Rapid Molecular Diagnostics for Lower Respiratory Tract Infections in Urgent Care: Filling a Selective Gap

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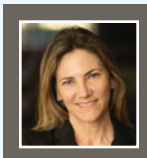
Diagnostic uncertainty and error contribute to inappropriate treatments, which, in turn, can increase morbidity and the costs associated with care.[1,2,3,4] Diagnostic errors can also contribute to unnecessary antibiotic prescribing, contributing to antimicrobial resistance (AMR).[1,5] Lower respiratory tract infections (LRTI) are among the most common urgent care (UC) and emergency department (ED) presentations, and are often associated with diagnostic errors that can invite additional morbidity and cost of care per episode.[6] This persistent clinical challenge calls for continued attention. Diagnostic insights can be a component of the solution.

Among LRTI, community-acquired pneumonia (CAP) remains a leading cause of infectious disease-related hospitalization and death in the United States.[7] Current guidelines recommend 'empiric' therapy based on the most likely pathogen when treating CAP.[8] There is persistent data on the continued opportunity for more selective antibiotic prescribing for LRTIs. That said, a clinician in the UC setting is challenged to balance the risk of a delayed diagnosis and intervention for CAP versus an incorrect intervention by prescribing an antibiotic for symptoms not of a bacterial etiology at the time of evaluation. Data suggests that further reductions in respiratory infection-related antibiotic prescribing should be possible without an increase in hospitalization for pneumonia.[9] Recently, in inpatient and ED settings, syndromic multiplex polymerase chain reaction (PCR)-based testing has shown efficacy in the detection of multiple pathogens simultaneously while facilitating early pathogen-directed treatment, reducing unnecessary use of antibiotics, and shortening the length of pneumonia-related hospitalization.[10-15] These recent findings have applications to the UC setting. Early identification of the infecting pathogen could improve CAP treatment and reduce unnecessary or inappropriate antibiotic use in the UC setting. Yet, access to such testing in outpatient settings has been limited.[16,17]



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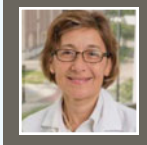

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Syndromic Multiplex PCR-based Test Panels

Multiplex PCR-based panels have high diagnostic accuracy for detecting both viral and bacterial respiratory pathogens with sensitivities and specificities >90% for most pathogens.[18-20] Further, these panels permit "syn-

drome-based" (eg, "area of infection") test ordering in patients with a high pre-test probability that their symptoms are caused by a pathogen and for whom empiric decision-making or available point-of-care testing have proved insufficient. It is postulated that clinical profiles of patients with potential LRTI infections in whom this testing could be beneficial include (1) those with worsening symptoms or recent antibiotic treatment; (2) comorbidities associated with increased risk of morbidity from a LRTI; (3) risk for polymicrobial pathogens; or (4) more severe clinical presentation inviting consideration of additional diagnostic insight (eg, chest x-ray or ED referral).[21,22]

Antimicrobial Selection

As community-acquired antibiotic-resistant infections continue to increase in incidence,[23] molecular diagnostics can offer earlier opportunities for data-driven antibiotic selection and an opportunity to monitor AMR rates faster through the detection of specific gene sequences.[24,25] More than 20 known resistance genes, including *mecA* in MRSA and extended-spectrum β-lactamase genes, can now be directly tested in patient specimens without requiring recovery of the organism.[26,27] The overall sensitivity and specificity of AMR gene targets (compared with culture and susceptibility) are high at 91% and 99%, respectively.[18]

Better Interpretation of Results to Make Treatment Decisions

When multiple organisms are detected in a specimen, a clear understanding of which to treat has been a longstanding microbiologic dilemma. Depending on host and environmental factors, many potentially pathogenic organisms can be found among the normal flora of the respiratory tract, asymptomatically colonizing the host for prolonged durations without causing disease.[28-30,31] As nucleic acids may be detected from nonviable, nonpathogenic, or colonizing organisms, the clinical relevance of the targets detected must be carefully considered.[32,33 34] This is why limiting testing to only patients with significant infectious signs and symptoms (ie, syndromic testing) is so critical. Ordering syndromic panels that are most appropriate to presenting clinical symptoms increases the likelihood that the organisms detected are pathogenic rather than incidental colonizers. Further, semi-quantification scales, which were developed to differentiate the significance of organisms recovered in culture, are now being applied to real-time PCR analysis wherein the semi-quantitative cycle threshold (Ct) value produced for the organism can be correlated with the equivalent value expected based on standard culture (eg, colony forming units [CFU]/ml). Applying Ct to culture based quantitative correlations has shown promising analytic concordance,[35,36] enabling clinicians to more effectively interpret results and make treatment decisions. Meaning, a "4+" pathogen organism finding as measured by "Ct" is likely clinically meaningful and a "1+" is not. Other methods for producing quantitative PCR results include calibration curves or internal calibrators. Molecular tests that couple organism detection with markers of pathogen viability[37] and/or host response[38] may further aid in determining the significance of organisms detected.

Urgent Care Center Workflow

As patient care expenditures face increasing scrutiny, clinicians and administrators are tasked with deciding when tests are worth their costs. Many patients can be evaluated and a care plan formulated without the use of diagnostics. (The expectation is that the clinician is leveraging evidence-based clinical practice guidelines.) Still others will be able to be fully evaluated using point of care (POC) testing. Multiplex PCR assays are positioned to follow. Well-constructed syndromic testing menus simplify test ordering, allowing parallel testing for the most common pathogens based on the patient's symptoms. Multiplex PCR assays provide scale and throughput benefits over single-target assays—a single specimen collected and tested by a single laboratory saves collection and processing time for providers in the clinic.

Operating Cost Considerations

In UC settings, where profitability is driven by patient volume,[39] the clinically judicious use of molecular diagnostics with clinically actionable results can have multiple favorable impacts. Incorporating syndromic, multiplex PCR testing with accurate and actionable results available next day, enables an opportunity for adding next-day patient follow-up in the clinical workflow to adjust treatment based on the diagnosis. Moreover, multiplex testing using a universal collection device simplifies clinical workflows. Clinicians report access to next morning results supports antibiotic stewardship.[40] Ultimately, in order to realize the full potential impact of complex molecular testing for respiratory infections, UC centers will require the lowest achievable cost per test and the ability for results to seamlessly cross into the electronic health record (EHR). Clinician practice and prescribing would also need to be adapted so that rapid results are incorporated into the patient's plan of care. The potential value realized from this change in the UC evaluation of

patients presenting with LRTI symptoms could be less overall testing, less provider time spent following up inappropriately ordered test results, decreased staff time spent in specimen collection, processing, packaging and shipping specimens for multiple tests, and potentially, improved patient satisfaction and outcomes. Certainly, clinical leadership of the UC center has a role in test stewardship to support the utilization of such testing at an evidenced-based point in the workup of patients presenting for a range of infectious disease complaints.[41]

If a clinician is working in a facility is seeing a patient whose care episode is paid for at a population level (eg, per member, per month) with the expectation that diagnostic testing is included in that schedule, additional testing needs to be especially judicious. Further, the clinician needs to be aware of the "payer" for the service, if there is a steered relationship to a preferred lab partner to generate the diagnostic insight, and if so, the coverage and reimbursement policy of the payer or managed services organization that applies to the specific utilized diagnostic insight.[42] All said, coverage and reimbursement policies are a "guide" and clinicians might be engaged in a request for additional clinical information in support of an overturn of a denial for reimbursement of a selected diagnostic test.

Adoption of PCR Testing: Future Research

Despite the value, use of multiplex molecular testing in the UC setting for CAP has faced adoption barriers, including provider training, patient expectations, and reimbursement.[43,44,45] Recent claims-based studies have shown reduced healthcare costs and utilization of multiplex PCR respiratory testing compared with evidenced-based empiric decision-making or the use of culture.[46,47] Despite technological advances, certain inherent limitations of molecular testing remain. For example, genotypic resistance testing that is an available component of molecular testing is directionally accurate but has limitations versus phenotype resistance testing obtained as part of "culture and sensitivity" testing. [18,48] Ideally, each specimen should undergo a quality check (eg, Gram stain assessment) prior to testing. But perhaps the most influential roadblock has been the lack of randomized control trials that have definitively and directly linked use of multiplex molecular respiratory tests with improved patient outcomes in the outpatient and UC setting. [17] Accordingly,[8] existing guidelines do not currently recommend routine microbiologic testing for CAP, citing the delay and overall poor yield of sputum culture for detecting organisms causing CAP and the lack of high-quality evidence demonstrating benefit.[8] Additional studies are required to confirm that real-world use of molecular PCR based multiplex testing in the UC setting indeed improves patient oriented outcomes, such as reducing the risk of hospitalization, return visit, and improving time to recovery. Overcoming these barriers with operational strategies and additional research into clinical utility is necessary for successful adoption.

Conclusion

For decades, rapid molecular testing has provided methodological benefits and proven beneficial for patient outcomes with certain viral infections.[49,50] Molecular-based tests are well-suited for improving diagnostic accuracy in UC settings; these tests are faster, more sensitive, and timelier (and therefore, clinically impactful) versus traditional culture methods. In clinical practice, these tests provide results which can guide effective pathogen-directed therapy. Data continues to emerge on the real-world experience and value of molecular pathogen detection.[12,51,52] Future randomized interventional studies examining the short- and long-term effects of such molecular testing will be important for clarifying the value of integrating rapid syndromic molecular diagnostics into routine outpatient clinical practice. Additionally, such evidence would support favorable reimbursement policies for such multiplex PCR array syndromic panels. Ultimately, incorporating these tests into patient care algorithms provides an opportunity for UC clinicians to reduce diagnostic error and, importantly, combat inappropriate empiric prescribing for the millions of patients seeking acute care for undifferentiated respiratory infections. ■

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