Viral Pneumonias in Immunocompromised Adult Hosts

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Abstract
Viral infections have always been considered pediatric diseases. However, viral pneumonia has become an important cause of morbidity and mortality in immunocompromised adults. Improved diagnostic techniques, such as the introduction of highly sensitive nucleic acid amplification tests, have not only allowed us to discover new viruses but also to determine the etiology of viral pneumonia in immunocompromised adult hosts. Unfortunately, only a few antiviral agents are available. Thus, early diagnosis and treatment are crucial to patient outcome. In this article, we review the most common viruses that have been implicated as etiologic agents of viral pneumonia in immunocompromised adults. We discuss the epidemiologic characteristics and clinical presentation of these viral infections and the most appropriate diagnostic approaches and therapies when available.

Keywords
virus, pneumonia, immunocompromised, transplantation, cancer

Introduction
Pneumonia is a common and potentially serious illness. Over the past 10 years, the incidence of viral pneumonia has increased primarily because of improved diagnostic techniques such as the introduction of highly sensitive nucleic acid amplification tests1 and a growing population of immunocompromised patients. Moreover, recent studies of community-acquired pneumonia in immunocompetent and immunocompromised adults indicate a viral etiology in 1% to 23% of cases, with influenza virus being the most common one.2,3

Pneumonia is more common in hosts with impaired immunity. Immunocompromised patients have a high susceptibility to infection with organisms with little native virulence. These patients experience longer infections with prolonged shedding, a higher nosocomial transmission rate, and a higher mortality rate than their immunocompetent counterparts.4 Lung infections remain the most common form of tissue-invasive infection in these patients.

The objective of this article is to provide a comprehensive and updated review of viral pneumonias in immunocompromised patients. We will discuss the etiology, epidemiologic characteristics, clinical presentation, diagnosis, and therapy of the most common viral infections that can cause pneumonia in immunocompromised hosts (Table 1).

Influenza Pneumonia
Influenza is an RNA virus that belongs to the family Orthomyxoviridae. It is classified into 3 distinct types, influenza A, B, and C on the basis of major antigenic differences. Influenza viruses are enveloped and covered with surface projections that are glycoproteins with hemagglutinin (HA) or neuraminidase (NA) activity. Major changes in these glycoproteins are referred to as antigenic shifts (associated with pandemics) and minor changes are called antigenic drifts (related to outbreaks).

Outbreaks of influenza infection occur during the winter months. The Centers for Disease Control and Prevention (CDC) tracks influenza virus isolates throughout the world to monitor disease activity and predicts the appropriate components of the annual influenza vaccine. Weekly updated information is available at www.cdc.gov/flu/weekly/.

Clinical Presentation
Influenza is transmitted via small-particle aerosols during sneezing, coughing, and talking. After an incubation period of 1 to 2 days, fever, headache, myalgia, and malaise develop accompanied by a sore throat and cough. However, patients may present with symptoms of an afebrile respiratory illness, similar to the common cold, or an illnesses in which systemic
signs and symptoms predominate, with relatively little clinical indication of respiratory tract involvement. The major complication of influenza is pneumonia, which occurs most frequently in patients with illnesses that involve the cardiovascular or pulmonary systems, patients with diabetes mellitus, renal disease, hemoglobinopathy, or immunosuppression, residents of nursing homes or chronic care facilities, and otherwise healthy individuals over age 65 years.\(^5\)

Influenza pneumonia presents in 1 of the 3 different forms. Primary influenza pneumonia develops when the influenza virus infection directly involves the lungs. Influenza virus affects the tracheobronchial epithelium, leading directly to a decrease in cell size and cilia loss; this in turn predisposes the patients to infection by other bacterial pathogens (secondary influenza pneumonia). Finally, there could be a mixed viral and bacterial pneumonia that is a co-infection with both.

**Hematopoietic stem cell transplant recipients.** Influenza pneumonia has an incidence of 0.4% in hematopoietic stem cell transplant (HSCT) recipients.\(^6\) Nichols et al\(^6\) found that among 62 patients who developed influenza infection after HSCT, 11 (17.7%) patients had pneumonia at presentation and 51 patients had only an upper respiratory infection. Of those who present with only an upper respiratory tract infection, 7 (13.7%) experienced progression to pneumonia. La Rosa et al\(^7\) found a pneumonia rate of 63% in HSCT recipients, with a 43% mortality whereas a most recent publication found a 30% incidence in HSCT recipients with influenza infection and a 13% mortality.\(^8\) The only risk factor that has been found for progression of upper respiratory infection to lower respiratory infection is lymphopenia. Surprisingly, systemic corticosteroids use and autologous HSCT appeared to be protective factors.\(^6\) Co-pathogens are found in 60% of pneumonia cases. The reported mortality of influenza pneumonia in HSCT recipients is as high as 28% and is usually secondary to respiratory failure.\(^6\) Radiologic images are characterized by a diffuse interstitial pattern; however, focal pulmonary infiltrates have been described. These infiltrates are associated with an aggressive and rapidly progressive disease.\(^9\)

**Solid organ transplant recipients.** Among solid organ transplant (SOT) recipients, lung transplant patients are at highest risk of infection.\(^10\) The clinical presentation depends on the host. Garantzioti et al\(^11\) found that in lung transplant recipients, the initial presentation did not always involve the respiratory tract but rather nonspecific gastrointestinal symptoms; however, pneumonia was present at onset requiring hospitalization. In addition, all patients experienced progression to bronchiolitis obliterans shortly after the influenza infection, which is generally thought to represent a manifestation of chronic lung allograft rejection. To our knowledge, no large series exist on influenza pneumonia in renal or liver transplant recipients, but it has been described in case reports. In renal transplant patients, influenza pneumonia has been described as acute, with rapid onset of high fever, nonproductive cough, dyspnea, and cyanosis and is associated with arterial hypoxemia, leukopenia, and thrombocytopenia.\(^12\)

**Patients with human immunodeficiency virus.** Few data exist on influenza pneumonia in patients with human immunodeficiency virus (HIV), mainly because it is not a major clinical problem in this population despite their immunodeficiency. In a study from 1997 to 1999, 43 cases of influenza were found and in 16% of these pneumonia was also diagnosed.\(^13\) The mean CD4 count in these patients was 304 cells/mm\(^3\) and the HIV viral load was 3.37 log copies/mL; these results were not statistically significantly different from those patients without pneumonia (346 cells/mm\(^3\) and 3.25 log copies/mL).\(^14\) The symptoms of influenza pneumonia in these patients with HIV included dyspnea, productive cough, and hypoxemia, although patients rarely required mechanical ventilation. Imaging studies showed patchy, nodular, or interstitial infiltrates. During the 1997-1998 winter season during which the vaccine failed to protect against the predominant circulating H3N2 strain (A/Sydney/5/97), there was a reported incidence of 57% in patients with HIV.\(^14\)

**Other immunosuppressed hosts.** Influenza infections result in higher morbidity and mortality rates in patients with cancer

### Table 1. Characteristics and Seasonality of Respiratory Viruses Reported to Cause Pneumonia in Adult Immunocompromised Hosts

<table>
<thead>
<tr>
<th>Virus</th>
<th>Nucleic Acid Type</th>
<th>Family</th>
<th>Seasonality in United States</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza virus</td>
<td>RNA ss(−)</td>
<td>Orthomyxoviridae</td>
<td>Winter</td>
</tr>
<tr>
<td>Parainfluenza virus</td>
<td>RNA ss(−)</td>
<td>Parainmyxoviridae</td>
<td>PIV-1 and PIV-2 fall</td>
</tr>
<tr>
<td>RSV</td>
<td>RNA ss(−)</td>
<td>Paramyxoviridae</td>
<td>PIV-3 spring and summer</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>DNA ds</td>
<td>Adenoviridae</td>
<td>Winter</td>
</tr>
<tr>
<td>CMV</td>
<td>DNA ds</td>
<td>Herpesviridae</td>
<td>Throughout the year</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td>DNA ds</td>
<td>Herpesviridae</td>
<td>Throughout the year</td>
</tr>
<tr>
<td>Rhinovirus</td>
<td>RNA ss</td>
<td>Picornaviridae</td>
<td>Peak in early fall and spring</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>RNA ss</td>
<td>Picornaviridae</td>
<td>Throughout the year, but with higher rates in summer and fall</td>
</tr>
<tr>
<td>Coronavirus</td>
<td>RNA ss (+)</td>
<td>Coronaviridae</td>
<td>Winter and spring</td>
</tr>
<tr>
<td>Metapneumovirus</td>
<td>RNA ss (−)</td>
<td>Paramyxoviridae</td>
<td>Late winter and early spring</td>
</tr>
</tbody>
</table>

Abbreviations: PIV, parainfluenza virus; RSV, respiratory syncytial virus; CMV, cytomegalovirus; RNA, ribonucleic acid; ss, single stranded; DNA, deoxyribonucleic acid; ds, double stranded.
than nonimmunocompromised hosts. In the largest reported series of patients with leukemia and influenza, 39% of patients developed pneumonia. Cough and dyspnea were the most frequent manifestations. Lymphopenia was found in half the patients and 25% of these developed a mold infection within 1 month of the onset of influenza.

**Diagnosis**

Influenza should be diagnosed clinically and confirmed in the laboratory. Viral culture is still the gold standard of laboratory diagnosis, but it takes 48 to 72 hours before the cytopathic effects of the virus become apparent in tissue culture. Sputum and nasal washes are superior to throat swabs for the isolation of the virus. Rapid viral diagnostic tests include immunofluorescence (IF) assays, enzyme immunoassays (EIA), and polymerase chain reaction (PCR)-based testing. The sensitivity of these tests ranges from 72% to 95% and the specificity ranges from 76% to 84%. The timing of the test in relation to clinical symptoms influences on sensitivity and is best when viral shedding is peaking (24-48 hours after the start of the illness). Polymerase chain reaction-based tests are more sensitive than culture, are specific for both influenza A and B, and can detect low quantities of influenza RNA in bronchoalveolar lavage (BAL) fluid and other specimens. However, they are rarely used in the clinical setting because of the cost.

**Treatment and Outcome**

Two types of drugs are available for the treatment of influenza: M2 inhibitors (amantadine and rimantadine) and NA inhibitors (zanamivir and oseltamivir). Amantadine and rimantadine are only active against influenza A; they target its M2 protein that forms a proton channel in the viral membrane that is essential for efficient viral replication. Resistance occurs through a single nucleotide change involving the transmembrane portion of the molecule and can develop as early as 2 to 3 days after the start of therapy. Central nervous system side effects (eg, anxiety, insomnia, impaired thinking, confusion, light-headedness, and hallucinations) are reported with amantadine and are more common in elderly patients. It also has anticholinergic effects and is contraindicated in patients with untreated angle closure glaucoma. Zanamivir and oseltamivir are active against influenza A and B, interfering with the release of progeny influenza virus from infected cells.

In adults, both drugs decrease the median duration of symptoms by a mean of 1 day. Administration of oseltamivir within 12 hours after fever onset reduces the median illness duration by 3.1 days more than if the intervention was delayed until 48 hours. In addition, oseltamivir has been shown to shorten the duration of shedding. Zanamivir and oseltamivir have also been shown to significantly decrease the incidence of complications associated with influenza such as pneumonia compared to placebo. However, zanamivir may have poor bioavailability in the peripheral lungs. Medeiros et al reported a case of a HSCT recipient who developed influenza pneumonia with a susceptible influenza A (H1N1) strain; the patient did not respond to inhaled zanamivir treatment but recovered after oseltamivir treatment was initiated.

Resistance can develop from changes in HA or NA and is more common in children and immunocompromised patients, and it is associated with fatal outcomes. Adverse effects of NA inhibitors are usually mild. Nausea and vomiting occurs in 15% of patients treated with oseltamivir but is usually limited to the first day of treatment. Other adverse effects include delirium, hallucinations, confusion, abnormal behavior, convulsions, encephalitis, and severe skin reactions. Zanamivir, which is administered inhaled, can cause bronchospasm and a decline in respiratory function in patients with chronic respiratory diseases including asthma and is contraindicated in patients with these underlying diseases.

Because of an increase in the number of M2 inhibitor-resistant strains (91% of H3N2 influenza isolates were resistant during the 2005-2006 influenza season), the CDC recommends against the use of these drugs in influenza treatment. During the 2007-2008 influenza season, there was a worldwide increase in the incidence of oseltamivir resistance among influenza A (H1N1) viruses secondary to the carriage of the H274Y mutation. As of March 2008, the frequency of resistance in the United States was 8.6%. The last CDC recommendations for the use of influenza antiviral medications for the 2008-2009 influenza season states that the prevalence of influenza A (H1N1) virus strains resistant to the antiviral medication oseltamivir is high. Therefore, zanamivir or a combination of oseltamivir and rimantadine are more appropriate options than oseltamivir alone.

In immunocompromised hosts, the main issues in influenza treatment are the higher levels of influenza virus and prolonged viral shedding. These patients also have a higher rate of extrapulmonary complications including graft dysfunction and rejection. To our knowledge, no clinical randomized control trials have been conducted on the use of antivirals for the treatment of influenza pneumonia in immunocompromised patients. Some studies have shown that M2 inhibitors decrease the rate of progression to pneumonia in patients with leukemia and HSCT recipients from 76% down to 35%. However, the rapid development of resistance to amantadine and rimantadine limits its use as Englund et al demonstrated. After being exposed to amantadine, 83% of patients with symptomatic diseases acquired drug resistant influenza. Newer drugs such as oseltamivir have been shown to reduce the incidence of progression to pneumonia from 18% to 0% in HSCT recipients, from 48% to 12% in influenza A patients, and from 32% to 7% in influenza B patients with hematologic malignancies. In a study of patients with leukemia, only 1 (7%) of the 14 patients treated with NA inhibitors experienced progression to pneumonia. Oseltamivir has also been shown to significantly reduce the mortality rate from 27% to 9% in patients with hematologic malignancy and 0% in patients with leukemia and HSCT recipients. In addition, oseltamivir has been found to resolve infections without complications in lung transplant recipients with influenza infection.
**Prevention/Vaccines/Prophylaxis**

The mainstay for prevention of influenza in immunosuppressed patients should be vaccination. However, standard infection control measures such as good hand hygiene as well as the use of contact and droplet isolation are recommended by the CDC to limit nosocomial spread. Because immunocompromised patients shed influenza virus for longer periods of time, isolation should be continued for the duration of the illness.

The 2007 Advisory Committee on Immunization Practices recommends that all immunosuppressed patients and health care personnel, family members, and visitors be vaccinated annually early in the influenza season. Hematopoietic stem cell transplant recipients should be vaccinated before SCT and at yearly intervals starting 6 months after transplantation. Machado et al found a vaccine effectiveness rate of 80% in a cohort of HSCT recipients.

Two types of influenza vaccine exist: an intramuscular influenza vaccine (inactivated virus or subvirion components) and an intranasal vaccine (attenuated cold adapted donor virus from which reassortants with H and N antigens are generated). The intranasal form is only approved for use in patients aged 49 years or younger and should not be used in immunosuppressed patients or people in contact with severely immunosuppressed patients. Egg anaphylaxis is a contraindication for both vaccine types, because they are prepared from viruses grown in eggs and a small amount of protein may be present in the vaccines. Skin testing with influenza vaccine or desensitization can be performed in patients with a history of egg allergy. An experimental trivalent influenza virus hemagglutinin (rHAO) that does not include embryonated eggs is under development and has already been shown to be effective against a drifted influenza A(H3N2) virus.

Although, prophylactic antivirals are not recommended for influenza except in nosocomial outbreaks, recent studies have shown that oseltamivir is safe and well tolerated in HSCT recipients and appears to prevent the development of influenza infection.

**Parainfluenza Virus Pneumonia**

Parainfluenza viruses (PIVs) are enveloped, single-stranded RNA viruses that belong to the genus Paramyxovirus in the Paramyxoviridae family along with human mumps, measles, and respiratory syncytial viruses (RSVs). There are 4 major serotypes of human PIV: PIV-1, -2, -3, and -4. Transmission occurs through person-to-person contact or large droplet inhalation. The incubation time is 1 to 4 days. Infections occur throughout the year and all over the world. In the developing and tropical countries, PIV viruses do not have seasonal variations; however, in the United States PIV-1 and PIV-2 appear every 2 years in the fall and PIV-3 occurs annually in spring or summer epidemics.

**Clinical Presentation**

**HSCT recipients.** In 1 study, the prevalence of PIV pneumonia in HSCT recipients was 1.5%; respiratory failure occurred in 31.5% of cases and resulted in 100% mortality. Parainfluenza usually presents as an upper respiratory tract infection. Progression to pneumonia is seen in 18% of cases, which is much less common than with other viruses. In 1 study, lymphopenia and the use of systemic corticosteroids were found to be risk factors for the development of pneumonia. The risk increased to 40% with 1 mg/kg of prednisone and 65% with 2 mg/kg. Other authors have reported that the presence of neutropenia or lymphopenia within 1 week, chemotherapy 1 month prior, and pulmonary co-infections 1 month prior to the onset of symptoms were risk factors for pneumonia.

Wendt et al found that parainfluenza pneumonia had a mortality rate of up to 30% in HSCT recipients. Hammoud et al found a mortality rate of 20% and it did not differ by ribavirin treatment. In one of the largest series, co-pathogens were present in 53% of the cases (Aspergillus fumigatus was the most common in 24% of cases); this and mechanical ventilation were risk factors for increased mortality.

**SOT recipients.** Fewer studies exist on PIV pneumonia in SOT than in HSCT recipients. Paramyxovirus infections were seen in 21% of lung transplant recipients during an 8-year period (9 cases of RSV and 10 of PIV). All patients developed pneumonia and 6 experienced a decline in spirometry that returned to baseline in only 4 cases. Other authors have found a prevalence of 12.8% for pneumonia in patients with PIV infections, with some degree of acute allograft rejection seen in all patients in whom transbronchial biopsy was performed.

**HIV patients.** Few data exist on PIV pneumonia in patients with HIV. Garbino et al reviewed the results of bronchoscopies performed in patients with HIV suspected to have lower respiratory infections; by using PCR techniques, they found a recovery rate of 5% for PIV. However, many patients had co-infections and PIV was not found to be the sole cause of disease in all cases.

**Other immunosuppressed hosts.** Parainfluenza virus infection outbreaks have been reported in the elderly patients in nursing homes and are associated with the subsequent development of pneumonia with community-acquired pathogens. In patients with leukemia, 52% of patients with PIV infection experienced progression to pneumonia, a significantly higher rate than in HSCT recipients. Of these patients, 96% had undergone chemotherapy within 1 month prior to the diagnosis of PIV infection. Three patients were treated with ribavirin and one died. Of the 25 patients not treated with ribavirin, 5 died (20%).

**Diagnosis**

Nasopharynx or lower respiratory tract culture is still the gold standard of diagnosis for PIV infections. Immunofluorescent
tests and EIA for the rapid detection of antigens are also available and have sensitivity rates of 75% to 95%. New PCR assays detect multiple respiratory viruses including PIV and have up to 100% sensitivity and 98% specificity.

Treatment

Currently, no licensed antiviral therapy exists for PIV. Ribavirin is active against PIV in vitro and in animal models and is sometimes used for the treatment of PIV pneumonia in immunocompromised hosts. However, studies of the effectiveness of aerosolized or systemic ribavirin in patients with PIV pneumonia have shown contradictory results. Nichols et al found that aerosolized ribavirin was not effective at reducing viral shedding or mortality once pneumonia was established in HSCT recipients, whereas the combination of systemic ribavirin and methylprednisolone was successful in the treatment of PIV pneumonia in cardiac transplant and HSCT recipients. Hammond et al found no difference between HSCT recipients treated with ribavirin and those who had not been treated, but in patients with leukemia, the mortality rate was reduced from 20% to 0% among patients treated with ribavirin, although only a small number of patients were treated.

Prevention/Vaccines/Prophylaxis

There is no commercially licensed vaccine currently available for PIV. Thus, infection control measures are the cornerstone of disease prevention. Early respiratory isolation of infected patients is required to avoid horizontal transmission. However, the lack of symptoms in immunocompetent individuals and HSCT recipients, asymptomatic shedding in infected patients, staff, and visitors; and the persistence of the virus on environmental surfaces make it difficult to control the spread of the virus; as a result multiple outbreaks are continuously reported in the outpatient and inpatient settings with attack rates as high as 17%.

Respiratory Syncytial Virus Pneumonia

Respiratory syncytial virus is an enveloped single-stranded RNA virus that belongs to the Paramyxoviridae family, Pneumoviridae subfamily, and Pneumovirus genera. There are 2 major groups of RSV: A (which causes more severe disease) and B, and there are several distinct genotypes within these groups that cause the dominant strains to shift annually.

In the Northern hemisphere, seasonal outbreaks occur from November to April with a peak in January or February. Transmission usually occurs through direct contact with virus-containing secretions or fomites but can also occur through large aerosol droplets.

Clinical Presentation

Immunocompromised patients such as severe combined immunodeficiency patients, patients with leukemia, HSCT or lung transplant recipients, patients with asthma, the institutionalized elderly individuals, and those with chronic pulmonary disease or functional disability as well as people who live at altitudes >2500 meters are at risk of developing RSV pneumonia.

HSCT recipients. Respiratory syncytial virus infection presents as an upper respiratory infection; it progresses to pneumonia in 36% of cases, usually less than 1 month after transplantation and in patients who have not experienced engraftment. Risk factors in HSCT recipients for progression to pneumonia are lymphopenia, old age, seasonality, malignancy relapse, graft versus host disease (GVHD), lack of engraftment, and lack of RSV-antiviral therapy. The usual symptoms on presentation are fever, cough, and dyspnea; upper respiratory tract symptoms are rare. Airflow decline has been found to be a consequence of RSV pneumonia in HSCT recipients. A mortality rate of 18% was reported in patients treated with aerosolized ribavirin; however, before the use of ribavirin, a small outbreak study reported mortality rates of up to 78%.

SOT recipients. Solid organ transplant patients with RSV infection can present with dyspnea (100%), cough (86%), purulent sputum (57%), fever (43%), rales (100%), and wheezing (29%). Hypoxemia is usually present with a mean PaO2 of 64 mm Hg. Respiratory syncytial virus infections progress to pneumonia in 72% of patients, 66% of whom have bilateral infiltrates. Among, SOT patients, lung transplant recipients have the highest incidence of pneumonia that can be complicated by bronchiolitis obliterans and organ rejection. However, the mortality rate in these patients as well as in kidney transplant recipients is insignificant. In adult liver transplant patients, RSV upper respiratory infections have been reported but not pneumonia. However, RSV pneumonia has been reported in 2.4% of pediatric liver transplant recipients, with a mortality rate of 17%. Early onsets of infection after transplantation as well as preexisting lung disease are predictive of more severe disease.

HIV patients. Data on RSV pneumonia in HIV patients are scarce. Bronchoalveolar lavage fluid from a cohort of 44 patients with lower respiratory tract infections during the winter season revealed no evidence of RSV.

Other immunosuppressed hosts. In children, genetic polymorphisms in cytokine- and chemokine-related genes (interleukin [IL]-4, IL-8, IL-10, IL-13, and CCR5) and genes related to potential virus-cell surface interactions or cell signaling (TLR-4, CX3CR1, SP-A, and SP-D) have been associated with severe RSV disease.

In patients with leukemia, RSV infection is associated with significant morbidity and mortality. Torres et al found that a high APACHE II score and lack of ribavirin treatment were independent predictors of progression to pneumonia. In addition, mortality secondary to RSV pneumonia in these patients was 18.5%.
Diagnosis

Respiratory syncytial virus pneumonia should be diagnosed clinically in the appropriate setting with laboratory confirmation. The gold standard diagnostic test is the identification of typical plaque morphology with syncytium formation through culture in HEp-2 cells. However, culture results take more than 4 days, reason why rapid antigen detection tests with sensitivity rates of >90% are now widely used for diagnosis. Bronchoalveolar lavage specimens are more sensitive than nasal wash or tracheal aspirate samples in immunocompromised adults but not children. Polymerase chain reaction tests have shown to be more sensitive than direct antigen detection but are still used mainly in research.

Treatment

Ribavirin is a nucleoside analogue that inhibits viral replication; it has been approved by the US Food and Drug Administration (FDA) for the treatment of RSV in children in its inhaled form. Ribavirin has been shown to reduce the mortality rate in HSCT recipients with RSV pneumonia, when it is used early in the course of treatment; however, in SOT recipients, the data are less conclusive. In addition, in patients with leukemia who present with RSV upper respiratory tract infections, aerosolized ribavirin has been shown to decrease the rate of development of pneumonia from 96% to 68%. Its use is contraindicated in pregnant women secondary to teratogenicity evidenced in rodents. Although no large randomized studies have been conducted, the concomitant early use of aerosolized ribavirin and intravenous immunoglobulin was shown in case series to reduce mortality from 100% to 22% in HSCT recipients, and it was also effective in lung transplant recipients.

Palivizumab is an RSV monoclonal antibody that is only FDA approved for prophylaxis, but it has been used to treat upper and lower respiratory tract RSV infections in severely immunocompromised patients. It has an excellent safety profile in HSCT recipients and good peak serum concentrations that effectively reduced RSV titers in cotton rats. In a series of 15 patients with established RSV infections, 12 of whom had pneumonia, palivizumab combined with ribavirin resulted in an 83% survival rate among the subgroup of patients with pneumonia, which compares favorably with the results of previous reports. In a retrospective review, 31 high-risk pediatric patients (18 immunocompromised patients including 13 patients with cancer or HSCT recipients) who received palivizumab for the treatment of RSV infections were evaluated. Lower respiratory tract infections were present in 58% of patients, and aerosolized or intravenous ribavirin was administered in 80% of patients. The treatment was well tolerated, with no reported adverse reactions, and the survival rate was 93.6%. In a retrospective study from France of 40 HSCT recipients with symptomatic RSV infections, palivizumab had no effect on progression to lower respiratory tract infection or on survival; palivizumab was well tolerated, with no adverse reactions. In a study by Khanna et al., palivizumab was used mainly in patients with severe immunodeficiency to prevent progression to lower respiratory tract infections; no conclusions on the efficacy of palivizumab in lower respiratory tract infections could be made.

Prevention/Vaccines/Prophylaxis

Standard infection control measures should be used to avoid nosocomial transmission of RSV (hand hygiene, use of gloves, gowns, masks, and eyes protection when there is a risk of exposure to aerosols). The isolation of patients in private rooms or rooms with other patients with RSV and limited transportation of patients outside their rooms are recommended. If an outbreak occurs, certain personnel should be restricted to care for only RSV-infected patients to limit the horizontal transmission of the virus to other patients.

No effective vaccine for RSV is available. For passive immunization, palivizumab is recommended in premature babies and children with bronchopulmonary dysplasia or congenital heart disease because randomized studies demonstrated that it significantly reduces RSV-associated hospitalizations. Although no randomized trials have been conducted in immunocompromised hosts, palivizumab’s use is recommended by the authors for individuals with RSV lower respiratory infections that are severely immunocompromised or have respiratory failure in combination with aerosolized ribavirin.

Adenovirus Pneumonia

Human adenoviruses are member of a family of DNA viruses that are an important cause of upper respiratory tract infections in children but can also cause pneumonia. Infections occur worldwide and throughout the year. Transmission is fecal—oral, through fomites, and droplets. Immunocompromised hosts may experience reactivation of latent infections. More than 50 serotypes exist based on antigenic determinants that are further classified into 6 subgroups (A-F) on the basis of hemagglutination patterns.

Clinical Presentation

Hematopoietic stem cell transplant recipients. In HSCT recipients, adenovirus pneumonia can occur as a solitary event or as part of a disseminated disease. It has been associated with delayed engraftment and graft failure. Isolated pneumonia has a reported incidence of 0.5% to 3% and is more common in allogeneic (73%) than in autologous HSCT recipients. However, the mortality rate is as high as 75% in both groups. Disseminated disease can occur without progressive respiratory tract infection and can develop in almost any organ causing hemorrhagic cystitis, gastrointestinal disease, hepatitis, nephritis, pneumonia, conjunctivitis, thrombotic thrombocytopenic purpura, or pancreatitis. Viremia is present in most but not all of the cases of disseminated disease. The most common clinical manifestations are fever and diarrhea. Differently from the other respiratory tract viruses, cases of fatal disease are also
reported in patients with no evidence of pneumonia. However, if pneumonia is present, the mortality rate is higher (80% vs 50%).

**Diagnosis**

Viral culture remains the gold standard for identifying adenovirus infections. Nasopharyngeal aspirates or swabs, throat swabs, and sputum samples are appropriate. Most strains of adenovirus (except 40 and 41A) have a cytopathic effect in human cell lines such as HeLa (cervix), A549 (lung), HEK (human embryonic kidney), and HEp-2 (larynx). Adenovirus types 40 and 41A grow well in HEK 293 cells, which express the Ad5 E1 region, complementing the poor E1 functions of the enteric adenoviruses.

The adenovirus antigen can be detected directly in clinical samples through adenovirus-specific EIA or IF assay. Although these tests are more rapid than culture, they are insensitive to adenovirus in sputum, reaching only 50% sensitivity in immunocompromised hosts.

Polymerase chain reaction can detect adenovirus DNA from a variety of clinical specimens and has improved sensitivity in diagnosis. Viral load quantification can be used as a surrogate for clinical response to therapy and is useful for determining prognosis. Viral loads >1 × 10^6 copies/mL have been shown to be associated with an increased likelihood of death in HSCT recipients. In addition, in HSCT recipients, early detection of adenovirus viremia by PCR has been used to identify asymptomatic patients who are at risk for progressive adenoviral disease.

**Treatment**

No randomized control trials have demonstrated the benefit of any specific therapy for adenoviral disease. Cidofovir is currently the drug of choice in immunocompromised patients because it has shown to decrease the viral loads. Cidofovir is active against all strains of adenovirus in vitro. However, only retrospective data are available on the effectiveness of cidofovir in HSCT and SOT recipients. Moreover, these studies did not include patients with pneumonia but with different manifestations of the disease showing clinical improvement and increased survival. Because of the risk of nephrotoxicity, this drug should be used with caution. Two regimens are typically used: 5 mg/kg every 1 to 2 weeks, or 1 mg/kg 3 times per week, the latter being associated with less nephrotoxicity.

New orally active ether–ester prodrugs of cidofovir have been developed and have promising results. When tested against 5 adenovirus serotypes, they showed to be 5- to 2500-fold more active than unmodified parent compounds, but they are still under investigation.

Ganciclovir, ribavirin, and foscarnet are not recommended for the treatment of adenovirus infections because they do not have any proven efficacy. In vitro studies have shown a role of ribavirin in the treatment of adenovirus infections. However, clinical data did not confirm this theoretical role.

Adenovirus-specific donor T-cells infusions have been proposed for adoptive transfer of immunity. They have shown to be feasible and effective at preventing adenovirus complications.
Clinical Presentation

HSCT recipients. Cytomegalovirus pneumonia is one of the most common life-threatening infectious complications after transplantation, with an incidence of 10% to 30% in allogeneic HSCT recipients, higher than in autologous HSCT recipients who also usually develop a less severe disease.127

The risk factors for the development of CMV pneumonia include positive serology of the HSCT donor, the use of granulocyte transfusions from seropositive donors, old age, GVHD, total-body irradiation, depleted antithymocyte globulins, the receipt of T-cell-depleted stem cells, and viruria or viremia.126,128 However, the use of leukocyte-depleted platelets and CMV-seronegative red blood cells reduces the risk of development of CMV pneumonitis.129

The mean time to onset of CMV pneumonia is 45 days (range 2 weeks to over 2 years).130 However, with the use of prophylaxis this has been delayed to a median of 169 days (range from 96-184 days).131

Patients with CMV pneumonia presents with rapid onset of fever (94%), nonproductive cough (63%), and dyspnea (50%).132 Hypoxemia is common and mechanical ventilation is frequently required. The severity and outcome of CMV interstitial pneumonia in HSCT recipients can be predicted with a clinical score system that was initially developed for renal transplant patients but has been validated in HSCT recipients (Table 2).133 Fever, cytopenias, superinfection, and involvement of other organs are part of this scoring system in which a value of 8 is the threshold to predict mortality with 100% sensitivity.

The spectrum of radiologic findings in CMV pneumonia is diverse, and it can also present with normal findings on chest X-ray. The most common findings are bilateral asymmetric ground-glass, air-space opacities and small centrilobular nodules.134

Previous reports have shown a high mortality rate of up to 84%.126 Interestingly, a recent autopsy-based study demonstrated that the incidence of fatal pneumonia has decreased from 4% to 0.8% (before and after 1997, respectively).135

SOT recipients. The latest series performed in patients receiving antiviral prophylaxis reported an incidence of CMV pneumonitis of 0% to 9.2% in liver transplant recipients,136 0.8% to 8% in heart transplant recipients,136 and <1% in renal transplant recipients.136

Cytomegalovirus pneumonia is more common in lung transplant than in other transplant recipients. The incidence in this population depends on the use of prophylaxis (10%-55% with routine viral prophylaxis136 to 75%-100% without prophylaxis [75% in CMV D−/R+ and 86%-100% in CMV D+/R−]). In addition, patients who do not receive prophylaxis developed CMV pneumonia between 16 and 60 days after transplant, whereas the use of prophylactic viral agents postponed the development of disease.137 One possible explanation to the high incidence of CMV pneumonia in lung transplant recipients is that the lungs have been found to have a significantly higher

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Attributable Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever &gt;38.3°C</td>
<td>1</td>
</tr>
<tr>
<td>2-20 days</td>
<td>1</td>
</tr>
<tr>
<td>&gt;21 days</td>
<td>3</td>
</tr>
<tr>
<td>Leucopenia (≤4 x 10⁹/L)</td>
<td>1</td>
</tr>
<tr>
<td>Thrombocytopenia (≤4 x 10⁹/L)</td>
<td>1</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>1</td>
</tr>
<tr>
<td>Degree of pulmonary disease</td>
<td>1</td>
</tr>
<tr>
<td>Infiltrate without symptoms</td>
<td>1</td>
</tr>
<tr>
<td>Infiltrate with symptoms</td>
<td>2</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>3</td>
</tr>
<tr>
<td>Gastrointestinal CMV infection</td>
<td>3</td>
</tr>
<tr>
<td>Central nervous system status</td>
<td>1</td>
</tr>
<tr>
<td>Lethargy</td>
<td>1</td>
</tr>
<tr>
<td>Stupor</td>
<td>2</td>
</tr>
<tr>
<td>Coma</td>
<td>3</td>
</tr>
<tr>
<td>Renal status</td>
<td>1</td>
</tr>
<tr>
<td>Creatinine level 2-4 times the best</td>
<td>1</td>
</tr>
<tr>
<td>value after transplantation</td>
<td>2</td>
</tr>
<tr>
<td>Creatinine level &gt;4 times the best</td>
<td>2</td>
</tr>
<tr>
<td>value after transplantation</td>
<td>3</td>
</tr>
<tr>
<td>Nephrectomy or permanent dialysis</td>
<td>3</td>
</tr>
<tr>
<td>Arthritis or muscle wasting</td>
<td>2</td>
</tr>
<tr>
<td>Superinfection</td>
<td>3</td>
</tr>
<tr>
<td>Death</td>
<td>4</td>
</tr>
</tbody>
</table>

Abbreviations: CMV, cytomegalovirus; HSCT, hematopoietic stem cell transplantation.

* A total score of >8 predicts mortality with 100% sensibility and 88% specificity.

in children after HSCT and causing a significant decrease in viral load.124

Prevention/Vaccines/Prophylaxis

Only routine infection control practices are recommended. Contact and droplet precautions should help prevent transmission. No vaccines are available.

Cytomegalovirus Pneumonia

Cytomegalovirus is a DNA herpes virus and the largest virus that infects humans. It causes a wide spectrum of diseases ranging from an asymptomatic state or a mononucleosis-like syndrome to severe disease in immunocompromised hosts.

After the resolution of acute infection, CMV establishes latent infection. In the general population, the proportion of people with evidence of previous CMV infection range from 40% to 100%, depending on ethnicity and country of residence.125 Secondary symptomatic disease can present later in life as reactivation or reinfection with a new strain.
burden of latent viral CMV genome than other organs. In addition, bronchoscopy, which detects subclinical disease, is routinely used in these patients. Cytomegalovirus pneumonia has been found to increase the risk of bronchiolitis obliterans. Combined CMV prophylaxis with ganciclovir and immunoglobulin has been shown to reduce the incidence of acute rejection and lymphocytic bronchitis/bronchiolitis, the main risk factor for chronic rejection.

Patients with CMV pneumonitis are asymptomatic in 10% to 15% of cases. When it is symptomatic, patients can develop 2 different clinical syndromes. One syndrome involves mild-to-moderate disease with cough, fever, and impaired oxygenation that does not require ventilatory support and that develops over several days. It is most common in seropositive (partially immune) patients and responds to antiviral therapy over 4 to 7 days. The second clinical syndrome—rare because of the use of prophylaxis—has a rapid onset of symptoms including hypoxia and is more common in D+/R− patients. It has a slower response to treatment and a higher mortality rate. The widespread use of prophylaxis has decreased the mortality rate in this population, which was reported to be 54% to 100%. However, this has led to the emergence of ganciclovir-resistant strains that are found in nearly 10% of lung transplant recipients, despite preemptive antiviral therapy, and are more common among D+/R− patients.

Heart transplant patients have a reported incidence of CMV pneumonia of 0.8% to 8%. Dry cough or hypoxia can be the first sign or symptom, usually starting gradually. Heart-lung transplant patients have a similar presentation; in these patients, CMV pneumonia is associated with a high mortality (32%) and abnormal lung function after resolution of the disease.

Renal transplant recipients have a low incidence of CMV pneumonia (<1%), and it may occur more than 6 months after transplantation. Risk factors include antilymphocyte induction, D+/R− status, and immunosuppressive regimens with tacrolimus and mycophenolate mofetil rather than cyclosporine. A correlation exists between CD4+ and CD8+ T lymphocytes levels and outcome in patients who develop acute respiratory distress syndrome (ARDS) secondary to CMV pneumonia. Sun et al found that patients who survived had increasing levels of CD4+ and CD8+ T lymphocytes during infection, whereas patients who died had levels of zero at the time of death. Serial PCR CMV-DNA of plasma levels may be predictive of CMV pneumonia. Viral loads of >10⁴ copies/mL plasma continuing for 3 weeks were found to be a cutoff to predict CMV pneumonia.

In liver transplant recipients, the incidence of CMV pneumonia is 9.2%; it is diagnosed at a median of 38 days after transplantation. It usually presents concomitantly with CMV hepatitis. D+/R− CMV serologic status, CMV viremia, abdominal re-exploration after transplantation, and invasive fungal disease are independent predictors of CMV pneumonia. The 1-year mortality rate is 84.6% at a median of 17 days after diagnosis.

HIV patients. In patients with AIDS, CMV is the most common viral opportunistic infection; CMV disease had a prevalence of 21% to 44% before highly active antiretroviral therapy. Cytomegalovirus retinitis is the most common form of CMV disease followed by polyradiculopathy and gastrointestinal disease. The connotation of CMV pneumonia in HIV-infected patients is not clear. Histological evidence of CMV lung infection was found in 57% to 81% of patients at autopsy, but it was often not the only pathogen, implying that it is not common at least until the late stages of HIV disease.

Patients having HIV with CMV pneumonia present with cough, dyspnea, fever, and hypoxemia. Elevated lactate dehydrogenase levels are seen. Pleural effusions have been found in 33% of patients. Salomon et al demonstrated that CD4 counts ≤12 cells/mL have been associated with the development of CMV pneumonia.

Cytomegalovirus pneumonia treatment is recommended in patients with HIV when CMV is the sole pathogen and when there is symptomatic disease. Some studies have found that treatment does not result in improved survival or outcome when other pathogens are present.

Other immunosuppressed hosts. There have been isolated reports of CMV pneumonia in other immunosuppressed patients, and usually with fatal outcome. In these patients, CMV pneumonia is associated with the use of high-dose corticosteroids either alone or as part of a more potent immunosuppressive regimen for the treatment of different diseases such as ulcerative colitis (high-dose steroids and leukocytapheresis), metastatic breast cancer (chemotherapy and systemic corticosteroids), and connective tissue diseases such as dermatomyositis (azathioprine, prednisolone, and cyclosporine), systemic lupus erythematosus (prednisolone and cyclophosphamide), and mixed connective tissue diseases (steroids and methotrexate). It is not known whether corticosteroids alone can predispose to CMV because an early study failed to isolate CMV from any patient receiving corticosteroids alone compared with patients receiving steroids and other cytoxic immunosuppressive drugs.

In patients with lymphoma, CMV pneumonia is the most common presentation of CMV disease (82%) and is more common in patients with non-Hodgkin lymphoma (89%). From 1997 to 2003, the incidence of CMV pneumonia increased in this population. The CMV pneumonia-attributed mortality rate was 30%, and a multivariate analysis showed that a high APACHE score (>16) at onset of infection and antiviral toxicities were independent predictors of death.

Diagnosis

The diagnosis of CMV pneumonia involves a compatible clinical picture, radiographic findings, and detection of CMV in BAL fluid or lung-tissue specimens by culture, cytology, immunohistochemical staining, histopathology examination, or in situ hybridization.
The identification of CMV in BAL fluid is highly correlated with its detection in lung biopsies and should be the preferred method of diagnosis. However, BAL fluid cultures are not sensitive or specific for the diagnosis of CMV pneumonia. Immunohistochemistry staining is superior to routine histopathology in the diagnosis of CMV pneumonia.

In HSCT recipients, PCR has been found to be the most sensitive assay for detecting CMV in BAL fluid. The sensitivity of alveolar cell immunostaining and PCR were 100% for the diagnosis of CMV pneumonia and the sensitivity of viral culture was only 85.7%. In lung transplant recipients, a high CMV viral load in BAL fluid was strongly associated with CMV pneumonia. In another study, quantitation of CMV (ie, determination of the viral load) in BAL and blood samples was used to discriminate between patients with and without CMV pneumonia.

In HSCT recipients, CMV antigenemia has been found to predict the development of CMV pneumonia.

**Treatment**

The current, marketed systemic antivirals against CMV include ganciclovir, foscarnet, and cidofovir. The standard therapy for CMV pneumonia is ganciclovir combined with high-dose immunoglobulin. However, this treatment has not been evaluated in a randomized controlled trial. A recent study has questioned whether the use of immunoglobulin improves outcome; however, its use is still recommended by experts. The use of ganciclovir is limited by the associated development of neutropenia. Foscarnet is used off-label in patients who experience myelosuppression with ganciclovir. However, its use is associated with nephrotoxicity and electrolyte imbalances (hypokalemia, hypocalcemia, hypomagnesemia, and hypophosphatemia). Cidofovir’s side effects include nephrotoxicity and occasionally neutropenia.

The emergence of resistance is another limitation of ganciclovir use. Resistance develops from mutations in UL97 (phosphotransferase), UL54 (viral DNA polymerase), or both, whereas cidofovir and foscarnet resistance results from mutations in UL54 only.

**Prevention/Vaccines/Prophylaxis**

One of the main goals of management is to prevent the development of CMV disease through the early detection of CMV DNA in plasma using PCR assays or CMV antigenemia. Antiviral therapy when given immediately after the detection of CMV in plasma can prevent the development of end-organ disease (preemptive therapy) and decrease mortality. However, some authors favor the use of prophylaxis. Valganciclovir, an oral prodrug of ganciclovir but with a 10-fold greater bioavailability than oral ganciclovir, is used as prophylaxis in high-risk kidney, heart, or pancreas transplant recipients. In a randomized double-blind study, ganciclovir has been shown to be more effective than valganciclovir in preventing CMV pneumonia in the first 100 days posttransplantation. Maribavir, a benzimidazole riboside with an unnatural L-sugar moiety that inhibits UL 97 kinase, an early viral gene product involved in viral DNA elongation, DNA packaging, and egress or shedding of capsids from viral nuclei, showed in a prophylactic study (phase II) to reduce the incidence of CMV infection without the potential side effect of myelosuppression of ganciclovir, providing promising results in the future management of CMV disease. However, phase III preliminary analysis failed to show any significant difference between maribavir and placebo in reducing the rate of CMV within 180 days posttransplant (Tables 3 and 4).

**Other Viruses**

**Herpes Simplex Virus Pneumonia**

Herpes simplex virus is a DNA virus that is associated with a wide variety of illnesses, including mucocutaneous infections, central nervous system infections, and visceral organs infections. Both, HSV types 1 and 2 have been reported to cause pneumonia. However, it is difficult to distinguish between asymptomatic shedding of the virus and disease.

In a cohort of 20 patients with autopsy-confirmed HSV pneumonia, 16 were HSCT recipients and all developed pneumonia within 2 months after transplantation. Twelve were neutropenic at the time of infection. Cough, dyspnea, and fever were the most common symptoms. All patients died of respiratory failure.

In a series of liver transplant patients with pneumonia, 6 cases of HSV-1 pneumonia were found. All 6 patients were treated with intravenous acyclovir, mechanical ventilation, and reduced immunosuppression with no HSV-1-attributable mortality.

In patients with cancer and solid tumors, the clinical manifestations of HSV pneumonia are nonspecific. Fever is seen in 44% of cases; other manifestations include dyspnea, pleuritic chest pain, and cough. Radiologic findings vary and include alveolar infiltrates (71%), interstitial infiltrates (16%), and even nodular infiltrates (9%). Cavitations and ARDS are rare. Having proven HSV pneumonia by positive cytopathic effect in BAL cytology appeared to be significantly associated with increased length of stay and mechanical ventilation. This subset of patients seems to benefit from acyclovir therapy.

**Varicella-Zoster Virus Pneumonia**

Varicella-zoster virus is 1 of the 8 DNA herpes viruses that infect humans and has a worldwide distribution. It causes 2 clinical forms of diseases: primary infection or chicken pox usually in children and reactivation or shingles in adults. Infecting particles can be found in secretions of the upper airways and fluid from the vesicles.

The virus can spread to different visceral organs causing hepatitis, pneumonitis, pancreatitis, small bowel obstruction, and encephalitis. Immunocompromised hosts are at risk of these complications. Graft versus host disease is a predictor of VZV dissemination. Primary VZV infection is more likely to cause pneumonia. Therefore, dissemination to the
Table 3. FDA-Approved Indication, Mechanism of Action and Common Side Effect of Available Antiviral Agents

<table>
<thead>
<tr>
<th>Antiviral Agent</th>
<th>FDA-Approved Indication</th>
<th>Mechanism of Action</th>
<th>Common Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valganciclovir</td>
<td>CMV retinitis in AIDS patients, prophylaxis</td>
<td>Inhibits DNA polymerase</td>
<td>Hematologic toxicities, gastrointestinal adverse effects</td>
</tr>
<tr>
<td></td>
<td>CMV infection in high-risk kidney, heart, or pancreas transplant patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>CMV retinitis, prophylaxis</td>
<td>Inhibits DNA polymerase</td>
<td>Hematologic toxicities, neurologic toxicity, abnormal liver function tests, fever, rash</td>
</tr>
<tr>
<td></td>
<td>CMV infection in transplant recipients at risk of CMV disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acyclovir</td>
<td>Treatment and prophylaxis of HSV infections</td>
<td>Inhibits DNA polymerase</td>
<td>Acute renal failure, neurologic toxicity</td>
</tr>
<tr>
<td>Famciclovir</td>
<td>Management of acute Herpes zoster and treatment of recurrent HSV infections</td>
<td>Inhibits DNA polymerase</td>
<td>Similar to acyclovir</td>
</tr>
<tr>
<td>Valacyclovir</td>
<td>Treatment of herpes zoster infections</td>
<td>Inhibits DNA polymerase</td>
<td>Thrombotic thrombocytopenic purpura</td>
</tr>
<tr>
<td>Cidofovir</td>
<td>CMV retinitis in patients with AIDS</td>
<td>Inhibits DNA polymerase</td>
<td>Nephrotoxicity, hematologic adverse effects</td>
</tr>
<tr>
<td>Foscarnet</td>
<td>HSV; CMV retinitis in patients with AIDS</td>
<td>Inhibits DNA polymerase</td>
<td>Nephrotoxicity, electrolyte imbalance (hypocalcemia), seizures, anemia.</td>
</tr>
<tr>
<td>Amantadines (amantadine, rimantadine)</td>
<td>Treatment of influenza A infections&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Inhibits the uncoating process preventing penetration of virus into the host</td>
<td>Nervousness, anxiety, difficulty concentrating, light-headedness, nausea, anorexia</td>
</tr>
<tr>
<td>Zanamivir and oseltamivir</td>
<td>Prophylaxis and treatment of influenza A and B infections</td>
<td>Inhibits virus neuraminidase</td>
<td>Diarrhea, nausea, vomiting, headache, neuropsychiatric events in children. Additionally zanamivir can cause cough and bronchospasm</td>
</tr>
<tr>
<td>Ribavirin (aerosolized)</td>
<td>RSV in immunocompromised children</td>
<td>Inhibits RNA polymerase activity</td>
<td>Fatigue, headache, bronchospasm, insomnia, nausea, anorexia, hemolytic anemia, teratogenic</td>
</tr>
</tbody>
</table>

Abbreviations: CMV, cytomegalovirus; AIDS, acquired immune deficiency syndrome; DNA, deoxyribonucleic acid; HSV, herpes simplex virus; RSV, respiratory syncitial virus; RNA, ribonucleic acid; CDC, Center for disease control and prevention.

<sup>a</sup> Currently not recommended by the CDC for influenza A H3N2 isolates because of the high level of resistance. However, it is recommended in combination with oseltamivir for influenza A (H1N1) oseltamivir-resistant viruses.
lungs is higher in children with primary varicella (50\%) than in patients with herpes zoster (5\%).\textsuperscript{184} Data in children demonstrated that the best predictor of pneumonitis is the absolute lymphocyte count (ALC) at the onset of infection and the risk of mortality increases with lower ALCs.\textsuperscript{184}

Rash precedes VZV pneumonia in HSCT or SOT recipients.\textsuperscript{185} Chest radiographs show nodular or interstitial infiltrates. Additionally, marked mediastinal adenopathy and interlobular septal thickening has been reported in lung transplant patients.\textsuperscript{186}

Intravenous acyclovir is the treatment of choice. Although infrequent, if there is no response or suspicious of resistance, forcarnet can be used.\textsuperscript{187}

### Rhinovirus Pneumonia

Rhinovirus, an RNA picornavirus, is responsible for one third to half of episodes of the common cold in adults\textsuperscript{188} but can also invade the lower respiratory tract causing pneumonia or triggering asthma exacerbations.

One of the first studies on rhinovirus infections in adult HSCT recipients found that 32\% of patients developed fatal pneumonia after rhinovirus infection.\textsuperscript{189} All had profound respiratory failure. Autopsies revealed a co-pathogen in 1 case only (\textit{Aspergillus} species); the others had histological findings of interstitial pneumonitis and/or ARDS. Another more recent European study confirmed these findings; 55\% of HSCT recipients with rhinovirus infections developed pneumonia, the attributable mortality rate was 33\%.\textsuperscript{190}

The latest study of community-acquired pneumonia among immunocompromised patients found that rhinovirus was responsible for 12\% of cases being the most common virus isolated,\textsuperscript{2} with a mortality rate of 18\% suggesting that it may have been an underappreciated pathogen.

New diagnostic methods such as the use of PCR may aid in the diagnosis of rhinovirus infection. Unfortunately, no effective antiviral treatment exists as of yet.

### Enterovirus Pneumonia

Enteroviruses are single-stranded RNA viruses of the family Picornaviridae that are enterically transmitted from person to person. Polioviruses are the prototypic and cause paralytic poliomyelitis. The nonpolio enteroviruses have a wide spectrum of manifestations depending on the host. In immunocompromised patients, central nervous system infections, a dermatomyositis-like syndrome, and chronic hepatitis are the most common.

In a prospective cohort of respiratory tract infections in patients with hematologic malignancies, 9 (3\%) cases of

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<table>
<thead>
<tr>
<th>Virus</th>
<th>Treatment</th>
<th>Prevention and/or Infection Control Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza virus</td>
<td>Oseltamivir: 75 mg PO bid times 5-10 days Zanamivir: 2 inhalations (2 times 5 mg) bid times 5-10 days</td>
<td>Contact and respiratory droplet isolation (gloves, gown, and mask); vaccination</td>
</tr>
<tr>
<td>Parainfluenza virus</td>
<td>No treatment available</td>
<td>Contact and respiratory droplet isolation (gloves, gown and mask)</td>
</tr>
<tr>
<td>Respiratory syncytial virus</td>
<td>Ribavirin: 6 g inhaled delivered over 18 hours each day or 2 g inhaled for 3 hours every 8 hours with palivizumab 15 mg/kg IV or IVIG 500 mg/kg every other day</td>
<td>Palivizumab: 15 mg/kg IV q month or IVIG 500 mg/kg every other day for 5 to 7 doses; contact and respiratory droplet isolation (gloves, gown, and mask)</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>Cidofovir: 5 mg/kg IV q weeks times 2, then q 2 weeks IV prehydration: probenecid must be used with each infusion</td>
<td>Contact and respiratory droplet isolation (gloves, gown, and mask)</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Ganciclovir: 5 mg/kg IV q 12 hours (induction); 5 mg/kg IV q 24 hours (maintenance); or Foscarnet: 90 mg/kg IV q 12 hours (induction); 90 mg/kg IV q 24 hours (maintenance)</td>
<td>Ganciclovir 5 mg/kg IV q 24 hours or Foscarnet 90 mg/kg IV q 24 hours or Valacyclovir 2 g 4 times daily; valgancyclovir 900 mg PO daily; standard infection control measures</td>
</tr>
<tr>
<td>Herpes simplex virus and varicella virus</td>
<td>Acyclovir: 10 mg/kg IV q 8 hours</td>
<td>Valacyclovir 500 mg bid; famciclovir 250 mg bid; contact and respiratory droplet isolation (gloves, gown, and mask) for varicella virus infections</td>
</tr>
</tbody>
</table>

Abbreviations: PO, by mouth; bid, twice a day; IV, intravenous; IVIG, intravenous immune globulin.

\* The treatment recommendations above are based on evidence III-A, except for cytomegalovirus treatment (II-A for ganciclovir, but III-A for foscarnet).\textsuperscript{6,8,16,51,52,81,117,121,179}

\* There is no specific treatment available for rhinovirus, enterovirus, coronavirus, or metapneumovirus pneumonia except supportive measures.
enterovirus infection were found (6 in HSCT recipients) of which 2 developed pneumonia. Another study performed in Spain on HSCT recipients, described 4 cases of enterovirus pneumonia. Three patients were neutropenic and 2 developed ARDS. Radiologic imaging demonstrated alveolar infiltrates in all cases. The mortality rate was 75%, revealing that enteroviral pulmonary infections may be a cause of severe pneumonia in immunocompromised hosts. The role of enterovirus in SOT recipients is unknown. Currently, no standard treatment is available.

**Coronavirus Pneumonia**

Coronaviruses are enveloped RNA viruses that are primarily respiratory pathogens but can also cause diarrhea and have been recently associated with demyelinating central nervous system diseases. Overall, they are estimated to cause 15% of common colds in adults. Four strains exist that can cause diseases in humans: HuCoV-OC43 and HuCoV-229E (associated with common colds), SARS-CoV (produces life-threatening severe acute respiratory syndrome), and HCoV-NL63 (associated with lower respiratory tract infections).

The most recent series of cases of coronavirus infections found a mean infection rate of 8.8% among immunocompromised patients, statistically significantly different from immunocompetent hosts (4.5%), but no patients developed pneumonia. There are no large series of coronavirus pneumonia in immunocompromised patients, but a few case reports. Folz et al reported the case of a young woman who developed fever, sore throat, cough, and severe hypoxia after autologous HSCT. She was diagnosed with coronavirus pneumonia by electron microscopic examination from BAL fluid and recovered successfully without any adjuvant treatment. Kumar et al described a liver transplant recipient who contracted SARS during an outbreak and died with subsequent transmission of infection to family members and several health care workers. A higher concentration of SARS-CoV was found in this patient’s tissue compared with the other immunocompetent patients, which could explain the fatal outcome. No specific treatment is available for coronavirus infections.

**Metapneumovirus Pneumonia**

Human metapneumovirus, a new member of the Paramyxoviridae family in the genus *Metapneumovirus*, was recently discovered in 2001. It is an enveloped RNA virus that causes upper and lower respiratory tract infection in all age groups. It appears to have a seasonal variation most common in late winter and early spring in the United States.

A total of 6 cases of human metapneumovirus (hMPV) infection were identified in 688 patients who underwent bronchoscopy. Of them, 4 (66%) were immunocompromised. All presented with fever, cough, dyspnea, and wheezing. Pathology of the lung tissue samples showed acute and organizing injury, and smudge cell formation.

Metapneumovirus infection was found in 9% of patients with hematologic malignancies, 73% of whom were HSCT recipients. Nine patients developed pneumonia with an associated mortality rate of 33%. In another study of HSCT recipients, human metapneumovirus was detected in 3% of BAL specimens. These patients became symptomatic within the first 40 days after transplantation with fever, cough, nasal congestion, and sore throat and were later complicated with respiratory failure, pulmonary hemorrhage, and culture-negative septic shock. The mortality rate was 80%. Radiographic findings varied from diffuse bilateral alveolar and interstitial infiltrates to emphysema without infiltrates.

Metapneumovirus was found in 25% of lung transplant recipients. All patients developed pneumonia, 44% of them had proven acute rejection and 33% died.

No established treatment exists for metapneumovirus pneumonia. In vitro studies have shown that intravenous immunoglobulin neutralizes human metapneumovirus and that ribavirin has antiviral activity. Raza et al recently reported the case of a lung transplant recipient who presented with respiratory failure and sepsis syndrome secondary to hMPV pneumonia that was successfully treated with intravenous ribavirin.

**Conclusion**

Viruses have become an important etiology of community-acquired and hospital-acquired pneumonia in immunocompromised patients and cause significant morbidity and mortality in this population. Newer molecular techniques have allowed us to discover new viral etiologies of pneumonia, expanding the spectrum of possible etiologies. However, large prospective studies are still needed to understand the role of newly discovered viruses. Although new diagnostic tests have become available, there is still a need for a sensitive, specific, cost-effective test that would allow us to perform earlier and faster diagnosis which is the key to a good clinical outcome. Treatment options for viral pneumonia are limited and their benefit in the treatment of pneumonia remains to be studied in randomized control trials. Therefore, preventive measures such as vaccination, preemptive, and prophylactic antivirals as well as infection control measures are the cornerstone of preventing disease transmission to susceptible hosts and decreasing the morbidity and mortality rates associated with viral pneumonia.

**Declaration of Conflicting Interests**

The author(s) declared no conflicts of interest with respect to the authorship and/or publication of this article.

**Funding**

The author(s) received no financial support for the research and/or authorship of this article.
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