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Viral Pneumonia and Acute Respiratory Distress Syndrome

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INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a severe form of inflammatory lung injury characterized by increased vascular permeability in the lung. Clinically, ARDS is defined by the presence of severe hypoxemia and bilateral opacities on chest imaging that are not explained by the presence of cardiac failure or volume overload. Community-acquired pneumonia (CAP) is the most common cause of ARDS that develops outside of the hospital. Respiratory viruses are increasingly recognized in patients with severe community-acquired pneumonia and acute respiratory distress syndrome (ARDS). Pandemic and seasonal respiratory viral infections have been implicated in the pathogenesis of ARDS in adults. Supportive care for adults with ARDS caused by respiratory viruses is similar to the care of patients with ARDS from other causes. Antiviral therapy is available for some respiratory viral infections; however, further research is needed to determine which groups of patients would benefit.

EPIDEMIOLOGY

Improved diagnostic testing, particularly multiplex reverse transcription polymerase chain reaction (RT-PCR) assays, have increased recognition that respiratory viruses cause critical illness in adults. Although no studies have reported the incidence of ARDS specifically caused by viral pneumonia, epidemiologic surveys of adults admitted to the intensive care unit (ICU) with pneumonia and respiratory failure suggest that respiratory viruses are a common cause of severe pneumonia. Community-acquired pneumonia (CAP) is the most common cause of ARDS that develops outside of the hospital. Respiratory viruses are increasingly recognized in patients with severe CAP and ARDS. This article reviews the epidemiology, diagnosis, and management of adult patients with severe pneumonia and ARDS caused by viral respiratory pathogens.

KEYWORDS

• Acute respiratory distress syndrome • Respiratory virus • Community-acquired pneumonia

KEY POINTS

• Respiratory viruses are increasingly recognized in patients with severe community-acquired pneumonia and acute respiratory distress syndrome (ARDS).
• Pandemic and seasonal respiratory viral infections have been implicated in the pathogenesis of ARDS in adults.
• Supportive care for adults with ARDS caused by respiratory viruses is similar to the care of patients with ARDS from other causes.
• Antiviral therapy is available for some respiratory viral infections; however, further research is needed to determine which groups of patients would benefit.

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these series, influenza virus and rhinovirus were the most commonly detected respiratory viruses, identified in approximately 6% and 8% of cases of viral pneumonia respectively. The prevalence of identified bacterial coinfection was low, and in 1 series the mortalities related to bacterial and viral pneumonia were comparable.

Epidemiologic studies have shown that respiratory viruses are an underappreciated cause of severe CAP. However, the results of these studies should be interpreted with caution for several reasons. First, the viruses most commonly detected in patients with CAP vary across reports, which likely reflects differences in patient populations, season, and geographic location. Although respiratory viruses are commonly detected in critically ill patients using RT-PCR, their role in the pathogenesis of severe pneumonia and ARDS is less clear. Respiratory viruses may be the sole cause of CAP and ARDS in some patients, or may be a risk factor predisposing patients to infections with other organisms, or may also represent concurrent upper respiratory tract infection, colonization, or prolonged viral shedding.

PATHOGENESIS

The pathogenesis of ARDS in patients infected with respiratory viruses is incompletely understood. Most adults with respiratory viral infections have mild symptoms. However, viral strains associated with ARDS, such as the 2009 pandemic influenza A virus strain, are identical to those seen in mild cases. A combination of variable host factors and the host immune response therefore likely leads to the development of severe pneumonia and ARDS. Detailed review of the pathologic mechanisms implicated in the development of ARDS caused by respiratory viruses is beyond the scope of this article, but several excellent reviews on this topic exist. Respiratory viruses initially infect the nasal and bronchial epithelium. This point of entry leads to respiratory airway and alveolar endothelial injury, elaboration of cytokines and chemokines, and recruitment of both innate and adaptive immune cells. Specific cytokine profiles vary by virus, but converge on a common end pathway, resulting in the pathologic hallmark of ARDS, diffuse alveolar damage. The mechanisms of acute lung injury caused by viral pathogens have important clinical implications: if ARDS results from the inflammatory host response rather than viral-mediated injury, then antiviral therapy alone may not be central to resolution of lung injury.

GENERAL APPROACH TO VIRAL PNEUMONIA AND ACUTE RESPIRATORY DISTRESS SYNDROME

Diagnosis

The diagnosis of ARDS should be considered in all patients with respiratory viral infection, hypoxemia, and bilateral opacities on chest radiography unless there is strong clinical suspicion for cardiogenic pulmonary edema or volume overload. Criteria for diagnosing ARDS, referred to as the Berlin criteria, are listed in Box 1. In resource-limited settings, diagnostic testing to ensure that patients meet each criterion, such as echocardiography or arterial blood gas analysis, may not be possible. In such situations, any patient with hypoxemia and bilateral opacities on chest radiography should be considered to have ARDS unless strong clinical suspicion for cardiogenic pulmonary edema or volume overload is present.

Diagnosis of respiratory viruses can be made using isolation of intact virus particles from cell culture, viral antigen detection by immunofluorescence, or multiplex RT-PCR. When available, multiplex RT-PCR provides more rapid diagnosis with equal or better sensitivity and specificity compared with viral culture and immunofluorescence testing. Multiplex RT-PCR testing using specimens collected from nasopharyngeal (NP)
aspirate or BAL have higher sensitivity compared with nasal swab. Studies comparing BAL and NP aspirate have not shown one method to be superior to the other. The optimal site of sampling depends on the particular respiratory virus, incubation time, and the duration of symptoms. For patients with viral pneumonia in whom bronchoscopy can safely be performed, the combination of RT-PCR testing from NP plus BAL specimens may increase the diagnostic yield compared with NP testing alone.37,38

**Treatment**

In additional antiviral therapy, special attention should be paid to ventilator management and other supportive care. Similar to ARDS of any other cause, patients who require invasive mechanical ventilation should be treated with a low-tidal-volume strategy targeting 6 mL/kg of ideal body weight.39-41 In cases of severe ARDS, consideration should be given to salvage therapies, including prone positioning and paralytic therapy for the first 48 hours following intubation.42-44 Although noninvasive positive pressure ventilation has been tried in patients with ARDS, reports from the 2009 H1N1 pandemic suggest that this strategy is not effective in patients with ARDS caused by influenza.47 Patients with severe viral infection are at risk for secondary bacterial pneumonia, because of both the effects of the virus alone and the risk of ventilator-associated pneumonia from prolonged mechanical ventilation.48,49 Invasive tests, such as bronchoscopy, may be helpful to differentiate bacterial infection from viral pneumonia alone.50 In general, the empiric use of antibiotic therapy in patients with viral pneumonia should be avoided and may increase the risk of antibiotic resistance and subsequent nosocomial infection.51,52 The use of intravenous corticosteroids in the treatment of ARDS has generally not improved outcomes.53,54 In patients with ARDS related to influenza and severe acute respiratory syndrome (SARS), adjunctive corticosteroids have not improved outcomes and may increase the risk subsequent nosocomial infection.55,56

Extracorporeal membrane oxygenation (ECMO) gained attention during the 2009 H1N1 influenza pandemic after several studies reported low mortality in patients with viral ARDS treated with this modality.57,58 The only randomized clinical trial that compared ARDS treatment with ECMO with conventional care, the CESAR trial, enrolled a significant proportion of patients with influenza.59 However, this trial had several significant methodological limitations; in particular, more patients in the ECMO arm were treated with a low-tidal-volume ventilation strategy compared with patients in the conventional arm. In a retrospective matched cohort study of patients with influenza A (H1N1) and ARDS, the mortality in patients treated with ECMO was similar to propensity score–matched controls not treated with ECMO.60

**PANDEMIC VIRUSES**

Over the past 15 years, 3 respiratory viruses have attracted special attention because of the high proportion of affected patients who develop critical illness and ARDS: influenza, particularly influenza A H1N1 2009; and 2 novel coronaviruses, Middle Eastern respiratory syndrome coronavirus (MERS-CoV) and SARS coronavirus (SARS-CoV).

**Influenza Virus**

Influenza A virus is the most frequently described cause of viral pneumonia and ARDS in adult patients.61 Influenza A virus has a wide variety of hosts and antigenic subtypes; this genetic diversity allows the virus to cause annual epidemics, as well as occasional pandemics. By contrast, humans are the primary host for influenza B and the virus relies mainly on genetic drift to propagate epidemics.62

Influenza causes seasonal epidemics during the winter months in the northern and southern hemispheres, and year-round in the tropics.63 Seasonal influenza is a self-limited infection in the general population, with an average annual mortality of 1.4 to 16.7 deaths per 100,000 persons. In the United States, seasonal influenza accounts for an estimated 18,491 to 95,390 ICU admissions yearly.64 Adults greater than 65 years of age, residents of nursing homes and chronic care facilities, pregnant women, patients with chronic medical conditions, immune-compromised individuals, and obese patients are at higher risk for more severe disease and death.55,66

In 2009, a novel H1N1 strain of influenza A virus was detected in the western United States and Mexico, and quickly spread globally, triggering the first influenza pandemic since 1968.67 The new strain caused a range of clinical syndromes in humans, ranging from mild self-limited illness to fulminant pneumonia and ARDS.57,68,69 During the 2009 pandemic in the United States, approximately 275,000 hospitalizations and in excess of 12,000 deaths were attributed to the 2009 H1N1 virus.70 ICU admission occurred in 9% to 31% of hospitalized adults, and 14% to 47% of critically ill adults died.71 Risk factors for poor outcomes in hospitalized patients with H1N1 were age less than 5 years, pregnancy (especially during the
third trimester), chronic medical illness, morbid obesity, and immune suppression.72

In adults with influenza virus, the principal clinical syndrome leading to ARDS is viral pneumonitis and severe hypoxemic respiratory failure, sometimes accompanied by shock and acute renal failure.28,67 This syndrome accounted for most of the ICU admissions during the 2009 pandemic.47,69,73 The radiographic presentation of influenza-induced ARDS is similar to ARDS of any other causes. On computed tomography scan of the chest, influenza classically presents with bilateral ground glass opacities, but areas of the alveolar consolidation and air bronchograms are also common.74 Bacterial and viral coinfection is common, particularly in patients greater than 65 years of age, and can complicate up to 34% of cases.75 Radiographic findings typical of bacterial pneumonia, such as alveolar consolidation or air bronchograms, are not specific enough to confirm or exclude the presence of secondary bacterial pneumonia.76 Other important complications of influenza in critically ill patients include venous thromboembolism, myocarditis, rhabdomyolysis, and neurologic manifestations (confusion, seizures, unconsciousness, encephalopathy, quadriaparesis, andencephalitis),77,78

The neuraminidase inhibitors, oseltamivir and zanamivir, are the mainstay of treatment of patients with influenza. Early administration of antiviral therapy may decrease progression to critical illness in hospitalized patients.71

Typical dosing of oseltamivir is 75 mg twice daily; however, optimal dosing and duration of oseltamivir therapy in patients with ARDS is not known. Treatment failure, as shown by persistent influenza detection in BAL samples of critically ill adults, was frequently reported during the H1N1 pandemic with standard-dose oseltamivir.67 Two clinical trials comparing oseltamivir 75 mg twice a day with 150 mg twice a day did not show any significant difference in clinical outcomes, but the proportion of critically ill subjects enrolled in each trial was low.79,80 The authors recommend administration of a higher dose of oseltamivir of 150 mg twice daily for up to 10 days for treatment of H1N1 or H5N1 influenza, and this dose should be considered for patients with ARDS related to seasonal influenza virus.

Zanamivir is available as an inhaled powder or intravenous therapy.81 Zanamivir is generally well tolerated but has not been extensively studied in critically ill adults. The inhaled powder should be avoided in patients with obstructive airways disease because it may provoke bronchospasm. The use of nebulized zanamivir in mechanically ventilated patients has been associated with ventilator dysfunction caused by the lactose carrier.82 During the 2009 H1N1 pandemic, sporadic reports of oseltamivir resistance were reported caused by a mutation in viral neuraminidase; these cases can be treated with intravenous zanamivir.83 Evidence for the use of adjuvant corticosteroid therapy in patients with influenza infection and ARDS is largely based on retrospective studies form the H1N1 pandemic, and is conflicting. Several studies have shown an increased risk of nosocomial infection and mortality.55,84,85 However, 1 study showed a reduction in the need for mechanical ventilation in patients with hematopoietic stem cell transplant hospitalized with H1N1 influenza.86 The authors recommend against the routine use of corticosteroid therapy in patients with influenza pneumonia and ARDS.

Middle Eastern respiratory syndrome coronavirus

MERS-CoV is a novel lineage B coronavirus first identified in Saudi Arabia in 2012.87,88 Since then, sporadic cases and outbreaks have been reported in people living in or recently traveling to the Arabian Peninsula.89 MERS-CoV infects both humans and camels via the CD26 receptor present on nonciliated bronchial epithelial cells found in the lower respiratory tract.90,91 Median incubation time of the virus is 5 to 6 days, but can be as long as 14 days.92 MERS-CoV should be suspected in patients with an acute febrile respiratory illness or CAP who live in or have recently traveled to the Arabian Peninsula. Clinically, patients with MERS-CoV can present with a range of symptoms from mild upper respiratory symptoms to severe pneumonia, acute renal failure, and ARDS.93 Gastrointestinal complaints, including diarrhea and abdominal pain, are common and may precede the onset of respiratory symptoms.94 In one case series of 47 hospitalized patients with laboratory-confirmed cases of MERS-CoV, 42 (89%) needed intensive care and 34 (72%) required mechanical ventilation.95 The reported mortality in most case series exceeds 50%.95,96

Most hospitalized patients with MERS-CoV have abnormal chest radiograph (CXR) or computed tomography findings consistent with infectious pneumonia, most commonly bilateral and subpleural ground-glass opacities, although lobular consolidation has also been described.97 In one series, microbiologic evidence from blood and respiratory samples of bacterial, viral, or fungal coinfection was not found in any patient, suggesting that MERS-CoV was the sole organism responsible for respiratory failure and ARDS.98 Diagnosis is made using RT-PCR obtained from
an NP, lower respiratory, or serum specimen. In patients presenting with lower respiratory symptoms or severe illness, RT-PCR testing from a lower respiratory source, such as sputum, endotracheal aspirate, or BAL, is more sensitive than testing from an upper respiratory source.

Treatment of SARS-CoV is supportive, and to date there are no prospective clinical trials of any specific treatment intervention. Glucocorticoids have been used as adjuvant therapy in patients with severe MERS-CoV; however, there is no clear evidence that this practice improves outcomes. Combination antiviral therapy with high-dose interferon alpha-2b and ribavirin administered shortly after inoculation of MERS-CoV in rhesus macaques showed a decrease in viral replication and radiographic evidence of pneumonia. A retrospective cohort study of 20 patients with MERS-CoV treated with combination interferon alpha-2b and ribavirin initiated a median of 3 days after diagnosis found reduced 14-day mortality compared with 24 patients treated with supportive care alone. In 2015, a MERS-CoV antibody, LCA60, was isolated from memory B cells of a human patient previously infected with the virus. This antibody has the potential to be used for postexposure prophylaxis and treatment of MERS-CoV, but data for its efficacy in human patients are lacking.

**Severe acute respiratory syndrome coronavirus**

SARS-CoV was discovered in 2002 during an outbreak of 300 cases of rapidly progressive pneumonia in the Guoduong Province of China. Between 2002 and mid-2004, a total of 8096 cases of SARS were reported, with a case fatality rate of 9.6%. The animal reservoir for SARS is not known, although both palm civets and bats have been implicated. During epidemics, SARS spread from person to person by respiratory droplets, and to a lesser extent by airborne and fecal-oral transmission. Because of increased transmission by close physical proximity, SARS was frequently contracted by health care workers caring for hospitalized patients.

The pathogenesis of SARS is incompletely understood, but is likely related to both viral infection and immunopathologic injury. The functional receptors for SARS coronavirus are angiotensin receptor enzyme 2 (ACE-2) and CD209L. Autopsy studies of patient who have died of SARS show that the lung and intestinal tract are the primary sites of infection. Lung histology often shows diffuse alveolar damage with varying degrees of organization. Downregulation of ACE-2 caused by viral replication, which plays a protective role in acute lung injury, has been implicated in the development of ARDS in patients with SARS.

Clinical manifestations of SARS are a mild prodrome of fever and myalgias lasting 3 to 7 days, during which viral replication occurs. Respiratory symptoms, usually cough followed by dyspnea and hypoxemia, occur during the second week of the illness. Clinical worsening occurs during a time of decreasing viral load, and may be caused by immunopathologic injury rather than direct injury from the virus. Dyspnea may progress to respiratory failure, ARDS, and need for mechanical ventilation. The radiographic pattern of SARS is nonspecific, but it most commonly presents as ill-defined airspace opacities or ground-glass opacities, with progression to multifocal airspace opacities in patients who develop ARDS. The diagnosis of SARS is made from the presence of symptoms along with radiographic abnormalities or autopsy consistent with pneumonia and/or ARDS, and detection of virus by RT-PCR from 2 body-fluid samples, cell culture from a single sample, or detection of viral antibodies by enzyme-linked immunosorbent assay and/or immunofluorescent assays.

During the SARS pandemic approximately 20% of hospitalized patients developed ARDS. The management of patients with SARS and ARDS is primarily supportive with low-tidal-volume ventilation and other rescue therapies as indicated. Strict infection control measures should be instituted, including the isolation of affected patients, and the rigorous use of masks, gloves, and gowns by health care workers to prevent human-to-human transmission. During 2003, the most severely ill patients with SARS were treated with high-dose ribavirin, corticosteroids, or both. However, most experts agree that these therapies were of little or no benefit, and adverse effects of these therapies were common. SARS-CoV has been dormant since the end of the outbreak in 2004. Vaccine development has been ongoing, but the best approach remains an area of debate.

**Seasonal Viruses**

Seasonal respiratory viruses are identified in 22% to 36% of adults with community-acquired pneumonia who require ICU admission. Influenza and rhinoviruses (human rhinoviruses [HRVs]) are the most frequently detected viruses, but respiratory syncytial virus (RSV), coronaviruses, parainfluenza virus (PIV), human metapneumovirus (hMPV), and adenovirus are also commonly reported. Whether these viruses are
the sole cause of pneumonia or ARDS is controversial; however, bacteria are less commonly identified than viruses even when invasive methods such as bronchoscopy are routinely used to test for the cause of pneumonia. Although the precise frequency of ARDS caused by seasonal respiratory viruses is unknown, the overall frequency is probably very low.

**Rhinovirus**

HRV, a single-stranded RNA virus of the Picornaviridae family, is the most common cause of upper respiratory tract infections in adults and children. HRV is also one of the most commonly identified viruses in adults admitted to hospital and ICU with CAP. Whether rhinovirus is the sole cause of pneumonia, an incidental finding, a risk factor for bacterial or viral coinfection, or asymptomatic carriage, is controversial. In adults with radiographically proven CAP, rhinovirus is identified more frequently in patients with CAP compared with asymptomatic controls. HRV has been shown to trigger cytokine release in both the lower respiratory epithelium and blood, suggesting a potential pathogenic link to both pneumonia and ARDS.

Rhinovirus has been reported as a cause of ARDS most frequently in elderly and immunocompromised adults. Autopsy findings of 4 bone marrow transplant patients with suspected HRV pneumonia showed findings consistent with viral pneumonia, including acute and chronic interstitial pneumonitis and diffuse alveolar damage with hyaline membrane consistent with ARDS. Among patients with pneumonia admitted to an ICU at a single center in South Korea, 96.2% of patients with HRV pneumonia required mechanical ventilation, and 59.3% had diffuse abnormalities on CXR suggestive of ARDS.

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**Respiratory Syncytial Virus**

RSV, an enveloped paramyxovirus, is an important cause of lower respiratory tract infection in children but can infect people at all ages. RSV subtypes A and B are responsible for most human disease. RSV epidemics occur during the winter months and overlap with seasonal influenza. In adults, RSV causes a range of clinical syndromes, including upper respiratory tract infection, bronchitis, respiratory failure, and ARDS. Adults with underlying cardiopulmonary disease, immunocompromised state, hematopoietic bone marrow transplant, and those more than 65 years of age are at risk for severe infection. In one study of elderly and hospitalized adults with RSV infection, 15% were admitted to the ICU, 13% required mechanical ventilation, and 8% died.

Antiviral therapy with ribavirin, in combination with human intravenous immunoglobulin (IVIG) or corticosteroids, may be beneficial in immunocompromised adults with severe pneumonia caused by RSV. A small case series suggested that both oral and inhaled ribavirin may improve morbidity and mortality in hematopoietic cell transplant recipients. Nonrandomized studies of adult lung transplant recipients with RSV infection suggested that combination therapy with corticosteroids and ribavirin is effective. Ribavirin should be used with caution in some patient populations. The inhaled formulation of ribavirin can provoke bronchospasm. Both inhaled and oral ribavirin are potential teratogens that should be used with caution in pregnant patients, and pregnant health care providers should avoid contact with patients receiving aerosolized ribavirin.

**Parainfluenza Virus**

PIVs are single-stranded, enveloped RNA viruses of the Paramyxoviridae family. Three serotypes cause clinical disease: PIV 1 and 2 are seen primarily in the fall and winter months, whereas PIV3 is seen in the spring and summer seasons. Although PIV infections are generally self-limited, hospitalization, ICU admission, and ARDS can occur. Patients with underlying obstructive lung disease and immunocompromised hosts may be more susceptible. In a retrospective cohort study of 253 hematopoietic cell transplant patients with PIV infection, 24.1% developed pneumonia and the associated mortality was 35%.
No antiviral agents have shown efficacy against PIV. Use of inhaled, oral, or intravenous ribavirin for the treatment of PIV has been described in case reports. However, a retrospective study of hematopoietic cell transplant recipients with parainfluenza who received inhaled ribavirin combined with IVIG or corticosteroids showed no benefit in terms of either viral shedding or mortality. DAS181, an investigational sialidase fusion protein, has in vitro activity against PIV but the efficacy of this drug in humans is not known.

**Human Metapneumovirus**

hMPV is an enveloped negative-sense RNA virus of the Paramyxoviridae family, discovered in 2001. hMPV infections show the seasonal variation typical of RSV and are usually mild and self-limiting. hMPV is difficult to culture in vitro, and the diagnosis is more readily made using RT-PCR from an NP or lower respiratory tract specimen. Respiratory failure and ARDS caused by hMPV have been reported in adults, including residents of long-term care facilities and severely immunocompromised patients, such as those with bone marrow transplant and acquired human deficiency syndrome. In a case series of 128 hospitalized adults with hMPV infection, 31% required ICU admission and 14.8% developed ARDS.

Animal models show that hMPV infects bronchial epithelial cells, leading to bronchial hyperresponsiveness, and induces proinflammatory cytokines, including interleukin (IL)-2, IL-8, IL-4, and interferon alfa. Histopathologic changes suggestive of ARDS, including hyaline membrane formation and organizing pneumonia–like reaction, have been described in open-lung or transbronchial biopsy specimens of immunocompromised patients with hMPV identified on BAL. Murine models have also shown that hMPV increases the risk of severe secondary pneumococcal infection similar to influenza A virus.

Antiviral therapy for hMPV is not well established, but several antiviral agents for severe hMPV are under investigation. Ribavirin limits viral replication and downregulates cytokine production in in vivo and mouse models; however, uncontrolled case series of patients with hMPV infection treated with ribavirin have not shown a consistent improvement in outcomes. A monoclonal antibody against the hMPV fusion protein seems to have both prophylactic and therapeutic benefit in mouse models but studies in human subjects are currently lacking.

**Adenovirus**

The adenovirus is part of the nonenveloped family of viruses with a double-stranded DNA genome. The true incidence of adenovirus in adults is difficult to estimate because testing for this virus is not routinely done; in most series, adenovirus is found in 1% of ICU patients. In addition to typical lower respiratory symptoms, adults with adenovirus pneumonia may also present with abdominal complaints, such as diarrhea, and neurologic manifestations, such as encephalitis and seizures. Outbreaks of severe adenovirus pneumonia have been reported in military recruits, residents of long-term care facilities, and immunocompromised individuals. Although rare, ARDS has been reported in immunocompetent adults. Adenovirus can be detected by RT-PCR from an NP, lower respiratory, or stool sample, but the diagnosis should be confirmed by PCR or cell culture detection from a sterile site such as blood, cerebrospinal fluid, or tissue biopsy.

In addition to supportive care, patients with severe adenovirus pneumonia and ARDS may benefit from antiviral therapy. Cidofovir, a mononucleotide analog of cytosine, reduces viral load and improves clinical symptoms in patients with hematopoietic stem cell transplant and invasive adenoviral disease compared with historical controls. In a case series of 7 immunocompetent adults with adenovirus pneumonia who were administered cidofovir within 48 hours of diagnosis, all survived and had radiographic resolution of pneumonia by 21 days. Brincidofovir, a lipid-linked derivative of cidofovir, is currently under phase III clinical trials in hematopoietic stem cell transplant patients. Pooled human IVIG has high levels of neutralizing antibodies against adenoviruses and can be used as adjunctive therapy. In a retrospective review, the use of corticosteroids in immunocompetent patients with adenovirus pneumonia did not show any benefit.

**SUMMARY**

Respiratory viruses are a common cause of severe pneumonia and ARDS in adults. The advent of new diagnostic technologies, particularly multiplex reaction-PCR, have increased the recognition of viral respiratory infections in critically ill adults. Supportive care for adults with ARDS caused by respiratory viruses is similar to the care of patients with ARDS from other causes. Although antiviral therapy is available for some respiratory viral infections, further research is needed to determine which groups of patients would benefit.
REFERENCES

1. Ashbaugh DG, Bigelow DB, Petty TL, et al. Acute respiratory distress in adults. Lancet 1967;2:319–23.
2. Force ADT, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307:2526–33.
3. Bernard GR, Artigas A, Brigham KL, et al. Report of the American-European Consensus Conference on Acute Respiratory Distress Syndrome: definitions, mechanisms, relevant outcomes, and clinical trial coordination. Consensus Committee 1994;9:72–81.
4. Torres A, Serra-Batlles J, Ferrer A, et al. Severe community-acquired pneumonia. Epidemiology and prognostic factors. Am Rev Respir Dis 1991;144:312–8.
5. Choi SH, Hong SB, Ko GB, et al. Viral infection in patients with severe pneumonia requiring intensive care unit admission. Am J Respir Crit Care Med 2012;186:325–32.
6. Nguyen C, Kaku S, Tutera D, et al. Viral respiratory infections of adults in the intensive care unit. J Intensive Care Med 2015;31(7):427–41.
7. Legoff J, Guerot E, Ndjoyi-Mbiguino A, et al. High prevalence of respiratory viral infections in patients hospitalized in an intensive care unit for acute respiratory infections as detected by nucleic acid-based assays. J Clin Microbiol 2005;43:455–7.
8. Wu X, Wang Q, Wang M, et al. Incidence of respiratory viral infections detected by PCR and real-time PCR in adult patients with community-acquired pneumonia: a meta-analysis. Respiration 2015;89:343–52.
9. Karhu J, Ala-Kokko TI, Vuorinen T, et al. Lower respiratory tract virus findings in mechanically ventilated patients with severe community-acquired pneumonia. Clin Infect Dis 2014;59:62–70.
10. Garg S, Jain S, Dawood FS, et al. Pneumonia among adults hospitalized with laboratory-confirmed seasonal influenza virus infection—United States, 2005–2008. BMC Infect Dis 2015;15:369.
11. Hong HL, Hong SB, Ko GB, et al. Viral infection is not uncommon in adult patients with severe hospital-acquired pneumonia. PLoS One 2014;9: e95865.
12. Jain S, Self WH, Wunderink RG. Community-acquired pneumonia requiring hospitalization. N Engl J Med 2015;373:2382.
13. Wiemken T, Peyrani P, Bryant K, et al. Incidence of respiratory viruses in patients with community-acquired pneumonia admitted to the intensive care unit: results from the Severe Influenza Pneumonia Surveillance (SIPS) project. Eur J Clin Microbiol Infect Dis 2013;32:705–10.
14. Self WH, Williams DJ, Zhu Y, et al. Respiratory viral detection in children and adults: comparing asymptomatic controls and patients with community-acquired pneumonia. J Infect Dis 2016;213:584–91.
15. Pavia AT. What is the role of respiratory viruses in community-acquired pneumonia? What is the best therapy for influenza and other viral causes of community-acquired pneumonia? Infect Dis Clin North Am 2013;27:157–75.
16. Gadsby NJ, Russell CD, McHugh MP, et al. Comprehensive molecular testing for respiratory pathogens in community-acquired pneumonia. Clin Infect Dis 2016;62:817–23.
17. Loffler B, Niemann S, Ehrhardt C, et al. Pathogenesis of Staphylococcus aureus necrotizing pneumonia: the role of PVL and an influenza coinfection. Expert Rev Anti Infect Ther 2013;11:1041–51.
18. Zhan Y, Yang Z, Chen R, et al. Respiratory virus is a real pathogen in immunocompetent community-acquired pneumonia: comparing to influenza like illness and volunteer controls. BMC Pulm Med 2014;14:144.
19. Campbell AP, Guthrie KA, Englund JA, et al. Clinical outcomes associated with respiratory virus detection before allogeneic hematopoietic stem cell transplant. Clin Infect Dis 2015;61:192–202.
20. Zlateva KT, de Vries JJ, Coenjaerts FE, et al. Prolonged shedding of rhinovirus and re-infection in adults with respiratory tract illness. Eur Respir J 2014;44:169–77.
21. Dawood FS, Jain S, Finelli L, et al. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. N Engl J Med 2009;360:2605–15.
22. Garten RJ, Davis CT, Russell CA, et al. Antigenic and genetic characteristics of swine-origin 2009 A(H1N1) influenza viruses circulating in humans. Science 2009;325:197–201.
23. Howard WA, Peiris M, Hayden FG. Report of the ‘mechanisms of lung injury and immunomodulator interventions in influenza’ workshop, 21 March 2010, Ventura, California, USA. Influenza Other Respir Viruses 2011;5:453–4. e458–75.
24. Hendrickson CM, Matthay MA. Viral pathogens and acute lung injury: investigations inspired by the SARS epidemic and the 2009 H1N1 influenza pandemic. Semin Respir Crit Care Med 2013;34:475–86.
25. Gralinski LE, Baric RS. Molecular pathology of emerging coronavirus infections. J Pathol 2015;235:185–95.
26. Herold S, Becker C, Ridge KM, et al. Influenza virus-induced lung injury: pathogenesis and implications for treatment. Eur Respir J 2015;45:1463–78.
27. Itoh Y, Shinya K, Kiso M, et al. In vitro and in vivo characterization of new swine-origin H1N1 influenza viruses. Nature 2009;460:1021–5.
28. Shieh WJ, Blau DM, Denison AM, et al. 2009 pandemic influenza A (H1N1): pathology and pathogenesis of 100 fatal cases in the United States. Am J Pathol 2010;177:166–75.

29. Fujita J, Ohtsuki Y, Higa H, et al. Clinicopathological findings of four cases of pure influenza virus A pneumonia. Intern Med 2014;53:1333–42.

30. Wang R, Xiao H, Guo R, et al. The role of C5a in acute lung injury induced by highly pathogenic viral infections. Emerg Microbes Infect 2015;4:e28.

31. To KK, Hung IF, Li IW, et al. Delayed clearance of viral load and marked cytokine activation in severe cases of pandemic H1N1 2009 influenza virus infection. Clin Infect Dis 2010;50:850–9.

32. Luks AM. Ventilatory strategies and supportive care in acute respiratory distress syndrome. Influenza other Respir viruses 2013;7(Suppl 3):8–17.

33. Liolios L, Jenney A, Spelman D, et al. Comparison of a multiplex reverse transcription-PCR-enzyme hybridization assay with conventional viral culture and immunofluorescence techniques for the detection of seven viral respiratory pathogens. J Clin Microbiol 2001;39:2779–83.

34. Puppe W, Weigl JA, Aron G, et al. Evaluation of a multiplex reverse transcriptase PCR ELISA for the detection of nine respiratory tract pathogens. J Clin Virol 2004;30:165–74.

35. Meerhoff TJ, Houben ML, Coenjaerts FE, et al. Detection of multiple respiratory pathogens during primary respiratory infection: nasal swab versus nasopharyngeal aspirate using real-time polymerase chain reaction. Eur J Clin Microbiol Infect Dis 2010;29:365–71.

36. Wurzel DF, Marchant JM, Clark JE, et al. Respiratory virus detection in nasopharyngeal aspirate versus bronchoalveolar lavage is dependent on virus type in children with chronic respiratory symptoms. J Clin Virol 2013;58:683–8.

37. Azadéh N, Sakata KK, Brighton AM, et al. FilmArray respiratory panel assay: comparison of nasopharyngeal swabs and bronchoalveolar lavage samples. J Clin Microbiol 2015;53:3784–7.

38. Hakki M, Strasfeld LM, Townes JM. Predictive value of testing nasopharyngeal samples for respiratory viruses in the setting of lower respiratory tract disease. J Clin Microbiol 2014;52:4020–2.

39. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 2000;342:1301–8.

40. Brochard L, Roudot-Thoraval F, Roupie E, et al. Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trail Group on Tidal Volume reduction in ARDS. Am J Respir Crit Care Med 1998;158:1831–8.

41. Amato MB, Barbas CS, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 1999;338:347–54.

42. Guerin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013;368:2159–68.

43. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010;363:1107–16.

44. Al-Dorzi HM, Alsolamy S, Arabi YM. Critically ill patients with Middle East respiratory syndrome coronavirus infection. Crit Care 2016;20:65.

45. Rana S, Jenad H, Gay PC, et al. Failure of noninvasive ventilation in patients with acute lung injury: observational cohort study. Crit Care 2006;10:R79.

46. Correa TD, Sanches PR, de Morais LC, et al. Performance of noninvasive ventilation in acute respiratory failure in critically ill patients: a prospective, observational, cohort study. BMC Pulm Med 2015;15:144.

47. Rello J, Rodriguez A, Ibanez P, et al. Intensive care adult patients with severe respiratory failure caused by Influenza A (H1N1)v in Spain. Crit Care (London, England) 2009;13:R148.

48. Viasus D, Pano-Pardo JR, Pachon J, et al. Pneumonia complicating pandemic (H1N1) 2009: risk factors, clinical features, and outcomes. Medicine 2011;90:328–36.

49. Palacios G, Hornig M, Cisterna D, et al. Streptococcus pneumoniae coinfection is correlated with the severity of H1N1 pandemic influenza. PLoS One 2009;4:e8540.

50. Choi SH, Hong SB, Hong HL, et al. Usefulness of cellular analysis of bronchoalveolar lavage fluid for predicting the etiology of pneumonia in critically ill patients. PLoS One 2014;9:e97346.

51. Barlow G, Moss P. A/H1N1 flu... as does policy on antibiotics. BMJ 2009;339:b2738.

52. Crotty MP, Meyers S, Hampton N, et al. Impact of antibacterials on subsequent resistance and clinical outcomes in adult patients with viral pneumonia: an opportunity for stewardship. Crit Care (London, England) 2015;19:404.

53. Bernard GR, Luce JM, Sprung CL, et al. High-dose corticosteroids in patients with the adult respiratory distress syndrome. N Engl J Med 1987;317:1565–70.

54. Steinberg KP, Hudson LD, Goodman RB, et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med 2006;354:1671–84.

55. Brun-Buisson C, Richard JC, Mercat A, et al. Early corticosteroids in severe influenza A/H1N1 pneumonia and acute respiratory distress syndrome. Am J Respir Crit Care Med 2011;183:1200–6.
56. Auyeung TW, Lee JS, Lai WK, et al. The use of corticosteroid as treatment in SARS was associated with adverse outcomes: a retrospective cohort study. J Infect 2005;51:98–102.
57. Combes A, Pellegrino V. Extracorporeal membrane oxygenation for 2009 influenza A (H1N1)-associated acute respiratory distress syndrome. Semin Respir Crit Care Med 2011;32:188–94.
58. Davies A, Jones D, Bailey M, et al. Extracorporeal membrane oxygenation for 2009 influenza A(H1N1) acute respiratory distress syndrome. JAMA 2009;302:1888–95.
59. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet 2009;374:1351–63.
60. Pham T, Combes A, Roze H, et al. Extracorporeal membrane oxygenation for pandemic influenza A(H1N1)-induced acute respiratory distress syndrome: a cohort study and propensity-matched analysis. Am J Respir Crit Care Med 2013;187:276–85.
61. Ortiz JR, Neuzil KM, Shay DK, et al. The burden of influenza-related critical illness hospitalizations. Crit Care Med 2014;42:2325–32.
62. Webster RG, Sharp GB, Claas EC. Interspecies transmission of influenza viruses. Am J Respir Crit Care Med 1995;152:S25–30.
63. Moura FE. Influenza in the tropics. Curr Opin Infect Dis 2010;23:415–20.
64. Reed C, Chaves SS, Daily Kirley P, et al. Estimating influenza disease burden from population-based surveillance data in the United States. PLoS One 2015;10:e0118369.
65. Harper SA, Bradley JS, Englund JA, et al. Seasonal influenza in adults and children—diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 2009;48:1003–32.
66. Shah NS, Greenberg JA, McNulty MC, et al. Severe influenza in 33 US hospitals, 2013-2014: complications and risk factors for death in 507 patients. Infect Control Hosp Epidemiol 2015;36:1251–60.
67. Bautista E, Chotpitayasunondh T, Gao Z, et al. Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. N Engl J Med 2010;362:1708–19.
68. Perez-Padilla R, de la Rosa-Zamboni D, Ponce de Leon S, et al. Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. N Engl J Med 2009;361:680–9.
69. Webb SA, Pettila V, Seppelt I, et al. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. N Engl J Med 2009;361:1925–34.
70. Shrestha SS, Swerdlow DL, Borse RH, et al. Estimating the burden of 2009 pandemic influenza A (H1N1) in the United States (April 2009-April 2010). Clin Infect Dis 2011;52(Suppl 1):S75–82.
71. Jain S, Kamimoto L, Bramley AM, et al. Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. N Engl J Med 2009;361:1935–44.
72. Louie JK, Acosta M, Winter K, et al. Factors associated with death or hospitalization due to pandemic 2009 influenza A(H1N1) infection in California. JAMA 2009;302:1896–902.
73. Kumar A, Zarychanski R, Pinto R, et al. Critically ill patients with 2009 influenza A(H1N1) infection in Canada. JAMA 2009;302:1872–9.
74. Kim EA, Lee KS, Primack SL, et al. Viral pneumonias in adults: radiologic and pathologic findings. Radiographics 2002;22 Spec No:S137–49.
75. Chertow DS, Memoli MJ. Bacterial coinfection in influenza: a grand rounds review. JAMA 2013;309:275–82.
76. Rice TW, Rubinson L, Uyeki TM, et al. Critical illness from 2009 pandemic influenza A virus and bacterial coinfection in the United States. Crit Care Med 2012;40:1487–98.
77. Rothberg MB, Haessler SD. Complications of seasonal and pandemic influenza. Crit Care Med 2010;38:e91–7.
78. Noriega LM, Verdugo RJ, Araos R, et al. Pandemic influenza A (H1N1) 2009 with neurological manifestations, a case series. Influenza other Respir viruses 2010;4:117–20.
79. South East Asia Infectious Disease Clinical Research Network. Effect of double dose oseltamivir on clinical and virological outcomes in children and adults admitted to hospital with severe influenza: double blind randomised controlled trial. BMJ 2013;346:f3039.
80. Lee N, Hui DS, Zuo Z, et al. A prospective intervention study on higher-dose oseltamivir treatment in adults hospitalized with influenza A and B infections. Clin Infect Dis 2013;57:1511–9.
81. Heneghan CJ, Onakpoya I, Thompson M, et al. Zanamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. BMJ 2014;348:g2547.
82. Kiatboonsri S, Kiatboonsri C, Theerawit P. Fatal respiratory events caused by zanamivir nebulization. Clin Infect Dis 2010;50:620.
83. Gaur AH, Bagga B, Barman S, et al. Intravenous zanamivir for oseltamivir-resistant 2009 H1N1 influenza. N Engl J Med 2010;362:88–9.
84. Delaney JW, Pinto R, Long J, et al. The influence of corticosteroid treatment on the outcome of influenza A(H1N1pdm09)-related critical illness. Crit Care (London, England) 2016;20:75.
85. Han K, Ma H, An X, et al. Early use of glucocorticoids was a risk factor for critical disease and death from pH1N1 infection. Clin Infect Dis 2011; 53:326–33.

86. Choi SM, Boudreault AA, Xie H, et al. Differences in clinical outcomes after 2009 influenza A/H1N1 and seasonal influenza among hematopoietic cell transplant recipients. Blood 2011;117:5050–6.

87. de Groot RJ, Baker SC, Baric RS, et al. Middle East respiratory syndrome coronavirus (MERS-CoV): announcement of the Coronavirus Study Group. J Virol 2013;87:7790–2.

88. Zaki AM, van Boheemen S, Bestebroer TM, et al. Middle East respiratory syndrome (MERS). Available at: http://www.cdc.gov/coronavirus/mers/about/index.html. Accessed December 3, 2016.

89. Middle East respiratory syndrome (MERS). Available at: http://www.cdc.gov/coronavirus/mers/about/index.html. Accessed December 3, 2016.

90. Raj VS, Mou H, Smits SL, et al. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature 2013;495:251–4.

91. Azhar EI, El-Kafrawy SA, Farraj SA, et al. Evidence for camel-to-human transmission of MERS coronavirus. N Engl J Med 2014;370:2499–505.

92. Assiri A, McGeer A, Perl TM, et al. Hospital outbreak of Middle East respiratory syndrome coronavirus. N Engl J Med 2013;369:407–16.

93. Alsolamy S. Middle East respiratory syndrome: knowledge to date. Crit Care Med 2015;43:1283–90.

94. Guery B, Poissy J, el Mansouf L, et al. Clinical features and viral diagnosis of two cases of infection with Middle East respiratory syndrome coronavirus: a report of nosocomial transmission. Lancet 2013; 381:2265–72.

95. Assiri A, Al-Tawfiq JA, Al-Rabeeah AA, et al. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. Lancet Infect Dis 2013;13:752–61.

96. Saad M, Omrani AS, Baig K, et al. Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: a single-center experience in Saudi Arabia. Int J Infect Dis 2014;29:301–6.

97. Aijan AM, Ahyad RA, Jamjoom LG, et al. Middle East respiratory syndrome coronavirus (MERS-CoV) infection: chest CT findings. AJR Am J Roentgenology 2014;203:782–7.

98. Centers for Disease Control and Prevention (CDC). Update: severe respiratory illness associated with Middle East respiratory syndrome coronavirus (MERS-CoV)–worldwide, 2012-2013. MMWR Morb Mortal Wkly Rep 2013;62:480–3.

99. Lee JH, Lee CS, Lee HB. An appropriate lower respiratory tract specimen is essential for diagnosis of Middle East respiratory syndrome (MERS). J Korean Med Sci 2015;30:1207–8.

100. Arabi YM, Arifi AA, Balkhy HH, et al. Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. Ann Intern Med 2014;160:389–97.

101. Omrani AS, Saad MM, Baig K, et al. Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study. Lancet Infect Dis 2014;14:1090–5.

102. Corti D, Zhao J, Pedotti M, et al. Prophylactic and postexposure efficacy of a potent human monoclonal antibody against MERS coronavirus. Proc Natl Acad Sci U SA 2015;112:10473–8.

103. Poon LL, Guan Y, Nicholls JM, et al. The aetiology, origins, and diagnosis of severe acute respiratory syndrome. Lancet Infect Dis 2004;4:663–71.

104. Christian MD, Poutanen SM, Loutfy MR, et al. Severe acute respiratory syndrome. Clin Infect Dis 2004;38:1420–7.

105. Shi Z, Hu Z. A review of studies on animal reservoirs of the SARS coronavirus. Virus Res 2008; 133:74–87.

106. Donnelly CA, Fisher MC, Fraser C, et al. Epidemiological and genetic analysis of severe acute respiratory syndrome. Lancet 2003;361:1767–72.

107. Frieman M, Yount B, Agnihothram S, et al. Molecular determinants of severe acute respiratory syndrome coronavirus pathogenesis and virulence in young and aged mouse models of human disease. J Virol 2012;86:884–97.

108. Lau YL, Peiris JS. Pathogenesis of severe acute respiratory syndrome. Curr Opin Immunol 2005;17:404–10.

109. Peiris JS, Lai ST, Poon LL, et al. Coronavirus as a possible cause of severe acute respiratory syndrome. Lancet 2003;361:1319–25.

110. Nicholls JM, Poon LL, Lee KC, et al. Lung pathology of fatal severe acute respiratory syndrome. Lancet 2003;361:1773–8.

111. Imai Y, Kuba K, Penninger JM. Angiotensin-converting enzyme 2 in acute respiratory distress syndrome. Cell Mol Life Sci 2007;64:2006–12.

112. Peiris JS, Chu CM, Cheng VC, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. Lancet 2003;361:1767–72.

113. Chan JW, Ng CK, Chan YH, et al. Short term outcome and risk factors for adverse clinical outcomes in adults with severe acute respiratory syndrome (SARS). Thorax 2003;58:686–9.

114. Ketai L, Paul NS, Wong KT. Radiology of severe acute respiratory syndrome (SARS): the emerging pathologic-radiologic correlates of an emerging disease. J Thorac Imaging 2006;21:276–83.

115. Wong KT, Antonio GE, Hui DS, et al. Severe acute respiratory syndrome: radiographic appearances
and pattern of progression in 138 patients. Radiology 2003;228:401–6.

116. Case definitions for the 4 diseases requiring notification to WHO in all circumstances under the IHR (2005). Wkly Epidemiol Rec 2009;84:52–6 [In English, French].

117. Booth CM, Stewart TE. Severe acute respiratory syndrome and critical care medicine: the Toronto experience. Crit Care Med 2005;33:S53–60.

118. Manocha S, Walley KR, Russell JA. Severe acute respiratory distress syndrome (SARS): a critical care perspective. Crit Care Med 2003;31:2684–92.

119. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. PLoS Med 2006;3:e343.

120. Wang JT, Chang SC. Severe acute respiratory syndrome. Curr Opin Infect Dis 2004;17:143–8.

121. Graham RL, Donaldson EF, Baric RS. A decade after SARS: strategies for controlling emerging coronaviruses. Nat Rev Microbiol 2013;11:836–48.

122. Ruuskanen O, Lahti E, Jennings LC, et al. Viral pneumonia. Lancet 2011;377:1264–75.

123. Mackay IM. Human rhinoviruses: the cold wars resume. J Clin Virol 2008;42:297–320.

124. Lieberman D, Shimoni A, Shemer-Avni Y, et al. Respiratory viruses in adults with community-acquired pneumonia. Chest 2010;138:811–6.

125. Papadopoulos NG, Bates PJ, Bardin PG, et al. Rhinoviruses infect the lower airways. J Infect Dis 2004;181:1875–84.

126. Hayden FG. Rhinovirus and the lower respiratory tract. Rev Med Virol 2004;14:235–55.

127. Falsey AR, Hennessey PA, Formica MA, et al. Respiratory syncytial virus infection in elderly and high-risk adults. N Engl J Med 2005;352:1749–59.

128. Hynicka LM, Ensor CR. Prophylaxis and treatment of respiratory syncytial virus infection in adult immunocompromised patients. Ann Pharmacother 2012;46:558–66.

129. McColl MD, Corser RB, Bremner J, et al. Respiratory syncytial virus infection in adult transplantation: effective therapy with short duration nebulised ribavirin. Bone Marrow Transplant 1998;21:423–5.

130. Kraft CS, Jacob JT, Sears MH, et al. Severity of human rhinovirus infection in immunocompromised adults is similar to that of 2009 H1N1 influenza. J Clin Microbiol 2012;50:1061–3.

131. Hayden FG, Herrington DT, Coats TL, et al. Efficacy and safety of oral pleconaril for treatment of colds due to picornaviruses in adults: results of 2 double-blind, randomized, placebo-controlled trials. Clin Infect Dis 2003;36:1523–32.

132. Hayden FG, Albrecht JK, Kaiser DL, et al. Prevention of natural colds by contact prophylaxis with intranasal alpha 2-interferon. N Engl J Med 1986;314:71–5.

133. Hayden FG, Kaiser DL, Albrecht JK. Intranasal recombinant alfalfa 2b interferon treatment of naturally occurring common colds. Antimicrob Agents Chemother 1988;32:224–30.

134. Walsh EE, Peterson DR, Falsey AR. Is clinical recognition of respiratory syncytial virus infection in hospitalized elderly and high-risk adults possible? J Infect Dis 2007;195:1046–51.

135. Falsey AR, Walsh EE. Respiratory syncytial virus infection in adults. Clin Microbiol Rev 2000;13:371–84.

136. Murata Y. Respiratory syncytial virus infection in adults. Curr Opin Pulm Med 2008;14:235–40.

137. Neemann K, Freifeld A. Respiratory syncytial virus in hematopoietic stem cell transplantation and solid-organ transplantation. Curr Infect Dis Rep 2015;17:490.

138. Falsey AR, Hennessey PA, Formica MA, et al. Respiratory syncytial virus infection in elderly and high-risk adults. N Engl J Med 2005;352:1749–59.

139. Johnstone J, Majumdar SR, Fox JD, et al. Viral lower respiratory tract disease in hematopoietic stem cell transplantation. Curr Heart Lung Transplant Rep 2005;17:490–5.

140. Waghmare A, Campbell AP, Xie H, et al. Respiratory syncytial virus lower respiratory disease in hematopoietic cell transplant recipients: viral RNA detection in blood, antiviral treatment, and clinical outcomes. Clin Infect Dis 2013;57:1731–41.

141. Pelaez A, Lyon GM, Force SD, et al. Efficacy of oral ribavirin in lung transplant patients with respiratory syncytial virus lower respiratory tract infection. J Heart Lung transplantation 2009;28:67–71.

142. Glanville AR, Scott AI, Morton JM, et al. Intravenous ribavirin is a safe and cost-effective treatment for respiratory syncytial virus infection after lung transplantation. J Heart Lung transplantation 2005;24:2114–9.

143. Gross AE, Bryson ML. Oral ribavirin for the treatment of noninfluenza respiratory viral infections: a systematic review. Ann Pharmacother 2015;49:1125–35.
147. Moscona A, Porotto M, Palmer S, et al. A recombinant sialidase fusion protein effectively inhibits human parainfluenza viral infection in vitro and in vivo. J Infect Dis 2010;202:234–41.

148. Dhakal B, D’Souza A, Pasquini M, et al. DAS181 treatment of severe parainfluenza virus 3 pneumonia in allogeneic hematopoietic stem cell transplant recipients requiring mechanical ventilation. Case Rep Med 2016;2016:8503275.

149. van den Hoogen BG, de Jong JC, Groen J, et al. A newly discovered human pneumovirus isolated from young children with respiratory tract disease. Nat Med 2001;7:719–24.

150. Feuillet F, Lina B, Rosa-Calatrava M, et al. Ten years of human metapneumovirus research. J Clin Virol 2012;53:97–105.

151. Liao RS, Appelgate DM, Pelz RK. An outbreak of severe respiratory tract infection due to human metapneumovirus in a long-term care facility for the elderly in Oregon. J Clin Virol 2012;53:171–3.

152. Boivin G, De Serres G, Hamelin ME, et al. An outbreak of severe respiratory tract infection due to human metapneumovirus in a long-term care facility. Clin Infect Dis 2007;44:1152–8.

153. Godet C, Le Goff J, Beby-Defaux A, et al. Human metapneumovirus pneumonia in patients with hematological malignancies. J Clin Virol 2014;61:593–6.

154. Hasvold J, Sjoding M, Pohl K, et al. The role of human metapneumovirus in the critically ill adult patient. J Crit Care 2016;31:233–7.

155. Kuiken T, van den Hoogen BG, van Riel DA, et al. Experimental human metapneumovirus infection of cynomolgus macaques (Macaca fascicularis) results in virus replication in ciliated epithelial cells and pneumocytes with associated lesions throughout the respiratory tract. Am J Pathol 2004;164:1893–900.

156. Schildgen V, van den Hoogen B, Fouchier R, et al. Human metapneumovirus: lessons learned over the first decade. Clin Microbiol Rev 2011;24:734–54.

157. Sumino KC, Agapov E, Pierce RA, et al. Detection of severe human metapneumovirus infection by real-time polymerase chain reaction and histopathological assessment. J Infect Dis 2005;192:1052–60.

158. Hamelin ME, Couture C, Sackett M, et al. The prophylactic administration of a monoclonal antibody against human metapneumovirus attenuates viral disease and airways hyperresponsiveness in mice. Antivir Ther 2008;13:39–46.

159. Tate JE, Bunning ML, Lott L, et al. Outbreak of severe respiratory disease associated with emergent human adenovirus serotype 14 at a US air force training facility in 2007. J Infect Dis 2009;199:1419–26.

160. Shields AF, Hackman RC, Fife KH, et al. Adenovirus infections in patients undergoing bone marrow transplantation. N Engl J Med 1985;312:529–33.

161. Ison MG. Respiratory viral infections in transplant recipients. Antivir Ther 2007;12:627–38.

162. Sun B, He H, Wang Z, et al. Emergent severe acute respiratory distress syndrome caused by adenovirus type 55 in immunocompetent adults in 2013: a prospective observational study. Crit Care 2014;18:456.

163. Hakim FA, Tleyjeh IM. Severe adenovirus pneumonia in immunocompetent adults: a case report and review of the literature. Eur J Clin Microbiol Infect Dis 2008;27:153–8.

164. Neofytos D, Ojha A, Mookerjee B, et al. Treatment of adenovirus disease in stem cell transplant recipients with cidofovir. Biol Blood Marrow Transplant 2007;13:74–81.

165. Kim SJ, Kim K, Park SB, et al. Outcomes of early administration of cidofovir in non-immunocompromised patients with severe adenovirus pneumonia. PLoS One 2015;10:e0122642.

166. Wold WS, Toth K. New drug on the horizon for treating adenovirus. Expert Opin Pharmacother 2015;16:2095–9.

167. Tan D, Zhu H, Fu Y, et al. Severe community-acquired pneumonia caused by human adenovirus in immunocompetent adults: a multicenter case series. PLoS One 2016;11:e0151199.