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Rapid ID from positive blood culture: Labs tally gains

Anne Paxton

Fresh from its Dec. 27, 2020 FDA clearance, the Bruker MALDI Sepsityper Kit US IVD promises to provide microbiology laboratories with a universal, rapid sepsis identification solution. With the Bruker MALDI Biotyper platform's reference library covering 491 organisms, the Sepsityper's ability to identify pathogens directly from positive blood cultures in suspected bacterial or fungal sepsis cases delivers an "order of magnitude increase" in the number of microorganisms that can be identified through PCR detection, said Wolfgang Pusch, Bruker Daltonics executive vice president of microbiology and diagnostics, in a company statement.


Mckinney

But that's no news to the microbiology laboratories in the United States that were early adopters of the Sepsityper Kit and have long taken advantage of its ability to return a pathogen identification in less than 30 minutes from a positive blood culture bottle alert. Finding that this feature can save up to 24 hours in time-to-result for many identifications, these laboratories started using Sepsityper more than six years ago when it was labeled research use only.

"A lot of laboratories are realizing they need to use MALDI-TOF MS technology for microbial identification," says one early adopter, Ike Northern, MT(ASCP)SM, director of infectious disease testing and immunology for CompuNet Clinical Laboratories in Ohio, which acquired a MALDI Biotyper in 2015. He has found that using the MALDI Sepsityper Kit 50 on the Biotyper is a more cost-effective means of fast identification than PCR syndromic panels.

For Tekita Mckinney, MT(ASCP), MEd, infectious disease and PCR laboratory manager at Le Bonheur Children's Hospital in Memphis, Sepsityper was the main reason her laboratory bought its MALDI-TOF instrument in 2012.

Mckinney's laboratory performs some 80,000 tests per year for pediatric patients throughout the mid-South. Before she heard about Bruker's MALDI-TOF in 2011, the laboratory was aiming for two improvements.

"We're a small pediatric hospital but we take care of west Tennessee and also Mississippi, Arkansas, and Georgia. Our patients are very sick. With almost half of our 255 beds being critical care beds and with such a high acuity rate, we need to be able to reliably identify organisms, especially in blood cultures and other cultures, quickly. You're talking about babies who may weigh only a couple of pounds and are fighting for their lives."

"Patients may come to the ED with fevers, and we take a blood culture and send them home." Typically the culture takes two days to become positive. "After that, we're not seeing many positives." But a positive would mean emotional turmoil for a child's family while the pathogen was being analyzed. "We would call to say, 'Your baby may be septic; you need to come into the hospital.' We would hook the child up to IV antibiotics. And 18 to 24 hours later we may say it's a contaminant, not a pathogen." Her laboratory wanted to be able to reduce the chances of that happening.

It also wanted to lessen the risk of resistance patterns. "You don't want that starting out on day 30 of life," Mckinney says. "By being able to identify things more quickly, we are able to intervene early and keep our kids on mild organism-targeted antibiotics and keep the resistance patterns from starting while they're here."

She met with instrument makers and soon convinced the hospital's infectious disease physicians of the need for Bruker's MALDI Biotyper, which was up, running, and reporting out clinically by February 2013, aided by the Vitek for antimicrobial susceptibility testing and Bactec FX for blood culture monitoring. Now, with the Sepsityper Kit 50, once the lab has a positive blood culture, "within the hour we will know what is causing the problem," Mckinney says.

"Before the Biotyper was FDA approved, we had validated 80 percent of the organisms we would see in a positive blood culture here at this hospital. Now that they've added the FDA-approved library, we're completely covered," Mckinney says. Some organisms can be seen in adults that don't tend to appear in kids, she notes, so her lab doesn't have all the resistance patterns and organisms that adults would see. "But everything we need, we have it with this instrument. With this new technology, even though there is a waiting period until the organism grows, once it grows or is identified in a blood culture environment, then you're down to minutes. This means that a person in the hospital can maybe go home a day earlier."

With the Biotyper, she explains, "you can perform the direct colony method from any agar plate" and get an identification from the MALDI. "If we have an organism we can identify with just drop biochemicals, like *Staphylococcus aureus*, we could do the drop test. We wouldn't necessarily put that on the MALDI. But if we had a Gram-negative rod that we couldn't identify with biochemicals, we would use the MALDI. And in a few minutes, we would know what we are dealing with. We'll put the identification in the computer instead of the susceptibility. So there again, we're still a day ahead."

Le Bonheur's infectious disease laboratory has one MALDI-TOF bench operating 24 hours a day with two people reading on day and night shifts. "By 3 AM, the doctors know everything we know. So they don't have to call us at 7 AM. It's already documented in the chart."

The payoffs from these time savings are so substantial that they make the upfront cost of the MALDI-TOF of minimal importance, Mckinney says. "We save so much money from not having to bring the patient back to the hospital to hook up to IVs for 24 hours. And it's not a lot out of our pocket because the consumables for this instrument are minor. We buy the Sepsityper Kit and the standard consumables, but it pays for itself in our being able to deliver this excellent patient care."

Her laboratory could well expand its MALDI uses in the future. "We've done preliminary type things that we haven't implemented yet, just having research students look at urines and spinal fluids tested directly on the MALDI-TOF," Mckinney says. "We're always interested in new technology here. As the hospital brings on more transplant children and others, the needs grow and change. So we try to grow with it."

The microbiology laboratory at CompuNet Clinical Laboratories, which is a regional reference lab and a core lab for Premier Health System, runs 60,000 blood cultures per year. CompuNet was not one of the first in line to buy a Bruker Biotyper, but that was not for lack of trying.

"We kind of struggled with getting good identifications for some organisms, just because there weren't great methods out there to identify them," Northern says. "The Bruker MALDI-TOF was in the budget for three years before the administration approved it." But in 2015, "they finally gave me approval. And we've been super happy with it." His laboratory is now contemplating acquiring a second instrument.

Standard culture samples as well as positive blood culture samples can be analyzed on the same MALDI Biotyper; they just entail different processes for getting the sample ready to put on the instrument, Northern explains. "If you're working off of a plate, as with a urine culture, you pick up some of the colony from the organism right off the plate and put it on the target plate. But when you're working with the Sepsityper, your organism is in the blood, so you have to process your sample to concentrate the organism in order to put it on the MALDI-TOF. So it uses different parameters when it knows that it's the Sepsityper versus a colony."

About two years ago, his laboratory began to use the Sepsityper Kit 50 to get a rapid identification from a positive blood culture bottle. That's been one of the areas of biggest impact, Northern says.

"Initially, we wanted to just be able to identify the organisms, the Gram-negative bacilli and staphylococci and so on, that our MicroScan, which we were using for susceptibility testing, could not identify. If we did a MicroScan and got a low probability ID, we'd have to do an API or some other method for identification. We had a special kit for *Neisseria*, a special kit for non-fermenters, a special kit for yeast. And we wanted to try to eliminate as many of those things as possible."

Next they began to test *Nocardia* and *Actinomyces* and the results were good, Northern says. "But where the Biotyper helped us the most on our identifications was with anaerobes."

Pre-MALDI-TOF, "we'd have to take the organism and streak it out and put it in three different environments to see if it was an anaerobic organism. And once you did that, you had to take another day to identify it. So it took two additional days to get an identification once you saw that organism on the plate." In the year after acquiring the MALDI-TOF, "we were getting identifications on the first day." That enabled the lab to cut the staff needed to do those anaerobic cultures each day from two to one.

Instead of doing aerotolerances, "we just identified everything on the plate the first day with the MALDI-TOF. All identifications of yeast are done on the same day, which is two or three days quicker than what we had before." Identifications of mycobacteria, fungi, and molds will also soon be online, he says.

At an upfront cost of roughly $200,000, the MALDI-TOF looks like an expensive instrument, and it is, Northern admits, even though it fits on a tabletop. "But in a hospital

environment, it's pretty easy to justify that expense. You can save several thousands of dollars per patient by reducing their length of stay by even one day. So it doesn't take a lot of patients for you to recoup that money."

Using the Sepsityper Kit 50 is less costly than using a large PCR panel, he says. An analysis of CompuNet's 60,000 blood cultures in 2019 found 6,600 positive blood cultures, an 11 percent positivity rate. Comparing the cost of analyzing half of those PBCs with a Sepsityper Kit (at $9.50 per test) versus half with a multiplex PCR test (at $105 per test) reveals a dramatic difference in cost-effectiveness.

Even adding in the tech time needed for the Sepsityper Kit 50, at an annual cost of $38,000, the savings from using the Sepsityper rather than the PCR test was $277,150 in a year's time.

Recently added options have enhanced the MALDI's usefulness, Northern says. "Bruker has a new [MBT Subtyping] module that allows you to do subtyping. So if you have an outbreak in your hospital—say you had five cases of *Staph aureus* that you think may be a nosocomial infection—you can take those five isolates and do the subtyping using the MALDI and tell whether it's the same organism or not." In the past, "we'd have had to send those off to different laboratories to do other types of tests."

Bruker is continuing to develop that module as well as a module to detect other resistance markers. "When you have a resistance gene, it's going to change the structure of the proteins, and if we can figure out exactly what those proteins are and where you can find them on the mass spectrometer, eventually we will be able to pick out resistant organisms when we put them on the MALDI."

CompuNet conducted a validation study of the Sepsityper Kit 50 in 2017 using the Biotyper when it was still research use only. The purpose was to verify the rapid identification ability of the system from positive blood culture bottles. Parallel identifications were performed on 106 PBC bottles once the bottle flagged positive on the blood culture instrument: one using the Sepsityper Kit 50 and the other using MALDI-TOF and conventional biochemical ID from solid media.

The laboratory obtained accurate identification in 87 of the 106 PBCs (82 percent), and 74 of the identifications, or 70 percent, were identified to the species level while 13 (12 percent) were identified to the genus level. The study demonstrated that the Sepsityper Kit 50 using MALDI-TOF technology is a suitable method for rapid identification from PBC bottles, Northern says.

Is it possible that the MALDI could eventually replace most identification testing in the microbiology lab? "I would say if you had enough MALDI-TOFs, you could replace 90 percent of it," Northern estimates. "Right now we don't have enough room in our MALDI-TOF to do all of our identifications. So we still use our MicroScan for identifications for most of our Gram-negative rods. We'd need one or two more MALDIs to do all of our identifications."

One potential pitfall of the MALDI's identification process, Northern says, is getting a decent sample. "If it grows on a plate, most of the time we're going to be able to identify it on the MALDI-TOF. But some different types of culture media are not always validated for use on the MALDI-TOF." He and colleagues have done their own validation of four or five other culture media commonly used by the laboratory.

Some microbes can be trickier to identify using a MALDI, Northern says. "It seems like there are a couple of organisms that might be a bit more finicky to work with and didn't identify quite so well." But it's more likely to be a question of the quality of the sample, in his view. "I think mostly it's because those blood cultures had a low number of organisms in the sample to begin with." While there are some organisms the lab has been unable to get the Biotyper to identify—for example, the MALDI-TOF in general cannot differentiate between *Shigella* and *Escherichia coli*—"it's been far fewer than with our old methods."

Case studies written by one of CompuNet's infectious disease physicians show how the Bruker Sepsityper solution had effectively helped a patient with postsurgical complications, another with a history of heroin drug use, and a third with weakness and failure to thrive. In the first case, there was a quick identification with the Sepsityper Kit 50 "and the physician was astute enough to realize that the patient had had the same organism [*Enterobacter cloacae*] months before, a carbapenemase-producing organism," Northern says. "So they put the patient immediately on antibiotics to treat a resistant organism. Without the Sepsityper, it would have taken them two more days to figure that out."

In the case of the patient with a history of heroin use, when blood cultures were positive for Gram-positive cocci based on Gram stain 18 hours after admission, the admitting hospital assumed endocarditis, due to the patient's history, and ordered a transesophageal echocardiogram to evaluate further. But one hour later, the Biotyper with Sepsityper Kit 50 identified *Streptococcus pyogenes*. That bacteria indicated, instead, targeted treatment with ampicillin and an ultrasound of the patient's arm, which revealed extensive thrombosis of the axillary and subclavian vein. The patient had a good clinical response after six weeks of IV ampicillin.

Similarly, therapy for a 77-year-old admitted to the emergency department for weakness and failure to thrive was initially vancomycin and piperacillin-tazobactam. But blood cultures were positive for Gram-positive cocci on the first day of hospitalization. Shortly afterward, the Sepsityper Kit 50 results showed *Enterococcus faecalis*. So within 24 hours of admission the patient was switched to

ampicillin and gentamicin, on which she remained for six weeks without issue.

The average physician, Northern says, may not be quick to change therapy based on just an identification off the MALDI-TOF or the Sepsityper. "But your infectious disease physicians are thrilled by this." When he began to have discussions at CompuNet about acquiring a MALDI-TOF instrument, they wanted to see reduced use of antibiotics or use of more appropriate therapies. "But I told them there were studies to show that if you did these rapid identification methods and you don't have a mechanism to make sure that someone makes a change when you get the positive result, it doesn't make sense" to acquire a MALDI-TOF.

"The facilities that had someone who would get the result and take action on it saw significant changes in treatment," Northern says. As a result, CompuNet took care to have the antibiotic stewardship committee work with the pharmacists. "They came up with a process that works well for our system. They're taking action on the results quickly after they get them."

The experience at Le Bonheur in Memphis is similar, Mckinney says. "We always ask the physicians what they are getting from the microbiology laboratory that they are most proud of," she says. "And they always say the MALDI-TOF. They say it has changed how they can get their jobs done." □

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