

Dr. James Musser and Dr. Katherine Perez showed how patient care improves and money is saved when MALDI-TOF mass spec, susceptibility testing, and antimicrobial stewardship are linked. "You get a bit of a sticker shock at first," Dr. Musser says, "but the downstream cost savings are tremendous."

While not exactly a call to arms, the study lays bare how labs generate data and send it on to other providers and (one would hope) to the bedside, and how they interact with colleagues. It's plain to Dr. Musser that re-engineering could strengthen pathology service.

"As we go forward—and by 'we,' I mean our pathology profession—it's going to be essential to examine very closely every process that we do, and ask the question, If we re-engineer an entire process, what sort of efficiencies, cost savings, and improved care, if any, will we achieve?" In this case, as the microbiology laboratory considered how best to use its recently acquired MALDI-TOF mass spectrometer, Dr. Musser and his colleagues identified three critical bottlenecks in patient care. The goal: bring more speed to each.

Hitting a triple, so to speak, has brought big improvements at The Methodist Hospital, a 1,000-bed quaternary care academic institution. The study included 112 patients in the preintervention group and 107 in the intervention group.

The authors report that in the preintervention period (August to November 2011), final ID and susceptibility results took 47.1 hours; in the intervention period (February to May 2012), final results took 24.4 hours. Mean time to gram-negative organism ID was 36.6 hours in the preintervention group versus 10.2 hours in the intervention arm. The most common primary source of bloodstream infection was urinary tract, followed by intravascular catheter-associated. *Escherichia coli* was isolated most frequently in both groups, followed by *Klebsiella* ssp.

During the intervention period, the lab used the MALDI-TOF MS for routine species identification of gram-negative bacteria from early-positive blood cultures. If a gram-negative organism was identified, the specimen was analyzed by MALDI-TOF MS and set up for direct, rapid antimicrobial susceptibility testing. The ID pharmacist was notified immediately of each result. The MALDI-TOF MS analysis was done three times daily at first, with a fourth shift, at night, added later.

Mean length of stay in the preintervention group (100 survivors) was 11.9 days, with a mean hospital cost of $45,709. In the intervention group (101 survivors), LOS was 9.3 days, with a cost of $26,162.

Dr. Musser says the overall cost savings would be $19 million per year for the main hospital, looking only at gram-negative pathogens. Extrapolating it to other pathogens, including gram positives, mycobacteria, yeast, and fungi, over the entire five-hospital Methodist system in Houston, savings could reach close to $30 million annually. (Since the study, Methodist has added gram-positives and plans to add other pathogens as well, including mycobacteria. It also purchased a second MALDI-TOF and will increase the run frequency on the instruments.) The cost-saving figures were generated by the hospital, not pathology, says Dr. Musser, who adds that he considers them to be accurate and conservative numbers.

During the intervention period, the ID pharmacist recommended 246 interventions to the prescribing physician; 225 were accepted. Overall, adjustments occurred, on average, 75 hours from time-to-positivity in 80 percent of patients preintervention, while in the intervention group the time dropped to 29 hours, on average, in 94 percent of patients. Furthermore, at 24 hours from onset of bloodstream infection, 19.6 percent of preintervention patients were on inactive therapy, versus 4.7 percent in the intervention group.

The ID pharmacist involved in the study, Katherine K. Perez, PharmD, doesn't mince words when she talks about what those differences mean. When she first heard how quickly the results would be made available to clinicians, she recalls thinking, "This was going to blow everything out of the water."

There's no shortage of literature showing that with bloodstream infections in general, and gram-negative bacteremia in particular, time is the enemy. "Each hour is directly correlated with an increased risk in mortality," says Dr. Perez, clinical specialist in infectious diseases, The Methodist Hospital-Pharmacy Services.

She was a highly enthusiastic supporter of the study—she personally volunteered to be on call round-the-clock. Granted, she was in residency at the time. "But I've always been a bug nerd, and I saw an opportunity to really change the way we manage patients with infectious diseases. I'm pretty passionate about this." Not responding immediately, she says, can't be justified when every hour counts.

Crucially, the laboratory reported results by phone. "We do not rely on simply conventional passive electronic communication," Dr. Musser says. The ID pharmacist (Dr. Perez now shares on-call duties with three other colleagues, including a resident) also has privileges to look at the patient's electronic medical record and will adjust antimicrobial therapy as needed, directly or in consultation with the treating physician. "It's active, rather than what labs have traditionally done for decades—passive electronic reporting," he says.

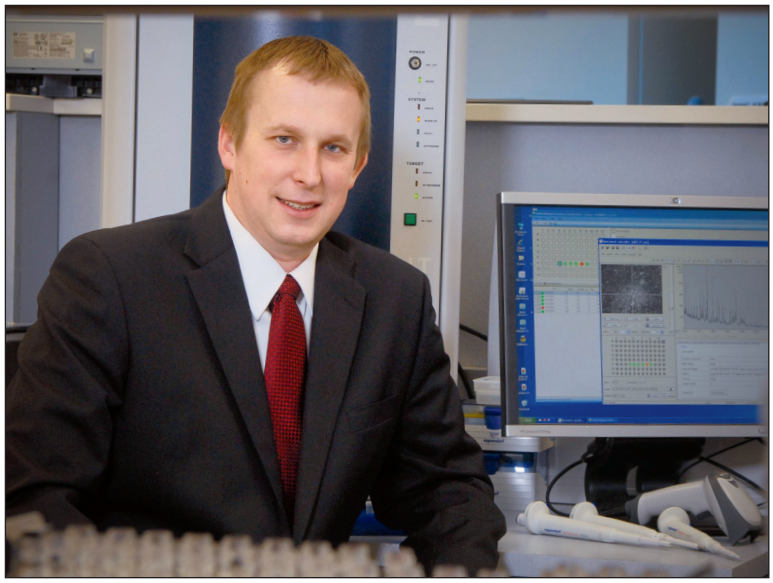
That required clinicians to make a mental shift as well. Dr. Perez says that when she first started calling treating physicians with results, some were miffed, asking, "Why hasn't anyone called me about this?" Dr. Perez laughs at the recollection. "That's exactly what I was doing."

Part of her job was filtering phone calls; not every call required active intervention. "That's something physicians like—not being paged with every single result. Rather, they're being paged with the results that matter."

These days, Dr. Perez is also trying to make things a little easier on the lab. Rather than interrupting workflow with phone calls to the ID pharmacists, she's been working with the IT department to have results paged through the medical record.

Not all her pharmacy colleagues shared her initial enthusiasm. "I wish I knew why," she says. It's possible, she theorizes, that no one could fully envision just how dramatic the difference would be, how rapidly results would come sailing in. In antimicrobial stewardship, acting 48 hours faster must seem almost magical, like waking up on a January morning and realizing you live in Santa Barbara, not South Bend.

An unexpected bonus: being able to share with laboratory staff (within the bounds of HIPAA, naturally) how the faster results helped patient care. About a month into the study, in a workshop she led with the microbiology staff, Dr. Perez showed how the data were affecting patient care. "After that, they began asking me how patients were doing," she says.



Dr. Ledeboer and his colleagues are using Nanosphere's Verigene gram-positive blood culture test for direct detection. "We're seeing a much more rapid response to our laboratory data," he says.

If it sounds like antimicrobial stewardship is just as important as the lab processes, well, yes. Ed Septimus, MD, clinical professor of internal medicine, Texas A&M Health Science Center, Houston, puts it bluntly. "If the information provided isn't used, it's a waste of money."

"Antimicrobial stewardship can't be done in a silo," he continues. "You have to close the loop. Which Dr. Musser did," says Dr. Septimus, who reviewed the article, at Dr. Musser's request, before its initial submission.

Nathan Ledeboer, PhD, echoes the Houston contingent. He points to a study published last year (Frye AM, et al. *J Clin Microbiol*. 2012;50:127–133), looking at the clinical impact of using RT-PCR to rapidly identify staphylococcal bacteremia. While time to identification dropped significantly, the authors wrote, time to optimal antibiotic therapy did not. Says Dr. Ledeboer: "The interesting thing about this study was that they didn't include an antimicrobial stewardship component. It's a nice piece of data to say, you have to have that multidisciplinary buy-in for this to be successful. And that's true whether it's MALDI-TOF, a nucleic acid test, whatever."

Dr. Ledeboer, assistant professor of pathology, Medical College of Wisconsin, and director of microbiology and molecular diagnostics, Dynacare Laboratories and Froedtert Hospital, Milwaukee, has also been looking at linking MALDI-TOF, susceptibility testing, and antimicrobial stewardship. His lab initially published a paper looking at MALDI-TOF for direct identification of blood cultures. A subsequent study (presented as an abstract at the Infectious Diseases Society of America annual meeting in 2011), using retrospective chart review, determined the impact of that direct identification had it been used clinically. As in the Methodist study, the results are intriguing.

"Our average duration of empiric antibiotic therapy at Froedtert Hospital is about 66 hours today," says Dr. Ledeboer. "Had we had that MALDI-TOF information, we would have been able to reduce it down to about 15 hours."

Because the FDA has not yet approved MALDI-TOF for clinical use, Dr. Ledeboer and his colleagues are using a nucleic acid test—Nanosphere's Verigene gram-positive blood culture test—for direct detection and have been for several months. "We're seeing a much more rapid response to our laboratory data," he says. The lab calls physicians directly to notify them of a positive gram stain result and identification. A report is also automatically sent, in real time, to the antimicrobial stewardship pharmacist, who also follows up with the clinician.

"The pharmacy has been incredibly supportive," Dr. Ledeboer says. It helped, he says, that the lab devoted plenty of time to educate everyone about the new process prior to launch. He and his colleagues talked about the test's advantages and limitations, what it could and couldn't identify, and how they would report the results. "There are so many players whose hands touch a positive blood culture," he says: critical care, ID, pharmacy, and hospitalists. The lab had to make them all comfortable.

Like Methodist, the lab is also exploring other uses for MALDI-TOF. It recently submitted a paper to the *Journal of Clinical Microbiology* describing a new database and a new extraction method for identifying *Mycobacterium* species. The data were presented at the 2012 ICAAC meeting.

Methodist is now studying how well its three-pronged approach will work in its other four system hospitals, which gets to the heart of an important question: Is it realistic for smaller facilities to start thinking about rapid testing and antimicrobial stewardship? "If one is a stand-alone 300-bed, largely community hospital with a different patient profile, this may not have as dramatic an impact," Dr. Musser says.

One obvious difference is that not all facilities enjoy the luxury of an ID pharmacist, Dr. Septimus notes—less than 10 percent of community hospitals can support one, he says. But, he hastens to add, clinical pharmacists can fill the role if they're given additional training in infectious diseases.

For a program like this to work elsewhere, it also requires a physician champion, Dr. Septimus says. In some places, the pharmacist-clinician relationship is rock solid. In others, physicians don't take kindly to a pharmacist telling them what to do. In such places, a physician will need to step in. "Because ultimately, stewardship is

about physician behavior. And sometimes you have to deal with a difficult physician. We all have them," says Dr. Septimus, who is also an adult infectious diseases physician and hospital epidemiologist. The best person to talk to physicians is often a fellow physician, albeit one who can talk to them collegially. "Stewardship is a big team sport," says Dr. Septimus, who, being from Texas, should know.

Real results have persuasive powers of their own, says Dr. Perez. "When you call physicians with objective data, it's very difficult for them to turn their heads away."

For his part, Dr. Musser says he encountered almost no resistance to the lab's bold proposal. When the vastly improved speeds became clear only a few patients into the study, in fact, "There was zero pushback." If anything, he says, he was met with incredulity from clinicians who were stunned by the speedy TATs. In one instance an intensivist said, "We don't believe they can do it this fast. Can they really do it this fast?" Adds Dr. Musser: "Seriously. I'm not making this up."

Smaller hospitals might also blanch at the price tag. MALDI-TOF is expensive—about $200,000. "It's like a new car," Dr. Musser says. "You get a bit of a sticker shock at first, but the downstream cost savings are tremendous. We can no longer do cost accounting with blinders on in the pathology department."

Sandra Richter, MD, and her colleagues at Cleveland Clinic have been doing clinical trial work using both of the MALDI-TOF mass spec instruments on the market, Bruker's Biotyper and bioMérieux's Vitek MS. "It seems like a no-brainer to bring this technology into the clinical lab," says Dr. Richter, director of bacteriology in the departments of Clinical Pathology and Molecular Pathology. Based on her work with both systems in the research lab, as well as what has been reported in the literature, "It's clear that this is a giant step forward in the accuracy and speed of organism identification routinely reported by the lab. Both systems provide reliable results that compare quite well to either reference biochemicals or molecular sequencing identification."

Dr. Richter finds it reasonable to look beyond the purchase price. The data she's seen suggest large institutions could recoup their costs within two years (Neville SA, et al. *J Clin Microbiol.* 2011;49:2980–2984; Gaillot O, et al. *J Clin Microbiol.* 2011;49:4412). Even the initial price doesn't leave her deeply unsettled. "Compared to, say, a chemistry analyzer, it doesn't seem expensive."

For now, the technology is for research use only. "We need some FDA-approved applications for MALDI so we can start billing," Dr. Ledeboer says.

Both bioMérieux and Bruker planned to submit their systems to the FDA in early 2013 and anticipate clearance during the year.

The companies are refreshingly understated when they talk about the future of MALDI-TOF.

Bruker's George Goedesky, executive director, MALDI Biotyper for the Americas, says laboratories will need to consider not only accuracy but also ease of use and throughput. "All technologies—sequencing, mass spec, NAT—will have a place," he says. "The issue is, what questions will best be answered by each of these technologies?"

When MALDI-TOF does become available for clinical use, it won't be as if the FDA has waved a magic wand over the technology, immediately freeing it for the masses. What labs may not fully appreciate, says bioMérieux's Nedal Safwat, PhD, is that the RUO and IVD databases will be treated differently. The MALDI-TOF database is a growing component, and new organisms or updates to existing organisms will be in the RUO database format, he says, while the IVD database (still in clinical trials) will reflect the new additions once FDA clearance is granted. The RUO database will be used more for research, and the database will grow in research settings. (Dr. Safwat says the regulation of both databases is under discussion now.) This is no small consideration if, as some predict, labs first run samples on the IVD database, and, if they can't make an identification, potentially turn to the RUO database. The biggest implications would be for smaller institutions.

"Not every institution would be able to access both databases. RUO databases are meant for larger institutions where they can conduct research with an open architecture where new data can be archived for database research and development," says Dr. Safwat, the company's director of product marketing, U.S. Clinical Microbiology.

Asked about how MALDI-TOF mass spec might fit into the community setting, Dr. Safwat says that he's seeing "big hype in the market about getting MALDI," in part because of the prestige it might confer on the institution. "It's image perception," he says.

MALDI-TOF might not be a good fit for every hospital right now, he allows, unless they have high volumes and a diversity of organisms. For slow-growing organisms—filamentous fungi, mycobacteria, molds, yeast—MALDI-TOF is a superior technology, he says. But for routine isolates, it might be harder to justify its use. "And the hospital has to enable the physician to act on the results as soon as they're available and have antibiotic susceptibility results shortly after to target therapy further," Dr. Safwat says.

While many are actively exploring applications for strain typing and resistance testing, Dr. Safwat speaks cautiously. "It's premature to say that it's going to be able to do either. We see some major challenges." He sees next-generation mass spec focusing on proteomic analysis, enzyme markers for resistance, and even drug metabolism.

As even the vendors make clear, MALDI-TOF isn't the only player on stage (and MALDI may not even be the final form of mass spec in the lab). Next-generation sequencing is quickly moving on the scene and can address limitations found in current MALDI-TOF and NAT technologies. Each approach, like a poem, has its strengths and mysteries.

Regardless of the specific characters and their roles, the unfolding story will be one of transformation for the microbiology laboratory, says Dr. Ledeboer.

Ask ID physicians today if they would like automatic typing in their next-generation identification system, says Dr. Ledeboer, and "They'll say it would be nice, but they won't rank it high on their list."

Ask the question differently, and the response will be far more enthusiastic, he predicts. "What if instead of typing being confirmatory of an outbreak, it could identify outbreaks early?" he says. If the lab used a technology like mass spec or next-gen sequencing, and included bioinformatics in the identification scheme, "We could actually look for sequences of enterococcus, sequences of staph, in real time, on a unit-by-unit basis."

"It's going to change the value of microbiology's data," Dr. Ledeboer says. "It's also going to change how microbiology does its work, in that we're going to depend a lot more on software, a lot more on bioinformatics."

That will shift the science of microbiology. Until now, microbiology has largely been a confirmatory science, for a very good reason: "We have to culture everything," he says. But now, he says, microbiology has the potential to become a prospective science. □

Karen Titus is CAP TODAY *contributing editor and co-managing editor.*