Review Article

Respiratory viruses and severe community-acquired pneumonia

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ABSTRACT

Community-acquired pneumonia remains a major cause of morbidity and mortality globally. Streptococcus pneumoniae is recognized the main pathogen related to pneumonia in all site of care. However, recent advances in molecular techniques have led to recognized that respiratory viruses are a common and important cause of severe CAP. Also, in the last 10 years new respiratory viruses are recognized as potential infectious agents in pneumonia. Recent studies show that in approximately 10 to 40% of pneumonia cases are involved viral pathogens being influenza virus the most common respiratory virus. A better knowledge of the role of respiratory viruses especially in cases of severe pneumonia may lead to better management of this population. This review aimed to describe the main respiratory viruses involved in severe pneumonia, specially focus in the clinical presentation, diagnosis, therapy and outcomes.

Key words: Community-acquired pneumonia, respiratory viruses, viral pneumonia

INTRODUCTION

Viral pneumonia occurs most frequently in the extreme ages of life, in young children, and elderly adults. Children do not have previous immunity, and their smaller immature airways facilitate infection, while in the case of the elderly, immunosenescence and the presence of chronic medical conditions increase their vulnerability.

Community-acquired pneumonia (CAP) is an acute pulmonary infection affecting individuals who have not recently been hospitalized and are not in regular contact with the health-care system. The usual clinical presentation is a newly recognized lung infiltrate on chest imaging, associated with fever, cough, sputum production, shortness of breath, physical findings of consolidation, and leukocytosis.[1] Nevertheless, CAP often does not present with the traditional signs and symptoms, especially in elderly patients.[2,3]

During the detection process, there are always cases, usually around 50%, for which the causal agent cannot be identified.[4] Recent advances in molecular virology have led to the discovery of previously unrecognized respiratory viruses. Polymerase chain reaction (PCR)-based testing has allowed detection of newer agents and improved the ability to detect old viral infections, such as influenza virus and rhinovirus. Commercially available PCR assays are able to detect most common respiratory virus, using samples from nasopharyngeal swabs, nasal washes, or nasopharyngeal aspirates.[5,6] Lower

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respiratory tract samples such as endotracheal aspirates and bronchoalveolar lavage can also be tested and might be more sensitive than upper respiratory samples for individuals with influenza-associated pneumonias.[7]

Viruses that require hospitalization and urgent intensive care have been poorly studied, although it is estimated that they account for 23%–36% of CAP cases, with variations according to geographic and seasonal factors, as well as detection techniques.[8,9] In addition, it can difficult to differentiate whether a virus was the cause of the infection or simply acted as a predisposing factor for a secondary bacterial infection.[10]

This report will describe the association of respiratory viruses with severe CAP.

VIRAL INFLUENZA

Influenza viruses belong to the *Orthomyxoviridae* family, with segmented RNA genomes, and are divided into three types (A, B, and C). The influenza viruses A and B cause seasonal epidemics, and influenza A can also sporadically cause pandemics when a new strain enters the human population from an animal host. In the past 100 years, there have been four such pandemics: the H1N1 "Spanish flu" in 1918 (from an avian host), the H2N2 Asian influenza in 1968 (avian virus), the H3N2 Hong Kong influenza in 1968 (avian virus), and the H1N1 swine influenza virus in 2009 (from a pig host).

Influenza A viruses are further classified into subtypes on the basis of the antigenic properties of their two surface glycoproteins, hemagglutinin and neuraminidase. There have been 16 hemagglutinin and 9 neuraminidase subtypes isolated from birds (H1 to H16 and N1 to N9, respectively), while 2 types of each glycoprotein have been identified in bats (H17 and H18 and N10 and N11). A similar animal reservoir does not exist for influenza B viruses.[11]

Clinical manifestation can range greatly, from a completely asymptomatic to a fulminant presentation, depending on the characteristics of both the virus and the host. Purely viral pneumonia is uncommon outside pandemic settings, in a nonimmunocompromised host (5% of the highly vaccinated adult population).[12] In addition to severity, it is also important to consider the virus propagation capacity. In a typical year of seasonal outbreaks in the Northern and Southern Hemispheres, influenza viruses can cause as many as 5 million cases of severe illness and approximately 500,000 deaths.[13] In a pandemic, these statistics are worse. During the great Spanish flu pandemic of 1918–1919, it is estimated that 50 million people were infected worldwide and that 50–100 million of those infected were killed.

Severe primary influenza pneumonia presents with typical influenza symptoms, followed by rapid respiratory decompensation with hypoxemia, shock, and multi-organ dysfunction, which necessitates endotracheal intubation and mechanical ventilation. Chest imaging reveals diffuse bilateral infiltrates, indicative of acute respiratory distress syndrome (ARDS), whose severity depends on viral respiratory tract infections, patients inflammatory response, and in some cases, secondary bacterial pneumonia.[14] Mortality tends to be high, and autopsies reveal severe pulmonary structural damage with necrotizing bronchitis, hyaline membranes, intra-alveolar hemorrhage, edema, and interstitial inflammation.[11]

Bacterial pneumonia as a complication of influenza can occur simultaneously with influenza or in a later phase.[15] The most common bacterial strains isolated from sputum are *Streptococcus pneumoniae*, *Staphylococcus aureus* (including community-acquired methicillin-resistant *S. aureus*), *Haemophilus influenzae*, other *Streptococcus* species, and other Gram-negative rods.[11]

In April 2009, the H1N1pdm09 influenza A virus caused the first pandemic of the 21st century. More than 18,500 deaths were reported worldwide though there are estimates that the actual mortality was 15 times greater.[16] In contrast to what is typically observed in seasonal viral outbreaks, many critically ill patients were young- to middle-aged adults. This younger population had fewer comorbidities, greater radiographic extension, and more severe respiratory compromise. They were more likely to be admitted to Intensive Care Units (ICUs) and faced a greater risk of death, compared to seasonal influenza pneumonia.[17-19] Most notably, since H1N1pdm09 affected a different population than expected, available CAP severity measures (CURB-65, pneumonia severity index) were not adapted to the atypical presentation and tended to underestimate the severity of the disease. They were thus not useful to determine hospitalization criteria.[20]

Treatment of influenza-associated severe CAP requires ICU admission, mechanical ventilation with low tidal volume, lung-protective ventilation, and an open lung approach, with increased positive end-expiratory pressure and mean airway pressure. Despite these ventilation strategies, many patients' illnesses can become extremely severe and necessitate rescue treatment, such as extracorporeal membrane oxygenation (ECMO). Prone positioning and ECMO appear to be associated with lower mortality in severe ARDS.[14]

Corticosteroids are contraindicated in these cases, as their use is associated with prolonged viral replication and secondary Gram-negative bacterial and fungal pneumonia and higher mortality.[21] Although the true incidence of secondary bacterial infections during influence is unknown, the severity of pneumonia associated with mixed etiology (viral and bacterial) requires empirical broad-spectrum antimicrobial therapy, to cover the aforementioned pathogens, and then

antibiotics can be scaled down, based on the results of cultures from the lower respiratory tract.

Existing evidence has not yet been able to clarify the benefits of using antivirals in critically ill patients with influenza. Nevertheless, by reducing viral load, antivirals could improve inflammatory response, and observational studies of critically ill patients suggest some clinical benefit of antivirals, especially if they are initiated early.[22] The use of oseltamivir is recommended as soon as possible, even before test results are received, and enteral administration of its standard dose has been found to be adequately absorbed by critically ill patients. Although higher doses have been used in hospitalized patients, no benefit was seen over standard dosing, and the ideal dosage and duration of treatment in these patients are still unknown. The emergence of oseltamivir resistance strains in severe influenza has been reported, especially in immunocompromised patients.[23] Given that replication of the influenza virus may be prolonged, serial lower respiratory tract samples for reverse-transcription PCR (RT-PCR) could provide information to estimate disease duration. Patients with contradictions for enteral administration or those with oseltamivir-resistant virus infections could be given intravenous zanamivir. Lack of effectiveness of oseltamivir is most likely due to the progression of acute pulmonary damage or other similar complication and less likely to the emergence of oseltamivir resistance.[14]

AVIAN INFLUENZA

Wild birds carry the influenza virus in their intestines and are usually not affected. However, the virus can be transmitted to other birds and tends to affect domesticated birds, (chickens, turkeys, ducks, and geese) which in turn can pass the virus onto humans. The contagion of susceptible individuals occurs through direct contact with infected birds or with their secretions or depositions. It should be highlighted that very few influenza A avian viruses have crossed over into humans, and that the strains H5N1 and H7N9 are responsible for the majority of infections in humans.

Asian lineage highly pathogenic avian influenza (HPAI) H5N1 viruses have caused the highest number of cases of severe illness and death among humans. Since November 2003, the World Health Organization (WHO) has received reports of more than 700 cases of individuals affected by H5N1 HPAI viruses of Asian origin, from 15 countries in Asia, Africa, the Pacific, Europe, and the Middle East. Cases of humans infected with these viruses are fortunately uncommon, as infection can cause pneumonia and respiratory failure, with a mortality rate of close to 60%. The majority of H5N1 cases have been seen in children and adults younger than 40 years of age. Although this virus is not spread efficiently among people, there have been some cases of limited and unsustainable transmissions, particularly among family members.[24]

Individuals infected by Asian lineage H7N9 avian viruses were first reported in China in March 2013. Since then, there have been annual epidemics of sporadic infections. According to the WHO, as of May 23, 2017, there have been a total of 1,486 cases of human infections, with a mortality rate of 40%. As with the H5N1 viruses, there are few cases of person-to-person contagion of H7N9, and although there have been some cases outside of Mainland China, most of these infections occurred in individuals who traveled to China before becoming ill. The pandemic potential of this virus is worrisome because influenza viruses constantly change, it is possible that the virus can acquire the ability to spread easily and sustainably among humans, which would trigger a global outbreak. Currently, the Asian H7N9 virus is considered to have the greatest potential to cause a pandemic.[24]

In terms of treatment, the Center for Disease Control and Prevention recommends the use of neuraminidase inhibitors for avian influenza. Observational evidence has shown that oseltamivir reduces mortality in the case of H5N1. While the majority of viruses are susceptible to oseltamivir, peramivir, and zanamivir, there is evidence to suggest that both avian viruses have some resistance to antivirals.[25] In light of this, the use of two or more antivirals in combination for severe pneumonias has been reported to enhance their effectiveness and avoid resistance, although better evidence is required.[23]

RESPIRATORY SYNCYTIAL VIRUS

Human respiratory syncytial virus (RSV) is a common respiratory virus during the winter months that was initially considered to be strictly pediatric, though it was later recognized to be a serious adult pathogen as well.[26] It is the second most commonly identified cause of viral pneumonia in elderly adults, and in some studies, it has been identified as the third leading cause of pneumonia in adults, behind *S. pneumoniae* and influenza. RSV is an enveloped RNA virus and is a member of the family *Paramyxoviridae*, subfamily *Pneumovirinae*, and genus *Pneumovirus*.[12] The clinical manifestations of RSV are difficult to distinguish from influenza, and small differences that have been described, such as increased frequency of rhinorrhea, sputum, and wheezing, are not sufficient to determine the etiological diagnosis. Radiographic findings range from subsegmental patching and alveolar densities to lobar consolidation. Opacities are usually basal, unilateral, and relatively subtle. A limited number of patients present diffuse interstitial infiltrates, considered typical of viral pneumonia.[12] Potential bacterial pathogens have been found in 15%–30% of adults with RSV. Specific laboratory tests such as viral cultures, rapid antigen tests, and RT-PCR are required for diagnosis. Unlike influenza, commercial rapid antigen tests for RSV are not sensitive for adults (indirect fluorescence assay has a sensitivity of only 23%). RT-PCR in adults performs much better, with 73% sensitivity and 99% specificity.[27]

RSV has a direct cytopathic effect on pulmonary epithelial cells, leading to loss of cellular functions such as ciliary movement and possible epithelial destruction. RSV pneumonia is characterized by inflammation of bronchial and alveolar epithelium, with peribronchial infiltrate of mononuclear cells, accompanied by submucosal edema and mucous secretion.[8] The incidence of hospitalizations for RSV-associated acute lower respiratory tract infection is estimated at 85 cases per 100,000 person-years. Mortality due to RSV is mainly observed among patients older than 65 years of age, although it is 3 times less frequent than among patients with influenza.[28]

LESS FREQUENT VIRUSES THAT CAUSE SEVERE COMMUNITY-ACQUIRED PNEUMONIA

Human parainfluenza viruses

Human parainfluenza viruses (HPIVs) belong to the *Paramyxoviridae* family. They are negative-sense, single-stranded, enveloped RNA viruses and have four types (1 through 4) and two subtypes (4a and 4b), which can vary in their clinical and epidemiological features. In the United States, infections associated with HPIV-1 are usually seen in odd-numbered years, whereas HPIV-2 and HPIV-3 infections are observed annually. HPIVs commonly infect infants and young children, though they can affect individuals of any age, and while each type can cause mild or severe diseases, HPIV-3 is most often associated with bronchiolitis, bronchitis, and pneumonia.[28,29]

Clinically, HPIVs behave like other respiratory viruses. Prospective studies in nursing homes have documented PIV infection in 4%–14% of respiratory illnesses, and fatal cases of bronchopneumonia caused by HPIVs have been described, as have severe cases associated with ARDS, interstitial pneumonitis, and cytoplasmic inclusions.[8,12] Viral cultures, RT-PCR, and serologic tests can be used to diagnose PIV, though there is no specific treatment.

Human metapneumovirus

Human metapneumovirus (hMPV) was discovered in 2001 and belongs to the *Paramyxovirus* family. Broader use of molecular diagnostic testing has increased identification and awareness of hMPV as an important cause of upper and lower respiratory infections in individuals of all ages. The clinical presentation does not differ from other respiratory viruses, and hMPV behaves very similarly to RSV.[30] In severe pneumonia with ARDS, alveolar septum congestion and hemorrhage have been described.[12] As there is no specific antiviral therapy for hMPV, all medical care is focused on support measures.

Adenovirus

To date, 55 serotypes of adenoviruses, family *Adenoviridae*, have been described. Human adenoviruses (HAdVs) are notorious pathogens in individuals with compromised immune function and represent a frequent cause of acute respiratory disease outbreaks among young children. Life-threatening adenoviral pneumonia has previously been documented among military trainees, patients with AIDS, and transplant recipients. Comparative studies have shown that the ability of HAdV to cause severe disease may be determined by the serotype, and severe pneumonia has been more closely related to HAdV-55 than to other serotypes (HAdV-3, HAdV-7, or HAdV-14). Since 2006, severe cases of HAdV-55 in immunocompetent adults have been reported sporadically in China, and the typical clinical features and outcomes of the most critically ill patients with severe ARDS caused by HAdV-55 are still being determined. Persistent high fever, dyspnea, and rapid progression to respiratory failure within 2 weeks, together with bilateral consolidations and infiltrates, appear to be the most frequent clinical manifestations of these patients, who present a mortality rate of 80%, despite appropriate respiratory support. Current knowledge of HAdV-55-induced ARDS requiring invasive mechanical ventilation and/or ECMO support in immunocompetent adults is derived from single case reports or relatively small, single-center series, and it is hoped that the evidence base will improve in the coming years.[31]

Coronavirus

This virus belongs to the *Coronaviridae* family, and although it is more known for being the second leading cause of the common cold, strains of the virus have also produced epidemic outbreaks with an important number of cases of severe pneumonia. The most known has been the Middle East respiratory syndrome coronavirus (MERS-CoV) and the SARS-associated coronavirus (SARS-CoV), which do not have a specific treatment.

First identified in 2012, MERS-CoV has emerged as a cause of severe acute respiratory illness in humans. As of May 1, 2016, a total of 1728 laboratory-confirmed cases, including 624 deaths, were reported globally. Fever is the most commonly reported symptom (74%), followed by cough (63%), shortness of breath (44%), and diarrhea (44%). The most severe form of the virus is associated with pneumonia and respiratory failure, with mortality in 36% of patients. All reported cases have been directly or indirectly linked to countries in or near the Arabian Peninsula, including a recent outbreak in South Korea resulting from a single-imported case in a person with recently traveled to Middle East. Increasing evidence suggests that dromedary camels are a natural host for MERS-CoV and that camel-to-human transmission can occur, initiating short chains of human-to-human transmission.[32] Health-care settings are important amplifiers of transmission. A 2014 case series of 255 MERS-CoV infections in Saudi Arabia found that 31% of cases occurred among healthcare personnel (HCP), and among patients who were not HCP, 87.5% had recent exposure with health services.[33]

SARS-CoV was first reported in Asia in February 2003. Over the following few months, the illness spreads to more than two dozen countries in North America, South America, Europe, and Asia, before the global outbreak was contained. According to the WHO, a total of 8439 people worldwide were affected, and of those, 812 (9.6%) passed away. The global health response was able to halt the outbreak, and no new cases have been reported since 2004.[34]

HANTAVIRUS PULMONARY SYNDROME

Cases of human illness caused by *Hantavirus* spp. were not seen in the Americas until May 1993. Since then, hantavirus infection has been reported in the United States, Argentina, Bolivia, Brazil, Chile, Ecuador, Paraguay, Panama, Uruguay, and Venezuela. Several types of New World hantaviruses (family *Bunyaviridae*) have been recognized, and their distribution is determined by the density of the rodent populations, which serve as the specific reservoir for the virus. The initial clinical presentation is similar to influenza, with high fever, myalgia, headache, or asthenia but without rhinorrhea, and often accompanied by abdominal symptoms. After a prodromal period (2–7 days), respiratory symptoms appear with dyspnea, respiratory failure, and hemodynamic instability. Chest X-rays show bilateral interstitial infiltrates, with different degrees of rapid progression, leading to acute respiratory distress and mortality in 32% of cases. In most cases, death occurs within one to 2 days of hospital admission. In the Andean strain of the virus, seen in Southern Chile and Argentina, hemorrhagic manifestations have been described in 39% of cases; this is the only strain that has reported person-to-person transmission.[35-37] There is no specific treatment.

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There are no conflicts of interest.

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