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Other Community Respiratory Viruses

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KEYWORDS

- Respiratory viral panel • Pneumonia • Acute respiratory distress syndrome • Ribavirin • Cidofovir
- Adenovirus • Coronavirus • Human metapneumovirus

KEY POINTS

- Polymerase chain reaction–based diagnosis has become the standard for viral pneumonia and other respiratory tract infections.
- Expanded respiratory viral panels (RVPs) lead to diagnosis of viral respiratory infections for which no specific treatment exists outside of influenza and, possibly, respiratory syncytial virus.
- Careful clinical evaluation, including source of sample, pattern of respiratory tract involvement and tempo of progression, degree of immunocompromise, and extrapulmonary involvement, of the patient with a positive RVP is critical, given the limited repertoire of treatments.
- Generic treatments with intravenous immunoglobulin, ribavirin, and interferons may benefit select severe viral pneumonia patients, whereas cidofovir has activity for severe adenoviral pneumonia.

INTRODUCTION

The advent of clinical use of polymerase chain reaction (PCR) technology has revolutionized the diagnosis of viral respiratory infections. Early studies demonstrated much greater sensitivity than viral culture with a clinically actionable time to results. PCR has, therefore, essentially replaced viral culture for acute clinical diagnosis. PCR has an unclear relationship to acute and convalescent serology, a prior diagnostic standard that was not clinically useful except for retrospective diagnosis. PCR detects presence of viral genomic material at the time of specimen acquisition. This usually represents acute infection, although prolonged shedding of viral genomic material after an acute infection can occur, especially in immunocompromised patients.

Multiplex platforms that perform a respiratory viral panel (RVP) have become the norm for many hospitals. The initial driving force for multiplex panels was the 2007 to 2008 seasonal influenza outbreak. During that year, 2 strains of influenza A were circulating: an H1 strain that was resistant to oseltamivir and an H3 strain that remained sensitive.[1] At that time, differentiation between influenza A and B, and between the 2 strains of influenza A, became critical in order to discontinue dual antiviral therapy. In the subsequent year, the pandemic strain of influenza A(H1N1) virus added an additional target for multiplex RVP assays.

To completely replace respiratory viral cultures, the RVPs included other clinically important viral assays used for epidemiologic purposes, such as respiratory syncytial virus (RSV) and adenovirus. Panels became progressively more extensive, including addition of newly discovered human respiratory viral pathogens such as the coronaviruses responsible for severe acute respiratory syndrome (SARS) and human metapneumovirus (HMPV). Initially perceived as simply a positive alternative when more significant pathogens were not detected, the frequent association of rhinovirus with respiratory tract disease[2] led to its

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routine inclusion in RVP panels. Increasingly, sub-species of viruses other than influenza A were added. This was made dramatically clear with the recent epidemic of enterovirus (EV)-D68[3] which was detected as human rhinovirus in some multiplex assays and not in others. The EV species seem to have distinct trophism with C and D, mainly causing respiratory tract disease. Finally, PCR for bacterial species difficult to grow, such as *Mycoplasma* spp and *Chlamydophila* spp, and in the differential of respiratory tract infections, such as *Bordetella pertussis*, were added for convenience and increased diagnostic yield. A spectrum of causes covered by most multiplex RVPs is listed in **Box 1**.

Unfortunately, current multiplex RVP panels now provide laboratory diagnoses of viral respiratory tract diseases that have few, if any, clinical treatment options. This disconnect between diagnosis and specific treatment raises difficult management issues and a tendency to ignore the results. For a positive assay on an RVP panel, influenza and atypical bacterial pathogens (if included) are clearly actionable and covered in other articles in this issue. In this article, evaluation and management of the other respiratory viruses commonly detected with multiplex RVPs are reviewed.

PCR is also the standard for diagnosis of many other viral infections that are either rare (eg, hantavirus syndrome or Middle East respiratory syndrome [MERS]) or which rarely involve the lung. Because high clinical suspicion for these infections is required before ordering a PCR assay, they will not be specifically discussed in this article.

GENERAL APPROACH

Given the limited repertoire of treatment options for viral respiratory tract infections, careful assessment of the clinical significance of a positive PCR for any virus other than influenza is needed. In general, the indication for treatment of a positive RVP (other than influenza) is presence of or high risk of subsequently developing lower respiratory tract (LRT) infection (LRTI). **Box 2** gives a general approach to evaluating a positive RVP.

Colonization Versus Active Infection

One of the major questions is whether a positive RVP represents disease or is simply colonization or prolonged shedding from a prior unrelated infection. Many viral syndromes may have minimal symptoms, yet lead to positive screening tests. Several viruses have also been demonstrated to have prolonged shedding after symptomatic illness. Prolonged shedding is a particular problem in the immunocompromised, the exact population in which viral pneumonia is most likely to require treatment.

A perspective on the frequency of colonization or prolonged asymptomatic shedding can be gained from studies of healthy patients presenting for noninfectious clinic visits. Colonization is clearly more common in asymptomatic children than in adults.[4] A pediatric case control study of community-acquired pneumonia (CAP) compared with normal healthy controls demonstrated that

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Box 1
Pathogens included in usual respiratory viral panels

Influenza A

- H1 lineage
- H3 lineage
- pdm2009 H1 lineage

Influenza B

Adenovirus

HMPV

Rhinovirus or EV

RSV

Parainfluenza

- Types 1 to 4

Coronavirus

- OC43, NL63, 229E, HKU1

Bocavirus

Atypical bacterial pathogens occasionally included

Mycoplasma pneumoniae

Chlamydophila pneumoniae

Bordetella pertussis

Box 2
Clinical evaluation of a positive respiratory viral panel

Colonization versus active infection

Upper respiratory tract versus LRT

Temporal pattern of symptoms

Immune status

Pattern of LRTI involvement

Extrarespiratory tract involvement

the odds ratio was greater than 10 for influenza, RSV, and HMPV, and at least greater than 1 for adenovirus.[5] For bocavirus, coronaviruses, EV, parainfluenza, and rhinovirus, the frequency of positive nasopharynx (NP) PCR tests was actually greater in asymptomatic controls than cases of pneumonia. In contrast, detection of any common respiratory virus in asymptomatic adults was only 2.1%.[4] In adults, even rhinovirus is highly associated with pneumonia with an odds ratio of greater than 13. The most common virus detected in asymptomatic adults was coronaviruses, although detection was still associated with an odds ratio for pneumonia of greater than 3.

Upper Versus Lower Respiratory Tract Disease

The second critical issue is the site of sampling. A positive sample from the LRT carries more significance than a positive sample from the NP or oropharynx (OP). Most positive viral samples are from NP or OP swabs because of the ease of obtaining the specimen. The lower in the respiratory tract that the sample is obtained, the greater the significance; that is, a positive bronchoalveolar lavage sample is much more likely to indicate viral pneumonia than an NP or OP swab. Expectorated sputum and endotracheal aspirates can represent viral tracheobronchitis or an intermediate risk of viral pneumonia.

Probably the most concerning aspect of site of sampling is the finding that patients with positive LRTI can occasionally have negative NP or OP swabs. This may result from poor sampling technique with the NP or OP swab or may actually represent a transition from upper respiratory tract (URT) to LRT disease. Of major concern is that this has been seen in patients with influenza A-induced acute respiratory distress syndrome (ARDS). Preliminary data suggest that high quality sputum samples in patients with radiographic pneumonia may be positive more often than NP or OP swabs, even for common viruses such as influenza. Obtaining an LRT sample from patient with CAP-induced respiratory failure is prudent even if the NP or OP swab is negative for influenza.

The risks for progression from viral URT infection to pneumonia or ARDS are generally unclear or nonspecific. Presence of peripheral monocytosis has been demonstrated to be associated with pneumonia in adenoviral infection.[6] For stem cell transplants, smoking, steroids, total body irradiation, and lymphopenia are associated with progression to LRTI.[7] Other investigators have suggested that detection of multiple respiratory viruses portends poor prognosis and may be a marker for occult immuncompromise.[8]

Temporal pattern of symptoms

Assessing the tempo of disease progression is also key to understanding the significance of a positive RVP. A long duration or interval since onset of URT symptoms followed by new or changed symptoms consistent with LRT or systemic infection suggests a pulmonary infiltrate in a patient with a positive NP or OP swab is more likely bacterial superinfection than primary viral pneumonia. In this case, the positive NP or OP RVP likely represents persistent shedding after an antecedent viral URI. Conversely, a negative RVP in this situation may result in seroconversion, leading to the discordant results between serology and RVPs seen in epidemiologic studies. Persistent or worsening URI symptoms suggest that a positive NP or OP RVP may be the cause of tracheobronchitis or pneumonia.

Immune status

By far the most important factor on the decision to treat a positive RVP is the immune status of the patient. Up to 50% of patients with viral pneumonia may be immunocompromised.[8] Disseminated disease, including viremia, is much more likely in the severely immunocompromised.

The type of immunocompromise associated with progression to viral pneumonia is poorly studied. Probably the greatest risk is to recent human stem cell and bone marrow transplant patients.[8] Recovery of T- and B-lymphocytes is delayed more than neutrophils and recent hematologic transplant patients may have low immunoglobulin levels. Lung transplant patients are also particularly prone to serious viral pneumonia. Use of B-cell suppressive therapy, for example, rituximab, may also predispose to progressive LRT viral infections when used for both malignancies and other immunoglobulin-mediated disease. Conversely, acute leukemia or chemotherapy-induced neutropenia may not have as important a role in severe viral infections as they do bacterial and fungal infections.

Despite the increased risk in hematologic and lung transplant recipients, most patients with viral pneumonia or viral-induced ARDS are not overtly immunocompromised. Given the frequency of infection with common respiratory viruses in both adults and children, the proportion developing LRTI is very small. Specific genetic defects in the normal host response to viral URT infection are likely in patients with these extreme manifestations.

Pattern of lower respiratory tract involvement

Four general patterns of LRTI with viruses are commonly seen: acute bronchitis or bronchiolitis in adults and children without prior lung disease,

acute exacerbation of obstructive lung diseases (asthma and chronic obstructive lung disease [COPD]), pneumonia, and ARDS. The potential benefit of nonspecific therapies increases with the latter 2, whereas supportive therapy alone is usually adequate for airway-only involvement.

Acute bronchiolitis in children and exacerbation of asthma or COPD are by far the most common reasons for hospitalization with an acute viral illness. Whether specific antiviral therapy improves outcome in these entities is still under investigation. The data on influenza antivirals in exacerbations of asthma or COPD are very mixed. Data on response to the various novel agents for RSV are pending. However, RSV is a major cause of pediatric hospitalizations and justification for treatment of airway disease alone should be available from the ongoing trials.

Extrarespiratory involvement

Involvement of extrapulmonary sites with a respiratory viral infection clearly increases the propensity to treat. Sites that may be involved with respiratory viruses are listed in Table 1.

Viremia occurs frequently in some viral LRTIs although it has not been reported in others. However, the technology for assessing viremia in the past has been poor and incompletely studied. Experience with human immunodeficiency virus (HIV) and hepatitis viruses, in which assessing serum viral load is commonplace, may lead to greater use of whole blood viral load for assessing indication and response to therapy of respiratory viruses. A serum assay for adenovirus is commercially available.

Neurologic complications are classic for EV, including the prototypical EV D68 strain,[3] with flaccid paralysis, encephalitis, and aseptic meningitis being the most prominent features. Central nervous system involvement in influenza includes encephalitis; transverse myelitis; aseptic meningitis; and, rarely, Guillain-Barré syndrome. Up to 10% of cases of viral encephalitis may be influenza, in both adults and children.[9] Encephalitis has been associated with HMPV in case reports.

Pericarditis and myocarditis are classic for the EV strain previously called coxsackievirus. Coxsackievirus is not routinely detected with the current commercially available RVPs. Myocarditis and pericarditis were reported in the 1918 influenza pandemic but have been infrequently reported since. However, during the Asian epidemic in 1957, signs of focal or diffuse myocarditis were found in a third of autopsies.

Hepatitis can clearly complicate several viral respiratory tract infections with the classic being adenovirus. EV is also a significant risk because the group includes hepatitis A, and EV A and B groups are also associated with hepatitis.

Rhabdomyolysis has been reported with viral pneumonia, particularly from the 2009 pandemic influenza A strain. A multicenter report of patients admitted to the intensive care units found that creatinine kinase was elevated in 24%, with greater risk of renal replacement therapy and prolonged ventilation.[10] In vitro studies suggest that muscle cells also express the α2,3 and α2,6-linked sialic acid receptors, identical to the receptors influenza use to bind respiratory epithelial cells.[11] Rhabdomyolysis, therefore, seems to likely be a manifestation of viremia. Case reports have associated rhabdomyolysis with other respiratory viruses as well.

Clinical Decisions

The clinical response to a positive RVP can take a variety of forms. In many ways, the most straightforward responses occur when specific treatments are available, such as for influenza and, potentially, RSV. Management of infection with other viruses in an RVP panel requires a much more nuanced approach. The primary clinical question is "Does providing a viral diagnosis lead to differential treatment?"

Antibiotic discontinuation

A major clinical question is whether a positive viral diagnosis in patients with LRTI allows safe avoidance or discontinuation of antibiotics. No randomized controlled trial has specifically addressed this issue. The most pertinent publications are before-and-after studies of introduction of a multiplex PCR into a specific institution. One large study suggested that a positive RVP did not decrease antibiotic utilization but did have a significant impact on increased antiviral use

Table 1 Extrapulmonary site of infection with respiratory viruses	
Manifestation	**Viruses Involved**
Viremia	? all: influenza, adenovirus, rhinovirus, EV
Encephalitis or cerebritis	Adenovirus, EV, influenza, RSV
Hepatitis	Adenovirus, influenza, RSV
Pericarditis	Influenza
Myocarditis	Adenovirus, influenza, EV, RSV
Rhabdomyolysis	Influenza

(purely oseltamivir) and a 6% decrease in chest computed tomography (CT) scans.[12]

The most pertinent study was a pilot randomized controlled trial of the combination of serum procalcitonin and multiplex RVP in subjects with nonpneumonic LRTI.[13] In this study, subjects with a positive RVP had significantly less discharge antibiotics and a trend toward shorter duration of antibiotic therapy, especially with high protocol adherence. The combination of a low procalcitonin and positive RVP is also demonstrated to be too few antibiotics in an observational study of pneumonia.[14]

Until true randomized control trials are available, the current data suggest that a positive RVP alone is insufficient evidence to discontinue antibiotics. However, a positive RVP seems to have a synergistic effect with procalcitonin, a biomarker that has independently been associated with decreased antibiotic therapy, to decrease the duration of antibiotic therapy. Avoiding all antibiotic therapy in patients with pneumonia seems to be an unlikely use of RVP. In addition, a positive RVP may give enough clinical assurance to avoid additional diagnostic procedures, such as chest CT scans or bronchoscopy for patients who are failing empirical antibiotic therapy. In contrast, avoidance of antibiotics in other LRTIs, including acute exacerbations of COPD and acute simple bronchitis based on a positive RVP and low procalcitonin may be clinically safe.

GENERIC TREATMENT

In addition to decisions regarding antibiotics, several other clinically relevant generic treatments may be affected by a positive RVP.

Anticholinergics for Bronchospasm

The initial resurgence use of anticholinergic bronchodilators was the recognition that postviral cough and bronchospasm seemed to respond better to anticholinergics than the then standard β-agonist bronchodilators. For COPD exacerbations, anticholinergics are now standard therapies, although significantly less so for asthma. Therefore, a positive RVP may suggest the need to add anticholinergics that the patient was not previously taking. More importantly, a positive RVP may generate less concern about prolonged exacerbation because certain viruses are associated with prolonged bronchospasm, including rhinovirus, influenza, parainfluenza, and RSV. In this situation, avoidance of escalation in corticosteroid dose or duration may result from knowledge of the viral trigger. No prospective randomized trial has addressed this issue.

Extracorporeal Membrane Oxygenation

Documentation of viral pneumonia causing ARDS is increasingly being recognized as an indication for venovenous (VV) extracorporeal membrane oxygenation (ECMO). Improvements in technical aspects of ECMO, including simplification of the membrane oxygenator, VV circuits, and use of a single catheter, have taken this from a rare intervention to becoming part of the standard armamentarium in tertiary referral centers.

In recent years, pneumonia secondary to the pandemic A(H1N1) strain has become the leading nontransplant indication for VV-ECMO. The LRT trophism of this influenza strain and the predilection for previously healthy young patients may be the main reasons. However, other respiratory viruses are associated with severe ARDS and need for rescue therapies. Viral-induced ARDS is less likely to respond to other rescue therapies such as prone positioning or high PEEP. In addition, lack of a reliable treatment of the underlying disease, as seen with bacterial pneumonia, may have pushed clinical care more toward this type of support.

GENERIC ANTIVIRAL THERAPIES

Lack of specific antiviral therapies has led to use of several more generic forms. Generally, these are reserved for patients with pneumonia or ARDS, or for patients with severe immunocompromise. In addition, they are often used in combination, making dissecting out to individual benefits very difficult.

A positive RVP may be a contraindication to other generic antiviral therapies. Patients infected with both SARS coronavirus and severe pandemic A(H1N1) virus seem to be worsened with the use of systemic corticosteroids.[15,16] Therefore, a positive RVP may be an indication to avoid steroids in patients with ARDS.

In patients with organ transplant, a positive RVP may be a consideration for decreasing the degree of immunosuppression. Although this may be possible in renal transplant and some other solid organ transplants, the combination of organ rejection or graft versus host disease and a positive RVP is often a lethal combination, mainly because high-dose immunosuppression cannot be decreased.

Intravenous Immunoglobulin

The rationale for use of intravenous immunoglobulin (IVIG) is the probability of virus-specific antibodies present in the pooled immunoglobulin extracted from multiple people. Because of the

pooled specimens and variable exposure and titers of virus-specific antibodies, the benefit may be inconsistent. Plasma from patients who have recently recovered from serious viral infections may have much more effectiveness but limited availability. Data from RSV antibody work suggest that the benefit of IVIG may be greatest when viremia is still occurring but may not stop direct cell-to-adjacent-cell spread of viruses.

Ribavirin

Ribavirin, a guanosine analog, seems to have activity against a broad spectrum of both RNA and DNA viruses and has been used for a variety of viral respiratory tract infections.[17] Greatest use has been in the immunocompromised population, often in combination with IVIG. Ribavirin treatment has been attempted in severe pneumonia from almost all the viruses in the usual RVP. Unfortunately, most of the studies are uncontrolled and nonblinded, making estimation of the true benefit of ribavirin difficult to determine. Also, most gave other immunomodulators, including IVIG and corticosteroids, further obscuring the potential benefit.

Aerosolized ribavirin has generally fallen into disfavor secondary to the significant teratogenic effects and difficulty in venting the drug from the patient's room without potentially affecting caregivers or visitors. Oral or intravenous ribavirin has been associated with hemolytic anemia and severe hypomagnesemia, requiring drug discontinuation in as many as 15% of cases.

Interferon

Recently, the availability of different interferon formulations has been explored in the treatment of severe viral respiratory infections. These pharmaceutical interferon medications have been developed principally for the treatment of chronic hepatitis. Interferon is a critical part of the normal host response to respiratory viral infections as well. Although it is tempting to suspect that immunocompetent patients who develop severe viral pneumonia or ARDS may have alterations in their interferon response, only limited data support this concept.[18]

The greatest support for interferon combination therapy in respiratory viral infections comes from a historical-control cohort series of treatment of the coronavirus-induced MERS.[19] Pegylated interferon alfa-2a weekly for 2 weeks and daily ribavirin were used to treat 20 subjects with documented MERS. Early survival at 14 days was significantly higher (70%) than a historical control at the same

site (29%). However, sustained survival was not demonstrated. The combination of interferon and ribavirin also seems to be synergistic for SARS coronavirus.[20]

Interferon-β-1a has been used to treat patients with ARDS,[21] many of which had pneumonia although the frequency of viral pneumonia was unknown. In a small pilot study, 28 day mortality was significantly improved compared with control. Interferon-β has also been used as an aerosol to treat viral-induced exacerbations of asthma with equivocal results.[22] The combination of interferon α2a and ribavirin has also been used to treat refractory serious rhinovirus respiratory tract infections in patients with hypogammaglobulinemia with good results.[23]

SPECIFIC ANTIVIRALS

The only specific antiviral treatment of pathogens, other than influenza and RSV, is cidofovir for serious adenoviral pneumonia. Released for treatment of cytomegalovirus retinitis in HIV patients, intravenous cidofovir has been used in both immunocompromised and immunocompetent patients. Treatment is clearly more effective in immunocompetent[24] than immunocompromised patients.[25,26] Cidofovir has significant nephrotoxicity. Adenoviral serum titer measurement is commercially available and can assist in determining the duration of therapy, although 1 or 2 doses weekly is usually sufficient for those patients likely to respond.

Pleconaril has been studied in neonatal EV sepsis with successful results.[27] Possible use in serious enteroviral or rhinoviral respiratory tract infections has not been studied and the drug is not clinically available yet. Side effects seem to be very tolerable.

SUMMARY

PCR-based diagnosis has become the standard for viral pneumonia and other respiratory tract infections. Expansion of RVPs outside of influenza, and possibly RSV, has led to the ability to diagnose viral infections for which no approved specific antiviral treatment exists. Careful clinical evaluation of the patient with a positive RVP is, therefore, critical given the limited repertoire of treatments. Generic treatments with IVIG, ribavirin, and interferons may benefit select severe viral pneumonia patients, whereas cidofovir has activity for severe adenoviral pneumonia. Development of new treatments will add significant value to the ability to detect viral respiratory pathogens.

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