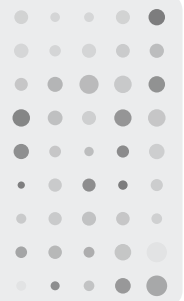


Molecular Tests Provide a Better Alternative to Stool Culture for GI Cases



Introduction

Clinical laboratories are increasingly adopting molecular assays as an alternative to the tedious, time-consuming stool cultures that have long been the mainstay for testing patients who might have infectious diarrhea or conditions such as *Salmonella* or *Campylobacter*. With an estimated 1.7 billion cases of childhood diarrheal disease occurring annually around the world, this is a significant advance for gastroenteritis testing.¹

One of the biggest challenges in diagnosing patients with diarrhea is the sheer number of possible causes, along with significant overlap in symptoms. Diarrheal disease can be caused by bacteria, viruses, and parasites, as well as non-infectious sources, such as toxins, food allergies, and medications. Conventional testing paradigms involve a broad range of methods, including culture and microscopy, which are plagued by low sensitivity, especially since the pathogens are all too easy to miss if the wrong part of the sample is examined.

Molecular tests for gastroenteritis offer many advantages to stool culture. These tests streamline the diagnostic process, covering a number of likely pathogens in a single assay with excellent sensitivity and specificity. Results are generated much faster than traditional culture techniques, allowing clinicians to get patients on the right treatment — or off the wrong treatment — in hours rather than days. The best molecular tests make it possible to choose from targeted or syndromic testing, or even to create custom subpanels as needed. Taken together, these advantages can make molecular assays far more cost-effective than conventional stool culture approaches.

Part of the reason the shift to molecular tests is happening now is the release of new clinical guidelines from the Infectious Diseases Society of America (IDSA). These guidelines include detailed recommendations for whether, when, who, and how to test for gastrointestinal infections.

New Guidelines

In late 2017 and early 2018, the IDSA released new clinical practice guidelines for the treatment and testing of infectious diarrhea and *Clostridium difficile*, respectively. Although best practices vary in the guidelines for each of these diseases, molecular testing has an important role in both.

For infectious diarrhea, testing is recommended based on patient-specific factors, such as exposure history, immune competency, clinical course of the illness, and symptoms; these factors also help guide which pathogens to test for. For example, IDSA recommends *C. diff* testing only for patients with a history of antibiotic use or who are experiencing nosocomial diarrhea.² Patients who have recently traveled to resource-challenged areas should be tested for parasites, while testing for bacterial pathogens is favored when patients present with fever, dysentery, severe pain, or signs of sepsis. Generally, patients with otherwise good health should get more targeted testing, while immunocompromised patients should be tested for a broader panel of possible pathogens.

The guidelines also offer recommendations for when and how molecular testing should be used, either to supplement or to replace standard cultures. For example, in cases where bacteremia or enteric fever is suspected, the IDSA's infectious diarrhea guidelines encourage the use of culture-independent methods such as "panel-based multiplex molecular diagnostics." The same document also highlights the importance of faster turnaround times for results from molecular methods. "Earlier, directed treatment may become more feasible with the increasing use of [culture-independent diagnostic testing], facilitating organism identification," according to the IDSA. Within the *C. diff* testing guidelines, molecular tests are recommended as a standalone option, or as part of a 2-step algorithm, depending on institutional criteria for patient testing.

Real-world Results

Some clinical laboratory professionals have recently presented results from their experiences in making the shift from stool culture to molecular tests for gastroenteritis cases. Daniel Rhoads, Associate Director of Microbiology at University Hospitals Cleveland Medical Center, and Jose Alexander, Medical & Public Health Microbiologist at Florida Hospital in Orlando, gave talks on this subject in a *CAP Today* webinar on April 25, 2018, entitled “Fecal Matters: Molecular GI Testing — An Approach Based on Clinical Guidelines.”³

Rhoads’ lab serves 12 acute care hospitals and several outpatient facilities; his team is responsible for more than 300 urine cultures and more than 200 blood cultures per day. The lab no longer routinely performs stool cultures, having adopted the VERIGENE® System⁴ and its rapid-result Enteric Pathogens Test (EP),⁵ which the lab runs an average of 12 times each day. This test includes norovirus, which was not covered by the lab’s previous methods, Rhoads said, pointing out that this is a major advantage since norovirus is a common source of gastroenteritis and its detection triggers specific protocols for healthcare workers. Last winter, 8% of the lab’s specimens came back positive for norovirus — a major improvement in diagnosing this highly contagious disease in the system’s patient population.

In the same webinar, Alexander presented data from seven hospitals and multiple nursing homes in Florida, including a large microbiology department with more than 40 full-time medical technologists. In 2017, his team ran 7,200 stool cultures, but the lab has now shifted to molecular assays also on the VERIGENE System. That decision was partly based on a cost analysis that revealed the cost per culture — when factoring in operator time — was nearly \$53. Switching to a PCR-based approach has allowed his team to accelerate turnaround time, reduce hands-on time, increase sensitivity, and redistribute staff and responsibilities, he said. Stool cultures routinely took five days to return results, but with the VERIGENE EP Test, Alexander is aiming to reduce turnaround time to six hours. Like Rhoads’ lab in Ohio, the Florida lab no longer offers stool culture as a standalone option on its test menu.

According to Alexander, molecular diagnostics are moving into microbiology faster than ever before, and any lab that has not yet faced this decision will have to do so in the near future. Molecular tests offer a notable improvement “for detection of the pathogen and the benefit of the patient [as well as] for the benefit of the laboratory itself,” he said. In his lab, the VERIGENE EP Test makes it possible to routinely screen for more organisms and a broader range of Shiga toxin-producing genes than they previously could. Alexander is using the system to create custom subpanels, including a bacterial panel, a viral panel, and individual tests for norovirus or rotavirus. This flexibility is particularly important for compliance with the IDSA guidelines. Some molecular assays include *C. diff* detection in GI panels that cannot be customized, Alexander noted, meaning that teams using those tests must ignore the IDSA recommendations about the very limited set of cases where *C. diff* testing is appropriate.

Two other clinical lab directors shared their molecular diagnostic adoption stories in a workshop at the 2018 ASM Microbe meeting.⁶ In one presentation, Mir Noorbash, Director of Microbiology and Molecular at the Sutter Health Shared Laboratory, spoke about the challenges his reference lab has in northern California serving 24 acute care hospital systems and 26 clinics or medical foundations. Bacterial stool cultures were particularly expensive in Noorbash’s lab due to California regulations about who can perform these tests, so molecular test alternatives were attractive for their potential to lower costs by reducing hands-on time. A shift to the VERIGENE EP Test, he believed, could lead to dramatically shorter turnaround times, easier use, and better reliability. The use of such tests has been shown to reduce the length of hospital stays, he told attendees.

The other presentation came from Morgan Pence, Director of Clinical and Molecular Microbiology at Cook Children’s Medical Center in Fort Worth, Texas. The lab serves a 400-bed pediatric hospital and previously performed about 3,000 stool cultures annually, but those take up to four days to produce useful results — and even longer if susceptibility testing is needed. In Pence’s lab, molecular tests cost more to run than stool cultures, but their use is still justified due

to their improved sensitivity and specificity, faster run times, ability to test for norovirus, and contribution to a reduction in unnecessary follow-up testing and imaging.

Pence's team brought in the VERIGENE EP Test in late 2016, starting with a validation study of 106 specimens including stool samples and rectal swabs. The lack of *C. diff* on the panel was one deciding factor in its implementation since children are not supposed to be tested for this organism, except in very specific situations. In the validation study, there were only three discordant results compared to stool culture, and further testing showed that the molecular test had been correct for two of those results. The study found accuracy was 99.1%, sensitivity was 98.6%, and specificity was 100%. "It actually was really impressive," Pence said. Since then, the lab has run more than 5,500 specimens and has gotten positive feedback from clinicians and technicians alike. The

molecular test has allowed the lab to discontinue some single-organism tests, both internal and send-out, which has helped streamline their test menu.

Conclusion

Molecular tests offer significant improvement over traditional stool cultures, generating more accurate results in a much shorter time frame for optimal patient care. Clinical labs looking to make the switch must consider many factors, such as compliance with the IDSA and other guidelines, the flexibility of testing, whether and when to include *C. diff* detection, and cost-effectiveness. A test platform that allows users to create custom subpanels and choose which organisms to include offers the greatest flexibility for meeting the needs of each lab's patient population and for adhering to evolving clinical practice guidelines, now and in the future.

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