Introduction

Background

Community-acquired pneumonia (CAP) is a heterogeneous illness caused by a wide range of respiratory pathogens. There is increasing recognition that respiratory viruses are frequent causative agents of CAP (1). CAP is typically diagnosed on the basis of clinical signs and symptoms, often with notable reliance on radiographic findings. In recent years, a number of additional diagnostic technologies have been introduced into clinical practice that are intended to aid clinicians in the identification of CAP-causing pathogens. The American Thoracic Society (ATS) and Infectious Diseases Society of America clinical practice guideline on the diagnosis and management of CAP was updated in 2019 (2). The revised guideline includes the recommendation that adults with CAP should have a respiratory sample tested for influenza virus at the time of diagnosis. The recommendation specifically endorses rapid influenza molecular assays such as influenza nucleic acid amplification tests (NAATs) over rapid antigen tests when influenza viruses are in circulation in the community. However, no recommendation is made regarding the role of testing for noninfluenza viruses.

Given the important etiologic contributions to CAP of noninfluenza respiratory viruses and the expanding commercial availability of multiplex testing for these viruses, the ATS commissioned the current document to provide an evidence-based clinical practice guidance regarding the pertinence of nucleic acid–based testing of respiratory samples for noninfluenza respiratory viruses in adults with suspected CAP.

At the time of document development, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was not a recognized CAP-causing pathogen. As such, the systematic literature review did not consider this virus, and no related recommendations are made. However, as SARS-CoV-2 has been well established as an important cause of CAP since the time of the literature review, discussions of how these recommendations may relate to viruses like SARS-CoV-2 are offered.

Introduction of Nucleic Acid–based Testing

NAATs first emerged in the 1980s for HIV and *Chlamydia trachomatis* and were eventually adapted for other microorganisms, including respiratory viral infections. The breadth of respiratory infections detectable by NAATs has drastically increased over the past several years, largely supplanting other diagnostic modalities as the principal means of respiratory viral testing. The role of NAATs in respiratory viral diagnosis was recently emphasized by the dependence of healthcare institutions on NAATs to detect SARS-CoV-2 infections in response to the coronavirus disease (COVID-19) pandemic. NAATs for the detection of noninfluenza respiratory viruses may be developed for use by individual clinical laboratories (laboratory-developed assays) or by private companies (commercially available assays). Within the United States, NAAT-based assays for respiratory viruses are classified as medical devices by the Food and Drug Administration (FDA). Therefore, all commercially available respiratory viral assays are subject to FDA approval and oversight to provide reasonable quality assurance and reliability. At the time of this writing, FDA approval is not required for laboratory-developed assays, though guidelines to assist in establishing performance specifications are routinely published by the Clinical and Laboratory Standards Institute; current legislation (Verifying Accurate and Leading-Edge *In Vitro* Clinical Test Development Act) proposes to enforce more stringent regulation (3). Assays may be designed for use in a central laboratory or at the point of care (POC). Many POC tests in the United States are Clinical Laboratory Improvement Amendments of 1988 waived, indicating that they are of low complexity, requiring little operator expertise and having a low potential for errors (4).

Commercially available assays for the detection of noninfluenza respiratory viruses employ several methodologies, including *1*) real-time RT-PCR, *2*) multiplex microarray competitive DNA hybridization, *3*) nested multiplex RT-PCR, *4*) isothermal nucleic acid amplification, *5*) loop-mediated isothermal DNA amplification, and *6*) RT-PCR followed by microarray hybridization. The most common approved specimen for testing is a nasopharyngeal swab, but other approved specimens may include nasal swabs, nasal aspirates, nasal washes, and throat swabs. Most assays are not approved for testing on BAL fluid, with some exceptions (e.g., FilmArray Pneumonia Panel [BioFire Diagnostics]) (5).

Both single-target and multiplex assays are available to detect noninfluenza respiratory virus targets. These can be divided into five categories: *1*) multiplex PCR assays (generally $\geqslant$4 targets) for influenza and noninfluenza respiratory viruses plus select atypical bacterial pathogens (e.g., FilmArray Pneumonia Panel and FilmArray Respiratory Panel by BioFire Diagnostics; ePlex Respiratory Pathogen Panel by GenMark Diagnostics); *2*) multiplex PCR assays (generally $\geqslant$4 targets) for influenza and noninfluenza respiratory viruses only (e.g., eSensor Respiratory Viral Panel by GenMark Diagnostics); *3*) multiplex PCR assays (3 targets) for influenza A/B plus respiratory syncytial virus (RSV) (e.g., Xpert Flu/RSV XC by Cepheid); *4*) multiplex PCR assays (generally 2–3 targets) for noninfluenza viruses only (e.g., Solana RSV + human metapneumovirus assay by Quidel; Panther Fusion Paraflu Assay by Hologic); and *5*) single-target assays for noninfluenza viruses (e.g., Alere I RSV by Abbott Laboratories) (5).

Upper respiratory tract testing for influenza using molecular panels is not sufficiently sensitive to exclude lower tract infections, particularly in critically ill and immunocompromised patients, nor is it sufficiently sensitive to exclude some strains of influenza (e.g., H1N1 and H5N1) that preferentially infect the lower respiratory tract (6–10). Relevant data for other

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