

Severe Respiratory Viral Infections

New Evidence and Changing Paradigms

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KEYWORDS

- Viral pneumonia • Community-acquired pneumonia • Rhinovirus
- Human adenovirus • Respiratory syncytial virus • Human metapneumovirus

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.

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.

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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

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

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