Moving Toward Prime Time: Host Signatures for Diagnosis of Respiratory Infections

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(See the major article by Suarez et al on pages 213–22.)

As eloquently stated in a recent position paper from the Infectious Diseases Society of America, “whether caring for an individual patient with an infectious disease or responding to a worldwide pandemic, the rapid and accurate establishment of a microbial cause is fundamental to quality care” [1, p S139]. The need for improved diagnostic tests for acute respiratory infections is tremendous, as they are one of the most common reasons for physician visits [2, 3] and account for a large proportion of antibacterial use in both emergency and outpatient settings [4, 5]. Limitations in our diagnostic capabilities for acute respiratory infections lead to overuse of antibacterial agents, one of the most vexing issues facing modern medicine. Both pathogen and host-based diagnostic tests aim to improve the timeliness and accuracy of infectious diseases diagnosis, allowing for targeted therapies and reduction of unwanted antibacterial use.

Pathogen-specific tests have and will continue to play an important role in the diagnosis of respiratory infections. However, the growing field of rapid, unbiased host-based diagnostic assays provides a promising complement to traditional microbiologic testing. The concept of host-derived biomarkers for infectious diseases diagnosis and management is not novel. The erythrocyte sedimentation rate, first described in 1917 [6], and C-reactive protein, described in 1930 [7], continue to play a role in infectious diseases management, albeit with limited specificity. The host-based diagnostics field remained relatively stagnant until the discovery of procalcitonin as an inflammatory biomarker in bacterial infection [8–10]. Secreted as an acute phase reactant by multiple cell types, procalcitonin levels reasonably distinguish bacterial infection from alternative diagnoses in a variety of settings, ranging from the clinic to the intensive care unit [8, 11–13]. However, procalcitonin levels demonstrate limited sensitivity and specificity, and thus the search continues for highly accurate host-based markers for infectious diseases diagnosis and classification. In 2007, Ramilo et al first described the use of host-based diagnostic tests for classifying viral and bacterial infections in pediatric patients [14]. The same group has now taken another step forward, with an article by Suarez et al in this issue of The Journal of Infectious Diseases, where they show that host transcriptional profiling is superior to procalcitonin in discriminating between bacterial and viral lower respiratory tract infections in hospitalized adults.

Recognition of the molecular specificity of the immune response to respiratory pathogens provided the backdrop for host-based diagnostic test development. First defined ex vivo [15], the host cellular immune response has been described for multiple respiratory pathogens and pathogen classes, including those associated with viral [14, 16, 17], bacterial [18, 19], and fungal infections [20–22]. Advances in gene expression technology and advanced analytical methods have moved the field rapidly from retrospective classification of viral illness in hospitalized children [14] to identification of a characteristic gene expression signature for viral respiratory infection in experimental [23] and emergency department real-world settings [24].

Suarez et al now capitalize on advanced analytical methods to classify individuals with bacterial, viral, or mixed illness in a cohort of hospitalized adults. This work moves the field forward in 3 notable ways. First, the authors use modular analysis [25] and prediction algorithms to identify pathways that characterize bacterial versus viral or mixed infections. This aspect of the authors’ analysis provide insight into the host mechanisms of pathogen recognition and fuel for future studies of host immune responses and how they can potentially be modulated. Second, the authors identify a classifier, comprising only 10 genes, that discriminates bacterial from viral infection with 95% sensitivity and 92% specificity. Determined by use
of an exceedingly manageable number of analytes, this finding strengthens the groundwork for development of a practical commercial product that could be used in clinical settings. Third, they demonstrate that their transcriptional signature is substantially more sensitive than procalcitonin (95% vs 38%), with approximately equal specificity (92% vs 91%), in distinguishing bacterial from viral infections in their cohort. Thus, this represents an important comparison of multiple-analyte host-based classifiers versus the currently available single-analyte diagnostic.

Significant in Suarez et al’s current findings is the reproducibility of the host response to viral infection. Of the 10 genes identified in the authors’ bacterial versus viral infection classifier, 7 are either the same or from the same gene family as those represented in a reverse transcription polymerase chain reaction (RT-PCR) assay we developed to distinguish symptomatic from asymptomatic response to viral challenge, which was validated in patients with community-onset bacterial or viral infection [24]. IFI27, RSAD2, and IFT14 generated the strongest median expression values in the current study and were among the most prominently discriminating genes in the previously published classifier. This overlap demonstrates a robust indication of the strength of interferon-related gene expression products for use as a potential diagnostic tool for detection of viral infection in human hosts. Taken together and with other supporting reports [26–29], these studies illustrate the potential for blood gene expression signatures for clinical application in infectious diseases.

What are the next steps in developing practical, host-based diagnostic tests to identify the pathogen class in individuals presenting with acute respiratory illness? Technical advances, such as rapid sample processing for RT-PCR analysis, are a critical step in bringing such a diagnostic test to the clinical setting. In addition, prospective validation of the classifier genes (particularly those shown in multiple studies) in a cohort of patients presenting with acute respiratory illness, both infectious and noninfectious, is a necessary component of bringing a host-based test to market. Additionally, inclusion of immunocompromised hosts and those with chronic inflammatory illnesses in the prospective validation would enhance the generalizability of the test. Confirmation that the test also appropriately classifies other bacterial causes of severe respiratory tract infection, such as Legionella and hospital-associated gram-negative pathogens, which were not represented here, is also critical to ensure the safety of such a test. Given the scope of the problem, host-based testing for classifying acute respiratory illness will be a welcome addition to our diagnostic armamentarium.

**Note**

**Potential conflicts of interest.** A. K. Z. and E. L. T. are holders of provisional patents to develop expression-based diagnostics for infectious diseases. M. M. certifies no potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**References**


