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Viral Pneumonia and Acute Respiratory Distress Syndrome

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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.

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a severe form of inflammatory lung injury characterized by increased vascular permeability in the lung.[1] 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.[2,3] Community-acquired pneumonia (CAP) is the most common cause of ARDS that develops outside of the hospital.[4] Respiratory viruses are increasingly recognized in patients with severe CAP and ARDS.[5,6] This article reviews the epidemiology, diagnosis, and management of adult patients with severe pneumonia and ARDS caused by viral respiratory pathogens.

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.[7–9] 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.[10,11] In the Etiology of Pneumonia in the Community (EPIC) study, a population-based surveillance for CAP, respiratory viruses were identified in 22% of adults admitted to the ICU with radiographically proven pneumonia.[12] In a prospective, observational study of consecutive patients admitted to an ICU with CAP in 6 hospitals in Kentucky, respiratory viruses were identified in 23% of adults.[13] In a retrospective study of 198 patients with pneumonia admitted to a single ICU in South Korea, 36.4% had evidence of viral pneumonia, including 23 patients with a virus identified in bronchoalveolar lavage (BAL).[5] In

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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[5] 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.[14,15] 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.[16–20]

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 the identical to those seen in mild cases.[21,22] 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.[23–26] 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.[27] Specific cytokine profiles vary by virus, but converge on a common end pathway, resulting in the pathologic hallmark of ARDS, diffuse alveolar damage.[28–30] 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.[31]

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,[2] 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.[32]

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.[33,34] Multiplex RT-PCR testing using specimens collected from nasopharyngeal (NP)

Box 1
Definition of acute respiratory distress syndrome, Berlin criteria

Within 1 week of known clinical insult or new or worsening respiratory symptoms.

Bilateral opacities on chest imaging not fully explained by effusions, lobar/lung collapse, or nodules.

Respiratory failure not explained by cardiac failure or fluid overload. Need objective assessment such as echocardiography to exclude hydrostatic edema if no risk factor present.

Impaired oxygenation:

- Mild: 200< P_aO_2/FiO_2 ≤300 with PEEP or CPAP ≥5 cm H_2O
- Moderate: 100< P_aO_2/FiO_2 ≤200 with PEEP ≥5 cm H_2O
- Severe: P_aO_2/FiO_2 ≤100 with PEEP ≥5 cm H_2O

Abbreviations: CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure.

Adapted from Force ADT, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307:2526–33.

aspirate or BAL have higher sensitivity compared with nasal swab.[35] Studies comparing BAL and NP aspirate have not shown one method to be superior to the other.[36] 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,[45,46] 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 coinfection from viral pneumonia alone.[5,50] 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.[26,61] 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 south 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.[65,66]

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.[47,68,69] 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 pnuemonia.[76] Other important complications of influenza in critically ill patients include venous thromboembolism, myocarditis, rhabdomyolysis, and neurologic manifestations (confusion, seizures, unconsciousness, encephalopathy, quadriparesis, and encephalitis).[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.[95] Diagnosis is made using RT-PCR obtained from

an NP, lower respiratory, or serum specimen.[98] 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.[99]

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.[100] Combination antiviral therapy with high-dose interferon alfa-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 alfa-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.[101] In 2015, a MERS-CoV antibody, LCA60, was isolated from memory B cells of a human patient previously infected with the virus.[102] 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.[103] Between 2002 and mid-2004, a total of 8096 cases of SARS were reported, with a case fatality rate of 9.6%.[104] The animal reservoir for SARS is not known, although both palm civets and bats have been implicated.[105] During epidemics, SARS spread from person to person by respiratory droplets, and to a lesser extent by airborne and fecal-oral transmission.[106] 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.[107,108] Autopsy studies of patient who have died of SARS show that the lung and intestinal tract are the primary sites of infection.[109] Lung histology often shows diffuse alveolar damage with varying degrees of organization.[110] 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.[111]

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.[112] Dyspnea may progress to respiratory failure, ARDS, and need for mechanical ventilation.[113] 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.[114,115] 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.[116]

During the SARS pandemic approximately 20% of hospitalized patients developed ARDS.[117,118] 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.[119,120] 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.[121]

Seasonal Viruses

Seasonal respiratory viruses are identified in 22% to 36% of adults with community-acquired-pneumonia who require ICU admission.[5,12,122] 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.[5] 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.[123] 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.[15] In adults with radiographically proven CAP, rhinovirus is identified more frequently in patients with CAP compared with asymptomatic controls.[14,124] 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.[125,126]

Rhinovirus has been reported as a cause of ARDS most frequently in elderly and immunocompromised adults.[127] 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.[128] 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.[129] In another retrospective analysis of 80 hospitalized adults with HRV infection, 27.4% of whom were immunocompromised, 50% had radiographic evidence of pneumonia and 11.3% required ICU admission.[130] In these cohorts, mortality related to HRV ranged from 2.3% to 55.7% and was highest among patients with an underlying immunocompromised state.

There is no clear role for antiviral therapy in critically ill adults with HRV pneumonia. The capsid-binding anti-HRV agent pleconaril reduces the duration of uncomplicated HRV upper respiratory infections by 1 day; however, the drug was not approved for clinical use because of concern for drug-drug interactions.[131] Intranasal recombinant interferon alfa-2b is effective in preventing HRV colds when used for postexposure prophylaxis but is not effective for treatment of established HRV infection.[132,133] Further studies of antiviral therapy in patients with HRV and critical illness are needed.

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.[134] In adults, RSV causes a range of clinical syndromes, including upper respiratory tract infection, bronchitis, respiratory failure, and ARDS.[135] 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.[136,137] In one study of elderly and hospitalized adults with RSV infection, 15% were admitted to the ICU, 13% required mechanical ventilation, and 8% died.[138]

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.[139] A small case series suggested that both oral and inhaled ribavirin may improve morbidity and mortality in hematopoietic cell transplant recipients.[140,141] Nonrandomized studies of adult lung transplant recipients with RSV infection suggested that combination therapy with corticosteroids and ribavirin is effective.[142,143] 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.[12,144] 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%.[145]

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.[146] 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.[145] DAS181, an investigational sialidase fusion protein, has in vitro activity against PIV but the efficacy of this drug in humans is not known.[147,148]

Human Metapneumovirus

hMPV is an enveloped negative-sense RNA virus of the Paramyxoviridae family, discovered in 2001.[149] 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.[150] Respiratory failure and ARDS caused by hMPV have been reported in adults, including residents of long-term care facilities[151,152] and severely immunocompromised patients, such as those with bone marrow transplant[153] and acquired human deficiency syndrome.[28] In a case series of 128 hospitalized adults with hMPV infection, 31% required ICU admission and 14.8% developed ARDS.[154]

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.[155,156] 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.[157] Murine models have also shown that hMPV increases the risk of severe secondary pneumococcal infection similar to influenza A virus.[158]

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 modelsl[159]; however, uncontrolled case series of patients with hMPV infection treated with ribavirin have not shown a consistent improvement in outcomes.[160,161] A monoclonal antibody against the hMPV fusion protein seems to have both prophylactic and therapeutic benefit in mouse models[162] 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.[5,12,13] 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,[163] residents of long-term care facilities,[164] and immunocompromised individuals.[165,166] Although rare, ARDS has been reported in immunocompetent adults.[167,168] 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.[169] 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.[170] Brincidofovir, a lipid-linked derivative of cidofovir, is currently under phase III clinical trials in hematopoietic stem cell transplant patients.[171] Pooled human IVIG has high levels of neutralizing antibodies against adenoviruses and can be used as adjunctive therapy.[169] In a retrospective review, the use of corticosteroids in immunocompetent patients with adenovirus pneumonia did not show any benefit.[172]

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.

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