FROM THE LAB

Infectious Disease Management:

Does PCR Make a Difference?

Physicians rely on their repertoire of knowledge to identify likely bacterial pathogens in patients and then initiate treatment. Based on a "best guess," the empiric selection of antibiotic(s) is the basis of antibiotic stewardship—picking the right antibiotic against the most likely pathogen while minimizing resistance[1] and then waiting for patient response. The waiting is what draws physicians' ire as they anxiously anticipate patient response or await culture results that will identify the bacteria and antibiotic sensitivities—all the while painfully aware that an antibiotic delay could significantly impact patient morbidity or mortality.

Each year 2 million people get an antibiotic-resistant infections, and close to 23,000 of those people die. The annual costs of fighting resistant bacterial infections in the U.S. are estimated to be between $21 billion and $34 billion.[1]

In response to the escalating endemic, the Federal Government established a Federal Task Force in 2015 to combat antibiotic-resistant bacteria. This task force created a national action plan, with the target goal of 2025, to support research institutions in developing innovative solutions to the problem; one goal is to advance the development and use of rapid and innovative diagnostic tests to identify and characterize resistant bacteria.[2]

Fortunately, real time-PCR (RT-PCR) has emerged as a practical tool that satisfies the growing demand for speed and accuracy in microbial identification and antibiotic sensitivity through advances in technology.

An Overview of PCR

Polymerase chain reaction (PCR) is a sensitive in-vitro technique that enzymatically replicates DNA segments using oligonucleotide primers that hybridize to the target DNA sequence. A fluid sample containing a pathogen usually has DNA levels too small to detect, but PCR exponentially amplifies the number of DNA copies to facilitate analysis.

Types of PCR: Over the last 20 years, modified versions of PCR have expanded their utility and versatility. Multiplex PCR allows simultaneous detection of several target sequences. Nested PCR is a technique that increases segment sensitivity and specificity, and reverse transcriptase PCR allows RNA transcription into complementary DNA that is easily amplified; the most significant advancement has been in developing quantitative real-time PCR. This technique combines amplification and detection of amplified products in a single reaction vessel so that the product's measurement coincides with DNA synthesis.[3] It has been through the National Center for Biotechnology Information's extraordinary efforts to create a national database of antibiotic-resistant organisms (NDARO) to enable researchers to sequence bacterial and viral genomes, which further allows the cataloging of genes to serve as amplification targets for many pathogens.[4]

Reliability and accuracy of PCR: There is evidence that RT-PCR is more sensitive for many organisms than cell culture in detecting pathogens.

In a study funded by the French Ministry of Health, Angelakis' group compared real-time quantitative PCR and culture to diagnose emerging rickettsioses. The group obtained skin biopsies from 145 patients suspected of having rickettsiosis. Collections of serology samples from 53 patients during the acute phase and 26 patients during an acute and convalescent-phase were used as a benchmark to measure qPCR and culture results' sensitivity. Compared to serology, qPCR sensitivity was 82%, whereas culture sensitivity was 29.4% compared to serology.[5]

In a study conducted by Sakaguchi, 23 pediatric cancer patients, ranging in age from one month to 18 years, BrRNA RT-qPCR was used to detect bacteria in blood samples from a patient population that commonly experiences febrile neutropenia. This study's significance is that primer sequences specific to genomic segments of bacteria widely known to be associated with febrile neutropenia enhanced specificity. The results of this study illustrate several essential points regarding qPCR;[6]

- The bacterial detection rate was significantly higher relative to standard blood culture. Blood culture detected four bacterial species, while BrRNA RT-qPCR was able to detect 16 bacteria, including those picked up by the blood culture. Included control samples eliminated the concern of cross-reactivity and false-positives.
- Processing time for preliminary culture results was 24 hours, while processing time for BrRNA RTqPCR was 5 hours.
- Required sample collection was quantitatively smaller using BrRNA RT-qPCR (e.g., 1 mL), relative to culture requirements (e.g., 10 mL).

Both studies clearly illustrate RT-PCR's advantages over culture results concerning smaller quantity detection, faster processing, and greater detection sensitivity. The second study further illustrates the benefit of enhanced RT-PCR specificity by using primer sequences to target bacteria.

RT-PCR has high specificity and sensitivity, but is there concordance between culture-derived antibiotic susceptibility and qPCR detection of DNA gene sequences known to confer antibiotic resistance in bacteria? To answer that question, Collins' group conducted a study comparing culture definitive identification/susceptibility testing against multiplexed PCR that rapidly identifies pathogens and detects gene sequences that confer antibiotic resistance. Using bronchoalveolar lavage fluid (BALF) samples from patients with pneumonia, they found 97% positive percent agreement and 99.9% negative percent agreement for microbial identification, and 77.8% concordance in detecting antibiotic resistance.[7]

PCR impact on treatment outcome: As illustrated from the previous studies, an early start in management with pathogen-specific antibiotics is clinically superior to empirical treatment and is associated with a lower risk of developing antibiotic-resistant bacteria.

Improved treatment outcome through the use of RT-PCR is conditional on the principle that early treatment using the correct antibiotic will result in quicker recovery (e.g., reduced sick-days from work, reduced hospital days, earlier resumption of normal lifestyle), a lower rate of disease complications, and greater patient satisfaction (e.g., less treatment ambiguity, faster positive results). A 2016 Study that supports this principle looked at retrospective data analysis; he showed that qPCR had 99% sensitivity and 100% specificity in detecting malarial parasites. By initiating treatment based on qPCR rather than by blood thick smear, he found that the duration of blood-stage parasitemia was shorted by 3.5 days and resulted in a 78% reduction in disease-related adverse events.[8]

Treatment outcome bearing on patient satisfaction and payor reimbursement: When gauging patient satisfaction, psychological studies have shown an association between satisfaction and embodiment. Patients want a tangible consequence that fits their perception of successful treatment outcome.[9] A concordance between clinical success and patient satisfaction requires early physician inclusion of the patient in the decision-making process. By exploring the patient's treatment expectation(s), the physician can then address management options that target patient expectations or address knowledge gaps if patient expectations are not realistic. Utilizing RT-PCR can shorten hospital days, prevent hospital readmissions, and reduce disease complications; these are the tangible outcomes patients expect.

Patient satisfaction and disease management outcomes are part of the measures reviewed by the Centers for Medicare & Medicaid Services (CMS) in determining reimbursement for hospital and physician services. They are part of the CMS's meaningful measures initiative in 2017 to identify high-priority areas for quality measurement and improvement to better patient outcomes. CMS reviews disease outcomes for inclusion in the 30-day risk-standardized mortality measure and the 30-day risk-standardized readmission measure in the hospital quality initiative. By improving treatment outcomes using qPCR, physician/institutions can realize more significant gains in payor reimbursement.

RT-PCR can improve patient satisfaction and
INCREASE PAYOR REIMBURSEMENT

So...Does PCR Make a Difference?

In addressing the topic question, "does PCR make a difference"? Real-time PCR (RT-PCR) relative to culture and blood thick smear makes a significant difference. While reviewing past clinical studies, RT-PCR demonstrated greater sensitivity and specificity than many cell cultures. With better treatment outcomes, RT-PCR can improve patient satisfaction and

increase Payor reimbursement by reducing hospital days and preventing hospital readmissions. But the most important benefit is that incorporating RT-PCR will enhance patient quality of care through improved antibiotic stewardship.

At Assurance Scientific Laboratories, our mission is to help arm clinicians with the data needed to be good antibiotic stewards. If you have any questions about how our testing solutions can help your practice or facility, contact us at ClientServices@AssuranceScientific.com or 855.319.4459.

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