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Severe Respiratory Viral Infections: New Evidence and Changing Paradigms

James M. Walter, MD[1], **Richard G. Wunderink, MD, FCCP**[*]

Division of Pulmonary and Critical Care, Department of Medicine, Northwestern University Feinberg School of Medicine, 676 North St Clair Street, Arkes 14-000, Chicago, IL 60611, USA

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Lower respiratory tract infection (LRTI) is a leading cause of death in the United States and the most common infection identified in patients admitted to the intensive care unit (ICU).[1,2] This burden will only increase as the population ages.[3]

The diagnosis and treatment of LRTIs including community-acquired pneumonia (CAP) has focused traditionally on bacterial pathogens.[4] Enthusiasm for the study of respiratory viral pathogens in severe respiratory illness has been tempered in the past by cumbersome diagnostic techniques and limited pharmacologic therapies. However, as pneumonia epidemiology and diagnostic platforms evolve, this focus has begun to change. The success of childhood vaccination programs and the aging of the US population have altered the landscape of severe respiratory infection.

Invasive pneumococcal disease has declined dramatically and viral pathogens that particularly impact the elderly are now recognized as common causal pathogens in severe disease.[5,6] Concurrently, the widespread use of nucleic acid amplification testing has markedly improved the detection of viral pathogens.[7]

This review focuses on the importance of respiratory viral pathogens in the pathogenesis of severe respiratory infections with a particular emphasis on community-acquired infections. Given widespread knowledge of influenza's important role in severe respiratory infections, we will focus on the noninfluenza viruses rhinovirus, human adenovirus (HAdV), respiratory syncytial virus (RSV), and human metapneumovirus (hMPV; Table 1).[8]

[*]Corresponding author. 676 North St. Clair Street, Arkes Pavilion 14-015, Chicago, IL 60611., r-wunderink@northwestern.edu.
[1]Present address: 240 E. Huron, McGaw M-300, Chicago, IL 60611.

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THE EVOLVING EPIDEMIOLOGY OF SEVERE RESPIRATORY INFECTIONS

As the US population ages, the number of homebound elderly, patients discharged to long-term care facilities, and adults with chronic medical conditions has increased.[3,9,10] It is, therefore, not surprising that the number of elderly patients admitted to the hospital with pneumonia is increasing. In 1 study, hospitalizations for pneumonia in patients 65 years of age or older increased by 20% over a 15-year period with an 11% increase in the number of patients with chronic cardiac or pulmonary disease.[3] Elderly and functionally limited adults are particularly prone to severe viral infection.[11] The incidence of rhinovirus infection in patients 65 years of age or older is 10 times higher than in younger adults; likewise, the majority of deaths attributable to RSV infection occur in patients older than 65 years of age.[12,13] Outbreaks of severe viral infections at long-term care facilities are common for numerous respiratory viral pathogens.[14–16]

As the number of adults susceptible to severe viral infections has increased, the incidence of invasive bacterial pneumonia has decreased owing to widespread pneumococcal vaccination, increased awareness of the importance of early antimicrobial therapy, and decreased rates of cigarette smoking. In 1 study, the incidence of invasive pneumococcal disease decreased by almost 30% over a 5-year period in adults greater than 50 years of age.[17] This shift in CAP pathogenesis may in part explain why the percentage of pneumonia hospitalizations with no reported pathogen increased by almost 20% from 1993 to 2011 despite improvements in diagnostic testing.[18]

Concurrently, our ability to diagnose viral infections rapidly and accurately has improved. Conventional diagnostic tests for respiratory viral pathogens include viral culture, acute and convalescent phase viral serologies, and direct fluorescence antibody staining. These methods are limited by slow turnaround time and limited sensitivity.[19] Nucleic acid amplification testing with the use of polymerase chain reaction (PCR) platforms has greatly improved the diagnosis of respiratory viral infections. The sensitivity of PCR testing is up to 5 times higher than conventional diagnostic methods, which may be particularly important in elderly patients who shed lower titers of virus.[20–23] PCR can also aid with viral subtyping and quantification of viral burden. Multiplex assays are now available, which allow for the testing of up to 19 viruses simultaneously.[19] Numerous clinical samples can be used for PCR testing including nasopharyngeal swabs, tracheal aspirates, bronchoalveolar lavage fluid, and pleural fluid.

The widespread use of PCR-based testing has allowed for a more accurate assessment of the role respiratory viral pathogens play in severe disease. In studies of hospitalized patients with CAP, between 15% and 35% have evidence of a viral infection.[21,24–27] This was best illustrated in the recent Centers for Disease Control and Prevention (CDC) EPIC study (Etiology of Pneumonia in the Community), a multicenter population-based surveillance study conducted in the United States, which used rigorous microbiologic testing in 2259 hospitalized adults with CAP.[12] Viruses were the most common type of pathogen isolated, found in 23% of patients compared with just 11% of patients with bacterial pathogens (Fig. 1).

Viral pathogens are also frequently isolated in patients with severe CAP requiring ICU admission. In a single-site study from Korea, viral pathogens were isolated by reverse transcription PCR (RT-PCR) from nasopharyngeal swabs or lavage fluid in 72 of 198 (36%) patients with severe CAP or health care-associated pneumonia.[28] Viral detection rates in similar studies of ICU patients have ranged from 16% to 41%.[29–31]

Studies have also found respiratory viral pathogens present in over 20% of patients with hospital-acquired pneumonia (HAP)[32,33] and between 14% and 29% of patients undergoing bronchoalveolar lavage for suspected infection.[22,34]

As our understanding of the importance of respiratory viral pathogens in the pathogenesis of severe respiratory infection continues to evolve, it is important for clinicians to be familiar with the unique characteristics of the most commonly identified pathogens.

RHINOVIRUS

Rhinoviruses are singe-stranded negative-sense RNA viruses that are divided into 3 species (rhinovirus-A, -B, -C) and more than 160 distinct serotypes.[35] Rhinovirus infections occur throughout the year with increased prevalence noted in the late spring and early fall.[36] Transmission occurs most commonly through autoinoculation after contact with contaminated objects, although aerosolization also contributes to viral spread.[37] Nosocomial outbreaks of rhinovirus have been reported and highlight the importance of infection control protocols when caring for infected patients.[38]

The clinical importance of rhinovirus is well described in children where it may be responsible for more than 70% of asthma exacerbations in children greater than 2 years of age.[39] Infection with rhinovirus early in childhood has been linked to asthma pathogenesis, particularly in children with a genetic predisposition to the disease.[40,41] Rhinovirus is also recognized as an important cause of pediatric CAP.[42]

Rhinovirus Infection in Adults

In immunocompetent adults, rhinovirus most commonly causes a self-limited upper respiratory tract infection (URI) and may be responsible for more than 80% of common colds during the fall and spring.[43] The frequent association with benign URIs has led many clinicians to question its relevance to pneumonia. However, rather than simply a precursor to more serious infections, rhinovirus can itself be an important pathogen. In the clearest example, immunocompromised patients are particularly prone to severe rhinovirus infection. Infection after lung transplantation is common and may contribute to graft dysfunction.[44] Rhinovirus is also a common cause of severe LRTIs in adults with hematologic malignancies, commonly in association with bacterial coinfection.[45–47]

In patients with chronic obstructive pulmonary disease (COPD), rhinovirus is an important cause of exacerbations. In a study of 77 patients with COPD and frequent exacerbations, rhinovirus prevalence and viral load, measured in sputum by quantitative RT-PCR, were significantly higher in patients during acute exacerbations. Of patients with rhinoviral infection, 73% were found to have bacteria in their sputum by day 14.[48] This association

between rhinovirus and bacterial coinfection may be due in part to changes in the host microbiome. A recent study of rhinovirus infection in patients with COPD and healthy controls found that rhinovirus altered the microbiome of COPD patients, allowing for an increase in pathogenic bacterial species such as *Haemophilus influenzae*.[49] Rhinovirus may also degrade antimicrobial peptides in the lung, predisposing susceptible patients to bacterial coinfection.[50]

Rhinovirus is isolated frequently in adult patients with CAP. In the CDC EPIC study, rhinovirus was the most common pathogen identified and was found in 9% of all patients.[12] Importantly, rhinovirus was rarely isolated in the study's healthy controls. In a single-center prospective study of 304 hospitalized patients with CAP in New Zealand, rhinovirus was also the most frequently identified pathogen and was isolated in 10% of patients.[26] The incidence of rhinovirus in other studies of CAP both in the United States and around the world have ranged from 1% to 4%.[24,25,27]

Several studies have focused specifically on patients with severe CAP requiring admission to the ICU. In a prospective multicenter study from Kentucky, rhinovirus was identified from nasopharyngeal swab in 33 of 393 patients (36%) with severe CAP.[31] In a study of 49 patients with CAP requiring mechanical ventilation in Finland, 15 (31%) were found to be infected with rhinovirus.[51] Similarly, rhinovirus was identified in 4 of 64 patients (6%) with severe CAP in Korea.[28]

Rhinovirus also plays an important role in HAP. Rhinovirus was identified in 15 of 262 patients (6%) with HAP requiring admission to an ICU in Korea.[28] Similarly, a retrospective single-center study found rhinovirus in 19 (11%) of 174 patients with non-ventilated HAP.[33]

Clinical Presentation and Diagnosis

Sore throat and rhinorrhea are typical early symptoms of rhinovirus infection.[52] Common presenting symptoms in patients with CAP secondary to rhinovirus are not well-described. In 1 study of 304 hospitalized patients with CAP, the most common symptoms in 31 patients with documented rhinovirus infection were cough (94%), lethargy (87%), anorexia (77%), sputum production (74%), and pleuritic pain (58%).[26]

RT-PCR is the preferred diagnostic test for severely ill patients with rhinovirus owing to improved sensitivity and more rapid turnaround time than conventional culturebased diagnostic methods.[53] In the future, identifying specific host transcriptional changes may help to differentiate between true infection and asymptomatic carriage.[54]

Treatment

Treatment of even severe rhinoviral infection is supportive. Case reports have described the use of pegylated interferon-α2A and ribavirin in immunosuppressed patients with evidence of persistent infection, but this strategy has not been tested in randomized trials.[55]

HUMAN ADENOVIRUSES

HAdVs are nonenveloped double-stranded DNA viruses that have long been recognized as an important cause of respiratory tract infections in children.[56] HAdVs are divided into seven species (HAdV-A through HAdV-G) with species B, C, and E most commonly associated with respiratory infections.[57] Based on serotypes and genomic analysis, 67 subtypes of adenovirus have been identified.[58]

Unlike other respiratory viruses, HAdV infections do not demonstrate clear seasonal variation.[58] Transmission can occur via inhalation of aerosolized droplets, direct conjunctival inoculation, fecal–oral spread, and contact with infected environmental surfaces.[59] HAdVs are resistant to many common disinfectants, so rigorous infection control policies, including the use of 95% ethanol for decontamination, are essential to prevent nosocomial spread of infection.[59,60]

Human Adenovirus Infection in Adults

Severe HAdV infection is most commonly encountered in immunocompromised hosts, where disease can range from asymptomatic viremia to invasive multiorgan disease. Patients with human immunodeficiency virus and those who have undergone solid organ transplantation or allogeneic stem cell transplantation are particularly at risk.[61] Common disease manifestations in the immunocompromised patient include pneumonia, colitis, hemorrhagic cystitis, hepatitis, and graft dysfunction.[58]

By adulthood, almost all immunocompetent individuals have evidence of prior HAdV exposure and exhibit HAdV-specific T cells.[57] As a result, HAdV infection is usually mild and self-limited. However, outbreaks of severe respiratory infection are well-described and it is important for clinicians to be aware of recent trends in HAdV epidemiology.

Crowded living environments are a risk factor for outbreaks of severe HAdV in otherwise healthy individuals. The best documented example is US military recruits who for decades have been found to be at high risk for severe HAdV infection.[61] Recognition of this association led to routine vaccination of military trainees against HAdV-4 and HAdV-7, which produced a dramatic decrease in HAdV disease.[62] However, a recent epidemic of HAdV pneumonia at a US Air Force base in Texas was found to be caused by HAdV-14, an uncommon subtype not usually associated with severe disease.[63] Of 66 hospitalized trainees, 23 (35%) were found to have HAdV-14 infection, including 4 (17%) who required ICU admission. HAdV infection has been responsible for outbreaks of febrile respiratory infections at military training facilities outside of the United States.[64–67] and infections requiring hospitalization at mental health facilities,[68] job training sites,[69] and boarding schools.[70]

Recent community outbreaks of HAdV-14 in the United States emphasize the increasing importance of this particular subtype even outside of communal living environments. In Oregon, 28 cases of HAdV-14 pneumonia were identified including 18 (47%) who required admission to the ICU and 7 (18%) who died.[71] Similarly, 46 cases of HAdV-14 respiratory illness were recently documented in an Alaskan community, including 11 patients who

required hospitalization.[72] In both of these outbreaks, elderly patients with underlying lung disease and other chronic health problems were at particular risk.

Outside of the United States, HAdV has emerged as an increasingly important cause of CAP. A recent multicenter surveillance study in China documented HAdV as a causative pathogen in 5% of all cases of CAP and found that infection with serotype HAdV-55 was associated with a particularly high pneumonia severity index score.[73] A retrospective analysis of all cases of CAP caused by HAdV-55 at 2 hospitals in northern China noted a 27% mortality rate.[74] Interestingly, 2 cases of severe CAP secondary to HAdV-55 were also recently described in France, perhaps signaling the importance of this serotype outside of Asia.[75]

Clinical Presentation and Diagnosis

Patients with pneumonia owing to HAdV present with symptoms indistinguishable from other types of pneumonia, including fever, cough, and shortness of breath.[71,72] No clinical factors reliably discriminate between pneumonia caused by HAdV and pneumonia caused by other pathogens. In a study of infected military personnel, those with HAdV infection were more likely to have cytopenias than those without HAdV infection.[76] This association between HAdV infection and cytopenias has been documented in other studies, but not with enough consistency to impact clinical practice.[68,77] Although chest imaging is usually abnormal, findings are nonspecific and can include focal areas of consolidation or interstitial abnormalities.[71,78]

Numerous methods are available to diagnose HAdV infection, although PCR is the most practical choice for acutely ill patients. Viral culture was previously considered the “gold standard” although the time needed to observe the characteristic cytopathic effect in human epithelial cells makes it impractical for use in critically ill patients.[61] Shell vial cultures have improved turnaround time although may have lower sensitivity.[58] HAdV-specific antigens can be identified by enzyme-specific immunoassays, although this method is not recommended in immunocompromised patients owing to poor sensitivity.[79] Although tissue sampling is rarely pursued in immunocompetent patients, HAdV can be diagnosed readily on histopathology by visualizing characteristic intranuclear viral inclusions. In recent years, PCR has become the test of choice owing to rapid turnaround time and high sensitivity and specificity.[80] Molecular typing, although helpful for epidemiologic studies, is not recommended for individual patients.

Treatment

The mainstay of therapy for immunocompetent patients with HAdV infection is supportive care. No high-quality randomized trials inform the decision to use pharmacologic therapy in any patient population. Of available antiviral agents, cidofovir, the nucleoside analogue of cytidine monophosphate, has the most supporting data and several case reports have described the safe and successful use of cidofovir in the treatment of severe HAdV infection in immunocompromised patients.[81,82] However, routine use is limited by significant side effects, including nephrotoxicity and neutropenia.[83,84]

RESPIRATORY SYNCYTIAL VIRUS

RSV is an enveloped, negative-sense, single-stranded RNA virus first identified more than 50 years ago.[85] The 2 serotypes, RSV-A and RSV-B, are discriminated by reactivity to monoclonal antibodies. RSV has a worldwide circulation and peak infectivity in temperate climates between December and February.[86] Exposure to the virus by 2 years of age is nearly universal.[85] RSV is highly infectious and can spread via aerosolized droplets or contact with infected secretions.[87] Outbreaks of RSV infections in hospitalized patients are well-described and strict infection control protocols are essential when caring for infected patients.[88]

The clinical and economic burden of RSV infection in children is substantial. Globally, RSV is the most common cause of LRTIs in children, with more than 3 million hospitalizations and up to 200,000 deaths in children less than 5 years of age per year.[89] Annual direct medical costs in the United States are estimated at more than $650 million.[90] Respiratory bronchiolitis, characterized by inflammation and obstruction of the small airways, is one of the most common manifestations of RSV infection and is a significant cause of pediatric morbidity and mortality in the United States.[91] Children with Down syndrome seem to be at particular risk of severe infection.[92] RSV infection early in life has also been associated with the development of asthma.[93] RSV can cause numerous extrapulmonary diseases in children, including myocarditis, hepatitis, and seizures.[94]

Respiratory Syncytial Virus Infection in Adults

As with other respiratory viruses, immunocompromised patients are at particular risk of severe RSV infection. Severe LRTIs have been described in multiple patient populations, including after hematopoietic stem cell transplantation, patients with hematologic malignancies, and after solid organ transplantation, where infection may predispose to graft dysfunction.[95–98] Outbreaks of severe RSV infections in bone marrow transplantation wards highlight the susceptibility of this patient population to infection.[99]

In otherwise healthy adults, RSV infection typically produces a URI characterized by a productive cough, nasal congestion, and sinus involvement.[100] In elderly patients and those with underlying cardiac and pulmonary disease, RSV is an important cause of LRTIs and pneumonia (Fig. 2). Studies using national mortality and viral surveillance data have found that more than 75% of deaths attributable to RSV infection occur in patients older than 65 years of age.[101] In this age group, RSV is responsible for an estimated 62,000 hospitalizations per year and 9% of all hospitalizations for pneumonia.[102] The numerous reports of RSV outbreaks at long-term care facilities highlight the susceptibility of elderly patients to severe RSV infection.[15,103]

In one of the most rigorous studies to date, Falsey and colleagues[13] prospectively evaluated the impact of RSV infection over 4 consecutive winters in 3 patient cohorts: healthy adults 65 years of age or older, elderly adults with chronic cardiac or pulmonary disease, and adult patients hospitalized with acute respiratory symptoms. Importantly, in addition to viral culture and serologies, RT-PCR was used to aid the diagnosis of RSV infection. The annual rate of RSV infection was 3% to 7% in healthy elderly patients and 4% to 10% in high-risk

adults. Of 56 high-risk patients with RSV infection, 25 (45%) were unable to perform activities of daily living owing to their acute illness, 9 (16%) required hospitalization, and 2 (4%) died. In the cohort of hospitalized patients with confirmed RSV infection, 20 (15%) required ICU admission, 17 (13%) required mechanical ventilation, and 10 (8%) died. During the study period, RSV accounted for 11% of hospitalizations for pneumonia, 11% for COPD, 5% for congestive heart failure, and 7% for asthma.

In studies of CAP, RSV has been found to be an important pathogen. In the CDC EPIC study, RSV was detected in 3% of adults hospitalized with CAP with detection rates varying significantly by season.[12] A similar detection rate has been found in other studies.[25,104] In patients with severe CAP requiring admission to the ICU, RSV may be responsible for up to 10% of cases.[28,29,31]

Patients with COPD seem to be at particular risk of RSV infection. Although persistent RSV infection in stable COPD seems to be uncommon,[105,106] RSV is a common trigger for COPD exacerbations.[107] COPD is frequently identified as a risk factor for severe RSV infection[108] and mortality rates in infected COPD patients may eclipse those of infected patients after stem cell transplantation.[109]

Clinical Presentation and Diagnosis

Among adults presenting to the hospital with confirmed RSV infection, wheezing is encountered more frequently than with other viral infections, including influenza.[104,110,111] Cough, shortness of breath, and fever are other common presenting symptoms.[13,104] Chest radiography is frequently normal, although radiographic evidence of pneumonia may be found more frequently than in patients with influenza.[13,104] On chest computed tomography scans, tree-in-bud opacities and abnormalities in a bronchocentric distribution are more common in RSV infection than with other respiratory viruses.[112,113]

As with other respiratory viruses, nucleic acid amplification, specifically with RT-PCR, has become the test of choice for suspected RSV infection in adults.[114] Culture techniques including shell vial culture are challenging given the unstable nature of the RSV virus and lack sensitivity.[85] Rapid antigen detection tests, which are used commonly in children, perform less well in adults likely owing to lower viral titers present in the secretions of elderly patients.[115] Detection of acute and convalescent phase serologies is useful for epidemiologic study and may increase the yield of RT-PCR, but is not widely used in clinical practice.[85]

Treatment

The mainstay of therapy for immunocompetent adults with severe RSV infection is supportive care. In immunocompromised patients and other select high-risk adult groups, additional therapy may be considered. The guanosine analogue ribavirin has been used with some success in patients with RSV infection after hematopoietic stem cell transplantation. In a recent single-center study of 280 patients after allogeneic stem cell transplantation, early use of aerosolized ribavirin was associated with a reduction in progression to LRTI and improved mortality.[116] Similar results were found in a recent review of published case series.[117] Concerns regarding cost, teratogenicity, and adverse effects including hemolytic

anemia have limited routine use in adults.[118] Immunotherapy with intravenous immunoglobulin in combination with ribavirin has been described in case reports, but has not been studied in randomized trials.[119]

In children, passive immunoprophylaxis with palivizumab, a monoclonal antibody directed against the RSV F glycoprotein, has been used with success and is recommended by the American Academy of Pediatrics for use in infants with hemodynamically significant heart disease or chronic lung disease of prematurity.[120] Unfortunately, results with the use of palivizumab in at-risk adult patients have been disappointing.[117,121] A novel oral viral replication inhibitor ALS-008176 was recently used with encouraging results in a small RSV challenge study in healthy adults, but further trials are required before it can be recommended for routine use.[122]

The substantial morbidity and mortality associated with RSV infection in the elderly has heightened calls for the development of an RSV vaccine.[13] Although progress has been made, no vaccines are currently available.[123]

HUMAN METAPNEUMOVIRUS

hMPV is a single-stranded, negative-sense RNA virus first isolated in 2001 from children with respiratory tract infections in the Netherlands.[124] The virus is present worldwide and exhibits clear seasonality with peak circulation in temperate climates between winter and spring.[125] Exposure to the virus by 5 years of age is nearly universal.[126] Modes of transmission are not well-described, but outbreaks of hMPV at long-term care facilities and hospital wards highlight the importance of infection control protocols when caring for infected patients.[14,16,127]

The clinical importance of hMPV is well-documented in children. In a recent prospective study in the United States, hMPV was identified in 6% of all children hospitalized with an acute respiratory illness and associated with increased ICU duration of stay.[128] hMPV may be responsible for more than 10% of all LRTIs in children in the United States and 5% to 7% of all pediatric respiratory tract infections worldwide.[129,130] Disease manifestations in children range from croup and bronchiolitis to exacerbations of asthma and severe pneumonia requiring mechanical ventilation.[129]

Human Metapneumovirus Infection in Adults

hMPV is recognized as an important respiratory pathogen in immunocompromised adults. Studies using RT-PCR have identified hMPV as the cause of severe pneumonia in hematopoietic stem cell transplant recipients,[131] patients with hematologic malignancies,[132] and solid organ transplant recipients where infection may increase the risk of graft dysfunction.[133–135] A recent systematic review found a 26% mortality in immunocompromised patients with hMPV LRTI.[135]

In immunocompetent adults with suspected viral infection, the incidence of hMPV ranges from 2% to 9%.[136–138] In the recent CDC EPIC study, hMPV was identified in 4% of hospitalized adults with CAP.[12] Although severe hMPV infection in immunocompetent

adults is uncommon, several at-risk patient populations deserve mention. Outbreaks of hMPV are common at long-term acute care facilities. In California, 26 residents and staff were infected with hMPV including 8 (31%) who developed radiographically confirmed pneumonia and 2 (5%) who required hospitalization.[14] Similarly, during an outbreak of severe respiratory infection at a long-term care facility in Quebec, hMPV was identified in 6 of 96 infected patients, with a 50% mortality.[16] Outbreaks have also been described at long-term care facilities in Oregon,[139] the Netherlands,[140] and Japan.[141]

Limited data suggest that hMPV may be an important cause of hospitalizations in patients with COPD. In a single-center, observational study of 50 adults hospitalized for a COPD exacerbation, RT-PCR of nasopharyngeal specimens identified 6 patients (12%) with hMPV infection.[142] Documented hMPV infection rates in other studies of patients with COPD exacerbations have ranged from 2.3% to 5.5%.[143,144]

Clinical Presentation and Diagnosis

Patients hospitalized with hMPV present with nonspecific symptoms. In 1 study of 91 hospitalized adults with hMPV, the most common symptoms were dyspnea (98%), cough (94%), wheezing (79%), and sputum production (74%).[145] High rates of wheezing have been noted in other studies and are similar to the incidence of bronchospasm found with RSV infection.[138,146] Chest imaging is similarly nonspecific and may be normal in more than one-third of hospitalized patients.[145] Reports of chest computed tomography findings in hPMV infection are limited. In 1 study of high-resolution computed tomography findings in 4 patients with hMPV, groundglass opacities, consolidation, and parenchymal bands were present in all patients.[147]

Although uncommon, hMPV infection can lead to severe disease. In a single study from Korea of 198 patients with severe pneumonia requiring admission to the ICU, hMPV infection was identified by RT-PCR in 13 patients including 5 (8%) with CAP.[28] Similarly, in a recent review of all admissions to a single ICU over 4 years, 40 cases of hMPV infection were identified, of which 55% required mechanical ventilation, 23% developed shock, and 48% met criteria for acute respiratory distress syndrome.[148] Importantly, 6 of these 40 patients (15%) had only minor comorbidities. Finally, in a study of 91 patients hospitalized with hMPV, 12 (13%) required admission to the ICU, 11 (12%) required mechanical ventilation, and 6 (7%) died.[145]

hMPV replicates slowly and is difficult to isolate with typical cell culture techniques, making viral culture impractical for routine use in the ICU.[149] RT-PCR is the preferred diagnostic test for hMPV and is now available as part of a multiplex PCR panel for simultaneous testing with other viruses.[138]

Treatment

Treatment of severe hMPV infection is supportive and no pharmacologic therapies are currently approved for use. Ribavirin has shown promising activity in murine models of infection[150] and several case reports describe the drug's potential efficacy in humans when used in conjunction with intravenous immunoglobulins.[151,152] However, concerns regarding

the cost of ribaviran, teratogenicity and reports showing underwhelming clinical results have tempered enthusiasm for more routine use.[153]

CHALLENGES AND FUTURE DIRECTIONS

With the improved sensitivity of PCR-based testing, a major challenge in the diagnosis and treatment of viral pneumonia is distinguishing true infection from asymptomatic carriage or isolated URI.[6] This is especially true for samples obtained from the upper respiratory tract in patients with suspected LRTI. The specificity of PCR testing likely depends on both the age of the patient and the pathogen identified and further studies are needed to refine test interpretation.[154] The results of the CDC EPIC study, where only 2% of 238 asymptomatic control subjects had a pathogen identified, suggest that the majority of identified respiratory viral pathogens play a causal role in disease pathogenesis.[12]

Measuring convalescent phase serum antibodies may help to improve the diagnostic yield and specificity of PCR-based testing although further studies are needed to validate this approach.[155] Transcriptional profiling of the host response to infection may also aid the diagnosis of viral pneumonia. Recently, an 11-gene influenza virusspecific host response signature was identified in human blood that accurately diagnosed influenza infection, identified bacterial coinfection, and predicted outcomes in patients with influenza pneumonia.[156] Similarly, a host transcriptional signature defined largely by the overexpression of interferon-related genes was found to discriminate between viral and bacterial pneumonia.[157]

Perhaps the greatest challenge facing both clinicians and researchers is the large number of patients with a clinical diagnosis of pneumonia in whom a causative pathogen is never identified. Of the more than 2000 patients in the CDC EPIC study, 62% had no identifiable pathogen despite a degree of microbiologic testing that exceeded usual clinical practice.[12] Over the past 2 decades, the percentage of patients hospitalized with pneumonia who had no reported pathogen increased by almost 20% in the United States.[18] Research that better characterizes this large group of patients has the potential to profoundly impact health care costs and antimicrobial stewardship.[158] Our evolving understanding of the link between the respiratory microbiome and pneumonia pathogenesis may prove an important engine of innovation in the coming years.[159]

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KEY POINTS

- The epidemiology of severe lower respiratory tract infection is changing due in part to the aging of the US population and the success of childhood vaccination programs.
- Diagnostic advances including nucleic acid amplification platforms have greatly improved the detection of respiratory viral pathogens.
- Respiratory viral pathogens are now recognized as an important cause of severe respiratory infection in both immunocompetent and immunocompromised adults.
- Despite advances in diagnostic testing, a large number of patients with severe community-acquired respiratory infections do not have a causative pathogen identified.
- Better characterizing this group of patients remains an ongoing challenge.

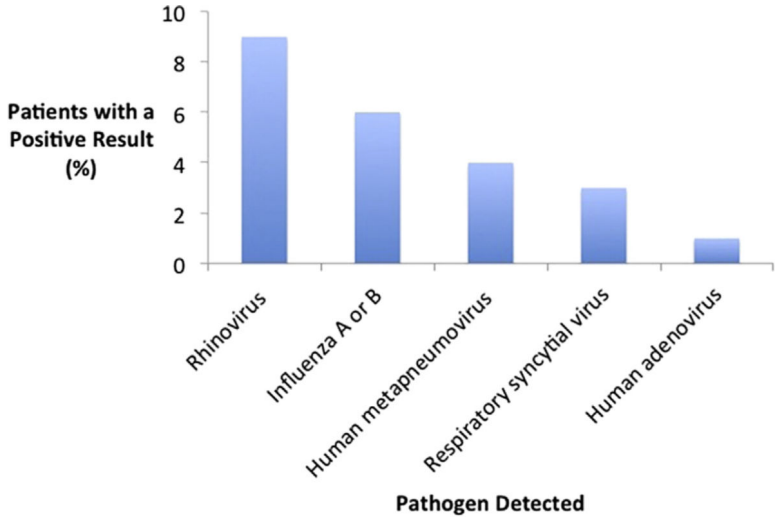

Fig. 1.

Percentage of all adults in the Centers for Disease Control and Prevention EPIC (Etiology of Pneumonia in the Community) study in whom specific respiratory viral pathogens were detected. (*Data from* Jain S, Self WH, Wunderink RG, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. N Engl J Med 2015;373(5):415–27.)

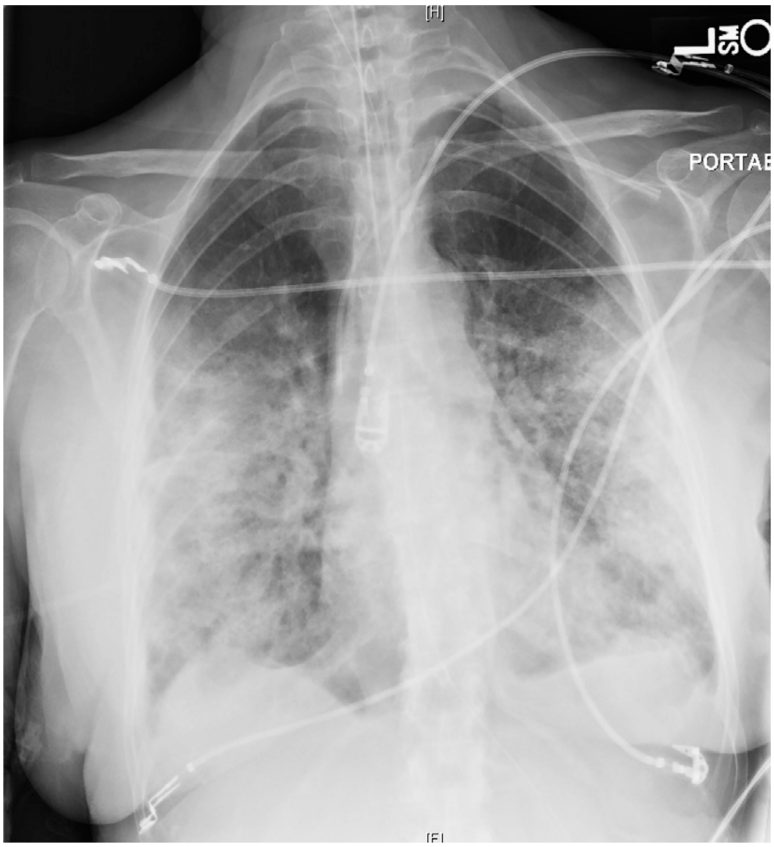

Fig. 2.

Posteroanterior chest radiograph in an elderly woman with acute hypoxemic respiratory failure secondary to respiratory syncytial virus pneumonia demonstrating dense bilateral airspace disease.

Table 1

Characteristics of common noninfluenza respiratory viral pathogens

Virus	Structure	Peak Infectivity	Notable Groups at Risk	Notable Features	Preferred Diagnostic Test	Investigational Therapies
Rhinovirus	Single-stranded negative-sense RNA virus	Late spring and early fall	• Immunocompromised patients • Patients with COPD	• Common cause of asthma exacerbations in children • Most common pathogen isolated in CDC EPIC study	RT-PCR	Pegylated interferon-α2A + ribavirin
Human adenovirus	Nonenveloped double-stranded DNA virus	No seasonal peak	• Immunocompromised patients • Adults in crowded living environments including military barracks and long-term care facilities	• HAdV-14 linked to outbreaks of severe respiratory infection in the US • HAdV-55 an important cause of CAP in China	PCR	Cidofivir
Respiratory syncytial virus	Enveloped negative-sense single-stranded RNA virus	December to February	• Immunocompromised patients • Elderly patients • Patients with COPD	• Most common cause of LRTIs in children • Commonly presents with wheezing	RT-PCR	• Ribavirin ± IVIG • Viral replication inhibitor ALS-008176
Human metapneumovirus	Single-stranded negative-sense RNA virus	Winter to spring	• Immunocompromised patients • Residents of long-term care facilities • Patients with COPD	• Commonly presents with wheezing	RT-PCR	Ribavirin + IVIG

Abbreviations: CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; EPIC, Etiology of Pneumonia in the Community; IVIG, intravenous immunoglobulin; LRTI, lower respiratory tract infection; PCR, polymerase chain reaction; RT-PCR, reverse-transcriptase polymerase chain reaction.