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REVIEW

New Developments in Clinical Bacteriology Laboratories

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Abstract

There are a number of changes underway in modern clinical bacteriology laboratories. Panel-based molecular diagnostics are now available for numerous applications, including, but not limited to, detection of bacteria and select antibacterial resistance markers in positive blood culture bottles, detection of acute gastroenteritis pathogens in stool, and detection of selected causes of acute meningitis and encephalitis in the cerebrospinal fluid. Today, rapid point-of-care nucleic acid amplification tests are bringing the accuracy of sophisticated molecular diagnostics closer to patients. A proteomic technology, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, is enabling rapid, accurate, and cost-effective identification of bacteria, as well as fungi, recovered in cultures. Laboratory automation, common in chemistry laboratories, is now available for clinical bacteriology laboratories. Finally, there are several technologies under development, such as rapid phenotypic antimicrobial susceptibility testing, whole-genome sequencing, and metagenomic analysis for the detection of bacteria in clinical specimens. It is helpful for clinicians to be aware of the pace of new development in their bacteriology laboratory to enable appropriate test ordering, to enable test interpretation, and to work with their laboratories and antimicrobial stewardship programs to ensure that new technology is implemented to optimally improve patient care.

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During the past several years, a number of transformations have taken place in clinical bacteriology laboratories, as they move away from traditional methods in place for over a century toward a new generation of tests. These changes, often made "behind the scenes" without the cognizance of clinicians, have the potential to improve patient care. Clinicians should be mindful of innovations in their laboratory, including the sensitivity, specificity, and advantages and disadvantages of the tests offered, to inform appropriate test utilization and interpretation. With the pace of the development of new technology, there is a potential gap between the laboratory and the end user of microbiology information. To address this issue, I will describe recent advances implemented in clinical bacteriology laboratories and highlight others that may be realized in the near future.

ADVANCES IN TRADITIONAL MOLECULAR DIAGNOSTICS

Nucleic acid amplification tests, such as polymerase chain reaction (PCR), have become part of daily clinical practice. They allow rapid and sensitive detection of microorganisms, including bacteria, as well as viruses, parasites, and fungi, directly from clinical specimens. Until recently, they have been the domain of large, sophisticated laboratories and have typically been ordered and performed one by one. An advantage of bacterial culture is that it enables growth of many different organism types in a single test. Today, molecular tests are increasingly being offered as automated, easy-to-use, rapid panels assembled on the basis of clinically significant organisms likely to be present in the specimen being tested. In some cases, antibacterial resistance genes are detected simultaneously. These new US Food and Drug Administration (FDA)–cleared diagnostics have been packaged into pouches, cartridges, and so on, that may be inoculated with clinical specimens after minimal processing and that are automatically run on specifically designed instruments, putting them within the technical reach of laboratories of all sizes and enabling 24/7 availability. Some provide results in as little as an hour.

ARTICLE HIGHLIGHTS

- Panel-based molecular diagnostics are available for numerous applications, including, but not limited to, detection of bacteria and antimicrobial resistance markers in positive blood culture bottles, detection of acute gastroenteritis pathogens in stool, and detection of select causes of acute meningitis and encephalitis in the cerebrospinal fluid.
- Rapid point-of-care nucleic acid amplification tests are available, bringing the accuracy of sophisticated molecular diagnostics to the bedside.
- Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry has been implemented in many clinical microbiology laboratories and is associated with rapid, accurate, and cost-effective identification of bacteria recovered in cultures.
- Laboratory automation, standard in chemistry laboratories, is now available for clinical bacteriology laboratories.
- Rapid phenotypic antimicrobial susceptibility testing, whole-genome sequencing, and metagenomic analysis are under development for clinical diagnostic testing.
- Cost-effectiveness and effect on clinical outcomes of new technologies need to be evaluated before widespread adoption; involvement of an antimicrobial stewardship team can be helpful.

Examples of panel-based molecular diagnostics include those designed for testing positive blood culture bottles and those designed for testing stool, respiratory specimens, and cerebrospinal fluid for acute gastrointestinal, respiratory, and central nervous system pathogens, respectively. One limitation is that molecular panels, despite their breadth, test only for the specific organisms targeted. A strategy to overcome this limitation is to use a broad-range bacterial (eg, 16S ribosomal RNA gene) nucleic acid amplification strategy such as PCR, along with sequencing of the amplified product to test normally sterile fluids and tissues.[1] However, broad-range bacterial PCR is not always as sensitive as organism-specific PCR[2,3] and is susceptible to nonspecificity because of the presence of "stray" bacterial DNA associated with specimens, containers, plastics, and/or reagents.

Two companies' broad molecular panels are approved by the FDA for testing positive blood culture bottles (Table 1): the FilmArray Blood Culture Identification Panel (Biofire Diagnostics, LLC) and the Verigene Gram-Positive Blood Culture Test and Gram-Negative Blood Culture Test (Nanosphere, Inc.). Today, instead of receiving a Gram stain morphology report when a blood culture bottle signals positive and waiting a day or more for the identification of the organism(s) involved, these assays provide microbial identification and detect select antibacterial resistance genes in a 1- to 2.5-h time frame. Although they are accurate and revolutionary in terms of the speed at which they identify bacteria and yeasts in positive blood culture bottles and, to some extent, characterize resistance of the associated bacteria, they have limitations. They do not always detect all bacteria and yeasts in mixed infections, even when pathogens are a part of the panel. Also, they do not assign resistance genes to individual species in mixed infections. For example, if *mecA* is detected in the context of mixed infection with *Staphylococcus aureus* and another species of *Staphylococcus*, it is impossible to determine which organism is methicillin-resistant (or whether both are methicillin-resistant). These assays do not detect organisms in all patients with positive blood cultures. In my laboratory experience, approximately four-fifths of patients with positive blood cultures will have positive results with the FilmArray Blood Culture Identification Panel.[4] Detection rates may be higher in locations where typical organisms are expected (eg, medical/surgical wards and intensive care units) than in those where more unusual organisms may be more frequent (eg, cancer or transplant centers). These assays are expensive and, because of the workflow involved, are not typically orderable by clinicians. Laboratories, if they choose to use these tests, must decide when to deploy them. In order for results to affect patient care, results must be immediately delivered to health care practitioners, who, in turn, are knowledgeable of the status of the patient involved and, more importantly, prepared to rapidly adjust treatment regimens on the basis of the results. Test results will be forthcoming from the laboratory at any time the laboratory is staffed (24/7 in our case). Our laboratory group performed a randomized controlled clinical trial evaluating rapid panel-based molecular testing of positive blood culture bottles, in which we found that

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