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Respiratory viral testing
New frontiers in diagnostics and implications for antimicrobial stewardship

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Millions of patients visit the doctor or emergency department annually for illnesses attributed to respiratory viruses, including influenza, but accurate and focused antimicrobial therapy often proves elusive. Appropriately targeted therapy is vital in cases of severe illness or resource scarcity, both of which can occur in the setting of pandemic influenza. The article in this issue of Virulence by Bogoch et al. provides insight into the use of deep respiratory samples for influenza viral detection in patients hospitalized with severe acute respiratory illness. They describe a subset of 15 patients undergoing deep respiratory secretions testing for influenza, with 10 patients having positive results. Eight of these 10 were positive by PCR testing from their lower respiratory tract sampling only. These results demonstrate the potential utility of molecular virologic testing of patients requiring invasive ventilator support for severe illness by providing physicians with relevant diagnostic data that would help drive appropriate antiviral use in cases where sampling from other sites or using antigen- or culture-based testing has yielded negative results.

Advancement of nucleic acid technology has not only proven pivotal in the clarification of previously unknown and uncultivated microorganisms, but has dramatically improved test performance parameters of clinical diagnostic tests compared with the traditional diagnostics of rapid antigen testing, DFA, and viral culture for influenza. Clinicians seek the least expensive and most rapid, comprehensive and accurate (highly sensitive and specific) test to diagnose respiratory viral illnesses. Nucleic acid amplification tests (NAATs), including PCR, have supplanted viral culture because of better turn-around time, accurate diagnosis, ability to detect multiple targets (multiplexing) and potential for positively aiding physician decision-making and patient management. Other modalities still play important roles in healthcare responses on patient, community and health-system levels. Culture for viruses like influenza will remain important for differentiating prolonged detection of nucleic acids from continued shedding of virus and potential antiviral resistance, subtyping of novel strains and propagation for vaccine manufacturing. Commonly-used rapid shell vial culturing techniques combined with specific direct fluorescent antibody demonstrated sensitivities ranging from 90–97% and 100% specificity for pandemic H1N1 (pH1N1), but complexity of use and 2–3 d turnarounds still limit their impact on clinical care. Rapid antigen tests are inexpensive and easy to use, making them ideal for point-of-care testing in places like physician offices and emergency rooms and their high specificity in times of high disease prevalence allows their high positive predictive value to aid in timely treatment, limiting unnecessary resource utilization. However, sensitivity for pH1N1 was lackluster (< 50%). When seeking best practices for which tests laboratories will adopt it is unlikely a one-size-fits-all solution will work. A combination of tests using a structured protocol will likely be necessary. This ideally would include using a rapid and cost-effective diagnostic test for influenza initially with reflex testing using a more comprehensive multiplexed NAAT-based respiratory panel or individual NAAT with high sensitivity and specificity in cases of negative rapid testing, especially if the patient will be admitted and/or antibiotics are being considered.

In their article, Bogoch et al. suggest the use of lower respiratory tract specimens as a potential alternative to nasopharyngeal or upper respiratory sampling. While there are now numerous single analyte NAATs for both influenza as well as respiratory panel assays, none are currently FDA-cleared for lower respiratory specimens. Laboratories must validate these specimen types, which can be a considerable undertaking. In our laboratory, where validation for BAL specimens was done for performing a respiratory panel multiplex assay, 611 specimens were received from November 2010 to September 2012, and 100 have been positive (unpublished data). For those patients who underwent both NP and BAL viral PCR testing (97 patients), 30 were BAL positive and 32 were NP positive. Discordant results

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The decrease in antiviral use was more pronounced in patients with a positive non-influenza virus test result than in those with completely negative PCR testing, which likely represents physicians’ concern of a false-negative result similar to that found in the case series by Bogoch et al. Additionally, physicians generally do not change antibiotic prescription practices based on viral testing results even in clinically unambiguous circumstances where a viral etiology is likely.6,11 This illustrates the core challenge facing clinicians and microbiologists alike when integrating respiratory viral testing into antimicrobial stewardship programs: how should a clinician select patients likely to benefit from antimicrobial discontinuation based on NAAT results? Blanket policy decisions will likely lead to misclassification of patients at high risk for bacterial infection not receiving necessary antibiotics, while overly-specific guidelines may be too cumbersome for physicians to utilize, resulting in the continuation of unnecessary antimicrobials for many patients.

The key to successfully utilizing these more sensitive virologic assays in clinical practice is to develop targeted interventions in clearly-defined patient populations with easily-recognizable viral syndromes, and to continue to allow physicians appropriate latitude in antimicrobial therapy—and diagnostic testing—in complex or uncertain cases. Deep respiratory specimen testing in patients with severe illness and/or multiple medical co-morbidities could provide the clinician with crucial insight into the etiology of a patient’s illness, prompt the addition of targeted antiviral therapy and help provide insight into the underlying epidemiology of respiratory viruses causing severe illness in the community, particularly during the early stages of a developing epidemic. This study by Bogoch et al. supports the need for reliable, validated respiratory viral testing from a variety of sites for severely-ill patients.

Disclosure of Potential Conflicts of Interest
K.C. receives support from Luminex and Genmark for research on respiratory viral infections.

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occurred in four patients where BAL was positive and NP sampling was negative, and in six patients where NP specimens were positive and BAL specimens negative. The higher rate of discordant results in the authors’ report compared with our data are likely due to the lower performance parameters of DFA, antigen and culture techniques for some of the NP and BAL comparisons. However, the potential for improved diagnosis in patients with active infection limited to the lower respiratory tract nonetheless exists using BAL/lower respiratory specimen sampling.

Despite the challenges posed by validating respiratory viral testing from multiple sites, the potential benefits of improving a physician’s ability to accurately determine the etiology of a patient’s acute respiratory symptoms is quite significant. Previous studies have shown that physicians will likely prescribe more anti-influenza medications when presented with positive test results and may decrease their utilization of ancillary diagnostic tests.7 Review of data from our own institution found that, during peak pH1N1 prevalence in our region, physicians increased their use of antiviral medication after a positive test result for influenza, and, perhaps more importantly, discontinued antiviral use in cases where patients were diagnosed with a non-influenza respiratory viral infection or negative NAAT.10 The decrease in antiviral use was more pronounced in patients with a positive non-influenza virus test result than in those with completely negative PCR testing, which likely represents physicians’ concern of a false-negative result similar to that found in the case series by Bogoch et al. Additionally, physicians generally do not change antibiotic prescription practices based on viral testing results even in clinically unambiguous circumstances where a viral etiology is likely.6,11 This illustrates the core challenge facing clinicians and microbiologists alike when integrating respiratory viral testing into antimicrobial stewardship programs: how should a clinician select patients likely to benefit from antimicrobial discontinuation based on NAAT results? Blanket policy decisions will likely lead to misclassification of patients at high risk for bacterial infection not receiving necessary antibiotics, while overly-specific guidelines may be too cumbersome for physicians to utilize, resulting in the continuation of unnecessary antimicrobials for many patients.

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