Community-acquired viral pneumonia in human immunodeficiency virus infected patients

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ABSTRACT

Respiratory viruses (RV) have become an important cause of community-acquired pneumonia in immunocompromised patients with the highest rates of morbidity and mortality. The advances in molecular diagnostic methods have increased our understanding of the role of viruses in pneumonia. However, little is known about their impact on patients with human immunodeficiency virus (HIV) infection. In this review, we focus on the most prevalent RV that has been implicated in viral respiratory infections, particularly in pneumonia in HIV infected patients. We discuss the epidemiologic characteristics and clinical presentations of these viral infections and the most appropriate diagnostic approaches and therapies if available.

Key words: Human immunodeficiency virus, respiratory virus, viral pneumonia

INTRODUCTION

Community-acquired pneumonia (CAP) is a serious health problem associated with high morbidity and mortality in all age groups worldwide.[1] CAP is the sixth cause of death across the world and is a major burden on healthcare resources.[1] Respiratory viruses (RV), in particular influenza viruses A and B, rhinoviruses, parainfluenza viruses 1, 2, and 3, and coronaviruses, are considered as the etiological agents in almost one-third of the CAP cases. It is estimated that 100 million cases of viral pneumonia occur every year globally.[2] The development of new diagnostic tools has aided better detection of viral pneumonia in the recent years, and viral etiologies have been reported in approximately 23% of pneumonia among immunocompromised patients.[3,4] However, there are only few studies on RV in patients with human immunodeficiency virus (HIV) infection summarized on Table 1.

Human immunodeficiency virus-infected patients present deficiencies in humoral and cell-mediated immunity that can potentially alter the course and severity of common infections.[9] Despite antiretroviral therapy (ART), some HIV patients, especially those with impaired antigen specific responses, may remain at risk for morbidity associated with respiratory viral infections.[9] Additional risk factors for the infections in HIV patients are active smoking and chronic lung comorbidities. The objective of this article is to review the main RV that cause CAP in HIV patients and to discuss their epidemiologies, clinical presentations, diagnosis, and treatments.

EPIDEMIOLOGY

Approximately, 100 million cases of viral pneumonia are reported in adults annually.[2] Recent studies of CAP in adult population demonstrated that approximately 1-30% of the cases are caused by RV; influenza viruses...
A and B, rhinoviruses, parainfluenza viruses 1, 2, and 3, and coronaviruses are the most frequent causes of pneumonia.\textsuperscript{[3,4,6-8]}

The H1N1 influenza pandemic of 2009-2010 gave us new insight into the role of the virus in immunocompromised patients.\textsuperscript{[10-12]} The World Health Organization estimated, approximately 16,000 deaths between April 2009 and January 2010. The majority of these deaths corresponded to patients with underlying risk factors, such as metabolic dysfunctions, pregnancy, obesity, and immunosuppression, contributing to worse outcomes.\textsuperscript{[12,13]} In HIV patients, 1.74% of deaths were caused by H1N1 virus. A recent study in Spain reported that the most frequent (5.4%) viruses involved in CAP in HIV patients were influenza A and rhinoviruses.

### PRINCIPAL RESPIRATORY VIRUSES IN PNEUMONIA

Details for individual virus discussed below are summarized in Table 2.

### Influenza virus

Influenza viruses are RNA viruses that are classified into types A, B and C. Antigenic drifts of surface proteins are responsible for seasonal epidemics, and is described for both influenza A and B. Severe outbreaks and pandemics due to antigenic shift are less frequent and occur only with influenza A virus.\textsuperscript{[14]} Transmission of influenza virus is by airborne particles or contaminated hands touching nose or mouth.\textsuperscript{[11]}

The incubation period is 24-48 h. The viral shedding starts 5 days before the onset of symptoms in healthy adults, but its duration is longer in immunocompromised patients.\textsuperscript{[16-18]}

Influenza is usually self-limiting, but severe complications (e.g., pneumonia) can occur particularly in high-risk individuals including HIV patients, and may lead to significant increases in hospitalization and mortality rates. Nonetheless, there are few data on influenza pneumonia in HIV patients. Recent studies demonstrated that influenza causes increased risk of hospitalization, death, and prolonged illness in HIV patients without ART in comparison to the general population.\textsuperscript{[19,20]}

### Respiratory syncytial virus

Respiratory syncytial virus (RSV) is an RNA virus that is classified into two antigenic subgroups A (causes more severe disease) and B. It causes seasonal outbreaks that occur from November to April in the Northern hemisphere and from April to September in the Southern hemisphere, which often last 4-5 months in a community.\textsuperscript{[21,22]} RSV infection is transmitted through direct contact with virus-containing secretions, fomites, or large aerosol droplets. Nasal congestion, dyspnea and wheezing are the typical symptoms in RSV pneumonia.

Respiratory syncytial virus has been identified as an important cause of pneumonia in adults. The prevalence of RSV in CAP is 2-5% throughout the year and 5-14% during winter.\textsuperscript{[21,24,25,26]} Individuals with higher-risk for
developing RSV pneumonia are: Children <6 months old, patients with chronic diseases or congenital heart disease, institutionalized elderlies, and immunosuppressed patients.\textsuperscript{[27]} Adults with severe immunodeficiency are at higher-risk for serious RSV infection.\textsuperscript{[28,29]} The clinical presentation in HIV patients is similar to non-HIV patients, but with significantly increased morbidity and mortality while the severity of the infection depends on the magnitude of immunosuppression in each patient. The overall mortality rate in adults varies from 1% to 5% in healthy individuals to 41% in bone marrow transplant recipients.\textsuperscript{[30]}

### Human rhinovirus

Human rhinoviruses (HRV) are RNA viruses with more than 100 different strains that are genetically divided into three classes: A, B, and C.\textsuperscript{[31]} They are the most common causative agents of acute upper respiratory tract disease. HRV infections are transmitted by either aerosol droplets or contact with infected secretions from the upper airway.

Advances in diagnosis methods have shown that RV may also cause pneumonia and induce asthma exacerbations.\textsuperscript{[27]} Respiratory symptoms are the result of the destruction of normal airway tissue by the virus and production of proinflammatory immune responses against the virus.\textsuperscript{[32]}

In adults, approximately 5-10% of viral pneumonia are caused by HRV.\textsuperscript{[33-35]} A recent study on CAP among immunocompromised patients found that HRV was responsible for 12% of the cases, making it the most common virus isolated; the mortality rate was 18% suggesting that it may have been an underestimated respiratory virus.\textsuperscript{[4]}

Human rhinoviruses are one of the most frequent pathogens implicated in mixed respiratory viral infections and was shown in 19.5% of bronchiolitis by such infection.\textsuperscript{[16]}

### Human parainfluenza virus

Human parainfluenza viruses (HPIV) are RNA viruses that are classified into four serotypes (HPIV1-4), all of which

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**Table 2: Summary of viral pneumonia**

<table>
<thead>
<tr>
<th>Respiratory viruses</th>
<th>Mode of transmission</th>
<th>Laboratory diagnosis</th>
<th>Therapy</th>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza virus</td>
<td>Person-to-person by airborne particles</td>
<td>Culture, Nucleic acid amplification, Antigen detection, Serology</td>
<td>Neuraminidase inhibitors: Oseltamivir, zanamivir (influenza A and B), M2 inhibitors: Amantadine, rimantadine (influenza A)</td>
<td>Inactivated influenza vaccine</td>
</tr>
<tr>
<td>Respiratory syncytial virus</td>
<td>Direct contact with virus-containing secretions, fomites, or large aerosol droplets</td>
<td>Culture, Nucleic acid amplification, Antigen detection, Serology</td>
<td>Ribavirin, palivizumab</td>
<td>Vaccine not available</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>Fecal — oral through fomites and droplets</td>
<td>Culture, Nucleic acid amplification, Antigen detection, Serology</td>
<td>Cidofovir, ribavirin</td>
<td>Vaccine not available</td>
</tr>
<tr>
<td>Rhinovirus</td>
<td>Aerosol droplets or contact with infected secretions from the upper airway</td>
<td>Nucleic acid amplification, Antigen detection, Serology</td>
<td>Pleconaril, interferon therapy</td>
<td>Vaccine not available</td>
</tr>
<tr>
<td>Human PIV</td>
<td>Respiratory droplets, fomites, or direct contact</td>
<td>Culture, Nucleic acid amplification, Imunoglobulin detection</td>
<td>Ribavirin</td>
<td>Vaccine not available</td>
</tr>
<tr>
<td>HMPV</td>
<td>Direct or close contact with contaminated secretions including saliva, droplets or large-particle aerosols</td>
<td>Nucleic acid amplification, Antigen detection</td>
<td>Ribavirin</td>
<td>Vaccine not available</td>
</tr>
<tr>
<td>Coronavirus</td>
<td>Airborn droplets, close personal contact</td>
<td>Cell culture, Nucleic acid amplification, Serology</td>
<td>No specific treatment is available</td>
<td>Vaccine not available</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Direct or close contact with contaminated secretions</td>
<td>Nucleic acid amplification, Antigen detection, Serology</td>
<td>Ganciclovir</td>
<td>Vaccine not available</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td>Close contact with an infected person who is shedding virus from the skin, in saliva, or in secretions from genitals</td>
<td>Nucleic acid amplification, Serology</td>
<td>Aciclovir</td>
<td>Vaccine not available</td>
</tr>
<tr>
<td>Human bocavirus</td>
<td>Aerosol and contact</td>
<td>Nucleic acid amplification, Serology</td>
<td>No specific treatment is available</td>
<td>Vaccine not available</td>
</tr>
</tbody>
</table>

PIV: Parainfluenza virus; HMPV: Human metapneumovirus
can cause lower respiratory infection (LRI) in humans such as bronchitis, asthma, and pneumonia especially in infants, young children, elders, and immunocompromised individuals.[53-57] Transmission can occur through respiratory droplets, fomites, or direct contact with an infected host.[38]

Human parainfluenza viruses type 1 and type 3 are among the major pathogens that cause hospitalization for viral respiratory infection in the world. They are with high prevalence in adults and associated with up to 12% of acute LRIs.[39,40] HPIV infection is generally limited to the respiratory tract and does not spread systemically unless the infected individual is severely immunocompromised.

Factors contributing to HPIV pathogenesis are young age and lack of prior exposure. Fewer data exist on HPIV pneumonia in patients with HIV. Garbino et al. showed that 5% of the HIV patients in their study were infected with HPIV, and were all in the context of co-infection with other pathogens.[5]

**Adenovirus**

Adenoviruses are DNA viruses with approximately 52 serotypes, but only few of them cause diseases in humans with a worldwide distribution throughout the year. Pulmonary infections are associated with serotypes 1, 2, 3, 4, 5, 7, 14, and 21. Serotype 14 is associated with severe pneumonia in susceptible adults and children including solid-organ transplant recipients, HIV patients, and individuals with other kinds of impaired cell-mediated immunity.[41] Respiratory infection by adenoviruses also accounts for 5-10% of the pediatric population and 1-7% of adults.[42] Transmission of adenovirus is fecal — oral through fomites and droplets, and the virus can persist on environmental surfaces for several weeks. Clinical presentation ranges from asymptomatic viremia to respiratory and gastrointestinal disease, hemorrhagic cystitis, and a severe disseminated disease, hemorrhagic cystitis, and a severe disseminated illness, but is typically characterized by fever, cough, and dyspnea. Pulmonary opacities are often patchy and irregular or reticular at radiological images, but consolidations can also be observed. However, the clinical spectrum of the disease is broad, and dissemination or pneumonia can be fatal in both immunocompetent and immunocompromised patients.[43] Khoo et al. found that the risk of adenovirus infection in patients with acquired immunodeficiency syndrome (AIDS) was 28% in the 1st year (17% if CD4+ T-cell count was >200/mm³ vs. 35% if the count was <200/mm³). Adenovirus infection is uncommon in HIV/AIDS patients until their immune systems are impaired.[44]

**Human metapneumovirus**

Human metapneumovirus (HMPV) is an RNA virus, and HMPV infection has been detected worldwide in the community or hospitalized patients at any age, with most severe cases reported in elderly and immunocompromised patients. HMPV is thought to be transmitted by direct or close contact with contaminated secretions including saliva, droplets, or large-particle aerosols. Symptoms are usually very similar to those caused by RSV, with a range of illness from mild respiratory symptoms to severe bronchiolitis and pneumonia. The incubation period is approximately 5 days, and clinical symptoms are similar to that of other viral infections, with nasal congestion, coughing, wheezing, fever and dyspnea. Chest images show bilateral alveolar opacities in 43% of cases, and nodular opacities and pleural effusion can also be observed.[45]

**Coronavirus**

Coronaviruses are RNA viruses that are primarily associated with respiratory infection at any age, worldwide, and cause epidemics every 2-3 years. Approximately 15% of the common cold in adults are caused by coronaviruses.[46-47] There are five strains associated with respiratory infection in humans: Severe acute respiratory syndrome (SARS) coronavirus produces life-threatening SARS and was identified in 2003 outbreak in China;[48] the human coronaviruses (HCoV)-OC43 and HCoV-229E are associated with common cold, and HCoV-NL63 and HCoV-HKU1 are associated with LRI infections, which were identified in The Netherlands in 2004 and in Hong Kong in 2005, respectively.[49,50] More recently, Middle East respiratory syndrome-CoV was reported in Saudi Arabia in 2012. The mode of transmission is through aerosol droplets or close personal contact. The infections by coronaviruses mainly occur in winter, with an incubation period of 2-5 days. The most common symptoms are: Myalgia, chills, and dyspnea, with possible progression to respiratory failure whereas fever, is uncommon. The radiological pattern is nonspecific, commonly characterized by diffuse pulmonary ground-glass opacities on chest tomography. In a retrospective study in Hong Kong, coronavirus was presented in 2.1% of patients hospitalized with acute respiratory illnesses.[51] Several studies demonstrated that coronavirus causes CAP in children and adults.[1,32,51] Garbino et al. found RV in 18.6% of bronchioalveolar lavage (BAL) samples of HIV patients in the study, and HCoV-OC43 was identified in 27.2% of such cases.[5] However, few such studies with HIV patients exist.

**Cytomegalovirus**

Cytomegalovirus (CMV) is a DNA virus that is highly prevalent in the general population. CMV is a common cause of acute LRI infections particularly in immunocompromised patients and is associated with a wide spectrum of diseases ranging from an asymptomatic disease or a mononucleosis-like syndrome to severe disease in immunocompromised patients.[54-56] The principal risk factors for CMV infection include HIV infection and immunosuppression by transplantation and conditions associated with significant morbidity and mortality.[14-56] CMV is transmitted by direct or close contact with contaminated secretions, and CMV infection is the most common viral opportunistic infection with a prevalence of 21-44% in the HIV population before ART therapy.[47] After the resolution of acute infection,
CMV establishes latent infection. Most HIV patients have latent CMV infection in many tissues including the lungs, and most cases of CMV pneumonia are believed to be caused by CMV reactivation due to severe immunosuppression.

Pneumonia caused by CMV is reported to be similar to that caused by Pneumocystis jirovecii; with fever, cough, hypoxemia, diffuse radiographic opacities, and pleural effusion in 33% of cases.

Salomon et al. demonstrated that CD4+ T-cell count ≤12 × 10^6 and extra-pulmonary CMV manifestations were independently associated with CMV pneumonia.

Herpes simplex virus

Herpes simplex virus (HSV) is a DNA virus with two types: HSV-1 and HSV-2, both of which produce lifelong infections and are very common in the general population. The primary infection by this virus is usually asymptomatic, but it establishes lifelong latency. Reactivation of the virus has been associated with asymptomatic virus excretion in saliva, producing ulceration of the mouth mucosa or herpes labialis, and immunocompromised patients develop a serious disease such as herpetic tracheobronchitis or pneumonia. The transmission is due to close contact with an infected person who is shedding virus from the skin, in saliva, or in secretions from genitals. HSV infections, both oral and genital, are frequent in HIV patients with severe immunodeficiency. Herpetic pneumonia is rare in HIV patients; while HSV-1 is the usual cause of the cases, pneumonia due to HSV-2 is extremely rare. Despite the low frequency of pulmonary infections, sporadic cases of HSV-mediated pneumonia and tracheitis in HIV patients have been reported.

Human bocavirus

Bocavirus was first isolated in nasopharyngeal aspirate specimens from children with LRI infections in 2005. It is a DNA virus, which likely is transmitted by respiratory droplets and has been detected worldwide. Several studies suggest that the human bocavirus is mainly a respiratory pathogen.

In a recent study, 17 RV were tested during the acute phase of CAP in children, and bocavirus was among the most frequently detected virus after RSV and HRV. In a different pediatric population from South Africa, Nunes et al. found presence of bocavirus in 9.5% of HIV-infected and in 13.3% of HIV-uninfected children with LRI. In the adult HIV patients, Garbino et al. found only 1 out of the 55 patients (3.1%) was positive for bocavirus. Unfortunately, clinical manifestations of bocavirus infection are not well defined, but it has been described to range from mild to severe upper respiratory tract infections.

MICROBIAL DIAGNOSIS

The key for successful detection of RV is the collection of good quality respiratory tract samples (nasal and oropharyngeal swabs placed in a single viral transport medium). Specimens should be collected preferably within 48 h from the onset of illness. Current diagnostic methods for RV are: Serology, virus culture, antigen detection, and nucleic acid testing.

Serology

Serology requires collection of paired blood samples from acute and convalescent phases. Greater than four-fold increase of virus specific IgG in the convalescent phase relative to the acute phase confirm the diagnosis. It is available for many RV including adenovirus, RSV, and seasonal influenza. However, the results do not affect clinical management of patients.

Virus isolation

Viral culture requires specific technical expertise, is labor-intensive and expensive, and takes several days to grow and identify the virus. Viral culture is more sensitive than antigen detection assays and is capable of recovering novel or highly divergent strains that were not detected by other tests. However, some viruses such as rhinovirus, metapneumovirus, coronaviruses, and human bocavirus, grow poorly or not at all in the culture. In addition, this method only detects viable viruses in contrast to the nucleic acid amplification test.

Antigen detection

Direct and indirect immunofluorescence assays use commercial type-specific monoclonal antibodies to detect viral antigens directly on clinical specimens or in cell culture. These tests mostly have a specificity greater than 80% and sensitivity of 47-93% depending on virus and viral load. These tests are not available for some viruses (e.g., bocavirus, coronavirus, and rhinovirus), and presents lower sensitivity for detection of viruses in co-infections compared with nucleic acid amplification methods.

NUCLEIC ACID AMPLIFICATION

Nucleic acid amplification is considered the most sensitive, specific, and versatile test for respiratory virus detection. In addition, it requires a significantly shorter time (1-5 h) to obtain the result in comparison to other methods. Today, there are many commercial tests and in-house assays. Real-time polymerase chain reaction (PCR) combines the amplification and detection steps, and can quantify the viral
load in clinical specimens for prognosis and to assess antiviral efficacy.[75] Also, it can simultaneously detect influenza and other RV.[76] Moreover, CMV, HSV, and varicella zoster virus can be detected by PCR in BALs from HIV patients with severe respiratory infection.[77]

**PREVENTION**

Influenza A and B virus infections can be prevented by prophylactic use of neuraminidase-inhibitors.[78] Preventive strategies are recommended in HIV-infected patients due to the possibility for highly morbid viral infections (immunodeficiency) and the high frequency of additional risk factors (e.g., smoking and chronic lung diseases). Current guidelines by prevention and treatment of opportunistic infections in HIV-infected patients recommend annual influenza vaccination to reduce the risk of influenza and postinfluenza bacterial pneumonia in the population.[79] In fact, the prolonged shedding and the increased risk for complications and death in HIV patients make this population an important target for influenza vaccination campaigns.

The protective efficacy of the inactivated influenza vaccine in healthy individuals achieves 70-90%.[80] While that of the HIV patient population is approximately 40%.[81,82] Reasons for decreased antibody responses to the influenza vaccine in HIV patients are not clear; nevertheless, two main predictors for induction of adequate response to influenza vaccine may be higher CD4+ T-cell count (≥200 cells/μL) and undetectable viral load (<50 copies/mL). Recent studies show that HIV patients reach higher levels of influenza seroprotection if vaccinated with high-dose influenza vaccine.[83,84]

For RSV, handwashing and use of gloves are the primary measures to prevent viral transmission from close contact with an infected patients or contaminated surfaces.

For RV infection, the combination of antiviral chemoprophylaxis and control measures such as handwashing would be expected to reduce the risk of LRI particularly in patients with comorbidities.

**ANTIVIRAL THERAPY**

For influenza pneumonia, two groups of antiviral drugs are currently available: Matrix protein 2 (M2) inhibitors and neuraminidase inhibitors. M2 inhibitors are only active against influenza A. Unfortunately, resistance against M2 inhibitors can develop as early as 2-3 days after administration of the drug. Therefore, these antivirals should be administered within 48 h from the onset of symptoms. Oral or inhaled neuraminidase-inhibitors are both effective against influenza A and B viruses. The rate of developing resistance is very low; however, some resistant cases were reported during the H1N1 pandemic.[85] In cases of severe pneumonia, the medication is recommended even after 48 h from the onset of symptoms.

Ribavirin is a nucleoside analogue that inhibits viral replication; the aerosol form is used for the treatment of RSV in children. Palivizumab is an anti-RSV monoclonal antibody that has been used for prophylaxis and to treat upper and lower respiratory tract RSV infections in severely immunocompromised patients.

Intranasal interferon demonstrated prophylactic efficacy against rhinovirus infection while it is not therapeutically effective in established rhinovirus colds.[86] Pleconaril is the first antiviral to be proven effective in clinical practice to reduce duration and severity of viral respiratory infection symptoms after establishment of the illness.[87]

Currently, there is no specific antiviral therapy for HIPV infection. Nonetheless, Chakrabarti et al. reported a good response to ribavirin in HIPV respiratory infections among hematopoietic stem cell transplant recipients.[88] Cidofovir has been used, and several reports demonstrated the efficacy of the combined therapy “cidofovir/ribavirin,” especially in patients with unfavorable evolution.[43]

There is no specific therapy for HMPV infection. However, Raza et al. reported a successful ribavirin treatment of a lung transplant recipient with severe HMPV pneumonia.[89]

To coronavirus infection, no specific treatment is available. However, in severe cases, protease inhibitors (lopinavir and ritonavir) and interferon (alpha and beta) can be administered.[90] There is no evidence of efficacy for ribavirin use.

For the treatment of CMV pneumonia, ganciclovir is recommended in combination with high-dose immunoglobulins while it has not been evaluated in a randomized controlled trial. CMV pneumonia treatment is recommended for patients with HIV if CMV is the sole pathogen and is symptomatic whereas treatment does not seem to result in improved outcome if other pathogens are present.[47]

For the treatment of HSV pneumonia, acyclovir has demonstrated beneficial effects in several studies, and the frequency of developing resistance is minimal.[91]

Currently, there is no antiviral treatment for bocavirus, and only supportive care is available.

**CONCLUSION**

The development of novel diagnostic tests has shown that viral involvements in CAP are more prevalent than was
described in the past. Community-acquired viral pneumonia is a more serious clinical disease in immunocompromised patients than in the general population. Further investigations are needed to understand the role and clinical impact of the newly identified RV, especially in HIV populations. Unfortunately, vaccines and specific therapies are available only for some RV. Preventive measures are keys to stop the transmissions of these viruses to susceptible hosts and will decrease the morbidity and mortality rates associated with the community-acquired viral pneumonia in the immunocompromised population. Finally, it is worth noting that a wide microbiological analysis is recommended in immunocompromised patients to optimize antimicrobial therapy.

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