AMERICAN THORACIC SOCIETY DOCUMENTS

Nucleic Acid–based Testing for Noninfluenza Viral Pathogens in Adults with Suspected Community-acquired Pneumonia

An Official American Thoracic Society Clinical Practice Guideline

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Background: This document provides evidence-based clinical practice guidelines on the diagnostic utility of nucleic acid–based testing of respiratory samples for viral pathogens other than influenza in adults with suspected community-acquired pneumonia (CAP).

Methods: A multidisciplinary panel developed a Population–Intervention–Comparison–Outcome question, conducted a pragmatic systematic review, and applied Grading of Recommendations, Assessment, Development, and Evaluation methodology for clinical recommendations.

Results: The panel evaluated the literature to develop recommendations regarding whether routine diagnostics should include nucleic acid–based testing of respiratory samples for viral pathogens other than influenza in suspected CAP. The evidence addressing this topic was generally adjudicated to be of very low quality because of risk of bias and imprecision. Furthermore, there was little direct evidence supporting a role for routine nucleic acid–based testing of respiratory samples in improving critical outcomes such as overall survival or antibiotic use patterns. However, on the basis of direct and indirect evidence, recommendations were made for both outpatient and hospitalized patients with suspected CAP. Testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was not addressed in the literature at the time of the evidence review.

Conclusions: The panel formulated and provided their rationale for recommendations on nucleic acid–based diagnostics for viral pathogens other than influenza for patients with suspected CAP.

Keywords: community-acquired pneumonia; pneumonia; viral diagnostics

Contents

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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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respiratory viruses are sparser. It is well established that rhinoviruses, coronaviruses, and adenoviruses infect both upper and lower respiratory tract epithelia. Moreover, cases of children infected with rhinovirus, adenovirus, and bocavirus have been documented to have positive testing in the lower respiratory tract but negative testing in the upper respiratory tract (11). In infants and immunocompromised adults with RSV, progression of infection from the upper to the lower respiratory tract often portends higher morbidity and mortality. In one study of immunocompromised adults with RSV, testing of lower respiratory tract specimens was significantly more sensitive than testing of upper respiratory tract specimens (nasal wash: 15%; endotracheal aspirate: 71.4%; BAL: 88.9%) (12). In another study of adult hematopoietic stem cell transplant (HSCT) recipients, high rates of discordance between upper and lower respiratory tract specimens were reported for adenovirus (100%), human metapneumovirus (44%), rhinovirus (34%), and parainfluenza virus type 3 (28%), whereas testing for RSV was highly concordant (92%) (13).

Given the variable diagnostic performance and clinical impact of multianalyte NAATs for different viruses and in difference clinical contexts, together with the lack of guidance from the most recent CAP guideline on this topic, the ATS initiated a project to investigate the role of molecular testing for noninfluenza viruses in the setting of suspected CAP.

Methods

A multidisciplinary, international panel of experts in respiratory infections convened to develop a single Population–Intervention–Comparison–Outcome (PICO) question regarding the use of nucleic acid–based viral diagnostic testing for viral pathogens (other than influenza) in patients with suspected CAP. The PICO question was finalized after multiple rounds of discussions via teleconference. Subsequently, we performed a systematic review of the literature and applied the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to evaluate quality of evidence and inform our recommendations. The detailed guideline-development methodology and conflict-of-interest management strategies are included in the online supplement. GRADE standards were used to determine the designation of the quality of evidence as high, moderate, low, or very low. On the basis of the quality of the evidence and committee discussions, recommendations were assigned as being strong or conditional. Recommendations based on a low or very low quality of evidence and that were not believed to represent standards of care were labeled as being conditional. The guideline document was subjected to expert peer review and was approved by the Board of Directors of the ATS. It will be reevaluated in 3–5 years to determine whether updating is necessary.

Group Composition

The PICO guideline co-chairs (S.E.E. and C.S.D.C.) were selected by the ATS. They led all aspects of project management and selected the panelists, who included 12 clinicians and researchers with experience in pneumonia. Two (B.C. and R.G.W.) participated in the initial design and discussions of the PICO questions and evidence but were not involved in the formulation of the recommendations or writing of the guideline. With the assistance of a librarian (A.M.), three methodologists (A.L.J., L.C.M., and E.O.) identified, collected, and synthesized the evidence; constructed the evidence profiles; and ensured that all methodological requirements were met. The methodologists presented the evidence to the co-chairs and panelists, who then formulated and finalized the recommendations. All panel members were required to disclose conflicts of interest on an ongoing basis throughout the process.

Recommendations

Question: In adults with suspected CAP, should routine diagnostics include nucleic acid–based testing of respiratory samples for viral pathogens other than influenza?

Recommendation 1. In outpatients with suspected CAP, we suggest not performing routine nucleic acid–based testing of respiratory samples for viral pathogens other than influenza (conditional recommendation, very-low-quality evidence).

Recommendation 2. In hospitalized patients with suspected CAP, we suggest nucleic acid–based testing of respiratory samples for viral pathogens other than influenza *only* in patients who meet one of the following conditions (conditional recommendation, very-low-quality evidence):

- Patients with severe CAP (i.e., patients with ⩾1 major or ⩾3 minor criteria [2]) and
- Immunocompromised patients (including those with neutropenia, those undergoing active cancer therapy, those with a history of solid-organ or blood-component transplantation, those with advanced HIV disease, or those with a history of chronic use of immunosuppressive medications, including systemic corticosteroids).

Summary of the evidence. There is limited evidence regarding the relationship between nucleic acid–based testing of respiratory samples for noninfluenza viral pathogens and patient-centered outcomes, specifically among patients with suspected or confirmed CAP. Few studies compare testing with "no testing" when assessing these associations (14, 15). Given the limited number of studies with a true comparison of testing with no testing, we also reviewed studies that compare a positive viral test result with a negative viral test result (16–18). In addition, we included studies that evaluated tests involving both viral and bacterial assays, if comparisons related to viral testing were reported (19–23). Most of the evaluated studies are observational in nature, and of the studies that involved clinical trials (14, 19, 20), data related to our question consist of comparisons other than the primary intervention versus the control.

Overall, available evidence is of very low quality because of methodological issues, most notably risk of bias and imprecision. Study findings and GRADE assessments for prespecified patient-centered outcomes are detailed in Tables 1 and 2. The evidence does not support a clinically significant relationship between testing for noninfluenza viral pathogens and antimicrobial treatment (14, 15, 17, 18). Once antibiotics are initiated, identification of viral pathogens using a NAAT may reduce the duration of antibiotic use (19, 20, 22), but this finding is not consistent (14, 15, 17). When viral PCR results become available to clinicians, most patients with positive test results continue to receive antibiotics (16, 18, 20, 21, 23).

Table 1. GRADE Evidence Table for Studies Assessing Viral Nucleic Acid–based Testing

Certainty Assessment									
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Impact	Certainty	Importance
Duration of antibiotics									
3*	Observational studies	Serious†	Not serious	Not serious	Serious‡	None	**Afzal *et al.*, 2016 (15):** In 19 patients whose clinicians were not notified of a positive viral PCR result, the median duration of antibiotic use was 12 d (IQR, 7 to 15 d). For the 11 patients whose clinicians were informed that a respiratory virus had been identified, the median duration of antibiotic use was 7 d (IQR, 6 to 10 d). **Blatt *et al.*, 2017 (17):** The median duration of antibiotic treatment for patients with a negative viral panel result was 4 d (IQR, 3 to 5 d), compared with 3 d (IQR, 2 to 6 d) for those with positive viral panel result. **Brendish *et al.*, 2017 (14):** For patients with pneumonia, the mean duration of antibiotic use did not significantly differ between those in the molecular viral-testing arm and those receiving usual care (difference in means [SD], 0.7 d [−0.9 to 2.2 d]; $P = 0.41$).	Very low	Critical
Antimicrobial treatment									
4§	Observational studies	Serious†	Not serious	Not serious	Serious‖	None	**Afzal *et al.*, 2016 (15):** In 19 patients whose clinicians were not notified of a positive viral PCR result, the median number of antibiotics used was 3 (IQR, 2 to 3). For the 11 patients whose clinicians were informed that a respiratory virus had been identified, the median number of antibiotics used was 2 (IQR, 1 to 3). **Blatt *et al.*, 2017 (17):** Among patients with a negative respiratory viral panel result, 90% continued antibiotic treatment for ⩾2 d after the diagnosis of pneumonia (vs. 72% of those who had a positive viral panel result). **Brendish *et al.*, 2017 (14):** For patients with pneumonia, 97.8% (92 of 94) of those in the molecular viral-testing arm were given antibiotics while hospitalized (up to 30 d); 98% (96 of 98) of those in the usual-care arm received antibiotics (OR, 0.96; 95% CI, 0.13 to 6.95). **Semret *et al.*, 2017 (18):** Among patients with suspected pneumonia, not empirically treated, 0% with a positive noninfluenza respiratory virus panel PCR result and 9% with a negative test result started oseltamivir ⩽48 h after testing. For this same patient group, 38% with a positive noninfluenza respiratory virus panel PCR result and 23% with a negative test result started antibiotics ⩽48 h after testing. Radiographic suspicion of pneumonia on admission was the only variable correlated with continuation of antibiotics among patients treated before test results or with initiation of antibiotics after the availability of test results.	Very low	Critical

(Continued)

Table 1. (*Continued*)

Certainty Assessment									
No. of Studies	**Study Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Considerations**	**Impact**	**Certainty**	**Importance**
Modification of antimicrobial treatment									
2[¶]	Observational studies	Serious**	Not serious	Not serious	Serious[††]	None	**Hernes *et al.*, 2014 (16):** When viral PCR results became available to clinicians, 12.5% (2 of 16) of symptomatic patients with positive test results had their antimicrobial treatment discontinued (both patients had a diagnosis of pneumonia). **Semret *et al.*, 2017 (18):** Among patients with suspected pneumonia who were empirically treated, 0% with a positive noninfluenza respiratory virus panel PCR result and 1% with a negative test result had oseltamivir continued. For this same patient group, 80% with a positive noninfluenza respiratory virus panel PCR result and 70% with a negative test result had antibiotics continued.	Very low	Critical
Hospital LOS									
2[‡‡]	Observational studies	Serious[§§]	Not serious	Not serious	Not serious	None	**Blatt *et al.*, 2017 (17):** Among patients with a negative viral panel result, the median hospital LOS was 5 d (IQR, 3.0 to 9.0 d); the same results were noted for those with a positive viral panel result. **Brendish *et al.*, 2017 (14):** For patients with pneumonia, the mean hospital LOS did not significantly differ between those in the molecular viral-testing arm and those receiving usual care (difference in means [SD], 0.5 d [−1.4 to 2.4 d]; $P = 0.58$).	Very low	Critical

Definition of abbreviations: CI = confidence interval; ED = emergency department; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; IQR = interquartile range; LOS = length of stay; OR = odds ratio.

Study comparison groups: Studies that compare viral testing with no viral testing (or not knowing the results of viral testing): Afzal and colleagues (2016) (15) and Brendish and colleagues (2017) (14). Studies that compare a positive viral test result with having a negative viral test result: Hernes and colleagues (2014) (16), Blatt and colleagues (2017) (17), and Semret and colleagues (2017) (18).

*References 15 and 17 are cohort studies. Reference 14 is a pragmatic, open-label, randomized controlled trial (data presented here are from a prespecified subgroup analysis based on the diagnostic group of subjects with pneumonia).

[†]In References 14, 15, and 17, comparisons are unadjusted, generating concern for significant residual confounding.

[‡]Reference 15 included few participants and few events.

[§]References 15, 17, and 18 are cohort studies. Reference 14 is a pragmatic, open-label, randomized controlled trial (data presented here are from a prespecified subgroup analysis based on the diagnostic group of subjects with pneumonia).

[‖]References 15 and 18 include few participants and few events.

[¶]References 16 and 18 are cohort studies.

**In Reference 16, analyses were either unadjusted or adjusted for a minimal number of variables, generating concern for significant residual confounding.

[††]References 16 and 18 included few participants and few events considering the outcomes selected for the guideline and/or the population of interest (i.e., individuals with CAP).

[‡‡]Reference 17 is a cohort study. Reference 14 is a pragmatic, open-label, randomized controlled trial (data presented here are from a prespecified subgroup analysis based on the diagnostic group of subjects with pneumonia).

[§§]In References 14 and 17, analyses are unadjusted, generating concerns for significant residual confounding.

Table 2. GRADE Evidence Table for Studies Assessing Viral + Bacterial Nucleic Acid–based Testing

Certainty Assessment									
No. of Studies	**Study Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Considerations**	**Impact**	**Certainty**	**Importance**
Duration of antibiotics									
3*	Observational studies	Serious†	Not serious	Not serious	Serious‡	None	**Gelfer *et al.*, 2015 (20):** Days of therapy (normalized to 1,000 patient days) were significantly fewer in the virus-only group, compared with groups with virus and bacteria or bacteria only identified as pathogens (1,188 ± 641, compared with 1,661 ± 387 and 1,484 ± 252, respectively; $P = 0.003$). **Gilbert *et al.*, 2016 (19):** The length of therapy (normalized to 1,000 patient days) was significantly lower in virus-only patients than in patients with bacterial infection (845 ± 252, compared with 1,380 ± 1,205; $P = 0.04$). **Rezkalla *et al.*, 2019 (22):** Among patients who underwent multiplex PCR testing ($n = 70$), 22 (31%) had a pathogen identified. The average duration of antibiotics for PCR-negative patients was 8.3 d (range, 0–15 d) compared with 4.9 d (range, 0–12 d) in the PCR-positive group with a viral pathogen ($P = 0.0004$).	Very low	Critical

(Continued)

Table 2. (*Continued*)

Certainty Assessment									
No. of Studies	**Study Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Considerations**	**Impact**	**Certainty**	**Importance**
Modification of antimicrobial treatment									
4[§]	Observational studies	Serious[‖]	Not serious	Not serious	Serious[¶]	None	**Gelfer *et al.*, 2015 (20):** In 18 patients, PCR identified a virus only; in only four of these patients were empiric antibiotics discontinued within 48 h of physician receipt of PCR results. **Gilbert *et al.*, 2016 (19):** In 25 patients, PCR identified a virus only; discontinuation of empiric antibiotics within 48 h of test results occurred in 8 of the 25 (32%) patients. **Guillon *et al.*, 2017 (21):** Pathogen identification using multiplex PCR led to changes in antibiotic treatment in 22% of patients (ICU, $n = 63$; pulmonary ward, $n = 8$). **Wittermans *et al.*, 2019 (23):** In multivariable analyses, PCR for atypical pathogens was associated with any alteration of antibiotic treatment by Hospital Day 3 (OR, 2.6; 95% CI, 1.4–4.9) and an alteration of atypical coverage (OR, 3.1 95% CI, 1.6–6.0). There was not a significant association between PCR for respiratory viruses and these outcomes.	Very low	Critical

Definition of abbreviations: CI = confidence interval; ED = emergency department; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; OR = odds ratio.
Study comparison groups: Studies that compare viral + bacterial testing with no viral + bacterial testing: Wittermans and colleagues (2019) (23). Studies that compare a positive viral + bacterial test result to having a negative viral + bacterial test result: Gelfer and colleagues (2015) (20), Gilbert and colleagues (2016) (19), Guillon and colleagues (2017) (21), and Rezkalla and colleagues (2019) (22).
*References 19 and 20 are cluster-randomized trials; however, results presented here are not a comparison of intervention versus control groups. Reference 22 is a cohort study.
[†]In References 19 and 20, patients were cluster randomized in 1-week blocks to undergo additional diagnostic testing with either a laboratory-generated respiratory pathogen PCR panel or a commercial, faster, and broader multiplex PCR panel. Presented results are a comparison of groups based on pathogen, not based on intervention, and these results are unadjusted. Results from Reference 22 are unadjusted.
[‡]References 19, 20, and 22 included few participants and few events.
[§]In References 19 and 20, patients were cluster randomized in 1-week blocks to undergo additional diagnostic testing with either a laboratory-generated respiratory pathogen PCR panel or a commercial, faster, and broader multiplex PCR panel. References 21 and 23 are cohort studies.
[‖]In References 19 and 20, patients were cluster randomized in 1-week blocks to undergo additional diagnostic testing with either a laboratory-generated respiratory pathogen PCR panel or a commercial, faster, and broader multiplex PCR panel. Presented results are a comparison of groups based on pathogen, not based on intervention, and these results are unadjusted. Results from References 21 and 23 are adjusted for no or a minimal number of variables.
[¶]References 19–21 included few participants and/or few events.

Table 3. Narrative Summary of Studies Including Patients with a Variety of Respiratory Illnesses; Comparison Group: Positive PCR versus Negative PCR Viral Results

Author, Year (Reference)	Study Design	Setting/Participants	Key Results
Kim *et al.*, 2018 (38)	Retrospective cohort study of multiplex PCR testing for viral pathogens, performed when severe pneumonia did not respond to empirical antibiotics, when imaging revealed ground-glass opacities suggestive of atypical pathogens, or when patients were immunocompromised	515 adult patients admitted to the medical ICU with severe pneumonia, including CAP, HCAP, or HAP; of 69 patients with positive PCR results, 24 received a diagnosis of CAP (34.8%)	Of the 515 patients who underwent testing for viral pathogens, 69 (13.4%) had a positive result. Detection of a viral pathogen led to changes in the disease management in 23 (33.3%) patients, including addition of antiviral therapy in 12 patients and discontinuation of antibiotics in 2 patients. Outcomes for patients with management changes were compared with those without management changes, with no significant difference seen in hospital or ICU LOS or in-hospital mortality.
Mayer *et al.*, 2017 (37)	Retrospective cohort study of patients in whom a multiplex PCR for respiratory viruses was performed	Pediatric ($n = 72$) and adult ($n = 182$) in- and outpatients with upper or lower RTI; among adults, 35.7% had a diagnosis of CAP	Excluding patients who received antibiotics for other indications, antibiotic treatment was stopped in 2 of 35 adults (5.7%) in whom a viral pathogen was detected by using PCR. In adults with a positive viral PCR result, management was judged to be correct in 34% (12 of 35) after PCR results became available.
Yee *et al.*, 2016 (36)	Retrospective cohort study comparing patients with a positive multiplex viral PCR result to patients with a negative test result	186 adults in a hospital setting (either ED or inpatient) with suspected ILI; 19.9% (37 of 186) of patients had suspected pneumonia	Among hospitalized patients, empiric oseltamivir was discontinued in 66.7% (10 of 15) of patients with a negative viral test result and in 100% (4 of 4) of patients who tested positive for a virus other than influenza. Empiric antibiotics were discontinued in 14.6% (6 of 41) of patients with a negative viral PCR result and in 26.3% (5 of 19) of patients with a positive viral PCR result.

Definition of abbreviations: CAP = community-acquired pneumonia; ED = emergency department; HAP = hospital-acquired pneumonia; HCAP = health care–associated pneumonia; ILI = influenza-like illness; LOS = length of stay; RTI = respiratory tract infection.

Lastly, the hospital length of stay does not differ significantly between hospitalized patients who undergo viral testing or have a positive viral test result and those who do not have tests performed or whose test results are negative (14, 17).

To supplement the evidence most directly informing our recommendations, we also provide a narrative summary of studies identified in our literature review that include patients with non-CAP respiratory illnesses, such as acute exacerbations of chronic obstructive pulmonary disease or bronchiectasis, in addition to patients with suspected or confirmed CAP; these studies are detailed in Tables 3–8. Although these findings are indirect, as our population of interest is individuals with suspected CAP, they include important data about outpatient testing and the use of NAATs in critically ill and immunocompromised individuals (24–39).

Rationale for Suggestion to Not Routinely Perform Multiplex Testing for Noninfluenza Viruses in Patients with Suspected CAP

Limited evidence of altered antibiotic use with viral testing. Although the panel anticipated that changes in antibiotic use would be among the most substantial effects of testing, there is little current evidence supporting the supposition that the use of nucleic acid–based testing of respiratory samples for viral pathogens other than influenza in patients with suspected or confirmed CAP impacts antibiotic management. In theory, identification of viruses without concomitant bacteria might prompt clinicians to withhold antibiotics for CAP. However, possibly because of time lags in obtaining results of the respiratory virus panel even with POC tests, no studies have found that these tests are associated with a significant decrease in the initiation of antibiotic therapy. Among patients hospitalized with CAP, over 95% received antibiotics, regardless of whether they were found to be respiratory virus panel positive

Table 4. Narrative Summary of Studies Including Patients with a Variety of Respiratory Illnesses; Comparison Group: Routine PCR versus Rapid PCR Viral Testing

Author, Year (Reference)	Study Design	Setting/Participants	Key Results
Vos *et al.*, 2019 (39)	Before–after study comparing an in-house multiplex PCR to a rapid multiplex PCR for 15 viral pathogens	419 immunocompromised adults (135 before and 284 after) who presented to the ED with suspicion of having an RTI and underwent PCR testing for viral pathogens; of the entire cohort (including patients who did not undergo testing), 43.2% (246 of 570) received a "working diagnosis" of pneumonia	Comparing outcomes before and after implementation of a rapid multiplex viral PCR, there were no significant differences in empiric antibiotic use, the duration of antibiotic use, or hospital LOS. Admissions to in-hospital isolation facilities were reduced (adjusted OR, 0.35; 95% CI, 0.19–0.64), and there were fewer prescriptions of oseltamivir (adjusted OR, 0.25; 95% CI, 0.15–0.43).

Definition of abbreviations: CI = confidence interval; ED = emergency department; LOS = length of stay; OR = odds ratio; RTI = respiratory tract infection.

or negative (17). Most of the literature addressing this issue focuses on the inpatient setting, so the panel extrapolates these reports to outpatients, in whom antibiotic use is presumed to be less prevalent.

Alternately, identification of respiratory viruses but not bacteria could support discontinuation of antibiotics. Yet in studies of patients with acute respiratory illness, only a minority have had antibiotics discontinued, despite the lack of identification of bacterial pathogens and positive respiratory virus panel NAAT results. The rate of antibiotics discontinuation has been reported to range from 12.5% to 32% of virus-positive/bacteria-negative patients, even when accompanied by a low procalcitonin concentration (16, 19). One study reported that pathogen identification using multiplex PCR resulted in changes to antibiotic treatment in only 22% of the patients, who were mostly in the ICU (21). Although identification of influenza is clearly associated with modifications in antibiotic and antiviral management, significant differences in the discontinuation of antibiotics have not generally been observed between patients who had only noninfluenza respiratory viruses isolated and patients who had only bacterial or mixed bacterial and viral infections (18). Other factors, such as clinician suspicion of pneumonia based on radiographic findings may be more important drivers of continuation of antibiotics than respiratory virus panel results (18).

Although results are mixed, several studies suggest that identification of respiratory viruses may be associated with a shorter duration of antibiotic therapy. Patients who were found to have only respiratory viruses, when compared with patients with bacterial or mixed pathogens, had fewer days of antibiotics (15, 19, 20) and were more likely to receive a single dose of antibiotics or receive antibiotics for

Table 5. Narrative Summary of Studies Including Patients with a Variety of Respiratory Illnesses; Comparison Group: Multiplex PCR versus No Multiplex PCR Viral Testing

Author, Year (Reference)	Study Design	Setting/Participants	Key Results
Rappo *et al.*, 2016 (27)	Before–after study comparing conventional diagnostics to rapid multiplex viral PCR	337 adults (198 before and 138 after) in the ED and inpatient setting who tested positive for a respiratory virus, no data regarding the number with suspected pneumonia; 45.9% (128 of 279) had radiographic abnormalities on chest images	Among patients with who were positive for noninfluenza viruses, there were no significant differences in hospital LOS or the duration of antimicrobial use when comparing conventional testing with rapid multiplex PCR. Compared with patients with influenza diagnosed with conventional testing, patients with influenza diagnosed by using rapid multiplex PCR had a shorter hospital LOS (−0.37; 95% CI, −0.73 to −0.018; $P = 0.04$) and duration of antimicrobial use (−0.68; 95% CI, −1.29 to −0.060; $P = 0.032$).

Definition of abbreviations: CI = confidence interval; ED = emergency department; LOS = length of stay.

Table 6. Narrative Summary of Studies Including Patients with a Variety of Respiratory Illnesses; Comparison: Positive PCR versus Negative PCR Viral + Bacterial Results

Author, Year (Reference)	Study Design	Setting/Participants	Key Results
Busson *et al.*, 2019 (25)	Prospective study in which all participants were tested with a multiplex PCR panel evaluating 14 viral and 3 bacterial targets	291 adults and children visiting the ED during influenza season, presenting with upper or lower respiratory symptoms; 149 adults (≥15 yr old), no data regarding the number with suspected pneumonia	Analyses comparing hospitalization status and prescription of antibiotics showed no significant difference between patients with a positive PCR result and those with a negative result. Among hospitalized adults, the difference in the LOS between those with a negative PCR result and those with a positive result was 15.7 vs. 9.3 d ($P = 0.056$, adjusted for age). Isolation practices for the 93 hospitalized adults, based on PCR results, were as follows: 6 for whom isolation was planned were not isolated, 7 for whom isolation was planned were isolated, and 34 for whom isolation was not planned were not isolated. For influenza-positive adults, oseltamivir was given in 31 of 53 patients, and it was avoided in 86 of 97 patients who were negative for influenza.
Green *et al.*, 2016 (24)	Retrospective study of antimicrobial prescriptions among outpatients tested with a multiplex PCR panel evaluating 14 viral and 3 bacterial targets	295 patients seen in an outpatient setting (e.g., EDs, outpatient clinics, or urgent care clinics) who were not hospitalized after evaluation; 9 of 295 (3.1%) had a clinical syndrome consistent with pneumonia	Antimicrobial prescription rates differed when comparing the three following groups: positive for influenza virus ($n = 105$), positive for a noninfluenza virus pathogen ($n = 109$), and negative for all pathogens tested ($n = 81$); antibiotic prescription rates were 29.5%, 48.6%, and 49.3%, respectively ($P = 0.005$), and oseltamivir prescription rates were 81.0%, 5.5%, and 2.5%, respectively ($P < 0.001$). There was no significant difference in antibiotic prescription rates between individuals who tested positive for a noninfluenza virus and those who tested negative (48.6% and 49.3%, respectively; $P = 1.0$).
Tang *et al.*, 2018 (26)	Retrospective study of the clinical efficacy of multiplex PCR evaluating atypical bacteria, *P. jirovecii*, and 27 viruses from samples obtained via flexible bronchoscopy	130 patients after allogeneic HSCT who underwent bronchoscopy for pulmonary infiltrates; of 77 cases of infection, 54 were viral pneumonia (CMV most common), 37 were fungal pneumonia, and 29 were bacterial pneumonia	61% had a treatment modification after bronchoscopy ($n = 79$): 73% in the group with positive results and 33% in those with negative results ($P = 0.000$). This included modifications of antibiotic ($n = 15$), antifungal ($n = 13$), and antiviral ($n = 36$) medications, and the addition of corticosteroids ($n = 15$).

Definition of abbreviations: CMV = cytomegalovirus; ED = emergency department; HSCT = hematopoietic stem cell transplant; LOS = length of stay; *P.* = *Pneumocystis*.

48 hours or fewer (14, 17). There is concern that these results may be more driven by patients with asthma and chronic obstructive pulmonary disease exacerbations after secondary analyses of the data (40). In a retrospective study of hospitalized patients with CAP, the average duration of antibiotics was also shorter for the group with a viral pathogen detected by using NAATs than for those who did not have a viruses detected (4.9 vs. 8.3 d) (22). However, in other studies, detection of respiratory viruses by using NAATs was not associated with any significant difference in antibiotic treatment or the median duration of therapy (17, 23).

Data on the influence of respiratory viral NAAT results used to inform antibiotic management in patients with CAP are limited by the number of studies and methodological concerns. Limitations

Table 7. Narrative Summary of Studies Including Patients with a Variety of Respiratory Illnesses; Comparison: Routine PCR versus Rapid PCR Viral + Bacterial Testing

Author, Year (Reference)	Study Design	Setting/Participants	Key Results
Andrews *et al.*, 2017 (28)	Quasirandomized trial with patients enrolled in the control arm on odd days of the month and enrolled in the intervention arm on even days of the month; the control consisted of in-house multiplex PCR for viruses, and the intervention consisted of a POC multiplex PCR panel for 17 viral and 3 bacterial targets	545 patients, ⩾16 yr of age, seen in both inpatient and outpatient settings, with symptoms suggestive of an URTI, ILI, or LRTI; no data regarding number with suspected pneumonia	There was no significant difference in the hospital LOS between the control and the intervention. The median hospital LOS was 79.6 h (IQR, 41.9 to 188.9 h) in the control arm and 98.6 h (IQR, 48.1 to 218.4 h) in intervention arm. Comparing the control arm with the intervention arm, no significant difference was detected in antibiotic use at any time during the hospital stay after enrollment or in duration of antibiotic use. Among patients with influenza, the time to the first dose of antiviral therapy was shorter in the intervention arm: median of 60.4 h in the control arm (IQR, 22.7 to 85.2 h) vs. median of 24 h in the intervention arm (IQR, 11.6 to 33.0 h).
Mercuro *et al.*, 2018 (29)	Single-center, quasiexperimental study evaluating antimicrobial use after implementation of an in-house multiplex PCR panel for 17 viral and 3 bacterial targets coupled with an antimicrobial stewardship audit	131 hospitalized, immunocompromised patients were tested with a respiratory viral panel (send-out testing, $n = 51$; compared with in-house testing, $n = 75$); pneumonia was diagnosed in 80 (61.1%) patients	Compared with send-out testing, the in-house multiplex panel did not significantly alter antimicrobial optimization interventions (30.7% vs. 35.7%) but did reduce the time to intervention from specimen collection from 52.1 to 13.9 h ($P < 0.001$). There was no significant difference between these groups for type of antimicrobial intervention (deescalation, discontinuation, or addition), hospital LOS, or empiric antibiotic duration.
Shengchen *et al.*, 2019 (30)	Single-center, open-label randomized trial with patients randomized to POC testing with a multiplex PCR panel for 17 viral and 3 bacterial targets plus routine PCR or to routine PCR for 10 viral pathogens	800 hospitalized patients (398 in the intervention group and 402 in the control group) with LRTI; 57% had received a final diagnosis of pneumonia	No significant difference was observed between the two groups regarding the proportion of patients given i.v. antibiotics (92.1% vs. 93.8%; 95% CI, −5.1% to 2.0%; $P = 0.38$). The median duration of i.v. antibiotic treatment in the intervention group was significantly shorter than that in the control group (7 vs. 8 d, 95% CI, −2.1 to −0.8 d; $P < 0.001$). More patients in the intervention group had antibiotic deescalation within 72 h (7.9% vs. 3.2%; 95% CI, 1.4% to 8.0%; $P = 0.005$) than in the control group. The median hospital LOS was significantly shorter in the intervention group than in the control group (8 vs. 9 d; 95% CI, −1.6 to −0.4 d; $P < 0.001$).

Definition of abbreviations: CI = confidence interval; ILI = influenza-like illness; IQR = interquartile range; i.v. = intravenous; LOS = length of stay; LRTI = lower respiratory tract illness/infection; POC = point of care; URTI = upper respiratory tract infection.

include small sample sizes, retrospective study designs, challenges in implementation of respiratory virus panel testing and obtaining results in a rapid manner, communicating findings in a standardized and consistent way to treating clinicians, inclusion of mixed populations of patients with acute respiratory illness not restricted to CAP, and a primary focus on elderly patients. As a result, the panel was unable to recommend the routine use of NAAT-based testing for noninfluenza viral pathogens in patients with suspected CAP in the outpatient or the inpatient setting because of very-low-quality evidence. Substantial work

Table 8. Narrative Summary of Studies Including Patients with a Variety of Respiratory Illnesses; Comparison: Multiplex PCR versus No Multiplex PCR Viral + Bacterial Testing

Author, Year (Reference)	Study Design	Setting/Participants	Key Results
Branche *et al.*, 2015 (31)	Open-label randomized trial; patients randomized 1:1 to standard care or procalcitonin-guided care in combination with multiplex PCR testing for viral and atypical bacterial pathogens	300 inpatients with LRTI; 19% had an admission diagnosis of pneumonia	When comparing the intervention group with the nonintervention group, antibiotic use for ⩽48 h was seen in 69 (46%) vs. 61 (41%) patients ($P = 0.42$), the number of patients discharged receiving oral antibiotics was 51 (35%) vs. 64 (44%) ($P = 0.09$), and the total number of antibiotic days [median (IQR)] was 3.0 (1.0–7.0) vs. 4.0 (0.0–8.0) ($P = 0.71$).
Brittain-Long *et al.*, 2011 (32)	Multicenter randomized trial with patients randomized to have the treating physician receive results of multiplex PCR analysis for viral and bacterial pathogens either on the day after inclusion (rapid result) or 8 to 12 d later (delayed result)	406 adult outpatients with a diagnosis of community-acquired acute RTI; no data regarding the number with suspected pneumonia	In patients randomized to the rapid-result group, 9 of 202 (4.5%) patients received an antibiotic, compared with 25 of 204 (12.3%) of patients in the delayed-result group ($P = 0.005$); 335 of 406 (83%) patients returned for an optional follow-up visit or were available for a telephone appointment. In total, 28 patients (13.9%) in the rapid-result group and 35 patients (17.2%) in the delayed-result group received antibiotic treatment at either the initial visit or the follow-up visit ($P = 0.359$).
Dowson *et al.*, 2019 (33)	Before–after design in which nurse-initiated multiplex PCR testing of respiratory specimens was implemented as part of evaluation of residents with suspected RTI or in the setting of possible ILI or outbreak	55 nursing home residents with suspected RTI; before intervention: 38.3% of recorded episodes of infection met criteria for pneumonia or LRTI; after intervention: 31.7% met criteria for pneumonia or LRTI; of those identified for PCR testing, 26.4% met criteria	Before the intervention vs. after the intervention with antibiotic therapy, the incidence rates of antibiotic prescribing, with clustering of antibiotic prescribing within nursing homes taken into consideration, was as follows: the IRR for antibiotic days of therapy was 0.94 (0.25–3.35) ($P = 0.92$), and the IRR for antibiotic courses was 0.77 (0.22–2.66) ($P = 0.67$).
Echavarría *et al.*, 2018 (34)	Randomized trial with patients randomized to a multiplex PCR panel for 17 viral and 3 bacterial targets or testing for viral pathogens via IFA	432 patients (156 children and 276 adults) visiting the ED with signs and symptoms of an acute LRTI; 22.5% of adults received a diagnosis of pneumonia	Among adults, the decrease in antibiotic prescriptions was more common in the multiplex group than in the IFA group in a multivariable model (OR, 15.52; 95% CI, 1.99 to 120.8; $P = 0.009$). In unadjusted analysis, a change from intention to treat with oseltamivir to a final decision not to treat occurred in 12% of influenza A/B–negative adults tested by using multiplex PCR vs. 9% of influenza A/B–negative adults tested by using IFA ($P = 0.042$).

(Continued)

Table 8. (*Continued*)

Author, Year (Reference)	Study Design	Setting/Participants	Key Results
Oosterheert *et al.*, 2005 (35)	Multicenter randomized trial with patients randomized to the intervention group in which the results of a multiplex PCR test for viral and bacterial pathogens was reported ⩽48 h after a sample obtained or to the control group in which PCR was performed but in which results were not made available to treating physicians	107 hospitalized patients with LRTI (55 randomized to the intervention and 52 randomized to control); 51.4% received a diagnosis of pneumonia	In the intervention group, antibiotic treatment was modified in six patients (11%). Compared with the control group, the relative reduction in the number of completed antibiotic courses was 4% (95% CI, −1% to 9%). There was no significant difference in the duration of antimicrobial treatment between groups: median of 10 d (range, 1 to 46 d) in the intervention group and median of 9 d (range, 1 to 31 d) in the control group. The intervention had no significant effect on hospital LOS: median, 8 d (range, 1 to 24 d) in the intervention group; median, 8 d (range, 1 to 19 d) in the control group.

Definition of abbreviations: CI = confidence interval; ED = emergency department; IFA = immunofluorescence assay; ILI = influenza-like illness; IQR = interquartile range; IRR = incidence rate ratio; LOS = length of stay; LRTI = lower respiratory tract illness/infection; OR = odds ratio; RTI = respiratory tract infection.

remains to be done to address this question. Future studies should consider implementation strategies that combine viral NAATs with measurements of biomarkers, such as procalcitonin, and antibiotic stewardship practices in an effort to have a meaningful impact on antibiotic management of CAP. The panel further recognizes that factors related to local test availability may impact adherence to the suggestion not to routinely test for noninfluenza viral pathogens while routinely performing guideline-compliant testing for influenza in patients with CAP. For instance, some hospitals may only offer influenza testing as part of a multiplex panel that also includes noninfluenza virus targets. In such cases, the panel offers no guidance regarding the composition of the multiplex assay and must defer to individual institutional judgment as to whether the avoidance of occasional unnecessary testing justifies the cost of purchasing influenza-only tests.

Limited evidence of changes in other clinical outcomes. Although antibiotic use and hospital length of stay were identified as critically important outcomes, the panel also sought evidence to suggest that the use of such testing could impact other important clinical outcomes, such as mortality and hospital or ICU admission rates. No high-quality data were identified to conclusively support an association between routine testing for noninfluenza viruses and these outcomes. The panel did not identify evidence that routine use of nucleic acid–based testing for noninfluenza respiratory viruses improved the survival rate of patients with suspected CAP, nor did it demonstrably reduce hospitalization, the use of ICU services, or the time to clinical stability. The absence of data supporting such benefits may result from studies that largely focused on other questions and were thus underpowered to detect these effects. Nonetheless, the panel did not find that there was sufficient evidence of improvement in these patient-centered outcomes to recommend routine testing for viruses other than influenza in patients with suspected CAP.

Rationale for Suggestion for Routine Testing in CAP in Certain Hospitalized Patients

Rationale for noninfluenza virus testing recommendation in hospitalized patients with severe CAP. Although there is little high-quality evidence to strongly support the use of molecular testing for noninfluenza respiratory virus testing in any setting, the panel identified certain situations in which the potential benefit of testing is perceived to be greater. The recommendation to routinely use nucleic acid–based testing of respiratory samples for viral pathogens other than influenza in patients with severe CAP is based on increasing recognition that noninfluenza viruses cause severe CAP and the panel's assertion that detection of these viruses may have important impacts on patient management as well as hospital antiinfective practices. Highly sensitive and specific NAATs allow improved detection of respiratory viruses, enhancing our understanding of the epidemiology and ecology of severe CAP (1, 41–47). Noninfluenza viruses are detected in a substantial proportion of severe CAP cases and have been associated with important complications in hospitalized adults, including the increased need for mechanical ventilation, the increased need for prolonged intensive-care support, and increased mortality (48). In fact, some series indicate that noninfluenza respiratory viruses have been associated with greater inpatient mortality than influenza (49). Furthermore, noninfluenza viruses have been reported to cause more severe CAP than influenza in patients with advanced age, chronic respiratory diseases, malignancy, and/or immunosuppression (49).

The yield of NAATs for respiratory viruses in reported series of adults with severe CAP ranges between 9% and 41%, although these numbers are influenced by the inclusion of influenza virus in these data sets (1, 41–47). Mixed viral and bacterial

infections are detected in about 12% of CAP cases, and rapid recognition of all contributing pathogens is critical for patients with severe CAP (41), for whom delays in appropriate antibiotic and antiviral selections can have serious consequences. The panel agreed that detection of noninfluenza viruses or mixed viral and bacterial infections in patients with severe CAP can promote appropriate antibiotic use and/or allow deescalation to prevent overuse of antimicrobial agents in the ICU, where antimicrobial use is significantly higher than in other settings (50). We explicitly support the stratification of patients on the basis of disease severity as outlined in the 2007 (and endorsed in the 2019) Infectious Diseases Society of America/ATS severe CAP criteria (Table 9) (2) rather than on the basis of hospital care setting or unit type, as this may vary among hospitals and practices.

Rationale for testing recommendation in hospitalized immunocompromised patients. Immunocompromised patients are at particularly high risk for death after developing an infectious pneumonia syndrome (51). This population may include patients with inherited or acquired immune deficiency or drug-induced neutropenia, such as patients actively receiving cancer chemotherapy, patients with HIV infection and CD4 counts <500 cells/mm^3, and solid organ transplant or HSCT recipients.

Certain immunocompromised populations, such as HSCT recipients, have a high annual incidence of respiratory viral infections (52), and the rate of progression from upper respiratory viral infection to fatal pneumonia is markedly higher than that in nonimmunocompromised hosts (53). Similarly, lung transplant recipients are at high risk of progression from upper respiratory tract infection to severe pneumonia (54, 55). Even in symptomatic, immunocompromised patients, the yield of causative pathogens from BAL fluid using culture-based techniques for bacterial pathogens remains low (56, 57). Because of the risk of progression or death after respiratory viral infection in immunocompromised hosts, early detection of viral infection may be useful for clinicians providing treatment. Although prospective, randomized studies are needed to draw better conclusions, noninfluenza respiratory viruses such as RSV and adenovirus have enhanced pathogenic potential in immunocompromised patients, potentially warranting more invasive testing if initial upper respiratory tract testing results are negative.

Thus, the panel supports routine testing for noninfluenza respiratory viruses in the immunocompromised population. Such testing in these patients has the further potential to enhance our understanding of the viral epidemiology in a population that is susceptible to uncommon and unusual pathogens. However, this recommendation is made while recognizing that the utility of viral testing in this population may be limited by certain key observations. First, despite the use of cidofovir for the treatment of adenovirus (58) and oral or inhaled ribavirin for the treatment of RSV pneumonia (59), only antiinfluenza medications have FDA-approved indications in immunocompromised adults with respiratory viral infection (60). Second, prolonged periods of viral shedding in immunocompromised hosts may lead to overdiagnosis and overtreatment in cases in which viral inflammation is inactive or minimal (61). Finally, in the absence of lower respiratory PCR panels that detect bacterial infection, clinicians may not be comfortable with stopping antibiotics after a negative bacterial culture from BAL fluid samples because of the low diagnostic yield (62). As in nonimmunocompromised patients, there is no current evidence demonstrating that viral respiratory PCR panels alter prescribing patterns of antimicrobial agents in immunocompromised hosts (29, 39). In light of these limitations, the consensus opinion of the committee was to recommend that nucleic acid–based testing of respiratory samples for viral pathogens other than influenza be considered in certain immunocompromised patients at high risk for death of respiratory viral infection, but the utility of this test will depend heavily on the development of novel effective antiviral therapies. It is further acknowledged that identifying viral pathogens in immunocompromised outpatients via nucleic acid–based testing may also provide important benefits, but the absence of even indirect evidence from that population limits the panel's capacity to suggest testing in that context.

Table 9. 2007 Infectious Diseases Society of America/American Thoracic Society Criteria for Severe CAP

Validated definition includes either one major criterion or three or more minor criteria

Minor criteria
- Respiratory rate >30 breaths/min; Pa_{O_2}/Fi_{O_2} ratio <250
- Multilobar infiltrates
- Confusion/disorientation
- Uremia (blood urea nitrogen level >20 mg/dl)
- Leukopenia* (white blood cell count $<4{,}000$ cells/ml)
- Thrombocytopenia (platelet count $<100{,}000$/ml)
- Hypothermia (core temperature $<36.8^{\circ}$C)
- Hypotension requiring aggressive fluid resuscitation

Major criteria
- Septic shock with need for vasopressors
- Respiratory failure requiring mechanical ventilation

Definition of abbreviation: CAP = community-acquired pneumonia.
The same criteria were used by the 2019 CAP guideline (2).
*Due to infection alone (i.e., not chemotherapy induced).

Additional Considerations

Impact on Antiviral Agent Use

Respiratory viral pathogens other than influenza cause a significant burden of disease and lead to poor outcomes in high-risk patients. Although the standard of care for patients infected with these pathogens is generally limited to supportive management, some patients may be candidates for antiviral therapy or passive immunization with virus-specific immunoglobulins, supporting our recommendation for testing viral pathogens in high-risk patients.

For example, human RSV is a common cause of acute upper respiratory tract illness that often leads to more severe disease and hospitalization in older adults and in those with compromised immunity (63). Although there are no formal guidelines for therapy of RSV in adults, off-label use of aerosolized ribavirin has been used to treat RSV infections in HSCT or lung transplant recipients, on the basis of mainly observational data (52). Treatment with oral ribavirin, which is significantly less

expensive and easier to administer than the aerosolized compound, may be an effective alternative in reducing progression to lower respiratory tract infection and mortality (59). Several new antiviral agents (presatovir, ALS-008176, and RSV604), as well as monoclonal antibodies to prevent acquisition of RSV, are currently at different phases of preclinical or clinical development (64). Human adenoviruses (HAdVs) typically cause short-lived upper respiratory tract manifestations in adults, but some species have been associated with severe viral pneumonia in outbreak settings. Furthermore, HAdVs are capable of establishing latent infections with subsequent reactivation during periods of immune suppression, allowing development of pneumonia and disseminated disease (65). Clinical experience with antivirals is limited, but cidofovir has been used to treat severe HAdV disease on the basis of *in vitro* activity and observational data (66, 67); trials for the safety and efficacy of brincidofovir are underway (68).

Other respiratory viruses, such as human metapneumovirus, parainfluenza types 1–4, rhinovirus/enterovirus, or human coronaviruses, may also cause severe pneumonia in adult patients, although agents with activity against them are not clinically available (69, 70). In such cases, their detection may become more relevant as effective antivirals become available.

Nonviral Target Pathogens

Although the focus of this guideline is testing for viral pathogens, the panel recognizes the clinical importance and diagnostic challenges related to detection of nonviral pathogens in CAP. Development and adoption of rapid molecular tests for nonviral pathogens may improve etiologic diagnosis and appropriate selection of antimicrobials (23). "Atypical" bacterial pathogens (e.g., *Legionella* spp, *Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae*) are common causes of CAP (1, 71) with distinct antimicrobial-susceptibility profiles. In endemic regions and high-risk patients, rapid molecular testing of *Mycobacterium tuberculosis* likely improves diagnostic accuracy and informs infection prevention interventions (72). Specific fungal pathogens can be common causes of CAP in endemic regions (e.g., coccidiomycosis in the American Southwest [73] and histoplasmosis and blastomycosis in the Mississippi and Ohio River valleys [74, 75]). Specific recommendations regarding their implementation are beyond the scope of the current document, but the panel notes that these organisms may also be detected by some NAAT arrays and thus recognizes that a potential further benefit may exist.

Role in infection control and outbreak management. Rapid nucleic acid–based tests for viral pathogens other than influenza could result in faster and more efficient infection-control measures in hospital settings through detection and prevention of nosocomial outbreaks. Alternately, when respiratory viral infections are suspected, rapid tests with a short turnaround time could provide economic benefit due to a reduced number of isolation days (39). A recent single-center study confirmed significant reductions in the mean number of days in isolation, mean number of days under contact precautions, and mean number of days under droplet precaution measures upon introduction of a rapid RT-PCR test for influenza (76). It is suspected that similar results might be observed for other respiratory viral infections, such as RSV.

Indeed, significant reductions in admissions to isolation facilities and the time of isolation have been described after implementation of a rapid PCR-based viral respiratory panel test targeting several respiratory viruses (39, 77). The impact on isolation use appears to relate mainly to the accelerated turnaround time for newly implemented POC test results. Thus, although it seems likely that nucleic acid–based tests for respiratory viruses other than influenza will improve infection control and outbreak measures while saving costs, studies confirming this in different healthcare settings are needed before such testing is recommended. Underscoring this potential, NAATs are the cornerstone of the CDC's U.S. SARS-CoV-2 Surveillance Plan, with NAAT data being used to characterize the spread of disease and inform pandemic management strategies. Furthermore, the U.S. FDA has issued emergency use authorizations for rapid nucleic acid amplification platforms on the basis of the expectation that reduced turnaround times will improve patient care and better contain viral spread.

Research Needs

The development of this document revealed a paucity of high-quality data related to the impact of diagnosing noninfluenza viral infections on patient outcomes in suspected CAP. This underscores the urgent need for prospective studies to determine the influence of nucleic acid–based viral diagnostics in the management of outpatient and inpatient CAP, including pragmatic and implementation studies. Studies are specifically needed to determine the clinical impact of these diagnostics on treatment decisions in patients with severe CAP and in those who are immunocompromised. Such studies may reveal the impact of turnaround time using NAAT technologies to diagnose viral pneumonias on important patient outcomes. Studies are also needed to better assess the impact of multiplex NAAT panel target composition. This can allow insight into the clinical benefit of differently sized panels, as well as into those that include pathogens that are often separately targeted (e.g., influenza viruses or SARS-CoV-2) or those that include nonviral pathogens (e.g., atypical bacteria).

Improved clinical identification of common respiratory viral pathogens may promote the development of novel therapies to manage and prevent these infections. Studies demonstrating efficacy of such viral agents could subsequently improve antimicrobial stewardship practices. Relatedly, health system–integrated clinical reminders after viral testing may further enhance NAAT impacts on antibiotic use patterns, although this also requires formal evaluation. Nucleic acid amplification testing has infection-control implications in the hospital setting, especially where patients with severe CAP are managed, and this should be formally investigated. Well-designed pragmatic clinical trials will be instrumental in informing the use of NAATs for noninfluenza viral pathogens. The SARS-CoV-2 pandemic has highlighted the importance of molecular diagnostics in the diagnosis, management, and surveillance of viral respiratory infections. Studies to assess the impact of such testing on patient outcomes and pandemic management are ongoing.

Conclusions

This guideline constitutes a rigorous PICO-guided evaluation of relevant and available literature for scientific evidence regarding recommendations pertaining to the use of nucleic acid–based diagnostics testing for noninfluenza viral pathogens in CAP for the outpatient and inpatient setting. On the basis of GRADE criteria, the quality of evidence on this topic was rated as being very low, with few studies assessing the effect of noninfluenza viral diagnoses on key patient-centered outcomes. The use of nucleic acid–based diagnostics for viral pathogens other than influenza only was not clearly associated with patterns of antibiotic use. The panel examined and discussed the role of nucleic acid–based viral diagnostics for hospitalized patients and believed their use for the routine evaluation of suspected CAP should be considered only for patients with severe disease or those with immunocompromising conditions. Neither of the recommendations in this guideline is considered to be an appropriate target for a performance measure. ■

This official clinical practice guideline was prepared by an *ad hoc* subcommittee of the ATS Assembly on Pulmonary Infection and Tuberculosis.

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