Rapid Blood Culture Identification: The Value of a Randomized Trial

Angela M. Caliendo

Department of Medicine, Alpert Medical School of Brown University, Providence, Rhode Island

(See the Major Article by Banerjee et al on pages 1071–80.)

Keywords. rapid molecular diagnostics; sepsis.

After decades of relatively modest technological advances in the clinical microbiology laboratory, in the past 10 years there has been an explosion of new technologies including a wide array of molecular methods, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS), and next-generation sequencing, as well as advances in laboratory automation. As our experience with these technologies has progressed, there is a marked improvement in the ability to rapidly identify pathogens using fully integrated systems that are simple to use. Remarkably, earlier this year the first Clinical Laboratory Improvement Amendments–waived molecular test was cleared by the US Food and Drug Administration for the detection of influenza A and B, meaning that the testing is so straightforward that it can be performed by nonlaboratory personnel. Moreover, the results are available in 20 minutes. This takes molecular testing out of the clinical laboratory and into clinics, offices, and emergency rooms closer to the patient, providing results in a time frame that can impact clinical decisions. Furthermore, fully automated highly multiplexed molecular methods are available that can detect 20 or more targets in a single assay and provide results in about an hour.

Although newer technologies may be more rapid and at times more accurate than traditional methods, some are also considerably more expensive. Given that clinical laboratories are experiencing extreme financial pressure, it is absolutely imperative that we show the value of these new, more costly methods. This is a challenging undertaking, as there are limited outcomes studies in clinical microbiology; we are more adept at validating the analytical performance of new tests than we are at establishing their clinical utility and cost effectiveness. Additional barriers arise because to have maximum impact, multicenter studies are often needed, which require considerable infrastructure and have no clear funding mechanism. All of these factors have contributed to the limited information regarding the most effective applications of these newer technologies.

The rapid diagnosis of sepsis remains an important unmet clinical need; while we await the development of the ideal biomarker to identify sepsis early or tests to detect bacterial pathogens directly from blood without the need for culture, we are left with approaches to improve on the identification of organisms once the blood cultures become positive. Two technologies have been used to rapidly identify bacteria and yeast directly from the blood cultures: MALDI-TOF MS and multiplexed molecular tests. MALDI-TOF MS is very rapid and can identify a wide array of bacteria and yeast, as the current databases are quite extensive. There are molecular assays that target a limited number of pathogens (Staphylococcus aureus and the mecA gene), whereas others detect the most common bacteria and yeast isolated from blood cultures and include a few resistance genes. Several studies [1–5] have been published using both of these technologies, and some patterns have emerged: Testing of the positive blood cultures needs to be done on demand rather than batch testing, and an active stewardship team is needed to act on the results. If results are just reported in the electronic medical record, there is little improvement in time to escalation and de-escalation of antibiotics. These initial studies have been intriguing and provided important information on the logistics of both the laboratory testing and stewardship programs needed to implement this type of program. In addition, some of these studies showed decreased mortality, decreased cost, and reduced length of stay. Although these studies were limited in their observational design and use of historical controls, the results were...
encouraging and important in moving the field forward.

In this issue of Clinical Infectious Diseases, Banerjee et al report the first prospective randomized controlled trial to demonstrate benefit of a rapid, highly multiplexed polymerase chain reaction (PCR)–based test in identifying bacteria and yeast from positive blood cultures [6]. The molecular testing was done with the FilmArray Blood Culture ID Panel (BioFire Diagnostics/bioMérieux, Salt Lake City, Utah), which identifies >20 common bacteria and Candida to either the genus or species level and detects the resistance genes mecA, vanA/B, and blaoXA. The study was designed to assess the value of the rapid molecular test as well as the role of the stewardship program. There were 3 arms to the study: (1) standard blood culture bottle processing, which at the Mayo Clinic includes routine use of MALDI-TOF MS for pathogen identification from colonies isolated from positive blood cultures; (2) rapid multiplex PCR with templated comments; and (3) rapid multiplex PCR with templated comments and real-time antimicrobial stewardship.

There are several important design features of this study. The FilmArray test was performed 24 hours a day, 7 days a week as soon as the bottle signaled positive, results of the PCR test and the template comments were both called to the clinical service and reported electronically, and the antimicrobial stewardship program paged an infectious diseases clinician or pharmacist with results 24/7.

As expected, the time from Gram stain result to organism identification was shorter in both intervention arms than in the control group (for organisms included in the PCR panel). The more important question is how the information is used to manage antibiotic utilization. In this regard, there are several interesting observations from this study, including that more appropriate antibiotic use (less broad-spectrum and more narrow-spectrum antibiotic use, and less treatment of contaminants) was seen in both the rapid molecular testing arms with or without antibiotic stewardship. This may be due to the effectiveness of the content of the template comments and/or the fact that the comments were called to the team in addition to being reported in the electronic medical record. Both intervention arms escalated antibiotics at the same rate, but only the intervention arm with the antibiotic stewardship program de-escalated antibiotics more rapidly than the control arm. Although the clinical service had the information, they were less likely than infectious diseases clinicians or pharmacists to narrow antibiotic coverage. Unfortunately, the study was not powered to show a difference in mortality, length of stay, or cost, all of which are important considerations for centers contemplating implementation of the program described in this study.

Banerjee et al also underscore some of the challenges associated with rapid diagnostics from positive blood cultures. The multiplex assay was able to detect 80% of the pathogens that grew in blood cultures. Whether this can be significantly improved upon is questionable, as there are a wide array of organisms that make up the 20% missed by the current panel, although studies such as this give manufacturers an idea of how to approach the next best group of pathogens to add to the panel. There were discrepancies between the identification and/or susceptibility result seen with the PCR test compared with conventional methods. The error rate was about 3%, and many of these discrepancies were due to mixed infections. Identification of all bacteria in the culture remains a limitation of both MALDI-TOF MS and multiplexed PCR technologies. It is unclear if this can be improved upon, given that the organisms in a mixed culture may not be present in the same concentration and may not replicate at the same rate.

The authors are to be commended on performing a well-designed outcomes study that contributes significant information to the field of rapid diagnostics. The study was designed to assess not only the value of the rapid molecular test but also what level of stewardship adds value.

An important consideration is whether this approach could or should be implemented in other medical centers. There are several issues to consider: The control arm used MALDI-TOF MS to rapidly identify colonies from the plate, which is considerably faster than would occur with conventional identification systems relying on bacterial growth; it is possible that the laboratories that rely on these slower methods of identification may see an even greater improvement in antibiotic usage than observed in this study. The value of rapid detection of resistance determinants may be influenced by the prevalence of Klebsiella pneumoniae carbapenemase–producing organisms; the authors report low resistance rates at the Mayo Clinic. An important question is whether laboratories can perform the FilmArray test 24/7; although the test is easy to perform, staffed throughout the night and weekends would be required for on-demand testing. The ability to implement a 24/7 stewardship program will be challenging for many centers. Although non–infectious diseases clinicians are comfortable escalating antibiotics, they appear to be less willing to de-escalate antibiotics. If a 24/7 stewardship program is not an option, calling and reporting the templated comments 24/7 clearly has value in guiding appropriate antibiotic usage.

This relatively large, well-designed study points to the difficulties in determining the cost effectiveness and value of rapid diagnostics. Although the authors showed more appropriate use of antibiotics and the most optimal use with a stewardship team, they were unable to show differences in clinical outcomes, length of stay, cost, and mortality. A large multicenter clinical study will be needed to address these important issues.

Note

Potential conflict of interest. The author has received grant support from T2 Biosystems and Hologic, and consulting fees from Roche Molecular, Abbott Molecular/IBIS, Quidel, Nanosphere, BioFire Diagnostics, InCellDx, and Cubist.
The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References