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Rapid Molecular Panels: What Is in the Best Interest of the Patient? A Review of Patient Outcome Studies for Multiplex Panels Used in Bloodstream, Respiratory, and Neurological Infections

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Abstract

In the clinical microbiology laboratory, the focus when choosing new tests is often on performance, turnaround time, and labor needs. This review examines available rapid, multiplexed tests from a different perspective: that of the patient. It considers whether published evidence supports the notion that use of rapid, on-demand tests (as opposed to batched testing) leads to better patient outcomes and whether broad, syndrome-based, multiplexed panels translate into better patient care than narrower monoplex or duplex assays. Finally, we examine how synergy between the clinical microbiology and antimicrobial stewardship programs is necessary to ensure that rapid tests, if implemented, impact the patients they are designed to support.

Introduction

The raison d'être of an antimicrobial stewardship program (ASP) was stated succinctly by the Infectious Diseases Society of America (IDSA) in an early guidance document on the subject: to "optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, including toxicity, the selection of pathogenic organisms and the emergence of resistance" [1]. What ASP interventions are effective? A recent systematic review published by the Cochrane Collaboration affirmed the positive impact of empirical treatment adherence to published guidelines, de-escalation of antimicrobial treatment, a switch from intravenous to oral, therapeutic drug monitoring, and the use of restricted antimicrobial lists on clinical outcomes and hospital costs [2].

The clinical microbiology laboratory is a critical partner in an ASP's quest to optimize antimicrobial utilization and patient outcomes and reduce hospital costs. Importantly, the emergence of rapid, user-friendly, multiplexed assays has great potential to facilitate earlier ASP intervention [3,4]. However, the impact of rapid diagnostic tests (RDTs) on patient outcomes is clearer for some assays and specimen types than for others. Even less clear is how to optimize collaboration between laboratories and ASPs to maximize impact at the bedside. Here, we review published data related to clinical outcomes attributed to the use of current RDTs that detect pathogens in patients with bloodstream infections, respiratory infections, and neurological infections. In each case, we consider the following. Do we need molecular testing? Would rapid, on-demand testing be worthwhile to patients, or would batched testing suffice? And, finally, is there evidence supporting the use of the broad, syndromic, multiplexed tests, or do narrower monoplex or duplex assays suffice?

Quality Measures

Before proceeding, it is useful to briefly review various metrics that studies have used to measure

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the effectiveness of ASP interventions, including the implementation of an RDT. They can be categorized into two groups: process measures and outcome measures [5]. Process measures include the duration of antimicrobial therapy and time to antimicrobial optimization (e.g., through escalation, in which a narrow-spectrum antimicrobial regimen is broadened, or through de-escalation, which involves the reverse). Examples of outcome measures include length of stay (LOS); clinical cure (e.g., "clearance" of a bloodstream infection from blood cultures); and incidence of 30-day mortality, 30-day readmission, and adverse drug reactions. Hospital costs are also considered outcome measures. Both process measures and outcome measures can be meaningful when assessing the impact of an ASP intervention on patients and costs [6].

RDTs in Bloodstream Infections

Bloodstream infections (BSIs) and their complications are associated with considerable morbidity and mortality. The wide spectrum of organisms to which BSIs are attributed, coupled with the urgency associated with BSI diagnosis, make rapid, highly sensitive, multiplexed assays attractive for this purpose. Not surprisingly, the impact of RDTs on patient care and outcomes has been most comprehensively studied in positive blood cultures. The goal of early provision of organism identification and antimicrobial susceptibility status is earlier optimization or discontinuation of antimicrobials. This, in turn, may translate into shorter LOS, reduced mortality, and decreased hospital costs.

Available RDTs detect and identify organisms present in positive blood culture bottles using a variety of different technologies, including real-time PCR (FilmArray BCID [bioMérieux, Durham, NC] and Xpert MRSA/SA BC [Cepheid, Sunnyvale, CA]), microarrays (Verigene BC-GP and Verigene BC-GN [Luminex, Austin, TX]), peptide nucleic acid hybridization (PNA) (PNA FISH [OpGen, Germantown, MD]), and matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS). Test turnaround time is typically 2 to 2.5 hours but may be shorter, with the PNA QuickFISH BC method (OpGen, Germantown, MD) having the shortest test time of 20 minutes. The FilmArray and Verigene assays detect Gram-positive and Gram-negative bacteria. FilmArray also detects *Candida* species. In addition, the FilmArray BCID has the ability to detect a limited group of antimicrobial resistance determinants, including *mecA*, *vanA*, and *blaKPC*. Verigene BC-GN also detects the extended-spectrum β-lactamase determinant *blaCTX-M* and the carbapenemase determinants *blaNDM*, *blaIMP*, *blaVIM*, and *blaOXA-48*. GenMark Diagnostics (Carlsbad, CA) recently announced CE Mark for ePlex Blood Culture Identification Gram-Positive and Gram-Negative Panels. Additionally, the recently FDA-cleared Accelerate Pheno assay (Accelerate Diagnostics, Tucson, AZ) uses time-lapse microscopy and image analysis to report antimicrobial susceptibility testing data for pre-defined panels of drugs on isolates in blood cultures within 6 hours.

Various systematic reviews, literature reviews, and commentaries have examined whether rapid testing in positive blood cultures improves patient outcomes [3,4,7,8]. In 2016, as part of updated guidelines on implementation of an ASP, IDSA and the Society for Healthcare Epidemiology (SHEA) performed a literature review focusing on this question [7]. Citing data based on implementation of FilmArray BCID, MALDI-TOF MS, PNA FISH assays, Xpert MRSA/SA BC, and the now unavailable BD GeneOhm StaphSR assay, the authors reported statistically significant reductions in time to initiation of appropriate antibiotic therapy, rates of recurrence of bacteremia, LOS, mortality, and hospital costs when RDTs in positive blood cultures were coupled with ASP intervention. This resulted in a recommendation supporting the use of RDTs on positive blood cultures combined with ASP [7].

One study deserves specific mention. Banerjee and colleagues published a non-blinded, randomized, controlled trial with patients stratified into three arms: standard blood culture processing (n = 207), FilmArray BCID with a templated report (n = 198), and BCID with a templated report plus ASP intervention in the form of real-time audit and feedback (n = 212). While the study was not adequately powered to show differences in LOS, mortality, or hospital costs, they found that time from Gram stain report to appropriate antimicrobial de-escalation or escalation was shortest in the BCID plus ASP intervention arm [9]. Banerjee et al., therefore, provided much needed, high-quality evidence that documented the incremental additional benefit of coupling RDTs with ASP intervention in positive blood cultures.

RDTs in Respiratory Infections

Prior to the emergence of widely available rapid molecular assays, rapid antigen detection tests (for influenza virus and respiratory syncytial virus), direct fluorescent antibody testing, viral culture, and laboratory-developed molecular tests (LDTs) were used for detection of respiratory viruses. The poor sensitivity of rapid antigen tests, direct fluorescent-antibody assay (DFA), and viral culture favored the use of molecular tests. However, while LDTs at the time were often highly sensitive and specific, the technical skill required to implement LDT panels was difficult to achieve in many laboratories, and the labor required necessitated batched testing.

Today, in many laboratories, these tests have largely given way to rapid, automated respiratory pathogen panel testing that can be performed on demand. These tests include the FilmArray Respiratory Panel (bioMérieux, Durham, NC; 17 viral targets plus *Bordetella pertussis*, *Chlamydophila pneumoniae*, and *Mycoplasma pneumoniae*), Verigene RP plus and RP flex (Luminex, Austin, TX; 13 viral targets plus *B. pertussis*, *Bordetella parapertussis/Bordetella bronchiseptica*, and *Bordetella holmesii*), various Xpert Flu/RSV assays (Cepheid, Sunnyvale, CA), and the Simplexa Flu/RSA assays (Focus Diagnostics, Cypress, CA).

Like RDTs in positive blood cultures, the use of rapid testing during respiratory illness provides opportunities to optimize antimicrobial administration. If a respiratory virus is detected and the illness is attributed to it, unnecessary antibiotics can be mitigated or discontinued early. In cases involving influenza A/B, RDTs may expedite treatment with antivirals (e.g., oseltamivir), potentially reducing the duration of the illness, although its impact on

preventing clinical complications remains unclear [10]. Additionally, it is uncertain if detection of respiratory viruses other than influenza virus (e.g., parainfluenza virus, respiratory syncytial virus, metapneumovirus, the coronaviruses, adenovirus, and rhinovirus) using molecular tests in panel-based assays (rapid or batched format) translates into benefits at the patient level. As antivirals are not routinely used to treat these viruses, to derive clinical benefit from rapid testing, clinical teams would need to feel a degree of reassurance from positive results to expedite discontinuation of antimicrobials and discharge from the hospital. This may be challenging, particularly with sick patients.

In the medical literature, data supporting the use of current RDTs for respiratory pathogen detection is sparser than for blood cultures. Rappo and colleagues [11] used a retrospective, quasi-experimental design to compare outcomes of patients with positive viral studies during the respiratory virus season prior to implementation of nasopharyngeal testing (n = 198) with FilmArray RP (BioFire, Salt Lake City, UT) and during the season when the assay was implemented (n = 139). Pre-implementation, a variety of respiratory viral tests were offered, including rapid antigen testing, the Luminex xTAG Respiratory Viral Panel (Luminex, Austin, TX), DFA, and viral culture on nasopharyngeal swabs, and in some cases, bronchoalveolar lavage specimens. Following statistical adjustment for potential confounders, including age, immune status, asthma diagnosis, and admission to the intensive care unit, in the multivariate analysis, among patients diagnosed with influenza, LOS, duration of antimicrobial administration, and number of chest radiographs performed were reduced after implementation of FilmArray RP. The same phenomenon was not observed in patients in whom respiratory viruses other than influenza virus were detected [11]. The study ultimately suggested that while rapid diagnosis of influenza virus infection may have a positive impact on patient outcomes, rapid detection of other respiratory viruses may not lead to similar benefits and may call into question the need for panel testing of a broad range of respiratory pathogens.

Rogers and colleagues [12] reported a lack of impact on LOS but a possible reduction in duration of antibiotic use after implementing the FilmArray RP in a pediatric population. Using a similar retrospective, quasi-experimental design, clinical outcomes during the respiratory viral season prior to implementation of FilmArray RP (n = 365) were compared with those during the season in which RP was implemented (n = 771). Prior to RP, a multiplexed LDT PCR assay detecting 11 viral targets was performed once daily, 7 days per week, for respiratory viral testing. Univariate analysis showed a mean reduction in antimicrobial days of 0.4 days that was statistically significant, but there was no change in LOS following implementation of FilmArray RP. Further, they reported that RP implementation reduced LOS only in patients with a positive result by FilmArray RP. This study suggested that a switch from batched PCR-based respiratory viral panel testing to a broader, rapid respiratory pathogen panel test may not robustly impact patient care or outcomes [12]. Notably, the prevalence of influenza virus, the only treatable virus in the cohort and perhaps the most severe of the respiratory infections, was not evenly matched between the pre- and post-intervention groups; therefore, bias may have been introduced, which could have affected the study conclusions.

Finally, in a non-blinded study, Brendish and colleagues compared outcomes for 362 patients randomized to FilmArray RP performed in a point-of-care format with those for 358 patients who were assigned to routine care (control) [13]. In the control group, the clinical team determined if testing needed to be pursued. When viral studies were requested, a PCR assay that included nine viral targets was performed in a centralized laboratory in a batched fashion. Following multivariable adjustment for a variety of possible confounding variables, there were no differences in the proportion of patients who were started on antimicrobials, duration of antimicrobial use, or isolation days between the two groups. However, there was a mean 1.1-day reduction in hospital stay (95% confidence interval, –2.2 to –0.3 days; P = 0.04). Of note, 17% of the RP group tested positive for influenza A/B virus, but only 10% were positive in the control group. Further, only 45% of the controls underwent testing for respiratory viruses. As in the study by Rappo et al., testing in the control group involved "routine clinical care" and the "judgment of the responsible clinical team," which is difficult to generalize to other settings.

In their guidelines on implementation of ASPs, IDSA and SHEA recommended that rapid viral testing be pursued for respiratory pathogens in an effort to reduce the use of inappropriate antibiotics, but the authors acknowledged that the recommendation was weak and based on low-quality evidence [7]. Assessment of the clinical impact of implementing rapid respiratory testing, therefore, appears to be ongoing and an emerging area of research. It is important to note that none of the studies described how ASP was integrated into the care of the study patients. We need to better define how to optimize the role of ASP when implementing RDTs in respiratory infections, as their role in this context is still unclear. Finally, these studies focus largely on diagnosis of community-acquired respiratory viral infections in immunocompetent patients. The optimal role of RDTs in the detection of nosocomial (hospital-acquired) viral infections and in immunocompromised patients would also benefit from investigation.

RDTs in Meningitis and Encephalitis

There are three rapid assays that are FDA cleared for molecular detection of pathogens from cerebrospinal fluid (CSF). The Xpert EV assay (Cepheid) was FDA cleared in 2007, Simplexa HSV 1 & 2 Direct (Focus Diagnostics) in 2014, and the FilmArray Meningitis/Encephalitis (BioFire, Salt Lake City, UT) in 2015. The last has 7 viral targets (herpes simplex virus 1 [HSV-1], HSV-2, enterovirus, human parechovirus, varicella zoster virus, cytomegalovirus, and human herpesvirus 6) and 6 bacterial targets (*Escherichia coli* K1, *Haemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Streptococcus agalactiae*); and also detects *Cryptococcus neoformans/Cryptococcus gattii*.

Infections of the central nervous system represent some of the most concerning conditions encountered in clinical medicine, with mortality almost certain without treatment. Because of increased morbidity and mortality associated with delayed therapy in HSV

encephalitis and bacterial meningitis, IDSA recommends that acyclovir be administered in patients presenting with encephalitis and that broad-spectrum antibiotics be initiated in suspected cases of bacterial meningitis without waiting for diagnostic testing [14-17]. As with their use in positive blood cultures, for the management of encephalitis and meningitis, RDTs facilitate optimization of antimicrobials that have already been started.

The opportunities for optimization of antimicrobial administration with implementation of these assays are clearest when HSV-1/HSV-2 or enteroviruses are detected and correlate with a clinical picture of viral meningitis. A CSF sample that rapidly tests positive for enterovirus in a patient with aseptic meningitis may be reassuring to a clinical team and lead to expedited discontinuation of antibiotics and acyclovir if the patient appears well. Similarly, HSV meningitis is common with primary genital HSV infection, and early detection could lead to the discontinuation of antibiotics but continuation of acyclovir. Conversely, in non-critical patients with meningitis, a negative result for HSV-1/HSV-2 may prompt discussion of discontinuing this nephrotoxic and neurotoxic antiviral. It is worth noting that in patients with encephalitis, the sensitivity of HSV PCR can vary, particularly early in the course of the illness [18]. In this context, clinicians may be reluctant to alter acyclovir therapy without repeatedly negative HSV-1/HSV-2 test results.

Clinician action based on detection of a bacterial target is more complex, and clinical teams may be reluctant to adjust antimicrobials until conventional cultures and antimicrobial susceptibility testing results are available, particularly if a patient is pediatric or has fulminant meningitis. On the other hand, antimicrobial susceptibility in *H. influenzae*, *L. monocytogenes*, *N. meningitidis*, and *S. agalactiae* tends to be relatively predictable. Detection of these organisms may allow some degree of optimization of the broad-spectrum antimicrobial regimens that are typically started empirically when bacterial meningitis is suspected in an immunocompetent patient [16].

The clinical impact of implementing molecular HSV-1/HSV-2 testing for diagnosis of meningitis and encephalitis has been without controversy, given the poor sensitivity of historical viral culture [19]. However, data supporting the benefit of molecular RDTs in these cases are scarce. Using a retrospective quasi-experimental study design, Van and colleagues [20] recently described the effect of switching from the realStar alphaherpesvirus PCR kit, a multiplex PCR LDT that detects HSV-1, HSV-2, and varicella zoster virus, (alTona Diagnostics, Hamburg, Germany) that was performed once per day, 6 days per week, to the Simplexa HSV 1 and 2 Direct assay, which was performed on demand, 24 hours per day, 7 days per week. This study did not report any positive results, but among their 182 patients with suspected meningitis and/or encephalitis who were tested prior to rapid testing and 181 patients tested post-implementation, the study reported a decrease in the median duration of acyclovir therapy from 29.2 hours to 14.3 hours. The authors felt that, given evidence that renal toxicity and neurotoxicity typically occur within the first 48 hours of intravenous acyclovir administration, this reduction in acyclovir use associated with rapid HSV-1/HSV-2 testing had the potential to be clinically impactful [20].

The positive impact of batched enterovirus PCR LDTs on curtailing unnecessary antibiotic days and LOS is also well documented in the medical literature [21-24] but data demonstrating the incremental benefit of rapid, on-demand provision of enterovirus status by PCR has been limited to very small single-center studies using quasi-experimental designs [25,26].

Regarding bacterial detection in spinal fluid, the FilmArray Meningitis/Encephalitis assay (bioMérieux, Durham, NC) is the first FDA-cleared molecular assay that detects a panel of bacterial targets. Leber et al. reported that the assay detected *H. influenzae* and *S. pneumoniae* from CSF in culture-negative cases that were confirmed using another arbiter PCR assay [27]. Dien Bard and colleagues reported the same for cases of *H. influenzae* and *L. monocytogenes* infection [28]. Of note, in their clinical trial, Leber et al. also reported false-positive results for *S. pneumoniae*, *S. agalactiae*, and *E. coli* and a false-negative result for *S. agalactiae*. Others who have reviewed these results have remarked that institutions using FilmArray ME may wish to consider implementing clinician counseling by clinical laboratories and/or ASP to ensure that positive and negative results are interpreted appropriately [29].

Patient Satisfaction

In addition to clinical outcomes, an equally important measure of quality of care is patient satisfaction, as this may also be an independent determinant of patient outcomes. In other words, if patients are happy with their care, their clinical outcomes may be enhanced. The drivers of patient satisfaction are complex, but a variety of different measurement tools have attempted to incorporate the key elements. Data derived from the federally administered Hospital Consumer Assessment of Healthcare Providers and Systems survey have suggested that patient satisfaction with discharge planning may be associated with lower 30-day hospital readmission rates [30]. More timely and accurate determination of the agent responsible for an infectious condition has great potential to enhance a clinical team's ability to formulate an ideal discharge plan and counsel a patient about the clinical course after discharge. However, this, too, needs evaluation, and any positive impact of rapid testing would need to be weighed against the costs that might be incurred by the patient for the testing.

Conclusions

Which test to choose, if any? In the management of BSIs, there appears to be sufficient evidence to support the use of rapid, multiplexed tests, if tightly coupled with ASP intervention. For patients with respiratory illness, however, we do not appear to have compelling published evidence to support the assertion that multiplexed, one-size-fits-all panels (whether rapid or not) are useful. Interestingly, at least one manufacturer has attempted to offer more flexible use of their respiratory panel. Finally, in patients with meningitis or encephalitis, molecular technologies have greatly enhanced our ability to detect the responsible agents, but we do not appear to have sufficient evidence to assert that rapid (panel

or duplex) testing improves patient care or outcomes. As others have stated previously, we need high-quality, adequately powered studies to determine the impact of available assays on health care processes and patient outcomes [31]. Finally, specific patient populations (e.g., children versus adults and immunocompromised versus immunocompetent individuals) need to be considered and integrated into our decision processes [31,32].

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